Supporting Information for

Synthesis and Cholinesterase Inhibitory Activity Study of Amaryllidaceae Alkaloid Analogues with N-Methyl Substitution

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1. General

All chemicals and reagents were used as received from commercial suppliers without further purification. ZnBr$_2$ (Fluorochem) was dried at 140 °C under reduced pressure for 4 hours before use. Tetrahydrofuran was dried by distillation from sodium/benzophenone, ethyl acetate was distilled and then dried and stored over 4Å molecular sieves. Anhydrous dichloromethane, $N,N$-dimethylformamide and acetonitrile were purchased from Acros Organics. BDSB was prepared according to the literature.$^{[1]}$ Analytical thin-layer chromatography (TLC) performed on Merck Silica gel 60-F254 coated aluminium plates was carried out to monitor reactions. UV light (254 nm) and/or suitable TLC stain followed by heating were used for visualisation. To stain TLCs, the following dips were used: phosphomolybdate dip: Ce(SO$_4$)$_2$·4H$_2$O (2 g), H$_2$P(Mo$_3$O$_{10}$)$_4$ (4g), H$_2$SO$_4$ (10 mL), H$_2$O (200 mL); anisaldehyde dip: CH$_3$COOH (99%) (6 mL), anisaldehyde (8 mL), CH$_3$CH$_2$OH (400 mL), H$_2$SO$_4$ (20 mL); KMnO$_4$ dip: KMnO$_4$ (3 g), K$_2$CO$_3$ (20 g), H$_2$O (300 mL), 10% NaOH (2.5 mL) or ninhydrin dip: ninhydrin [(0.3 g), n-BuOH (100 mL), CH$_3$COOH (99%) (3.0 mL)]. Column chromatography was performed on Acros Silica gel 60 A (35–70 µm). NMR spectra were recorded on Bruker AVANCE III 600, Bruker AVANCE III HD 400 spectrometers. The $^1$H NMR spectra were recorded at room temperature in deuterated; chloroform [referenced to residual CHCl$_3$ signal ($^1$H, δ = 7.26)], methanol [referenced to residual CH$_3$OH ($^1$H, δ = 3.31)], water [referenced to residual H$_2$O ($^1$H, δ = 4.79)], dichloromethane [referenced to residual CH$_2$Cl$_2$ ($^1$H, δ = 5.32)] or dimethyl sulfoxide [referenced to residual ($CH_3$)$_2$SO ($^1$H, δ = 2.50)]. The $^{13}$C NMR spectra were recorded at room temperature and referenced to residual solvent signal of CDCl$_3$ ($^{13}$C, δ = 77.16), CD$_3$OD ($^{13}$C, δ = 49.00), CD$_2$Cl$_2$ ($^{13}$C, δ = 53.84) or (CD$_3$)$_2$SO ($^{13}$C, δ = 39.52). Chemical shifts are reported in parts per million (δ scale) downfield from tetramethylsilane, coupling constants (J) are given in Hertz. Multiplicity is defined as s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet or combination of the above. Infrared spectra were recorded in the range between 4000 and 400 cm$^{-1}$ with Thermo Nicolet AVATAR 370 FT-IR spectrometer in KBr via DRIFT method and are reported in wavenumbers (cm$^{-1}$). Low-resolution mass spectra were measured using time-of-flight mass spectrometer GCT Premier (Waters), Q-Tof micro (Waters). The exact mass was measured using an LTQ Orbitrap XL hybrid mass spectrometer (Thermo Fisher Scientific). Melting points were measured on Büchi Melting Point B-545 using a capillary method and are uncorrected. Optical rotations measured on an automatic polarimeter, Autopol III are given in deg·mL·g$^{-1}$·dm$^{-1}$ with accuracy ±2 and the mass concentrations (marked as c are given in g/100 mL). Chiral HPLC was carried out using an LC20AD Shimadzu liquid chromatograph with SPD-M20A diode array detector with columns Daicel Chiralpak® IA, Daicel Chiralpak® IC, Daicel Chiralcel® OD-H.
2. Synthesis of starting material

2-Iodocyclopent-2-en-1-one (SI1)

Ketone SI1 was prepared using a procedure reported earlier[2] as a yellowish solid with yields in the range of 79-88%. The recorded spectral data were in agreement with previously reported values.[2]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.01 (t, \(J = 2.9\) Hz, 1H), 2.80 – 2.74 (m, 2H), 2.53 – 2.47 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 204.1, 169.7, 103.0, 31.4, 31.0.

2-Iodocyclopent-2-en-1-ol (2)

Alcohol 2 was prepared from ketone SI1 using the procedure reported earlier[2] as a white solid with yields in the range of 82-94%. The recorded spectral data were in agreement with previously reported values.[2]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 6.29 (td, \(J = 2.5, 1.0\) Hz, 1H), 4.73 – 4.66 (m, 1H), 2.55 – 2.45 (m, 1H), 2.38 – 2.25 (m, 2H), 1.94 – 1.81 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 142.8, 100.4, 82.4, 32.9, 31.6.
3. Approach I: N-oxide cyclisation

3.1. Synthesis of starting alkyne 3

\[
\begin{align*}
\text{OH} & \quad \text{I} \\
\text{MeCN} & \quad \text{MsCl, Et}_3\text{N} \\
\text{DCM} & \quad \text{OMs} & \quad \text{Me} & \quad \text{N} & \quad \text{Me} & \quad \text{I} \\
\text{DCM} & \quad \text{LiHMDS, Et}_3\text{SiCl} & \quad \text{THF} & \quad \text{Me} & \quad \text{N} & \quad \text{SiEt}_3 \\
2 & \quad \text{II} & \quad \text{SI2, 56\%} & \quad 3 & \quad 56\% \\
\end{align*}
\]

2-Iodo-N-methyl-N-(prop-2-yn-1-yl)cyclopent-2-en-1-amine (SI2)

Compound 2 (420 mg, 2.00 mmol) was dissolved in dry DCM (3.5 mL) under argon atmosphere and cooled down to 0 °C. Et$_3$N (0.6 mL, 4.60 mmol) and methanesulfonyl chloride (0.2 mL, 2.40 mmol) were added to the solution. The reaction mixture was stirred at 0 °C for 1 h before the addition of a saturated aqueous solution of NH$_4$Cl (3 mL). The mixture was extracted between EtOAc (3 × 30 mL) and water (20 mL), then combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude mesylate was dissolved in DCM (3.5 mL), cooled down to 0 °C and treated with Et$_3$N (0.6 mL, 4.00 mmol) and N-methyl propargylamine (371 uL, 4.40 mmol) before being allowed to warm up and then stirred at room temperature for 67 h. The reaction mixture was extracted between 1M aqueous solution of Na$_2$CO$_3$ (30 mL) and EtOAc (3 × 30 mL) and combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient elution 9/1 → 8/2 hexanes/EtOAc) to give the title compound as an orange oil (296 mg, 57%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 6.31 (td, J = 2.6, 1.7 Hz, 1H), 4.03 – 3.94 (m, 1H), 3.40 (dd, J = 16.8, 2.5 Hz, 1H), 3.30 (dd, J = 16.8, 2.4 Hz, 1H), 2.40 – 2.28 (m, 2H), 2.28 (s, 3H), 2.20 (t, J = 2.5 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.83 (dt, J = 13.7, 8.8, 5.9 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.5, 99.3, 81.0, 74.7, 72.3, 42.9, 35.8, 33.7, 20.3; IR (KBr) ν 3294, 2938, 2845, 2789, 1604, 1452, 1362, 1207, 1129, 1033, 911, 812, 656 cm$^{-1}$; MS (ESI) $m/z$ (%) 262.0 (100, [M+H$^+$]), 193.0 (41), 137.1 (4), 70.1 (47); HRMS (ESI) $m/z$ calcd for C$_9$H$_{13}$NI 262.0087, found 262.0088.

5,5'-Oxybis(1-iodocyclopent-1-ene) (SI3)

The title compound was synthesized as an unexpected product of mesylation under the different conditions. The compound was prepared from alcohol 2 (56 mg, 0.27 mmol) dissolved in dry DCM
(1.1 mL) under argon atmosphere to which dry Et₃N (111 uL, 0.80 mmol) and silver trifluoromethanesulfonate (136 mg, 0.53 mmol) were added. The resulting mixture was cooled to 0 °C and methanesulfonyl chloride (31 uL, 0.40 mmol) was dropped in within 5 min. The mixture was allowed to warm to room temperature and stirred for 23 h before being extracted with DCM (3 × 20 mL) and a saturated aqueous solution of NaHCO₃. Combined organic layers were dried over Na₂SO₄ and after filtration concentrated under reduced pressure. 25 % (NMR yield based on mesitylene as an internal standard) of the title compound was formed. The crude can be purified by short column chromatography on silica gel using DCM as a mobile phase.

