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PALLADIUM CATALYZED ENE-HALOGENOCYCLIZATION OF α-HALOESTER HAVING INTERNAL DOUBLE BOND WITH THE LOW-VALENT METAL COMPLEX

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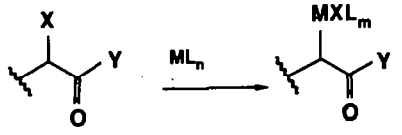
Abstract- α-Haloester having internal double bond was reacted with a catalytic amount of $Pd(PPh_3)_4$ to afford the cyclized product in good yield and the same product was obtained by treatment of ketene silyl acetal with divalent palladium complex.

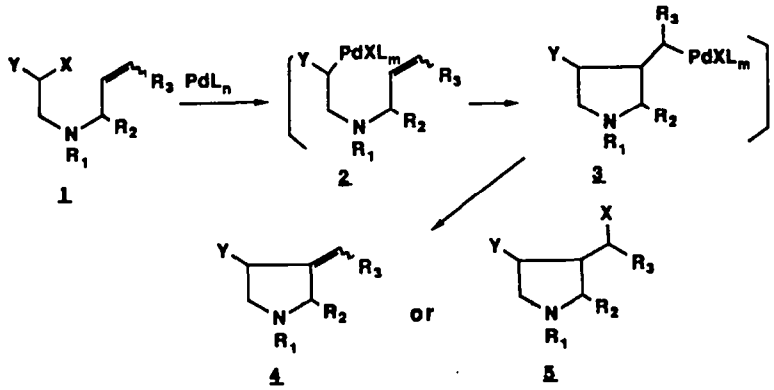
In general, an aryl or vinyl halide can oxidatively add to the low-valent metal complex to afford an aryl or vinylmetal complex, while an alkyl halide can not afford such an alkylmetal complex.[2] We have found that α-haloamide having internal double bond could oxidatively add to the low-valent metal complex to afford σ-alkylmetal complex.[3] These result suggests that the alkyl halide having sp^2-carbon at the α-position could oxidatively add to the low-valent metal complex to afford σ-alkyl metal complex.



α-Halocarbonyl compound

σ-Alkylmetal complex

X=Br, I
Y=NRR',OR



1 2 3 4 5

The idea was substantially realized, which reaction of 1[4] smoothly proceeded to afford the cyclized product 5 as main product along with 4. When the ketene silyl acetal having internal double bond was reacted with an equimolar amount of divalent palladium complex, the cyclized product was obtained via the same σ-alkylmetal complex derived from the α-haloester.

Cyclization of α-Haloesters Having Internal Double Bond by Use of $Pd(PPh_3)_4$

The initial α-haloester having internal double bond as the substrate were prepared from the amino acid. The preparation of α-iodoester was effected through the bromination of ketene silyl acetal[5] followed by treatment with potassium iodide in acetone. When α-iodoester 1a was warmed with 10 mol % of $Pd(PPh_3)_4$ at 65°C for 15 min in HMPA in the presence of proton sponge(1,8-dimetylaminonaphthalene) as a scabenger of hydrogen iodide, pyrrolidine derivative 5a was obtained as inseparable two isomers in 75 % yield. The ratio of cis and trans isomers of compound 5a was determined as 2:3 by the result of HPLC. Similarly, compound 1b also afforded the pyrrolidine derivative 5b in 76 % yield.

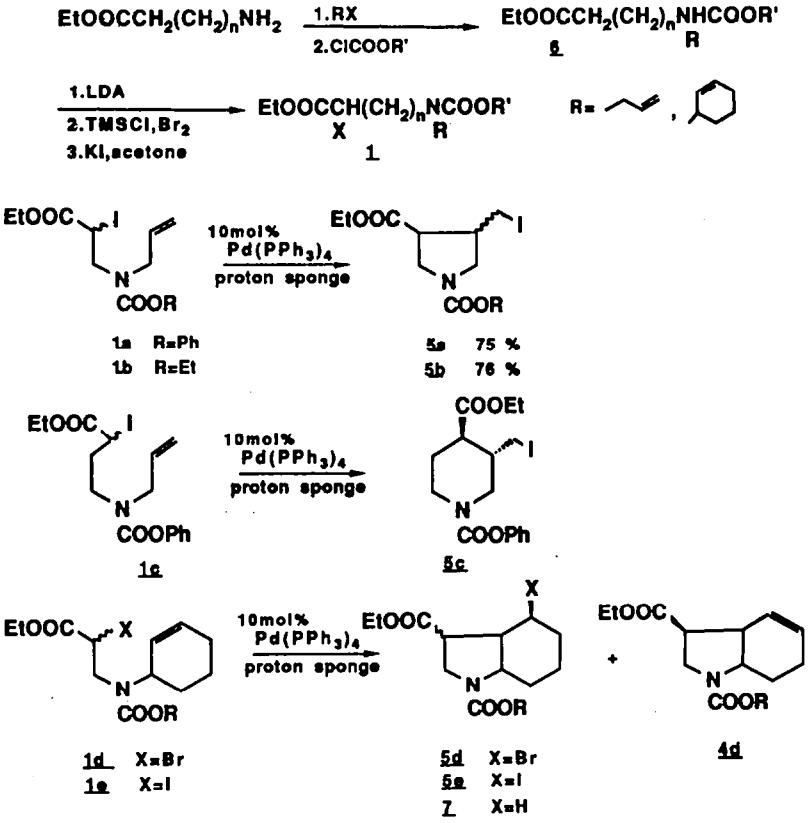
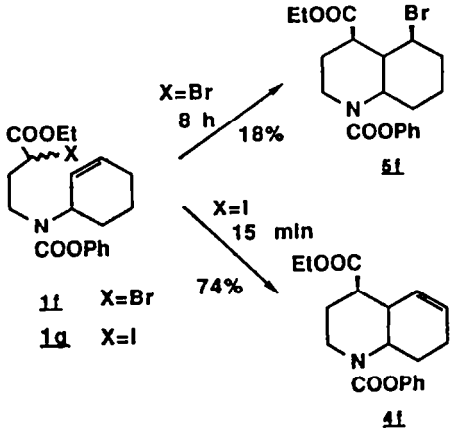


Table 1 Reaction of α-haloesters 1d and 1e with $Pd(PPh_3)_4$

Run	X	$Pd(PPh_3)_4$	Reaction Temp	Time	yield of 5d	4d	7
1	Br	10 mol %	65°C	4 h	65	6	
2	I	10	65	15 min	30	34	-
3	I	1	rt	15 min	80	-	-

Piperidine derivative 5c was obtained from compound 1c on the same treatment of $Pd(PPh_3)_4$. The cyclohexenyl derivative 1d gave the indoline derivative 5d in the yield of 65 % along with 4d and 7(7 % yield). Though the starting material was disappeared after 4 h on the reaction of 1d, only 15 min was enough for the completion of the cyclization of 1e(Table 1). The use of 1 mol % of palladium catalyst improved the yield of the desired compound 5d. Though an octahydroquinoline derivative 4f was obtained from 1g on treatment of $Pd(PPh_3)_4$ in good yield, -bromoester 1f gave the cyclized product 5f in 18 % yield. These results suggest that the reactivity of α-iodoester is much superior to that of the α-bromoesters. Though the reason why the cyclized iodo-compound was obtained was not clear yet, the results were very interesting and useful.

