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DEBENZYLATION OF N-BENZYL-β-LACTAMS BY USE OF ANODIC OXIDATION

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Abstract——Anodic oxidation of *N-benzyl-3-methylene-β-lactam* 1a followed by hydrolysis with TsOH in 2-butanone gave 3-methylene-β-lactam 4a. To examine the effect of the substituents on the aromatic ring of N-benzyl group for the anodic oxidation, N-p-carbomethoxy, N-p-methyl and N-p-methoxybenzyl-3-methylene-β-lactams were electrolyzed under the same conditions. N-p-Methyl and N-p-methoxybenzyl-β-lactams gave only the exo-methoxylated compounds.

In the previous paper, it has been shown that the anodic oxidation of N-alkyl-β-lactams 1 in MeOH afforded the methoxylated compounds 2 and 3 at the exo- and endo-cyclic carbons α to nitrogen, though five, six and seven membered lactams were regioselectively electrolyzed under the same conditions.[1] It was very interesting that the major product on the electrochemical oxidation of N-benzyl-3-methylene-β-lactam(1a) was methoxylated compound 2a at the exo-position.[2] If the acid treatment of this compound 2a could afford *N-non*-substituted-β-lactam 4a, the anodic oxidation might be a useful method for debenzylation of N-benzyl-β-lactams.[3]

Thus, a solution of N-benzyl-3-methylene-β-lactam[4](1a, 85 mg, 0.49 mmol) was electrolyzed in MeOH(6 ml) containing Et_4NClO_4(0.1 mol solution) in an undivided cell with platinum plates as anode and cathode under constant current(30 mA, 4.4 F/mol) to afford N-methoxybenzyl-3-methylene-β-lactam(2a, 55 mg, 54 %), N-benzyl-3-methylene-4-methoxy-β-lactam(3a, 12 mg, 12 %) and the starting material(1a, 7 mg, 8.2 %). The former compound 2a was treated with TsOH in *aqueous acetone(5 %) to afford* 3-*methylene*-β-lactam(4a) in the yield of 50 %. Similarly, compound 1b[4] was electrolyzed under the same conditions to produce the methoxylated compound 3b and 4b in the yield of 62 % and 11 %, respectively, along with the starting material(1b, 9 %). Compound 2b was treated with TsOH in aqueous acetone to afford the desired compound 4b[mp 106.5-108°C, Mass m/e

Chart 1

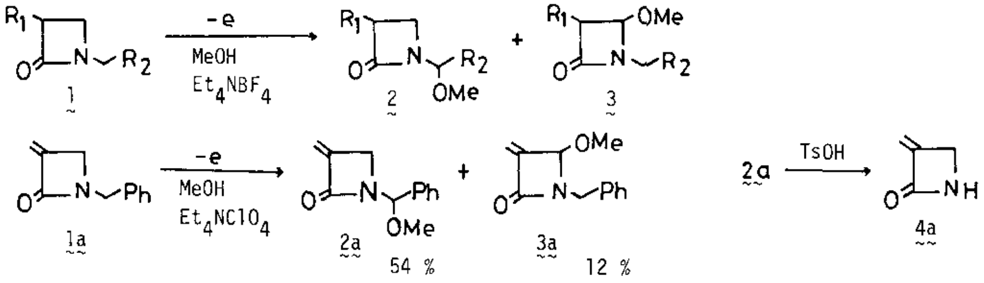
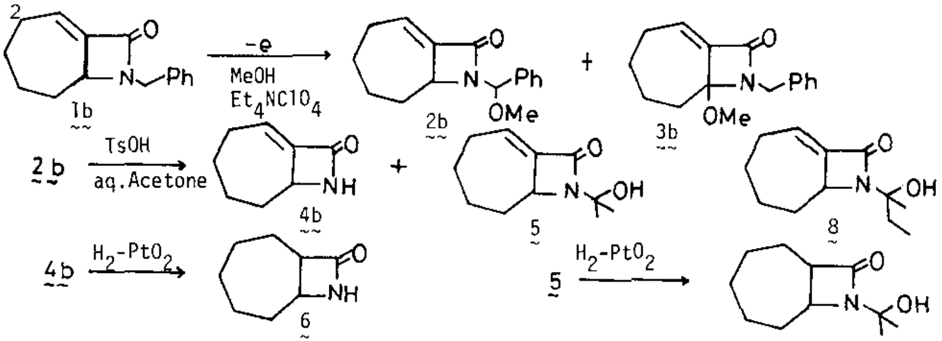


