5,6-Dihydroindolizines as Convenient Precursors of Indolizidine 167B and Analogues

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Abstract: Starting from 5-carboxyethyl-5,6-dihydroindolizine, the title alkaloid was obtained in 25% overall yield via differently C5-substituted 5,6-dihydroindolizines and final exhaustive hydrogenation. An alternative strategy for the synthesis of optically active indolizidine 167B and analogues still based on 5,6-dihydroindolizine intermediates is given.

Keywords, (–)-indolizidine 167B, 5,6-dihydroindolizines, synthesis, 4-(pyrrol-1-yl)butanal, enantioselective hydrogenation

Indolizidine alkaloids are a class of compounds widely diffused in nature and characterized by interesting wide ranging biological properties. Many indolizidines with alkyl chains of various length in different positions of the bicyclic core have been identified as venomous constituents of ant species or neotropical frogs,[1] some of these being non-competitive blockers of nicotinic acetylcholine receptor channels.[2] Indolizidine 167B (Figure **1**) was originally identified as a trace component in the skin secretions of a frog belonging to the genus *Dendrobates* on the Isla de Còlon, Panama, and later identified in a single population of *D. speciosu*s.[3]
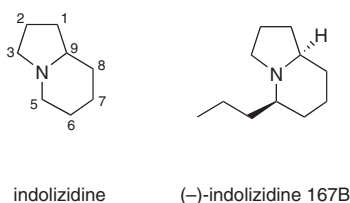
indolizidine   (–)-indolizidine 167B

Figure 1

Although the structure has recently been questioned,[4] this alkaloid remains a target for many research groups,[5] both in its racemic and optically active form. Most of the synthetic strategies proposed for the total synthesis of indolizidine 167B begin with the pyrrolidine ring and then construction of the piperidine ring, the most frequent disconnection being at the N4–C5 bond,[6] although cyclisation via the C8–C9 bond is also known.[7]

We recently described an approach to 5,6-dihydroindolizine core, based on the C8–C9 bond formation via an intramolecular cyclodehydration of 4-(pyrrol-1-yl)butanals, coming from rhodium-catalysed hydroformylation of *N*-allylpyrroles.[8] 5,6-Dihydroindolizines are rare and we employed them in a formal synthesis of Myrmicarin 217.[9] We now show that these compounds can be used as precursors of indolizidine 167B and analogues.

As depicted in Scheme 1 we envisaged that the saturated 5-alkylindolizidine [alkyl = *n*-Pr in (–)-indolizidine 167B (**1**)] could be directly obtained from 5,6-dihydroindolizine **2**, where the alkyl group present in position 5 of the ring skeleton is the same or a direct precursor of that in the target molecule.

Compound **2** could be obtained through a functional group transformation starting from indolizine ester **3**. This compound has been synthesized from glutamic acid, the crucial step being the cyclodehydration of the pyrrolylbutanal **4**.[9] 5-Carboxyethyl-5,6-dihydroindolizine (**3**) represents a key intermediate; in fact, while the manipulation of the ester group allows access to various 5-substituted-5,6-dihydroindolizines, the independent use of both the double bond and/or the pyrrole positions could allow synthesis of more complex indolizidine derivatives.