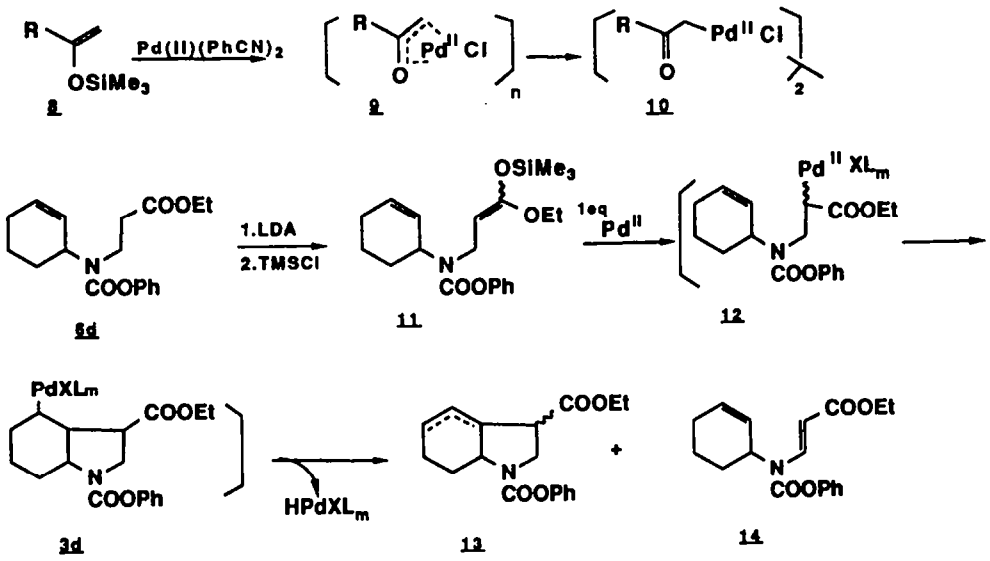


Reaction of Silyl Enol Ether and Divalent Palladium Complex

It was expected that the intermediate 3 was formed from ketene silyl acetal and divalent palladium complex.[6] Compound 6d was reacted with lithium diisopropylamide(LDA)(eq.molar) followed by treatment with trimethyl silyl chloride(TMSCl, 2 mol) in THF[6] to give the ketene silyl acetal 11. After evaporation of the solvent and base, an equimolar amount of divalent palladium complex was added to the residue in acetonitrile. The desired cyclized product 13 was obtained though a yield was rather low. The results were shown in Table 2. A fair amount of β-hydride elimination product 14 was obtained from 12. As for the catalyst, $PdCl_2(CH_3CN)_2$ and $PdCl_2(PhCN)_2$ did not give the good results and no reaction occurrs in the absence of TMSCl. It was very interesting that the low-valent metal complex[$Pd(PPh_3)_4$] could be reacted with α-haloester to produce σ-alkylmetal complex, while the same σ-alkylmetal complex could be formed from ketene silyl acetal and the divalent metal complex.

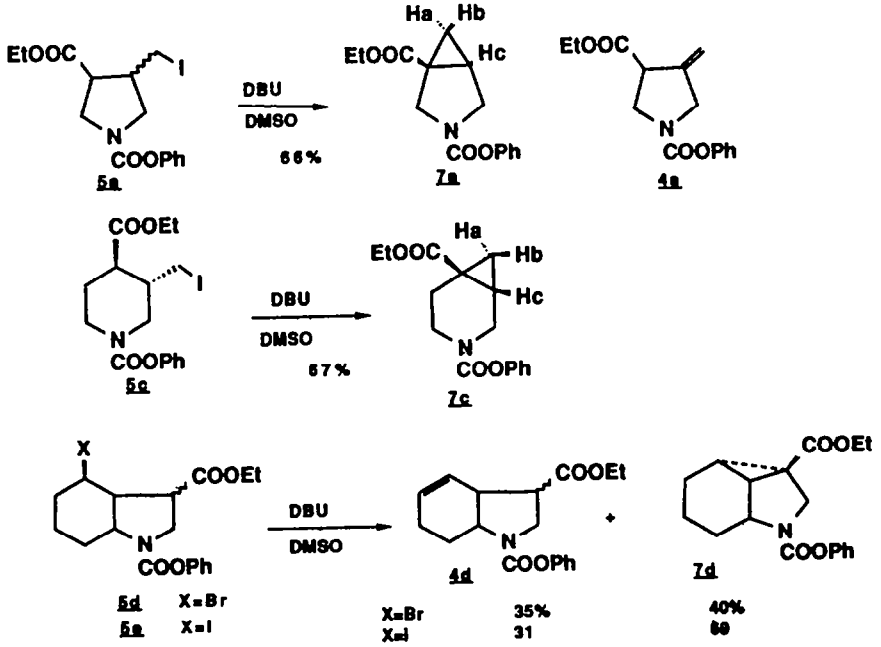
Table 2 Reaction of ketene silyl acetal 11 with divalent palladium complex

Run	TMSCl		yield of 13	14	6d
1	$PdCl_2(CH_3CN)_2$	1 eq	8 %	- %	39 %
2	$PdCl_2(PhCN)_2$	1	-	-	57
3	$Pd(OAc)_2$	1	16	29	18
4	$Pd(OAc)_2$	2	17	40	12
5	$Pd(OAc)_2$	0	-	-	36



Stereochemistry of the Cyclized Products prepared from α-Haloesters

For the structure determiation of the cyclized products, iodo compound 5a was treated with DBU in DMSO to give the three membered product 7a in 66 % yield instead of the olefinic compound 4a. The results indicated that compound 5a having trans substituents should form the three membered ring after epimerization of the ester group.[7] ^{13}C-NMR spectrum of 5a showed a pair of each peak due to the rotational isomer of C=N$^+$ bond. Because of the steric compression effect between the iodomethyl group and the ester group, the peaks of the iodomethyl group of the cis form were appeared at the higher field(δ3.5 and 3.9) compaired with those of the trans form(δ8.0 and 8.1). Compound 5c, whose substituents should be in trans because the HPLC of compound 5c indicated the single peak, was treated with DBU in DMSO afforded also fused three membered compound 7c in moderate yield.