Chart 2



137(M^+), IR ν max 1740 cm^{-1}] in 57 % yield, on which a fairly amount of a condensation product with acetone was obtained[5, 16.7 %, Mass m/e 178(M^+-OH); IRν max 1740 cm^{-1}; NMRδ ($CDCl_3$) 1.80(s, 6 H, CH_3), 4.05(bs, 1 H, NCH), 6.45(bs, 1 H, vinyl)]. To confirm the structures of these compounds, hydrogenation of 4b and 5 with PtO_2 in EtOH afforded 6[Mass m/e 139(M^+)] and 7[Mass m/e 180(M^+-OH)], respectively, in quantitative yield. On hydrolysis of methoxylated compound 2b with TsOH, the use of aqueous THF or 2-butanone as a solvent gave a better result. In the case of 2-butanone, the desired product(4b, 84 % yield) was obtained with a small amount of a condensation product with 2-butanone(8, Mass m/e 192(M^+-OH)]. These results demonstrated that the anodic oxidation could be a useful method for debenzylation of N-benzyl-β-lactams.

It was anticipated that the substituents on the aromatic ring may exert an influence on the reaction site in electrolysis. Therefore, N-p-carbomethoxy, N-p-methyl and N-p-methoxybenzyl-3-methylene-β-lactams were synthesized by use of palladium catalyzed carbonylation according to the method shown in Chart 3.[4] The anodic oxidation of 1c, 1d and 1e were carried out in the same manner to afford the exo- and endo-methoxylated compounds in good yields(Table 1). When 2.2 F/mol was passed through the solution of N-p-methylbenzyl-3-methylene-β-lactam 1d in MeOH, the desired product 2d was obtained in the yield of 39 % along with 12 (15 % yield), in which methyl group was oxidized to methoxymethyl group. After 4.4 F/mol was passed, the yield of the desired product 2d decreased and compound 13 was obtained(10 % yield). It was very interesting that the anodic oxidation of N-p-methoxybenzyl-3-methylene-β-lactam(1e) gave an exo-methoxylated compound 2e in 54 % yield along with a dimethoxylated compound(14, 8 % yield). These results suggest that compound 1 having electron-donating group at the para position on the aromatic ring gives only the desired exo-methoxylated compound 2.

Chart 3

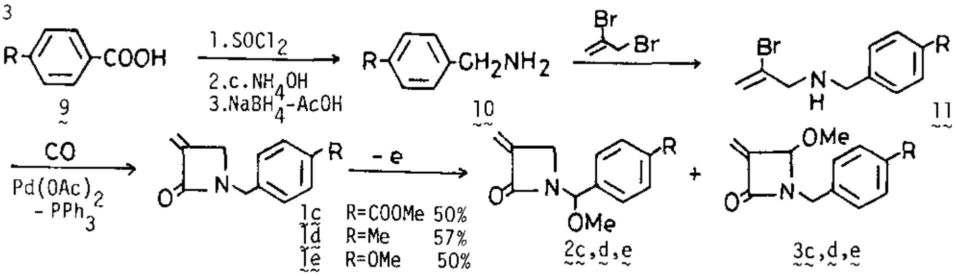
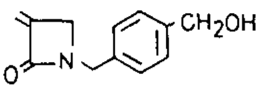


Table 1 Anodic oxidation of N-p-substituted-benzyl-3-methylene-β-lactams

	R	F/mol	2	3	1	2 : 3
1c	COOMe	5.4	48 %	23 %	9 %	1 : 0.5
1a	H	4.4	54	12	8	1 : 0.2
1d	Me	2.2	39	-	39	1 : 0
1d	Me	4.4	21	-	-	1 : 0
1e	OMe	2.2	54	-	17	1 : 0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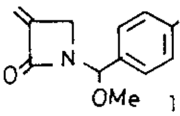
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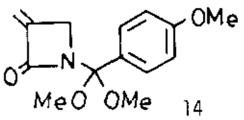
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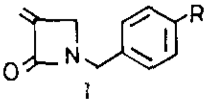
From the cyclic voltammograms of compound 1, p-substituted toluenes 15 and various β-lactams in CH_3CN containing Et_4NClO_4, the peak potentials were measured.[5] N-Alkyl- or N-benzyl-β-lactams showed no oxidation peaks below 2.2 V, but oxidation peaks of N-p-methoxy- and N-p-methyl-3-methylene-β-lactams were shown to be 1.7-2.2 V. These data suggest that the electron-donating substituents such as p-methoxy and p-methyl group on the aromatic ring would make the initial oxidation step easier and the oxidation for compound 1d and 1e should be initiated by the electron transfer from aromatic ring to anode. However, the first electron abstraction of N-benzyl-β-lactams having p-hydrogen or p-carbomethoxy group on the aromatic ring occurs from the amide nitrogen or both of them.