**1H NMR** (400 MHz, CDCl₃) δ 6.37 – 6.29 (m, 2H), 4.61 – 4.51 (m, 2H), 2.59 – 2.43 (m, 2H), 2.34 – 2.19 (m, 4H), 2.15 – 2.06 (m, 1H), 2.05 – 1.94 (m, 1H); **13C NMR** (100 MHz, CDCl₃) δ 144.0, 143.8, 97.0, 96.9, 90.0, 88.7, 33.1, 32.8, 31.0, 30.8; **IR** (KBr): ν 2960, 2916, 2848, 1734, 1604, 1456, 1331, 1153, 1084, 924, 818 cm⁻¹; **MS** (ESI) m/z (%) 424.8 (100, [M+Na]+), 381.3 (38), 353.2 (36), 312.9 (20), 264.9 (14), 257.0 (5), 192.9 (21); **HRMS** (ESI) m/z calcd for C₁₀H₁₂O₁I₂Na 424.8870, found 424.8869.

**2-Iodo-N-methyl-N-(3-(triethylsilyl)prop-2-yn-1-yl)cyclopent-2-en-1-amine (3)**

Compound SI2 (695 mg, 2.66 mmol) was dissolved in dry THF (2.7 mL) under argon atmosphere and cooled to -78 °C. LiHMDS (3.2 mL of 1 M solution in THF, 3.20 mmol) was added dropwise and the mixture was stirred for 1 h at the same temperature. Then chlorotriethylsilane (546 uL, 3.19 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. A saturated aqueous solution of NH₄Cl (4 mL) was added and the resulting mixture was extracted between EtOAc (3 × 40 mL) and water (25 mL). The combined organic layers were dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (93/7 hexanes/EtOAc) to provide the title compound as a light yellow (976 mg, 98%).

**1H NMR** (400 MHz, CDCl₃) δ 6.31 (td, J = 2.5, 1.7 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.46 (d, J = 17.1 Hz, 1H), 3.39 (d, J = 17.1 Hz, 1H), 2.42 – 2.25 (m, 2H), 2.28 (s, 3H), 2.17 (ddt, J = 13.4, 8.8, 4.4 Hz, 1H), 1.82 (ddt, J = 13.7, 9.0, 5.7 Hz, 1H), 0.99 (t, J = 7.9 Hz, 9H), 0.64 – 0.55 (m, 6H); **13C NMR** (100 MHz, CDCl₃) δ 142.6, 104.4, 99.7, 86.5, 74.8, 44.2, 35.7, 33.8, 20.5, 7.6, 4.5; **IR** (KBr): ν 2950, 2905, 2872, 2842, 2783, 1458, 1413, 1234, 1204, 1126, 1042, 1015, 979, 815, 743, 725 cm⁻¹; **MS** (EI) m/z (%) 375.1 (51, M⁺), 248.2 (87), 220.2 (35), 154.1 (35), 132.1 (95), 115.1 (44), 97.0 (48), 87.0 (100), 68.0 (60), 66.0 (59), 59.0 (59), 55.0 (41); **HRMS** (ESI) m/z calcd for C₁₅H₂₆INISi 375.0879, found 375.0876.
3.2. Synthesis of polycyclic compounds

Table S1. Halocyclisation of tertiary and quaternary amines and N-oxides 4 and 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reagent (a)</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Result</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4b</td>
<td>NIS</td>
<td>DCM/HFIP</td>
<td>0 °C - r.t. (2 days)</td>
<td>---</td>
<td>4b (s.m.)</td>
</tr>
<tr>
<td>2</td>
<td>4a</td>
<td>NIS</td>
<td>MeCN</td>
<td>r.t. (4 h)</td>
<td>---</td>
<td>4a (s.m.)</td>
</tr>
<tr>
<td>3</td>
<td>4a</td>
<td>NIS</td>
<td>MeCN</td>
<td>r.t. (22 h)</td>
<td>decomp.</td>
<td>4a (s.m.)</td>
</tr>
<tr>
<td>4</td>
<td>4a</td>
<td>BDSB (b)</td>
<td>MeCN</td>
<td>r.t. (0.3 h)</td>
<td>5a (33%)</td>
<td>4a (s.m.)</td>
</tr>
<tr>
<td>5</td>
<td>6b</td>
<td>NIS (c)</td>
<td>HFIP</td>
<td>0 °C - r.t. (3 days)</td>
<td>side prod.</td>
<td>6b (s.m.)</td>
</tr>
<tr>
<td>6</td>
<td>6b</td>
<td>BDSB</td>
<td>MeCN</td>
<td>r.t. (1 h)</td>
<td>5b (traces) (d)</td>
<td>4b, decomp.</td>
</tr>
<tr>
<td>7</td>
<td>6a</td>
<td>NIS</td>
<td>MeCN</td>
<td>r.t. (20 h), 40 °C (1 h)</td>
<td>side prod.</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>6a</td>
<td>BDSB</td>
<td>MeCN</td>
<td>0 °C (1 h)</td>
<td>5a (traces)</td>
<td>---</td>
</tr>
<tr>
<td>9</td>
<td>6a</td>
<td>BDSB</td>
<td>MeCN</td>
<td>r.t. (3 h), 40 °C (3 h), 60 °C (0.5 h), r.t.(17 h)</td>
<td>5a (49%)</td>
<td>SI8a (10%) (d)</td>
</tr>
<tr>
<td>10</td>
<td>6a</td>
<td>BDSB</td>
<td>MeCN</td>
<td>40 °C (7 h), r.t. (16 h)</td>
<td>5a (traces)</td>
<td>---</td>
</tr>
<tr>
<td>11</td>
<td>6a</td>
<td>BDSB</td>
<td>MeCN</td>
<td>60 °C (3 h)</td>
<td>decomp.</td>
<td>---</td>
</tr>
<tr>
<td>12</td>
<td>6a</td>
<td>Me₂S</td>
<td>MeCN</td>
<td>r.t. (2 days)</td>
<td>---</td>
<td>6a (s.m.)</td>
</tr>
<tr>
<td>13</td>
<td>6a</td>
<td>Me₂S</td>
<td>MeCN</td>
<td>60 °C (6 h)</td>
<td>---</td>
<td>6a (s.m.)</td>
</tr>
<tr>
<td>14</td>
<td>6c</td>
<td>NIS</td>
<td>DCM</td>
<td>r.t. (3 h)</td>
<td>---</td>
<td>6c (s.m.)</td>
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<tr>
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<td>6c</td>
<td>BDSB</td>
<td>DCM</td>
<td>r.t. (3 h)</td>
<td>---</td>
<td>6c (s.m.)</td>
</tr>
</tbody>
</table>

\(a\) NIS (1.2 eq.), BDSB (1.05 eq.) or Me₂S (1-11eq.) were used. \(b\) Bromodiethylsulfonium bromopentachloroantimonate (see ref. \([1]\)). \(c\) Morfoline (1.4 eq.) was used as an additive. \(d\) The compound was not fully characterised.
(Z)-3-(Benzo[d][1,3]dioxol-5-yl(triethylsilyl)methylene)-1-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[b]pyrrole ((Z)-4a)

Compound 3 (208 mg, 0.55 mmol) was dissolved in mixture of THF (9.1 mL) and H₂O (0.9 mL), followed by addition of 3,4-(methylenedioxy)phenylboronic acid (149 mg, 0.88 mmol) and caesium carbonate (364 mg, 1.11 mmol). The mixture was degassed by evacuation and backfilling with argon (2x), then Pd(PPh₃)₄ (32 mg, 0.028 mmol) was added and the degassing procedure was repeated again. Then it was warmed to 70 °C, stirred for 20 h under argon atmosphere and cooled to room temperature before being extracted between EtOAc (3 × 40 mL) and brine (40 mL). The combined organic layers were dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (90/10/1.5 hexanes/EtOAc/Et₃N) to provide the title compound as an orange oil (195 mg, 96%).

