Supporting Information

One-pot Synthesis of Azabicycles via Cascade nitro-Mannich Reaction and N-Alkylation

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1. General information

Unless otherwise noted, all commercial reagents were used without further purification. Anhydrous solvents and reagents were purified and dried according to the standard procedure. Column chromatography was carried out using silica gel. Thin layer chromatography (TLC) and preparative thin layer chromatography (PTLC) were carried out on aluminum and glass plates, respectively, precoated with 0.25 mm silica gel 60 F254. Flash column chromatography was performed on 230-400 mesh silica gel. 1H NMR spectra were recorded on a 300 MHz NMR instrument. Chemical shifts (δ values) for 1H nuclear magnetic resonance (NMR) spectra were reported in parts per million (ppm) downfield from tetramethylsilane (δ = 0.00 ppm) as internal reference and coupling constants (J values) in Hz. Multiplicity was indicated using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m), broad (br). 13C Spectra were recorded on a 75 MHz NMR spectrometer with CDCl3 (δ = 77.00 ppm) as internal reference and complete proton decoupling. Infrared (IR) spectra were obtained using Universal Attenuated Total Reflectance (UATR) technique and reported in wavenumbers (cm⁻¹). High resolution mass spectrometry (HRMS) was performed using time-of-flight (TOF). Optical rotations were recorded on a polarimeter. Melting points (m.p.) were determined and reported without correction. HPLC analysis was performed on a chiral column with UV/VIS detector.

2. General experimental procedures

2.1 Typical procedure for the preparation of N-(nitroalkyl)phthalimides 1a-f

For commercially unavailable N-(nitroalkyl)phthalimides (1c-f), they were prepared from the corresponding commercially available N-(haloalkyl)phthalimides. ¹

To a solution mixture of NaNO₂ (0.54 g, 7.8 mmol, 1.1 equiv) and KI (1.29 g, 7.8 mmol, 1.1 equiv) in DMSO (35 mL) was added N-(bromoalkyl)phthalimide (7.0 mmol, 1.0 equiv) and the mixture was stirred at RT for 2 h. The reaction was quenched with water (50 mL) and the mixture was extracted with AcOEt (30 mL x 2). The organic part was successively washed with water, dried over Na₂SO₄, and concentrated in vacuo. Crude products were purified by column chromatography
to obtain the corresponding \(N\)-(nitroalkyl)phthalimides 1.

\[
\begin{align*}
\text{N-(5-Nitropentyl)phthalimide (1c):}^{[2]} \\
72\% \text{ yield, white solid, m.p. 51.2–52.5 } ^\circ\text{C;}
\end{align*}
\]
\[{}^{1}\text{H NMR (300 MHz, CDCl}_3\text{)} \delta 7.87–7.81 \text{ (m, 2H), 7.76–7.70 (m, 2H), 4.40 (t, } J = 7.0 \text{ Hz, 2H), 3.70 (t, } J = 7.1 \text{ Hz, 2H), 2.12–2.03 \text{ (m, 2H), 1.81–1.71 (m, 2H), 1.51–1.40 (m, 2H);}
\]
\[{}^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta 168.24, 133.89, 131.90, 123.11, 75.20, 37.19, 27.71, 26.65, 23.39;
\]
\[\text{IR (UATR) } \nu_{\text{max}} 2942, 1772, 1705, 1548, 1436, 1396, 1136, 1052, 878, 717 \text{ cm}^{-1};
\]
\[\text{HRMS (ESI}^+\text{) calcd for C}_{13}\text{H}_{14}\text{N}_{2}\text{NaO}_{4} \text{(M+Na)}^+ 285.0846, \text{ found 285.0851.}
\]

\[
\begin{align*}
\text{N-(6-Nitrohexyl)phthalimide (1d):} \\
76\% \text{ yield, white solid, m.p. 92.3–93.8 } ^\circ\text{C;}
\end{align*}
\]
\[{}^{1}\text{H NMR (300 MHz, CDCl}_3\text{)} \delta 7.87–7.81 \text{ (m, 2H), 7.75–7.69 (m, 2H), 4.38 (t, } J = 7.0 \text{ Hz, 2H), 3.69 (t, } J = 7.1 \text{ Hz, 2H), 2.06–1.97 \text{ (m, 2H), 1.75–1.66 (m, 2H), 1.51–1.36 (m, 4H);}
\]
\[{}^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta 168.33, 133.87, 132.04, 123.13, 75.42, 37.55, 28.16, 27.12, 26.01, 25.72;
\]
\[\text{IR (UATR) } \nu_{\text{max}} 2939, 1766, 1702, 1543, 1367, 1187, 1058, 893, 723 \text{ cm}^{-1};
\]
\[\text{HRMS (ESI}^+\text{) calcd for C}_{14}\text{H}_{16}\text{N}_{2}\text{NaO}_{4} \text{(M+Na)}^+ 299.1002, \text{ found 299.1008.}
\]

\[
\begin{align*}
\text{N-(3-Nitro-2-methylpropyl)phthalimide (1e):} \\
58\% \text{ yield, yellow solid, m.p. 88.1–89.5 } ^\circ\text{C;}
\end{align*}
\]
\[{}^{1}\text{H NMR (300 MHz, CDCl}_3\text{)} \delta 7.83–7.77 \text{ (m, 2H), 7.71–7.66 (m, 2H), 4.38 (dd, } J = 12.7, 5.6 \text{ Hz, 1H), 4.20 (dd, } J = 12.7, 8.4 \text{ Hz, 1H), 3.65 (d, } J = 6.5 \text{ Hz, 2H), 2.86–2.71 \text{ (m, 1H), 1.04 (d, } J = 6.8 \text{ Hz, 3H);}
\]
\[{}^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta 168.35, 134.31, 131.72, 123.54, 79.33, 40.89, 32.69, 15.52;
\]
IR (UATR) $\nu_{\text{max}}$ 2931, 1774, 1706, 1548, 1398, 1190, 1050, 901, 795, 721, 712 cm$^{-1}$; HRMS (ESI$^+$) calcd for C$_{12}$H$_{12}$N$_2$Na$_1$O$_4$ (M+Na)$^+$ 271.0689, found 271.0692.

N-(3-Nitrobutyl)phthalimide (1f):
26% yield, pale yellow solid, m.p. 85.1–86.6 °C;
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.89–7.83 (m, 2H), 7.77–7.71 (m, 1H), 4.60 (sex, $J = 6.7$ Hz, 1H), 3.78 (t, $J = 6.8$ Hz, 2H), 2.48 (td, $J = 7.7$, 7.0 Hz, 1H), 2.16–2.05 (m, 1H), 1.63 (d, $J = 6.7$ Hz, 3H);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.04, 134.19, 131.82, 123.43, 80.82, 34.42, 33.45, 19.33;
IR (UATR) $\nu_{\text{max}}$ 2943, 1773, 1705, 1545, 1391, 1050, 967, 858, 794, 716 cm$^{-1}$
HRMS (ESI$^+$) calcd for C$_{12}$H$_{12}$N$_2$Na$_1$O$_4$ (M+Na)$^+$ 271.0689, found 271.0693.

2.2 Typical procedure for the preparation of aldehydes 2a-i

Step 1: For commercially unavailable mono-OTs alcohol, they were prepared according to literatures.$^{[3]}$

A solution of diol (3.0 mmol, 1.0 equiv) in dichloromethane or toluene (30 mL) was added into a two-neck round-bottom flask containing a mixture of silver (I) oxide (1.05 g, 99%, 4.5 mmol, 1.5 equiv), potassium iodide (0.10 g, 0.6 mmol, 0.2 equiv), and $p$-toluenesulfonic acid monohydrate (0.63 g, 3.3 mmol, 1.1 equiv) under atmosphere of argon and the resulting suspension was vigorously stirred at room temperature for 14 h. The mixture was filtered through a celite pad, and the pad was successively washed with dichloromethane. The filtrate was concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding monotosylated alcohol.
Step 2: For commercially unavailable aldehydes, they were prepared accordingly.

A solution of dimethyl sulfoxide (0.37 mL, 5.2 mmol, 1.4 equiv) in dichloromethane (4.0 mL) was added dropwise into a two-neck round-bottom flask containing a solution of oxalyl chloride (0.39 mL, 4.5 mmol, 1.2 equiv) in dichloromethane (4.0 mL) under atmosphere of argon at −78 °C and further stirred for 20 min. Then, a solution of monotosylated alcohol (3.8 mmol, 1.0 equiv) in dichloromethane (8.0 mL) was added dropwise, and the mixture was stirred for an additional 30 min. Triethylamine (2.1 mL, 15.1 mmol, 4.0 equiv) was added, and the reaction was allowed to gradually warm to room temperature over 1 h. After that, the reaction was cooled down to 0 °C, quenched with an aqueous solution of 10% citric acid (20 mL), further stirred at room temperature for 30 min, and extracted with dichloromethane (2 x 30 mL). The combined organic part was washed with water, dried over anhydrous sodium sulfate, and the solvent was concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding aldehyde 2.

6-Hydroxyhexyl 4-methylbenzenesulfonate:[4]

51% yield, pale yellow oil;

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.79 (d, $J = 8.2$ Hz, 2H), 7.35 (d, $J = 8.2$ Hz, 2H), 4.03 (t, $J = 6.4$ Hz, 2H), 3.60 (t, $J = 6.4$ Hz, 2H), 2.45 (s, 3H), 1.66 (qui, $J = 6.7$ Hz, 2H), 1.52 (qui, $J = 6.8$ Hz, 2H), 1.41–1.25 (m, 4H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 144.66, 133.11, 129.76, 127.79, 70.48, 62.54, 32.35, 28.72, 25.08, 25.02, 21.55;

IR (UATR) $\nu_{\max}$ 3394, 2935, 1598, 1456, 1353, 1173, 1097, 923, 814, 663 cm$^{-1}$

HRMS (ESI$^+$) calcd for C$_{13}$H$_{20}$Na$_1$O$_4$S$_1$ (M+Na)$^+$ 295.0975, found 295.0977.

6-Oxohexyl 4-methylbenzenesulfonate (2c):[4]

75% yield, pale yellow oil;

$^1$H NMR (300 MHz, CDCl$_3$) δ 9.71 (t, $J = 1.5$ Hz, 1H), 7.77 (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.2$ Hz, 2H), 4.02 (t, $J = 6.4$ Hz, 2H), 2.44 (s, 3H), 2.40 (td, $J = 7.3$, 1.5 Hz, 2H), 1.70–1.31 (m, 6H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 201.85, 144.50, 132.61, 129.55, 127.41, 69.96, 43.09, 28.17, 24.50, 21.17, 20.89;

IR (UATR) $\nu_{\max}$ 2942, 1723, 1598, 1459, 1356, 1175, 1098, 925, 816 cm$^{-1}$

HRMS (ESI$^+$) calcd for C$_{13}$H$_{18}$Na$_1$O$_4$S$_1$ (M+Na)$^+$ 293.0818, found 293.0808.
7-Hydroxyheptyl 4-methylbenzenesulfonate:\textsuperscript{[5]}

55\% yield, colorless oil;

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.78 (d, \(J = 8.2\) Hz, 2H), 7.36 (d, \(J = 8.2\) Hz, 2H), 4.02 (t, \(J = 6.5\) Hz, 2H), 3.59 (t, \(J = 6.5\) Hz, 2H), 2.45 (s, 3H), 2.08 (s, 1H), 1.70–1.45 (m, 4H), 1.36–1.20 (m, 6H);

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.59, 132.91, 129.68, 127.65, 70.53, 62.46, 32.31, 28.52, 28.49, 25.32, 25.09, 21.42;

IR (UATR) \(\nu_{\text{max}}\) 3422, 2932, 1598, 1457, 1354, 1174, 1097, 935, 814, 662 cm\(^{-1}\);

HRMS (ESI\(^+\)) calcd for C\(_{14}\)H\(_{22}\)Na\(_1\)O\(_4\)S\(_1\) (M+Na\(^+\)) 309.1131, found 309.1140.

7-Oxoheptyl 4-methylbenzenesulfonate (2d):\textsuperscript{[5]}

51\% yield, colorless oil;

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.73 (t, \(J = 1.5\) Hz, 1H), 7.78 (d, \(J = 8.2\) Hz, 2H), 7.36 (d, \(J = 8.2\) Hz, 2H), 4.02 (t, \(J = 6.4\) Hz, 2H), 2.45 (s, 3H), 2.40 (td, \(J = 7.3, 1.5\) Hz, 2H), 1.68–1.25 (m, 8H);

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 202.29, 144.59, 132.91, 129.67, 127.62, 70.28, 43.41, 28.37, 28.17, 24.92, 21.52, 21.39;

IR (UATR) \(\nu_{\text{max}}\) 2937, 1722, 1598, 1463, 1355, 1174, 1097, 933, 815 cm\(^{-1}\);

HRMS (ESI\(^+\)) calcd for C\(_{14}\)H\(_{20}\)Na\(_1\)O\(_4\)S\(_1\) (M+Na\(^+\)) 307.0975, found 307.0980.

5-Hydroxyhexyl 4-methylbenzenesulfonate:\textsuperscript{[6]}

45\% yield, colorless oil;

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.79 (d, \(J = 8.3\) Hz, 2H), 7.35 (d, \(J = 8.0\) Hz, 2H), 4.03 (t, \(J = 6.4\) Hz, 2H), 3.79–3.69 (m, 1H), 2.45 (s, 3H), 1.69–1.62 (m, 2H), 1.48–1.30 (m, 4H), 1.15 (d, \(J = 6.2\) Hz, 3H);

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.67, 133.06, 129.78, 127.80, 70.43, 67.63, 38.31, 28.73, 23.43, 21.55;

IR (UATR) \(\nu_{\text{max}}\) 3394, 2932, 1598, 1457, 1354, 1173, 1097, 931, 815, 776, 663 cm\(^{-1}\);

HRMS (ESI\(^+\)) calcd for C\(_{13}\)H\(_{20}\)Na\(_1\)O\(_4\)S\(_1\) (M+Na\(^+\)) 295.0975, found 295.0981.

