2-OXOTETRAHYDRO-1,3-OXAZINE : A USEFUL INTERMEDIATE FOR THE PREPARATION OF TETRAHYDROPYRIDINE, INDOLIZIDINE, AND QUINOLIZIDINE SKELETONS#

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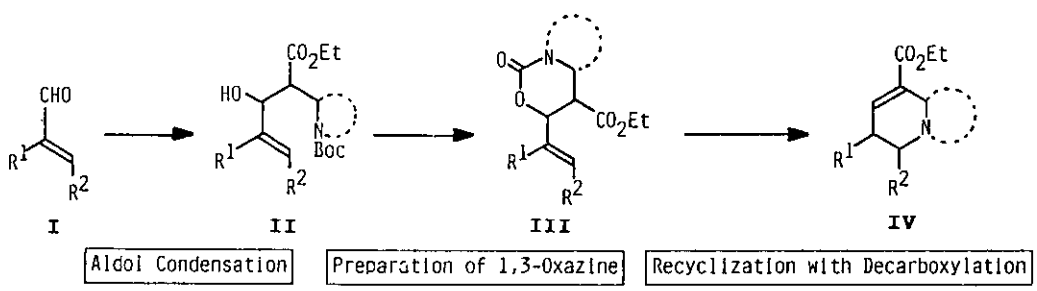
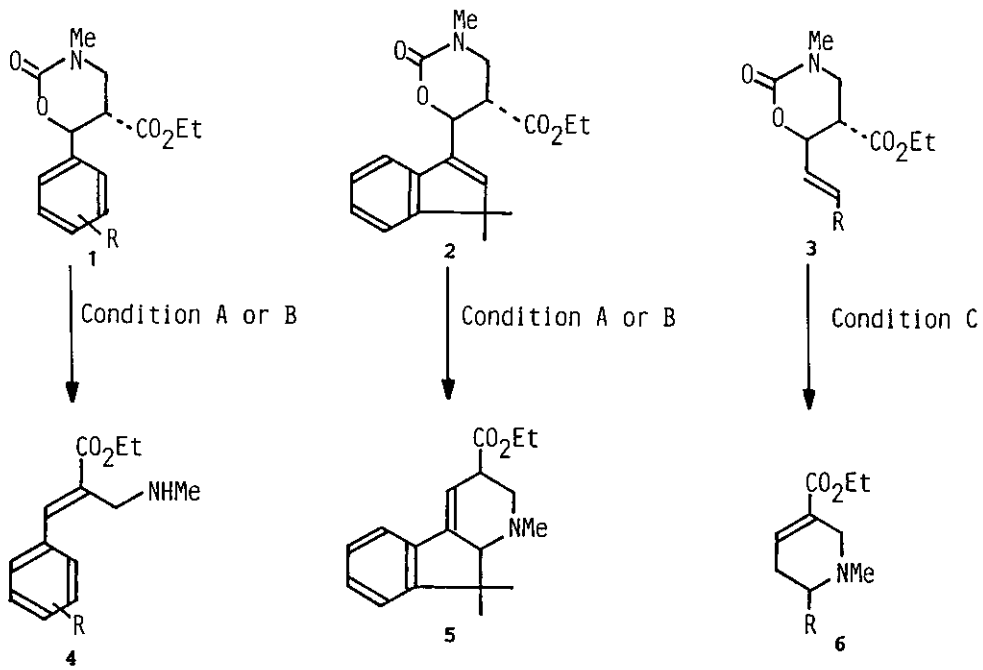
Abstract —— Conversion of 2-oxotetrahydro-1,3-oxazines into tetrahydropyridines was applied to the synthesis of indolizidine and quinolizidine alkaloids.

We have recently reported a transformation of α,β-unsaturated aldehyde (I) into tetrahydropyridine (IV). This sequence consists of three steps described in Scheme: (1) an aldol condensation of I with ethyl 3-(N-Boc)aminopropionate (LDA), (2) a transformation of the threo-alcohol (II) into the 2-oxotetrahydro-1,3-oxazine (III) (MsCl and TEA),[1] and (3) a recyclization of III accompanied by a decarboxylation into IV (DBU in DMSO).[2] We report here its synthetic application to the quinolizidine and nuphar indolizidine alkaloids as well as a full account of the work reported in a previous short communication.[2]



