FORMAL TOTAL SYNTHESIS OF ENANTIOPURE TRICYCLIC (S)-MYRMICARIN ALKALOIDS 217, 215A AND 215B

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Abstract – We described herein a formal synthesis of the enantiopure tricyclic (4aS)-myrmicarin alkaloids 217, 215A and 215B owing to the obtention of a common pyrroloindolizidine intermediate, starting from a chiral cis-(2S,5R)-disubstituted pyrrolidine. An intramolecular one-pot aldolization-crotonization-aromatization process of a diketo indolizidine constitutes the key step for the formation of the pyrrole ring of the target compound.

INTRODUCTION
Myrmicarins constitute a new family of oligocyclic air-sensitive alkaloids recently isolated by Schröder et al.1 as the major constituents of the poison gland of the African ant species Myrmicaria opaciventris. Among the simplest members of this group, tricyclic myrmicarins 217, 215A and 215B possess a pyrrolo[2,1,5-cd]indolizidine core whose pyrrole ring is substituted both by an ethyl group and either a propyl or a (Z) or (E)-prop-1-enyl group (Figure 1). So far, only a few syntheses of these alkaloids have been reported.2 In particular, Vallée and co-workers2b described in 2000 the first non racemic synthesis of (R)- and (S)-myrmicarins 217. In this synthesis the pyrrole ring was formed early in the sequence by condensation of D- or L-glutamic acid, as the chiral source, with tetrahydro-2,5-hydroxyfuran. More recently, Movassaghi and Ondrus2e achieved the total synthesis of the enantiomerically enriched (R)-myrmicarins 217, 215A and 215B (ee = 85%). Their approach included a stereospecific palladium-catalyzed N-vinylation of a substituted pyrrole from a vinyl triflate. Actually, all these syntheses2b,2e featured a common enantiopure tricyclic keto intermediate (I) (Figure 1), that provided rapid access to pure tricyclic myrmicarins 217, 215A and 215B.

In our continuing effort aimed at the synthesis of enantiopure alkaloids, we describe herein a new synthesis of pyrroloindolizidine (4aS)-(I), thus achieving a formal synthesis of the three tricyclic (4aS)-myrmicarins.
RESULTS AND DISCUSSION

From a retrosynthetic point of view, we envisioned that the pyrrole ring of compound (4aS)-(1) could stem from the intramolecular cyclization of diketo indolizidine (8aS)-(2) in which the C-3 position would be substituted by an oxobutyl group (R = Et). The latter could arise from an intramolecular reductive amination of 2,5-disubstituted pyrrolidine (3) which in turn would stem from enantiopure cis-(2S,5R)-disubstituted pyrrolidine (4) (Scheme 1). Indeed, we recently described the preparation of the latter compound that was used as a key intermediate in the formal synthesis of (+)-gephyrotoxin.3

Our approach relies on the formation of the pyrrole ring at the last stage as the key step of our synthesis. As a preliminary study, we first explored the access to bicyclic A-C substructure via the obtention of 2,3-dihydro-1H-pyrrolizine (5) (Scheme 2) as a model molecule of tricyclic compound (1). We reasoned that the bicyclic pyrrole (5) could result from an intramolecular aldolization-erotionization sequence from diketo derivative (6), followed by subsequent one-pot aromatization.4 Compound (6) was prepared starting from commercially available methyl pyrrolidineacetate (7) (Scheme 2).

Figure 1

Scheme 1

Scheme 2
We initially converted pyrrolidine (7) into diesters (8) by condensation of methyl α-bromopropionate in 66% isolated yield (1:1 mixture of separable isomers). Diethylketo pyrrolidine (6) was then obtained from 8, following a two-step procedure by reacting ethyl Grignard reagent with the corresponding non isolated Weinreb diamide in 72% overall yield (Scheme 3).

The required intermediate (6) in hand, we next examined the aldolization reaction under basic conditions. The use of LDA at −78 °C turned out to be ineffective, whereas LHMDS allowed the regioselective aldolization to afford the expected cyclization product (9) as a single isomer in quantitative yield. The latter was then submitted to dehydration in acidic medium. Refluxing in toluene in the presence of p-TSA (0.1 to 1 equivalent) left the product unchanged. Using HCl in refluxing ethanol led to degradation products. In contrast, when compound (9) was treated under basic conditions with lithium hydroxide monohydrate in refluxing ethanol, crotonization occurred followed by in situ aromatization leading to the expected pyrrole derivative (5) in a moderate 30% yield. We then tried to optimize the sequence by using lithium hydroxide in the initial aldolization reaction, thus allowing a one pot three-step process. Effectively, when reacting with lithium hydroxide, diketopyrrolidine (6) directly afforded pyrrole (5) in 62% yield (Scheme 3). So, we have succeeded in developing a new simple access to 2,3-dihydro-1H-pyrrolizine (5) which constitutes a properly substituted model for tricyclic compound (1).

Scheme 3

The results of this preliminary methodological study in hand, we then turned our attention to the synthesis of tricyclic compound (4aS)-(1) starting from enantiopure pyrrolidineacetate (4).³

Pyrrolidine (4) was firstly submitted to hydrogenolysis under an hydrogen atmosphere in the presence of Pd/C as a catalyst, followed by the protection of the amine function of the crude product as a benzylcarbamate to afford pyrrolidineacetate (10a). However, silica gel column chromatography did not allow the separation of the latter compound from phenylethanol. To allow easier isolation, compound (4)
was initially subjected to acetylation. This three-step procedure allowed us to isolate expected compound (10a) in 57% overall yield. Deprotection of the tetrahydropyranyl protected alcohol function was then performed by treatment with pyridinium para-toluene sulfonate in ethanol to give rise to alcohol (11a) in 84% yield. Swern oxidation of the latter afforded aldehyde (12a) in 71% yield. Horner-Wadsworth-Emmons condensation of 12a with the reactive 3,3-diethoxy-2-oxopentylphosphonate in refluxing THF in the presence of KHMDS as the base,\(^6\) provided E-unsaturated ketone (13a) in 76% yield. The double bond was then chemoselectively reduced under an hydrogen atmosphere in the presence of a catalytic amount of PtO\(_2\) to give pyrrolidine (14a) in 74% yield (Scheme 4).

