Addition of Trimethylsilyl Enol Ethers to Isoquinolinium Salts: A Facile Synthesis of 1-(2-Oxoalkyl)-2-(ethoxycarbonyl)(or acetyl)-1,2-dihydroisoquinolines and Their Cyclization for the Synthesis of the Isoquinoline Alkaloid Skeleton

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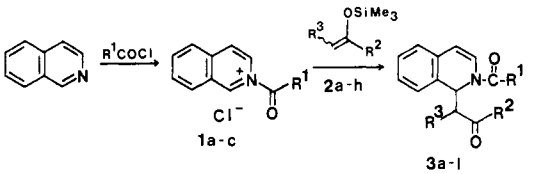
Received June 15, 1984

The addition of trimethylsilyl enol ethers to 2-acylisoquinolinium salts afforded 1-(2-oxoalkyl)-2-(ethoxycarbonyl)(or acetyl)-1,2-dihydroisoquinolines (**3**) in excellent yields. These compounds were cyclized with bases to give benzo[*a*]quinolizine derivatives (**4**) in good yields. Formation of the cis or trans isomer of **4** at C(1)–C(11b) was explained by steric effect in the transition states. This two-step process was applied to 6,7-dimethoxy-3,4-dihydroisoquinoline to obtain a precursor (**11**) for emetine synthesis.

Activation of nitrogen containing heteroaromatics by quaternization permits introduction of substituents into these rings, as in acylation to give Reissert compounds.[1] Recently, we and others have presented some results on regioselective introduction of alkyl and aryl groups at the 4-position of pyridine and quinoline by acylation of these rings.[2,3]

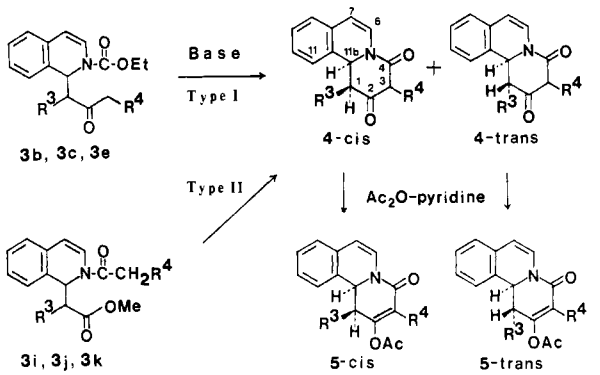
It is quite useful to introduce carbon substituents containing a β-carbonyl group into the 1-position of isoquinoline for preparation of isoquinoline alkaloids. In order to realize this, Yamanaka et al.[4] and Sheinkman et al.[5] reported the reaction of isoquinoline with methyl ketones in the presence of acetic anhydride or benzoyl chloride. However, the reactions are sluggish and the yields are low. In a preliminary study on the same project, we reported on addition of boron enolates, which can be generated from ketones, to isoquinolinium salts at room temperature to obtain the expected 1,2-dihydroisoquinolines in 64–98% yields.[6] We have now extended the scope of this reaction by employing silyl enol ethers, because these reagents can be derived not only from ketones but also from aldehydes and esters.[7] This paper describes an efficient synthesis of a variety of 1-(2-oxoalkyl)-2-acyl-1,2-dihydroisoquinolines (**3**) by the reaction of 2-acylisoquinolinium salts (**1**) and trimethylsilyl enol ethers (**2**) and cyclization of **3** with some stereochemical considerations.[8]

Scheme I[a]



[a] **1a**, R^1 = EtO; **1b**, R^1 = Me; **1c**, R^1 = Et; **2a**, R^2 = Ph, R^3 = H; **2b**, R^2 = Pr, R^3 = H; **2c**, R^2 = $PhCH_2CH_2$, R^3 = H; **2d**, R^2,R^3 = $-(CH_2)_4-$; **2e**, R^2 = Et, R^3 = Me; **2f**, R^2 = MeO, R^3 = Ph; **2g**, R^2 = MeO, R^3 = Me; **2h**, R^2 = H, R^3 = $PhCH_2$.

Scheme II



Results and Discussion

During the course of the reaction of dibutylboron enolate of ketones and **1**, ether was found to be the best solvent and the adducts (**3**) were obtained in satisfactory yields.[6a] For example, kinetic boron enolate of 4-phenyl-2-butanone reacted with **1a** to afford 2-(ethoxycarbonyl)-1-(2-oxo-2-phenylethyl)-1,2-dihydroisoquinoline (**3a**) in 64% yield. But boron enolates attacked also the carbonyl group of **1** as a side reaction to give back isoquinoline. To circumvent this side reaction, we tried the reaction of trimethylsilyl

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(6) (a) Akiba, K.; Araki, K.; Nakatani, M.; Wada, M. *Tetrahedron Lett.* **1981**, *22*, 4961. (b) Portions of this work have been communicated in preliminary form: Wada, M.; Nakatani, M.; Akiba, K. *Chem. Lett.* **1983**, 39.

(7) (a) Colvin, E. W. "Silicon in Organic Synthesis"; Butterworths: London, 1981. (b) Weber, W. P. "Silicon Reagents for Organic Synthesis"; Springer-Verlag: Berlin, 1983. (c) Recently we developed a simple and efficient method of the regioselective preparation of some silyl enol ethers. That is, (trimethylsilyl)methyl copper reagent was reacted with acid chloride to give β-keto silanes, which can be rearranged with catalytic trimethylsilyl triflate. A detail description of this method was reported recently: Yamamoto, Y.; Ohdoi, K.; Nakatani, M.; Akiba, K. *Chem. Lett.* **1984**, 1967. Cf. Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248. Emde, H.; Götz, A.; Hofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1981**, 1643.

(8) The ratios of some diastereomers of **3** were estimated on the basis of ^1H NMR data: Integral ratio of methoxy protons at room temperature for **3k** (1:1), at 100 °C for **3j** (1.1:1). Integral ratio of methylene protons in ethoxy group in the presence of $Eu(dpm)_3$ for **3e** (1.5:1). Peak height ratio of acetyl protons at 100 °C for **3g** (1.3:1).

0022-3263/85/1950-0063$01.50/0

Table I. Synthesis of 1-(2-Oxoalkyl)-1,2-dihydroisoquinolines (3) from 1 and 2

entry	compd 3	R^1	R^2	R^3	yield, %[a]	reactn temp,[d] °C	cond[b] time, h
1	**3a**	EtO	Ph	H	98	0	1
2	**3b**	EtO	*n*-Pr	H	84	rt	2
3	**3c**	EtO	$PhCH_2CH_2$	H	90	rt	2
4	**3d**	EtO	$-(CH_2)_4-$		88[c]	0	1.5
5	**3e**	EtO	Et	Me	98[c]	rt	1.5
6	**3f**	Me	Ph	H	96	rt	0.5
7	**3g**	Me	Et	Me	98[c]	rt	1.5
8	**3h**	EtO	MeO	Ph	94[c]	0	0.5
9	**3i**	Me	MeO	Ph	97[c]	0	0.5
10	**3j**	Me	MeO	Me	95[c]	0	2
11	**3k**	Et	MeO	Me	97[c]	rt	1
12	**3l**	EtO	H	$PhCH_2$	63[c]	30-40	2.5

[a] Isolated yield by flash column chromatography (SiO_2, hexane–ethyl acetate). [b] Acetonitrile was used as a solvent. [c] A mixture of diastereomers. [d] rt = room temperature.