¹H NMR (400 MHz, CDCl₃) δ 6.74 (d, J = 8.2 Hz, 1H), 6.52 – 6.33 (m, 2H), 5.97 – 5.89 (m, 2H), 4.57 – 4.50 (m, 1H), 2.60 – 2.36 (m, 2H), 2.34 (s, 3H), 2.01 (ddt, J = 11.7, 6.4, 1.1 Hz, 1H), 1.48 (ddt, J = 11.8, 10.4, 8.9 Hz, 1H), 0.90 (t, J = 7.9 Hz, 9H), 0.62 – 0.52 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 147.8, 147.7, 147.4, 145.29, 145.27, 143.7, 139.3, 139.2, 135.8, 124.9, 124.6, 120.1, 120.0, 108.9, 108.2, 108.0, 100.7, 77.5, 67.0, 41.2, 37.3, 31.2, 7.7, 3.7, All the aromatic signals are doubled due to the presence of atropoisomers; IR (KBr) ν 2953, 2869, 2833, 2765, 1479, 1323, 1240, 1225, 1213, 1039, 1006, 937, 725 cm⁻¹; MS (EI) m/z (%) 370.2 (10), 369.2 (45, [M⁺]), 340.2 (9), 255.1 (25), 254.1 (100), 248.2 (10), 134.1 (8), 87.1 (5), 59.0 (4); HRMS (EI) m/z calcd for C₂₂H₃₁NO₂Si 369.2124, found 369.2118.

(Z)-3-((4-Methoxyphenyl)(triethylsilyl)methylene)-1-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[b]pyrrole (4b)

Compound 3 (526 mg, 1.40 mmol) was dissolved in the mixture THF (10.5 mL) and H₂O (2.1 mL). 4-methoxyphenylboronic acid (341 mg, 2.24 mmol) and caesium carbonate (912 mg, 2.80 mmol) were added. The mixture was degassed by evacuation and backfilling with argon (2x), then Pd(PPh₃)₄ (41 mg, 0.04 mmol) was added and the degassing procedure was repeated again. Then it was warmed to 70 °C, stirred for 23 h under argon atmosphere, cooled to room temperature and extracted between EtOAc (3 × 40 mL) and water (35 mL). The combined organic layers were dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by
column chromatography (gradient elution 90/10/1 → 70/30/1 hexanes/EtOAc/Et₃N) to provide the title compound (418 mg, 80%) in ratio of Z/E isomers 85/15 from which (Z)-4b (60 mg, 11%) was isolated in pure form as a brown oil.

(Z)-4b. ¹H NMR (400 MHz, CDCl₃) δ 6.95 – 6.79 (m, 4H), 4.39 – 4.35 (m, 1H), 4.04 (d, J = 13.1 Hz, 1H), 3.79 (s, 3H), 3.29 – 3.21 (m, 2H), 2.56 – 2.34 (m, 2H), 2.34 (s, 3H), 1.99 (dt, J = 12.4, 6.4 Hz, 1H), 1.52 – 1.40 (m, 1H), 0.90 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.6 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 148.1, 143.5, 137.8, 135.8, 128.4, 128.3, 124.4, 114.3, 113.3, 77.6, 67.1, 55.3, 41.3, 37.3, 31.2, 7.7, 3.7; IR (KBr) ν 2950, 2869, 2836, 2768, 1607, 1509, 1461, 1278, 1242, 1186, 1039, 920, 716 cm⁻¹; MS (Cl) m/z (%) 356.2 (57, [M+H]+), 355.2 (100, M⁺), 340.2 (5), 326.2 (26), 240.1 (34); HRMS (Cl) m/z calcd for C₂₂H₃₄NOSi 356.2410, found 356.2408.

(Z)-3-(Benzo[d][1,3]dioxol-5-yl(triethylsilylmethylene)-1-methyl-1,2,3,5,6,6a-hexahydro-cyclopenta[b]pyrrole 1-oxide (6a)

Compound (Z)-4a (50 mg, 0.14 mmol) was dissolved in dry DCM (4 mL) under argon atmosphere. The flask was covered with aluminium foil and cooled to 0 °C. At this temperature, m-chloroperoxybenzoic acid (26 mg, 0.15 mmol) was added and the reaction mixture was stirred for 3 h. The reaction was quenched with water (10 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (gradient elution 95/5 → 90/10 DCM/MeOH) to give the title compound as a brown foam (47 mg, 90%). The reaction was repeated several times with the yields in the range of 77-90%.

¹H NMR (400 MHz, CDCl₃) δ 6.76 – 6.70 (m, 1H), 6.58 – 6.48 (m, 1H), 6.37 – 6.29 (m, 1H), 5.95 – 5.89 (m, 2H), 4.83 – 4.78 (m, 1H), 4.67 – 4.54 (m, 3H), 3.25 (s, 3H), 2.65 – 2.48 (m, 3H), 1.91 – 1.83 (m, 1H), 0.89 (t, J = 7.9 Hz, 9H), 0.62 – 0.50 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 147.9, 147.5, 145.7, 140.9, 140.7, 137.9, 133.7, 130.3, 129.8, 120.2, 119.7, 108.9, 108.2, 108.1, 107.6, 100.94, 100.88, 87.3, 80.3, 55.7, 37.3, 22.0, 7.6, 3.7; IR (KBr) ν 3434, 2956, 2878, 1604, 1485, 1431, 1329, 1237, 1222, 1036, 1003, 943, 719 cm⁻¹; MS (ESI) m/z (%) 1178.6 (13, [3M+Na]+), 771.4 (100, [2M+H]+), 408.2 (18, [M+Na]+), 386.2 (17, [M+H]+); HRMS (ESI) m/z calcd for C₂₂H₃₄O₃NSi 386.2146, found 386.2144.
(Z)-3-((4-Methoxyphenyl)(triethylsilyl)methylene)-1-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[b]pyrrole 1-oxide (6b)

Compound (Z)-4b (62 mg, 0.17 mmol) was dissolved in dry DCM (5.2 mL) under argon atmosphere. The flask was covered with aluminium foil and cooled to 0 °C. At this temperature, m-chloroperoxybenzoic acid (33 mg, 0.19 mmol) was added and the reaction mixture was stirred for 3.5 h. The reaction was quenched with water (20 mL) and the mixture was extracted with DCM (6 × 40 ml). The combined organic layers were dried with Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (gradient elution 100 → 90/10 DCM/MeOH) to give the title compound as a white amorphous solid (51 mg, 79%).

$^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.00–6.91 (m, 1H), 6.91–6.80 (m, 3H), 4.67–4.57 (m, 3H), 4.45 (d, $J = 13.6$ Hz, 1H), 3.79 (s, 3H), 3.17 (s, 3H), 2.56–2.35 (m, 3H), 1.88–1.79 (m, 1H), 0.92 (t, $J = 7.9$ Hz, 9H), 0.65–0.53 (m, 6H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) δ 158.4, 142.3, 140.5, 138.6, 136.9, 129.3, 128.4, 128.2, 114.8, 113.7, 87.3, 80.6, 55.7, 55.5, 37.4, 22.1, 7.6, 4.0; IR (KBr) ν 3324, 2953, 2869, 2839, 1601, 1509, 1284, 1216, 1186, 1045, 1006, 946, 872, 722 cm$^{-1}$; MS (ESI) m/z (%) 743.4 (28, [2M+H]$^+$), 394.2 (26, [M+Na]$^+$), 372.2 (100, [M+H]$^+$); HRMS (ESI) m/z calced for C$_{22}$H$_{34}$O$_2$NSi 372.2353, found 372.2351.

1-Bromo-4-methyl-6-(triethylsilyl)-1,2,3,3a,4,5-hexahydro-[1,3]dioxolo[4',5':5,6]indenol[1,2-c]cyclopenta[b]pyrrole (5a)

Compound 6a (30 mg, 0.08 mmol) was dissolved in dry MeCN (1.6 mL) under argon atmosphere. The BDSB (45 mg, 0.08 mmol) was added and the reaction warmed up and stirred at room temperature for 3 h, 40 °C for 3 h, 60 °C for 0.5 h and then left to stir at room temperature for 16 h. The reaction was quenched (based on TLC developed in mobile phase 10/4 acetone/MeOH with 5 drops of Et$_3$N) with the saturated aqueous solution of N$_2$S$_2$O$_3$ (10 mL) and the resulting mixture was extracted between EtOAc (25 mL) and DCM (3 × 25 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (gradient elution 100/0 → 90/10 DCM/MeOH) to give the title compound as an amorphous brown solid (17 mg, 49%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 6.80 (s, 1H), 6.64 (s, 1H), 5.93 (s, 2H), 4.41 (dd, $J = 9.8$, 7.5 Hz, 1H), 4.06 (d, $J = 13.6$ Hz, 1H), 3.11 (d, $J = 13.7$ Hz, 1H), 2.78 (d, $J = 3.7$ Hz, 1H), 2.71–2.49 (m, 2H), 2.42 (s, 3H), 2.12 (dd, $J = 13.3$, 6.4 Hz, 1H), 1.83–1.73 (m, 1H), 0.99 (t, $J = 7.8$ Hz, 9H),
0.85 – 0.78 (m, 6H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 147.2, 145.1, 144.1, 143.1, 103.7, 103.5, 101.2, 73.7, 72.2, 56.1, 54.9, 41.9, 37.2, 32.5, 7.7, 3.9 (two signals of quaternary aromatic carbons were not found due to low intensity); \(\text{IR}\) (KBr): \(\nu\) 2956, 2872, 1607, 1473, 1290, 1242, 1156, 1036, 1006, 943, 863, 731 cm\(^{-1}\); \(\text{MS}\) (ESI) \(m/z\) (%) 450.1 (38, [M+H]\(^{+}\)), 448.1 (37, [M+H]\(^{+}\)), 369.2 (25), 368.2 (100, M-Br); \(\text{HRMS}\) (ESI) \(m/z\) calcd for C\(_{22}\)H\(_{31}\)BrNO\(_2\)Si [M+H]\(^{+}\) 448.1302, found 448.1302.
4. Approach II: Boc protection of nitrogen

