Diversity-oriented synthesis of bicyclic and tricyclic alkaloids

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1. General experimental details

Reactions were performed using oven-dried glassware under an atmosphere of nitrogen with anhydrous, freshly distilled solvents when indicated only. Dichloromethane, ethyl acetate, methanol and n-hexane were distilled from calcium hydride. Anhydrous dimethylformamide (DMF) was used as obtained from commercial sources. All other reagents were used as obtained from commercial sources. Room temperature refers to ambient temperature. Temperatures of 0°C were maintained using an ice-water bath and temperatures below 0°C were maintained using an acetone-cardice bath. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. All flash chromatography was carried out using slurry-packed Merck 9325 Keiselgel 60 silica gel. Where possible, reactions were monitored by thin layer chromatography (TLC) performed on commercially prepared glass plates precoated with Merck silica gel 60 F254 or aluminium oxide 60 F254. Visualisation was by the quenching of UV fluorescence ($\lambda_{\text{max}} = 254$ nm) or by staining with ceric ammonium molybdate, potassium permanganate, iodine or Dragendorff’s reagent (0.08% w/v bismuth subnitrate and 2% w/v KI in 3M aq. AcOH). Infrared spectra were recorded on a Perkin-Elmer Spectrum One spectrometer with internal referencing. Selected absorption maxima ($\nu_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$). Melting points were obtained using a Büchi® melting point apparatus (model B-545) and are uncorrected. Proton magnetic resonance spectra were recorded using an internal deuterium lock at ambient probe temperatures on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz), Bruker Avance 500 BB ATM (500 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). Chemical shifts ($\delta_H$) are quoted in ppm, to the nearest 0.01 ppm, and are referenced to the residual non-deuterated solvent peak. Coupling constants ($J$) are reported in Hertz to the nearest 0.5 Hz. Data are reported as follows: chemical shift,
multiplicity [b, broad; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sept, septet; m, multiplet; or as a combination of these (e.g. dd, dt, etc.)], coupling constant(s), integration and assignment. Proton assignments were determined either on the basis of unambiguous chemical shift or coupling pattern, by patterns observed in 2D experiments ($^1$H-$^1$H COSY, HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds. NOESY experiments were used to determine the stereochemistry when necessary. Numbering of compounds for NMR assignment does not correspond to the numbering for nomenclature. Carbon magnetic resonance spectra were recorded by broadband proton spin decoupling at ambient probe temperatures using an internal deuterium lock on the following instruments: Bruker DPX-400 (100 MHz), Bruker Avance 400 QNP (100 MHz), Bruker Avance 500 BB ATM (125 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz). Chemical shifts ($\delta_C$) are quoted in ppm, to the nearest 0.1 ppm, and are referenced to the residual non-deuterated solvent peak. Assignments were supported by DEPT editing and determined either on the basis of unambiguous chemical shift, by patterns observed in 2D experiments (HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds. High resolution mass spectroscopy measurements were made by the EPSRC mass spectrometry service (Swansea) or recorded in-house using a Waters LCT Premier Mass Spectrometer or a Micromass Quadrupole-Time of Flight (Q-ToF) spectrometer. Mass values are reported within the error limits of ±5 ppm mass units. ESI = electrospray ionisation.
2. Synthesis of N-Boc-aminodialkenes

Undeca-1,10-dien-6-ol\textsuperscript{1,2}

\[
\begin{align*}
&\text{Br} \quad \text{O} \quad \text{H} \\
&\quad 5' \quad 3' \quad 1 \quad 2 \quad 4 \quad 5 \\
&\quad 6' \quad 4' \quad 2 \quad 3 \quad 3' \quad 2' \quad 5' \quad 4' \quad 3' \quad 2' \quad 5' \quad 4'
\end{align*}
\]

A suspension of magnesium turnings (2.5 equiv) and iodine (cat) in dry THF (2 mL/mmol of bromide) was prepared under nitrogen atmosphere. To this mixture, 5-bromo-1-pentene (2.5 equiv) was slowly added at rt. While the addition, an increase in the temperature of the reaction mixture confirmed the initiation of the Grignard formation. Once the addition of the bromide was completed, the mixture was allowed to stir at rt during 45 min, after which it was cooled down to 0 °C for the slow addition of ethyl formate (1.0 equiv). After the addition, the cold bath was removed and the mixture was stirred at rt overnight. The reaction was cooled down to 0 °C for quenching by addition of aqueous ammonium chloride (saturated solution). The resulting aqueous phase was extracted with diethyl ether (x3) and the final organic phase dried over magnesium sulphate, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica (elution with petrol ether (30/40):diethyl ether 15:1) to afford the final alcohol (98%) as a yellow oil ($R_f$ 0.22 (petroleum ether (30-40):diethyl ether 6:1)].

$\nu_{\text{max}} \text{ (CH}_2\text{Cl}_2/\text{cm}^{-1})$ 3329, 3077, 2978, 2931, 2860, 2338, 1827, 1641, 1458, 1440, 1415, 1325, 1068, 993, 908, 826 and 741; $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 5.80 (ddt, $J_1 = 17.0$ Hz, $J_2 = 10.2$ Hz, $J_3 = 6.7$ Hz, 2H, H-5, 5'), 4.99 (dq, $J_1 = 17.1$ Hz, $J_2 = 1.6$ Hz, 2H, H$_\text{trans-6A}$, 6'A), 4.94 (ddt, $J_1 = 10.2$ Hz, $J_2 = 2.3$ Hz, $J_3 = 1.2$ Hz, 2H, H$_\text{cis-6B}$, 6'B), 3.60 (m, 1H, H-1), 2.13-1.99 (m, 4H, H-4, 4'), 1.60-1.35 (m, 8H, H-2, 2', 3, 3'); $\delta_{\text{C}}$ (100 MHz; CDCl$_3$) 138.7 (CH-5 and 5'), 114.6 (CH-2 and 6'), 71.7 (CH-1), 36.9, 33.7 (CH$_2$-2, 2', 4 and 4'), 24.9 (CH$_2$-3 and 3').

Nona-1,8-dien-5-ol\textsuperscript{3,4}

\[
\begin{array}{c}
\text{Br} \\
\text{OH}
\end{array}
\xrightarrow{\text{O} \text{H}}
\begin{array}{c}
\text{OH} \\
\text{3' 4' 5'}
\end{array}
\]

The procedure described for the preparation of undeca-1,10-dien-6-ol was followed, using this time the Grignard of 4-bromo-1-butene. After the addition of ethyl formate at 0 °C, the reaction was stirred at rt, overnight. Quenching as described above and purification by flash chromatography on silica (elution with petroleum ether (30/40):diethyl ether 10:1), afforded the alcohol as a yellow oil in 94% yield [$R_f$ 0.31 (petroleum ether (30-40):diethyl ether 6:1)].

\[\nu_{\text{max}} (\text{CH}_2\text{Cl}_2/\text{cm}^{-1}) \quad 3345, 3078, 2978, 2933, 2848, 1641, 1449, 1416, 993, 908; \delta_{\text{H}} (400 \text{MHz}; \text{CDCl}_3) \quad 5.83 \text{ (ddt, } J_1 = 17.2 \text{ Hz, } J_2 = 10.4 \text{ Hz, } J_3 = 6.7 \text{ Hz, } \text{H-4, 4')}, \quad 5.04 \text{ (dq, } J_1 = 17.2 \text{ Hz, } J_2 = 1.6 \text{ Hz, } \text{H}_{\text{trans}}\text{-5A, 5'A}), \quad 4.96 \text{ (m, 2H, H}_{\text{cis}}\text{-5B, 5'B}), \quad 3.64 \text{ (m, 1H, H-1), 2.25-2.06 \text{ (m, 4H, H-3, 3')}, 1.62-1.47 \text{ (m, 4H, H-2, 2')}; \delta_{\text{C}} (100 \text{ MHz}; \text{CDCl}_3) \quad 138.5 \text{ (CH-4 and 4'), 114.8 (CH}_2\text{-5 and 5'), 71.0 (CH-1), 36.5, 30.0 (\text{CH}_2\text{-2, 2', 3 and 3'}).}

Deca-1,9-dien-5-ol\textsuperscript{1}

\[
\begin{array}{c}
\text{O} \\
\text{H}
\end{array}
\xrightarrow{\text{Br}}
\begin{array}{c}
\text{OH} \\
\text{5'} 4' 6'
\end{array}
\]

A suspension of magnesium turnings (2.0 equiv) and iodine (cat.) in dry THF (2 mL/mmol of bromide) was prepared at rt, under nitrogen atmosphere. To this mixture, 4-bromo-1-butene (2.0 equiv) was added slowly at rt While the addition, an increase in the temperature of the reaction mixture confirmed the initiation of the Grignard formation. Once the addition of the bromide was completed, the mixture was allowed to stir at rt during 1 h, after which it was cooled down to 0 °C for the slow addition of a solution of 5-hexenal (1.0 equiv) in dry THF (1mL/mmol of aldehyde). After the addition, the cold bath was removed and the mixture was stirred at rt overnight. The

reaction was cooled down to 0 °C for quenching by addition of aqueous ammonium chloride (saturated solution). The resulting aqueous phase was extracted with diethyl ether (x3) and the final organic phase dried over magnesium sulphate, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica (elution with petroleum ether (30/40):diethyl ether 8:1), to furnish the alcohol as a yellow oil in 51% yield \( [R_f 0.24 \text{ (petroleum ether (30-40):diethyl ether 4:1)}] \)

\[ \nu_{\text{max}} (\text{CH}_2\text{Cl}_2/\text{cm}^{-1}) \] 3327, 3078, 2977, 2931, 2858, 1641, 1440, 1416, 993, 908; \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 5.77 (ddt, \( J_1 = 17.0 \) Hz, \( J_2 = 10.3 \) Hz, \( J_3 = 6.6 \) Hz, 1H, H-5 or 5'), 5.74 (ddt, \( J_1 = 16.0 \) Hz, \( J_2 = 10.2 \) Hz, \( J_3 = 6.6 \) Hz, 1H, H-5 or 5'), 5.01-4.86 (m, 4H, H-6, 6'), 3.56 (m, 1H, H-1), 2.19-1.96 (m, 4H, H-4, 4'), 1.55-1.30 (m, 6H, H-2, 2', 3); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 139.1, 139.0 (CH-5 and 5'), 115.2, 115.0 (CH-6 and 6'), 71.7 (CH-1), 37.3, 36.9, 34.1, 30.5, 28.3, 25.3 (CH\(_2\)-2, 2', 3, 4 and 4').

