Potent Inhibitors of Secretory Phospholipase A2: Synthesis and Inhibitory Activities of Indolizine and Indene Derivatives

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Phospholipase A2 is an enzyme which hydrolyzes the *sn*-2 position of certain cellular phospholipids. The liberated lysophospholipid and arachidonic acid are precursors in the biosynthesis of various biologically active products. As human nonpancreatic sPLA2 is present in high levels in the blood of patients in several pathological conditions, the potent sPLA2 inhibitors have been suggested to be useful drugs. Here we describe the synthesis, structure−activity relationship, and inhibitory activities of indolizine and indene derivatives. 1-(Carbamoylmethyl)indolizine derivatives and 1-oxamoylindolizine derivatives exhibited very potent inhibitory activity. The former was unstable to air oxidation, but the latter exhibited an improvement both in stability and in potency. Some compounds approached the stoichiometric limit of the chromogenic assay.

Introduction

Phospholipase A2 (PLA2) is an enzyme that specifically hydrolyzes the *sn*-2-acyl ester bond of phosphoglycerides of cell membranes and is distributed widely in nature. Activation of PLA2 leads to the release of fatty acids and lysophospholipid, which are then converted to mediators of inflammation and allergy, such as prostaglandins, leukotrienes, and platelet activating factor.[1] Therefore, blockade of PLA2 can result in the suppression of three important classes of lipid mediators and offers an attractive therapeutic approach to inflammation. Over the past decade, a number of distinct types of PLA2 have been isolated and characterized. Pancreatic type I secretory PLA2, nonpancreatic 14-kDa type II secretory PLA2 (sPLA2), and 85-kDa cytosolic PLA2[2] are especially well-known in relation to pathology. Among these types, mammalian nonpancreatic sPLA2 has been detected in high levels in the blood of patients with septic shock[2] and pancreatitis[3] and also in the synovial fluid of those suffering from rheumatoid arthritis.[4] Because of this involvement of sPLA2 in such inflammatory processes, it has been suggested that a potent sPLA2 inhibitor can be a therapeutically useful drug in the treatment of septic shock, acute respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, rheumatoid arthritis, gout, and other diseases.

Various PLA2 inhibitors have been described by many research groups.[5] Researchers at Lilly have recently found a highly potent sPLA2 inhibitor[6] having a novel indole structure by using computer-aided drug design and chemical modification of a lead compound, which was discovered in the course of high-volume screening. This information prompted us to study the structural effects of the closely related indolizine and indene compounds on sPLA2 activity. The indolizine nucleus is similar to indole with a delocalized 10 π-electron aromatic system. Owing to its electronic and stereochemical similarity to indole, the indolizine system was considered likely to show similar sPLA2 inhibitory activity.

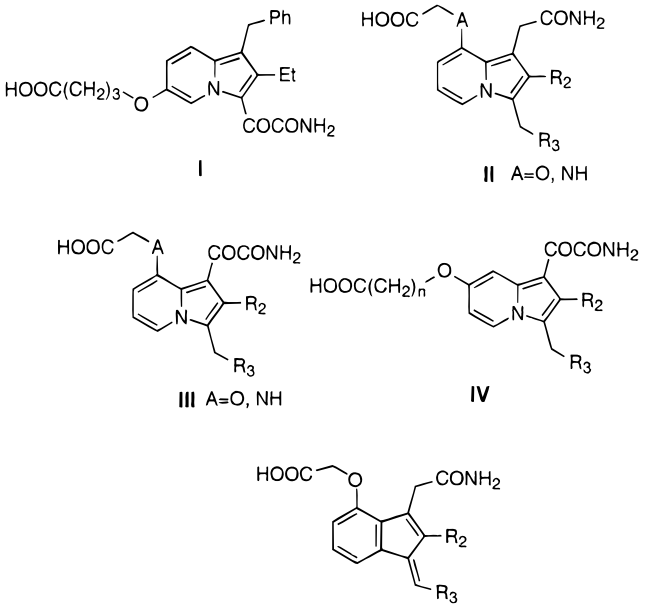

Figure 1. Prepared compounds.

In this paper, we describe the synthesis and evaluation of sPLA2 inhibitory activity of four types of indolizine derivatives, **I**−**IV**, and the indene derivative depicted in Figure 1 (also see Table 1). These derivatives have not only a (carbamoylmethyl) group or an oxamoyl group at the C-1 position but also a carboxylic acid to co-ordinate with the Ca^{2+} ion located in the hydrophilic domain at the active site. Also chemical modification of the hydrophobic part located in the hydrophobic domain was carried out using SAR study to pursue the effective substituents.

Synthesis

(1) Synthesis of Type I Compound (Scheme 1). The carbanion of 2-methyl-5-methoxypyridine[7] was reacted with benzonitrile to produce **2**.[8] The

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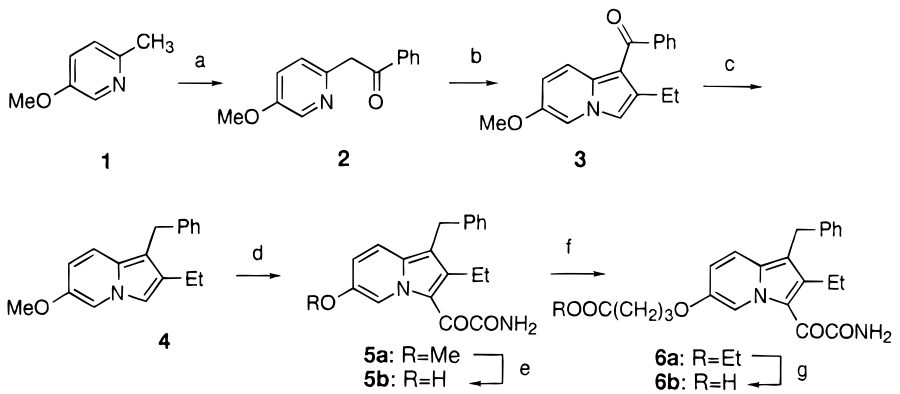
Table 1. Substituents of Indolizine and Indene Derivatives

compd	R_2	R_3	compd	R_2	R_3
11−15					
a	Et	Ph	**e**	cycloPr	*o*-Ph-C_6H_4
b	Et	*o*-Ph-C_6H_4	**f**	Et	Ph
c	Et	*m*-Cl-C_6H_4	**g**	Et	1-Naphthyl
d	Et	*m*-Cl-C_6H_4			
18−20, 25−28, 31, 32					
i	Et	Ph	**xxii**	Et	*trans*-4-(*m*-*n*-pentyl)cyclohexyl
ii	Et	*o*-Ph-C_6H_4	**xxiii**	Me	1-adamantyl
iii	Et	*m*-Cl-C_6H_4	**xxiv**	Me	*o*-Ph-C_6H_4
iv	Et	*m*-CF_3-C_6H_4	**xxv**	cycloPr	Ph
v	Et	1-naphthyl	**xxvi**	Et	*p*-*n*-Bu-C_6H_4
vi	cycloPr	*o*-Ph-C_6H_4	**xxvii**	Me	cyclohexyl
vii	Me	Ph	**xxviii**	cycloPr	cyclopentyl
viii	Et	*p*-Ph-C_6H_4	**xxix**	Me	cyclopentyl
ix	Et	cyclohexyl	**xxx**	cycloPr	cyclohexyl
x	Et	cyclopentyl	**xxxi**	iPr	*o*-Ph-C_6H_4
xi	Et	cycloheptyl	**xxxii**	tBu	*o*-Ph-C_6H_4
xii	Et	*n*-Bu	**xxxiii**	cyclopentyl	*o*-Ph-C_6H_4
xiii	Et	pent-4-yl	**xxxiv**	Et	*m*-Ph-C_6H_4
xiv	Et	2-naphthyl	**xxxv**	Et	cinnamyl
xv	Et	3,5-(t-Bu)$_2$-C_6H_3	**xxxvi**	Et	phenethyl
xvi	Et	Bn	**xxxvii**	cycloPr	1-naphthyl
xvii	Et	*o*-Bn-C_6H_4	**xxxviii**	OMe	*o*-Ph-C_6H_4
xviii	Et	2-thienyl	**xxxix**	SMe	*o*-Ph-C_6H_4
xix	Et	3-(thienyl-2-yl)thienyl-2-yl	**xl**	Me	Ph
xx	Et	*m*-MeO-C_6H_4	**xli**	Me	cyclohexyl
xxi	Et	*o*-NO_2-C_6H_4			
38−43					
a	Et	Ph	**e**	Et	*o*-Ph-C_6H_4
b	cycloPr	*o*-Ph-C_6H_4	**f**	Et	*o*-Ph-C_6H_4
c	Et	*o*-Ph-C_6H_4	**g**	Et	*o*-Ph-C_6H_4
d	Et	cyclohexyl			
61−65					
a	Me	Ph	**f**	Et	*m*-Cl-C_6H_4
b	Me	Ph	**g**	Et	*o*,*m*-Cl_2-C_6H_3
c	Et	Ph	**h**	Et	*m*-CF_3-C_6H_4
d	Et	*o*-Ph-C_6H_4	**i**	Et	1-naphthyl
e	Et	*o*-Bn-C_6H_4	**j**	Et	2-naphthyl

Scheme 1[a]

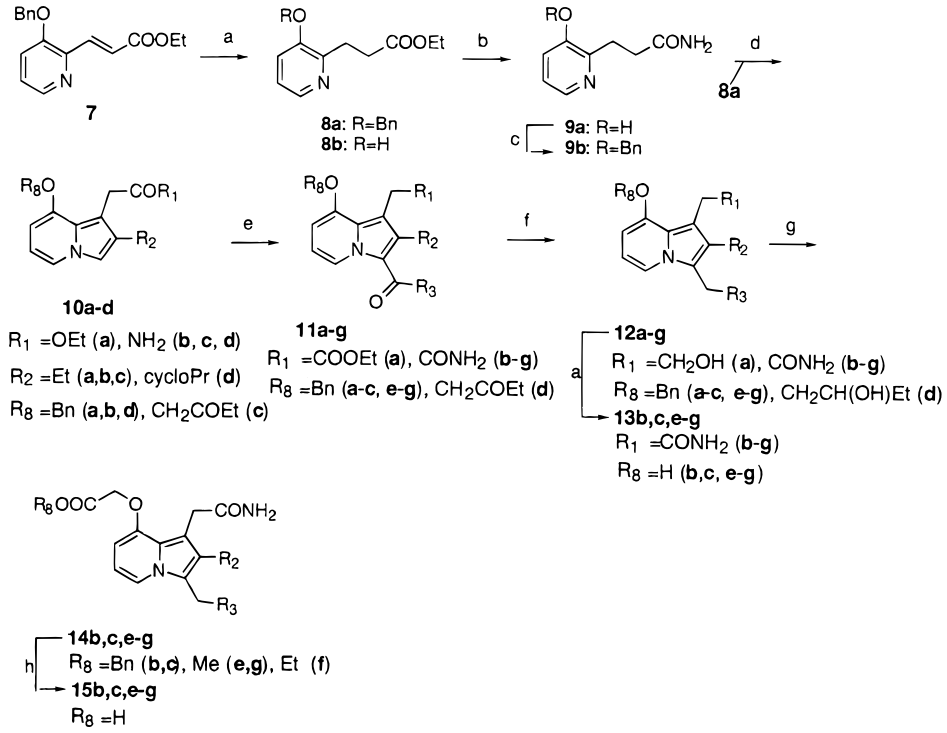


[a] Reagents: (a) LDA, C_6H_5CN; (b) 1-bromo-2-butanone, $NaHCO_3$; (c) $LiAlH_4$; (d) (1) $(COCl)_2$, (2) NH_4OH; (e) BBr_3; (f) NaH, $Br(CH_2)_3COOEt$; (g) LiOH.

Tschitschibabin reaction, that is, alkylation of the nitrogen of **2** with 1-bromo-2-butanone to the N-alkylated intermediate, followed by cyclization with $NaHCO_3$ gave **3**.[9] Although indolizine is generally unstable to air oxidation because of its electron-rich character, electron-withdrawing groups on the indolizine nucleus have the effect of making the compounds much less susceptible to oxidation by air. The benzoyl group of **3** was reduced to the benzyl group with $LiAlH_4$ to give compound **4**, which was very reactive to an electrophile and was acylated with oxalyl chloride without any catalyst. Sequential treatment with NH_4OH gave **5a** in excellent yield. Demethylation of **5a** with BBr_3 yielded **5b**, which was O-alkylated using NaH and ethyl 4-bromobutylate to form **6a**.

(2) Synthesis of Type II Compound (Scheme 2). Compound **7**[10] was reduced by catalytic hydrogenation until no starting material was detected to give a mixture of compounds **8a** and **8b**. As ammonolysis of **8a** gave **9b** in poor yield, **8b** was used instead to obtain **9a** in good yield. The hydroxy group of **9a** was protected to give **9b**, and then cyclization by the Tschitschibabin reaction was done with 1-bromo-2-butanone and chloromethyl cyclopropyl ketone to obtain **10b** accompanied by **10c** and **10d**, respectively. Ester **8a** was also cyclized to furnish **10a**. In order to modify the substituent at

Scheme 2[a,b]



[a] Reagents: (a) H_2, Pd−C: (b) NH_4OH; (c) BnCl, K_2CO_3; (d) XCH_2COR_2, $NaHCO_3$; (e) R_3COCl; (f) t-$BuNH_2$−BH_3, $AlCl_3$; (g) NaH, $BrCH_2COOR_8$; (h) LiOH or H_2, Pd−C. [b] R_2 and R_3 of **a**−**g**: see Table 1.

the C-3 position of indolizine, **10** was acylated without any catalyst with various hydrophobic acyl chloride: *o*-phenylbenzoyl chloride, *m*-chlorobenzoyl chloride, benzoyl chloride, and 1-naphthyl chloride. Selective reduction of the carbonyl group at the C-3 position of **11**, except for **10a**, to methylene was carried out with t-$BuNH_2$−BH_3 complex and $AlCl_3$[11] to give **12**, which was converted to the desired type **II** compound **15** as shown in Scheme 2 by deprotection of the benzyl group, followed by alkylation at the C-8 position.

(3) Synthesis of Type III Compound (Schemes 3−5). Compound **16b**, obtained by O-benzylation of **16a**[12] was N-alkylated with 1-bromo-2-butanone or bromomethyl cyclopropyl ketone and cyclized by the Tschitschibabin reaction to give **17**. Although **17** has an electron-withdrawing group at the indolizine nucleus, the acylation was possible at the C-3 position in good yield without any catalyst, and several acyl chloride were used to vary the R_3 group. Hydrolysis of **18** required a drastic condition, using KOH in DMSO at 140 °C. The carboxylic acid was thermally decarboxylated to give **19**, which was reduced with $LiAlH_4$ to yield **20**. Alternatively, **16b** was treated with 3-bromo-4-phenyl-2-butanone[13] **21** under Tschitschibabin reaction conditions to give **22**, which was then converted to **20vii**, having a methyl group at the C-2 position, by the same procedure cited above. Sequential treatment of **20** with oxalyl chloride and NH_4OH formed **25**, which was then treated by the same procedure cited for the preparation of **15** to give **28**. The merit of this synthetic pathway from **16** to **28** is that the compounds of each step, except for **20**, are stable to oxidation by air and can be treated easily. Unfortunately, the starting material **16** is not easily prepared by the reported method.[12]

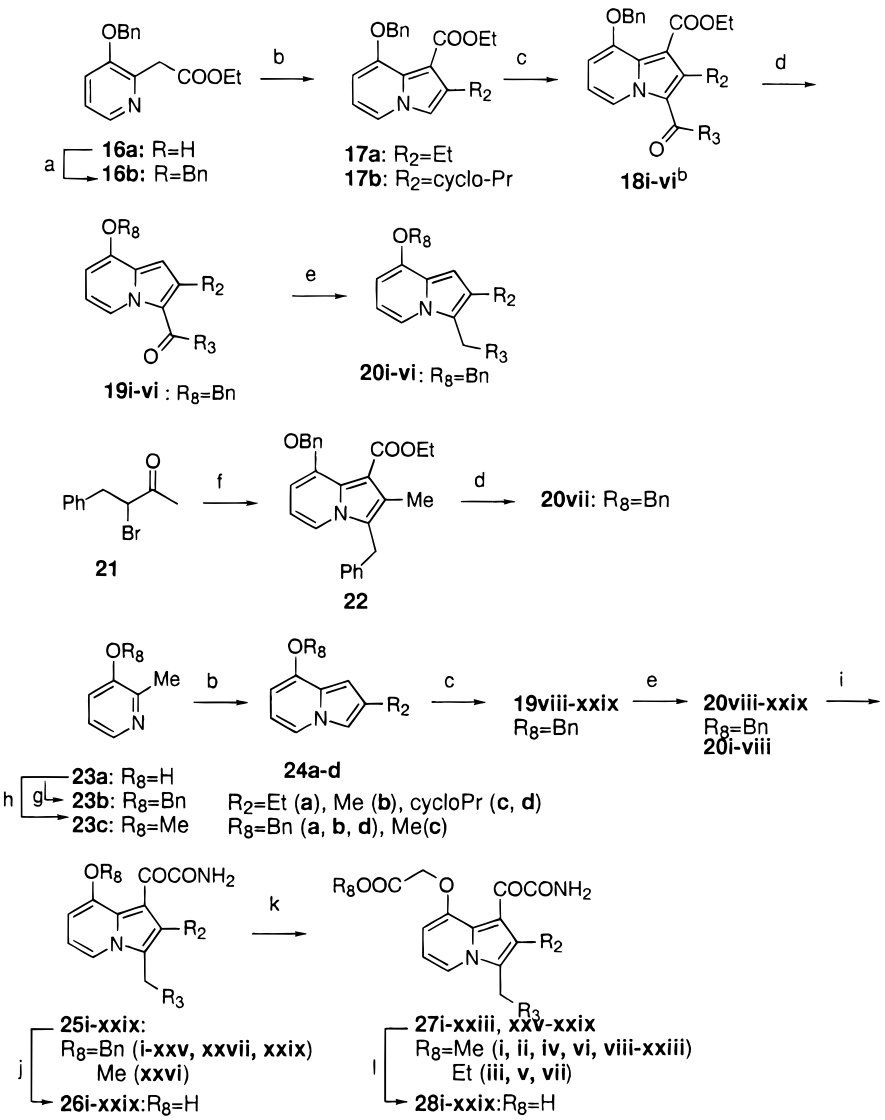
We next tried using 3-hydroxypicoline[14] **23a** as a starting material (Scheme 3). Heating the protected compound **23b** or **23c** with 2-halo ketone compounds gave an N-alkylated pyridinium intermediate which was cyclized to **24**. Various kinds of hydrophobic acyl groups were introduced at the C-3 position of indolizine by this method. Ketone **19** was converted to the desired compounds **28** by the same procedure from **20** or **28**.

In order to shorten the synthetic steps, the processes of protection and deprotection of the hydroxy group were eliminated (Scheme 4). Hydroxypicoline **23a** was O-alkylated with methyl bromoacetate to produce **29**, which was cyclized by the same procedure cited above to give **30**. To also remove the step of reduction of the carbonyl group at the C-3 position, **30** was treated with various benzyl halides, which gave compounds alkylated at the C-3 position, accompanied by 1,3-dialkylated derivatives. The electrophilic substituent of the indolizine nucleus has been established, and the most reactive positions are the C-3 and C-1 positions, in that order,[15] but the difference in reactivities seems to be small. Alternatively, compound **31** was obtained by acylation of **30**, followed by selective reduction of the carbonyl group with $NaBH_4$−$AlCl_3$. Although the method required reduction of the newly produced ketone, the yield and procedure for purification of the product were improved.

Chemical modification at the C-2 position was achieved with a methoxy or a methylthio group (Scheme 5). Treatment of **16b** with excess methyl bromoacetate, followed by cyclization with K_2CO_3, gave a hydroxy compound that was difficult to isolate and was used directly for the next O-methylation to furnish **17c**. Compound **17c** was hydrolyzed and decarboxylated thermally to give **24f**, which was C-alkylated at the C-3 position with *o*-(iodomethyl)biphenyl and treated by a procedure similar to that described above to yield **28xxxviii** with a methoxy group at the C-2 position.

According to the procedure of Kakehi et al.,[16] 2-benzyloxypyridine **23a** was converted to **33**, which was also

Scheme 3[a,b]



[a] Reagents: (a) NaH, BnCl; (b) XCH_2COR_8, $NaHCO_3$; (c) R_3COCl; (d) (1) KOH−DMSO; (2) △; (e) $LiAlH_4$ or $NaBH_4$−$AlCl_3$; (f) **16b**, △; (g) BnBr, KOH, TBAB; (h) MeI, K_2CO_3; (i) (1) $(COCl)_2$, (2) NH_4OH (j) H_2, Pd−C or BBr_3; (k) $BrCH_2COOMe$, K_2CO_3, KI; (l) OH^-. [b] R_2 and R_3 of **i**−**xxix**: see Table 1.

cyclized to give an ca. 10:1 mixture of 8- and 6-benzyloxy derivatives **34a** + **34b**. Treatment of the mixture with KOtBu eliminated ethyl acrylate[16] to form **35**, the isomers of which were separated from each other, and the 6-benzyloxy derivative was then S-alkylated to give **35b**. Hydrolysis of **35b** with KOH in DMSO under reflux for 8 h formed the dicarboxylic acid, which was thermally decarboxylated to give **24g**. Compound **24g** was treated with *o*-phenylbenzyl iodide as above to furnish a C-3 alkylated compound with contamination by a C-1 alkylated compound. Sequential treatment with oxalyl chloride and then NH_4OH as above gave **25xxxix**, which was separated from the C-1 alkylated derivative. Compound **25xxxix** was converted to **28xxxix**, having a methylthio group at the C-2 position by the above-mentioned procedure.

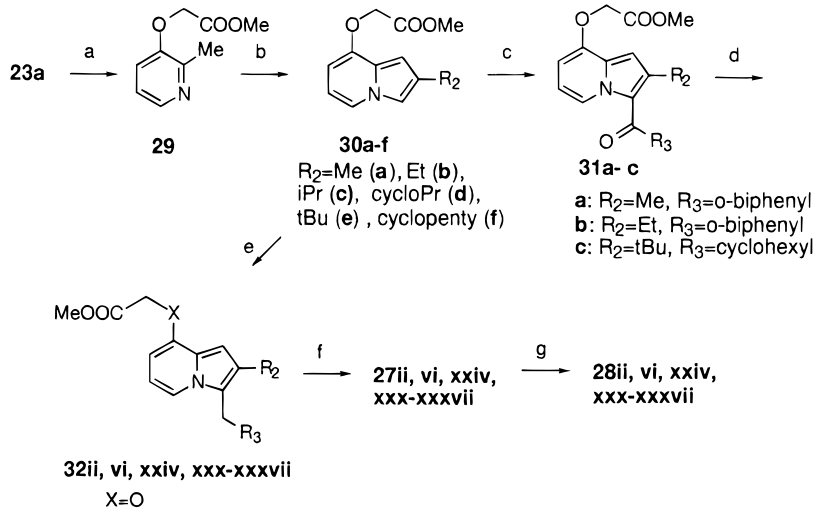
(4) Synthesis of Type IV Compound (Scheme 6). This type of compound was prepared by applying the second method (Scheme 3) for the preparation of compounds of type **III** to 4-methoxypicoline **36** to give **41** via several steps as shown in Scheme 6. O-Alkylation of **41** was carried out with ω-bromoalkyl ester, $Br(CH_2)_n$-COOEt (n = 1, 3, and 4), to give **42a**−**f**. In the case of n = 2, β-propiolactone[17] was used and **43g** was obtained. The oxamoyl group of **42** was selectively reduced with t-$BuNH_2$−BH_3 complex and $AlCl_3$ to the (carbamoylmethyl) group to give **44a**.

(5) Synthesis of Amino Derivatives (Scheme 7). Aminopicoline **45a** was converted to its N-Cbz derivative **45b**, of which the anion was alkylated with methyl bromoacetate to produce **46**. Reaction of **46** with **21** or 3-bromo-4-cyclohexyl-2-butanone in the presence of $NaHCO_3$ furnished **32xl** or **32xli**, which was converted to the desired compound **28** by treatment similar to that described above. The oxamoyl group of **27xli** was selectively reduced as in the case of **42** to give **48a**.

(6) Other Modifications (Scheme 8). Chemical modification at the C-8 position was carried out. Compound **26ii** was O-alkylated with alkyl halide to give basic compounds **49c**−**e** and acidic compounds **49b** and **49g**, following by deprotection. The methylene chain was also changed by addition of β-propiolactone as above. Tetrazole derivative **50b** was also prepared via the cyano derivative **50a** from **26iii**.

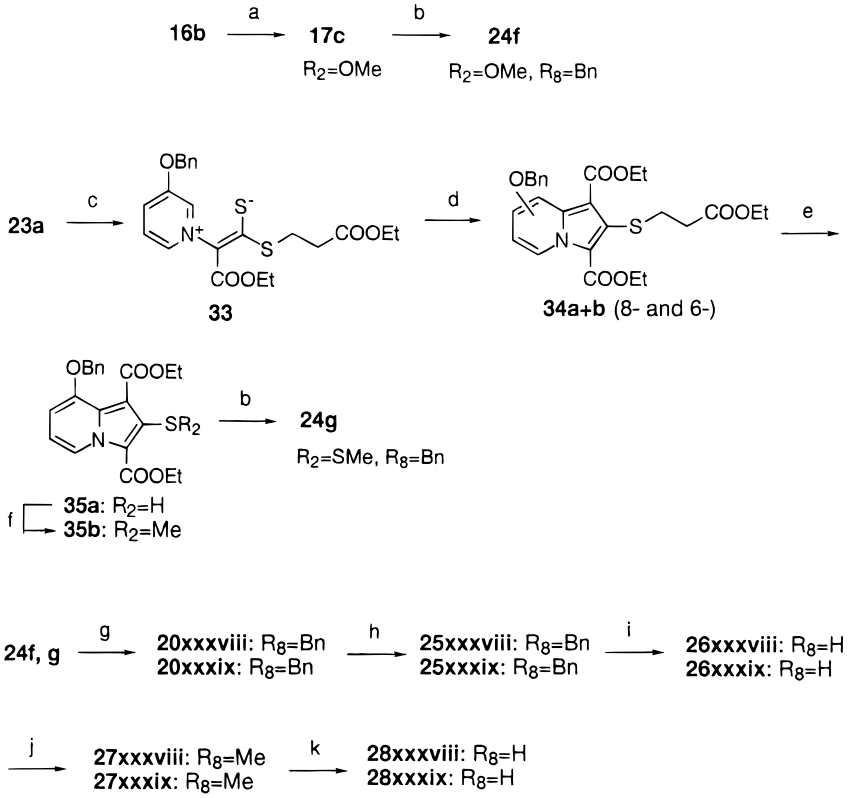
After the reaction with $(COCl)_2$, **20i** was treated with methylamine or dimethylamine instead of NH_4OH to

Scheme 4[a,b]



[a] Reagents: (a) KOH, $BrCH_2COOMe$; (b) (1) XCH_2COR_2, (2) DBU; (c) R_3COCl; (d) $NaBH_4$, $AlCl_3$; (e) R_3CH_2X; (f) (1) $(COCl)_2$, (2) NH_4OH; (g) OH^-. [b] R_2 and R_3 of **ii**, **vi**, **xxiv**, and **xxx**−**xxxvii**: see Table 1.

