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A short and modular approach towards 3,5-disubstituted indolizidine alkaloids†

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3,5-Dialkyl indolizidines have been prepared in four linear steps from commercially available starting materials. The sequence involves two direct α -functionalization steps and a subsequent reductive amination and provides diastereoselective access to both C-3 epimers of the 5,9-*trans*-substituted indolizines. The naturally occurring indolizidines **195B** and **223AB** have been synthesized using this methodology.

Introduction

The indolizidine framework is part of a large number and variety of natural products which occur in microorganisms, plants, terrestrial animals, as well as marine creatures.¹ Indolizidine alkaloids from terrestrial animals were essentially isolated from arthropods, *i.e.* ants and mites, as well as amphibians,^{2,3} the latter of which supposedly consume them *via* their arthropod prey (“dietary hypothesis”).⁴ An important class of these indolizidine alkaloids represented by at least 30 compounds, are the 3,5-disubstituted indolizidines, among which (+)-monomorine I (**1**, Fig. 1), a trail pheromone of the pharaoh ant, has received particular attention.^{2,5} Numerous synthetic approaches towards this class of alkaloids have been reported, most of which target a 5,9-*cis*-geometry, in

which the residues at C-5 and C-9 occupy the same face of the molecule in a *syn*-fashion.^{6–14} This is certainly due to the more frequent occurrence of this relative configuration in nature. There are, however, also several examples of natural indolizidines featuring a 5,9-*trans* (*anti*-relation at C-5 and C-9) substitution (Fig. 1),² and only a few synthetic methods selectively accessing this configuration have been reported so far.^{15–18} We herein report a four step modular access towards 3,5-disubstituted indolizidines, selectively producing a 5,9-*trans* substitution pattern. The developed route was applied to the synthesis of the naturally occurring 5,9-*trans*-dialkyl-indolizidines **195B** and **223AB**. In this way the (5*E*,9*Z*)-(**2a** and **3a**) as well as the (5*Z*,9*E*)-isomers (**2b** and **3b**) could be prepared.¹⁹

Results and discussion

Our retrosynthetic approach for the synthesis of 3,5-disubstituted indolizidines (**A**) is shown in Scheme 1. The strategy involves the sequential double α -alkylation of an *N*-protected piperidine with an iodoalkane and an enone through the α -lithio-derivatives resulting in 2,6-*trans*-disubstitution (**B**), followed by an intramolecular reductive amination to form the

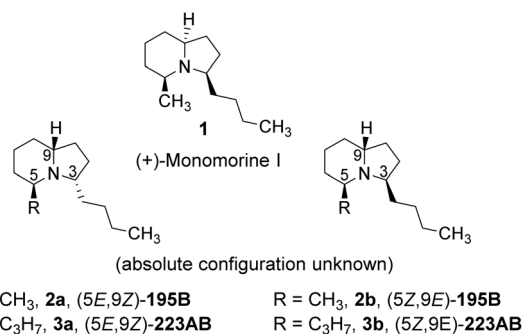
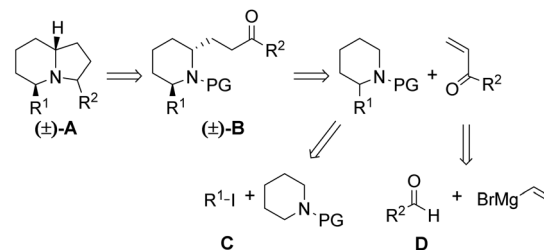


Fig. 1 Absolute stereostructure of (+)-monomorine I (**1**) and relative stereostructures of 5,9-*trans* indolizidines **195B** (**2a** and **2b**) and **223AB** (**3a** and **3b**).

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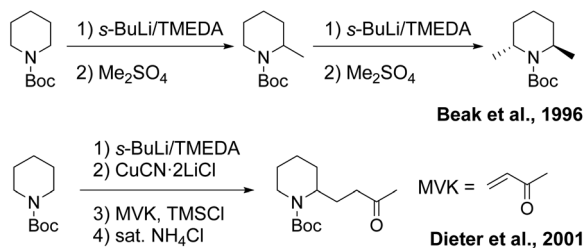
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Scheme 1 Retrosynthetic approach for the synthesis of 3,5-dialkylindolizidines.



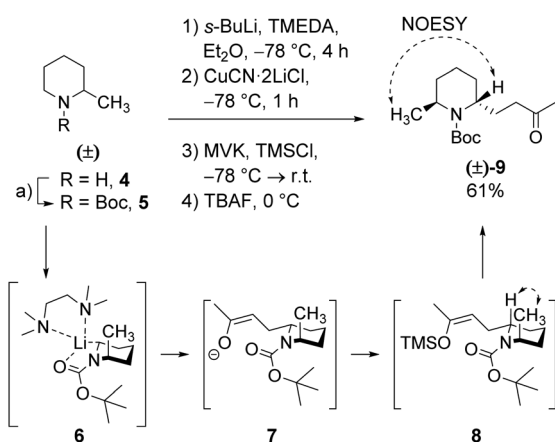


Scheme 2 Lithiation/alkylation reactions developed by Beak and Dieter.

bicyclic structure. This sequence would allow the formation of indolizidines bearing the desired substitution pattern, in which the substituents R^1 and R^2 are selected by the choice of iodoalkane **C** and the aldehyde **D** employed.

The consecutive α -lithiation/alkylation to form 2,6-disubstituted piperidines **B** has originally been developed by Beak and Hoppe and has been extensively applied since.^{20–22} The reaction was later extended by Dieter *et al.* who introduced a transmetalation to copper(i) for the monoalkylation, allowing the utilization of softer electrophiles such as iodoalkanes as well as Michael-acceptors in the subsequent alkylation step (Scheme 2).²³ Due to the inherent *trans*-selectivity of the second alkylation, the less common 2,6-*trans*-dialkylpiperidines and consequently the resulting 5,9-*trans*-indolizidines were expected to be the favored products of this sequence.²⁰

In search for a general protocol for the preparation of 3,5-dialkylindolizidines, we first focused on the model compound 3,5-dimethylindolizidine which should be accessible from commercially available 2-methylpiperidine and butenone (methyl vinyl ketone, MVK). The synthesis of the 2,6-*trans*-disubstituted piperidine **9** was achieved by a slightly modified protocol of Dieter *et al.*, as displayed in Scheme 3.²³ Deprotonation of the *N*-Boc-protected 2-methylpiperidine with *s*-BuLi in the presence of TMEDA leads to the formation of the intermediate complex **6**, which undergoes Michael-addition to the α,β -unsaturated ketone after transmetalation to copper(i).



