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Rearrangement of Isoxazoline-5-spiro Derivatives. Part 10.[1] Regioselective Nitrone Cycloadditions to Methoxycarbonylmethylenecyclopropane: Synthesis of Precursors of (±)-Lupinine, (±)-Epilupinine and (±)-Elaeokanine A

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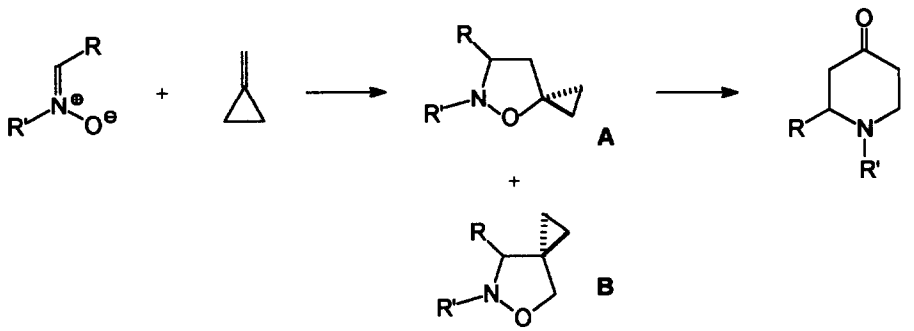
Abstract The cycloaddition of cyclic nitrones to methoxycarbonylmethylenecyclopropane (**1**) gives adducts having the methoxycarbonyl group on C-4 of the isoxazolidine ring with high regioselectivity The thermal rearrangement of the adducts gives quinolizidinone **6** and indolizidinones **8** bearing the methoxycarbonyl group selectively at C-1 and at C-8, respectively The two compounds are intermediates for new formal syntheses of the alkaloids (±)-Lupinine and (±)-Epilupinine, and (±)-Elaeokanine A, respectively

The thermal rearrangement of isoxazolidine-5-spirocyclopropanes **A**, available by nitrone cycloaddition to methylenecyclopropane, has shown its potential as a new method for the synthesis of azaheterocycles (Scheme 1) [2] Particularly interesting appears to be the new access to *N*-bridgehead bicyclic structures widespread in natural alkaloids [3]



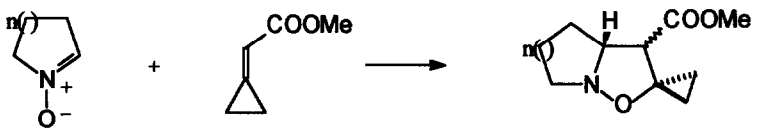
SCHEME 1

The selectivity of the process in the presence of various substituents on the reagents is a goal for a wider application of the method Since the overall process consists of two steps, a cycloaddition of a nitrone to a methylenecyclopropane derivative followed by a thermal rearrangement (Scheme 1),

different substituents on the 1,3-dipole as well as on the methylenecyclopropane, may reasonably affect the process In particular, the substitution on the exocyclic double bond of the methylenecyclopropane may affect the regiochemical outcome of the cycloaddition [4]

Unsubstituted or ring substituted methylenecyclopropanes have been shown[2] to react with nitrones to give mixtures of regioisomers **A** and **B** The 4-spiro regioisomers **B**, unreactive under the rearrangement conditions, sometimes accounts for as much as 37% (relative yield)[2] of the reaction mixture In a recent study[4] we demonstrated that an electronwithdrawing substituent on the exocyclic double bond of methylenecyclopropanes, such as the methoxycarbonyl group in **1**, gives rise to a significant change in the polarization of that bond, leading to highly regioselective cycloadditions The observed regiochemistry in this reaction was the same as that observed in the reactions of the related methyl 3,3-dimethylacrylate with nitrones,[5] that is regiospecific formation of the 4-methoxycarbonyl adduct

In this paper we want to show that this selectivity, combined with a thermal rearrangement, constitutes an useful protocol for the construction of selectively substituted intermediates for the synthesis of quinolizidine and indolizidine alkaloids