However, when compound (14a) was submitted to an hydrogen atmosphere either at room temperature or at 50 °C in the presence of Pd/C as the catalyst, the in situ expected cyclization to yield the corresponding indolizidine did not occur. Pyrrolidine acetate (3), resulting from the hydrogenolysis of the carbamate moiety of 14a was the only isolated compound (Scheme 5).

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**Scheme 4**

**Scheme 5**
We thought that this lack of reactivity might stem from the bulkiness of the acetal group which would prevent cyclization of \textit{cis} 2,5-disubstituted pyrrolidine (3). We thus envisaged to initially deprotect the keto function of compound (14a) (Scheme 4). This was achieved in presence of aqueous TFA to give rise to diketopyrrolidine (15a) in 86% yield. The latter was then submitted to an hydrogen atmosphere in the presence of Pd/C as the catalyst. To our delight, the intramolecular cyclization effectively occurred even at room temperature to afford indolizidine (2a) in 46% yield (Scheme 4).\textsuperscript{7} Noteworthy, indolizidine (2a) was obtained as a single isomer whose stereochemistry at the C-5 center was postulated to be (\textit{R}), according to previous results.\textsuperscript{8}

At this stage, to complete our synthesis toward pyrroloindolizidine (1), we had to prepare indolizidine (2b) (R = Et) by transformation of the ester moiety of 2a into an oxo-1-propyl one, which could be achieved via the Weinreb amide. Since this strategy required protecting the keto group of indolizidine (2a), thus increasing the number of steps, we rather planned to install the oxo-2-butyl side chain at an earlier step, from ester pyrrolidine (10a) (Scheme 4). Ester (10a) was transformed into ketone (10b) by a two-step procedure in 65% overall yield, via an intermediate Weinreb amide that was treated with ethyl Grignard reagent. According to the sequence previously described from ester analogue (10a), deprotection of the alcohol function in the presence of PPTS and subsequent Swern oxidation afforded aldehyde (12b) in high yield. Chemoselective condensation of 3,3-diethoxy-2-oxopentylphosphonate on the aldehyde function of 12b gave pyrrolidine (13b) in 89% yield. Successive double bond reduction (H\textsubscript{2}, PtO\textsubscript{2}, 89%) and deprotection of the acetal group (aq. TFA, CHCl\textsubscript{3}, 93%) allowed the efficient obtention of triketo derivative (15b). Subsequent hydrogenolysis and in situ cyclization provided the expected diketo indolizidine (2b) in 50% yield, as a single isomer. This key intermediate in hand, we then envisaged the ultimate step in line with the reaction we previously studied, i.e. a one-pot aldolization-crotonization-aromatization reaction to lead to the target pyrroloindolizidine derivative (1) (Scheme 6).

As expected, when treated in the presence of lithium hydroxide monohydrate in refluxing ethanol, compound (2b) gave rise to the expected compound (\textit{S})-(1) in 64% yield. The spectroscopic data of this compound were identical to those reported in the literature and the optical rotation ([\textit{\alpha}]\textsubscript{D}\textsuperscript{20} −65 (c 0.52; CH\textsubscript{2}Cl\textsubscript{2})) was in accordance with the one given for its enantiomer (for (\textit{R})-1: [\textit{\alpha}]\textsubscript{D}\textsuperscript{20} +64.8 (c 0.50; CH\textsubscript{2}Cl\textsubscript{2})\textsuperscript{2b}).

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\begin{align*}
2b & \xrightarrow{\text{LiOH.H}_{2}O, \text{80°C}} \text{(S)-1} \\
& \xrightarrow{\text{EtOH, 80°C}} (64\%) \\
\end{align*}
\]

\textbf{Scheme 6}
In conclusion, we have completed an efficient formal synthesis of enantiopure tricyclic (S)-myrmicarin alkaloids via enantiopure pyrroloindolizidine (S)-(1), in 12 steps and 7.4% overall yield starting from enantiopure cis-(2S,5R)-disubstituted pyrrolidine 4. Noteworthy, naturally occurring enantiomer (R)-myrmicarin can be equally prepared according to a similar way starting from (2R,5S)-4 obtained from (R)-phenylglycinol. Our strategy relies on the obtention of diketoindolizidine (2b), generated by the intramolecular reductive amination of an enantiopure 2,5-disubstituted pyrrolidine (15b). Compound (2b) was then successfully submitted to a one-pot aldolization-crotonization-aromatization reaction, as a method for the formation of the pyrrole ring. This new methodology is currently under generalization in the Laboratory.

EXPERIMENTAL

General: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone ketyl immediately prior to use. CH2Cl2 was distilled from calcium hydride. All reactions were carried out under argon. Thin layer chromatography analyses were performed on Merck precoated silica gel (60 F254) plates and column chromatography on silica gel Gerudan SI 60 (40-60 μm) (Merck). Melting points are uncorrected. IR: Philips PU 9706. Optical rotation: Perkin-Elmer 341 polarimeter. HMRS were recorded on a JEOL MS 700 mass spectrometer. NMR: Bruker ARX 250 and ARX 400 spectrometers. Spectra were recorded in CDCl3 or C6D6 as solvents. Chemical shifts (δ) were expressed in ppm relative to TMS at δ = 0 for 1H NMR, and relative to CDCl3 at δ = 77.16 in this solvent or to TMS at δ=0 in C6D6 for 13C NMR. Coupling constants (J) are expressed in Hertz.

It is of note that the NMR studies at room temperature in CDCl3 of all benzyl carbamate compounds showed that these compounds are present as a mixture of rotamers, which renders their NMR spectroscopic description often unclear and difficult, in particular for 13C spectra. For this reason, these spectra have equally been recorded in C6D6 at 343 °K, this temperature generally allowing the coalescence of the 13C signals.

