116. Short, Enantiospecific Syntheses of Indolizidines 209B and 209D, and Piclavine A from Diethyl-L-Glutamate

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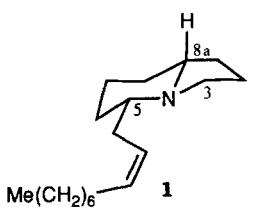
(29.V.95)

The 1*H*-pyrrole derivative obtained from diethyl L-glutamate hydrochloride and tetrahydro-2,5-dimethoxyfuran was cyclized with BBr_3 to ethyl (5*S*)-5,6,7,8-tetrahydro-8-oxoindolizine-5-carboxylate (**18**). Catalytic hydrogenation of **18** over Pd/C in AcOH gave ethyl (5*S*,8a*R*)-octahydroindolizine-5-carboxylate (**21**), whereas hydrogenation over Rh/Al_2O_3 in EtOH/AcOH 99:1 afforded mainly ethyl (5*S*,8*S*,8a*S*)-octahydro-8-hydroxyindolizine-5-carboxylate (**22**). By functional-group interconversions, **21** was transformed into piclavine A (**1**) and indolizidine 209D (**2**). Similarly, (5*R*,8*R*,8a*S*)-octahydro-5-pentylindolizine-8-methanol (**37**), the final relay for indolizidine 209B (**3**), was obtained from **22**.

Introduction. – Indolizidine (= octahydroindolizine) alkaloids attract attention because of their diverse biological properties and scarce occurrence in exotic organisms [1]. Of particular relevance are the 5-alkyl- and 5,8-dialkylindolizidines which, despite their seemingly simple structures, are not easy to prepare in an enantiomerically pure state. A typical example is piclavine A (**1**), an antimicrobial constituent extracted from the tunicate *Clavelina picta,* which represents the first indolizidine occurring in the marine biosphere [2]. Equally typical are the highly toxic indolizidines 209D[1]) (**2**) and 209B (**3**) which were isolated in infinitesimally small amounts from the skin of neotropical frogs of the *Dendrobatidae* family [4] [5]. Several approaches to **2** and **3** have been undertaken, whereas **1** has yet to be synthesized. The stereochemical problem centers on the construction of the bicyclic entity of the desired configuration at the C(5) and C(8a) positions and, in the case of **3**, the creation of the *trans*-disposed Me group. A variety of solutions have been propounded. Most make use of chiral auxiliaries, whereas some exploit optically active starting materials of natural origin which were incorporated to various degrees in the final product [6–10]. However, they usually require many steps and, with few exceptions, are characterized by low yields.



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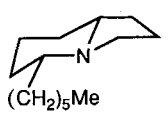

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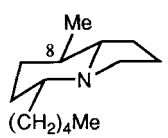

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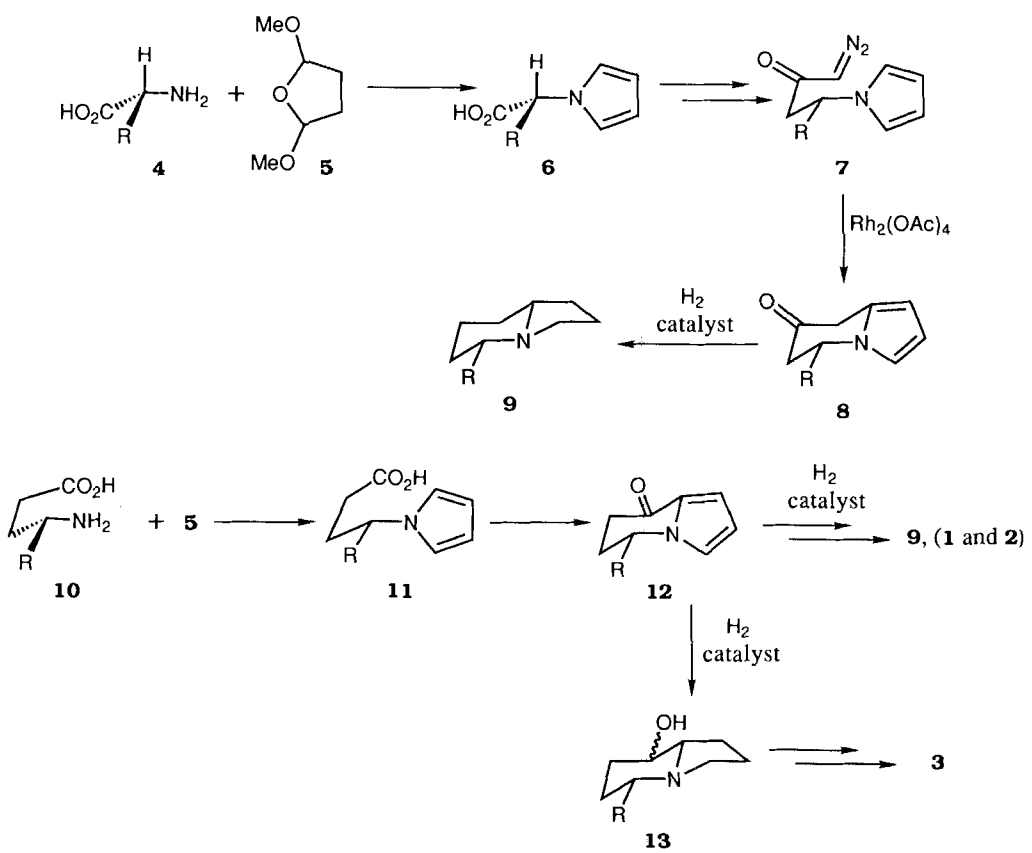
[1]) The absolute configuration of indolizidine 209D was inferred from that of 223 AB [3].

We now describe straightforward, enantioselective syntheses of **1**–**3** which are based on an adaptation of our previous method for preparing enantiomerically pure 5-alkyl- and *cis*-3,5-dialkylindolizidines [11]. This method consists of three stages. In the first, a chiral α-amino acid **4** is converted into its 1*H*-pyrrole derivative **6** by condensation with tetrahydro-2,5-dimethoxyfuran (**5**; *Scheme 1*). The second entails elongation of the side-chain by *Arndt-Eistert* homologation. The resulting α-diazoketone **7**, on $Rh_2(OAc)_4$ catalysis, is cyclized to the bicyclic nonconjugated ketone **8**. In the third stage, catalytic hydrogenation of **8**, thanks to control by the stereogenic center, produces the required diastereoisomeric 5-substituted indolizidine **9**. The new synthetic strategy depends, as before, on the dissymmetry implanted into a bicyclic pyrrole building block, but involves important modifications in all three stages (for a preliminary communication, see [12]). By taking a γ-amino acid **10** as the chiral component, the corresponding 1*H*-pyrrole derivative **11**, on intramolecular acylation, would afford the pivotal isomeric bicyclic ketone **12** (*Scheme 1*). Substituent-controlled hydrogenation should be subject to steric constraints similar to those operating in **8** and, depending on the catalyst, could proceed with full reduction of the bicyclic entity to the 5-substituted indolizidine **9**. Thus, a more direct

Scheme 1

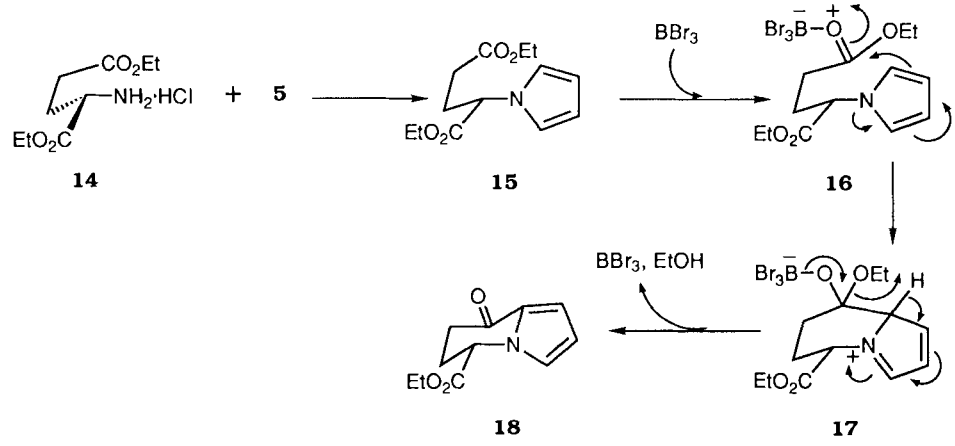


route to 5-alkylindolizidines (*e.g.* **1** and **2**) becomes available. Partial hydrogenation should afford indolizidinol **13**. The latter, by appropriate conversion of the functional groups, would then provide the 5,8-dialkylindolizidines (*e.g.* **3**).