Scheme 3 Synthesis of compound **9**. (a) Boc₂O, THF, 0 °C → r.t., 99%.

Due to steric hindrance imposed by the *tert*-butyl group in the complex **6**, the methyl group adopts an axial position, which leads to the above mentioned 2,6-*trans* configuration of the product. This was confirmed by a NOESY experiment which shows an intensive cross-peak between the protons of the methyl group at C-6 and the proton at C-2, which corresponds to a 1,3-diaxial arrangement of these substituents. The *cis*-isomer (**10**) shows no corresponding NOESY-contact as expected for an axial-equatorial arrangement of H-2 and CH₃-6. We observed that the stereoselectivity is highly dependent on the temperature at which the transmetalation is carried out, as well as on the addition-sequence of MVK and TMSCl (see Table 1). While the transmetalation at -50 °C (entry 1), as described by Dieter *et al.* for the monoalkylation, leads to diastereomeric ratios ranging from 2.6:1 to 6:1, a ratio of >95:5 was obtained, when all steps were carried out at -78 °C (entry 3). A ratio of 1.8:1 in favor of the *cis*-isomer was observed when the TMSCl was added 30 minutes after the addition of MVK (entry 2). This could be due to a configurational instability of the intermediate enolate **7** or to a low reactivity of the electrophile resulting in a configurational scrambling of the α -cuprated amine when no scavenger is present. Moreover, no reaction was observed, when the transmetalation-step was omitted (entry 4). It is noteworthy that this reaction exhibits a somewhat poor reproducibility and significant variations from one experiment to another can be observed in terms of yield and diastereomeric ratio. The same was reported by Dieter and coworkers for the corresponding reaction with unsubstituted *N*-Boc-piperidine. When the reaction parameters are thoroughly controlled, a satisfactory reproducibility can however be achieved and the dr is usually in excess of 95:5.

The conversion of **9** to the corresponding indolizidine was carried out by acidic deprotection with subsequent reductive amination *in situ* (Scheme 4).

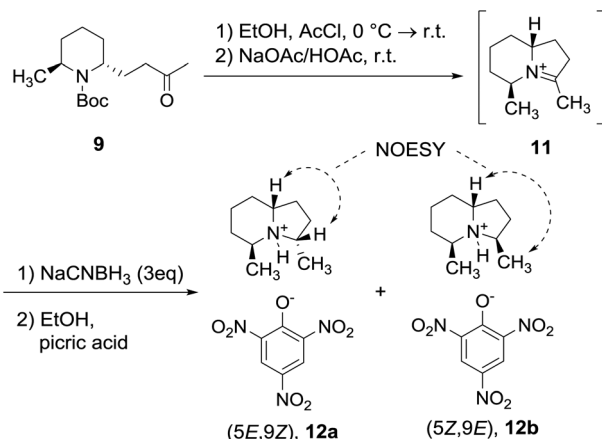
Addition of acetyl chloride to an ethanolic solution of **9** leads to the formation of HCl, which efficiently cleaved the

Table 1 Reaction conditions for the deprotonation/alkylation of **5** with MVK^a

Entry	T_t [°C]	t_A (min)	Yield [%]	dr (9 : 10) ^b
1	-50	0	42 ^c	2.6 : 1–6 : 1
2	-50	30	39 ^b	1 : 1.8
3	-78	0	61 ^c	>95 : 5
4 ^d	—	0	no conv.	—

^a (1) *s*-BuLi (1.3 eq.), TMEDA (2.2 eq.), Et₂O, -78 °C, 4 h, (2) CuCN·2LiCl (0.3 M in THF, 1 eq.), T_t , 1 h, (3) butenone (1 eq.), t_A, TMSCl (5 eq.), -78 °C–r.t. ^b Determined by ¹H-NMR-spectroscopy. ^c Isolated yield. ^d Reaction performed without the transmetalation step.

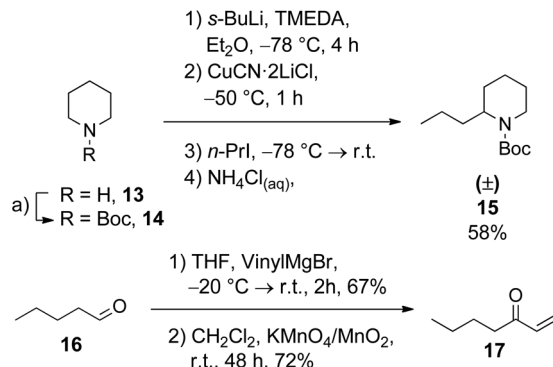




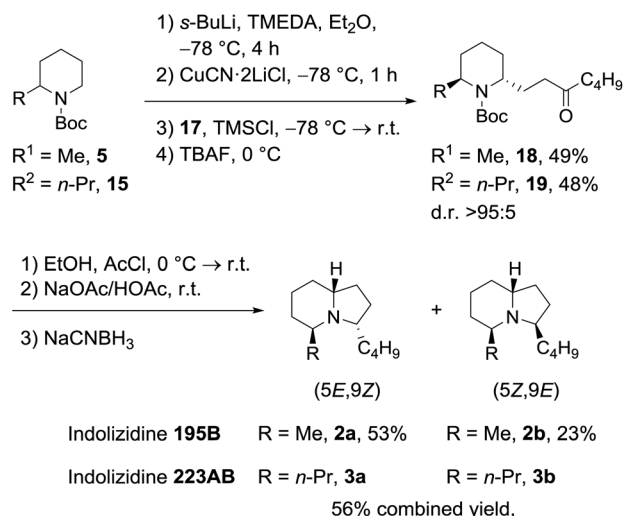
Scheme 4 Synthesis of 3,5-dimethyloctahydroindolizinium picrates **12a** and **12b**.