Methyl 2-(2-(2-methoxy-2-oxoethyl)pyrrolidin-1-yl)propanoate (8). To a solution of aminoester (7) (0.5 g, 3.5 mmol) in THF (30 mL) at 0 °C were added K2CO3 (0.53 g, 3.80 mmol) and tetrabutylammonium iodide (0.13 g, 0.35 mmol). Methyl 2-bromopropionate (0.43 mL, 3.80 mmol) was then added dropwise. The reaction mixture was stirred at reflux temperature for 16 h. After cooling to room temperature, the mixture was filtered and the solvent removed in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) allowed the separation of two diastereomers (8a) and (8b) in
equimolar amount as pale yellow oils (0.53 g, 66% overall).

For 8a: Rf = 0.25; IR (neat) 1675 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 1.34 (d, \(J = 7.5\) Hz, 3H), 1.53–1.63 (m, 1H), 1.70–1.80 (m, 2H), 1.95–2.09 (m, 1H), 2.26 (dd, \(J = 7.5, 15\) Hz, 1H), 2.56 (dd, \(J = 5, 15\) Hz, 1H), 2.73–2.83 (m, 1H), 2.97–3.04 (m, 1H), 3.22–3.32 (m, 1H), 3.63 (q, \(J = 7.5\) Hz, 1H), 3.66 (s, 3H), 3.69 (s, 3H); 13C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 17.2, 22.9, 31.2, 40.0, 47.3, 51.0, 51.3, 56.5, 57.8, 172.6, 173.8; HRMS (ESI): m/z calcd for C\(_{11}\)H\(_{20}\)NO\(_4\) (MH\(^+\)) 230.1386, found 230.1389.

For 8b: Rf = 0.24; \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 1.27 (d, \(J = 7.5\) Hz, 3H), 1.50–1.61 (m, 1H), 1.67–1.77 (m, 2H), 1.88–2.00 (m, 1H), 2.25 (dd, \(J = 10, 15\) Hz, 1H), 2.48 (dd, \(J = 5, 15\) Hz, 1H), 2.53–2.64 (m, 1H), 2.88–2.96 (m, 1H), 3.26–3.36 (m, 1H), 3.51 (q, \(J = 7.5\) Hz, 1H), 3.62 (s, 3H), 3.66 (s, 3H); 13C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 14.5, 23.3, 31.1, 41.0, 50.0, 51.5, 51.7, 57.0, 58.6, 172.7, 174.6.

2-(2-(2-Oxobutyl)pyrrolidine-1-yl)pentan-3-one (6). To a cooled solution of N,O-dimethylhydroxylamine hydrochloride (1.70 g, 17.4 mmol) in THF (40 mL) at −78 °C was added dropwise a 2.5 M n-BuLi solution in hexanes (13.9 mL, 34.8 mmol). The reaction mixture was stirred for 15 min. after removing the cooling bath, then cooled to −78 °C and a solution of compound (8) (0.30 g, 1.30 mmol) diluted in THF (15 mL) was slowly added. After stirring for 1 h at −78 °C, the reaction was quenched by addition of saturated aqueous solution of NH\(_4\)Cl (10 mL) and allowed to warm to room temperature. The aqueous layer was extracted with AcOEt. The organic layer was washed with brine (10 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to afford the crude intermediate diamide. The latter was dissolved in THF (20 mL) and cooled to −78 °C. Ethylmagnesium bromide (3 M in Et\(_2\)O, 1.80 mL, 5.56 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched by addition of saturated aqueous NH\(_4\)Cl solution (15 mL). The aqueous layer was extracted with AcOEt. The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) yielding diketone (6) as a yellow oil (0.21g, 72%). IR (neat) 1695 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 0.72–0.92 (m, 6H), 1.12 (d, \(J = 7.5\) Hz, 3H), 1.21–1.34 (m, 1H), 1.54–1.61 (m, 2H), 1.65–1.91 (m, 1H), 2.18–2.45 (m, 6H), 2.59–2.65 (m, 1H), 2.77–2.82 (m, 1H), 3.07–3.18 (m, 1H), 3.39 (q, \(J = 7.5\) Hz, 1H); 13C NMR (CDCl\(_3\), 62.5MHz) \(\delta\) 7.6 (2C), 15.0, 23.1, 31.6, 32.9, 36.7, 48.5, 49.9, 56.0, 63.8, 210.8, 213.8; HRMS (ESI): m/z calcd for C\(_{13}\)H\(_{24}\)NO\(_2\) (MH\(^+\)) 226.1801, found 226.1800.

1-(2-Ethyl-2-hydroxy-3-methylhexahdro-1H-pyrrolizin-1-yl)propan-1-one (9). To a solution of diketone (6) (0.28 g, 1.24 mmol) in THF (10 mL) at −78 °C was added dropwise LHMDS (1 M in Et\(_2\)O, 1.86 mL, 1.86 mmol). The reaction mixture was stirred for 2h at −78 °C and quenched by addition of
acetic acid (1 mL). Saturated aqueous potassium carbonate was added until pH = 9. The aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo to yield compound (9) as a colorless oil which was pure enough to be used in the next step (0.28 g, 100%). IR (neat) 3365, 1710 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.72–1.01 (m, 9H), 1.10–1.17 (m, 2H), 1.30–1.95 (m, 4H), 2.38–2.53 (m, 4H), 2.60–2.64 (m, 1H), 2.78–2.99 (m, 1H), 3.58–3.71 (m, 1H), 4.30 (ls, 1H); ¹³C NMR (CDCl₃, 62.5MHz) δ 7.2, 9.2, 13.0, 26.3, 29.4, 32.1, 38.2, 53.2, 62.0, 66.2, 69.1, 85.7, 214.2; HRMS (ESI): m/z calcd for C₁₃H₂₄NO₂ (MH⁺) 226.1801, found 226.1800.

