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Studies on Indenopyridine Derivatives and Related Compounds. VI.[1] Synthesis and Stereochemistry of Ethyl 9,9-Dimethyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylate as a Possible Intermediate for the Total Synthesis of Lysergic Acid

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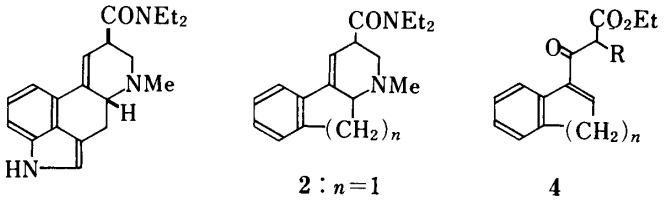
Reaction of 1,1-dimethylindene-3-carbonyl chloride (**9**), prepared from 3,3-dimethylindanone (**5**) *via* a four step sequence, with ethyl 3-(*N*-*tert*-butoxycarbonyl-*N*-methyl)aminopropionate (**14**) or its 2-methyl derivative (**15**) in the presence of lithium diisopropylamide (LDA) gave the β-keto esters (**16** and **17**). De-*tert*-butoxycarbonylation of **16** followed by treatment with sodium bicarbonate did not give **12**, while **17** afforded the cyclized β-keto ester (**19**) in good yield. Sodium borohydride reduction of **19** followed by treatment with methanesulfonyl chloride gave the mesylate (**21**), which was reacted with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) to give the unsaturated ester (**22**). By analogous reaction sequences, the diethylamide derivative (**2**) was synthesized in moderate yield. Reaction of the β-keto ester (**16**) with diethyl phosphorochloridate in the presence of LDA gave the enolphosphate (**30**), which was converted to the unsaturated esters (**31a** and **31b**) in good yields. However, dephosphorylation of **31** failed. Sodium borohydride reduction of **16** gave the alcohol (**33**), which was converted to the diene ester (**34**) or the mesylate (**36**). These were successfully converted to the ethyl 1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylates (**32a** and **32b**), which were found to exist in an equilibrium mixture, in excellent yields, respectively. The stereochemistry of some of the key intermediates and of the target compounds is discussed.

Keywords——1-indanone; indenecarbonyl chloride; ethyl 3-aminopropionate; lithium diisopropylamide; mesylation; tetrahydro-9*H*-indeno[2,1-*b*]pyridine; lysergic acid analog; 1,8-diazabicyclo[5.4.0]-7-undecene

Extensive studies have been done on the synthesis of simplified analogs of ergot alkaloids in the hope of obtaining compounds with potent pharmacological activity.[2] Previously, Horii reported the synthesis of *N*,*N*-diethyl-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[*f*]quinoline-2-carboxamide (**3**) as an LSD_{25} (**1**) analog lacking only a pyrrole ring *via* the Mannich condensation of **4** ($n=2$, $R=CONEt_2$) with methylamine and formalin as a key reaction.[3] Craig and co-workers reported a synthesis of the simplified analog of **1**, *N*,*N*-diethyl-1-methyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxamide (**2**), from indene *via* a ten-step sequence.[4] They found that the Mannich reaction of **4** [$n=1$, R=H or $CO_2C(CH_3)_3$] for the construction of the tetrahydropyridine ring (C ring) failed, because of high reactivity of the allylic protons in the indene nucleus and the resulting side reactions. We now describe a convenient and useful synthetic method for the preparation of the 1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine skeleton having a carbonyl function at the C-3 position starting from 1,1-dimethylindene-3-carboxylic acid (**8**). Such a product may be useful in the total synthesis of lysergic acid.



1 2 : $n=1$, 3 : $n=2$ 4

Chart 1

Synthesis

Previously, we have developed a new synthetic method for α,β-unsaturated nitriles from aromatic ketones *via* cyanophosphorylation with diethyl phosphorocyanidate (DEPC) and lithium cyanide (LiCN) followed by treatment with boron trifluoride etherate ($BF_3 \cdot Et_2O$).[5]

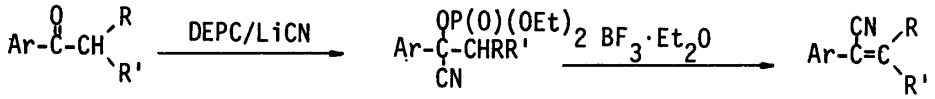


Chart 2

According to this methodology, we successfully prepared the carboxylic acid (**8**) from 3,3-dimethyl-1-indanone (**5**)[6] in 93% overall yield: namely reaction of **5** with DEPC (3 eq) and LiCN (3 eq) in dry tetrahydrofuran (THF) at room temperature for 40 min gave the cyanophosphate (**6**). Without purification **6** was treated with $BF_3 \cdot Et_2O$ in dry benzene to afford the pure α,β-unsaturated nitrile (**7**), which was subsequently hydrolyzed with potassium hydroxide (KOH) in 75% ethanol (EtOH) to give **8**. It was possible to isolate **7** by distillation [bp_2 65—80 °C (Kugelrohr)] in 80% overall yield from **5**. Chlorination of **8** with thionyl chloride ($SOCl_2$) gave 1,1-dimethylindene-3-carbonyl chloride (**9**) quantitatively. Reaction of **9** with ethyl acetate in the presence of lithium diisopropylamide (LDA)[7] or diethyl

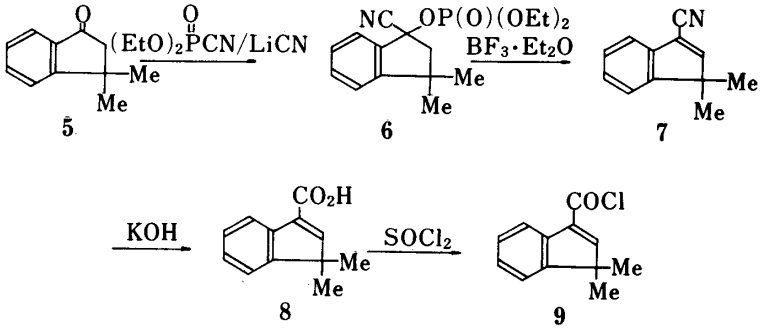


Chart 3

ethoxymagnesiummalonate gave the β-keto ester (**10**) or β-keto diester (**11**) in 86% or 89% yield, respectively. However, attempts to synthesize **12** or **13** by the Mannich reactions of **10** or **11** with methylamine and formalin under the conditions described previously[3] failed in spite of the absence of highly reactive allylic protons in the indene nucleus of **10** or **11**. Thus, another route to introduce nitrogen at C-2 in indene was attempted. Reaction of **9** with ethyl 3-(*N*-*tert*-butoxycarbonyl-*N*-methyl)aminopropionate (**14**), prepared from ethyl 3-methylaminopropionate[8] and di-*tert*-butyl dicarbonate, in the presence of LDA at −78 °C gave the β-keto ester (**16**) in 79% yield. The infrared (IR) spectrum of **16** showed strong carbonyl absorptions at 1725 and 1680 cm^{-1}. Removal of the *tert*-butoxycarbonyl (*t*-Boc) group by treatment with a solution of saturated dry hydrogen chloride gas in ethyl acetate (EtOAc)