When inseparable two isomers indicated by HPLC of compound 5d were treated with DBU in DMSO, compound 7d(40 % yield) having three membered ring was obtained along with the elimination product 4d(35 % yield). Similar treatment of 5e afforded compound 7d in good yield. The structure of 7d was determined by ^{1}H-NMR and ^{13}C-NMR spectra. The C-2 methylene signal on ^{1}H-NMR spectrum of 7d in DMSO showed two pairs of quartet. When the spectrum was measured at higher temperature(100°C) in DMSO, these peaks were broadened. At 150°C, they were changed to sharp peaks as AB quartet. These phenomena were due to the rotatory conformational isomers of amide group of 7d(Chart 1). Since the epimerization of compound 5e(α : β=2:1) with t-BuOK in t-BuOH afforded single isomer 5e', the results indicated that compound 5e was a mixture of two isomers in regard to the ester group.We have already reported that the formation of three membered ring proceeded via W-shaped syn-1,3-elimination.[7] Since the iodo group and β-hydrogen at C-3 position of compound 5e could easily form W-shaped transition state, compound 7d should be derived from compound 5e having β-hydrogen at C-3 position. Compound 4d should be formed via 1,2-elimination of compound 5e' having α-hydrogen at C-3 position because it could not form W-shaped transition state without epimerization of carboethoxy group of 5e'. The formation of 7d suggests that the ring junction of compound 5d was in cis.

Chart 1

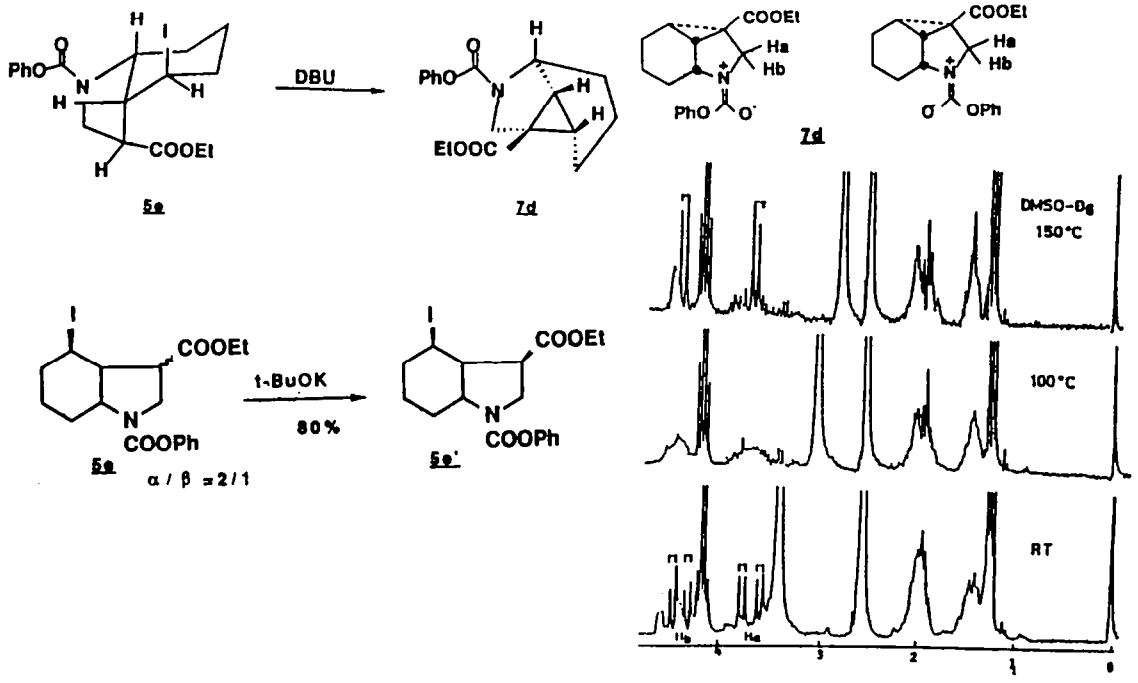
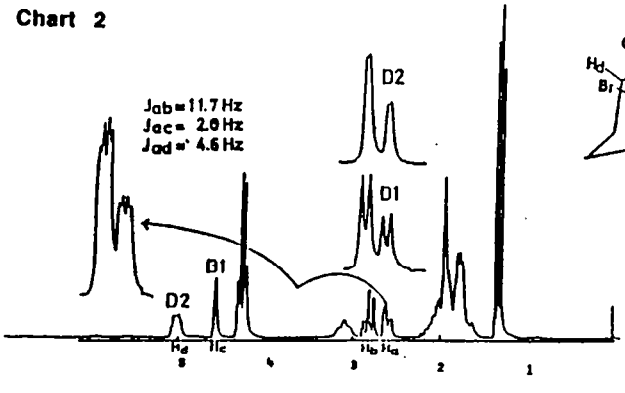


Chart 2



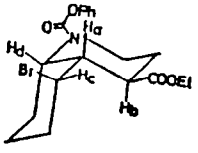
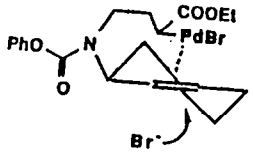


Fig 1



On the other hand, the stereochemistry of perhydroquinoline 5f was determined by decoupling of ^{1}H-NMR. As shown in Chart 2, Ha proton observed as octet changed to qurtet by irradiation of Hc proton. The irradiation of Hd proton showed that the Ha proton changed to qurtet from octet. On the basis of these results, the coupling constants Jab, Jac and Jad were determined as 11.7, 2.0, and 4.6 Hz, respectively. Thus, the ring junction of perhydroquinoline was determined as cis from the coupling constant.

These highly regio- and stereoselective syntheses of perhydroindole and perhydroquinoline were considered to be the perpendicular attack to the internal olefin by σ-alkylpalladium complex(Fig 1) followed by back side attack by halogen.

In addition to the reaction of α-haloamide with the low-valent metal complex,[3] the reaction of α-haloesters with the low-valent metal complex should be useful for the synthesis of the cyclic compounds.

