

Synthesis of Indolizidines (-)-195B, (-)-223AB and (-)-239AB : (2S,5R)-1-[(Benzyloxy)carbonyl]-2-methoxycarbonyl-5-(4-pentenyl)pyrrolidine as a Versatile Chiral Building Block¹

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Abstract: The total syntheses of three levogyre 3,5-disubstituted indolizidines, (-)-195B, (-)-223AB and (-)-239AB are described. The employed strategy is based on the utilization of the common enantiopure *trans* 2,5-disubstituted pyrrolidine **3**, which is assembled by addition of pent-4-enylcopper to N-acyl iminium ion derived from (S)-proline. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Indolizidine alkaloids exuded by the skin of batrachians of Central America have been attractive targets for synthesis because of their potential biological activities,² unique origin and varied structures.³ A subclass of this family composed of 3,5-disubstituted indolizidines occurs in some *dendrobatidae* species (figure 1). Among the four members of this subclass, (-) indolizidine **223AB** has been the most popular synthesis target.^{4,5} In most of the previous multisteps syntheses, at least one of the two substituents (R¹ and/or R²) is installed at the start. Accordingly, each of the four indolizidines **1a-d** requires an appropriate starting material. One exception is due to C. Kibayashi *et al*⁵ who reported a general method for the preparation of both enantiomers of the four indolizidines **1**. However the preparation of the advanced common synthetic intermediate of the four indolizidines, requires more than twenty steps, starting from D-mannitol.

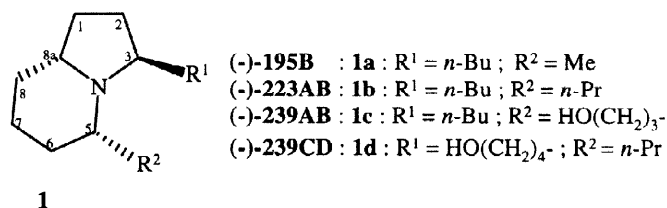


Figure 1

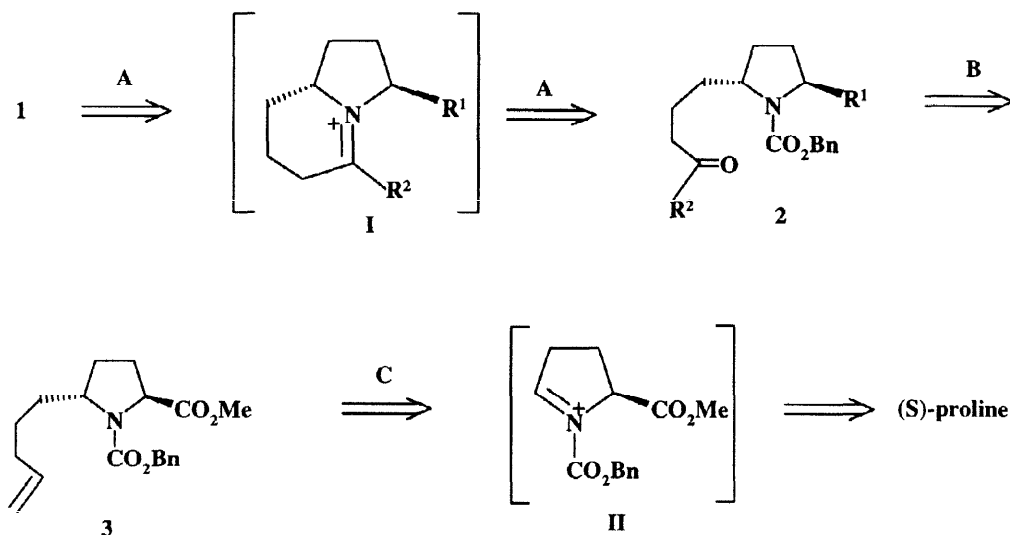
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We now report efficient and short synthesis of enantiopure levogyre indolizidines **1a**,⁶ **1b** and **1c**, based on appropriate homologations of the common intermediate **3** (scheme 1).

SYNTHETIC STRATEGY

As shows the disconnective analysis, our plan for the synthesis of **1a-c** depends on the diastereoselectivities of two critical steps: A and C (Scheme 1). The achievement of the indolizidine skeleton **1** (step A) with a *cis* relative arrangement of the C5 and C8a hydrogen atoms will be based on the reduction of the transient iminium ion **I**, *in situ* generated from **2**. A literature survey shows that the stereochemical outcome of this intramolecular reductive amination *via* iminium ion **I** only depends on the C8a configuration. Indeed whatever the reducing agent (H_2/Pd or hydrides)^{4,5,7} and the C3 configuration (C1 in pyrrolidine numbering), the incoming C5 hydrogen atom is mainly delivered *syn* to that of C8a. For the synthesis of **2**, appropriate series of transformations ought to ensure the elaboration of R^1 radical from the ester group and that of R^2CO from the olefin moiety of intermediate **3**. Finally the chirality of the natural (S)-proline which will become that of C3 in **1**, must allow the control of the configuration of C8a center during an *anti* addition of a suitable five carbons nucleophile to the *in situ* generated N-acyliminium ion **II**. The stereocontrol of our synthetic plan depends on the diastereoselectivity of this most crucial C step. It is well established that π -type nucleophiles give selectively a *syn* addition to N-acyliminiums **II**, derived from (S)-proline.⁸ To achieve an *anti* addition of our five carbons nucleophile, we decided to react the *in situ* generated iminium **II** with pent-4-enylcopper following the procedure reported by L.G. Wistrand and M. Skrinjar.⁹