Scheme 5[a,b]

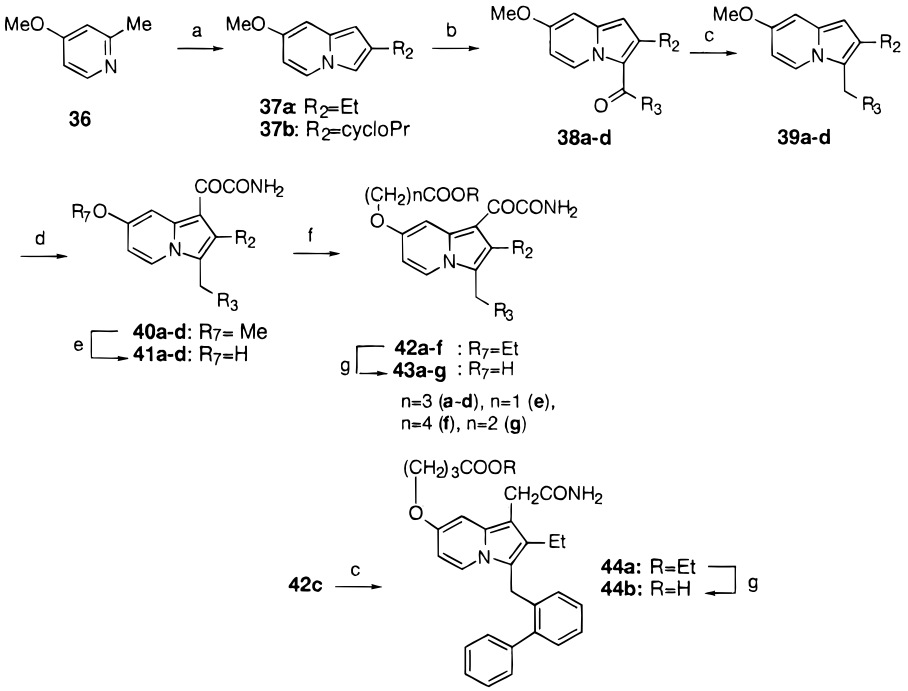


[a] Reagents: (a) (1) $BrCH_2COOMe$, (2) K_2CO_3, (3) Me_2SO_4, K_2CO_3; (b) (1) KOH-DMSO, (2) △; (c) (1) $BrCH_2COOEt$, NaH, (2) CS_2, (3) CH_2=$CHCOOEt$; (d) $BrCH_2COOEt$, DBU; (e) KOtBu; (f) NaH, MeI; (g) *o*-Ph-Bnl; (h) (1) $(COCl)_2$, (2) NH_4OH; (i) H_2, Pd−C; (j) $BrCH_2COOMe$, K_2CO_3, KI; (k) OH^-. [b] R_2 and R_3 of **xxxviii** and **xxxix**: see Table 1.

give mono- or dimethylglyoxylamide, which were then converted to **51a** or **51b** via a synthetic procedure similar to that cited in the Scheme 3.

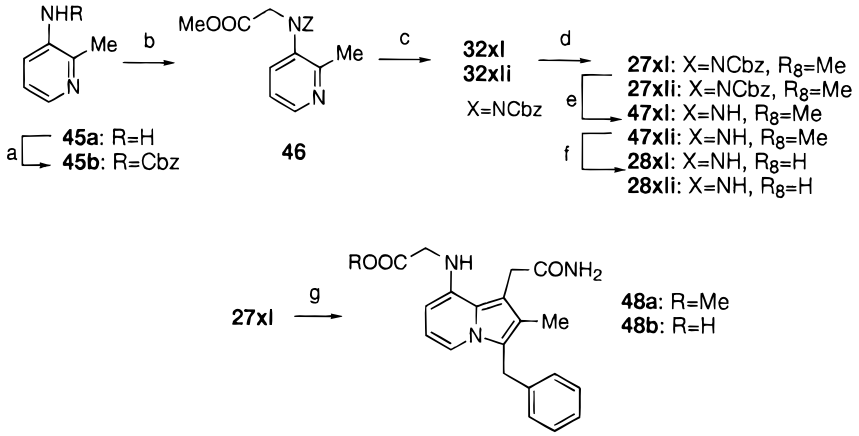
(7) Synthesis of Indene Derivatives (Scheme 9). To obtain **53**, *m*- or *p*-anisaldehyde was treated with propionic or butyric anhydride under the Perkin reaction condition. Compound **53** was reduced by catalytic hydrogenation to give **54**. Acidic cyclization of **54** yielded **57**. Alternatively, the position para to the methoxy group of **54c** was blocked by bromination to give **55**, which was cyclized to **56** by acidic treatment and then debrominated using catalytic hydrogenolysis to give **57c**. Reaction of **57** with triethyl phosphonoacetate produced **58a** and/or **59b**,**c**. Radical bromination of **59b**,**c** gave **60**, which on reduction catalytically yielded **58b** and **58c**. Compound **58** was condensed with benzaldehyde and its derivatives in the presence of MeONa to give **61**, which was converted to the amide **62** via the active ester. After demethylation of **62** with BBr_3, the compound **63** formed was O-alkylated as above to give **64**, which was reduced by catalytic hydrogenation to give **66** and **67**.

Scheme 6[a,b]



[a] Reagents: (a) (1) XCH_2COR_2, (2) DBU; (b) R_3COCl; (c) t-$BuNH_2$−$AlCl_3$; (d) (1) $(COCl)_2$, (2) NH_4OH; (e) BBr_3; (f) $Br(CH_2)_nCOOEt$, NaH or propiolactone; (g) OH^-. [b] R_2 and R_3 of **38**−**43**: see Table 1.

Scheme 7[a,b]



[a] Reagents: (a) N-(benzyloxycarbonyl)succinimide; (b) NaH, $BrCH_2COOMe$; (c) **21** or 3-bromo-4-cyclohexyl-2-butanone, $NaHCO_3$; (d) (1) $(COCl)_2$, (2) NH_4OH; (e) H_2, Pd−C; (f) OH^-; (g) (1) t-$BuNH_2$−BH_3, $AlCl_3$, (2) H_2, Pd−C. [b] R_2 and R_3 of **xi** and **xli**: see Table 1.

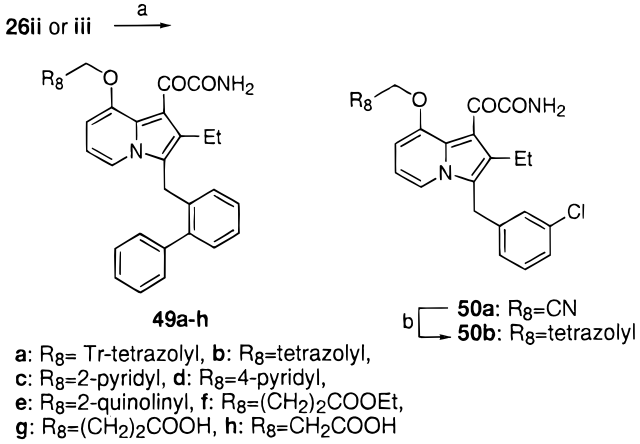
Enzyme Inhibitory Activity and Discussion

The chromogenic screening assay procedure[18] using a thiol substrate analogue was used to identify and evaluate inhibitors of recombinant human sPLA2. IC_{50} values of the prepared compounds are shown in Table 2. We also used a slightly modified phosphatidyl choline/deoxycholate assay that had been developed for the evaluation of patient samples of human sPLA2,[19,20] and IC_{50} values are shown in Table 2. As mentioned above, for the structure−activity relationships study, the indolizine derivatives were grouped into four categories according to their structure. Compound **6b** of type **I** did not exceed the micromolar order of inhibitory activity. Compound **12d**, bearing the hydroxyl group at the C-8 position, also did not show potent activity. But replacement of the substituent by methylene amide, **15b**−**g**, at this position (type **II**) had a favorable effect on the enzyme interaction. Crystals of human type II PLA2 complexed with **15f** were grown and analyzed by X-ray crystallography, which will be submitted for publication in due course. However, as mentioned above, these compounds were not stable to air oxidation.

Replacing the methylene amide by an oxamoyl group (type **III**) made the derivative stable and also increased the potency of PLA2 inhibition. Variation of the residue at the C-2 position did not have a major influence on the inhibitory activity. However, bulky substituents such as t-Bu or cyclopentyl groups revealed an unfavorable influence on the ability to inhibit PLA2. The ethyl group appeared to be best.

Efforts to optimize compounds of type **III** included structural variation of the substituent at the C-3 position. Chemical modification giving benzyl-type substituents increased the potency in the following order, depending on the position in the benzene ring: *p*- < *m*- < *o*-position (**28viii** < **28xxxiv** < **28ii**), although the difference was not statistically important. An electron-withdrawing group, **28iv**, seemed to be better than an

Scheme 8[a]



[a] Reagents: (a) R_8CH_2X, (b) (1) Me_3SnN_3, (2) HCl.

electron-donating group, **28xx**, but compound **28xxi**, having a nitro group at the ortho-position, showed lower potency. The electronic effect of the substituent is not a major factor influencing the inhibitory activity. Other benzyl-type compounds, such as **28v**, **28xvii**, and **28xxvi**, showed highly potent activity, and substituted benzyl groups were potent except when the substituent was very bulky (**28xv**). Elongation of the methylene decreased the activity, as demonstrated by **28xvi**, **28xxxv**, and **28xxxvi**. A 2-fold or greater decrease in potency was observed in compounds with hydrophobic substituents such as alkyl- (**28xiii** and **28xvi**) and cycloalkyl- (**28ix**, **28x** and **28xxii**) groups. Hydrophobic heteroaromatic substituents (**27xviii** and **28xix**) helped retain the activity.

Co-ordination of the substituents at the C-1 and the C-7 or C-8 positions with the calcium ion is necessary to produce the activity as pointed out by the Lilly workers,[6] and chemical modification at the C-1 and the C-8 positions of indolizine compounds of type **III** was achieved. The inhibitory activity disappeared on chemical modification of the ether linkage at the C-8 position to the amino function (**28xl**), probably due to a conformational change caused by hydrogen bonding between the NH group and the carbonyl group at the C-1 position. The activity was improved by reducing the carbonyl group (**28xli**) but still the conformation did not seem to be suitable for co-ordination with the calcium, because of the hydrogen bonding of the amino group with the amide group.

The tetrazole group provided an additional ligand for the calcium, as shown in **49b** and **50b**. Pyridine and quinoline rings still may co-ordinate with the calcium (**49c**, **49d**, and **49e**), while the compound with a phenyl group (**25ii**) did not show activity at all. Methylenic homologation with one and two carbon units at the carboxylic acid function of the C-8 position lowered the activity in that order. Introduction of a methyl or a dimethyl group seemed to disturb co-ordination of the amide group with the calcium (**51a** and **51b**).

We also examined whether the indolizine skeleton could be replaced by an indene ring. Although indene derivatives **65a**−**j** having an *exo*-methylene group generally showed 10 times or more decreased potency, compared with the corresponding indolizine derivatives **15b**−**g**, 1-naphthyl derivative (**65a**) showed an IC_{50} value of 25 nM. Partially reduced compounds **67a** and **67b** showed further lower potency. The introduction of an oxamoyl group to the indene ring was tried to improve the activity but was fruitless. The skeleton seems to need an electron-rich character for sPLA2 inhibition, in addition to the geometric 6−5 fused ring.

Summary

In this report, we have described the preparation of indolizine and indene derivatives that are designed to inhibit human nonpancreatic PLA2. 1-(Carbamoylmethyl)indolizine derivatives were potent inhibitors, but were not stable to air oxidation. Introduction of an oxamoyl group to the C-1 position made the derivative stable and highly potent. By chemical modification at the C-3 position with various hydrophobic substituents and at the C-1 or C-8 position with hydrophilic substituents, some compounds approached the stoichiometric limit of the chromogenic assay.

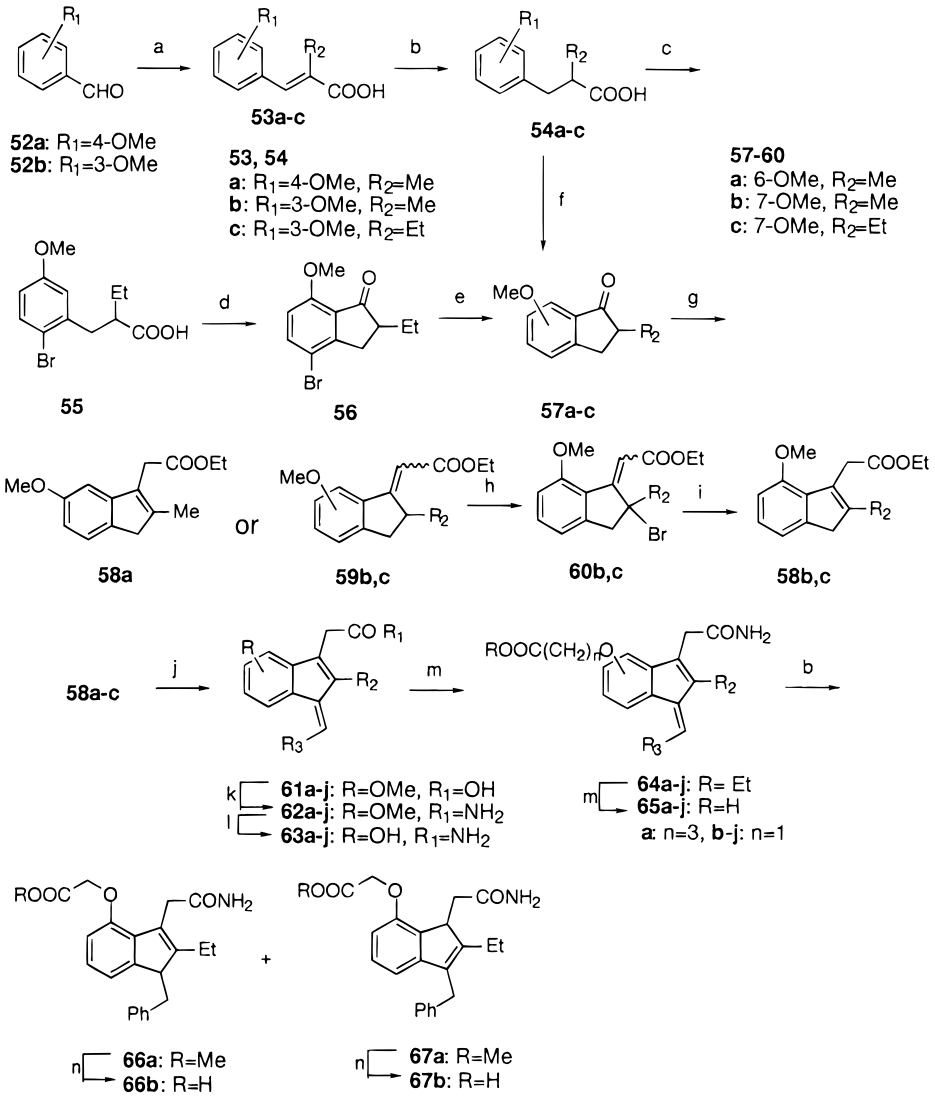
Experimental Section

General Methods. Melting points were not corrected. IR spectra were recorded on a Nicolet 20SXB FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian VXR-200 and VXR-300 FT-NMR spectrometer with tetramethylsilane as internal reference. Mass spectra were measured on a JEOL JMS-SX/S102A or a HITACHI M-90 mass spectrometer. Column chromatography was performed on Merck Kiesel gel 60 with a medium pressure unless otherwise noted. Drying of an organic phase over anhydrous Na_2SO_4 is simply indicated by the word "dried". Solvents were removed by evaporation under reduced pressure unless otherwise noted.

5-Methoxy-2-phenacylpyridine (2). A solution of n-BuLi in hexane (1.6 M, 11.4 mL, 18.2 mmol) was added dropwise to a solution of diisopropylamine (1.81 g, 17.9 mmol) in THF (50 mL) at −60 to −70 °C under N_2. The mixture was stirred for 10 min. A solution of 5-methoxy-2-methylpyridine[7] (2.20 g, 17.9 mmol) in THF (4 mL) was added dropwise. The mixture was stirred for 10 min. A solution of benzonitrile (1.84 g, 17.9 mmol) in THF (8 mL) was added dropwise at −70 °C. The mixture was stirred at −78 °C for 1 h and at room temperature for 2 h and poured to ice-cold aqueous NH_4Cl. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were extracted with dilute HCl. The extracts were washed with ether, basified with 10% aqueous NaOH, and extracted with ether. The extracts were washed with water and dried. After removal of the solvent, the residue was chromatographed by eluting with hexane:AcOEt (3:2) and crystallized from benzene:hexane to give **3**, 2.32 g (57.0% yield). The NMR showed the product to be a mixture of the keto and the enol tautomers: IR ν_{max} (Nujol) 1685, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84−3.88 (3H, m), 4.45 (2H, m), 7.0−7.3 (3H, m), 7.82 (1H, m), 8.07 (2H, m), 8.27 (1H, m). Anal. ($C_{14}H_{13}NO_2$) C, H, N.

1-Benzoyl-2-ethyl-6-methoxyindolizine (3). A mixture of the pyridine derivative **2** (2.146 g, 9.44 mmol), 1-bromo-2-butanone (2.14 g, 14.2 mmol), and $NaHCO_3$ (1.60 g, 19 mmol) in acetone (50 mL) was heated under reflux for 20 h. The insoluble materials were removed off by filtration. The filtrate was concentrated. The residue was recrystallized from benzene:hexane to give **3**: 2.39 g (90.7% yield); mp 138−139 °C; IR ν_{max} (Nujol) 1600, 1592, 1505 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19

Scheme 9[a,b]



[a] Reagents: (a) $(R_2CO)_2O$, R_2COONa; (b) H_2, Pd−C; (c) Br_2; (d) PPA; (e) H_2, Pd−C, AcONa; (f) PPA or TFA; (g) $(EtO)_2POCH_2COOEt$, NaH; (h) NBS, BPO; (i) H_2, PtO_2; (j) RCHO, MeONa; (k) (1) BPO, (2) NH_4OH; (l) BBr_3; (m) NaH, $Br(CH_2)_nCOOEt$; (n) NaOH. [b] R_2 and R_3 of **61**−**65**: see Table 1.

(3H, t, J = 7.5 Hz), 2.72 (2H, q, J = 7.4 Hz), 3.80 (3H, s), 6.69 (1H, dd, J = 2.0, 9.8 Hz), 7.10 (1H, s), 7.26 (1H, d, J = 9.6 Hz), 7.35−7.55 (4H, m), 7.67 (2H, m). Anal. ($C_{14}H_{14}NO_2$) C, H, N.

1-Benzyl-2-ethyl-6-methoxyindolizine (4). The benzoyl derivative **3** (1.37 g, 4.90 mmol) was added in small portions to a slurry of $LiAlH_4$ (1.03 g, 27.1 mmol) in ether (100 mL) with cooling in ice under N_2. The mixture was then heated under reflux for 4.5 h. After cooling, the mixture was poured into ice-cold 5% aqueous NaOH and extracted with ether. The extracts were washed with water and dried. The solvent was removed to give 1.23 g (94.5% yield). The oily residue was used in the next preparation without further purification owing to its unstability: IR ν_{max} (film) 1642, 1550, 1218 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (3H, t, J = 7.6 Hz), 2.57 (2H, q, J = 7.5 Hz), 3.75 (3H, s), 4.06 (2H, s), 6.38 (1H, dd, J = 9.6, 2.2 Hz), 7.0−7.3 (7H, m), 7.39 (1H, d, J = 2.2 Hz).

(1-Benzyl-2-ethyl-6-methoxyindolizin-3-yl)glyoxylamide (5a). A solution of the indolizine compound **4** (1.288 g, 4.85 mmol) in THF (25 mL) was added dropwise to a solution of $(COCl)_2$ (3.18 g, 25 mmol) in THF (5 mL) with cooling in ice. The mixture was stirred at 0 °C for 1 h and added dropwise to 28% NH_4OH (50 mL) with cooling in ice. The mixture was stirred for 1 h at room temperature. Water was added. The mixture was extracted with CH_2Cl_2. The extracts were washed with water and dried. After removal of the solvent, the residue was crystallized from ethyl acetate: benzene to give **5a**: 1.27 g (73.6% yield); mp 159−160 °C; IR ν_{max} (Nujol) 3342, 3166, 1664, 1571 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (3H, t, J = 7.4 Hz), 2.90 (2H, q, J = 7.4 Hz), 3.84 (3H, s), 4.07 (2H, s), 5.83 (1H, br s), 6.55 (1H, br s), 6.96 (1H, dd, J = 9.4, 2.4 Hz), 7.1−7.3 (6H, m), 9.59 (1H, d, J = 2.4 Hz). Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

(1-Benzyl-2-ethyl-6-hydroxyindolizin-3-yl)glyoxylamide (5b). A solution of BBr_3 (976 mg, 3.89 mmol) in CH_2Cl_2 (5 mL) was added to a solution of the methoxy compound **5a** (437 mg, 1.30 mmol) in CH_2Cl_2 (50 mL) at −20 °C. The mixture was stirred at room temperature for 24 h and poured to ice water. A small amount of MeOH was added. The organic phase was separated and washed with water. After removal of the solvent, The residue was crystallized from CH_2Cl_2: mp 219−220 °C (dec); IR ν_{max} (Nujol) 3388, 3261, 3193, 1678, 1530 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD) δ 1.14 (3H, t, J = 7.6 Hz), 2.85 (2H, q, J = 7.8 Hz), 4.06 (2H, s), 7.01 (1H, dd, J = 9.4, 2.4 Hz), 7.05−7.25 (6H, m), 9.64 (1H, d, J = 2.4 Hz). Anal. ($C_{19}H_{18}N_2O_3 \cdot 0.9H_2O$) C, H, N.

(1-Benzyl-6-[(3-carbethoxypropyl)oxy]-2-ethylindolizin-3-yl)glyoxylamide (6a). NaH (60%, 52 mg, 1.32 mmol) was added to a solution of the alcohol **5b** (213 mg, 0.661 mmol) and ethyl 4-bromo-2-butylate (283 mg, 1.45 mmol) in DMF (5 mL) with cooling in ice under N_2. The mixture was stirred at room temperature for 8.5 h, poured to ice water and extracted with ethyl acetate. The extracts were washed with water and dried. After removal of the solvent, the residue was chro-

Table 2. Inhibitory Activity against Human sPLA2 and Arachidonic Acid[a]

	IC_{50} (μM)			IC_{50} (μM)	
compd	chromogenic assay	PC/DOC assay	compd	chromogenic assay	PC/DOC assay
6b	1.1		**28xxxiii**	0.28	
12d	19		**28xxxiv**	0.009	0.0042
15b	0.014	0.014	**28xxxv**	0.038	0.08
15c	0.015	0.052	**28xxxvi**	0.051	
15e	0.013	0.026	**28xxxvii**	0.023	0.2
15f	0.013	0.028	**28xxxviii**	0.015	0.013
15g	0.03	0.135	**28xxxix**	0.016	
28i	0.008	0.005	**28xl**	>50	
27ii	0.017		**28xli**	>50	
28ii	0.006	0.003	**43a**	0.2	
28iii	0.006	0.003	**43b**	4.4	
28iv	0.009	0.003	**43c**	0.14	
28v	0.005	0.024	**43d**	3.4	
28vi	0.009	0.006	**43e**	1.4	
28vii	0.008	0.003	**43f**	1.3	
28viii	0.018	0.013	**43g**	0.24	
28xi	0.021	0.03	**44**	0.08	
28x	0.019	0.019	**48b**	22	
28xi	0.023	0.1	**49b**	0.007	0.007
28xii	0.062		**49c**	0.046	
28xiii	0.017	0.078	**49d**	0.083	
28xiv	0.017	0.0073	**49e**	0.055	
28xv	6.6		**49g**	0.08	0.21
28xvi	0.051		**49h**	0.044	0.13
28xvii	0.006	0.0013	**50b**	0.03	0.045
28xviii	0.011	0.013	**51a**	>50	
28xix	0.01	0.011	**51b**	>50	
28xx	0.021	0.03	**65a**	0.91	
28xxi	0.036	0.12	**65b**	0.42	
28xxii	0.025	0.02	**65c**	0.16	
28xxiii	0.12		**65d**	0.1	0.42
28xxiv	0.008	0.0014	**65e**	0.4	
28xxv	0.046	0.049	**65f**	0.2	
28xxvi	0.011	0.005	**65g**	0.067	
28xxvii	0.01	0.015	**65h**	0.24	
28xxviii	0.029	0.088	**65i**	0.025	0.13
28xxix	0.014	0.022	**65j**	0.17	
28xxx	0.043	0.16	**67a**	15	
28xxxi	0.035		**67b**	12	
28xxxii	0.1				

[a] IC_{50} values are the means of at least two experiments.

matographed by eluting with hexane:EtOAc (1:2) and recrystallized from benzene to give **6a**: 162 mg (56.2% yield); mp 143−144 °C. Anal. ($C_{25}H_{28}N_2O_5$) C, H, N.

(1-Benzyl-6-[(3-carboxypropyl)oxy]-2-ethylindolizin-3-yl)glyoxylamide (6b). A mixture of the ester **6a** (125 mg, 0.286 mmol) in MeOH (1.2 mL) and 10% aqueous LiOH (1.2 mL) was stirred at room temperature for 3 h, acidified with dilute HCl, and extracted with CH_2Cl_2. The extracts were washed with water and dried. After removal of the solvent at reduced pressure, the residue was chromatographed by eluting with $CHCl_3$:MeOH (10:1) and recrystallized from EtOAc to give **6b**: 58.4 mg (49.9% yield); mp 176−178 °C; IR ν_{max} (Nujol) 3391, 3203, 1722, 1663, 1569, 1263 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, J = 7.5 Hz), 2.13 (2H, m), 2.52 (2H, t, J = 6.9 Hz), 2.87 (2H, q, J = 7.8 Hz), 4.06 (2H, t, J = 6.3 Hz), 7.00 (1H, dd, J = 9.3, 2.1 Hz), 7.05−7.3 (6H, m), 9.78 (1H, d, J = 1.5 Hz). Anal. ($C_{23}H_{24}N_2O_5 \cdot 0.5H_2O$) C, H, N.

Ethyl 3-(3-(Benzyloxy)-2-pyridinyl)propanoate (8a). A mixture of (E)-ethyl 3-(3-(benzyloxy)-2-pyridinyl)propenoate[10] (12.2 g, 43.0 mmol), and 10% Pd−C (0.5 g) in EtOAc (250 mL) was stirred in an H_2 atmosphere until no more starting material remained. The catalyst was filtered and the filtrate was concentrated. The residue was chromatographed by eluting with hexane:AcOEt (2:1 and 1:2). The fraction with the larger R_f value (6.0 g (48.8% yield)) was the title compound: ^1H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.2 Hz), 2.80 (2H, t, J = 7.5 Hz), 3.22 (2H, t, J = 8.1 Hz), 4.13 (2H, q, J = 7.2 Hz), 5.10 (2H, s), 7.07 (1H, dd, J = 4.5, 8.4 Hz), 7.13 (1H, dd, J = 1.5, 8.4 Hz), 7.3−7.5 (5H, m), 8.11 (1H, dd, J = 1.5, 4.5 Hz). The fraction with the smaller R_f value (3.95 g, 47.0% yield) was ethyl 3-(3-hydroxy-2-pyridinyl)propanoate (**8b**).[10]

3-(3-Hydroxy-2-pyridinyl)propanamide (9a). A solution of the ester **8b** (7.47 g) in 28% NH_4OH (50 mL) was allowed to stand at room temperature overnight, and the volatile materials were removed by distillation. The residue was crystallized from EtOAc to give **9a**: 6.49 g (94.7% yield); mp 130−134 °C; IR ν_{max} (Nujol) 3292, 3112, 1682, 1632 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD) δ 2.71 (2H, t, J = 6.9 Hz), 3.06 (2H, t, J = 6.6 Hz), 7.09 (1H, dd, J = 4.8, 8.1 Hz), 7.23 (1H, dd, J = 1.5, 7.8 Hz), 8.00 (1H, dd, J = 1.2, 4.5 Hz). Anal. ($C_8H_{10}N_2O_2$) C, H, N.