5-Oxoheptyl 4-methylbenzenesulfonate (2e):\textsuperscript{[6]}

70\% yield, colorless oil;

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.78 (d, \(J = 8.3\) Hz, 2H), 7.35 (d, \(J = 8.0\) Hz, 2H), 4.02 (t, \(J = 6.0\) Hz, 2H), 2.45 (s, 3H), 2.43–2.39 (m, 2H), 2.11 (s, 3H), 1.71–1.54 (m, 4H);
13C NMR (75 MHz, CDCl3) δ 207.98, 144.73, 132.99, 129.80, 127.80, 70.09, 42.47, 29.82, 28.11, 21.56, 19.54;

IR (UATR) \( \nu_{\text{max}} \) 2926, 1714, 1598, 1354, 1173, 1097, 922, 815, 764, 662 cm\(^{-1}\);

HRMS (ESI\(^+\)) calcd for C\(_{13}\)H\(_{18}\)Na\(_1\)O\(_3\)S\(_1\) (M+Na)\(^+\) 293.0818, found 293.0828.

Preparation of 6-hydroxyhexan-2-yl 4-methylbenzenesulfonate

To a two-neck round-bottom flask containing a suspension of sodium hydride (341 mg, 60% in mineral oil, 8.5 mmol, 1.0 equiv) in tetrahydrofuran (4.0 mL) under atmosphere of argon was added dropwise a solution of 1,5-diols (1.00 g, 8.4 mmol, 1.0 equiv) in tetrahydrofuran (20 mL) at 0 °C. After 30 min, the reaction was added benzyl bromide (1.1 mL, 9.2 mmol, 1.1 equiv) and the resulting mixture was warmed to room temperature and further stirred for 17 h. The reaction was cooled down to room temperature, quenched with a saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic part was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford 6-(benzyloxy)hexan-2-ol (916.4 mg, 52% yield) as a colorless oil.

A solution of alcohol (898.3 mg, 4.3 mmol, 1.0 equiv) in dichloroethane (15 mL) was added p-toluenesulfonyl chloride (821.7 mg, 4.3 mmol, 1.0 equiv), triethylamine (0.6 mL, 4.3 mmol, 1 equiv) and 4-(dimethylamino)pyridine (53 mg, 0.4 mmol, 0.1 equiv), and the resulting mixture under atmosphere of argon was gentle refluxed at 50 °C for 1 h. The reaction was cooled down to room temperature, quenched with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic part was washed with a saturated sodium hydrogen carbonate solution (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford 6-(benzyloxy)hexan-2-yl 4-methylbenzenesulfonate (1.3511 g, 86% yield) as a colorless oil.

To a pressure vessel containing a solution of benzyl ether (1.00 g, 2.8 mmol) in ethanol (50 mL) was added Pd/C (10 mol%, 210.0 mg). The reaction mixture was vigorously stirred under atmosphere of hydrogen (75 psi) at room temperature for 3 h. The reaction mixture was filtered
through a celite pad, successively washed with ethanol, and the filtrate was concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford 6-hydroxyhexan-2-yl 4-methylbenzenesulfonate (695.1 mg, 93% yield) as a colorless oil.

6-Oxohexan-2-yl 4-methylbenzenesulfonate (2f) was prepared according to a typical procedure for the preparation of aldehyde to afford the desired aldehyde (554.3 mg, 80% yield) as a colorless oil.

6-(Benzyloxy)hexan-2-ol:[7] 52% yield, colorless oil;

\[ \text{H NMR (300 MHz, CDCl}_3\text{)} \delta 7.33–7.23 \text{ (m, 5H), 4.49 (s, 2H), 3.80–3.70 \text{ (m, 1H), 3.46 (t, } J = 6.4 \text{ Hz, 2H), 2.00 (br s, 1H), 1.68–1.58 \text{ (m, 2H), 1.52–1.36 \text{ (m, 4H), 1.15 (d, } J = 6.2 \text{ Hz, 3H);}} \]

\[ \text{C NMR (75 MHz, CDCl}_3\text{)} \delta 138.43, 128.23, 127.53, 127.40, 72.76, 70.16, 67.68, 38.90, 29.54, 23.31, 22.29; \]

IR (UATR) \( \nu_{\text{max}} \) 3393, 2934, 1454, 1366, 1098, 941, 734, 697 cm\(^{-1}\)

HRMS (ESI\(^{+}\)) calcd for C\(_{13}\)H\(_{20}\)Na\(_1\)O\(_2\) (M+Na\(^{+}\)) 231.1356, found 231.1364.

6-(Benzyloxy)hexan-2-yl 4-methylbenzenesulfonate:
86% yield, colorless oil;

\[ \text{H NMR (300 MHz, CDCl}_3\text{)} \delta 7.78 \text{ (d, } J = 8.2 \text{ Hz, 2H), 7.40–7.20 \text{ (m, 7H), 4.66–4.55 \text{ (m, 1H), 4.46 \text{ (s, 2H), 3.38 \text{ (t, } J = 6.3 \text{ Hz, 2H), 2.41 \text{ (s, 3H), 1.70–1.20 \text{ (m, 6H), 1.24 \text{ (d, } J = 6.3 \text{ Hz, 2H);}} \]

\[ \text{C NMR (75 MHz, CDCl}_3\text{)} \delta 144.31, 138.45, 134.49, 129.62, 128.26, 127.59, 127.49, 127.43, 80.32, 72.80, 69.83, 36.17, 29.17, 21.54, 21.49, 20.67; \]

IR (UATR) \( \nu_{\text{max}} \) 2937, 1599, 1454, 1357, 1174, 1094, 890, 815, 735, 698, 663 cm\(^{-1}\)

HRMS (ESI\(^{+}\)) calcd for C\(_{20}\)H\(_{26}\)Na\(_1\)O\(_4\)S\(_1\) (M+Na\(^{+}\)) 385.1444, found 385.1441.

6-Hydroxyhexan-2-yl 4-methylbenzenesulfonate:
93% yield, colorless oil;

\[ \text{H NMR (300 MHz, CDCl}_3\text{)} \delta 7.72 \text{ (d, } J = 8.3 \text{ Hz, 2H), 7.26 \text{ (d, } J = 8.0 \text{ Hz, 2H), 4.57 \text{ (sex, } J = 6.3 \text{ Hz, 1H), 3.50 \text{ (t, } J = 6.3 \text{ Hz, 2H), 2.38 \text{ (s, 3H), 1.62–1.30 \text{ (m, 6H), 1.18 \text{ (d, } J = 6.3 \text{ Hz, 3H);}} \]

\[ \text{C NMR (75 MHz, CDCl}_3\text{)} \delta 144.45, 134.33, 129.65, 127.54, 80.36, 62.25, 36.08, 31.88, 21.48, 21.01, 20.59; \]

IR (UATR) \( \nu_{\text{max}} \) 3368, 2940, 1350, 1173, 1123, 1008, 895, 815, 684 cm\(^{-1}\)

HRMS (ESI\(^{+}\)) calcd for C\(_{13}\)H\(_{20}\)Na\(_1\)O\(_4\)S\(_1\) (M+Na\(^{+}\)) 295.0975, found 295.0981.

6-Oxohexan-2-yl 4-methylbenzenesulfonate (2f):
80% yield, colorless oil;
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.69 (t, $J = 1.4$ Hz, 1H), 7.79 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 4.67–4.57 (m, 1H), 2.45 (s, 3H), 2.36 (td, $J = 6.9$, 1.4 Hz, 2H), 1.69–1.47 (m, 4H), 1.25 (d, $J = 6.3$ Hz, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 201.55, 144.54, 134.23, 129.70, 127.55, 79.62, 42.96, 35.57, 21.48, 20.59, 17.29;

IR (UATR) $\nu_{\text{max}}$ 2938, 1717, 1598, 1352, 1173, 1098, 892, 816, 663 cm$^{-1}$

HRMS (ESI$^+$) calcd for C$_{13}$H$_{18}$Na$_1$O$_4$S$_1$ (M+Na)$^+$ 293.0818, found 293.0822.

Preparation of $(+)$-$(2S,3S)$-2,3-bis(benzyloxy)-1,4-butanediol

To a two-neck round-bottom flask containing a suspension of sodium hydride (0.77 g, 60% in mineral oil, 19.3 mmol, 2.0 equiv) in tetrahydrofuran (10 mL) under atmosphere of argon was added dropwise a solution of diethyl L-tartrate (2.00 g, 9.7 mmol, 1.0 equiv) in tetrahydrofuran (7 mL) at 0 °C. After 1 h, the reaction was added tetrabutylammonium iodide (0.75 g, 2.0 mmol, 0.2 equiv) and a catalytic amount of 18-crown-6 (0.01 g, 0.04 mmol, 0.004 equiv) were directly added in one portion. Benzyl bromide (2.3 mL, 19.4 mmol, 2.0 equiv) was slowly added dropwise to this mixture at 0 °C. The resulting mixture was warmed to room temperature and further stirred for 3.5 h. The reaction was cooled down under ice-bath, quenched with 1 N aq. HCl (30 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic part was washed with saturated aq. NaHCO$_3$ (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding bis(benzyloxy)-diethyl L-tartrate (948.7 mg, 25% yield) as a colorless oil.

A solution of tartrate derivative (500.0 mg, 1.3 mmol, 1.0 equiv) in diethyl ether (3 mL) was added dropwise to a suspension of lithium aluminum hydride (103.1 mg, 95% purity, 2.6 mmol, 2.0 equiv) in diethyl ether (3 mL) at 0 °C. After heating at 40 °C for 3 h, the mixture was cooled down under ice-bath, quenched with water (0.1 mL), followed by 15% aq. NaOH (0.1 mL) and water (0.3 mL), and further stirred at room temperature for 1 h. Then, the resulting slurry was added potassium carbonate (excess) to remove water, and the solution was collected by filtration through a sintered glass funnel and successively washed a cake with ether. After evaporation, crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding bis(benzyloxy)-1,4-butanediol (357.2 mg, 92% yield) as a colorless oil, which crystallized as white solid on standing at -18 °C.
(+)-(2S,3S)-2,3-Bis(benzyloxy)-1,4-butanediol:[8]
56% yield (over 2 steps from diethyl L-tartrate), white solid, m.p. 41.1–41.9 °C, \([\alpha]_D^{27} = +14.1\) (c = 1.2, MeOH);

1H NMR (300 MHz, CDCl₃) δ 7.36–7.24 (m, 10H), 4.62 (s, 4H), 3.80–3.64 (m, 6H), 2.72 (br s, 2H);

13C NMR (75 MHz, CDCl₃) δ 137.91, 128.43, 127.85, 78.96, 72.51, 60.69;
IR (UATR) ν\(_{\text{max}}\) 3421, 2877, 1454, 1208, 1048, 735, 696 cm\(^{-1}\);
HRMS (ESI\(^+\)) calcd for C\(_{18}\)H\(_{22}\)Na\(_1\)O\(_4\)(M+Na)\(^+\) 325.1410, found 325.1410.

(+)-(2S,3S)-2,3-Bis(benzyloxy)-4-hydroxybutyl 4-methylbenzenesulfonate:[3]
67% yield, white solid, m.p. 59.5–61.5 °C, \([\alpha]_D^{26} = +5.6\) (c 1.3, CHCl₃);

1H NMR (300 MHz, CDCl₃) δ 7.75 (d, J = 8.2 Hz, 2H), 7.34–7.20 (m, 12H), 4.61 (d, J = 11.7 Hz, 1H), 4.51 (s, 2H), 4.50 (d, J = 11.7 Hz, 1H), 4.27 (dd, J = 10.7, 3.5 Hz, 1H), 4.15 (dd, J = 10.7, 6.6 Hz, 1H), 3.88–3.81 (m, 1H), 3.72–3.65 (m, 1H), 3.61–3.52 (m, 2H), 2.75 (br s, 1H), 2.40 (s, 3H);
13C NMR (75 MHz, CDCl₃) δ 144.80, 137.59, 137.43, 132.65, 129.78, 128.39, 128.34, 127.96, 127.87, 127.84, 127.72, 77.86, 76.61, 73.18, 72.63, 69.76, 60.81, 21.53;
IR (UATR) ν\(_{\text{max}}\) 3349, 2871, 1598, 1455, 1360, 1175, 1095, 967, 665 cm\(^{-1}\);
HRMS (ESI\(^+\)) calcd for C\(_{25}\)H\(_{28}\)Na\(_1\)O\(_6\)S\(_1\)(M+Na)\(^+\) 479.1499, found 479.1511.

