*Tetrahedron* Vol. 41, No. 23, pp. 5465 to 5474, 1985
Printed in Great Britain.

0040-4020/85 $3.00+.00


# NEW SYNTHESIS OF HETEROCYCLES BY USE OF PALLADIUM CATALYZED CYCLIZATION OF α-HALOAMIDE WITH INTERNAL DOUBLE BOND

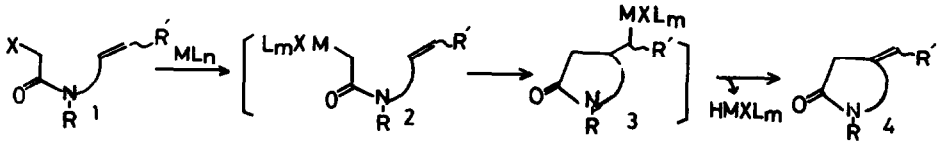
Miwako Mori*, Nana Kanda, Izumi Oda, and Yoshio Ban

Faculty of Pharmaceutical Sciences, Hokkaido University,
Sapporo 060, Japan

(*Received in Japan* 24 *June* 1985)

Abstract ---- α-Haloamide having internal double bond was allowed to react with a catalytic amount of $Pd(PPh_3)_4$ in the presence of base to produce a cyclized product in a fairly good yield possibly through the intermediate of -alkylmetal complex. By use of this method, five and six membered lactams, pyrrolizidine and quinolizidine derivatives were synthesized in fairly good yields.

It is generally known that aryl or vinyl halides can oxidatively add to the low-valent transition metal complexes to produce the reactive intermediates (=-$MXL_m$), which are useful for organic syntheses. We have already reported the new synthetic methods of heterocycles via aryl or vinylmetal complexes,[1] and now tried to extend this reaction to alkyl halides. According to the literature, it was already known that an alkyl halide such as methyl, allyl or benzyl halide afforded an alkylmetal complex.[2] However, other alkylmetal complexes($RMXL_m$) could not be obtained by reaction of alkyl halides with the low-valent transition metal complexes because such alkylmetal complexes convert easily to olefins and hydride metal complexes when they possess the β-hydrogen with respect to the metal. Recently, Ito et al. reported that a fairly stable α-alkylmetal complex could be formed from silyl enol ether and the divallent palladium complex via oxo-π-allylpalladium complex(eq.1).[3] The reaction of α-halocarbonyl compound 1 having internal double bond with the low-valent transition metal complex, however, could be expected to afford a fairly stable σ-alkylmetal complex 2, because such a complex does not possess the β-hydrogen. These σ-alkylmetal complex 2 should react with the internal double bond to afford a cyclized product 4 via an organometallic complex 3. We report in this paper these types of successful reactions for the synthesis of heterocycles.[4]



Syntheses of Five and Six Membered Lactams

N-Benzyl-N-iodoacetyl-2-propenylamine 1a was allowed to react with an equimolar amount of $Pd(PPh_3)_4$ at 65° for 5.5 h to afford the cyclized products 4a and 5a in the yield of 14 % and 23 %, respectively. The former compound was an expected product via the intermediate of σ-alkylmetal complex 3, and the latter 5a was considered to be a reductive elimination product from 3. Compound 1b was treated in the same manner to afford the cyclized products 4b, 4b' and 5b. To confirm the structure of these products, compound 5b and 4b, 4b' were reduced to N-benzyl-3-ethyl-2-pyrrolidone 7 with $NaBH_4$ in the presence of $n\text{-}Bu_4NBr$[5] and with $PtO_2$ in EtOH, respectively. In order to increase the yield of the desired products and to investigate the reaction mechanism, this reaction was examined under the various reaction conditions. These results were summarized in Table 1 and 2. There is no reaction in the absence of the metal catalyst(Run 2). Though the reaction proceeded catalytically for $Pd(PPh_3)_4$(Run 4), even an equimolar amount of $Ni(PPh_3)_4$ gave only a small amount of a cyclized product 4a(Run 3). Divalent palladium complex [$Pd(acac)_2$] or a catalytic amount of $Pd(OAc)_2$-$PPh_3$ did not afford a good result(Run 5 and 6). In order to avoid the formation of the triphenylphosphonium salt of α-haloamide, o-tolyl triphenylphosphine was used instead of $PPh_3$, but, the desired compound could not be obtained(Run 7). On the other hand, N-Benzyl-N-bromoacetyl-2-propenylamine was treated in the same manner to afford only low yields of the cyclized compounds 4a(6 %) and 6a(2 %).

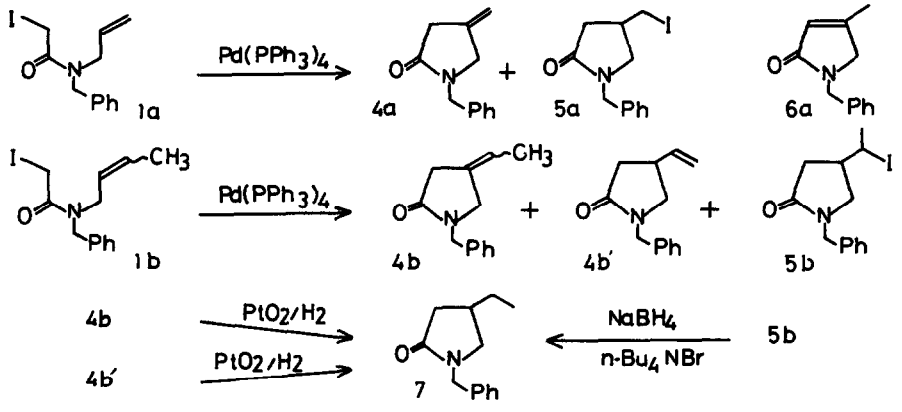



Table 1 Reaction of compound 1a with the various metal catalysts

| Run | Catalyst(mol eq.) | Yield of Cyclized Products | Recovery of 1 | Ratio of 4a : 5a |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ (1.00) | 37 % | - | 1 : 1.6 |
| 2 | $PPh_3$ (0.25) | 0 | 58 % | |
| 3 | $Ni(PPh_3)_4$ (1.00) | 10 | - | 1 : 0 |
| 4 | $Pd(PPh_3)_4$ (0.10) | 25 | - | 0 : 1 |
| 5 | $Pd(acac)_2$ (0.05) | 0 | 71 | |
| 6 | $Pd(OAc)_2$ (0.05) -$PPh_3$ (0.20) | 4 | 53 | 0 : 1 |
| 7 | $Pd(OAc)_2$ (0.05) -(o-tolyl-$PPh_3$)(0.20) | 0 | 61 | |