4.1 Synthesis of starting alkyne 8

![Chemical structure](image)

**2-Iodo-N-(prop-2-yn-1-yl)cyclopent-2-en-1-amine (SI4)**

Alcohol 2 (4.20 g, 20.02 mmol) is dissolved in DCM (54 mL) and cooled to 0 °C before Et$_3$N (8.4 mL, 60.05 mmol) was added. Methanesulfonyl chloride (2.3 mL, 30.02 mmol) was added slowly and the resulting mixture was stirred for 2 h at 0 °C and then for 1.5 h at room temperature before being extracted between DCM (3 × 50 mL) and a saturated aqueous solution of NaHCO$_3$ (40 mL). Combined organic layers were dried over Na$_2$SO$_4$, filtered, concentrated under reduced pressure (100 mbar, 30 °C). Prop-2-yn-1-amine (4.8 mL, 60.05 mmol) was added to the crude mesylate at 0 °C under argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for an additional 13 h. The crude was purified by column chromatography on silica gel (9/1 hexanes/EtOAc) to give the title compound as light brown oil (3.61 g, 73%). The reaction was repeated several times with the yields in the range of 70-73%.

$^1$H NMR (400 MHz, CDCl$_3$) δ 6.27 (td, J = 2.5, 1.5 Hz, 1H), 3.93 (dddd, J = 7.9, 4.4, 2.9, 1.5 Hz, 1H), 3.50 (dd, J = 16.9, 2.5 Hz, 1H), 3.37 (dd, J = 16.9, 2.5 Hz, 1H), 2.51 – 2.37 (m, 1H), 2.38 – 2.24 (m, 1H), 2.22 (t, J = 2.5 Hz, 1H), 2.25 – 2.12 (m, 1H), 1.82 (ddt, J = 13.1, 9.1, 5.1 Hz, 1H), 1.67 (bs, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.2, 99.4, 82.2, 71.5, 68.5, 35.1, 33.2, 28.7; IR (KBr) ν 3297, 2923, 2845, 1607, 1455, 1329, 1159, 1114, 1042, 920, 815, 647 cm$^{-1}$; MS (EI) m/z (%) 247.0 (72, M$^+$), 246.0 (38), 208.0 (11), 193.0 (8), 127.9 (26), 120.1 (100, [M-I]$^+$), 118.1 (44), 103.1 (19), 91.1 (37), 80.0 (46), 77.0 (32), 69.0 (32), 66.0 (48), 54.0 (10); HRMS (EI) m/z calcd for C$_8$H$_{10}$NI 246.9858, found 246.9859.

**2-Iodo-N-(3-(triethylsilyl)prop-2-yn-1-yl)cyclopent-2-en-1-amine (7)**

Amine SI4 (2.69 g, 10.88 mmol) was dissolved in dry THF (15 mL) under argon atmosphere and cooled to -78 °C. LiHMDS (13.1 mL of 1M solution in THF) was added and the mixture was stirred at the same temperature for 2 h before the addition of chlorotriethylsilane (2.2 mL, 13.05 mmol). The reaction was allowed to warm up to room
temperature and stirred for an additional 4 h before being quenched with a saturated aqueous solution of NH₄Cl (1 mL). The mixture was extracted with EtOAc (3 × 40 mL) and water (20 mL) and combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 hexanes/EtOAc) to give the title compound as orange liquid (3.39 g, 86%). The reaction was repeated several times with the yields in the range of 74-86%. The compound is a little volatile under reduced pressure (10 mbar, 20 °C).

**1H NMR** (400 MHz, CDCl₃) δ 6.25 (td, J = 2.5, 1.5 Hz, 1H), 3.94 (dddt, J = 7.7, 4.5, 2.9, 1.5 Hz, 1H), 3.52 (d, J = 17.2 Hz, 1H), 3.39 (d, J = 17.2 Hz, 1H), 2.48 – 2.37 (m, 1H), 2.35 – 2.24 (m, 1H), 2.21 – 2.11 (m, 1H), 1.83 (ddt, J = 13.1, 9.0, 4.9 Hz, 1H), 1.60 (bs, 1H), 0.99 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 7.8 Hz, 6H); **13C NMR** (100 MHz, CDCl₃) δ 142.1, 105.6, 99.6, 85.4, 68.5, 36.4, 33.2, 28.8, 7.6, 4.5; **IR** (KBr) ν 3306, 2953, 2878, 2167, 1604, 1458, 1323, 1237, 1108, 1018, 985, 728 cm⁻¹; **MS** (Cl) m/z (%) 362.1 (41, M⁺), 332.0 (100), 246.0 (12), 234.2 (42), 222.0 (41), 208.0 (24), 193.0 (12), 170.1 (97), 118.1 (7), 87.1 (11); **HRMS** (Cl) m/z calcd for C₁₄H₂₅NSiI 362.0801, found 362.0799.

**tert-Butyl (S)-(2-iodocyclopent-2-en-1-yl)(3-(triethylsilyl)prop-2-yn-1-yl)carbamate (8)**

The title compound was prepared using the procedure reported earlier[2] and obtained in a quantitative yield as a light yellow oil. The recorded spectra were in agreement with those already reported.[2]

### 4.2. Synthesis of polycyclic compounds

![Polycyclic Compounds Synthesis Diagram](image-url)
Table S2. Optimisation of conditions for Boc cleavage