(+)-(2S,3R)-2,3-Bis(benzyloxy)-4-oxobutyl 4-methylbenzenesulfonate (2g):
60% yield, pale brown oil, \([\alpha]_D^{28} = +27.3\) (2.2, CHCl₃);

1H NMR (300 MHz, CDCl₃) δ 9.58 (d, J = 0.9 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.33–7.18 (m, 12H), 4.67 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 4.50 (d, J = 11.7 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.20 (dd, J = 10.0, 5.7 Hz, 1H), 4.09 (dd, J = 15.6, 5.5 Hz, 1H), 4.09–4.00 (m, 1H), 3.88 (dd, J = 3.6, 1.0 Hz, 1H), 2.42 (s, 3H);
13C NMR (75 MHz, CDCl₃) δ 201.88, 145.04, 136.76, 136.50, 132.42, 129.86, 128.52, 128.40, 128.27, 128.23, 128.11, 127.88, 81.84, 73.59, 73.41, 67.39, 21.59;
IR (UATR) ν\(_{\text{max}}\) 2872, 1733, 1598, 1497, 1455, 1361, 1175, 1095, 976, 814, 737, 697, 665 cm\(^{-1}\);
HRMS (ESI\(^+\)) calcd for C\(_{25}\)H\(_{36}\)Na\(_1\)O\(_6\)S\(_1\)(M+Na)\(^+\) 477.1342, found 477.1341.
Preparation of 2,3,4-[tris(benzyloxy)]pentane-1,5-diol

To a two-neck round-bottom flask containing adonitol (2.00 g, 13.1 mmol, 1.0 equiv), trityl chloride (7.33 g, 26.3 mmol, 2.0 equiv) and a catalytic amount of 4-(dimethylamino)pyridine (0.32 g, 2.6 mmol, 0.2 equiv) under atmosphere of argon was added pyridine (16 mL), and the resulting mixture was stirred at room temperature for 30 h. The reaction was quenched with a saturated ammonium chloride solution (60 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic part was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude 1,5-di-O-trityladonitol (9.11 g, quant.) as a yellow oil, which was used in the next step without purification.

To a two-neck round-bottom flask containing a suspension of sodium hydride (1.50 g, 60% in mineral oil, 37.5 mmol, 4.9 equiv) in tetrahydrofuran (30 mL) under atmosphere of argon was added dropwise a solution of 1,5-di-O-trityladonitol (crude 4.91 g, 7.7 mmol, 1.0 equiv) in tetrahydrofuran (20 mL) at 0 °C. After 1 h, the white suspension was added tetrabutylammonium iodide (0.57 g, 1.5 mmol, 0.2 equiv) and a catalytic amount of 18-crown-6 (0.10 g, 0.38 mmol, 0.05 equiv) were directly added in one portion. Benzyl bromide (3.7 mL, 31.1 mmol, 4.0 equiv) was slowly added dropwise to this mixture at 0 °C. The resulting mixture was refluxed for 23 h. The reaction was cooled down under ice-bath, quenched with saturated ammonium chloride (100 mL) and extracted with diethyl ether (2 x 200 mL). The combined organic part was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the crude 1,5-di-O-trityl-2,3,4-tri-O-benzyladonitol (7.10 g) as a dark brown oil, which was used in the next step without purification. Next, the solution of crude material from above in methanol (50 mL) was added p-toluenesulfonic acid monohydrate (3.01 g, 15.8 mmol, 2.1 equiv) and refluxed for 16 h. The reaction was concentrated under reduced pressure. The obtained yellow oil was diluted with DCM (100 mL) and quenched with saturated sodium hydrogen carbonate (160 mL). The organic part was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Crude products
were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding **2,3,4-{(tris(benzyloxy)}pentane-1,5-diol** (1.67 g, 51% yield) as white solid.

**(2S*,3S*,4R*)-2,3,4-{Tris(benzyloxy)}pentane-1,5-diol**:\(^{[9]}\)

51% yield (over 3 steps from adonitol), white solid, m.p. 41.3–42.1 °C;

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35–7.20 (m, 15H), 4.69 (s, 2H), 4.56 (s, 4H), 3.92 (t, \(J = 4.8\) Hz, 1H), 3.75–3.66 (m, 6H), 2.58 (br s, 2H);

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 137.73, 128.25, 127.89, 127.71, 127.62, 78.82, 78.60, 73.92, 71.81, 60.97;

IR (UATR) \(\nu_{\text{max}}\) 3349, 2873, 1598, 1454, 1359, 1175, 1096, 978, 814, 737, 697, 665 cm\(^{-1}\);


**(2S*,3R*,4R*)-2,3,4-Tris(benzyloxy)-5-hydroxypentyl 4-methylbenzenesulfonate**: 50% yield, colorless oil;

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.72 (d, \(J = 8.3\) Hz, 2H), 7.35–7.19 (m, 17H), 4.61 (s, 1H), 4.60 (s, 1H), 4.58 (s, 1H), 4.55 (s, 1H), 4.54 (s, 2H), 4.28 (dd, \(J = 10.8\), 3.3 Hz, 1H), 4.19 (dd, \(J = 10.8\), 5.8 Hz, 1H), 3.92 (ddd, \(J = 5.8\), 4.4, 3.3 Hz, 1H), 3.80 (dd, \(J = 5.8\), 4.4 Hz, 1H), 3.69 (s, 1H), 3.68 (s, 1H), 3.63 (dd, \(J = 5.8\), 3.3, 1H), 2.39 (s, 3H), 2.00 (br s, 1H);

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.69, 137.69, 137.56, 137.54, 132.84, 129.75, 128.49, 128.41, 128.33, 128.08, 127.92, 127.89, 127.88, 127.86, 127.77, 78.37, 78.18, 76.84, 73.89, 72.57, 72.08, 69.72, 60.94, 21.59;

IR (UATR) \(\nu_{\text{max}}\) 3349, 2873, 1598, 1454, 1359, 1175, 1096, 978, 814, 737, 697, 665 cm\(^{-1}\);

HRMS (ESI\(^+\)) calcd for Ca\(_{26}\)H\(_{36}\)Na\(_4\)O\(_3\)S\(_1\) (M+Na\(^+\)) 599.2074, found 599.2075.

**(2S*,3S*,4S*)-2,3,4-Tris(benzyloxy)-5-oxopentyl 4-methylbenzenesulfonate (2h/ent-2h)**: 65% yield, white solid, m.p. 74.5–75.0 °C;

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.40 (s, 1H), 7.70 (d, \(J = 8.2\) Hz, 2H), 7.29–7.13 (m, 17H), 4.70 (d, \(J = 12.0\) Hz, 1H), 4.64 (d, \(J = 12.0\) Hz, 1H), 4.51 (d, \(J = 11.0\) Hz, 2H), 4.45 (d, \(J = 11.2\) Hz, 1H), 4.39 (d, \(J = 11.2\) Hz, 1H), 4.26 (d, \(J = 10.8\) Hz, 1H), 4.13 (dd, \(J = 10.7\), 3.4 Hz, 1H), 4.05 (s, 1H), 3.92 (d, \(J = 12.0\) Hz, 1H), 3.88 (d, \(J = 10.2\) Hz, 1H), 2.34 (s, 3H);

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 200.63, 144.64, 137.02, 136.93, 136.89, 132.57, 129.66, 128.37, 128.31, 128.15, 127.91, 127.87, 127.78, 127.76, 127.63, 81.56, 79.40, 74.79, 73.09, 72.55, 72.48, 68.51, 21.43;

IR (UATR) \(\nu_{\text{max}}\) 2871, 1731, 1598, 1455, 1362, 1176, 1097, 973, 814, 738, 697, 665 cm\(^{-1}\);

HRMS (ESI\(^+\)) calcd for Ca\(_{25}\)H\(_{34}\)Na\(_4\)O\(_3\)S\(_1\) (M+Na\(^+\)) 597.1918, found 597.1909.
To a solution of alcohol (1.69 g, 9.3 mmol, 1.0 equiv) in dichloromethane (20 mL) was added p-toluenesulfonyl chloride (1.77 g, 9.3 mmol, 1.0 equiv), triethylamine (2.5 mL, 17.9 mmol, 1.9 equiv) and 4-(dimethylamino)pyridine (230 mg, 1.9 mmol, 0.2 equiv), and the resulting mixture under atmosphere of argon was stirred at room temperature for 15 h. The reaction was quenched with saturated ammonium chloride (50 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic part was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford 3,4-dimethoxyphe

To a solution of 3,4-dimethoxyphenethyl 4-methylbenzenesulfonate (971.4 mg, 3.0 mmol, 1.0 equiv) in dichloromethane (7 mL) at –40 °C under argon atmosphere was added dropwise dichloromethyl methyl ether (0.4 mL, 4.4 mmol, 1.5 equiv) and a solution of tin(IV) chloride (928.0 mg, 3.6 mmol, 1.2 equiv) in dichloromethane (3.6 mL). The reaction was allowed to warm up to room temperature over 16 h. Then, the mixture was cooled down under ice-bath, quenched with saturated sodium hydrogen carbonate (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic part was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford 2-formyl-4,5-dimethoxyphenethyl 4-methylbenzenesulfonate (830.1 mg, 77% yield) as yellow solid.

3,4-Dimethoxyphenethyl 4-methylbenzenesulfonate:[11]
73% yield, white solid, m.p. 51.5–53.8 °C;

1H NMR (300 MHz, CDCl3) δ 7.67 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.75 (d, J = 8.1 Hz, 1H), 6.66 (dd, J = 8.1, 2.0 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 4.19 (t, J = 6.9 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 2.89 (t, J = 6.9 Hz, 2H), 2.43 (s, 3H);

13C NMR (75 MHz, CDCl3) δ 148.85, 147.91, 144.57, 132.92, 129.64, 128.69, 127.71, 120.92, 111.94, 111.19, 70.74, 55.82, 55.68, 34.87, 21.51;

IR (UATR) νmax 2957, 1596, 1517, 1465, 1355, 1262, 1174, 1028, 964, 908, 813 cm⁻¹;

HRMS (ESI⁺) calcd for C17H20NaO5S1 (M+Na)⁺ 359.0924, found 359.0914.

2-Formyl-4,5-dimethoxyphenethyl 4-methylbenzenesulfonate (2i): 77% yield, yellow solid, m.p. 103.9–105.1 °C;
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.94 (s, 1H), 7.64 (d, $J = 8.3$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.23 (s, 1H), 6.71 (s, 1H), 4.27 (t, $J = 6.4$ Hz, 2H), 3.93 (s, 6H), 3.34 (t, $J = 6.4$ Hz, 2H), 2.42 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 190.41, 153.36, 148.09, 144.64, 133.55, 132.83, 129.66, 127.67, 126.83, 114.31, 114.24, 70.37, 56.17, 56.03, 31.84, 21.54;

IR (UATR) $\nu_{\text{max}}$ 2939, 1676, 1598, 1515, 1463, 1354, 1270, 1173, 1100, 959, 903, 814, 768 cm$^{-1}$;

HRMS (ESI$^+$) calcd for C$_{18}$H$_{20}$Na$_1$O$_6$S$_1$ (M+Na)$^+$ 387.0873, found 387.0885.

2.3 Typical procedure for the synthesis of nitro alkylamine 1a', 4 and 5

In a round-bottom flask equipped with a condenser containing N-(nitropropyl)phthalimide 1a (902.7 mg, 3.9 mmol, 1.0 equiv) was added a solution of hydrazine monohydrate (210.0 mg, 4.2 mmol, 1.1 equiv) in methanol (2.1 mL) and the mixture was stirred at 80 °C for 2 h. After cooling down to room temperature, the suspension was quenched with 6 N HCl (4.2 mL), and the resulting mixture was further refluxed at 70 °C for 1 h. The solvent was removed under reduced pressure and the resulting mixture was diluted with cold water (5.0 mL). The obtained solid was filtered out using a paper pad and the pad was washed with cold water (2.0 mL). The aqueous filtrate was collected and concentrated under reduced pressure to afford pale yellow solid 1a' (433.0 mg, 80%), after washing with cold ethanol.

3-Nitropropan-1-ammonium chloride (1a'):
80% yield, pale yellow solid, m.p. 119.3–121.0 °C;
$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.04 (br s, 3H), 4.68 (t, $J = 6.8$ Hz, 2H), 2.4–2.81 (m, 2H), 2.21 (t, $J = 6.8$ Hz, 1H), 2.16 (t, $J = 6.8$ Hz, 1H);

$^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 72.30, 35.92, 24.40;

IR (UATR) $\nu_{\text{max}}$ 3377, 2946, 1710, 1551, 1381, 1142, 997, 786, 720 cm$^{-1}$;

HRMS (ESI$^+$) calcd for C$_3$H$_9$N$_2$O$_2$ (M+H)$^+$ 105.0659, found 105.0661.

Lithium hexamethyldisilazane (LHMDS, 1 M in tetrahydrofuran, 6.5 mL, 6.5 mmol, 1.3 equiv) was added dropwise to a two-neck round-bottom flask containing a solution of nitrostyrene derivative (1.01 g, 4.8 mmol, 1.0 equiv) and arylacetonitrile (0.75 mL, 6.5 mmol, 1.3 equiv) in
tetrahydrofuran (30 mL) under atmosphere of argon at -78°C and the reaction was further stirred for 30 min. Then, the mixture was quenched with a saturated ammonium chloride solution (30 mL), gradually warmed up to room temperature and extracted with ethyl acetate (2 x 50 mL). The combined organic part was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude products (isomeric ratio = 56 : 44, using $^1$H NMR) were crystalized with ethyl acetate to obtain the corresponding diaryl nitro alkynitrile (1.55 g, 98% with isomeric ratio = 3 : 2) as white solid. These mixture isomers were re-crystallized with dichloromethane at -18°C to obtain one pure isomer of nitro alkynitrile (550.9 mg, 35%) as white solid.