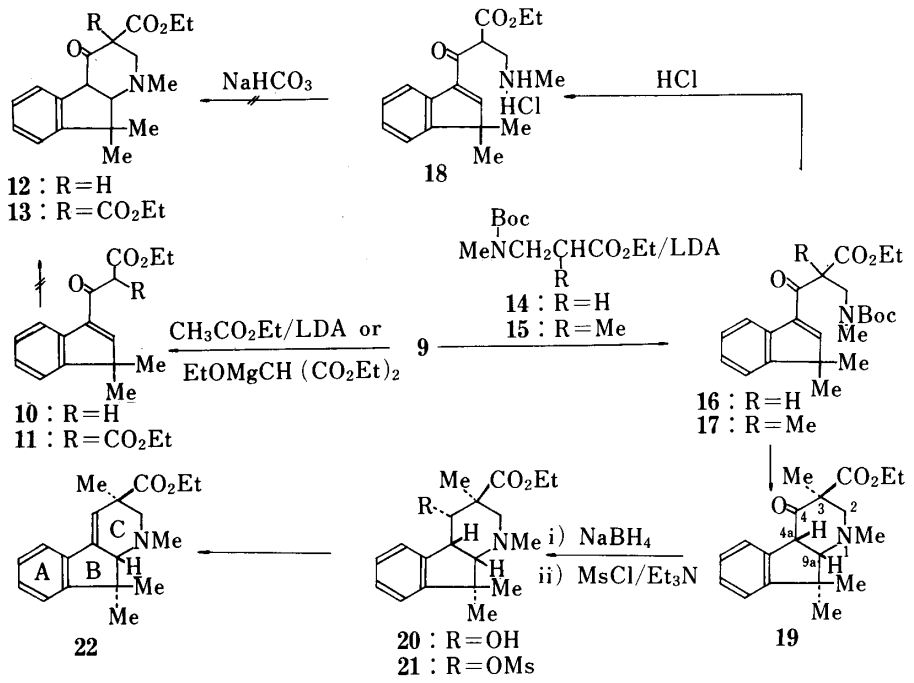


Chart 4

(2.3 N HCl in EtOAc) gave the hydrochloride (**18**) in quantitative yield. Unfortunately, treatment of **18** with sodium bicarbonate ($NaHCO_3$) gave a complex mixture, and we could not isolate **12**, presumably because of its susceptibility to fission of the C-2 and nitrogen bond induced by the active C-3 hydrogen. This was confirmed by the following experiments. Namely, analogous condensation of **9** with **15** gave the β-keto ester (**17**). Without purification **17** was subjected to the de-*tert*-butoxycarbonylation sequence (2.3 N HCl in EtOAc) at room temperature and then treated with saturated aqueous $NaHCO_3$. The resulting reaction mixture was purified by silica gel (SiO_2) column chromatography to give ethyl 1,3,9,9-tetramethyl-4-oxo-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylate (**19**) in 73% overall yield from **9**. The IR spectrum of **19** showed two strong carbonyl absorptions at 1740 and 1720 cm^{-1}. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed an AB quartet at δ 2.74 and 3.58 (J = 12 Hz) due to the C-2 protons, and two doublets (J = 10 Hz) at δ 3.37 and 4.24 due to the C-4a and C-9a protons, respectively. Sodium borohydride ($NaBH_4$) reduction of the ketone (**19**) afforded the alcohol (**20**) as a sole product in 83% yield. Dehydration of **20** with $SOCl_2$ and pyridine or phosphorus oxychloride and pyridine containing a trace of phosphoric acid gave a complex mixture, from which **22** could not be isolated. Therefore, **20** was treated with methanesulfonyl chloride (MsCl) and triethylamine (Et_3N) in dichloromethane (CH_2Cl_2) to give the mesylate (**21**) in 71% yield. The mesylate was smoothly converted to the unsaturated ester (**22**) by heating with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) in dimethylsulfoxide (DMSO) or lithium bromide (LiBr) in dimethylformamide (DMF) in 69% or 88% yield, respectively. The ultraviolet (UV) spectrum showed absorption maxima at 250 ($\log\varepsilon$ 4.14), 286 (3.60), and 295 nm (3.53), and the ^{1}H-NMR spectrum revealed the presence of an olefinic proton at δ 6.12.

Efforts were then directed to the preparation of the cyclic β-keto amide (**25**) which has a less reactive C-3 hydrogen as compared with **12**, and might be isolable. Reaction of **9** with *N,N*-diethyl-3-(*N*-*tert*-butoxycarbonyl-*N*-methyl)aminopropionamide (**23**) [prepared from *N,N*-diethyl-3-(*N*-methyl)propionamide[9] by treatment with di-*tert*-butyl dicarbonate] in the presence of *n*-butyl lithium (*n*-BuLi) (3 eq)[10] at -78 °C gave the β-keto amide (**24**) in 45% yield. Usual cleavage of the *t*-Boc group of **24** followed by treatment with $NaHCO_3$ afforded

the cyclic β-keto amide (**25**) [mass spectrum (MS) *m/e*: 328 (M^+). High-resolution MS Calcd for $C_{20}H_{28}N_2O_2$: 328.2149. Found: 328.2152].[11] Without purification, **25** was reduced with $NaBH_4$ in EtOH under ice cooling to give the alcohol (**26**), mp 129—131 °C, in 57% overall yield from **24** as a sole product. This was converted into the mesylate (**27**) by treatment with MsCl and Et_3N in CH_2Cl_2 in 96% yield. Then, the mesylate (**27**) was converted into *N,N*-diethyl-1,9,9-trimethyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxamide (**2**) under the following conditions. i) Treatment with DBU in DMSO gave **2** in 44% yield. ii) Treatment with a mixture of LiBr and lithium carbonate (Li_2CO_3) in DMF[12] gave **2** in 51% yield together with the 5-bromo derivative (**28**)[13] in 2% yield. iii) Treatment with LiCl in DMF gave **2** in 6% yield together with the 5-chloro derivative (**29**)[13] in 16% yield. The structure of **2** was readily confirmed by comparison of the spectroscopic data with those of **22**. Thus, we have succeeded in the preparation of a simplified analog of LSD_{25}.

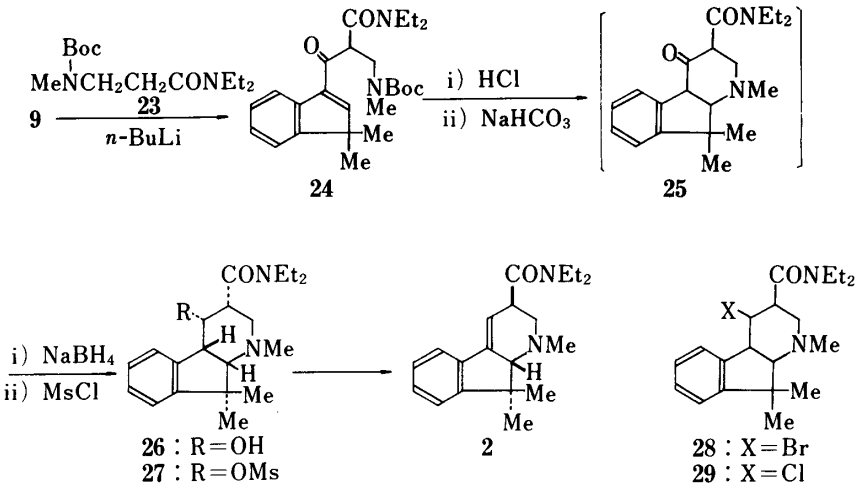


Chart 5

We next investigated the synthesis of compound **31** by a different approach from that used in the synthesis of **22**. Reaction of **16** with diethyl phosphorochloridate in the presence of LDA in THF at −78 °C gave the enol phosphate (**30**) in 72% yield. Usual cleavage of the *t*-Boc group of **30** followed by treatment with $NaHCO_3$ gave ethyl 4-diethylphosphonooxy-1,9,9-trimethyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylates (**31a** and **31b**) in 98% combined yield. These were separated by SiO_2 column chromatography. The IR spectra showed strong carbonyl absorption at 1730 cm^{-1} as well as strong absorptions at 1280, 1180, and 1030 cm^{-1} due to the $-OP(O)(OEt)_2$ group. The ^{1}H-NMR spectrum of **31a** was very similar to that of **31b** except for the chemical shift of the C-3 proton [δ 3.76 in **31b** and δ 3.9—4.3 (overlapped with three $-OCH_2CH_3$ groups) in **31a**]. The two compounds (**31a** and **31b**) are therfore epimeric at C-3. It is known, in general, that the enol phosphates undergo reductive dephosphorylation upon Birch reduction.[14] However, attempts to cleave the C-4 and O bond in **31** by this method in order to get **32** failed. Nevertheless, the result was encouraging because the diene ester (**30**) was a good precursor for the introduction of a nitrogen function at C-2 of the indene nucleus. From these points of view, **16** was reduced with $NaBH_4$ in EtOH to give the alcohol (**33**) in quantitative yield. Dehydration of **33** with $SOCl_2$ and pyridine gave the diene ester (**34**) in 38% yield. The ^{1}H-NMR spectrum revealed the presence of two olefinic protons [δ 6.46 (1H, br s) and 7.32 (overlapped with the aromatic protons)]. Cleavage of the *t*-Boc group of **34** followed by treatment with $NaHCO_3$ gave the desired ethyl 1,9,9-trimethyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylates (**32a** and **32b**) in 92% combined overall yield from **34** as an isomeric mixture in the ratio of 5:4 (by ^{1}H-NMR spectroscopy). Complete separation of two isomers was unsuccessful,

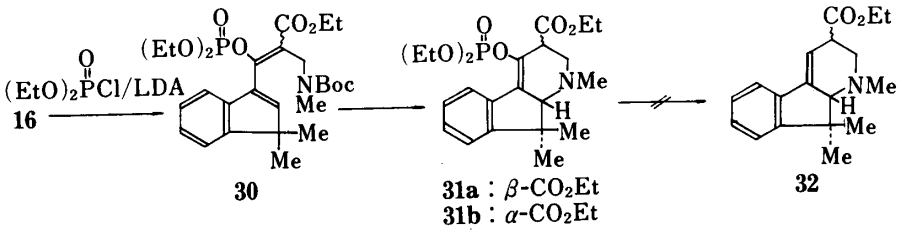


Chart 6

though **32a** was isolated in a small amount. However, **32a** was found to isomerize to an equilibrium mixture of these two esters on standing in ethanol for several hours.[15] When a solution of a mixture of **32a** and **32b** in deuterium methoxide was refluxed, complete hydrogen–deuterium exchange at the C-3 proton was observed in the ^{1}H-NMR spectrum. These results are in good agreement with those reported in benzo[*f*]quinoline analogs by Ninomiya *et al.*[15] In order to improve the yield of the diene ester (**34**), **33** was mesylated with MsCl/Et_3N to give **36** (45%), which was then treated with DBU in DMSO to give **34**, but the yield was very poor. Therefore, **36** was first subjected to de-*tert*-butoxycarbonylation, then treated with DBU in DMSO at room temperature to give a mixture of **32a**/**32b** in quantitative overall yield from **36**.