Table II. Synthesis of Benzo[*a*]quinolizine 4 from 3 and Their Stereochemistry

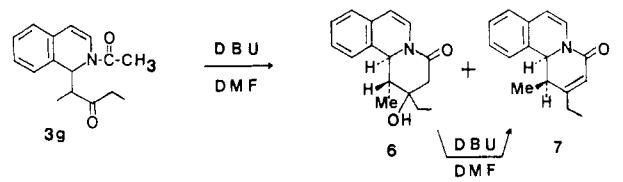
type	3	4	R^3	R^4	yield, %	cis:trans	bases
I	**3b**	**4a**	H	Et	78		NaOEt
	3c	**4b**	H	$PhCH_2$	73		NaOEt
	3e	**4c**	Me	Me	63	trans only	NaOEt
					56	1:18	NaH
					64	1:1.3	*t*-BuOK
II	**3k**	**4c**	Me	Me	74	3.2:1	*t*-BuOK
	3j	**4d**	Me	H	62	5:1	*t*-BuOK
	3i	**4e**	Ph	H	51	10 > 1	*t*-BuOK

enol ethers (**2**) with **1**, where acetonitile was found superior to ether as a solvent.[6b] Some of the results are summarized in Table I. As is evident from Table I, silyl enol ethers of ketones (**2a–e**) and esters (**2f,g**) reacted smoothly with **1** to give **3** in almost quantitative yields at zero to room temperature. When that of an aldehyde (**2h**) was used, however, **3** was obtained in only 63% yield, probably due to lower nucleophilicity of **2h**. The adducts (**3d, 3e, 3g–3l**) were isolated as a mixture of erythro and threo isomers. The ratios of these diastereomers were close to unity (1.0–1.5:1.0).[8] In this reaction, it is noteworthy that **2** did not attack the carbonyl group of **1** but reacted chemoselectively at the 1-position, as evidenced by the absence of recovered isoquinoline. The present procedure provides a facile method for the synthesis of **3** under very mild conditions.

Cyclization of the Adducts (3). Cyclization of the adducts (**3**) by Dieckmann condensation to benzo[*a*]quinolizine derivatives **4** can occur in two ways as shown in Scheme II. In type I condensation, the enolate ion is generated on the substituent at the 1-position (**3b, 3c, 3e**), and the enolate ion is generated on the acylating group in type II condensation (**3i, 3j, 3k**). The relative stereochemistry between the C(1) and C(11b) in **4** was different according to each type (Table II). When **3e** was treated with 2.3–2.4 equiv of NaOEt in refluxing ether for 4–5 h, **4c** was obtained in 63% yield. The relative stereochemistry of **4c** at C(1) and C(11b) was assigned trans due to the observed large coupling constant (J = 10 Hz) in ^1H NMR compared with that of the cis isomer (J = 3 Hz, vide infra). When NaH (2.9 equiv) was used in refluxing benzene with **3e**, trans isomer was the major product (53%) and cis isomer was also isolated (3%:trans/cis = 18). But by the use of *t*-BuOK as a base, selectivity became very poor (64% yield, trans/cis = 1.3). When **3b** and **3c** were similarly cyclized with NaOEt in refluxing ether, **4a** and **4b** were obtained in 78% and 73% yield, respectively.

Similar treatment of **3i–3k** with sodium methoxide caused decomposition, resulting in isoquinoline, hence, bulkier *t*-BuOK was employed. Treatment of **3i** with 2.4 equiv of *t*-BuOK in ether at room temperature for 7 h afforded **4e** in 51% yield. ^1H NMR of **4e** showed a small

Scheme III



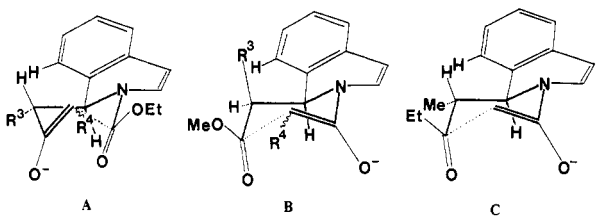
coupling constant (J = 4.5 Hz) between protons at C(1) and C(11b), indicating that the cis isomer was almost the sole product. In a similar manner, **3j** and **3k** were cyclized to give **4d** and **4c** in good yields (62% and 74%, respectively), and cis isomers were major products in both cases (cis/trans = 5 and 3.2, respectively). Therefore, it is possible to prepare each of the diastereomers of **4** by choosing type I or type II condensation as exemplified for **4c**. The cyclized products (**4**) were slowly oxidized and were somewhat unstable on silica gel. They were readily acetylated (except **4e**) to the more stable acetates (**5**) in nearly quantitative yields (91–99%).

We observed no cis–trans isomerization of **4c**, when each isomer was separately subjected to the reaction conditions (*t*-BuOK in ether at room temperature for several hours). Therefore it can be concluded that these are kinetically controlled products.

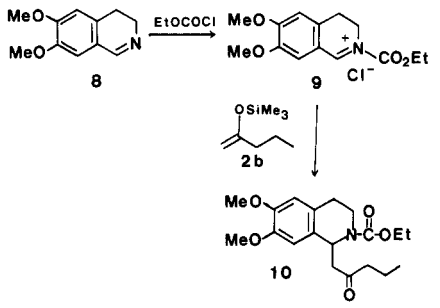
As the adducts (**3**) are ca. 1:1 mixture of diastereomers,[8] the cyclization should proceed with isomerization of **3**. In fact, by monitoring the reaction on TLC, it was clearly observed that one of the diastereomers of **3** disappeared first and the other slowly did.

In addition to the above Dieckmann condensation, intramolecular aldol condensation was also performed with **3g**. It was cyclized by DBU (3 equiv) in DMF at 100 °C for 4 h to give **6** and **7** in 31% and 53% yield, respectively. To our surprise, ^1H NMR showed that the coupling constant between protons at C(1) and C(11b) in **6** was 11 Hz and that in **7** was 3 Hz. This result indicates that **6** has trans and **7** has cis configuration. After isolation, **6** was converted to **7** with DBU in 61% yield. During the latter process, no **3g** was observed to show that dehydration was much faster than retro aldol condensation and **6**-*trans* was a kinetically controlled product.[9] On the other hand,

Chart I



Scheme IV



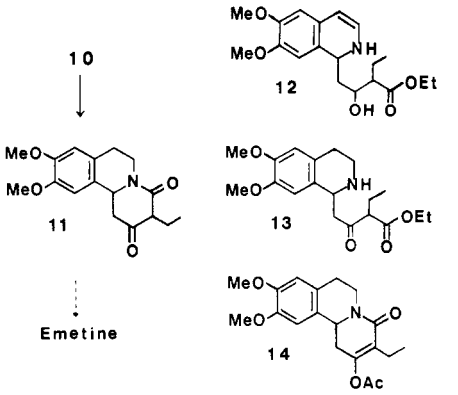
thermodynamically stable **7** with cis configuration was formed through isomerization catalyzed by DBU. Apparently, this cyclization resembles the type II cyclization, but the stereochemical outcome was the opposite.