Since 5-ethoxycarbonyl-2-oxotetrahydro-1,3-oxazine is regarded as a β-amidoxy ester, the behaviors of three types of oxazines (**1**, **2** and **3**) upon the bases were investigated first. Although treatment of the 6-aryloxazines (**1a** and **1b**) with LDA in THF (-78 °C) (Condition A) gave the unsaturated esters (**4a** and **4b**) in 82 and 70% yields, the reaction proceeded quantitatively when DBU (1 eq.) was used as base in DMSO at room temperature (Condition B). 6-(3-Indenyl)-2-oxotetrahydro-1,3-oxazine (**2**) was also recyclized successively to the indeno[2,1-b]pyridine (**5**) by Conditions A (68%) and B (100%). On the other hand, the recyclization with decarboxylation of the 6-(vinyl-, 1-propenyl- or styryl-)-2-oxotetrahydro-1,3-oxazines (**3a**, **3b** and **3c**) into the tetrahydropyridines (**6a**, **6b** and **6c**) could be accomplished cleanly by heating with DBU (2.0 eq) in DMSO at 120 °C (Condition C) (quantitative yields). Thus, application of these reaction conditions to structually related bicyclic oxazinones (**9a**, **9b** and **15**) would provide the useful method for the preparation of indolizidine and quinolizidine skeletons.