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reagent</th>
<th>Eq.</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time (h)</th>
<th>Product, yield (%)</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a</td>
<td>TFA</td>
<td>10</td>
<td>DCM</td>
<td>r.t.</td>
<td>2.5</td>
<td>12a, 0</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>11a</td>
<td>H₃PO₄</td>
<td>4</td>
<td>DCM</td>
<td>r.t.</td>
<td>72</td>
<td>12a, 0</td>
<td>11a, side prod.</td>
</tr>
<tr>
<td>3</td>
<td>11a</td>
<td>H₃PO₄</td>
<td>20</td>
<td>THF</td>
<td>r.t.</td>
<td>72</td>
<td>12a, 0</td>
<td>11a, 10% complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>11a</td>
<td>HCl c)</td>
<td>30</td>
<td>dioxane</td>
<td>r.t.</td>
<td>1</td>
<td>12a, 0</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>11a</td>
<td>HCl d)</td>
<td>30</td>
<td>ether</td>
<td>r.t.</td>
<td>1</td>
<td>12a, 0</td>
<td>complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>11a</td>
<td>---</td>
<td>---</td>
<td>H₂O</td>
<td>100 °C</td>
<td>1</td>
<td>12a, 0</td>
<td>11a, 13%</td>
</tr>
<tr>
<td>7</td>
<td>11a</td>
<td>---</td>
<td>---</td>
<td>DMSO</td>
<td>140 °C</td>
<td>2</td>
<td>12a, 0</td>
<td>11a, side prod. complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>11a</td>
<td>TMSI</td>
<td>1.2</td>
<td>CHCl₃</td>
<td>r.t.</td>
<td>0.5</td>
<td>12a, 0</td>
<td>side prod.</td>
</tr>
<tr>
<td>9</td>
<td>11a</td>
<td>I₂</td>
<td>0.1</td>
<td>CHCl₃</td>
<td>r.t.</td>
<td>19</td>
<td>12a, 0</td>
<td>side prod.</td>
</tr>
<tr>
<td>10</td>
<td>11a</td>
<td>AlCl₃</td>
<td>1</td>
<td>DCM</td>
<td>r.t.</td>
<td>3</td>
<td>12a, 0</td>
<td>side prod.</td>
</tr>
<tr>
<td>11</td>
<td>11b</td>
<td>BF₃.OEt₂</td>
<td>1.4</td>
<td>DCM</td>
<td>r.t.</td>
<td>0.5</td>
<td>12b, 0</td>
<td>side prod.</td>
</tr>
<tr>
<td>12</td>
<td>11b</td>
<td>---</td>
<td>---</td>
<td>HFIP</td>
<td>150 °C</td>
<td>2</td>
<td>12b, 0</td>
<td>side prod.</td>
</tr>
<tr>
<td>13</td>
<td>11b</td>
<td>---</td>
<td>---</td>
<td>HFIP</td>
<td>100 °C</td>
<td>5</td>
<td>12b, 0</td>
<td>side prod.</td>
</tr>
<tr>
<td>14</td>
<td>11b</td>
<td>ZnCl₂</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>26</td>
<td>12b, 37</td>
<td>---</td>
</tr>
<tr>
<td>15</td>
<td>11a</td>
<td>ZnBr₂</td>
<td>5</td>
<td>DMF</td>
<td>r.t.</td>
<td>17</td>
<td>12a, 0</td>
<td>11a, 65%</td>
</tr>
<tr>
<td>16</td>
<td>11a</td>
<td>ZnBr₂</td>
<td>5</td>
<td>MeOH</td>
<td>r.t.</td>
<td>19</td>
<td>12a, 0</td>
<td>11a, 39%</td>
</tr>
<tr>
<td>17</td>
<td>11a</td>
<td>ZnBr₂ g)</td>
<td>2.2</td>
<td>DCM</td>
<td>r.t.</td>
<td>22</td>
<td>12a, 5</td>
<td>---</td>
</tr>
<tr>
<td>18</td>
<td>11a h)</td>
<td>ZnBr₂</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>18</td>
<td>12a, 46</td>
<td>---</td>
</tr>
<tr>
<td>19</td>
<td>11a i)</td>
<td>ZnBr₂</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>18</td>
<td>12a, 75 (61) j)</td>
<td>---</td>
</tr>
<tr>
<td>20</td>
<td>11b</td>
<td>ZnBr₂</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>22</td>
<td>SI6b, 84 k)</td>
<td>12b, (42) j) ---</td>
</tr>
<tr>
<td>21</td>
<td>11b</td>
<td>ZnBr₂</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>19</td>
<td>12b, 81 l) (39) j)</td>
<td>---</td>
</tr>
</tbody>
</table>

a) Zinc salts were vacuum-dried at 140°C for 4 h prior to reaction. b) ¹H NMR yield. Mesitylene was used as an internal standard. Isolated yields in brackets. c) 4M HCl in dioxane. d) 4M HCl in dry dioxane. e) Starting material did not dissolve. f) Microwave irradiation. g) Not dried prior to reaction. h) Solid 11a was added to the reaction mixture. i) 11a was added as a solution in DCM. j) Isolated yield after column chromatography on neutralised SiO₂. k) Filtration work-up. l) Extraction work-up.
Table S3. Boc cleavage/methylation sequence optimisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reagent 1 (eq.)</th>
<th>Reagent 2 (eq.)</th>
<th>Additive (eq.)</th>
<th>Solvent</th>
<th>Overall Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11b</td>
<td>HCHO (1)</td>
<td>NaBH₃CN (1)</td>
<td>--</td>
<td>MeCN</td>
<td>1b, 44</td>
</tr>
<tr>
<td>2</td>
<td>11b</td>
<td>HCHO (5)</td>
<td>NaBH₃CN (1)</td>
<td>ZnCl₂ (0.4)</td>
<td>MeOH</td>
<td>1b, 74</td>
</tr>
<tr>
<td>3</td>
<td>11b</td>
<td>LiHMDS (2)</td>
<td>Mel (3)</td>
<td>--</td>
<td>THF</td>
<td>1b, 0&lt;sup&gt;b)&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>11b</td>
<td>HCHO (2.2)</td>
<td>HCOOH (5)</td>
<td>--</td>
<td>--</td>
<td>1b, 0</td>
</tr>
<tr>
<td>5</td>
<td>11a</td>
<td>HCHO (1)</td>
<td>NaBH₃CN (3)</td>
<td>--</td>
<td>MeCN</td>
<td>1a, 28&lt;sup&gt;c)&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>11a</td>
<td>HCHO (5)</td>
<td>NaBH₃CN (2)</td>
<td>ZnCl₂ (0.4)</td>
<td>MeOH</td>
<td>1a, 21</td>
</tr>
<tr>
<td>7</td>
<td>11a</td>
<td>HCHO (5)</td>
<td>NaBH₃CN (3)</td>
<td>--</td>
<td>MeOH</td>
<td>1a, 54</td>
</tr>
<tr>
<td>8</td>
<td>11a</td>
<td>HCHO (9)</td>
<td>NaBH₃CN (3)</td>
<td>--</td>
<td>MeOH</td>
<td>1a, 24</td>
</tr>
</tbody>
</table>

Dried ZnBr₂ (5 eq.) in dry DCM was always used. The reaction was performed at r.t. for 17–21 h, followed by a basic extraction work-up. <sup>a)</sup> Isolated yield. <sup>b)</sup> The quaternary salt (13b) was isolated in 18% yield. <sup>c)</sup> <sup>1</sup>H NMR yield. Mesitylene was used as an internal standard.
**Table S4. Optimisation of the elimination/desilylation method**

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Scale (mmol)</th>
<th>F’ source (eq.)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Yield of SI5 (%)</th>
<th>Yield of 11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10b</td>
<td>0.06</td>
<td>TBAF (4)</td>
<td>THF</td>
<td>20</td>
<td>4 days</td>
<td>SI5b, 72</td>
<td>11b, 0</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>0.07</td>
<td>TBAF (4)</td>
<td>THF</td>
<td>70</td>
<td>5 h</td>
<td>SI5b, 79</td>
<td>11b, 0</td>
</tr>
<tr>
<td>3</td>
<td>10b</td>
<td>0.04</td>
<td>TBAF (4)</td>
<td>THF</td>
<td>70</td>
<td>3 days</td>
<td>SI5b, 85</td>
<td>11b, 7</td>
</tr>
<tr>
<td>4</td>
<td>10b</td>
<td>0.03</td>
<td>KF (2.2)</td>
<td>DMF</td>
<td>70</td>
<td>3 days</td>
<td>SI5b, 0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11b, 0</td>
</tr>
<tr>
<td>5</td>
<td>10b</td>
<td>0.04</td>
<td>TBAF (4)</td>
<td>DMF</td>
<td>75</td>
<td>7 h</td>
<td>SI5b, 0</td>
<td>11b, 52</td>
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<tr>
<td>6</td>
<td>10b</td>
<td>0.14</td>
<td>TBAF (4)</td>
<td>DMF</td>
<td>80</td>
<td>16 h</td>
<td>SI5b, 0</td>
<td>11b, 57</td>
</tr>
<tr>
<td>7</td>
<td>10b</td>
<td>0.02</td>
<td>TBAF (4)</td>
<td>DMF</td>
<td>90</td>
<td>9 h</td>
<td>SI5b, 0</td>
<td>11b, 76</td>
</tr>
<tr>
<td>8</td>
<td>10b</td>
<td>0.03</td>
<td>TBAF (4)</td>
<td>DMF</td>
<td>95</td>
<td>16 h</td>
<td>SI5b, 0</td>
<td>11b, 85</td>
</tr>
<tr>
<td>9</td>
<td>10b</td>
<td>0.13</td>
<td>TBAF (4)</td>
<td>DMF</td>
<td>95</td>
<td>16 h</td>
<td>SI5b, 0</td>
<td>11b, 91</td>
</tr>
<tr>
<td>10</td>
<td>10a</td>
<td>0.07</td>
<td>TBAF (4)</td>
<td>THF</td>
<td>70</td>
<td>20 h</td>
<td>SI5a, 0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11a, 98</td>
</tr>
<tr>
<td>11</td>
<td>10a</td>
<td>1.03</td>
<td>TBAF (4)</td>
<td>THF</td>
<td>70</td>
<td>3 days</td>
<td>SI5a, 0</td>
<td>11a, 98</td>
</tr>
<tr>
<td>12</td>
<td>10a</td>
<td>0.45</td>
<td>TBAF (4)</td>
<td>DMF</td>
<td>95</td>
<td>2 h</td>
<td>SI5a, 0</td>
<td>11a, 95</td>
</tr>
</tbody>
</table>

<sup>a</sup> Starting material was partially regenerated (34%).<sup>b</sup> The compound was not fully characterised.
**tert-Butyl 3-(benzo[d][1,3]dioxol-5-yl(triethylsilyl)methylene)-3,5,6,6a-tetrahydrocyclopenta[b]pyrrole-1(2H)-carboxylate (9a)**

The title compound was prepared using a modified procedure reported earlier.[2] Compound 8 (692 mg, 1.50 mmol) was dissolved in a mixture of THF (22.5 mL) and water (2.3 mL), then 3,4-(methylenedioxy)phenylboronic acid (498 mg, 3.00 mmol) and caesium carbonate (1086 mg, 3.30 mmol) were added. The mixture was degassed by evacuation and backfilling with argon (2x), then Pd(PPh₃)₄ (88 mg, 0.075 mmol) was added and the degassing procedure was repeated again. The mixture was warmed to 75 °C and stirred at this temperature for 18 h. Then it was allowed to cool to room temperature and extracted between EtOAc (3 × 80 mL) and brine (50 mL). Combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient elution: 99/1 → 95/5 hexanes/EtOAc) to provide the title compound (546 mg, 80%) in ratio of Z/E isomers 80/20 from which (Z)-9a (379 mg, 55%) and (E)-9a (7 mg, 1%) were isolated in pure form. The reaction was successfully scaled up to gram scale (1.63 g of 8, 77%).