These rather complex stereochemical results are rationalized by assuming a six-membered chair-like transition state for each type. In each type, the enolate carbanion is arranged to attack the requisite carbonyl group from the direction to keep a slightly larger angle than 90°.[10] Thus for type I, transition state A is assumed. Examination of Dreiding models reveals that a severe nonbonded interaction by the $A^{1,3}$ strain exists in the enolate anion, when R^3 stays at an axial position. This effect seems to overcome the interaction between R^3 and the peri hydrogen at C(11) (vide infra). Consequently the major product had trans structure. For type II, transition state B was supposed. The substituent (R^3) of the ester group is assumed to exist predominantly in axial orientation in order to avoid a nonbonded interaction with the peri hydrogen at C(11). Therefore the cis isomer of **4** became the major product. However in B, nonbonded interaction between R^3 and the OMe group exists as a secondary factor. In transition state C for **3g**, this effect became a main factor to place R^3 (= Me) in the equatorial position, because it was much larger with the Et group when the latter was placed instead of the OMe group as in B; therefore **6**-*trans* was formed.

Thus the stereochemical outcome of the cyclization of **3** was rationalized by assuming chair-like transition states and it was found that the adducts (**3**) were effective precursors for cyclization to form the third ring of the isoquinoline skeleton.

Preparation of a Precursor (11) for Emetine Synthesis. In order to demonstrate the synthetic application of these reactions, we tried to prepare a precursor (**11**)[11]

Scheme V



for emetine synthesis. 6,7-Dimethoxy-3,4-dihydroisoquinolinium salt (**9**) was prepared from **8**[12] and ethyl chloroformate in acetonitrile, silyl enol ether (**2b**) was added, and the mixture was stirred at room temperature for two days. The adduct (**10**) was obtained in 80% yield. Treatment of **10** with NaOEt or LDA resulted in a complex mixture, whereas **12** (46% yield) was obtained with *t*-BuOK, and **12** (18%) and **13** (45%) were the products with KH. Only when the benzene solution of **10** was added dropwise to the suspension of NaH in refluxing benzene could **11** be isolated in 47% yield with 16% of recovered **10**. And **11** was readily acetylated to **14** in 93% yield. Already **11** had been shown to be the precursor for emetine[11] and this method provided a simple and short route to **11**.

Experimental Section

Melting points were taken on a micro melting point apparatus and are uncorrected. IR spectra were obtained on a Hitachi 215 spectrometer. ^1H NMR spectra were recorded on Varian T-60 or Hitachi R-90H spectrometer. Mass spectra were recorded on a Hitachi RMU-6L spectrometer. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, Hiroshima University. Flash column chromatography was carried out on Merck silica gel 60, 230–400 mesh. Thin-layer chromatography (TLC) was performed by using Merck silica gel GF-254 plates. All solvents were distilled before use.

Synthesis of 2-(Ethoxycarbonyl)(or Acetyl)-1-(2-oxoalkyl)-1,2-dihydroisoquinoline (3) with Trimethylsilyl Enol Ethers (2). General Procedure. Isoquinolinium salt (**1**) was prepared from isoquinoline (0.26 g, 2.0 mmol) and ethyl chloroformate (0.22 g, 2.0 mmol) in 5 mL of CH_3CN at 0 °C. To this solution was added trimethylsilyl enol ether **3** (2.2 mmol) through a syringe and the reaction mixture was stirred under nitrogen or argon at 0 °C or room temperature. The resulting reaction mixture was treated with 5% $NaHCO_3$ (20 mL), then the product was extracted with ether (25 mL × 3). After drying over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The crude product was purified on flash column chromatography with hexane and ethyl acetate (9:1–8:2) as eluent to afford **3**.

2-(Ethoxycarbonyl)-1-(2-oxo-2-phenylethyl)-1,2-dihydroisoquinoline (3a). Yield 98%; mp 89–91 °C; IR (Nujol) 1710, 1680, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, *J* = 7 Hz), 3.27 (d, 2 H, *J* = 7 Hz), 4.13 (q, 2 H, *J* = 7 Hz), 5.67–6.15 (m, 2 H), 6.67–7.55 (m, 8 H), 7.67–8.18 (m, 2 H); MS, *m/e* (relative intensity) 321 (M^+, 5), 202 ($M^+ - PhCOCH_2$, 100), 158 (202 – OEt + H, 24). Anal. Calcd for $C_{20}H_{19}O_3N$: C, 74.74; H, 5.96; N, 4.36. Found: C, 75.02; H, 6.10; N, 4.28.

2-(Ethoxycarbonyl)-1-(2-oxopentyl)-1,2-dihydroisoquinoline (3b). Yield 84%; IR (neat) 1700, 1630, 1570, 1450 cm^{-1};

(9) As the stereochemistry at C(2) of **6** was unknown, we could not remove the possibility that the rate of dehydration of cis isomer of **6** was much faster than that of **6**-*trans*. But when we stopped the reaction halfway, we could isolate **3g** (30% yield, diastereomer ratio about 1.8:1), **6** (32% yield, almost only trans), and **7** (30% yield, only cis). Therefore, it seems certain that **6**-*trans* was almost the sole kinetic product.

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^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3 H, J = 6 Hz), 1.00–2.00 (m, 5 H), 2.00–2.50 (m, 2 H), 2.87 (t, 2 H, J = 7 Hz), 4.23 (q, 2 H, J = 6 Hz), 5.57–6.03 (m, 2 H), 6.67–7.73 (m, 5 H); MS, m/e (relative intensity) 287 (M^+, 9), 202 ($M^+ - CH_3CH_2CH_2COCH_2$, 9), 158 (202 – OEt + H, 96), 130 (158 – CO, 100). Anal. Calcd for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.78; H, 7.58; N, 4.68.

2-(Ethoxycarbonyl)-1-(2-oxo-4-phenylbutyl)-1,2-dihydroisoquinoline (3c). Yield 90%; mp 53.5–54.5 °C; IR (KBr) 1710, 1630 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.30 (t, 3 H, J = 7 Hz), 2.15–3.00 (m, 6 H), 4.15 (q, 2 H, J = 7 Hz), 5.50–5.90 (m, 2 H), 6.60–7.30 (m, 10 H); MS, m/e (relative intensity) 349 (M^+, 4), 202 ($M^+ - CH_2COCH_2CH_2Ph$, 8), 158 (202 – OEt + H, 13), 130 (158 – CO, 100). Anal. Calcd for $C_{22}H_{23}O_3N$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.56; H, 6.65; N, 4.01.

2-(Ethoxycarbonyl)-1-(2-oxocyclohexyl)-1,2-dihydroisoquinoline (3d). Total yield 88%. The initially eluted diastereomer of **3d** from flash column chromatography (hexane-AcOEt, 9:1): mp 103–104 °C; IR (nujol) 1700, 1630, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz); 1.50–3.00 (m, 9 H), 4.23 (q, 2 H, J = 7 Hz), 5.63–6.07 (m, 2 H), 6.57–7.60 (m, 5 H); MS, m/e (relative intensity) 299 (M^+, 3), 202 (M^+ – cyclohexanoyl, 100), 130 (202 – CO_2Et + H, 88). Anal. Calcd for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.47; H, 7.18; N, 4.51. Another diastereomer: oil; IR (neat) 1700, 1630, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz), 1.47–3.00 (m, 9 H), 4.18 (q, 2 H, J = 7 Hz), 5.70–6.07 (m, 2 H), 6.60–7.33 (m, 5 H).