Boc-protecting group. Subsequent adjustment to pH 4–5 by addition of an acetate buffer facilitated the cyclization to the iminium ion **11**, which could be monitored *via* LC-MS. The reduction to the tertiary amine was achieved by addition of sodium cyanoborohydride. Due to the high volatility of the tertiary amine, an isolation on a small scale was somewhat troublesome, hence crystallization as the picrate salt was performed. In this way, the indolizidine was isolated in 55% yield as a 1:1.2 mixture of the two C-3 epimers. The relative configuration could again be determined by NOESY-experiments which showed intensive cross-peaks between the proton at C-9 and the proton ((*5E,9Z*), **12a**) or the methyl group ((*5Z,9E*), **12b**) at C-3, respectively. Switching of the reducing agent to sodium triacetoxyborohydride surprisingly did not lead to the reduction of the intermediate iminium ion while upon treatment with hydrogen and Pd/C, only an incomplete conversion and a yield of 13% were obtained.

The optimized reaction sequence was then applied to the synthesis of (*5E,9Z*)- and (*5Z,9E*)-indolizidines **195B** (**2a**, **2b**) and **223AB** (**3a**, **3b**). The starting materials required for the desired substitution patterns of the indolizidines were prepared according to known procedures (Scheme 5). Boc-2-propylpiperidine (Boc-coniine, **15**) was obtained in 58% yield similarly to **9** by a deprotonation/alkylation sequence of Boc-piperidine (**14**) with 1-iodopropane, based on a procedure described by Pizzuti *et al.* (Scheme 5).²⁴ Hept-1-en-3-one (**17**) was prepared in two steps *via* a Grignard addition with subsequent oxidation from valeraldehyde (**16**) and vinyl magnesium bromide.^{25,26} Deprotonation of the 2-substituted *N*-Boc-piperidines **5** and **15** with subsequent Michael-addition to hept-1-en-3-one (**17**) selectively furnished the respective 2,6-*trans*-disubstituted piperidines **18** and **19** in 49% and 48% yield (Scheme 6). The 2,6-*trans*-configuration could again be verified by NOESY. Reductive amination with sodium cyanoborohydride produced the two C-3 epimers of indolizidines **2** and **3** in 78% and 56% combined yield, respectively.



Scheme 5 Synthesis of Boc-coniine (**15**) and hept-1-en-3-one (**17**). (a) Boc₂O, DCM, r.t., 94%.



Scheme 6 Synthesis of (*5E,9Z*) and (*5Z,9E*) diastereomers of indolizidines **195B** (**2**) and **223AB** (**3**).

As for the model compound, the isolation and purification of these alkaloids was somewhat challenging due to the still substantial volatility of these compounds, as well as their sensitivity towards aerial oxygen. When a purification by crystallization as described for picrate salts **12a** and **12b** was attempted, no precipitation of the respective salts could be accomplished upon the addition of picric acid. The same applied to acetic acid, trifluoroacetic acid, as well as HBr and HCl. Although chromatographic purification could be achieved on an NH₂-functionalized silica gel, a successful separation of the two diastereomers was only achieved for indolizidines **2a** and **2b**. Chromatographic separation on silica gel or aluminum oxide as described in the literature was unsuccessful since no compound could be recovered from the column.^{27,28}

The NMR-spectra of the isolated compounds were in agreement with the literature and the relative configuration could thus easily be assigned.^{16,27–29} As for compound **12**, the (*5E,9Z*)-diastereomer was slightly favored in both cases over



the (5*Z*,9*E*)-diastereomer with selectivities of 2.3 : 1 and 1.7 : 1, respectively.

Conclusion

In summary, a highly modular synthetic protocol for the preparation of 3,5-dialkylindolizidines in only four linear steps from commercially available starting materials was developed. The nature of the two alkyl moieties is solely dependent on the alkyl iodide and aldehyde employed. The sequence involves two direct α -metalation steps of Boc-piperidine with a subsequent reductive amination. Due to the *trans*-selectivity of the second metalation, 5,9-*trans*-indolizidines were obtained selectively. To the best of our knowledge, no shorter access to this compound class bearing the indicated stereochemistry has been reported so far.

Experimental section

General methods

All reactions including air or moisture sensitive compounds were carried out under an inert atmosphere of argon in flame- or oven dried glassware. *sec*-Butyllithium was purchased in solution (1.3 M in cyclohexane/*n*-hexane 92/8) from a commercial supplier and titrated against *N*-benzylbenzamide prior to use.³⁰ All other reagents were reagent grade and used as purchased unless otherwise noted. The stated reaction temperatures refer to the temperature of the respective cooling bath. Melting points were determined in open capillary tubes using an electronic apparatus. NMR spectra were recorded on 300 MHz, 400 MHz or 600 MHz spectrometers equipped with a 5 mm BBFO probe head with *z*-gradient and ATM capability. Chemical shifts were referenced to the deuterated solvent (CDCl₃, δ = 7.26 ppm and 77.16 ppm for ¹H and ¹³C NMR, respectively) and reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ = 0.00 ppm).³¹ Coupling constants (*J*) are stated in Hz using the splitting abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Standard pulse sequences were used for the 2D experiments. FT-Infrared spectra were recorded using a diamond ATR unit. High-resolution mass spectrometry was executed on a QToF-Instrument with a dual electrospray source and a suitable external calibrant. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (60F₂₅₄) visualizing with UV-light and developing with an anisaldehyde solution (4.1 mL of *p*-anisaldehyde, 1.7 mL AcOH and 5.6 mL H₂SO₄ in 450 mL EtOH) or potassium permanganate solution (2.0 g KMnO₄ and 5.5 g NaCO₃ in 250 mL H₂O). Flash chromatography was carried out using the indicated solvent system on 35–70 μ m silica gel or KP-NH silica gel from Biotage.

General procedure for the preparation of CuCN·2LiCl solution

Lithium chloride (2.0 equiv.) was flame dried under vacuum at 140 °C for at least 4 h. Copper(I)-cyanide (1.0 equiv.) and THF (3.33 mL mol⁻¹, producing a 0.3 M solution) were added

under argon and the resulting mixture was stirred until all the solids had completely dissolved (usually about 1 h).

