# A NEW SYNTHESIS OF THE SYNTHONS FOR THE FUNCTIONALIZED ASPIDOSPERMA ALKALOIDS *via* α-KETOCARBONIUM ION INTERMEDIATE

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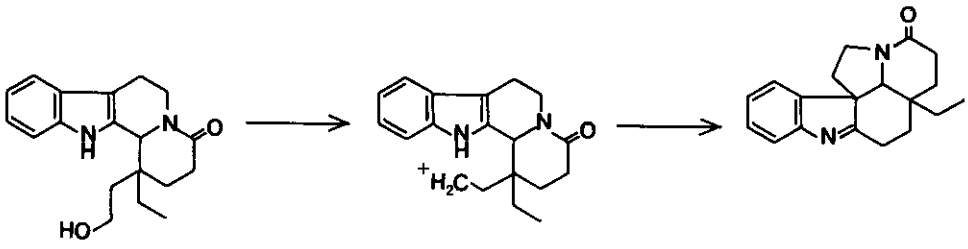
Acid catalyzed rearrangements of the diazoketones, 14 and 29 (a and b) have been examined. On acidic treatments 14 gives the α,β-unsaturated ketone(21), while 29(a and b) give the vinylogous amides 7(a and b) which are converted into the aminoketones 5 (a and b), synthons for the synthesis of the functionalized aspidosperma alkaloids, by the dissolving metal reduction.

Harley-Mason and Kaplan[1] reported an interesting acid catalyzed rearrangement of the carboline 1 into the indolenine 3 through a carbonium ion intermediate 2. Although the reaction provided a simple and efficient synthesis of simple aspidosperma alkaloids, such as aspidospermidine[2], it seemed to be unapplicable for the synthesis of the highly functionalized aspidosperma alkaloids, vindoline[2](4a) and vindorosine[2](4b), which have been elegantly synthesized from the key intermediates, 5a and 5b, by Büchi and co-workers[3,4] in connection with the synthetic studies towards the oncolytic dimeric alkaloids, vinblastine[2] and vincristine[2].

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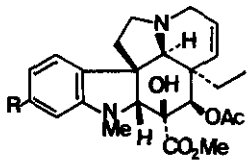
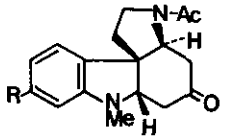
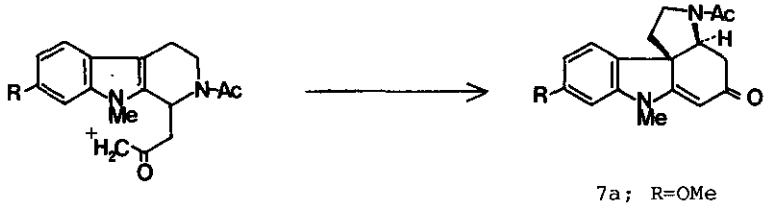


4a; R=OMe
b; R=H



5a; R=OMe
b; R=H

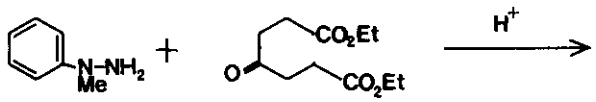
In order to make an application of the carbonium ion rearrangement to the synthesis of the highly functionalized systems, we have examined the synthesis of the tetracyclic conjugated amides, 7a and 7b, which could lead to the Büchi's intermediates, 5a and 5b, through the intermediacy of α-ketocarbonium ions, 6a and 6b, respectively. Since the formation of an α-ketocarbonium ion and its strong electrophillic nature have been recognized by Mander and co-workers[5] by treating a diazoketone with a strong acid in a polar medium, we initially examined the acid catalyzed rearrangement of the diazoketone 14 which was possessed an essential chromophore to test the reaction as a model experiment.



6a; R=OMe
b; R=H

7a; R=OMe
b; R=H

The synthesis of the diazoketone 14 was achieved by a four step sequence. Fischer indole synthesis using N-methylphenylhydrazine(8) and diethyl α-ketopimerate[6](9) gave the diester(10) which on controlled hydrolysis with ethanolic potassium hydroxide afforded the half ester(11). Transformation to the diazoketone 14 was accomplished by a mixed anhydride formation[7] of 11 to 12 with ethyl chloroformate in the presence of triethylamine, followed by treating with an excess of diazomethane.