a: R=H, b: R=3,4-OCH_2O-

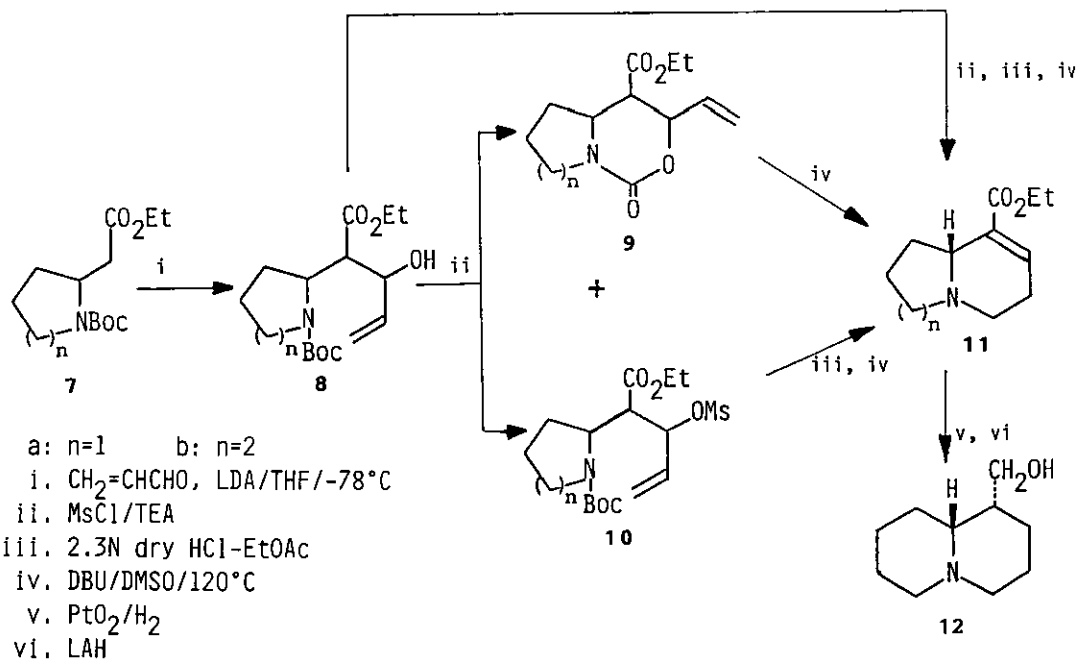
a: R=H, b: R=Me, c: R=Ph

Conditions

A: LDA/THF/-78°C B: DBU (1 eq.)/DMSO/r.t. C: DBU (2 eq.)/DMSO/120°C

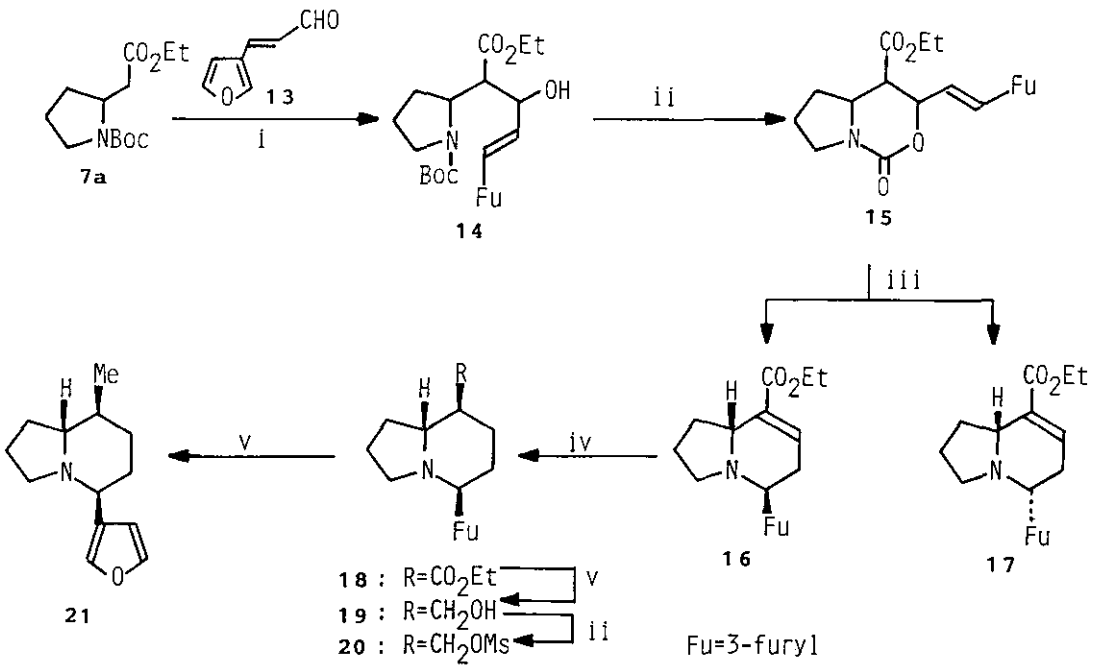
Aldol condensation of ethyl N-Boc-2-pyrrolidineacetate (**7a**)[3] with acrolein in the presence of LDA at -78°C in THF gave the allyl alcohol (**8a**) as an oily mixture of

diastereoisomers (95% yield). This was treated with MsCl and TEA at room temperature in CH_2Cl_2 to give the bicyclic oxazinone (**9a**)[4] and the mesylate (**10a**) in 68% and 22% yields, respectively. Heating **9a** with DBU (2 eq.) in DMSO at 120°C afforded **11a** in 87% yield. Removal of the Boc group of **10a** (2.3N dry HCl-EtOAc) followed by heating with DBU in DMSO[5] gave the indolizidine (**11a**) in 64% yield. This sequence could be carried out in a single synthetic operation. For this purpose, **8a** was subjected to the following sequence in turn: 1) MsCl/TEA/r.t., 2) 2.3N dry HCl-EtOAc/r.t., 3) DBU in DMSO/120°C. The final product was purified by column chromatography to give **11a** in 81% overall yield. Application of the same sequences to ethyl N-Boc-2-piperidineacetate (**7b**)[3] provided a route to the quinolizidine (**11b**),[6] after purification by column chromatography at the end of the process, in 85% overall yield. Similarly, the intermediates [bicyclic oxazinone (**9b**)[4] (45%) and mesylate (**10b**) (40%)] were separated and converted to **11b** in 82% from the former and 67% from the latter under the same conditions as above. Catalytic hydrogenation of **11b** on PtO_2 gave the saturated ester, which was then reduced with $LiAlH_4$ (LAH) to lead (±)-lupinine (**12**). The ir and ^1H nmr spectral data were identical with those reported.[7]



5-(3-Furyl)-8-methyloctahydroindolizine (**21**), which is a minor component of the dried scent glands of the Canadian beaver, has hitherto been synthesized by three

groups.[8] The accurate stereochemistry, however, of this natural product was not assigned, because the structural formula of **21** was determined solely by fragmentation pattern displayed in the ms spectrum.[9] Then, we carried out the synthesis of this product by our methodology. Aldol condensation of **7a** with 3-(3-furyl)-



i, LDA/THF/-78°C; ii, MsCl/TEA; iii, DBU/DMSO/120°C; iv, 5% Pd-C/H_2; v, LAH

acrolein[10] in the presence of LDA afforded the allyl alcohol (**14**), which was treated with MsCl/TEA in CH_2Cl_2 at -7 °C to give only the bicyclic oxazinone (**15**)[4] in 86% yield without formation the mesylate. Heating **15** with an equivalent amount of DBU in DMSO at 120 °C for 20 min provided the indolizidine (**16**) in 86% yield as a sole product, which showed no Bohlmann bands in the ir spectrum. When recyclization was attempted with two equivalents amount of DBU at 120°C for 2 h, the isomer (**17**), whose ir spectrum displayed a strong Bohlmann bands at 2880 and 2790 cm^{-1}, was isolated in 19% yield, along with **16** (31%). The compound(**16**) epimerized to **17** partially when heated with DBU in DMSO. The two compounds (**16** and **17**) are therefore epimeric at C-5, and **17** is a more stable isomer than **16**. Upon irradiation of 8a-H, a NOE enhancement was observed at 5-H in **17**, but not in **16** in their ^1H nmr spectra. Thus, the A/B trans fusion, as well as the trans relative configuration between 5-H and 8a-H in **16** and the cis in **17**, were deduced. Catalytic

hydrogenation of **16** (5% Pd-C) in MeOH occurs predominantly from the α-side to afford the saturated ester (**18**) in 91 % yield. The LAH reduction of **18** followed by mesylation (MsCl/TEA/0 °C) gave the mesylate (**20**), which was then treated with LAH in Et_2O. The final product was purified by column chromatography to give the nuphar indolizidine (**21**) in 49% from **18**. The ir spectrum of **21** displayed no Bohlmann bands. The selected ^1H nmr data (CH_3, 5-H, and protons of furan ring) of **21** were comparable to those reported by Ban.[8b] The ms spectrum of synthetic compound **21** was completely identical to that of the natural product reported by Ohloff[9] as shown in Figure.