Experimental Section

^{1}H-NMR spectra were recorded in the indicated solvent on a JEOL JNM-FX 100 (100 MHz), and JEOL-FX 200 (200 MHz) spectrophotometer with Me_4Si as an internal standard. A Jasco JNM-IRA-2 diffraction-grating infrared spectrophotometer and a Hitachi RMU-7M double focussing mass spectrophotometer are used to determine IR and mass spectra, respectively. HPLC was performed on a Cica-Merk prepacked column RT-250-4 eqipped with a ERMA Optical Works ERC-7520 RI detector.

2-(N-Allyl-N-phenoxycarbonylamino)-1-ethoxycarbonylethane. A solution of acrylic acid(9.1 g, 9.1 mmol) and allylamine(7.8 g, 13.6 mmol) was allowed to stand overnight in a refrigerator. After the solvent was removed, a residual oil(11.9 g) of 2-allylamino-1-ethoxycarbonylethane was dissolved in acetone(130 mL) and K_2CO_3(13 g, 96 mmol) was added to the solution. A solution of phenyl chloroformate(7.6 g, 48 mmol) in acetone(130 mL) was added to the solution and the mixture was stirred for 1 h. After the solvent was removed and water was added to the residue. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with 10 % HCl solution and brine, dried over $MgSO_4$ and concentrated. The residual oil was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(5:1) to give colorless oil of 2-(N-allyl-N-phenoxycarbonylamino)-1-ethoxycarbonylethane(5.0 g, 56 %). IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) 1.35(t, J=6.8 Hz, 3 H), 2.65(t, J=6.0 Hz, 2 H), 3.65(t, J=6.0 Hz, 2 H), 3.9-4.3(m, 4 H), 5.0-5.4(m, 2 H), 5.5-6.2(m, 1 H), 7.0-7.5(m, 5 H); MS m/e 277(M^+), 232, 204, 184, 142(base).

2-(N-Allyl-N-ethoxycarbonylamino)-1-ethoxycarbonyl-1-ethane(6a). A crude product which was prepared from 2-allylamino-1-ethoxycarbonylethane(3.5 g, 22 mmol), and ethyl chlorformate(3.63 g, 33 mmol) and K_2CO_3(9.2 g, 67 mmol) in acetone(70 mL) was purified by distillation to give colorless oil of 2-(N-Allyl-N-ethoxycarbonylamino)-1-ethoxycarbonylethane(3.8 g, 75 %); bp_{18} 133-136°; IR ν(neat) 1735, 1700 cm^{-1}; NMR ($CDCl_3$) δ1.25(t, J=6.7 Hz, 6 H), 2.55(t, J=6.7 Hz, 2 H), 3.05(t, J=6.7 Hz), 3.9(m, 2 H), 4.20(q, J=6.7 Hz, 4 H), 5.2(m, 2 H), 5.5-6.1(m, 1 H); MS m/e 229(M^+), 184, 156(base).

General procedure for the synthesis of ω-ethoxycarbonyl-N-phenoxycarbonyl amine(6). To a mixture of amino acid ethyl ester hydrochloride(1 eq.) and K_2CO_3)(2 eq.) in CH_3CN was added a solution of allyl bromide(1.5 eq) and the mixture was vigorously stirred for several hours. To the solution were added K_2CO_3(2 eq.) and phenyl chloroformate(1.5 eq.) in CH_3CN and the solution was stirred for several hours. Water was added to the solution and an aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give 6.

2-[N-(2-cyclohexen-1-yl)-N-phenoxycarbonylamino]-1-ethoxycarbonylethane(6b). A crude product which was prepared from β-alanine ethyl ester hydrochloride(2.0 g, 13 mmol), K_2CO_3(5.4 g, 39 mmol), 3-bromocyclohexene(2.1 g, 13 mmol) in CH_3CN(80 mL) followed by treatment with phenyl chloroformate(2.0 g, 13 mmol) and K_2CO_3(5.4 g, 39 mmol) in CH_3CN(10 mL) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(7:1) to give colorless oil of 6b(3.0 g, 73 %): IR ν(neat) 1720 cm^{-1}; NMR δ1.20(t, J=7.0 Hz, 3 H); 1.5-2.3(m, 6 H), 2.2(m, 2 H), 3.6(m, 2 H), 4.1(q, J=7.0 Hz, 2 H), 4.8(brs, 1 H), 5.4-6.1(m, 2 H), 7.0-7.6(m, 5 H).

3-(N-Allyl-N-phenoxycarbonylamino)-1-ethoxycarbonylpropane(6c). A crude product which was prepared from eythyl α-amino-n-butylate hydrochloride(2.1 g, 13 mmol), K_2CO_3(3.6 g, 26 mmol), and allyl bromide(1.8 g, 15 mmol) in CH_3CN(90 mL) followed by treatment with phenyl chloroformate(2.3 g, 15 mmol) and K_2CO_3(3.6 g, 26 mmol)in CH_3CN(90 mL) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(8:1) to give colorless oil of 6a(998 mg, 26 %): IR ν(neat)1720 cm^{-1}; NMR δ($CDCl_3$) 1.20(t, J=6.2Hz, 3 H), 1.8-2.5(m, 4 H), 3.3-3.6(m, 2 H), 3.9-4.3(m, 4 H), 5.0-5.4(m, 2 H), 5.6-6.2(m, 1 H), 7.0-7.5(m, 5 H); MS m/e 291(M^+), 246, 218, 198, 152, 87(base).

2-(N-2-Cyclohexen-1-yl-N-pnenoxycarbonyamino)-1-ethoxycarbonylethane(6d). A crude product which was prepared from 2-ethoxycarbonyl-1-aminoethane hydrochloride(2.0 g, 13 mmol), K_2CO_3(5.4 g, 39 mmol), and 3-bromocyclohexene(2.1 g, 13 mmol) in CH_3CN(90 mL) followed by treatment with phenyl chloroformate(2.0 g, 13 mmol) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(7:1) to give colorless oil of 6d(3.0 g, 73 %):IR ν(neat) 1720 cm^{-1}; NMR δ ($CDCl_3$) 1.20(t, J=7.0 Hz, 3 H), 1.5-2.3(m, 6 H), 2.2(m, 2 H), 3.6(m, 2 H), 4.1(q, J=7.0 Hz, 2 H), 4.8(brs, 1 H), 5.4-6.1(m, 2 H), 7.0-7.6(m, 5 H).