2-(Ethoxycarbonyl)-1-(1-methyl-2-oxobutyl)-1,2-dihydroisoquinoline (3e). Total yield 98% (diastereomer ratio 1.5: 1[8]). The initially eluted minor diastereomer of **3e** from flash column chromatography (hexane–AcOEt, 9:1): mp 55–56 °C; IR (KBr) 1710, 1630, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, 3 H, J = 7 Hz), 1.02 (d, 3 H, J = 7 Hz), 1.34 (t, 3 H, J = 7 Hz), 2.10 (q, 2 H, J = 7 Hz), 2.74–3.40 (m, 1 H), 4.28 (q, 2 H, J = 7 Hz), 5.35–6.15 (m, 2 H), 6.76–7.38 (m, 5 H). Another major diastereomer: oil; IR (neat) 1700, 1630, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.50–1.50 (m, 9 H), 2.00–3.33 (m, 3 H), 4.20 (q, 2 H, J = 7 Hz), 5.50 (d, 1 H, J = 8 Hz), 5.67–6.17 (m, 1 H), 6.67–7.50 (m, 5 H); MS, m/e (relative intensity) 287 (M^+, 5), 202 ($M^+ - CH_3CH_2COCH_2CH_2$, 91), 158 (202 – OEt + H, 33), 130 (158 – CO, 100). Anal. Calcd for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.83. Found: C, 70.90; H, 7.29; N, 4.71.

2-Acetyl-1-(2-oxo-2-phenylethyl)-1,2-dihydroisoquinoline (3f). Yield 96%; mp 112–113 °C; IR (nujol) 1675, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.13, 2.37 (s, 3 H), 3.10–3.40 (m, 2 H); 5.95 (d, 1 H, J = 7 Hz), 6.14–6.45 (m, 1 H), 6.60 (d, 1 H, J = 7 Hz), 6.83–7.67 (m, 7 H), 7.67–8.17 (m, 2 H); MS, m/e (relative intensity) 291 (M^+, 4), 172 (M^+ – $PhCOCH_2$, 33), 130 (172 – CH_3CO + H, 100). Anal. Calcd for $C_{19}H_{17}O_2N$: C, 78.33; H, 4.81; N, 5.88. Found: C, 78.43; H, 4.79; N, 5.82.

2-Acetyl-1-(1-methyl-2-oxobutyl)-1,2-dihydroisoquinoline (3g). Total yield 98% (diastereomer ratio (1.3:1[8]). The initially eluted minor diastereomer of **3g** from flash column chromatography (hexane–AcOEt, 9:1): mp 101–102 °C; IR (KBr) 1710, 1680, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.70–1.30 (m, 6 H), 2.10–3.30 (m, 6 H), 5.90 (d, 1 H, J = 8 Hz), 6.02 (d, 1 H, J = 7.5 Hz), 6.70 (d, 1 H, J = 7.5 Hz), 6.90–7.45 (m, 4 H); MS, m/e (relative intensity) 257 (M^+, 2), 172 ($M^+ - CH_3CHCOCH_2CH_3$, 68), 130 (172 – $COCH_3$ + H, 100). Anal. Calcd for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.65; H, 7.53; N, 5.42. Another major diastereomer: mp 56–61 °C; IR (neat) 1710, 1675, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.58–1.35 (m, 6 H), 1.70–2.50 (m, 5 H), 2.70–3.60 (m, 1 H), 5.90–6.25 (m, 2 H), 6.70 (d, 1 H, J = 7.5 Hz), 6.90–7.45 (m, 4 H); MS, m/e (relative intensity) 257 (M^+, 1), 172 ($M^+ - CH_3CHCOCH_2CH_3$, 32), 130 (172 – $COCH_3$ + H, 100).

2-(Ethoxycarbonyl)-1-[1-(methoxycarbonyl)benzyl]-1,2-dihydroisoquinoline (3h). Total yield 94%. The initially eluted diastereomer of **3h** from flash column chromatography (hexane–AcOEt, 9:1): mp 78–80 °C; IR (KBr) 1750–1730, 1630 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.77–1.30 (m, 3 H), 3.30–4.10 (m, 6 H), 5.73 (d, 1 H, J = 11 Hz), 6.05 (d, 1 H, J = 8 Hz), 6.55–7.05 (m, 10 H); MS, m/e (relative intensity) 202 (M^+ – $PhCHCO_2CH_3$, 100), 174 (202 – Et + H, 22), 158 (174 – O, 40), 130 (158 – CO, 50). Anal. Calcd for $C_{21}H_{21}O_4N$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.58; H, 6.06; N, 3.88. Another diastereomer: mp 80–82 °C; IR (KBr) 1755–1700, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3 H, J = 7 Hz), 3.69 (s, 3 H), 3.92 (d, 1 H, J = 9 Hz), 4.30 (q, 2 H, J = 7 Hz), 5.70–6.15 (m, 2 H), 6.36 (d, 1 H, J = 8 Hz), 6.66–7.22 (m, 9 H); MS, m/e (relative intensity) 351 (M^+, 0.1), 202 (M^+ – $PhCHCO_2CH_3$, 100), 174 (202 – Et + H, 4), 158 (174 – O, 8), 130 (158 – CO, 47). Anal. Calcd for $C_{21}H_{21}O_4N$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.54; H, 6.02; N, 3.91.

2-Acetyl-1-[α-(methoxycarbonyl)benzyl]-1,2-dihydroisoquinoline (3i). Total yield 97%. The initially eluted diastereomer of **3i** from flash column chromatography (hexane–AcOEt, 8:2): mp 143.5–144.5 °C; IR (KBr) 1720, 1668, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.59, 1.73 (s, 3 H), 3.45, 3.50 (s, 3 H), 3.92, 4.03 (d, 1 H, J = 11 Hz), 6.12 (d, 1 H, J = 7.5 Hz), 6.52 (d, 1 H, J = 7.5 Hz), 6.55 (d, 1 H, J = 11 Hz), 7.07–7.58 (m, 9 H); MS, m/e (relative intensity) 217 (M^+ – CH_3CO – CO_2CH_3, 0.8), 172 (M^+ – $PhCHCO_2CH_3$, 44), 130 (172 – CH_3CO + H, 100). Anal. Calcd for $C_{20}H_{19}O_3N$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.44; H, 5.95; N, 4.30. Another diastereomer: mp 111–112 °C; IR (KBr) 1725, 1680, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.18, 2.50 (s, 3 H), 3.67 (s, 3 H), 3.90, 4.30 (d, 1 H, J = 9.5 Hz), 5.90–7.43 (m, 12 H); MS, m/e (relative intensity) 217 (M^+ – CH_3CO – CO_2CH_3, 1), 172 (M^+ – $PhCHCO_2CH_3$, 47), 130 (172 – CH_3CO + H, 100). Anal. Calcd for $C_{20}H_{19}O_3N$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.61; H, 5.98; N, 4.29.