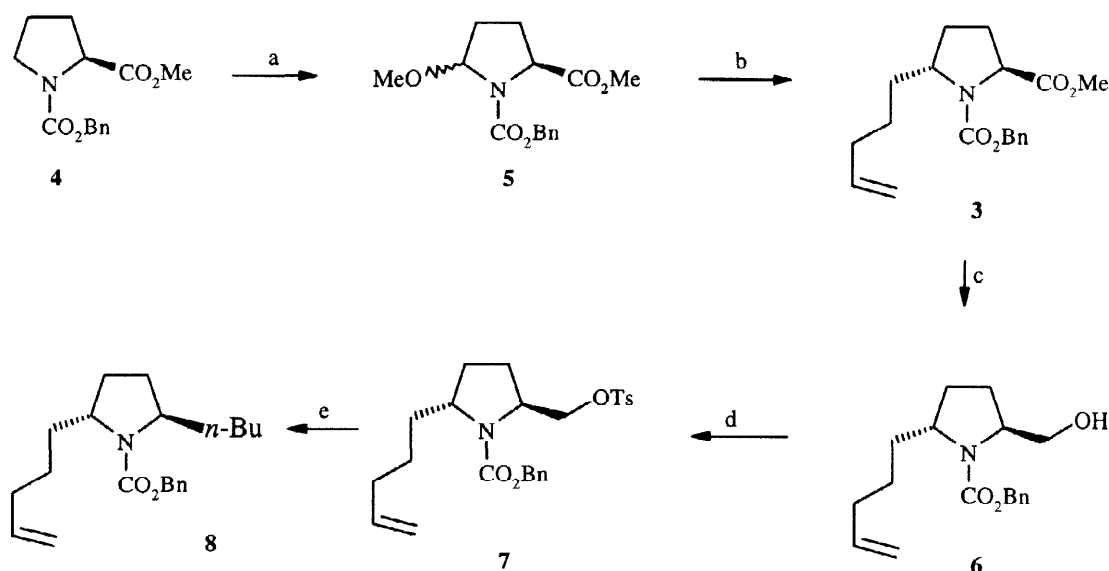


Scheme 1

RESULTS AND DISCUSSION

The feasibility of the above described plan was first put to the test by selecting (-)-indolizidine **195B** [(-)-**1a**]⁶ as the target. The synthesis of the corresponding intermediate **2a** ($R^1 = n\text{-Bu}$, $R^2 = \text{Me}$) only requires the establishment of a *n*-butyl group from the ester one and the methylketone moiety from the terminal carbon-carbon double bond (Scheme 1). As precursor of iminium ion **II** we decided to use the methyl-1-benzyloxycarbonyl-5-methoxyproline **5**. Thus, with some modifications¹⁰ to the conditions of T. Shono, **5** was obtained in 75% yield by anodic α -methoxylation of **4**. Boron trifluoride-mediated addition of pent-4-enylcopper to **5** generated adduct **3** with high stereoselectivity (*trans/cis* : 96/4 as estimated by GC) in 79% yield (Scheme 2). Isolation of the major *trans* isomer failed at this stage. However pure *trans* alcohol **6** was

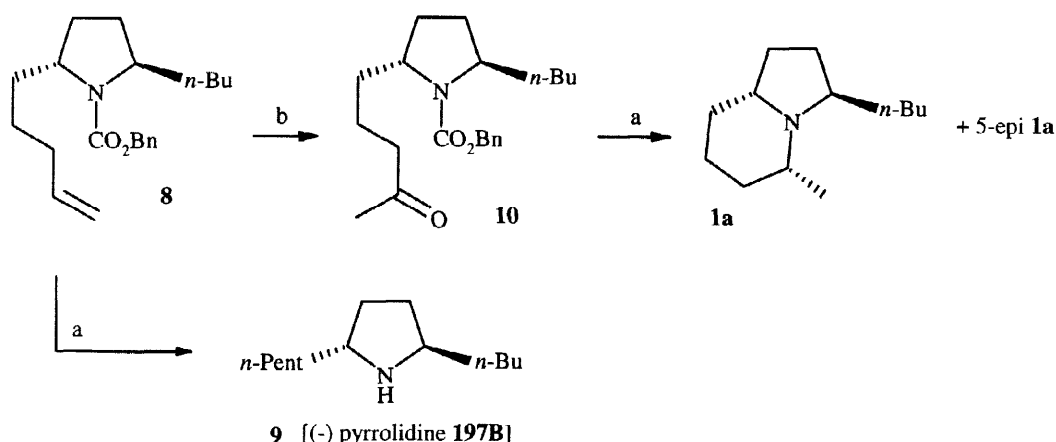
isolated in 73% yield after a chemoselective reduction of the ester group with sodium borohydride in the presence of calcium chloride following the procedure described by J. R. Luly and coworkers.¹¹ It is essential to keep the reaction temperature below 0°C, otherwise (*eg* at room temperature) alcohol **6** is obtained along with benzyl alcohol and (5*R*,7*aR*)-5-(4-pentenyl)-tetrahydropyrrolo[1,2-*c*]oxazolo-3-one **19** (see note 13 for structure) which is the result of an intramolecular transesterification of the carbamate group. The alcohol **6** was uneventfully converted to the corresponding tosylate **7**¹³ in 96% yield. The three-carbon homologation necessary to prepare **8** was performed in 75% yield, by nucleophilic displacement of the tosylate group when **7** was treated with an excess (6 equiv) of *n*-Pr₂CuLi in diethylether at -20°C for 36 h.



Scheme 2 a) -2e-(c-c)-MeOH-Et₄NOTs, -5°C; b) CH₂=CH(CH₂)₃Cu, BF₃·OEt₂, -78°C to rt; c) NaBH₄/CaCl₂, THF/EtOH, -5°C; d) TsCl/NEt₃; e) *n*-Pr₂CuLi, Et₂O, -20°C

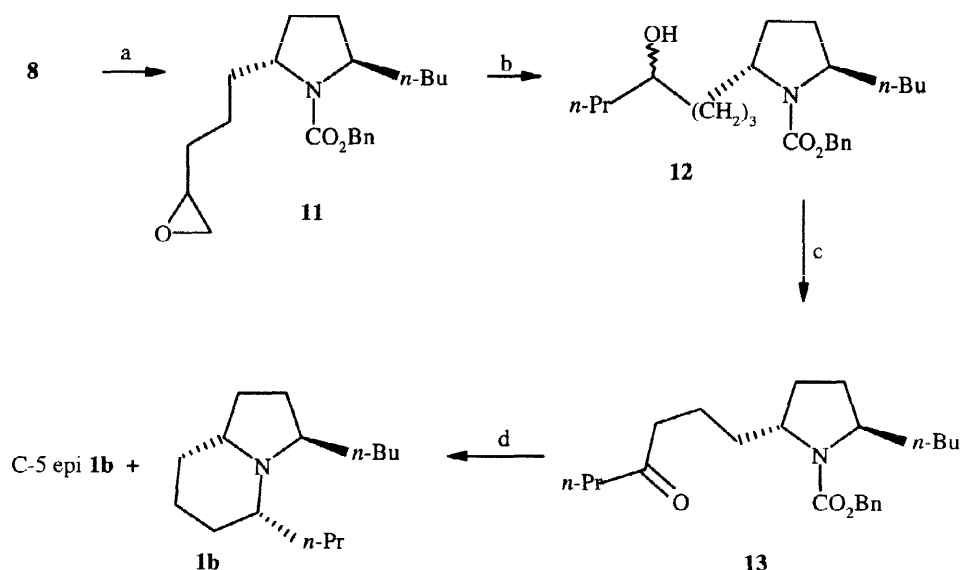
The *trans* stereochemistry of **8** was established after its conversion to the pyrrolidine **9** which was identical in all respects to the known¹³ (-)-pyrrolidine **197B** (Scheme 3). Since **9**, in our hands, was formed as a single product, it can be assumed that the operations, as well as the conditions employed, did not compromise the configuration of the original chiral center in **4**. Having secured the absolute configuration of **8**, the synthesis of (-)-indolizidine **195B**, was next undertaken. The Wacker process using bis-benzonitrile palladium (II)¹⁴ chloride was applied to the olefinic compound **8**, affording the methyl ketone (-)-**10**⁵ in 77% yield. Finally, submission of **10** to hydrogen under atmospheric pressure with Pd/BaSO₄ (or Pd/C) as catalyst resulted in carbamate cleavage and subsequent intramolecular reductive amination leading to (-)-indolizidine **195B** [(-) **1a**], along with its C-5 epimer in a ratio of 84/16 (Scheme 3). The ¹³C NMR spectrum of a pure synthetic sample of (-)-**1a** thus obtained after purification by column chromatography, was identical with that of synthetic (3*R*,5*R*,8*aR*)-3-butyl-5-methyloctahydroindolizidine, while the ¹H NMR spectra broadly agreed.^{5,15} The optical rotation of **1a** was -99 (*c* = 0.215, MeOH), which is very close to the value of -97.1 cited for the sample obtained by C. Kibayashi *et al.*^{5,15}

This result having demonstrated that the experimental plan in its stereochemical aspect was realizable, the syntheses of (-)-indolizidine **223AB** [(-) **1b**] and (-)-indolizidine **239AB** [(-) **1c**] with a three-carbons chain at C-5 position, were then undertaken.