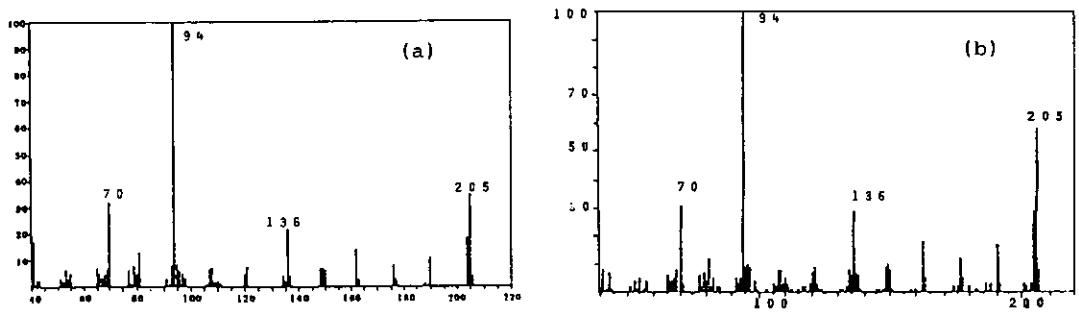


Figure The mass spectra of nuphar indolizidine (**21**) of natural product (a) and synthetic compound (b).

In conclusion, we provided an excellent method for the conversion of 2-oxotetrahydro-1,3-oxazines bearing vinyl substituents at the 6-position into tetrahydropyridine skeletons and the application to the synthesis of indolizidine and quinolizidine alkaloids.

EXPERIMENTAL

All melting and boiling points are uncorrected. Ir spectra were determined using a Shimadzu IR-435 spectrophotometer. ^1H Nmr spectra were obtained using a Varian Gemini-200 spectrometer with TMS as the internal standard. Ms spectra were measured with a Hitachi M-80 instrument. For column chromatography, SiO_2 (Merck Art 7734 and 9835) was used.

General Procedure for Base Treatment of 2-Oxotetrahydro-1,3-oxazines (**1**, **2** and **3**)

Condition A: The preparation of LDA was carried out as follows: n-BuLi (1.6 M hexane solution, 0.38 ml, 0.6 mmol) was added to a solution of diisopropylamine (0.08 ml, 0.6 mmol) in THF (3 ml) at -78°C under N_2, and the mixture was stirred for 20 min. A solution of **1a** (132 mg, 0.5 mmol) in THF (3 ml) was added in one

portion to the solution at -78°C, and the whole was stirred for 10 min. The reaction mixture was quenched by the addition of H_2O (5 ml), and THF was removed by evaporation. The residue was extracted with $CHCl_3$, and the extract was washed with brine, dried over anhyd. Na_2SO_4, and evaporated. The residual oil was purified by column chromatography [$CHCl_3$-MeOH (10:1)].

Condition B: DBU (76 mg, 0.5 mmol) was added to a solution of **1a** (132 mg, 0.5 mmol) in DMSO (1 ml), and the mixture was stirred for 15 min at room temperature. The reaction mixture was then diluted with H_2O (5 ml), and extracted with $CHCl_3$. The extract was washed with brine, dried over anhyd. Na_2SO_4, and evaporated. The residual oil was purified as above.

Condition C: DBU (152 mg, 1 mmol) was added to a solution of **3a** (107 mg, 0.5 mmol), and the mixture was heated at 120°C for 45 min. The cooled reaction mixture was worked up as described in Condition B.

(E)-Ethyl 2-(N-Methyl)aminomethyl-3-phenyl-2-propenate (**4a**)

Yields: 82% (Condition A) and 100% (Condition B), pale brown oil; ir (Neat) 3330 (NH) and 1690 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.33 (3H, t, J=7.3 Hz, $CO_2CH_2CH_3$), 2.41 (3H, s, NCH_3), 3.55 (2H, s, CH_2), 4.28 (2H, q, J=7.3 Hz, $CO_2CH_2CH_3$), 7.30-7.49 (5H, m, Ar-H), and 7.80 (1H, s, =CH); ms m/z 219 (M^+). Calcd for $C_{13}H_{17}NO_2$: M^+, 219.1252. Found: 219.1237.