Results and Discussion. – For practical reasons, the foregoing plan was realized by taking diethyl L-glutamate hydrochloride (**14**), rather than the acid, as the starting material. Full details were discussed elsewhere [13], but suffice it to say that the usual procedure for condensing α-amino acids with **5**, namely dissolution in warm AcOH with or without added AcONa, led to partial racemization of the resulting 1*H*-pyrrole derivative. Consequently, the use of the ester hydrochloride in a two-phase solvent system is essential to conserve optical integrity. It will be seen that the ester functions of **14** can be differentiated and conveniently fashioned into the appropriate 5- and 8-substituents of the target molecules **1–3**.

The chiral foundation for the construction of the indolizidine edifice common to **1–3** was laid by converting **14** into 1*H*-pyrrole derivative **15** by reaction with **5** under non-racemizing conditions, namely, in a stirred mixture of warm water and 1,2-dichloroethane (*Scheme 2*). The cyclization of the pyrrole ester **15** into the bicyclic pyrrole **18** was problematical, because esters do not usually undergo acylation under the *Friedel-Crafts* conditions [14]. Nevertheless, an old report [15] that BBr_3 supposedly reacts with esters and lactones to give boronic derivatives which behave like acylating agents provided a sufficient incentive for trying out this reagent on **15**. Treatment of **15** with BBr_3 brought about efficient closure to **18** with complete retention of configuration.

Scheme 2



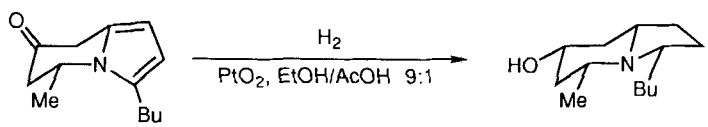
14 **15** **16** **17** **18**

Although the mechanism of this new reaction is open to conjecture, the intermediacy of a boronic derivative seems unlikely, because the ester substituent of **18** survived even when an excess of BBr_3 was used [16]. It can be supposed that the distal ester group is activated by complexation with BBr_3 (→ **16**) thereby triggering attack by the 1*H*-pyrrole ring at the α-position to give the zwitterion **17**. Formally, excision of a molecule each of EtOH and BBr_3 would account for the formation of **18**. In synthetic terms, this new procedure has distinct advantages when compared to conventional *Friedel-Crafts* reactions of related

(1*H*-pyrrol-1-yl)butyric and -propionic acids, which are characterized by poor yields (< 50%) [17].

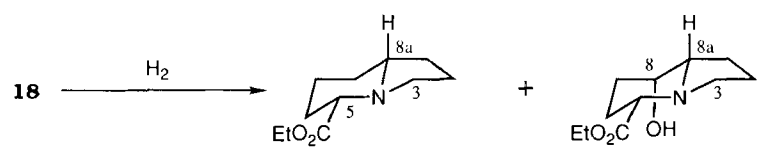
The next step, the catalytic hydrogenation of **18** was also critical. We discovered earlier [18] [19] that the catalysts commonly employed for reducing aromatic ketones, Pt and Pd/C [20], also worked well with derivatives of 5,6-dihydroindolizin-7(8*H*)-one. Under the normal conditions, in AcOH or EtOH as solvent, hydrogenation of the pyrrole ring was substituent-directed, but stopped short of completion. *E.g.*, the monomorine precursor **19** on hydrogenation over Pt in AcOH/EtOH gave solely the all-*cis*-substituted indolizidin-7-ol **20** [19] (*Scheme 3*). Consequently, to bring about hydrogenolysis of an isolated carbonyl group in pyrroles such as **8**, a strong acid medium (6N HCl in AcOH) had to be utilized [11]. Of course, in the present instance, forcing conditions would be superfluous, since the carbonyl group in **18** is adjacent to the aromatic ring and, therefore, susceptible to hydrogenolysis. Solution in AcOH was perfectly adequate, and hydrogenation over Pd/C proceeded fully and stereospecifically (*Scheme 4*). Reduction occurred with hydrogenolysis of the carbonyl group to give ethyl (5*S*,8a*R*)-indolizidine-5-carboxylate (**21**) in an enantiomeric excess of > 98% and in 75% yield.

Scheme 3



19 **20**

Scheme 4



	21	**22**
10% Pd/C, AcOH	75%	0%
EtOH/AcOH 50:50	66%	9%
EtOH/AcOH 99:1	39%	51%
5% Rh/Al_2O_3, EtOH/AcOH 99:1	5%	89%
AcOH	16%	63%

Nevertheless, the role of acid was important. When it was progressively diluted with EtOH, hydrogenolysis was hampered leading to increasing amounts of ethyl (5*S*,8*S*,8a*S*)-8-hydroxyindolizidine-5-carboxylate (**22**) (> 98% ee). The configuration of both products attest to the all-*cis* delivery of H_2 to the least hindered side of **18**. Thus, the vested chirality has completely determined the creation of the new chiral centers at C(8) and C(8a).

The foregoing result contrasted with those recently reported for certain 3,5-dialkyl-5,6,7,8-tetrahydroindolizines [21] [22]. These non-ketonic derivatives were found to decompose on attempted catalytic hydrogenation in 6N HCl/AcOH solution. When milder conditions were used, saturation of the pyrrole ring could be achieved but with little stereoselectivity. It can, therefore, be concluded that the presence of a ketone function within the six-membered ring is needed so that an asymmetric center at C(5) may exert its directional effect. To be sure, acid conditions, weak or strong, depending on whether the carbonyl group is conjugated or not, are indispensable for hydrogenolysis, otherwise they are clearly inadvisable [21].

Although partial reduction of **18** with Pd/C was possible, only roughly equal amounts of **21** and **22** could be obtained, albeit in high yield, under weakly acid conditions (*Scheme 4*). Therefore, recourse was made to Rh/Al_2O_3 as it is known to be a more selective catalyst, especially in its action on 2,3-dihydro-1*H*-pyrrolizin-1*H*-one, which is a pertinent model for **18** [23]. Once again, hydrogenation in EtOH containing a little AcOH was entirely *cis*-directed giving this time mainly **22** (89%) together with a minor amount of **21** (*Scheme 4*). Even when the hydrogenation was conducted in AcOH alone, **22** still predominated, although the proportion of the fully reduced, minor product **21** increased somewhat (*Scheme 4*). The configurations of **21** and **22** were confirmed by their NOESY spectra (see *Exper. Part*). The strong dipolar coupling observed between H–C(8a) and H–C(5) and between H_{ax}–C(3) and H–C(5) means that both pairs of protons are contiguous[2]). Similarly, the intensity of the IR maxima at 2790 and 2796 cm^{-1}, the so-called *Bohlmann* bands [24], further attests to the *trans*-diaxial arrangement of the aforementioned H-atoms with respect to the N-lone pair.

The assembly of the indolizidine building blocks **21** and **22** constitutes the crux of the synthesis. Once the chiral centers have been planted, **1** and **2** are attainable by simply elaborating the pendent ester group of **21** into the desired alkyl group. Access to **3** from **22** will be more difficult, because, apart from changing an ester to a pentyl group, an OH group has to be converted to a Me group with inversion of configuration.

As a test of the practicality of functional-group interconversion, the synthesis of the structurally simpler, known indolizidine 209D (**2**) was tackled to start with. Reduction of **21** with a 2.5-fold excess of diisobutylaluminium hydride (DIBAH) gave aldehyde **23** accompanied by the merest trace of the corresponding primary alcohol [25] (*Scheme 5*). When the quantity of DIBAH was diminished (1 to 1.5 equiv.), reduction was not complete even after 24 h. A similar lack of reactivity was already observed with α-amino esters protected as *Schiff* bases [26]. As attempts to purify **23** failed, it was directly treated with pentyltriphenylphosphonium bromide and potassium hexamethyldisilazide (KHMDS) in THF under salt-free conditions [27]. As expected, only the (*Z*)-olefin **24** was obtained, and in 61% yield for the two steps. Finally, hydrogenation of **24** over *Adams* catalyst in AcOEt delivered indolizidine 209D (**2**) in 97% yield or in 33% overall yield from diethyl L-glutamate hydrochloride (**14**). This synthetic sample has an optical rotation (−87.6) somewhat higher than those previously reported (−83.6 [6], −80.4 [8], and −76.5 [7]) which may be ascribed to its higher optical purity. In any event, all four samples have concordant spectral data.