**Colorless foam.** ¹H NMR (400 MHz, CDCl₃) δ 6.74 (d, J = 7.9 Hz, 1H), 6.53 – 6.26 (m, 2H), 5.92 (s, 2H), 4.75 (s, 1H), 4.48 (d, J = 15.8 Hz, 1H), 4.43 – 4.33 (m, 1H), 4.34 (d, J = 15.9 Hz, 1H), 2.54 – 2.22 (m, 3H), 1.74 – 1.57 (m, 1H), 1.46 (s, 9H), 0.89 (t, J = 7.9 Hz, 9H), 0.66 – 0.50 (m, 6H). Other spectral data were in agreement with those already reported.[2]

**Colorless foam;** ¹H NMR (400 MHz, CDCl₃) δ 6.71 (d, J = 7.7 Hz, 1H), 6.39 (d, J = 1.7 Hz, 1H), 6.32 (dd, J = 7.8, 1.7 Hz, 1H), 6.01 (dt, J = 4.4, 2.3 Hz, 1H), 5.92 (s, 2H), 4.61 – 4.52 (m, 1H), 3.99 (d, J = 16.6 Hz, 1H), 3.91 (d, J = 16.6 Hz, 1H), 2.77 – 2.40 (m, 3H), 1.86 – 1.71 (m, 1H), 1.41 (s, 9H), 0.87 (t, J = 7.9 Hz, 9H), 0.70 – 0.51 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 155.0, 147.6, 145.5, 145.4, 141.7, 138.2, 137.1, 127.1, 119.8, 108.5, 107.8, 100.9, 79.4, 69.1, 56.4, 36.8, 35.8, 28.6, 7.7, 3.8; IR (KBr) ν 2950, 2875, 1700, 1365, 1338, 1237, 1177, 1120, 1039, 1000, 937, 731 cm⁻¹; MS (ESI) m/z (%) 933.6 (18, [2M+Na]+), 478.3 (100, [M+Na]+), 410.1 (5), 400.2 (13), 454.3 (9), 398.2 (4); HRMS (ESI) m/z calcd for C₂₆H₃₇O₄NNaSi 478.2384, found 478.2381.

**tert-Butyl 3-((4-methoxyphenyl)(triethylsilyl)methylene)-3,5,6,6a-tetrahydrocyclopenta[b]pyrrole-1(2H)-carboxylate (9b)**

Compound 8 (1.13 g, 2.46 mmol) was dissolved in a mixture of THF (32 mL) and water (3.2 mL), then 4-methoxyphenylboronic acid (0.71 g, 4.92 mmol) and caesium carbonate (1.78 g, 5.41 mmol) were added. The mixture was degassed by evacuation and backfilling with argon (2x), then Pd(PPh₃)₄ (143 mg, 0.12
tert-Butyl 1-iodo-6-(triethylsilyl)-1,2,3,3a-tetrahydro-[1,3]dioxolo-[4',5':5,6]indeno[1,2-c]cyclopenta-[b]pyrrole-4(5H)-carboxylate (10a)

The title compound was prepared using a modified procedure reported earlier.[2] Compound 9a (274 mg, 0.60 mmol) was dissolved in dry MeCN (12 mL) under argon atmosphere. The solution was cooled to 0 °C, covered with aluminum foil and then N-iodosuccinimide (162 mg, 0.72 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h before being extracted between brine (25 mL) and EtOAc (3 × 40 mL). Combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 hexanes/EtOAc) to give the

mmol) was added and the degassing procedure was repeated again. The resulting mixture was heated to 70 °C and stirred at this temperature 23 h before being allowed to cool to room temperature and extracted between EtOAc (3 × 50 mL) and brine (20 mL).

Combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 hexanes/EtOAc) to provide the title compound (0.96g, 89%) in ratio of Z/E isomers 87/13 from which (Z)-9b (0.83 g, 85%) and (E)-9b (65 mg, 7%) were isolated in pure form.

(Z)-9b: White crystalline solid, m.p. = 177.7 °C (recrystallized from Et₂O/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 6.90 – 6.80 (m, 4H), 4.62 – 4.58 (m, 1H), 4.56 – 4.32 (m, 3H), 3.80 (s, 3H), 2.50 – 2.22 (m, 3H), 1.71 – 1.59 (m, 1H), 1.47 (s, 9H), 0.90 (t, J = 7.9 Hz, 9H), 0.66 – 0.51 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 155.4, 146.4, 140.4, 137.3, 136.9, 128.3, 127.0, 113.5, 79.6, 68.3, 56.5, 55.3, 36.1, 36.0, 28.6, 7.6, 3.6.; IR (KBr) ν 2947, 2875, 2836, 1706, 1607, 1509, 1392, 1278, 1242, 1171, 1120, 1030, 1006, 911, 722 cm⁻¹; MS (ESI) m/z (%) 905.6 (30, [2M+Na]+), 464.3 (100, [M+Na]+), 386.2 (4); HRMS (ESI) m/z calcld for C₂₆H₃₉O₃NNaSi 464.2591, found 464.2589.

(E)-9b: Light yellow amorphous solid; ¹H NMR (400 MHz, CDCl₃) δ 6.88 – 6.73 (m, 4H), 6.04 – 5.97 (m, 1H), 4.61 – 4.51 (m, 1H), 3.96 (d, J = 16.6 Hz, 1H), 3.86 (d, J = 16.6 Hz, 1H), 3.79 (s, 3H), 2.79 – 2.41 (m, 3H), 1.85 – 1.71 (m, 1H), 1.40 (s, 9H), 0.86 (t, J = 7.8 Hz, 9H), 0.67 – 0.51 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 155.0, 145.5, 141.5, 137.0, 136.7, 128.0, 126.9, 114.0, 79.3, 69.1, 56.5, 55.3, 36.8, 35.8, 28.6, 7.7, 3.9; IR (KBr) ν 2947, 2869, 1697, 1697, 1610, 1512, 1395, 1278, 1245, 1180, 1033, 973, 728 cm⁻¹; MS (ESI) m/z (%) 905.6 (10, [2M+Na]+), 464.3(100, [M+Na]+), 412.2 (2), 386.2 (14); HRMS (ESI) m/z calcld for C₂₆H₄₆O₃NSi 442.2772, found 442.2766.
title compound (265 mg, 76%) as a light yellow solid. The reaction was repeated several times with the yields in the range of 74-76%. The recorded spectra were in agreement with those already reported.[2]