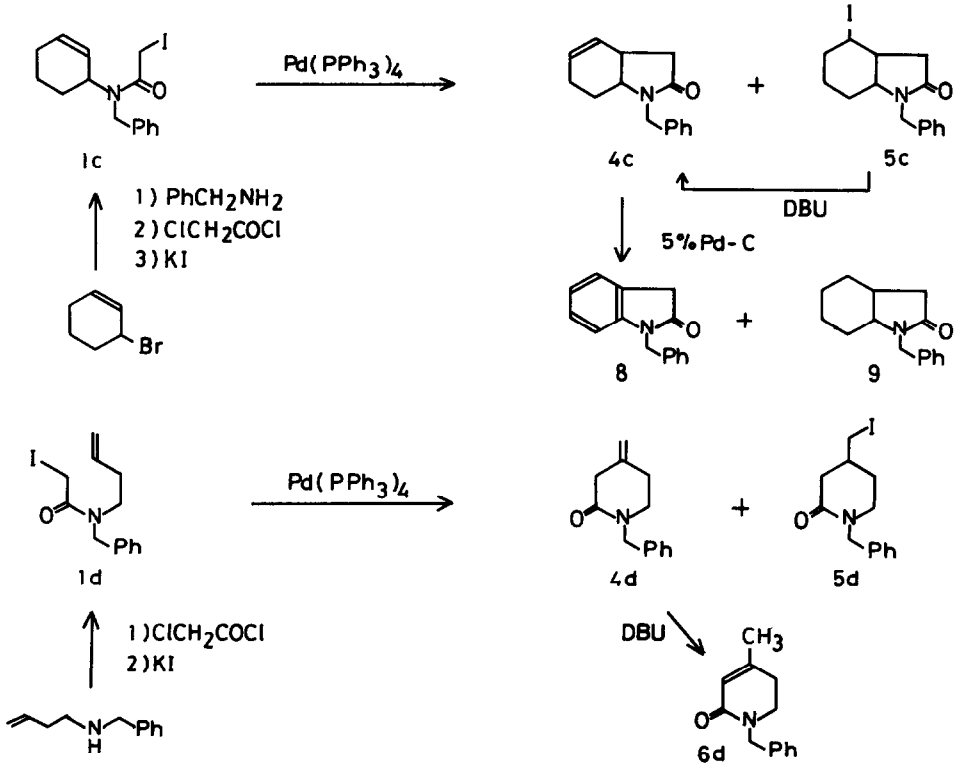
Solvent: DMF

Table 2 Reaction of compound 1 with $Pd(PPh_3)_4$(10 mol %) in the presence of proton sponge

| Run | Starting Material | Solvent | Yield of Cyclized Products | Ratio of 4 : 5 : 6 |
|---|---|---|---|---|
| 1 | 1a | DMF | 48 % | 0 : 2 : 1 |
| 2 | 1a | HMPA | 80 | 3 : 2 : 1 |
| 3 | 1b | DMF | 45 | 0 : 1 : 0 |
| 4 | 1b | HMPA | 67 | 1.6 : 1 : 0 |

To regenerate the zerovalent metal complex from hydride metal complex, the base such as $NEt_3$ or n-$Bu_3N$ was required. Since these bases should afford the ammonium salts of the starting material, the reaction was carried out in the presence of bis(1,8-dimethylamino)-naphthalene (proton sponge) as a base to afford the desired cyclized products in fairly good yields(Table 2). Though acetonitrile($CH_3CN$), dimethylformamide(DMF), toluene and hexamethylphosphoroamide (HMPA) can be used as the solvent, HMPA gave a good result.

For the synthesis of indole derivative, cyclohexenyl derivative 1c was prepared by the condensation of 2-bromocyclohexene with benzylamine followed by treatment with chloroacetyl chloride and then potassium iodide. Compound 1c was warmed at 65° with $Pd(PPh_3)_4$ in the presence of proton sponge in DMF for 6 h to afford the cyclized compounds 4c and 5c in the yield of 26 % and 20 %, respectively. The same reaction was carried out by use of HMPA as solvent to produce compound 4c as a sole product in the yield of 62 %. Compound 5c was treated with 1,8-diazabicyclo[5,4,0]-7-undecene(DBU)[6] in DMSO to give the dehydrohalogenation product 4c. To confirm the structure of these cyclized products, compound 4c was treated with 5% Pd-C in p-cymene[7] under an atmosphere of argon to produce N-benzyl oxindole[8] 8 and N-benzyl-hexahydro-oxindole[9] 9 in the yield of 33 % and 41 %, respectively.



This reaction was extended to the synthesis of six membered lactams 5d and 4d from compound 1d in the same manner. The latter compound 4d was easily converted to compound 6d by treatment with DBU.

Synthesis of Pyrrolizidine and Indolizidine Derivatives

It was tried to synthesize the pyrrolizidine and indolizidine derivatives by use of this palladium catalyzed cyclization of α-haloamide. For its purpose, N-iodoacetyl-2-vinylpyrrolidine 1e or piperidine derivative 1f was required as the starting material. L-Proline 11e was converted to N-benzyloxycarbonyl-2-prolinol 12e, which was oxidized with PCC followed by treatment with Wittig reagent to afford N-benzyloxycarbonyl-2-vinylpyrrolidine(14e). Removal of carbobenzyloxy group with HBr-AcOH followed by treatment with chloroacetyl-chloride and then potassium iodide gave N-iodoacetyl-2-vinylpyrrolidine(1e) in a fairly good yield. Reaction of this compound 1e with $Pd(PPh_3)_4$ was carried out in DMF at 65° for 3 h to give the desired pyrrolizidine derivatives, 5e, 4e and 6e in the yield of 3 %, 3 % and 18 %, respectively. However, only 5 min was required in $CH_3CN$ as solvent for this reaction to produce the cyclized products in the yield of 50 %. For the synthesis of indolizidine derivative 5f, N-iodo-acetyl-2-vinylpiperidine 1f was prepared from pipecolinic acid 11f in the same route. Compound 1f was treated with $Pd(PPh_3)_4$ in DMF at 65 ° for 6 h to afford indolizidine derivative 5f in the yield of 33 %.