The strategy was successful, as demonstrated by the synthesis of optically active indolizidine 167B and analogues. The synthetic pathway we adopted is described in Scheme 2 and utilises 5,6-dihydroindolizine ester **3** as the starting material and introduces some new 5,6-dihydroindolizines as convenient intermediates.
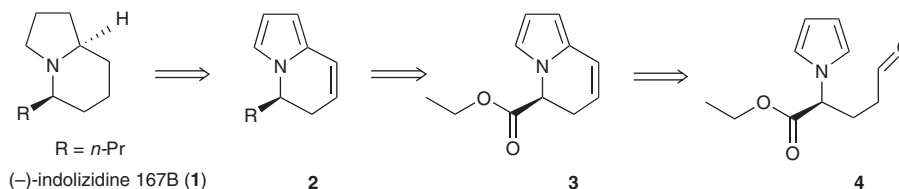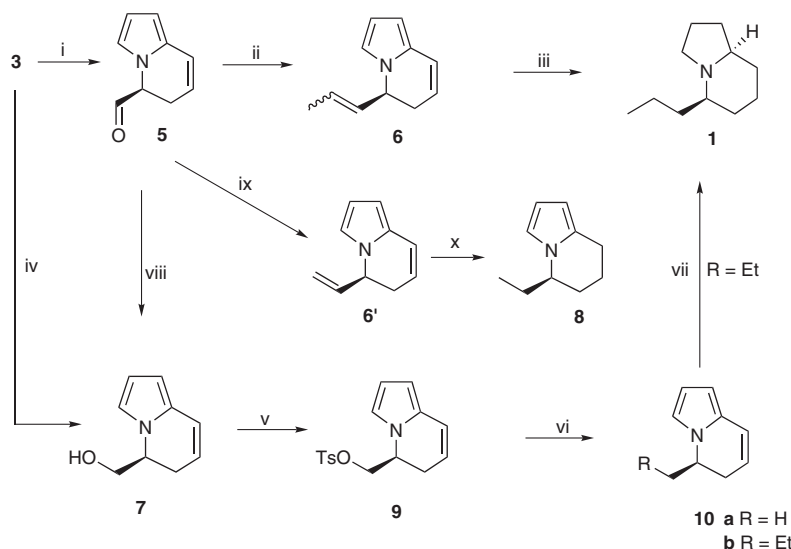
R = *n*-Pr
(–)-indolizidine 167B (**1**)   **2**   **3**   **4**

Scheme 1

Scheme 2 **A**: i) DIBAL-H–hexane (1.9 equiv), THF, –78 °C, 1.5 h, –78 °C, workup from –78 °C → r.t., 61% yield; ii) CH₃CH₂PPh₃Br–NaNH₂, THF, from –30 °C → r.t., 22.5 h, 52% yield; iii) H₂, Rh/C (5%), 10 atm, 90 min, 80% yield **B**: iv) LiAlH₄, THF, 0 °C → r.t., 1 h, 99% yield; v) Et₃N, TsCl, CH₂Cl₂, r.t., 5 h, 69% yield; vi) LiAlH₄, Et₂O, 0 °C → r.t., 22 h, 55% yield for **10a**; Li₂CuCl₄, EtMgBr, THF, –78 °C → r.t., 63 h, 52% yield for **10b**; vii) H₂, Rh/C (5%), 10 atm, 60 min, 65% yield; viii) NaBH₄, MeOH, r.t.; ix) CH₃PPh₃Br–NaNH₂, THF, –30 °C → r.t.; x) H₂, Rh/C (5%), r.t.

The pathway is diastereoselective and only the diastereomer corresponding to indolizidine 167B (–)-(**1**) was formed, as evidenced by the comparison of the obtained ¹H and ¹³C NMR data with those reported for the same isomer.[10]

Pathway A

The reduction of (–)-**3** to aldehyde (–)-**5** was carried out at –78 °C. From our previous work on an analogous transformation in the synthesis of optically active 1-allylpyrroles from the corresponding α-aminoacids,[11] we knew that the ester reduction might cause racemisation but only in a low extent if the addition of tartrate solution occurs at –78 °C. In this case we obtained (–)-(S)-5-formyl-5,6-dihydroindolizine (**5**) with an optical purity of 80%. In particular this datum was valued by transforming the aldehyde (–)-**5** into the corresponding alcohol (+)-**7**, its αmax value[9] being known (Scheme 2). The olefination of (–)-**5** into (+)-**6** was carried out with the Schlosser–Schaub instant ylide reagent (ethyltriphenyl phosphonium bromide and sodium amide) by addition of the aldehyde to the preformed ylide cooled at low temperature (–30 °C) to avoid racemisation. This has proven to be the lowest temperature at which we can observe any reaction between the reagents, but the reaction mixture must be heated to room temperature to obtain a complete conversion of the starting material. When the isolate **6** was submitted to hydrogenation with Rh/C catalytic system, (–)-indolizidine167B was obtained, with an optical purity of 42%, as determined from the comparison of its specific rotation with the αmax value reported in the literature.[10] The olefination or hydrogenation step or both could be in principle responsible for racemisation. Preliminary attempts of elution of **6** on chiral chromato-

graphic column, which is convenient with other similar structures, were unsuccessful.[12,13] On the other hand no racemisation has been previously observed[11] by us for the transformation of a formyl group into a terminal double bond under the same methylenation conditions. In order to clarify if the formation of an internal instead of a terminal double bond could play a crucial role in racemisation, the synthesis of (–)-5-vinyl-5,6-dihydroindolizine (**6′**) was accomplished via methylenation of **5** with commercial methyltriphenylphosphonium bromide/NaNH₂ instant ylide (Scheme 2).