2-Acetyl-1-[1-(methoxycarbonyl)ethyl]-1,2-dihydroisoquinoline (3j). A mixture of diastereomers **3j**: yield 95% (diastereomer ratio 1.1:1[8]); IR (neat) 1730–1710, 1675–1640, 1615 cm^{-1}; ^{1}H NMR (Me_2SO-d_6, 100 °C) δ 0.90, 1.07 (d, 3 H, J = 7 Hz), 2.18, 2.22 (s, 3 H), 2.50–2.97 (m, 1 H), 3.48, 3.60 (s, 3 H), 5.65–5.75 (m, 1 H), 6.04 (d, 1 H, J = 8 Hz), 6.83–7.30 (m, 6 H); MS, m/e (relative intensity) 259 (M^+, 2), 172 (M^+ – $CH_3CHCO_2CH_3$, 29), 130 (172 – CH_3CO + H, 100).

1-[1-(Methoxycarbonyl)ethyl]-2-(1-oxopropyl)-1,2-dihydroisoquinoline (3k). A mixture of diastereomers **3k**: yield 97% (diastereomer ratio 1:1[8]); IR (neat) 1740–1720, 1690–1660, 1630–1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.73–1.27 (m, 6 H), 2.10–3.05 (m, 3 H), 3.40, 3.50 (s, 3 H), 5.71–6.20 (m, 2 H), 6.50–6.76 (m, 1 H), 6.87–7.37 (m, 4 H); MS, m/e (relative intensity) 273 (M^+, 2), 186 (M^+ – $CH_3CHCO_2CH_3$, 32), 130 (186 – CH_3CH_2CO + H, 100).

2-(Ethoxycarbonyl)-1-(1-formyl-2-phenylethyl)-1,2-dihydroisoquinoline (3l). A mixture of diastereomers **3l**: yield 63%; IR (neat) 1725–1690, 1625 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.31 (t, 3 H, J = 7 Hz), 2.52–3.15 (m, 3 H), 4.25 (q, 2 H, J = 7 Hz), 5.50–6.05 (m, 2 H), 6.60–7.40 (m, 10 H), 9.50–9.63 (m, 1 H); MS, m/e (relative intensity) 335 (M^+, 1), 202 (M^+ – $PhCH_2CHCHO$, 100), 158 (202 – OEt + H, 1), 143 (M^+ – CO_2Et – $PhCH_2$ – CHO, 22), 130 (158 – CO, 65).

Preparation of 3-Ethyl-2,4-dioxo-1,2,3,4-tetrahydro-11b*H*-benzo[*a*]quinolizine (4a). To a suspension of NaOEt (668 mg, 9.8 mmol) in ether (5 mL) was added 25 mL of ether solution of **3b** (1.18 g, 4.09 mmol) at room temperature. The mixture was refluxed with stirring for 4 h. The resulting mixture was poured into 60 mL of water. The aqueous layer was washed with ether (50 mL × 2), followed by addition of 1 M HCl until pH 6, and extracted with ether (60 mL × 3). After drying over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The crude product **4a** was obtained in 78% yield. It was recrystallized from petroleum ether and ethanol: mp 182–183 °C; IR (KBr) 3600–2500, 1675, 1640, 1600 cm^{-1}; ^{1}H NMR (pyridine-d_5) δ 1.25 (t, 3 H, J = 7 Hz), 2.81 (q, 2 H, J = 7 Hz), 3.13 (dd, 1 H, J = 13, 16 Hz), 3.30 (dd, 1 H, J = 6, 13 Hz), 5.12 (dd, 1 H, J = 13, 6 Hz), 5.80 (d, 1 H, J = 8 Hz), 6.85–7.38 (m, 4 H), 7.80 (d, 1 H, J = 8 Hz), 10.6 (bs, 1 H); MS, m/e (relative intensity) 241 (M^+, 43), 171 (M^+ – $COCHCH_2CH_3$, 18), 130 (171 – $COCH_2$, 100). In pyridine-d_5, **4a** exists as a conjugated enol exclusively. Anal. Calcd for $C_{15}H_{15}O_2N$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.95; H, 6.30; N, 5.70.

3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydro-11b*H*-benzo[*a*]quinolizine (4b). **4b** was synthesized from **3c** by a similar method described above in 73% yield: mp 183–184 °C; IR (KBr) 3600–2500, 1665, 1640, 1595 cm^{-1}; ^{1}H NMR (pyridine-d_5) δ 3.10 (dd, 1 H, J = 12, 17 Hz), 3.30 (dd, 1 H, J = 6, 17 Hz), 4.05 (s, 2 H), 5.05 (dd, 1 H, J = 12, 6 Hz), 5.70 (d, 1 H, J = 8 Hz), 6.80–7.60 (m, 9 H), 7.65 (d, 1 H, J = 8 Hz), 9.23 (bs, 1 H); MS, m/e (relative intensity) 303 (M^+, 28), 212 (M^+ – CH_2Ph, 44), 130 (212 – $CH_2COCHCO$, 100). In pyridine-d_5, **4b** exists as a conjugated enol exclusively. Anal. Calcd for $C_{20}H_{17}O_2N$: C, 79.18; H, 5.65; N, 4.62. Found: C, 78.89; H, 5.61; N, 4.45.

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-11b*H*-benzo[*a*]quinolizine (4c). (a) By use of a procedure described for the preparation of **4a**, **4c**-*trans* was obtained from **3e** in 63% yield. **4c**-*cis* was not detected in the crude product by TLC and ^{1}H NMR ($CDCl_3$). **4c**-*trans*: mp 122–123 °C; IR (KBr) 1730, 1695, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 3 H, J = 8 Hz), 1.35 (d, 3 H, J = 6 Hz), 2.67 (dq, 1 H, J = 10, 8 Hz), 3.73 (q, 1 H, J = 6 Hz), 5.32 (d, 1 H, J = 10 Hz), 5.70 (d, 1 H, J = 8 Hz), 6.81–7.42 (m, 5 H); MS, m/e (relative intensity) 241 (M^+, 67), 157 (M^+ – COCHMeCO, 47), 130 (157 – $CHCH_3$ + H, 100). Anal. Calcd for $C_{15}H_{15}O_2N$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.58; H, 6.27; N, 5.76.

(b) NaH (453 mg, 11.6 mmol) dispersed in mineral oil (61.4%) was added to a flask and the mineral oil was removed by washing with 10-mL portions of benzene for three times. The benzene was removed with a syringe after the sodium hydride was allowed to settle. Benzene (10 mL) was added to the sodium hydride, and the mixture was heated to reflux. A solution of **3e** (prepared in situ by the above method from 4 mmol of isoquinoline) in 20 mL of benzene was added dropwise over a period of 2 h. After the addition was complete, this mixture was allowed to reflux for an additional 1 h. Acetic acid (3 mL) and ice-cold water (ca. 70 mL) were added dropwise in portions. The benzene layer was separated, and the aqueous layer was extracted with benzene (50 mL × 3). After the combined benzene was dried over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The solidified product **4c** was filtered and washed with ether. This compound was confirmed to be **4c**-*trans* by ^{1}H NMR (43% yield). The filtrate was concentrated and it was subjected to TLC (hexane–AcOEt, 1:1). **4c**-*trans* and **4c**-*cis* were obtained in 10% and 3% yield, respectively. **4c**-*cis*: oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3 H, J = 7 Hz), 1.34 (d, 3 H, J = 6 Hz), 2.89 (dq, 1 H, J = 3, 7 Hz), 3.69 (q, 1 H, J = 6 Hz), 5.58 (d, 1 H, J = 8 Hz), 5.93 (d, 1 H, J = 3 Hz), 6.8–7.5 (m, 5 H).