**tert-Butyl N-(p-toluenesulfonyl)-N-[1-(4-pentenyl)-5-hexenyl]carbamate**

A mixture of triphenylphosphine (1.5 equiv), undeca-1,10-dien-6-ol (1.0 equiv) and tert-butyltosylcarbamate (1.5 equiv) in anhydrous THF (10 mL/mmol of alcohol), was prepared under nitrogen at rt. The mixture was stirred and cooled at -10 °C and diisopropyl azodicarboxylate (1.5 equiv) was added dropwise. The mixture was then stirred at that temperature for 30 min before heating up to 40 °C. After 24 h stirring, the solvent was removed under reduced pressure and the residue was purified by column chromatography (stepped gradient elution with petroleum ether (30/40) and petroleum ether:diethyl ether 50:1) to afford tert-butyl N-(p-toluenesulfonyl)-N-[1-(4-pentenyl)-5-hexenyl]carbamate as a yellow oil in 65% yield \( [R_f 0.23 \text{ (petroleum ether (30-40):diethyl ether 10:1)}] \)

\[ \nu_{\text{max}} (\text{CH}_2\text{Cl}_2/\text{cm}^{-1}) \] 3076, 2979, 2931, 2864, 1724, 1640, 1598, 1457, 1395, 1351, 1275, 1252, 1149, 1087, 992, 911, 841, 812, 770, 723, 669; \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 7.82 (d, \( J = \)
8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 5.78 (ddt, J₁ = 17.1 Hz, J₂ = 10.4 Hz, J₃ = 6.7 Hz, 2H, H-13, 13’), 4.99 (dq, J₁ = 17.5 Hz, J₂ = 1.2 Hz, 2H, Htrans-14A, 14’A), 4.95 (dq, J₁ = 10.9 Hz, J₂ = 1.2 Hz, 2H, Hcis-14B, 14’B), 4.39 (tt, J₁ = 8.4 Hz, J₂ = 6.4 Hz, 1H, H-9), 2.43 (s, 3H, H-8), 2.13-2.02 (m, 4H, H-12, 12’), 1.96-1.89 (m, 2H), 1.74-1.65 (m, 2H), 1.47-1.39 (m, 4H), 1.37 (s, 9H, H-3); δC (100 MHz; CDCl3) 151.0 (C-1), 143.8 (C-4), 138.3 (CH), 137.6 (C-7), 128.9 (CH), 128.3 (CH), 114.6 (CH₂-14 and 14’), 83.8 (C-2), 59.9 (CH-9), 33.3, 33.0 (CH₂-10, 10’, 12 and 12’), 27.5 (CH₃-3), 25.6 (CH₂-11 and 11’), 21.5 (CH₃-8); HRMS (ESI+) calcd for C₂₃H₃₅NO₄NaS (M + Na)+ 444.2185, found 444.2195.

*tert*-Butyl N-(p-toluenesulfonyl)-N-[1-(3-butenyl)-4-pentenyl]carbamate⁴,⁵

Compound *tert*-butyl N-(p-toluenesulfonyl)-N-[1-(3-butenyl)-4-pentenyl]carbamate was prepared from nona-1,8-dien-5-ol, according to the procedure described for the preparation of *tert*-butyl N-(p-toluenesulfonyl)-N-[1-(4-pentenyl)-5-hexenyl]carbamate. The reaction was stirred for 18 h at 40 °C, after which the solvent was removed under reduced pressure and the residue was purified by column chromatography (stepped gradient elution with petroleum ether (30/40) and petroleum ether (30/40):diethyl ether 30:1), to afford *tert*-butyl N-(p-toluenesulfonyl)-N-[1-(3-butenyl)-4-pentenyl]carbamate as a pale yellow oil in 65% yield [Rf 0.26 (petroleum ether (30-40):diethyl ether 15:1)]

νmax (CH₂Cl₂/cm⁻¹) 2979, 2929, 1724, 1641, 1598, 1455, 1395, 1352, 1278, 1253, 1149, 1087, 978, 911, 843, 813, 770, 724, 705, 670; δH (400 MHz; CDCl₃) 7.82 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.83 (ddt, J₁ = 16.9 Hz, J₂ = 10.3 Hz, J₃ = 6.4 Hz, 2H, H-12, 12’), 5.04 (dd, J₁ = 17.0 Hz, J₂ = 1.2 Hz, 2H, Htrans-13A, 13’A), 4.99 (dd, J₁ = 10.4 Hz, J₂ = 1.2 Hz, 2H, Hcis-13B, 13’B), 4.39 (btt, J₁ = 8.1 Hz, J₂ = 6.4 Hz, 1H, H-9), 2.43 (s, 3H, H-8), 2.15-1.97 (m, 4H, H-11, 11’, 10A, 10’A), 1.86-1.77 (m, 2H, H-10B, 10’B), 1.37 (s, 9H, H-3); δC (100 MHz; CDCl₃) 151.4 (C-1), 144.3 (C-4), 138.2 (CH), 138.0

(C-7), 129.4 (CH), 128.8 (CH), 115.4 (CH2-13 and 13'), 84.4 (C-2), 59.6 (CH-9), 33.4, 31.5 (CH2-10, 10', 11 and 11'), 28.4 (CH3-3), 22.0 (CH3-8); HRMS (ESI+) calcd for C21H31NO4NaS (M + Na)+ 416.1871, found 416.1889.

tert-Butyl N-(p-toluenesulfonyl)-N-[1-(3-butenyl)-5-hexenyl]carbamate


tert-Butyl N-(p-toluenesulfonyl)-N-[1-(3-butenyl)-5-hexenyl]carbamate was prepared from deca-1,9-dien-5-ol, according to the procedure described for the preparation of tert-butyl N-(p-toluenesulfonyl)-N-[1-(4-pentenyl)-5-hexenyl]carbamate. The reaction was stirred for 18 h at 40 °C, after which the solvent was removed under reduced pressure and the residue was purified by column chromatography (stepped gradient elution with petroleum ether (30/40) and petroleum ether (30/40):diethyl ether 50:1, 30:1 and 20:1), to afford tert-butyl N-(p-toluenesulfonyl)-N-[1-(3-butenyl)-5-hexenyl]carbamate as a yellow oil in 78% yield [Rf 0.21 (petroleum ether (30-40):diethyl ether 20:1)]

νmax (CH2Cl2/cm⁻¹) 3076, 2979, 2931, 2866, 1776, 1724, 1641, 1598, 1456, 1395, 1350, 1276, 1250, 1149, 1087, 991, 911, 841, 813, 770, 723, 706, 669; δH (400 MHz; CDCl3) 7.82 (d, J = 8.0 Hz, 2HAr), 7.29 (d, J = 8.0 Hz, 2HAr), 5.83 (ddt, J1 = 17.0 Hz, J2 = 10.4 Hz, J3 = 6.4 Hz, 1H, H-13'), 5.78 (ddt, J1 = 17.1 Hz, J2 = 10.3 Hz, J3 = 6.7 Hz, 1H, H-13'), 5.07-4.93 (m, 4H, H-14, 14'), 4.41 (m, 1H, H-9), 2.43 (s, 3H, H-8), 2.16-2.00 (m, 4H, H-12, 12'), 2.06-1.64 (m, 4H), 1.46-1.38 (m, 2H), 1.37 (s, 9H, H-3); δC (100 MHz; CDCl3) 149.2 (C-1), 142.1 (C-4), 136.6, 136.1 (CH-13 and 13'), 135.9 (C-7), 127.2, 126.6 (CH-5, 5', 6, 6'), 113.2, 112.9 (CH2-14 and 14'), 82.1 (C-2), 57.8 (CH-9), 31.6, 31.3, 31.1, 29.4 (CH2-10, 10', 12 and 12'), 26.2 (CH3-3), 24.4 (CH2-11), 19.8 (CH3-8); HRMS (ESI+) calcd for C22H33NO4NaS (M + Na)+ 430.2028, found 430.2011.
**tert-Butyl N-[1-(4-pentenyl)-5-hexenyl]carbamate**

Magnesium turnings (5.0 equiv) were added to a solution of tert-butyl N-(p-toluenesulfonyl)-N-[1-(4-pentenyl)-5-hexenyl]carbamate (1.0 equiv) in anhydrous methanol (18 mL/mmol of tert-butyl N-(p-toluenesulfonyl)-N-[1-(4-pentenyl)-5-hexenyl]carbamate) and the mixture was sonicated until the total consumption of the starting material (4 h). The reaction was then stopped by dilution with dichloromethane and quenching with diluted hydrochloric acid (10%). The phases were separated and the aqueous phase was extracted with dichloromethane. The final organic phase was dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica, eluting with petroleum ether (30/40):diethyl ether 20:1, 15:1 and 10:1, to furnish the desired product as a pale cream oil in 62% yield [Rf 0.4 (petroleum ether (30/40):diethyl ether 10:1)]

$\nu_{\text{max}}$ (CH$_2$Cl$_2$/cm$^{-1}$) 3348, 2977, 2931, 2859, 1686, 1641, 1522, 1456, 1442, 1390, 1365, 1248, 1172, 1053, 1026, 994, 909, 868, 778; $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 5.78 (ddt, $J_1 = 17.1$ Hz, $J_2 = 10.3$ Hz, $J_3 = 6.8$ Hz, 2H, H-8, 8'), 4.99 (dq, $J_1 = 17.2$ Hz, $J_2 = 1.5$ Hz, 2H, H$_{\text{trans}}$-9A, 9'A), 4.94 (bdq, $J_1 = 10.4$ Hz, 2H, H$_{\text{cis}}$-9B, 9'B), 4.22 (bb, 1H, NH), 3.56 (bb, 1H, H-4), 2.05 (m, 4H, H-7, 7'), 1.50-1.30 (m, 8H, H-5, 5', 6, 6'), 1.44 (s, 9H, H-3); $\delta_{\text{C}}$ (100 MHz; CDCl$_3$) 153.9 (C-1), 136.9 (CH-8 and 8'), 112.8 (CH$_2$-9 and 9'), 77.1 (C-2), 48.6 (CH-4), 33.3, 31.8 (CH$_2$-5, 5', 7 and 7'), 26.7 (CH$_3$-3), 25.5 (CH$_2$-6 and 6'); HRMS (ESI$^+$) calcd for C$_{16}$H$_{29}$NO$_2$Na (M + Na)$^+$ 290.2096, found 290.2076.
**tert-Butyl N-[1-(3-butenyl)-4-pentenyl]carbamate**

The carbamate following the procedure described above. The reaction mixture was subjected to sonication until complete consumption of the starting material (4 h, tlc analysis). As described, the reaction was stopped by dilution with dichloromethane and quenching with diluted hydrochloric acid (10%). The phases were separated and the aqueous phase was extracted with dichloromethane. The final organic phase was dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica, eluting with petroleum ether (30/40):diethyl ether 10:1, to furnish the desired product as a low melting point white solid in 89% yield [mp 35.8-36.8 °C (petroleum ether (30/40):diethyl ether), $R_f$ 0.33 (petroleum ether (30/40):diethyl ether 10:1)]

$\nu_{\text{max}}$ (CH$_2$Cl$_2$/cm$^{-1}$) 3334, 2977, 2928, 2854, 2163, 2010, 1688, 1591, 1366, 1247, 1169, 1119, 1072, 993, 909, 776; $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 5.81 (ddt, $J_1 = 16.9$ Hz, $J_2 = 10.3$ Hz, $J_3 = 6.6$ Hz, 2H, H-7, 7'), 5.02 (dq, $J_1 = 17.2$ Hz, $J_2 = 1.6$ Hz, 2H, H$_\text{trans}$-8A, 8'A), 4.96 (bdq, $J_1 = 10.2$ Hz, 2H, H$_\text{cis}$-8B, 8'B), 4.26 (bd, $J = 8.8$ Hz, 1H, NH), 3.56 (bm, 1H, H-4), 2.10 (m, 4H, H-6, 6'), 1.59-1.52 (m, 2H, H-5A, 5'A), 1.48-1.38 (m, 2H, H-5B, 5'B), 1.44 (s, 9H, H-3); $\delta_{\text{C}}$ (100 MHz; CDCl$_3$) 156.0 (C-1), 138.6 (CH-7 and 7'), 115.2 (CH$_2$-8 and 8'), 79.3 (C-2), 50.3 (CH-4), 35.3, 30.6 (CH$_3$-5, 5', 6 and 6'), 28.8 (CH$_3$-3); HRMS (ESI$^+$) calcd for C$_{14}$H$_{25}$NO$_2$Na (M + Na)$^+$ 262.1783, found 262.1782.