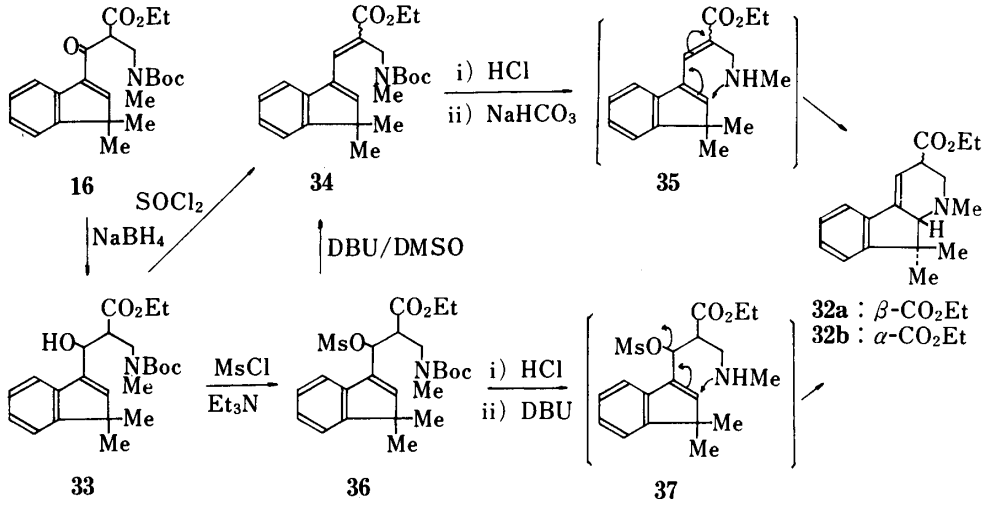


Chart 7

In conclusion, we have developed new methods for the construction of the 1,2,3,9a-tetrahydroindeno[2,1-*b*]pyridine skeleton a having carbonyl function at the C-3 position, and these methods should be applicable to the total synthesis of lysergic acid and its analogs.

Stereochemistry

As we have mentioned in the previous paper,[16] three possible conformations of hexahydroindeno[2,1-*b*]pyridines, *i.e.*, B/C *trans*-fused form, a stable B/C *cis*-fused form, and an unstable B/C *cis*-fused form, may be considered.[17] By inspection of the Dreiding model of the hexahydroindeno[2,1-*b*]pyridine system, it is apparent that strong deshielding of the aromatic C-5 proton is caused by the steric effect[18] when the substituent at C-4 is in an equatorial orientation in the unstable B/C *cis*-fused form in which the bond between C-4a and C-4b is axial with respect to the piperidine ring.[4] The ^{1}H-NMR spectrum of **20** showed no aromatic proton clearly deshielded as compared with the other three protons. The *cis*-stereochemistry of the ring junction was assigned on the basis of the coupling constant (J=9 Hz)[19] of the C-9a proton, which appeared as a doublet at δ 2.85. The assignment of an

axial configuration of the C-4 hydroxyl group in **20** was made on the basis of the coupling constant (2 Hz) of the C-4 proton, which appeared as a doublet at δ 4.25. Lithium aluminum hydride (LAH) reduction of **20** gave the diol (**38**), which was reacted with 2,2-dimethoxypropane[20] in the presence of *p*-toluenesulfonic acid (TsOH) to give the octahydro-2*H*-*m*-dioxino[5,4-*c*]indeno[1,2-*c*]pyridine (**39**); the structure was assigned on the basis of the spectroscopic evidence (see Experimental). In particular, **39** showed one aromatic proton (C-11 proton) at δ 7.75 clearly deshielded from the other three in its ^{1}H-NMR spectrum. The result clearly indicates that the O-1 atom of the 1,3-dioxane ring of **39** is in a position very close to the C-11 aromatic proton. This proximity is presumably caused by the conformational change (from a stable B/C *cis*-fused form with the C-3 hydroxymethyl group axial in **38** to an unstable B/C *cis*-fused form with the C-3 hydroxymethyl group equatorial) that occurs during the reaction of **38** with 2,2-dimethoxypropane. If the hydroxymethyl group at C-3 in **38** has an equatorial orientation, the structure **39′** will be possible for the tetracyclic 1,3-dioxane derivative. However, this is very unlikely since there is severe crowding between

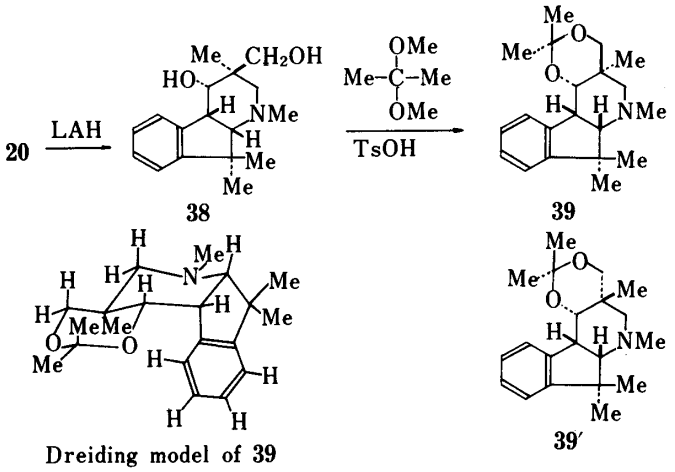


Chart 8

the methyl group on the 1,3-dioxane ring and the aromatic ring, as observed by the inspection of the Dreiding model of **39′**. On the basis of these results, the stereostructure of **39** was assigned as depicted in Chart 8. Therefore, a stable B/C *cis*-fused form with an axial ethoxycarbonyl group at C-3 and an axial hydroxyl group at C-4 was assumed for **20**. The stereochemistry of **26**, having a stable *cis*-B/C ring junction with an axial hydroxyl group at C-4, was determined on the basis of the following ^{1}H-NMR spectral data, *i.e.*, i) no aromatic proton clearly deshielded from the other three was observed, ii) the signals assignable to H-4, H-4a, and H-9a are compatible with those of **20**, shown in Table I. The equatorial position of the large diethylaminocarbonyl group in **26** appears to be preferable from the viewpoint of stereochemical stability.[21]

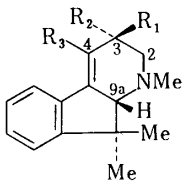
Finally, we investigated the stereochemistries of the unsaturated esters (**31a**, **31b**, **32a**, and **32b**) and the unsaturated amide (**2**). The ^{1}H-NMR spectral data for H-2, H-3, H-4 and H-9a of these compounds are summarized in Table II together with the data for the corresponding protons of the benzo[*f*]quinoline group (**40a** and **40b**)[22] for comparison. In compounds **2**, **31a**, and **32b** having C-3β substituents, the C-2 axial proton appears as a triplet with a large coupling constant (11—12 Hz) coupled with the C-2 equatorial and C-3 axial protons. This is in good agreement with **40a**. On the other hand, in compounds **31b** and **32b** having C-3 substituents, the couplings of the C-2 axial proton with the C-3 equatorial proton are very small (J=4.5—5 Hz). All otherproton signals of the indeno[2,1-*b*]pyridine group also coincide with those of the benzo[*f*]quinoline group.[22] Thus, it was concluded that the C-3 substituents

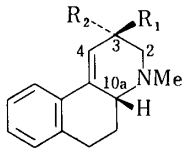
TABLE I. The ^{1}H-NMR Data for Compounds **20** and **26** ($CDCl_3$, 300 MHz)

Proton	**20**		**26**	
	δ (ppm)	J (Hz)	δ (ppm)	J (Hz)
2-H_2	2.70 (d)	12	2.63 (dd)	12, 11
	2.90 (d)	12	2.85 (dd)	11, 8
3-H			3.28 (ddd)	11, 8, 2
4-H	4.25 (d)	2	4.16 (t)	3[a]
4a-H	3.35 (dd)	9, 2	3.78 (dd)	9, 3
9a-H	2.85 (d)	9	2.84 (d)	9

a) Solvent: $CDCl_3+D_2O$.