(E)-Ethyl 2-(N-Methyl)aminomethyl-3-(3,4-methylenedioxyphenyl)-2-propenate (**4b**)

Yields: 70% (Condition A) and 100% (Condition B), pale brown oil; ir (Neat) 3330 (NH) and 1690 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.35 (3H, t, J=7.4 Hz, $CO_2CH_2CH_3$), 2.46 (3H, s, NCH_3), 3.54 (2H, s, NCH_2), 4.27 (2H, q, J=7.4 Hz, $CO_2CH_2CH_3$), 6.00 (2H, s, OCH_2O), 6.84 (1H, d, J=8.4 Hz, Ar-H), 7.01 (1H, dd, J=8.4, 1.6 Hz, Ar-H), 7.10 (1H, d, J=1.6 Hz, Ar-H), and 7.22 (1H, s, =CH); ms m/z 263 (M^+). Calcd for $C_{14}H_{17}NO_4$: M^+, 263.1157. Found: 263.1164.

Ethyl 1,9,9-Trimethyl-1,2,3,9a-tetrahydro-9H-indeno[2,1-b]pyridine-3-carboxylate (**5**)

Yields: 68% (Condition A) and 100% (Condition B). The ir and ^1H nmr spectral data were identical with those of the authentic sample.[11]

Ethyl 1-Methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**6a**)

Yield: 100% (Condition C), pale brown oil; ir (Neat) 1710 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.29 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 2.37 (2H, m, 5-H_2), 2.41 (3H, s, NCH_3), 2.49 (2H, t, J=5.0 Hz, 6-H_2), 3.14 (2H, dd, J=5.0 and 3.0 Hz, 2-H_2), 4.20 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 6.99 (1H, m, 4-H); ms m/z 169 (M^+). Calcd for

$C_9H_{15}NO_2$: M^+, 169.1104. Found: 169.1102.

Ethyl 1,6-Dimethyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**6b**)

Yield: 98% (Condition C), colorless oil; ir (Neat) 1710 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.09 (3H, d, J=6.8 Hz, $CHCH_3$), 1.29 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 2.09 and 2.35 (each 1H, each m, 5-H_2), 2.37 (3H, s, NCH_3), 2.46 (1H, m, 6-H), 3.05 and 3.45 (each 1H, each m, 2-H_2), 4.20 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), and 6.95 (1H, m, 4-H); ms m/z 183 (M^+). Calcd for $C_{10}H_{17}NO_2$: M^+, 183.1260. Found: 183.1258.

Ethyl 1-Methyl-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**6c**)

Yield: 100% (Condition C), pale yellow oil; ir (Neat) 1710 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.30 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 2.12 (3H, s, NCH_3), 2.45-2.60 (2H, m, 5-H_2), 3.06 and 3.70 (each 1H, each m, 2-H_2), 3.22 (1H, dd, J=8.5, 5.0 Hz, 6-H), 4.23 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 7.06 (1H, br s, 4-H), 7.20-7.40 (5H, m, Ar-H); ms m/z 245 (M^+). Calcd for $C_{15}H_{19}NO_2$: M^+, 245.1416. Found: 245.1415.

General Procedure for Aldol Condensation of **7a,b** with Acrolein

A solution of acetate (**7**) (2 mmol) in THF (5 ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (2.4 mmol)] in THF (3 ml) at -78°C under N_2, and the mixture was stirred for 20 min. A solution of 90% acrolein (2.4 mmol) in THF (3 ml) was added in one portion at -78°C, and the whole was stirred for 40 min. After usual work-up as described for **4** or **5** (Condition A), the resulting crude oil was purified by column chromatography [benzene-EtOAc (10:1)] to give **8** as a colorless oil.

Ethyl 1-tert-Butoxycarbonyl-α-(1-hydroxy-2-propenyl)pyrrolidine-2-acetate (**8a**)

Yield: 95%; ir (Neat) 3380 (OH), 1730 and 1665 (CO) cm^{-1}. The ^1H nmr spectrum was not sufficiently well resolved for assignment of the signals. Ms m/z 313 (M^+). Calcd for $C_{16}H_{27}NO_5$: M^+, 313.1888. Found: 313.1863.

Ethyl 1-tert-Butoxycarbonyl-α-(1-hydroxy-2-propenyl)piperidine-2-acetate (**8b**)

Yield: 98%; ir (Neat) 3450 (OH), 1730 and 1690 (CO) cm^{-1}. The ^1H nmr spectrum was not sufficiently well resolved for assignment of the signals. Ms m/z 327 (M^+). Calcd for $C_{17}H_{29}NO_5$: M^+, 327.2044. Found: 327.2036.