General procedure (A) for the Michael-addition of 2 substituted *tert*-butylpiperidine-1-carboxylates to enones

The respective 2-substituted *tert*-butylpiperidine-1-carboxylate (1.0 equiv.) was dissolved in dry Et₂O (3–5 mL mmol⁻¹) under argon and TMEDA (2.3 equiv.) was added. The resulting solution was cooled to –78 °C and *sec*-butyllithium (1.2–1.4 equiv.) was added dropwise. The solution was stirred for 4 h at –78 °C, after which a 0.3 M solution of CuCN·2LiCl in THF (3.3 mL mmol⁻¹, 1.0 equiv.) was added slowly. The resulting solution was stirred at –78 °C for 30 min. The respective enone (1.0 equiv.) and TMSCl (5.0 equiv.) were added dropwise and the resulting solution was warmed to ambient temperature overnight. To the resulting black solution was added TBAF (1 M in THF, 5.0 equiv.) at 0 °C and the mixture was stirred for 1 h. The mixture was filtered over a short plug of silica, eluting with hexanes/EtOAc (5 : 1), the solvents were removed under reduced pressure and the crude product was purified by silica gel column chromatography.

General procedure (B) for the synthesis of indolizidines *via* deblocking–reductive–amination sequence

The respective 2,6-disubstituted *tert*-butylpiperidine-1-carboxylate (1.0 equiv.) was dissolved in dry EtOH (*ca.* 5–15 mL mmol⁻¹) under an inert nitrogen atmosphere. The solution was cooled to 0 °C and acetyl chloride was added portion-wise, generating an ethanolic HCl-solution. Stirring was continued overnight until LC-MS indicated full conversion of the starting material. A 1 M aqueous solution of NaOAc/HOAc (*ca.* 50 mL mmol⁻¹) was added to adjust the pH to 4–5 and stirring was continued until LC-MS indicated complete formation of the Iminium-Ion (5–20 h). A portion of NaCNBH₃ (3–4 equiv.) was added every 12 h, until LC-MS indicated complete reduction of the Iminium Ion. 2 M HCl_(aq) (10 mL mmol⁻¹) was added and the emerging HCN was removed by a constant stream of nitrogen (CAUTION!!!). The solution was washed with EtOAc (2 × 20 mL mmol⁻¹) and the organic extracts were back-extracted with 2 M HCl_(aq) (2 × 5 mL mmol⁻¹). The combined aqueous phases were set to pH 10 by the addition of 2 M NaOH_(aq) and extracted with CH₂Cl₂ (6 × 15 mL mmol⁻¹). The combined organic extracts were dried over MgSO₄ and the solvent was evaporated at a minimum pressure of 500 mbar.

tert-Butyl 2-methylpiperidine-1-carboxylate (5)

Di-*tert*-butyl dicarbonate (10.68 g, 48.93 mmol, 1.0 equiv.) was dissolved in dry THF (50 mL) under argon at 0 °C. 2-Methylpiperidine (5.90 mL, 49.97 mmol, 1.0 equiv.) was added dropwise. The mixture was stirred at 0 °C for 30 min and then at ambient temperature overnight. The mixture was washed with sat. aq. NaHCO₃ (50 mL) and the aqueous phase extracted with Et₂O (3 × 50 mL). The combined organic extracts were washed with sat. aq. NaHCO₃, then brine (50 mL), dried over MgSO₄ and the solvent was evaporated under reduced pressure to yield 5 (9.69 g, 48.62 mmol, 99%) as a colorless oil. *R*_f = 0.23



(SiO₂, hexanes/EtOAc 20 : 1); IR (ATR) $\tilde{\nu}$ (cm⁻¹) = 2934, 1687, 1406, 1364, 1337, 1274, 1172, 1141, 1075, 770; ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 4.33–4.24 (m, 1H, 2-H), 3.83 (d, br, J = 13.1 Hz, 1H, CH_{2A}-6), 2.72 (td, J = 13.1, 2.8 Hz, 1H, CH_{2B}-6), 1.63–1.19 (m, 6H, 3-H, 4-H, 5-H), 1.37 (s, 9H, C(CH₃)₃), 1.04 (d, J = 7.0 Hz, 3H, CH₃-1'); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) = 155.2 (C=O), 79.1 (C(CH₃)₃), 46.2 (C-2), 38.8 (C-6), 30.2 (C-3), 28.7 (3C, C(CH₃)₃), 25.8 (C-5), 18.8 (C-4), 15.8 (CH₃). The analytical data are in accordance with the literature.³²

tert-Butyl piperidine-1-carboxylate (14)

Di-*tert*-butyl dicarbonate (3.70 g, 16.95 mmol, 1.0 equiv.) was dissolved in CH₂Cl₂ (50 mL) and piperidine (1.85 mL, 18.68 mmol, 1.1 equiv.) was added dropwise. The solution was stirred overnight and the solvent was removed under reduced pressure. Purification by bulb-to-bulb distillation (7 mbar, 150 °C) yielded **14** (2.96 g, 15.99 mmol, 94%) as a colorless oil. R_f = 0.67 (SiO₂, cyclohexane/EtOAc 5 : 1); IR (ATR) $\tilde{\nu}$ (cm⁻¹) = 2976, 2934, 2858, 1690, 1411, 1365, 1268, 1170, 1147; ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 3.36–3.32 (m, 4H, 2,6-H), 1.60–1.45 (m, 6H, 3,5-H; 4-H), 1.44 (s, 9H, CH₃); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) = 155.1 (C=O), 79.2 (C(CH₃)₃), 44.9 (br, C-2,6), 28.6 (3C, CH₃), 25.9 (C-3,5), 24.6 (C-4). The analytical data are in accordance with the literature.³²

Hept-1-en-3-one (17)