3-(3-(Benzyloxy)-2-pyridinyl)propanamide (9b). A mixture of the hydroxy compound **9a** (4.85 g, 29.2 mmol), benzyl chloride (4.06 g, 32.1 mmol), and K_2CO_3 (8.07 g, 58.4 mmol) in methyl ethyl ketone (100 mL) was heated under reflux for 9 h. The insoluble materials were removed by filtration. The filtrate was concentrated. The residue was dissolved in CH_2Cl_2. The solution was washed with water and dried. After removal of the solvent, the residue was crystallized from benzene to give **9b**: 5.10 g (68.2% yield); mp 126−127 °C; IR ν_{max} (Nujol) 3412, 3270, 3090, 1665, 1614, 1283 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.75 (2H, t, J = 6.9 Hz), 3.23 (2H, t, J = 7.5 Hz), 5.10 (2H, s), 5.34 (1H, br s), 6.54 (1H, br s), 7.10 (1H, dd, J = 4.2, 8.4 Hz), 7.16 (1H, dd, J = 8.4, 1.5 Hz), 7.3-7.45 (5H, m), 8.10 (1H, dd, J = 1.5, 4.5 Hz). Anal. ($C_{15}H_{16}N_2O_2$) C, H, N.

Ethyl 2-(8-(Benzyloxy)-2-ethylindolizin-1-yl)acetate (10a). A mixture of the ester **8a** (1.0 g, 3.51 mmol), 1-bromo-2-butanone (0.79 g, 5.23 mmol), and $NaHCO_3$ (0.70 g, 8.23 mmol) in methyl ethyl ketone (10 mL) was heated under reflux for 20 h. The solid was filtered off. After removal of the solvent of the filtrate, the residue was chromatographed by eluting with hexane:AcOEt (5:1) to give **10a** (283 mg, 23.9% yield) as an oil: ^1H NMR ($CDCl_3$) δ 1.15 (3H, t, J = 7.2 Hz), 1.25 (3H, t, J = 7.5 Hz), 2.61 (2H, q, J = 7.6 Hz), 3.97 (2H, s), 4.04 (2H, q, J = 7.2 Hz), 5.11 (2H, s), 5.93 (1H, d, J = 7.4 Hz), 6.23 (1H, t, J = 7.0 Hz), 7.08 (1H, s), 7.3−7.5 (6H, m).

2-(8-(Benzyloxy)-2-ethylindolizin-1-yl)acetamide (10b) and 2-(2-Ethyl-8-[(2-oxobutyl)oxy]indolizin-1-yl)acetamide (10c). The residue was chromatographed by eluting with hexane:EtOAc (1:2) and with EtOAc. The first fraction was crystallized from benzene:hexane to give **10b**: 2.32 g (48.2% yield); mp 117−119 °C; IR ν_{max} (Nujol) 3384, 3188, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.5 Hz), 2.65 (2H, q, J = 7.4 Hz), 3.87 (2H, s), 5.15 (2H, s), 5.21 (1H, br s), 5.63 (1H, br s), 6.01 (1H, d, J = 7.4 Hz), 6.29 (1H, t, J = 7.1 Hz), 7.11 (1H, s), 7.3−7.5 (6H, m). Anal. ($C_{19}H_{20}N_2O_2$) C, H, N.

The second fraction was crystallized from AcOEt:hexane to give **10c**: 0.208 g (4.6% yield); mp 156−157 °C; IR ν_{max} (Nujol) 3390, 3167, 1717, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.6 Hz), 2.63 (2H, q, J = 7.2 Hz), 2.72 (2H, q, J = 7.6 Hz), 3.92 (2H, s), 4.69 (2H, s), 5.26 (1H, br s), 5.80 (1H, d, J = 7.2 Hz), 6.26 (1H, t, J = 7.1 Hz), 6.28 (1H, br s), 7.13 (1H, s), 7.51 (1H, d, J = 6.8 Hz). Anal ($C_{16}H_{20}N_2O_3 \cdot 0.1$AcOEt) C, H, N.

2-(8-(Benzyloxy)-2-cyclopropylindolizin-1-yl)acetamide (10d): 30.8% yield; mp 128−131 °C; IR ν_{max} (Nujol) 3386, 3197, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.54 (1H, dd, J = 4.2, 1.8 Hz), 0.55 (1H, dd, J = 3.9, 2.1 Hz), 0.90 (1H, dd, J = 1.5, 4.2 Hz), 0.93 (1H, dd, J = 3.2, 2.1 Hz), 4.00 (2H, s), 5.15 (2H, s), 5.22 (1H, br s), 5.65 (1H, br s), 6.00 (1H, d, J = 7.5 Hz), 6.27 (1H, t, J = 6.9 Hz), 7.3−7.5 (6H, m). Anal. ($C_{19}H_{18}N_2O_2 \cdot 0.2C_6H_6 \cdot 0.1H_2O$) C, H, N.

3-(Substituted benzoyl)indolizine (11). General procedure: the indolizine derivative **10** (1 equiv) and substituted benzoyl chloride (1.5 equiv) in benzene were heated under reflux for 4 h and washed with aqueous $NaHCO_3$ and dried. After removal of the solvent, the residue was purified by recrystallization or column chromatography.

Ethyl 2-(8-(Benzyloxy)-2-ethyl-3-(*o*-phenylbenzoyl)indolizin-1-yl)acetate (11a). Column chromatography (hexane:AcOEt (5:1)) yielded 73.2% of an amorphous solid: IR ν_{max} (Nujol) 1736, 1589, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (3H, t, J = 7.4 Hz), 1.08 (3H, t, J = 7.2 Hz), 2.14 (2H, br s), 3.78 (2H, s), 3.94 (2H, q, J = 7.0 Hz), 5.10 (2H, s), 6.40 (1H, d, J = 7.2 Hz), 6.59 (1H, t, J = 7.3 Hz), 7.1−7.6 (14H, m), 9.32 (1H, d, J = 6.6 Hz). Anal. ($C_{34}H_{31}NO_4$) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-(*o*-phenylbenzoyl)indolizin-1-yl)acetamide (11b). Column chromatography (hexane:AcOEt (1:2)) yielded 71.3% of an amorphous solid: ^{1}H NMR ($CDCl_3$) δ 0.78 (3H, t, J = 7.5 Hz), 2.05 (2H, br s), 3.65 (2H, br s), 4.82 (1H, br s), 5.06 (1H, br s), 5.14 (2H, s), 6.42 (1H, d, J = 7.5 Hz), 6.63 (1H, t, J = 7.5 Hz), 6.95 (3H, m), 7.3−7.65 (11H, m), 9.14 (1H, d, J = 6.9 Hz).

2-(8-(Benzyloxy)-3-(*m*-chlorobenzoyl)-2-ethylindolizin-1-yl)acetamide (11c): mp 239−240 °C (dec) (benzene); 96.2% yield; IR ν_{max} (Nujol) 3474, 3166, 1680, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD) δ 0.90 (3H, t, J = 7.6 Hz), 2.32 (2H, q, J = 7.5 Hz), 3.84 (2H, s), 5.21 (2H, s), 6.54 (1H, d, J = 7.8 Hz), 6.70 (1H, t, J = 7.2 Hz), 7.35−7.6 (8H, m), 9.15 (1H, d, J = 7.0 Hz).

2-(3-(*m*-Chlorobenzoyl)-2-ethyl-8-[(2-oxobutyl)oxy]indolizin-1-yl)acetamide (11d): mp 191−192 °C (AcOEt:benzene); 68.4% yield; IR ν_{max} (KBr) 1725, 1668, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, J = 7.4 Hz), 1.18 (3H, t, J = 7.2 Hz), 2.44 (2H, q, J = 7.3 Hz), 2.61 (2H, q, J = 7.4 Hz), 3.94 (2H, s), 4.81 (2H, s), 5.25 (1H, br s), 6.30 (1H, d, J = 7.4 Hz), 6.49 (1H, br s), 6.65 (1H, t, J = 7.3 Hz), 7.35−7.6 (3H, m), 7.64 (1H, m), 9.16 (1H, d, J = 6.6 Hz). Anal. ($C_{22}H_{23}ClN_2O_4 \cdot 0.1C_6H_6$) C, H, Cl, N.

2-(8-(Benzyloxy)-2-cyclopropyl-3-(*o*-phenylbenzoyl)indolizin-1-yl)acetamide (11e). Column chromatography (hexane:AcOEt (1:2)) yielded 56.6% of an amorphous solid.

3-(Substituted benzyl)indolizine (12). General procedure: BH_3−t-$BuNH_2$ complex (6 equiv) was added in small portions to a mixture of pulverized $AlCl_3$ (3 equiv) in CH_2Cl_2 with cooling in ice. After stirring for 10 min, the mixture became clear. A solution of the ketone **11** (1 equiv) in CH_2Cl_2 was added dropwise to the solution. The reddish orange solution was stirred for 5 h. Dilute HCl was added dropwise. The organic phase was separated, washed with aqueous $NaHCO_3$ and water successively, and dried. After removal of the solvent, the residue was purified by chromatography or recrystallization.

2-(8-(Benzyloxy)-2-ethyl-3-(*o*-phenylbenzoyl)indolizin-3-yl)ethanol (12a). Column chromatography (hexane:AcOEt (1:1)) gave viscous oil in 45.1% yield: ^{1}H NMR ($CDCl_3$) δ 1.09 (3H, t, J = 7.6 Hz), 2.61 (2H, q, J = 7.5 Hz), 3.16 (2H, t, J = 6.9 Hz), 3.73 (2H, q, J = 6.3 Hz), 4.10 (2H, s), 5.11 (2H, s), 5.94 (1H, d, J = 7.5 Hz), 6.16 (1H, t, J = 7.2 Hz), 6.66 (1H, d, J = 7.8 Hz), 6.91 (1H, d, J = 7.2 Hz), 7.1−7.6 (13H, m).

2-(8-(Benzyloxy)-2-ethyl-3-(*o*-phenylbenzyl)indolizin-1-yl)acetamide (12b): mp 134−136 °C (benzene:hexane); 59.7% yield; IR ν_{max} (Nujol) 3451, 3171, 1677, 1526, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, t J = 7.5 Hz), 2.63 (2H, q, J = 7.8 Hz), 3.92 (2H, s), 4.11 (2H, s), 5.13 (2H, s), 5.20 (1H, br s), 5.65 (1H, br s), 5.99 (1H, d, J = 7.5 Hz), 6.19 (1H, t, J = 7.1 Hz), 6.67 (1H, d, J = 7.5 Hz), 6.92 (1H, d, J = 7.2 Hz), 7.13 (1H, dt, J = 1.8, 7.2 Hz), 7.2−7.5 (12H, m). Anal. ($C_{32}H_{30}N_2O_2$) C, H, N.

2-(8-(Benzyloxy)-3-(*m*-chlorobenzyl)-2-ethylindolizin-1-yl)acetamide (12c): mp 167−168 °C (benzene:hexane); 69.7% yield; IR ν_{max} (Nujol) 3389, 3191, 1650, 1527 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, t J = 7.6 Hz), 2.70 (2H, q, J = 7.6 Hz), 3.94 (2H, s), 4.20 (2H, s) 5.16 (2H, s), 5.19 (1H, br s), 5.69 (1H, br s), 6.05 (1H, d, J = 7.2 Hz), 6.27 (1H, t, J = 7.1 Hz), 6.88 (1H, t, J = 4.4 Hz), 7.05 (1H, s), 7.1−7.25 (3H, m), 7.3−7.5 (5H, m). Anal ($C_{26}H_{25}ClN_2O_2$) C, H, Cl, N.

2-(3-(*m*-Chlorobenzyl)-2-ethyl-8-(2-hydroxybutyloxy)-indolizin-1-yl)acetamide (12d): mp 131 °C (benzene:hexane); 73.0% yield; IR ν_{max} (Nujol) 3378, 3185, 1656, 1527 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, t J = 7.5 Hz), 1.16 (3H, t, J = 7.5 Hz), 1.64 (2H, m), 2.70 (2H, q, J = 7.8 Hz), 3.8−4.05 (5H, m), 4.20 (2H, s), 5.55 (1H, br s), 5.68 (1H, br s), 5.93 (1H, d, J = 7.2 Hz), 6.30 (1H, t, J = 7.2 Hz), 6.88 (1H, m), 7.04 (1H, s), 7.1−7.2 (3H, m). Anal. ($C_{23}H_{27}ClN_2O_3$) C, H, Cl, N.

2-(8-(Benzyloxy)-2-cyclopropyl-3-(*o*-phenylbenzyl)indolizin-1-yl)acetamide (12e): mp 208−210 °C (benzene); 37.9% yield. Anal. ($C_{33}H_{30}N_2O_2$) C, H, N.

2-(3-Benzyl-8-(benzyloxy)-2-ethylindolizin-1-yl)acetamide (12f): mp 174−176 °C (ether:hexane); 77.3% yield. Anal. ($C_{26}H_{26}N_2O_2$) C, H, N.

2-(3-Naphthyl-8-(benzyloxy)-2-ethylindolizin-1-yl)-acetamide (12g): mp 166−169 °C (dec) (ether:hexane); 43.5% yield. Anal. ($C_{30}H_{28}N_2O_2$) C, H, N.

8-Hydroxyindolizine Compounds (13). General procedure: A mixture of the 8-(benzyloxy)indolizine derivative **12** and 10% Pd−C in EtOAc was stirred in hydrogen for 9h to 3 d.

2-(2-Ethyl-8-hydroxy-3-(*o*-phenylbenzyl)indolizin-1-yl)acetamide (13b): amorphous solid; 59.6% yield; ^{1}H NMR ($CDCl_3$:CD_3OD) δ 1.10 (3H, t, J = 7.5 Hz), 2.63 (2H, q, J = 7.5 Hz), 3.89 (2H, s), 4.10 (2H, s), 5.84 (1H, d, J = 7.2 Hz), 6.18 (1H, t, J = 7.1 Hz), 6.67 (1H, d, J = 7.6 Hz), 6.88 (1H, d, J = 6.8 Hz), 7.1−7.55 (8H, m).

2-(3-(*m*-Chlorobenzyl)-2-ethyl-8-hydroxyindolizin-1-yl)acetamide (13c): amorphous solid; 58.3% yield.

2-(2-Cyclopropyl-8-hydroxy-3-(*o*-phenylbenzyl)indolizin-1-yl)acetamide (13e): amorphous solid; 55.8% yield.

2-(3-Benzyl-8-hydroxy-2-ethylindolizin-1-yl)acetamide (13f): mp 138−141 °C (ether:hexane); 45% yield. Anal. ($C_{19}H_{20}N_2O_2$) C, H, N.

2-(3-Naphthyl-8-hydroxy-2-ethylindolizin-1-yl)acetamide (13g): mp 138−142 °C (powder) (ether-hexane:AcOEt). 32% yield.

(Indolizin-8-yloxy)acetate Compounds (14 and 15). General procedure: 60% NaH (1.5 equiv) was added in small portions to a mixture of the 8-hydroxyindolizine compound **13** (1.0 equiv) and benzyl, ethyl, or methyl bromoacetate (3.0 equiv) in DMF. The mixture was stirred at room temperature for 4−10 h. Dilute HCl was added. The mixture was extracted with EtOAc. The extracts were washed with water and dried. After removal of the solvent, the residue was purified by chromatography or recrystallization.

2-(8-[[(Benzyloxycarbonyl)methyl]oxy]-2-ethyl-3-(*o*-phenylbenzyl)indolizin-1-yl)acetamide (14b) and carboxylic acid 15b: amorphous solid; 45.4% yield.

15b: mp 164−165 °C (AcOEt); 61.1% yield; IR ν_{max} (Nujol) 3410, 3228, 1732, 1666, 1603, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD) δ 1.12 (3H, t, J = 7.5 Hz), 2.69 (2H, q, J = 7.5 Hz), 3.95 (2H, s), 4.11 (2H, s), 4.67 (2H, s), 5.86 (1H, d, J = 7.2 Hz), 6.18 (2H, t, J = 7.2 Hz) 6.67 (1H, d, J = 7.5 Hz), 6.93 (1H, d, J = 6.9 Hz), 7.12 (1H, m), 7.2−7.3 (2H, m), 7.3−7.5 (5H, m). Anal. ($C_{27}H_{26}N_2O_4 \cdot 1.4H_2O$) C, H, N.

2-(8-[[(Benzyloxycarbonyl)methyl]oxy]-3-(*m*-chlorobenzyl)-2-ethylindolizin-1-yl)acetamide (14c) and carboxylic acid 15c: mp 157−158 °C (benzene); 38.8% yield.

15c: mp 216−219 °C (dec) (AcOEt); 57.5% yield; IR ν_{max} (KBr) 3416, 3311, 1739, 1707, 1643, 1620, 1572, 1552, 1529, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD) δ 1.16 (3H, t, J = 7.5 Hz), 2.76 (2H, q, J = 7.5 Hz), 3.98 (2H, s), 4.21 (2H, s), 4.70 (2H, s), 5.92 (1H, d, J = 7.5 Hz), 6.27 (1H, t, J = 6.9 Hz), 6.89 (1H, t, J = 4.2 Hz), 7.04 (1H, s), 7.17 (3H, m). Anal. ($C_{21}H_{21}ClN_2O_4 \cdot 0.1H_2O$) C, H, Cl, N.

2-(8-[(Carbomethoxymethyl)oxy]-2-cyclopropyl-3-(*o*-phenylbenzyl)indolizin-1-yl)acetamide (14e) and carboxylic acid 15e: amorphous solid; 43.8% yield.

15e: 65.5% yield; ^{1}H NMR ($CDCl_3$) δ 0.51 (2H, m), 0.89 (2H, m), 1.76 (1H, m), 4.06 (2H, s), 4.22 (2H, s), 4.63 (2H, s), 5.82 (1H, d, J = 7.5 Hz), 6.16 (1H, t, J = 7.2 Hz), 6.56 (1H, d, J = 7.5 Hz), 6.88 (1H, d, J = 7.2 Hz), 7.11 (1H, dt, J = 7.5, 1.5 Hz), 7.26 (2H, m), 7.3−7.5 (5H, m).

Methyl ((3-benzyl-1-(carbamoylmethyl)-2-ethylindolizin-8-yl)oxy)acetate (14f) and carboxylic acid 15f: mp 159−163 °C (ether:hexane); 42.2% yield. Anal. ($C_{22}H_{24}N_2O_4 \cdot 0.2H_2O$) C, H, N.

15f: mp 213−218 °C (dec) (ether:hexane); 79% yield; IR ν_{max} (Nujol) 3418, 1735, 1718, 1638, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD 7:1) δ 1.16 (3H, t, J = 7.7 Hz), 2.77 (2H, q, J = 7.7 Hz), 3.99 (2H, s), 4.24 (2H, s), 4.69 (2H, s), 5.89 (1H, d, J = 7.0 Hz), 6.23 (1H, t, J = 7.0 Hz), 7.01−7.25 (6H, m). Anal. ($C_{21}H_{22}N_2O_4 \cdot 0.2H_2O$) C, H, N.

Methyl ((3-naphthyl-1-(carbamoylmethyl)-2-ethylindolizin-8-yl)oxy)acetate (14g) and carboxylic acid 15g: amorphous solid; 38% yield; IR ν_{max} ($CHCl_3$) 3498, 3384, 1754, 1671, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, t, J = 7.4 Hz), 2.77 (2H, q, J = 7.4 Hz), 3.85 (3H, s), 4.04 (2H, s), 4.64 (2H, s), 4.75 (2H, s), 5.37 (1H, br s), 5.84 (1H, d, J = 7.2 Hz), 6.18

(1H, t, J = 7.2 Hz), 6.54 (1H + 1H, br s + d, J = 7.2 Hz), 7.06 (1H, d, J = 6.9 Hz), 7.19−7.27 (1H, m), 7.55−7.63 (2H, m), 7.71 (1H, d, J = 7.8 Hz), 7.91 (1H, d, J = 8.1 Hz), 8.24 (1H, d, J = 8.1 Hz).

15g: mp 129−133 °C (hexane:AcOEt); 65% yield; IR ν_{max} (Nujol) 3198, 1729, 1672, 1599, 1527 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD 7:1) δ 1.12 (3H, t, J = 7.6 Hz), 2.76 (2H, q, J = 7.6 Hz), 4.03 (2H, s), 4.65 (2H, s), 4.73 (2H, s), 5.92 (1H, d, J = 7.6 Hz), 6.21 (1H, t, J = 7.0 Hz), 6.54 (1H, d, J = 6.8 Hz), 7.08 (1H, d, J = 7.6 Hz), 7.23 (1H, t, J = 7.0 Hz), 7.56−7.65 (2H, m), 7.73 (1H, d, J = 7.6 Hz), 7.92 (1H, d, J = 7.4 Hz), 8.25 (1H, d, J = 9.0 Hz).

Ethyl 3-Hydroxy-2-pyridineacetate (16b). NaH (60%, 2.69 g, 66.2 mmol) was added in small portions to a solution of ethyl 3-hydroxy-2-pyridineacetate (**16a**) (12.0 g, 66.2 mmol)[12] in DMF (220 mL) at 0 °C. The mixture was stirred at 0 °C for 50 min. Benzyl chloride (8.4 mL, 72.8 mmol) was added dropwise to the mixture, which was stirred overnight. EtOAc was added. The mixture was washed with 5% aqueous $NaHCO_3$ and water and dried. After removal of the solvent, the residue was chromatographed by eluting with AcOEt:toluene (1:19 to 1:1) to give **16b** (16.17 g, 90.0% yield) as an oil: IR ν_{max} (film) 1736, 1446, 1278 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, J = 7.2 Hz), 3.93 (2H, s), 4.14 (2H, q, J = 7.2 Hz), 5.10 (2H, s), 7.13−7.22 (2H, m), 7.32−7.43 (5H, m), 8.16 (1H, dd, J = 4.0, 3.0 Hz). Anal. ($C_{16}H_{17}NO_3$) C, H, N.

Ethyl 8-(Benzyloxy)-2-ethylindolizine-1-carboxylate (17a). A mixture of pyridine derivative **16b** (15.15 g, 55.8 mmol), $NaHCO_3$ (23.45 g, 279 mmol), and 1-bromo-2-butanone (11.4 mL, 113 mmol) in methyl ethyl ketone (250 mL) was heated under reflux for 24 h, washed with water, and dried. After removal of the solvent, The residue was chromatographed by eluting with AcOEt:hexane (1:19 to 1:9) to give **17a** (16.66 g, 92.0% yield) as an oil. Anal. ($C_{20}H_{21}NO_3$·$0.1H_2O$) C, H, N.

Ethyl 8-(benzyloxy)-2-cyclopropylindolizine-1-carboxylate (17b): oil; 78% yield; IR ν_{max} (film) 1693, 1525, 1304, 1227, 1094, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.55−0.62 (2H, m), 0.89−0.94 (2H, m), 1.16 (3H, t, J = 7.2 Hz), 2.14−2.26 (1H, m), 4.14 (2H, q, J = 7.2 Hz), 5.16 (2H, s), 6.21 (1H, d, J = 7.5 Hz), 6.43 (1H, t, J = 7.2 Hz), 6.87 (1H, s), 7.28−7.42 (3H, m), 7.45−7.52 (3H, m). Anal. ($C_{21}H_{21}NO_3$·$0.1H_2O$) C, H, N.

Ethyl 8-(Benzyloxy)-2-ethyl-3-(substituted benzoyl)-indolizine-1-carboxylate (18). General procedure: A mixture of the indolizine **17** (1 equiv), substituted benzoyl chloride (2.0 equiv), and Et_3N (5.0 equiv) was heated at 90 °C (bath temperature) for 2−8h. EtOAc was added. The mixture was washed with dilute HCl and water and dried. After removal of the solvent, the residue was chromatographed by eluting with AcOEt:hexane (1:2) and recrystallized.

Ethyl 3-benzoyl-8-(benzyloxy)-2-ethylindolizine-1-carboxylate (18i): mp 124−125 °C (AcOEt:hexane); 79% yield; IR ν_{max} (KBr) 2969, 1593, 1571, 1552, 1326, 1275, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 5.0 Hz), 1.12 (3H, t, J = 4.8 Hz), 2.43 (2H, q, J = 5.0 Hz), 4.03 (2H, q, J = 4.8 Hz), 5.18 (2H, s), 6.57 (1H, s, J = 5.0 Hz), 6.72 (1H, dd, J = 5.0 Hz), 7.3−7.6 (8H, m), 7.55−7.7 (2H, m), 8.99 (1H, d, J = 4.8 Hz); EIMS m/z 427 [M$^+$]. Anal. ($C_{27}H_{25}NO_4$·$0.1H_2O$) C, H, N.

Ethyl 8-(benzyloxy)-2-ethyl-3-(*o*-phenylbenzoyl)indolizine-1-carboxylate (18ii): mp 110−112 °C (ether:hexane); 46.0% yield. Anal. ($C_{33}H_{29}NO_4$) C, H, N.

Ethyl 8-(benzyloxy)-3-(*m*-chlorobenzoyl)-2-ethylindolizine-1-carboxylate (18iii): mp 115.0−116.5 °C (ether:hexane); 92% yield. Anal. ($C_{27}H_{24}NO_4Cl$) C, H, N, Cl.

Ethyl 8-(benzyloxy)-2-ethyl-3-(*m*-(trifluoromethyl)-benzoyl)indolizine-1-carboxylate (18iv): mp 129.0−129.5 °C (ether:hexane); 82% yield. Anal. ($C_{28}H_{24}NO_4F_3$) C, H, N, F.

Ethyl 8-(benzyloxy)-2-ethyl-3-(1-naphthoyl)indolizine-1-carboxylate (18v): mp 169−170 °C (benzene:hexane); 59.3% yield. Anal. ($C_{31}H_{27}NO_4$) C, H, N.

Ethyl 8-(benzyloxy)-2-cyclopropyl-3-(*o*-phenylbenzoyl)-indolizine-1-carboxylate (18vi): mp 143−145 °C (AcOEt:hexane); 52% yield. Anal. ($C_{34}H_{29}NO_4$) C, H, N.

8-(Benzyloxy)-2-ethyl-3-(substituted benzoyl)indolizine-1-carboxylic Acid and 8-(Benzyloxy)-2-ethyl-3-(substituted benzoyl)indolizine (19). General procedure: To a solution of the ester **18** (1.0 mmol) in DMSO (10 mL) was added 50% aqueous KOH (3 mL). The mixture was heated at 140 °C for 2−24 h. After cooling, the mixture was acidified with dilute HCl and extracted with EtOAc. The extracts were washed with water and dried. After removal of the solvent, the residue was purified by recrystallization to give the carboxylic acid.

The acid in toluene was heated under reflux for 1 h and the solvent was removed by distillation. The residue was purified by recrystallization.

3-Benzoyl-8-(benzyloxy)-2-ethylindolizine (19i): mp 92−93 °C (AcOEt:hexane); IR ν_{max} (KBr) 2965, 1593, 1571, 1552, 1326, 1275, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, t, J = 7.4 Hz), 2.42 (2H, q, J = 7.4 Hz), 5.21 (2H, s), 6.47 (1H, d, J = 7.4 Hz), 6.62−6.71 (2H, m), 7.25−7.52 (8H, m), 7.61−7.65 (2H, m), 9.23 (1H, d, J = 7.2 Hz); EIMS m/z 355 [M$^+$]. Anal. ($C_{24}H_{21}NO_2$·$0.1H_2O$) C, H, N.