General Procedure for Reaction of **8a,b** with Methanesulfony Chloride and Triethylamine

MsCl (7.5 mmol) was added to a solution of **8** (5 mmol) and TEA (5 mmol) in CH_2Cl_2 (10 ml) under ice cooling, and the mixture was stirred for 40 min at room temperature. The reaction mixture was quenched by the addition of H_2O (5 ml), and extracted with $CHCl_3$. The extract was washed with brine, dried over anhyd. Na_2SO_4,

and evaporated. The residue was purified by column chromatography [benzene-EtOAc (2:1)] to give **10** from the earlier fraction and **9** from the later fraction, each as an oil.

Ethyl 1-Oxo-3-vinyl-3,4,4a,5,6,7-hexahydro-1H-pyrrolo[1,2-c][1,3]oxzine-4-carboxylate (**9a**)

Yield: 68%, colorless oily mixture of diastereomers; ir (Neat) 1720 and 1690 (CO) cm^{-1}. The ^1H nmr spectrum was not sufficiently well resolved for assignment of the signals. Ms m/z 239 (M^+). Calcd for $C_{12}H_{17}NO_4$: M^+, 239.1157. Found: 239.1160.

Ethyl 1-Oxo-3-vinyl-4,4a,5,6,7,8-hexahydro-1H,3H-pyrido[1,2-c][1,3]oxazine-4-carboxylate (**9b**)

Yield: 45%, colorless oily mixture of diastereomers; ir (Neat) 1730 and 1680 (CO) cm^{-1}. The ^1H nmr spectrum was not sufficiently well resolved for assignment of the signals. Ms m/z 253 (M^+). Calcd for $C_{13}H_{19}NO_4$: M^+, 253.1313. Found: 253.1308.

Ethyl 1-tert-Butoxycarbonyl-α-(1-methanesulfonyloxy-2-propenyl)pyrrolidine-2-acetate (**10a**)

Yield: 22%, pale brown oily mixture of diastereomers; ir (Neat) 1720, 1680 (CO), and 1345, 1160 (SO_2) cm^{-1}. The ^1H nmr spectrum was not sufficiently well resolved for the assignment of the signals. Ms m/z 391 (M^+). Calcd for $C_{17}H_{29}NO_7S$: M^+, 391.1663. Found: 391.1741.

Ethyl 1-tert-Butoxycarbonyl-α-(1-methanesulfonyloxy-2-propenyl)piperidine-2-acetate (**10b**)

Yield: 40%, pale brown oily mixture of diastereomers; ir (Neat) 1725, 1690 (CO) and 1345, 1165 (SO_2) cm^{-1}. The ^1H nmr spectrum was not sufficiently well resolved for assignment of the signals. Ms m/z 405 (M^+). Calcd for $C_{18}H_{31}NO_7S$: M^+, 405.1819. Found: 405.1818.

Ethyl 1,2,3,5,6,8a-Hexahydroindolizine-8-carboxylate (**11a**)

Method A ----- DBU (304 mg, 2 mmol) was added to a solution of **9a** (239 mg, 1 mmol) in DMSO (1 ml), and the mixture was heated at 120°C for 4 h. Work-up was the same as described for **6**, affording **11a** (170 mg, 87%) as a pale brown oil; ir (Neat) 2870, 2795 (Bohlmann bands), 1710 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ1.21 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 3.40 (1H, m, 9a-H), 6.90 (1H, m, 7-H); ms m/z 195 (M^+). Calcd for $C_{11}H_{17}NO_2$: M^+, 195.1257. Found: 195.1256.

Method B ----- **10a** (100 mg, 0.25 mmol) was dissolved in 2.3N dry HCl-EtOAc (0.6 ml) and the mixture was stirred for 1.5 h. After removal of the solvent by evaporation, the residue was dissolved in DMSO (0.5 ml) containing DBU (76 mg, 0.5

mmol). The mixture was heated at 120 °C for 4 h. Work-up was the same as described for **6**, affording **11a** (31 mg, 64%), which was identical with the sample obtained by Method A.

Method C ----- Without isolation of the intermediates, **8a** (579 mg, 1.85 mmol) was subjected to the following sequence in turn: i) MsCl (0.21 ml, 2.78 mmol)/TEA (0.78 ml, 5.55 mmol) at room temperature for 40 min, ii) 2.3N dry HCl-EtOAc (4 ml) at room temperature for 1.5 h, iii) DBU (562 mg, 3.7 mmol) in DMSO (3 ml) at 120°C for 4 h. Works-up as described above gave an oil, which was purified by column chromatography [$CHCl_3$-MeOH (10:1)] to give **11a** (305 mg, 81%).