To a solution of an isomeric pure nitro alkynitrile (1.52 g, 4.7 mmol, 1.0 equiv) in tetrahydrofuran (30 mL) was added dropwise a solution of boran dimethylsulfide complex (2 M in tetrahydrofuran, 6.0 mL, 12.0 mmol, 2.5 equiv) at room temperature and the reaction was refluxed at 80 °C for 3 h. Then, the reaction was cooled down to room temperature, quenched with methanol (10 mL) and 3N aq. HCl (10 mL) and the mixture was heated to 90 °C for 1.5 h. The reaction was concentrated under reduced pressure to remove volatile materials. The mixture was cooled down under ice-bath, basified with 20% NaOH to pH 12 at 0 °C, and extracted with ethyl acetate (3 x 30 mL). The combined organic part was dried over anhydrous potassium carbonate, and the solvent was concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using ethyl acetate as eluents to afford the corresponding nitro alkylamine 4 (1.50 g, 97% yield) as pale brown solid.

(±)-(2R*,3S*)-3-(3,4-Dimethoxyphenyl)-4-nitro-2-phenylbutanenitrile:

35% yield, white solid, m.p. 159.3–161.0 °C;
$^1$H NMR (300 MHz, CDCl$_3$) δ 7.37–7.30 (m, 3H), 7.16–7.08 (m, 2H), 6.79 (d, J = 8.3 Hz, 1H), 6.67 (dd, J = 8.3, 2.1 Hz, 1H), 6.41 (d, J = 2.1 Hz, 1H), 4.88 (dd, J = 13.5, 7.8 Hz, 1H), 4.77 (dd, J = 13.5, 7.2 Hz, 1H), 4.30 (d, J = 6.1 Hz, 1H), 3.90–3.78 (m, 1H), 3.86 (s, 3H), 3.72 (s, 3H);
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 149.36, 148.90, 132.47, 129.11, 128.76, 128.00, 125.93, 120.24, 118.16, 111.63, 111.26, 76.99, 55.79, 47.84, 41.48;
IR (UATR) $\tilde{\nu}_{\text{max}}$ 2936, 2242, 1595, 1552, 1517, 1456, 1380, 1261, 1147, 1024, 903, 866, 810, 761, 699, 661 cm$^{-1}$;
HRMS (ESI$^+$) calcd for C$_{18}$H$_{18}$N$_2$NaO$_4$ (M+Na)$^+$ 349.1159, found 349.1156.

(±)-(2R*,3S*)-3-(3,4-Dimethoxyphenyl)-4-nitro-2-phenylbutan-1-amine (4):

97% yield, pale brown solid, m.p. 79.8–81.6 °C;
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.46–7.38 (m, 2H), 7.36–7.29 (m, 3H), 6.85 (s, 2H), 6.76 (s, 1H), 4.44 (dd, $J$ = 12.4, 11.2 Hz, 1H), 4.23 (dd, $J$ = 12.4, 4.3 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.66 (td, $J$ = 11.2, 4.3 Hz, 1H), 2.95–2.65 (m, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 149.29, 148.68, 139.89, 130.45, 129.40, 128.14, 127.83, 120.02, 111.54, 110.88, 80.00, 55.98, 55.86, 52.38, 47.98, 45.59;

IR (UATR) $\nu_{\text{max}}$ 3373, 2935, 1592, 1549, 1516, 1454, 1380, 1262, 1144, 1026, 901, 813, 767, 703, 657 cm$^{-1}$;

HRMS (ESI$^+$) calcd for C$_{18}$H$_{23}$N$_2$O$_4$ (M+H)$^+$ 331.1652, found 331.1645.

To a round-bottom flask containing a solution of 4-methoxycinnamaldehyde (500.0 mg, 3.1 mmol, 1.0 equiv), (S)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (78.0 mg, 0.3 mmol, 0.1 equiv), benzoic acid (75.0 mg, 0.6 mmol, 0.2 equiv) in methanol (5.0 mL) under atmosphere of argon at room temperature was added nitromethane (0.5 mL, 9.2 mmol, 3.0 equiv) and the reaction was further stirred for 17 h. Then, the mixture was quenched with a saturated sodium hydrogen carbonate solution (10 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic part was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained crude products in methanol (10 mL) were added sodium borohydride (300 mg, 98% purity, 7.8 mmol, 2.5 equiv) in a small portion and the mixture was stirred for 30 min. The reaction was quenched with a saturated ammonium chloride solution (10 mL) and the resulting mixtures were concentrated under reduced pressure. The obtained solid was dried over water (10 mL) and extracted with dichloromethane (2 x 30 mL). The organic part was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding (−)-(S)-3-(4-methoxyphenyl)-4-nitrobutan-1-ol (520.8 mg, 75% yield) as a yellow oil.
To a solution of alcohol (310.5 mg, 1.4 mmol, 1.0 equiv) in dichloromethane (3.0 mL) was directly added triphenylphosphane (434.0 mg, 1.7 mmol, 1.2 equiv) under ice-bath. After stirring for 10 min, the reaction was added tetrabromomethane (503.0 mg, 1.5 mmol, 1.1 equiv) and further stirred for 3 h. Then, the mixture was quenched with water (20 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic part was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crude alkylbromide product was dissolved in tetrahydrofuran (4.0 mL) and water (1.0 mL) and sodium azide (110.0 mg, 1.7 mmol, 1.2 equiv) was directly added and stirred at room temperature for 2.5 h. Then, triphenylphosphene (540.0 mg, 2.1 mmol, 1.5 equiv) was added and the mixture was further stirred for 16 h. The reaction was quenched with water (10 mL) and extracted with dichloromethane (2 x 20 mL). The organic part was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using dichloromethane and an increasing proportion of methanol (<10%) as eluents to afford the corresponding nitro alkylphosphazene 5 (576.3 mg, 85% yield) as brown solid.

(−)-(S)-3-(4-Methoxyphenyl)-4-nitrobutan-1-ol: \[1^{12} \]
75% yield (over 2 steps), yellow oil; \([\alpha]_D^{26} -53.3 \text{ (c 0.8, CHCl}_3)\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.14 (d, J = 8.7 \text{ Hz}, 2H), 6.87 (d, J = 8.7 \text{ Hz}, 2H), 4.63 (dd, J = 12.2, 7.3 \text{ Hz}, 1H), 4.55 (dd, J = 12.2, 8.3 \text{ Hz}, 1H), 3.79 (s, 3H), 3.71–3.57 (m, 2H), 3.55–3.44 (m, 1H), 2.05–1.80 (m, 2H);

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 159.01, 130.66, 128.52, 114.39, 80.84, 59.83, 55.21, 40.34, 35.64; \)

IR (UATR) \(\nu_{\text{max}} 3393, 2938, 1611, 1547, 1513, 1380, 1247, 1180, 1029, 831, 691 \text{ cm}^{-1}; \)

HRMS (ESI\(^+\)) calcd for C\(_{11}\)H\(_{15}\)N\(_1\)Na\(_1\)O\(_4\) (M+Na\(^+\)) 248.0893, found 248.0893.

(−)-(S)-3-(4-methoxyphenyl)-4-nitro-N-(triphenylphosphoranylidene)butan-1-amine (5): 85% yield, brown solid, m.p. 64.6–65.5 °C, \([\alpha]_D^{26} -25.5 \text{ (c 1.0, CHCl}_3)\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.80–7.69 (m, 9H), 7.66–7.56 (m, 6H), 6.93 (d, J = 8.7 \text{ Hz}, 2H), 6.72 (d, J = 8.7 \text{ Hz}, 2H), 4.57 (dd, J =12.4, 6.1 \text{ Hz}, 1H), 4.43 (dd, J = 12.4, 9.0 \text{ Hz}, 1H), 3.75 (s, 3H), 3.52–3.38 (m, 1H), 3.35–2.80 (m, 2H), 2.41–2.25 (m, 1H), 2.05–1.87 (m, 1H);

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 158.73, 134.70, 134.66, 133.43, 133.28, 129.86, 129.68, 128.39, 121.68, 120.32, 114.18, 80.68, 55.11, 40.68, 40.03, 33.64, 33.55;

IR (UATR) \(\nu_{\text{max}} 2960, 2834, 1611, 1546, 1513, 1438, 1380, 1249, 1181, 1114, 1028, 834, 725, 691 \text{ cm}^{-1}; \)

HRMS (ESI\(^+\)) calcd for C\(_{29}\)H\(_{30}\)N\(_2\)O\(_3\)P\(_1\) (M+H\(^+\)) 485.1989, found 485.2006.
2.4 Typical procedure for the synthesis of azabicycles 3a-q

A One-pot process from an isolable nitro alkyamine 1a' for the synthesis of (±)-3a

In a reaction flask containing a suspension of of 3-nitro-1-propylammonium chloride 1a' (120.0 mg, 0.85 mmol, 1.0 equiv) in ethanol (2.0 mL) was added potassium carbonate (240.1 mg, 1.7 mmol, 2.0 equiv) and further stirred at room temperature for 5 min. To this suspension was added a solution of aldehyde 2a (252.0 mg, 0.98 mmol, 1.2 equiv) in ethanol (2.5 mL) and the resulting mixture was further vigorously stirred at room temperature for 14 h. The solvent was removed under reduced pressure, and the resulting solid was diluted with water (20 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic part was dried over anhydrous sodium sulfate, and the solvent was concentrated under reduced pressure. Crude product was purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding azabicycle (±)-3a (104.2 mg, 72% yield, isomeric ratio = 3:1). The cis-isomer was preferentially formed as a major product, as assigned by comparing NMR data with previously reported relative molecules.[13]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield of (±)-3a (%)</th>
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<tbody>
<tr>
<td>MeOH</td>
<td>73</td>
</tr>
<tr>
<td>DCM</td>
<td>18</td>
</tr>
<tr>
<td>THF</td>
<td>trace on TLC</td>
</tr>
<tr>
<td>MeCN</td>
<td>trace on TLC</td>
</tr>
<tr>
<td>1:1 MeOH-DCM</td>
<td>68</td>
</tr>
</tbody>
</table>

Further attempts to optimize the solvents (with the use of EtOH to MeOH, DCM, THF, and MeCN) revealed that alcoholic solvents gave better reaction conversion by enhancing the basicity and solubility of the carbonate base. The use of alcohol as a single solvent should be beneficial for all the sequential steps in the one-pot process.

A One-pot process from N-(nitroalkyl)phthalimide 1a for the synthesis of (±)-3a (Table 1)

In a reaction flask equipped with and condenser containing N-(nitroalkyl)phthalimide 1a (0.35 mmol, 1.0 equiv) was added a solution of hydrazine monohydrate (28 mg, 0.56 mmol, 1.2 equiv) in methanol (0.3 mL), and the reaction was stirred at 80 °C for 2 h. After cooling down to
room temperature, the suspension was added potassium carbonate (53 mg 0.39 mmol, 1.1 equiv) and a solution of aldehyde 2 (0.39 mmol, 1.1 equiv) in methanol (1.0 mL) and the resulting mixture was further vigorously stirred at room temperature for 14 h. The solvent was removed under reduced pressure to dryness. The resulting solid was diluted with dichloromethane (10 mL) and the undissolved solid was separated by filtration through a paper pad. The filtrate was concentrated under reduced pressure to give crude product. Calculated percentage yield and isomeric ratio of 3a were determined from crude product using GC-MS analysis with an internal calibration method and N-butyl piperidine as the internal standard. Crude products were purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding azabicycles 3a.

**Condition for GC-MS analysis**

- **Column type:** 5%-phenyl arylene/95%-dimethylpolysiloxane, Zebron (ZB-5MS, Phenomenex)  
  (L = 30 m x ID = 0.25 mm x df = 0.25 um)
- **Inlet temp:** 220 °C
- **Carrier gas flow:** 20 ml/min
- **Oven program:** 40 °C (2 min), to 200 °C at 10 °C/min (hold 3 min), to 280 °C at 20 °C/min (hold 10 min) for a total run time of 33 min.

A One-pot process from N-(nitroalkyl)phthalimide 1a-f for the synthesis of 3b-o (Table 2)

![Reaction Scheme]

In a reaction flask equipped with and condenser containing N-(nitroalkyl)phthalimide 1 (0.35 mmol, 1.0 equiv) was added a solution of hydrazine monohydrate (28 mg, 0.56 mmol, 1.2 equiv) in methanol (0.3 mL), and the reaction was stirred at 80 °C for 2 h. After cooling down to room temperature, the suspension was added potassium carbonate (53 mg 0.39 mmol, 1.1 equiv) and a solution of aldehyde 2 (0.39 mmol, 1.1 equiv) in methanol (1.0 mL) and the resulting mixture was further vigorously stirred at room temperature for 14 h (except for 3m, 3n, and 3o; the reactions were performed at 100 °C for 3 h, in a pressure tube). The solvent was removed under reduced pressure to dryness. The resulting solid was diluted with dichloromethane (10 mL) and the undissolved solid was separated by filtration through a paper pad. The filtrate was concentrated under reduced pressure. Isomeric ratios of 3b-l were determined from crude product using GC-MS analysis (condition as previously described for 3a). For compounds 3m-o having high melting point, isomeric ratios were determined by 1H-NMR analysis. Crude products were purified by column
chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding azabicycles 3b-o.

A One-pot process from an isolable nitro alkylamine 4 for the synthesis of (±)-3p

![Synthesis Reaction](image)

In a reaction flask containing a solution of 3,4-diaryl nitrobutylamine (±)-4 (130.1 mg, 0.39 mmol, 1.0 equiv) in methanol (0.9 mL) was added potassium carbonate (60.0 mg, 0.43 mmol, 1.1 equiv), and a solution of aldehyde 2b (106.5 mg, 0.44 mmol, 1.1 equiv) in methanol (1.1 mL). The resulting mixture was further vigorously stirred at room temperature for 14 h. The solvent was removed under reduced pressure, and the resulting solid was diluted with water (20 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic part was dried over anhydrous sodium sulfate, and the solvent was concentrated under reduced pressure. An isomer ratio of product (3 : 1) was determined by $^1$H-NMR analysis. Crude product was purified by column chromatography on silica gel using hexanes and an increasing proportion of ethyl acetate as eluents to afford the corresponding azabicycle (±)-3p (83.7 mg as a major isomer and 26.3 mg as mixture of two isomers, total 79% yield).