8-(Benzyloxy)-2-ethyl-3-(*o*-phenylbenzoyl)indolizine (19ii): quantitative yield. Anal. ($C_{30}H_{25}NO_2$·$0.1H_2O$) C, H, N.

8-(Benzyloxy)-3-(*m*-chlorobenzoyl)-2-ethylindolizine (19iii). mp 95.5−96.5 °C (ether:hexane); 87% yield. Anal. ($C_{24}H_{20}NO_2Cl$) C, H, N, Cl.

8-(Benzyloxy)-2-ethyl-3-(*m*-(trifluoromethyl)benzoyl)-indolizine (19iv): mp 97−98 °C (ether:hexane); 84% yield. Anal. ($C_{25}H_{20}NO_2F_3$) C, H, N, F.

8-(Benzyloxy)-2-ethyl-3-(1-naphthoyl)indolizine (19v): amorphous solid; 66.1% yield.

8-(Benzyloxy)-2-cyclopropyl-3-(*o*-phenylbenzoyl)indolizine (19vi): amorphous solid; 82% yield. Anal. ($C_{31}H_{25}NO_2$ $0.1H_2O$) C, H, N.

8-(Benzyloxy)-3-(substituted methyl)-2-ethylindolizine (20). General procedure: (1) these compound were prepared from **19**, according to the procedure described for the preparation of **4** from **3**.

(2) A mixture of **19**, $NaBH_4$ (5 molar equiv), and pulverized $AlCl_3$ (3 molar equiv) in THF was heated under reflux for 45 min. Ice water was added. The mixture was extracted with EtOAc. The extracts were washed with water and dried. After removal of the solvent, the residue was purified by recrystallization or column chromatography.

3-Benzyl-8-(benzyloxy)-2-ethylindolizine (20i): ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, t, J = 7.4 Hz), 2.71 (2H, q, J = 7.4 Hz), 4.22 (2H, s), 5.16 (2H, s), 5.99 (1H, d, J = 7.4 Hz), 6.24 (1H, dd, J = 7.4, 7.4 Hz), 6.61 (1H, s), 7.02−7.51 (11H, m).

8-(Benzyloxy)-2-ethyl-3-(*o*-phenylbenzyl)indolizine (20ii): quantitative yield; IR ν_{max} ($CHCl_3$) 1525, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.5 Hz), 2.64 (2H, q, J = 7.5 Hz), 4.12 (2H, s), 5.15 (2H, s), 5.97 (1H, d, J = 7.2 Hz), 6.20 (1H, t, J = 7.1 Hz), 6.57 (1H, s), 6.69 (1H, d, J = 7.4 Hz), 6.94 (1H, d, J = 6.8 Hz), 7.06−7.55 (13H, m).

8-(Benzyloxy)-3-(*m*-chlorobenzyl)-2-ethylindolizine (20iii): quantitative yield; IR ν_{max} ($CHCl_3$) 1551, 1258 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, t, J = 7.5 Hz), 2.70 (2H, q, J = 7.5 Hz), 4.20 (2H, s), 5.18 (2H, s), 6.03 (1H, d, J = 7.5 Hz), 6.28 (1H, t, J = 7.1 Hz), 6.61 (1H, s), 6.88−6.93 (1H, m), 7.06 (1H, br s), 7.19−7.23 (3H, m), 7.29−7.53 (5H, m).

8-(Benzyloxy)-2-ethyl-3-(*m*-(trifluoromethyl)benzyl)-indolizine (20iv): mp 73−75 °C (hexane); quantitative yield; IR ν_{max} (Nujol) 1332, 1163, 1114 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, t, J = 7.5 Hz), 2.71 (2H, q, J = 7.5 Hz), 4.28 (2H, s), 5.18 (2H, s), 6.03 (1H, d, J = 7.5 Hz), 6.29 (1H, t, J = 7.2 Hz), 6.62 (1H, s), 7.09−7.18 (2H, m), 7.30−7.54 (8H, m).

8-(Benzyloxy)-2-ethyl-3-(1-naphthylmethyl)indolizine-1-carboxylate (20v): mp 119−120 °C (hexane); 89.0% yield; IR ν_{max} (Nujol) 1530, 1263, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, t, J = 7.5 Hz), 2.69 (2H, q, J = 7.2 Hz), 4.65 (2H, s), 5.20 (2H, s), 6.03 (1H, d, J = 7.2 Hz), 6.23 (1H, t, J = 6.9 Hz), 6.59 (1H, d, J = 6.9 Hz), 6.68 (1H, s), 7.10 (1H, d, J = 6.9 Hz), 7.21 (1H, d, J = 7.8 Hz), 7.3−7.65 (7H, m), 7.71 (1H, d, J = 8.4 Hz), 7.91 (1H, d, J = 8.1 Hz), 8.25 (1H, d, J = 8.1 Hz). Anal. ($C_{28}H_{25}NO$·$0.2H_2O$) C, H, N.

8-(Benzyloxy)-2-cyclopropyl-3-(*o*-phenylbenzyl)indolizine (20vi): 91% yield; IR ν_{max} ($CHCl_3$) 1527, 1448, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.64−0.72 (2H, m), 0.83−0.93 (2H,

m), 1.85 (1H, tt, J = 8.6 Hz, 5.0 Hz), 4.24 (2H, s), 5.13 (2H, s), 5.96 (1H, d, J = 7.2 Hz), 6.19 (1H, t, J = 7.2 Hz), 6.27 (1H, s), 6.80 (1H, d, J = 7.5 Hz), 6.91 (1H, d, J = 7.2 Hz), 7.14 (1H, td, J = 7.5 Hz, 2.1 Hz), 7.19−7.52 (12H, m).

Ethyl 3-benzyl-8-(benzyloxy)-2-methylindolizine-1-carboxylate (22): A mixture of 3-bromo-4-phenyl-butan-2-one[13] (1.3 equiv), ethyl pyridine-2-acetate (1.0 equiv), and $NaHCO_3$ (10 equiv) was heated at 165 °C for 1−4 h and chromatographed by eluting with hexane:AcOEt (5−2:1): mp 117−118 °C (hexane); 47.4% yield; IR ν_{max} (Nujol) 1707, 1535, 1233 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, t, J = 7.5 Hz), 2.43 (3H, s), 4.13 (2H, q, J = 7.2 Hz), 4.22 (2H, s), 5.16 (2H, s), 6.23 (1H, d, J = 7.5 Hz), 6.39 (1H, t, J = 6.6 Hz), 7.06 (2H, m), 7.15−7.45 (7H, m), 7.48 (2H, m). Anal. ($C_{26}H_{25}NO_3$) C, H, N.

3-Benzyl-8-(benzyloxy)-2-methylindolizine-1-carboxylic acid: mp 132 °C (dec); 68.4% yield; IR ν_{max} (Nujol) 3295, 1670, 1535, 1259 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (3H, s), 4.25 (2H, s), 5.33 (2H, s), 6.51 (1H, d, J = 0.8 Hz), 6.53 (1H, s), 7.0−7.1 (2H, m), 7.15−7.3 (2H, m), 7.35−7.50 (6H, m). Anal. ($C_{24}H_{21}NO_3$) C, H, N.

3-Benzyl-8-(benzyloxy)-2-methylindolizine (20vii): quantitative yield; ^1H NMR ($CDCl_3$) δ 2.34 (3H, s), 4.22 (2H, s), 5.17 (2H, s) 6.00 (1H, d, J = 7.6 Hz), 6.25 (1H, t, J = 7.1 Hz), 6.56 (1H, s), 7.0−7.5 (11H, m).

3-(Benzyloxy)-2-methylpyridine (23b). A mixture of 2-methyl-3-pyridinol **23a**[14] (16.4 g, 0.15 mol), pulverized KOH (12.72 g, 0.195 mol), tetrabutylammonium bromide (2.42 g, 7.5 mmol), and benzyl bromide (18.7 mL, 0.158 mol) in THF (380 mL) was stirred at room temperature for 1.5 h. Water was added. The mixture was concentrated and then extracted with EtOAc. The extracts were washed with water and dried. After removal of the solvent, 28.3 g (90% yield) of the title compound was obtained: ^1H NMR ($CDCl_3$) δ 2.56 (3H, s), 5.11 (2H, s), 7.04−7.16 (2H, m), 7.35−7.45 (5H, m), 8.08 (1H, dd, J = 4.5, 1.5 Hz).

8-(Benzyloxy)-2-ethylindolizine (24a). A mixture of **23b** (29.7 g, 0.149 mol) in EtOAc (17 mL) and 1-bromo-2-butanone (22.5 g, 0.149 mol) was stirred at 70 °C for 0.5 h. EtOAc (23 mL) was added to the reaction mixture and the solid was recrystallized from EtOAc to give the quaternary salt (47.04 g, 90.1%).

The quaternary salt (47.04 g, 0.134 mol) in benzene (150 mL) and DBU (44.2 mL, 0.295 mol) were refluxed for 0.75 h, poured into ice water, and extracted with EtOAc. The extracts were washed with water and dried. After removal of the solvent, the title oily compound (**46a**) (26.62 g, 79% yield) was obtained: ^1H NMR ($CDCl_3$) δ 1.28 (3H, t, J = 7.6 Hz), 2.70 (2H, q, J = 7.6 Hz), 5.16 (2H, s), 5.99 (1H, d, J = 7.5 Hz), 6.29 (1H, t, J = 7.1 Hz), 6.48 (1H, s), 7.10−7.52 (7H, m).

8-(Benzyloxy)-2-methylindolizine (24b): 92% yield; oil; ^1H NMR ($CDCl_3$) δ 2.31 (3H, s), 5.16 (2H, s), 5.98 (1H, d, J = 7.6 Hz), 6.28 (1H, t, J = 7.0 Hz), 6.44 (1H, s), 7.08 (1H, s), 7.34−7.55 (6H, m).

2-Cyclopropyl-8-methoxyindolizine (24c): 72% yield; ^1H NMR ($CDCl_3$) δ 0.60−0.68 (2H, m), 0.86−0.96 (2H, m), 1.83−1.97 (1H, m), 3.89 (3H, s), 5.92 (1H, d, J = 7.4 Hz), 6.25−6.34 (1H + 1H, m), 7.11 (1H, d, J = 1.6 Hz), 7.47 (1H, d, J = 7.0 Hz).

8-(Benzyloxy)-2-cyclopropylindolizine (24d): 69% yield; ^1H NMR ($CDCl_3$) δ 0.61−0.69 (2H, m), 0.86−0.96 (2H, m), 1.84−1.97 (1H, m), 5.15 (2H, s), 5.98 (1H, d, J = 7.6 Hz), 6.25−6.32 (1H + 1H, m), 7.12 (1H, d, J = 2.0 Hz), 7.35−7.49 (6H, m).

8-(Benzyloxy)-2-ethyl-3-(substituted carbonyl)indolizine (19). General procedure: This compound was prepared from **24**, according to the procedure described for the preparation of **11** from **10**.

8-(Benzyloxy)-2-ethyl-3-(*p*-phenylbenzoyl)indolizine (19viii): mp 114−115 °C; 80% yield.

8-(Benzyloxy)-3-(cyclohexylcarbonyl)-2-ethylindolizine (19ix): mp 88−89 °C (hexane:EtOAc); 77% yield. Anal. ($C_{24}H_{27}NO_2 \cdot 0.1H_2O$) C, H, N.

8-(Benzyloxy)-3-(cyclopentylcarbonyl)-2-ethylindolizine (19x): mp 63−64 °C (hexane); 68% yield. Anal. ($C_{23}H_{25}NO_2 \cdot 0.1H_2O$) C, H, N.

8-(Benzyloxy)-3-(cycloheptylcarbonyl)-2-ethylindolizine (19xi): mp 85−86 °C (hexane); 74% yield. Anal. ($C_{25}H_{29}NO_2$) C, H, N.

8-(Benzyloxy)-2-ethyl-3-(2-oxopentyl)indolizine (19xii): mp 84 °C (hexane:EtOAc); 89% yield. Anal. ($C_{22}H_{25}NO_2$) C, H, N.

8-(Benzyloxy)-2-ethyl-3-(1-oxo-2-propylpentyl)indolizine (19xiii): mp 137−138 °C (hexane:EtOAc); 25% yield.

8-(Benzyloxy)-2-ethyl-3-(naphth-2-ylcarbonyl)indolizine (19xiv): amorphous solid; 70% yield. Anal. ($C_{28}H_{23}NO_2$) C, H, N.

8-(Benzyloxy)-3-(3,5-di-*tert*-butylbenzoyl)-2-ethylindolizine (19xv): mp 131 °C (hexane:EtOAc); 82% yield. Anal. ($C_{32}H_{37}NO_2$) C, H, N.

8-(Benzyloxy)-2-ethyl-3-(1-oxo-2-phenylethyl)indolizine (19xvi): mp 139−140 °C (hexane:EtOAc); 58% yield. Anal. ($C_{25}H_{23}NO_2$) C, H, N.

3-(*o*-Benzylbenzoyl)-8-(benzyloxy)-2-ethylindolizine (19xvii): yellow oil; 58% yield. Anal. ($C_{31}H_{27}NO_2 \cdot 0.5H_2O$) C, H, N.

8-(Benzyloxy)-2-ethyl-3-thien-2-ylindolizine (19xviii): mp 141−142 °C (hexane:EtOAc); 82% yield. Anal. ($C_{22}H_{19}NO_2S$) C, H, N, S.

8-(Benzyloxy)-2-ethyl-3-(3-thien-2-ylthien-2-yl)indolizine (19xix). 3-(Thiophene-2-yl)thiophene-2-carboxylic acid was prepared by hydrolysis of the methyl ester:[21] mp 137−138 °C (hexane:EtOAc); ^1H NMR ($CDCl_3$) δ 7.10 (1H, dd, J = 3.6, 5.0 Hz), 7.26 (1H, d, J = 5.0 Hz), 7.39 (1H, dd, J = 1.0, 5.0 Hz), 7.55−7.60 (2H, m); IR ν_{max} (KBr) 2845, 2606, 1671, 1273, 1245 cm^{-1}; The acid chloride was treated as above, but the product could not be purified and used in the next preparation without further purification.

8-(Benzyloxy)-2-ethyl-3-(*m*-methoxybenzoyl)indolizine (19xx): mp 64−67 °C; 77% yield. Anal. ($C_{25}H_{23}NO_3$) C, H, N.

8-(Benzyloxy)-2-ethyl-3-(1-oxo-2-(4-*n*-pentylcyclohexyl)ethyl)indolizine (19xxii): mp 64−65 °C (hexane); 41% yield. Anal. ($C_{29}H_{37}NO_2$) C, H, N.

8-(Benzyloxy)-2-methy-3-(*o*-phenylbenzoyl)indolizine (19xxiv): mp 114−116 °C; 66.9% yield.

8-(Benzyloxy)-3-benzoyl-2-cyclopropylindolizine (19xxv): mp 144−146 °C; 81.4% yield. Anal. ($C_{25}H_{21}NO_2 \cdot 0.1H_2O$) C, H, N.

3-(*p*-*n*-Butylbenzoyl)-2-ethyl-8-methoxyindolizine (19xxvi): mp 90−91 °C (hexane); 72.8% yield. Anal. ($C_{22}H_{25}NO_2$) C, H, N.

8-(Benzyloxy)-2-methyl-3-(1-oxo-2-cyclohexylethyl)-lindolizine (19xxvii): mp 105−106 °C (hexane:EtOAc); 61% yield. Anal. ($C_{23}H_{25}NO_2$) C, H, N.

8-(Benzyloxy)-3-(cyclopentylcarbonyl)-2-methylindolizine (19xxix): mp 93.5−94.5 °C; 24% yield. Anal. ($C_{22}H_{23}NO_2$) C, H, N.

8-(Benzyloxy)-2-ethyl-3-(*p*-phenylbenzyl)indolizine (20viii): quantitative yield; ^1H NMR ($CDCl_3$) δ 1.26 (3H, t, J = 7.2 Hz), 2.74 (2H, q, J = 7.8 Hz), 4.28 (2H, s), 5.18 (2H, s), 6.02 (1H, d, J = 7.2 Hz), 6.28 (1H, t, J = 7.2 Hz), 7.11 (1H, d, J = 8.4 Hz), 7.23−7.71 (14H, m).

8-(Benzyloxy)-3-(cyclopentylmethyl)-2-ethylindolizine (20x): ^1H NMR ($CDCl_3$) δ 1.15−1.34 (5H, m), 1.41−1.74 (6H, m), 2.18 (1H, quint, J = 7.8 Hz), 2.65 (2H, q, J = 7.4 Hz), 2.82 (2H, d, J = 7.2 Hz), 5.17 (2H, s), 5.98 (1H, d, J = 7.0 Hz), 6.34 (1H, dd, J = 7.0, 7.4 Hz), 6.53 (1H, s), 7.3−7.5 (6H, m).

8-(Benzyloxy)-2-ethyl-3-pentylindolizine (20xii): IR ν_{max} (KBr) 2950, 2920, 1550, 1520, 1365, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3H, br s), 1.20−1.66 (9H, m), 2.61 (2H, q, J = 7.4 Hz), 2.84 (2H, t, J = 7.8 Hz), 5.16 (2H, s), 6.06 (1H, d, J = 7.2 Hz), 6.38 (2H, m), 7.3−7.5 (6H, m).

8-(Benzyloxy)-2-ethyl-3-(2-propylpentyl)indolizine (20xiii): 25% yield; ^1H NMR ($CDCl_3$) δ 0.82−0.88 (6H, m), 1.16−1.49 (12H, m), 1.64−1.86 (1H, m), 2.57−2.74 (4H, m), 5.16 (2H, s), 5.98 (1H, d, J = 7.4 Hz), 6.34 (1H, dd, J = 7.2, 7.4 Hz), 6.53 (1H, s), 7.31−7.50 (6H, m).

8-(Benzyloxy)-2-ethyl-3-(naphth-2-ylmethyl)indolizine (20xiv): ^1H NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.4 Hz), 2.76

(2H, q, J = 7.4 Hz), 4.39 (2H, s), 5.17 (2H, s), 6.00 (1H, d, J = 7.4 Hz), 6.22 (1H, dd, J = 7.0, 7.4 Hz), 6.64 (1H, s), 7.22−7.8 (13H, m).

8-(Benzyloxy)-3-(*o*-benzylbenzyl)-2-ethylindolizine (20xvii): 91% yield; IR ν_{max} (neat) 2922, 1523, 1371, 1312 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, J = 7.4 Hz), 2.54 (2H, q, J = 7.4 Hz), 4.07 (2H, s), 4.18 (2H, s), 5.16 (2H, s), 5.97 (1H, d, J = 7.4 Hz), 6.13 (1H, dd, J = 6.6, 7.4 Hz), 6.48 (1H, d, J = 7.8 Hz), 6.58 (1H, s), 6.69 (1H, d, J = 6.8 Hz) 6.98−7.51 (13H, m).

8-(Benzyloxy)-2-ethyl-3-((3-thiophene-2-ylthiophen-2-yl)methyl)indolizine (20xix): ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.4 Hz), 2.63 (2H, q, J = 7.4 Hz), 4.41 (2H, s), 5.06 (2H, s), 5.92 (1H, d, J = 7.0 Hz), 6.17 (1H, dd, J = 7.0, 7.2 Hz), 6.51 (1H, s), 6.91−7.42 (11H, m).

8-(Benzyloxy)-2-ethyl-3-(*m*-methoxybenzyl)indolizine (20xx): quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, t, J = 7.5 Hz), 2.72 (2H, q, J = 7.5 Hz), 3.72 (3H, s), 4.21 (2H, s), 5.17 (2H, s), 6.01 (1H, d, J = 7.2 Hz), 6.26 (1H, t, J = 7.2 Hz), 6.58−6.75 (4H, m), 7.11−7.44 (5H, m), 7.46−7.63 (2H, m).

8-(Benzyloxy)-2-ethyl-3-(4-*n*-pentylcyclohexyl)methylindolizine (20xxii): ^{1}H NMR ($CDCl_3$) δ 0.70−1.80 (24H, m), 2.57−2.71 (4H, m), 5.17 (2H, s), 5.98 (1H, d, J = 7.4 Hz), 6.34 (1H, dd, J = 7.0, 7.4 Hz), 6.53 (1H, s), 7.26−7.51 (6H, m).

8-(Benzyloxy)-3-(biphenyl-2-ylmethyl)-2-methylindolizine (20xxiv): mp 98−99 °C; quantitative yield; ^{1}H NMR ($CDCl_3$) δ 2.26 (3H, s), 4.11 (2H, s), 5.15 (2H, s), 5.97 (1H, d, J = 6.9 Hz), 6.19 (1H, t, J = 7.1 Hz), 6.52 (1H, s), 6.72 (1H, d, J = 6.9 Hz), 6.93 (1H, d, J = 6.9 Hz), 7.10−7.16 (1H, m), 7.23−7.54 (12H, m).

3-Benzyl-8-(benzyloxy)-2-cyclopropylindolizine (20xxv): 94% yield; ^{1}H NMR ($CDCl_3$) δ 0.67−0.75 (2H, m), 0.87−0.97 (2H, m), 1.86−2.00 (1H, m), 4.34 (2H, s), 5.14 (2H, s), 5.98 (1H, d, J = 7.4 Hz), 6.21−6.31 (1H + 1H, m), 7.09−7.49 (11H, m).

3-(*p*-*n*-Butylbenzyl)-2-ethyl-8-methoxyindolizine (20xxvi): oil; 67.9% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.5 Hz), 1.32 (2H, m), 1.55 (2H, m), 2.54 (2H, t, J = 7.6 Hz), 2.71 (2H, m), 3.92 (3H, s), 4.19 (2H, s), 5.90 (1H, d, J = 7.2 Hz), 6.28 (1H, t, J = 7.1 Hz), 6.94 (1H, d, J = 8.2 Hz), 7.04 (1H, d, J = 8.0 Hz), 7.23 (1H, d, J = 7.0 Hz).

8-(Benzyloxy)-2-ethyl-3-(cyclohexylmethyl)indolizine (20xxvii): ^{1}H NMR ($CDCl_3$) δ 1.00−1.26 (5H, m), 1.55−2.25 (6H, m), 2.25 (3H, s), 2.68 (2H, d, J = 6.9 Hz), 5.16 (2H, s), 5.98 (1H, d, J = 7.2 Hz), 6.34 (1H, dd, J = 6.9, 7.2 Hz), 6.47 (1H, s), 7.30−7.49 (6H, m).

2-(8-(Benzyloxy)-2-ethyl-3-(substituted methyl)indolizin-1-yl)glyoxylamide (25). These compounds were prepared from **20**, according to the procedure described for the synthesis of **5a** from **4**.

2-(3-Benzyl-8-(benzyloxy)-2-ethylindolizin-1-yl)glyoxylamide (25i): mp 188−189 °C; 63% yield; IR ν_{max} (Nujol) 3425, 3203, 2968, 2929, 1693, 1621, 1313 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.4 Hz), 2.85 (2H, q, J = 7.4 Hz), 4.24 (3H, s), 4.78 (1H, br s), 5.13 (1H, s), 6.16 (1H, br s), 6.38 (1H, d, J = 7.0 Hz), 6.49 (1H, dd, J = 6.6, 7.4, Hz), 7.04−7.14 (2H, m), 7.20−7.49 (9H, m). Anal. ($C_{26}H_{24}N_2O_3$·0.2H_2O) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (25ii): mp 183−185 °C (ether:hexane); 79.0% yield. Anal. ($C_{32}H_{28}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-3-(*m*-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide (25iii). mp 145−148 °C (ether:hexane); 80% yield; LSIMS m/z 446 $[M]^{+\bullet}$, 447 $[M + H]^+$, 893 $[2M + H]^+$.

(8-(Benzyloxy)-2-ethyl-3-(*m*-(trifluoromethyl)benzyl)-indolizin-1-yl)glyoxylamide (25iv): mp 182−185 °C (CH_2Cl_2:hexane); 76% yield.

(8-(Benzyloxy)-2-ethyl-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide (25v): mp 189−190 °C (benzene); 76.0% yield. Anal. ($C_{30}H_{26}N_2O_3$) C, H, N.

(8-(Benzyloxy)-2-cyclopropyl-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (25vi): mp 185−186 °C (CH_2Cl_2:hexane); quantitative yield. Anal. ($C_{33}H_{28}N_2O_3$ 0.3H_2O) C, H, N.

2-(3-Benzyl-8-(benzyloxy)-2-methylindolizin-1-yl)glyoxylamide (25vii): mp 212−214 °C; 96.2% yield. Anal. ($C_{25}H_{22}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-(*p*-phenylbenzyl)indolizine-1-yl)glyoxylamide (25viii): mp 196−199 °C; 61% yield. Anal. ($C_{32}H_{28}N_2O_3$·0.2H_2O) C, H, N.

2-(8-(Benzyloxy)-3-(cyclohexylmethyl)-2-ethylindolizin-1-yl)glyoxylamide (25ix): mp 176 °C (hexane:EtOAc); 85% yield. Anal. ($C_{26}H_{30}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-3-(cyclopentylmethyl)-2-ethylindolizin-1-yl)glyoxylamide (25x): mp 161−162 °C (hexane:AcOEt); 77% yield. Anal. ($C_{25}H_{28}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-3-(cycloheptylmethyl)-2-ethylindolizin-1-yl)glyoxylamide (25xi): mp 144−145 °C (hexane); 76% yield. Anal. ($C_{27}H_{32}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-(oxopentyl)indolizin-1-yl)-glyoxylamide (25xii): mp 141−142 °C (hexane:EtOAc); 77% yield. Anal. ($C_{24}H_{28}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-(2-propylpentyl)indolizin-1-yl)glyoxylamide (25xiii): mp 159−160 °C (hexane:EtOAc); 82% yield. Anal. ($C_{27}H_{34}N_2O_3$·1.6H_2O) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-(naphth-2-ylmethyl)indolizin-1-yl)glyoxylamide (25xiv): mp 209−210 °C (EtOAc); 77% yield. Anal. ($C_{30}H_{26}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-3-(3,5-di-*tert*-butylbenzyl)-2-ethylindolizin-1-yl)glyoxylamide (25xv): mp 230−231 °C (EtOAc); 59% yield. Anal. ($C_{34}H_{40}N_2O_3$·0.2H_2O) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-(2-phenylethyl)indolizin-1-yl)glyoxylamide (25xvi): mp 188−189 °C (EtOAc); 79% yield. Anal. ($C_{27}H_{26}N_2O_3$·0.3H_2O) C, H, N.

2-(8-(Benzyloxy)-3-(*o*-benzylbenzyl)-2-ethylindolizin-1-yl)glyoxylamide (25xvii): mp 178−179 °C (hexane:EtOAc); 93% yield. Anal. ($C_{33}H_{30}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-(thiophene-2-ylmethyl)indolizin-1-yl)glyoxylamide (25xviii): mp 191−192 °C (EtOAc); 73% yield. Anal. ($C_{24}H_{22}N_2O_3S$) C, H, N, S.

2-(8-(Benzyloxy)-2-ethyl-3-((3-thiophene-2-ylthiophene-2-yl)methyl)indolizin-1-yl)glyoxylamide (25xix): mp 208−209 °C (EtOAc); 10% Yield (two steps).

2-(8-(Benzyloxy)-2-ethyl-3-(*m*-methoxybenzyl)indolizine-1-yl)glyoxylamide (25xx): mp 180−182 °C; 61% yield. Anal. ($C_{27}H_{26}N_2O_4$·0.1H_2O) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-(*o*-nitrobenzyl)indolizine-1-yl)glyoxylamide (25xxi): mp 205−208 °C; 8% yield. Anal. ($C_{26}H_{23}N_3O_5$) C, H, N.