3-(N-2-cyclohexen-1y-N-phenoxycarbonylamino)-1-ethoxycarbonylpropane(6f). A crude product which was prepared from ethyl-α-aminobutylate hydrochloride(200 mg, 1.2 mmol), K_2CO_3(324 mg, 2.4 mmol) and 3-bromocyclohexene(225 mg, 1.4 mmol) in CH_3CN(10 mL) followed by treatment with phenyl chloroformate(282 mg, 1.8 mmol) and K_2CO_3(324 mg, 2.4 mmol) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(7:1) to give a colorless oil of 6f(279 mg, 70 %): IR ν(neat) 1780, 1710, 1600 cm^{-1}; NMR δ($CDCl_3$) 1.20(t, J=6.7 Hz, 3 H), 1.5-2.5(m, 10 H), 3.3(m, 2 H), 4.10(q, J=6.7 Hz, 2 H), 4.75(brs, 1 H), 5.4-6.1(m, 2 H), 7.25(m, 5 H); MS m/e 331(M^+), 238, 210, 80, 81(base).

General procedure for the synthesis of 1. A solution of LDA(1 eq.) in THF was added to 6 in THF at -78°C under an argon atmospher and the solution was stirred for 40 min at the same temperature. To the solution was added a solution of Me_3SiCl(1 eq.)in THF and the solution was stirred for 50 min. A pentane solution of bromine(1 eq.) was added to the above solution and the solution was stirred for 10 min at the same temperature. 10 % HCl solution was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on SiO_2 silica gel eluted with appropriate solvent to afford the desired bromide. A mixture of the bromide(1 eq.), KI or NaI and a catalytic amount of crown ether in acetone was stirred at room temperature overnight. Solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with 10 % thiosulfate solution and brine, and dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel to give the iodide 1.

2-(N-Allyl-N-phenoxycarbonylamino)-1-ethoxycarbonyl-1-iodoethane(1a). A crude product which was prepared from 2-(N-allyl-N-phenoxycarbonylamino)-1-ethoxycarbonylethane(2.5 g, 9.1 mmol), LDA(9.1 mmol), Me_3SiCl(1.15 mL, 9.1 mmol), and bromine(4.7 mL of 10 % pentane solution, 9.1 mmol) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(9:1) to give colorless oil of the desired bromide(1.8 g, 55 %); IR ν(neat) 1720 cm^{-1}; NMR δ($CDCl_3$) 1.30(t, J=7.5 Hz, 3 H), 3.7-4.2(m, 4 H), 4.25(q, J=7.5 Hz, 2 H), 4.5-4.8(m, 1 H), 5.25(m, 2 H), 5.8(m, 1 H), 6.9-7.6(m, 5 H); MS m/e 357, 355(M^+), 312, 310, 276, 264, 262, 236, 234, 218, 216, 41(base). A mixture of bromide(951 mg, 2.7 mmol), KI(1.33 g, 8.0 mmol) and a catalytic amount of 18-crown-6 in acetone(16 mL) was stirred overnight. After the usual work up, the residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(3:1) to give colorless oil of 1a(1.0 g, 93 %): IR ν(neat) 1720 cm^{-1}; NMR δ($CDCl_3$) 1.30(t, J=7.1 Hz, 3 H), 3.6-4.4(m, 6 H), 4.8-5.0(m, 1 H), 5.1-5.4(m, 2 H), 5.6-6.1(m, 1 H), 7.0-7.5(m, 5 H); MS m/e 403(M^+), 358, 310(base).

2-(N-Allyl-N-ethoxycarbonylamino)-1-ethoxycarbonyl-1-iodoethane(1b). A crude product which was prepared from 2-(N-allyl-N-ethoxycarbonylamino)-1-ethoxycarbonylethane(2.0 g, 8.7 mmol), LDA(8.7 mmol), Me_3SiCl(1.3 mL, 10.4 mmol), and Br_2(4.5 mL of 10 % pentane solution, 8.7 mmol) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(3:1) to give colorless oil of the desired bromide(0.75 g, 28 %). IRν(neat)1740 , 1700 cm^{-1}; NMR δ($CDCl_3$) 1.28(t, J=6.8 Hz, 3 H), 1.32(t, J=6.8 Hz, 3 H), 3.7-4.7(m, 9 H), 4.9-5.3(m, 2 H), 5.5-6.0(m, 1 H); MS m/e 309, 307(M^+), 264, 262, 236, 234, 228, 42(base). A mixture of bromide(486 mg, 1.6 mmol), NaI(710 mg, 4.7 mmol) and a catalytic amount of 15-crown-5 in acetone(5 mL) was stirred overnight. After usual work up, the residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(3:1) to give pale yellow oil of 1b(472 mg, 84 %): IR ν(neat) 1730, 1700 cm^{-1}; NMR δ($CDCl_3$) 1.27(t, J=7.1 Hz, 3 H), 1.28(t, J=7.1 Hz, 3 H), 3.5-4.3(m, 8 H), 4.7(brs, 1 H), 5.0-5.3(m, 2 H), 5.5-6.0(m, 1 H); MS m/e 355(M^+), 310, 282, 228, 142, 128(base).

3-N-Allyl-N-phenoxycarnbonylamino)-1-ethoxycarbonyl-1-iodopropane(1c). A crude product which was prepared from 6c(1.9 g, 6.5 mmol), Me_3SiCl(0.83 mmol, 6.5 mmol) and bromine(3.4 mL of 10 % pentane solution, 6.5 mmol)was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(8:1) to give colorless oil of bromide(406 mg, 17 %): IR ν(neat) 1730, 1720, 1690 cm^{-1}; NMR δ($CDCl_3$) 1.25(t, J=6.7 Hz, 3 H), 2.2-2.6(m, 2 H), 3.3-3.7(m, 2 H), 3.9-4.4(m, 4 H), 5.0-5.4(m, 2 H), 5.5-6.1(m, 2 H), 7.0-7.5(m, 5 H); MS m/e 371, 369(M^+), 278, 276, 250, 248, 232, 230, 41(base). A crude product which was prepared from the bromide(269 mg, 0.73 mmol), KI(364 mg, 2.19 mmol) and a catalytic amount of 18-crown-6 was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(8:1) to give colorless oil of 1c(212 mg, 70 %): IR ν(neat) 1720-1700 cm^{-1}; NMR δ($CDCl_3$) 1.2-1.4(m, 3 H), 2.2-2.5(m, 2 H), 3.3-3.6(m, 2 H), 3.9-4.5(m, 5 H), 5.1-5.3(m, 2 H), 5.7-6.1(m, 1 H), 7.1-7.5(m, 5); MS m/e 417(M^+), 372, 324, 290, 278, 41(base).