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**tert-Butyl N-[1-(3-butenyl)-5-hexenyl]carbamate**

The carbamate following the procedure described above. The reaction mixture was subjected to sonication until complete consumption of the starting material (4 h, tlc analysis). As described, the reaction was stopped by dilution with dichloromethane and quenching with diluted hydrochloric acid (10%). The phases were separated and the aqueous phase was extracted with dichloromethane. The final organic phase was dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica, eluting with petroleum ether (30/40):diethyl ether 20:1, to furnish the desired product as a pale yellow oil, in 80% yield [\(R_f\) 0.28 (petroleum ether (30/40):diethyl ether 15:1)]

\[\nu_{\text{max}} (\text{CH}_2\text{Cl}_2/\text{cm}^{-1}) 3337, 3077, 2978, 2931, 2859, 1685, 1641, 1521 (\text{bb}), 1452, 1390, 1365, 1246, 1169, 1050, 994, 908, 864, 778, 748; \delta_\text{H} (400 \text{ MHz; CDCl}_3) 5.81 (\text{ddt}, J_1 = 17.2 \text{ Hz}, J_2 = 10.7 \text{ Hz}, J_3 = 6.6 \text{ Hz}, 1\text{H, H-8 or 8'}), 5.78 (\text{ddt}, J_1 = 17.2 \text{ Hz}, J_2 = 10.4 \text{ Hz}, J_3 = 6.8 \text{ Hz}, 1\text{H, H-8 or 8'}), 5.02 (\text{dq}, J_1 = 17.1 \text{ Hz}, J_2 = 1.6 \text{ Hz}, 1\text{H, H}_{\text{trans}}-8\text{A or 8' A}), 5.00 (\text{dq}, J_1 = 17.2 \text{ Hz}, J_2 = 1.6 \text{ Hz}, 1\text{H, H}_{\text{trans}}-8\text{A or 8' A}), 4.97-4.92 (\text{m}, 2\text{H, H}_{\text{cis}}-8\text{B, 8'B}), 4.24 (\text{bd}, J = 7.6 \text{ Hz}, 1\text{H, NH}), 3.58 (\text{bb}, 1\text{H, H-4}), 2.15-2.00 (\text{m}, 4\text{H, H-7, 7'}), 1.62-1.25 (\text{m}, 6\text{H, H-5, 5', 6}), 1.44 (\text{s}, 9\text{H, H-3}); \delta_\text{C} (100 \text{ MHz; CDCl}_3) 156.0 (\text{C-1}), 138.6, 138.2 (\text{CH-8 and 8'}), 114.7, 114.6 (\text{CH}_2-9 \text{ and 9'}), 78.0 (\text{C-2}), 50.1 (\text{CH-4}), 34.9, 33.6, 30.2 (\text{CH}_3-5, 5', 7 and 7'), 28.3 (\text{CH}_3-3), 25.1 (\text{CH}_2-6); \text{HRMS (ESI') calcd for C}_{15}\text{H}_{25}\text{NO}_2\text{Na (M+Na)}^+ 276.1939, \text{found 276.1895.}
(2E, 11E)-Diethyl 7-(tert-butoxycarbonylamino)trideca-2,11-dienedioate 1a

In a dry flask, a 0.08M solution of tert-butyl N-[1-(4-pentenyl)-5-hexenyl]carbamate (1.0 equiv) in ethyl acrylate was prepared and degassed (nitrogen bubbling during 10-15 min), at rt. To the degassed solution, Hoveyda-Grubbs second generation catalyst (3 mol%) was added solid and nitrogen was again bubbled in the reaction mixture for 10 min more. After this time, the mixture was allowed to stir under nitrogen atmosphere for 24 h. The reaction crude was then loaded directly in a column for removal of the ethyl acrylate and purification of the final product. Gradient elution with petroleum ether (30/40):diethyl ether from 6:1 to 1:1, afforded the desired (E,E) isomer 1a [95%, yellow oil, Rf 0.23 (petroleum ether (30/40):diethyl ether 2:1)], along with the isomer (E,Z)-1a [3%, colorless oil, Rf 0.28 (petroleum ether (30/40):diethyl ether 2:1)].

1a: \( \nu_{\text{max}} \) (CH\textsubscript{2}Cl\textsubscript{2}/cm\textsuperscript{-1}) 3361, 2980, 2931, 2856, 1805, 1697 (bb), 1653, 1519, 1455, 1391, 1366, 1266, 1170, 1096, 1044, 983, 859, 780; \( \delta_H \) (400 MHz; CDCl\textsubscript{3}) 6.92 (dt, \( J_{\text{trans}} = 15.7 \) Hz, \( J_2 = J_3 = 6.9 \) Hz, 2H, H-8, 8'), 5.81 (dt, \( J_{\text{trans}} = 15.7 \) Hz, \( J_2 = J_3 = 1.4 \) Hz, 2H, H-9, 9'), 4.20 (bb, 1H, NH), 4.16 (q, \( J = 7.3 \) Hz, 4H, H-11, 11'), 3.56 (bb, 1H, H-4), 2.17 (m, 4H, H-7, 7'), 1.55-1.44 (m, 6H, H-5, 5', 6, 6'), 1.44 (s, 9H, H-3), 1.40-1.30 (m, 2H, H-5, 5', 6, 6'), 1.28 (t, \( J = 7.3 \) Hz, 6H, H-12, 12'); \( \delta_C \) (100 MHz; CDCl\textsubscript{3}) 167.0 (C-10 and 10'), 156.1 (C-1), 149.0 (CH-8 and 8'), 122.0 (CH-9 and 9'), 79.5 (C-2), 60.6 (CH\textsubscript{2}-11 and 11'), 50.5 (CH-4), 35.6, 32.3 (CH\textsubscript{2}-5, 5', 7 and 7'), 28.8 (CH\textsubscript{3}-3), 24.8 (CH\textsubscript{2}-6 and 6'), 14.7 (CH\textsubscript{3}-12); HRMS (ESI\textsuperscript{+}) calcd for C\textsubscript{22}H\textsubscript{37}NO\textsubscript{6}Na (M + Na)
\textsuperscript{+} 434.2519, found 434.2541.
\( (2Z, 11E) \)-Diethyl 7-\((\text{tert-butoxycarbonylamino})\)trideca-2,11-dienedioate \((E,Z)-1a: \)

\[ \delta_H (400 \text{ MHz}; \text{CDCl}_3) 6.92 (1 \text{H}, H-8), 6.17 (\text{dt}, J_{\text{cis}} = 11.5 \text{ Hz}, J_2 = J_3 = 7.7 \text{ Hz}, 1 \text{H}, H-8'), 5.81 (1 \text{H}, H-9), 5.75 (\text{dt}, J_{\text{cis}} = 11.5 \text{ Hz}, J_2 = J_3 = 1.5 \text{ Hz}, 1 \text{H}, H-9'), 4.20 (\text{bb}, 1 \text{H}, \text{NH}), 4.16 (4 \text{H}, H-11, 11'), 3.56 (\text{bb}, 1 \text{H}, H-4), 2.64 (\text{m}, 2 \text{H}, H-7'), 2.17 (\text{m}, 2 \text{H}, H-7), 1.55-1.44 (\text{m}, 6 \text{H}, H-5, 5', 6, 6'), 1.44 (\text{s}, 9 \text{H}, H-3), 1.40-1.30 (\text{m}, 2 \text{H}, H-5, 5', 6, 6'), 1.28 (6 \text{H}, H-12, 12').
\]

\( (2E, 9E) \)-Diethyl 6-\((\text{tert-butoxycarbonylamino})\)undeca-2,9-dienedioate \(1b\)

The carbamate \(1b\) was prepared following the procedure described above. After 24 h stirring at rt, the reaction crude was loaded directly in a column for removal of the ethyl acrylate and purification of the final product. Stepped gradient elution with petroleum ether (30/40):ethyl acetate 10:1, 8:1, 6:1, 5:1 and 4:1, afforded the desired \((E,E)\) isomer \(1b\) [96%, colorless oil, \(R_f 0.33\) (petroleum ether (30/40):ethyl acetate 4:1)], along with the isomer \((E,Z)-1b\) [4%, colorless oil, \(R_f 0.42\) (petroleum ether (30/40):ethyl acetate 4:1)].

\(1b: \nu_{\text{max}} (\text{CH}_2\text{Cl}_2/\text{cm}^{-1}) 3362, 2979, 2928, 2163, 2014, 1713 (\text{bb}), 1654, 1520, 1450, 1391, 1366, 1265, 1244, 1169, 1095, 1044, 981, 863; \delta_H (400 \text{ MHz}; \text{CDCl}_3) 6.92 (\text{dt}, J_{\text{trans}} = 15.6 \text{ Hz}, J_2 = J_3 = 6.8 \text{ Hz}, 2 \text{H}, H-7, 7'), 5.81 (\text{bd}, J_{\text{trans}} = 15.6 \text{ Hz}, 2 \text{H}, H-8, 8'), 4.28 (\text{bd}, J = 8.4 \text{ Hz}, 1 \text{H}, \text{NH}), 4.17 (\text{q}, J = 7.1 \text{ Hz}, 4 \text{H}, H-10, 10'), 3.59 (\text{bb}, 1 \text{H}, H-4), 3.56 (\text{bb}, 1 \text{H}, H-4),
\]
2.25 (m, 4H, H-6, 6'), 1.67-1.55 (m, 2H, H-5¸, 5'¸), 1.55-1.45 (m, 2H, H-5B, 5'B), 1.43 (s, 9H, H-3), 1.27 (t, J = 7.2 Hz, 6H, H-11, 11'); δ 1H (400 MHz; CDCl3) 6.87 (dt, Jtrans = 15.6 Hz, J2 = J3 = 6.8 Hz, 1H, H-7), 6.16 (dt, Jcis = 11.2 Hz, J2 = J3 = 7.6 Hz, 1H, H-7'), 5.75 (bdt, Jtrans = 15.6 Hz, 1H, H-8), 5.71 (bdt, Jcis = 11.6 Hz, J2 = J3 = 1.4 Hz, 1H, H-8'), 4.32 (bd, J = 8.4 Hz, 1H, NH), 4.11 (q, J = 7.2 Hz, 2H, H-10 or H-10'), 4.10 (q, J = 7.2 Hz, 2H, H-10 or H-10'), 3.54 (bb, 1H, H-4), 2.72-2.61 (m, 1H, H-6' A), 2.62-2.50 (m, 1H, H-6' B), 2.26-2.13 (m, 2H, H-6), 1.64-1.52 (m, 2H, H-5¸, 5'¸), 1.52-1.40 (m, 2H, H-5B, 5'B), 1.37 (s, 9H, H-3), 1.22 (t, J = 7.1 Hz, 3H, H-11 or 11'), 1.21 (t, J = 7.1 Hz, 3H, H-11 or 11'); HRMS (ESI⁺) calcd for C_{20}H_{33}NO_6Na (M + Na)⁺ 406.2206, found 406.2202.