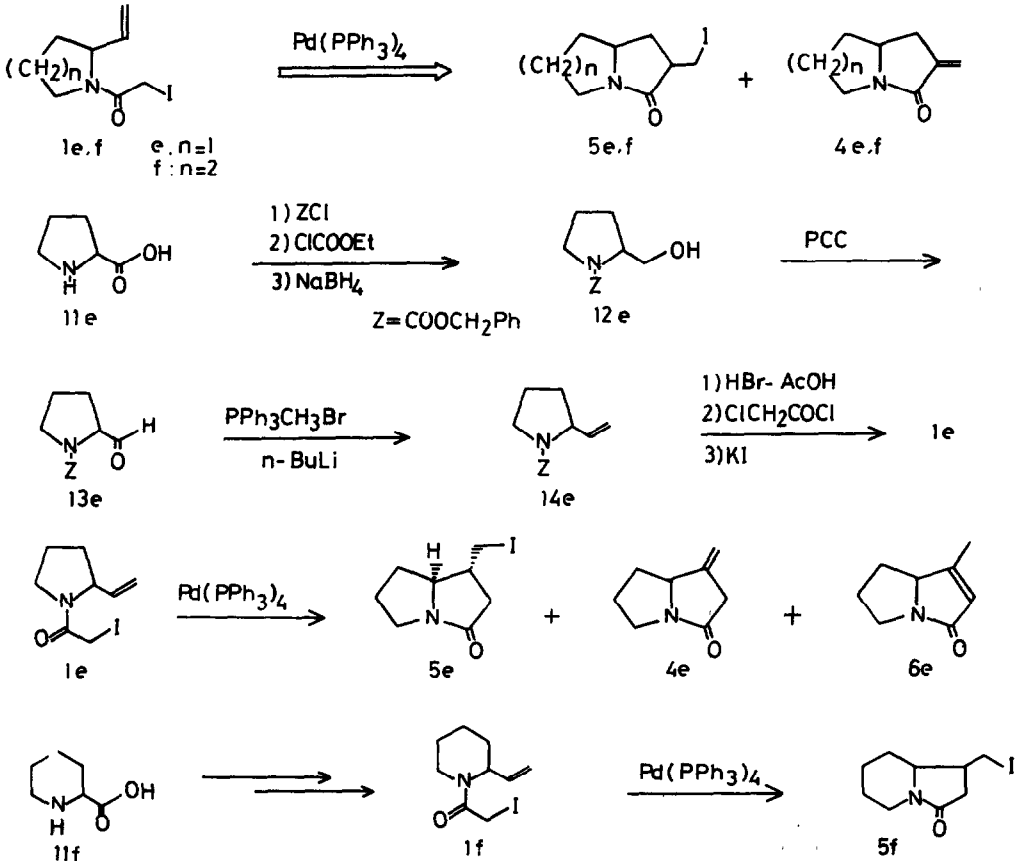


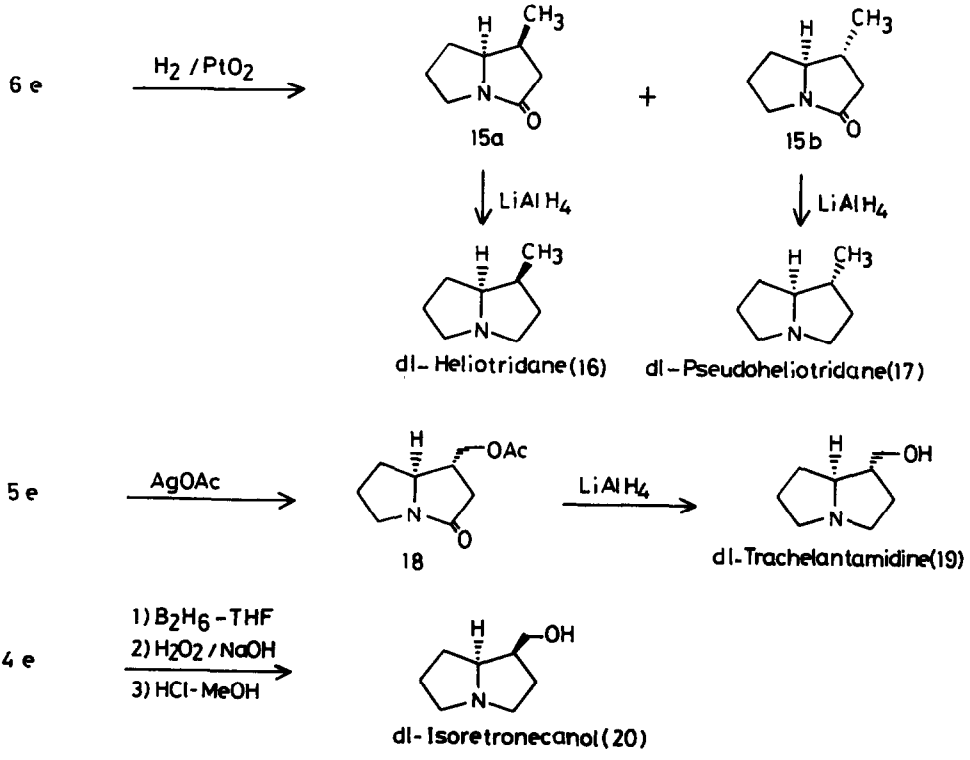
Table 3 Reaction of compound 1e with $Pd(PPh_3)_4$

| Solvent | Reaction Time | Yield of Cyclized Product | Ratio of 5e : 4e : 6e |
|---|---|---|---|
| DMF | 3 h | 24 % | 1 : 1 : 6 |
| HMPA | 6 h | 28 * | 1 : 0 : 8 |
| $CH_3CN$ | 5 min | 50 | 4 : 2 : 1 |

* N-Acetyl-2-vinyl-pyrrolidine was obtained in the yield of 35 %.

Subsequently, some pyrrolizidine alkaloids were synthesized from these pyrrolizidine derivatives. Hydrogenation of compound 6e in the presence of $PtO_2$ under an atmosphere of hydrogen smoothly proceeded to afford 15a and 15b in the yield of 48 % and 12 %, respectively. The former compound 15a was reduced with $LiAlH_4$ in THF to give dl-heriotridane(16)[10] and the latter was converted to dl-pseudoheliotridane(17)[10] in the same manner. The iodomethyl group of compound 5e was easily converted into the acetoxymethyl group by treatment with AgOAc at 65° for 40 h(93 % yield). Reduction of 18 with $LiAlH_4$ in THF afforded dl-trachelantamidine(19)[11] in the yield of 89 %. The melting point of its picrate was agreed with that of the natural product already reported.[11] These results mean that compound 5e is considered to be one isomer and the ring junction of this palladium catalyzed cyclization product 5e should be a thermodynamically stable cis form.[12] dl-Isoretronechanol[8](20) was synthesized from compound 4e by hydroboration followed by treatment of its amine-borane complex with dil.HCl.

These results suggested that α-haloamides having internal double bond was allowed to react with the low-valent transition metal complex to afford various five and six membered lactams in fairly good yields presumably through the σ-alkylmetal complexes.



## Experimental Section

Melting points were measured with a hot stage microscope(Yanaco MP-J2) and with a melting point apparatus(Yanaco MP-1) and are uncorrected. $^1$H NMR spectra were recorded in the indicated solvent on a Hitachi R-20B (60 MHz), a JEOL JNM-FX 100 (100 MHz), and a JEOL-FX 200 (200 MHz) spectrometers with $Me_4Si$ as an internal standard. A Jasco IRA-2 diffraction-grating infrared spectrophotometer and a Hitachi RMU-7M double-focussing mass spectrophotometer were used to determine IR and mass spectra, respectively.

General procedure of the synthesis of N-iodoacetylamine derivatives(1). To a solution of amine derivative (10 mmol) in acetone (20 ml) containing $K_2CO_3$ (20 mmol) was added a solution of chloroacetyl chloride (15 mmol) in ether (3 ml) under ice-cooling and a solution was allowed to stir at room temperature for several hours. Solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate to afford N-chloroacetylamine derivative. A solution of N-chloroacetyamine derivative (10 mmol) and potassium iodide (12 mmol) in 2-butanone (70 mL) was refluxed for 3 h. An dissolved material was filtered off and the residue was purified by suitable method to afford 1.