A solution of vinylmagnesium bromide (0.7 M, 50 mL, 35.00 mmol, 1.2 equiv.) was added to a solution of pentanal (3.20 mL, 29.74 mmol, 1.0 equiv.) in dry THF (50 mL) under argon at –20 °C. After complete addition, the cooling bath was removed and the mixture was allowed to warm to ambient temperature. After TLC indicated full consumption of the starting material (2 h), 1 M aq. HCl (60 mL) was added and stirring was continued for 10 min. The organic layer was separated and the aqueous phase was extracted with Et₂O (3 × 60 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and the solvents removed under reduced pressure (40 °C, 100 mbar). Purification by bulb-to-bulb distillation (10–20 mbar, 90–100 °C) yielded hept-1-en-3-ol (2.28 g, 19.97 mmol, 67%) as a colorless liquid. R_f = 0.21 (SiO₂, hexanes/EtOAc 5 : 1); IR (ATR) $\tilde{\nu}$ (cm⁻¹) = 3417, 2957, 2933, 2872, 2864, 1720, 1466, 1379, 1146, 962; ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 5.86 (ddd, J = 17.1, 10.4, 6.3 Hz, 1H, 2-H), 5.20 (d pseudo-t, J_d = 17.1, $J_{\text{pseudo-t}}$ ≈ 1 Hz, 1H, CH_{2A}-1), 5.09 (d pseudo-t, J_d = 10.4, $J_{\text{pseudo-t}}$ ≈ 1 Hz, 1H, CH_{2B}-1), 4.08 (pseudo-q pseudo-t, $J_{\text{pseudo-q}}$ ≈ 6 Hz, $J_{\text{pseudo-t}}$ ≈ 1 Hz, 1H, 3-H), 1.66 (s br, 1H, OH), 1.57–1.48 (m, 2H, 4-H), 1.42–1.24 (m, 4H, 5-H, 6-H), 0.91 (m, 3H, 7-H); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) = 141.5 (C-2), 114.7 (C-1), 73.4 (C-3), 36.9 (C-4), 27.6, 22.8 (C-5, C-6), 14.2 (C-7). The analytical data are in accordance with the literature.²⁶ Hept-1-en-3-ol (2.51 g, 21.98 mmol, 1.0 equiv.) was dissolved in CH₂Cl₂ (50 mL) and a freshly ground mixture of KMnO₄ (2.0 g, 12.66 mmol, 0.58 equiv.) and freshly prepared MnO₂³³ (6.0 g, 69.01 mmol, 3.1 equiv.) was added. The resulting suspension was stirred at ambient temperature for 48 h.

After filtration over Celite with CH₂Cl₂, the solvent was evaporated under reduced pressure (40 °C, 200 mbar) to yield **17** (1.73 g, 15.42 mmol, 72%) as a colorless liquid. R_f = 0.51 (SiO₂, hexanes/EtOAc 5 : 1); IR (ATR) $\tilde{\nu}$ (cm⁻¹) = 2958, 2929, 2872, 1727, 1465, 1380, 1368, 1286, 1126, 1074; ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 6.35 (dd, J = 17.7, 10.5 Hz, 1H, 2-H), 6.21 (dd, J = 17.7, 1.3 Hz, 1H, CH_{2A}-1), 5.81 (dd, J = 10.5, 1.3 Hz, 1H, CH_{2B}-1), 2.59 (t, J = 7.4 Hz, 2H, 4-H), 1.64–1.56 (m, 2H, 5-H), 1.38–1.29 (m, 2H, 6-H), 0.91 (t, J = 7.3 Hz, 3H, 7-H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) = 201.3 (C-3), 136.7 (C-1), 128.0 (C-2), 39.5 (C-4), 26.3, 22.5 (C-5, C-6), 14.0 (C-7). The analytical data are in accordance with the literature.³⁴

tert-Butyl 2-propylpiperidine-1-carboxylate (15)

tert-Butyl piperidine-1-carboxylate (**14**, 1.03 g, 5.53 mmol, 1.0 equiv.) was dissolved in dry Et₂O (40 mL) under argon and TMEDA (2.0 mL, 13.25 mmol, 2.4 equiv.) was added. The resulting solution was cooled to –78 °C and *sec*-butyllithium (13.25 mmol, 2.4 equiv.) was added dropwise. The solution was stirred for 4 h at –78 °C, after which a 0.3 M solution of CuCN·2LiCl in THF (44.1 mL, 13.23 mmol, 2.4 equiv.) was added slowly. The resulting solution was allowed to warm to –50 °C and stirred at this temperature for 1 h. It was again cooled to –78 °C and 1-iodopropane (1.3 mL, 13.31 mmol, 2.4 equiv.) was added dropwise and the resulting solution was warmed to ambient temperature overnight. To the resulting black solution was added sat. NH₄Cl(aq) (50 mL) and the mixture was stirred for 1 h. The aqueous phase was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with water (60 mL) and brine (60 mL), dried over MgSO₄ and the solvent was evaporated under reduced pressure. Purification by column chromatography (SiO₂, hexanes/EtOAc 30 : 1, 1% NEt₃) yielded **15** (0.73 g, 3.21 mmol, 58%) as a colorless oil. R_f = 0.41 (SiO₂, cyclohexane/EtOAc 5 : 1); IR (ATR) $\tilde{\nu}$ (cm⁻¹) = 2955, 2931, 2865, 1687, 1414, 1364, 1244, 1170, 1144, 767; ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 4.20 (s br, 1H, 2-H), 3.95 (d, br, J = 12.4 Hz, 1H, CH_{2A}-6), 2.74 (m, 1H, CH_{2B}-6), 1.71–1.16 (m, 10H, 3-H, 4-H, 5-H, 1'-H, 2'-H), 1.44 (s, 9H, C(CH₃)₃), 0.91 (d, J = 7.3 Hz, 3H, 3'-H); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) = 154.8 (C=O), 78.8 (C(CH₃)₃), 50.2 (C-2), 38.7 (C-6), 31.7 (C-1'), 28.5 (4C, C-3, C(CH₃)₃), 25.7 (C-5), 19.5 (C-2'), 19.0 (C-4), 14.1 (C-3'). The analytical data are in accordance with the literature.³⁵

tert-Butyl *trans*-2-methyl-6-(3-oxobutyl)piperidine-1-carboxylate (9)

The title compound was prepared according to general procedure A using *tert*-butyl 2-methylpiperidine-1-carboxylate (1.06 g, 5.32 mmol, 1.0 equiv.), Et₂O (20 mL), TMEDA (1.8 mL, 11.93 mmol, 2.2 equiv.), *sec*-butyllithium (1.3 M, 5.4 mL, 7.02 mmol, 1.3 equiv.), CuCN·2LiCl (0.3 min dry THF, 18 mL, 5.4 mmol, 1.0 equiv.), TMSCl (3.4 mL, 26.60 mmol, 5.0 equiv.) and butenone (0.46 mL, 5.45 mmol, 1.0 equiv.). Purification by column chromatography (SiO₂, hexanes/EtOAc 30 : 1) yielded **9** (0.88 g, 3.27 mmol, 61%) as a colorless oil. R_f = 0.17 (SiO₂, cyclohexane/EtOAc 5 : 1); IR (ATR) $\tilde{\nu}$ (cm⁻¹) = 2967, 2931, 2872,