TABLE II. The ^{1}H-NMR Data for the Indeno[2,1-*b*]pyridine and Benzo[*f*]quinoline Moieties in $CDCl_3$ (300 MHz) [δ (ppm)/J (Hz)]





31a: $R_1=CO_2Et$, $R_2=H$, $R_3=OP(O)(OEt)_2$
31b: $R_1=H$, $R_2=CO_2Et$, $R_3=OP(O)(OEt)_2$
32a: $R_1=CO_2Et$, $R_2=R_3=H$
32b: $R_1=H$, $R_2=CO_2Et$, $R_3=H$
2: $R_1=CONEt_2$, $R_2=R_3=H$

40a: $R_1=CO_2Me$, $R_2=H$
40b: $R_1=H$, $R_2=CO_2Me$

	2ax-H	2eq-H	3-H	4-H	9a-H
31a	2.63, t, $J=11$ Hz	3.22, dd, $J=11$, 6.5 Hz	[a]		3.03, t, $J=3.5$ Hz
31b	2.78, dd, $J=12$, 4.5 Hz	3.25, dd, $J=12$, 2 Hz	3.76, br s		2.94, dd,[b] $J=5$, 2.5 Hz
32a	2.56, t, $J=11.5$ Hz	3.17, ddd, $J=11.5$, 5.5, 1 Hz	3.65, m,	6.13, dt, $J=3$, 1 Hz	2.86, dd, $J=4$, 3 Hz
32b	2.54, dd, $J=11.5$, 5 Hz	3.33, dt, $J=11.5$, 1 Hz	3.13, m	6.15, m	2.79, t, $J=3$ Hz
2	2.79, t, $J=11$ Hz	3.0, dd, $J=11$, 6 Hz	3.86, m[c]	5.92, t, $J=2$ Hz	2.99
40a	2.56, t	3.22, dd, $J=11.5$, 6 Hz	3.66, m	6.42, br s	2.80, dq,[d] $J=12$, 3 Hz
40b	2.62, 2.44, m	3.37, br d, $J=12$ Hz	3.21, m	6.39, br d, $J=5$ Hz	2.77, br d,[d] $J=13$ Hz

a) Signals for this proton are ambigous due to overlapping with other proton signals at δ 4.0—4.2. *b*) It was found by the irradiation technique that this proton couples with 3-H and the phosphorus atom with coupling constants of 5 and 2.5 Hz, respectively. *c*) Signal for this proton collapsed to a doublet of doublets of doublets ($J=11$, 6, 4 Hz) on irradiation of 4-H. *d*) These are signals of 10a-H.

in **2**, **31a**, and **32a** are in a β-equatorial orientation, while they take an α-axial orientation in **31b** and **32b**.

Experimental

All melting points and boiling points are uncorrected. The IR spectra were recorded on a JASCO IRA-1

spectrometer, UV spectra were determined on a JASCO UVIDEC-505 spectrometer, and ^{1}H-NMR spectra on Hitachi R-40 (90 MHz) and Varian XL-300 (300 MHz) spectrometers with tetramethylsilane as an internal standard. MS were recorded with a Hitachi M-80 spectrometer. The solvent for extraction was a mixture of benzene–EtOAc (1 : 1) unless otherwise noted. For column chromatography, SiO_2 (Merck 7734, 7739, and 9385) was used.

1,1-Dimethylindene-3-carbonitrile (7)——A solution of **5** (481 mg, 3 mmol), DEPC (1.49 g, 9 mmol), and LiCN (297 mg, 9 mmol) in THF (7 ml) was stirred at room temperature for 40 min. After removal of the solvent, the residue was dissolved in benzene–EtOAc. The organic solution was washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent gave the crude cyanophosphate (**6**) as an oil, which was then stirred with $BF_3 \cdot Et_2O$ (1.28 g, 9 mmol) in benzene (8 ml) at room temperature for 2 h. After the addition of benzene (20 ml) and H_2O (10 ml), the organic layer was separated, washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography [benzene–EtOAc (10 : 1)] to give **7** (408 mg, 80%). bp_2 65—80 °C (Kugelrohr). IR ν_{max}^{film} cm^{-1}: 2210 (CN). ^{1}H-NMR ($CDCl_3$) δ: 1.33 [6H, s, 1-$(CH_3)_2$], 7.05 (1H, s, =CH), 7.2—7.6 (4H, m, Ar-H). *Anal.* Calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.13; H, 6.34; N, 8.56.

1,1-Dimethylindene-3-carboxylic Acid (8)——A solution of **7** (340 mg, 2 mmol) and KOH (1 g) in 75% EtOH (5 ml) was refluxed for 19 h. After removal of the solvent, the residue was stirred with a mixture of H_2O (10 ml) and hexane (10 ml). The aqueous layer was separated, acidified by the addition of conc. HCl under ice cooling and then extracted. The extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent gave crude solid, which was recrystallized from benzene to give **8** (360 mg, 98%) as colorless crystals, mp 171—173 °C. IR ν_{max}^{Nujol} cm^{-1}: 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.38 [6H, s, 1-$(CH_3)_2$], 7.1—7.4 (3H, m, Ar-H), 7.45 (1H, s, =CH), 8.0 (1H, m, 7-H), 8.3—10.0 (1H, m, OH). *Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.52; H, 6.27.

Reaction of **5** (140 g, 0.87 mol) with DEPC (287 g, 1.74 mol) and LiCN (30 g, 0.91 mol), followed by treatment with $BF_3 \cdot Et_2O$ (330 g, 2.34 mol) under the same conditions as described above gave the diene nitriles (**7**) *via* the cyanophosphate (**6**). Without purification, the nitrile was hydrolyzed with KOH in 75% EtOH to give the carboxylic acid (**8**) (151 g) in 93% overall yield from **5**.

1,1-Dimethylindene-3-carbonyl Chloride (9)——A suspension of **8** (2.07 g, 11 mmol) in $SOCl_2$ (2 ml) was heated at 80 °C for 2 h. After removal of excess $SOCl_2$, the residue was distilled (bp_4 104—105 °C) to give **9** (2.26 g, 100%). IR ν_{max}^{film} cm^{-1}: 1770 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.36 [6H, s, 1-$(CH_3)_2$], 7.30 (3H, m, Ar-H), 7.61 (1H, s, =CH), 7.73—7.96 (1H, m, Ar-H). *Anal.* Calcd for $C_{12}H_{11}ClO$: C, 69.73; H, 5.36. Found: C, 69.85; H, 5.37.

Ethyl 3-(1,1-Dimethylinden-3-yl)-3-oxopropionate (10)——The preparation of LDA was carried out as follows: *n*-butyl lithium (15% hexane solution, 3.2 ml, 5.1 mmol) was added to a solution of diisopropylamine (506 mg, 5 mmol) in THF (3 ml) at −78 °C under N_2, and the mixture was stirred at −78 °C for 20 min. A solution of ethyl acetate (463 mg, 4.95 mmol) in THF (4 ml) was then added dropwise to this solution at −78 °C, and the reaction mixture was stirred at −78 °C for 10 min. A solution of **9** (207 mg, 1 mmol) in THF (4 ml) was added dropwise, and whole was stirred at −78——10 °C for 1.5 h. The mixture was quenched by the addition of H_2O, and THF was removed by evaporation. The residue was extracted, and the extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography (benzene) to give pure **13** (221 mg, 86%) as an oil. bp_2 80—100 °C (Kugelrohr). IR ν_{max}^{film} cm^{-1}: 1740, 1670 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.40 [6H, s, 1-$(CH_3)_2$], 3.92 (2H, s, CH_2), 4.35 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 7.4 (4H, m, Ar-H and =CH), 8.3 (1H, m, Ar-H). *Anal.* Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found; C, 74.51; H, 7.06.

Diethyl 1,1-Dimethylinden-3-ylcarbonylmalonate (11)——A solution of diethyl malonate (961 mg, 6 mmol) in dry benzene (5 ml) and EtOH (3 ml) was added dropwise to a suspension of magnesium (144 mg, 6 mmol) in dry benzene (5 ml) and EtOH (3 ml) containing a drop of CCl_4 with stirring at room temperature. The mixture was refluxed until all the magnesium had dissolved (*ca.* 1.5 h). After removal of the solvent under reduced pressure, the residue was diluted with dry benzene (10 ml). A solution of **9** (620 mg, 3 mmol) in dry benzene (5 ml) was then added dropwise at room temperature, and the mixture was refluxed for 1 h. The reaction mixture was quenched by the addition of cold H_2O, then extracted. The extract was washed with sat. aq. $NaHCO_3$, and H_2O, then dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography (benzene) to give **11** (880 mg, 89%) as an oil. IR ν_{max}^{film} cm^{-1}: 1750, 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, t, J=7 Hz, 2 × $CO_2CH_2C\underline{H}_3$), 1.42 [6H, s, 3-$(CH_3)_2$], 4.27 (4H, q, J=7 Hz, 2 × $CO_2C\underline{H}_2CH_3$), 5.11 (1H, s, CH), 7.10 (1H, s, =CH), 7.25 (3H, m, Ar-H). MS *m/e*: 330 (M^+).