N-Benzyl-N-iodoacetyl-2-propenylamine(1a). A crude product which was prepared from N-benzyl-N-chloroacetyl-2-propenylamine (2.47 g, 11 mmol) and KI (2.21 g, 13.3 mmol) in 2-butanone (78 ml) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(4:1) to give a pale yellow oil of 1a (2.97 g, 86 %). IR $\nu$(neat)cm$^{-1}$: 1630(C=O). NMR ($CDCl_3$): $\delta$3.71, 3.77(s and s, 2 H, $COCH_2$), 3.86, 4.02(bd and bd, 2 H, $NCH_2C$=), 4.55, 4.60(s and s, 2 H, $NCH_2$), 5.12(bd, 1 H, vinyl), 5.24(bs, 1 H, vinyl), 5.6-6.0(m, 1 H, vinyl), 7.3(m, 5 H, aromatic). MS m/e 315($M^+$), 188($M^+$-I), 91.

N-Benzyl-N-iodoacetyl-2-butenylamine(1b). A crude product which was prepared from N-benzyl-N-chloroacetyl-2-butenylamine(1.33 g, 5.63 mmol) and KI(1.10 g, 6.62 mmol) in 2-butanone(40 ml) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(4:1) to afford a pale yellow oil of 1b(1.73 g, 93 %); IR $\nu$(neat)cm$^{-1}$: 1640(C=O). NMR ($CDCl_3$): $\delta$1.70 (bd, 3 H, $CH_3$), 3.7-4.0(m, 4 H), 4.5-4.7(m, 2 H), 5.50(m, 2 H, vinyl), 7.3(s, 5 H, aromatic). MS m/e 329($M^+$), 202($M^+$-I), 132, 106, 91.

N-Benzyl-N-iodoacetyl-2-cyclohexenylamine(1c). To a solution of benzylamine (799.2 mg, 7.47 mmol) in $CH_3CN$(30 mL) containing $K_2CO_3$(3 g, 21.6 mmol) was added a solution of 3-bromocyclohexene(1.00 g, 6.23 mmol) in $CH_3CN$(6 ml) and a mixture was allowed to stir at room temperature overnight. Solvent was removed under reduced pressure and the residue was dissolved in acetone(30 ml). Excess solid $K_2CO_3$(4 g, 28.8 mmol) was added to the solution and a solution of chloroacetyl chloride(0.9 ml) in ether(6 ml) was added to the solution in ice-bath and the solution was allowed to stir at room temperature overnight. Solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(4:1) to afford N-benzyl-N-chloroacetyl-2-cyclohexenylamine(1.27 g, 78 %). IR $\nu$(neat)cm$^{-1}$: 1645(C=O). NMR ($CDCl_3$): $\delta$ 1.3-2.2(m, 6 H), 3.9, 4.2(s and s, 2 H, $COCH_2I$), 4.4-4.8(m, 1 H), 4.6(s, 2 H, $NCH_2Ph$), 5.1-6.1(m, 2 H, vinyl), 7.3(s, 5 H, aromatic). The chloroacetyl derivative(1.273 g, 4.83 mmol) was converted to iodoacetyl derivative(1c, 1.578 g, 92 %) with KI(970 mg, 5.84 mmol) in 2-butanone(40 ml). IR $\nu$(neat)cm$^{-1}$: 1650(C=O). NMR ($CDCl_3$): $\delta$1.2-2.2(m, 6 H), 3.55-3.90(s and s, 2 H, $COCH_2I$), 4.2-4.9(m, 3 H), 5.2-6.2(m, 2 H, vinyl). MS m/e 355($M^+$), 228, 91.

N-Benzyl-N-iodoacetyl-3-butenylamine(1d). A crude product which was prepared from N-chloroacetyl-3-butenylamine(538 mg, 2.264 mmol) and KI(453 mg, 2.72 mmol) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(4:1) to afford a pale yellow oil of 1d(694 mg, 93 %); IR $\nu$(neat)cm$^{-1}$: 1640(C=O). NMR ($CDCl_3$): $\delta$ 2.38(t, J=7 Hz, 2 H, $CH_2C$=), 3.32(t, J=7 Hz, 2 H, $NCH_2$), 3.67, 3.80(s and s, 2 H, $COCH_2I$), 4.55, 4.61(s and s, 2 H, $NCH_2Ph$), 4.9-6.0(m, 3 H, vinyl), 7.28(s, 5 H, aromatic).

General Procedure of the reaction of N-iodoacetylamine derivative(1) with $Pd(PPh_3)_4$. A solution of N-iodoacetylamine derivative(1, 1 eq.), $Pd(PPh_3)_4$(10 mol %) and proton sponge(1 eq.) in solvent(DMF, HMPA, $CH_3CN$ or toluene) was warmed for several hours. Ethyl acetate was added to the reaction mixture and an organic layer was washed with 10 % HCl, dried over $Na_2SO_4$ and concentrated. The residue was purified by column or preparative thin layer chromatography on silica gel to afford the cyclized products 4, 5 and 6.

Cyclization of N-benzyl-N-iodoacetyl-2-propenylamine(1a) with $Pd(PPh_3)_4$. A crude product which was prepared from 1a(107 mg, 0.34 mmol), $Pd(PPh_3)_4$(39 mg, 10 mol%) and proton sponge(73 mg, 1.02 mmol) in HMPA(0.5 ml) at 50° for 10 min was purified by preparative thin layer chromatography on silica gel eluted with n-

hexane-acetone(3:2) to afford 4a(25 mg, 39 %), 5a(30 mg, 28 %) and 6a(8 mg, 13 %). 4a: IR ν (neat)cm$^{-1}$: 1680(C=O). NMR ($CDCl_3$): δ 3.19(bs, 2 H, $COCH_2$), 3.89(bt, 2 H, $NCH_2$), 4.50(s, 2 H, $NCH_2$), 5.15(m, 2 H, vinyl), 7.30(s, 5 H, aromatic); MS m/e 187($M^+$), 132, 96, 91, High resolution mass spectrum calc for $C_{12}H_{13}NO$ m/e 187.09960, found m/e 187.09960. 5a: IR ν(neat)cm$^{-1}$: 1695(C=O). NMR ($CDCl_3$): δ 2.1-2.4(m, 1 H), 2.5-2.9(m, 2 H, $COCH_2$), 2.95-3.55(m, 6 H), 4.44(q, 2 H, $NCH_2Ph$), 7.2-7.4(m, 5 H, aromatic). MS m/e 315($M^+$), 224($M^+$-91), 146, 132, 120, 91. High resolution mass spectrum calc for $C_{12}H_{14}NOI$ m/e 315.01213, found m/e 315.01043. 6a: IR ν(neat)cm$^{-1}$: 1670(C=O). NMR δ ($CDCl_3$): 2.00(bd, 3 H, $CH_3$), 3.70(s, 2 H, $NCH_2$), 4.59(s, 2 H, $NCH_2Ph$), 5.86(bs, 1 H, vinyl), 7.25(bs, 5 H, aromatic). MS m/e 187($M^+$), 110, 91, High resolution mass spectrum calc for $C_{12}H_{13}NO$ m/e 187.09965, found 187.09895.