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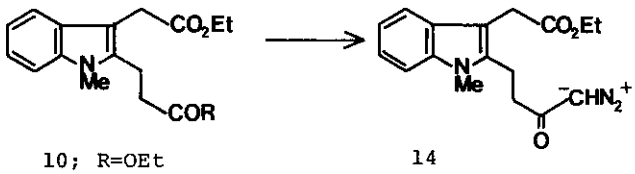
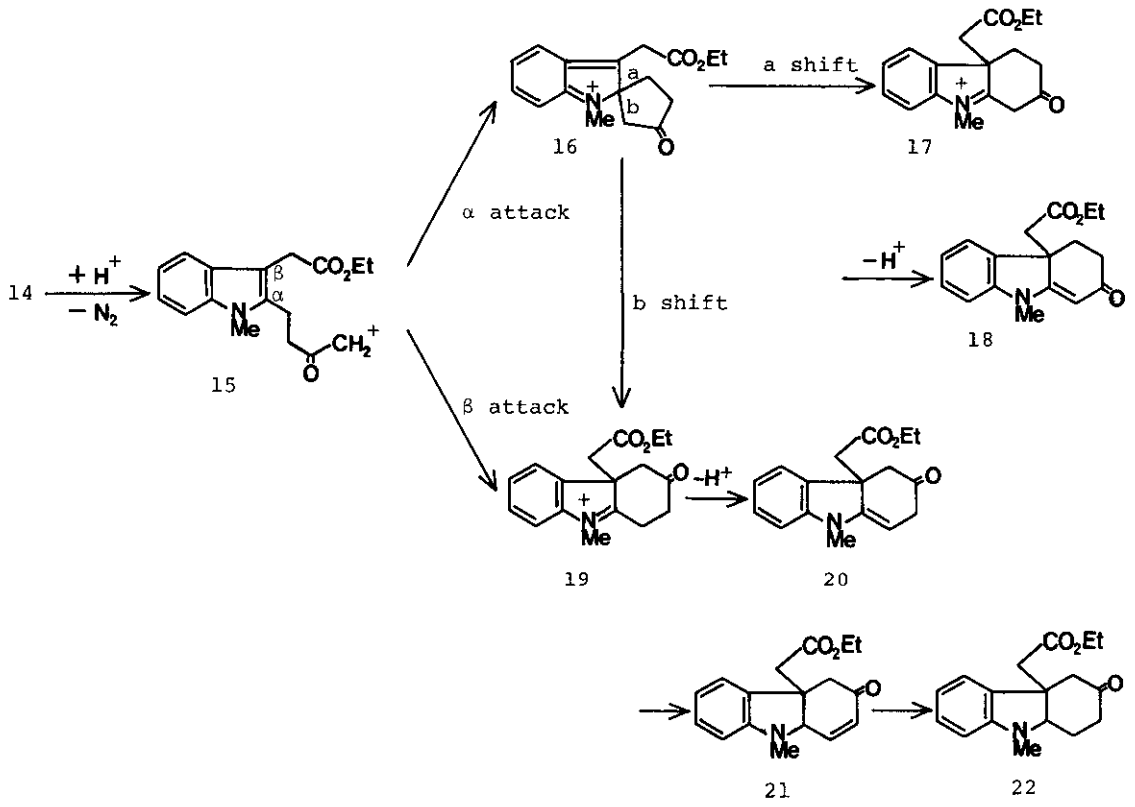


10; R=OEt
11; R=OH
12; R=$OCO_2Et$
13; R=$CH_2OH$

14

Exposure of the diazoketone 14 with boron trifluoride etherate in nitromethane at -10∿0 °C[5] did not give the expected vinylogous amide 18, but the α,β-unsaturated ketone 21 in 57 % yield as a sole isolable product. The structure of 21 was determined by its spectroscopic properties whose uv spectrum did not indicate vinylogous amide system[8] 18 and the nmr spectrum which shows four aromatic protons and two vinylic protons in aromatic region did not support the structure 18, too. Moreover, a facile hydrogen uptake under catalytic hydrogenation with Adams catalyst giving the ketone 22 was also inconsistent with structure 18, since a vinylogous amide system would be quite stable under ordinary hydrogenation conditions. Formation of the α,β-unsatureted ketone 21 could be rationalized by two routes[9] as shown, but it was seemingly formed by initial bond formation of an α-ketocarbonium ion 15 at the β position of the indole ring giving an indolenium base 19 which was then rearranged to a more stable form 21 *via* an enamine 20. Treatment of the diazoketone 14 with trifluoroacetic acid[5], however, did not give a rearranged product but the α-hydroxyketone(13) as a sole isolable product.

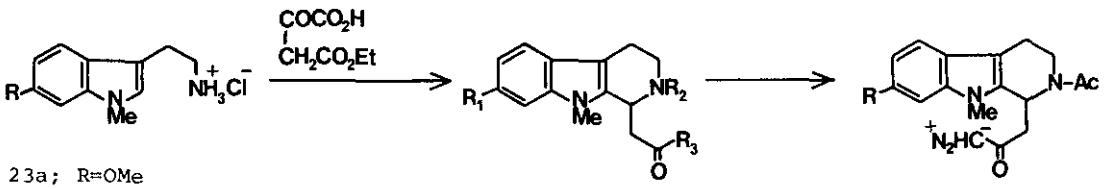
Examination of the reaction using the diazoketones, 29a and 29b, possessing more rigid structure was next carried out. The synthesis of the required β-carboline diazoketones, 29a and 29b, was achieved by a standard fashion. Condensation of 6-methoxy-1-methyltryptamine[10] hydrochloride 23a with carbethoxypyruvic acid[11] in ethanol at boiling temperature gave the β-carboline derivative 24a in 94 % yield losing carbon dioxide spontaneously. Resulting secondary amine 24a was acetylated to give the acetamide 25a which upon hydrolysis with refluxing ethanolic potassium




hydroxide afforded the carboxylic acid 26a in 59 % overall yield from 24a. Conversion of the carboxylic acid 26a into the diazoketone 29a was attained in 65.2 % yield *via* the mixed anhydride 27a. Similarly, l-methyltryptamine[10] hydrochloride 23b was converted into the diazoketone derivative 29b *via* the acid chloride(27b).