2-[N-(2-cyclohexene-1-yl)-N-phenoxycarbonylamino]-1-ethoxycarbonyl-1-iodo ethane(1e). A crude product which was prepared from 6d(500 mg, 1.6 mmol), LDA(1.6 mmol), Me_3SiCl(0.3 mL, 2.4 mmol) and bromine(0.8 mL of 10 % pentane solution, 1.6 mmol) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(8:1) to give colorless oil of 1d(454 mg, 73 %): IR ν(neat) 1740, 1720 cm^{-1}; NMR δ($CDCl_3$) 1.25(t, J=7.4 Hz, 3 H), 1.5-2.2(m, 6 H), 3.7-4.0(m, 2 H), 4.25(q, J=7.4 Hz, 2 H), 4.5-5.0(m, 2 H), 5.4-6.1(m, 2 H), 7.0-7.6(m, 5 H); MS m/e 397, 395(M^+), 352, 350, 304, 302, 276, 274, 80(base). A mixture of 1d(1.2 g, 3.0 mmol), NaI(1.4 g, 9.0 mmol) and a catalytic amount of 15-crown-5 in acetone(10 mL) was stirred overnight. After usual work up, the residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(8:1) to give pale yellow oil of 1e(1.3 g, 98 %): IR ν(neat) 1720, 1590 cm^{-1}; NMR δ($CDCl_3$) 1.30(t, J=7.2 Hz, 3 H), 1.5-2.2(m, 6 H), 3.8-4.0(brs, 2 H), 4.20(q, J=7.2 Hz, 2 H), 4.4-5.0(m, 2 H), 5.4-6.0(m, 2 H), 7.0-7.5(m, 5 H); MS m/e 398(M^+-45), 350, 270, 81(base).

3-[N-(2-Cyclohexen-1-yl)-N-phenoxycarbonylamino]-1-ethoxycarbonyl-1-iodo propane(1g). A crude product which was prepared from 6f(1.32 g, 4.0 mmol), LDA(4.0 mmol), Me_3SiCl(0.51 mL, 4.0 mmol), and bromine(2.1 mL of 10 % pentane solution, 4.0 mmol) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(5:1) to give colorless oil of 1f(606 mg, 37 %); IR ν(neat) 1720, 1690 cm^{-1}; NMR δ($CDCl_3$) 1.30(t, J=7.1 Hz, 3 H), 1.6-2.2(m, 6 H), 2.2-2.6(m, 2 H), 3.2-3.6(m, 2 H), 4.0-4.4(m, 3 H), 4.8(brs, 1 H), 5.4-5.7(m, 1 H), 5.8-6.1(m, 1 H), 7.0-7.5(m, 5 H); MS m/e 411, 409(M^+), 318, 316, 290, 288, 238, 236, 81, 80(base). A mixture of 1f(410 mg, 1.0 mmol), KI(498 mg, 3.0 mmol) and a catalytic amount of 18-crown-6 in acetone(5 mL) was stirred overnight. After usual work up, the residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(5:1) to give pale yellow oil of 1g(324 mg, 71 %); IR ν(neat) 1720, 1700 cm^{-1}; NMR δ($CDCl_3$) 1.30(t, J=7.1 Hz, 3 H), 1.5-2.2(m, 6 H), 2.2-2.5(m, 2 H), 3.1-3.5(m, 2 H), 4.0-4.5(m, 3 H), 4.6-4.9(brs, 1 H), 5.4-5.7(m, 1 H), 5.8-6.1(m, 1 H), 7.0-7.5(m, 5 H); MS m/e 457(M^+), 364, 336, 332, 330, 284, 80(base).

General procedure for the syntheses of palladium catalyzed cyclization of -haloesters. To a solution of $Pd(PPh_3)_4$(10 mol %) in HMPA was added a solution of α-haloester(1 eq.) and 1,8-dimethylaminonaphthalene(proton sponge, 1 eq.)in HMPA at room temperature under an atmosphere of argon. After the solution was stirred at room temperature or at 65°C, ethyl acetate was added to the solution. The organic layer was washed with 5 % H_2SO_4 solution and brine, dried over Na_2SO_4 and concentrated. The residue was purified by an appropriate method to give the cyclized product.

Cyclization of 1a with $Pd(PPh_3)_4$. A crude product which was prepared from 1a(1.0 g, 2.5 mmol), $Pd(PPh_3)_4$(10 mol %), and proton sponge(535 mg, 2.5 mmol) in HMPA(3 mL) at 65°C for 15 min was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(4:1) to give pale yellow oil of 3-ethoxycarbonyl-4-iodomethyl-1-phenoxycarbonylpyrrolidine(5a)(750 mg, 75 %), 5a(trans): IR ν(neat) 1720 cm^{-1}; NMR ν($CDCl_3$) 1.30(t, J=7.1 Hz, 3 H), 2.6-4.1(m, 8 H), 4.24(q, J=7.1 Hz, 2 H), 8.1-8.6(m, 5 H); ^{13}C-NMR (DMSO-D_6, at room temperarure) 8.0, 8.1, 13.8, 42.2, 43.1, 47.0, 47.7, 48.1, 48.3, 52.1, 60.6, 121.5, 124.9, 129.0, 150.8, 151.7, 170.9; MS m/e 403(M^+), 358, 310(base), 282, 276; High resolution mass spectrum calcd for $C_{15}H_{18}NO_4I$ 403.0281, found 403.0262. 5a'(cis): IR ν(neat) 1720 cm^{-1}; NMR δ($CDCl_3$) 1.30(t, J=7.1 Hz, 3 H), 2.6-4.1(m, 8 H), 4.24(q, J=7.1 Hz, 2 H), 8.1-8.6(m, 5 H); ^{13}C-NMR(DMSO-D_6, at room temperature) 3.5, 3.9, 14.0, 42.7, 43.5, 45.4, 46.2, 47.9, 48.3, 50.9, 51.1, 60.5, 121.6, 125.1, 129.0, 150.9, 152.0, 171.0; MS m/e 403(M^+), 358, 310(base), 282, 276; High resolution mass spectrum calcd for $C_{15}H_{18}NO_4$ 403.0262, found 403.0262.

Cyclization of 1b with $Pd(PPh_3)_4$. A crude product which was prepared from 1b(250 mg, 0.70 mmol), $Pd(PPh_3)_4$(10 mol %) and proton sponge(150 mg, 0.70 mmol) in HMPA(3 mL) at 65°C for 15 min was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(3:1) to give pale yellow oil of 1,3-

diethoxycarbonyl-4-iodomethylpyrrolidine(5b)(189 mg, 76 %): IR ν(neat) 1730, 1700 cm^{-1}; NMR δ($CDCl_3$) 1.26(t, J=7.1 Hz, 3 H), 1.30(t, J=7.1 Hz, 3 H), 2.5-3.9(m, 8 H), 4.0-4.3(m, 4 H); MS m/e 355(M^+), 326, 310, 282(base), 228; High resolution mass spectrum calcd for $C_{11}H_{18}NO_4I-C_2H_5$ 325.9936, found 325.9914.