A One-pot process from an isolable nitro alkylphosphazene 5 for the synthesis of (-)-3q

A solution of chiral alkylphosphazene (-)-5 (201.5 mg, 0.4 mmol, 1.0 equiv) and aldehyde 2a (320.3 mg, 1.2 mmol, 3.0 equiv) in methanol (3 mL) was added dropwise triethylamine (0.09 mL, 0.6 mmol, 1.5 equiv) and the reaction was refluxed at 60 °C for 12 h. After cooling down to room temperature, the volatile materials were removed under reduced pressure, and the resulting crude product was quenched with water (10 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic part was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. An isomer ratio of product (7 : 1) was determined by $^1$H-NMR analysis. Crude product was purified by column chromatography on silica gel using hexane and an increasing proportion of ethyl acetate as eluents to afford the corresponding nitro azabicycle (-)-3q (60.0 mg as a pure major isomer, and 30.5 mg as mixture isomers, total yield 90.5 mg, 75%) as brown solid. An enantiomeric excess (ee) of a major isomer (-)-3q was determined to be 97% using chiral RP-HPLC (column type: Daicel CHAIRALPAK® IF: 4.6 mm-Ø x 250 mm-L, particle size = 5 µm; solvent system: MeCN-H$_2$O = 70 : 30; flow rate: 0.5 mL/min; temp: 25°C)
(±)-(1S*, 8aR*)-1-Nitrooctahydroindolizine (3a):
70% yield, yellow oil;

1H NMR (300 MHz, CDCl₃) d.r. 3 : 1, major diastereomer: δ 4.59 (ddd, J = 9.3, 8.4, 5.1 Hz, 1H), 3.08 (ddd, J = 9.3, 7.1, 2.4 Hz, 2H), 2.47 (t, J = 8.4 Hz, 1H), 2.40–2.25 (m, 2H), 2.17–2.03 (m, 2H), 1.90–1.80 (m, 1H), 1.72–1.60 (m, 1H), 1.60–1.21 (m, 4H); minor diastereomer observable: δ 4.98 (m, 1H), 3.30 (dd, J = 8.9, 7.1 Hz, 1H), 3.20 (dt, J = 10.9, 3.0 Hz, 1H), 2.50 (t, J = 8.1 Hz, 1H), 2.65–2.55 (m, 1H), 2.20 (qd, J = 8.3, 1.2 Hz, 1H), 1.94 (td, J = 11.4, 3.4 Hz, 1H), 1.72–1.60 (m, 1H), 1.05 (m, 1H);

13C NMR (75 MHz, CDCl₃) major diastereomer: δ 88.74, 69.10, 53.07, 52.80, 29.40, 27.89, 24.75, 23.62; minor diastereomer observable: δ 88.32, 67.33, 53.21, 53.13, 27.29, 26.55, 24.68, 23.69;

IR (UATR) νmax 2924, 1550, 1444, 1363, 1264, 1176, 1097, 958, 816, 664 cm⁻¹;

HRMS (ESI⁺) calcd for C₈H₁₅N₂O₂ (M+H)⁺ 171.1128, found 171.1121.

(±)-(1S*, 9aR*)-1-Nitrooctahydropyrrolo[1,2-a]azepine (3c):[13]
51% yield, yellow oil;

1H NMR (300 MHz, CDCl₃) d.r. 3 : 1, major diastereomer: δ 4.58 (ddd, J = 8.7, 5.6, 3.2 Hz, 1H), 3.14–3.00 (m, 2H), 2.90 (ddd, J = 10.6, 5.5, 3.0 Hz, 1H), 2.77 (ddd, J = 10.6, 9.4, 7.0 Hz, 1H), 2.46–2.23 (m, 3H), 2.14–2.04 (m, 1H), 1.82–1.50 (m, 7H); minor diastereomer observable: δ 5.01 (td, J = 7.5, 4.3 Hz, 1H), 3.31 (td, J = 8.5, 2.3 Hz, 1H); 2.71–2.53 (m, 2H);

13C NMR (75 MHz, CDCl₃) major diastereomer: δ 92.03, 70.81, 55.64, 54.73, 34.01, 29.44, 28.13, 25.71, 25.34;

IR (UATR) νmax 2924, 1552, 1463, 1363, 1223, 1176, 963, 819, 722 cm⁻¹;

HRMS (ESI⁺) calcd for C₉H₁₇N₂O₂ (M+H)⁺ 185.1285, found 185.1281.

(±)-(1S*, 10aR*)-1-Nitrodecahydropyrrolo[1,2-a]azocine (3d):[13]
24% yield, yellow oil;
\[^1\]H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.56 (ddd, \(J = 7.6, 4.3, 2.6\) Hz, 1H), 3.19–3.08 (m, 2H), 2.85 (dt, \(J = 13.3, 6.8\) Hz, 1H), 2.79 (ddd, \(J = 11.0, 9.2, 6.8\) Hz, 1H), 2.55 (dt, \(J = 12.8, 4.7\) Hz, 1H), 2.39–2.12 (m, 2H), 1.90–1.40 (m, 10H); 
\[^13\]C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 91.81, 68.17, 55.46, 54.77, 33.59, 29.28, 27.60, 26.87, 25.78, 22.70; 
IR (UATR) \(\nu_{\text{max}}\) 2920, 1553, 1462, 1377, 1261, 1171, 1090, 804, 721 cm\(^{-1}\); 
HRMS (ESI\(^+\)) calcd for C\(_{10}\)H\(_{19}\)N\(_2\)O\(_2\) (M+H)\(^+\) 199.1441, found 199.1433.

(±)-6-[(2R*,3S*)-3-Nitropyrrolidin-2-yl]hexyl 4-methylbenzenesulfonate (3d\(^{'}\)):
58% yield, yellow oil;
\[^1\]H NMR (300 MHz, CDCl\(_3\)) d.r. 3 : 1, major diastereomer : \(\delta\) 7.78 (d, \(J = 8.2\) Hz, 2H), 7.35 (d, \(J = 8.2\) Hz, 2H), 4.63 (dt, \(J = 8.8, 3.7\) Hz, 1H), 4.01 (td, \(J = 6.4, 2.3\) Hz, 2H), 3.50–3.42 (m, 1H), 3.25–3.08 (m, 1H), 2.71 (br s, 1H), 2.45 (s, 3H), 2.49–2.38 (m, 1H), 2.30–2.09 (m, 1H), 1.69–1.20 (m, 9 H); minor diastereomer observable : \(\delta\) 7.70 (d, \(J = 8.2\) Hz, 2H), 7.20 (d, \(J = 8.1\) Hz, 2H), 5.02 (ddd, \(J = 7.0, 5.1, 1.8\) Hz, 1H), 3.46–3.36 (m, 1H), 3.25–3.08 (m, 1H), 2.95 (ddd, \(J = 14, 9.4, 6.5\) Hz, 1H), 2.49–2.38 (m, 1H), 2.30–2.09 (m, 1H), 1.69–1.20 (m, 9 H);
\[^13\]C NMR (75 MHz, CDCl\(_3\)) major diastereomer : \(\delta\) 144.61, 132.99, 129.72, 127.70, 90.33, 70.40, 66.18, 45.83, 33.68, 32.27, 28.51, 28.48, 26.16, 25.03, 21.47; minor diastereomer observable : \(\delta\) 128.94, 125.59, 89.38, 65.74, 45.79, 32.43, 28.96, 28.62, 26.93, 24.93; 
IR (UATR) \(\nu_{\text{max}}\) 3376, 2930, 1549, 1456, 1356, 1175, 1122, 1010, 952, 816, 682, 664 cm\(^{-1}\); 
HRMS (ESI\(^+\)) calcd for C\(_{17}\)H\(_{27}\)N\(_2\)O\(_5\)S\(_1\) (M+H)\(^+\) 371.1635, found 371.1646.

(±)-(8S*,8aR*)-8-Nitrooctahydroindolizine (3e):
65% yield, yellow oil;
\[^1\]H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.27 (ddd, \(J = 11.3, 9.5, 4.0\) Hz, 1H), 3.15–3.02 (m, 2H), 2.39–2.30 (m, 2H), 2.26 (q, \(J = 8.9\) Hz, 1H), 2.09 (td, \(J = 11.7, 2.8\) Hz, 1H), 2.03–1.55 (m, 7H); 
\[^13\]C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 87.87, 65.71, 53.90, 51.25, 30.11, 28.96, 28.62, 26.93, 24.93; 
IR (UATR) \(\nu_{\text{max}}\) 2924, 1550, 1456, 1363, 1264, 1176, 1097, 958, 816, 664 cm\(^{-1}\); 
HRMS (ESI\(^+\)) calcd for C\(_8\)H\(_{13}\)N\(_2\)O\(_2\) (M+H)\(^+\) 171.1128, found 171.1134.
(±)-(1S*,9aR*)-1-Nitrooctahydroquinolizine (3f):[13]

72% yield, yellow oil;

$^1$H NMR (300 MHz, CDCl$_3$) δ 4.30 (ddd, $J = 12.1, 9.6, 4.1$ Hz, 1H), 2.88 (d, $J = 11.4$ Hz, 1H), 2.79 (d, $J = 11.7$ Hz, 1H), 2.32–2.23 (m, 2H), 2.20–2.07 (m, 2H), 1.95 (qd, $J = 12.3, 4.6$ Hz, 1H), 1.85–1.49 (m, 6H), 1.40–1.20 (m, 2H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 89.40, 63.98, 56.10, 55.28, 30.48, 28.84, 25.32, 23.48, 23.03;

IR (UATR) $\nu_{\text{max}}$ 2923, 1551, 1465, 1377, 1272, 1186, 964, 795, 720 cm$^{-1}$;

HRMS (ESI$^+$) calcd for C$_9$H$_{17}$N$_2$O$_2$ (M+H)$^+$ 185.1285, found 185.1278.

(±)-(10S*,10aR*)-10-Nitrodecahydropyrido[1,2-a]azepine (3g):

45% yield, yellow oil;

$^1$H NMR (300 MHz, CDCl$_3$) d.r. 4 : 1, major diastereomer : δ 4.58 (td, $J = 9.3, 2.6$ Hz, 1H), 3.10 (td, $J = 8.1, 3.0$ Hz, 1H), 2.88–2.73 (m, 3H), 2.63–2.53 (m, 1H), 2.40–2.37 (m, 1H), 2.16–2.03 (m, 1H), 1.98–1.40 (m, 10H); minor diastereomer observable : δ 4.78 (ddd, $J = 8.4, 7.6, 1.0$ Hz, 1H), 2.96–2.70 (m, 3H), 2.53–2.47 (m, 1H), 2.30–2.20 (m, 1H), 2.16–2.03 (m, 1H), 1.98–1.40 (m, 10H);

$^{13}$C NMR (75 MHz, CDCl$_3$) major diastereomer : δ 91.88, 63.69, 54.64, 53.30, 31.07, 28.85, 27.33, 24.89, 23.38, 22.00; minor diastereomer : δ 90.70, 63.94, 57.72, 54.75, 29.60, 26.48, 26.06, 26.00, 25.68, 23.73;

IR (UATR) $\nu_{\text{max}}$ 2933, 1547, 1441, 1349, 1298, 1114, 1059, 964, 938, 904, 787, 697 cm$^{-1}$;

HRMS (ESI$^+$) calcd for C$_{10}$H$_{19}$N$_2$O$_2$ (M+H)$^+$ 199.1441, found 199.1441.

(±)-(1S*,2R*,8aR*)-2-Methyl-1-nitrooctahydroindolizine (3i):

One could be isolated as a pure major isomer.

52% yield, yellow oil;

$^1$H NMR (300 MHz, CDCl$_3$) δ 4.53 (dd, $J = 7.1, 3.7$ Hz, 1H), 3.42 (dd, $J = 8.6, 8.0$ Hz, 1H), 3.17 (dt, $J = 11.4, 3.6$ Hz, 1H), 3.11–2.96 (m, 1H), 2.26 (ddd, $J = 10.3, 7.2, 2.5$ Hz, 1H), 1.93 (td, $J =$
11.4, 3.4 Hz, 2H), 1.88–1.74 (m, 2H), 1.65–1.45 (m, 2H), 1.35–1.20 (m, 2H), 1.16 (d, \( J = 7.2 \) Hz, 3H);

\( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 95.59, 66.87, 61.98, 53.11, 36.36, 26.20, 24.57, 23.69, 17.68;

IR (UATR) \( \nu_{\text{max}} \) 2934, 1546, 1456, 1362, 1330, 1151, 1065, 879, 777, 686 cm\(^{-1} \);

HRMS (ESI\(^+\)) calcd for C\(_9\)H\(_{17}\)N\(_2\)O\(_2\) (M+H)\(^+\) 185.1285, found 185.1284.

Others isomers could be isolated as mixtures. Only major peaks were interpreted.