Ethyl 3-(*N*-*tert*-Butoxycarbonyl-*N*-methyl)aminopropionate (14)——A solution of di-*tert*-butyl dicarbonate (2.18 g, 10 mmol) in THF (10 ml) was added dropwise to a solution of ethyl 3-methylaminopropionate (1.31 g, 9 mmol) in THF (10 ml) under ice cooling, then stirred at room temperature for 1 h. Removal of the solvent gave an oil, which was distilled (bp_3 86—88 °C) to give **14** (2.4 g, 100%). IR ν_{max}^{film} cm^{-1}: 1730, 1690 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.47 [9H, s, $C(CH_3)_3$], 2.52 (2H, t, J=7 Hz, NCH_2), 2.87 (3H, s, NCH_3), 3.50 (2H, t, J=7 Hz, CH_2CO), 4.12 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$). *Anal.* Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 56.95; H, 9.05; N, 6.19.

Ethyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-methyl)aminomethyl-3-(1,1-dimethylinden-3-yl)-3-oxopropionate (16)——A solution of **14** (6.55 g, 24 mmol) in THF (8 ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (2.83 g, 28 mmol)] in THF (8 ml) at −78 °C under N_2, and the mixture was stirred at −78 °C for

20 min. A solution of **9** (4.13 g, 20 mmol) in THF (8 ml) was added dropwise at −78 °C, and the whole was stirred at room temperature for 2 h. Work-up as described for the preparation of **10** gave an oil, which was purified by column chromatography [benzene–EtOAc (10 : 1)] to give **16** (6.33 g, 79%) as an oil. IR ν_{max}^{film} cm^{-1}: 1725, 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.40 [6H, s, 3-$(CH_3)_2$], 1.44 [9H, s, $C(CH_3)_3$], 2.87 (3H, s, NCH_3), 3.83 (2H, d, J=8 Hz, NCH_2), 4.18 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.40—5.50 (1H, m, CHCO), 7.30 (4H, m, Ar-H and =CH), 8.13 (1H, m, Ar-H). MS *m/e*: 401 (M^+). High-resolution MS Calcd for $C_{23}H_{31}NO_5$: 401.2203. Found: 401.2199.

Ethyl 3-(1,1-Dimethylinden-3-yl)-2-(*N*-methyl)aminomethyl-3-oxopropionate Hydrochloride (18)——A solution of **16** (635 mg, 1.6 mmol) in 2.3 N HCl in EtOAc (10 ml) was kept at room temperature for 1 h. Evaporation of the solvent gave a crude solid, which was washed with dry Et_2O to give **18** (550 mg, 100%) as colorless crystals. mp 104—107 °C (from benzene–ether). IR ν_{max}^{KBr} cm^{-1}: 2760 (NH), 1725, 1670 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.43 [6H, s, 3-$(CH_3)_2$], 2.77 (3H, s, NCH_3), 3.60 (2H, t, J=7 Hz, NCH_2), 4.23 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.24 (1H, t, J=7 Hz, CHCO), 7.34 (3H, m, Ar-H), 7.78 (1H, s, =CH), 8.06 (1H, m, Ar-H), 9.1—10.2 (2H, br m, NH_2Cl). *Anal.* Calcd for $C_{18}H_{23}NO_3 \cdot HCl$: C, 63.98; H, 7.16; N, 4.14. Found: C, 63.75; H, 7.15; N, 4.23.

Ethyl 3-(*N*-*tert*-Butoxycarbonyl-*N*-methyl)amino-2-methylpropionate (15)——A solution of di-*tert*-butyl dicarbonate (21.83 g, 100 mmol) in THF (50 ml) was added dropwise to a solution of ethyl 2-methyl-3-methylaminopropionate (14.42 g, 99 mmol) in THF (45 ml) under ice cooling and the whole was stirred at room temperature for 1 h. Removal of the solvent gave an oil, which was distilled (bp_4 97—98 °C) to give **15** (25 g, 100%). IR ν_{max}^{film} cm^{-1}: 1740, 1700 (CO).^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.48 [9H, s, $C(CH_3)_3$], 2.87 (3H, s, NCH_3), 3.39 (2H, d, J=7 Hz, NCH_2), 4.16 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$). *Anal.* Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.98; H, 9.45; N, 5.93.

Ethyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-methyl)aminomethyl-3-(1,1-dimethylinden-3-yl)-2-methyl-3-oxopropionate(17)——A solution of **15** (14.7 g, 60 mmol) in THF (30 ml) was added to a solution of LDA [prepared from diisopropylamine (6.03 g, 60 mmol)] in THF (15 ml) at −78 °C under N_2, and the mixture was stirred at −78 °C for 20 min. A solution of **9** (10.33 g, 50 mmol) in THF (50 ml) was added dropwise at −78 °C, and the whole was stirred at room temperature for 2 h. Work-up as described for the preparation of **10** gave an oil, which was purified by column chromatography [benzene–EtOAc (10 : 1)] to give **17** (14.49 g, 70%) as an oil. IR ν_{max}^{film} cm^{-1}: 1730, 1700 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.35 [6H, s, 3-$(CH_3)_2$], 1.41 [9H, s, $C(CH_3)_3$], 1.55 (3H, s, CH_3), 2.81 (3H, s, NCH_3), 6.94 (1H, s, =CH), 7.30 (3H, m, Ar-H), 8.08 (1H, m, Ar-H). MS *m/e*: 415 (M^+). High-resolution MS Calcd for $C_{24}H_{33}NO_5$: 415.2360. Found: 415.2356.

Ethyl 1,3,9,9-Tetramethyl-4-oxo-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylate (19)——A solution of **17** (3.40 g, 8 mmol) in 2.3 N HCl in EtOAc (20 ml) was kept at room temperature for 2 h. Evaporation of the solvent gave ethyl 2-methyl-2-(*N*-methyl)aminomethyl-3-(1,1-dimethylinden-3-yl)-3-oxopropionate hydrochloride. mp 144—150 °C (from EtOAc) as colorless crystals. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.33, 1.37, and 1.92 [each 3H, each s, 9-$(CH_3)_2$ and /or CH_3], 2.89 (3H, s, NCH_3), 3.49 (2H, s, NCH_2), 4.32 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 7.10 (1H, s, =CH), 7.3—7.4 (3H, m, Ar-H), 8.02 (1H, m, Ar-H), 9.30 and 9.70 (each 1H, each br s, NH_2Cl). *Anal.* Calcd for $C_{19}H_{25}NO_3 \cdot HCl$: C, 64.85; H, 7.45; N, 3.98. Found: C, 64.64; H, 7.57; N, 4.18. The hydrochloride was added to sat. aq. $NaHCO_3$ (20 ml) and the mixture was stirred at room temperature for 40 min, then extracted. The extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by column chromatography (benzene) to give **19** (1.88 g, 73%) as an oil. IR ν_{max}^{film} cm^{-1}: 1740, 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.97, 1.47 and 1.50 (each 3H, each s, 3 × CH_3), 1.29 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.54 (3H, s, NCH_3), 2.74 and 3.58 (each 1H, each d, J=12 Hz, 2-H_2), 3.37 (1H, d, J=10 Hz, 4a-H), 4.19 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.24 (1H, d, J=10 Hz, 9a-H), 7.1—7.3 (4H, m, Ar-H). MS *m/e*: 315 (M^+). High-resolution MS Calcd for $C_{19}H_{25}NO_3$: 315.1835. Found: 315.1832.

Ethyl 4-Hydroxy-1,3,9,9-tetramethyl-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylate (20)——A solution of **19** (6.18 g, 19.6 mmol) and $NaBH_4$ (2.97 g, 78 mmol) in EtOH (50 ml) was stirred at 50 °C for 1 h. After evaporation of the solvent, the residue was neutralized with aq. AcOH under ice cooling and extracted. The extract was washed with sat. aq. $NaHCO_3$, and H_2O, and then dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography [benzene–EtOAc (10 : 1)] to give **20** (5.2 g, 83%) as an oil. IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1710 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.60—3.40 (1H, br s, OH), 2.45 (3H, s, NCH_3), 2.70 and 2.90 (2H, AB-q, J=12 Hz, 2-H_2), 2.85 (1H, d, J=9 Hz, 9a-H), 3.35 (1H, dd, J=9, 2 Hz, 4a-H), 4.21 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 7.24 (4H, m, Ar-H). MS *m/e*: 317 (M^+). High-resolution MS Calcd for $C_{19}H_{27}NO_3$: 317.1992. Found: 317.1989.

Ethyl 4-Methanesulfonyloxy-1,3,9,9-tetramethyl-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylate (21)——Methanesulfonyl chloride (276 mg, 2.4 mmol) was added to a solution of **20** (635 mg, 2 mmol) and Et_3N (304 mg, 3 mmol) in CH_2Cl_2 (50 ml), and the mixture was stirred at room temperature for 1 h. The solution was washed with cold H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography [benzene–EtOAc (10 : 1)] to give **21** (560 mg, 71%) as colorless crystals. mp 105—107 °C (from petr. ether). IR ν_{max}^{Nujol} cm^{-1}: 1720 (CO), 1350, 1180 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.84 (3H, s, SCH_3), 2.63 (3H, s, NCH_3), 2.83 and 2.93 (each 1H, each d, J=12 Hz, 2-H_2), 3.15 (1H, d,

J=9 Hz, 9a-H), 3.73 (1H, dd, J=9, 4 Hz, 4a-H), 4.25 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 5.62 (1H, d, J=4 Hz, 4-H), 7.10—7.40 (4H, m, Ar-H). MS *m/e*: 395 (M^+). *Anal.* Calcd for $C_{20}H_{29}NO_5S$: C, 60.73; H, 7.39; N, 3.54. Found: C, 60.84; H, 7.38; N, 3.56.