1

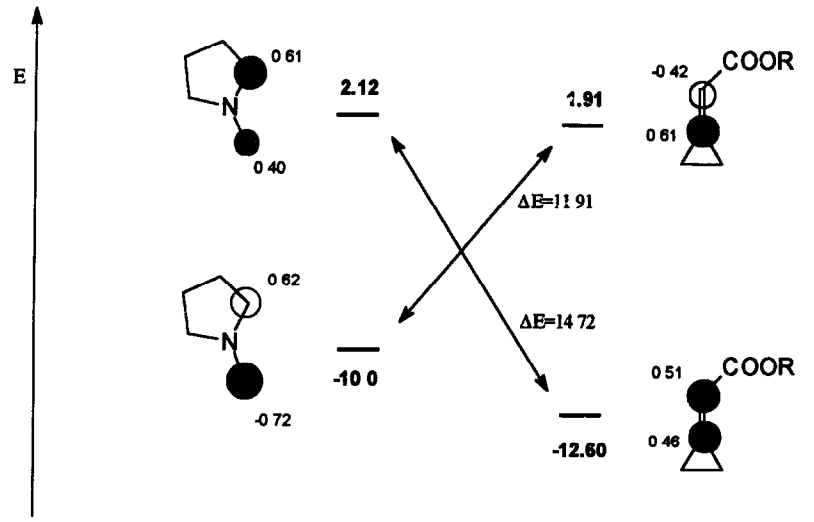
n = 2	**2**				
n = 1	**4**	**3a,b**	2 3 1	78%	
		5a,b	2 1 1	64%	

SCHEME 2

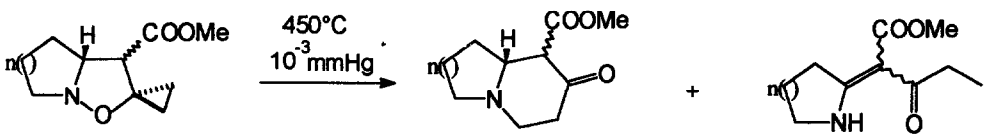
Methoxycarbonylmethylenecyclopropane (**1**) and 3,4,5,6-tetrahydropyridine-*N*-oxide (**2**) gave a mixture of two diastereomeric isoxazolidines **3a** and **3b** (78%) in 2 3 1 ratio under heating at 80°C in toluene (Scheme 2) The assignment of the regiochemistry was made on the observation of a doublet (δ 3 33 ppm for **3a** and δ 3 11 ppm for **3b**) for the proton α to the methoxycarbonyl group coupled with the bridgehead proton The major isomer **3a** was assigned as the exo product in force of the smaller coupling constant (7 5 Hz vs 9 9 Hz) typical of a trans H-H relationship in a five membered ring Pyrroline-*N*-oxide (**4**) gave with **1** a similar mixture of adducts **5a** and **5b** in 2 1 1 ratio and somewhat more modest yield (64%) H3-H4 (isoxazolidine numberings) coupling constant in the major compound **5a** (8 4 Hz vs 4 3 Hz in **5b**) attested for the preference of an endo approach in the cycloaddition of this nitrone [6]

The observed regioselectivity is in agreement with the results of a study of the coefficients and energy of the frontier molecular orbitals of methylenecyclopropane 1 and nitrone 4 (Figure 1) [7] In the favored $HOMO_{nitrone}$-$LUMO_{dipolarophile}$ interaction the larger coefficients are located on the oxygen of the nitrone and on the cyclopropylidene carbon of the methylenecyclopropane as required for the observed regioselectivity A quantitative evaluation of the differences in charge transfer energies of the two regioisomeric oriented complexes ($\Delta\Delta E = \Delta E_{5\text{-spiro}} - \Delta E_{4\text{-spiro}} = -0\,30$ Kcal mol^{-1}) again predicts the 5-spiro regioisomer as being the dominant isomer in the cycloaddition

FIGURE 1 Coefficients and Energies of the Frontier Molecular Orbitals of Methoxycarbonylmethylenecyclopropane (1) and Pyrroline-*N*-oxide (4)



Isoxazolidines **3** and **5** were particularly resistant to thermal rearrangement, if compared with other substrates [2] On the other hand, heating in mesitylene at reflux (160°C) for several hours gave poor yields of rearranged products, mainly consisting in the open chain enaminones **7** and **9** [2] By heating **3a,b** under Flash Vacuum Thermolysis (FVT) conditions (450°C, 10^{-3} mmHg) the quinolizidinone **6** and the enaminones **7** were obtained, and they were isolated in 46% and 20% yield, respectively, after flash column chromatography Both the diastereomeric isoxazolidines gave a single diastereomeric ketone probably as a result of a tautomerism towards the more stable isomer The assignment of methoxycarbonyl group substitution on C1 carbon relied on the multiplicity of the α proton in the ^{1}H-NMR spectrum The value of the coupling constant (10 9 Hz) is diagnostic for a trans H1-H9a relationship in **6**, that implies the carbomethoxy group to be placed in equatorial position cis to the bridgehead proton An analogue FVT treatment of isoxazolidines **5a,b** followed by chromatographic separation, gave both the diastereomeric indolizidinones **8a,b** in 2 4 1 ratio (45%) besides the enaminones **9** (19%) Again, a coupling constant of 11 1 Hz testifies for a trans H8-H8a relationship in the major isomer **8a**