1-(6-Ethyl-5-methyl-2,3-dihydro-1H-pyrrolizin-7-yl)propan-1-one (5). To a solution of diketone (6) (0.14 g, 0.62 mmol) in EtOH (4 mL) was added lithium hydroxide monohydrate (39 mg, 0.93 mmol). The reaction mixture was stirred at 80 °C for 18 h. The solvent was removed in vacuo and the residue purified by silica gel column chromatography (cyclohexane/AcOEt 7:3) to afford pyrrole (5) (80 mg, 62%) as a yellow solid. mp 69 °C; IR (neat) 1642 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 1.12 (t, J = 7.5 Hz, 3H), 1.16 (m, J = 7.5 Hz, 3H), 2.11 (s, 3H), 2.53 (quint, J = 7.5 Hz, 2H), 2.67 (q, J = 7.5 Hz, 2H), 2.71 (q, J = 7.5 Hz, 2H), 3.12 (t, J = 7.5 Hz, 2H); ¹³C NMR (CDCl₃, 62.5 MHz) δ 8.8, 9.6, 16.2, 19.5, 26.6, 28.2, 34.4, 45.2, 115.3, 121.5, 127.2, 141.4, 196.6; HRMS (ESI) m/z calcd for C₁₃H₁₉NONa (MNa⁺) 228.1358, found 228.1361.

(2S,5R)-Benzyl 2-(2-methoxy-2-oxoethyl)-5-(2-(tetrahydro-2H-pyran-2-yl oxy)ethyl)pyrrolidine-1-carboxylate (10a). To a solution of compound (4)³ (3.8 g, 9.71 mmol) in CH₂Cl₂ (95 mL) were successively added NEt₃ (2 mL, 14.5 mmol), DMAP (0.12 g, 0.97 mmol) and acetyl chloride (2.1 mL, 29.1 mmol). The reaction mixture was stirred at room temperature for 16 h. The organic layer was washed with water (2 × 20 mL) and brine (15 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude product was then dissolved in MeOH (150 mL) and subjected to hydrogenation (1 atm) in the presence of 5% Pd/C (0.78 g) at room temperature for 16 h. The reaction mixture was filtered over a Celite pad and the residue washed with MeOH. Concentration in vacuo afforded a crude yellow oil, which was dissolved in CH₂Cl₂ (100 mL). To the ice-cooled solution was added K₂CO₃ (1.53 g, 13.3 mmol) followed by dropwise addition of benzyl chloroformate (1.4 mL, 9.8 mmol). The reaction mixture was stirred at room temperature for 14 h, filtered and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (10a) (2.3 g, 57% for 3 steps) as a yellow oil (1:1 mixture of epimers at C-2 center of the THP group). IR (neat) 1732, 1690 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz, 343 °K) δ 1.22–1.60 (m, 9H), 1.65–1.84 (m, 2H), 2.07–2.24 (m, 1H), 2.27–2.33 (m, 1H),
3.00–3.03 (m, 1H), 3.35 (s, 3H), 3.36–3.43 (m, 2H), 3.70–3.84 (m, 2H), 3.90–4.05 (m, 1H), 4.25–4.31 (m, 1H), 4.47–4.59 (m, 1H), 5.09–5.14 (m, 2H), 7.05–7.30 (m, 5H); 13C NMR (C6D6, 100 MHz, 343 °K) δ 19.2 and 19.3, 25.4, 29.1 and 29.2, 29.5, 30.5, 35.5 and 35.7, 40.0, 50.3, 55.4, 56.7, 61.3 and 61.4, 64.4 and 64.5, 66.3, 98.2 and 98.3, 127.4, 127.7, 128.0, 137.3, 154.6, 170.7; HRMS (ESI): m/z calcd for C22H31NO6Na (MNa+) 428.2043, found 428.2037.

(2R,5S)-Benzyl 2-(2-hydroxyethyl)-5-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (11a). To a solution of compound (10a) (0.30 g, 0.74 mmol) in EtOH (20 mL) was added PPTS (93 mg, 0.37 mmol). The reaction mixture was stirred at 50 °C for 16 h. The solvent was removed in vacuo and the residue was dissolved in CH2Cl2 (10 mL). The organic layer was washed with water (2 × 5 mL), dried over Na2SO4, filtrated and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 3:7) afforded compound (11a) (0.2 g, 84%) as a yellow oil. [α]D20 −20.8 (c 2.00, CHCl3); IR (neat) 3496 cm−1; 1H NMR (C6D6, 400 MHz, 343 °K) δ 1.19–1.25 (m, 1H), 1.43–1.55 (m, 4H), 1.72–1.80 (m, 1H), 2.19–2.25 (m, 1H), 2.82–2.86 (m, 1H), 3.31 (s, 3H), 3.56 (m, 2H), 4.08–4.13 (m, 2H), 5.06 (m, 2H), 7.06–7.27 (m, 5H); 13C NMR (C6D6, 100 MHz, 343 °K) δ 29.5, 29.8, 38.8, 40.2, 50.3, 55.3, 55.9, 58.9, 66.7, 98.2 and 98.3, 127.4, 127.7, 128.0, 136.7, 156.2, 170.4; HRMS (ESI) m/z calcd for C17H23NO5Na (MNa+) 344.1468, found 344.1461.