Ethyl 1,3,9,9-Tetramethyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylate (22)——Method A: A solution of **21** (229 mg, 0.56 mmol) and DBU (106 mg, 0.7 mmol) in DMSO (2 ml) was heated at 100 °C for 20 h. The mixture was poured into ice water, and extracted. The extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography (benzene) to give **22** (120 mg, 69%) as an oil. IR ν_{max}^{film} cm^{-1}: 1730 (CO). UV λ_{max}^{EtOH} nm (log ε): 250 (4.14), 286 (3.60), 295 (3.53). ^{1}H-NMR ($CDCl_3$) δ: 1.08, 1.49 and 1.55 (each 3H, each s, 3×CH_3), 1.31 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 2.48 (3H, s, NCH_3), 2.71 (1H, d, J=12 Hz, 2-H), 2.81 (1H, d, J=2 Hz, 9a-H), 2.85 (1H, dd, J=12, 1 Hz, 2-H), 4.22 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 6.12 (1H, dd, J=2, 1 Hz, =CH), 7.23 (3H, m, Ar-H), 7.50 (1H, m, 5-H). MS *m/e*: 299 (M^+). High-resolution MS Calcd for $C_{19}H_{25}NO_2$: 299.1887. Found: 299.1884.

Method B: A solution of **21** (158 mg, 0.4 mmol) and LiBr (174 mg, 2 mmol) in DMF (5 ml) was heated at 100 °C for 2 h. Work-up as usual gave an oil, which was purified by column chromatography to give **22** (105 mg, 88%). This was identical with an authentic sample (IR and ^{1}H-NMR spectral comparisons).

***N,N*-Diethyl-3-(*N*-*tert*-butoxycarbonyl-*N*-methyl)aminopropionamide (23)**——A solution of di-*tert*-butyl dicarbonate (18.01 g, 82.5 mmol) in THF (50 ml) was added dropwise to a solution of *N,N*-diethyl-3-(*N*-methyl)propionamide (13.06 g, 82.5 mmol) in THF (40 ml) under ice cooling and the mixture was stirred at room temperature for 2 h. Removal of the solvent gave an oil, which was distilled (bp_{14} 159—164 °C) to give **23** (21 g, 99%). IR ν_{max}^{film} cm^{-1}: 1690, 1640 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.02—1.30 (6H, m, 2×NCH_2CH_3), 1.46 [9H, s, $C(CH_3)_3$], 2.52 (2H, t, J=7 Hz, NCH_2), 2.87 (3H, s, NCH_3), 3.40 (6H, m, 2×NCH_2CH_3 and CH_2CO). *Anal.* Calcd for $C_{13}H_{26}N_2O_3$: C, 60.43; H, 10.14; N, 10.85. Found: C, 60.36; H, 9.88; N, 10.95.

***N,N*-Diethyl-2-(*N*-*tert*-butoxycarbonyl-*N*-methyl)aminomethyl-3-(1,1-dimethylinden-3-yl)-3-oxopropionamide (24)**——*n*-Butyl lithium (15% hexane solution, 153 ml, 240 mmol) was added dropwise to a solution of **23** (62 g, 240 mmol) in THF (150 ml) at −78 °C under N_2, and the mixture was stirred at −78 °C for 20 min. A solution of **9** (16.5 g, 80 mmol) in THF (150 ml) was added dropwise at −78 °C, and the whole was stirred at room temperature for 1 h. Work-up as described for the preparation of **10** gave an oil, which was purified by column chromatography [benzene–EtOAc (5 : 1)] to give **24** (15.5 g, 45%) as an oil. IR ν_{max}^{film} cm^{-1}: 1690, 1640 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.12 (6H, m, 2×NCH_2CH_3), 1.38 [6H, s, 3-$(CH_3)_2$], 1.43 [9H, s, $C(CH_3)_3$], 2.83 (3H, s, NCH_3), 3.10—3.55 (4H, m, 2×NCH_2CH_3), 3.80 (2H, br d, J=7 Hz, NCH_2), 4.80 (1H, br s, CH), 7.30 (4H, m, Ar-H and =CH), 8.10 (1H, m, Ar-H). MS *m/e*: 428 (M^+). High-resolution MS Calcd for $C_{25}H_{36}N_2O_4$: 428.2676. Found: 428.2673.

***N,N*-Diethyl-4-hydroxyl-1,9,9-trimethyl-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxamide (26)**——A solution of **24** (320 mg, 0.75 mmol) in 2.3 N HCl in EtOAc (2 ml) was kept at room temperature for 4 h. Removal of the solvent gave crude solid, which was added to sat. aq. $NaHCO_3$. The mixture was stirred for 10 min, and extracted. The extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent afforded *N,N*-diethyl-1,9,9-trimethyl-4-oxo-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxamide (**25**) [MS *m/e* 328 (M^+). High-resolution MS Calcd for $C_{20}H_{28}N_2O_2$: 328.2152. Found: 328.2149]. $NaBH_4$ (34 mg, 0.9 mmol) was added to a solution of **25** without purification in EtOH (10 ml), and the mixture was stirred at room temperature for 4 h. After evaporation of the solvent, the residue was neutralized with aq. AcOH under ice cooling, and extracted. The extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography (EtOAc) to give **26** (142 mg, 57% overall yield from **24**) as an oil, which soon solidified. mp 129—131 °C (from benzene–ligroin) as colorless crystals. IR ν_{max}^{Nujol} cm^{-1}: 3380 (OH), 1610 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.14 and 1.21 (each 3H, each t, J=7 Hz, 2×NCH_2CH_3), 1.34 and 1.42 (each 3H, each s, 2×CH_3), 2.39 (3H, s, NCH_3), 2.63 (1H, dd, J=12, 11 Hz, 2ax-H), 2.84 (1H, d, J=9 Hz, 9a-H), 2.85 (1H, dd, J=11, 8 Hz, 2eq-H), 3.28 (1H, ddd, J=12,8, 2 Hz, 3-H), 3.40 (4H, m, 2×NCH_2CH_3), 3.78 (1H, dd, J=9, 3 Hz, 4a-H), 4.16 (1H, br s, 4-H), 7.10—7.40 (4H, m, Ar-H). MS *m/e*: 330 (M^+). High-resolution MS Calcd for $C_{20}H_{30}N_2O_2$: 330.2309. Found: 330.2306. *Anal.* Calcd for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.77; H, 9.11; N, 8.23.

***N,N*-Diethyl-4-melthanesulfonyloxy-1,9,9-trimethyl-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxamide (27)**——A mixture of **26** (330 mg, 1 mmol), Et_3N (152 mg, 1.5 mmol), and MsCl (137 mg, 1.2 mmol) in CH_2Cl_2 (5 ml) was treated as described for the preparation of **21** to give an oil, which was purified by column chromatography [benzene–EtOAc (1 : 1)] to give **27** (392 mg, 96%) as an oil. IR ν_{max}^{film} cm^{-1}: 1620 (CO), 1350, 1170 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.14 and 1.22 (each 3H, each t, J=7 Hz, 2×NCH_2CH_3), 1.38 and 1.40 (each 3H, each s, 2×CH_3), 2.35 and 2.45 (each 3H, each s, NCH_3 and /or SCH_3), 2.90 (1H, d, J=9 Hz, 9a-H), 3.30—3.55 (5H, m, 2×NCH_2CH_3 and 3-H), 4.0 (1H, dd, J=9, 4 Hz, 4a-H), 5.32 (1H, dd, J=4, 2 Hz, 4-H), 7.20 (3H, m, Ar-H), 7.43 (1H, m, 5-H). MS *m/e*: 408 (M^+). High-resolution MS Calcd for $C_{21}H_{32}N_2O_4S$: 408.2085. Found: 408.2080.

The perchlorate of **27** was recrystallized from EtOH to give an analytical sample of mp 210—211 °C as colorless crystals. *Anal.* Calcd for $C_{21}H_{33}ClN_2O_8S$: C, 49.55; H, 6.53; N, 5.50. Found: C, 49.59; H, 6.32; N, 5.38.