Cyclization of N-benzyl-N-iodoacetyl-2-butenylamine(1b) with $Pd(PPh_3)_4$. A crude product which was prepared from 1b(102 mg, 0.31 mmol), $Pd(PPh_3)_4$(10 mol %) and proton sponge(66 mg, 0.31 mmol) in HMPA(0.5 mL) at 50° for 20 min was purified by preparative thin layer chromatography on silica gel eluted with n-hexane-acetone(3:2) to afford the oily products of 4b'(12 mg, 19.3 %), 4b(4 mg, 7 %) and 5b(41.8 mg, 41 %). 4b': IR ν(neat)cm$^{-1}$: 1680(C=O). NMR ($CDCl_3$): δ 2.0-3.6(m, 5 H), 4.42(s, 2 H, $NCH_2$), 5.0-6.0(m, 3 H, $CH=CH_2$), 7.3(m, 5 H, aromatic), MS m/e 201($M^+$), 146, 120, 110, 91, High resolution mass spectrum calc for $C_{13}H_{15}NO$ m/e 201.11530, found 201.11340. 4b: IR ν(neat)cm$^{-1}$: 1670(C=O). NMR ($CDCl_3$): δ 1.50, 1.60(d and d, 3 H, $CH_3$), 3.10(bs, 2 H, $COCH_2$), 3.82(bs, 2 H, $NCH_2$), 4.50(s, 2 H, $NCH_2$), 5.45(bs, 1 H, vinyl), MS m/e 201($M^+$), 91, High resolution mass spectrum calc for $C_{13}H_{15}NO$ m/e 201.11533, found m/e 201.11453. 5b: IR ν(neat)cm$^{-1}$: 1680(C=O). NMR ($CDCl_3$): δ1.82, 1.88(d and d, J=7 Hz, 3 H, $CH_3$), 2.1-2.9(m, 3 H, $COCH_2CH$), 2.9-3.5(m, 2 H, $NCH_2$), 4.16(m, 1 H, CHI), 4.5(bs, 2 H, $NCH_2Ph$), 7.3(bs, 5 H, aromatic). MS m/e 329($M^+$), 202, 91. High resolution mass spectrum calc for $C_{13}H_{16}NOI$ m/e 329.02540, found m/e 329.02660.

Cyclization of N-benzyl-N-iodoacetyl-2-cyclohexenylamine(1c) with $Pd(PPh_3)_4$. Method a) A crude product which was prepared from 1e(507 mg, 1.43 mmol), $Pd(PPh_3)_4$(10 mol %) and proton sponge(363 mg, 1.69 mmol) at 65° for 6 h was purified by column chromatography on silica gel and then preparative thin layer chromatography on silica gel to afford 5c(95 mg, 19 %) and 4c(80 mg, 25 %). 4c: IR ν(neat)cm$^{-1}$: 1685(C=O). NMR ($CDCl_3$): δ 1.5-2.2(m, 4 H), 2.2-2.9(m, 3 H), 3.60(m, 1 H), 4.00(d, J=15Hz, 1 H, NCHPh), 5.05(d, J=15 Hz, 1 H, NCHPh), 5.68(m, 2 H, vinyl), 7.30(s, 5 H, aromatic). MS m/e 227($M^+$), 91. High resolution mass spectrum calc for $C_{15}H_{17}NO$ m/e 227.13108, found 227.13138. 5c: IR (neat)cm$^{-1}$: 1680(C=O). NMR ($CDCl_3$): δ1.0-2.9(m, 9 H), 3.50(m, 1 H, NCH), 4.05(m, 1 H, CHI), 4.03(d, J=15 Hz, 1 H, NCHPh), 4.89(d, 1 H, J=15 Hz, NCHPh), 7.30(s, 5 H, aromatic). MS m/e 355($M^+$), 228, 91. High resolution mass spectrum calc for $C_{15}H_{18}NOI$ m/e 355.04344. found 355.04324. Method b) A crude product which was prepared from 1c(105 mg, 0.30 mmol), $Pd(PPh_3)_4$(17 mg, 5 mol %), and proton sponge(63 mg, 0.30 mmol) in HMPA(0.5 ml) at 60° for 1.5 h was purified by preparative thin layer chromatography on silica gel to afford 4c(41 mg, 62 %).

Cyclization of N-benzyl-N-iodoacetyl-3-butenylamine(1d) with $Pd(PPh_3)_4$. A crude product which was prepared from 1d(420.1 mg, 1.28 mmol), $Pd(PPh_3)_4$(10 mol %) and proton sponge(328 mg, 1.54 mmol) at 90° for 6 h was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(2:1). The first fraction was pale brown oil of 5d(108 mg, 26 %) and the second fraction was 4d(33 mg, 13 %). 4d: IR ν(neat)cm$^{-1}$: 1640 cm(C=O). NMR ($CDCl_3$):δ 2.42(t, J=6 Hz), 2 H, $CH_2C$=), 3.10-3.40(m, 5 H), 4.63(s, 2 H, $NCH_2Ph$), 4.55(bs, 1 H, vinyl), 4.85(bs, 1 H, vinyl). MS m/e 201($M^+$), 120, 91. 5d: IR ν(neat)cm$^{-1}$: 1640(C=O). NMR ($CDCl_3$):δ 1.9-2.9(m, 5 H), 3.1-3.5(m, 4 H), 4.65(s, 2 H, $NCH_2Ph$), 7.33(s, 5 H, aromatic). MS m/e 329($M^+$), 238($M^+$-$PhCH_2$), 91. High resolution mass spectrum calc for $C_{13}H_{16}NOI$ 329.0274, found m/e 329.0273.

N-Benzyl-3-ethyl-2-pyrrolidone(7) From 5b:To a solution of 5b(200 mg, 0.61 mmol) in $n\text{-}Bu_4NBr$(20 mg, 0.61 mmol) in toluene(1 ml) was added a solution of $NaBH_4$(231 mg, 6.1 mmol) in water(4 ml) at room temperature for 30 min. The solution was stirred at room temperature and warmed at 78° for 18 h. Water was added to the solution and the solution was extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by preparative thin layer chromatography on silica gel eluted with n-hexane-ethyl acetate(1:1) to afford a colorless oil of 7(45 mg, 36 %). IR ν (neat) cm$^{-1}$:1680(C=O). NMR ($CDCl_3$): δ 0.97(t, 3 H, $CH_3$), 1.2-1.8(m, 2 H), 2.0-2.7(m, 3 H), 2.7-3.6(m, 2 H), 4.43(s, 2 H, $NCH_2$), 7.3(s, 5 H, aromatic). MS m/e 203($M^+$), 174($M^+$-Et), 91. From 4b': To a solution of 4b'(33 mg) in EtOH was added $PtO_2$(5 mg) and a solution was stirred under an atmosphere of hydrogen for 4 h. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by preparative thin layer chromatography on silica gel eluted with n-hexane-ethyl acetate(4:1) to give 5b(10 mg, 31 %). From 4b: A solution of 4b(20 mg) and $PtO_2$ in EtOH(5 ml) was stirred under hydrogen overnight. After usual work up, a colorless oil of 7(2.6 mg, 13 %) was obtained.