1717, 1684, 1454, 1392, 1364, 1324, 1175; ¹H NMR, COSY, NOESY (600 MHz, CDCl₃) δ (ppm) = 3.90–3.86 (m, 1H, H-2), 3.85–3.80 (m, 1H, H-6), 2.47 (t, *J* = 7.7 Hz, 2H, H-2''), 2.14 (s, 3H, H-4''), 1.95–1.89 (m, 1H, CH_{2A}-1''), 1.88–1.78 (m, 2H, CH_{2A}-3, CH_{2A}-5), 1.77–1.70 (m, 1H, CH_{2B}-1''), 1.66–1.56 (m, 3H, CH₂-4, CH_{2B}-5), 1.54–1.48 (m, 1H, CH_{2B}-3), 1.45 (s, 9H, C(CH₃)₃), 1.22 (d, *J* = 6.7 Hz, 3H, CH₃-1'); ¹³C NMR, HSQC, HMBC (75.5 MHz, CDCl₃) δ (ppm) = 208.9 (C-3''), 155.7 (NCO₂), 79.2 (C(CH₃)₃), 51.1 (C-6), 47.5 (C-2), 41.3 (C-2''), 30.2 (C-4''), 28.7 (C(CH₃)₃), 28.6 (C-1''), 27.1 (C-3), 24.6 (C-5), 20.8 (C-1'), 14.2 (C-4); HRMS (ESI) *m/z* 292.1877 ([M + Na]⁺, calcd for C₁₅H₂₇NO₃Na 292.1889).

tert-Butyl *trans*-2-methyl-6-(3-oxoheptyl)piperidine-1-carboxylate (18)

The title compound was prepared according to general procedure A using *tert*-butyl 2-methylpiperidine-1-carboxylate (0.97 g, 4.87 mmol, 1.0 equiv.), Et₂O (20 mL), TMEDA (1.68 mL, 11.13 mmol, 2.3 equiv.), *sec*-butyllithium (1.3 M, 5.22 mL, 6.79 mmol, 1.4 equiv.), CuCN·2LiCl (0.3 min dry THF, 16.3 mL, 4.89 mmol, 1.0 equiv.), TMSCl (3.1 mL, 24.25 mmol, 5.0 equiv.) and hept-1-en-3-one (**17**, 0.65 mL, 4.87 mmol, 1.0 equiv.). Purification by column chromatography (SiO₂, hexanes/EtOAc 15 : 1) yielded **18** (0.75 g, 2.40 mmol, 49%) as a slight yellow oil. *R*_f = 0.34 (SiO₂, cyclohexane/EtOAc 5 : 1); IR (ATR) $\tilde{\nu}$ (cm⁻¹) = 2957, 2933, 2872, 1684, 1456, 1392, 1364, 1324, 1174, 1121, 772; ¹H NMR, COSY, NOESY (600 MHz, CDCl₃) δ (ppm) = 3.90–3.86 (m, 1H, H-2), 3.84–3.80 (m, 1H, H-6), 2.43 (t, *J* = 7.7 Hz, 2H, H-2''), 2.40 (t, *J* = 7.5 Hz, 2H, H-4''), 1.95–1.89 (m, 1H, CH_{2A}-1''), 1.88–1.78 (m, 2H, CH_{2A}-3, CH_{2A}-5), 1.77–1.70 (m, 1H, CH_{2B}-1''), 1.66–1.48 (m, 6H, CH_{2B}-3, CH₂-4, CH_{2B}-5, CH₂-5''), 1.45 (s, 9H, C(CH₃)₃), 1.33–1.26 (m, 2H, CH₂-6''), 1.22 (d, *J* = 6.7 Hz, 3H, CH₃-1'); 0.89 (t, *J* = 7.4 Hz, 3H, CH₃-7''); ¹³C NMR, HSQC, HMBC (75.5 MHz, CDCl₃) δ (ppm) = 211.3 (C-3''), 155.7 (NCO₂), 79.2 (C(CH₃)₃), 51.3 (C-6), 47.5 (C-2), 42.8 (C-4''), 40.4 (C-2''), 28.7 (C(CH₃)₃), 28.6 (C-1''), 27.1 (C-3), 26.2 (C-5''), 24.6 (C-5), 22.5 (C-6''), 20.8 (C-1'), 14.3 (C-4), 14.0 (C-7''); HRMS (ESI) *m/z* 334.2354 ([M + Na]⁺, calcd for C₁₈H₃₃NO₃Na 334.2358).

tert-Butyl *trans*-2-(3-oxoheptyl)-6-propylpiperidine-1-carboxylate (19)

The title compound was prepared according to general procedure A using *tert*-butyl 2-propylpiperidine-1-carboxylate (0.43 g, 1.88 mmol, 1.0 equiv.), Et₂O (10 mL), TMEDA (0.66 mL, 4.37 mmol, 2.3 equiv.), *sec*-butyllithium (1.3 M, 2.05 mL, 2.67 mmol, 1.4 equiv.), CuCN·2LiCl (0.3 min dry THF, 6.3 mL, 1.89 mmol, 1.0 equiv.), TMSCl (1.2 mL, 9.39 mmol, 5.0 equiv.) and hept-1-en-3-one (**17**, 0.25 mL, 1.87 mmol, 1.0 equiv.). Purification by column chromatography (SiO₂, hexanes/EtOAc 15 : 1) yielded **19** (0.30 g, 0.89 mmol, 48%) as a slight yellow oil. *R*_f = 0.33 (SiO₂, cyclohexane/EtOAc 5 : 1); IR (ATR) $\tilde{\nu}$ (cm⁻¹) = 2957, 2933, 2872, 1713, 1682, 1455, 1391, 1364, 1170, 773; ¹H NMR, COSY, NOESY (600 MHz, CDCl₃) δ (ppm) = 3.71–3.66 (m, 2H, H-2, H-6), 2.45–2.38 (m, 4H, H-2', H-4'), 2.00–1.94 (m, 1H, CH_{2A}-1'), 1.77–1.51 (m, 10H, CH₂-3, CH₂-4,

CH₂-5, CH_{2B}-1', CH_{2A}-1''), 1.47–1.39 (m, 1H, CH_{2B}-1''), 1.45 (s, 9H, C(CH₃)₃), 1.33–1.26 (m, 4H, CH₂-6', CH₂-2''), 0.91 (t, *J* = 7.5 Hz, 3H, CH₃-3''); 0.89 (t, *J* = 7.5 Hz, 3H, CH₃-7'); ¹³C NMR, HSQC, HMBC (75.5 MHz, CDCl₃) δ (ppm) = 211.4 (C-3''), 155.9 (NCO₂), 79.2 (C(CH₃)₃), 52.3 (C-6), 51.7 (C-2), 42.8 (C-4'), 40.3 (C-2'), 36.2 (C-1''), 28.7 (C(CH₃)₃), 28.2 (C-1'), 26.1 (C-5'), 25.7, 24.8 (C-3, C-5), 22.5 (C-6'), 20.4 (C-2''), 15.6 (C-4), 14.2 (C-3''), 14.0 (C-7'); HRMS (ESI) *m/z* 362.2664 ([M + Na]⁺, calcd for C₂₀H₃₇NO₃Na 362.2671).