In contrast to the model experiment, the diazoketone 29a, upon treatment with trifluoroacetic acid[5] in methylene chloride at -20 °C gave the expected vinylogous amide[12,13] 7a in 35 % yield accompanied by 16.5 % of the β-hydroxyketone 28a. Similarly, the diazoketone 29b afforded the vinylogous amide[13] 7b in 12 % yield accompanied by the β-hydroxy ketone 28b. On the other hand, any fruitful results could not be obtained by treating the diazoketones, 29a and 29b, with boron trifluoride etherate in various solvents.

In these reactions, the formation of the vinylogous amides, 7a and 7b,

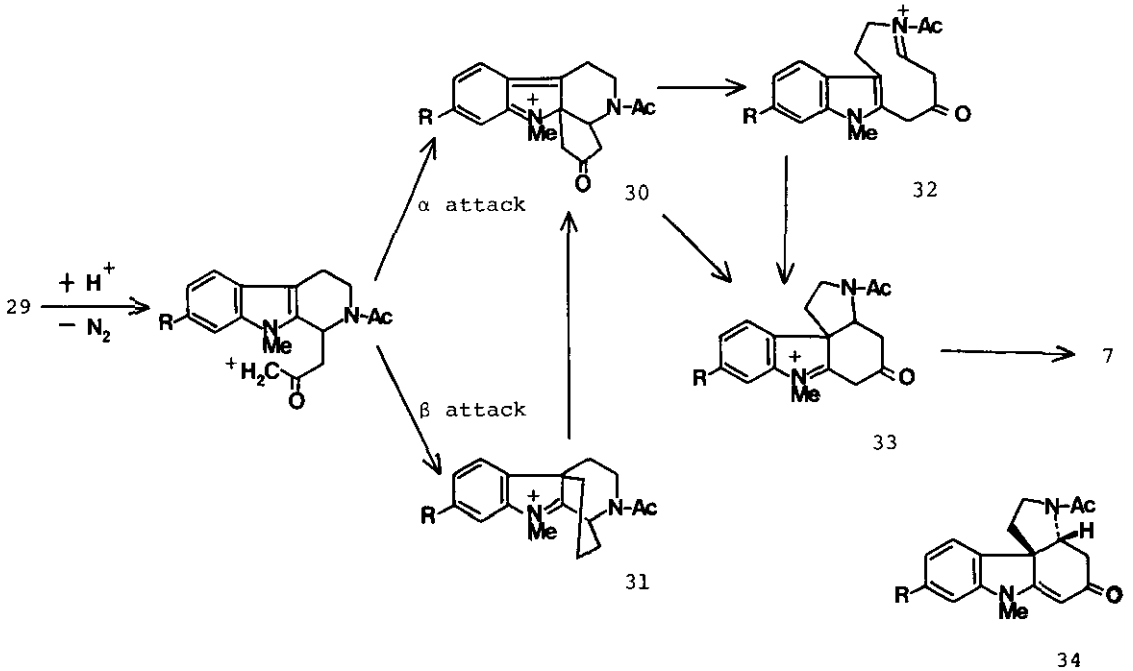


23a; R=OMe
b; R=H

24a; $R_1$=OMe, $R_2$=H, $R_3$=OEt
b; $R_1$=$R_2$=H, $R_3$=OEt
25a; $R_1$=OMe, $R_2$=Ac, $R_3$=OEt
b; $R_1$=H, $R_2$=Ac, $R_3$=OEt
26a; $R_1$=OMe, $R_2$=Ac, $R_3$=OH
b; $R_1$=H, $R_2$=Ac, $R_3$=OH
27a; $R_1$=OMe, $R_2$=Ac, $R_3$=$OCO_2Et$
b; $R_1$=H, $R_2$=Ac, $R_3$=Cl
28a; $R_1$=OMe, $R_2$=Ac, $R_3$=$CH_2OH$
b; $R_1$=H, $R_2$=Ac, $R_3$=$CH_2OH$

29a; R=OMe
b; R=H

could be rationalized by the initial bond formation at the ß position of the indole ring including two rearrangements as the model experiment indicated. However, an alternative route involving the initial bond formation at the α position including one rearrangement would also be attractive, since the diazoketone 29a carried an electron donator at $C_7$ gave much better yield than the diazoketone 29b carried no electron donator.



Examination of the nmr spectra of the vinylogous amide 7a in both deuteriochloroform and dimethyl sulfoxide d-6 indicated that the material consisted of two components in a 5:3 ratio showing two 5:3 singlets(total 3H, $COCH_3$) at δ 2.14 and 2.19, two 5:3 triplets(total 1H, J=6 Hz, respectively, >CH-N(Ac)-) at δ 4.33 and 4.75, in deuteriochloroform and two 3:5 singlets(total 3H, $COCH_3$) at δ 2.10 and 2.12, two overlapped triplets(total 1H, J=6 Hz, respectively, >CH-N(Ac)-) at δ 4.43 and 4.50, two 5:3 doublets(total 1H, J=6 Hz, respectively, aromatic H) at δ 6.79 and 6.98 in dimethyl sulfoxide d-6, respectively. Because of no distinctive change was observed in these spectra at 90 °C and its thin layer chromatography and high pressure liquid chromatography clearly showed a presence of two components in a 5:3 ratio though they were too close to be separated, we initially assigned one of the components to be 34 possessed highly strained framework. However, its inconsistency was revealed by further examination of the nmr spectrum at higher temperature. Since the spectrum in dimethyl sulfoxide d-6 at 120 °C showed an equillibration of two components exhibiting a singlet(3H, $COCH_3$) at δ 2.16, a coalescent one protone signal(>CH-N(Ac)-) centered at 4.59 ppm, and a coalescent aromatic one proton signal centered at δ 7.08, which reverted to the original spectrum after cooling, the compound 7a was concluded to be existed in two rotamers about the acetamide bond[14]. The other vinylogous amide 7b should also consist of two rotamers in a 5:3 ratio since its nmr spectrum as well as its chromatographical behaviors(tlc and lpc) showed quite similar patterns to those of 7a, though we did not carried out the temperature-dependent nmr measurements.