Ethyl 3,4,7,8,9,9a-hexahydro-6H-quinolizine-1-carboxylate (**11b**)

Method A ----- **9b** (264 mg, 1.04 mmol) was treated with DBU (316 mg, 2.08 mmol) as described for **11a** (Method A) to give **11b** (178 mg, 82%) as pale brown oil; ir (Neat) 2800, 2755 (Bohlmann bands), 1705 (CO) cm^{-1}; ^1H nmr ($CDCl_3$)δ 1.25 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 4.15 (2H, q, J=7.2 Hz, $CO_2CH_2CH_3$), 6.82 (1H, m, 2-H); ms m/z 209 (M^+). Calcd for $C_{12}H_{19}NO_2$: M^+, 209.1415. Found: 209.1413.

Method B ----- **10b** (150 mg, 0.37 mmol) was treated with 2.3N dry HCl-EtOAc (0.8 ml), followed by DBU (112 mg, 0.74 mmol) to give **11b** (52 mg, 67%), which was identical with the sample obtained by Method A.

Method C ----- Without isolation of the intermediates, **8b** (810 mg, 2 mmol) was successively converted to **11b** (357 mg, 85%) after works-up as described for **11a** (Method C).

(±)-Lupinine (**12**)

According to the method of literatures, **11b** (21 mg, 0.1 mmol) was hydrogenated with PtO_2 (15 mg)[6a] to give a saturated ester, which was reduced with LAH (15 mg) in THF (2 ml)[12] to give a solid, which was recrystallized from hexane to give **12** (8.3 mg, 49%), mp 55-57 °C (lit.,[7] 57.5-58.5 °C). The compound prepared was identical with an authentic sample[7] in terms of the ir and ^1H nmr spectral data.

3-(3-Furyl)acrolein (**13**)

This was prepared from 3-furanaldehyde according to the method for the synthesis of 3-(2-furyl)acrolein[10] in 60% yield, bp 94-96 °C/10 mm Hg; ^1H nmr ($CDCl_3$)δ 6.36 (1H, dd, J=15.8, 7.8 Hz, =C<u>H</u>CHO), 6.55, 7.40 and 7.70 (each 1H, each s, Fu-H), 7.33 (1H, d, J=15.8 Hz, C<u>H</u>=CHCHO), 9.54 (1H, s, CHO).

Ethyl 1-tert-Butoxycarbonyl-2-[3-(3-furyl)-1-hydroxy-2-propenyl]pyrrolidine-2-acetate (**14**)

A solution of the ester (**7a**) (5.68 g, 22.1 mmol) in THF (10 ml) was added

dropwise to a solution of LDA [prepared from diisopropylamine (26.6 mmol)] in THF (15 ml) at -78 ℃ under N_2, and the mixture was stirred for 20 min. A solution of **13** (3.25 g, 26.6 mmol) in THF (10 ml) was added dropwise at -78°C, and the whole was stirred for 30 min. Work-up as described for the preparation of **8** gave an oil, which was purified by column chromatography [benzene-EtOAc (5:1)] to give **14** (7.78 g, 93%) as an oily mixture of diastereomers; ir (Neat) 3450 (OH), 1725 and 1680 (CO) cm^{-1}. The ^1H nmr spectrum was not sufficiently well resolved for assignment of the signals. Ms m/z 379 (M^+). Calcd for $C_{20}H_{29}NO_6$: M^+, 379.1992. Found: 379.1974.

Ethyl 3-[2-(3-Furyl)vinylene]-1-oxo-3,4,4a,5,6,7-hexahydro-1H-pyrrolo[1,2-c]-[1,3]oxazine-4-carboxylate (**15**)

A solution of MsCl (0.53 ml, 6.9 mmol) in CH_2Cl_2 (23 ml) was added to a solution of **14** (1.74 g, 4.6 mmol) and TEA (1.93 ml, 13.8 mmol) in CH_2Cl_2 (45 ml) at -7°C over a period of 30 min, and the mixture was stirred for 5 min. Work-up as described for **9** (or **10**) gave an oil, which was purified by column chromatography [benzene-EtOAc (5:1)] to give **15** (1.20 g, 86%) as a pale yellow oily mixture of diastereomers; ir (Neat) 1725 and 1695 (CO) cm^{-1}. The ^1H nmr spectrum was not sufficiently well resolved for assignment of the signals. Ms m/z 305 (M^+). Calcd for $C_{16}H_{19}NO_5$: M^+, 305.1262. Found: 305.1266.