Chart 4 Peak potentials of various β-lactams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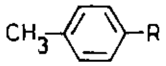
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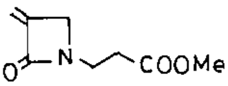
Table 2 Peak potentials of compound 1 and 15

Compound	Anode Potential			
	OMe	Me	H	COOMe
1	1.73	2.15	2.25	2.42
15	1.55	1.95	2.19	2.47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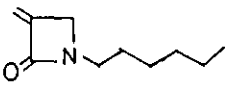
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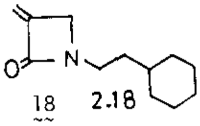
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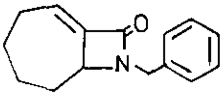
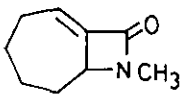

19 2.28


20 2.20

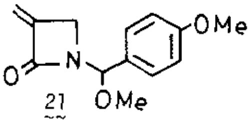
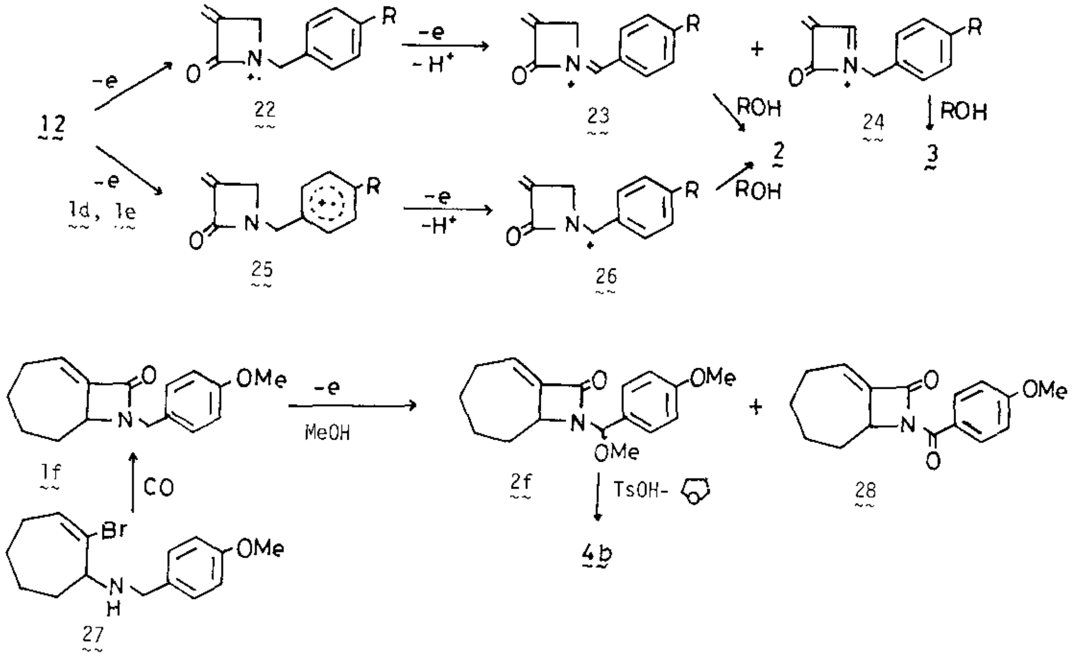

21 1.77

Chart 5



A plausible reaction scheme is shown in Chart 5.

It was anticipated that the p-methoxybenzyl group should be a good protecting group for the amide nitrogen of the β-lactams.[6] Thus, compound 1f which was prepared from 2-bromo-cycloheptenylamine derivative 27 and carbon monoxide[4] was electrolyzed in MeOH in the usual manner to afford the desired compounds 2f and 28 in the yield of 60 % and 13 %, respectively, along with a starting material(1f, 17 %). Hydrolysis of 2f with TsOH in aqueous THF gave 4b in a quantitative yield.