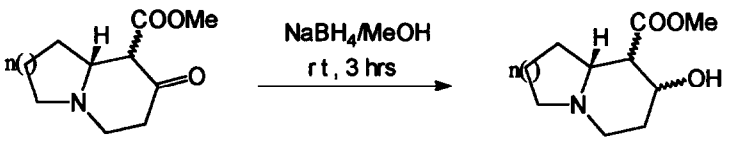
n = 2	**3a,b**	**6**	46%	**7a,b**	20%
n = 1	**5a,b**	**8a,b**	45%	**9a,b**	19%

SCHEME 3

The formation of the open chain isomers in the rearrangement originates from a 1,5-hydrogen shift of the diradical intermediate[8] and can only be diminished by using FVT conditions In both rearrangements the yields of the bicyclic products **6** and **8** were only modest, but this seems to depend on the thermal stability of these compounds In fact, due to the low volatility of the rearranged products, a film of decomposed material is always found at the hot end of the FVT tube Decomposition processes, like retro-Michael and Grob fragmentation,[9] are likely to occur in these compounds due to their nature of γ-aminoketones

The simple two-step cycloaddition-rearrangement protocol has been able to provide a new direct access to selectively functionalised quinolizidine and indolizidine compounds. Many synthetically useful applications can be foreseen for these compounds, as a new entry to unnatural and natural azaheterocycles [10] In this paper we report on their use as precursors for the formal synthesis of (±)-Lupinine (**10**), (±)-Epilupinine (**11**) and (±)-Elaeokanine A (**12**) alkaloids

Reduction of ketones **6** and **8a,b** with sodium borohydride gave the stable quinolizidinol **13** and indolizidinol **14** as mixtures of diastereoisomers with good yields (Scheme 4)

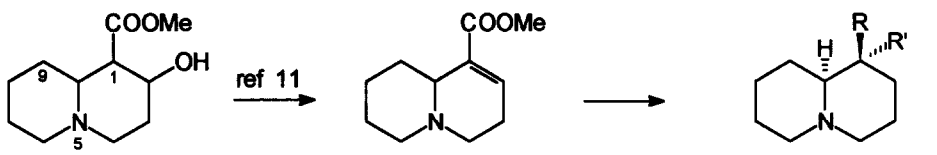


n = 2 **6** **13a,b** 81 %

n = 1 **8a,b** **14a-d** 83 %

SCHEME 4

The alcohol **13** was used by J J Tufariello as intermediate for the synthesis of both *Lupine* alkaloids (±)-**10** and (±)-**11** via the unsaturated compound **15** (Scheme 5) [11]



13 **15**

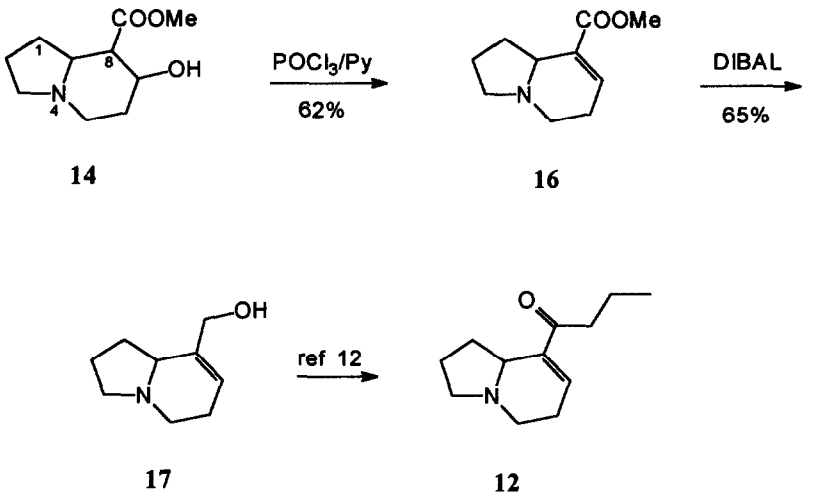
10 R=CH_2OH R'=H

11 R=H R'=CH_2OH

SCHEME 5

The indolizidinols **14** can be conveniently applied to a new synthesis of the alcohol **17**, used by D F Taber in the total synthesis of (±)-Elaeokanine A (**12**) (Scheme 6) [12]