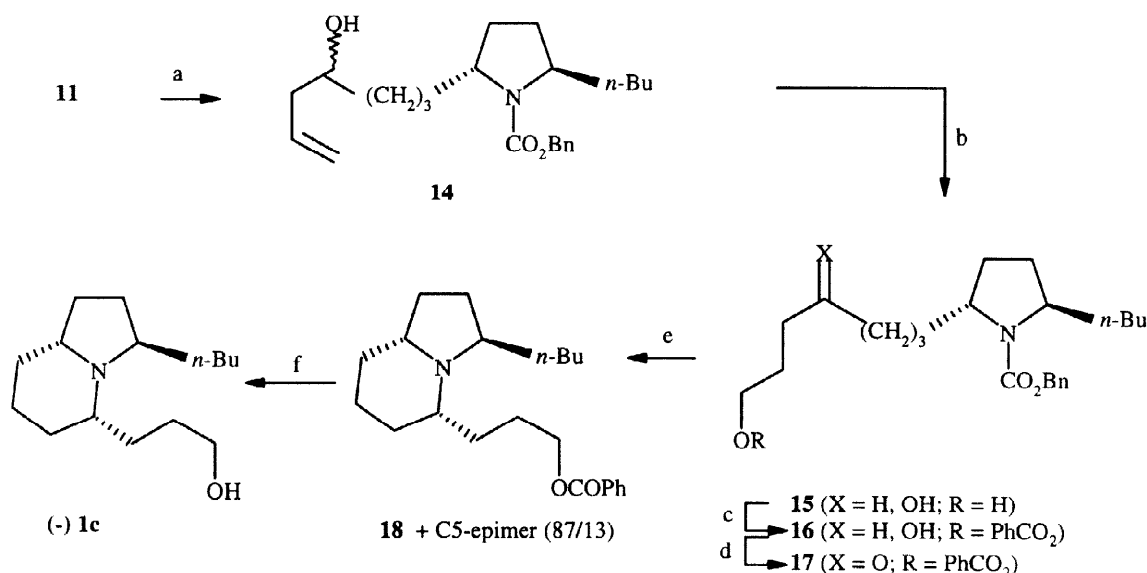
Scheme 3 a) H₂ (1 atm), catalytic Pd/C (or Pd/BaSO₄), MeOH; b) O₂, PdCl₂(PhCN)₂, CuCl, H₂O-DMF (7/1), 60°C.

Treatment of the olefin **8** with *m*-chloroperbenzoic acid, in the presence of a phosphate buffer (NaH₂PO₄/Na₂HPO₄, pH = 8) afforded the epoxide **11** as a mixture of two diastereomers in 69% yield. Submission of **11** to excess ethylmagnesium bromide and catalytic (0.1 eq) copper iodide in THF at -20°C furnished the alcohol **12** which was readily oxidized with pyridinium dichromate (PDC) leading to the key propyl ketone **13**^{4,5} in an overall yield of 63% from **11**. Lastly, on hydrogenation over palladium on carbon, **13** provided (-)-indolizidine **223AB** [(-)-**1b**] along with its C-5 epimer in a ratio of 86:14 (Scheme 4). Our synthetic sample of (-)-**1b** thus obtained exhibited after separation by column chromatography, ¹³C and ¹H NMR spectra identical to those of the natural³ and others synthetic^{4,5} materials. The optical rotation [α]_D²² was determined to be -97 (c = 0.815, hexane). This value compares favorably with those (-88 to -102)^{3,4} obtained previously for synthetic samples.¹⁶



Scheme 4 a) *m*-CPBA, CH₂Cl₂, Na₂HPO₄/NaH₂PO₄ (pH = 8); b) EtMgBr (excess), CuI (0.1 eq), THF, -20°C; c) PDC, CH₂Cl₂; d) H₂, 10% Pd/C, MeOH.

In a slightly modified manner, the epoxide **11** was readily converted to (-)-indolizidine **239AB** [(-) **1c**] (Scheme 5). This time we needed a nucleophilic addition of a 2-hydroxymethylene group equivalent to the epoxide **11**. Such an organometallic being unstable, we undertook its introduction in two steps. Thus, treatment of **11** with excess of vinylmagnesium bromide in the presence of catalytic amount of copper(I) iodide (-20°C, THF) resulted in the regioselective opening of the ring epoxide to give the homoallylic alcohol **14** in 88% yield. Regioselective hydroboration-oxidation of **14** proceeded smoothly on treatment with 0.67 equivalent of boron-methyl sulfide (Et₂O, room temperature) and subsequent oxidation using hydrogen peroxide in the presence of sodium hydroxide to afford the diol **15** in 82% yield. Subsequent to unsuccessful attempts to protect the primary alcohol as a trityl ether, we prepared the corresponding benzoate **16** in 72% yield, by slow addition of benzoyl chloride (1 equiv) to a cooled (-40°C) solution of diol **15** and pyridine in chloroform. Then, the secondary alcohol readily underwent oxidation with pyridinium dichromate (PDC) to provide in a quantitative manner (96% yield) the ketone (-)-**17**. Exposure of the latter to an atmosphere of hydrogen in the presence of Pd/C in methanol led stereoselectively, *via* debenzoyloxycarbonylation and subsequent reductive amination, to a 87/13 diastereomeric mixture of (-) indolizidine **18** and its C5-epimer (Scheme 5). Transesterification of pure **18** {[α]_D²² -37 (c 0.72, MeOH)}, performed on treatment with an excess of sodium methoxide afforded (-)-indolizidine **239AB** [(-)-**1c**], in 86% yield, as shown by comparison of its optical rotation {[α]_D²⁰ -95 (c 0.35, MeOH)}, ¹H and ¹³C-NMR data with those previously reported.^{5,17}



Scheme 5 a) CH₂=CHMgBr (excess), CuI (0.05 eq), THF, -40 to -20°C; b) BH₃.DMS then H₂O₂/NaOH; c) PhCOCl, pyridine; d) PDC, CH₂Cl₂; e) H₂, 10% Pd/C, MeOH; f) MeONa, MeOH

CONCLUSION

We established a general strategy for successful approach to the enantiopure indolizidines (-) **195B**, (-)-**223AB** and (-)-**239AB**, which bear a *n*-butyl group at C3 position. These practical syntheses have been accomplished starting from a common pyrrolidine **8**, which is readily available (4 steps) from natural (S)-proline. In terms of shortness and especially stereoselectivity, our strategy compares favorably with those previously reported.

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EXPERIMENTAL SECTION

General. Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF and Et₂O were distilled from Na-benzophenone ketyl immediately prior to use. CH₂Cl₂ was distilled from calcium hydride. All reactions involving organometallic reagents were carried out under an argon atmosphere. The 1-lithiopent-4-ene was prepared from 5-bromopent-1-ene¹⁸ and lithium in Et₂O at -20°C (in *ca* 70% yield) and the concentration were typically between 0.6 and 0.8 M as determined by titration.¹⁹ Analytical TLC was performed on Merck precoated silica gel (60 F₂₅₄) plates and column chromatography on silica gel Geduran SI 60 (40–60 μm) (Merck). Optical rotations were measured on a digital polarimeter in a 1 dm cell. ¹H NMR spectra were recorded in CDCl₃ solution at 250 MHz and ¹³C NMR spectra in CDCl₃ solution at 62.9 MHz unless stated otherwise. ¹H chemical shifts are expressed relative to CHCl₃ at δ 7.27 and ¹³C chemical shifts relative to CDCl₃ at δ 77.1 ppm. When a carbamate moiety is present in a molecule two rotamers are observed in ¹H and ¹³C NMR. Mass spectra were recorded on a Varian (Saturn type) GC/MS (ion trap) instrument. Elemental analysis were performed by the Service Régional de Microanalyse de l'Université P. & M. Curie.