EXPERIMENTAL

Melting points were measured with a hot-stage microscope(Yanaco MP-J2) apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in the indicated solvent on JEOL JNM-FX100(100 mHz) and Hitachi R-20B(60 MHz) spectrometers. A Jasco IRA-2 diffraction grating infrared spectrophotometer and Hitachi RMU-7M double focussing mass spectrometer were used to determine infrared(IR) and mass spectra(MS), respectively. Anodic oxidation was carried out with Yanaco VE-8 controlled potential electrolyser and cyclic voltammogram was measured by Yanaco Poralographic Analyzer P-1100.

General procedure for the synthesis of 3-methylene-β-lactams(1).[4] For carbonylation, a baloon filled with a carbon monoxide was connected with a top of the reaction vassel. A solution of 2-bromoallylamine derivative(1 eq.), $Pd(OAc)_2$ or $Pd(acac)_2$(2 mol %), PPh_3(4 mol %) and $n-Bu_3N$(1.2 eq.) in HMPA was warmed at 100 °C for several hours under carbon monoxide. Ethyl acetate was added to the reaction mixture and the organic layer was washed with 5 % HCl dried over

Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel to afford the desired 3-methylene-β-lactam(1).

N-p-Methoxycarbonylbenzyl-3-methylene-β-lactam(1c). Yield, 50 %. Colorless prisms, mp 116-116.5°C(from ethyl acetate-n-hexane). IR ν(Nujol) 1730, 1710, 1605 cm^{-1}; NMR δ ($CDCl_3$) 3.68(s, 2 H), 3.92(s, 1 H, OMe), 4.57(s, 2 H, NCH_2Ar), 5.20(bs, 1 H, vinyl), 5.75(bs, 1 H, vinyl), 7.33, 8.10(q, 4 H, aromatic). MS m/e 231(M^+), 200(M^+-OMe), 191, 172, 160, 149, 132. Anal Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found, C, 67.64; H, 5.70; N, 6.04.

N-p-Methylbenzyl-3-methylene-β-lactam(1d). Yield, 57%. Colorless needles, mp 63-63.5°C(from ether-hexane). NMR δ ($CDCl_3$) 2.34(s, 3 H, CH_3) 3.62(bs, 2 H), 4.47(s, 2 H, NCH_2Ar), 5.14(bs, 1 H, vinyl), 5.72(bs, 1 H, vinyl), 7.15(s, 4 H, aromatic). MS m/e 187(M^+), 172(M^+-CH_3), 147, 132, 105. Anal calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found, C, 76.81; H, 7.11; N, 7.51.

N-p-Methoxybenzyl-3-methylene-β-lactam(1e). Yield, 50 %. Colorless needles, mp 71-71.5°C(from ether-n-hexane). IR ν (Nujol) 1740, 1605 cm^{-1}; NMR δ ($CDCl_3$) 3.62(m, 2 H), 3.80(s, 3 H, OMe), 4.45(s, 2 H, NCH_2Ar), 5.14(bs, 1 H, vinyl), 5.71(bs, 1 H, vinyl), 6.88, 7.19(q, 4 H, aromatic); MS m/e 203(M), 188(M^+-CH_3), 172(M^+-OMe), 121; Anal calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found, C; 70.79; H, 6.29; N, 7.02.

8-p-Methoxybenzyl-8-aza-bicyclo-[5,2,0]-1-nonen-9-one(1f). Yield, 80 %. IR ν(Nujol) 1735, 1700 cm^{-1}. NMR δ ($CDCl_3$) 1.0-2.6(m, 8 H), 3.80(s, 3 H, OMe), 3.80(bs, 1 H), 4.22, 4.61(q, 2 H, NCH_2Ar), 6.4(m, 1 H, vinyl), 6.84, 7.21(q, 4 H, aromatic); MS m/e 257(M^+), 229(M^+-CO), 228, 226, 214, 121.

Anodic oxidation of β-lactams(1). A solution of β-lactams(1) were electrolyzed in MeOH containing Et_4NClO_4(0.1 M solution) in an undivided cell with platinum plates as anode and cathode under constant current(30 mA). Solvent was removed under reduced pressure and the residue was purified by preparative thin layer chromatography on silica gel to afford compounds 2 and 3.