5,9-*trans*-3,5-Dimethyloctahydroindolizinium 2,4,6-trinitrophenolate (12)

The title compound was prepared according to general procedure B using *tert*-butyl *trans*-2-methyl-6-(3-oxobutyl)piperidine-1-carboxylate (**9**, 174 mg, 0.646 mmol, 1.0 equiv.), EtOH (4.5 mL), AcCl (2 × 0.4 mL), 1 M NaOAc/HOAc-buffer (12.5 mL), NaCNBH₃ (1 × 145 mg, 2.31 mmol, 3.6 eq.). The product was isolated as its picrate-salt, by dissolving in EtOH (4 mL) and adding a saturated solution of picric acid in EtOH (4 mL). The resulting solution was heated to reflux briefly and cooled until full precipitation. The salt was filtered and washed with EtOH to yield **12** (136 mg, 0.356 mmol, 55%) as a yellow solid. The product was isolated as a 1 : 1.2 mixture (¹H NMR) of C-3 epimers. *Mp* 200–201 °C dec. (EtOH); *R*_f = 0.26 (SiO₂, CHCl₃/MeOH); IR (ATR) $\tilde{\nu}$ (cm⁻¹) = 3025, 2954, 2918, 2849, 1631, 1564, 1365, 1316, 1297, 1269; ¹H NMR, COSY, NOESY, TOCSY (600 MHz, CDCl₃) δ (ppm) = Major Isomer (5*E*,9*Z*, **12a**): 9.49 (br, s, 1H, NH), 8.86 (s, 2H, Ar-H), 4.20–4.14 (m, 1H, H-5), 3.28–3.20 (m, 1H, H-3), 3.19–3.11 (m, 1H, H-9), 2.39–1.94 (m, 5H, H-1, H_a-2, H_a-6, H_a-8), 1.93–1.79 (m, 2H, H_b-2, H_b-8), 1.79–1.57 (m, 3H, H_b-6, H-7), 1.36 (d, *J* = 6.5 Hz, 3H, C3-CH₃), 1.29 (d, *J* = 7.1 Hz, 3H, C5-CH₃); Minor Isomer (5*Z*,9*E*, **12b**): 9.49 (br, s, 1H, NH), 8.86 (s, 2H, Ar-H), 4.20–4.14 (m, 1H, H-9), 3.83–3.73 (m, 1H, H-3), 3.40–3.33 (m, 1H, H-5), 2.39–1.94 (m, 3H, H_a-1, H_a-2, H_a-8), 1.93–1.79 (m, 3H, H_b-1, H_b-2, H_a-6), 1.79–1.57 (m, 4H, H_b-6, H-7, H_b-8), 1.52 (d, *J* = 6.7 Hz, 3H, C5-CH₃), 1.49 (d, *J* = 6.7 Hz, 3H, C3-CH₃); ¹³C NMR, HSQC, HMBC, HSQC-TOCSY (75.5, 150.9 MHz, CDCl₃) δ (ppm) = Major Isomer (5*E*,9*Z*, **12a**): 161.7 (C_{Ar}-1), 141.9 (C_{Ar}-2,6), 128.0 (C_{Ar}-4), 126.5 (C_{Ar}-3,5), 60.1 (C-9), 59.0 (C-3), 50.9 (C-5), 28.7 (C-6), 28.5 (C-8), 27.9 (C-2), 26.2 (C-1), 17.5 (C-7), 14.6 (C3-CH₃), 10.0 (C5-CH₃); Minor Isomer (5*Z*,9*E*, **12b**): 161.7 (C_{Ar}-1), 141.9 (C_{Ar}-2,6), 128.0 (C_{Ar}-4), 126.5 (C_{Ar}-3,5), 59.8 (C-3), 59.2 (C-9), 53.3 (C-5), 29.3 (C-2), 27.2 (C-6), 26.8 (C-1), 25.3 (C-8), 18.1 (C3-CH₃), 17.4 (C5-CH₃), 16.9 (C-7); HRMS (ESI) *m/z* 154.1595 ([M + H]⁺, calcd for C₁₀H₂₀N 154.1596).

5,9-*trans*-3-Butyl-5-methyloctahydroindolizine (2)

The title compound was prepared according to general procedure B using *tert*-butyl *trans*-2-methyl-6-(3-oxoheptyl)piperidine-1-carboxylate (**18**, 84 mg, 0.270 mmol, 1.0 equiv.), EtOH (5 mL), AcCl (3 × 0.3 mL), 1 M NaOAc/HOAc-buffer (25 mL), NaCNBH₃ (2 × 63 mg, 1.00 mmol, 3.7 eq.). Purification by column chromatography (*KP-NH*, *n*-pentane/Et₂O 100 : 1) yielded **2a** (5*E*,9*Z*, 28 mg, 0.143 mmol, 53%) and **2b** (5*Z*,9*E*, 12 mg, 0.061 mmol, 23%) as colorless oils. *R*_{fa} = 0.42 (*KP-NH*,