The olefin **6′** having the same optical purity as the starting aldehyde **5** was obtained,[13,14] thus the aldehyde **5** proved configurationally stable in the adopted conditions. Taking into account that the reaction to **6** is slower than that forming **6′**, enolisation of the aldehyde group could probably occur in the former transformation, with the consequent racemisation observed.

Pathway B

To avoid the drawback of the C5 configurational lability in (–)-**5** during the olefination step to (+)-**6**, we looked to an alternative enantioselective synthesis having (+)-(S)-5-hydroxymethyl-5,6-dihydroindolizine (**7**) as key intermediate. As reported above, this species can be obtained in high optical purity (80%) via reduction of the aldehyde (–)-**5** (Scheme 2) with NaBH₄ in MeOH. However, we have previously obtained it in enantiomerically pure form[9] (98%) directly from (–)-(S)-5-carboxyethyl-5,6-dihydroindolizine (**3**) by treatment with LiAlH₄ in THF. In the current work, we have studied yet another synthetic pathway in a preliminary way to (–)-indolizidine 167B

starting from (–)-(*S*)-5-carboxyethyl-5,6-dihydroindolizine (**3**) (steps iv, v, vi, vii, Scheme 2).

With respect to the previous procedure (steps i, ii, iii Scheme 2), an additional step was present in this reaction sequence. The reduction of **3** was carried out as previously reported.[9] After one hour, the conversion was complete and the reaction was quenched with MeOH and saturated aqueous solution of mixed sodium potassium tartrate. The reaction was relatively fast and furnished (+)-(*S*)-hydroxymethyl-5,6-dihydroindolizine (**7**) in almost quantitative yield. The tosylation step also occurred very easily; the reactants were mixed together and stirred at room temperature, providing (+)-(*S*)-5-(*p*-toluenesulfonyloxymethyl)-5,6-dihydroindolizine (**9**) in good yield (69%).

Some attempts of substitution reactions at C5 on **9** were carried out. For the first time the introduction of a hydride has been accomplished by treatment of **9** with LiAlH₄, at room temperature. The simplest 5-alkyl-5,6-dihydroindolizine, i.e. (–)-(*R*)-5-methyl-5,6-dihydroindolizine (**10a**) was obtained with the same ee value as the starting **3**.[15,16] Tamura and Kochi's Cu(II) system[17] seemed to be the proper reagent for the introduction of an ethyl group instead of the tosyl one in forming the *n*-propyl substituent at C5. Preliminary tests showed that by using catalytic quantities (5%) of Li₂CuCl₄ (added as a THF solution) with high excess of EtMgBr (9-fold) (–)-(*R*)-*n*-propyl-5,6-dihydroindolizine (**10b**) was formed but only partial conversion (20%) of the starting material was observed. Increasing the quantity of racemic reagent (50%), the conversion of the starting material rose to 70%, but also side-products started to appear. In both cases (–)-(*R*)-*n*-propyl-5,6-dihydroindolizine with an ee of 98% was obtained,[15,16] giving pure (–)-indolizidine 167B via final enantioselective rhodium-catalyzed hydrogenation.

In conclusion we have disclosed a new three-step synthesis of indolizidine 167B from 5-carboxyethyl-5,6-dihydroindolizine (**3**) in a 25% overall yield. By means of some transformations of the carboxyethyl group into different functionality at the 5-position many new 5,6-dihydroindolizines were prepared. Other 5-alkyl-substituted indolizidines can be obtained in a similar manner via the same synthetic iteration; the availability of the Wittig reagent to introduce the proper alkenyl group at C5 in 5-formyl-5,6-dihydroindolizine **5** being the sole crucial key. The enantiopure (–)-167B was also obtained via an enantioselective four-step synthesis, still based on 5,6-dihydroindolizine derivatives. The above findings indicate that the 5,6-dihydroindolizine core, owing to the stability shown in different experimental conditions as well as to the possibility to an independent use of the C7–C8 double bond, seem to be a very useful scaffold for fine chemicals.