2-(8-(Benzyloxy)-2-ethyl-3-((4-*n*-pentylcyclohexyl)-methyl)indolizin-1-yl)glyoxylamide (25xxii): mp 169−170 °C (EtOAc); 80% yield. Anal. ($C_{31}H_{40}N_2O_3$·0.4H_2O) C, H, N.

2-(3-(Adamant-1-yl)-8-(benzyloxy)-2-ethylindolizin-1-yl)glyoxylamide (25xxiii): mp 225−226 °C (EtOAc); 21% Yield (three steps). Anal. ($C_{29}H_{32}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-3-(biphenyl-2-ylmethyl)-2-methylindolizin-1-yl)-glyoxylamide (25xxiv): mp 198−200 °C; 82.7% yield. Anal. ($C_{31}H_{26}N_2O_3$·0.2H_2O) C, H, N.

2-(3-Benzyl-8-(benzyloxy)-2-cyclopropylindolizin-1-yl)-glyoxylamide (25xxv): mp 206−207 °C; 30% yield. Anal. ($C_{27}H_{24}N_2O_3$·0.3H_2O) C, H, N.

2-(3-(*p*-*n*-Butylbenzyl)-2-ethyl-8-methoxyindolizin-1-yl)glyoxylamide (25xxvi): mp 195−196 °C (benzene); 96.8% yield. Anal. ($C_{24}H_{28}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-3-cyclohexyl-2-methylindolizin-1-yl)-glyoxylamide (25xxvii): mp 222−223 °C (EtOAc); 88% yield. Anal. ($C_{25}H_{18}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-3-cyclopentylmethyl-2-cyclopropylindolizin-1-yl)glyoxylamide (25xxviii). Compounds **19xxviii** and **20xxviii** were prepared by the above procedure and used in the next preparation without further purification: mp 186−187 °C; 28% yield. Anal. ($C_{26}H_{28}N_2O_3$) C, H, N.

2-(8-(Benzyloxy)-3-(cyclopentylmethyl)-2-methylindolizin-1-yl)glyoxylamide (25xxix): Compound **20xxix** was prepared by the general procedure 2 cited above and used in the next preparation without further purification: mp 174−175 °C; 66% yield. Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

2-(3-(Substituted methyl)-8-hydroxy-2-ethylindolizin-1-yl)glyoxylamide (26). General procedure 1: These com-

pounds were prepared from **25**, according to the procedure described for the synthesis of **12** from **13**.

General procedure 2: A 1 M solution of BBr_3 in CH_2Cl_2 (3.3 molar equiv) was added to a solution of **25** in CH_2Cl_2. The mixture was stirred for 3 h to 1 d. Ice water was added. The organic phase was washed with water and dried. After removal of the solvent, the residue was purified by recrystallization or column chromatography.

2-(3-Benzyl-2-ethyl-8-hydroxyindolizin-1-yl)glyoxylamide (26i): mp 194−195 °C (AcOEt); IR ν_{max} (KBr) 3469, 3308, 2969, 1688, 1567, 1317 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD) δ 1.23 (3H, t, J = 7.8 Hz), 2.90 (2H, q, J = 7.8 Hz), 4.22 (2H, s), 6.71 (1H, d, J = 7.4 Hz), 6.78 (1H, dd, J = 6.6, 7.4 Hz), 7.02−7.09 (2H, m), 7.18−7.33 (4H, m). Anal. ($C_{19}H_{18}N_2O_3$ $0.1H_2O$) C, H, N.

2-(2-Ethyl-8-hydroxy-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (26ii): mp 195−196 °C (dec) (ether:hexane); 95.0% yield. Anal. ($C_{25}H_{22}N_2O_3$·$0.1H_2O$) C, H, N.

2-(3-(*m*-Chlorobenzyl)-2-ethyl-8-hydroxyindolizin-1-yl)glyoxylamide (26iii): mp 144−146 °C (AcOEt:hexane); 88% yield; LSIMS m/z 356 $[M]^{+\bullet}$, 357 $[M + H]^+$, 713 $[2M + H]^+$.

2-(2-Ethyl-8-hydroxy-3-(*m*-(trifluoromethyl)benzyl)-indolizin-1-yl)glyoxylamide (26iv): mp 142−146 °C (AcOEt: hexane); 96% yield.

2-(2-Ethyl-8-hydroxy-3-(1-naphthylmethyl)indolizin-1-yl)glyoxylamide (26v): mp 176−178 °C (benzene); 84.5% yield. Anal. ($C_{23}H_{20}N_2O_3$·$0.5C_6H_6$) C, H, N.

2-(2-Cyclopropyl-8-hydroxy-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (26vi): mp 189−191 °C (AcOEt: hexane); 95% yield. Anal. ($C_{26}H_{22}N_2O_3$·$0.2H_2O$) C, H, N.

2-(3-Benzyl-8-hydroxy-2-methylindolizin-1-yl)glyoxylamide (26vii): mp 189−192 °C; 94.9% yield. Anal. ($C_{18}H_{16}N_2O_3$) C, H, N.

2-(2-Ethyl-8-hydroxy-3-(*o*-phenylbenzyl)indolizine-1-yl)glyoxylamide (26viii): quantitative yield; ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.5 Hz), 2.93 (2H, q, J = 7.5 Hz), 4.25 (2H, s), 5.76 (1H, br s), 6.39 (1H, br s), 6.70 (1H, d, J = 7.2 Hz), 6.79 (1H, t, J = 7.1 Hz), 7.08−7.78 (10H, m), 12.90 (1H, s).

2-(3-(Cyclopentylmethyl)-2-ethyl-8-hydroxyindolizin-1-yl)glyoxylamide (26x): ^1H NMR ($CDCl_3$) δ 1.1−1.3 (6H, m), 1.46−1.76 (5H, m), 2.06−2.24 (1H, m), 2.78−2.91 (4H, m), 5.70 (1H, br s), 6.3 (1H, br s), 6.72 (1H, d, J = 7.8 Hz), 6.91 (1H, dd, J = 6.8, 7.8 Hz), 7.54 (1H, d, J = 6.8 Hz), 12.93 (1H, s).

2-(3-(Cycloheptylmethyl)-2-ethyl-8-hydroxyindolizin-1-yl)glyoxylamide (26xi): ^1H NMR ($CDCl_3$) δ 1.13−1.9 (16H, m), 2.67 (2H, d, J = 7.4 Hz), 2.83 (2H, q, J = 7.8 Hz), 5.70 (1H, br s), 6.30 (1H, br s), 6.72 (1H, d, J = 7.5 Hz), 6.92 (1H, dd, J = 6.2, 7.8 Hz), 7.48 (1H, d, J = 6.2 Hz), 12.94 (1H, s).

2-(2-Ethyl-8-hydroxy-3-oxopentylindolizin-1-yl)glyoxylamide (26xii). Anal. ($C_{17}H_{22}N_2O_3$) C, H, N.

2-(2,5-Di-*tert*-butylbenzyl)-8-hydroxy-2-ethylindolizin-1-yl)glyoxylamide (26xv): ^1H NMR ($CDCl_3$) δ 1.18−1.80 (21H, m), 2.91 (2H, q, J = 7.4 Hz), 4.20 (2H, s), 5.71 (1H, br s), 6.31 (1H, br s), 6.70−6.88 (4H, m), 7.26−7.33 (2H, m), 12.90 (1H, s).

2-(2-Ethyl-8-hydroxy-3-thien-2-ylindolizin-1-yl)glyoxylamide (26xviii): mp 163−164 °C (hexane:EtOAc); 40% yield; MS m/z 328 $[M]^+$.

2-(2-Ethyl-8-hydroxy-3-((3-thien-2-ylthien-2-yl)methyl)-indolizin-1-yl)glyoxylamide (26xix): ^1H NMR ($CDCl_3$:CD_3-OD) δ 1.28 (3H, t, J = 7.4 Hz), 2.91 (2H, q, J = 7.4 Hz), 4.50 (2H, s), 6.72 (1H, d, J = 7.8 Hz), 6.80 (1H, dd, J = 6.2, 7.8 Hz), 7.10−7.43 (6H, m).

2-(2-Ethyl-8-hydroxy-3-(*m*-methoxybenzyl)indolizin-1-yl)glyoxylamide (26xx): mp 140−143 °C; 86% yield.

2-(2-Ethyl-8-hydroxy-3-(*o*-nitrobenzyl)indolizin-1-yl)-glyoxylamide (26xxi): mp 174−178 °C (dec); 85% yield. Anal. ($C_{19}H_{17}N_3O_5$) C, H, N.

8-Hydroxy-2-ethyl-3-(4-*n*-pentylcyclohexyl)indolizin-1-yl)glyoxylamide (26xxii): mp 99−100 °C (hexane:EtOAc). Anal. ($C_{24}H_{34}N_2O_3$) C, H, N.

2-(3-(Biphenyl-2-ylmethyl)-8-hydroxy-2-methylindolizin-1-yl)glyoxylamide (26xxiv): mp 129−130 °C; 77.6% yield. Anal. ($C_{24}H_{20}N_2O_3$·$0.2H_2O$) C, H, N.

2-(3-Benzyl-2-cyclopropyl-8-hydroxyindolizin-1-yl)glyoxylamide (26xxv): mp 188−190 °C; 96.7% yield. Anal. ($C_{20}H_{18}N_2O_3$·0.5AcOEt) C, H, N.

2-(3-(*p*-*n*-Butylbenzyl)-2-ethyl-8-hydroxyindolizin-1-yl)glyoxylamide (26xxvi): mp 145−148 °C (benzene); 59.3% yield. Anal. ($C_{23}H_{26}N_2O_3$·$0.1H_2O$) C, H, N.

2-(3-(Cyclohexylmethyl)-8-hydroxy-2-methylindolizin-1-yl)glyoxylamide (26xxvii): ^1H NMR ($CDCl_3$) δ 1.00−1.80 (11H, m), 2.33 (3H, s), 2.65 (2H, d, J = 6.9 Hz), 5.7 (1H, br s), 6.24 (1H, br s), 6.71 (1H, d, J = 7.8 Hz), 6.91 (1H, dd, J = 6.3, 7.8 Hz), 7.46 (1H, d, J = 6.3 Hz), 12.97 (1H, s).

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(substituted methyl)indolizin-1-yl)glyoxylamide (27). General procedure: Compound **26** (1 mmol), methyl bromoacetate (1.1 mmol), K_2CO_3 (3 mmol), KI (0.2 mmol), and DMF (3 mL) were stirred for 5 h. Water was added. The mixture was extracted with EtOAc. The extracts were washed with water and dried. After removal of the solvent, the residue was purified by recrystallization or column chromatography.

(8-((Carboxymethyl)oxy)indolizin-1-yl)glyoxylamide (28). General procedure: Aqueous KOH (1 N, 4 mL) was added to a solution of the ester **27** (2 mmol) in MeOH (21 mL). The solution was stirred at room temperature for 40 min, washed with ether, acidified with 2 N HCl, and extracted with EtOAc. The extracts were washed with water and dried. After removal of the solvent, the residue was recrystallized.

(3-Benzyl-8-((carbethoxymethyl)oxy)-2-ethylindolizin-1-yl)glyoxylamide (27i) and carboxylic acid 28i: mp 191−192 °C (AcOEt:hexane); 23% yield; IR ν_{max} (KBr) 3409, 3161, 2968, 1727, 1686, 1630, 1319, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20−1.32 (6H, m), 2.88 (2H, q, J = 7.4 Hz), 4.18−4.29 (4H, m), 4.72 (2H, s), 6.12 (1H, br s), 6.25 (1H, d, J = 7.4 Hz), 6.49 (1H, dd, J = 7.0, 7.4 Hz), 6.69 (1H, br s), 7.07−7.11 (2H, m), 7.20−7.35 (4H, m). Anal. ($C_{23}H_{24}N_2O_5$ $0.8H_2O$) C, H, N.

28i: mp 244−245 °C (AcOEt:ether); 42% yield; IR ν_{max} (KBr) 3855, 2974, 2931, 1703, 1660, 1625, 1312, 1092 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD) δ 1.22 (3H, t, J = 7.4 Hz), 2.90 (2H, q, J = 7.4 Hz), 4.27 (2H, s), 4.73 (2H, s), 6.37 (1H, d, J = 7.8 Hz), 6.73 (1H, dd, J = 6.6, 7.8 Hz), 7.06−7.43 (6H, m); EIMS m/z 380 $[M^+]$. Anal. ($C_{21}H_{20}N_2O_5$ $0.7H_2O$) C, H, N.

(8-((Carbethoxymethyl)oxy)-2-ethyl-3-(*o*-phenylbenzyl)-indolizin-1-yl)glyoxylamide (27ii) and carboxylic acid 28ii: mp 127−129 °C (ether:hexane); 86.0% yield. Anal. ($C_{29}H_{28}N_2O_5$) C, H, N.

28ii: mp 209−212 °C (dec) (ether:hexane); 93% yield. Anal. ($C_{27}H_{24}N_2O_5$·$0.3H_2O$) C, H, N.

(8-((Carbethoxymethyl)oxy)-3-(*m*-chlorobenzyl)-2-ethylindolizin-1-yl)glyoxylamide (27iii): mp 172−175 °C (AcOEt:hexane); 73% yield; LSIMS m/z 442 $[M]^{+\bullet}$, 443 $[M + H]^+$, 885 $[2M + H]^+$.

28iii: mp 230−233 °C (dec) (ether:hexane); 79% yield; LSIMS m/z 414 $[M]^{+\bullet}$, 415 $[M + H]^+$, 829 $[2M + H]^+$.

(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(*m*-(trifluoromethyl)benzyl)indolizin-1-yl)glyoxylamide (27iv) and carboxylic acid 28iv: mp 136−137 °C (AcOEt:hexane); 59% yield. Anal. ($C_{23}H_{21}N_2O_5F_3$·$0.2H_2O$) C, H, N, F.

28iv: mp 235−237 °C (dec) (CH_2Cl_2:hexane); 97% yield.

(8-Carbethoxymethyloxy-2-ethyl-3-(1-naphthylmethyl)-indolizin-1-yl)glyoxylamide (27v) and carboxylic acid 28v: 37.8% yield.

28v: 68.4% yield.

(8-((Carbomethoxymethyl)oxy)-2-cyclopropyl-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (27vi) and carboxylic acid 28vi: mp 178−179 °C (AcOEt:hexane); 69% yield. Anal. ($C_{29}H_{26}N_2O_5$·$0.2H_2O$) C, H, N.

28vi: mp 205−207 °C (dec) (AcOEt:hexane); 93% yield. Anal. ($C_{28}H_{24}N_2O_5$·$0.3H_2O$) C, H, N.

(3-Benzyl-8-((carbethoxymethyl)oxy)-2-methylindolizin-1-yl)glyoxylamide (27vii) and carboxylic acid 28vii: mp 193−195 °C; 41.4% yield. Anal. ($C_{22}H_{22}N_2O_5$) C, H, N.

28vii: mp 245−246 °C (dec); 86.7% yield. Anal. ($C_{20}H_{18}N_2O_5$ $0.2H_2O$) C, H, N.

2-(2-Ethyl-8-((carbomethoxymethyl)oxy)-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (27viii) and carboxylic acid 28viii: mp 221−222 °C, 54% yield. Anal. ($C_{28}H_{26}N_2O_5$) C, H, N.

28viii: mp 229−234 °C (dec); 84% yield. Anal. ($C_{27}H_{24}N_2O_5 \cdot 0.1H_2O$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-3-(cyclohexylmethyl)-2-ethylindolizin-1-yl)glyoxylamide (27ix) and carboxylic acid 28ix: mp 149−150 °C, (hexane:EtOAc); 19% yield from **25ix**. Anal. ($C_{22}H_{28}N_2O_5$) C, H, N.

28ix: mp 224−225 °C (AcOEt); MS *m*/*z* 386 $[M]^+$.

2-(8-((Carbomethoxymethyl)oxy)-3-(cyclopentylmethyl)-2-ethylindolizin-1-yl)glyoxylamide (27x) and carboxylic acid 28x: mp 158−159 °C (AcOEt); quantitative yield. Anal. ($C_{21}H_{26}N_2O_5$) C, H, N.

28x: 43% yield. Anal. ($C_{20}H_{24}N_2O_5 \cdot 0.4H_2O$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-3-(cycloheptylmethyl)-2-ethylindolizin-1-yl)glyoxylamide (27xi) and carboxylic acid 28xi: mp 147−148 °C (AcOEt); 79% yield. Anal. ($C_{23}H_{30}N_2O_5$) C, H, N.

28xi: 76% yield. Anal. ($C_{22}H_{28}N_2O_5$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(oxopentyl-)indolizin-1-yl)glyoxylamide (27xii) and carboxylic acid 28xii: mp 140−141 °C (hexane:EtOAc); 36% yield. Anal. ($C_{20}H_{26}N_2O_5 \cdot 0.5H_2O$) C, H, N.

28xii: mp 232−233 °C (acetone:AcOEt); 37% yield; MS *m*/*z* 360 $[M]^+$.

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(2-propylpentyl)indolizin-1-yl)glyoxylamide (27xiii) and carboxylic acid 28xiii: mp 114−115 °C (hexane:EtOAc); 84% yield. Anal. ($C_{23}H_{32}N_2O_5$) C, H, N.

28xiii: mp 176−177 °C (hexane:AcOEt); 81% yield; MS *m*/*z* 402 $[M]^+$. Anal. ($C_{22}H_{30}N_2O_5 \cdot 1.1H_2O$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(naphth-2-ylmethyl)indolizin-1-yl)glyoxylamide (27xiv) and carboxylic acid 28xiv: mp 195−196 °C (EtOAc); quantitative yield. Anal. ($C_{26}H_{24}N_2O_5 \cdot 0.3H_2O$) C, H, N.

28xiv: mp 236−237 °C (AcOEt); 33% yield. Anal. ($C_{25}H_{22}N_2O_5 \cdot 0.6H_2O$) C, H, N.

2-(8-((Carboxymethyl)oxy)-3-(3,5-di-*tert*-butyl)benzyl)-2-ethylindolizin-1-yl)glyoxylamide (27xv) and carboxylic acid 28xv: mp 186−187 °C (EtOAc); 83% Yield (two steps). Anal. ($C_{30}H_{38}N_2O_5 \cdot 0.2H_2O$) C, H, N.

28xv: mp 144−145 °C (hexane:EtOAc); 43% yield; MS *m*/*z* 492 $[M]^+$. Anal. ($C_{29}H_{26}N_2O_5 \cdot 1.7H_2O$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy-2-ethyl-3-(2-phenylethyl)indolizin-1-yl)glyoxylamide (27xvi) and carboxylic acid 28xvi: mp 175−176 °C (EtOAc); 47% Yield (two steps). Anal. ($C_{23}H_{24}N_2O_5 \cdot 0.1H_2O$) C, H, N.

28xvi: mp 233−234 °C (EtOAc); 48% yield. Anal. ($C_{22}H_{22}N_2O_5$) C, H, N.

2-(3-*o*-Benzylbenzyl)-8-((carbomethoxymethyl)oxy)-2-ethylindolizin-1-yl)glyoxylamide (27xvii) and carboxylic acid 28xvii: mp 190−191 °C (EtOAc); 65% Yield (two steps). Anal. ($C_{29}H_{28}N_2O_5 \cdot 0.5H_2O$) C, H, N.

28xvii: mp 220−221 °C (EtOAc); 42% yield. Anal. ($C_{28}H_{26}N_2O_5$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-thien-2-ylindolizin-1-yl)glyoxylamide (27xviii) and carboxylic acid 28xviii: mp 182 °C (hexane:EtOAc); 75% yield. Anal. ($C_{20}H_{20}N_2O_5\,S \cdot 0.2H_2O$) C, H, N, S.

28xviii: mp 251−252 °C (EtOAc); 32% yield. Anal. ($C_{19}H_{18}N_2O_5S \cdot 0.6H_2O$) C, H, N, S.

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-((3-thien-2-ylthien-2-yl)methyl)indolizin-1-yl)glyoxylamide (27xix) and carboxylic acid 28xix: mp 176−177 °C. Anal. ($C_{24}H_{22}N_2O_5\,S_2 \cdot 0.2H_2O$) C, H, N, S.

28xix: mp 209−210 °C; 54.5% yield. Anal. ($C_{23}H_{20}N_2O_5S_2$) C, H, N, S.

2-(2-Ethyl-8-((carbomethoxymethyl)oxy)-3-(*m*-methoxybenzyl)indolizin-1-yl)glyoxylamide (27xx) and carboxylic acid 28xx: mp 155−157 °C; 85% yield. Anal. ($C_{23}H_{24}N_2O_6$) C, H, N.

28xx: mp 219−221 °C (dec); 80% yield. Anal. ($C_{22}H_{22}N_2O_6 \cdot 0.8H_2O$) C, H, N.

2-(2-Ethyl-8-((carbomethoxymethyl)oxy)-3-(*o*-nitrobenzyl)indolizin-1-yl)glyoxylamide (27xxi) and carboxylic acid 28xxi: mp 156−157 °C; 96% yield.

28xxi: mp 208−210 °C (dec); 69% yield. Anal. ($C_{21}H_{19}N_3O_7 \cdot 0.3H_2O$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-((4-*n*-pentylcyclohexyl)methyl)indolizin-1-yl)glyoxylamide (27xxii) and carboxylic acid 28xxi: mp 175−176 °C (hexane:EtOAc), 92% yield (two steps). Anal. ($C_{27}H_{38}N_2O_5$) C, H, N.

28xxii: mp 224−225 °C (EtOAc); 59% yield (from Na salt). Anal. ($C_{26}H_{36}N_2O_5 \cdot 0.7H_2O$) C, H, N.

2-(3-(Adamant-1-yl-8-((carbomethoxymethyl)oxy)-2-methylindolizin-1-yl)glyoxylamide (27xxiii) and carboxylic acid 28xxiii: mp 191−192 °C (EtOAc); 38% yield (two steps); MS *m*/*z* 438 $[M]^+$.

28xxiii: mp 237−238 °C (EtOAc); 60% yield; MS *m*/*z* 424 $[M]^+$.

2-(3-Benzyl-8-(carbomethoxymethyl)oxy-2-cyclopropylindolizin-1-yl)-glyoxylamide (27xxv) and carboxylic acid 28xxv: mp 186−188 °C; 74.5% yield; IR ν_{max} ($CHCl_3$) 3502, 3390, 1759, 1737, 1697, 1642 cm^{-1}. Anal. ($C_{23}H_{22}N_2O_5 \cdot 0.1H_2O$) C, H, N.

28xxv: mp 235−237 °C; 74.6% yield. Anal. ($C_{22}H_{20}N_2O_5 \cdot 0.2H_2O$) C, H, N.

2-(3-(*p*-*n*-Butylbenzyl)-8-((carbomethoxymethyl)oxy)-2-ethylindolizin-1-yl)glyoxylamide (27xxvi) and carboxylic acid 28xxvi: mp 174−176 °C (EtOAc:benzene); 70.9% yield. Anal. ($C_{23}H_{26}N_2O_3 \cdot 0.1H_2O$) C, H, N.

28xxvi: mp 217−220 °C (EtOAc); 92.4% yield. Anal. ($C_{23}H_{26}N_2O_3 \cdot 0.1H_2O$) C, H, N.

2-(8-(Carbomethoxymethyoxy-3-(cyclohexylmethyl)-2-methylindolizin-1-yl)glyoxylamide (27xxvii) and carboxylic acid 28xxvii: mp 177−178 °C (hexane:EtOAc); 68% yield (two steps). Anal. ($C_{21}H_{26}N_2O_5 \cdot 0.6H_2O$) C, H, N.

28xxvii: mp 235−236 °C (hexane:EtOAc). Anal. ($C_{20}H_{24}N_2O_5 \cdot 0.8H_2O$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-3-(cyclopentylmethyl)-2-cyclopropylindolizin-1-yl)glyoxylamide (27xxviii) and carboxylic acid 28xxviii. Compound **26xxviii** was prepared as cited above and used in the next preparation without further purification: mp 175−176 °C, 70.4% yield. Anal. ($C_{22}H_{26}N_2O_5$) C, H, N.

28xxviii: mp 237−238 °C, 20% yield. Anal. ($C_{21}H_{24}N_2O_5$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-3-(cyclopentylmethyl)-2-methylindolizin-1-yl)glyoxylamide (27xxix) and carboxylic acid 28xxix: mp 149−150 °C, 63% yield. Anal. ($C_{20}H_{24}N_2O_5$) C, H, N.

28xxix: mp 249−251 °C (dec), 85% yield. Anal. ($C_{19}H_{22}N_2O_5$) C, H, N.

3-((Carbomethoxymethyl)oxy)-2-methylpyridine (29). This compound was prepared from 3-hydroxy-2-methylpyridine by the procedure cited for the preparation of **14** from **13**. The residue was chromatographed (25 g) in EtOAc:hexane (2:1) to give an oil (791 mg, 60.1%): ^1H NMR ($CDCl_3$) δ 2.55 (3H, s), 3.81 (3H, s), 4.67 (2H, s), 6.97 (1H, dd, J = 8.2 Hz), 7.09 (1H, dd, J = 8.2, 4.8 Hz), 8.14 (1H, dd, J = 1.4, 4.6 Hz).

8-(Carbomethoxymethyl)oxy)-2-methylindolizine (30a). ((2-Methylpyridin-3-yl)oxy)acetic acid methyl ester (**29**) (1.75 g, 9.66 mmol) and chloroacetone (0.77 mL, 9.66 mmol) were heated at 95 °C under N_2 for 2 h. DBU (3.2 mL, 21.3 mmol) in benzene (11 mL) was added to the salt. The mixture was then refluxed under N_2 for 1 h, poured into ice water, and then extracted with EtOAc. The extracts were washed with water and dried. After removal of the solvents at reduced pressure, the residue was recrystallized from ether:hexane to give 804 mg (40% yield) of the title compound: mp 59−62 °C; ^1H NMR ($CDCl_3$) δ 2.30 (3H, s), 3.80 (3H, s), 4.72 (2H, s), 5.82 (1H, d, J = 7.5 Hz), 6.26 (1H, t, J = 6.9 Hz), 6.46 (1H, s), 7.08 (1H, s), 7.51 (1H, d, J = 6.6 Hz).

8-((Carbomethoxymethyl)oxy)-2-ethylindolizine (30b): oil; 601 mg (82.6% from **53**); ^1H NMR ($CDCl_3$) δ 1.29 (3H, t, J = 7.5 Hz), 2.70 (2H, q, J = 7.8 Hz), 3.81 (3H, s), 4.74 (2H, s), 5.86 (1H, d, J = 6.9 Hz), 6.30 (1H, t, J = 7.1 Hz), 6.51 (1H, s), 7.11 (1H, s), 7.56 (1H, d, J = 4.2 Hz).

((2-Isopropylindolizin-8-yl)oxy)acetic acid methyl ester (30c): oil, 59% yield; ^1H NMR ($CDCl_3$) δ 1.30 (6H, d, J = 6.6 Hz), 3.02 (1H, sept, J = 6.6 Hz), 3.81 (3H, s), 4.73 (2H, s), 5.82 (1H, d, J = 7.4 Hz), 6.27 (1H, t, J = 7.0 Hz), 6.53 (1H, s), 7.12 (1H, s), 7.53 (1H, d, J = 7.0 Hz).