n-pentane/Et₂O 10 : 1), $R_{fb} = 0.25$ (*KP-NH*, *n*-pentane/Et₂O 10 : 1); **IR** (ATR) $\tilde{\nu}$ (cm⁻¹) = 2953, 2921, 2852, 1646, 1465, 1377, 1299, 1242; **¹H NMR**, **COSY**, **NOESY**, **TOCSY** (400, 600 MHz, CDCl₃) δ (ppm) = Major Isomer (*5E,9Z*, **2a**): 3.39–3.34 (m, 1H, H-5), 2.45–2.38 (m, 2H, H-3, H-9), 1.79–1.65 (m, 5H, H_a-1, H_a-2, H_a-6, H_a-8, H_a-1'), 1.55–1.50 (m, 2H, H_b-6, H_a-7), 1.49–1.41 (m, 1H, H_b-7), 1.37–1.08 (m, 8H, H_b-1, H_b-2, H_b-8, H_b-1', H-2', H-3'), 0.91–0.86 (m, 6H, 4'-CH₃, C5-CH₃); Minor Isomer (*5Z,9E*, **2b**): 3.31–3.28 (m, 1H, H-9), 2.95–2.90 (m, 1H, H-3), 2.88–2.84 (m, 1H, H-5), 2.04–1.98 (m, 1H, H_a-2), 1.79–1.65 (m, 2H, H_a-1, H_a-6), 1.63–1.52 (m, 2H, H_a-7, H_a-1'), 1.50–1.41 (m, 2H, H_b-1, H_b-7), 1.40–1.20 (m, 9H, H_b-2, H_b-6, H-8, H_b-1', H-2', H-3'), 1.17 (d, *J* = 6.7 Hz, 3H, C5-CH₃); 0.89 (t, *J* = 7.0 Hz, 3H, H-4'); **¹³C NMR**, **HSQC**, **HMBC**, **H2BC**, **HSQC-TOCSY** (150.9 MHz, CDCl₃) δ (ppm) = Major Isomer (*5E,9Z*, **2a**): 59.3 (C-3), 55.5 (C-9), 47.5 (C-5), 32.6 (C-8), 32.5 (C-1'), 31.7 (C-6), 29.4 (C-2), 29.0 (C-2'), 28.3 (C-1), 23.3 (C-3'), 19.5 (C-7), 14.3 (C-4'), 7.7 (C5-CH₃); Minor Isomer (*5Z,9E*, **2b**): 59.8 (C-3), 55.4 (C-9), 48.7 (C-5), 36.4 (C-1'), 29.3 (C-2'), 29.1 (C-2), 28.7 (C-1), 27.1 (C-8), 27.0 (C-6), 23.2 (C-3'), 20.7 (C5-CH₃), 19.2 (C-7), 14.3 (C-4'); **HRMS** (ESI) *m/z* 196.2058 ([M + H]⁺, calcd for C₁₃H₂₆N 196.2065). The analytical data are in accordance with the literature.²⁸

5,9-*trans*-3-Butyl-5-propyloctahydroindolizine (3)

The title compound was prepared according to general procedure B using *tert*-butyl *trans*-2-(3-oxoheptyl)-6-propylpiperidine-1-carboxylate (**19**, 108 mg, 0.318 mmol, 1.0 equiv.), EtOH (5 mL), AcCl (3 × 0.3 mL), 1 M NaOAc/HOAc-buffer (25 mL), NaCNBH₃ (2 × 63 mg, 1.00 mmol, 3.7 eq.). Purification by column chromatography (*KP-NH*, *n*-pentane/Et₂O 100 : 1) yielded **3** (40 mg, 0.179 mmol, 56%) as a colorless oil. The product was isolated as a 1 : 1.7 mixture (determined by ¹H NMR) of C-3 epimers. $R_{fa} = 0.58$ (*KP-NH*, *n*-pentane/Et₂O 10 : 1), $R_{fb} = 0.44$ (*KP-NH*, *n*-pentane/Et₂O 10 : 1); **IR** (ATR) $\tilde{\nu}$ (cm⁻¹) = 2955, 2922, 2852, 1647, 1464, 1377, 1299, 1243; **¹H NMR**, **COSY**, **NOESY**, **TOCSY** (600 MHz, CDCl₃) δ (ppm) = Major Isomer (*5E,9Z*, **3a**): 3.07–3.04 (m, 1H, H-5), 2.57–2.52 (m, 1H, H-3), 2.43–2.38 (m, 1H, H-9), 1.80–1.73 (m, 2H, H_a-2, H_a-1'), 1.71–1.62 (m, 4H, H_a-1, H_a-6, H_a-8, H_a-1''), 1.59–1.49 (m, 2H, H_b-6, H_a-7), 1.48–1.39 (m, 1H, H_b-7), 1.38–1.08 (m, 11H, H_b-1, H_b-2, H_b-8, H_b-1', H_b-1'', H-2', H-2'', H-3'), 0.93–0.87 (m, 6H, 4'-CH₃, 3''-CH₃); Minor Isomer (*5Z,9E*, **3b**): 3.25–3.22 (m, 1H, H-9), 2.94–2.89 (m, 1H, H-3), 2.72–2.68 (m, 1H, H-5), 2.02–1.95 (m, 1H, H_a-2), 1.80–1.73 (m, 1H, H_a-1), 1.71–1.62 (m, 1H, H_a-6), 1.59–1.49 (m, 3H, H_a-7, H_a-1', H_a-1''), 1.48–1.39 (m, 2H, H_b-7, H_b-1''), 1.38–1.08 (m, 12H, H_b-1, H_b-2, H_b-6, H-8, H_b-1', H-2', H-2'', H-3'), 0.93–0.87 (m, 6H, 4'-CH₃, 3''-CH₃); **¹³C NMR**, **HSQC**, **HMBC**, **H2BC**, **HSQC-TOCSY** (100.6, 150.9 MHz, CDCl₃) δ (ppm) = Major Isomer (*5E,9Z*, **3a**): 58.6 (C-5), 56.3 (C-9), 52.6 (C-5), 32.7 (C-1'), 32.6 (C-8), 29.6 (C-1), 28.9 (C-2'), 28.5 (C-2), 27.9 (C-6), 23.3 (C-3'), 23.0 (C-1''), 21.0 (C-2''), 19.5 (C-7), 14.7 (C-3''), 14.3 (C-4'); Minor Isomer (*5Z,9E*, **3b**): 58.6 (C-5), 55.1 (C-9), 52.4 (C-5), 36.1 (C-1'), 35.6 (C-1''), 29.2 (C-1), 28.9 (C-2'), 28.8 (C-2), 27.4 (C-8), 23.3 (C-3'), 23.0 (C-6), 20.5 (C-2''), 19.5 (C-7), 14.4, 14.3 (C-3'', C-4'); **HRMS** (ESI) *m/z*

224.2375 ([M + H]⁺, calcd for C₁₅H₃₀N 224.2378). The analytical data are in accordance with the literature.¹⁶

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