Dehydrohalogenation of N-benzyl-4-iodo-2-oxo-perhydroindole(5c). A solution of 5c(85 mg, 0.24 mmol) and DBU(39 mg, 0.26 mmol) in DMSO(1 ml) was warmed at 90° for 8 h. Ethyl acetate was added to the reaction mixture and an organic layer was washed with 10 % HCl, dried over $Na_2SO_4$ and concentrated. The residue was purified by preparative thin layer chromatography on silica gel eluted with n-hexane-ethyl acetate(2:1) to afford 4c(41 mg, 74 %).

Dehydrogenation of N-benzyl-2-oxo-hexahydroindole(4c). A solution of 4c(107 mg, 0.47 mmol) and 10 % Pd-C in p-cymene(3 ml) was refluxed for 7 h. The solution was filtered and the filtrate was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel eluted with n-hexane-ethyl acetate(2:1). The first fraction was 8(34 mg, 41 %) and the second fraction was 9(44 mg, 41 %). 8: IR $\nu$(neat)$cm^{-1}$: 1710(C=O), 1610(C=C). NMR ($CDCl_3$): $\delta$3.63(s, 2 H, $COCH_2$), 4.92(s, 2 H, $NCH_2$), 6.7-7.4(4 H, m, aromatic), 7.30(s, 5 H, aromatic). MS m/e 223($M^+$), 194, 186, 132, 91. 9: IR $\nu$(neat)$cm^{-1}$: 1680(C=O). NMR ($CDCl_3$):$\delta$1.1-1.9(m, 8 H), 2.3(m, 3 H), 3.48(m, 1 H, NCH), 4.11(d, 2H, J=15 Hz), 5.13(d, 2 H, J=15 Hz), 7.33(s, 5 H, aromatic). MS m/e 229($M^+$), 91. High resolution mass spectrum calc for $C_{15}H_{19}NO$ m/e 229.14663, found 229.14583.

Isomerization of 4d to 6d. To a solution of 4d(33 mg, 0.16 mmol) in DMSO(1 ml) was added DBU(2 drops) and a mixture was warmed at 90° for several hours. Ethyl acetate was added to the solution and an organic layer was washed with 10 % HCl dried over $Na_2SO_4$ and evaporated. The residue was purified by preparative thin layer chromatography on silica gel eluted with n-hexane-ethyl acetate(2:1) to afford 6d(20 mg, 61 %). IR $\nu$(neat)$cm^{-1}$: 1670(C=O), 1620(C=C). NMR ($CDCl_3$):$\delta$ 1.90(bs, 3 H, $CH_3$), 2.25(t, J=7 Hz, $CH_2C$=), 3.32(t, J=7 Hz, 2 H, $NCH_2$), 4.65(s, 2 H, $NCH_2Ph$), 5.85(bs, 1 H, vinyl), 7.31(s, 5 H, aromatic). MS m/e 201($M^+$), 124, 110, 97, 91. High resolution mass spectrum calc for $C_{13}H_{15}NO$ m/e 201.11534, found 201.11424.

N-Benzyloxycarbonyl-2-formyl-pyrrolidine(13e). A solution of N-benzyloxycarbonyl-2-hydroxymethylpyrrolidine(12e, 1.30 g, 5.58 mmol) in $CH_2Cl_2$(30 ml) was added a solution of PCC(1.80 g, 8.37 mmol) in $CH_2Cl_2$(30 ml) under ice-cooling and the solution was stirred at room temperature for 5 h. Undissolved materail was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with benzene-ethyl acetate(2:1) to afford a colorless oil of 13e(840 mg, 64 %). IR $\nu$(neat)$cm^{-1}$: 2700(CHO), 1730(C=O), 1700(C=O). NMR ($CDCl_3$): $\delta$1.57-2.29(m, 4 H), 3.42-3.74(m, 2 H, $NCH_2$), 7.38(s, 5 H, aromatic), 9.08, 9.15(bs, 1 H, CHO).

N-Benzyloxycarbonyl-2-formylpiperidine(13f). A crude product which was prepared from 12f(2.02 g, 8.12 mmol) and PCC(2.10 g, 9.74 mmol) in $CH_2Cl_2$(150 ml) in the same procedure as the synthesis of 13e was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(4:1) to afford 13f(1.00 g, 50 %). IR $\nu$(neat)$cm^{-1}$: 2700(CHO), 1730(C=O), 1700(C=O). NMR ($CDCl_3$): $\delta$1.0-2.5(m, 6 H), 3.0(m, 1 H), 4.15(m, 1 H), 5.18(s, 2 H, $NCH_2Ph$), 7.37(s, 5 H, aromatic), 9.65(s, 1 H, CHO).

N-Benzyloxycarbonyl-2-vinylpyrrolidine(14e). To a solution of methyl triphenylphosphonium bromide(2.19 g, 6.15 mmol) in THF(20 ml) was added a solution of n-BuLi(15 % hexane solution, 4.3 ml, 5.59 mmol) by syringe in ice-bath under argon and the solution was stirred for 40 min. To a solution of 13e(1.03 g, 5.59 mmol) in THF(10 ml) was added the above solution of Wittig reagent by syringe in water bath under argon and a mixture was stirred at room temperature. After 2 hr, solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with water, dried over $Na_2SO_4$ and concentrated. The crude product was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(3:1) to afford the oily product of 13e(659 mg, 51 %). IR $\nu$(neat)$cm^{-1}$: 1700(C=O): NMR ($CDCl_3$):$\delta$ 1.5-2.3(m, 6 H), 3.49(bt, 2 H), 4.40(m, 1 H), 5.15(s, 2 H, $NCH_2$), 4.9-6.1(m, 3 H, vinyl), 7.36(s, 5 H, aromatic).

N-Benzyloxycarbonyl-2-vinylpiperidine(14f). A crude product which was prepared from 13f(241 mg, 0.98 mmol), $MePPh_3Br$(418 mg, 1.18 mmol) and n-BuLi(15 % hexane solution, 0.9 ml, 0.98 mmol) in benzene(5 ml), in the same procedure as the synthesis of 14e was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(4:1) to afford 14f(82 mg, 34 %). NMR ($CDCl_3$):$\delta$1.1-2.0(m, 6 H), 2.5-3.2(m, 1 H), 3.8-4.2(m, 2 H), 4.90(m, 1 H), 5.15(s, 2 H, $NCH_2$), 5.05-6.1(m, 3 H, vinyl), 7.35(s, 5 H, aromatic). MS m/e 245($M^+$), 174($M^+$-$PhCH_2$), 110($M^+$-$COOCH_2Ph$).