(E,Z)-1b: v_{max} (CH_2Cl_2/cm^{-1}) 3362, 2928, 2846, 2163, 2006, 1718 (bb), 1667, 1523, 1456, 1367, 1264, 1176, 1042; δ 1H (400 MHz; CDCl3) 6.87 (dt, Jtrans = 15.6 Hz, J2 = J3 = 6.8 Hz, 1H, H-7), 6.16 (dt, Jcis = 11.2 Hz, J2 = J3 = 7.6 Hz, 1H, H-7'), 5.75 (bdt, Jtrans = 15.6 Hz, 1H, H-8), 5.71 (bdt, Jcis = 11.6 Hz, J2 = J3 = 1.4 Hz, 1H, H-8'), 4.32 (bd, J = 8.4 Hz, 1H, NH), 4.11 (q, J = 7.2 Hz, 2H, H-10 or H-10'), 4.10 (q, J = 7.2 Hz, 2H, H-10 or H-10'), 3.54 (bb, 1H, H-4), 2.72-2.61 (m, 1H, H-6' A), 2.62-2.50 (m, 1H, H-6' B), 2.26-2.13 (m, 2H, H-6), 1.64-1.52 (m, 2H, H-5¸, 5'¸), 1.52-1.40 (m, 2H, H-5B, 5'B), 1.37 (s, 9H, H-3), 1.22 (t, J = 7.1 Hz, 3H, H-11 or 11'), 1.21 (t, J = 7.1 Hz, 3H, H-11 or 11'); HRMS (ESI⁺) calcd for C_{20}H_{33}NO_6Na (M + Na)⁺ 406.2206, found 406.2202.

(2E, 10E)-Diethyl 6-(tert-butoxycarbonylamino)dodeca-2,10-dienedioate 1c

The carbamate 1c was prepared following the procedure described above. After 24 h stirring at rt, the reaction crude was loaded directly in a column for removal of the ethyl acrylate and purification of the final product. Stepped gradient elution with petroleum ether (30/40):diethyl ether 20:1, 15:1, 6:1, 3:1 and 2:1, afforded the desired (E,E) isomer 1c [81%, colorless oil, R: 0.16 (petroleum ether (30/40):diethyl ether 2:1)], along
with traces of an \((E,Z)\) isomer [5%, yellow oil, \(R_f\) 0.21 (petroleum ether (30/40):diethyl ether 2:1)].

\[\text{max (CH}_2\text{Cl}_2/\text{cm}^{-1})\] 3353, 2997, 2936, 2359, 2191, 1713 (bb), 1653, 1519, 1446, 1366, 1265, 1169, 1041, 979, 853; \(\delta_1\) (400 MHz; CDCl_3) 6.94 (dt, \(J_{\text{trans}} = 15.6\) Hz, \(J_2 = J_3 = 6.6\) Hz, 1H, H-8 or 8'), 6.92 (dt, \(J_{\text{trans}} = 15.6\) Hz, \(J_2 = J_3 = 6.6\) Hz, 1H, H-8 or 8'), 5.82 (dt, \(J_{\text{trans}} = 15.6\) Hz, \(J_2 = 1.6\) Hz, 1H, H-9 or 9'), 5.81 (dt, \(J_{\text{trans}} = 15.6\) Hz, \(J_2 = 1.6\) Hz, 1H, H-9 or 9'), 4.23 (bb, 1H, NH), 4.18 (2q, \(J = 7.2\) Hz, 4H, H-11, 11'), 3.58 (bb, 1H, H-4), 2.28-2.15 (m, 4H, H-7, 7'), 1.67-1.35 (m, 6H, H-5, 5', 6), 1.44 (s, 9H, H-3), 1.27 (2t, \(J = 7.2\) Hz, 6H, H-12, 12'); \(\delta_c\) (100 MHz; CDCl_3) 164.5 (C-10 and 10'), 153.5 (C-1), 146.4, 146.1 (CH-8 and 8'), 119.7 (CH-9 and 9'), 77.5 (C-2), 58.1 (CH_2-11 and 11'), 48.1 (CH-4), 33.1, 32.1, 29.8, 26.8, 22.3 (CH_2-5, 5', 6, 7 and 7'), 26.3 (CH_3-3), 12.2 (CH_3-12); HRMS (ESI^+) calcd for C_{21}H_{35}NO_6Na (M + Na)^+ 420.2362, found 420.2356.

3. Folding cascades from aminodialkenes

\((1R, 3aS, 6aR, 9aR)/(1S, 3aR, 6aS, 9aS)-\text{Ethyl 2-oxododecahydropyrido[2,1,6-de]quinolizine-1-carboxylate 3a}\)

A dry flask was equipped with a Dean-Stark trap containing anhydrous toluene and a few pieces of sodium metal. In the flask, a solution of 1a (1.0 equiv) was prepared in anhydrous toluene (30mL/mmol of 1a), at rt, under nitrogen atmosphere. On this solution, stannous (II) triflate (0.5 equiv) was added solid in one portion and the mixture was heated up to reflux. After 24 h, no starting material could be observed on tlc and the reaction was stopped by cooling down to rt. The reaction mixture was then diluted with ethyl acetate and a saturated aqueous solution of sodium bicarbonate. The phases were separated and the aqueous phase was extracted (x3) with ethyl acetate. The final combination of the organic phases was dried over magnesium sulfate and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (gradient
elution using mixtures dichloromethane:acetone 10:0.5 and 10:1), to obtain 3a as a white solid [mp 60.4-61.4 °C (DCM)] in 72% yield: \( R_f 0.6 \) (silica, DCM:acetone 9:1); crystallization by slow evaporation of a solution in dichloromethane, at rt]. Along with 1a, trans-2a [colorless oil, 2%, \( R_f 0.3 \) (silica, DCM:acetone 9:1)] and cis-2a [colorless oil, 7%, \( R_f 0.1 \) (silica, DCM:acetone 9:1)] were isolated.

1a: \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)/cm\(^{-1}\)) 2930, 2860, 2800, 1743, 1700, 1445, 1370, 1338, 1324, 1303, 1264, 1182, 1152, 1139, 1112, 1046, 982, 856, 756, 678; \( \delta_H \) (400 MHz; CDCl\(_3\)) 4.19 (dq, \( J_{\text{gem}} = 10.8 \) Hz, \( J_{\text{vec}} = 7.2 \) Hz, 1H, H-14\(_A\)), 4.14 (dq, \( J_{\text{gem}} = 10.8 \) Hz, \( J_{\text{vec}} = 7.2 \) Hz, 1H, H-14\(_B\)), 3.25 (d, \( J = 11.6 \) Hz, 1H, H-1), 2.58 (bddd, \( J_1 = J_2 = 10.6 \) Hz, \( J_3 = 2.4 \) Hz, 1H, H-12), 2.33 (dd, \( J_{\text{gem}} = 25.3 \) Hz, \( J_{\text{vec}} = 13.2 \) Hz, 1H, H-3\(_A\)), 2.29 (m, 1H, H-4), 2.28 (dd, \( J_{\text{gem}} = 25.3 \) Hz, \( J_{\text{vec}} = 2.0 \) Hz, 1H, H-3\(_B\)), 1.93 (bt, \( J = 8.2 \) Hz, 1H, H-8), 1.67-1.54 (m, 6H, H-5\(_A\), 6\(_A\), 7\(_A\), 9\(_A\), 10\(_A\), 11\(_A\)), 1.43-1.27 (m, 6H, H-5\(_B\), 6\(_B\), 7\(_B\), 9\(_B\), 10\(_B\), 11\(_B\)), 1.22 (t, \( J = 7.2 \) Hz, 3H, H-15); \( \delta_C \) (125 MHz; CDCl\(_3\)) 203.0 (C-2), 168.7 (C-13), 64.3 (CH-12), 63.7 (CH-1), 62.7 (CH-8), 61.8 (CH-4), 61.0 (CH\(_2\)-14), 48.3 (CH\(_2\)-3), 34.5 (CH\(_2\)-5), 33.8, 33.5 (CH\(_2\)-7 and 9), 33.0 (CH\(_2\)-11), 23.7, 23.6 (CH\(_2\)-6 and 10), 14.17 (CH\(_3\)-15); HRMS (ESI\(^+\)) calcd for C\(_{15}\)H\(_{24}\)NO\(_3\) (M + H\(^+\)) 266.1751, found 266.1716.

Crystallization and X-ray diffraction on 3a: Suitable crystals of 3a were obtained after dissolving this compound in a small volume of dichloromethane. A vial with a screw top allowed the slow evaporation of the solvents at rt, to the formation of colorless crystals. Relevant crystal data: empirical formula C\(_{15}\)H\(_{23}\)NO\(_3\), \( M_w = 265.34 \), \( T = 100(2) \) K, crystal system triclinic, space group P-1, unit cell dimensions \( a=8.6717(2) \) Å, \( b=8.8865(2) \) Å, \( c=9.6551(2) \) Å and \( \alpha=86.555(1)^\circ \), \( \beta=72.478(1)^\circ \), \( \gamma=80.643^\circ \), \( V = 700.02(3) \) Å\(^3\), \( Z=2 \), \( D=1.259 \) Mg/m\(^3\) (calculated), \( \mu(\text{MoK})=0.087 \) mm\(^{-1}\), collected/independent reflections 12,361/4060 \( [R_{\text{int}}=0.0271] \), final \( R \) indices \( [I>2\sigma(I)] R_{I}=0.0412 \) and \( wR_2=0.1107 \), GOF=1.080. CCDC number 746888.
(±)-Diethyl octahydro-1H-quinolizine-4,6-diyl)diacetate, \( \text{trans-}2a \): \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)/cm\(^{-1}\)) 2923, 2852, 1736; \( \delta_H \) (500 MHz; CDCl\(_3\)) 4.13 (qd, \( J_1 = 7.2 \) Hz, \( J_2 = 1.5 \) Hz, 3H, H-13), 4.12 (q, \( J = 7.2 \) Hz, 3H, H-13'), 3.59 (m, 1H, H-12), 2.81 (dd, \( J_{\text{gem}} = 14.6 \) Hz, \( J_{\text{vec}} = 4.3 \) Hz, 1H, H-2\(_A\)), 2.70 (m, 1H, H-4), 2.61 (dd, \( J_{\text{gem}} = 14.3 \) Hz, \( J_{\text{vec}} = 3.0 \) Hz, 1H, H-2'\(_A\)), 2.49 (dd, \( J_{\text{gem}} = 14.3 \) Hz, \( J_{\text{vec}} = 10.7 \) Hz, 1H, H-2'\(_B\)), 2.23 (dddd, \( J_1 = J_2 = 10.8 \) Hz, \( J_3 = J_4 = 2.5 \) Hz, 1H, H-8), 2.19 (dd, \( J_{\text{gem}} = 14.6 \) Hz, \( J_{\text{vec}} = 8.5 \) Hz, 1H, H-2\(_B\)), 1.70-1.67 (m, 1H, H-5\(_A\)), 1.67-1.45 (m, 8H), 1.35-1.31 (m, 1H, H-5\(_B\)), 1.30-1.12 (m, 2H), 1.25 (t, \( J = 7.1 \) Hz, 3H, 14 or 14'), 1.24 (t, \( J = 7.1 \) Hz, 3H, H-14 or 14'); \( \delta_C \) (125 MHz; CDCl\(_3\)) 173.3 (C-1'), 172.5 (C-1), 60.4 (CH\(_2\)-13 and 13'), 55.1 (CH-4), 54.3 (CH-8), 50.9 (CH-12), 39.0 (CH\(_2\)-2), 34.7 (CH\(_2\)), 34.4 (CH\(_2\), 32.7 (CH\(_2\)-5), 29.4 (CH\(_2\)), 27.5 (CH\(_2\)-2'), 23.8 (CH\(_2\)), 18.5 (CH\(_2\)), 14.2 (CH\(_3\)-14 and 14'); HRMS (ESI\(^+\)) caleld for C\(_{17}\)H\(_{30}\)NO\(_4\) (M + H\(^+\)) 312.2175, found 312.2171.