Dehydration of **14** by phosphorus oxychloride in pyridine[13] gave the unsaturated indolizidine **16** in fair yield Other conditions to run the elimination ($SOCl_2$/DBU, MsCl/Py at 0°C) were tested, but were found less effective The formal synthesis of (±)-Elaeokanine A (**12**) was completed by DIBAL reduction of the unsaturated ester **16** to the allylic alcohol **17** in 65% yield (Scheme 6)



SCHEME 6

Further studies on the synthetic utility of quinolizidinone **6** and indolizidinones **8** are in progress in our laboratory

EXPERIMENTAL

All the reactions were carried out under inert atmosphere (N_2) and the solvents were appropriately dried before the use The R_f values refer to TLC on 0 25 mm silica gel plates (Merck F_{254}) obtained using the same eluant as in the column chromatographies NMR spectra ($CDCl_3$ as solvent) were recorded on a Varian Gemini (^1H, 200 MHz) Chemical shift values are reported in ppm from tetramethylsilane notation s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively The coupling constants *J* are given in Hz IR spectra (in $CDCl_3$ solution) were recorded on a Perkin-Elmer 881 spectrophotometer Mass spectra were recorded at 70 eV by GC inlet on a 5790A-5970A Hewlett-Packard instrument or by direct inlet on a QMD1000 Carlo Erba instrument Combustion analyses were carried out with a Perkin-Elmer 240 C elemental analyzer Nitrones **2** and **4** were synthesized according to ref 14 and 15, respectively Methoxycarbonylmethylenecyclopropane (**1**) was synthesized according to ref 16 ^1H-NMR δ 6 22 (quintet, J=1 9 Hz, 1H), 3 73 (s, 3H), 1 50-1 37 (m, 2H), 1 28-1 13 (m, 2H) ^{13}C-NMR δ 166 4 s, 145 4 s, 110 6 d, 51 4 q, 4 6 t, 2 1 t IR 2981, 1759, 1704, 1437, 1340 cm^{-1} MS m/z (relative intensity) 112 (M^+, 17), 111 (20), 97 (19), 82 (66), 81 (100), 59 (20), 53 (76), 51 (35)

Cycloaddition of Nitrone 2 to Methylenecyclopropane 1

A solution of **2** (459 mg, 4 5 mmol) and **1** (337 mg, 3 mmol) in 7 mL of toluene was heated at reflux for 16 h After concentration in vacuo the crude mixture was filtered through a short pad of silica gel, eluting with ethyl acetate Removal of the solvent in vacuo gave 493 mg (2 3 mmol, 78%) of a mixture of two cycloadducts **3a** and **3b** in 2 3 1 ratio The two diastereoisomers were separated by flash chromatography (eluant petroleum ether-ethyl acetate 70 30) and characterized, but there is no need of separation for further steps

(3'R,3a'R*) - 3' - (1-Methoxy-1-oxomethyl)-octahydrospiro[cyclopropane-1,2'-isoxazole[2,3a] pyridine] (exo isomer)* (**3a**) R_f = 0 28 ^{1}H-NMR δ 3 69 (s, 3H), 3 54-3 43 (m, 1H) , 3 33 (d, *J*=7 5 Hz, 1H), 2 74 (ddd, *J*=10 1, 7 5, 2 5 Hz, 1H), 2 46-2 02 (m, 1H), 1 93-0 96 (m, 8H), 0 81-0 58 (m, 2H) ^{13}C-NMR δ 171 3 s, 70 9 d, 63 7s, 55 8 t, 55 1 d, 51 4 q, 26 0 t, 24 1 t, 23 3 t, 12 2 t, 9 6 t IR 3004, 2952, 2838, 1739, 1722, 1437, 1269, 1192, 1165 cm^{-1} MS m/z (relative intensity) 211 (M^+, 15), 140 (39), 124 (58), 110 (35), 96 (90), 82 (58), 68 (39), 55 (100), 41 (87) Anal Calcd for $C_{11}H_{17}NO_3$ C, 62 54, H, 8 11, N, 6 63% Found C, 62 04, H, 8 27, N, 6 65%