Reactions requiring an inert atmosphere were conducted under anhyd N₂, and the glassware were oven-dried (120 °C). Anhydrous solvents were purified prior to use as follows. CH₂Cl₂ was distilled from CaCl₂, THF and Et₂O were distilled from sodium under N₂. All reagents were purchased in the highest quality available and were used without further purification. 5-Carboxyethyl-5,6-dihydroindolizine (**3**) was prepared as reported in the literature.[9] TLC analyses were performed on aluminium oxide 60 F₂₅₄ neutral plates from Merck. For preparative chromatography Merck aluminium oxide 90 active (neutral, 70–230 mesh) was used. Optical rotations were measured with a JASCO DIP-370 digital polarimeter at the given temperature. Melting points were taken using a Reichart Thermovar apparatus and are uncorrected. Microanalyses were performed at Laboratorio di Microanalisi, Istituto di Chimica Organica, Facoltà di Farmacia, Università di Pisa. ¹H NMR and ¹³C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Varian Gemini 200 spectrometer. Chemical shifts are given in δ (ppm) relative to CDCl₃.

(–)-(*S*)-5-Formyl-5,6-dihydroindolizine (5)

To a solution of (–)-(*S*)-5-carboxyethyl-5,6-dihydroindolizine (**3**; 4.9 g, 25.6 mmol) in THF–hexane (1:4) cooled at –78 °C a 1 M hexane solution of DIBAL-H (50 mL, 50 mmol) was added and stirring was continued at that temperature for 1.5 h. The reaction mixture was then quenched with MeOH (9 mL) at –78 °C and a sat. aq solution of mixed sodium potassium tartrate (100 mL) was added. When the temperature was raised to the r.t., the two phases separated, the aqueous phase was extracted with Et₂O (3 × 150 mL) and the combined organic layers washed with water (4 × 150 mL). The organic layers were dried (Na₂SO₄), concentrated in vacuo and purified by vacuum distillation (70 °C, 0.05 mm Hg) to afford (–)-(*S*)-**5** as a yellow oil (2.3 g, 15.6 mmol, 61%); $[\alpha]_D^{25}$ –161.2 (*c* = 1.4, benzene).

¹H NMR: δ = 9.54 (br s, 1 H, CHO), 6.71 (t, *J* = 1.4 Hz, 1 H, H_Pyr), 6.47 (dt, *J* = 2.0, 9.8 Hz, 1 H, PyrCH=), 6.27 (t, *J* = 3 Hz, 1 H, H_Pyr), 6.18 (dd, *J* = 1.2, 3.4 Hz, 1 H, H_Pyr), 5.59 (m, 1 H, CH₂CH=), 4.52 (t, *J* = 5.6 Hz, 1 H, NCH), 2.87 (m, 2 H, CH₂).

¹³C NMR: δ = 25.6, 62.6, 107.9, 109.9, 116.6, 120.9, 121.2, 129.0, 200.5.

MS: *m/z* = 147 (31) [M⁺], 118 (100), 91 (20), 63 (11).

Anal. Calcd for C₁₂H₉NO: C, 73.50; H, 6.12; N, 9.52. Found: C, 72.90; H, 6.30; N, 9.58.

(+)-(*S*)-5-(Propen-1-yl)-5,6-dihydroindolizine (6)

A mixture of ethyltriphenylphosphonium bromide and NaNH₂ (10 g, 24 mmol) in anhyd THF (280 mL) was stirred at r.t. for 1 h and then cooled to –30 °C. A solution of (–)-(*S*)-**5** (1.89 g, 12.9 mmol) in anhyd THF (80 mL) was added and the mixture was stirred at –30 °C for 1.5 h and allowed to warm to 0 °C. After stirring for 17 h at 0 °C and for further 4 h at r.t., the crude mixture was hydrolysed (200 mL of water). The aqueous phase was extracted with hexane (3 × 150 mL) and the combined organic layers were washed until neutral, dried (Na₂SO₄), concentrated in vacuo and submitted to vacuum distillation to afford (+)-(*S*)-5-(propen-1-yl)-5,6-dihydroindolizine (**6**; 80 °C, 0.01 mm Hg) as an orange viscous liquid (1.1 g, 6.70 mmol, 52%); $[\alpha]_D^{20}$ +10.31 (*c* = 1.8, CH₂Cl₂).