(2S,5R)-Benzyl 2-(2-methoxy-2-oxoethyl)-5-(2-oxoethyl)pyrrolidine-1-carboxylate (12a). To a cooled solution of oxalyl chloride (0.62 mL of 2M solution in CH2Cl2, 1.24 mmol) in CH2Cl2 (10 mL) at −60 °C was added dropwise DMSO (0.14 mL, 1.86 mmol). After stirring for 5 min, a solution of alcohol (11a) (0.2 g, 0.62 mmol) in CH2Cl2 (10 mL) was added dropwise. The reaction mixture was stirred at −60 °C for 40 min, then NEt3 (0.52 mL, 3.73 mmol) was added. The reaction mixture was allowed to warm to room temperature over 30 min. Saturated aqueous NaHCO3 solution (20 mL) was added and the aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with saturated aqueous solution of NH4Cl (10 mL), dried over Na2SO4, filtered and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 4:6) afforded compound (12a) (0.14 g, 71%) as an oil. [α]D20 −3.7 (c 0.70, CHCl3); IR (neat) 1752 cm−1; 1H NMR (CDCl3, 250 MHz, 295 °K, rotamers) δ 1.63–1.86 (m, 2H), 2.00–2.17 (m, 2H), 2.25–2.41 (m, 2H), 2.61–3.03 (m, 2H), 3.63 and 3.65 (s, 3H), 4.26–4.34 (m, 2H), 5.12 (m, 2H), 7.29–7.34 (m, 5H), 9.63 and 9.75 (s, 1H); 13C NMR (C6D6, 100 MHz, 343 °K) δ 29.2, 29.6, 39.6, 49.5, 50.5, 53.9, 55.4, 66.7, 127.6, 127.7, 128.1, 137.0, 154.4, 170.6, 198.4; HRMS (ESI): m/z calcd for C17H21NO5Na (MNa+) 320.1492, found 320.1488.
(2R,5S)-Benzyl 2-((E)-5,5-diethoxy-4-oxohept-2-enyl)-5-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (13a). To a solution of KHMDS (0.10 g, 0.53 mmol) in THF (5 mL) at 0 °C was added dropwise a solution of 3,3-diethoxy-2-oxopentylphosphonate (0.14 g, 0.48 mmol) in THF (5 mL). The reaction mixture was stirred at 0 °C for 15 min, then a solution of aldehyde (12a) (0.14 g, 0.44 mmol) in THF (5 mL) was added. Stirring was continued at 0 °C for 10 min then at 80 °C for 16 h. The reaction was quenched by addition of saturated aqueous solution of NH₄Cl (10 mL) and water (5 mL). The aqueous layer was extracted with Et₂O (6 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (13a) (0.62 g, 76%) as a yellow oil. [α]D²⁰ +1.4 (c 0.80, CHCl₃); IR (neat) 1744, 1735 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz, 295 °K, rotamers) δ 0.65 (t, J = 7.5 Hz, 3H), 1.11 (t, J = 7.5 Hz, 6H), 1.55–1.74 (m, 4H), 1.90–2.15 (m, 2H), 2.23–2.43 (m, 2H), 2.62–3.07 (m, 2H), 3.26–3.45 (m, 4H), 3.56 and 3.58 (s, 3H), 3.85–4.02 (m, 1H), 4.08–4.26 (m, 1H), 5.02–5.09 (m, 2H), 6.60–6.68 (m, 1H), 6.80–6.92 (m, 1H), 7.22–7.29 (m, 5H); ¹³C NMR (C₆D₆, 100 MHz, 343 °K) δ 7.3, 15.1, 26.8, 28.5, 29.4, 39.8, 50.4, 55.6, 57.1, 57.8, 66.6, 104.4, 127.6, 127.9, 128.0, 128.2, 137.2, 143.3, 154.6, 170.7, 195.6; HRMS (ESI): m/z calcd for C₂₆H₃₇NO₇Na (MNa⁺) 498.2462, found 498.2446.

(2R,5S)-Benzyl 2-(5,5-diethoxy-4-oxoheptyl)-5-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (14a). A solution of compound (13a) (0.15 g, 0.32 mmol) in anhydrous MeOH (10 mL) was subjected to hydrogenation (1 atm) in the presence of PtO₂ (15 mg) at room temperature for 5 h. The mixture was filtered over a Celite pad and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (14a) (0.11 g, 74%) as a colorless oil. [α]D²⁰ −1.6 (c 0.60, CHCl₃); IR (neat) 1737, 1691 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz, 295 °K) δ 0.68 (t, J = 7.5 Hz, 3H), 1.15 (t, J = 7.5 Hz, 6H), 1.21–1.57 (m, 3H), 1.59–1.76 (m, 8H), 2.29 (dd, J = 10, 15 Hz, 1H), 2.44–2.63 (m, 2H), 3.24–3.61 (m, 4H), 3.59–3.61 (s, 3H), 3.73–3.82 (m, 1H), 4.10–4.26 (m, 1H), 5.01–5.11 (m, 2H), 7.24–7.32 (m, 5H); ¹³C NMR (C₆D₆, 100 MHz, 343 °K) δ 7.3, 14.9, 19.8, 26.6, 28.8, 29.6, 35.1, 39.0, 40.1, 50.3, 55.5, 56.9, 58.5, 66.3, 104.6, 127.2, 127.5, 127.7, 137.3, 154.6, 170.6, 207.7; HRMS (ESI): m/z calcd for C₂₆H₃₉NO₇Na (MNa⁺) 500.2619, found 500.2602.

Methyl 2-((2S,5S)-5-(5,5-diethoxy-4-oxoheptyl)pyrrolidin-2-yl)acetate (3). A solution of compound (14a) (0.10 g, 0.21 mmol) in anhydrous MeOH (10 mL) was subjected to hydrogenation (1 atm) in the presence of 5% Pd/C (0.1 g) at 60 °C for 16 h. The mixture was filtered over a Celite pad and concentrated in vacuo. Silica gel column chromatography (CH₂Cl₂/7N NH₃ solution in MeOH 98:2) afforded compound (3) (0.35 g, 49%) as a colorless oil. [α]D²₀ +7.3 (c 3.00, CHCl₃); IR (neat) 3368 cm⁻¹;
\(^1\)H NMR (CDCl\(_3\), 250 MHz, 295 °K, rotamers) \(\delta\) 0.71 (t, \(J = 7.5\) Hz, 3H), 1.15 (t, \(J = 7.5\) Hz, 6H), 1.38–1.43 (m, 4H), 1.49–1.59 (m, 2H), 1.74–1.88 (m, 4H), 2.07 (ls, 1H), 2.42–2.46 (m, 2H), 2.51–2.66 (m, 2H), 3.01–3.06 (m, 1H), 3.31–3.55 (m, 5H), 3.65 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz, 295 °K) \(\delta\) 7.7, 15.4, 21.0, 26.9, 30.6, 30.7, 36.6, 39.7, 41.0, 51.4, 54.8, 57.2, 58.9, 104.7, 173.1, 210.2; HRMS (ESI): m/z calcd for C\(_{18}\)H\(_{34}\)NO\(_5\) (MH\(^+\)) 344.2431, found 344.2423.