Selective reduction of the double bond of the vinylogous amide 7a was very difficult and the desired aminoketone 5a could be only obtained by the dissolving metal reduction[15] using limited amount of an alkali metal. Thus, treatment of the vinylogous amide 7a with an equimolar amount of potassium in a mixture of tetrahydrofuran and liquid ammonia gave the aminoketone 5a in 92 % yield. Similar treatment on 7b using sodium afforded the corresponding aminoketone 5b in 70 % yield. Spectroscopic and physical data of these compounds were completely identical with those of reported data[3,4]. Furthermore, structure confirmation was made by a comparison with samples obtained *via* the Fischer base intermediates[13].

As mentioned these two products have been converted into vindoline[4] and vindorosine[3], present study implied that the carbonium ion promoted rearrangement, of which prototype has been shown by Harley-Mason and Kaplan[1], could be applicable to the synthesis of the highly functionalized aspidosperma alkaloids. Further

studies in this direction are in progress.

## Experimental Section

Melting points were determined on a Yanagimoto MP-S2 apparatus and were uncorrected. Infrared apsorption spectra were recorded on a shimadzu IR 400 instrument, ultraviolet spectra were recorded on a Hitachi 124 instrument, and proton magnetic resonance spectra were recorded on Jeol PS 100, PMX 60 and Hitachi H-60 spectrometers with tetramethylsilane as an internal reference. Mass spectra were recorded on a Hitachi RMU-7 spectrometer. High pressure liquid chromatography was carried out using a Hitachi 635 instrument equipped with a column packed with Hitachi gel 3011 and monitored by UV absorption.

2-(2-Carbethoxyethyl)-3-carbethoxymethyl-1-methylindole(10) A mixture of N*a*-methylphenylhydrazine(10.1 g, 82.5 mmol) and diethyl γ-ketopimerate(15.2 g, 75 mmol) in EtOH(55 ml) was refluxed with concd. sulfuric acid(6.0 ml) overnight. After evaporation of the solvent *in vacuo*, to a residue was added water(70 ml) and was extracted with benzene. The extract was washed with 5 % $NaHCO_3$, brine and was dried over $Na_2SO_4$. After evaporation of the solvent *in vacuo*, the oily residue was distilled under reduced pressure to give 10(15.6 g, 65.7 %) as a pale yellow oil : bp 205∿210 °C(1∿2 mmHg); IR(neat) 1715 $cm^{-1}$; NMR($CDCl_3$) δ 1.18(3H, t, J=7 Hz), 1.20(3H, t, J=7 Hz) 2.60∿3.30(4H, m), 3.65(3H, s), 3.70(2H, s), 4.10(4H, q, J=7 Hz), 6.92∿7.69(4H, m); MS m/e 317($M^+$), 244, 158(100 %).

*Anal.* ($C_{18}H_{23}NO_4$) C, H, N.

2-(2-Carboxyethyl)-3-carbethoxymethyl-1-methylindole(11) Diester(10)(54 g, 170 mmol) was refluxed with potassium hydroxide(14.3 g, 255 mmol) in EtOH(200 ml) for 20 h. After evaporation of the solvent *in vacuo*, the residue was taken up in water(200 ml) and the aqueous layer was washed thoroughly with benzene. The aqueous layer was made acidic with concd. HCl and was extracted with brine, drid over $Na_2SO_4$. The solvent was evaporated to give a crystalline residue which on recrystallization from a mixture of n-hexane and ethanol gave 11(10.2 g, 20.8 %) as pale yellow prisms : mp 120∿123 °C; IR(Nujol) 3150∿2550, 1717 $cm^{-1}$; NMR($CDCl_3$+ $CF_3CO_2H$) 1.14(3H, t, J=7 Hz), 2.90∿3.55(4H, m), 3.58(2H, s), 4.02(2H, q, J=7 Hz), 4.06(3H, s), 7.10∿7.90(4H, m); MS m/s 289($M^+$), 216(100 %).

*Anal.* ($C_{16}H_{19}NO_4$) C, H, N.

3-Carbethoxymethyl-2-(2-diazomethylenecarbonylethyl)-1-methylindole(14) Half ester(11)(5.20 g, 18 mmol) in methylene chloride(70 ml) was mixed with $Et_3N$

(1.82 g, 18 mmol) at -10∿-20 °C and the mixture was treated with ethyl chloroformate(5.86 g, 54.8 mmol) at the same temperature. After stirring for 1.5 h, the reaction mixture was washed with water, 5 % $NaHCO_3$, brine, and was dried over $Na_2SO_4$. Evaporation of the solvent under vacuum left a crude mixed anhydride(12) (4.54 g) as a pale yellow oil; IR(neat) 1810, 1720 $cm^{-1}$; NMR($CDCl_3$) δ 1.20(3H, t, J=7 Hz), 1.31(3H, t, J=7 Hz), 2.59∿2.95(2H, m), 2.98∿3.36(2H, m), 3.63(3H, s), 3.69(2H, s), 4.03(2H, q, J=7 Hz), 4.18(2H, q, J=7 Hz), 6.96∿7.70(4H, m).