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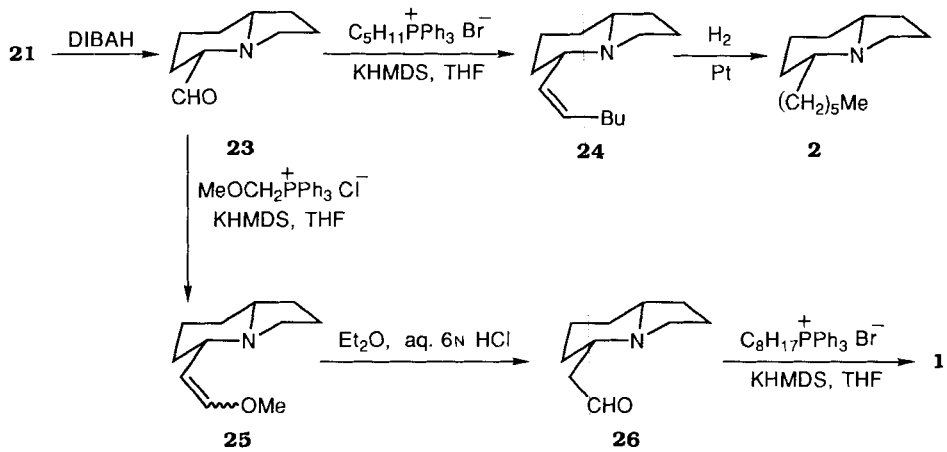
[2]) Although H–C(3) is embodied in a five-membered ring, the term axial (ax) is used to designate the H-atom which lies closest to H–C(8a).

Scheme 5



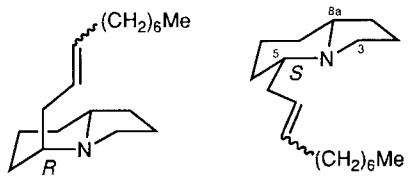
The configuration of **24** was deduced from the characteristic *Bohlmann* band at 2780 cm^{-1} and the ^{1}H-NMR spectrum. By irradiation of the resonance at 2.10 ppm, the allylic methylene protons were decoupled. Analysis of the resulting *ABX* spectrum of the allylic fragment yielded a *J* of 11 Hz for the *AB* part, thereby enabling the olefin geometry to be defined as (*Z*). Furthermore, as no bands were seen in the 960–990 cm^{-1} region of the IR spectrum, an (*E*)-olefin can be ruled out.

In view of this success, it was obvious that aldehyde **23** could be put to good use for synthesizing piclavine A (**1**). The homologous aldehyde **26** was prepared by acid hydrolysis of the mixture of methyl enol ethers **25** ((*E*)/(*Z*) 98:2) obtained from **23** by *Wittig* reaction (*Scheme 5*). Treatment of **26** with octyltriphenylphosphonium bromide and KHMDS under salt-free conditions produced **1** in 61% yield from **25** or in 17% overall yield from **14**. The (*Z*)-geometry of the alkenyl side chain and the (5*S*,8a*R*)-configuration of **1** were fully substantiated by the IR and NMR spectra.

Strong irradiation at 2.08 ppm, midway between the signals showing at 2.05 and 2.12 ppm for three of the allylic H-atoms, gave an *ABX* spectrum for the olefinic moiety, from which a *J* of 11 Hz was extracted for the *AB* part. This value taken together with the absence of a band lying between 960 and 990 cm^{-1} confirms the (*Z*)-geometry. The *Bohlmann* band at 2780 cm^{-1} and the chemical shifts of the atoms adjacent to the N-atom are typical of the equatorial placement of the C(5) substituent (*vide infra*).

This synthetic sample of piclavine (**1**) serves as a stereochemical marker for all the piclavines. In fact, the natural material comprises four isomers which, on chromatographic separation, were eluted in the order A1–A4 with abundances of 1:3:6:6, respectively [2] (*Fig. 1*)[3]). Their gross structure was ascertained from the ^{1}H-NMR spectrum of the mixture of isomers. The relative configuration and the olefin geometry of the individual isomers were deduced from the IR spectra. However, comparison of our NMR data for **1** (see A4) with those reported for the major components, originally designated as A3 and A4, indicates that they must be the 5-axial isomers and should be re-assigned as A1 and A2. The clues to configuration are the chemical shifts of H–C(5) H–C(8a), and H–C(3) (*Fig. 2*).

[3]) For the sake of clarity, only the diastereoisomers having the (8a*S*)-configuration are depicted.



Structure	A1 (*E*)	A2 (*Z*)	A3 (*E*)	A4 (*Z*) (≡ **1**)
Abundance (revised)	6	6	1	3
Abundance [2]	1	3	6	6

Fig. 1. *Abundance and assigned relative structures of piclavins A1–4*

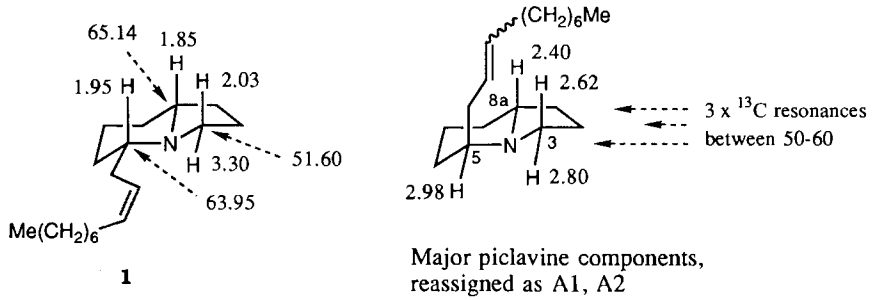
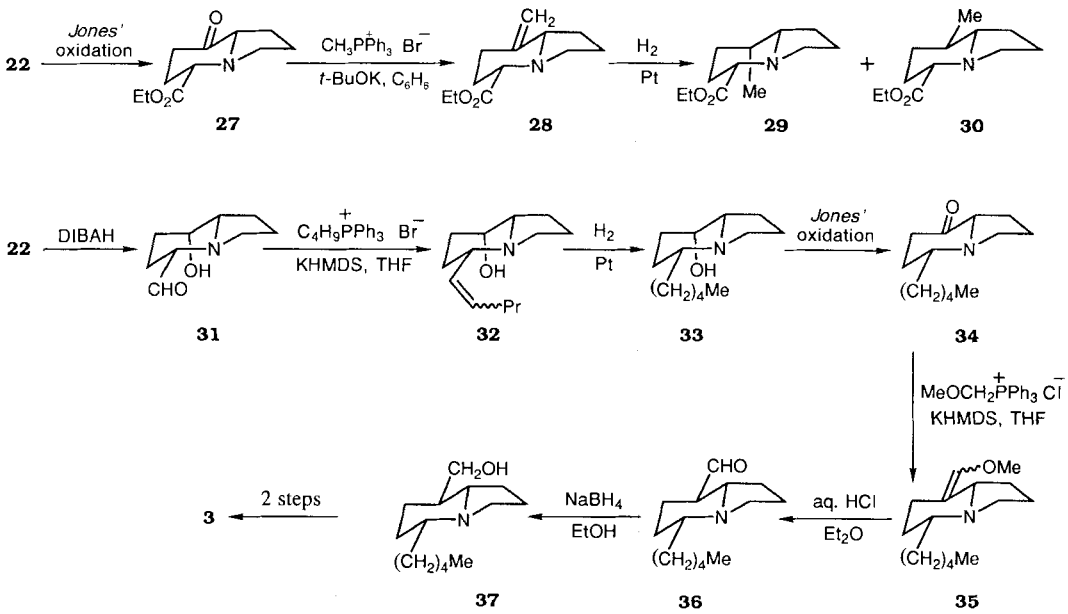


Fig. 2. *Some ^{1}H- and ^{13}C-NMR chemical shifts* (in ppm) *of* **1** *and the major piclavine components*

E.g., the values of 1.95 and 1.85 ppm in **1** are an index of *cis*-disposed protons at C(5) and C(8a). For the major pair of natural components, the analogous shifts are quite different, namely, 2.98 and 2.4 ppm, and characterize the *trans*-arrangement found in the axial epimers A1 and A2. Differential shielding effects are also seen for H–C(3). The equatorial 5-(alkenyl) substituent in **1** deshields the contiguous H_{eq}–C(3) so that H_{eq}–C(3) and H_{ax}–C(3) appear at 3.30 and 2.03 ppm, respectively. In the major components, these shifts show at 2.80 (H_{eq}–C(3)) and 2.62 ppm (H_{ax}–C(3)) in keeping with the deshielding exerted on H_{ax}–C(3) by the nearby axially disposed 5-substituent of A1 and A2. Such correlations were noted previously for the (5*S*)- and (5*R*)-epimers of several (8a*R*)-5-alkylindolizidines, not only for the ^{1}H-, but also for the ^{13}C-chemical shifts [8] [28]. It may be added that the values of the chemical shifts exhibited by the C(3), C(5), and C(8a) atoms of **1** are entirely compatible with the (5*S*,8a*R*)-configuration. Moreover, the observation [2] that the main fraction of natural piclavine displayed just three ^{13}C-signals between 50–60 ppm could have been interpreted in favor of the axial isomers A1 and A2.