(5S)-2-Methoxy-1-[(benzyloxy)carbonyl]-5-methoxycarbonylpyrrolidine (5). A 150 mL undivided jacketed cell was charged with a magnetic stir-bar, 14.8 g (56.2 mmol) of (2S)-1-[(benzyloxy)carbonyl]-5-methoxycarbonylpyrrolidine, 50 mL of dry methanol and 0.61 g (2 mmol) of tetraethylammonium *p*-toluenesulfonate. Two graphite plates spaced 4 mm apart were immersed into the solution in order to have a working electrode surface of 20 cm². While the electrolysis cell temperature was maintained at -5°C, under inert atmosphere, a constant current of 0.5A (voltage 8–12V) was passed through the solution. Progress of the anodic oxidation was monitored by gas chromatography. After 5.5 F/mol have been passed through the solution, the electrolysis was stopped, and the reaction mixture was concentrated in *vacuum*. The resulting residue was dissolved in 80 mL of CH₂Cl₂ and washed with H₂O (2 x 20 mL). The combined aqueous phases were extracted with CH₂Cl₂ (20 mL) and the combined organic extracts dried over sodium sulfate. Filtration, concentration and purification of the residue by column chromatography (1:2 AcOEt/cyclohexane) gave 12.36 g (75%) of **5** as a pale yellow oil: IR (neat) 1730, 1700, 1580, 1490 cm⁻¹; ¹H NMR δ 1.75–2.50 (m, 4H), 3.26, 3.33, 3.42, 3.45, 3.49, 3.64, 3.73, 3.76 (8s, 2 OCH₃), 4.30–4.50 (m, 1H), 4.95–5.20 (m, 3H), 7.30–7.42 (m, 5H); ¹³C NMR δ 26.90, 27.95, 28.02, 30.00, 30.69, 32.06, 32.65, 51.87, 52.00, 52.11, 55.36, 55.65, 58.85, 58.91, 59.04, 59.15, 67.14, 67.36, 67.49, 88.60, 89.15, 89.79, 127.85, 127.89, 127.96, 128.29, 128.35, 135.96, 136.08, 157.76, 172.55, 172.70, 172.73.

(2S,5R)-1-[(Benzyloxy)carbonyl]-2-methoxycarbonyl-5-(pent-4-enyl)pyrrolidine (3). To a vigorously stirred suspension of CuBr.DMS (16.03 g, 78 mmol) in Et₂O (150 mL) was slowly added a solution of 1-lithiopent-4-ene (0.8 M in Et₂O, 97 mL, 77.6 mmol) *via* cannula at -50°C under an argon atmosphere. The resulting dark brown mixture was stirred for 30 min at -45 to -35°C, then cooled to -78°C. Boron trifluoride etherate (14.7 mL, 117 mmol) was added dropwise *via* syringe. After 15 min of stirring at the same temperature, a solution of α-aminoether **5** (11.47 g, 39 mmol) in Et₂O (20 mL) was slowly added *via* cannula under argon atmosphere, then the dark reaction mixture was allowed to attain ambient temperature over 4 to 5 h. The reaction was quenched at room temperature with a mixture of saturated aqueous NH₄Cl (40 mL) and concentrated aqueous ammonia (40 mL). The resulting mixture was vigorously stirred for 30 min then passed through a plug of celite eluting with CH₂Cl₂ (300 mL). The organic effluent was washed with water (30 mL), then dried over sodium sulfate. Filtration, concentration and purification of the residue by flash chromatography (1:2 AcOEt/cyclohexane) gave 10.31 g (79.5%) of **3** as a pale yellow oil: [α]_D²⁵ -72 (c = 1.08, MeOH); IR

(neat) 1730, 1700, 1650, 1590, 1490 cm^{-1} ; ^1H NMR δ 1.24–2.09 (m, 10H), 3.49 and 3.70 (2s, 3H), 3.92–4.09 (m, 1H), 4.34 (bt, $J = 8.6$ Hz, 1H), 4.90–5.20 (m, 4H), 5.62–5.89 (m, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR δ 25.66, 25.76, 27.32, 27.56, 28.22, 28.60, 33.23, 33.45, 33.63, 33.88, 51.90, 52.09, 57.93, 58.69, 59.36, 59.53, 66.69, 66.90, 114.59, 127.85, 128.33, 136.59, 138.32, 138.54, 154.17, 154.76, 173.01, 173.21; MS (EI) m/z (%) 272 ($\text{M}^+ - \text{CO}_2\text{Me}$, 6), 244 (4), 228 (22), 218 (17), 196 (14), 91 (100).

(2S,5R)-1-[(Benzyloxy)carbonyl]-2-hydroxymethyl-5-(pent-4-enyl)pyrrolidine (6). To a stirred cold (-5°C) suspension of anhydrous calcium chloride (1.91 g, 17.2 mmol) and sodium borohydride (1.3 g, 34.8 mmol) in dry THF (20 mL) was added a solution of **3** (2.85 g, 8.6 mmol) in dry ethanol (24 mL) under an argon atmosphere. The resulting suspension was stirred for 18 h at -5°C and then concentrated under *vacuum*. To the pasty residue was added ethyl acetate (50 mL), then under stirring 1M aqueous citric acid solution was carefully added at 0°C until the precipitate disappeared. The mixture was extracted with ethyl acetate (5 x 20 mL). The combined extracts were washed with aqueous saturated NaHCO_3 (2 x 20 mL), brine (1 x 20 mL), dried over sodium sulfate, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (1:1 AcOEt/cyclohexane) gave 0.26 g (9.9%) as a mixture of alcohol **6** and its *cis* isomer, and 1.92 g (73.6%) of pure *trans* **6** as colorless oils: $[\alpha]_D^{22} -67$ ($c = 1$, MeOH); IR (neat) 3460, 1690, 1600, 1510, 1460 cm^{-1} ; ^1H NMR δ 1.19–1.42 (m, 4H), 1.53–1.80 (m, 2H), 1.80–2.20 (m, 4H), 3.69 (m, 3H), 3.83 (m, 1H), 4.06 (m, 1H), 4.83–5.25 (m, 4H), 5.60–5.85 (m, 1H), 7.36 (bs, 5H); ^{13}C NMR δ 26.36, 26.59, 27.02, 27.40, 28.66, 31.97, 33.09, 34.10, 34.31, 59.29, 59.40, 60.75, 66.47, 66.87, 67.24, 67.72, 115.14, 115.32, 128.60, 129.09, 137.03, 137.64, 138.99, 139.32, 155.14, 156.92. MS (CI, *i*-butane) m/z (%) 304 ($\text{M}+1^+$, 99), 286 (4), 272 (14), 260 (49), 236 (5), 225 (12), 196 (100), 168 (4), 152 (5), 126 (12), 91 (19); Anal. Calcd. for $\text{C}_{18}\text{H}_{25}\text{NO}_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.07; H, 8.31; N, 4.49.