(3'S,3a'R*) - 3' - (1-Methoxy-1-oxomethyl)-octahydrospiro [cyclopropane-1,2'-isoxazole[2,3-a] pyridine] (endo isomer)* (**3b**) R_f = 0 39 ^{1}H-NMR δ 3 69 (s, 3H), 3 48-3 33 (m, 1H), 3 11 (d, *J*=9 9 Hz, 1H), 2 86 (td, *J*=9 9, 1 7 Hz, 1H), 2 61-2 47 (m, 1H), 2 08-0 62 (m, 10H) ^{13}C-NMR δ 171 9 s, 72 0 d, 64 0 s, 56 6 d, 55 3 t, 51 8 q, 28 5 t, 24 3 t, 23 3 t, 14 5 t, 7 2 t MS m/z (relative intensity) (M^+, 13), 140 (32), 124 (44), 110 (31), 96 (62), 82 (40), 69 (30), 55 (100), 41 (69)

Cycloaddition of Nitrone 4 to Methylenecyclopropane 1

A solution of **4** (2 125 g, 25 0 mmol) and **1** (1 121 g, 10 0 mmol) in 3 5 mL of benzene was stirred at r t for 18 h After concentration in vacuo the crude mixture was filtered through a short pad of silica gel, eluting first with petroleum ether-ethyl acetate 50 50, then with ethyl acetate Removal of the solvent in vacuo gave 1 264 g (6 4 mmol, 64%) of a mixture of two cycloadducts **5a** and **5b** in 2 1 1 ratio The two diastereoisomers were separated by flash chromatography (eluant ethyl acetate) and characterized, but there is no need of separation for further steps

(3'R,3a'S*) - 3' - (1- Methoxy -1- oxomethyl)-hexahydrospiro[cyclopropane-1,2'-pyrrolo[1,2-b] isoxazole] (endo isomer)* (**5a**) R_f =0 27 ^{1}H-NMR δ 4 07 (q, *J*=7 8 Hz, 1H), 3 65 (s, 3H), 3 58 (d, *J*=8 4 Hz, 1H), 3 40-3 22 (m, 1H), 3 13-2 95 (m, 1H), 2 10-1 61 (m, 4H), 1 18-0 56 (m, 4H) ^{13}C-NMR δ 170 7 s, 68 7 d, 63 1 s, 56 7 t, 54 1 d, 51 7 q, 27 8 t, 24 8 t, 10 4 t, 8 5 t IR 3095, 2954, 2877, 1738, 1436, 1363, 1194, 1170 cm^{-1} MS m/z (relative intensity) 197 (M^+, 22), 138 (24), 110 (74), 108 (52), 98 (52), 82 (93), 69 (88), 55 (52), 43 (77), 41 (100) Anal Calcd for $C_{10}H_{15}NO_3$ C, 60 90, H, 7 67, N, 7 10% Found C, 61 16, H, 7 86, N, 6 82%

(3'S,3a'S*) - 3' -(1 - Methoxy -1- oxomethyl)-hexahydrospiro[cyclopropane-1,2'-pyrrolo[1,2-b] isoxazole] (exo isomer)* (**5b**) R_f =0 39 ^{1}H-NMR δ 4 25-4 18 (m, 1H), 3 68 (s, 3H), 3 35-3 20 (m, 1H), 3 12-2 98 (m, 1H), 3 05 (d, *J*=4 3 Hz, 1H), 2 14-1 62 (m, 4H), 1 29-0 64 (m, 4H) ^{13}C-NMR δ 171 2 s, 68 9 d, 64 1 s, 58 1 t, 56 6 d, 52 1 q, 31 2 t, 23 8 t, 10 5 t, 7 5 t

Thermal Rearrangement of 3a,b

The mixture of spiroisoxazolidines **3a,b** (211 mg, 1 mmol) was subjected to FVT (450°C, 10^{-3} mmHg) by vaporization at 80-100°C ^{1}H-NMR analysis of the crude reaction product (175 mg, 82%) showed the presence of **6** and **7a,b** in 2 3 1 ratio The mixture was subjected to flash chromatography (eluant ethyl acetate) to yield 97 mg (46%) of **6** and 42 mg (20%) of an unseparable mixture of **7a** and **7b** in 1 3 1 ratio