(±)-Diethyl octahydro-1H-quinolizine-4,6-diyl)diacetate, \( \text{cis-}2a \): \( \delta_H \) (500 MHz; CDCl\(_3\)) 4.14 (dq, \( J_{\text{gem}} = 10.8 \) Hz, \( J_{\text{vec}} = 7.1 \) Hz, 2H, H-13\(_A\), 13\(_A'\)\), 4.10 (dq, \( J_{\text{gem}} = 10.8 \) Hz, \( J_{\text{vec}} = 7.1 \) Hz, 2H, H-13\(_B\), 13\(_B'\)\), 3.42 (m, 1H, H-4, 12), 3.16 (m, 1H, H-8), 2.71 (dd, \( J_{\text{gem}} = 14.9 \) Hz, \( J_{\text{vec}} = 7.0 \) Hz, 2H, H-2\(_A\), 2'\(_A\)\), 2.26 (dd, \( J_{\text{gem}} = 14.9 \) Hz, \( J_{\text{vec}} = 6.3 \) Hz, 2H, H-2\(_B\), 2'\(_B\)\), 1.74 (m, 2H, H-5\(_A\), 11\(_A\)\), 1.65 (m, 2H, H-5\(_B\), 11\(_B\)\), 1.60-1.50 (m, 4H, H-6\(_A\), 6\(_B\), 10\(_A\), 10\(_B\)\), 1.28 (m, 2H, H-7\(_A\), 9\(_A\)\), 1.15 (m, 2H, 7\(_B\), 9\(_B\)\); \( \delta_C \) (125 MHz; CDCl\(_3\)) 172.8 (C-1 and 1'), 60.2 (CH\(_2\)-13 and 13'), 50.2 (CH-4 and 12), 49.9 (CH-8), 39.4 (CH\(_2\)-2 and 2'), 27.7 (CH\(_2\)-7 and 9), 27.3 (CH\(_2\)-5 and 11), 20.0 (CH\(_2\)-6 and 10), 14.3 (CH\(_3\)-14 and 14').
(4R,6R)/(4S,6S)-Diethyl 2,2′-(octahydro-1H-quinolizine-4,6-diyl)diacetate, 
trans-2a²

In a dry flask, a solution of 1a (1.0 equiv) was prepared in anhydrous toluene (30 mL/mmol of 1a), at rt, under nitrogen atmosphere. The solution was cooled to 0 °C before the addition of 3.0 equiv of the Lewis acid (aluminium chloride (1M in nitrobenzene) or scandium triflate), after which the cold bath was removed and the mixture was heated up to reflux. After 20 h, no starting material could be observed on tlc and the reaction was stopped by cooling down to rt and dilution with ethyl acetate and a saturated aqueous solution of sodium bicarbonate. The phases were separated and the aqueous phase was extracted (x3) with ethyl acetate. The final combination of the organic phases was dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica gel. Elution with mixtures petroleum ether (30/40):diethyl ether 2:1→ 1.5:1, afforded trans-2a as a colorless oil in 43% (AlCl₃) or 50% yield (Sc(OTf)₃), and elution with mixtures ethyl acetate:acetone 1:1 and 0:1 afforded the monocycle in 13% (AlCl₃) or 21% yield (Sc(OTf)₃).

Decahydro-1H-pyrido[2,1,6-de]quinolin-2-one

A solution of 3a (1.0 equiv) in ethanol (26 mL/mmol of 3a) was prepared at rt. On this solution, sodium carbonate (5.0 equiv, 10% solution in water) was added at rt and the mixture was taken to a 100 °C preheated oil bath. After stirring 24 h at this temperature,
no starting material could be detected on tlc analysis. After cooling down to rt, the reaction was diluted with distilled water and dichloromethane and the phases were separated. The basic aqueous phase was extracted (x 3) with dichloromethane and the resulting organic phases were combined, dried over magnesium sulfate and evaporated under vacuum. The residue was purified by flash chromatography using Alumina (pH 7, activity I) and eluting with dichloromethane:acetone 9:1 mixture. This way, decahydro-1H-pyrido[2,1,6-de]quinolizin-2-one was obtained as a colorless oil in 76% yield [RF 0.2 (alumina plate, dichloromethane); RF 0.4 (silica plate, dichloromethane:acetone 2:1)].

\[ \nu_{\text{max}}(\text{CH}_2\text{Cl}_2/cm^{-1}) \, 2928, \, 2860, \, 2789, \, 1740, \, 1444, \, 1385, \, 1327, \, 1278, \, 1178, \, 1117, \, 1107, \, 1090, \, 1061, \, 1033, \, 995, \, 869, \, 746; \delta (\text{CDCl}_3) \, 2.37 \, (dd, J_{\text{gem}} = 13.3 \, \text{Hz}, J_{\text{vec}} = 13.3 \, \text{Hz}, 2H, \, H-1A, \, 3A), \, 2.24 \, (dd, J_{\text{gem}} = 13.3 \, \text{Hz}, J_{\text{vec}} = 1.1 \, \text{Hz}, 1H, \, H-1B, \, 3B), \, 2.22 \, (m, \, 2H, \, H-4, \, 12), \, 1.90 \, (bddd, \, J_1 = J_2 = 10.5 \, \text{Hz}, J_3 = J_4 = 2.1 \, \text{Hz}, 1H, \, H-8), \, 1.71-1.68 \, (m, \, 2H, \, H-6A, \, 10A), \, 1.64-1.60 \, (m, \, 2H, \, H-5A, \, 11A), \, 1.62-1.60 \, (m, \, 2H, \, H-7A, \, 9A), \, 1.48-1.29 \, (m, \, 6H, \, H-5B, \, 6B, \, 7B, \, 9B, \, 10B, \, 11B); \delta_C \, (125 \, \text{MHz}; \, \text{CDCl}_3) \, 208.2 \, (C-2), \, 62.8 \, (CH-8), \, 62.4 \, (CH-4 \, and \, 12), \, 48.8 \, (CH_2-1 \, and \, 3), \, 34.4 \, (CH_2-5 \, and \, 11), \, 33.6 \, (CH_2-7 \, and \, 9), \, 23.8 \, (CH_2-6 \, and \, 10); \, \text{HRMS (ESI+)} \, \text{calcd for C}_{12}H_{20}NO \, (M + H)^+ \, 194.1545, \, \text{found 194.1541.}

2-Methylenedecahydropyrido[2,1,6-de]quinolizine 4

Methyltriphenylphosphonium bromide (1.8 equiv) was dried in the reaction flask, by heating at 120 °C, under high vacuum, for 2 h. After this time, the flask was allowed to cool down to rt, after which it was purged with nitrogen. Anhydrous tetrahydrofuran (12 mL/mmol of phosphonium salt) was then added to the flask to make a white suspension that was then cooled to -78 °C for the addition of n-butyllithium (1.5M in hexanes, 1.5 equiv). The cold bath was then removed and the bright yellow mixture was stirred at rt for 2 h. After this time, a solution of the ketone (1.0 equiv) in anhydrous THF (12
mL/mmol of ketone) was slowly added at rt and the final mixture was heated up to 69 °C. After 3 h stirring at this temperature, no starting material could be observed on tlc and the reaction was stopped by cooling down to rt and dilution with ethyl acetate and distilled water. The phases were separated and the organic phase was washed with distilled water (x 3), dried over magnesium sulfate and evaporated under vacuum. The residue was purified by flash chromatography (Alumina pH 7, activity I). Elution with petroleum ether (30/40): ethyl acetate 25:1 mixture, afforded the product 4 in 61% yield [colorless oil, \( R_f \) 0.3 (alumina plate, petroleum ether (30/40):diethyl ether 15:1); \( R_f \) 0.2 (silica plate, dichloromethane:acetone 4:1)].

\[ \nu_{\text{max}} (\text{CH}_2\text{Cl}_2/\text{cm}^{-1}) \] 2926, 2858, 2789, 2753, 2728, 2619, 1657, 1444, 1383, 1320, 1115, 1036, 997, 967, 880, 868, 745; \( \delta_\text{H} \) (500 MHz; CDCl\(_3\)) 4.57 (s, 2H, H-13), 2.15-2.05 (m, \( J_{1A-12} = J_{3A-4} = 2.3 \text{ Hz}, J_{1B-12} = J_{3B-4} = 12.8 \text{ Hz}, 4H, H-1A, 1B, 3A, 3B), 1.86-1.81 (m, 3H, H-4, 8, 12), 1.67-1.65 (m, 2H, H-6A, 10A), 1.60-1.54 (m, 4H, H-5A, 7A, 9A, 11A), 1.41-1.27 (m, 6H, H-5B, 6B, 7B, 9B, 10B, 11B); \( \delta_\text{C} \) (125 MHz; CDCl\(_3\)) 146.2 (C-2), 106.1 (CH\(_2\)-13), 63.5 (CH-4 and 12), 62.6 (CH-8), 42.4 (CH\(_2\)-1 and 3), 34.0, 33.9 (CH\(_2\)-5, 7, 9 and 11), 24.0 (CH\(_2\)-6 and 10); HRMS (ESI\(^+\)) calcd for C\(_{13}\)H\(_{22}\)N (M + H\(^+\)) 192.1752, found 192.1750.

(2r, 3aR, 7ar, 10aS)-2-Methyldecahydropyrido-1H-[2,1,6-de]quinolizine, myrrhine\(^7\)

A solution of 4 (1.0 equiv) in methanol was prepared at rt. On this solution, \( p \)-toluenesulfonic acid (1.5 equiv) was added and the mixture was stirred at rt for 15 min, to allow the formation of the \( p \)-toluenesulfonic salt of 4. After this time, Raney Nickel\(^\circledast\) (slurry in water) was added and the flask was purged with hydrogen (slightly higher

pressure of hydrogen than the atmospheric was required for the reaction to proceed. The progress of the reaction was controlled by tlc and until consumption of the starting material could be verified by tlc (after 3-9 h stirring at rt). The catalyst was then removed by filtration through a thin lay of Celite® while washing with methanol. Evaporation of the filtrate under vacuum yielded a white solid that was identified as the \( p \)-toluenesulfonic salt of myrrhine [mp 192.0-194 °C (MeOH)]. The solid was dissolved in distilled water and this aqueous phase was washed with ethyl acetate (x3). The final aqueous phase was then taken to pH 8-10 by addition of sodium bicarbonate (saturated solution in water) and the basic aqueous phase was extracted with dichloromethane (x3). The final organic phase was dried over magnesium sulfate and evaporated under vacuum. \(^1\)H- and \(^13\)C-NMR of the residue showed the peaks corresponding to myrrhine as the only visible diastereoisomer. Further purification was performed by flash chromatography (Alumina pH 7, activity I; elution with mixture petroleum ether (30/40):ethyl acetate 25:1), to yield two colorless oils that were identified as myrrhine (52%) and its epimer \textit{epi-myrrhine} (5%).

\[ \text{myrrhine}^9: \nu_{\text{max}} (\text{CH}_2\text{Cl}_2/cm^{-1}) 2926, 2857, 2787, 2726, 2616, 1446, 1386, 1324, 1256, 1222, 1131, 1122, 1067, 1044, 1022, 997, 747; \delta_H (500 MHz; \text{CDCl}_3) 1.88-1.76 (m, H-4, 8, 12), 1.68-1.60 (bb, 2H, H-6A, 10A), 1.58-1.48 (bm, 6H, H-1A, 3A, 5A, 7A, 9A, 11A), 1.49-1.42 (bb, 1H, H-2), 1.39-1.28 (bm, 6H, H-5B, 6B, 7B, 9B, 10B, 11B), 1.09-0.97 (bm, 2H, H-1B, 3B), 0.85 (d, \( J = 6.2 \) Hz, 3H, H-13); \delta_C (125 MHz; \text{CDCl}_3) 62.5 (CH-8), 62.1 (CH-4 and 12), 42.6 (CH\textsubscript{2}-1 and 3), 34.0, 33.9 (CH\textsubscript{2}-5, 7, 9 and 11), 30.3 (CH-2), 20.3 (CH-6)\].