(2S,5R)-1-[(Benzyloxy)carbonyl]-2-tosyloxymethyl-5-(pent-4-enyl)pyrrolidine (7). A solution of alcohol **6** (2.70 g, 8.9 mmol) and *p*-toluenesulfonyl chloride (2.06 g, 10.8 mmol) in triethylamine (6.2 mL, 44.5 mmol) was stirred for 3 h under argon atmosphere. To achieve the hydrolysis of the excess of *p*-toluenesulfonyl chloride, water (40 mL) was added and the resulting mixture stirred for additional 3 h at room temperature then extracted with dichloromethane (5 x 10 mL). The combined extracts were washed with saturated aqueous NaHCO_3 (2 x 20 mL) and water (1 x 20 mL). The organic phase was dried over sodium sulfate, filtered and concentrated to give an oily residue, which was purified by flash chromatography (1:1 AcOEt/cyclohexane) to give 3.9 g (96%) of the tosylate **7** as a colorless solid: mp $38\text{--}40^\circ\text{C}$ (uncorrected); $[\alpha]_D^{21} -73$ ($c = 1$, MeOH); IR (neat) 1740, 1710, 1695, 1645, 1600, 1550, 1460 cm^{-1} ; ^1H NMR δ 1.25 (m, 3H), 1.65 (m, 1H), 1.69 (m, 6H), 2.35 and 2.36 (2s, 3H), 3.66–4.18 (m, 4H), 4.85–5.20 (m, 4H), 5.60–5.80 (m, 1H), 7.18–7.28 (m, 7H), 7.62 and 7.69 (2 bd, $J = 7.9$ Hz, 2H); ^{13}C NMR δ 20.98, 24.98, 25.26, 25.34, 25.86, 26.12, 30.89, 32.79, 32.94, 55.00, 55.64, 57.63, 58.21, 66.09, 66.87, 68.58, 68.98, 114.09, 114.18, 126.48, 127.29, 127.40, 129.11, 132.37, 132.52, 136.04, 136.13, 137.83, 138.01, 144.24, 144.36, 152.90, 153.60.

(2R,5R)-1-[(Benzyloxy)carbonyl]-2-butyl-5-(pent-4-enyl)pyrrolidine (8). To a stirred suspension of CuI (2.3 g, 12.1 mmol) in Et_2O (10 mL) was added a solution of *n*-propyllithium (0.77 M in Et_2O , 31.5 mL, 24.2 mmol) *via* cannula at -50°C under an argon atmosphere. The resulting dark brown solution was stirred for 30 min at -40 to -30°C before being cooled to -60°C . A solution of tosylate **7** (0.89 g, 1.9 mmol) in Et_2O (4 mL) was added, then the reaction mixture was allowed to warm to -20°C . After 36 h stirring at -20°C the reaction mixture was quenched at *ca* 0°C with a mixture of concentrated NH_4OH (20 mL) and saturated aqueous NH_4Cl (20 mL). The mixture was vigorously stirred for 30 min and extracted following the procedure described for compound **3**. Purification by flash chromatography (1:2 Et_2O /pentane) gave 0.48 g (75%) of the 2,5-dialkylpyrrolidine **8** as a colorless oil: $[\alpha]_D^{20} -78$ ($c = 1$, MeOH); IR (neat) 1700, 1650, 1460, 1410 cm^{-1} ; ^1H NMR δ 0.84 and 0.89 (2 t, $J = 5.1$ Hz, 3H), 1.09–1.31 (m, 7H), 1.57–1.67 (m, 4H), 1.80–2.17 (m, 5H) 3.67–3.90 (m, 2H), 4.70–4.99 (m, 2H), 5.07 (ABq, $J = 16$ Hz, 1H), 5.20 (ABq, $J = 16$ Hz, 1H), 5.77–6.01 (m, 1H), 7.37–7.65 (m, 5H); ^{13}C NMR δ 13.82, 13.94, 22.38, 22.53, 25.84, 26.54, 27.51, 28.66, 32.14, 57.42, 57.54, 57.90,

58.01, 66.19, 114.31, 114.39, 127.63, 127.79, 128.20, 137.70, 137.97, 138.33, 138.55, 154.07; Anal. Calcd. for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.36; H, 9.68; N, 4.10.

(2R,5R)-2-Butyl-5-pentylpyrrolidine [(-)-Pyrrolidine 197B] (9). To a solution of 1-[(benzyloxy)carbonyl]-2-butyl-5-(pent-4-enyl)pyrrolidine **8** (20 mg, 0.06 mmol) in methanol (2 mL) was added 10% Pd/C (20 mg) and the resulting mixture stirred under hydrogen atmosphere for 30 min. The reaction mixture was passed through a plug of celite eluting with Et_2O (40 mL) and the effluent was concentrated under *vacuum* (at 20 mm Hg, *bath temperature below 30°C*). The residue was purified by flash chromatography [10:1 $CHCl_3/(MeOH/NH_4OH$ 95:5)] to give 11 mg (92 %) of (-)-pyrrolidine **197B** (**9**): $[\alpha]^{21}_D$ -6.3 ($c = 0.72$, $CHCl_3$) [lit.¹³ $[\alpha]^{27}_D$ -5.8 ($c = 0.61$, $CHCl_3$)]; IR (neat) 3350, 2960, 2920, 2860, 1640, 1530, 1460 cm^{-1} ; 1H NMR δ 0.85 (t, $J = 6.9$ Hz, 3H), 0.87 (t, $J = 6.9$ Hz, 3H), 1.15–1.54 (m, 16H), 1.84–2.00 (m, 2H), 2.03–2.19 (m, 1H), 3.04–3.18 (m, 2H); ^{13}C NMR δ 14.14 (2C), 22.72, 22.91, 27.05, 29.55, 32.07, 32.45 (2C), 36.68, 36.95, 58.15 (2C); MS (EI) m/z (%) 196 (3), 152 (21), 138 (100); MS (CI, NH_3) m/z 198 ($M+1^+$, 100).

(2R,5R)-1-[(Benzyloxy)carbonyl]-2-butyl-5-(4-oxopentyl)pyrrolidine (10). Oxygen was bubbled during 1 h in a suspension of bis(benzonitrile)dichloropalladium (56 mg, 0.14 mmol) and CuCl (14 mg, 0.14 mmol) in 15 mL of DMF/ H_2O (7/1) mixture at 60°C. A solution of substrate **8** (0.48 g, 1.45 mmol) in 5 mL of DMF/ H_2O (7/1) mixture was added. After 3 days of oxygen bubbling at 60°C, aqueous solution of HCl (3M, 15 mL) was added at room temperature and the mixture extracted with Et_2O (3 x 10 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and dried over Na_2SO_4 . After filtration and concentration, the brown oily residue was subjected to purification by flash chromatography on silica gel (1:1 AcOEt/cyclohexane) to give 0.39 g (77 %) of **10** as a colorless oil: $[\alpha]^{22}_D$ -64 ($c = 1$, $CHCl_3$) [lit.⁵ $[\alpha]^{23}_D$ -63 ($c = 0.94$, $CHCl_3$)]; IR (neat) 1720, 1690, 1590, 1490 cm^{-1} ; 1H NMR δ 0.83 and 0.89 (2t, $J = 6.5$ Hz, 3H), 1.25 (m, 6H), 1.58 (m, 5H), 1.96 (m, 3H), 2.03 and 2.12 (2s, 3H), 2.25 (m, 1H), 2.45 (m, 1H), 3.63–3.90 (m, 2H), 5.02 and 5.25 (ABq, $J = 12.5$ Hz, 2H), 7.20–7.43 (m, 5H); ^{13}C NMR δ 13.92; 14.04, 20.53, 22.46, 22.60, 26.62, 27.57, 28.72, 29.87, 31.99, 32.19, 33.45, 33.54, 43.14, 43.33, 57.22, 57.71, 58.16, 66.34, 127.82, 128.01, 128.35, 137.00, 154.09, 154.25, 208.39, 208.77.