(c) To a suspension of *t*-BuOK (0.85 g, 7.5 mmol) in 10 mL of ether was added the solution of **3e** (prepared in situ by the above method from 3 mmol of isoquinoline) in 30 mL of ether with stirring at room temperature. The mixture was stirred for 5 h, and the resulting mixture was worked up according to the procedure described for the preparation of **4a**. The crude product **4c** was acetylated with pyridine (5 mL) and Ac_2O (1.7 mL). The resulting mixture was diluted with 200 mL of ether and washed with three 100-mL portions of 1 M HCl, 5% $NaHCO_3$, and brine. After drying ($MgSO_4$) and evaporation of ether, the crude product was separated on flash column chromatography (hexane–AcOEt, 7:3). 2-Acetoxy-1,3-dimethyl-4-oxo-1,4-dihydro-11b*H*-benzo[*a*]quinolizine (**5c**) was obtained in 64% yield (cis:trans, 1:1.3) from isoquinoline. **5c**-*trans*: mp 122–125 °C; IR (KBr) 1760, 1695, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3 H, J= 7 Hz), 1.75 (d, 3 H, J = 2 Hz), 2.15 (s, 3 H), 3.62 (ddq, 1 H, J = 11, 2, 7 Hz), 4.40 (d, 1 H, J = 11 Hz), 6.05 (d, 1 H, J = 8 Hz), 6.85–7.25 (m, 4 H), 7.35 (d, 1 H, J = 8 Hz): MS, m/e (relative intensity) 283 (M^+, 10), 154 ($CH_3CHCOAcCMeCO$, 29), 130 (M^+ – 154 + H, 57), 112 (100). Anal. Calcd for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.00; H, 6.11; N, 4.88. **5c**-*cis*: mp 112–114 °C; IR (KBr) 1765, 1755, 1685, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 7 Hz), 1.80 (s, 3 H), 2.28 (s, 3 H), 3.00 (dq, 1 H, J = 4, 7 Hz), 5.58 (d, 1 H, J = 8 Hz), 5.62 (d, 1 H, J = 4 Hz), 6.80–7.33 (m, 4 H), 7.33 (d, 1 H, J = 8 Hz); MS, m/e (relative intensity) 283 (M^+, 15), 154 (28), 130 (68), 112 (100). Anal. Found: C, 72.29; H, 6.01; N, 4.84. And in addition, 2-acetoxy-1,3-dimethyl-4-oxo-4*H*-benzo[*a*]quinolizine was obtained in 4% yield: mp 172–177 °C; IR (KBr) 1755, 1650, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.42 (s, 3 H), 2.52 (s, 3 H), 6.96 (d, 1 H, J = 8 Hz), 7.27–7.69 (m, 3 H), 8.07–8.43 (m, 1 H), 8.75 (d, 1 H, J = 8 Hz); MS, m/e (relative intensity) 281 (M^+, 60), 239 (M^+ – $COCH_3$ + H, 100), 210 (36), 154 (49). Dehydrogenation of **4** and **5** occurs easily on handling in the air.

2-Acetoxy-1,3-dimethyl-4-oxo-1,4-dihydro-11b*H*-benzo[*a*]quinolizine (5c). By use of a procedure described for the preparation of **4c** (c), **5c** was obtained from **3k** in 74% yield (cis:trans, 3.2:1) and the dehydrogenated product in 8% yield (from isoquinoline).

1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-11b*H*-benzo[*a*]quinolizine (4d). Without acetylation, the crude product was subjected to flash column chromatography (hexane–AcOEt, 3:2) and **4d** was obtained in 62% yield from isoquinoline (cis:trans, 5:1). **4d**-*cis*: mp 169–172 °C; IR (KBr) 1720, 1690–1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 3 H, J = 7.5 Hz), 2.74 (dq, 1 H, J = 3, 7.5 Hz), 3.43, 3.63 (ABq, 2 H, J = 18 Hz), 5.64 (d, 1 H, J = 8 Hz), 5.81 (d, 1 H, J = 3 Hz), 6.90–7.35 (m, 5 H); MS, m/e (relative intensity) 227 (M^+, 29), 130 (100). Anal. Calcd for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.70; H, 5.61; N, 6.21. **4d**-*trans*: IR (neat) 1725, 1690–1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3 H, J = 7 Hz), 2.95 (dq, 1 H, J = 10, 7 Hz), 3.52, 3.62 (ABq, 2 H, J = 18 Hz), 4.95 (d, 1 H, J = 10 Hz), 5.92 (d, 1 H, J = 7.5 Hz), 6.96–7.40 (m, 5 H).

2,4-Dioxo-1-phenyl-1,2,3,4-tetrahydro-11b*H*-benzo[*a*]quinolizine (4e). The crude product **4e** was obtained and recrystallized from ethanol to afford **4e**-*cis* in 51% yield: mp 194–198 °C; IR (KBr) 3250–2050, 1645, 1635, 1610 cm^{-1}; ^{1}H NMR (pyridine-d_5) δ 4.16 (d, 1 H, J = 4.5 Hz), 5.30 (s, 1 H), 5.47 (s, 1 H), 6.06 (d, 1 H, J = 4.5 Hz), 6.50–7.65 (m, 11 H); MS, m/e (relative intensity) 289 (M^+, 19), 130 (100).

Study of the Cis–Trans Isomerization of 4c. **4c**-*trans* was treated with 2.5 equiv of *t*-BuOK in ether at room temperature for 6 h, and the resulting mixture was worked up in a similar manner as described above to recover the starting material **4c**-*trans* quantitatively. By a separate experiment, **4c**-*cis* was also recovered from the above conditions. Therefore, it was confirmed that no isomerization took place during the cyclization reaction.

2-Acetoxy-3-ethyl-4-oxo-1,4-dihydro-11b*H*-benzo[*a*]quinolizine (5a). **4a** (0.16 g, 0.66 mmol) was dissolved in 0.78 g (ca. 15 equiv) of pyridine and stirred for 1 day after addition of 0.30 g (ca. 5 equiv) of Ac_2O. The resulting mixture was diluted with 30 mL of ether and washed with 2 M HCl, 5% $NaHCO_3$, and brine. After drying ($MgSO_4$), the solvent was evaporated in vacuo to afford **5a** in 91% yield. It was recrystallized from AcOEt. **5a**: mp 109–114 °C; IR (KBr) 1755, 1690, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7 Hz), 2.27 (s, 3 H), 2.33 (q, 2 H, J = 7 Hz), 3.05 (d, 2 H, J = 9.5 Hz), 5.10 (t, 1 H, J = 9.5 Hz), 5.75 (d, 1 H, J = 8 Hz), 6.80–7.20 (m, 4 H), 7.35 (d, 1 H, J = 8 Hz); MS, m/e (relative intensity) 283 (M^+, 40), 224 (M^+ – OAc, 24), 205 (64), 130 (100). Anal. Calcd for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.76; H, 5.84; N, 5.04.