1H NMR (400 MHz, CDCl3, mixture of rotamers, signals of both rotamers are listed) δ 6.84 (s, 1H), 6.82 (s, 1H#), 6.69 (s, 1H), 6.68 (s, 1H), 5.96 – 5.93 (m, 2H, 2H#), 4.36 (dd, J = 11.7, 6.8 Hz, 1H), 4.35 (dd, J = 11.9, 7.0 Hz, 1H#), 4.29 (d, J = 13.7 Hz, 1H), 4.20 (d, J = 13.5 Hz, 1H#), 4.06 (d, J = 13.7 Hz, 1H), 4.05 (d, J = 13.5 Hz, 1H#), 3.87 (d, J = 3.8 Hz, 1H#), 3.80 (d, J = 3.8 Hz, 1H), 2.53 – 2.27 (m, 3H, 3H#), 1.87 – 1.75 (m, 2H), 1.45 (s, 9H#), 1.44 (s, 9H), 1.03 – 0.97 (m, 9H, 9H#), 0.88 – 0.79 (m, 6H, 6H#); 13C NMR (100 MHz, CDCl3, mixture of rotamers, signals of both rotamers are listed) δ 163.8#, 163.6, 153.5 (1C, 1C#), 147.52#, 147.50, 145.6#, 145.5, 143.8, 143.5#, 141.6#, 141.5, 134.1, 133.9#, 103.84, 103.80#, 103.74#, 103.68, 101.4 (1C, 1C#), 80.1, 79.9#, 71.9, 71.2#, 63.62, 63.56#, 48.1#, 47.8, 38.3#, 38.0, 36.0, 35.0#, 31.3#, 31.1, 28.6 (1C, 1C#), 7.7 (1C, 1C#), 4.1 (1C, 1C#) (*rotamer signals – the signals are in pairs but could not be assigned to the particular rotamer, lower intensity signal of the pair is always marked by #)

tert-Butyl 1-iodo-9-methoxy-6-(triethylsilyl)-1,2,3,3a-tetrahydrocyclopenta[b]inden[1,2-c]pyrrole-4(5H)-carboxylate (10b)

Alkene 9b (35 mg, 0.08 mmol) was dissolved in dry MeCN (1.6 mL) under an argon atmosphere. The solution was cooled to 0 °C and covered with aluminium foil before N-iodosuccimide (21 mg, 0.10 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h before being extracted with EtOAc (3 × 20 mL) and brine (15 mL). Combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 hexanes/EtOAc) to give the title compound as a transparent crystalline solid (31 mg, 68%), m.p. = 148.2 °C (recrystallized from EtOAc). The reaction was repeated several times with the yields in the range of 62-68% and was successfully scaled up (0.91 g, 62%).

1H NMR (400 MHz, CDCl3, mixture of rotamers, signals of both rotamers are listed) δ 7.24 – 7.19 (m, 1H, 1H#), 6.78 – 6.74 (m, 2H, 2H#), 4.41 (dd, J = 6.7, 5.1 Hz, 1H#), 4.38 (dd, J = 6.7, 5.1 Hz, 1H), 4.31 (d, J = 13.6 Hz, 1H), 4.23 (d, J = 13.4 Hz, 1H#), 4.07 (d, J = 13.6 Hz, 1H), 4.06 (d, J = 13.4 Hz, 1H#), 3.90 (d, J = 3.8 Hz, 1H#), 3.83 (d, J = 3.7 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H#), 2.55 – 2.29 (m, 3H, 3H#), 1.91 – 1.78 (m, 1H, 1H#), 1.45 (s, 9H#), 1.44 (s, 9H), 1.04 – 0.97 (m, 9H, 9H#), 0.89 – 0.81 (m, 6H, 6H#); 13C NMR (100 MHz, CDCl3, mixture of rotamers, signals of both rotamers are listed) δ 162.5#, 162.3, 157.9#, 157.8, 153.6 (1C, 1C#), 149.9#, 149.8, 143.1, 142.8#, 134.0, 133.7#, 122.73, 122.65#, 112.0 (1C, 1C#), 109.73#, 109.65, 80.0, 79.9#, 72.2, 71.4#, 63.6, 63.5#, 55.7 (1C, 1C#), 48.2#, 47.9, 38.5#, 38.2,
36.1, 35.1°, 32.0°, 31.8, 28.6 (1C, 1C°), 7.7 (1C, 1C°), 4.1 (1C, 1C°) (°rotamer signals – the signals are in pairs but could not be assigned to the particular rotamer, lower intensity signal of the pair is always marked by °); IR (KBr) v 2959, 2866, 2839, 1679, 1619, 1580, 1392, 1245, 1210, 1180, 1105, 1045, 997, 875, 743, 695 cm⁻¹; MS (ESI) m/z (%) 1157.4 (30, [2M+Na]+), 590.2 (100, [M+Na]+), 512.1 (22), 462.3 (82), 440.3 (4), 270.1 (7); HRMS (ESI) m/z calcd for C_{26}H_{38}O_{3}NINaSi 590.1558, found 590.1552.

**tert-Butyl 3,3a-dihydro-[1,3]dioxolo[4',5':5,6]indeno[1,2-c]cyclopenta[b]pyrrole-4(5H)-carboxylate (11a)**

Compound 10a (45 mg, 0.08 mmol) was dissolved in dry DMF (0.7 mL) and then TBAF (0.3 mL of 1M solution in THF, 0.31 mmol) was added. The reaction mixture was heated to 90 °C and stirred for 2.5 h. Then it was cooled to room temperature, diluted with Et₂O (35 mL) and washed with water (3 × 10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient elution: 100/0 → 98/2 hexanes/EtOAc) to provide the title compound as a light yellow foam (25 mg, 96%). The reaction was repeated several times with the yields in the range of 90-96%.

**1H NMR** (400 MHz, CDCl₃, mixture of rotamers, signals of both rotamers are listed) δ 6.77 (s, 1H), 6.76 (s, 1H°), 6.63 (d, 1H°), 6.62 (s, 1H), 6.44 – 6.40 (m, 1H, 1H°), 6.09 – 6.02 (m, 1H, 1H°), 5.95 – 5.91 (m, 2H, 2H°), 5.34 – 5.28 (m, 1H, 1H°), 4.22 (d, J = 13.2 Hz, 1H), 4.11 (d, J = 13.2 Hz, 1H°), 4.02 – 3.88 (m, 2H, 2H°), 3.00 – 2.76 (m, 2H, 2H°), 1.46 (s, 9H°), 1.45 (s, 9H); **13C NMR** (100 MHz, CDCl₃, mixture of rotamers, signals of both rotamers are listed) δ 154.21, 154.16°, 151.0°, 150.8, 147.51, 147.48°, 145.8°, 145.7, 140.5°, 140.4, 139.4, 139.3°, 133.5°, 133.0, 132.6, 132.3°, 123.7, 123.6°, 105.4°, 105.3, 102.8, 102.6°, 101.2 (1C, 1C°), 79.8, 79.6°, 75.2, 74.5°, 63.0, 62.8°, 45.4°, 44.9, 42.0, 40.9°, 28.7 (1C, 1C°) (°rotamer signals – the signals are in pairs but could not be assigned to the particular rotamer, lower intensity signal of the pair is always marked by °); IR (KBr) v 2971, 2926, 1688, 1470, 1389, 1269, 1163, 1102, 1036, 943, 866, 782, 731 cm⁻¹; MS (ESI) m/z (%) 701.3 (28, [2M+Na]+), 362.1 (100, [M+Na]+), 340.1 (5, [M+H]+), 300.1 (6), 284.1 (44); HRMS (ESI) m/z calcd for C_{20}H_{21}O_{4}NINa 362.1363, found 362.1362.

**tert-Butyl 9-methoxy-6-(triethylsilyl)-3,3a-dihydrocyclopenta[b]indeno[1,2-c]pyrrole-4(5H)-carboxylate (SI5b)**

Compound 10b (38 mg, 0.07 mmol) was dissolved in dry THF (0.7 mL) under argon atmosphere and then TBAF (0.26 mL of 1M solution in THF, 0.26 mmol) was added. The reaction mixture was warmed to
70 °C and stirred for 5 h before cooling down and extracted with EtOAc (3 × 20 mL) and water (20 mL). Combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 hexanes/EtOAc) to give the title compound as an orange amorphous solid (22 mg, 77%). The product is sensitive to acids.