(3R,5R,8aR)-3-Butyl-5-methyloctahydroindolizidine [(-)-Indolizidine 195B] (1a). A slurry of **8** (0.36 g, 1.04 mmol) and Pd/ $BaSO_4$ (19 mg) in MeOH (5 mL) was stirred under 1 atmosphere of hydrogen for 30 min. Filtration of the mixture through a plug of celite, washing with Et_2O (40 mL) and concentration (*below 30°C at 20 mm Hg*) gave a brown oily residue which contain indolizidine (-) **1a** and its C-5 epimer in an 86:14 ratio (by GC). Purification by flash chromatography on Al_2O_3 (1:3 $CHCl_3$ /hexane) gave 30 mg (14%) as a diastereomeric mixture and 164 mg (81%) of pure (-) **1a**: $[\alpha]^{22}_D$ -99 ($c = 0.21$, MeOH) [lit.^{5,15} $[\alpha]^{24}_D$ -101.3 ($c = 0.15$, MeOH)]; 1H NMR (200 MHz) δ 0.87 (t, $J = 7.2$ Hz, 3H), 0.97–1.98 (m, 19H, including d at 1.07, $J = 6.4$ Hz, 3H), 2.24–2.43 (m, 2H), 3.16–3.33 (m, 1H); ^{13}C NMR (50 MHz) δ 14.29, 20.55, 23.09, 24.80, 24.93, 26.40, 29.27, 30.11, 32.51, 34.64, 52.01, 58.81, 59.01; MS (EI) m/z (%) 195 (M^+ , 24), 180 (57), 166 (10), 152 (30), 138 (100); HRMS Calcd. for $C_{13}H_{25}N$: 195.1887, Found 195.1987.

(2R,5R)-1-[(Benzyloxy)carbonyl]-2-butyl-5-(4,5-epoxypentyl)pyrrolidine (11). To a cooled (ice bath) solution of **8** (1.33 g, 4.04 mmol) in CH_2Cl_2 (5 mL) and 5 mL of phosphate buffer (Na_2HPO_4/NaH_2PO_4 , pH = 8) was slowly added *m*-chloroperbenzoic acid (1.4 g, 8.08 mmol). The resulting solution was allowed to warm to room temperature, stirred for an additional 3 h period then extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were washed with saturated aqueous Na_2CO_3 (5 mL), brine (5 mL) and dried over Na_2SO_4 . Filtration, concentration and purification of the oily residue by flash chromatography (2:1 Et_2O /pentane) gave 0.97 g (69%) of **11** (diastereomeric mixture) as a pale yellow oil: IR (neat) 1720, 1710, 1690, 1560, 1525, 1480, 1440 cm^{-1} ; 1H NMR δ 0.81 and 0.88 (2t, $J = 6.7$ Hz, 3H), 1.12–1.88 (m, 16H), 2.30–2.41 (m, 1H), 2.60–2.88 (m, 2H), 3.68–3.73 (m, 2H), 4.98 and 5.12 (ABq, $J = 12.2$ Hz, 2H), 7.27–7.34 (m, 5H); ^{13}C NMR δ 13.92, 14.05, 22.44, 22.60, 22.85, 23.01, 23.16, 26.57, 27.52, 28.72, 32.04, 32.16, 32.50, 33.51, 33.76, 47.08, 51.98, 52.35, 57.36,

57.46, 57.70, 57.82, 66.44, 127.85, 127.97, 128.33, 136.87, 154.25, 154.35. Anal. Calcd. for $C_{21}H_{31}NO_3$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.03; H, 9.16; N, 3.94.

(2R,5R)-1-[(Benzyloxy)carbonyl]-2-butyl-5-(4-hydroxyheptyl)pyrrolidine (12). To a stirred suspension of CuI (13 mg, 0.07 mmol) in Et_2O (5 mL) was added a solution of ethylmagnesium bromide (2.5 M in Et_2O , 4 mL, 10 mmol) *via* a syringe at $-15^\circ C$ under an argon atmosphere. To the resulting solution, cooled to $-40^\circ C$ was added dropwise a solution of epoxide **11** (1 g, 2.89 mmol) in Et_2O (5 mL). After 2 h stirring at $-15^\circ C$, the reaction mixture was quenched with aqueous solution of HCl (5 mL, 1M) and extracted with Et_2O (2 x 10 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried over Na_2SO_4 . Filtration, concentration, then purification of the residue by flash chromatography on silica gel (2:1 Et_2O /pentane) gave 0.79g (73%) of alcohol **12** as a colorless oil: IR (neat) 3430, 1680, 1590, 1500, 1450 cm^{-1} ; 1H NMR δ 0.75-0.84 (m, 6H), 1.12-1.87 (m, 21H), 3.35-3.70 (m, 3H), 4.99 and 5.12 (ABq, $J = 12.4$ Hz, 2H), 7.19-7.28 (m, 5H); ^{13}C NMR δ 14.02, 14.16, 18.84, 22.39, 22.54, 22.70, 23.02, 26.53, 27.51, 28.82, 32.02, 32.27, 33.60, 33.85, 34.10, 36.25, 37.21, 39.72, 40.30, 57.29, 57.79, 58.04, 58.22, 66.45, 70.66, 71.39, 127.87, 127.95, 128.44, 137.04, 154.39, 154.41. Anal. Calcd. for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.39; H, 9.82; N, 3.85.

(2R,5R)-1-[(Benzyloxy)carbonyl]-2-butyl-5-(4-oxoheptyl)pyrrolidine (13). To a stirred suspension of pyridinium dichromate (1.53 g, 4.07 mmol), in CH_2Cl_2 (5 mL), was added a solution of alcohol **12** (0.61 g, 1.62 mmol) in CH_2Cl_2 (3 mL). The dark mixture was stirred at room temperature for 30 h, then diluted with Et_2O (20 mL). The resulting dark slurry was filtered through a pad of celite, and washed with Et_2O (60 mL). The combined filtrates were washed with brine (10 mL), dried over Na_2SO_4 . Filtration, concentration and purification of the residue by flash chromatography on silica gel (2:1 Et_2O /pentane) gave 0.52 g (86%) of ketone **13** as a colorless oil: $[\alpha]_D^{22} -60$ ($c = 1$, $CHCl_3$) [lit.⁵ $[\alpha]_D^{26} -58.5$ ($c = 1$, $CHCl_3$)]; IR (neat) 1690, 1500, 1450, 1400, 1350 cm^{-1} ; 1H NMR δ 0.77-0.92 (m, 6H), 1.15-2.98 (m, 16H), 2.21-2.36 (m, 4H), 3.64-3.82 (m, 2H), 4.98 and 5.11 (ABq, $J = 12.5$ Hz, 2H), 7.26-7.31 (m, 5H); ^{13}C NMR δ 13.81, 14.04, 14.18, 17.34, 20.63, 22.58, 22.73, 26.67, 27.64, 28.84, 32.03, 33.62, 42.36, 42.52, 44.83, 57.36, 57.82, 58.26, 66.44, 127.93, 128.09, 128.46, 137.12, 154.54, 211.33; MS (CI, *i*-Butane) m/z 374 ($M+1^+$, 100), 330 (8), 238 (20), 222 (9). Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.69; H, 9.37; N, 3.56.