\(^8\) Both isomers present similar \( R_f \) on alumina plates \([R_f 0.3 \text{ (petroleum ether (30/40):ethyl acetate 20:1)}\] and silica plates \([R_f 0.24 \text{ (acetone)}]\). Myrrhine elutes in the first fractions while its epimer elutes afterwards.

24.2 (CH2-6 and 10), 22.0 (CH3-13); HRMS (ESI+) calcd for C13H24N (M + H)+ 194.1909, found 194.1918.

**epi-myrrhine:** \(v_{\text{max}}\) (CH2Cl2/cm\(^{-1}\)) 2926, 2850, 2497, 2100, 1744, 1463; \(\delta_H\) (500 MHz; CDCl3) 2.65-2.61 (m, 3H, H-4, 8, 12), 2.28 (ddt, \(J_1 = 26.4\) Hz, \(J_2 = 13.7\) Hz, \(J_3 = J_4 = 4.0\) Hz, 4H, H-5\(_A\), 7\(_A\), 9\(_A\), 11\(_A\)), 1.98 (ddd, \(J_1 = 25.3\) Hz, \(J_2 = 13.1\) Hz, \(J_3 = 1.5\) Hz, 2H, H-1\(_A\), 3\(_A\)), 1.87 (dquint, \(J_{\text{gem}} = 13.5\) Hz, \(J_2 = J_3 = J_4 = J_5 = 3.3\) Hz, 2H, H-6\(_A\), 10\(_A\)), 1.71 (m, 7H, H-1\(_B\), 2, 3\(_B\), 5\(_B\), 7\(_B\), 9\(_B\), 11\(_B\)), 1.48 (qt, \(J_1 = J_2 = J_3 = 13.5\) Hz, \(J_4 = J_5 = 3.7\) Hz, 2H, H-6\(_B\), 10\(_B\)), 0.98 (d, \(J = 6.5\) Hz, 3H, H-13); \(\delta_C\) (125 MHz; CDCl3) 65.4 (CH-8), 65.2 (CH-4 and 12), 38.5 (CH2-1 and 3), 30.4, 30.3 (CH2-5, 7, 9 and 11), 29.6 (CH-2), 22.7 (CH2-6 and 10), 21.0 (CH3-13); HRMS (ESI+) calcd for C13H24N (M + H)+ 194.1909, found 194.1958.

**myrrhine:pTsOH:** \(v_{\text{max}}\) (CH2Cl2/cm\(^{-1}\)) 3399, 2952, 2873, 2711, 2652, 2167, 1599, 1496, 1453, 1428, 1226, 1200, 1168, 1118, 1036, 1012, 998, 970, 949, 827, 799, 680; \(\delta_H\) (500 MHz; CD3OD) 7.70 (bd, \(J = 7.7\) Hz, 2H, H-2', 6'), 7.23 (bd, \(J = 7.1\) Hz, 2H, H-3', 5'), 3.07-2.98 (m, 3H, H-4, 8, 12), 2.36 (s, 3H, CH3-Ar), 1.89-1.84 (m, 6H, H-1\(_A\), 3\(_A\), 5\(_A\), 7\(_A\), 9\(_A\), 11\(_A\)), 1.82-1.76 (m, 3H, H-2, 6\(_A\), 10\(_A\)), 1.66-1.50 (m, 6H, H-5\(_B\), 6\(_B\), 7\(_B\), 9\(_B\), 10\(_B\), 11\(_B\)), 1.15 (m, 2H, H-1\(_B\), 3\(_B\)), 0.94 (d, \(J = 6.5\) Hz, 3H, H-13); \(\delta_C\) (125 MHz; CDCl3) 143.6 (C-1'), 141.8 (C-4'), 130.0 (CH-3' and 5'), 127.0 (CH-2' and 6'), 65.5 (CH-8), 65.2 (CH-4 and 12), 40.5 (CH2-1 and 3), 32.4, 33.3 (CH2-5, 7, 9 and 11), 29.7 (CH-2),
(2r, 3aR, 7aR, 10aS)-2-Methyl dodecahydro-1H-pyrido[2,1,6-de]quinolizine-4-oxide; myrrhine-N-oxide

A solution of 1 (1.0 equiv) in dichloromethane (100 mL/mmol of 1) was prepared at rt and cooled to 0 °C for the addition of solid m-chloroperbenzoic acid (57-86%, 1.6-2.4 equiv). The mixture was stirred at 0 °C for 4 h, after which the consumption of the starting material and the formation of the new product were checked by tlc and LCMS. The reaction was then stopped by removal of the solvent under vacuum. Myrrhine-N-oxide was purified by flash chromatography on alumina (pH 7, activity I), eluting with a mixture dichloromethane:methanol 10:0.3 [white solid, 96%, Rf 0.2 (silica plate, acetone:methanol 3:1)].

\[ \text{max (CH}_2\text{Cl}_2/\text{cm}^{-1}) \text{ 2923, 2870, 1646, 1445, 975, 922, 761; } \delta_H (500 \text{ MHz; CDCl}_3) \text{ 3.20-2.90 (m, 3H, H-4, 8, 12), 2.13 (dddd, } J_1 = J_2 = J_3 = 13.1 \text{ Hz, } J_4 = 3.6 \text{ Hz, } 4H, H-5_A, 7_A, 9_A, 11_A), 1.87 \text{ (ddd, } J_1 = J_2 = J_3 = 12.7 \text{ Hz, } 2H, H-1_A, 3_A), 1.68 \text{ (dquint, } J_{\text{gem}} = 13.3 \text{ Hz, } J_2 = J_3 = J_4 = J_5 = 2.6 \text{ Hz, } 2H, H-6_A, 10_A), 1.64 \text{ (bb, 1H, H-2), 1.49-1.38 (m, 2H, H-6_B, 10_B), 1.34-1.28 (m, 6H, H-1_B, 3_B, 5_B, 7_B, 9_B, 11_B), 0.90 (d, } J = 6.5 \text{ Hz, } 3H, H-13); \delta_C (125 \text{ MHz; CDCl}_3) \text{ 73.6 (CH-8), 73.3 (CH-4 and 12), 35.5 (CH}_2\text{-1 and 3), 27.3, 27.2 (CH}_2\text{-5, 7, 9 and 11), 29.7 (CH-2), 23.0 (CH}_2\text{-6 and 10), 21.3 (CH}_3\text{-13); HRMS (ESI+) calcd for C}_{13}\text{H}_{24}\text{NO (M + H)}^+ \text{ 210.1858, found 210.1864.} \]
Method A (Lewis acid mediated): In a dry flask, a solution of 1b (1.0 equiv) was prepared in anhydrous dichloromethane (30 mL/mmol of 1b), at rt, under nitrogen atmosphere. The solution was cooled to 0 °C before the addition of 1.1 equiv of aluminium chloride (1M in nitrobenzene), after which the cold bath was removed and the mixture was allowed to stir at rt. After 24 h, no starting material could be observed on tlc and the reaction was stopped by cooling down to rt and dilution with dichloromethane. The organic phase was washed with sodium bicarbonate (saturated solution in water). The phases were separated and the organic phase was dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica gel. First, elution with mixtures petroleum ether (30/40):ethyl acetate 2:1, 1:2 and 0:1, afforded cis-2b as a colorless oil in 28% yield, and elution with ethyl acetate:acetone 1:1 afforded trans-2b as a colorless oil in 42% yield.

Method B (Trifluoroacetic acid mediated): The acyclic compound 1b was dissolved in a mixture of anhydrous dichloromethane/trifluoroacetic acid 4/1 (60 mL/mmol of 1b), at rt, under nitrogen. The mixture was allowed to stir during 24 h, after which no starting material was visible on tlc. The reaction was stopped by dilution with dichloromethane and washes of the organic phase with sodium bicarbonate (saturated solution in water). The final organic phase was dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was purified by flash chromatography, as described above, to furnish cis-2b in 34% and trans-2b in 53% yield.

cis-2b: Rf 0.28 (ethyl acetate:acetone 1:1); νmax (CH2Cl2/cm⁻¹) 2966, 2925, 2854, 1728, 1464, 1369, 1269, 1173, 1107, 1031, 952, 720; δH (400 MHz; CDCl3) 4.13 (bq, J = 7.2

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Hz, 4H, H-11 and 11’), 3.59 (m, 1H, H-7), 3.20 (bquint, J = 6.5 Hz, 2H, H-4, 10), 2.55 (dd, \( J_{\text{gem}} = 15.0 \) Hz, \( J_{\text{vec}} = 5.8 \) Hz, 2H, H-2\(_{\Lambda}\), 2’\(_{\Lambda}\)), 2.25 (dd, \( J_{\text{gem}} = 14.8 \) Hz, \( J_{\text{vec}} = 8.0 \) Hz, 1H, H-2\(_{\Pi}\), 2’\(_{\Pi}\)), 2.05-1.91 (m, 4H, H-5\(_{\Lambda}\), 6\(_{\Lambda}\), 8\(_{\Lambda}\), 9\(_{\Lambda}\)), 1.54-1.39 (m, 4H, 5\(_{\Pi}\), 6\(_{\Pi}\), 8\(_{\Pi}\), 9\(_{\Pi}\)), 1.26 (t, \( J = 7.2 \) Hz, 6H, H-12, 12’); \( \delta \text{C} \) (100 MHz; CDCl\(_3\)) 172.0 (C-1 and 1’), 64.8 (CH-7), 63.3 (CH-4 and 10), 60.6 (CH\(_2\)-11 and 11’), 42.0 (CH\(_2\)-2 and 2’), 31.8, 31.6 (CH\(_2\)-5, 6, 8 and 9), 14.6 (CH\(_3\)-12 and 12’); HRMS (ESI\(^+\)) calcd for C\(_{15}\)H\(_{26}\)NO\(_4\) (M + H\(^+\)) 284.1862, found 284.1877.