***N,N*-Diethyl-1,9,9-trimethyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxamide (2)**——Method A: A solution of **27** (475 mg, 1.1 mmol) and DBU (183 mg, 1.2 mmol) in DMSO (10 ml) was heated at 70 °C for 4 d. Work-up, as described for the preparation of **22**, gave an oil, which was purified by column chromatography

[benzene–EtOAc (3 : 2)] to give **2** (138 mg, 44%) as an oil. IR ν_{max}^{film} cm^{-1}: 1620 (CO). UV λ_{max}^{EtOH} nm (log ε): 252 (4.16), 286 (3.65), 295 (3.57). ^{1}H-NMR ($CDCl_3$) δ: 1.10 and 1.56 (each 3H, each s, 2 × CH_3), 1.15 and 1.23 (each 3H, each t, J=7 Hz, 2 × $NCH_2C\underline{H}_3$), 2.52 (3H, s, NCH_3), 2.79 (1H, t, J=11 Hz, 2ax-H), 3.0 (1H, dd, J=11, 6 Hz, 2eq-H), 3.43 (4H, m, 2 × $NC\underline{H}_2CH_3$), 3.86 (1H, m, 3-H), 5.92 (1H, t, J=2 Hz, 4-H), 7.26 (3H, m, Ar-H), 7.45 (1H, m, 5-H). MS *m/e*: 312 (M^+). High-resolution MS Calcd for $C_{20}H_{28}N_2O$: 312.2203. Found: 312.2200.

The picrate of **2** was recrystallized from EtOH to give an analytical sample of mp 195—197 °C as yellow crystals. *Anal.* Calcd for $C_{26}H_{31}N_5O_8$:C, 57.66; H, 5.77; N, 12.93. Found: C, 57.72: H, 5.91; N, 12.78.

Method B: A mixture of **27** (1.47 g, 3.6 mmol), LiBr (1.56 g, 18 mmol) and Li_2CO_3 (1.33 g, 18 mmol) in DMF (10 ml) was heated with stirring at 90 °C for 3 h. Work-up gave an oil, which was subjected to column chromatography. The first eluate with benzene–EtOAc (3 : 2) gave 4-bromo-*N,N*-diethyl-1,9,9-trimethyl-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxamide (**28**) (25 mg, 2%) as an oil. IR ν_{max}^{film} cm^{-1}: 1640 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.13 and 1.31 (each 3H, each t, J=7 Hz, 2 × $NCH_2C\underline{H}_3$), 1.37 and 1.40 (each 3H, each s, 2 × CH_3), 2.79 (3H, s, NCH_3), 3.28 (1H, d, J=8 Hz, 9a-H), 3.40 (4H, m, 2 × $NC\underline{H}_2CH_3$), 3.63 (1H, dd, J=11, 8 Hz, 4a-H), 4.57 (1H, t, J=11 Hz, 4-H), 7.24 (3H, m, Ar-H), 7.67 (1H, m, 5-H). MS *m/e*: 392 (M^+). High-resolution MS Calcd for $C_{20}H_{29}BrN_2O$: 392.1465. Found: 392.1462. The second eluate with benzene–EtOAc (3 : 2) gave **2** (573 mg, 51%) as an oil, which was identical with an authentic sample (IR and ^{1}H-NMR spectral comparisons).

Method C: A solution of **27** (204 mg, 0.5 mmol) and LiCl (106 mg, 2.5 mmol) in DMF (5 ml) was heated at 90 °C for 30 min. Work-up gave an oil, which was subjected to column chromatography. The first eluate with benzene–EtOAc (3 : 2) gave 4-chloro-*N,N*-diethyl-1,9,9-trimethyl-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxamide (**29**) (27 mg, 16%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.12 and 1.30 (each 3H, each t, J=7 Hz, 2 × $NCH_2C\underline{H}_3$), 1.35 and 1.42 (each 3H, each s, 2 × CH_3), 2.78 (3H, s, NCH_3), 4.44 (1H, t, J=11 Hz, 4-H), 7.24 (3H, m, Ar-H), 7.60 (1H, m, 5-H). MS *m/e*: 348 (M^+). High-resolution MS Calcd for $C_{20}H_{29}ClN_2O$: 348.1971. Found: 348.1966. The second eluate with benzene–EtOAc (3 : 2) gave **2** (10 mg, 6%), which was identical with an authentic sample (IR spectral comparison).

Ethyl 2-(*N-tert*-Butoxycarbonyl-*N*-methyl)aminomethyl-3-diethylphosphonooxy-3-(1,1-dimethylinden-3-yl)acrylate (30)——A solution of **16** (530 mg, 1.32 mmol) in THF (5 ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (160 mg, 1.6 mmol)] in THF (5 ml) at −78 °C, and the mixture was stirred at −78 °C for 20 min. A solution of diethyl phosphorochloridate (251 mg, 1.6 mmol) in THF (4 ml) was added dropwise to this solution at −78 °C, then the reaction mixture was stirred at room temperature for 2.5 h. Work-up as described for the preparation of **10** gave an oil, which was purified by column chromatography [benzene–EtOAc (1 : 10)] to give **30** (510 mg, 72%) as an oil. IR ν_{max}^{film} cm^{-1}: 1730, 1690 (CO), 1290, 1150, 1030 [P(O)(OEt)$_2$]. ^{1}H-NMR ($CDCl_3$) δ: 1.15 [9H, m, 2 × P(O)($OCH_2C\underline{H}_3$)$_2$ and $CO_2CH_2C\underline{H}_3$], 1.39 [6H, s, 3-(CH_3)$_2$], 1.41 [9H s, $C(CH_3)_3$], 2.70 (3H, s, NCH_3), 6.54 (1H, s, =CH), 7.30 (4H, m, Ar-H). MS *m/e*: 537 (M^+). High-resolution MS Calcd for $C_{27}H_{40}NO_8P$: 537.2493. Found: 537.2489.

Ethyl 4-Diethylphosphonooxy-1,9,9-trimethyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylates (31a and 31b)——A solution of **30** (1.7 g, 3.17 mmol) in 2.3 N HCl in EtOAc (5 ml) was kept at room temperature for 1.5 h. Removal of the solvent gave crude solid, which was added to sat. aq. $NaHCO_3$ solution. The mixture was stirred for 40 min and extracted. The extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was subjected to column chromatography. The first eluate with benzene–EtOAc (1 : 10) gave **31b** (633 mg, 46%), and **31a** (720 mg, 52%) was obtained from the second eluate with benzene–EtOAc (1 : 10).

31a: IR ν_{max}^{film} cm^{-1}: 1730 (CO), 1280, 1180, 1030 [P(O)(OEt)$_2$]. UV λ_{max}^{EtOH} nm (log ε): 252 (4.20), 284 (3.62), 294 (3.57). ^{1}H-NMR ($CDCl_3$) δ: 1.16 and 1.30 [9H, m, 2 × P(O)($OCH_2C\underline{H}_3$)$_2$ and $CO_2CH_2C\underline{H}_3$], 1.09 and 1.53 (each 3H, each s, 2 × CH_3), 2.63 (1H, t, J=11 Hz, 2ax-H), 2.48 (3H, s, NCH_3), 3.03 (1H, t, J=3.5 Hz, 9a-H), 3.22 (1H, dd, J=11, 6.5 Hz, 2eq-H), 3.9—4.3 [7H, m, P(O)($OC\underline{H}_2CH_3$)$_2$, $CO_2C\underline{H}_2CH_3$, and 3-H], 7.30 (3H, m, Ar-H), 7.78 (1H, m, 5-H). MS *m/e*: 437 (M^+). High-resolution MS Calcd for $C_{22}H_{32}NO_6P$: 437.1968. Found: 437.1966.

31b: IR ν_{max}^{film} cm^{-1}: 1730 (CO), 1280, 1160, 1030 [P(O)(OEt)$_2$]. UV λ_{max}^{EtOH} nm (log ε): 252 (4.16), 284 (3.66). 293 (3.60). ^{1}H-NMR ($CDCl_3$) δ: 1.22, 1.33 and 1.37 [9H, m, P(O)($OCH_2C\underline{H}_3$)$_2$ and $CO_2CH_2C\underline{H}_3$], 1.06 and 1.52 (each 3H, each s, 2 × CH_3), 2.78 (1H, dd, J=12, 4.5 Hz, 2ax-H), 2.94 (1H, dd, J=5, 2.5 Hz, 9a-H), 3.25 (1H, dd, J=12, 2 Hz, 2eq-H), 3.76 (1H, br s, 3-H), 4.18 [6H, m, 2 × P(O)($OC\underline{H}_2CH_3$)$_2$ and $CO_2C\underline{H}_2CH_3$], 7.28 (4H, m, Ar-H), 7.80 (1H, m, 5-H). MS *m/e*: 437 (M^+). High-resolution MS Calcd for $C_{22}H_{32}NO_6P$: 437.1968. Found: 437.1964.

Without isolation of the enol phosphate (**30**) a mixture of **31a** and **31b** was obtained in 73% overall yield from **16**.

Ethyl 2-(*N-tert*-Butoxycarbonyl-*N*-methyl)aminomethyl-3-(1,1-dimethylinden-3-yl)-3-hydroxypropionate (33)——A solution of **16** (5.65 g, 14 mmol) and $NaBH_4$ (533 mg, 14 mmol) in EtOH (20 ml) was stirred at room temperature for 15 min. Work-up as described for the preparation of **20** gave an oil, which was purified by column chromatography [benzene–EtOAc (5 : 1)] to give **33** (5.53 g, 98%) as an oil. IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1700 (CO). The ^{1}H-NMR spectrum was not sufficiently well resolved for the assignment of the protons. MS *m/e*: 403 (M^+). High-resolution MS Calcd for $C_{23}H_{33}NO_5$: 403.2360. Found: 403.2357.