Anodic oxidation of 1a. 2a: Yield, 54 %. IR ν(neat) 1750 cm^{-1}; NMR δ ($CDCl_3$) 3.50(s, 3 H, OMe), 5.22(s, 1 H, vinyl), 5.82(s, 1 H, vinyl), 5.98(s, 1 H, NCHOMe), 7.32(s, 5 H, aromatic); MS m/e 203(M^+), 188(M^+-CH_3), 172(M^+-OMe). 3a: Yield, 12 %; IR ν(neat) 1750 cm^{-1}; NMR δ ($CDCl_3$) 3.21(s, 3 H, OMe), 4.25, 4.70(q, 2 H, $PhCH_2$), 5.34(s, 1 H, vinyl), 5.38(s, 1 H, NCHOMe), 5.82(s, 1 H, vinyl), 7.32(s, 5 H, aromatic); MS m/e 203(M^+), 188(M^+-CH_3), 172(M^+-OMe), 151, 112, 91, 70. Starting material, 8.2 %.

Anodic oxidation of 1b. 2b: Yield, 62 %. IR ν(neat) 1750, 1710 cm^{-1}; NMR δ($CDCl_3$) 1.0-2.6(m, 8 H), 3.48, 3.52(ss, 3 H, OMe), 4.06(m, 1 H), 6.00, 6.02(ss, 1 H, NCHOMe), 7.00(m, 1 H, vinyl), 7.38(s, 5 H aromatic); MS m/e 257(M^+), 256(M^+-1), 227(M^+-OMe), 226(M^+-MeOH), 121. 3b: Yield, 11 %. IR ν (neat) 1750, 1710 cm^{-1}; NMR δ ($CDCl_3$) 1.0-2.4(m, 8 H), 3.06(s, 3 H, OMe), 4.22, 4.55(q, 2 H, J=15 Hz, $PhCH_2$), 6.43(m, 1 H, vinyl), 7.31(s, 5 H, aromatic); MS m/e 257(M^+), 242(M^+-CH_3), 226(M^+-OMe), 137, 109, 91. Starting material, 9 %.

Anodic oxidation of 1c. 2c: Yield, 48 %; IR ν(neat) 1760, 1620, 1607 cm^{-1}; NMR δ(CDCl$_3$) 3.51(s, 3 H, OMe), 3.92(s, 3 H, OMe), 3.38, 3.63(q, J=10 Hz, NCH$_2$, 2 H), 5.26(bs, 1 H, vinyl), 5.84(bs, 1 H, vinyl), 6.03(s, 1 H, NCHOMe), 7.48, 8.06(q, 4 H, aromatic); MS m/e 261(M$^+$), 230(M$^+$-OMe), 179. 3c: Yield, 23 %; IR ν(neat) 1760, 1620, 1605 cm^{-1}; NMR δ (CDCl$_3$) 3.18(s, 3 H, OMe), 3.92(s, 3 H, OMe), 4.36, 4.71(q, J=15 Hz, 2 H, NCH$_2$),5.35(bs, 1 H, vinyl), 5.82(s, 1 H, vinyl), 7.43, 8.01(q, 4 H, aromatic), MS m/e 261(M$^+$), 246(M$^+$-CH$_3$), 230(M$^+$-OMe), 201(M$^+$-COOMe), 149, 112, 70. Starting material, 9 %.

Anodic oxidation of 1d. When 2.2 F/mol was passed through the solution, 2d(39 % yield), 12(15 % yield) and the starting material(39 % yield) were obtained. 2d: IR ν(neat) 1750, 1605 cm^{-1}; NMR δ (CDCl$_3$) 2.35(s, 3 H, CH$_3$), 3.48(s, 3 H, OMe), 3.41, 3.76(q, J=8 Hz, NCH$_2$, 2 H), 5.22(bs, 1 H, vinyl), 5.80(bs, 1 H, vinyl), 5.96(s, 1 H, NCHOMe), 7.17, 7.28(q, 4 H, aromatic). MS m/e 217(M$^+$), 186(M$^+$-OMe), 135. 12: IR ν(neat) 1750, 1605 cm^{-1}; NMR δ (CDCl$_3$) 3.40,(s, 3 H, OMe), 3.64(s, 2 H, NCH$_2$), 4.45(s, 2 H, CH$_2$Ar), 4.51(s, 2 H, CH$_2$Ar), 5.15(s, 1 H, vinyl), 5.73(s, 1 H, vinyl), 7.3(m, 4 H, aromatic); MS m/e 217(M$^+$), 186(M$^+$-OMe), 185(M$^+$-MeOH), 172(M$^+$-CH$_2$OMe), 135, 121. When 4.4 F/mol was passed through the solution, 2(21 % yield) and 13(10 % yield) were obtained. 13: IR ν (neat) 1750, 1605 cm^{-1}; NMR δ (CDCl$_3$) 3.39(s, 3 H, OMe), 3.49(s, 3 H, OMe), 4.45(s, 2 H, CH$_2$Ar), 5.23(s, 1 H, vinyl), 5.80(s, 1 H, vinyl), 5.98(s, 1 H, NCHOMe), 7.34(s, 4 H, aromatic); MS m/e 247(M$^+$), 216(M$^+$-OMe), 165.