**(2S,5S)-Benzyl 2-(4,5-dioxoheptyl)-5-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (15a).** A mixture of compound (14a) (0.5 g, 1.04 mmol) in CHCl\(_3\) (3 mL) and 50% aqueous TFA (6 mL) was stirred at room temperature for 16 h. The organic layer was decanted. The aqueous layer was extracted with CHCl\(_3\) (3 × 10 mL). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (15a) (0.36 g, 86%) as a yellow oil. \([\alpha]_{D20} \text{ (c 3.00, CHCl3)}\); IR (neat) 1698, 1675 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 250 MHz, 295 °K, rotamers) \(\delta\) 0.97 (t, \(J = 7.5\) Hz, 3H), 1.12–1.25 (m, 2H), 1.94–1.97 (m, 4H), 1.80–2.09 (m, 2H), 2.24 (dd, \(J = 10, 15\) Hz, 1H), 2.39–2.46 (m, 2H), 2.87–3.00 (m, 1H), 3.60 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz, 295 °K, rotamers) \(\delta\) 6.8, 19.6, 29.0, 29.4, 29.9, 34.6 and 34.9, 35.8, 39.9 and 40.4, 51.5, 55.2 and 55.5, 58.2 and 58.8, 66.7, 127.8, 127.9, 128.4, 136.7, 155.0, 171.6, 199.3, 200.0; HRMS (ESI): m/z calcd for C\(_{22}\)H\(_{29}\)NO\(_6\)Na (MNa\(^+\)) 426.1887, found 426.1887.

**Methyl 2-((3S,5R,8aS)-5-propionyloctahydroindolizin-3-yl)acetate (2a).** A solution of compound (15a) (0.2g, 0.49 mmol) in MeOH (10 mL) was subjected to hydrogenation (1 atm) in the presence of 10% Pd/C (0.2 g) at room temperature for 16 h. The mixture was filtered over a Celite pad and concentrated in vacuo at 20 °C. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (2a) (57 mg, 46%) as a colorless oil. \([\alpha]_{D20}^{0.70} \text{ (c 0.70, CHCl3)}\); IR (neat) 1740, 1680 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 250 MHz, 295 °K) \(\delta\) 0.97 (t, \(J = 7.5\) Hz, 3H), 1.12–1.52 (m, 5H), 1.63–2.12 (m, 6H), 2.18 (dd, \(J = 10, 15\) Hz, 1H), 2.38–2.75 (m, 4H), 2.93 (dd, \(J = 2.5, 10\) Hz, 1H), 3.60 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz, 295 °K) \(\delta\) 7.7, 24.2, 28.4, 29.4, 30.2, 30.4, 33.9, 40.7, 51.5, 61.2, 66.1, 73.6, 172.7, 213.4; HRMS (ESI): m/z calcd for C\(_{14}\)H\(_{24}\)NO\(_3\) (MH\(^+\)) 254.1750, found 254.747.

**(2S,5R)-Benzyl 2-(2-methylenebutyl)-5-(2-(tetrahydro-2H-pyran-2-oloxo)ethyl)pyrrolidine-1-carboxylate (10b).** To a cooled solution of N,O-dimethylhydroxylamine hydrochloride (0.94 g, 9.62 mmol) in THF (20 mL) at −78 °C was added dropwise a 2.5 M n-BuLi solution in hexanes (7.7 mL, 19.2 mmol). The reaction mixture was stirred for 15 min, then a solution of compound (10a) (0.39 g, 0.96
mmol) in THF (20 mL) was slowly added. After stirring for 2 h at −78 °C, the reaction was quenched by addition of saturated aqueous solution of NH₄Cl (15 mL) and allowed to warm to room temperature. The aqueous layer was extracted with AcOEt (3 × 15 mL). The organic layer was washed with brine (15 ml), dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude intermediate amide (0.4 g). The latter was dissolved in THF (45 mL) and cooled to −78 °C. Ethylmagnesium bromide (3 M in Et₂O, 1.3 mL, 3.68 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched by addition of saturated aqueous NH₄Cl solution (20 mL). The aqueous layer was extracted with AcOEt (2 × 10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (10b) (0.25 g, 65%) as a yellow oil (1:1 mixture of epimers at C-2 center of the THP group). IR (neat) 1697, 1682 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz, 343 °K) δ 0.90 (t, J = 8 Hz, 3H), 1.24–1.64 (m, 9H), 1.70–1.78 (m, 1H), 1.82–1.92 (m, 1H), 2.01–2.07 (m, 2H), 2.15–2.2 (m, 2H), 3.00–3.04 (m, 1H), 3.35–3.44 (m, 2H), 3.68–3.84 (m, 2H), 3.88–4.01 (m, 1H), 4.18–4.26 (m, 1H), 4.53–4.56 (m, 1H), 5.10 (s, 2H), 7.06–7.29 (m, 5H); ¹³C NMR (C₆D₆, 100 MHz, 343 °K) δ 7.3, 19.3, 25.5, 29.3, 29.4, 30.1, 30.7, 35.7, 35.8, 48.2, 55.1, 56.6, 61.5, 61.6, 64.6, 64.9, 66.4, 98.4 and 98.5, 127.6, 127.8, 128.2, 137.2, 154.5 and 154.6, 207.3; HRMS (ESI): m/z calcd for C₂₃H₃₃NO₅Na (MNa⁺) 426.2250, found 426.2248.

(2R,5S)-Benzyl 2-(2-hydroxyethyl)-5-(2-methylenebutyl)pyrrolidine-1-carboxylate (11b). To a solution of compound (10b) (0.16 g, 0.39 mmol) in EtOH (10 mL) was added PPTS (30 mg, 0.12 mmol). The reaction mixture was stirred at 50 °C for 16 h. The solvent was removed under vacuo and the residue was dissolved in CH₂Cl₂ (10 mL). The organic layer was washed with water (2 × 5 mL), dried over Na₂SO₄, filtrated and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (11b) (0.11 g, 84%) as a yellow oil. [α]D²⁰ −3.6 (c 2.00, CHCl₃); IR (neat) 3450, 1696 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz, 295 °K) δ 0.98 (t, J = 7.5 Hz, 3H), 1.55–1.68 (m, 4H), 1.96–2.04 (m, 1H), 2.24–2.44 (m, 4H), 3.02–3.09 (m, 1H), 3.54–3.71 (m, 2H), 4.08–4.25 (m, 3H), 5.08–5.22 (m, 2H), 7.28–7.35 (m, 5H); ¹³C NMR (CDCl₃, 62.5 MHz, 295 °K) δ 7.6, 30.1, 31.1, 36.4, 38.5, 49.1, 54.7, 55.6, 59.0, 67.3, 128.0, 128.2, 136.3, 156.5, 209.4; HRMS (ESI): m/z calcd for C₁₈H₂₆NO₄ (MH⁺) 320.1856, found 320.1860.