(3R,5R,8aR)-3-Butyl-5-propyloctahydroindolizidine [(-)-indolizidine 223AB] (1b). A mixture of ketone **13** (1 g, 2.68 mmol) and 5% Pd/BaSO₄ (1 g) in MeOH (5 mL) was stirred under an atmosphere of hydrogen (1 atm). After 5 h stirring, the TLC monitoring showed no cyclization. The mixture was filtered through Celite, washed with MeOH (20 mL). After drying over Na_2SO_4 , the filtrate was submitted to the hydrogenation conditions in the presence of 5% Pd/C (1 g). Workup and purification as for **1a** gave 0.24 g (40%) of pure **1b** as a volatile colorless oil: $[\alpha]_D^{22} -97$ ($c = 0.81$, hexane) [lit.^{5,16} $[\alpha]_D^{20} -101$ ($c = 2.3$, hexane)]; IR (neat) 2960, 2930, 2850, 2800, 1460, 1380 cm^{-1} ; 1H NMR δ 0.85-0.92 (m, 6H), 0.97-1.91 (m, 20H), 2.31-2.38 (m, 2H), 3.20 (bt, $J = 9.2$ Hz, 1H); ^{13}C NMR δ 14.25, 14.60, 19.38, 23.03, 24.73, 24.99, 26.40, 29.19, 30.12, 31.02, 32.47, 35.94, 56.63, 58.54, 59.02; MS (EI) m/z : 224 ($M+1^+$, 7), 180 (95), 166 (100), 124 (37). Anal. Calcd. for $C_{15}H_{29}N$: C, 80.64; H, 13.09; N, 6.27. Found: C, 80.50; H, 12.98; N, 6.19.

(2R,5R)-1-[(Benzyloxy)carbonyl]-2-butyl-5-(4-hydroxyhept-6-enyl)pyrrolidine (14). To a cold ($-20^\circ C$) suspension of CuI (10 mg, 0.05 mmol) in THF (5 mL), was added a solution of vinylmagnesium bromide (1 M in THF, 10 mL, 10 mmol) *via* a syringe under an argon atmosphere. The resulting mixture was stirred for 5 min, then cooled to $-40^\circ C$ before adding a solution of epoxide **11** (0.69 g, 2 mmol) in THF (3 mL). The reaction mixture was allowed to warm to $-20^\circ C$ and stirred for 2 h at this temperature before being quenched with aqueous solution of HCl (1 M, 5 mL) and extracted with Et_2O (4 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated under *vacuum*. Purification of the residue by flash chromatography (2:1 Et_2O /pentane) gave 0.66 g (88%) of alcohol **14** as a pale yellow oil: IR (neat) 3410,

1680, 1590, 1500, 1410 cm^{-1} ; ^1H NMR δ 0.75 and 0.82 (t, J = 6.9 Hz, 3H), 1.09–2.35 (m, 19H), 3.42–3.88 (m, 3H), 4.99–5.25 (m, 4H), 5.68–5.90 (m, 1H), 7.29–7.39 (m, 5H); ^{13}C NMR δ 13.95, 14.09, 22.32, 22.48, 22.64, 22.78, 26.57, 26.65, 27.54, 28.75, 32.25, 32.38, 33.58, 33.80, 34.00, 36.36, 36.50, 41.95, 42.11, 57.43, 57.69, 57.92, 58.13, 66.35, 70.35, 117.63, 117.76, 117.90, 127.79, 127.86, 127.94, 128.35, 134.80, 135.04, 137.02, 154.18, 154.20. Anal. Calcd. for $\text{C}_{23}\text{H}_{35}\text{NO}_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.59; H, 9.69; N, 3.46.

(2R,5R)-1-[(Benzyloxy)carbonyl]-2-butyl-5-(4,7-dihydroxyheptyl)pyrrolidine (15). To a cold (ice bath) solution of homoallylic alcohol **14** (0.66 g, 1.77 mmol) in dry Et_2O (5 mL) was added dropwise $\text{BH}_3\cdot\text{SMe}_2$ (2 M in THF, 0.59 mL, 1.18 mmol) and the solution was stirred for 3 h at room temperature before addition of EtOH (2 mL) and aqueous NaOH (3 M, 0.3 mL). After addition of 0.3 mL of H_2O_2 (33%) at 0°C the reaction mixture was heated at reflux for 1 h. To the cooled solution (0°C) was added cold water (10 mL) and the mixture was extracted with Et_2O (3 x 10 mL). The combined extracts were washed with water (2 x 10 mL), brine (10 mL) and dried over Na_2SO_4 . Filtration, concentration and purification of the residue by flash chromatography (2:1 AcOEt/cyclohexane) gave 0.57 g (82%) of diol **15** as a pale yellow oil: IR (neat) 3400, 1700, 1680, 1595, 1500, 1460, 1410 cm^{-1} ; ^1H NMR δ 0.64–0.81 (m, 3H), 0.95–2.20 (m, 22H), 3.39–3.88 (m, 5H), 5.03 and 5.15 (ABq, J = 12.4 Hz, 2H), 7.19–7.27 (m, 5H); ^{13}C NMR δ 14.02, 14.16, 22.54, 22.71, 22.84, 26.75, 27.60, 28.82, 29.06, 29.19, 32.29, 32.41, 33.59, 33.92, 34.10, 34.51, 37.15, 57.80, 58.06, 58.23, 62.84, 66.41, 66.50, 71.11, 71.36, 127.91, 128.43, 136.94, 137.11, 154.31, 154.48. Anal. Calcd. for $\text{C}_{23}\text{H}_{37}\text{NO}_4$: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.60; H, 9.51; N, 3.74.

(2R,5R)-1-[(Benzyloxy)carbonyl]-5-butyl-2-(4-hydroxy-7-benzoyloxyheptyl)pyrrolidine (16). To a cooled (-40°C) solution of diol **15** (0.57 g, 1.46 mmol) in dry CH_2Cl_2 (5 mL) was added benzoyl chloride (0.15 mL, 1.46 mmol) and pyridine (0.12 mL, 1.46 mmol) under an argon atmosphere. The resulting solution was stirred at -40°C for 3 h and additional 18 h at room temperature. To the mixture was added CH_2Cl_2 (5 mL) and aqueous HCl (1 M, 2 mL). The organic phase was washed with saturated aqueous NaHCO_3 (3 mL), water (3 mL) and dried over Na_2SO_4 . Filtration, concentration and purification of the residue by flash chromatography (1:1 AcOEt/cyclohexane) gave 0.52 g (72%) of benzoate **16** as a yellow oil: IR (neat) 3430, 1720, 1690, 1600, 1500, 1450, 1410 cm^{-1} ; ^1H NMR δ 0.75 and 0.78 (2t, J = 6.6 Hz, 3H), 1.00–1.97 (m, 21H), 3.53–3.74 (m, 3H), 4.25–4.30 (m, 2H), 4.97 and 5.11 (bABq, J = 12.5 Hz, 2H), 7.21–7.28 (m, 5H), 7.36 (bt, J = 7.7 Hz, 2H), 7.47 (bt, J = 6.3 Hz, 1H), 7.96 (d, J = 5.1 Hz, 2H); ^{13}C NMR δ 14.02, 14.16, 22.53, 22.55, 22.57, 25.11, 26.78, 26.80, 27.63, 28.82, 32.29, 32.49, 33.61, 33.82, 33.84, 37.21, 57.78, 57.93, 58.21, 65.06, 66.42, 71.14, 127.92, 128.38, 129.56, 130.38, 132.87, 137.23, 137.24, 154.68, 154.70, 166.67, 166.69. Anal. Calcd. for $\text{C}_{30}\text{H}_{41}\text{NO}_5$: C, 72.69; H, 8.34; N, 2.83. Found: C, 72.86; H, 8.50; N, 2.74.