Cyclization of 1c with $Pd(PPh_3)_4$. A crude product which was prepared from 1c(199 mg, 0.48 mmol), $Pd(PPh_3)_4$(10 mol %) and proton sponge(103 mg, 0.48 mmol) in HMPA(1 mL) at 60°C for 15 min was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(8:1) to give pale yellow oil of 4-ethoxycarbonyl-3-iodomethyl-1-phenoxycarbonylpiperidine(1c)(113 mg, 57 %): IR ν(neat) 1730, 1710 cm^{-1}; NMR δ($CDCl_3$) 1.30(t, J=7.1 Hz, 3 H), 1.8-3.0(m, 4 H), 3.1-3.7(m, 2 H), 3.8-4.6(m, 6 H), 7.0-7.5(m, 5 H), MS m/e 417(M^+), 372, 324(base), 296, 290, 278, 250; High resolution mass spectrum calcd for $C_{16}H_{20}NO_4I$ 417.0439, found 417.0468.

Cyclization of 1d with $Pd(PPh_3)_4$. A crude product which was prepared from 1d(250 mg, 0.63 mmol), $Pd(PPh_3)_4$(10 mol %), and proton sponge(135 mg, 0.63 mmol) in HMPA(1 mL) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(3:1) to give colorless oil of 5d(163 mg, 65 %) and a mixture of 4d and 7(12 mg, 6 %). 5d: IR ν(neat)1720 cm^{-1}; NMR δ($CDCl_3$) 1.30 (t, J=7.1 Hz), 1.32(t, J=7.1 Hz), 1.4-2.4(m, 6 H), 2.9-3.3(m, 2 H), 3.7-4.8(m, 6 H), 7.1-7.5(m, 5 H); MS m/e 397, 395(M^+), 352, 350, 304, 302, 258, 256, 230, 228, 222(base). High resolution mass spectrum calcd for $C_{18}H_{22}NO_4Br$ 397.0713, 395.0733, found 397.0730, 395.0739.

Cyclization of 1e with $Pd(PPh_3)_4$. A crude product which was prepared from 1e(170 mg, 0.38 mmol), $Pd(PPh_3)_4$(10 mol %), and proton sponge(81 mg, 0.38 mmol) in HMPA(1 mL) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(3:1) to give colorless oil of 5e(50 mg, 30 %) and 4d(41 mg, 34 %). 5e: IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) 1.30(t, J=7.1 Hz), 1.33(t, J=7.1 Hz), 1.4-2.4(m, 6 H), 3.0-3.4(m, 2 H), 3.6-4.1(m, 2 H), 4.1-4.6(m, 3 H), 4.9(brs, 1 H), 7.1-7.5(m, 5 H); MS m/e 443(M^+), 398, 350(base), 304, 222; High resolution mass spectrum calcd for $C_{18}H_{22}NO_4I$ 443.0603, found 443.0599. 4d: IRν(neat) 1720 cm^{-1}; NMR δ($CDCl_3$) 1.23(t, J=7.4 Hz, 3 H), 1.50(m, 1 H), 2.0-2.2(m, 3 H), 2.8-2.9(m, 2 H), 3.6-3.8(m, 2 H), 4.0(brs, 1 H), 4.15(q, J=7.4 Hz, 2 H), 5.68(d, J=10.3 Hz, 1 H), 5.82(d, J=9.7 Hz, 1 H), 7.1-7.5(m, 5 H); ^{13}C-NMR (DMSO-d_6, 100°C) 14.0, 22.4, 24.4, 41.4, 47.5, 48.1, 56.2, 60.5, 121.5, 124.9, 126.0, 128.8, 129.1, 151.5, 152.1, 171.8; MS m/e 315(M^+), 270, 222(base), 193; High resolution mass spectrum calcd for $C_{18}H_{21}NO_4$ 315.1470, found 315.1448.

Cyclization of 1f with $Pd(PPh_3)_4$. A crude product which was prepared from 1f(200 mg, 0.49 mmol), $Pd(PPh_3)_4$(10 mol %), and proton sponge(105 mg, 0.49 mmol) at 65°C for 8 h was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(5:1) to give colorless oil of 5f(36 mg, 18 %); IR ν(neat) 1740, 1700 cm^{-1}; NMR δ($CDCl_3$) 1.29(t, J=7.0 Hz, 3 H), 1.5-2.2(m, 8 H), 2.54(ddd, J=2.0, 4.6, 11.7 Hz, 1 H), 2.76(ddd, J=3.9, 11.7, 11.7 Hz, 1 H), 3.05(m, 1 H), 4.1-4.3(brs, 1 H), 4.20(q, J=7.0 Hz, 2 H), 4.51(brs, 1 H), 4.95(m, 1 H), 7.1-7.5(m, 5 H); MS m/e 411, 409(M^+), 366, 364, 338, 336, 318, 316, 236(base), 190, 162; High resolution mass spectrum calcd for $C_{19}H_{24}NO_4Br$ 411.0869, 409.0889; found 411.0897, 409.0912.

Cyclization of 1g with $Pd(PPh_3)_4$. A crude product which was prepared from 1g(200 mg, 0.44 mmol), $Pd(PPh_3)_4$(10 mol %), and proton sponge(94 mg, 0.44 mmol) at 65°C for 15 min was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(8:1) to afford 4f(107 mg, 74 %): IRν(neat) 1720 cm^{-1}; NMR δ($CDCl_3$) 1.29(t, J=7.0 Hz, 3 H), 1.6-2.1(m, 4 H), 2.23(brs, 2 H), 2.55(m, 2 H), 3.08(m, 1 H), 4.19(q, J=7.0 Hz, 2 H), 4.3(brs, 1 H), 4.55(m, 1 H), 5.69(brs, 2 H), 7.0-7.5(m, 5 H),; ^{13}C-NMR ($CDCl_3$, at room temperature) 14.3, 20.7, 22.0, 25.7, 29.0, 36.8, 39.0, 39.3, 45.2, 50.7, 51.2, 60.7, 121.7, 125.2, 127.5, 128.0, 129.2, 151.5, 155.9, 174.3; MS m/e 329(M^+), 284, 256, 236(base), 190; High resolution mass spectrum calcd for $C_{19}H_{23}NO_4$ 329.1627, found 329.1611.