2-Acetoxy-3-benzyl-4-oxo-1,4-dihydro-11b*H*-benzo[*a*]quinolizine (5b). **5b** was obtained similarly in 98% yield: mp 149–151 °C; IR (KBr) 1760, 1680, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 3.10 (d, 2 H, J = 9.5 Hz), 3.70 (s, 2 H), 5.10 (t, 1 H, J = 9.5 Hz), 5.67 (d, 1 H, J = 8 Hz), 6.80–7.20 (m, 9 H), 7.25 (d, 1 H, J = 8 Hz); MS, m/e (relative intensity) 345 (M^+, 41), 301 (M^+ – $COCH_3$ – H, 21), 210 (301 – CH_2Ph, 42), 174 (53), 130 (100). Anal. Calcd for $C_{22}H_{19}O_3N$: C, 79.18; H, 5.65; N, 4.62. Found: C, 78.89; H, 5.61; N, 4.45.

2-Acetoxy-1,3-dimethyl-4-oxo-1,4-dihydro-11b*H*-benzo[*a*]quinolizine (5c-*trans*). **5c**-*trans* was synthesized by using the above method from **4c**-*trans* in 99% yield.

2-Acetoxy-1-methyl-4-oxo-1,4-dihydro-11b*H*-benzo[*a*]quinolizine (5d-*cis*). **5d**-*cis* was synthesized in a similar fashion from **4d**-*cis* in a quantitative yield: mp 122–124 °C; IR (KBr) 1750, 1670, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 3 H, J = 7 Hz), 2.25 (s, 3 H), 3.02 (dq, 1 H, J = 4, 7 Hz), 5.63 (d, 1 H, J = 9 Hz), 5.65 (d, 1 H, J = 4 Hz), 6.02 (s, 1 H), 6.84–7.50 (m, 5 H); MS, m/e (relative intensity) 269 (M^+, 31), 226 (M^+ – $COCH_3$, 3), 130 (100). Anal. Calcd for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.38; H, 5.65; N, 5.12.

2-Ethyl-1-methyl-4-oxo-1,4-dihydro-11b*H*-benzo[*a*]quinolizine (7). **3g** (prepared in situ from 3 mmol of isoquinoline) was dissolved in 15 mL of DMF, and 3.5 equiv of DBU was added to the mixture. It was heated to 100 °C with stirring for 4 h, and the resulting mixture was poured into ca. 60 mL of water and extracted with ether (50 mL × 3). After drying ($MgSO_4$) and evaporation of the solvent, the crude mixture was separated by flash column chromatography (hexane–AcOEt, 5:1–1:1) to afford **6** and **7** in 31% and 53% yield, respectively. 2-Ethyl-2-hydroxy-1-methyl-4-oxo-1,2,3,4-tetrahydro-11b*H*-benzo[*a*]quinolizine (**6**): mp 200–206 °C; IR (KBr) 3370, 1640, 1625 cm^{-1}; ^{1}H NMR (CD_3OD and $CDCl_3$) δ 1.02 (t, 3 H, J = 7 Hz), 1.30 (d, 3 H, J = 6 Hz), 1.75 (q, 2 H, J = 7 Hz), 2.48 (dq, 1 H, J = 11, 6 Hz), 2.52 (s, 2 H), 4.20 (d, 1 H, J = 11 Hz), 4.51 (s, 1 H), 6.26 (d, 1 H, J = 7.5 Hz), 7.0–7.4 (m, 5 H); MS, m/e (relative intensity) 257 (M^+, 29), 171 (58), 143 (100), 130 (92). Anal. Calcd for

$C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.42; H, 7.58; N, 5.34. **7**: mp 105–109 °C; IR (KBr) 1670, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 7 Hz), 1.19 (t, 3 H, J = 8 Hz), 2.34 (dq, 2 H, J = 1, 8 Hz), 2.74 (dq, 1 H, J = 3, 7 Hz), 5.48 (d, 1 H, J = 3 Hz), 5.59 (d, 1 H, J = 8 Hz), 5.81 (t, 1 H, J = 1 Hz), 6.85–7.40 (m, 5 H); MS, m/e (relative intensity) 239 (M^+, 23), 130 (100). Anal. Calcd for $C_{16}H_{17}ON$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.05; H, 7.26; N, 5.85. **6** was converted to **7** in 61% yield by heating with DBU (DMF, 100 °C, 1.5 h) in a similar fashion.

Preparation of 2-(Ethoxycarbonyl)-6,7-dimethoxy-1-(2-oxopentyl)-1,2,3,4-tetrahydroisoquinoline (10). 6,7-Dimethoxy-3,4-dihydroisoquinoline **8** was prepared by the procedure of K. D. Paull et al.[12] By the reaction with **2b** for 2 days as described for the preparation of **3**, **10** was obtained in 80% yield: IR (neat) 1715–1690 cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (t, 3 H, J = 7 Hz), 1.22 (t, 3 H, J = 7 Hz), 1.52 (ses, 2 H, J = 7 Hz), 2.10–2.80 (m, 6 H), 2.80–3.50 (m, 2 H), 3.70 (s, 6 H), 4.05 (q, 2 H, J = 7 Hz), 5.40 (t, 1 H, J = 6.5 Hz), 6.45 (s, 1 H), 6.60 (s, 1 H); MS, m/e (relative intensity) 349 (M^+, 6), 276 ($M^+ - CO_2Et$, 21), 264 ($M^+ - CH_2C(OCH_2CH_2CH_3)$, 100), 236 (264 – CH_2CH_3, 22), 192 (236 – CO_2, 11). Anal. Calcd for $C_{19}H_{27}O_5N$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.18; H, 8.00; N, 3.98. By use of the corresponding boron enolate, **10** was obtained in 53% yield with some recovered **8**.

Reaction of 10 with *t*-BuOK. To a suspension of *t*-BuOK (0.55 g, 3.5 equiv) in ether (5 mL) was added 20 mL of ether solution of **10** (0.489 g, 1.4 mmol) at room temperature, and the mixture was stirred for 2 h. The resulting one was poured into ca. 60 mL of 1 M HCl and extracted with ether (50 mL × 3). After drying ($MgSO_4$) and evaporation of the solvent, the residue was subjected to flash column chromatography (hexane–AcOEt, 3:2). The starting material **10** was recovered in 24% yield and **12**, which is the intramolecular oxidation–reduction product, was obtained in 46% yield and recrystallized from THF and ether. 1-[3-(Ethoxycarbonyl)-2-hydroxypentyl]-6,7-dimethoxy-1,2-dihydroisoquinoline (**12**): mp 124–126 °C; IR (KBr) 3300, 1680, 1645, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7 Hz), 1.21 (t, 3 H, J = 7 Hz), 1.80 (dq, 2 H, J = 8, 7 Hz), 2.56–3.57 (m, 6 H), 3.89 (s, 6 H), 4.10 (q, 2 H, J = 7 Hz), 4.70–5.19 (bs, 1 H), 6.55 (d, 1 H, J = 16 Hz), 6.68 (s, 1 H), 7.08 (s, 1 H), 7.83 (d, 1 H, J = 16 Hz); MS, m/e (relative intensity) 349 (M^+, 31), 276 ($M^+ - CO_2Et$, 15), 259 (276 – H_2O or M^+ – 6,7-dimethoxy-1,2-dihydroisoquinoline, 45), 205 (100), 190 (6,7-dimethoxyisoquinoline + H, 28). Anal. Calcd for $C_{19}H_{27}O_5N$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.28; N, 7.95; N, 3.98.