16% yield, yellow oil;

\( ^{1} \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 4.66 (dd, \( J = 10.4, 8.8 \) Hz, 1H), 3.22 (dd, \( J = 8.6, 7.3 \) Hz, 1H), 3.07 (d, \( J = 10.8 \) Hz, 1H), 2.85–2.65 (m, 2H), 2.10 (t, \( J = 9.1 \) Hz, 2H), 1.98–1.77 (m, 2H), 1.77–1.40 (m, 4H), 0.97 (d, \( J = 7.1 \) Hz, 3H);

\( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 92.04, 66.71, 61.63, 52.87, 33.96, 29.09, 24.90, 23.72, 13.05;

(\( \pm \))-\( (1S^*, 8aR^*) \)-1-Methyl-1-nitrooctahydroindolizine (3j):

67% yield, yellow oil;

\( ^{1} \)H NMR (300 MHz, CDCl\(_3\)) d.r. 1:1, mixture of two diastereomers: \( \delta \) 3.30 (td, \( J = 8.8, 2.0 \) Hz, 1H), 3.21–3.04 (m, 3H), 2.98 (dt, \( J = 14.0, 8.8 \) Hz, 1H), 2.73 (dd, \( J = 14.0, 8.0, 1.0 \) Hz, 1H), 2.43–2.33 (m, 2H), 2.22 (q, \( J = 8.8 \) Hz, 1H), 2.08 (td, \( J = 11.8, 3.0 \) Hz, 1H), 2.00–1.73 (m, 8H), 1.67 (s, 3H), 1.62 (s, 3H), 1.56–1.40 (m, 2H), 1.40–1.16 (m, 2H), 1.00–0.80 (m, 2H);

\( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) mixture of two diastereomers: \( \delta \) 94.76, 93.75, 73.77, 71.62, 53.76, 53.42, 53.30, 52.83, 36.42, 35.13, 24.66, 24.56, 23.73, 23.62, 23.47, 22.91.

One could be isolated as a pure isomer.

\( ^{1} \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 3.30 (td, \( J = 8.8, 2.0 \) Hz, 1H), 3.17 (dt, \( J = 11.0, 3.3 \) Hz, 1H), 2.98 (dt, \( J = 14.0, 8.8 \) Hz, 1H), 2.22 (q, \( J = 8.8 \) Hz, 1H), 1.94 (td, \( J = 11.4, 3.3 \) Hz, 1H), 1.89–1.73 (m, 4H), 1.67 (s, 3H), 1.56–1.47 (m, 1H), 1.29–1.16 (m, 1H), 0.99–0.85 (m, 1H);

\( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 94.81, 73.81, 53.46, 52.89, 35.19, 26.05, 24.62, 23.77, 23.52;

IR (UATR) \( \nu_{\text{max}} \) 2938, 1536, 1439, 1389, 1330, 1271, 1129, 864, 664 cm\(^{-1} \);

HRMS (ESI\(^+\)) calcd for C\(_9\)H\(_{17}\)N\(_2\)O\(_2\) (M+H)\(^+\) 185.1285, found 185.1283.
(±)-(1S*,8aR*)-8a-Methyl-1-nitrooctahydroindolizine (3k):
69% yield, yellow oil;

1H NMR (300 MHz, CDCl3) d.r. 5 : 3, major diastereomer : δ 4.73 (dd, J = 8.7, 3.7 Hz, 1H), 3.28–3.17 (m, 1H), 2.90–2.80 (m, 1H), 2.72–2.57 (m, 4H), 2.27–2.10 (m, 1H), 1.72–1.48 (m, 3H), 1.48–1.38 (m, 1H), 1.30–1.22 (m, 1H), 1.17 (s, 3H); minor diastereomer observable : δ 4.59 (dd, J = 9.3, 6.5 Hz, 1H), 2.99 (td, J = 9.3, 4.2 Hz, 1H), 2.90–2.80 (m, 1H), 2.77–2.52 (m, 3H), 2.47–2.27 (m, 1H), 1.87 (dd, J = 9.1, 3.7 Hz, 1H), 1.72–1.48 (m, 5H), 0.92 (s, 3H);

13C NMR (75 MHz, CDCl3) major diastereomer : δ 94.02, 62.85, 47.98, 44.61, 29.39, 25.39, 22.28, 19.81, 15.68; minor diastereomer : δ 93.23, 62.23, 47.97, 45.28, 34.63, 24.68, 23.09, 20.19, 10.16; IR (UATR) νmax 2927, 1547, 1453, 1369, 1330, 1246, 1191, 1108, 933, 802, 756 cm⁻¹;
HRMS (ESI⁺) calcd for C₉H₁₇N₂O₂ (M+H)⁺ 185.1285, found 185.1284.

(±)-(1S*,5S*,8aR*)-5-Methyl-1-nitrooctahydroindolizine (3l):
67% yield, yellow oil;

1H NMR (300 MHz, CDCl3) d.r. 7 : 1, major diastereomer : δ 4.65 (td, J = 9.1, 4.5 Hz, 1H), 3.31 (t, J = 6.9 Hz, 1H), 2.50–2.32 (m, 4H), 2.32–2.12 (m, 1H), 2.12–2.02 (m, 1H), 1.88–1.79 (m, 1H), 1.68–1.59 (m, 1H), 1.49–1.19 (m, 2H), 1.34 (dt, J = 12.7, 3.4 Hz, 1H), 1.13 (d, J = 6.2 Hz, 3H); minor diastereomer observable : δ 4.98 (ddd, J = 10.4, 7.0, 3.5 Hz, 1H), 3.45 (td, J = 9.0, 1.5 Hz, 1H), 2.57 (ddt, J = 12.8, 9.0, 3.5 Hz, 1H), 2.20–2.12 (m, 1H), 2.05–1.98 (m, 1H), 1.13 (d, J = 6.2 Hz, 3H);

13C NMR (75 MHz, CDCl3) major diastereomer : δ 88.73, 69.44, 58.83, 50.38, 33.39, 29.17, 27.57, 23.82, 20.55; minor diastereomer observable : δ 88.55, 67.63, 59.33, 50.78, 27.03, 26.54, 24.13, 20.76;
IR (UATR) νmax 2934, 1548, 1440, 1374, 1294, 1189, 1082, 819, 678 cm⁻¹;
HRMS (ESI⁺) calcd for C₉H₁₇N₂O₂ (M+H)⁺ 185.1285, found 185.1287.

SI-25
(+)-(1S,2S,8S,8aS)-1,2-Bis(benzyloxy)-8-nitrooctahydroindolizine or (8S)-1,2-Bis(benzyloxy)-8-nitro-lentiginosine (3m):
75% yield, brown oil, [α]D^26+41.2 (c 0.9, CHCl₃);
1H NMR (300 MHz, CDCl₃) δ 7.37–7.17 (m, 10H), 4.57 (d, J = 12.0 Hz, 1H), 4.51 (ddd, J = 9.6, 7.7, 2.1 Hz, 1H), 4.44 (d, J = 11.1 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.35 (d, J = 11.1 Hz, 1H), 4.01 (dd, J = 7.0, 1.2 Hz, 1H), 3.87 (dd, J = 5.8, 1.2 Hz, 1H), 3.12 (d, J = 10.4 Hz, 1H), 2.96 (dt, J = 10.8, 3.0 Hz, 1H), 2.52 (dd, J = 10.4, 5.8 Hz, 1H), 2.43 (dd, J = 9.6, 7.0, 1H), 2.23 (dq, J = 12.6, 3.6 Hz, 1H), 2.08 (dd, J = 11.3, 3.5 Hz, 1H), 1.93 (qd, J = 12.6, 4.8 Hz, 1H), 1.80–1.64 (m, 2H);
13C NMR (75 MHz, CDCl₃) δ 137.48, 137.29, 128.31, 128.16, 127.95, 127.78, 127.76, 127.57, 88.14, 46.01, 81.17, 72.32, 71.41, 69.91, 57.94, 51.11, 29.05, 22.73;
IR (UATR) ν_max 3032, 2947, 1548, 1454, 1368, 1266, 1100, 975, 911, 734, 697 cm⁻¹;
HRMS (ESI⁺) calcd for C₂₂H₂₆N₂O₄ (M+H)⁺ 405.1785, found 405.1795.

(±)-(1S*,6S*,7S*,8R*,8aS*)-6,7,8-Tris(benzyloxy)-1-nitrooctahydroindolizine (3n):
79% yield, yellow oil;
1H NMR (300 MHz, CDCl₃) δ 7.42–7.22 (m, 15H), 4.94 (d, J = 11.8 Hz, 1H), 4.83 (d, J = 12.8 Hz, 1H), 4.78 (d, J = 11.8 Hz, 1H), 4.65 (d, J = 12.8 Hz, 1H), 4.57 (s, 2H), 4.09 (t, J = 2.9 Hz, 1H), 3.71–3.78 (br m, 1H), 3.52 (br s, 1H), 3.18–3.06 (m, 2H), 2.90–2.76 (br s, 1H), 2.67–2.41 (m, 2H), 2.35–2.23 (m, 2H);
13C NMR (75 MHz, CDCl₃) δ 137.48, 137.29, 128.31, 128.16, 127.95, 127.78, 127.76, 127.57, 88.14, 46.01, 81.17, 72.32, 71.41, 69.91, 57.94, 51.11, 29.05, 22.73;
IR (UATR) ν_max 3032, 2947, 1548, 1454, 1368, 1266, 1100, 975, 911, 734, 697 cm⁻¹;
HRMS (ESI⁺) calcd for C₂₉H₃₂N₂O₅ (M+H)⁺ 511.2203, found 511.2223.

(±)-(1S*,10bR*)-8,9-Dimethoxy-1-nitro-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (3o):
81% yield, yellow solid, m.p. 97.1–99.3 °C;
1H NMR (300 MHz, CDCl₃) d.r. = 7 : 1, major diastereomer : δ 6.68 (s, 1H), 6.61 (s, 1H), 4.99 (q, J = 6.3 Hz, 1H), 4.23 (d, J = 6.3 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.21–3.12 (m, 2H), 3.00–2.80 (m, 4H), 2.54–2.45 (m, 2H); minor diastereomer observable : δ 6.41 (s, 1H), 5.47 (ddd, J = 10.1, 6.6, 3.5 Hz, 1H), 3.96 (d, J = 6.6 Hz, 1H), 3.44 (m, 1H), 3.34 (dt, J = 10.8, 5.0 Hz, 1H);
$^{13}$C NMR (75 MHz, CDCl$_3$) major diastereomer: $\delta$ 148.29, 147.82, 126.32, 126.28, 111.42, 108.55, 90.74, 68.56, 55.94, 55.90, 52.61, 47.41, 30.65, 27.53; minor diastereomer observable: $\delta$ 111.59, 108.88, 88.29, 67.78, 56.03, 55.80, 52.54, 47.51, 29.97, 28.69;
IR (UATR) $\nu_{max}$ 2936, 1611, 1543, 1516, 1464, 1370, 1259, 1223, 1109, 1014, 857, 773 cm$^{-1}$;
HRMS (ESI$^+$) calcd for C$_{14}$H$_{19}$N$_2$O$_4$ (M+H)$^+$ 279.1339, found 279.1349.

(±)-(6R*,7S*,8S*,8aR*)-7-(3,4-Dimethoxyphenyl)-8-nitro-6-phenyloctahydroindolizine (3p):
79% yield, pale yellow solid, m.p. 171.4–172.6 °C;
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.25–7.10 (m, 5H), 6.62 (d, $J$ = 8.2 Hz, 1H), 6.40 (dd, $J$ = 8.2, 2.0 Hz, 1H), 5.94 (d, $J$ = 2.0 Hz, 1H), 4.87 (dd, $J$ = 11.9, 9.2 Hz, 1H), 3.79 (s, 3H), 3.63 (dd, $J$ = 11.9, 5.6 Hz, 1H), 3.48 (s, 3H), 3.41 (dd, $J$ = 11.4, 1.2 Hz, 1H), 3.22 (t, $J$ = 8.4 Hz, 1H), 3.16 (t, $J$ = 4.3 Hz, 1H), 2.79 (dd, $J$ = 11.4, 4.0 Hz, 1H), 2.63 (dt, $J$ = 9.2, 6.0 Hz, 1H), 2.30 (q, $J$ = 8.4 Hz, 1H), 2.07–1.76 (m, 4H);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 148.10, 147.98, 141.07, 130.29, 129.52, 127.69, 126.60, 120.86, 111.00, 89.24, 67.46, 56.28, 55.65, 55.36, 53.79, 51.08, 47.01, 28.28, 21.08;
IR (UATR) $\nu_{max}$ 2937, 1547, 1519, 1464, 1378, 1266, 1144, 1028, 808, 704 cm$^{-1}$;
HRMS (ESI$^+$) calcd for C$_{22}$H$_{26}$N$_2$O$_4$Na (M+Na)$^+$ 405.1785, found 405.1780.

(-)-(1S,2S,9aR)-2-(4-Methoxyphenyl)-1-nitrooctahydroquinolizine (3q):
75% yield, yellow solid, m.p. 102.6–104.5 °C, $[\alpha]_D^{27}$ = –42.5 ( c 0.8, CHCl$_3$);
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.11 (d, $J$ = 8.7 Hz, 2H), 6.83 (d, $J$ = 8.7 Hz, 2H), 4.43 (dd, $J$ = 11.2, 9.5 Hz, 1H), 3.77 (s, 3H), 3.14 (td, $J$ = 11.4, 5.5 Hz, 1H), 3.00–2.87 (m, 2H), 2.38 (td, $J$ = 10.9, 2.3 Hz, 1H), 2.33 (td, $J$ = 11.6, 3.7 Hz, 1H), 2.17 (td, $J$ = 11.8, 3.3 Hz, 1H), 2.05–1.87 (m, 2H), 1.85–1.74 (m, 1H), 1.74–1.50 (m, 3H), 1.46–1.18 (m, 2H);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.02, 131.56, 128.14, 114.28, 95.38, 64.31, 56.03, 55.36, 55.20, 46.82, 31.38, 29.02, 25.23, 23.36;
IR (UATR) $\nu_{max}$ 2939, 1613, 1546, 1515, 1368, 1249, 1178, 1127, 1034, 826, 743 cm$^{-1}$;
HRMS (ESI$^+$) calcd for C$_{16}$H$_{23}$N$_2$O$_3$ (M+H)$^+$ 291.1703, found 291.1704.
2.5 Functional group conversion to natural product cores 6-10

Preparation of (-)-6 from (±)-3q

To a round-bottom flask containing a solution of azabicycle (-)-3q (50.0 mg, 0.17 mmol, 1.0 equiv) in ethanol (10 mL) was added nickel chloride hexahydrate (47.1 mg, 0.20 mmol, 1.2 equiv) and sodium borohydride (18.1 mg, 98% purity, 0.45 mmol, 2.6 equiv) at 0 °C and the mixture was warmed up to room temperature and further stirred for 30 min. The reaction was quenched with a saturated ammonium chloride solution (3.0 mL) and the resulting mixtures were concentrated under reduced pressure. The obtained solid was diluted with water (10 mL) and extracted with dichloromethane (2 x 20 mL). The organic part was dried over anhydrous potassium carbonate, and concentrated under reduced pressure to afford the corresponding amine (45.0 mg, quant.) as pale yellow solid, which was used in the next step without purification.