(2R,5R)-1-[(Benzyloxy)carbonyl]-2-butyl-5-(4-oxo-7-benzoyloxyheptyl)pyrrolidine (17). Following the procedure employed for the oxidation of **12**, alcohol **16** (0.49 g, 1 mmol) gave, after purification by flash chromatography (1:1 AcOEt/cyclohexane), 0.47 g (96%) of ketone **17** as a pale yellow oil: $[\alpha]_{\text{D}}^{18}$ -54 (c = 1.0, MeOH); IR (neat) 1700, 1600, 1580, 1500, 1490, 1450, 1400 cm^{-1} ; ^1H NMR δ 0.74 and 0.82 (2bt, J = 6.9 Hz, 3H), 0.95–2.01 (m, 17H), 2.18–2.52 (m, 3H), 3.55–3.78 (m, 2H), 4.23–4.25 (m, 2H), 4.97 and 5.10 (ABq, J = 12.4 Hz, 2H), 7.26 (m, 5H), 7.37 (bt, J = 7.3 Hz, 2H), 7.47 (bt, J = 6.5 Hz, 1H), 7.95 (d, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.06, 14.08, 20.56, 22.53, 22.69, 22.87, 26.66, 27.60, 28.79, 32.05, 32.25, 33.57, 39.06, 42.43, 42.59, 57.25, 57.76, 58.23, 64.19, 66.43, 127.89, 128.04, 129.56, 130.02, 133.85, 137.01, 154.33, 155.16, 166.53, 209.42, 209.79. Calcd. for $\text{C}_{30}\text{H}_{39}\text{NO}_5$: C, 72.99; H, 7.96; N, 2.84. Found: C, 72.90; H, 8.03; N, 2.86.

(3R,5S,8aR)-3-Butyl-5-(3-benzoyloxypropyl)octahydroindolizidine (18). According to the procedure described for **1a** and **1b**, treatment of **17** (400 mg, 0.81 mmol) with 10% Pd/C (400 mg) under hydrogen atmosphere in MeOH (5 mL), gave a mixture of indolizidine **18** and its C-5 epimer in a 87:13 ratio. Purification by flash chromatography [9:1 CHCl_3 /(MeOH/ NH_4OH 20:1)] provided 25 mg (9%) as a mixture of epimers and 230 mg (82%) of pure **18** as colorless oils: $[\alpha]_{\text{D}}^{22}$ -37 (c = 0.72, MeOH); IR (neat) 2930, 2860, 2790, 1720,

1600, 1580, 1450 cm^{-1} ; ^1H NMR δ 0.81 (t, $J = 6.7$ Hz, 3H), 0.84–2.06 (m, 20H), 2.31–2.56 (m, 2H), 3.17–3.32 (m, 1H), 4.31 (t, $J = 5.8$ Hz, 2H), 7.38 (bt, $J = 7.2$ Hz, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 8.01 (dd, $J = 7.4$, 0.9 Hz, 2H); ^{13}C NMR δ 14.27, 23.05, 24.58, 24.98, 25.17, 26.37, 29.19, 30.00 (2C), 30.78, 32.26, 56.35, 58.61, 59.06, 65.25, 128.36, 129.57, 130.42, 132.90, 166.68.

(3R,5S,8aR)-3-Butyl-5-(3-hydroxypropyl)octahydroindolizidine [(-) Indolizidine 239AB, (-) 1c]. A solution of indolizidine **18** (0.20 g, 0.58 mmol) in MeOH (2 mL) was added to a freshly prepared solution of sodium methoxide (1M in MeOH, 3 mL, 3 mmol) and stirred for 10 min at room temperature. Methanol was removed under reduced pressure and brine (5 mL) was added to the residue. Extraction of the mixture with Et_2O (2 x 10 mL), drying of the combined organic layers over Na_2SO_4 , filtration, concentration and purification by flash chromatography [9:1 $\text{CHCl}_3/(\text{MeOH}/\text{NH}_4\text{OH}$ 20:1)] gave 120 mg (86%) of (-) indolizidine 239AB (**1c**) as a colorless oil: $[\alpha]_D^{20} -95$ ($c = 0.35$, MeOH), $[\text{lit}^5 [\alpha]_D^{25} -87.5$ ($c = 0.16$, MeOH); $\text{lit}^{17} [\alpha]_D^{21} -96$ ($c = 0.14$, MeOH)]; IR (neat) 3450, 2940, 2860, 2790, 1450 cm^{-1} ; ^1H NMR δ 0.89 (t, $J = 7.2$ Hz, 3H), 1.01–2.05 (m, 21H), 2.34–2.51 (m, 1H), 2.54 (bsext, $J = 4.2$ Hz, 1H), 3.29 (bt, $J = 8.8$ Hz, 1H), 3.50 (dt, $J = 11.4$, 3.1 Hz, 1H), 3.65 (dt, $J = 11.4$, 4.3 Hz, 1H); ^{13}C NMR δ 14.24, 22.94, 24.37, 25.09, 26.01, 27.89, 28.94, 29.07, 29.64, 30.64, 31.32, 55.25, 58.69, 59.39, 63.12; MS(EI) m/z (%) 240 ($\text{M}+1^+$, 100), 182 (92), 124 (21); MS (CI, NH_3) m/z (%) 240 ($\text{M}+1^+$, 100).

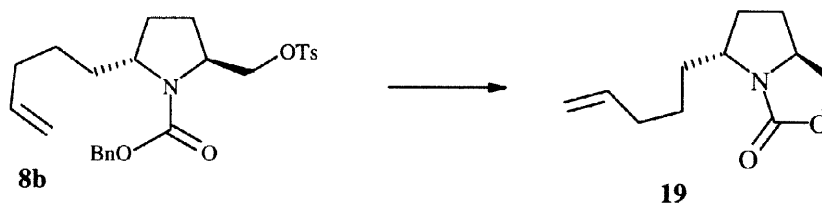
(2S, 5R)-5-(4-pentenyl)-tetrahydro-pyrrolo[1,2-c]oxazol-3-one (19). Obtained as byproduct during the reduction of **3** or tosylation of **6**: $[\alpha]_D^{26} -64$ ($c = 1$, MeOH); IR (neat) 1750, 1640 cm^{-1} ; ^1H NMR δ 1.40 (m, 6H), 2.02 (m, 3H), 2.20 (m, 1H), 3.60–3.91 (m, 2H), 4.09 (dd, $J = 3.1$, 8.8 Hz, 1H), 4.42 (dd, $J = 7.9$, 8.8 Hz, 1H), 4.85–4.98 (m, 2H), 5.64–5.78 (m, 1H); ^{13}C NMR δ 25.58, 31.29, 32.65, 33.32, 35.86, 58.61, 58.84, 67.27, 114.48, 138.43, 161.65. Anal. Calcd. for $\text{C}_{11}\text{H}_{17}\text{NO}_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.57; H, 8.85; N, 7.15.

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