Ethyl 5-(3-Furyl)-1,2,3,5,6,8a-hexahydroindolizine-8-carboxylate (**16** and **17**)

Method A ----- DBU (263 mg, 1.73 mmol) was added to a solution of **15** (528 mg, 1.73 mmol) in DMSO (1 ml), and the mixture was heated at 120℃ for 20 min. Work-up as described for the preparation of **11** gave a crude oil, which was purified by column chromatography [benzene-EtOAc (1:1)] to give **16** (391 mg, 86%) as a sole oily product; ir (Neat) 1705 (CO) cm^{-1} and no Bohlmann bands; ^1H nmr (C_6D_6) δ 0.97 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 1.38-1.62 (3H, m, 1-H and 2-H_2), 2.14 (2H, ddd, J=5.5, 4.5 and 2.8 Hz, 6-H), 2.37 (1H, m, 1-H), 2.57 (1H, m, 3-H), 2.71 (1H, m, 3-H), 3.46 (1H, t, J=5.5 Hz, 5-H), 3.87 (1H, m, 8a-H), 4.00 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 6.29 (1H, s, Fu-H), 6.96 (1H, td, J=4.5 and 1.9 Hz, 7-H) and 7.80 (2H, s, Fu-H); ms m/z 261 (M^+). Calcd for $C_{15}H_{19}NO_3$: M^+, 261.1363. Found: 261.1361.

Method B ----- DBU (760 mg, 5 mmol) was added to a solution of **15** (761 mg, 2.5 mmol) in DMSO (2 ml), and the mixture was heated at 120°C for 2 h. Work-up as described for the preparation of **11** gave a crude oil, which was purified by column chromatography [benzene-EtOAc (1:1)] to give **17** as an oil(127 mg, 19%) [ir (Neat) 2880 and 2790 (Bohlmann band), and 1705 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.24 (3H, t,

J=7.4 Hz, $CO_2CH_2CH_3$), 1.40-1.75 (3H, m, 1-H and 2-H_2), 2.13-2.70 (5H, m, 1-H, 3-H_2 and 6-H_2), 3.38 (1H, m, 8a-H), 3.62 (1H, dd, J=10.0 and 4.2 Hz, 5-H), 4.15 (2H, q, J=7.4 Hz, $CO_2CH_2CH_3$), 6.43 (1H, s, Fu-H), 6.92 (1H, dt, J=5.3 and 2.5 Hz, 7-H), and 7.33 (2H, br s, Fu-H); ms m/z 261 (M^+). Calcd for $C_{15}H_{19}NO_3$: M^+, 261.1363. Found: 261.1362] from the earlier fraction and **16** (200 mg, 31 %) from the later fraction, each as an oil.

Ethyl 5-(3-Furyl)octahydroindolizine-8-carboxylate (**18**)

A solution of **16** (322 mg, 1.23 mmol) in MeOH (15 ml) was hydrogenated using a Skita apparatus (initial pressure: 1.2 Kg/cm^2) with 5% Pd-C (161 mg) for 3 h. Catalyst was removed by filtration through Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography [benzene-EtOAc (1:1)] to give **18** (295 mg, 91%) as a colorless oil; ir (Neat) 1720 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.22 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 2.79 (1H, dt, J=8.8 and 3.0 Hz, 8a-H), 4.12 (3H, q, J=7.2 Hz, $CO_2CH_2CH_3$ and 5-H), 6.34 (1H, s, Fu-H), and 7.35 (2H, s, Fu-H); ms m/z 263 (M^+). Calcd for $C_{15}H_{21}NO_3$: M^+, 263.1519. Found: 263.1510.

5-(3-Furyl)-8-methyloctahydroindolizine (**21**)

A solution of **18** (295 mg, 1.12 mmol) in Et_2O (9 ml) was added to a suspension of LAH (51 mg, 1.35 mmol) in Et_2O (9 ml), and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched by the addition of H_2O (3 ml), 4% NaOH (2 ml) and H_2O (3 ml) in turn under ice cooling, and filtered by passing through the Celite pad. The separated aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over anhyd. $MgSO_4$, and concentrated to give **19** as an oil [ir (Neat) 3355 (OH) cm^{-1}; ms m/z 221 (M^+)]. This was treated with MsCl (0.13 ml, 1.67 mmol) and TEA (0.47 ml, 3.35 mmol) at 0 °C in CH_2Cl_2 (5 ml). Work-up as described for the preparation of **10** gave a crude mesylate (**20**), which was subsequently dissolved in ether (10 ml). The solution was added to a suspension of LAH (102 mg, 2.7 mmol) in Et_2O (10 ml). Work-up as described above gave an oil, which was purified by column chromatoglraphy (EtOAc) to give pure **21** (112 mg, 49% from **18**) as an oil; ir (Neat) no Bohlmann bands; ^1H nmr ($CDCl_3$) δ 0.90 (3H, d, J=6.0 Hz, $CHCH_3$), 2.80 (1H, dt, J=8.7 and 2.0 Hz, 8a-H), 4.12 (1H, br d, J=5.0 Hz, 5-H), 6.31 (1H, s, Fu-H), and 7.32 (2H, s, Fu-H); ms m/z 205 (M^+). Calcd for $C_{13}H_{19}NO$: M^+, 205.1466. Found: 205.1482.

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References and Notes

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