A solution of amine (45.0 mg) in dichloromethane (1.0 mL) was added pyridine (0.1 mL) and acetic anhydride (0.1 mL) and the reaction was stirred at room temperature for 20 h. The volatile materials were removed under reduced pressure, and the resulting crude product was diluted with ethyl acetate (50 mL). The organic part was washed with saturated copper sulfate solution (3 x 10 mL) and dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Crude product was purified by column chromatography on silica gel using hexane and an increasing proportion of ethyl acetate as eluents to afford the corresponding quinamide derivative (-)-6 (38.8 mg, 75%) as pale brown solid.

\[
\text{N-}\{(1S,2S,9aR)-2-(4-Methoxyphenyl)octahydroquinolinizin-1-yl\}acetamide (6):} \\
78\% \text{ yield, pale brown solid, m.p. 217.2–218.2 °C; [a]_D^{27} -20.6 (c 1.0, CHCl}_3); \\
\text{H NMR (300 MHz, CDCl}_3) \delta 7.11 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 4.98 (d, J = 9.7 Hz, 1H), 3.93 (q, J = 10.2 Hz, 1H), 3.77 (s, 3H), 2.96–2.83 (m, 2H), 2.45 (td, J = 11.2, 4.8 Hz, 1H), 2.19 (td, J = 11.5, 3.5 Hz, 1H), 2.11–2.00 (m, 1H), 1.96–1.72 (m, 5H), 1.71 (s, 3H), 1.68–1.56 (m, 2H), 1.43–1.28 (m, 1H), 1.27–1.10 (m, 1H); \\
\]
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.58, 158.17, 134.94, 128.27, 113.83, 67.55, 56.37, 56.06, 55.60, 55.13, 48.66, 33.67, 29.21, 25.54, 24.27, 23.19;
IR (UATR) $\nu_{\text{max}}$ 3299, 2932, 1649, 1553, 1514, 1372, 1248, 1179, 1036, 832 cm$^{-1}$;
HRMS (ESI$^+$) calcd for C$_{18}$H$_{27}$N$_2$O$_2$ (M+H)$^+$ 303.2067, found 303.2061.

**Preparation of (+)-7 from (+)-3m**

To a pressure vessel containing a solution of chiral nitro-azabicycle 3m (36.0 mg, 0.08 mmol, 1.0 equiv) in ethanol (4.0 mL) was added palladium on carbon (10 wt.% loading, 30.2 mg). The reaction was purged with hydrogen and vigorously stirred under atmospheric pressure of hydrogen (ca. 300 psi) at room temperature for 16 h. The catalyst was separated by filtration through a celite pad and the pad was successively washed with ethanol. The combined organic part was concentrated under reduced pressure to afford the desired amine. To this crude product was diluted with methanol (5 mL) and basified by the addition of Ambersep® 900 hydroxide form (20-50 mesh, ca. 100 mg) and further stirred for 10 min. The solid was separated and the filtrate was evaporated to dryness. Crude product was purified by column chromatography on Sephadex™ LH-20 using methanol as eluent to give bicyclic azasugar (+)-7 (12.1 mg, 89%) as pale brown solid.

**(+)-(1S,2S,8S,8aS)-8-Aminooctahydroindolizine-1,2-diol or (8S)-8-Amino-lentiginosine (7):**
89% yield, brown solid, m.p. 129.5–131.5 °C, $[\alpha]_D^{27} +21.3$ (c 1.0, MeOH);
$^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 3.94 (ddd, $J = 6.9, 4.6, 3.1$ Hz, 1H), 3.82 (dd, $J = 8.0, 3.1$ Hz, 1H), 2.90–2.83 (m, 2H), 2.70 (dd, $J = 13.3, 9.3, 4.1$ Hz, 1H), 2.56 (dd, $J = 10.4, 6.9$ Hz, 1H), 2.02–1.88 (m, 2H), 1.74–1.60 (m, 2H), 1.60 (dd, $J = 9.2, 8.0$ Hz, 1H), 1.17–1.03 (m, 1H);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 85.30, 78.14, 75.74, 62.25, 53.89, 53.29, 34.24, 34.24, 25.20;
IR (UATR) $\nu_{\text{max}}$ 3348, 2924, 1651, 1598, 1559, 1449, 1375, 1325, 1237, 1120, 1041, 948, 860, 758 cm$^{-1}$;
HRMS (ESI$^+$) calcd for C$_8$H$_{17}$N$_2$O$_2$ (M+H)$^+$ 173.1285, found 173.1284.
Preparation of (±)-8 from (±)-3n

To a pressure vessel containing a solution of nitro-azabicycle 3n (43.3 mg, 0.09 mmol, 1.0 equiv) in ethanol (4.0 mL) was added platinum (IV) oxide hydrate (11.1 mg). The reaction was purged with hydrogen and vigorously stirred under atmospheric pressure of hydrogen (ca. 70 psi) at 70 °C for 14 h. The reaction was cooled down to room temperature and hydrogen gas was released. The catalyst was separated by filtration through a celite pad and the pad was successively washed with ethanol. The combined organic part was concentrated under reduced pressure. Crude product was purified by column chromatography on Sephadex™ LH-20 using methanol as eluent to give bicyclic azasugar (±)-8 (37.9 mg, 93%) as thick brown oil.

(±)-(1S*,6S*,7S*,8R*,8aS*)-6,7,8-Tris(benzyloxy)octahydroindolizin-1-amine (8)

93% yield, thick brown oil;

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.47–7.20 (m, 15H), 4.98 (d, J = 12.2 Hz, 1H), 4.91 (d, J = 13.0 Hz, 1H), 4.86 (d, J =12.2 Hz, 1H), 4.67 (d, J = 13.0 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 3.97 (br dd, J = 3.0, 2.8 Hz, 1H), 3.78 (br d, J = 2.5 Hz, 1H), 3.65 (m, 1H), 3.36 (br dd, J = 2.8, 2.5 Hz, 1H), 3.20 (dd, J = 11.8, 3.2 Hz, 1H), 3.05 (dd, J = 10.8, 8.4 Hz, 1H), 2.40–2.20 (m, 2H), 2.05 (dd, J = 11.8, 1.7 Hz, 1H), 1.70 (br d, J = 7.7 Hz, 1H), 1.40–1.22 (m, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 139.17, 139.13, 138.46, 128.66, 128.30, 128.17, 128.06, 127.99, 127.44, 127.22, 127.14, 80.91, 74.09, 73.30, 72.11, 71.97, 71.13, 71.06, 54.32, 52.28, 50.52, 32.21;

IR (UATR) $\nu_{max}$ 3060, 3030, 2870, 1496, 1454, 1356, 1130, 1094, 734, 697 cm$^{-1}$;

HRMS (ESI$^+$) calcd for C$_{29}$H$_{34}$N$_2$Na$_1$O$_3$ (M+Na)$^+$ 481.2462, found 481.2460.

Preparation of (±)-9 from (±)-3o

To a round-bottom flask containing a solution of potassium dichromate (450.0 mg, 1.5 mmol, 7.0 equiv) in 6 N aq. HCl (7.0 mL) was added zinc powder (777.0 mg, 11.9 mmol, 54.0
equiv) in a small portion under an argon atmosphere. The mixture was stirred at room temperature for 1 h, to afford the in situ generated chromium (II) chloride.

In a round-bottom flask equipped with a condenser containing a solution of nitro-azabicycle 3o (60.1 mg, 0.22 mmol, 1.0 equiv) in MeOH (7.0 mL) under heating at 75°C was added dropwise a solution of the in situ generated chromium (II) chloride in aq. HCl and the mixture was further stirred at 75 °C for 15 min. After cooling down to room temperature, the volatile substrates were removed under reduced pressure and the obtained crude product was diluted with water (10 mL), poured into saturated sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3 x 20 mL). The organic part was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Crude product was purified by column chromatography on silica gel using hexane and an increasing proportion of ethyl acetate as eluents to afford the corresponding oxime (±)-9 (25.5 mg, 45%) as yellow solid.

![Image of (±)-9](image.png)

(±)-(10bR*)-8,9-Dimethoxy-2,3,5,6,10b-pentahydropyrrolo[2,1-a]isoquinolin-1-one oxime (9): 45% yield, yellow solid, m.p. 139.2–140.6 °C;

1H NMR (300 MHz, CDCl3) δ 7.04 (s, 1H), 6.57 (s, 1H), 4.56 (s, 1H), 3.84 (s, 6H), 3.15–2.99 (m, 4H), 2.99–2.86 (m, 1H), 2.71 (t, J = 6.8 Hz, 2H), 2.66 (dt, J = 11.5, 4.6 Hz, 1H);

13C NMR (75 MHz, CDCl3) δ 164.02, 147.96, 147.40, 125.78, 124.25, 111.26, 110.60, 62.11, 55.83, 55.82, 48.47, 45.71, 25.64, 24.68;

IR (UATR) νmax 3196, 3068, 2836, 1606, 1516, 1467, 1355, 1311, 1256, 1229, 1210, 1115, 1089, 984, 927, 885, 825, 790, 764, 734 cm⁻¹;

HRMS (ESI⁺) calcd for C14H19N2O3 (M+H)⁺ 263.1390, found 263.1386.

Preparation of (±)-10 from (±)-3p

To a pressure vessel containing a solution of nitro-azabicycle 3p (51.0 mg, 0.14 mmol, 1.0 equiv) in ethanol (5.0 mL) was added platinum (IV) oxide hydrate (16.1 mg). The reaction was purged with hydrogen and vigorously stirred under atmospheric pressure of hydrogen (ca. 70 psi) at
70 °C for 14 h. The reaction was cooled down to room temperature and hydrogen gas was released. The catalyst was separated by filtration through a celite pad and the pad was successively washed with ethanol. The combined organic part was concentrated under reduced pressure to afford the desired amine (46.3 mg, quant), which was used in the next reaction without purification.

To a round-bottom flask containing a solution of amine (46.3 mg, 0.14 mmol, 1.0 equiv) in ethanol (2.0 mL) was added formic acid (98–100% purity, 0.3 mL) and a solution of formaldehyde (37% purity, 0.3 mL), and the reaction was heated at 90 °C for 12 h. Then, the reaction was cooled down to room temperature, diluted with water (5.0 mL), basified with 20% NaOH to pH 12 at 0 °C, and extracted with ethyl acetate (3 x 10 mL). The combined organic part was dried over anhydrous sodium sulfate, and the solvent was concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel using ethyl acetate as eluents to afford the corresponding naphthyridine 10 (29.3 mg, 55% yield) as pale brown solid.