Cyclization of compound 11 with divalent palladium complex. To a solution of LDA(0.63 mmol) in THF(2 mL) was added a solution of 6d(200 mg, 0.63 mmol) in THF(5 mL) at -78°C under argon. The solution was stirred at the same temperature for 40 min. A solution of Me_3SiCl(0.16 mL, 1.26 mmol) was added to the solution and the whole mixture was stirred for 40 min. Solvent was removed under reduced pressure in ice-bath and CH_3CN(3 mL) was added to the mixture. $Pd(OAc)_2$(141 mg, 0.63 mmol) was added to the solution and the mixture was stirred overnight at room temperature. Ethyl acetate was added to the mixture and the organic layed was washed with 10 % HCl solution and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(8:1) to give colorless oil of 13(33 mg, 17 %) and 14(79 mg, 40 %). 13: IR ν (neat) 1720cm^{-1}; NMR δ($CDCl_3$) 1.50(t, J=7.1 Hz, 3 H), 1.8-2.4(m, 4 H), 2.6-3.2(m, 2 H), 3.7-3.9(m, 2 H), 4.1-4.3(m, 3 H), 5.7-5.9(m, 2 H), 7.1-7.5(m, 5 H); MS m/e 315(M^+), 222(base), 193; High resolution mass spectrum calcd for $C_{18}H_{21}NO_4$ 315.1468, found 315.1462. 14: IRν(neat) 1740, 1710 cm^{-1}; NMR

δ($CDCl_3$) 1.29(t, J=7.1 Hz, 3 H), 1.6-2.4(m, 6 H), 4.20(q, J=7.4 Hz, 2 H), 5.1(brs, 1 H), 5.6-6.0(m, 2 H), 5.74(d, J=14.5 Hz, 1 H), 7.1-7.5(m, 5 H), 8.13(d, J=14.5 Hz, 1 H); MS m/e 315(M^+), 270, 242, 222, 81(base), 80.

General procedure for the formation of three membered ring. A solution of 5(1 eq.) and DBU(2 eq.) in DMSO(10 mL) was warmed at 90°C for 2 days. Ethyl acetate was added to the solution and the organic layer was washed with 10 % HCl, 10 % thiosulfate solution and brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give 7.

1-Ethoxycarbonyl-3-phenoxycarbonyl-3-azabicyclo[3,1,0]hexane(7a). A crude product which was prepared from 5a(750 mg, 1.9 mmol) and DBU(0.56 mL, 3.7 mmol) in DMSO(1 mL) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(6:1) to give colorless oil of 7a(340 mg, 66 %): IR (neat)ν 1720 cm^{-1}; NMR ($CDCl_3$)δ0.95 (dd, J=4.9, 5.4 Hz, 1 H), 1.27(t, J=7.4 Hz, 3 H), 1.67(dd, J=4.9, 8.3 Hz, 1 H), 2.14(ddd, J=8.3, 5.4, 4.2 Hz, 1 H), 3.6-4.1(m, 4 H), 4.18(q, J=7.4 Hz, 2 H), 7.1-7.4(m, 5 H); ^{13}C-NMR ($CDCl_3$) 12.2, 16.6, 24.3, 25.2, 27.2, 28.0, 46.0, 58.8, 119.6, 123.1, 127.1, 149.2, 151.2, 169.4; MS m/e 275(M^+), 230, 182(base), 154; High resolution mass spectrum calcd for $C_{15}H_{17}NO_4$ 275.1157, found 275.1157.

1-Ethoxycarbonyl-4-phenoxycarbonyl-4-azabicyclo[4,1,0]heptane(7c). A crude product which was prepared from 5c(52 mg, 0.12 mmol) and DBU(49 mg, 0.32 mmol) in DMSO(1 mL) was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(6:1) to give colorlessoil of 7c(23 mg, 67 %): IRν(neat) 1715 cm^{-1}; NMR ($CDCl_3$) δ0.86(dd, J=5.4, 5.4Hz, 1 H), 1.26(t, J=7.4 Hz, 3 H), 1.51(dd, J=4.9, 9.3 Hz, 1 H), 1.8-2.0(m, 2 H), 2.7(m, 1 H), 3.1-3.4(m, 1 H), 3.5-4.0(m, 3 H), 5.14(q, J=7.4 Hz, 2 H), 7.2-7.5(m, 5 H); ^{13}C-NMR ($CDCl_3$) 14.2, 18.9, 21.1, 21.9, 23.3, 41.0, 41.9, 60.9, 121.6, 125.2, 129.2, 151.4, 154.0, 174.3; MS m/e 289(M^+), 244, 216, 196(base), 168; High resolution mass spectrum calcd for $C_{16}H_{19}NO_4$ 289.1314, found 289.1330.

9-Ethoxycarbonyl-7-phenoxycarbonyl-7-azatricyclo[4,3,0,$0^{2,9}$]nonane(7d). A crude product which was prepared from 5e(50 mg, 0.11 mmol) and DBU(35 mg, 0.23 mmol) in DMSO(1 mL) at 90°C for 6 days was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(6:1) to give colorless oil of 4e(11 mg, 31 %) and 7d(24 mg, 69 %). 7d: IRν(neat) 1720 cm^{-1}; NMR ($CDCl_3$)δ1.20(t, J=7.0 Hz, 3 H), 1.3-1.5(m, 4 H), 1.7-1.5(m, 3 H), 2.47(dd, J=6.8, 15.6 Hz, 1 H), 3.54(d, J=11.7 Hz), 3.64(d, J=12.2 Hz), 4.01(q, J=7.0 Hz, 2 H), 4.39(d, J=11.7 Hz), 4.45(d, J=12.2 Hz), 4.4-4.6(m, 1 H), 7.1-7.5(m, 5 H); ^{13}C-NMR (DMSO-d_6, at room temperature) 14.0, 15.3, 16.6, 16.9, 24.8, 23.7, 25.7, 30.5, 31.7, 33.5, 34.0, 47.0, 47.3, 52.8, 53.0, 60.2, 60.5, 121.7, 125.0, 129.0, 150.8, 151.0, 171.6; MS m/e 315(M^+), 270, 222(base); High Resolution mass spectrum calcd for $C_{18}H_{21}NO_4$ 315.1471, found 315.1474.

Epimerization of compound 5e with t-BuOK. A solution of 5e(C-3- α: β=2:1, 41 mg, 0.09 mmol) and t-BuOK(2 mg) in t-BuOH was refluxed for 30 min under argon. solvent was removed and ethyl acetate was added to the solution. The organic layer was washed with 10 % HCl solution, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluted with n-hexane-ethyl acetate(3:1) to give colorless oil of 5e'(33 mg, 80 %).

References and Notes

1. Emeritus Professor of Hokkaido University .
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