(1R,9aR*)-1-Methoxycarbonyloctahydro-[2H]-quinolizin-2-one* (**6**) R_f = 0 20 ^{1}H-NMR δ 3 74 (s, 3H), 3 25 (d, *J*=10 9 Hz, 1H), 3 12-2.98 (m, 2H), 2 78-2 34 (m, 4H), 2 12 (td, *J*=11 4, 3 4 Hz, 1H), 1 76-1 11 (m, 6H) ^{13}C-NMR δ 203 6 s, 169 1 s, 63 3 d, 63 1 d, 55 1 t, 54 8 t, 51 7 q, 40 6 t, 31 9 t, 25 0 t, 22 6 t IR 2944, 2813, 1741, 1715 cm^{-1} MS m/z (relative intensity) 211 (M^+, 19), 152 (54), 110 (40), 96 (42), 83 (100), 82 (25), 69 (17), 55 (51), 41 (37) Anal Calcd for $C_{11}H_{17}NO_3$ C, 62 54, H, 8 11, N, 6 63% Found C, 61 97, H,8 26, N, 6 63%

2-(1-Methoxycarbonyl-2-oxobutylidene)-piperidine (E and Z) (**7a,b**) R_f = 0 73 ^{1}H-NMR δ (major isomer) 5 53 (s, NH), 3 67 (s, 3H), 2 85 (t, *J*=6 0 Hz, 2H), 2 38 (q, *J*=7 4 Hz, 3H), 1 82-1 57 (m, 6H), 1 09 (t, *J*=7 4 Hz, 2H), (minor isomer) 5 57 (s, NH), 3 67 (s, 3H), 3 39-3 28 (m, 1H), 2 61 (t, *J*=6 2 Hz, 1H), 2 48 (q, *J*=7 4 Hz, 3H), 1 82-1 57 (m, 6H), 1 03 (t, *J*=7 4 Hz, 2H) IR 3692, 2950, 1735, 1599, 1194 cm^{-1} MS m/z (relative intensity) (M^+, 1), 141 (21), 125 (27), 97 (55), 84 (35), 83 (35), 70 (32), 60 (21), 56 (100) Anal Calcd for $C_{11}H_{17}NO_3$ C, 62 54, H, 8 11, N, 6 63% Found C, 62 34, H, 8 14, N, 6 96%

Thermal Rearrangement of 5a,b

The mixture of spiroisoxazolidines **5a,b** (119 mg, 0 6 mmol) was subjected to FVT (450°C, 10^{-3} mmHg) by vaporization at 70-90°C ^{1}H-NMR analysis of the crude reaction mixture (103 mg, 87%) showed the presence of the compounds **8a**, **8b** and **9a,b** in 2 4 1 0 9 ratio The mixture was subjected to flash chromatography (silica gel, eluant ethyl acetate) to yield 53 mg (45%) of an unseparable mixture of **8a,b** and 22 mg (19%) of a mixture of **9a,b**

(8R,8aR*) and (8R*,8aS*)-8-Methoxycarbonyloctahydroindolizin-7-one* (**8a** and **8b**) R_f = 0 10 ^{1}H-NMR δ (**8a**) 3 73 (s, 3H), 3 30 (d, *J*=11 1 Hz, 1H), 3 12 (td, *J*=8 0, 2 9 Hz, 1H), 2 66-2 50 (m, 2H), 2 49-2 36 (m, 2H), 2 35-2 19 (m, 1H), 2 11-1 72 (m, 4H), 1 66-1 40 (m, 1H) (**8b**) 3 27 (d, *J*=7 8 Hz, 1H) ^{13}C-NMR δ (**8a**) 203 7 s, 168 7 s, 65 7 d, 62 9 d, 52 8 t, 52 0 q, 49 9 t, 40 2 t, 30 3 t, 22 4 t IR 2956, 2881, 2811, 1745, 1718 cm^{-1} MS m/z (relative intensity) 197 (M^+, 14), 166 (25), 138 (97), 110 (31), 96 (100), 82 (48), 69 (56), 55 (38), 41 (100) Anal Calcd for $C_{10}H_{15}NO_3$ C, 60 90, H, 7 67, N, 7 10% Found C, 60 62, H, 7 81, N, 6 61%