(±)-(3aR*,3bS*,9bS*,10R*)-7,8-Dimethoxy-4-methyl-10-phenyl-1,2,3,3a,3b,4,5,9b,10,11-decahydrobenzo[c]pyrrolo[1,2-h][1,7]naphthyridine (10):
55% yield, yellow solid, m.p. 188.5–190.3 °C;
1H NMR (300 MHz, CDCl3) δ 7.44 (dd, J = 8.1, 1.5 Hz, 2H), 7.08–6.98 (m, 3H), 6.77 (s, 1H), 6.32 (s, 1H), 4.02 (d, J = 16.1 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.67 (br s, 1H), 3.42 (d, J = 16.1 Hz, 1H), 3.29 (dd, J = 11.2, 1.5 Hz, 1H), 3.08 (s, 1H), 3.06 (s, 1H), 2.98 (td, J = 8.4, 1.5 Hz, 1H), 2.57 (dd, J = 11.2, 3.9 Hz, 1H), 2.28 (s, 3H), 2.14–1.98 (m, 2H), 1.90–1.60 (m, 3H);
13C NMR (75 MHz, CDCl3) δ 147.01, 146.99, 142.38, 130.47, 127.47, 126.99, 125.99, 125.79, 110.35, 109.76, 67.00, 61.16, 58.40, 57.79, 55.92, 55.61, 54.21, 42.70, 38.20, 35.25, 28.78, 21.46;
IR (UATR) νmax 2962, 2766, 1607, 1514, 1454, 1326, 1254, 1223, 1125, 1039, 867, 781, 705 cm⁻¹; HRMS (ESI⁺) calcd for C26H31N2O2 (M+H)⁺ 379.2380, found 379.2382.
Table S1. Summary of relative configuration of major isomer of azabicycles 3a-q and 6-10 using $^3$J$_{H,H}$ coupling constants and/or NOE techniques comparing with previously reported or relative values.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Relative structure, Experiment $^3$J and/or NOE values of Major isomer</th>
<th>Reference no. and Reported $^3$J values</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-3a</td>
<td><img src="image1" alt="Structure" /> $^3$J$_{H1/8a} = 9.3$ Hz</td>
<td>New compound</td>
</tr>
<tr>
<td>(±)-3c</td>
<td><img src="image2" alt="Structure" /> $^3$J$_{H1/9a} = 8.7$ Hz</td>
<td>[13] reported value $^3$J$_{H1/9a} = 8.5$ Hz</td>
</tr>
<tr>
<td>(±)-3d</td>
<td><img src="image3" alt="Structure" /> $^3$J$_{H1/10a} = 7.6$ Hz</td>
<td>[13] reported value $^3$J$_{H1/10a} = 8.0$ Hz</td>
</tr>
<tr>
<td>(±)-3d'</td>
<td><img src="image4" alt="Structure" /> $^3$J$_{H2/3} = 8.8$ Hz</td>
<td>New compound</td>
</tr>
<tr>
<td>(±)-3e</td>
<td><img src="image5" alt="Structure" /> $^3$J$_{H8/8a} = 9.3$ Hz</td>
<td>[13] reported value $^3$J$_{H8/8a} = 9.5$ Hz</td>
</tr>
<tr>
<td>(±)-3f</td>
<td><img src="image6" alt="Structure" /> $^3$J$_{H1/9a} = 9.6$ Hz</td>
<td>[13] reported value $^3$J$_{H1/9a} = 9.5$ Hz</td>
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<td>(±)-3g</td>
<td><img src="image7" alt="Structure" /> $^3$J$_{H10/10a} = 9.3$ Hz</td>
<td>New compound</td>
</tr>
<tr>
<td>Compound No.</td>
<td>Relative structure, Experiment $^3J$ and/or NOE values of Major isomer</td>
<td>Reference no. and Reported $^3J$ values</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------</td>
<td>---------------------------------</td>
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<tr>
<td>(±)-3i</td>
<td><img src="image" alt="Structure of (±)-3i" /> $^3J_{H1/8a} = 7.1$ Hz $^3J_{H1/2} = 3.7$ Hz major isomer</td>
<td>New compound</td>
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<tr>
<td>(±)-3j</td>
<td><img src="image" alt="Structure of (±)-3j" /> $^3J_{H1/8a} = 8.8$ Hz $^3J_{H1/2} = 10.4$ Hz minor isomer</td>
<td>New compound</td>
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<td>(±)-3k</td>
<td><img src="image" alt="Structure of (±)-3k" /> $^3J_{H1/2} = 8.7$, $3.7$ Hz</td>
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<tr>
<td>(±)-3l</td>
<td><img src="image" alt="Structure of (±)-3l" /> $^3J_{H1/8a} = 9.0$ Hz</td>
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<tr>
<td>(±)-3m</td>
<td><img src="image" alt="Structure of (±)-3m" /> $^3J_{H8/8a} = 10.4$ Hz $^3J_{H1/8a} = 7.0$ Hz $^3J_{H1/2} = 5.7$ Hz</td>
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<td>(±)-3n</td>
<td><img src="image" alt="Structure of (±)-3n" /> $^3J_{H1/8a} = 6.1$ Hz $^3J_{H8/8a} = 3.0$ Hz $^3J_{H7/8} = 1.9$ Hz $^3J_{H6/7} = 1.9$ Hz</td>
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<td>Compound No.</td>
<td>Relative structure, Experiment $^3J$ and/or NOE values of Major isomer</td>
<td>Reference no. and Reported $^3J$ values</td>
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<td>---------------------------------------------------------------------</td>
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<tr>
<td>(±)-3p</td>
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</tr>
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<td>(-)-3q</td>
<td><img src="image" alt="Compound Diagram" /> $^3J_{H1/9a} = 9.5$ Hz $^3J_{H1/2} = 11.2$ Hz</td>
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<td>(-)-6</td>
<td><img src="image" alt="Compound Diagram" /> $^3J_{H1/9a} = 10.2$ Hz $^3J_{H1/2} = 11.2$ Hz</td>
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</tr>
<tr>
<td>(+)-7</td>
<td><img src="image" alt="Compound Diagram" /> $^3J_{H8/8a} = 9.3$ Hz $^3J_{H1/8a} = 8.0$ Hz $^3J_{H1/2} = 3.1$ Hz</td>
<td>New compound</td>
</tr>
<tr>
<td>(±)-8</td>
<td><img src="image" alt="Compound Diagram" /> $^3J_{H8/8a} = 7.7$ Hz $^3J_{H8/8a} = 3.0$ Hz $^3J_{H7/8} = 2.8$ Hz $^3J_{H6/7} = 2.5$ Hz</td>
<td>New compound</td>
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<td>(±)-9</td>
<td><img src="image" alt="Compound Diagram" /></td>
<td>New compound</td>
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<tr>
<td>(±)-10</td>
<td><img src="image" alt="Compound Diagram" /> $^3J_{H8/8a}$ $^3J_{H7/8}$ $^3J_{H6/7}$ = ND</td>
<td>New compound</td>
</tr>
</tbody>
</table>

*ND = could not be determined, due to complex or overlap signals

Relative stereochemistry was designed according to previous nitro intermediate 3.
2.6 References


3. NMR spectra of new compounds, GC-MS data analysis of compounds 3a-l and HPLC data analysis of compound (-)-3q
NMR spectra of new compounds

$^1$H NMR (300 MHz, CDCl$_3$): 1d

![Molecular structure of 1d](image)

SI-37
$^{13}$C NMR (75 MHz, CDCl$_3$); 1d
$^1$H NMR (300 MHz, CDCl$_3$); 1e
$^{13}$C NMR (75 MHz, CDCl$_3$); 1e
$^1$H NMR (300 MHz, CDCl$_3$); 1f
$^{13}$C NMR (75 MHz, CDCl$_3$); 1f
$^{13}$C NMR (75 MHz, CDCl$_3$); substrate for 2f

TsO\[\text{CH}\_2\]CH\_2\[\text{CH}\_2\]OBn
$^1$H NMR (300 MHz, CDCl₃); substrate for 2f

![NMR spectrum diagram]

TsO$\text{ }$\text{ }$\text{ }$\text{ }\text{ }$\text{ }\text{ }OH
$^{13}$C NMR (75 MHz, CDCl$_3$); substrate for 2f
$^{13}$C NMR (75 MHz, CDCl$_3$): 2f

TsO

2f
$^1$H NMR (300 MHz, CDCl$_3$); (+)-2g
$^{13}$C NMR (75 MHz, CDCl$_3$); (+)-2g

![NMR spectrum image]

SI-50
$^1$H NMR (300 MHz, CDCl$_3$); substrate for (±)-2h

![NMR Spectrogram]

HO

O

OBn

OTs

OBn

OBn

SI-51
$^{13}$C NMR (75 MHz, CDCl$_3$); substrate for (+)-2h
$^1$H NMR (300 MHz, CDCl$_3$); (+)-2h

![NMR spectrum of (+)-2h with chemical shifts and peaks labeled]

SI-53
$^{13}$C NMR (75 MHz, CDCl$_3$); (+)-2h

![Carbon NMR spectrum](image)

SI-54
$^1$H NMR (300 MHz, CDCl$_3$); 2i

![NMR spectrum of compound 2i](image-url)
$^{13}$C NMR (75 MHz, CDCl$_3$); 2i

![Chemical Structure](image)

SI-56
$^1$H NMR (300 MHz, DMSO-$d_6$); 1a'
$^{13}$C NMR (75 MHz, DMSO-$d_6$); 1a'
$^1$H NMR (300 MHz, CDCl$_3$); substrate for (±)-4
$^{13}$C NMR (75 MHz, CDCl$_3$); substrate for (±)-4
$^1$H NMR (300 MHz, CDCl$_3$); (+)-4

(±)-4

MeO

MeO

NO$_2$

NH$_2$
$^{13}$C NMR (75 MHz, CDCl$_3$); (±)-4

![Chemical Structure of (±)-4](image-url)
\(^1\)H NMR (300 MHz, CDCl\(_3\)); (-)-5

![Diagram of the (-)-5 compound](image-url)

SI-63
$^{13}$C NMR (75 MHz, CDCl$_3$); (-)-5

![Chemical Structure](image)
$^1$H NMR (300 MHz, CDCl$_3$); (+)-3a

mixture of two isomers
$^{13}$C NMR (75 MHz, CDCl$_3$); (±)-3a

mixture of two isomers
$^1$H NMR (300 MHz, CDCl$_3$); (±)-3d'

mixture of two isomers
$^{13}$C NMR (75 MHz, CDCl$_3$); (±)-3d′

mixture of two isomers
$^1$H NMR (300 MHz, CDCl$_3$); (±)-3g

mixture of two isomers
$^{13}$C NMR (75 MHz, CDCl$_3$): (±)-3g

mixture of two isomers
$^1$H NMR (300 MHz, CDCl$_3$); (±)-3i

major isomer
$^1$H NMR (75 MHz, CDCl$_3$); (±)-3i

![NMR Spectrum](image)

major isomer
$^1$H NMR (300 MHz, CDCl$_3$); $(\pm)$-3i

mixture of minor isomers
$^{13}$C NMR (75 MHz, CDCl$_3$); $(\pm)$-3i

mixture of minor isomers
1H NMR (300 MHz, CDCl3); (±)-3j

mixture of two isomers
$^{13}$C NMR (75 MHz, CDCl$_3$); (±)-3j

mixture of two isomers
{\textsuperscript{1}H} NMR (300 MHz, CDCl_{3}); \((\pm)-3j\)

one pure isomer
$^{13}$C NMR (75 MHz, CDCl$_3$); (+)-3j

one pure isomer
$^1$H NMR (300 MHz, CDCl$_3$); (±)-3k

mixture of two isomers

SI-79
$^{13}$C NMR (75 MHz, CDCl$_3$); (+)-3k

mixture of two isomers
$^1$H NMR (300 MHz, CDCl$_3$); (+)-31

mixture of two isomers
$^{13}$C NMR (75 MHz, CDCl$_3$); (±)-3l

mixture of two isomers
$^1$H NMR (300 MHz, CDCl$_3$); (+)-3m
$^{13}$C NMR (75 MHz, CDCl$_3$); (+)-3m

![NMR spectrum of (+)-3m](image)
COSY NMR (300 MHz, CDCl₃); (+)-3m

WD15099A1+2−F6−8 (300 MHz, CDCl₃)
NOE 1D NMR (300 MHz, CDCl₃); (+)-3m
$^1$H NMR (300 MHz, CDCl$_3$); (±)-3n
$^{13}$C NMR (75 MHz, CDCl$_3$); (±)-3n
COSY NMR (300 MHz, CDCl₃); (±)-3n
NOE 1D NMR (300 MHz, CDCl₃); (+)-3n
NOE 1D NMR (300 MHz, CDCl₃); (±)-3n

Chemical shifts with peak labels:
- H1
- H8
- H6
- H7
- H8a

SI-91
^1^H NMR (300 MHz, CDCl\textsubscript{3}); (±)-3o

mixture of two isomers
$^{13}$C NMR (75 MHz, CDCl$_3$); (+)-3o

mixture of two isomers
$^{1}$H NMR (300 MHz, CDCl$_3$); (+)-3p

![Chemical Structure](image-url)
$^{13}$C NMR (75 MHz, CDCl$_3$); (+)-3p

![Chemical Structure Image]
COSY NMR (300 MHz, CDCl₃); (+)-3p
NOE 1D NMR (300 MHz, CDCl₃); (±)-3p
\(^1\)H NMR (300 MHz, CDCl\(_3\)); (-)-3q

(-)-3q
$^{13}$C NMR (75 MHz, CDCl$_3$); (-)-3q
COSY NMR (300 MHz, CDCl₃); (-)-3q
NOE 1D NMR (300 MHz, CDCl₃); (-)-3q
$^1$H NMR (300 MHz, CDCl$_3$); (-)-6
$^{13}$C NMR (75 MHz, CDCl$_3$); (-)-6

(-)-6

169.578 158.166 134.935 128.270 113.929

77.423 77.000 76.576 67.547 56.372 56.056 55.597 55.134 55.672 48.660 33.673 23.188

SI-103
$^1$H NMR (300 MHz, MeOH-$d_4$); (+)-7
$^{13}$C NMR (75 MHz, MeOH-d4); (+)-7
$^1$H NMR (300 MHz, CDCl$_3$); (+)-8
$^{13}$C NMR (75 MHz, CDCl$_3$); (**)-8
$^1$H NMR (300 MHz, CDCl$_3$); (±)-9
$^{13}$C NMR (75 MHz, CDCl$_3$); (±)-9

![Chemical structure of (±)-9](image)

- $164.017$
- $147.957$
- $147.400$
- $125.777$
- $124.246$
- $111.259$
- $110.602$
- $77.423$
- $77.000$
- $62.110$
- $55.831$
- $55.822$
- $48.472$
- $45.714$
- $25.644$
- $24.681$

ppm
$^1$H NMR (300 MHz, CDCl$_3$); (±)-10

(±)-10

SI-110
$^{13}$C NMR (75 MHz, CDCl$_3$); (±)-10
07_WD13158A-1-filtrate_met02_inj1ul_nodi__01 #791 RT: 13.15 AV: 1 NL: 5.95E6
T: + c Full ms [30.00-500.00]

07_WD13158A-1-filtrate_met02_inj1ul_nodi__01 #861 RT: 14.05 AV: 1 SB: 2197 14.44-32.90 , 3.08-12.82 NL: 6.29E4
T: + c Full ms [30.00-500.00]

O₂N

H

1

9a

O

N

(➕)-3f

NL:

4.29E7

TIC MS

07_WD13158
A-1-
filtrate_met02
_inj1ul_nodi_
01
HPLC data analysis of compound (-)-3q