¹H NMR: δ = 6.67 (t, *J* = 2.0 Hz, 1 H, H_Pyr), 6.49 (dd, *J* = 2.2, 9.6 Hz, 1 H, PyrCH=), 6.16 (t, *J* = 3.1 Hz, 1 H, H_Pyr), 6.11 (dd, *J* = 1.6, 3.2 Hz, 1 H, H_Pyr), 5.92–5.55 (m, 3 H, CH₃CH=, CH₂CH=, CHCH=), 4.79 (m, 1 H, NCH), 2.40 (m, 2 H, CH₂), 1.77 (dd, *J* = 1.8, 7.0 Hz, 3 H, CH₃).

¹³C NMR: δ = 13.2, 27.9, 31.2, 50.7, 106.5, 107.8, 118.1, 119.3, 120.3, 128.4, 129.4.

MS: *m/z* = 159 (100) [M⁺], 144 (43), 130 (20), 118 (48), 117 (50), 104 (10), 91 (20), 80 (16), 63 (12).

Anal. Calcd for C₁₁H₁₃N: C, 83.02; H, 8.80; N, 7.55. Found: C, 82.88; H, 8.63; N, 7.62.

(–)-(S)-5-Ethenyl-5,6-dihydroindolizine (6′)

A mixture of methyltriphenylphosphonium bromide and NaNH$_2$ (10 g, 24 mmol) in anhyd THF (160 mL) was stirred at r.t. for 1 h. To the yellow suspension cooled at –30 °C a solution of (–)-**5** (1.32 g, 8.9 mmol) in anhyd THF (70 mL) was added. After 1.25 h the temperature was increased to r.t. and the mixture was stirred for 19 h. The reaction mixture was then hydrolysed with water (150 mL). The aqueous phase was extracted with hexane (3 × 150 mL) and the combined organic layers were washed until neutral. After drying (Na$_2$SO$_4$), the hexane solution was concentrated in vacuo affording, after vacuum distillation (40 °C, 0.01 mm Hg), (–)-(S)-5-ethenyl-5,6-dihydroindolizine (**6′**) as an orange liquid (0.55 g, 3.80 mmol, 42%); $[\alpha]_D^{25}$ –60.9 (c = 1.2, CH$_2$Cl$_2$).

^{1}H NMR: δ = 6.67 (br s, 1 H, H$_{Pyr}$), 6.47 (d, J = 9.4 Hz, 1 H, PyrCH=), 6.17 (t, J = 3.1 Hz, 1 H, H$_{Pyr}$), 6.10 (br s, 1 H, H$_{Pyr}$), 5.95 (m, 1 H, CHCH=), 5.68 (m, 1 H, CH$_2$CH=), 5.25 (d, J = 10.0 Hz, 1 H, *trans*-CH=CH$_2$), 5.03 (d, J = 16.8 Hz, 1 H, *cis*-CH=CH$_2$), 4.53 (q, J = 7.2 Hz, 1 H, NCH), 2.63 (m, 1 H, CH$_2$), 2.44 (m, 1 H, CH$_2$).

^{13}C NMR: δ = 31.0, 57.5, 106.7, 108.2, 117.6, 117.7, 120.1, 120.4, 129.5, 137.8.

MS: m/z = 145 (100) [M$^+$], 144 (97), 130 (24), 118 (81), 117 (78), 115 (11), 104 (27), 91 (22), 90 (18), 89 (19), 80 (10), 78 (10), 77 (14), 65 (13), 63 (13).

Anal. Calcd for C$_{12}$H$_{11}$N: C, 82.76; H, 7.59; N, 9.66. Found: C, 82.85; H, 7.63; N, 9.71.