Having demonstrated the utility of **21** as a chiral building block, the synthesis of indolizidine 209B (**3**) was finally undertaken by carrying out analogous conversions on **22**. Formation of the Me group was attempted first. Oxidation of **22** with *Jones'* reagent [18] [29] (→**27**) followed by *Wittig* olefination [30] gave the methylidene derivative **28** without epimerization at C(5) or C(8a) (*Scheme 6*). It is worth noting that ketones unless activated by an α-alkoxy substituent usually give poor yields with the *Wittig* reagent [27]. In the present instance, it can be supposed that the bridgehead N-atom was responsible for the good yield, perhaps through transannular interaction with the carbonyl group. The expectation that haptophilic binding between the catalyst, the N-atom, and the underside of the double bond [31] might control the direction of hydrogenation to favor the formation of an equatorially disposed Me group, was not fulfilled. Hydrogenation of **28** over Pt as catalyst in AcOEt gave mostly the unwanted axial epimer **29** (*Scheme 6*).

Scheme 6



Clearly, the directivity exerted by the ester substituent and the ring fusion was overriding since only a negligible amount of the equatorial epimer **30** was produced.

The structures of **29** and **30** followed from the δ(H)'s and δ(C)'s of Me–C(8) (see *Exper. Part*). The axially disposed Me group in **29** displayed a δ(H) downfield from that of the equatorial Me group in **30** (1.01 *vs.* 0.89 ppm). Conversely, the corresponding δ(C) of **29** was upfield from that of **30** (12.15 *vs.* 18.62 ppm). These correlations were in full agreement with those made for epimeric 5-(alkynyl)-8-methylindolizidines [32].

Confronted with this minor setback, it was decided to deal with the ester group initially and convert the OH into the Me group later. Reduction of **22** with 3.5 equiv. of DIBAH gave the equatorial aldehyde **31** in high yield accompanied by a small amount of the axial isomer (eq/ax 96.5:3.5) (*Scheme 6*). Fortunately, like previous cases involving indolizidine (*e.g.* **21**) and α-amino esters [25], no overreduction was observed. Treatment of **31** with butyltriphenylphosphonium bromide and KHMDS in THF gave a mixture of the (*E*)- and (*Z*)-pentenyl derivatives **32** ((*E*)/(*Z*) 5:95). Their joint hydrogenation over Pt furnished the desired (5*R*,8*S*,8a*S*)-8-hydroxy-5-pentylindolizidine (**33**), contaminated with traces of the 5-epimer which were easily removed by chromatography. Next, preparations were made for creating Me–C(8). Oxidation of **33** with *Jones'* reagent to the bicyclic ketone **34** followed by reaction with (methoxymethyl)triphenylphosphonium bromide and KHMDS in THF yielded a mixture of the (*E*)- and (*Z*)-methyl enol ethers **35** (major/minor 73:27). Acid hydrolysis liberated the equatorial aldehyde **36** together with a minor amount of the axial epimer (eq/ax 97:3). This result is perfectly satisfactory given the unavoidable use of base and acid and is certainly no worse than that previously experienced when **36** was expressly prepared by base-equilibration of the 8-axial epimer [10]. Reduction with $NaBH_4$ gave the relay, the methanol derivative **37**, the optical and

spectral properties of which were identical to those of a sample previously prepared from L-glutamic acid in a multi-step sequence [10]. As **37** has already been transformed to indolizidine 209B (**3**) in two standard steps and in 87% yield, the synthesis may be deemed complete.

Conclusion. – The present syntheses are short requiring a minimum number of steps to deliver enantiomerically pure products in preparatively acceptable yields from a cheap, readily available starting material, diethyl L-glutamate hydrochloride (**14**). Piclavine A (**1**) and indolizidine 209D (**2**) were each prepared in 7 and 6 steps in overall yields of 17 and 33%, respectively, from **14**, whereas indolizidine 209B (**3**) was procured in some 12 steps with an overall yield of 9%. The procedure is simple to perform and sufficiently versatile to be used for synthesizing other homochiral 5-alkyl- and 5,8-dialkylindolizidines. Further manipulation of the methylidene intermediate **28** should permit convenient access to alkaloids of the pumiliotoxin type [33].

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Experimental Part

General. Diethyl L-glutamate hydrochloride (**14**) (ee > 99%) was purchased from *Fluka*. Solvents: THF and Et_2O were distilled over sodio-benzophenone; CH_2Cl_2 and benzene (*puriss. p.a.*) were kept over molecular sieves (4 Å). Moisture-sensitive reactions were carried out under Ar. TLC: silica gel $60F_{254}$ (*Merck*) or alumina F_{254} (*Fluka*) visualized with 3% anisaldehyde/4% H_2SO_4 in EtOH or 1% $KMnO_4$/4% Na_2CO_3 in H_2O. Flash chromatography (FC): silica gel *60* (230–400 mesh, *Merck*) or alumina (*5016A*, basic, or *507C*, neutral; *Brockmann* grade II; *Fluka*). The enantiomeric excesses (ee) of **15** and **18** were determined by gas chromatography at 135 and 180°, resp., over *Lipodex E* (octakis(2,6-di-*O*-pentyl-3-*O*-butyryl)-γ-cyclodextrin) coated on a fused-silica column (25 m × 0.25 mm) (*Macherey-Nagel*) in a *Hewlett-Packard-5890* apparatus. The optical purities of **21** and **22** were estimated from ^{1}H-NMR spectra in the presence of [Eu(hfc)$_3$]. M.p. (uncorrected): *Reichert* hot-stage instrument. $[\alpha]_D^{20}$: *Perkin-Elmer-241* polarimeter. IR Spectra: *Perkin-Elmer-1600* (FTIR) spectrometer; $\tilde{\nu}_{max}$ in cm^{-1}. NMR: $CDCl_3$ soln., chemical shifts in ppm rel. to internal Me_4Si, coupling constants J in Hz; *Bruker-AMX-400* and *Varian-XL-200* spectrometers, signal assignments by H,H- and H,X-COSY. MS: *Finnigan-4023* (EI, 70 eV) and *VJ-7070* instruments, *m/z* (rel. intensity in %). Elemental analyses were performed by Dr. *H.J. Eder*, Microchemistry Service, Department of Pharmaceutical Chemistry, University of Geneva.

(2S)-Diethyl 2-(1H-Pyrrol-1-yl)pentanedioate (**15**). A soln. of **14** (2.397 g, 10 mmol) and tetrahydro-2,5-dimethoxyfuran (**5**; 1.322 g, 10 mmol) in H_2O (15 ml) and 1,2-dichloroethane (15 ml) was heated at 80° with vigorous stirring for 45 min. After cooling, the aq. layer was extracted with CH_2Cl_2, the comb. org. extract dried (Na_2SO_4) and evaporated, and the residue purified by FC (SiO_2, hexane/Et_2O 1:1): **15** (2.051 g, 81%; ee > 99%). Colorless oil. $[\alpha]_D^{20} = -12.2$ (*c* = 1.3, $CHCl_3$). ^{1}H-NMR: 1.22–1.27 (*m*, 6 H); 2.09–2.32 (*m*, 3 H); 2.39–2.44 (*m*, 1 H); 4.12 (*q*, *J* = 7.4, 2 H); 4.20 (*qd*, *J* = 7.0, 2.2, 2 H); 4.70 (*dd*, *J* = 9.9, 5.5, 1 H); 6.18 (*t*, *J* = 2.2, 2 H); 6.72 (*t*, *J* = 2.2, 2 H). ^{13}C-NMR: 14.02 (Me); 14.13 (Me); 28.04 (CH_2); 29.92 (CH_2); 60.57 (CH_2); 60.78 (CH); 61.60 (CH_2); 108.82 (CH); 120.02 (CH); 170.20 (C=O); 173.32 (C=O). MS: 253 (32, M^+), 208 (30), 180 (45), 134 (30), 106 (100). Anal. calc. for $C_{13}H_{19}NO_4$: C 61.64, H 7.56, N 5.53; found: C 61.38, H 7.51, N 5.48.