8-((Carbomethoxymethyl)oxy)-2-cyclopropylindolizine (30d): oil; 76% yield; ^{1}H NMR ($CDCl_3$) δ 0.65 (2H, m), 0.92 (2H, m), 1.90 (1H, m), 3.81 (3H, s), 4.71 (2H, s), 5.82 (1H, d, J = 7.4 Hz), 6.28 (1H, d, J = 7.4 Hz), 6.28 (1H, t, J = 7.2 Hz), 6.34 (1H, s), 7.13 (1H, d, J = 1.4 Hz), 7.50 (1H, d, J = 6.8 Hz).

2-*tert*-Butyl-8-((carbomethoxymethyl)oxy)indolizine (30e): oil; 48.0% yield; ^{1}H NMR ($CDCl_3$) δ 1.34 (9H, s), 3.82 (3H, s), 4.73 (2H, s), 5.82 (1H, d, J = 7.5 Hz), 6.27 (1H, t, J = 6.9 Hz), 6.27 (1H, t, J = 6.9 Hz), 6.56 (1H, s), 7.13 (1H, s), 7.53 (1H, d, J = 7.2 Hz).

8-((Carbomethoxymethyl)oxy)-2-cyclopentylindolizine (30f): oil; 14.3% yield; ^{1}H NMR ($CDCl_3$) δ 1.6−2.2 (8H, m), 3.11 (1H, m), 3.83 (3H, s), 4.74 (2H, s), 5.84 (1H, d, J = 7.4 Hz), 6.29 (1H, t, J = 7.0 Hz), 6.53 (1H, s), 7.14 (1H, s), 7.34 (1H, d, J = 7.2 Hz).

8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(*o*-phenylbenzoyl)indolizine (31b). This compound was prepared from **30b**, according to the procedure cited for the preparation of **20** from **19**: 83% yield; ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, t, J = 7.5 Hz), 2.07 (2H, q, J = 7.5 Hz), 3.82 (3H, s), 4.74 (2H, s), 6.31 (1H, d, J = 7.4 Hz), 6.49 (1H, d, J = 0.6 Hz), 6.65 (1H, t, J = 7.4 Hz), 7.10−7.25 (3H, m), 7.30−7.40 (2H, m), 7.42−7.58 (5H, m), 9.40 (1H, d, J = 7.4 Hz).

8-((Carbomethoxymethyl)oxy)-3-(cyclohexylcarbonyl)-2-cyclopropylindolizine (31c): mp 110−111.5 °C; 74% yield.

2-Alkyl-8-((carbomethoxymethyl)oxy)-3-(substituted methyl)indolizine (32). General procedure: A solution of **30** (1.30 mmol) and alkyl iodide (1.56 mmol) in benzene (5 mL) was allowed to stand at room temperature for 2 d. EtOAc was added. The mixture was washed with $NaHCO_3$ and with water, dried, and concentrated. The residue was chromatographed in hexane:benzene (1:2).

8-((Carbomethoxymethyl)oxy)-3-(cyclohexylmethyl)-2-cyclopropylindolizine (32xxx): 42.8% yield; ^{1}H NMR ($CDCl_3$) δ 0.64−0.69 (2H, m), 0.88−0.94 (2H, m), 1.04−1.17 (5H, m), 1.62−1.74 (6H, m), 1.80−1.89 (1H, m), 2.80 (2H, d, J = 6.6 Hz), 3.81 (3H, s), 4.72 (2H, s), 5.81 (1H, d, J = 6.9 Hz), 6.22 (1H, s), 6.33 (1H, t, J = 7.1 Hz), 7.40 (1H, d, J = 7.2 Hz).

8-((Carbomethoxymethyl)oxy)-2-isopropyl-3-(*o*-phenylbenzyl)indolizine (32xxxi): mp 115−117 °C; 37% yield. Anal. ($C_{27}H_{27}NO_3 \cdot 0.3C_6H_6$) C, H, N.

1,3-Bis(*o*-phenylbenzyl)-8-((carbomethoxymethyl)oxy)-2-isopropylindolizine: mp 215−219 °C (AcOEt:hexane); 9.2% yield. Anal. ($C_{40}H_{37}NO_3 \cdot 0.6H_2O$) C, H, N.

2-*tert*-Butyl-8-((carbomethoxymethyl)oxy)-3-(*o*-phenylbenzyl)indolizine (32xxxii): mp 155−157 °C (hexane); 22.5% yield. Anal. ($C_{28}H_{29}NO_3 \cdot 0.4C_6H_6$) C, H, N.

1,3-Bis(*o*-phenylbenzyl)-2-*tert*-butyl-8-((carbomethoxymethyl)oxy)indolizine: mp 230−234 °C; 1.8% yield; IR ν_{max} (Nujol) 1767, 1732, 1472, 1450, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (9H, s), 3.64 (3H, s), 4.29 (2H, s), 4.44 (2H, s), 4.61 (2H, br s), 5.73 (1H, d, J = 7.2 Hz), 6.16 (1H, t, J = 7.2 Hz), 6.54 (1H, d, J = 7.8 Hz), 6.81 (1H, t, J = 7.5 Hz), 6.99 (1H, d, J = 7.5 Hz), 7.1−7.55 (8H, m).

8-((Carbomethoxymethyl)oxy)-2-cyclopentyl-3-(*o*-phenylbenzyl)indolizine (32xxxiii): mp 145−148 °C (hexane); 26.2% yield. Anal. ($C_{31}H_{30}N_2O_5 \cdot 0.3H_2O$) C, H, N.

1,3-Bis-(*o*-phenylbenzyl)-8-((carbomethoxymethyl)oxy)-2-cyclopropylindolizine: mp 194−195 °C; 5.2% yield. Anal. ($C_{42}H_{39}NO_3 \cdot 0.3H_2O$) C, H, N.

8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(*m*-phenylbenzyl)indolizine (32xxxiv), 8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(3-phenyl-2-propenyl)indolizine (32xxxv) and 8-((Carbomethoxymethyl)oxy)-2-cyclopropyl-3-(1-naphthylmethyl)indolizine (56j). These products could not be isolated from 1,3-disubstituted indolizine and used in the next preparation without further purification.

2-(2-Alkyl-8-((carbomethoxymethyl)oxy)-3-(substituted methyl)indolizin-1-yl)glyoxylamide (27). General procedure: These compounds were prepared from **32**, according to the procedure described for the synthesis of **5a**.

2-(8-((Carbomethoxymethyl)oxy)-3-(cyclohexylmethyl)-2-cyclopropylindolizin-1-yl)glyoxylamide (27xxx) and carboxylic acid 28xxx: mp 153−157 °C; 53.7% yield. Anal. ($C_{23}H_{28}N_2O_5 \cdot 0.4$AcOEt) C, H, N.

28xxx: mp 229−234 °C; 79% yield; IR ν_{max} (Nujol) 3434, 3334, 1731, 1650(sh), 1620, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.41−0.46 (2H, m), 0.91−1.01 (2H, m), 1.08−1.79 (11H, m), 1.89−2.05 (1H, m), 2.85 (2H, d, J = 6.6 Hz), 4.73 (2H, s), 6.38 (1H, d, J = 7.4 Hz), 6.59 (1H, br s), 6.71 (1H, t, J = 7.2 Hz), 7.00 (1H, br s), 7.59 (1H, d, J = 7.0 Hz).

2-(3-(Biphenyl-2-ylmethyl)-8-((carbomethoxymethyl)oxy)-2-isopropylindolizin-1-yl)glyoxylamide (27xxxi) and carboxylic acid 28xxxi: mp 124−130 °C; 48.6% yield. Anal. ($C_{29}H_{28}N_2O_5 \cdot 0.2H_2O$) C, H, N.

28xxxi: mp 139−141 °C. 59% yield. Anal. ($C_{28}H_{26}N_2O_5 \cdot 1.3H_2O$) C, H, N.

2-(2-*tert*-Butyl-8-((carbomethoxymethyl)oxy)-3-(*o*-phenylbenzyl)indolin-1-yl)glyoxylamide (27xxxii) and carboxylic acid 28xxxii: mp 206−207 °C (EtOAc); 77.6% yield. Anal. ($C_{30}H_{30}N_2O_5 \cdot 0.7H_2O$) C, H, N.

28xxxii: mp 221−222 °C (EtOAc); quantitative yield. Anal. ($C_{29}H_{28}N_2O_5 \cdot 0.6C_6H_6$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-2-cyclopentyl-3-(*o*-phenylbenzyl)indolin-1-yl)glyoxylamide (27xxxiii) and carboxylic acid 28xxxiii: mp 119−121 °C (benzene); 77.6% yield. Anal. ($C_{30}H_{28}N_2O_5 \cdot 0.7H_2O$) C, H, N.

28xxxiii: mp 147−148 °C (EtOAc); 73.4% yield.

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(*m*-phenylbenzyl)indolin-1-yl)glyoxylamide (27xxxiv) and carboxylic acid 28xxxiv: mp 204−205 °C (EtOAc); 11.5% yield. Anal. ($C_{28}H_{26}N_2O_5 \cdot 0.2H_2O$) C, H, N.

28xxxiv: mp 241−244 °C (EtOAc); 73.5% yield.

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(3-phenyl-2-propenyl)indolin-1-yl)glyoxylamide (27xxxv) and carboxylic acid 28xxxv: mp 260−262 °C (EtOAc); 73.7% yield; IR ν_{max} (Nujol) 3350, 3199, 1754, 1664, 1611, 1493 cm^{-1}. Anal. ($C_{24}H_{24}N_2O_5 \cdot 0.2H_2O$) C, H, N.

28xxxv: mp 222−224 °C (EtOAc); 71.3% yield. Anal. ($C_{23}H_{22}N_2O_5$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-2-ethyl-3-(3-phenyl-2-propanyl)indolin-1-yl)glyoxylamide (27xxxvi) and Carboxylic Acid 28xxxvi. A mixture of the olefin **27xxxv** (180 mg, 0.428 mmol) and 10% Pd−C (13 mg) in EtOAc (15 mL) was stirred in hydrogen for 4 h. The catalyst was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was recrystallized from EtOAc to yield 103 mg (56.9%); mp 167 °C. Anal. ($C_{24}H_{26}N_2O_5 \cdot 0.1H_2O$) C, H, N.

28xxxvi: mp 215−217 °C; 93.1% yield. Anal. ($C_{23}H_{24}N_2O_5 \cdot 0.4H_2O$) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-2-cyclopropyl-3-(1-naphthylmethyl)indolin-1-yl)glyoxylamide (27xxxvii) and carboxylic acid 28xxxvii: amorphous solid; 44.3% yield. Anal. ($C_{27}H_{24}N_2O_5 \cdot 0.8C_6H_6$) C, H, N.

28xxxvii: mp 205−207 °C (EtOAc); 70.7% yield. Anal. ($C_{26}H_{22}N_2O_5 \cdot 0.4H_2O$) C, H, N.

8-(Benzyloxy)-1-carbethoxy-2-methoxyindolizine (17c). A mixture of **16b** (1 g, 3.69 mmol) and methyl bromoacetate (10 mL) was stirred at 50°C for 18 h in N_2. Ether was added to the reaction mixture. The insoluble oil was washed with ether, dried, and concentrated. A mixture of the pyridinium salt and K_2CO_3 (4.2g, 36.85 mmol) was stirred in 2-butanone (17 mL) at room temperature for 4 h. Dimethyl sulfate (2.5 mL, 26.38 mmol) in 2-butanone (3 mL) was added, then the mixture was heated to 60 °C. Water was added. The mixture was extracted with EtOAc. The extracts were dried. After removal of the solvent, the residue was chromatographed in hexane:EtOAc 5:1 to give **17c**: 382 mg (32% yield); IR ν_{max} (neat) 2970, 1693, 1555, 1527, 1452, 1370, 1304 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, t, J = 7.0 Hz), 3.86 (3H, s), 4.12 (2H, q, J = 7.0 Hz), 5.15 (2H, s), 6.30 (1H, d, J = 7.8 Hz), 6.46 (1H, dd, J = 6.6, J = 7.8 Hz), 7.26−7.54 (5H, m).

2-(8-(Benzyloxy)-2-methoxy-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (25xxxviii): mp 183−184 °C (hexane:EtOAc). Anal. ($C_{31}H_{26}N_2O_4$ 0.2H_2O) C, H, N.

2-(8-((Carbomethoxymethyl)oxy)-2-methoxy-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (27xxxviii) and carboxylic acid 28xxxviii: mp 188−189 °C (hexane:EtOAc). 56% yield (two steps). Anal. ($C_{27}H_{24}N_2O_6 \cdot 0.2H_2O$) C, H, N.

28xxxviii: mp 197−198 °C (EtOAc); 32% yield. Anal. ($C_{26}H_{22}N_2O_6$) C, H, N.

Diethyl 2-(3-Benzyloxypyridinio)-3-thionio-4-thiahept-2-enedioate (33). A solution of benzyloxypyridine (21.73 g, 0.117 mol) and ethyl bromoacetate (19.6 g, 0.117 mol) in benzene (85 mL) was stirred at 65 °C for 2 h and concentrated. The residue was washed with EtOAc.

A solution of aqueous NaOH (11.80 g, 0.295 mol, 35 mL) was added dropwise to a solution of the residue, CS_2 (10.8 g, 0.142 mol), water (24 mL), and EtOH (120 mL). The mixture was stirred for 30 min. Ethyl acrylate (11.8 g, 0.118 mol) was added dropwise. The mixture was stirred for 1 h. Ice water was added. The solid was collected by filtration, washed with water, dried (10.9 g, 20.8%), and recrystallized from $CHCl_3$: ether: mp 162−164 °C; IR ν_{max} (Nujol) 1719, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (3H, t, J = 6.9 Hz), 1.26 (3H, t, J = 7.2 Hz), 2.80 (2H, t, J = 7.5 Hz), 3.58 (2H, t, J = 7.5 Hz), 4.13 (2H, q, J = 6.9 Hz), 4.15 (2H, q, J = 7.2 Hz), 5.21 (2H, s), 7.42 (5H, s), 7.73 (1H, dd, J = 9.0, 6.0 Hz), 7.87 (1H, ddd, J = 8.7, 2.4, 1.2 Hz), 8.12 (1H, dt, J = 6.0, 1.2 Hz), 8.22 (1H, dd, J = 2.1, 0.9 Hz). Anal. ($C_{22}H_{25}NO_5S_2 \cdot 0.05CHCl_3 \cdot 0.3H_2O$) C, H, N, S, Cl.

8- and 6-(Benzyloxy)-1,3-dicarbethoxy-2-(2-(carbethoxyethyl)thio)indolizine (34a + 34b). A solution of ethyl bromoacetate (2.70 g, 16.2 mmol) and the salt **33** (6.03 g, 13.5 mmol) in $CHCl_3$ (40 mL) was allowed to stand for 3 d and cooled in ice. A solution of DBU (2.47 g, 16.2 mmol) and chloranil (3.32 g, 13.5 mmol) was added. The mixture was stirred at 0 °C for 6 h and chromatographed (120 g) in $CHCl_3$ to give a ca. 10:1 mixture of **34a** and **34b**, (6.0 g, 89.1%) as an oil.

8-(Benzyloxy)-1,3-dicarbethoxy-2-mercaptoindolizine (35a). KOtBu (2.73 g, 24.3 mmol) was added in small portions to a solution of the ester **34a**+**b** (9.88 g, 19.8 mmol) in DMF (25 mL) with cooling in ice. The mixture was stirred at 50 °C for 5 h. Ice water and then dilute HCl were added. The mixture was extracted with EtOAc. The extracts were washed with water, dried, and concentrated. The residue was chromatographed (200 g) in hexane:EtOAc (2:1). Both fractions of larger and smaller R_f values were crystallized from benzene:hexane.

35a, the fraction having the larger R_f value: mp 125−127 °C; 1.12 g (16.7%); IR ν_{max} (Nujol) 1661, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (3H, t, J = 6.9 Hz), 1.48 (3H, t, J = 7.5 Hz), 4.42 (2H, q, J = 6.9 Hz), 4.46 (2H, q, J = 7.2 Hz), 5.09 (2H, s), 7.04 (1H, s), 7.15 (1H, dd, J = 9.9, 2.4 Hz), 7.3−7.55 (5H, m), 8.09 (1H, dd, J = 9.6, 0.6 Hz), 9.41 (1H, s). Anal. ($C_{21}H_{21}NO_5S$) C, H, N, S.

The fraction having the smaller R_f value: mp 81−82 °C; 4.59 g (58.1%); IR ν_{max} (Nujol) 1686, 1655, 1543, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (3H, t, J = 6.9 Hz), 1.47 (3H, t, J = 7.2 Hz), 4.45 (2H, q, J = 7.5 Hz), 5.16 (2H, s), 5.56 (1H, s), 6.58 (1H, d, J = 7.5 Hz), 6.73 (1H, t J = 6.9 Hz), 7.3−7.5 (5H, m), 9.15 (1H, dd, J = 7.2, 0.9 Hz). Anal. ($C_{21}H_{21}NO_5S \cdot 0.4H_2O$) C, H, N, S.

8-(Benzyloxy)-1,3-dicarbethoxy-2-(methylthio)indolizine (35b). NaH (60%, 76 mg) was added to a solution of the thiol **35a** (690 mg, 1.73 mmol) in DMF (4 mL) with cooling in ice under N_2. A solution of iodomethane (295 mg, 2.08 mmol) in DMF (1 mL) was added dropwise to the mixture with cooling in ice. The mixture was stirred at room temperature for 2 h, acidified with dilute HCl, and extracted with EtOAc. The extracts were washed with water, dried, and concentrated. The residue was chromatographed in hexane: EtOAc (5:1 to 3:2) to give 732 mg of an oil (quantitative yield): ^1H NMR ($CDCl_3$) δ 1.13 (3H, t, J = 6.9 Hz), 1.45 (3H, t, J = 7.2 Hz), 2.47 (3H, s), 4.00 (2H, q, J = 7.2 Hz), 4.45 (2H, q, J = 7.5 Hz), 5.13 (2H, s), 6.46 (1H, d, J = 7.5 Hz), 6.70 (1H, t J = 7.2 Hz), 7.3−7.5 (5H, m), 9.06 (1H, dd, J = 6.9, 0.6 Hz).

8- and 6-(Benzyloxy)-2-(methylthio)indolizine (24g). Aqueous KOH (10%, 5 mL) was added to a solution of the diester **35b** (337 mg, 0.815 mmol) in DMSO (5 mL). The mixture was heated under reflux for 8 h. After cooling, the mixture was acidified with dilute HCl with cooling in ice and extracted with EtOAc. The extracts were washed with water, dried, and concentrated to give a mixture of **24g** and the dicarboxylic acid.

The solid in toluene (5 mL) was heated under reflux for 1 h and concentrated. The residue was chromatographed (25 g) in hexane:EtOAc (5:1) and crystallized from hexane: 191 mg (87.0%); mp 94 °C. Anal. ($C_{16}H_{15}NOS \cdot 0.05C_6H_6$) C, H, N, S.

2-(8-(Benzyloxy)-2-(methylthio)-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (25xxxix): mp 199−201 °C; 28.5% Yield from **24g**. Anal. ($C_{31}H_{26}N_2O_3S$) C, H, N, S.

2-(8-Hydroxy-2-(methylthio)-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (26xxxix). A 1 N solution of BBr_3 in CH_2Cl_2 (0.7 mL, 0.7 mmol) was added to a solution of the benzyl ether **25xxxix** (85 mg, 0.168 mmol) in CH_2Cl_2 (1 mL) with cooling in ice. The mixture was stirred at 0 °C for 1 h. Ice water was added. The mixture was extracted with CH_2Cl_2:MeOH. The extracts were washed with water, dried, and concentrated. The residue was recrystallized from EtOAc (mp 138−142 °C).

2-(8- and 6-((Carbomethoxymethyl)oxy)-2-(methylthio)-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (27xxxix) and carboxylic acid 28xxxix: mp 88−91 °C; 41.3% yield.

28xxxix: mp 200−205 °C; 65.4% yield. Anal. ($C_{26}H_{22}N_2O_5S$) C, H, N, S.

2-Ethyl-7-methoxyindolizine (37a) and 2-Cyclopropyl-7-methoxyindolizine (37b). 4-Methoxypicoline was treated as in the procedure for the preparation of **24** from **23**.

37a: 29.4% yield; IR ν_{max} (KBr) 2962, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, J = 7.2 Hz), 2.67 (2H, q, J = 7.4 Hz), 3.77 (3H, s), 6.06 (1H, s), 6.14 (1H, dd, J = 7.6, 2.6 Hz), 6.52 (1H, d, J = 2.4 Hz), 6.94 (1H, s), 7.66 (1H, d, J = 7.6 Hz). MS m/z 175.0982 $[M]^+$.

37b: mp 101−102 °C (hexane); 27.3% yield. Anal. ($C_{12}H_{13}NO$) C, H, N.

2-Alkyl-7-methoxy-3-(substituted carbonyl)indolizine (38). Indolizine compound **37** was converted to **38** by the same procedure cited for the preparation of **11** from **10**.

3-Benzoyl-2-ethyl-7-methoxyindolizine (38a): mp 105−106 °C (hexane); 70.5% yield; IR ν_{max} (KBr) 3057, 2966, 2926, 2868, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (3H, t, J = 7.5 Hz), 2.17 (2H, q, J = 7.5 Hz), 3.88 (3H, s), 6.23 (1H, s), 6.54 (1H, dd, J = 2.7, 7.8 Hz), 6.72 (1H, d, J = 2.1 Hz), 7.40−7.49 (3H, m), 7.56−7.60 (2H, m), 9.67 (1H, d, J = 7.5 Hz). Anal. ($C_{18}H_{17}NO_2 \cdot 0.5H_2O$) C, H, N.

2-Cyclopropyl-7-methoxy-3-(*o*-phenylbenzoyl)indolizine (38b): a yellow oil; quantitative yield; ^1H NMR ($CDCl_3$) δ 0.48 −0.69 (2H, m), 1.11 (1H, m), 3.82 (3H, s), 5.71 (1H, s), 6.45 (1H, dd, J = 2.8, 7.6 Hz), 6.57 (1H, d, J = 2.6 Hz), 7.15−7.54 (9H, m), 9.76 (1H, d, J = 7.6 Hz).

2-Ethyl-7-methoxy-3-(*o*-phenylbenzoyl)indolizine (38c): mp 140−141 °C (ether); 90.2% yield. Anal. ($C_{24}H_{23}NO$) C, H, N.

3-(Cyclohexylcarbonyl)-2-ethyl-7-methoxyindolizine (38d): mp 112−113 °C (hexane); 41.1% yield; IR ν_{max} (KBr) 2923, 2848, 1644 cm^{-1}. Anal. ($C_{18}H_{23}NO_2 \cdot 0.1H_2O$) C, H, N.

3-Benzyl-2-ethyl-7-methoxyindolizine (39a): amorphous solid; 22.0% yield; IR ν_{max} (KBr) 3002, 2956, 2926, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, dt, J = 7.5, 1.2 Hz), 2.69 (2H, q, J = 7.5 Hz), 3.76 (3H, s), 4.20 (2H, s), 6.09 (1H, dd, J = 2.4, 7.5 Hz), 6.18 (1H, s), 6.59 (1H, d, J = 2.1 Hz), 7.04 (2H, d, J = 7.2 Hz), 7.14−7.27 (3H, m), 7.25 (1H, d, J = 7.2 Hz).

2-Cyclopropyl-7-methoxy-3-(*o*-phenylbenzyl)indolizine (39b): mp 109−110 °C (hexane); 44.3% yield. Anal. ($C_{25}H_{23}NO$) C, H, N.

2-Ethyl-7-methoxy-3-(*o*-phenylbenzyl)indolizine (39c): mp 100−101 °C (hexane); 39.2% yield. Anal. ($C_{24}H_{23}NO$) C, H, N.

3-(Cyclohexylmethyl)-2-ethyl-7-methoxyindolizine (39d): amorphous yellow solid; 48.2% yield.

2-(3-Benzyl-2-ethyl-7-methoxyindolizin-1-yl)glyoxylamide (40a): amorphous solid; 78.9% yield; IR ν_{max} (KBr) 3500, 3386, 3004, 2962, 1689, 1644, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (3H, dt, J = 7.5, 1.2 Hz), 2.98 (2H, q, J = 7.8 Hz), 3.87 (3H, s), 4.21 (2H, s), 5.57 (1H, br s), 6.42 (1H, dd, J = 2.7, 7.5 Hz), 6.79 (1H, br s), 7.08 (1H, d, J = 6.9 Hz), 7.21 (3H, m), 7.51 (1H, d, J = 7.5 Hz), 7.82 (1H, d, J = 2.7 Hz).

2-(2-Cyclopropyl-7-methoxy-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (40b): mp 194−195 °C (benzene:hexane); 50.1% yield. Anal. ($C_{27}H_{24}N_2O_3$) C, H, N.

2-(2-Ethyl-7-methoxy-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylylamide (40c): mp 101−106 °C (benzene:hexane); 75.9% yield. Anal. ($C_{26}H_{24}N_2O_3 \cdot 0.3C_6H_6$) C, H, N.

2-(3-(Cyclohexylmethyl)-2-ethyl-7-methoxyindolizin-1-yl)glyoxylamide (40d): mp 178−180 °C (THF:hexane); 50.4% yield. Anal. ($C_{20}H_{25}N_2O_3 \cdot 0.2$THF) C, H, N.

2-(3-Benzyl-2-ethyl-7-hydroxyindolizin-1-yl)glyoxylamide (41a): amorphous solid; 49% yield; ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, t, J = 7.2 Hz), 2.86 (2H, t, J = 7.2 Hz), 4.24 (2H, s), 6.52 (1H, dd, J = 2.1, 7.5 Hz), 7.08−7.30 (6H, m), 7.43 (1H, d, J = 2.4 Hz), 7.51 (1H, s), 7.92 (1H, d, J = 6.9 Hz), 7.98 (1H, s).

2-(2-Cyclopropyl-7-hydroxy-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (41b): amorphous solid; 12.6% yield.

2-(2-Ethyl-7-hydroxy-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylylamide (41c): mp 125−129 °C (benzene:hexane); 36.9% yield. Anal. ($C_{25}H_{22}N_2O_3 \cdot 0.2C_6H_6 \cdot 0.5H_2O$) C, H, N.

2-(3-(Cyclohexylmethyl)-2-ethyl-7-hydroxyindolizin-1-yl)glyoxylamide (41d): amorphous solid; 28.0% yield.

2-(3-Benzyl-7-((3-carbethoxypropyl)oxy)-2-ethylindolizin-1-yl)glyoxylamide (42a) and carboxylic acid 43a: mp 146−149 °C; 54.% yield; IR ν_{max} (KBr) 3430, 3170, 2958, 2928, 1731, 1674, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.5 Hz), 1.25 (3H, t, J = 7.2 Hz), 2.13 (2H, m), 2.49 (2H, q, J = 7.2 Hz), 2.97 (2H, q, J = 7.5 Hz), 4.08 (2H, t, J = 6.3 Hz), 4.14 (2H, q, J = 7.2 Hz), 4.21 (2H, s), 5.56 (1H, br s), 6.40 (1H, dd, J = 2.7, 7.2 Hz), 6.78 (1H, br s), 7.08 (2H, d, J = 7.8 Hz), 7.21−7.29 (3H, m), 7.50 (1H, d, J = 7.2 Hz), 7.78 (1H, d, J = 2.7 Hz). Anal. ($C_{25}H_{28}N_2O_3 \cdot 0.2H_2O$) C, H, N.

43a: mp 178−183 °C (dec); 77.0% yield; IR ν_{max} (KBr) 3700−2400, 3085, 2925, 1710, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.5 Hz), 2.14 (2H, t, J = 6.9 Hz), 2.97 (2H, q, J = 7.5 Hz), 4.11 (2H, t, J = 6.3 Hz), 4.20 (2H, s), 6.38 (1H, br s), 6.41 (1H, dd, J = 7.2, 2.4 Hz), 6.96 (2H, br s), 7.08 (2H, d, J = 6.9 Hz), 7.23−7.26 (3H, m), 7.51 (1H, d, J = 7.5 Hz), 7.75 (1H, d, J = 2.7 Hz). Anal. ($C_{23}H_{24}N_2O_3 \cdot 0.3H_2O$) C, H, N.