Crude mixed anhydride(12)(4.2 g, 11.5 mmol) in $Et_2O$(50 ml) was mixed with an excess of ethereal diazomethane at 0 °C and the mixture was stirred for 3 h at 0 °C and for 20 h at room temperature. Evaporation of the solvent *in vacuo* left a crude diazoketone(14)(4.05 g) as unstable brown semicrystals : IR(neat) 2100, 1720, 1645 $cm^{-1}$; NMR($CDCl_3$) δ 1.20(3H, t, J=7 Hz), 2.38∿2.74(2H, m), 2.86∿3.34(2H, m), 3.58(3H, s), 3.67(2H, s), 4.07(2H, q, J=7 Hz), 5.12(1H, s), 6.91∿7.65(4H, m).

5b-Carbethoxymethyl-5b,6,7,9a-tetrahydro-7-keto-1-methylcarbazole(21)

Crude diazoketone(14)(247 mg, 0.79 mmol) in nitromethane(10 ml) was stirred and cooled to -10 °C and to a mixture 5 drops of boron trifluoride etherate was added. After the stirring was continued for 1 h at -10∿0 °C, then for 1 h at room temperature, the reaction mixture was treated with water(40 ml) and was extracted with methylene chloride and the extract was washed with 5 % $NaHCO_3$, brine, and was dried over $Na_2SO_4$. Evaporation of the solvent *in vacuo* left a brown oil(214 ml) of which half amount was purified with a preparative tlc($SiO_2$) to give the α,β-unsaturated ketone(21)(64 mg, 57.1 %) as a pale yellow oil : IR(neat) 1710, 1680 $cm^{-1}$; UV(EtOH) max 209, 225, 277nm; NMR($CDCl_3$) δ 1.20(3H, t, J=7 Hz), 2.40∿3.50(5H, m), 3.70(3H, s), 4.10(2H, q, J=7 Hz), 6.30∿7.60(6H, m); MS m/e 285($M^+$), 257, 244, 230, 212, 198, 197, 184, 169(100 %). *Anal.* ($C_{17}H_{19}NO_3$) C, H, N.

5b-Carbethoxymethyl-5b,6,7,8,9,9a-hexahydro-7-keto-1-methylcarbazole(22)

The α,β-unsaturated ketone(21)(220 mg, 0.79 mmol) in EtOH(10 ml) containing few drops of AcOH was stirred under hydrogen at atmospheric pressure at room temperature in the presence of platinum oxide(100 mg). After hydrogen was uptaken(ca 50 ml), the catalyst was removed by filtration and the filtrate was evaporated to give the saturated ketone(22)(200 mg, 90.3 %) as a pale yellow oil : IR(neat) 1725, 1715 $cm^{-1}$; NMR($CDCl_3$) 1.16(3H, t, J=7 Hz), 2.78(3H, s), 4.05(2H, q, J=7 Hz), 6.27∿7.23(4H, m); MS m/e 287($M^+$), 214, 200, 144(100 %). *Anal.* ($C_{17}H_{21}NO_3$) C, H, N.

3-Carbethoxymethyl-2-(4-hydroxy-3-ketobutyl)-1-methylindole(13) Crude diazoketone(14)(363 mg, 12 mmol) was added to stirred trifluoroacetic acid(11 ml)

at 0 °C and the stirring was continued for 2 h at the same temperature. To a mixture was added water(50 ml) and was extracted with methylene chloride. The extract was washed with water, 10 % NaOH, brine and was dried over $Na_2SO_4$. Evaporation of the solvent *in vacuo* left a brown oil which on purification by a silica gel preparative tlc gave the α-hydroxyketone(13)(97 mg, 27.6 %) as pale yellow prisms : mp 93∿95 °C; IR(Nujol) 3425, 1715 $cm^{-1}$; NMR($CDCl_3$) δ 1.23(3H, t, J=7 Hz), 2.57∿2.90(4H, m), 2.71(1H, s, disappeared with $D_2O$), 3.00∿3.30(2H, m), 3.67(3H, s), 3.68(2H, s), 4.10(2H, q, J=7 Hz), 4.17(2H, s), 6.97∿7.68(4H, m); MS m/e 303($M^+$), 170(100 %). *Anal.* ($C_{17}H_{21}NO_4$) C, H, N.

1-Carbethoxymethyl-1,2,3,4-tetrahydro-7-methoxy-9-methylcarboline(24a)

A mixture of 6-methoxy-1-methyltryptamine hydrochoride(23a)(2.27 g, 10 mmol) and carbethoxypyruvic acid(1.75 g, 11 mmol) in EtOH(50 ml) was refluxed for 24 h. After the solvent was evaporated *in vacuo*, the residue was made basic with 5% $NaHCO_3$ and extracted with methylene chloride. The extract was washed with brine, dried over $Na_2SO_4$, and the solvent was evaporated *in vacuo* to give the secondary amine(24a)(2.83 g, 93.7 %) as yellow prisms : mp 78∿80 °C(n-hexane); IR(neat) 3340, 1725 $cm^{-1}$; NMR($CDCl_3$) δ 1.25(3H, t, J=7 Hz), 2.2(1H, s, disappeared with $D_2O$), 3.55(3H, s), 3.86(3H, s), 4.20(2H, q, J=7 Hz), 4.5(1H, m), 6.60∿6.85(2H, m), 7.3 (1H, d, J=8 Hz); MS m/e 302($M^+$), 215(100 %). *Anal.* ($C_{17}H_{22}N_2O_3$) C, H, N.