(2S,5R)-Benzyl 2-(2-oxobutyl)-5-(2-oxoethyl)pyrrolidine-1-carboxylate (12b). To a cooled solution of oxalyl chloride (0.31 mL of 2 M solution in CH₂Cl₂, 0.62 mmol) in CH₂Cl₂ (2 mL) at −60 °C was added dropwise DMSO (66 mL, 0.94 mmol). After stirring for 5 min, a solution of alcohol (11b) (0.1 g, 0.31 mmol) in CH₂Cl₂ (2 mL) was added dropwise. The reaction mixture was stirred at −60 °C for 40 min,
then NEt₃ (0.26 mL, 1.88 mmol) was added. The reaction mixture was allowed to warm to room temperature over 30 min. Saturated aqueous NaHCO₃ solution (15 mL) was added and the aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with saturated aqueous solution of NH₄Cl (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 4:6) afforded compound (12b) (0.09 g, 91%) as an oil. 

\[ \alpha_D^{20} -7.7 \ (c \ 1.00, \ CHCl_3); \ IR \ (neat) \ 1765, 1742 \ cm^{-1}; \ 1^H NMR \ (C_6D_6, 400 MHz, 343 ^\circ K) \ \delta \ 0.86 \ (t, \ J = 8 \ Hz, \ 3H), 1.17–1.23 \ (m, \ 1H), 1.28–1.33 \ (m, \ 1H), 1.53–1.58 \ (m, \ 1H), 1.68–1.73 \ (m, \ 1H), 1.98 \ (q, \ J = 8 \ Hz, \ 2H), 2.07–2.14 \ (m, \ 2H), 2.56–2.59 \ (m, \ 1H), 2.80–2.84 \ (m, \ 1H), 4.02–4.05 \ (m, \ 1H), 5.01–5.09 \ (m, \ 2H), 7.03–7.23 \ (m, \ 5H), 9.47 \ (s, \ 1H); \ 13^C NMR \ (C_6D_6, 100 MHz, 343^\circ K) \ \delta \ 7.1, 29.5 \ (2C), 35.7, 47.3, 49.4, 53.5, 54.8, 66.4, 127.1, 127.6, 128.1, 136.8, 154.1, 198.4, 207.0; \ HRMS \ (ESI): m/z \ calcd \ for \ C_{18}H_{24}NO_4 (MH^+) 318.1699, \ found 318.1703.

(2R,5S)-Benzyl 2-((E)-5,5-diethoxy-4-oxohept-2-enyl)-5-(2-oxobutyl)pyrrolidine-1-carboxylate (13b). To a solution of KHMDS (0.12 g, 0.62 mmol) in THF (10 mL) at 0 °C was added dropwise a solution of 3,3-diethoxy-2-oxopentylphosphonate (0.16 g, 0.57 mmol) in THF (5 mL). The reaction mixture was stirred at 0 °C for 15 min, then a solution of aldehyde (12b) (0.16 g, 0.52 mmol) in THF (5 mL) was added. Stirring was continued at 0 °C for 10 min then at 70 °C for 16 h. The reaction was quenched by addition of saturated aqueous solution of NH₄Cl (10 mL) and water (5 mL). The aqueous layer was extracted with Et₂O (6 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (13b) (0.2 g, 89%) as a yellow oil. 

\[ \alpha_D^{20} -2.5 \ (c \ 0.60, \ CHCl_3); \ IR \ (neat) \ 1740, 1696 \ cm^{-1}; \ 1^H NMR \ (C_6D_6, 400 MHz, 343^\circ K) \ \delta \ 0.80 \ (t, \ J = 8 \ Hz , \ 3H), 0.88 \ (t, \ J = 8 \ Hz, \ 3H), 1.11 \ (t, \ J = 8 \ Hz, \ 6H), 1.24–1.39 \ (m, \ 3H), 1.72–1.79 \ (m, \ 1H), 1.86 \ (q, \ J = 8 \ Hz, \ 2H), 2.02 \ (q, \ J = 8 \ Hz, \ 2H), 2.15 \ (dd, \ J = 12, 16 \ Hz, \ 1H), 2.22–2.31 \ (m, \ 1H), 2.40–2.52 \ (m, \ 1H), 2.95–2.99 \ (m, \ 1H), 3.38–3.50 \ (m, \ 4H), 3.75–3.84 \ (m, \ 1H), 4.16–4.23 \ (m, \ 1H), 5.04–5.15 \ (m, \ 2H), 6.83–7.07 \ (m, \ 2H), 7.12–7.27 \ (m, \ 5H); \ 13^C NMR \ (C_6D_6, 100 MHz, 343^\circ K) \ \delta \ 7.8 \ (2C), 15.6, 27.3, 29.1, 30.4, 36.4, 38.3, 48.2, 55.7, 57.6, 58.1, 67.1, 105.0, 128.2, 128.4, 128.5, 128.8, 137.7, 143.9, 155.0, 196.2, 207.7; \ HRMS \ (ESI): m/z \ calcd \ for \ C_{27}H_{39}NO_6Na (MNa^+) 496.2669, \ found 496.2669.