2-(7-((3-Carbethoxypropyl)oxy)-2-cyclopropyl-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (42b) and carboxylic acid 43b: amorphous solid; 84.2% yield.

43b: mp 112−121 °C, (dec); 69.6% yield. Anal. ($C_{30}H_{28}N_2O_5 \cdot 1.2H_2O$) C, H, N.

2-(7-((3-Carbethoxypropyl)oxy)-2-ethyl-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylylamide (42c) and carboxylic acid 43c: mp 131−133 °C (benzene:hexane); 70.9% yield. Anal. ($C_{31}H_{32}N_2O_5 \cdot 0.2H_2O$) C, H, N.

(43c): mp 112−116 °C (dec); 67.0% yield. Anal. ($C_{29}H_{28}N_2O_5 \cdot 0.9H_2O$) C, H, N.

2-(7-((3-Carbethoxypropyl)oxy)-3-(cyclohexylmethyl)-2-ethyl-hydroxyindolizin-1-yl)glyoxylamide (42d) and carboxylic acid 43d: mp 150−151 °C (THF:hexane); 87.0% yield. Anal. ($C_{25}H_{34}N_2O_5$) C, H, N.

43d: mp 201−202.5 °C; 92.4% yield. Anal. ($C_{23}H_{30}N_2O_5 \cdot 0.3H_2O$) C, H, N.

2-(7-((Carbethoxymethyl)oxy)-2-ethyl-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (42e) and carboxylic acid 43e: mp 119−121 °C (THF:hexane); 86.6% yield. Anal. ($C_{29}H_{28}N_2O_5 \cdot 0.3H_2O$) C, H, N.

43e: mp 226 °C (dec); 81.0% yield. Anal. ($C_{27}H_{24}N_2O_5 \cdot 0.3$EtOAc$\cdot 0.7H_2O$) C, H, N.

2-(7-((5-Carbethoxypentyl)oxy)-2-ethyl-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (42f) and carboxylic acid 43f: mp 122−123 °C (MeOH:Et_2O:hexane); 81.0% yield. Anal. ($C_{32}H_{34}N_2O_5 \cdot 0.3H_2O$) C, H, N.

43f: mp 84−94 °C (dec); 72.0% yield. Anal. ($C_{30}H_{30}N_2O_5 \cdot 0.9H_2O$) C, H, N.

2-(7-((2-Carboxyethyl)oxy)-2-ethyl-3-(*o*-phenylbenzyl)-indolizin-1-yl)glyoxylamide (43g). Propiolactone (25 mg, 0.336 mmol) was added dropwise to a solution of **41c** (133.7 mg, 0.336 mmol) and KOt-Bu (37.6 mg, 0.336 mmol) in THF (4 mL) under N_2. The mixture was stirred for 21 h. Water was added. The mixture was washed with EtOAc. The aqueous phase was acidified with HCl. The precipitate was collected with filtration to give **43g**: 96.2 mg (60.9%); mp 99−108 °C (dec). Anal. ($C_{28}H_{26}N_2O_5 \cdot 1.2H_2O$) C, H, N.

2-(7-((3-Carbethoxypropyl)oxy)-2-ethyl-3-(*o*-phenylbenzyl)indolizin-1-yl)acetamide (44a) and Carboxylic Acid 44b. BH_3−t-BuNH_2 complex (125 mg, 1.44 mmol) was added to a mixture of $AlCl_3$ (13 mg, 0.097 mmol) in toluene (10 mL) with cooling in ice. The mixture was stirred at 0 °C for 10 min. A solution of the glyoxylamide **42c** (246 mg, 0.48 mmol) in toluene (5 mL) was added to the solution. The solution was heated at 60 °C for 2 h. After cooling, the solution was poured to ice-cold dilute HCl. The mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried, and concentrated. The residue was chromatographed in EtOAc:hexane (4:1) and recrystallized from hexane: 190 mg (79.4%); mp 128−130 °C. Anal. ($C_{31}H_{34}N_2O_4 \cdot 0.6H_2O$) C, H, N.

44b: mp 105−120 °C (dec); 62.0% yield. Anal. ($C_{31}H_{34}N_2O_4 \cdot 0.6H_2O$) C, H, N.

3-((Benzyloxycarbonyl)amino)-2-methylpyridine (45b). A mixture of 3-aminopicoline **45a** (0.60 g, 5.5 mmol), *N*-(benzyloxycarbonyl)succinimide (2.1 g, 8.3 mmol), and DMF (2 mL) was left for 2 d. The reaction mixture was poured into water, extracted with EtOAc, washed with water, and dried. The solvent was removed. The residue was chromatographed by eluting with EtOAc:hexane to give **45b** (0.92 g, 68%), mp 76−78 °C; IR ν_{max} (Nujol) 1725, 1551, 1227, 1061 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49 (3H, s), 5.22 (3H, s), 7.16 (1H, m), J = 8.7 Hz), 7.36−7.45 (5H, m), 8.15−8.27 (2H, m). Anal. ($C_{14}H_{14}N_2O_2$) C, H, N.

3-(*N*-(Benzyloxycarbonyl)-*N*-((methoxycarbonyl)-methyl)amino)-2-methylpyridine (46). To a suspension of NaH (60% dispersion in oil, 0.17 g, 4.2 mmol) in DMF (3 mL) was added **45b** (0.92 g, 3.8 mmol) in DMF (5 mL) at 0 °C with stirring under N_2. Stirring was continued for 1 h, at which time methyl bromoacetate (0.40 mL, 4.2 mmol) was added. The reaction mixture was stirred at room temperature for an additional 2.5 h. The reaction mixture was poured into water, extracted with EtOAc, washed with water, and dried. The solvent was removed. The product was purified by column chromatography in EtOAc:hexane (1:1) to yield **46** (1.07 g, 90%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.43 (3/4H, s), 2.51 (1/4H, m), 3.68 (1/4H, m), 3.76 (3/4H, s), 3.85 (1H, d, J = 18 Hz), 4.69 (1H, d, J = 18 Hz), 5.06−5.21 (3/2H, m), 5.22 (1/2H, s), 7.13−7.37 (6H, m), 7.73 (1H, m), 8.45 (1H, m).

3-Benzyl-8-(*N*-(benzyloxycarbonyl)-*N*-((methoxycarbonyl)methyl)amino)-2-methylindolizine (32xl): 42% yield; ^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s), 3.67−3.77 (3H, m), 4.21−4.46 (4H, m), 5.15 (2/3H, s), 5.25 (1/3H, s), 6.28−6.37 (2H, m), 6.77 (1H, m), 7.04−7.50 (11H, m).

8-(*N*-(Benzyloxycarbonyl)-*N*-((methoxycarbonyl)-methyl)amino)-3-(cyclohexylmethyl)-2-methylindolizine (32xli): 31% yield; ^{1}H NMR ($CDCl_3$) δ 0.82−1.80 (11H, m), 2.25 (3H, s), 2.70 (2H, d, J = 7 Hz), 3.66 (3/4H, s), 3.74 (9/4H, s), 4.10−4.55 (2H, m), 5.15 (3/2H, s), 5.23 (1/2H, s), 6.19 (3/4H, s), 6.23 (1/4H, s), 6.43 (1H, m), 6.73 (3/4H, d, J = 7 Hz), 6.79 (1/4H, d, J = 7 Hz), 7.12−7.42 (5H, m), 7.64 (1H, d, J = 7 Hz).

2-(3-Benzyl-8-(*N*-(benzyloxycarbonyl)-*N*-((methoxycarbonyl)methyl)amino)-2-methylindolizin-1-yl)glyoxylamide (27xl): 66% yield; ^{1}H NMR ($CDCl_3$) δ 2.44 (1H, s), 2.45 (2H, s), 3.67 (1H, s), 3.73 (2H, s), 3.80 (1H, d, J = 18 Hz), 4.24 (2H, s), 4.71 (1H, d, J = 18 Hz), 5.00−5.31 (2H, m), 6.64 (1H, m), 7.04−7.42 (11H, m), 7.62 (1H, m).

2-(8-(*N*-(benzyloxycarbonyl)-*N*-((methoxycarbonyl)-methyl)amino)-3-(cyclohexylmethyl)-2-methylindolizin-1-yl)glyoxylamide (27xli): 72% yield; ^{1}H NMR ($CDCl_3$) δ 1.00−1.26 (4H, m), 1.50−1.78 (7H, m), 2.32 (1H, s), 2.33 (2H, s), 2.70 (2H, d, J = 7 Hz), 3.67 (1H, s), 3.73 (2H, s), 3.78 (2/3H, d, J = 18 Hz), 3.79 (1/3H, d, J = 18 Hz), 4.60 (1/3H, d, J = 18 Hz), 4.69 (2/3H, d, J = 18 Hz), 5.03 (2/3H, d, J = 13 Hz), 5.19 (1/3H, d, J = 13 Hz), 5.23 (2/3H, d, J = 13 Hz), 5.25 (1/3H, d, J = 13 Hz), 6.73 (2/3H, t, J = 7 Hz), 6.79 (1/3H, t, J = 7 Hz), 7.14−7.43 (6H, m), 7.79 (1H, m).

2-(3-Benzyl-8-((methoxycarbonyl)methyl)amino)-2-methylindolizin-1-yl)glyoxylamide (47xl) and Carboxylic Acid 28xl. A mixture of the indolizine **27xl** (88 mg, 0.17

mmol) and 10% Pd−C (0.02 g) in EtOAc (5 mL) was stirred in H_2 atmosphere for 3 h. The catalyst was filtered and the filtrate was concentrated. Crystallization of the residue from THF:ether afforded **47xl** (51 mg, 78%): mp 186−188 °C. Anal. ($C_{21}H_{21}N_3O_4$) C, H, N.

28xl: mp 293 °C (dec) (MeOH:ether); 61% yield.

2-(8-((methoxycarbonyl)methyl)amino)-3-(cyclohexylmethyl)-2-methylindolizin-1-yl)glyoxylamide (47xli) and carboxylic acid 28xli: mp 173−177 °C (MeOH:ether:hexane); 90% yield. Anal. ($C_{21}H_{27}N_3O_4 \cdot 0.2H_2O$) C, H, N.

28xl: mp >300 °C (MeOH:ether); 47% yield.

2-(3-Benzyl-8-((methoxycarbonyl)methyl)amino)-2-methylindolizin-1-yl)acetamide (48a) and carboxylic acid 48b: mp 147−150 °C (dec) (EtOH:ether:hexane); 55% yield.

48b: 60% yield.

2-(3-(Biphenyl-2-ylmethyl)-2-ethyl-8-(substituted methyloxy)indolizin-1-yl)glyoxylamide (49a−e). General procedure: 2-(3-(Biphenyl-2-ylmethyl)-2-ethyl-8-((hydroxymethyl)oxy)indolizin-1-yl)glyoxylamide (**26ii**) was treated with the same procedure as for the preparation of **27** from **26**.

2-(3-(Biphenyl-2-yl-methyl)-2-ethyl-8-(((2-trityltetrazolyl)methyl)oxy)indolizin-1-yl)glyoxylamide (49a): mp 119−121 °C; 66% yield; IR ν_{max} (Nujol) 3439, 3363, 3166, 1734, 1685, 1607, 1495, 1249 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3H, t, $J = 7.5$ Hz), 2.78 (2H, q, $J = 7.5$ Hz), 4.10 (2H, s), 4.85 (1H, br s), 5.42 (2H, s), 6.05 (1H, br s), 6.45 (1H, t, $J = 7.2$ Hz), 6.58 (1H, d, $J = 7.2$ Hz), 6.77 (1H, d, $J = 7.5$ Hz), 7.03 (1H, d, $J = 6.9$ Hz), 7.08−7.18 (7H, m), 7.22−7.54 (16H, m).

2-(3-(Biphenyl-2-ylmethyl)-2-ethyl-8-((tetrazolylmethyl)oxy)indolizin-1-yl)glyoxylamide (49b). mp 206−209 °C (dec); 60% yield. Anal. ($C_{27}H_{24}N_6O_3 \cdot 0.1H_2O$) C, H, N.

2-(3-(Biphenyl-2-ylmethyl)-2-methyl-8-(pyridin-2-ylmethoxy)indolizin-1-yl)glyoxylamide (49c): mp 196−197 °C (hexane:AcOEt); 4.2% yield; ^1H NMR ($CDCl_3$) δ 2.38 (3H, s), 4.11 (2H, s), 4.81 (1H, br s), 5.11 (2H, s), 6.13 (1H, br s), 6.35 (1H, d, $J = 7.5$ Hz), 6.44 (1H, t, $J = 7.2$ Hz), 6.81 (1H, d, $J = 7.2$ Hz), 7.02 (1H, d, $J = 6.0$ Hz), 7.14−7.20 (1H, m), 7.25−7.33 (1H, m), 7.35−7.55 (9H, m).

2-(3-(Biphenyl-2-ylmethyl)-2-methyl-8-(pyridin-4-ylmethoxy)indolizin-1-yl)glyoxylamide (49d): mp 195−197 °C (hexane:AcOEt); 3.4% yield.

2-(3-(Biphenyl-2-ylmethyl)-2-methyl-8-(quinolin-2-ylmethoxy)indolizin-1-yl)glyoxylamide (49e): mp 165−167 °C (hexane:AcOEt); 3.4% yield; ^1H NMR ($CDCl_3$) δ 2.41 (3H, s), 4.11 (2H, s), 5.31 (1H, br s), 5.47 (2H, s), 6.26−6.38 (2H, m), 6.51 (1H, br s), 6.83 (1H, d, $J = 7.8$ Hz), 6.98−7.01 (1H, m), 7.14−7.24 (1H, m), 7.25−7.31 (3H, m), 7.40−7.60 (5H, m), 7.69−7.82 (3H, m), 8.04−8.17 (2H, m).

2-(8-((3-Carbomethoxypropyl)oxy)-2-ethyl-3-(*o*-phenylbenzyl)indolizin-1-yl)glyoxylamide (49f) and carboxylic acid 49g: mp 126−127 °C; 42% yield. Anal. ($C_{31}H_{32}N_2O_5 \cdot 0.5H_2O$) C, H, N.

49g: mp 185−187 °C; 71% yield. Anal. ($C_{29}H_{28}N_2O_5 \cdot 0.3H_2O$) C, H, N.

2-(8-((2-Carboxyethyl)oxy)-2-ethyl-3-(*o*-phenylbenzyl)-indolizin-1-yl)glyoxylamide (49h): mp 185−187 °C; 11% yield;

2-(8-((Cyanomethyl)oxy)-2-ethyl-3-(1-naphthylmethyl)-indolizin-1-yl)glyoxylamide (50a): mp 212−215 °C (ether); 45% yield. Anal. ($C_{21}H_{18}N_3O_3Cl$) C, H, N.

2-(8-((Cyanomethyl)oxy)-2-ethyl-3-(1-naphthylmethyl)-indolizin-1-yl)glyoxylamide (50b). A mixture of the nitrile derivative **50a** (100 mg, 0.253 mmol) and trimethyltin azide (68 mg, 0.329 mmol) in toluene (2.5 mL) was heated under reflux for 23 h. The precipitate was collected by filtration and suspended in toluene (2 mL). HCl gas was introduced. The mixture was stirred at room temperature for 20 min and then concentrated. EtOAc was added. The mixture was extracted with 1 N KOH. The aqueous phase was washed with CH_2Cl_2, acidified with dilute HCl, and extracted with EtOAc. The extracts were washed with water and dried. After removal of the solvent, the residue was dissolved in ether. The insoluble materials were removed by filtration and hexane was added to the filtrate to give **50b** (25 mg, 23% yield): mp 140−143 °C (dec) (ether:hexane).

2-(3-Benzyl-8-((carboxymethyl)oxy)-2-ethylindolizin-1-yl)-*N*-methylglyoxylamide (51a): mp 212−213 °C (AcOEt); 47% yield; IR ν_{max} (KBr) 3361, 2965, 2931, 1766, 1609, 1308, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3H, t, $J = 7.6$ Hz), 2.87 (2H, q, $J = 7.6$ Hz), 3.05 (3H, d, $J = 5.4$ Hz), 4.26 (2H, s), 4.73 (2H, s), 6.39 (1H, d, $J = 7.6$ Hz), 6.59 (1H, dd, $J = 6.4$, 7.6 Hz), 7.66-7.11 (2H, m), 7.22−7.29 (3H, m), 7.42 (1H, d, $J = 6.4$ Hz). Anal. ($C_22H_22N_2O_5$) C, H, N.

(3-Benzyl-8-((carboxymethyl)oxy)-2-ethylindolizin-1-yl)*N*,*N*-dimethylglyoxylamide (51b): mp 166−167 °C (AcOEt); 49% yield; IR ν_{max} (KBr) 3435, 2937, 1764, 1608, 1195 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (3H, t, $J = 7.6$ Hz), 2.99 (2H, q, $J = 7.6$ Hz), 3.15 (3H, s), 4.26 (2H, s), 4.21 (3H, s), 4.27 (2H, s), 4.74 (2H, s), 6.50 (1H, d, $J = 8.0$ Hz), 6.63 (1H, dd, $J = 6.4$, 8.0 Hz), 7.05−7.10 (2H, m), 7.22−7.29 (3H, m), 7.44 (1H, d, $J = 6.4$ Hz). Anal. ($C_23H_24N_2O_5 \cdot 0.9H_2O$) C, H, N.

3-(4-Methoxyphenyl)-2-methylacrylic Acid (53a): A mixture of *p*-anisaldehyde (26.6 g, 0.195 mol), propionic anhydride (43.0 mL, 0.347 mol) and sodium propionate (18.8 g, 0.195 mol) was heated at 150 °C overnight. After cooling, the reaction mixture was basified with 4N NaOH and washed with ether. The aqueous phase was acidified with conc. HCl and the precipitate was filtered to yield **53a**, 28.5 g (76%), mp 152−155 °C. ^1H NMR ($CDCl_3$) δ 2.16 (3H, d, $J = 1.2$ Hz), 3.85 (3H, s), 6.95 (2H, d, $J = 8.7$ Hz), 7.44 (2H, d, $J = 8.7$ Hz), 7.78 (1H, br s); IR ν_{max} (KBr) 1662, 1605, 1570, 1510 cm^{-1}; EIMS m/z 192 (M^+, base peak). Anal. ($C_{11}H_{12}O_3$) C, H.

3-(3-Methoxyphenyl)-2-methylacrylic acid (53b): mp 78−79 °C; 93% yield. Anal. ($C_{11}H_{12}O_3$) C, H.

2-Ethyl-3-(3-methoxyphenyl)acrylic acid (53c): mp 89−90 °C; 24% yield. Anal. ($C_{12}H_{14}O_3$) C, H.

3-(4-Methoxyphenyl)-2-methylpropionic Acid (54a). A mixture of the acrylic acid **53a** (28.3 g, 0.147 mol) and 10% palladium−coal (2.49 g) in methanol (350 mL) was hydrogenated under 3 atm overnight. The catalyst was filtered off and the solvent was evaporated to give **54a** (21.2 g, 74%): mp 43−44 °C; ^1H NMR ($CDCl_3$) δ 1.17 (3H, d $J = 6.8$ Hz), 2.54−2.83 (2H, m), 3.01 (1H, dd, $J = 5.4$, 12.4 Hz), 3.79 (3H, s), 6.83 (2H, d, $J = 8.7$ Hz), 7.10 (2H, d, $J = 8.7$ Hz); IR ν_{max} (film) 3424, 1709, 1612, 1584 cm^{-1}; EIMS m/z 121 (base peak), 194 (M^+). Anal. ($C_{11}H_{14}O_3$) C, H.

3-(3-Methoxyphenyl)-2-methylpropionic acid (54b): 75% yield. Anal. ($C_{11}H_{14}O_3 \cdot 0.1H_2O$) C, H.

2-(3-Methoxybenzyl)butyric acid (54c): quantitative yield. Anal. ($C_{12}H_{16}O_3$) C, H.

2-(2-Bromo-5-methoxybenzyl)butyric Acid (55). To a solution of the butyric acid **54a** (33.9 g, 0.163 mmol) in acetic acid (50 mL) was added a solution of bromine (10.5 mL, 0.204 mmol) in acetic acid (20 mL) at 0 °C. The resulting solution was stirred at room temperature for 2.5 h and then the mixture was partitioned between water and AcOEt. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with saturated $Na_2S_2O_3$ and water, dried, and evaporated. The residue **55** (51.8 g) was used to the next preparation without further purification: mp 39-42 °C; ^1H NMR ($CDCl_3$) δ 1.00 (3H, t, $J = 7.4$ Hz), 1.55−1.83 (2H, m), 2.68−3.08 (3H, m), 3.75 (3H, s), 6.65 (1H, dd, $J = 8.8$, 3.0 Hz), 6.78 (1H, d, $J = 3.0$ Hz), 7.41 (1H, d, $J = 8.8$ Hz). IR ν_{max} (KBr) 3010, 1689, 1593, 1577 cm^{-1}.

4-Bromo-2-ethyl-7-methoxy-1-indanone (56). A mixture of the butyric acid **55** (51.6 g) and polyphosphoric acid (511 g) was heated at 100 °C for 2.5 h. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with water, 5% $NaHCO_3$, and brine and dried. After removal of the solvent, the residue was chromatographed by eluting with hexane:AcOEt (4:1 to 1:2) to give **56** (30.0 g): ^1H NMR ($CDCl_3$) δ 1.02 (3H, s, $J = 7.4$ Hz), 1.40−1.66 (1H, m), 1.85−2.10 (1H, m), 2.52−2.76 (2H, m), 3.19 (1H, dd, $J = 18.2$, 8.0 Hz), 3.94 (3H, s), 6.72 (1H, d, $J = 8.8$ Hz), 7.64 (1H, d, $J = 8.8$ Hz); IR ν_{max} (film) 1712, 1585 cm^{-1}; EIMS m/z 240 (base peak), 268 (M^+); HR-EIMS calcd for $C_{12}H_{13}BrO_2$ 268.0098, found 268.0079.

6-Methoxy-2-methyl-1-indanone (57a). To the propionic acid **54a** (21.0 g, 0.108 mol) was added polyphosphoric acid (200 g) at 50 °C. The reaction was maintained at 90 °C for 2 h. The mixture was poured into water, stirred at room

temperature overnight, and extracted with ether. The combined extracts were washed with aqueous $NaHCO_3$ and brine and dried. After removal of the solvent, the residue was chromatographed by eluting with CH_2Cl_2:MeOH (10:0 to 9:1) and hexane:AcOEt (9:1 to 4:1) to give **57a** (7.45 g, 39%): ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d J = 7.2 Hz), 2.58−2.84 (2H, m), 3.33 (1H, dd, J = 16.1, 7.1 Hz), 3.84 (3H, s), 7.15−7.23 (2H, m), 7.30−7.40 (1H, m).

7-Methoxy-2-methyl-1-indanone (57b): 17% yield. Anal. ($C_{11}H_{12}O_2$·0.1H_2O) C, H.

2-Ethyl-7-methoxy-1-indanone (57c): three steps yield 51%; mp 67−69 °C. Anal. ($C_{12}H_{14}O_2$) C, H.

Ethyl (6-Methoxy-2-methyl-3*H*-inden-1-yl)acetate (58a). To a solution of triethyl phosphonoacetate (17.2 g, 76.7 mmol) in toluene (100 mL) was added 60% NaH (3.06 g, 76.5 mmol) at 0 °C. After the reaction mixture was stirred for 1 h at this temperature, a solution of the indanone **57a** (1.35 g, 7.63 mmol) in toluene (25 mL) was slowly added. The mixture was refluxed for 4 h and then was poured into 1 N HCl and extracted with AcOEt. The extract was washed with water, dried, and concentrated to produce a crude residue, which was chromatographed by eluting with hexane:AcOEt (19:1) to give the mixture of the compound **58a** and its positional isomer (1.65 g, 88%). The mixture was used to the next preparation without further purification: ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7.2 Hz), 2.12 (3H, s), 3.27 (2H, s), 3.49 (2H, s), 3.83 (3H, s), 4.14 (2H, q, J = 7.2 Hz), 6.68 (1H, dd, J = 2.5, 8.1 Hz), 6.86 (1H, d, J = 2.5 Hz), 7.24 (1H, d, J = 8.1 Hz).

Ethyl (7-methoxy-2-methylinden-1-ylidene)acetate (59b): 49% yield; ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, d, J = 6.6 Hz), 1.27 (3H, t, J = 7.0 Hz), 2.50−2.71 (1H, m), 2.93−3.19 (2H, m), 3.81 (3H, s), 4.21 (2H, q, J = 7.0 Hz), 5.81 (1H, d, J = 2.0 Hz), 6.70 (1H, d, J = 8.4 Hz), 6.86 (1H, d, J = 7.6 Hz), 7.25 (1H, t, J = 7.8 Hz).

Ethyl (2-ethyl-7-methoxyindan-1-ylidene)acetate (59c): 36% yield. Anal. ($C_{16}H_{20}O_3$·0.1H_2O) C, H.

Ethyl (2-Bromo-7-methoxy-2-methylindan-1-ylidene)-acetate (60b). To a solution of the ester compound **59a** (1.39 g, 5.65 mmol) in CCl_4 (15 mL) were added NBS (1.11 g, 6.22 mmol) and benzoyl peroxide (68.5 mg, 0.283 mmol). The mixture was stirred at 50 °C for 6 h, filtered, washed with saturated $Na_2S_2O_3$, and dried. After removal of the solvent, the residue was chromatographed by eluting with hexane: AcOEt (19:1) to afford **60b** (0.424 g, 23%): mp 85−91 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.2 Hz), 2.12 (3H, s), 3.42 (2H, s), 3.84 (3H, s), 4.22 (2H, qd, J = 7.2, 1.0 Hz), 6.02 (1H, s), 6.79 (1H, d, J = 8.0 Hz), 7.01 (1H, dd, J = 7.2, 0.8 Hz), 7.13 (1H, t, J = 7.7 Hz); IR ν_{max} (KBr) 1750, 1580 cm^{-1}; EIMS m/z 199 (base peak), 324 (M^+); HR-EIMS calcd for $C_{15}H_{17}BrO_3$ 324.0361, found 324.0377.

Ethyl (2-Bromo-2-ethyl-7-methoxyindan-1-ylidene)-acetate (60c). This compound was used in the next step without purification.

Ethyl (7-Methoxy-2-methyl-3*H*-inden-1-yl)acetate (58b). The mixture of the ester compound **60b** (388 mg, 1.19 mmol) and PtO_2 (38.4 mg) in AcOH (4.0 mL) was hydrogenated under ordinary atmosphere overnight. The catalyst was filtered off and the solvent was evaporated. The residue was chromatographed by eluting with hexane:AcOEt (97:3 to 9:1) and crystallized from hexane:AcOEt to give **58b** (170 mg, 59%): mp 76−79 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, s, J = 7.0 Hz), 2.04 (3H, s), 3.32 (2H, s), 3.67 (2H, s), 3.78 (3H, s), 4.16 (2H, q, J = 7.0 Hz), 6.73 (1H, d, J = 7.8 Hz), 6.98 (1H, d, J = 6.6 Hz), 7.06 (1H, t, J = 7.7 Hz); IR ν_{max} (KBr) 1735, 1578 cm^{-1}; EIMS m/z 172 (base peak), 246 (M^+). Anal. ($C_{15}H_{18}O_3$·0.1H_2O) C, H.