1-Carbethoxymethyl-1,2,3,4-tetrahydro-9-methylcarboline(24b) A mixture of 1-methyltryptamine hydrochloride(23b)(3.0 g, 14.3 mmol) and carbethoxypyruvic acid (2.5 g, 15.6 mmol) in EtOH(50 ml) was refluxed for 24 h to give the secondary amine (24b) hydrochloride(1.3 g, 29.5 %) as pale yellow needles : mp 170∿173 °C(EtOH). Free base; pale yellow oil; IR(neat) 3340, 1725 $cm^{-1}$; NMR($CDCl_3$) δ 1.30(3H, t, J=7 Hz), 2.30(1H, s, disappeared with $D_2O$), 3.50(3H, s), 4.20(2H, q, J=7 Hz), 4.05(1H, m), 6.55∿7.62(4H, m); MS m/e 272($M^+$), 185(100 %). *Anal.* ($C_{16}H_{19}NO_3 \cdot HCl$) C, H, N.

2-Acetyl-1-carbethoxymethyl-1,2,3,4-tetrahydro-7-methoxy-9-methylcarboline (25a) To a stirred mixture of the secondary amine(24a)(2.8 g, 9.3 mmol) and acetyl chloride(1.09 g, 14 mmol) in benzene(60 ml) was added triethylamine(7.1 g, 70 mmol) dropwise under ice-cooling. After stirring for 30 min, water was added to decompose an excess acetyl chloride and the organic layer was separated, and was washed with 5 % $NaHCO_3$, brine, and dried over $Na_2SO_4$. After evaporation of the solvent, the brown viscous residue was purified with a silica gel column chromatography to give pale yellow crystals which on recrystalization from EtOH gave the

pure amide(25a)(2.6 g, 81.5 %) as colorless needles : mp 102∿103 °C; IR(Nujol) 1720, 1620 $cm^{-1}$; NMR($CDCl_3$) δ 1.24(2H, t, J=7 Hz), 1.26(1H, t, J=7 Hz), 2.30(2H, s), 2.45(1H, s), 3.64(1H, s), 3.66(2H, s), 3.82(3H, s), 4.15(4/3 H, t, J=7 Hz), 4.25(2/3 H, t, J=7 Hz), 4.90(1/3 H, m), 5.45(2/3 H, m), 6.20(1H, m), 6.35∿6.40(2H, m), 7.26∿7.40(1H, m). *Anal.* ($C_{19}H_{24}N_2O_4$) C, H, N.

2-Acetyl-1-carbethoxymethyl-1,2,3,4-tetrahydro-9-methylcarboline(25b)

To a stirred mixture of the secondary amine(24b) hydrochloride(1.0 g, 3.25 mmol) and acetyl chloride(314 mg, 4 mmol) in benzene(30 ml) was added triethylamine(2.02 g, 20 mmol) dropwise under ice-cooling. After stirring at room temperature for 15 min, water was added to decompose an excess acetyl chloride and the organic layer was separated, and was washed with 5 % $NaHCO_3$, brine, and dried over $Na_2SO_4$. After evaporation of the solvent, the brown viscous residue was purified with a silica gel column chromatography to give the pure amide(25b)(1.0 g, 98 %) as a pale brown viscous oil : IR(neat) 1720, 1635 $cm^{-1}$; NMR($CDCl_3$) δ 1.21(2H, t, J=7 Hz), 1.23(1H, t, J=7 Hz), 2.12(2H, s), 2.23(1H, s), 3.60(3H, s), 4.13(4/3 H, q, J=7 Hz), 4.20(2/3 H, q, J=7 Hz), 6.20(1H, br.t, J=6 Hz), 7.0∿7.7(4H, m). *Anal.* ($C_{18}H_{22}N_2O_3$) C, H, N.

2-Acetyl-1-carboxymethyl-7-methoxy-9-methylcarboline(26a) A mixture of the amide(25a)(2.3 g, 6.7 mmol) and potassium hydroxide(0.56 g, 10 mmol) in EtOH (20 ml) was refluxed for 40 min. After evaporation of the solvent *in vacuo*, the residue was taken up in water(20 ml) and the aqueous layer was washed thoroughly with benzene. The aqueous layer was made acidic with concd. HCl and was extracted with methylene chloride. The extract, washed with brine and dried over $Na_2SO_4$, was evaporated *in vacuo* to leave a crystalline mass which on recrystallization from acetone gave the carboxylic acid(26a)(1.53 g, 72.5 %) as pale yellow prisms : mp 252∿254 °C; IR(Nujol) 3330∿2400, 1722, 1595 $cm^{-1}$; NMR($CDCl_3$+$CF_3CO_2H$) δ 2.36(3H, s), 3.70(3H, s), 3.90(3H, s), 6.20(1H, m), 6.60∿6.95(2H, m), 7.35(1H, d, J=8 Hz); MS m/e 316($M^+$), 257, 215. *Anal.*($C_{17}H_{20}N_2O_4$) C, H, N.