(5S)-Ethyl 5,6,7,8-Tetrahydro-8-oxoindolizine-5-carboxylate (**18**). To a soln. of **15** (2.532 g, 10 mmol) in dry CH_2Cl_2 (100 ml) cooled to 5° (ice-H_2O) was added dropwise 1M BBr_3 in CH_2Cl_2 (11 ml, 11 mmol). The cooling bath was removed and the soln. stirred for an additional 15 min. The soln. was quenched with sat. aq. $NaHCO_3$ soln. (40 ml) with cooling and vigorously stirred for a few min. Next the aq. layer was extracted with CH_2Cl_2 and the org. phase dried and evaporated. FC (SiO_2, Et_2O) gave **18** (1.900 g, 92%; ee > 98%). Yellowish oil. $[\alpha]_D^{20} = +12.7$ (*c* = 1.2, CH_2Cl_2). ^{1}H-NMR: 1.28 (*t*, *J* = 9.2, 3 H); 2.50–2.66 (*m*, 4 H); 4.19–4.30 (*m*, 2 H); 4.91–4.95 (*m*, 1 H); 6.33 (*dd*, *J* = 5.1, 3.2, 1 H); 6.90 (*dd*, *J* = 3.2, 2.3, 1 H); 7.08 (*dd*, *J* = 5.1, 2.3, 1 H). ^{13}C-NMR: 14.08 (Me); 26.24 (CH_2);

33.12 (CH_2); 56.62 (CH); 62.18 (CH_2); 110.98 (CH); 114.61 (CH); 126.54 (CH); 130.49 (C); 169.50 (C=O); 186.01 (C=O). MS: 207 (30, M^+), 134 (100), 106 (20). Anal. calc. for $C_{11}H_{13}NO_3$: C 63.75, H 6.32, N 6.76; found: C 63.55, H 6.40, N 6.93.

(5S,8aR)-Ethyl Octahydroindolizine-5-carboxylate (**21**). A soln. of **18** (345 mg, 1.66 mmol) in AcOH (20 ml) was hydrogenated over 10% Pd/C (345 mg) in a *Parr* apparatus at 55 psi for 5 h at r.t. The mixture was filtered over *Celite* and the filtrate evaporated at r.t. The residue was treated with Et_2O (10 ml) and H_2O (10 ml), basified by addition of solid Na_2CO_3, and extracted with Et_2O. The org. phase was dried (Na_2SO_4) and evaporated and the residual oil purified by FC (neutral Al_2O_3, hexane/Et_2O 1:1): **21** (245 mg, 75%; ee > 98%). $[\alpha]_D^{20} = -106.3$ ($c = 1.2$, CH_2Cl_2). IR (neat): 2935, 2845, 2790 (*Bohlmann*), 2703, 1748. ^{1}H-NMR: 1.26 (*t*, $J = 7.0$, 3 H); 1.28–1.42 (*m*, 2 H); 1.45–1.67 (*m*, 3 H); 1.73–1.91 (*m*, 6 H, including H–C(8a) at 1.87); 1.96 (*q*, $J = 8.8$, H_{ax}–C(3)); 2.73 (*dd*, $J = 11.4$, 2.6, H–C(5)); 3.22 (*td*, $J = 8.5$, 1.8, H_{eq}–C(3)); 4.13–4.26 (*m*, 2 H). NOESY Cross peaks: H–C(5)/H–C(8a), H–C(5)/H_{ax}–C(3). ^{13}C-NMR: 14.26 (Me); 20.46 (CH_2); 24.24 (CH_2); 29.72 (CH_2); 29.74 (CH_2); 30.03 (CH_2); 52.13 (C(3)); 60.56 (CH_2); 64.14 (C(8a)); 67.38 (C(5)); 173.20 (C=O). MS: 198 (5, $[M + 1]^+$), 196 (2), 124 (100), 96 (8). Anal. calc. for $C_{11}H_{19}NO_2$: C 66.97, H 9.71, N 7.10; found: C 66.72, H 9.59, N 7.10.

(5S,8S,8aS)-Ethyl Octahydro-8-hydroxyindolizine-5-carboxylate (**22**). A soln. of **18** (518 mg, 2.5 mmol) in EtOH (25 ml) containing AcOH (0.25 ml) was hydrogenated over 5% Rh/Al_2O_3 at 55 psi for 3 h at r.t. in a *Parr* apparatus. The soln. was filtered through *Celite* and evaporated. The residue was then treated with a sat. $NaHCO_3$ soln. and extracted with CH_2Cl_2. After drying of the org. extract, evaporation and FC (neutral Al_2O_3, Et_2O) gave **22** (476 mg, 89%; ee > 98%) and **21** (24 mg, 5%). **22**: Colorless solid. M.p. 36–37°. $[\alpha]_D^{20} = -88.3$ ($c = 1.5$, CH_2Cl_2). IR (neat): 3499, 2973, 2948, 2875, 2854, 2796 (*Bohlmann*), 2719, 1732. ^{1}H-NMR: 1.28 (*t*, $J = 7.0$, 3 H); 1.50 (*tdd*, $J = 13.6$, 5.2, 2.6, H_{ax}–C(7)); 1.63–2.02 (*m*, 7 H); 2.05 (*q*, $J = 8.8$, H_{ax}–C(3)); 2.18 (*m*, H–C(8a)); 2.64 (*br. d*, $J = 7.7$, OH); 2.83 (*dd*, $J = 11.8$, 3.3, H–C(5)); 3.25 (*td*, $J = 8.1$, 1.8, H_{eq}–C(3)); 3.82 (*br. s*, H–C(8)); 4.20 (*q*, $J = 7.0$, 2 H). NOESY Cross peaks: H–C(8a)/H–C(8), H–C(8a)/H–C(5), H–C(8)/H_{ax}–C(7), H–C(5)/H_{ax}–C(3)). ^{13}C-NMR: 14.19 (Me); 20.56 (CH_2); 23.91 (CH_2); 24.75 (CH_2); 31.40 (C(7)); 52.23 (C(3)); 60.66 (CH_2); 64.89 (C(8)); 66.83 (C(8a)); 66.89 (C(5)); 172.72 (C=O). MS: 213 (1, M^+), 140 (100), 122 (10), 96 (18). Anal. calc. for $C_{11}H_{19}NO_3$: C 61.95, H 8.98, N 6.57; found: C 61.72, H 8.77, N 6.51.

(5S,8aR)-Octahydroindolizine-5-carbaldehyde (**23**). To a soln. of **21** (197 mg, 1 mmol) in dry Et_2O (5 ml) was added dropwise a soln. of 1M DIBAH in hexane (2.5 equiv., 2.5 ml) while maintaining the temp. below −70° [25]. The mixture was stirred for 1 h at −70°, then quenched with MeOH (0.3 ml), and allowed to warm to r.t. A sat. aq. potassium-sodium tartrate (*Rochelle*'s salt) soln. (2.5 ml) was added and the mixture vigorously stirred for 1 h. Next, the aq. layer was extracted (Et_2O) and the comb. org. phase dried and evaporated: **23** (150 mg, 98%) which was used further without purification. IR (neat): 2932, 2860, 2792 (*Bohlmann*), 2714, 1730. ^{1}H-NMR: 1.18–1.97 (*m*, 11 H); 2.01 (*q*, $J = 9.1$, H_{ax}–C(3)); 2.63 (*dt*, $J = 11.4$, 3.1, H–C(5)); 3.25 (*td*, $J = 8.8$, 2.2, H_{eq}–C(3)); 9.57 (*d*, $J = 3.3$, 1 H). ^{13}C-NMR: 20.73 (CH_2); 23.69 (CH_2); 25.97 (CH_2); 29.49 (CH_2); 30.08 (CH_2); 52.13 (C(3)); 63.59 (C(8a)); 72.24 (C(5)); 202.64 (CHO). MS: 153 (1, M^+), 124 (100), 96 (20).