2-(1-Methoxycarbonyl-2-oxobutylidene)-pyrrolidine (E and Z) (**9a,b**) R_f = 0 73 ^{1}H-NMR δ (major isomer) 11 6 (s, 1H), 3 68 (s, 3H), 3 60 (t, *J*=7 1 Hz, 2H), 3 07 (t, *J*=7 8 Hz, 2H), 2 74 (q, *J*=7 3 Hz, 2H), 1 98 (quintet, *J*=7 4 Hz, 2H), 1 04 (t, *J*=7 3 Hz, 3H) ^{13}C-NMR δ (major isomer) 201 0 s, 174 3 s, 169 2 s, 98 5 s, 50 5 q, 47 8 t, 35 0 t, 34 7 t, 20 9 t, 9 7 q IR 3620, 1678, 1597, 1546, 1438 cm^{-1}

Reduction of 6

A stirred solution of **6** (200 mg, 0 95 mmol) in 10 mL of methanol was treated with sodium borohydride (18 mg, 0 47 mmol) at 0°C and after 5 min it was allowed to warm to r t and stirred for 3 h The reaction was quenched with saturated aqueous sodium chloride (7 mL) and the mixture was extracted with chloroform (3 x 10 mL) The combined organic layers were dried over sodium sulfate and filtered, and the solvent was removed in vacuo The crude product was chromatographed on a short pad of silica gel eluting sequentially with petroleum ether-ethyl acetate 50 50, ethyl acetate and methanol to give 163 mg (0 76 mmol, 81%) of a 1 1 mixture of **13a,b** Attempted chromatographic separation gave only mixtures enriched in one of the two components

(1R,2R*,9aR*) and (1R*,2S*,9aR*)-1-Methoxycarbonyloctahydro-[2H]-quinolizin-2-ol* (**13a** and **13b**) R_f (ethyl acetate) = 0 11 ^{1}H-NMR δ (**13a**) 3 80 (ddd, *J*=10 6, 10 2, 4 8 Hz, 1H), 3 71 (s, 3H), 2 96-2 76 (m, 2H), 2 70-2 52 (m, 2H), 2 28 (t, *J*=10 2 Hz, 1H), 2 23-1 15 (m, 10H), (**13b**) 4 18-4 12 (m, 1H), 3 69 (s, 3H), 2 99-2 75 (m, 3H), 2 60-2 42 (m, 3H), 2 28 (t, *J*=10 2 Hz, 1H), 2 21-1 10 (m, 8H) ^{13}C-NMR δ (**13a**) 174 8 s, 64 9 d, 57 3 d, 56 1 d, 51 7 t, 51 6 q, 49 2 t, 31 0 t, 30 8 t, 25 4 t, 24 1 t, (**13b**) 173 9 s, 70 7 d, 62 2 d, 57 9 d, 55 7 t, 54 0 t, 51 7 q, 33 7 t, 30 7 t, 25 2 t, 23 6 t IR 3611, 3497 br, 2941, 2768 and 2680 (Bohlmann's bands),[18] 1723, 1625, 1436 cm^{-1} MS m/z (relative intensity) 213 (M^+, 11), 196 (9), 182 (8), 168 (21), 154 (11), 136 (11), 111 (50), 97 (79), 83 (100) Anal Calcd for $C_{11}H_{19}NO_3$ C, 61 95, H, 8 98, N, 6 57% Found C, 61 99, H, 9 01, N, 6 28%

Reduction of 8a,b

Sodium borohydride (13 mg, 0 34 mmol) was added to the mixture of **8a** and **8b** (133 mg, 0 68 mmol) stirred in 5 mL of methanol at 0°C After 5 min at this temperature, the mixture was allowed to warm to room temperature and stirred for 3 h The reaction was quenched with saturated aqueous sodium chloride (3 mL) and the mixture was extracted with three 10 mL portions of chloroform The combined organic layers were dried over sodium sulfate and filtered, and the solvent was removed in vacuo The crude product was chromatographed on a short pad of silica gel eluting sequentially with petroleum ether-ethyl acetate 50 50, ethyl acetate and methanol to give 113 mg (0 57 mmol, 83%) of a mixture of the four alcohols **14a-d** Attempted chromatographic separation gave only mixtures enriched in one of the two major components