2-Acetyl-1-carboxymethyl-9-methylcarboline(26b) A mixture of the amide (25b)(2.4 g, 7.64 mmol) and potassium hydroxide(0.64 g, 11.5 mmol) in EtOH(10 ml) was refluxed for 1 h. After evaporation of the solvent *in vacuo*, the residue was taken up in water(20 ml) and the aqueous layer was washed thoroughly with benzene. The aqueous layer was made acidic with concd. HCl and was extracted with methylene chloride. The extract, washed with brine and dried over $Na_2SO_4$, was evaporated *in vacuo* to leave a crystalline mass which on recrystallization from EtOH gave the

carboxylic acid(26b)(1.50 g, 68.8 %) as pale brown prisms : mp 223∿225 °C; IR (Noujol) 3330∿2400, 1715, 1590 $cm^{-1}$; NMR($CDCl_3$) δ 2.40(3H, s), 3.73(3H, s), 6.30 (1H, m), 7.0∿7.65(4H, m), 10.57(1H, s, disappeared with $D_2O$); MS m/e 286($M^+$), 227, 185. *Anal.* ($C_{16}H_{18}N_2O_3$) C, H, N.

2-Acetyl-1-diazomethylenecarbonylmethyl-7-methoxy-9-methylcarboline(29a)

To a stirred mixture of the carboxylic acid(26a)(730 mg, 2.3 mmol) and triethylamine(280 mg, 2.7 mmol) in methylene chloride(30 ml) was added ethyl chloroformate (750 mg, 6.9 mmol) dropwise at 0 °C and the stirring was continued for 3.5 h at the same temperature. The reaction mixture was washed with brine, 5 % $NaHCO_3$, brine, and dried over $Na_2SO_4$ and the solvent was evaporated to leave the crude mixed anhydride(27a)(1.0 g) as a pale yellow oil. The crude 27a, without further purification, was dissolved in benzene(10 ml) and the solution was treated with an excess of ethereal diazomethane at 0 °C. After standing for 20 h at 0 °C, the diazoketone(29a) was separated and was collected by suction to give practically pure(29a)(0.51 g, 65.2 %) as yellow needles : mp 76∿79 °C; IR(Nujol) 2110, 1615 $cm^{-1}$; NMR($CDCl_3$) δ 2.16(2H, s), 2.23(1H, s), 3.60(2H, s), 3.63(1H, s), 3.86 (3H, s), 5.27(2/3 H, s), 5.56(1/3 H, s), 6.60∿6.90(2H, m), 7.3(1H, m); MS m/e 340 ($M^+$, very weak), 312, 270, 257(100 %).

2-Acetyl-1-diazomethylenecarbonylmethyl-9-methylcarboline(29b) The carboxylic acid(26b)(1.0 g, 2.8 mmol) in benzene(100 ml) was added thionyl chloride(3.66 ml, 40 mmol) at 0 °C with stirring. After stirring for 3 h, volatile materials were removed under vacuum to leave the crude acid chloride(27b)(ca. 1.0 g) as a pale brown oil. The crude acid chloride(27b)(1.0 g), without further purification, was dissolved in benzene(20 ml) and the solution was treated with an excess of ethereal diazomethane at 0 °C. After standing for 20 h at 0 °C, the solvent was filtered and the filtrate was evaporated *in vacuo* to give the crude diazoketone (29b)(1.1 g) as a pale brown oil; IR(neat) 2090, 1620 $cm^{-1}$; NMR($CDCl_3$) δ 2.1(2H, s), 2.16(1H, s), 3.63(3H, s), 5.29(1/3 H, s), 5.45(2/3 H, s), 6.10(1H, br.t, J=7 Hz), 6.80∿7.45(4H, m).

Treatment of the diazoketone(29a) with trifluoroacetic acid To trifluoroacetic acid(1.5 ml) was added the crude diazoketone(29a)(75 mg, 0.22 mmol) in methylene chloride(3 ml) at -20 °C with stirring and the stirring was continued for 30 min at the same temperature. The reaction mixture was treated with water and the organic layer was separated. The organic layer, washed with 5 % $NaHCO_3$, brine, and dried over $Na_2SO_4$, was evaporated *in vacuo* to give an yellow oil(65 mg).

Purification with a preparative tlc(silica gel) afforded pale brown crystals and a pale yellow oil. The crystalline fraction was recrystallized from acetone to give the vinylogous amide(7a)(24 mg, 34.8 %) as colorless needles : mp 126∿128 °C (lit.[12] 130∿133 °C); IR($CHCl_3$) 1640, 1590 $cm^{-1}$; UV(EtOH) max 338(3.94), 243(3.83), 257(3.91) nm; NMR($CDCl_3$)(28 °C) δ 2.14(1.8 H, s), 2.19(1.2 H, s), 3.11(3H, s), 3.82(3H, s), 4.33(0.6 H, t, J=6 Hz), 4.75(0.4 H, t, J=6 Hz), 5.43(1H, s), 6.40∿6.58(2H, m), 6.92(1H, d, J=6 Hz); NMR(DMSOd-6)(28 °C) δ 2.10(1.2 H, s), 2.12(1.8 H, s), 3.23(3H, s), 3.81(3H, s), 4.43(0.4 H, t, J=6 Hz), 4.50(0.6 H, t, J=6 Hz), 5.39 (0.4 H, s), 5.40(0.6 H, s), 6.41∿6.72(2H, m), 6.79(0.6 H, d, J=6 Hz), 6.98(0.4 H, d, J=6 Hz); NMR(DMSOd-6)(120 °C) δ 2.16(3H, s), 3.35(3H, s), 3.92(3H, s), 4.40∿4.78(1H, br.s), 5.48(1H, s), 6.60∿6.84(2H, m), 6.90∿7.26(1H, br.s); MS m/e 312($M^+$), 270, 227, 214(100 %). *Anal.* ($C_{18}H_{20}N_2O_3 \cdot 1/2\ H_2O$) C, H, N.