(5S,8aR)-5-[(Z)-Hex-1-enyl]octahydroindolizine (**24**). To a suspension of pentyltriphenylphosphonium bromide (*Aldrich*; 413 mg, 1 mmol) in dry THF (5 ml) was added a soln. of potassium hexamethyldisilazide (KHMDS; 200 mg, 1 mmol) in THF (2 ml) at −78°. The cooling bath was removed and the mixture allowed to warm to r.t. over 25 min. Then, with further cooling at −78°, a soln. of **23** (76 mg, *ca.* 0.5 mmol) in THF (2 ml) was added. The mixture was stirred at r.t. overnight, then quenched with H_2O (5 ml) and extracted with Et_2O. The combined org. extract was dried and evaporated and the oily residue treated with hexane. The hexane soln. was filtered and evaporated. FC (basic Al_2O_3, hexane/Et_2O 1:1) gave **24** (64 mg, 61% from **21**). Colorless oil. $[\alpha]_D^{20} = -71.8$ ($c = 0.55$, CH_2Cl_2). IR (neat): 3005, 2957, 2929, 2856, 2780 (*Bohlmann*), 2703. ^{1}H-NMR: 0.90 (*t*, $J = 7.0$, 3 H); 1.16–1.90 (*m*, 13 H, including H–C(8a) at 1.85); 1.93 (*q*, $J = 9.2$, H_{ax}–C(3)); 2.10 (*m*, allylic CH_2); 2.77–2.86 (*m*, H–C(5)); 3.14 (*td*, $J = 9.2$, 2.2, H_{eq}–C(3)); 5.35–5.43 (*m*, 2 olef. H). ^{13}C-NMR: 13.97 (Me); 20.16, 22.34, 24.47 (CH_2's); 27.50 (allylic CH_2); 30.42, 30.81, 31.93, 32.49 (CH_2's); 52.59 (C(3)); 60.90 (C(5)); 64.31 (C(8a)); 130.46 (=CH); 132.75 (=CH). MS: 207 (65, M^+), 206 (45), 178 (53), 164 (100), 150 (75), 136 (30), 124 (97), 122 (50), 108 (15), 96 (75). Anal. calc. for $C_{14}H_{25}N$: C 81.09, H 12.15, N 6.76; found: C 80.98, H 12.02, N 6.90.

(5R,8aR)-5-Hexyloctahydroindolizine (*= (−)-Indolizidine 209D;* **2**). A soln. of **24** (52 mg, 0.25 mmol) in AcOEt (5 ml) was hydrogenated at 40 psi over PtO_2 (5 mol-%) at r.t. overnight. The mixture was filtered through *Celite* the solvent evaporated, the residue treated with H_2O (2 ml), the aq. phase basified with sat. aq. $NaHCO_3$ soln. (1 ml) and extracted with CH_2Cl_2, the combined org. extract dried and evaporated, and the residual oil purified by FC (basic Al_2O_3, hexane/Et_2O, 1:1): **2** (50 mg, 97%). Colorless oil. $[\alpha]_D^{20} = -87.6$ ($c = 1$, CH_2Cl_2). IR (neat): 2958, 2929, 2857, 2781 (*Bohlmann*), 2709. ^{1}H-NMR: 0.88 (*t*, $J = 6.8$, 3 H); 1.09–1.92 (*m*, 22 H); 1.97 (*q*, $J = 8.8$, H_{ax}–C(3)); 3.26 (*td*, $J = 8.7$, 1.8, H_{eq}–C(3)). ^{13}C-NMR: 14.09 (Me); 20.42, 22.63, 24.71, 25.85, 29.75,

30.55, 30.86, 31.00, 31.84, 34.63 (CH_2's); 51.55 (C(3)); 63.93 (C(5)); 65.06 (C(8a)). MS: 209 (1, M^+), 208 (2), 124 (100), 96 (10). Anal. calc. for $C_{14}H_{27}N$: C 80.31, H 13.00, N 6.69; found: C 80.35, H 12.83, N 6.61.

(5S,8aR)-Octahydro-5-(2-methoxyethenyl)indolizine (**25**). As described for **24**, with (methoxymethyl)-triphenylphosphonium chloride (*Fluka*; 895 mg, 2.60 mmol), THF (10 ml), KHMDS (520 mg, 2.60 mmol), THF (3 ml), **23** (100 mg, *ca.* 0.65 mmol), THF (2 ml), and H_2O (5 ml). Workup with Et_2O and FC (Al_2O_3 basic, Et_2O) gave **25** (60 mg, 50% from **21**; (*E*)/(*Z*) 98:2). When the reaction was performed at 0°, the (*E*)/(*Z*) ratio changed to 80:20. IR (neat): 3005, 2928, 2844, 2778 (*Bohlmann*), 2712, 1655, 1209, 1176, 1120, 1049, 932. ^{1}H-NMR: (*E*)-isomer: 1.16–1.90 (*m*, 11 H); 1.95 (*q*, *J* = 9.2, H_{ax}–C(3)); 2.36 (*td*, *J* = 9.9, 2.6, H–C(5)); 3.17 (*td*, *J* = 9.0, 1.8, H_{eq}–C(3)); 3.51 (*s*, 3 H); 4.77 (*dd*, *J* = 12.5, 9.2, 1 H); 6.48 (*d*, *J* = 12.5, 1 H); (*Z*)-isomer (partial): 3.59 (*s*, 3 H); 4.45 (br. *t*, *J* = 8.1, 1 H); 5.91 (*d*, *J* = 6.6, 1 H). ^{13}C-NMR (*E*-isomer): 19.97 (CH_2); 24.62 (CH_2); 30.74 (CH_2); 34.15 (CH_2); 52.80 (C(3)); 55.71 (CH_3); 63.19 (C(5)); 64.51 (C(8a)); 106.65 (=CH); 147.90 (=CH). MS: 181 (70, M^+), 166 (100), 150 (25), 138 (50), 124 (15), 122 (45), 108 (20), 98 (17). Anal. calc. for $C_{11}H_{19}NO$: C 72.88, H 10.57, N 7.73; found: C 72.74, H 10.24, N 7.35.

(5S,8aR)-Octahydroindolizine-5-acetaldehyde (**26**). A soln. of **25** (50 mg, 0.28 mmol) in Et_2O (3 ml) was treated with aq. 6N HCl (1 ml) and stirred at r.t. overnight. The mixture was diluted with H_2O (2 ml), basified with solid Na_2CO_3, and extracted with Et_2O. The org. phases were dried and evaporated: **26** (55 mg, 100%) which was used without further purification. IR (neat): 2932, 2847, 2787 (*Bohlmann*), 2708, 1723. ^{1}H-NMR: 1.13–1.48 (*m*, 5 H); 1.61–1.97 (*m*, 6 H); 2.03 (*q*, *J* = 8.8, H_{ax}–C(3)); 2.50 (*ABXY* (*ddd*), *J* = 15.6, 7.0, 2.2, 1 H); 2.57 (*m*, H–C(5)); 2.70 (*ABXY* (*ddd*), *J* = 15.6, 3.7, 2.2, 1 H); 3.13 (*td*, *J* = 8.5, 2.2, H_{eq}–C(3)); 9.84 (*t*, *J* = 2.2, 1 H). ^{13}C-NMR: 20.34 (CH_2); 24.46 (CH_2); 30.44 (CH_2); 30.63 (CH_2); 32.15 (CH_2); 49.29 (CH_2); 51.93 (C(3)); 58.44 (C(5)); 64.88 (C(8a)); 202.02 (CHO). MS: 167 (1, M^+), 166 (2), 139 (10), 124 (100), 110 (5), 96 (35).

(5S,8aR)-5-[(Z)-Dec-2-enyl]octahydroindolizine (*Piclavine A*; **1**). Triphenylphosphine (6.56 g, 25 mmol) and 1-bromooctane (5.41 g, 28 mmol) in dry benzene (6 ml) were heated under reflux for 24 h. The solvent and excess bromooctane were carefully evaporated and the residual oil subjected to FC (SiO_2, CH_2Cl_2/MeOH 15:1) to give, after drying *in vacuo* over *Carnauba* wax, *octyltriphenylphosphonium bromide* as a glassy solid (19.40 g, 84%). ^{1}H-NMR: 0.83 (*t*, *J* = 7.0, 3 H); 1.20 (*m*, 8 H); 1.62 (*m*, 4 H); 3.80 (*m*, 2 H); 7.69–7.88 (*m*, 15 H). MS: 375 (2, M^+), 262 (100), 183 (50), 152 (5), 108 (30).

As described for **24**, with the above bromide (273 mg, 0.6 mmol), THF (2.5 ml), KHMDS (120 mg, 0.6 mmol), THF (1 ml), **26** (50 mg, *ca.* 0.30 mmol) THF (1 ml), and H_2O (2.5 ml). Workup with Et_2O and FC (Al_2O_3 basic, hexane/Et_2O 1:1) furnished **1** (41 mg, 61% from **25**). Colorless oil. $[\alpha]_D^{20} = -74.8$ (*c* = 0.5, CH_2Cl_2). IR (neat): 3006, 2956, 2926, 2853, 2780 (*Bohlmann*) 2706, 1454, 1439, 1378, 1365, 1332, 1320, 1127. ^{1}H-NMR: 0.88 (*t*, *J* = 6.9, 3 H); 1.11–2.08 (*m*, 25 H, including 2.05 (*m*, 2 allylic H)); 2.03 (*q*, *J* = 7.0, H_{ax}–C(3)); 1.95 (*m*, H–C(5)), and 1.85 (*m*, H–C(8a)); 2.12 (*m*, 1 allylic H); 2.42 (*m*, 1 allylic H); 3.30 (br. *t*, *J* = 8.5, H_{eq}–C(3)); 5.36 (*m*, 1 H); 5.44 (*m*, 1 H). ^{13}C-NMR: 14.08 (Me); 20.44, 22.65, 24.61 (CH_2's); 27.43 (allylic CH_2); 29.19, 29.31, 29.63, 30.48, 30.91, 31.02, 31.86 (CH_2's); 32.68 (allylic CH_2); 51.60 (C(3)); 63.95 (C(5)); 65.14 (C(8a)); 126.36 (=CH); 131.59 (=CH). MS: 263 (3, M^+), 262 (10), 124 (100), 96 (7). Anal. calc. for $C_{18}H_{33}N$: C 82.06, H 12.63, N 5.32; found: C 81.89, H 12.45, N 5.21.