Ethyl (2-Ethyl-7-methoxy-3*H*-inden-1-yl)acetate (58c). Method A yielded 32% in two steps.

Method B: To a solution of the ester compound **59c** (4.15 g, 0.0160 mol) in $CHCl_3$ (40 mL) was added three drops of concentrated H_2SO_4. The resulting solution was refluxed for 40 min and dried over K_2CO_3. After removal of the solvent, the residue was chromatographed by eluting with hexane: AcOEt (98:2 to 95:5) to give **58c** (3.55 g, 85%). Anal. ($C_{16}H_{20}O_3$·0.5H_2O) C, H.

[(3*Z*)-Benzylidene-6-methoxy-2-methyl-3*H*-inden-1-yl]-acetic acid (61a). To a solution of the crude indene **58a** (1.64 g, 6.66 mmol) in MeOH (20 mL) were added benzaldehyde (1.35 mL, 13.3 mmol) and 1 N NaOMe (20.0 mL, 20 mmol) at room temperature. The resulting solution was refluxed for 160 min, evaporated, poured into 1 N HCl, and extracted with AcOEt. The organic layer was washed with water, dried, and concentrated. The residue was chromatographed by eluting with hexane:AcOEt (9:1) and then $CHCl_3$:MeOH (9:1) and recrystallized (hexane:AcOEt) to afford **61a**: 0.841 g (41% yield); mp 146−160 °C; ^{1}H NMR ($CDCl_3$) δ 2.19 (3H, s), 3.59 (2H, s), 3.78 (3H, s), 6.40 (1H, dd, J = 8.2, 2.4 Hz), 6.75 (1H, d, J = 2.4 Hz), 7.12 (1H, s), 7.24 (1H, d, J = 8.2 Hz), 7.30−7.56 (5H, m); IR ν_{max} (KBr) 3428, , 2834, 1701, 1611, 1582 cm^{-1}; EIMS m/z 306 (M^+, base peak). Anal. ($C_{20}H_{18}O_3$·0.2H_2O) C, H.

[3(*Z*)-Benzilidene-7-methoxy-2-methyl-3*H*-inden-1-yl]-acetic acid (61b): mp 165−175 °C; 59% yield. Anal. ($C_{20}H_{18}O_3$·0.6H_2O) C, H.

[3(*Z*)-Benzylidene-2-ethyl-7-methoxy-3*H*-inden-1-yl]-acetic acid (61c): 166−188 °C (dec); 47% yield. Anal. (C_{21}-$H_{20}O_3$·0.4H_2O): C, H.

(*Z*)-2-[3-(Biphenyl-2-ylmethylene)-2-ethyl-7-methoxy-3*H*-inden-1-yl]acetic acid (61d): mp 230−232 °C; 39% yield; EIMS m/z 165 (base peak), 396 (M^+); HR-EIMS calcd for $C_{27}H_{24}O_3$ 396.1774, found 396.1772.

(*E/Z*)-[3-(2-Benzylbenzylidene)-2-ethyl-7-methoxy-3*H*-inden-1-yl]acetic acid (61e): mp 119.5−136 °C; 62% yield. Anal. ($C_{28}H_{26}O_3$·0.3H_2O) C, H.

(*Z*)-[3-(3-Chlorobenzylidene)-2-ethyl-7-methoxy-3*H*-inden-1-yl]acetic acid (61f): mp 173−178 °C; 79% yield. Anal. ($C_{21}H_{19}O_3Cl$ 0.3H_2O) C, H, Cl.

(*Z*)-[3-(2,3-Dichlorobenzylidene)-2-ethyl-7-methoxy-3*H*-inden-1-yl]acetic acid (61g): mp 214.5−222 °C; 63% yield; EIMS m/z 388 (M^+, base peak); HR-EIMS calcd for $C_{21}H_{18}O_3Cl_2$ 388.0632, found 388.0619.

(*Z*)-(2-Ethyl-7-methoxy-3-(naphthalen-1-ylmethylene)-3*H*-inden-1-yl)acetic acid (61i): mp 188−191 °C; 46% yield. Anal. ($C_{25}H_{22}O_3$) C, H.

(*Z*)-(2-Ethyl-7-methoxy-3-(naphthalen-2-ylmethylene)-3*H*-inden-1-yl)acetic acid (61j): mp 188−192.5 °C; 56% yield. Anal. ($C_{25}H_{22}O_3$) C, H.

2-[3(*Z*)-Benzylidene-6-methoxy-2-methyl-3*H*-inden-1-yl]acetamide (62a). To a solution of the acetic acid derivatve **61a** (200 mg, 0.645 mmol) in CH_3CN (10.0 mL) were added Et_3N (0.140 mL, 1.00 mmol) and benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (434 mg, 0.981 mmol) at 0 °C. The resulting solution was stirred at room temperature for 45 min, and then 28% NH_4OH (0.440 mL) was added. After 30 min, the mixture was poured into 2 N HCl and extracted with AcOEt. The organic layer was washed with water and dried. After removal of the solvent, the residue was chromatographed twice by eluting with CH_2-Cl_2:MeOH (99:1 to 98.5:1.5) and hexane:AcOEt (1:1 to 1:9) to give **62a**: 183 mg (92%); mp 174−178 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (3H, s), 3.55 (2H, s), 3.79 (3H, s), 5.44 (1H, br s), 5.64 (1H, br s), 6.44 (1H, dd, J = 8.4, 2.4 Hz), 6.73 (1H, d, J = 2.4 Hz), 7.16 (1H, s), 7.29 (1H, d, J = 8.4 Hz), 7.32−7.60 (5H, m); IR ν_{max} (KBr) 3389, 3196, 1653, 1614 cm^{-1}; EIMS m/z 305 (M^+, base peak). Anal. ($C_{20}H_{19}NO_2$·0.3H_2O) C, H, N.

2-[3(*Z*)-Benzilidene-7-methoxy-2-methyl-3*H*-inden-1-yl]acetamide (62b): mp 175−177 °C; 96% yield; EIMS m/z 305 (base peak, M^+); HR-EIMS calcd for $C_{20}H_{19}NO_2$ 305.1414, found 305.1416.

2-[3(*Z*)-Benzylidene-2-ethyl-7-methoxy-3*H*-inden-1-yl]-acetamide (62c): mp 153−156 °C; 99% yield; EIMS m/z 260 (base peak), 319 (M^+).

(*Z*)-2-[3-(Biphenyl-2-ylmethylene)-2-ethyl-7-methoxy-3*H*-inden-1-yl]acetamide (62d): mp 190−200 °C; 91% yield; EIMS m/z 165 (base peak), 395 (M^+); HR-EIMS calcd for $C_{27}H_{25}NO_2$ 395.1883, found 395.1885.

(*E/Z*)-2-[3-(2-Benzylbenzylidene)-2-ethyl-7-methoxy-3*H*-inden-1-yl]acetamide (62e): mp 133−147 °C; 74% yield; EIMS m/z 409 (M^+, base peak).

(*Z*)-2-[3-(3-Chlorobenzylidene)-2-ethyl-7-methoxy-3*H*-inden-1-yl]acetamide (62f): mp 204−208 °C; 85% yield;

EIMS *m*/*z* 294 (base peak), 353 (M^+); HR-EIMS calcd for $C_{21}H_{20}NO_2Cl$ 353.1181, found 353.1160.

(*Z*)-2-[3-(2,3-Dichlorobenzylidene)-2-ethyl-7-methoxy-3*H*-inden-1-yl]acetamide (62g): mp 170−176.5 °C; 81% yield; HR-EIMS calcd for $C_{21}H_{19}NO_2Cl_2$ 387.0791, found 387.0798.

(*Z*)-2-[2-Ethyl-7-methoxy-3-(3-(trifluoromethyl)benzylidene)-3*H*-inden-1-yl]acetamide (62h): mp 205.5−208 °C; 32% yield (two steps). Anal. ($C_{22}H_{20}NO_2F_3$) C, H, N, F.

(*Z*)-2-(2-Ethyl-7-methoxy-3-(naphthalen-1-ylmethylene)-3*H*-inden-1-yl)acetamide (62i): mp 172−175.5 °C; 91% yield. Anal. ($C_{25}H_{23}NO_2 \cdot 0.1H_2O$) C, H, N.

(*Z*)-2-(2-Ethyl-7-methoxy-3-(naphthalen-2-ylmethylene)-3*H*-inden-1-yl)acetamide (62j): mp 221−223 °C; 80% yield. Anal. ($C_{25}H_{23}NO_2 \cdot 0.3H_2O$) C, H, N.

2-[3(*Z*)-Benzylidene-6-hydroxy-2-methyl-3*H*-inden-1-yl]acetamide (63a): 49% yield; mp 178−180 °C; ^{1}H NMR ($CDCl_3$) δ 2.20 (3H, s), 3.56 (2H, s), 5.55 (1H, br s), 5.77 (1H, br s), 6.41 (1H, d, J = 8.4, 2.4 Hz), 6.69 (1H, d, J = 2.4 Hz), 7.14 (1H, s), 7.25 (1H, d, J = 8.4 Hz), 7.30−7.56 (6H, m); IR ν_{max} (KBr) 3212, 1657, 1602 cm^{-1}; EIMS *m*/*z* 232 (base peak), 291 (M^+). Anal. ($C_{19}H_{17}NO_2 \cdot 0.4H_2O$) C, H, N.

2-[3(*Z*)-Benzilidene-7-hydroxy-2-methyl-3*H*-inden-1-yl]-acetamide (63b): mp 200−203 °C; quantitative yield; EIMS *m*/*z* 274 (base peak), 291 (M^+); HR-EIMS calcd for $C_{19}H_{17}NO_2$ 291.1258, found 291.1253.

(*Z*)-2-(3-Benzylidene-2-ethyl-7-hydroxy-3*H*-inden-1-yl)-acetamide (63c): mp 176−180 °C (dec); 87% yield. Anal. ($C_{20}H_{19}NO_2 \cdot 0.8H_2O$) C, H, N.

(*Z*)-2-[3-(Biphenyl-2-ylmethylene)-2-ethyl-7-hydroxy-3*H*-inden-1-yl]acetamide (63d): mp 168−172 °C; 49% yield. Anal. ($C_{26}H_{23}NO_2 \cdot 0.2H_2O$) C, H, N.

(*Z*)-2-[3-(2-Benzylbenzylidene)-2-ethyl-7-hydroxy-3*H*-inden-1-yl]acetamide (63e): mp 137.5−153.5 °C; 72% yield. Anal. ($C_{27}H_{25}NO_2 \cdot 0.2H_2O$) C, H, N.

(*Z*)-2-[3-(3-Chlorobenzylidene)-2-ethyl-7-hydroxy-3*H*-inden-1-yl]acetamide (63f): mp 185−185.5 °C; 79% yield. Anal. ($C_{20}H_{18}NO_2Cl \cdot 0.2H_2O$) C, H, N, Cl.

(*Z*)-2-[3-(2,3-Dichlorobenzylidene)-2-ethyl-7-hydroxy-3*H*-inden-1-yl]acetamide (63g): mp 193−194.5 °C; 90% yield. Anal. ($C_{20}H_{17}NO_2Cl_2$) C, H, N, Cl.

(*Z*)-2-[2-Ethyl-7-hydroxy-3-(3-(trifluoromethyl)benzylidene)-3*H*-inden-1-yl]acetamide (63h): mp 184.5−186 °C; 96% yield. Anal. ($C_{21}H_{18}NO_2F_3$) C, H, N, F.

(*Z*)-2-(2-Ethyl-7-hydroxy-3-(naphthalen-1-ylmethylene)-3*H*-inden-1-yl)acetamide (63i): mp 189−189.5 °C; 92% yield. Anal. ($C_{24}H_{21}NO_2 \cdot 0.3H_2O$) C, H, N.

(*Z*)-2-(2-Ethyl-7-hydroxy-3-(naphthalen-2-ylmethylene)-3*H*-inden-1-yl)-acetamide (63j): mp 200−201.5 °C; 65% yield. Anal. ($C_{24}H_{21}NO_2 \cdot 0.2H_2O$) C, H, N.

Ethyl 4-[[1(*Z*)-Benzylidene-3-(carbamoylmethyl)-2-methyl-1*H*-inden-5-yl]oxy]butanate (64a). To compound **63a** (43.7 mg, 0.150 mmol) in DMF (1.0 mL) was added 60% NaH (21.3 mg, 0.533 mmol). After addition, the mixture was stirred at room temperature for 60 min, and then ethyl 4-bromobutyrate (75 μL, 0.524 mmol) was added. The mixture was stirred at 0 °C for 45 min and then at room temperature for 75 min and partitioned between 1 N HCl and AcOEt. The organic layer was separated, washed with water, dried, filtered, and concentrated. The residue was purified by preparative TLC (200 × 200 × 0.25 mm, elution with AcOEt) to give **64a** (38.0 mg, 63%): mp 124−128 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.0 Hz), 1.99−2.17 (2H, m), 2.21 (3H, s), 2.50 (2H, t, J = 7.2 Hz), 3.54 (2H, s), 3.98 (2H, t, J = 6.3 Hz), 4.14 (2H, q, J = 7.0 Hz), 5.50 (1H, br s), 5.67 (1H, br s), 6.42 (1H, dd, J = 8.2, 2.4 Hz), 6.73 (1H, d, J = 2.4 Hz), 7.16 (1H, s), 7.27 (1H, d, J = 8.2 Hz), 7.32−7.58 (5H, m); IR ν_{max} (KBr) 2972, 2919, 1739, 1687, 1655, 1614 cm^{-1}; EIMS *m*/*z* 115 (base peak), 405 (M^+). Anal. ($C_{25}H_{27}NO_4 \cdot 0.9H_2O$) C, H, N.

Ethyl [[1(*Z*)-benzylidene-3-(carbamoylmethyl)-2-methyl-1*H*-inden-4-yl]oxy]acetate (64b): 77% yield; mp 162−165 °C. Anal. ($C_{23}H_{23}NO_4 \cdot 0.8H_2O$) C, H, N.

(*Z*)-Ethyl ((3-benzylidene-1-(carbamoylmethyl)-2-ethyl-3*H*-inden-7-yl)oxy)acetate (64c): mp 139−142 °C; 61% yield. Anal. ($C_{24}H_{25}NO_4 \cdot 0.1H_2O$) C, H, N.

(*Z*)-Ethyl [[3-(biphenyl-2-ylmethylene)-1-(carbamoylmethyl)-2-ethyl-3*H*-inden-7-yl]oxy]acetate (64d): mp 161−163 °C; 76% yield. Anal. ($C_{30}H_{29}NO_4 \cdot 1.5H_2O$) C, H, N.

Ethyl (*Z*)-[[1-(2-benzylbenzylidene)-3-(carbamoylmethyl)-2-ethyl-1*H*-inden-4-yl]oxy]acetate (64e): mp 157.5−158.5 °C; 83% yield. Anal. ($C_{31}H_{31}NO_4 \cdot 0.4H_2O$) C, H, N.

Ethyl (*Z*)-[[3-(carbamoylmethyl)-1-(3-chlorobenzylidene)-2-ethyl-1*H*-inden-4-yl]oxy]acetate (64f): mp 182.5−184 °C; 57% yield. Anal. ($C_{24}H_{24}NO_4Cl$) C, H, N, Cl.

Ethyl (*Z*)-[[3-(carbamoylmethyl)-1-(2,3-dichlorobenzylidene)-2-ethyl-1*H*-inden-4-yl]oxy]acetate (64g): mp 185.5−187.5 °C; 83% yield. Anal. ($C_{24}H_{23}NO_4Cl_2$) C, H, N, Cl.

Ethyl (*Z*)-[[3-(carbamoylmethyl)-2-ethyl-1-(3-(trifluoromethyl)benzylidene)-1*H*-inden-4-yl]oxy]acetate (64h): mp 175.5−182.5 °C; 76% yield; EIMS *m*/*z* 400 (base peak), 459 (M^+); HR-EIMS calcd for $C_{25}H_{24}NO_4F_3$ 459.1656, found 459.1669.

Ethyl (*Z*)-((3-(carbamoylmethyl)-2-ethyl-1-(naphthalen-1-ylmethylene)-1*H*-inden-4-yl)oxy)acetate (64i): mp 153.5−160 °C; 64% yield. Anal. ($C_{28}H_{27}NO_4 \cdot 0.4H_2O$) C, H, N.

Ethyl (*Z*)-((3-(carbamoylmethyl)-2-ethyl-1-(naphthalen-2-ylmethylene)-1*H*-inden-4-yl)oxy)acetate (64j): mp 201−204 °C; 77% yield. Anal. ($C_{28}H_{27}NO_4 \cdot 0.8H_2O$) C, H, N.

4-[[1(*Z*)-Benzylidene-3-(carbamoylmethyl)-2-methyl-1*H*-inden-5-yl]oxy]butanoic Acid (65a). NaOH (1 N, 0.200 mL, 0.200 mmol) was added to a solution of **64a** (39.4 mg, 0.0972 mmol) in DMSO (1.0 mL) at room temperature. The solution was stirred at room temperature for 75 min and partitioned between 1 N HCl and AcOEt. The organic layer was separated, washed with water, dried, and evaporated. Recrystallization from AcOEt afforded **65a** (19.5 mg, 53%): mp 187−188 °C; ^{1}H NMR (d_6-DMSO) δ 1.82−2.02 (2H, m), 2.14 (3H, s), 2.36 (2H, t, J = 7.0 Hz), 3.94 (1H, t, J = 6.3 Hz), 6.42 (1H, dd, J = 8.4, 2.0 Hz), 6.85 (1H, d, J = 2.0 Hz), 6.96 (1H, br s), 7.13 (1H, d, J = 8.4 Hz), 7.16 (1H, s), 7.32−7.57 (6H, m); IR ν_{max} (KBr) 3462, 3342, 1715, 1697, 1647, 1613, 1582 cm^{-1}; EIMS *m*/*z* 232 (base peak), 377 (M^+). Anal. ($C_{23}H_{23}NO_4 \cdot 0.5H_2O$) C, H, N.

[[1(*Z*)-Benzylidene-3-(carbamoylmethyl)-2-methyl-1*H*-inden-4-yl]oxy]acetic acid (65b): mp 224−226 °C; 55% yield; EIMS *m*/*z* 349 (base peak, M^+); HR-EIMS calcd for $C_{21}H_{19}NO_4$ 349.1312, found 349.1311.

(*Z*)-((3-Benzylidene-1-(carbamoylmethyl)-2-ethyl-3*H*-inden-7-yl)oxy)acetic acid (65c): mp 119−205 °C; 91% yield; EIMS *m*/*z* 304 (base peak), 363 (M^+); HR-EIMS calcd $C_{22}H_{21}NO_4$ 363.1469, found 363.1485.

(*Z*)-[[1-(Biphenyl-2-ylmethylene)-3-(carbamoylmethyl)-2-ethyl-1*H*-inden-4-yl]oxy]acetic acid (65d): mp 205−209 °C; 93% yield; Anal ($C_{28}H_{25}NO_4 \cdot 0.3H_2O$) C, H, N.

(*Z*)-[[1-(2-Benzylbenzylidene)-3-(carbamoylmethyl)-2-ethyl-1*H*-inden-4-yl]oxy]acetic acid (65e): mp 194−200 °C; quantitative yield; EIMS *m*/*z* 179 (base peak), 453 (M^+); HR-EIMS calcd for $C_{29}H_{27}NO_4$ 453.1938, found 453.1944.

(*Z*)-[[3-(Carbamoylmethyl)-1-(3-chlorobenzylidene)-2-ethyl-1*H*-inden-4-yl]oxy]acetic acid (65f): mp 213.5−214 °C; 82% yield. Anal. ($C_{22}H_{20}NO_4Cl \cdot 0.3H_2O$) C, H, N, Cl.

(*Z*)-[[3-(Carbamoylmethyl)-1-(2,3-dichlorobenzylidene)-2-ethyl-1*H*-inden-4-yl]oxy]acetic acid (65g): mp 226−228.5 °C; 89% yield; EIMS *m*/*z* 378 (base peak), 431 (M^+); HR-EIMS calcd for $C_{22}H_{19}NO_4Cl_2$ 431.0689, found 431.0685.

(*Z*)-[[3-(Carbamoylmethyl)-2-ethyl-1-(3-(trifluoromethyl)benzylidene)-1*H*-inden-4-yl]oxy]acetic acid (65h): mp 207−211.5 °C; 70% yield. Anal. ($C_{23}H_{20}NO_4F_3$) C, H, N, F.

(*Z*)-((3-(Carbamoylmethyl)-2-ethyl-1-naphthalen-1-ylmethylene-1*H*-inden-4-yl)oxy)acetic acid (65i): mp 210.5−213 °C; 90% yield; EIMS *m*/*z* 354 (base peak), 413 (M^+); HR-EIMS calcd for $C_{26}H_{23}NO_4$ 413.1624, found 413.1621.

(*Z*)-((3-(Carbamoylmethyl)-2-ethyl-1-naphthalen-2-ylmethylene-1*H*-inden-4-yl)oxy)acetic acid (65j): mp 210.5−215.5 °C; 70% yield; EIMS *m*/*z* 354 (base peak), 413 (M^+); HR-EIMS calcd for $C_{26}H_{23}NO_4$ 413.1626, found 413.1629.

(*Z*)-Methyl ((3-Benzyl-1-(carbamoylmethyl)-2-ethyl-3*H*-inden-7-yl)oxy)acetate (66a) and (*Z*)-Methyl ((3-Benzyl-1-(carbamoylmethyl)-2-ethyl-1*H*-inden-7-yl)oxy)-

acetate (67a). A mixture of the methyl ester of **65a** (113 mg, 0.300 mmol) and 5% Pd−C (11.9 mg) in MeOH (5.0 mL) was hydrogenated under normal atmosphere for 18 min. The catalyst was filtered off and the solvent was evaporated. The residue was purified by preparative TLC (200 × 200 × 0.25 mm, eluting with AcOEt) to give the crude product which was recrystallized from CHCl3:hexane to afford the pure product **66a** (48.8 mg, 43%): mp 118−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, t, J = 7.5 Hz), 2.40 (1H, qd, J = 7.5, 15.0 Hz), 2.71 (1H, qd, J = 7.5, 15.0 Hz), 2.78 (1H, dd, J = 7.8, 13.8 Hz), 3.37 (1H, dd, J = 4.2, 13.8 Hz), 3.56 (1H, d, J = 15.3 Hz), 3.73 (1H, d, J = 14.7 Hz), 3.72−3.83 (1H, m), 3.79 (3H, s), 4.65 (2H, s), 4.97 (1H, br s), 5.75 (1H, br s), 6.62 (1H, d, J = 8.4 Hz), 6.76 (1H, d, J = 7.2 Hz), 6.91−7.00 (2H, m), 7.01 (1H, t, J = 7.8 Hz), 7.07−7.28 (3H, m); IR ν_{max} (KBr) 3136, 3023, 1743, 1686 cm^{-1}; EIMS m/z 334 (base peak), 379 (M^+). Anal. ($C_{23}H_{25}NO_4$) C, H, N.

67a: mp 183−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, t, J = 7.5 Hz), 2.62 (1H, qd, J = 7.5, 15.0 Hz), 2.73 (1H, qd, J = 7.5, 15.0 Hz), 2.89 (1H, dd, J = 4.5, 13.8 Hz), 3.25 (1H, dd, J = 5.3, 13.8 Hz), 3.80 (1H, s), 3.89−3.95 (3H, m), 4.72 (1H, ABq, A part J = 16.7 Hz), 4.81 (1H, ABq, B part J = 16.7 Hz), 4.90 (1H, br s), 5.97 (1H, br s), 6.48 (1H, d, J = 8.1 Hz), 6.75 (1H, d, J = 7.2 Hz), 7.11 (1H, t, J = 7.8 Hz), 7.10−7.28 (5H, m); IR ν_{max} (KBr) 3387, 3195, 1750, 1646 cm^{-1}; EIMS m/z 334 (base peak), 379 (M^+).

(*Z*)-(3-Benzyl-1-(carbamoylmethyl)-2-ethyl-3*H*-inden-7-yloxy)acetic acid (66b): 50% Yield, mp 193−197 °C ($CHCl_3$:hexane). Anal. ($C_{22}H_{23}NO_4 \cdot 0.4H_2O$) C, H, N.

(*Z*)-((3-Benzyl-1-(carbamoylmethyl)-2-ethyl-1*H*-inden-7-yl)oxy)acetic acid (67b): 90% yield; EIMS m/z 231 (base peak), 365 (M^+); HR-EIMS calcd for $C_{22}H_{23}NO_4$ 365.1626, found 365.1630.

Enzyme Assay. Phospholipase A2 activity was measured by established procedures using racemic diheptanoylthiophosphatidylcholine/Triton mixed micelle (chromogenic assay)[18] or 1-palmitoyl-2-oleoyl-*sn*-phosphatidylcholine/deoxycholic acid mixed micelle (PC/DOC assay)[19,20] as substrate.

Chromogenic Assay. A 200 μL portion of the reaction mixture containing 1 mM diheptanoylthiophosphatidylcholine, 0.3 mM Triton, 0.12 mM DTNB, 10 mM $CaCl_2$, 0.1 M KCl, and 0.1% BSA in 25 mM Tris-HCl buffer (pH 7.5) was added to the wells of a microplate. Test compounds (10 μL) were added to each well as DMSO solutions. To the control wells was added 10 μL of DMSO. Reactions were initiated by addition of 50 ng of the enzyme in 10 μL of AcONa buffer (pH 4.5) containing 0.2 M NaCl and incubated at 40 °C for 30 min. The reaction was monitored by the absorbance of wells at 405 nm with an automatic plate reader. The IC_{50} values were determined by diluting test compounds serially 5-fold. Inhibition measured at 405 nm, generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions, was determined. Each sample was titrated in triplicate, and result values were averaged for plotting and calculation of IC_{50} values. IC_{50} values were determined by plotting log concentration versus inhibition values in the range from 10 to 90% inhibition.

PC/DOC Assay. A 160 μL portion of the reaction mixture containing 1 mM 1-palmitoyl-2-oleoylphosphatidylcholine, 3 mM sodium deoxycholic acid, 10 mM $CaCl_2$, 150 mM NaCl, and 0.1% BSA in 100 mM Tris-HCl buffer (pH 8.0) was added to the test tube. Test compounds (20 μL) were added to each tube as DMSO solution and preincubated at 40 °C for 10 min. Reactions were initiated by addition of 20 ng of the enzyme in 20 μL of AcONa buffer (pH 4.5) containing 0.2 M NaCl and incubated at 40 °C for 30 min. Reactions were stopped by addition of 800 μL of Dole reagent.[22] Margaric acid (6 nM) in heptane (12 μL) was added as an internal standard. Then 320 μL of distilled water and 480 μL of heptane were added, and the solution was shaken for 10 s. After centrifugation at 20 °C for 30 s at 10 000 rpm, 400 μL of the upper phase was pipetted into another tube containing 15−20 mg of silicic acid powder, and then the solution was shaken for 30 s. After centrifugation for 30 s at 10 000 rpm, 150 μL of heptane was transfered into another tube, and the heptane was removed using a water aspirator. Then 100 μL of 0.05% 9-anthryldiazomethane solution was added. The mixture was incubated for 15 min at room temperature. An aliquot (10−15 μL) of the mixture was injected onto a Supersphere RP-8 column and eluted with 93% CH_3CN. The amount of released oleic acid was calculated by the ratio to margaric acid. Each sample was titrated in duplicate, and the values were averaged for plotting and calculation of IC_{50} values. Inhibition generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions were calculated. IC_{50} values were determined by plotting log concentration versus inhibition values in the range from 10 to 90% inhibition.

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