A pale yellow oil(12 mg, 16.5 %) was assigned to be 1-acetyl-1,2,3,4-tetrahydro-1-(3-hydroxy-2-ketopropyl)-7-methoxy-9-methylcarboline(28a) : IR(neat) 3300, 1710, 1620 $cm^{-1}$; NMR($CDCl_3$) δ 2.25(3H, s), 3.73(3H, s), 3.93(3H, s), 4.30(2H, s), 6.30(1H, m), 6.70∿7.10(2H, m), 7.45(1H, d, J=6 Hz).

Treatment of the diazoketone(29b) with trifluoroacetic acid To trifluoroacetic acid(15 ml) was added the crude diazoketone(29b)(1.0 g) in methylene chloride(15 ml) at -20 °C with stirring and the stirring was continued for 1 h at the same temperature. The reaction mixture was treated with water and the organic layer was separated. The organic layer, washed with 5 % $NaHCO_3$, brine, and dried over $Na_2SO_4$, was evaporated *in vacuo* to give a brown oil(1.1 g). Purification with a silica gel(20 g) column chromatography afforded colorless crystals and a pale yellow oil. The crystalline fraction was recrystallized from acetone-EtOH to give the vinylogous amide(7b)(100 mg, 11.6 %) as colorless prisms : mp 224∿225 °C; IR(Nujol) 1640, 1600, 1580 $cm^{-1}$; UV(EtOH) max 338, 295, 232 nm; NMR($CDCl_3$) δ 2.18 (1.8 H, s), 2.22(1.2 H, s), 3.25(1.2 H, s), 3.28(1.8 H, s), 4.40(0.6 H, t, J=7 Hz), 4.82(0.4 H, t, J=7 Hz), 5.43(0.4 H, s), 5.45(0.6 H, s), 6.80∿7.40(4H, m); MS m/e 282($M^+$), 240, 197, 184(100 %). *Anal.* ($C_{17}H_{18}N_2O_2$) C, H, N.

A pale yellow oil(180 mg, 19.6 %) was assigned to be 1-acetyl-1,2,3,4-tetrahydro-1-(3-hydroxy-2-ketopropyl)-9-methylcarboline(28b) : IR(neat) 3330, 1710, 1620 $cm^{-1}$; UV(EtOH) max 277, 285, 293 nm; NMR($CDCl_3$) δ 2.20(3H, s), 3.76(3H, s), 4.30 (2H, s), 6.25(1H, m), 6.90∿7.60(4H, m); MS m/e 300($M^+$), 257, 227(100 %), 185. *Anal.* ($C_{17}H_{20}N_2O_3$) C, H, N.

Reduction of the vinylogous amide(7a) To a stirred solution of the vinylo-

gous amide(7a)(624 mg, 2 mmol) in tetrahydrofuran(30 ml) and liq. $NH_3$(300 ml) was added lithium(14 mg, 2 mg atom). After blue color was faded(ca. 1 h), $NH_4Cl$ was added and the solvent was evaporated. The residue was extracted with methylene chloride and the extract was washed with water, dried over $Na_2SO_4$. Evaporation of the solvent afforded a glass(660 mg) which on purification with a preparative tlc (silica gel) followed by recrystallization form acetone afforded the aminoketone (5a)(577 mg, 91.9 %) as colorless needles : mp 177∿179 °C(lit.[4] 176∿177 °C); IR($CHCl_3$) 1720, 1640 $cm^{-1}$; NMR($CDCl_3$) δ 2.1(3H, s), 2.7(3H, s), 3.8(3H, s), 4.1 (1H, m), 3.05(1H, d, J=1 Hz), 3.14(1H, dd, J=1 and 6 Hz), 3.90(1H, d, J=6 Hz); MS m/e 314($M^+$), 271, 257, 228, 200, 188, 174(100 %). *Anal.* ($C_{18}H_{22}N_2O_3$) C, H, N.

Reduction of the vinylogous amide(7b) To a stirred suspension of the vinylogous amide(7b)(5.64 g, 20 mmol) in tetrahydrofuran(100 ml) and liq. $NH_3$ (1200 ml) was added sodium(ca. 0.7 g, ca. 30 mg atom) portionwise until no starting material was detected and then $NH_4Cl$ was added. After evaporation of the solvent, the residue was dissolved in water and was extracted with methylene chloride. The extract, washed with water, dried over $K_2CO_3$, was evaporated *in vacuo* to leave a brown oil which on purification using a silica gel(150 g) column chromatography, followed by recrystallization from EtOH gave the aminoketone(5b) (4.0 g, 70.4 %) as colorless needles : mp 195∿197 °C(lit.[3] 195∿197 °C); IR(Nujol) 1710, 1640, 1600 $cm^{-1}$; NMR($CDCl_3$) δ 2.13(3H, s), 2.75(3H, s), 6.5 7.3(4H, m); MS m/e 284($M^+$), 227, 198, 147, 134. *Anal.* ($C_{17}H_{20}N_2O_2$) C, H, N.

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