Ethyl 2-(*N-tert*-Butoxycarbonyl-*N*-methyl)aminomethyl-3-(1,1-dimethylinden-1-yl)acrylate (34)——A mixture of **33** (5.05 g, 12.5 mmol) and $SOCl_2$ (3 ml) in anhyd. pyridine (5 ml) was kept at room temperature for 1 h. The reaction mixture was poured into ice water and extracted with Et_2O. The extract was washed with sat. aq. $NaHCO_3$ and H_2O

and then dried over anhyd. $MgSO_4$. Removal of the solvent gave an oil, which was purified by column chromatography [benzene–EtOAc (10 : 1)] to give **34** (1.86 g, 38%)] as an oil. IR ν_{max}^{film} cm^{-1}: 1700 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (9H, m, 2 × CH_3 and $CO_2CH_2C\underline{H}_3$), 1.44 [9H, s, $C(CH_3)_3$], 2.70 (3H, s, NCH_3), 4.29 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.45 (2H, br s, CH_2), 6.46 (1H, br s, =CH), 7.32 (4H, m, Ar-H and =CH), 7.76 (1H, m, Ar-H). MS *m/e*: 385 (M^+). High-resolution MS Calcd for $C_{23}H_{31}NO_4$: 385.2254. Found: 385.2251.

Ethyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-methyl)aminomethyl-3-(1,1-dimethylinden-3-yl)-3-methanesulfonyloxypropionate (36)——A mixture of **33** (1.48 g, 3.37 mmol), Et_3N (512 mg, 5.06 mmol) and MsCl (463 mg, 4.04 mmol) was treated as described for the preparation of **21** to give an oil, which was purified by column chromatography [benzene–EtOAc (10 : 1)] to give **36** (730 mg, 45%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680 (CO), 1370, 1170 (SO_2). The ^{1}H-NMR spectrum was not sufficiently well resolved for the assignment of the protons. MS *m/e*: 481 (M^+). High-resolution MS Calcd for $C_{24}H_{35}NO_7S$: 481.2135. Found: 481.2131.

Treatment of 36 with DBU——A solution of **36** (481 mg, 1 mmol) and DBU (182 mg, 1.2 mmol) in DMSO (5 ml) was heated at 70 °C for 4 h. Work-up, as described for the preparation of **22**, gave an oil, which was purified by column chromatography [benzene–EtOAc (10 : 1)] to give **34** (52 mg, 13%). This was identical with an authentic sample (IR and ^{1}H-NMR spectral comparisons).

Ethyl 1,9,9-Trimethyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine-3-carboxylates (32a and 32b)——Method A: A solution of **34** (280 mg, 0.72 mmol) was treated as described for the preparation of **31a** and **31b** to give an oil, which was purified by column chromatography [benzene–EtOAc (15 : 1)] to give a mixture of **32a** and **32b** (190 mg, 92%) as an oil. By careful chromatographical separation a small amount of **32a** was obtained, but this readily isomerized to an equilibrium mixture of **32a** and **32b**.

32a: IR ν_{max}^{film} cm^{-1}: 1725 (CO). UV λ_{max}^{EtOH} nm (log ε): 251 (3.92), 286 (3.49), 295 (3.41). ^{1}H-NMR ($CDCl_3$) δ: 1.07 and 1.55 (each 3H, each s, 2 × CH_3), 1.31 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.50 (3H, s, NCH_3), 2.56 (1H, t, J=11.5 Hz, 2ax-H), 2.86 (1H, dd, J=4, 3 Hz, 9a-H), 3.17 (1H, ddd, J=11.5, 5.5, 1 Hz, 2eq-H), 3.65 (1H, m, 3-H), 4.21 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 6.13 (1H, td, J=3, 1 Hz, 4-H), 7.22 (3H, m, Ar-H), 7.43 (1H, m, 5-H). MS *m/e*: 285 (M^+). High-resolution MS Calcd for $C_{18}H_{23}NO_2$: 285.1730. Found: 285.1727. The perchlorate of **32a** was recrystallized from EtOH to give an analytical sample of mp 194—197 °C as colorless crystals. *Anal.* Calcd for $C_{18}H_{24}ClNO_6$: C, 56.03; H, 6.27; N, 3.63. Found: C, 55.85; H, 6.56; N, 3.77.

32b: (The ^{1}H-NMR spectral data for **32b** were obtained from the spectrum of a mixture of the two isomers) ^{1}H-NMR ($CDCl_3$) δ: 1.02 and 1.53 (each 3H, each s, 2 × CH_3), 1.23 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.45 (3H, s, NCH_3), 2.54 (1H, dd, J=11.5, 5 Hz, 2ax-H), 2.79 (1H, t, J=3 Hz, 9a-H), 3.13 (1H, m, 3-H), 3.33 (1H, dt, J=11.5, 1 Hz, 2eq-H), 4.18 (2H, m, $CO_2C\underline{H}_2CH_3$), 6.15 (1H, m, 4-H).

Method B: A solution of **36** (100 mg, 0.21 mmol) in 2.3 N HCl in EtOAc (2 ml) was kept at room temperature. Removal of the solvent gave a crude solid, which was stirred with DBU (63 mg, 0.42 mmol) in DMSO (5 ml) at room temperature for 15 min. The mixture was poured into H_2O and extracted. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography [benzene–EtOAc (15 : 1)] to give a mixture of **32a** and **32b** (58 mg, 100%), which was identical with an authentic mixture (^{1}H-NMR spectral comparison).

Treatment of a Mixture of 32a and 32b with MeOD——A solution of a mixture of **32a** and **32b** (11 mg) in MeOD (1 ml) was refluxed for 10 min. Removal of the solvent gave an oil, whose ^{1}H-NMR spectrum showed the disappearance of the signals due to 3-H, seen at δ 3.13 and 3.65 in **32a** and **32b**. [MS *m/e*: 286 (M^+)].

4-Hydroxy-3-hydroxymethyl-1,3,9,9-tetramethyl-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridine (38)——A solution of **20** (1.23 g, 4.5 mmol) in dry Et_2O (20 ml) was added to a stirred suspension of LAH (1.97 g, 22.5 mmol) in dry Et_2O (10 ml) under ice cooling. The mixture was stirred at room temperature for 30 min. After addition of EtOAc (20 ml) followed by H_2O (10 ml) under ice cooling, the organic layer was separated and the aqueous layer was extracted with Et_2O. The combined extracts were washed with brine and dried over anhyd. $MgSO_4$. Removal of the solvent gave a solid, which was recrystallized from EtOH–Et_2O to give **38** (1.03 g, 83%) as colorless crystals, mp 140—143 °C. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.06, 1.38 and 1.48 (each 3H, each s, 3 × CH_3), 2.26 and 2.82 (each 1H, each d, J=12 Hz, 2-H_2), 2.52 (3H, s, NCH_3), 2.99 (1H, d, J=9 Hz, 9a-H), 3.55 and 3.62 (each 1H, each d, J=11 Hz, CH_2O), 3.64 (1H, dd, J=9, 3 Hz, 4a-H), 3.80 [1H, m, (collapsed to doublet (J=3 Hz) on D_2O treatment), 4-H], 7.21 (4H, m, Ar-H). *Anal.* Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.23; H, 9.24; N, 5.19.

2,2,4a,6,7,7-Hexamethyl-4,4a,5,6,6a,7,11b,11c-octahydro-2*H*-*m*-dioxino[5,4-*c*]indeno[1,2-*c*]pyridine (39)——2,2-Dimethoxypropane (3.75 ml) was added to a solution of **38** (145 mg, 0.5 mmol) and TsOH (95 mg, 0.5 mmol) in DMF (5 ml), and the mixture was stirred at room temperature overnight. The reaction mixture was poured into H_2O, made alkaline with aq. K_2CO_3 and extracted. The extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography [$CHCl_3$–MeOH (100 : 1)] to give **39** (87 mg, 55%). ^{1}H-NMR ($CDCl_3$) δ: 0.88, 1.09 and 1.60 (each 3H, each s, 3 × CH_3), 1.55 [6H, s, 2-$(CH_3)_2$], 1.90 and 2.39 (each 1H, each d, J=11 Hz, 5-H_2), 2.32 (3H, s, NCH_3), 2.69 (1H, d, J=6 Hz, 6a-H), 3.25 and 3.61 (each 1H, each d, J=11 Hz, CH_2O), 3.73 (1H, br t, J=6 Hz, 11b-H), 4.12 (1H, d, J=6 Hz, 11c-H), 7.10 (3H, m, Ar-H), 7.75 (1H, m, 11-H). MS *m/e*: 315 (M^+). High-resolution MS Calcd for $C_{20}H_{29}NO_2$: 315.2200. Found: 315.2197.

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