Reaction of 10 with KH. KH (1.47 g, 22.2%, 8.14 mmol) in mineral oil was washed with benzene (5 mL × 2) and 5 mL of ether. Potassium hydride was suspended in ether (10 mL), a solution of **10** (1.21 g, 3.47 mmol) in 25 mL of ether was added dropwise over a period of 25 min, and stirring was continued for additional half an hour. The resulting mixture was poured into ca. 80 mL of water and extracted with ether (50 mL × 3). After drying ($MgSO_4$) and evaporation of the solvent, the residue was separated on flash column chromatography (hexane–AcOEt, 3:2). **10** was recovered in 28% yield, and **12** and **13** were obtained in 18% and 45% yield, respectively. 1-[3-(Ethoxycarbonyl)-2-oxopentyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**13**): viscous oil and a mixture of diastereomers; IR (nujol) 3350, 1725–1660 cm^{-1}; MS, m/e (relative intensity) 349 (M^+, 11), 276 ($M^+ - CO_2Et$, 24), 264 (100), 235 (276 – $CHCH_2CH_3$, 22), 206 (235 – CO, 24).

Reaction of 10 with NaH. Preparation of 3-Ethyl-9,10-dimethoxy-2,4-dioxo-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (11). NaH (0.655 g, 16.8 mmol) in mineral oil (61.4%) was washed with benzene (10 mL × 2) and the suspension in 10 mL of benzene was heated to reflux. A solution of **10** (1.88 g, 5.37 mmol) in 20 mL of benzene was added dropwise over a period of 3 h and the mixture was refluxed for an additional 3 h. Then the reaction mixture was poured into ca. 60 mL of 1 M HCl, the benzene layer was separated, and the aqueous layer was extracted with ether (50 mL × 3). After drying ($MgSO_4$) and concentration of the combined organic layer, the residue was allowed to stand in a refrigerator for 1 day so that **11** was crystallized. The crystaline **11** was filtered, washed with ether, and obtained in 21% yield. The filtrate was concentrated and it was subjected to TLC (hexane–AcOEt, 1:1) to afford **10**, **11**, and **12** in 16%, 26%, and 3% yield, respectively. **11** was recrystallized from petroleum ether and ethanol. **11**: mp 260-270 °C dec (lit.[11] oil); IR (KBr) 3300–1980, 1675, 1640, 1610 cm^{-1}; ^1H NMR (Me_2SO-d_6 and $CDCl_3$) δ 1.00 (t, 3 H, J = 7 Hz), 1.66–5.37 (m, 16 H), 6.72 (s, 2 H); MS, m/e (relative intensity) 303 (M^+, 82), 191 ($M^+ - CH_2COCHEtCO$, 100). Anal. Calcd for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.11; H, 7.17, N, 4.51. Compound **11** has been prepared by T. Shono et al. as compound **44a** in their paper (*J. Org. Chem.* **1983**, *48*, 1621) and is described as an oil. Prof. Shono admitted that they might have had a mixture (ca. 7:3) of keto and enol isomers but used the compound for further synthesis without much attention to crystallization. Our compound (**11**) also has a wide melting point range and the solid is almost enol by IR, although the ratio of keto and enol in solution could not be clearly determined by ^1H NMR. There is a definite trend that 1,3-diketones (**4**) have (much) higher melting points than their acetates (**5**) as amply exemplified in this paper, and such is the case for **11** and its acetate **14**.

2-Acetoxy-3-ethyl-9,10-dimethoxy-4-oxo-1,4,6,7-tetrahydro-11b*H*-benzo[*a*]quinolizine (14). By using a procedure described for the preparation of **5a**, **14** and its dehydrogenated product (**15**) were obtained in 93% and 4% yield, respectively. **14** was recrystallized from hexane and ethyl acetate: mp 129–130 °C; IR (KBr) 1760, 1675, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7 Hz), 2.02–3.17 (m, 10 H), 3.86 (s, 6 H), 4.50–5.10 (m, 2 H), 6.56 (s, 1 H), 6.63 (s, 1 H); MS, m/e (relative intensity) 345 (M^+, 67), 302 (M^+ – OAc, 39), 191 (302 – $CH_2COCEtCO$, 100). Anal. Calcd for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.79; H, 6.87; N, 3.87. **15**: mp 202–203 °C; IR (KBr) 1765, 1635, 1595 cm^{-1}; MS, m/e (relative intensity) 343 (M^+, 55), 300 ($M^+ - COCH_3$, 47), 285 (300 – O, 100).

Registry No. **1a**, 81357-89-3; **1b**, 81357-90-6; **1c**, 93605-16-4; **2a**, 13735-81-4; **2b**, 40911-68-0; **2c**, 59417-89-9; **2d**, 6651-36-1; **2e**, 17510-47-3; **2f**, 40195-27-5; **2g**, 34880-70-1; **2h**, 51075-22-0; **3a**, 81357-96-2; **3b**, 81358-08-9; **3c**, 81358-09-0; **3d** (isomer 1), 81357-99-5; **3d** (isomer 2), 81358-00-1; **3e** (isomer 1), 81358-01-2; **3e** (isomer 2), 81358-02-3; **3f**, 63488-74-4; **3g** (isomer 1), 84955-94-2; **3g** (isomer 2), 84955-99-7; **3h** (isomer 1), 84955-95-3; **3h** (isomer 2), 84956-02-5; **3i** (isomer 1), 84955-96-4; **3i** (isomer 2), 84956-03-6; **3j** (isomer 1), 93605-17-5; **3j** (isomer 2), 93605-31-3; **3k** (isomer 1), 93605-18-6; **3k** (isomer 2), 93605-32-4; **3l** (isomer 1), 84955-97-5; **3l** (isomer 2), 84955-98-6; **4a**, 93605-19-7; **4b**, 93605-20-0; **4c**-*trans*, 93712-81-3; **4c**-*cis*, 93712-82-4; **4d**-*cis*, 93605-24-4; **4d**-*trans*, 93605-33-5; **4e**-*trans*, 93605-34-6; **5a**, 81358-06-7; **5b**, 93605-25-5; **5c**-*trans*, 93605-21-1; **5c**-*cis*, 93605-22-2; **5d**-*cis*, 93605-22-2; **6**, 84956-01-4; **7**, 93605-26-6; **8**, 3382-18-1; **10**, 93605-27-7; **11**, 85222-87-3; **12**, 93605-28-8; **13**, 93605-29-9; **14**, 93644-90-7; **15**, 93605-30-2; 2-acetoxy-1,3-dimethyl-4-oxo-4*H*-benzo[*a*]quinolizine, 93605-23-3; isoquinoline, 119-65-3.