(2S,5S)-Benzyl 2-(5,5-diethoxy-4-oxoheptyl)-5-(2-oxobutyl)pyrrolidine-1-carboxylate (14b). A solution of compound (13b) (0.22 g, 0.45 mmol) in anhydrous MeOH (10 mL) was subjected to hydrogenation (1 atm) in the presence of PtO2 (22 mg) at room temperature for 16 h. The mixture was filtered over a Celite pad and concentrated in vacuo. Silica gel column chromatography
(cyclohexane/AcOEt 6:4) afforded compound (14b) (0.20 g, 93%) as a colorless oil. $[\alpha]_{D}^{20} +2.2$ (c 0.50, CHCl$_3$); IR (neat) 1733, 1669 cm$^{-1}$; $^1$H NMR (C$_6$D$_6$, 400 MHz, 343 °K) $\delta$ 0.75 (t, $J = 8$ Hz, 3H), 0.89 (t, $J = 8$ Hz, 3H), 1.11 (t, $J = 8$ Hz, 6H), 1.27–1.65 (m, 7H), 1.79–1.85 (m, 5H), 2.03 (q, $J = 8$ Hz, 2H), 2.20 (dd, $J = 8$, 16 Hz, 1H), 2.61 (t, $J = 8$ Hz, 2H), 3.00–3.04 (m, 1H), 3.35–3.39 (m, 2H), 3.75–3.85 (m, 1H), 4.22–4.30 (m, 1H), 5.12 (s, 2H), 7.07–7.30 (m, 5H); $^{13}$C NMR (C$_6$D$_6$, 100 MHz, 343 °K) $\delta$ 7.1, 7.2, 14.9, 19.8, 26.6, 28.8, 29.9, 35.1, 35.6, 38.9, 48.0, 55.0, 56.8, 58.3, 66.2, 104.5, 127.4, 127.6, 128.0, 137.2, 154.5, 207.1, 207.7; HRMS (ESI): m/z calcd for C$_{27}$H$_{41}$NO$_6$Na (MNa$^+$) 498.2826, found 498.2811.

(2S,5S)-Benzyl 2-(4,5-dioxoheptyl)-5-(2-oxobutyl)pyrrolidine-1-carboxylate (15b). A mixture of compound (14b) (0.25 g, 0.50 mmol) in CHCl$_3$ (2 mL) and 50% aqueous TFA (3 mL) was stirred at room temperature for 16 h. An aqueous saturated Na$_2$CO$_3$ solution was added (15 mL) and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (15b) (0.20 g, 99%) as a yellow oil. $[\alpha]_{D}^{20}$ $-$6.5 (c 1.00, CHCl$_3$); IR (neat) 1765, 1727 cm$^{-1}$; $^1$H NMR (C$_6$D$_6$, 400 MHz, 343 °K) $\delta$ 0.92–0.92 (m, 6H), 1.20–1.43 (m, 6H), 1.69–2.11 (m, 6H), 2.25–2.41 (m, 4H), 2.46–2.75 (m, 2H), 2.92 (dd, $J = 2.5$, 10 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 62.5 MHz, 295 °K) $\delta$ 6.8, 7.6, 19.6, 28.9 and 29.2, 29.45, 29.9 and 30.5, 34.6 and 34.9, 35.8, 36.3, 48.2 and 48.5, 54.5 and 55.2, 57.9 and 58.5, 66.7, 127.8, 127.9, 128.4, 136.7, 155.1, 199.5, 200.1, 209.7; HRMS (ESI): m/z calcd for C$_{23}$H$_{32}$NO$_5$ (MH$^+$) 402.2275, found 402.2271.

1-((3S,5R,8aS)-5-Propionyloctahydroindolizin-3-yl)butan-2-one (2b). A solution of compound (15b) (0.2 g, 0.49 mmol) in MeOH (10 mL) was subjected to hydrogenation (1 atm) in the presence of 5% Pd/C (40 mg) at room temperature for 16 h. The mixture was filtered over a Celite pad and concentrated in vacuo at 20 °C. Silica gel column chromatography (cyclohexane/AcOEt 6:4) afforded compound (2b) (60 mg, 50%) as a yellow oil. $[\alpha]_{D}^{20}$ $-$4.5 (c 1.00, CHCl$_3$); IR (neat) 1695 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz, 295 °K) $\delta$ 0.92 (t, $J = 7.5$ Hz, 3H), 0.94 (t, $J = 7.5$ Hz, 3H), 1.20–1.43 (m, 6H), 1.69–2.11 (m, 6H), 2.25–2.41 (m, 4H), 2.46–2.75 (m, 2H), 2.92 (dd, $J = 2.5$, 10 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 62.5 MHz, 295 °K) $\delta$ 7.7 (2C), 24.4,28.4, 29.9, 30.3, 30.7, 34.0, 36.5, 48.9, 60.1, 66.1, 73.4, 210.8, 213.2; HRMS (ESI): m/z calcd for C$_{15}$H$_{26}$NO$_2$ (MH$^+$) 252.1958, found 252.1955.

(4aS)-1-(1-Ethyl-3,4,4a,5,6,7-hexahydropyrrolo[2,1,5-c,d]indolizin-2-yl)propan-1-one (1).$^{2b}$ To a solution of compound (2b) (60 mg, 0.24 mmol) in EtOH (4 mL) was added lithium hydroxide
monohydrate (15 mg, 0.36 mmol). The reaction mixture was stirred at 80 °C for 18 h. The solvent was removed in vacuo and the residue purified by silica gel column chromatography (cyclohexane/AcOEt 7:3) to afford compound (1) (35 mg, 64%) as a yellow solid. mp 72-73 °C; [α]D 20 −65 (c 0.52, CH2Cl2); IR (neat) 1650 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 250 MHz, 295 °K) \(\delta\) 1.12 (t, \(J = 7.5\) Hz, 3H), 1.15 (t, \(J = 7.5\) Hz, 3H), 1.18–1.45 (m, 1H), 1.65–1.83 (m, 1H), 1.99–2.14 (m, 3H), 2.45–2.74 (m, 7H), 3.01–3.07 (m, 2H), 3.81–3.93 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz, 295 °K) \(\delta\) 8.7, 15.5, 19.3, 19.6, 22.3, 28.3, 29.9, 34.2, 63.1, 56.2, 116.1, 121.2, 125.0, 138.0, 196.7; HRMS (ESI): m/z calcd for C\(_{15}\)H\(_{22}\)NO (MH\(^+\)) 232.1695, found 232.1691.

REFERENCES


7. In order to optimize this reaction we attempted to obtain 2a directly from 14a by treating the latter under an hydrogen atmosphere in acidic medium in order to realize the in situ deprotection of the ketone function. However, the expected product (2a) was isolated in only 22% yield, showing that a two-step procedure was preferable.