(7R,8R*,8aR*), (7S*,8R*,8aR*), (7R*,8S*,8aR*) and (7S*,8S*,8aR*)-8-methoxycarbonyl-octahydroindolizin-7-ol* (**14a-d**) R_f (ethyl acetate)= 0 11 ^{1}H-NMR δ (first isomer) 3 83 (ddd, *J*=11 0, 9 9, 4 8 Hz, 1H), 3 70 (s, 3H), 3 06-2 99 (m, 2H), 2 27 (t, *J*=9 9 Hz, 1H), 2 18-1 42 (m, 10H), (second isomer) 4 29-4 23 (m, 1H), 3 70 (s, 3H), 3 12-2 95 (m, 2H), 2 90-2 78 (m, 1H), 2 54-2 40 (m, 1H), 2 18 (t, *J*=8 9 Hz, 1H), 2 16-1 18 (m, 8H) ^{13}C-NMR δ (first isomer) 173 6 s, 70 8 d, 64 2 d, 55 9 d, 53 1 t, 51 8 q, 49 5 t, 33 4 t, 28 9 t, 21 6 t, (second isomer) 174 4 s, 74 3 d, 65 3 d, 58 6 d, 53 6 t, 51 9 q, 46 2 t, 31 7 t, 29 2 t, 20 4 t IR 3618, 3575-3240, 2960, 2810, 1720, 1440 cm^{-1} MS m/z (relative intensity) 199 (M^+, 28), 198 (12), 184 (31), 182 (21), 168 (24), 140 (24), 122 (32), 97 (100), 96 (90), 83 (62), 69 (79) Anal Calcd for $C_{10}H_{17}NO_3$ C, 60 28, H, 8 60, N, 7 03% Found C, 59 96, H, 8 61, N, 6 99%

Dehydration of 14a-d

To a solution of the alcohols **14a-d** (76 mg, 0 38 mmol) in 2 mL of pyridine at 0°C was added freshly distilled phosphorus oxychloride (117 mg, 0 76 mmol) dropwise The mixture was allowed to warm to room temperature and stirred overnight After concentration in vacuo some ice was added to the crude mixture, then the aqueous solution was brought to basic pH with solid potassium carbonate, diluted with 8 mL of ether and dried over sodium sulfate for 1 h The solution was filtered, concentrated in vacuo and the crude product was chromatographed on a short pad of silica gel, eluting sequentially with ethyl acetate, ethyl acetate-methanol 90 10 and methanol, to give 43 mg (0 24 mmol, 62%) of **16**

1,2,3,5,6,8a-Hexahydro-8-methoxycarbonylindolizine (**16**) R_f (ethyl acetate-methanol 70 30)= 0 13 ^{1}H-NMR δ 6 97 (td, *J*=4 1, 1 8 Hz, 1H), 3 71 (s, 3H), 3 56-3 42 (m, 1H), 2 95-2 72 (m, 3H), 2 68-2 54 (m, 1H), 2 42-2 20 (m, 3H), 1 90-1 72 (m, 2H), 1 58-1 38 (m, 1H) ^{13}C-NMR δ 166 6 s, 137 5 d, 132 7 s, 58 6 d, 52 4 t, 51 4 q, 44 9 t, 29 7 t, 24 7 t, 22 4 t IR 2955, 2810, 1708, 1641, 1437, 1272 cm^{-1} MS m/z (relative intensity) 181 (M^+, 27), 166 (42), 153 (52), 122 (100), 120 (39), 94 (26), 41 (21) Anal Calcd for $C_{10}H_{15}NO_2$ C, 66 28, H, 8 34, N, 7 73% Found C, 66 31, H, 7 99, N, 8 16%

Reduction of 16

A solution of **16** (24 mg, 0 13 mmol) in 2 mL of tetrahydrofuran was cooled to 0°C in an ice bath Diisobuthylaluminum hydride (DIBAL) (0 52 mL of a 1 M solution in toluene, 0 52 mmol) was added dropwise The mixture was stirred at 0°C for 30 min and then was allowed to warm to r t and stirred for 5 h Ether (5 mL) was added, followed by sodium fluoride (87 mg, 2 08 mmol) Water (28 μL, 1 56 mmol) was added dropwise and the resulting mixture was stirred for 10 min, diluted with acetone and filtered The filtrate was concentrated in vacuo to yield 13 mg (0 085 mmol, 65%) of **17**

1,2,3,5,6,8a-Hexahydroindolizine-8-methanol (**17**) ^{1}H-NMR δ 5 76 (m, 1H), 4 76 (s, OH), 4 09 (s, 2H), 2 97 (t, *J*=7 5 Hz, 1H), 2 88 (m, 1H), 2 34 (m, 2H), 2 30 (m, 2H), 1 98-1 35 (m, 5H) MS m/z (relative intensity) 153 (M^+, 12), 152 (35), 134 (28), 125 (32), 122 (100), 120 (20) (Spectra identical to the data reported in ref 12)

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