(5S,8aS)-Ethyl Octahydro-8-oxoindolizine-5-carboxylate (**27**). To a vigorously stirred soln. of **22** (345 mg, 1.62 mmol) in acetone (30 ml) was added dropwise 2.67M *Jones'* reagent (1.21 ml, 3.24 mmol) at r.t. under Ar [18] [29]. After 2.5 h, i-PrOH (3 ml) was added, followed by sat. aq. $NaHCO_3$ soln. (5 ml). The mixture was vigorously stirred for 10 min, the solid removed by filtration through *Celite*, CH_2Cl_2 (30 ml) added, the aq. phase extracted with CH_2Cl_2 (3 × 30 ml), and the combined org. extract dried ($MgSO_4$) and evaporated: **27** (250 mg, 73%; yields of other runs 40–76%, average 60%). Yellow oil. IR (neat): 2976, 2867, 2799 (*Bohlmann*), 1731, 1442, 1375, 1329, 1211, 1164, 1092, 1061, 1025, 912, 727. ^{1}H-NMR: 1.30 (*t*, *J* = 7.0, 3 H); 1.68–1.90 (*m*, 4 H); 1.98–2.20 (*m*, 2 H); 2.23–2.31 (*m*, 2 H); 2.38 (*m*, 1 H); 2.58 (*m*, 1 H); 2.80 ('*t*', *J* = 8.0, 1 H); 3.29 (*m*, 1 H); 4.24 (*qd*, *J* = 7.0, 1.1, 2 H). ^{13}C-NMR: 14.21; 20.67; 22.88; 28.81; 38.01; 52.41; 61.13; 64.55; 69.92; 172.05; 205.79. MS: 186 (12, $[M - CO]^+$), 140 (14), 124 (100), 96 (19).

(–)-(5S,8aS)-Ethyl Octahydro-8-methylideneindolizine-5-carboxylate (**28**). Methyltriphenylphosphonium bromide (1.69 g, 4.73 mmol) and K(*t*-BuO) (53 mg, 4.73 mmol) in benzene (20 ml) were heated under reflux for 1 h [30]. The soln. was cooled to 5°, and **27** (465 mg, 2.20 mmol) was added dropwise. After stirring overnight, H_2O (20 ml) was added, the aq. layer extracted with Et_2O (3 × 20 ml), the combined org. extract dried ($MgSO_4$) and evaporated, and the residue submitted to FC (neutral Al_2O_3, Et_2O/hexane 1:2): **28** (332 mg, 72%). Colorless oil. $[\alpha]_D^{20} = -68.5$ (*c* = 1.36, CH_2Cl_2). IR (neat): 2939, 2867, 2790 (*Bohlmann*), 2692, 1746, 1730, 1654, 1442, 1371, 1278, 1175, 1147, 1104, 1033, 897. ^{1}H-NMR: 1.27 (*t*, *J* = 7.0, 3 H); 1.68–2.18 (*m*, 8 H); 2.44 (*m*, 2 H); 2.90 (*dd*, *J* = 11.6, 2.8, 1 H); 3.29 (*m*, 1 H); 4.21 (*m*, 2 H); 4.80 (*m*, 2 H). ^{13}C-NMR: 14.21; 20.18; 25.55; 30.80; 32.95; 52.58;

60.64; 66.02; 67.15; 107.24; 144.94; 172.68. MS: 209 (12, M^+), 180 (19), 166 (9), 149 (15), 136 (100). Anal. calc. for $C_{12}H_{19}NO_2$: C 68.87, H 9.15, N 6.69; found: C 68.62, H 9.14, N 6.76.

(−)-(5S,8S,8aS)- and (5S,8R,8aS)-Ethyl Octahydro-8-methylindolizine-5-carboxylate (**29** and **30**, resp.). A soln. of **28** (199 mg, 0.95 mmol) in AcOEt (5 ml) was shaken with pre-reduced Pt black (5% *w/w*) under H_2 at 40 psi for 19 h. Filtration over *Celite*, which was washed afterwards with AcOEt, gave a filtrate which on evaporation and FC (neutral Al_2O_3; Et_2O/hexane 1:2) furnished **29** (139 mg, 69%) and **30** (4.5 mg, 2.2%) as colorless oils.

29: $[\alpha]_D^{20} = -101.8$ ($c = 1.09$, CH_2Cl_2). IR (neat): 2970, 2936, 2881, 2790 (*Bohlmann*), 1747, 1461, 1386, 1270, 1169, 1144, 1084, 1033. ^{1}H-NMR: 1.01 (*d*, $J = 7.0$, 3 H); 1.27 (*t*, $J = 7.0$, 3 H); 1.52–1.95 (*m*, 10 H); 2.06 (*m*, 1 H); 2.66 (*dd*, $J = 11.4$, 2.9, 1 H); 3.21 (*m*, 1 H); 4.22 (*m*, 2 H). ^{13}C-NMR: 12.15; 14.23; 20.34; 24.72; 26.18; 29.17; 31.47; 52.80; 60.42; 66.83; 68.43; 173.39. MS: 211 (6, M^+), 138 (100), 96 (22).

30: ^{1}H-NMR: 0.89 (*d*, $J = 6.2$, 3 H); 1.27 (*t*, $J = 7.0$, 3 H); 1.40–2.05 (*m*, 11 H); 2.74 (*dt*, $J = 11.4$, 2.2, 1 H); 3.24 (*'t'*, $J = 8.5$, 1 H); 4.21 (*m*, 2 H). ^{13}C-NMR: 14.26; 18.62; 20.37; 28.28; 29.99; 33.00; 35.71; 52.43; 60.57; 67.16; 70.49; 173.20.

(5S,8S,8aS)-Octahydro-8-hydroxyindolizine-5-carbaldehyde (**31**). As described for **23**, with **22** (202 mg, 0.95 mmol), DIBAH in hexane (3.30 ml, 3.30 mmol; 1.5 h at −78°), H_2O/MeOH (1:1, 3 ml) instead of MeOH, and *Rochelle's* salt (20 ml; 0.5 h). Workup with Et_2O (3 × 20 ml) and then CH_2Cl_2 (20 ml); **31** (139 mg, 87%) together with a small amount of (5-axial) 5-epi-**31** (5eq/5ax 96.5:3.5). IR (neat): 3374, 2932, 2878, 2801 (*Bohlmann*), 1730, 1600, 1447, 1111, 1017. ^{1}H-NMR: 1.27 (*dt*, $J = 14.0$, 7.0, 1 H); 1.52 (*dtd*, $J = 13.6$, 4.8, 2.6, 1 H); 1.62 (*m*, 1 H); 1.70–1.85 (*m*, 5 H); 2.06 (*m*, 2 H); 2.19 (*m*, 1 H); 2.71 (*dt*, $J = 11.8$, 3.3, 1 H); 3.26 (*m*, 1 H); 3.87 (br. *s*, 1 H); 9.55 (*d*, $J = 3.3$, 1 H); 5-epi-**31**: 9.57 (*d*, $J = 3.7$, 1 H). ^{13}C-NMR: 20.11; 20.88; 24.26; 30.83; 52.27; 64.70; 66.36; 71.93; 201.62. MS: dec.