(–)-(5R,9R)-Octahydroindolizine (1)

Step iii: A solution of (+)-(S)-**6** (80 mg, 0.50 mmol) in Et$_2$O (5 mL) containing 5% Rh-C (85 mg) was hydrogenated under vigorous stirring in a steel vessel at r.t. and at 10 atm for 1.5 h. The catalyst was removed by filtration and the solution was concentrated in vacuo to afford (–)-**1** (69 mg, 0.41 mmol, 80%) as a colourless oil (42% optical purity). The spectroscopic data of this product are in complete agreement with the reported data.[10]

Step vii: Compound (–)-(**1**) was obtained from (–)-(R)-**10b** under the above reported reduction conditions in 65% yield and 98% optical purity.[10]

(+)-(S)-5-Hydroxymethyl-5,6-dihydroindolizine (7)

To a suspension of LiAlH$_4$ (0.960 g, 25.3 mmol) in anhyd THF (60 mL) cooled at 0 °C a solution of (–)-**3** (1.99 g, 10.4 mmol) in anhyd THF was added. The reaction mixture was heated to r.t. and, after 1 h stirring, MeOH (8 mL) and a sat. aq solution of mixed sodium potassium tartrate (50 mL) were added. The aqueous phase was extracted with Et$_2$O (3 × 70 mL) and the combined organic phases were washed with water (3 × 150 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to afford (+)-(S)-5-hydroxymethyl-5,6-dihydroindolizine (**7**)[9] (1.54 g, 10.3 mmol, 99%) as an orange oil, in 98% optical purity; $[\alpha]_D^{20}$ +69.6 (c = 1, CH$_2$Cl$_2$).

To a solution of (–)-(S)-5-formyl-5,6-dihydroindolizine (**5**; 56.5 mg, 0.38 mmol) in MeOH (1.5 mL) NaBH$_4$ (80 mg, 2.1 mmol) was added. After stirring at r.t. for 45 min, the reaction was quenched with a sat. aq solution of NH$_4$Cl (3 mL). Addition of Et$_2$O (5 mL) was followed by separation and extraction of the aqueous phase with Et$_2$O (3 × 3 mL). The combined organic layers were washed with water (3 × 10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to afford (+)-(S)-5-hydroxymethyl-5,6-dihydroindolizine (**7**)[9] (47.7 mg, 0.32 mmol, 84%) in 80% optical purity; $[\alpha]_D^{20}$ = +55.7 (c = 1, CH$_2$Cl$_2$).

(+)-(S)-5-(p-Toluenesulfonyloxymethyl)-5,6-dihydroindolizine (9)

The alcohol (+)-**7** (0.71 g, 4.76 mmol), tosyl chloride (1.65 g, 8.7 mmol) and Et$_3$N (1.78 g, 17.6 mmol) were stirred in anhyd CH$_2$Cl$_2$ at r.t. for 5 h. The brown solution was poured into sat. aq NaHCO$_3$ solution (30 mL) and the aqueous layers were extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic phases were washed (4 × 250 mL), dried and evaporated in vacuo. Column chromatography (CH$_2$Cl$_2$–hexane 1:1 as eluent) gave (+)-(S)-5-(p-toluenesulfonyloxymethyl)-5,6-dihydroindolizine (**9**; 0.99 g, 3.27 mmol, 69%) as an orange solid (mp 50–52 °C); $[\alpha]_D^{24}$ = +4.60 (c = 1.0, CH$_2$Cl$_2$).

^{1}H NMR: δ = 7.72 (d, J = 8.2 Hz, 2 H, H$_{Ph}$), 7.34 (d, J = 8.2 Hz, 2 H, H$_{Ph}$), 6.63 (br s, 1 H, H$_{Pyr}$), 6.36 (dd, J = 2.8, 9.6 Hz, 1 H, PyrCH=), 6.12 (t, J = 3.2 Hz, 1 H, H$_{Pyr}$), 6.02 (br s, 1 H, H$_{Pyr}$), 5.49 (m, 1 H, CH$_2$CH=), 4.38 (m, 1 H, NCH), 4.01 (m, 2 H, CH$_2$O), 2.70 (m, 1 H, CH$_2$), 2.48–2.33 (m, 4 H, CH$_2$, CH$_3$).

^{13}C NMR: δ = 22.0, 25.8, 52.9, 69.6, 107.2, 108.9, 116.1, 120.4, 121.1, 128.1 (3 × C), 130.2 (2 × C), 132.7, 145.5.

MS: m/z = 303 (52) [M$^+$], 131 (29), 118 (100), 91 (32), 65 (41).

Anal. Calcd for C$_{16}$H$_{17}$NO$_3$S: C, 63.37; H, 5.61; N, 4.62; S, 10.56. Found: C, 63.45; H, 5.65; N, 4.58; S, 10.60.