**trans-2b**: \( R_f 0.12 \) (ethyl acetate:acetone 1:1); \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)/cm\(^{-1}\)) 2962, 2921, 2839, 1733, 1472, 1369, 1175, 1030; \( \delta \text{H} \) (400 MHz; CDCl\(_3\)) 4.21-4.10 (m, 4H, H-11 and 11’), 3.65 (m, 1H, H-7), 3.55 (m, 1H, H-10), 3.37 (bquint, \( J = 6.8 \) Hz, 1H, H-4), 2.85 (dd, \( J_{\text{gem}} = 14.5 \) Hz, \( J_{\text{vec}} = 5.3 \) Hz, 1H, H-2\(_{\Lambda}\)), 2.53 (dd, \( J_{\text{gem}} = 15.2 \) Hz, \( J_{\text{vec}} = 5.1 \) Hz, 1H, H-2\(_{\Pi}\)), 2.33 (dd, \( J_{\text{gem}} = 15.2 \) Hz, \( J_{\text{vec}} = 8.5 \) Hz, 1H, H-2\(_{\Pi}\)), 2.27 (dd, \( J_{\text{gem}} = 14.5 \) Hz, \( J_{\text{vec}} = 9.6 \) Hz, 1H, H-2\(_{\Pi}\)), 2.12 (tdd, \( J_1 = 13.56 \) Hz, \( J_2 = 5.4 \) Hz, \( J_3 = 1.3 \) Hz, 1H, H-6\(_{\Lambda}\)), 2.06-1.98 (m, 2H, H-5\(_{\Lambda}\), 8\(_{\Lambda}\)), 1.88 (m, 1H, H-9\(_{\Lambda}\)), 1.68-1.56 (m, 2H, H-5\(_{\Pi}\), 6\(_{\Pi}\)), 1.46-1.30 (m, 2H, H-8\(_{\Lambda}\), 9\(_{\Pi}\)), 1.26 (t, \( J = 7.2 \) Hz, 6H, H-12, 12’); \( \delta \text{C} \) (100 MHz; CDCl\(_3\)) 172.5, 172.4 (C-1 and 1’), 66.5 (CH-7), 60.9, 60.7 (CH\(_2\)-11 and 11’), 58.6 (CH-10), 55.1 (CH-4), 42.7 (CH\(_2\)-2), 37.0 (CH\(_2\)-2’), 34.4 (CH\(_2\)-6), 32.6 (CH\(_2\)-8), 32.4 (CH\(_2\)-5), 30.5 (CH\(_2\)-9), 14.6 (CH\(_3\)-12 and 12’); HRMS (ESI\(^+\)) calcd for C\(_{15}\)H\(_{26}\)NO\(_4\) (M + H\(^+\)) 284.1862, found 284.1880.

\[ \text{(2aS,4aS,7aR)/(2aR,4aR,7aS)-Ethyl 6-hydroxy-1,2,2a,3,4,4a,7,7a-octahydropyrrolo[2,1,5-cd]indolizine-5-carboxylate, cis-3b} \]

In a dry flask, a solution of diisopropylamine (2.5 equiv) in dry THF (3 mL/mmol of diisopropylamine) was prepared under nitrogen, at rt. The solution was cooled to -18 °C and \( n \)-butyllithium (1.5 equiv) was added dropwise. The mixture was stirred at -18 °C for 30 min,\(^{11}\) after which a solution of **cis-2b** (1.0 equiv) in dry THF (5 mL/mmol) was

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slowly added. The reaction was stirred at -18 °C for 24 h, after which analysis by tlc revealed the permanence of only traces of the starting material. The reaction was then cooled down to -78 °C, quenched by addition of distilled water, and transferred to a separating funnel. There, it was diluted with ethyl acetate and a saturated aqueous solution of sodium bicarbonate and the phases were separated. The aqueous phase was still extracted with ethyl acetate (x 3), and the final combination of the organic phases was dried over magnesium sulfate and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (stepped gradient elution using mixtures chloroform:2.0M methanolic ammonia:methanol 10:0.1:0.1, 10:0.1:0.2 and 10:0.1:0.5) to furnish the final tricycle as a yellow oil in 38% yield \([R_f 0.24 \text{ (silica, chloroform:2.0M methanolic ammonia:methanol 10:0.1:0.7)}]\)

\[v_{\text{max}} \text{(CH}_2\text{Cl}_2/cm^{−1}) 3415 (bb), 3323 (bb), 2947, 2926, 1731, 1665, 1615, 1543, 1463, 1262, 1217, 1172, 1097; δ_{\text{H}} (500 MHz; CDCl}_3 4.20 (dq, J_1 = 10.8 Hz, J_2 = 7.1 Hz, 1H, H-12a), 4.08 (dq, J_1 = 10.8 Hz, J_2 = 7.1 Hz, 1H, H-12b), 4.02 (bb, 1H, H-7), 3.24 (bb, 1H, H-10), 3.01 (bb, 1H, H-4), 2.76 (dt, J_1 = 13.5 Hz, J_3 = 8.3 Hz, 1H, H-6a), 2.51 (bm, 1H, H-9a), 2.27 (dd, J_{\text{gem}} = 16.7 Hz, J_{\text{vec}} = 10.6 Hz, 1H, H-3a), 1.90-1.66 (m, 7H, H-3b, 5a, 5b, 6b, 8a, 8b, 9b), 1.26 (t, J = 7.1 Hz, 3H, H-13); δ_{\text{C}} (125 MHz; CDCl}_3 63.0 (CH-4), 58.9 (CH-12), 48.8 (CH-7), 46.8 (CH-10), 40.6 (CH-6), 35.8 (CH-9), 30.7 (CH-3), 27.7, 25.6 (CH-5 and 8), 14.5 (CH-13); HRMS (ESI\(^+\)) calcd for C_{13}H_{19}NO_3 (M) 237.1365, found 237.1627.

\((2aR,4aR,7aR)/(2aS,4aS,7aS)-\text{Ethyl 6-hydroxy-1,2,2a,3,4,4a,7,7a-octahydropyrrolo[2,1,5-cd]indolizine-5-carboxylate trans-3b}\)

The tricycle \(\text{trans-3b}\) was prepared from the bicycle \(\text{trans-2b}\), following the procedure above. After 24 h stirring at -18°C, analysis by tlc showed the permanence of only traces of the starting material and the formation of a new product. The reaction was then cooled down to -78 °C, quenched by addition of distilled water, and transferred to a
There, it was diluted with ethyl acetate and a saturated aqueous solution of sodium bicarbonate and the phases were separated. The aqueous phase was still extracted with ethyl acetate (x 3), and the final combination of the organic phases was dried over magnesium sulfate and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (stepped gradient elution using mixtures chloroform:2.0M methanolic ammonia:methanol 10:0.1:0.1 and 10:0.1:2) to furnish the final tricycle as a yellow solid in 91% yield [mp 71.0-72.0 °C (CHCl₃:MeOH); Rₖ 0.29 (silica, chloroform:2.0M methanolic ammonia:methanol 10:0.1:0.4)]

ν max (CH₂Cl₂/cm⁻¹) 2961, 2899, 2869, 1732, 1646, 1610, 1466, 1407, 1377, 1352, 1280, 1262, 1226, 1179, 1064, 840; δH (400 MHz; CDCl₃) 4.26 (dq, J₁ = 10.8 Hz, J₂ = 7.0 Hz, 1H, H-12A), 4.20 (dq, J₁ = 10.8 Hz, J₂ = 7.0 Hz, 1H, H-12B), 3.80 (dd, J₁ = 9.6 Hz, J₂ = 6.4 Hz, 1H, H-4), 3.58 (m, 1H, H-7), 2.62 (tt, J₁ = 10.4 Hz, J₂ = 4.0 Hz, 1H, H-10), 2.40 (dd, J gem = 16.8 Hz, J vec = 4.0 Hz, 1H, H-3A), 2.33 (ddd, J gem = 16.8 Hz, J vec = 10.4 Hz, J₂ = 0.8 Hz, 1H, H-3B), 2.32-2.24 (m, 1H, H-8A), 2.17-2.04 (m, 2H, H-5A, 6A), 2.00-1.91 (m, 1H, H-9A), 1.76-1.66 (m, 1H, H-5B), 1.65-1.46 (m, 3H, H-6B, 8B, 9B), 1.30 (t, J = 7.2 Hz, 3H, H-13); δC (100 MHz; CDCl₃) 172.6 (C-2), 172.4 (C-11), 100.9 (C-1), 62.2 (CH-7), 60.1 (CH₂-12), 57.9 (CH-4), 54.4 (CH-10), 36.0 (CH₂-3), 34.1 (CH₂-6), 31.8 (CH₂-9), 31.6 (CH₂-8), 30.7 (CH₂-5), 14.6 (CH₃-13); HRMS (ESI⁺) calcd for C₁₃H₂₀NO₃ (M + H)⁺ 238.1443, found 238.1464.
(3R,5R,8aR)/(3S,5S,8aS)-Diethyl 2,2’-(octahydroindolizine-3,5-diyl)diacetate, trans-2c and (3S,5S,8aR)/(3R,5R,8aS)-Diethyl 2,2’-(octahydroindolizine-3,5-diyl)diacetate, trans-2c’

Method A (Aluminium chloride): The reaction was set up following the procedure described above for the preparation of trans-2b and cis-2b (Method A) (1c (1.0 equiv), aluminium chloride (1.1 equiv, 1M in nitrobenzene), anhydrous dichloromethane (30 mL/mmol of 3c), rt, 24 h). The reaction was stopped by cooling down to rt and dilution with dichloromethane. The organic phase was washed with sodium bicarbonate (saturated solution in water). The phases were separated and the organic phase was dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica gel. Gradient elution with mixtures petroleum ether (30/40):ethyl acetate 6:1→0:1, afforded pure trans-2c as a colorless oil in 55% yield \( R_f \) 0.64 (petroleum ether:ethyl acetate 1:2), \( R_f \) 0.39 (dichloromethane:acetone 9:1), along with 30% trans-2c’ \( R_f \) 0.51 (petroleum ether:ethyl acetate 1:2)] and 8% cis-2c \( R_f \) 0.28 (petroleum ether:ethyl acetate 1:2)].

Method B (Stannous(II) triflate): A solution of 3c (1.0 equiv) in dry acetonitrile (30 mL/mmol of 3c) was prepared at rt, under nitrogen. To this solution, stannous triflate (0.5 equiv) was added and the mixture was refluxed for 24 h, after which the reaction was stopped by dilution with dichloromethane and washes of the organic phase with sodium bicarbonate (saturated solution in water). The final organic phase was dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was purified by flash chromatography on silica, using mixtures dichloromethane:acetone 10:1, 10:1.5 and 0:112, to furnish 8c-trans-1 in 10% yield, 8c-trans-2 in 69% yield [colorless oil, \( R_f \) 0.25 (dichloromethane:acetone 9:1), \( R_f \) 0.55 (chloroform:acetone 9:1)] and cis-2c in 15% yield [\( R_f \) 0.24 (chloroform:acetone 9:1)].

12 Elution with dichloromethane:acetone 10:1 affords pure trans-2c. The best results for the separation of trans-2c’and cis-2c are obtained using chloroform:acetone 10:1.
trans-2c: $\nu_{\text{max}}$ (CH$_2$Cl$_2$/cm$^{-1}$) 2930, 2851, 1738, 1719, 1463, 1372, 1334, 1257, 1174, 1152, 1115, 1032; $\delta_H$ (500 MHz; CDCl$_3$) 4.06 (q, $J = 7.1$ Hz, 4H, H-12 and 12'), 3.55 (m, 1H, H-11), 2.91 (m, 1H, H-4), 2.67 (dd, $J_{\text{gem}} = 15.0$ Hz, $J_{\text{sec}} = 4.2$ Hz, 1H, H-2A), 2.54 (dd, $J_{\text{gem}} = 14.5$ Hz, $J_{\text{sec}} = 4.2$ Hz, 1H, H-2'A), 2.40 (tdd, $J_1 = 9.8$ Hz, $J_2 = 6.5$ Hz, $J_3 = 2.8$ Hz, 1H, H-7), 2.35 (dd, $J_{\text{gem}} = 14.5$ Hz, $J_{\text{sec}} = 9.3$ Hz, 1H, H-2'B), 2.19 (dd, $J_{\text{gem}} = 14.9$ Hz, $J_{\text{sec}} = 8.9$ Hz, 1H, H-2'B), 1.87 (dq, $J_1 = 12.8$ Hz, $J_2 = 8.5$ Hz, 1H, H-5A), 1.76 (m, 1H, 8A), 1.72 (tdd, $J_1 = 12.5$ Hz, $J_2 = 6.1$ Hz, $J_3 = 3.35$ Hz, 1H, H-6A), 1.65-1.55 (m, 3H, H-9A, 10A, 10B), 1.48-1.36 (m, 2H, H-5B, 9B), 1.23 (bt, $J = 7.2$ Hz, 6H, H-13, 13'), 1.30-1.20 (m, 1H, H6B), 1.09 (qd, $J_1 = 11.9$ Hz, $J_2 = 3.8$ Hz, 1H, H-8B); $\delta_C$ (125 MHz; CDCl$_3$) 173.4 (C-1'), 172.4 (C-1), 60.4, 60.2 (CH$_2$-12 and 12'), 56.0 (CH-7), 55.2 (CH-4), 50.2 (CH-11), 38.9 (CH$_2$-2), 32.2 (CH$_2$-8), 29.6 (CH$_2$-6), 29.3 (CH$_2$-10), 28.5 (CH$_2$-5), 28.1 (CH$_2$-2'), 19.2 (CH$_2$-9), 14.2 (CH$_3$-13 and 13'); HRMS (ESI$^+$) calcd for C$_{16}$H$_{28}$NO$_4$ (M + H)$^+$ 298.2018, found 298.2018.