N-Iodoacetyl-2-vinylpyrrolidine(1e). A solution of HBr-AcOH(25 %, 9.5 mml, 25.4 mmol) was added a solution of 14e(1.17 g, 5.08 mmol) in $CH_2Cl_2$(6 ml) under ice-cooling and the solution was stirred at room temperature for 4 h. Solvent was removed under reduced pressure and the residue was dissolved in acetone(40 ml). Excess solid $K_2CO_3$(5.5 g, 40 mmol) was added to a solution and a mixture was

stirred vigorously. To the solution was added a solution of chloroacetyl chloride(0.6 ml, 7.62 mmol) in ether under ice-cooling and a mixture was stirred at room temperature for 4 h. Solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with water, dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(2:1) to afford an oily product of N-chloroacetyl-2-vinylpyrrolidine(809 mg, 92 %). IR ν(neat)$cm^{-1}$: 1690(C=O). NMR δ($CDCl_3$): 1.6-2.2(m, 4 H), 3.2-3.8(m, 2 H), 3.92(s, 2 H, $COCH_2Cl$), 4.4-4.7(m, 1 H), 4.9-6.2(m, 3 H, vinyl). MS m/e 173($M^+$), 138, 128. A solution of N-chloroacetyl-2-vinylpyrrolidine(809 mg, 4.66 mmol) and KI(928 mg, 5.59 mmol) in 2-butanone(25 ml) was refluxed under argon for 12 h. Undissolved material was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(1:1) to afford an oily product of 1e(1.07 g, 88 %). IR ν(neat)$cm^{-1}$: 1690(C=O). NMR ($CDCl_3$):δ 1.6-2.2(m, 4 H), 3.2-3.8(m, 2 H9, 3.62(s, 2 H, $CH_2I$), 4.4-4.7(m, 1 H), 4.9-5.3(m, 2 H, vinyl), 5.5-6.2(m, 1 H, vinyl). MS m/e 265($M^+$), 138, 124, 96.

N-Iodoacetyl-2-vinylpiperidine(1f). N-Chloroacetyl-2-vinylpiperidine was prepared from N-carbobenzyloxy-2-vinylpiperidine(14f, 194 mg, 0.79 mmol) and HBr-AcOH(25 %, 1 ml) in $CH_2Cl_2$(1 ml) followed by treatment with chroloacetyl chloride(0.15 ml) and $K_2CO_3$(550 mg, 3.96 mmol) in acetone(20 ml). A crude product was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(2:1) to afford an oily product(97 mg, 71 %), which was dissolved in 2-butanone(5 ml) containing KI(103 mg, 6.24 mmol). The solution was refluxed for 3 h and an undissolved material was filtered off. The filtrate was concentrated and the residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(2:1) to afford an oily product of 1f(120 mg, 83 %). IR ν(neat)$cm^{-1}$: 1640(C=O). NMR ($CDCl_3$): δ1.2-2.0(m, 6 H), 4.08(s, 2 H, $COCH_2Cl$), 2.5-4.0(m, 2 H), 5.0-6.2(m, 4 H, vinyl and NCH). MS m/e 279($M^+$), 252, 152($M^+$-I), 110, 84.

Cyclization of N-iodoacetyl-2-vinylpyrrolidine(1e). A solution of 1e(325 mg, 1.23 mmol), proton sponge(315 mg, 1.48 mmol) and $Pd(PPh_3)_4$(10 mol %) in $CH_3CN$(1.5 ml)) was warmed at 65° for 5 min under argon. After usual work up, the residue was purified by preparative thin layer chromatography on silica gel eluted with n-hexane-ethyl acetate-MeOH(1:1:0.1) to afford 4e(25 mg, 15 %), 5e(90 mg, 28 %), and 6e(11 mg, 7 %). 4e: IR ν(neat)$cm^{-1}$: 1690($cm^{-1}$). NMR ($CDCl_3$): δ 1.9-2.2(m, 4 H), 3.05(d, 1 H, J=10 Hz, COCH), 3.42(d, 1 H, J=10 Hz, COCH), 3.1(m, 1 H, NCH), 3.68(m, 1 H, NCH), 4.35(m, 1 H), 5.04(m, 2 H, vinyl). 5e: IR ν(neat)$cm^{-1}$: 1680(C=O). NMR ($CDCl_3$): δ1.9-2.2(m, 4 H), 2.2-2.7(m, 3 H), 2.9-3.4(m, 3 H), 3.4-3.8(m, 2 H). MS m/e 265($M^+$), 138, 70. High resolution mass spectrum calc for $C_8H_{12}NOI$, 264.9960, found 264.9994. 6e: IRν(neat) $cm^{-1}$:1680(C=O). NMR ($CDCl_3$):δ1.9-2.4(m, 4 H), 2.04(d, J=2 Hz, $CH_3$), 3.2-3.7(m, 2 H), 4.05(m, 1 H), 5.69(q, 1 H, vinyl). MS m/e 197($M^+$), 154, 137. High resolution mass spectrum calc for $C_8H_{11}NO$ m/e 197.1048, found 197.1065.

Cyclization of N-iodoacetyl-2-vinylpiperidine(1f). A solution of 1f(120 mg, 0.43 mmol), $Pd(PPh_3)_4$(10 mol %) and proton sponge(110 mg, 0.52 mmol) in DMF(2.5 ml) was allowed to warm at 65° for 6 h. After usual work up, the crude product was purified by thin layer chromatography on silica gel eluted with n-hexane-ethyl acetate(2:1) to afford 5f(39 mg, 33 %). IR ν(neat)$cm^{-1}$: 1670(C=O). NMR ($CDCl_3$): δ1.9-2.4(m, 4 H), 2.4-2.8(m, 2 H, $COCH_2$), 3.2(m, 1 H, NCH), 3.28(d, J=6 Hz, $CH_2I$), 4.0-4.3(m, 2 H, 2NCH). MS m/e 279($M^+$), 152($M^+$-I), 84. High resolution mass spectrm calc for $C_9H_{14}NOI$ m/e 279.01217, found 279.01157.

1-Methyl-3-oxo-hexahydropyrrolizine(15a and 15b). A solution of 5e(53 mg, 0.39 mmol) in EtOH(10 ml) was stirred under an atmosphere of hydrogen in the presence of $PtO_2$(5 mg) overnight. The solution was filtered and the filtrate was concentrated. The residue was purified by preparative thin layer chromatography on silca gel eluted with n-hexane-ethyl acetate-MeOH(1:1:0.1). The faster fraction was a colorless oil of 15a(26 mg, 48 %) and the slower fraction was 15b(6 mg, 12 %). 15a: IR ν(neat)$cm^{-1}$: 1680 cm(C=O). NMR ($CDCl_3$)δ0.98(d, J=7 Hz, 3 H, $CH_3$), 1.40-2.2(m, 4 H), 2.4-3.0(m, 2 H, $COCH_2$), 3.1(m, 1 H, NCH), 3.6(m, 1 H, NCH), 4.0(m, 1 H, NCH). MS m/e 139($M^+$), 111, 70. 15b: NMR ($CDCl_3$):δ 1.15(d, J=6 Hz, 3 H, $CH_3$), 1.6-2.4(m, 5 H), 2.2-2.7(m, 2 H, $COCH_2$), 3.05(m, 1 H, NCH), 3.5(m, 2 H, NCH).