(–)-(R)-5-Methyl-5,6-dihydroindolizine (10a)

To a suspension of LiAlH$_4$ (1.450 g, 11.8 mmol) in anhyd Et$_2$O, (+)-(S)-5-(p-toluenesulfonyloxymethyl)-5,6-dihydroindolizine (**9**; 0.725 g, 2.39 mmol) was added at 0 °C. The reaction mixture was warmed to r.t. and stirred for 22 h. The reaction mixture was hydrolysed with humid Et$_2$O (60 mL) and a sat. aq solution of NH$_4$Cl (70 mL), and the aqueous layer was extracted with Et$_2$O (3 × 100 mL). The combined organic phases were washed (3 × 200 mL), dried (Na$_2$SO$_4$) and evaporated carefully in vacuo. After purification by column chromatography (hexane as eluant), (–)-(S)-5-methyl-5,6-dihydroindolizine (**10a**)[15,16] was obtained as a yellow oil (0.173 g, 1.30 mmol, 55%); ee 98%; $[\alpha]_D^{21}$ = – 107.5 (c = 1.18, CH$_2$Cl$_2$).

(–)-(R)-5-Propyl-5,6-dihydroindolizine (10b)

To a solution of (+)-(S)-5-(p-toluenesulfonyloxymethyl)-5,6-dihydroindolizine (**9**; 0.194 g, 0.64 mmol) in anhyd THF were added at –78 °C a 3 M ethereal solution of EtMgBr (12 mmol, 19 equiv, 4 mL) and a THF solution of Li$_2$CuCl$_4$ (0.28 M, 0.756 mmol, 1.18 equiv, 2.7 mL). After allowing the reaction mixture to warm to r.t. very slowly (63 h), a sat. aq solution of NH$_4$Cl (40 mL) was added, and the aqueous layers were extracted with Et$_2$O (3 × 60 mL). The combined organic phases were washed (3 × 100 mL), dried (Na$_2$SO$_4$) and concentrated at atmospheric pressure. Purification by column chromatography (hexane as eluent) afforded (–)-(R)-5-propyl-5,6-dihydroindolizine (**10b**) as an orange oil (0.054 g, 0.33 mmol, 52%); ee 98%; $[\alpha]_D^{26}$ –46.3 (c = 0.86, CH$_2$Cl$_2$)}.

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(12) Chiral gas chromatography was performed on chiral capillary column CHIRALDEX G-TA (γ-cyclodextrin trifluoroacetyl, 50 m × 0.25 mm).

(13) The evaluation of ee of the olefin (–)-**6′** was accomplished by transforming it into the new partially hydrogenated 5-ethyl-5,6,7,8-tetrahydroindolizine (**8**; Scheme 2) which, unlike **6′**, was separated into its enantiomers by chiral gas chromatography [CHIRALDEX G-TA (γ-cyclodextrin trifluoroacetyl, 50 m × 0.25 mm) capillary column]. The chromatographic conditions were set up for analysing a racemic sample of **8**[14] prepared in the same manner. The compound **8** showed the same ee value as the starting aldehyde **5**. This result gives evidence that the vinyl group hydrogenation as well as the endocyclic double bond hydrogenation do not influence the configuration of the asymmetric centre, accounting for the internal bond formation in the alkyl chain of **6**, and not for its hydrogenation, as the sole step responsible for racemisation observed in the synthesis of (–)-indolizidine 167B.

(14) Selected data for **8**: ^{1}H NMR: δ = 6.67 (br s, 1 H), 6.15 (t, J = 3.1 Hz, 1 H), 5.81 (br s, 1 H), 3.94 (m, 1 H), 2.75 (m, 2 H), 2.07 (m, 2 H), 1.91 (m, 2 H), 1.68 (m, 2 H), 0.98 (t, J = 7.3 Hz, 3 H).
MS: *m/z* = 149 (78) [M⁺], 121 (43), 120 (100), 106 (15), 93 (14), 80 (14), 65 (7).

(15) The ee evaluation was accomplished via GC chiral gas chromatography under the same analytical conditions previously adopted for the same substrate prepared in an alternative way.[16]

(16) Settambolo, R.; Guazzelli, G.; Mandoli, A.; Lazzaroni, R. *Tetrahedron: Asymmetry* **2004**, *15*, 1821.

(17) (a) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303. (b) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82.