trans-2c': $\nu_{\text{max}}$ (CH$_2$Cl$_2$/cm$^{-1}$) 2928, 2852, 1733, 1444, 1370, 1295, 1242, 1158, 1133, 1097, 1033; $\delta_H$ (500 MHz; CDCl$_3$) 4.13 (m, 4H, H-12, 12'), 3.76 (bqd, $J_1 = 7.3$ Hz, $J_2 = 3.1$ Hz, 1H, H-4), 2.78 (dd, $J_{\text{gem}} = 14.6$ Hz, $J_{\text{sec}} = 3.6$ Hz, 1H, CH$_2$-2'A), 2.79-2.72 (m, 1H, H-11), 2.54 (dd, $J_{\text{gem}} = 13.8$ Hz, $J_{\text{sec}} = 3.0$ Hz, 1H, H-2A), 2.37 (m, 1H, H-7), 2.23 (dd, $J_{\text{gem}} = 14.4$ Hz, $J_{\text{sec}} = 9.5$ Hz, 1H, H-2'B), 2.14 (dd, $J_{\text{gem}} = 14.0$ Hz, $J_{\text{sec}} = 11.0$ Hz, 1H, H-2'B), 1.98-1.90 (m, 1H, H-5A), 1.83-1.63 (m, 3H, H-9A, 10A, 9B), 1.55-1.46 (m, 2H, H-6A, 8A), 1.46-1.37 (m, 1H, H-5B), 1.30-1.10 (m, 9H, H-6B, 8B, 10B, 13, 13'); $\delta_C$ (125 MHz; CDCl$_3$) 172.9 (C-1), 172.0 (C-1'), 60.4, 60.3 (CH$_2$-12 and 12'), 58.9 (CH-7), 55.9 (CH-4), 53.8 (CH-11), 39.6 (CH$_2$-2'), 31.7 (CH$_2$-2 and 10), 29.6, 29.5 (CH$_2$-6 and 8), 26.9 (CH$_2$-5), 24.1 (CH$_2$-9), 14.2, 14.0 (CH$_3$-13 and 13'); HRMS (ESI$^+$) calcd for C$_{16}$H$_{28}$NO$_4$ (M + H)$^+$ 298.2018, found 298.2017.
(2aR, 5S, 5aS, 9aR)/(2aS, 5R, 5aR, 9aS)-Ethyl 4-oxodecahydro-1H-pyrrolo[2,1,5-de]quinolizine-5-carboxylate (3c) and (2aR, 3S, 5aR, 5aR)/(2aS, 3R, 5aS, 5aS)-ethyl 4-oxodecahydro-1H-pyrrolo[2,1,5-de]quinolizine-3-carboxylate (3c’)

A dry flask was equipped with a Dean-Stark trap containing anhydrous toluene and a few pieces of sodium metal. In the flask, a solution of 1c (1.0 equiv) was prepared in anhydrous toluene (30 mL/mmol of 1c), at rt, under nitrogen atmosphere. On this solution, stannous (II) triflate (1.1 equiv) was added solid in one portion and the mixture was heated up to reflux. After 24 h, the reaction was stopped by cooling down to rt and dilution with ethyl acetate and a saturated aqueous solution of sodium bicarbonate. The phases were separated and the aqueous phase was extracted (x3) with ethyl acetate. The final combination of the organic phases was dried over magnesium sulfate and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (stepped gradient elution using mixtures dichloromethane:acetone 10:0.5, 10:1, 10:1.25 and 8:1), to obtain an inseparable 4:1 mixture of 3c:3c’ in 50% yield [white solid, mp 60.4-61.4 °C (DCM), Rf 0.62 (silica, DCM:acetone 9:1)], along with the bicycle cis-2c in 13% yield [yellow oil, Rf 0.07 (silica, DCM:acetone 9:1), Rf 0.14 (silica, petroleum ether (30/40):diethyl ether 1:1), Rf 0.28 (petroleum ether:ethyl acetate 1:2)]

3c + 3c’: $\nu_{\text{max}}$ (CH$_2$Cl$_2$/cm$^{-1}$) 2934 (bb), 1745, 1717, 1372, 1336, 1261, 1152; HRMS (ESI$^+$) calcd for C$_{14}$H$_{22}$NO$_3$ (M + H)$^+$ 252.1600, found 252.1604.

3c: $\delta_H$ (500 MHz; CDCl$_3$) 4.23 (m, 2H, H-13), 3.20 (d, J = 10.6 Hz, 1H, H-1), 2.63 (ddd, $J_1 = J_2 = 10.5$ Hz, $J_3 = 2.8$ Hz, 1H, H-11), 2.60 (dd, $J_1 = 12.5$ Hz, $J_2 = 1.7$ Hz, 1H, H-3A), 2.42 (m, 1H, H-4), 2.42-2.30 (m, 1H, H-3B), 2.05 (bm, 1H, H-7), 1.95-1.78 (m, 4H, H-5A, 6A, 8A, 9A), 1.75-1.65 (m, 1H, H-10A), 1.55-1.40 (m, 2H, H-5B, 6B), 1.32-1.20 (m, 3H, H-8B, 9B, 10B), 1.28 (t, J = 7.1 Hz, 3H, H-14); $\delta_C$ (125 MHz; CDCl$_3$) 203.9 (C-
2), 168.7 (C-12), 62.9 (CH-1), 62.3 (CH-7), 62.5 (CH-4), 61.0 (CH-13), 61.0 (CH-11),
47.2 (CH$_2$-3), 31.5 (CH$_2$-10), 30.4 (CH$_2$-8), 28.9 (CH$_2$-6), 28.4 (CH$_2$-5), 24.0 (CH$_2$-9),
14.19 (CH$_3$-14).

3c': $\delta$$_H$ (500 MHz; CDCl$_3$) 4.21 (m, 2H, H-13), 3.33 (d, $J = 11.3$ Hz, 1H, H-1), 2.70 (m,
1H, H-4), 2.42 (m, 1H, H-11), 2.42-2.30 (m, 2H, H-3), 2.05 (bm, 1H, H-7), 1.95-1.78
(m, 4H, H-5$_A$, H-5$_B$, H-8$_A$, H-8$_B$), 1.75-1.65 (m, 1H, H-10$_A$), 1.55-1.40 (m, 2H, H-5$_B$, H-6$_B$), 1.42-
1.32 (m, 1H, H-9$_B$), 1.32-1.20 (m, 2H, H-8$_B$, H-10$_B$), 1.28 (t, $J = 7.1$ Hz, 3H, H-14); $\delta$$_C$
(125 MHz; CDCl$_3$) 203.7 (C-2), 168.3 (C-12), 64.5, 58.8 (CH-4 and CH-7), 63.4 (CH-
1), 62.4 (CH-11), 61.0 (CH$_2$-13), 47.1 (CH$_2$-3), 32.7 (CH$_2$-10), 30.5 (CH$_2$-8), 29.0
(CH$_2$-6), 27.5 (CH$_2$-5), 24.1 (CH$_2$-9), 14.19 (CH$_3$-14).

cis-2c: (3$S$,5$R$,8a$R$)/(3$R$,5$S$,8a$S$)-Diethyl 2,2’-(octahydropindolizine-3,5-
diyldiacetate) $\nu$_max (CH$_2$Cl$_2$/cm$^{-1}$) 2925, 2853, 1728, 1445, 1369, 1160, 1038; $\delta$$_H$
(500 MHz; CDCl$_3$) 4.18-4.02 (m, 4H, H-12', 12''), 3.34 (m, 2H, H-4, H-11), 3.22 (m, 1H, H-7),
2.73 (dd, $J_{gem} = 14.4$ Hz, $J_{vec} = 9.2$ Hz, 1H, H-2''$_A$), 2.59 (dd, $J_{gem} = 15.2$ Hz, $J_{vec} = 3.9$
Hz, 1H, H-2''$_A$), 2.35 (dd, $J_{gem} = 14.4$ Hz, $J_{vec} = 6.4$ Hz, 1H, H-2''$_B$), 2.09 (dd, $J_{gem} = 15.3$
Hz, $J_{vec} = 9.2$ Hz, 1H, H-2$_B$), 2.12-2.08 (m, 1H, H-5$_A$), 2.02-1.98 (m, 1H, H-9$_A$), 1.83-1.77
(m, 1H, H-6$_A$), 1.77-1.69 (m, 1H, H-10$_A$), 1.50-1.43 (m, 1H, H-5$_B$), 1.41-1.33 (m, 1H, H-
6$_B$), 1.33-1.17 (m, 4H, H-10$_B$, H-8$_A$, H-8$_B$), 1.24 (bt, $J = 7.1$ Hz, 6H, H-13, 13''); $\delta$$_C$
(125 MHz; CDCl$_3$) 172.8 (C-1), 172.5 (C-1'), 60.1 (CH$_2$-12 and 12''), 55.5 (CH-4), 54.3
(CH-7), 50.0 (CH-11), 41.4 (CH$_2$-2), 38.8 (CH$_2$-2''), 29.7 (CH$_2$-8), 29.1 (CH$_2$-6), 28.6
(CH$_2$-5), 27.1 (CH$_2$-9), 22.9 (CH$_2$-10), 14.3, 14.2 (CH$_3$-13 and 13''); HRMS (ESI$^+$) caled
for C$_{16}$H$_{28}$NO$_4$ (M + H)$^+$ 298.2018, found 298.2029.
4. Scaffold Hunter analysis

We have visually assessed the skeletal diversity of the DOS through the use of “Scaffold Hunter”, a computer-based tool developed by Waldmann et al., which extracts the molecular scaffolds present in a compound collection and correlates the relationship between them in a hierarchical tree-like arrangement (Fig. 1).

Figure 1: Hierarchical classification determined by “Scaffold Hunter” illustrating the molecular scaffolds present in the DOS and the relationship between scaffolds at different levels of hierarchy. Key: parental scaffolds (black), daughter scaffolds (blue), and molecular scaffolds (red).

Terminal side chains are first removed from each molecule to give a series of distinct frameworks which are defined by the rings and unsaturated groups that rigidify the molecule. According to a set of prioritisation rules rings are then iteratively removed.
from each of these molecular scaffolds to reveal the last remaining ring which defines the ‘parental’ scaffold. Out of the 14 final compounds synthesised, 7 distinct molecular scaffolds were prepared.

\[ \text{For a recent example see: D. Morton, S. Leach, C. Cordier, S. Warriner and A. Nelson, } \textit{Angew. Chem. Int. Edit.}, 2009, \textit{48}, 104-109. \]
$^1$H and $^{13}$C NMR spectra
Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2009

[Chemical structure and spectra diagram]
cis-2b
trans-2c
trans-2c"
cis-3b
trans-3b
Myrrhine
Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2009

Myrrhine-\(\beta\)TsOH

![Diagram of molecules](image)

![NMR spectrum](image)
Mynrhine N-oxide
Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2009