Anodic oxidation of 1e. 2: Yield, 54 %; IR ν(neat) 1750, 1605 cm^{-1}; NMR δ(CDCl$_3$) 3.49(s, 3 H, OMe), 3.82(s, 3 H, OMe), 5.26(bs, 1 H, vinyl), 5.83(bs, 1 H, vinyl), 5.97(s, 1 H, NCHOMe), 6.92, 7.36(q, 4 H, aromatic); MS m/e 233(M$^+$), 232(M$^+$-OMe), 151, 135, 121. 14: Yield, 8 %; NMR δ (CDCl$_3$) 3.26(s, 6 H, OMe), 3.60(bs, 2 H), 3.82(s, 3 H, OMe), 5.20(bs, 1 H, vinyl), 5.77(bs, 1 H, vinyl), 6.92, 7.52(bs, 4 H, aromatic). MS m/e 263(M$^+$), 232(M$^+$-OMe), 181, 151, 135.

Anodic oxidation of 1f. 2f: Yield 60 %; NMR δ (CDCl$_3$) 1.0-2.4(m, 8 H), 3.46, 3.50(s,s, 3 H, OMe), 3.80, 3.81(s,s, 3 H, OMe), 4.2(m, 1 H), 5.92, 5.97(s,s, 1 H, NCHOMe), 6.5(m, 1 H, vinyl), 6.8-7.4(m, 4 H, aromatic),; MS m/e 287(M$^+$), 256(M$^+$-OMe), 151. 28: IR ν(neat) 1765, 1655, 1605, 1575 cm^{-1}; NMR δ (CDCl$_3$) 1.2-2.8(m, 8 H), 3.87(s, 3 H, OMe), 4.6(m, 1 H), 6.8(m, 1 H, vinyl), 7.23, 8.02(q, 4 H, aromatic); MS m/e 217(M$^+$), 202(M$^+$-CH$_3$), 135.

General procedure for the hydrolysis of 2. A solution of 2 and a catalytic amount of TsOH in aq.THF(5 %) was allowed to stand for 8 h. A small amount of solid NaHCO$_3$ was added to the reaction mixture, and a solution was stirred for 30 min. Undissolved material was filtered off and the filtrate was dried over Na$_2$SO$_4$. Solvent was evaporated and the residue was purified by preparative thin layer chromatography on silica gel to afford compound 4.

Hydrolysis of 2a. 4a: Yield, 50 %; IR ν(CHCl$_3$) 1750 cm^{-1}; NMR δ (CDCl$_3$) 3.83(m, 2 H), 5.26(m, 1 H, vinyl), 5.78(m, 1 H, vinyl), 6.43(bs, 1 H, NH).

Hydrolysis of 2b. When aq.acetone(5 %) was used for the solvent, the desired compound(4b, 57 % yield) and the condensation product with acetone(5, 16.7 % yield) were obtained. 4b: colorless prisms, mp 106.5-108°C(from ethyl acetate-n-hexane); IR ν(Nujol) 3200, 1740 cm^{-1}; NMR δ ($CDCl_3$) 1.05-2.5(8 H, m), 4.10(m, 1 H), 5.40(bt, 1 H, vinyl), 6.80(bs, 1 H, NH); MS m/e 137(M^+), 94, 79; Anal calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found, C,70.05; H, 7.90; N, 10.08. 5: Yield, 16.7 %; IR ν(neat) 3400, 1730, 1705 cm^{-1}; NMR δ ($CDCl_3$) 1.80(s, 6 H, CH_3), 1.0-2.5(m, 8 H), 4.05(bs, 1 H, NCH), 6.45(bs, 1 H, vinyl), 7.4(m, 1 H, OH); MS m/e 178(M^+-OH), 149, 121, 93.

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