(−)-(5S,8S,8aS)-Octahydro-5-(pent-1-enyl)indolizin-8-ol (**32**). As described for **24**, with butyltriphenylphosphonium bromide (1.33 g, 3.30 mmol), THF (10 ml), KHMDS (66 mg, 3.30 mmol), THF (10 ml; 0.5 h at r.t.), **31** (139 mg, 0.82 mmol), THF (5 ml), and H_2O (10 ml). Workup with Et_2O (3 × 20 ml) and FC (basic Al_2O_3, Et_2O) gave **32** ((*E*)/(*Z*) 5:95; 102 mg, 59.3%). Colorless oil. IR (neat): 3442, 3005, 2957, 2934, 2872, 2857, 2790 (*Bohlmann*), 1657, 1458, 1430, 1398, 1371, 1305, 1180, 1120, 1080, 1040, 999, 919, 886. ^{1}H-NMR: 0.93 (*t*, $J = 7.4$, 3 H); 1.34–2.17 (*m*, 14 H); 2.58 (*m*, 1 H); 2.80 (*m*, 1 H); 3.11 (*m*, 1 H); 3.80 (br. *s*, 1 H); 5.37 (*m*, 2 H, major (*Z*)-isomer); 5.57 (*dt*, $J = 19.0$, 8.3, minor (*E*)-isomer). ^{13}C-NMR: 13.85, 20.48, 22.87; 25.19; 26.67; 29.88; 31.68; 52.67; 60.79; 65.38; 67.09; 130.55; 132.41. HR-MS: 209.1773 (M^+, $C_{13}H_{23}NO^+$; calc. 209.1779). MS: 209 (13, M^+), 180 (11), 166 (6), 150 (13), 138 (9), 122 (10), 96 (13), 81 (13), 70 (100), 54 (18).

Occasionally, a small quantity of the supposed 5-axial 5-epi-**32** arose from base-isomerized **31** (see above). It was easily removed by FC. 5-epi-**32**: ^{1}H-NMR: 0.92 (*t*, $J = 7.2$, 3 H); 1.30–2.11 (*m*, 15 H); 2.86 (*m*, 1 H); 3.21 (*m*, 1 H); 5.06 (br. *s*, 1 H); 5.40 (*m*, 2 H). ^{13}C-NMR: 13.82; 19.69; 21.47; 22.85; 25.13; 27.49; 29.01; 29.86; 52.62; 60.68; 65.50; 67.95; 130.92; 132.08.

(−)-(5R,8S,8aS)-Octahydro-5-pentylindolizin-8-ol (**33**). As described for **29**/**30**, with **32** (61 mg, 0.293 mmol) in AcOEt (5 ml): **33** (57 mg, 92%). Crystalline solid. M.p. 42.0° (sharp). $[\alpha]_D^{20} = -69.3$ ($c = 1.07$, CH_2Cl_2). IR (neat): 3382, 2921, 2845, 2780 (*Bohlmann*), 1447, 1376, 1262, 1115, 1017. ^{1}H-NMR: 0.89 (*t*, $J = 7.0$, 3 H); 1.20–2.10 (*m*, 19 H); 2.16 (*m*, 1 H); 3.24 (*m*, 1 H); 3.78 (br. *s*, 1 H). ^{13}C-NMR: 14.07; 20.65; 22.65; 24.87; 25.24; 31.90; 32.24; 34.28; 51.60; 63.66; 65.45; 68.00; 77.21. HR-MS: 211.1923 (M^+, $C_{13}H_{25}NO^+$, 211.1936). MS: 211 (2, M^+), 154 (3), 140 (100), 122 (10), 96 (10).

(5R,8aS)-Octahydro-8-(methoxymethylidene)-5-pentylindolizine (**35**). As described for **27**, with **33** (30.5 mg, 0.144 mmol), acetone (5 ml), and *Jones'* reagent (0.14 ml, 0.36 mmol): **34** (26 mg, 86%). Yellow oil. IR (neat): 2930, 2852, 2800 (*Bohlmann*), 1719, 1453, 1419, 1371, 1264, 1109, 1022. ^{1}H-NMR: 0.89 (*t*, $J = 7.0$, 3 H); 1.20–1.45 (*m*, 8 H); 1.60–1.85 (*m*, 5 H); 1.96–2.16 (*m*, 2 H); 2.22 (*q*, $J = 8.8$, 1 H); 2.28–2.38 (*m*, 1 H); 2.46–2.52 (*m*, 1 H); 2.73 (*'t'*, $J = 8.0$, 1 H); 3.21 (*dtd*, $J = 8.8$, 3.3, 1 H). ^{13}C-NMR: 14.04; 20.61; 22.60; 23.0; 25.37; 30.95; 32.19; 34.10; 39.32; 51.30; 61.50; 70.93; 208.0. MS: dec.

As described for **24**, with (methoxymethyl)triphenylphosphonium bromide (771 mg, 2.25 mmol), THF (5 ml; under Ar), KHMDS (449 mg, 2.25 mmol), THF (5 ml; 0.5 h), **34** (98 mg, 0.466 mmol), and THF (2 ml). Workup as described for **28** gave **35** (60 mg, 54%; (*E*)/(*Z*) not assigned, major/minor 73:27). Colorless oil. Data for the major isomer unless stated otherwise: IR (neat): 2932, 2856, 2769 (*Bohlmann*), 2681, 1692, 1462, 1371, 1217, 1130, 1109, 1028, 1017, 924, 886, 842, 799. ^{1}H-NMR: 0.88 (*t*, $J = 7.0$, 3 H); 1.15–1.42 (*m*, 9 H); 1.61–2.15 (*m*, 8 H); 2.34 (*m*, 1 H); 2.85 (*ddd*, $J = 14.0$, 4.8, 2.2, 1 H); 3.29 (*'t'*, $J = 8.5$, 1 H); 3.48 (*s*, 3 H, minor isomer); 3.56 (*s*, 3 H); 5.76 (br. *'s'*, 1 H, minor isomer); 5.85 (br. *'s'*, 1 H). ^{13}C-NMR: 14.04; 20.41; 22.65; 23.94; 25.39; 25.81; 28.28; 32.30; 34.37; 51.68; 59.49; 63.96; 64.78; 139.62. HR-MS: (237.2087 M^+, $C_{15}H_{27}NO^+$, calc. 237.2092). MS: 237 (17, M^+), 236 (21), 222 (39), 206 (8), 180 (10), 166 (100), 134 (22), 122 (13), 96 (18).

(5R,8R,8aS)-Octahydro-5-pentylindolizine-8-carbaldehyde (**36**). A mixture of **35** (58 mg, 0.246 mmol), aq. 6N HCl (2.5 ml), and Et_2O (5 ml) was stirred at r.t. overnight. A sat. aq. $NaHCO_3$ soln. (10 ml) was added and the aq. layer extracted with Et_2O (4 × 20 ml); **36** (52 mg, 94%; 8eq/8ax 97:3 by ^{1}H-NMR). Light-yellow oil. IR (neat): 2953, 2927, 2857, 2781 (*Bohlmann*), 2705, 1726, 1462, 1378, 1154, 1105. ^{1}H-NMR: 0.86 (*t*, *J* = 6.8, 3 H); 0.96–1.40 (*m*, 20 H); 3.27 (*dt*, *J* = 8.3, 2.4, 1 H); 9.65 (*d*, *J* = 2.0, 1 H); (minor isomer 10.0 (*d*, *J* = 2.0)). ^{13}C-NMR: 14.07; 20.69; 22.63; 24.88; 25.31; 28.87; 29.81; 32.25; 34.33; 55.02; 62.86; 63.99; 76.69; 203.26. MS: 223 (12, M^+), 194 (15), 180 (8), 166 (22), 152 (100), 96 (12), 70 (18).

(–)-(5R,8R,8aS)-Octahydro-5-pentylindolizine-8-methanol (**37**). A sample of **36** (35 mg, 0.157 mmol) in EtOH was reduced with $NaBH_4$ and worked up according to [10]: **37** (27 mg, 75%). Colorless oil. $[\alpha]_D^{20} = -93.6$ (*c* = 0.51, MeOH; [10]: –93.3 (*c* = 0.58, MeOH)). IR (neat): 3300 (br.), 2927, 2851, 2798 (*Bohlmann*), 2701, 1470, 1446, 1379, 1330, 1303, 1244, 1169, 1142, 1089, 1046, 938, 911, 879. ^{1}H-NMR: 0.86 (*t*, *J* = 7.0, 3 H); 1.11 (*qd*, *J* = 12.9, 3.7, 1 H); 1.19–1.43 (*m*, 12 H); 1.54 (*qd*, *J* = 11.4, 7.0, 1 H); 1.62–2.00 (*m*, 6 H); 2.00 (*q*, *J* = 8.8, 1 H); 3.30 (*dt*, *J* = 8.8, 1.8, 1 H); 3.47 (*dd*, *J* = 10.7, 6.6, 1 H); 3.65 (*dd*, *J* = 10.7, 4.4, 1 H). ^{13}C-NMR: 14.01; 20.54; 22.59; 25.46; 27.83; 28.95; 30.50; 32.21; 34.33; 44.12; 51.38; 63.56; 65.65; 66.97. HR-MS: (225.2090 M^+, $C_{14}H_{27}NO^+$; calc. 225.2092). MS: 225 (3, M^+), 224 (4), 154 (100), 96 (11), 70 (12).

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