(±)-Heliotridane(16). A solution of 15a(24 mg, 0.17 mmol) and $LiAlH_4$(20 mg, 0.53 mmol) in THF(2 ml) was refluxed for 7 h. Excess $Na_2SO_4 \cdot 10H_2O$ was added to the solution and the solution was stirred overnight. Undissolved material was filtered off and washed with ether. The organic layer was concentrated and the residue(27 mg) was dissolved in ether. Picric acid in ether solution was added to the solution to afford (±)-heliotridane picrate. mp 245-247°(yellow needles from MeOH, lit.243-244°[10]). NMR ($CDCl_3$): δ1.15(d, J=7 Hz, $CH_3$), 1.6-2.4(m, 7 H), 2.4-3.0(m, 2 H), 3.15(m, 1 H), 3.7(m, 1 H), 3.9-4.5(m, 2 H), 8.90(s, 2 H, aromatic). High resolution mass spectrum calc for $C_8H_{15}N$ m/e 125.1201, found m/e

125.1201.

(±)-Pseudoheliotridane(17). A solution of 15b(6 mg, 0.04 mmol) and $LiAlH_4$(18 mg, 0.47 mmol) in THF(1 ml) was refluxed for 5 h. After usual work up, the residue was treated with picric acid in ether solution to afford (±)-pseudo heliotridane picrate. mp 234-236°(yellow needles from MeOH, lit 234-236°[10]). NMR ($CDCl_3$): δ 1.28(d, J=6 Hz, 3 H), 1.6-2.4(m, 6 H), 2.6-4.2(m, 6 H), 8.88(s, 2 H, aromatic). High resolution mass spectrum calc for $C_8H_{15}N$ m/e 125.1201, found 125.1202.

1-Acetoxymethyl-3-oxo-hexahydropyrrolizine(18). A solution of 1-iodomethyl-3-oxo-hexahydropyrrolizine(5e, 56 mg, 0.21 mmol) and AgOAc(140 mg, 0.84 mmol) in AcOH(1 ml) was stirred at 65° under argon for 40 h. Undissolved material was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate-MeOH(1:1:0.1) to aford a colorless oil of 18(39 mg, 93 %). IR ν(neat)$cm^{-1}$: 1740(C=O), 1680(C=O). NMR ($CDCl_3$): δ1.9-2.2(m, 4 H), 2.08(s, 3 H, $COCH_3$), 2.53(bs, 2 H, $COCH_2$), 3.1(m, 1 H), 3.4-3.8(m, 2 H), 4.1(m, 2 H, $OCOCH_3$). MS m/e 197($M^+$), 154, 137. High resolution mass spectrum calc for $C_{10}H_{15}NO_3$ m/e 197.1048, found 197.1065.

(±)-Trachelantamidine(19). A solution of 4e(32 mg, 0.16 mmol) and $LiAlH_4$(25 mg, 0.64 mmol) in THF(1 ml) was refluxed for 2 h. Excess $Na_2SO_4.10H_2O$ was added to the solution and a mixture was stirred overnight. Undissloved material was filterted off and the filtrate was concentrated to afford a colorless oil of (±)-trachelantamidine(20 mg, 89 %). IR ν(neat)$cm^{-1}$: 3400(OH). NMR ($CDCl_3$):δ 1.4-2.2(m, 7 H), 2.3-2.8(m, 2 H, NCH), 2.8-3.4(m, 3 H, $NCH_2$), 3.59(d, 2 H, $CH_2OH$), 3.5-3.9(m, 1 H, NCH), 3.80(t, 1 H, OH). MS m/e 141($M^+$), 140. High resolution mass spectrum calc for $C_8H_{15}NO$ m/e 141.1150, found 141.1155. Picrate mp 172-175°(from MeOH, lit 174-175°[11]).

(±)-Isoretronecanol(20). To a solution of 6e(37 mg, 0.27 mmol) in THF(1 ml) was added a solution of diborane(1 M THF solution, 1.5 ml, 1.35 mmol) under argon in an ice-bath and the solution was refluxed for 1.5 h. After the solution was cooled, water(0.35 ml) was added. To the solution were added 3 N NaOH solution(0.25 ml) and 30 % $H_2O_2$(0.25 ml) and the mixture was stirred for 1 h. Ethyl acetate was added to the solution and the organic layer was dried over $K_2CO_3$ and evaporated. The residue was purified by preparative thin layer chromatography on silica gel eluted with n-hexane-ethyl acetate-MeOH(1:1:0.2) to afford an amine-borane complex(61 mg). A solution of amine-borane complex in 2.5 % HCl-MeOH(1 ml) and the solution was refluxed for 1.5 h. Solvent was removed and ethyl acetate was added. Excess solid $K_2CO_3$ was added to the solution and a mixture was stirred. The solid was filtered and the filtrate was concentrated to afford (±)-isoretronecanol(10 mg, 26 %). IR ν (neat)$cm^{-1}$: 3400(OH). NMR ($CDCl_3$): δ1.3-2.1(m, 7 H), 2.2-2.7(m, 2 H), 2.8-3.3(m, 2 H), 3.3-3.8(m, 4 H, NCH and OH). MS m/e 141($M^+$), 140. High resolution mass spectrum calc for $C_8H_{15}NO$ 141.1150, found 141.1164. Picrate mp 194.5-195°(from MeOH, lit mp 189.5-190°[11], 199°[13]).

## References and Notes


1. M. Mori, Y. Washioka, T. Urayama, K. Yoshiura, K. Chiba and Y. Ban, J. Org. Chem., 48, 4085 (1983). References are herein.
2. P. Fitton, M. P. Johnson and J. E. Mckepn, J. C. S. Chem. Comm., 1968, 6. G. Pearson and P. E. Figdore, J. Am. Chem. Soc., 102, 1541(1980).
3. a) Y. Ito, H. Aoyama and T. Saegusa, J. Am. Chem. Soc., 102, 4521 (1980). b) Y. Ito, T. Hirao and T. Saegusa, J. Org. Chem., 43, 1011 (1978).
4. For a preliminary report on this work, see M. Mori, I. Oda and Y. Ban, Tetrahedron Lett., 23, 5315 (1982).
5. F. Rolla, J. Org. Chem., 46, 3909 (1981).
6. H. Oediger anfd Fr. Moller, Angew. Chem. Inter. Ed., 6, 76, (1967).
7. D. Rosenthal, J. Fries, P. Grabowich and E. F. Sabo, J. Am. Chem. Soc., 84, 877 (1962).
8. H. Rindernecht, H. Koechlin and C. J. Niemann, J. Org. Chem., 18, 971 (1953).
9. A. Bertho and J. F. Schmidt, Ber, 97, 3284 (1964).
10. N. J. Leonard and D. L. Felley, J. Am. Chem. Soc., 72, 2536 (1950).
11. N. J. Leonard and T. Sato, J. Org. Chem., 34, 1066, (1969).
12. S. Braudange and C. Lundin, J. Am. Chem. Soc., 105, 4096 (1983).
13. K. Tatsuta, H. Takahashi, Y. Amemiya and M. Kinoshita, J. Am. Chem. Soc., 105, 4096 (1983).