**1H NMR** (400 MHz, CDCl₃, mixture of rotamers, signals of both rotamers are listed) δ 7.26 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 6.77 (dd, J = 8.4, 2.5 Hz, 1H), 6.08 – 6.04 (m, 1H, 1H), 5.31 – 5.26 (m, 1H, 1H), 4.29 (d, J = 13.6 Hz, 1H), 4.21 (d, J = 13.5 Hz, 1H), 6.71 (d, J = 2.5 Hz, 1H), 6.69 (d, J = 2.5 Hz, 1H), 6.08 – 6.04 (m, 1H, 1H), 5.31 – 5.26 (m, 1H, 1H), 4.29 (d, J = 13.6 Hz, 1H), 4.21 (d, J = 13.5 Hz, 1H), 1.46 (s, 9H), 1.03 – 0.92 (m, 9H), 0.90 – 0.78 (m, 6H);

**13C NMR** (100 MHz, CDCl₃, mixture of rotamers, signals of both rotamers are listed) δ 161.0, 160.7, 157.7, 157.6, 154.29, 154.25, 148.6, 148.5, 143.1, 142.9, 134.0, 133.5, 133.1, 132.4, 131.9, 131.7, 122.7, 122.6, 112.4 (1C, 1C), 110.5, 110.3, 79.7, 79.6, 77.4, 76.7, 62.33, 62.27, 55.7 (1C, 1C), 46.2, 45.9, 42.1, 41.2, 28.7 (1C, 1C), 7.6 (1C, 1C), 3.99, 3.95 (rotamer signals – the signals are in pairs but could not be assigned to the particular rotamer, lower intensity signal of the pair is always marked by *)

**IR** (KBr) ν 3059, 2954, 2912, 2873, 1699, 1604, 1577, 1466, 1387, 1365, 1284, 1165, 1101, 1034, 1001, 744 cm⁻¹; **MS (ESI)** m/z (%) 440.3 (11, [M+H]+), 385.2 (15), 384.2 (100), 286.1 (12); **HRMS (ESI)** m/z calcd for C₂₆H₃₈O₃NSi 440.2616, found 440.2611.

tert-Butyl 9-methoxy-3,3a-dihydrocyclopenta[b]inden[1,2-c]pyrrole-4(5H)-carboxylate (11b)

Compound 10b (77 mg, 0.14 mmol) was dissolved in dry DMF (4 mL) under argon atmosphere and then TBAF (0.5 mL of 1M solution in THF, 0.54 mmol) was added. The reaction mixture was heated to 90 °C and stirred for 16 h. Then it was cooled to room temperature, diluted with Et₂O (35 mL) and washed with water (3 × 10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified on a short plug of silica gel (9/1 hexanes/EtOAc) to provide the title compound as brown-orange oil (40 mg, 91%). The compound is rather unstable.

**1H NMR** (400 MHz, CDCl₃, mixture of rotamers, signals of both rotamers are listed) δ 7.16 (d, J = 8.2 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 6.81 – 6.76 (m, 1H, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.48 – 6.47 (m, 1H), 6.47 – 6.45 (m, 1H, 1H), 6.10 – 6.04 (m, 1H, 1H), 5.37 – 5.31 (m, 1H, 1H), 4.24 (d, J = 13.2 Hz, 1H), 4.14 (d, J = 13.2 Hz, 1H), 4.03 – 3.94 (m, 2H, 2H), 3.79 (s, 3H, 3H), 3.01 – 2.77 (m, 2H, 2H), 1.46 (s, 9H), 1.45 (s, 9H); **13C NMR** (150 MHz, CDCl₃, mixture of rotamers, signals of both rotamers are listed) δ 158.12, 158.09, 154.3, 154.2, 149.8, 149.5, 148.49, 148.45,
3,3a,4,5-Tetrahydro-[1,3]dioxolo[4',5':5,6]indeno[1,2-c]cyclopenta[b]pyrrole (12a)

Compound 12a was synthesized using a modified literature procedure.\[^3\] Compound 11a (41 mg, 0.12 mmol) was dissolved in dry DCM (4 mL) under argon atmosphere and the solution was transferred to the flask with a vacuum-dried (4 h, 140 °C) ZnBr\(_2\) (135 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for 20 h before being quenched with 1M aqueous solution of NaOH (2 mL) and vigorously stirred for an additional 5 min. The mixture was extracted between DCM (4 × 25 mL) and 1M solution of NaOH (15 mL). Combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure to give NMR yield (82% with mesitylene as internal standard). The purification by column chromatography on silica gel (90/10 DCM/14% ammonia in methanol) is possible but about a quarter of the product is lost. The compound is also sensitive to acids and evaporation with silica gel.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 6.73 (s, 1H), 6.59 (s, 1H), 6.39 (dt, \(J = 1.8, 0.8\) Hz, 1H), 6.10 – 6.06 (m, 1H), 5.93 – 5.89 (m, 2H), 5.46 – 5.41 (m, 1H), 3.74 (dd, \(J = 13.2, 2.1\) Hz, 1H), 3.53 (d, \(J = 13.1, 1\)H), 3.46 (d, \(J = 5.2\) Hz, 1H), 2.95 (dddd, \(J = 17.5, 5.4, 2.8, 1.8\) Hz, 1H), 2.58 (bs, 1H), 2.45 (ddd, \(J = 17.4, 2.7, 1.5\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 157.8, 147.2, 145.2, 140.3, 140.1, 133.5, 132.6, 123.0, 105.1, 102.3, 100.9, 75.8, 61.6, 43.7, 42.7; IR (KBr) v 3227, 3055, 2897, 1693, 1476, 1392, 1311, 1159, 939, 862, 812, 727 cm\(^{-1}\); MS (ESI) \(m/z\) (%) 673.4 (41, [2M+Na]\(^+\)), 349.2 (18), 349.2 (100, [M+Na]\(^+\)), 292.1 (9), 270.1 (23); HRMS (ESI) \(m/z\) calcd for C\(_{20}\)H\(_{24}\)O\(_3\)N 326.1751, found 326.1748.

9-Methoxy-3,3a,4,5-tetrahydrocyclopenta[b]indeno[1,2-c]pyrrole (12b)

Compound 12b was synthesized using a modified literature procedure.\[^3\] Compound 11b (42 mg, 0.13 mmol) was dissolved in dry DCM (4 mL) under argon atmosphere and the solution was transferred to the flask with a vacuum-dried (4 h, 150 °C) ZnBr\(_2\) (145 mg, 0.14 mmol). The reaction mixture was stirred at room temperature for 20 h before being quenched with 1M aqueous solution of NaOH (2 mL) and vigorously stirred for an additional 5 min. The mixture was extracted between DCM (4 × 25 mL) and 1M solution of NaOH (15 mL). Combined organic
layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give NMR yield (81% with mesitylene as internal standard). The purification by column chromatography on silica gel (97/3 DCM/14% ammonia in methanol) is possible but about half of the product (isolated as a dark grey oil) is lost. The compound is also sensitive to acids and evaporation with silica gel.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.12 (d, J = 8.2 Hz, 1H), 6.77 (dd, J = 8.2, 2.4 Hz, 1H), 6.67 (d, J = 2.2 Hz, 1H), 6.44 (s, 1H), 6.13 – 6.08 (m, 1H), 5.47 – 5.43 (m, 1H), 3.78 (s, 3H), 3.74 (dd, J = 13.1, 1.8 Hz, 1H), 3.54 (d, J = 13.1 Hz, 1H), 3.50 (d, J = 5.3 Hz, 1H), 2.98 (ddt, J = 17.5, 5.1, 2.2 Hz, 1H), 2.55 (bs, 1H), 2.48 (d, J = 17.4 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 157.8, 156.6, 148.6, 139.6, 133.7, 132.8, 122.8, 121.2, 112.4, 110.7, 76.2, 61.6, 55.7, 44.0, 42.9; IR (KBr) $\nu$ 3400, 3059, 2927, 2871, 2733, 1693, 1606, 1581, 1469, 1385, 1284, 1223, 1161, 1028, 972, 849, 806, 721 cm$^{-1}$; MS (ESI) m/z (%) 226.1 (100, [M+H]$^+$), 209.1 (28), 197.1 (11); HRMS (ESI) m/z calcd for C$_{15}$H$_{16}$ON 226.1226, found 226.1224.

9-Methoxy-3,3a,4,5-tetrahydrocyclopenta[b]indenol[1,2-c]pyrrol-4-ium bromide (SI6b)

Compound SI6b was synthesized using a modified literature procedure.$[^3]$ Compound 11b (20 mg, 0.06 mmol) was dissolved in dry DCM (2 mL) under argon atmosphere and the solution was transferred to the flask with a vacuum-dried (4 h, 150 °C) ZnBr$_2$ (71 mg, 0.32 mmol). The reaction mixture was stirred at room temperature for 22 h before being filtered through a piece of cotton. The filtrate was concentrated under reduced pressure and further dried at 10 mbar to provide the title compound as a white amorphous solid (84% NMR yield with mesitylene as an internal standard).

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.27 – 7.23 (m, 1H), 6.87 (dd, J = 8.3, 2.4 Hz, 1H), 6.81 – 6.77 (m, 2H), 6.28 – 6.24 (m, 1H), 5.53 – 5.49 (m, 1H), 4.06 (d, J = 13.4 Hz, 1H), 3.97 – 3.86 (m, 2H), 3.78 (s, 3H), 3.29 – 3.20 (m, 1H), 2.97 – 2.89 (m, 1H); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 160.2, 147.6, 139.3, 134.0, 133.6, 128.9, 123.6, 114.5, 111.8, 76.1, 64.5, 56.1, 44.2, 40.1 (one signal in the aromatic region is overlapped); IR (KBr) $\nu$ 3530, 3064, 1607, 1577, 1473, 1287, 1219, 1156, 1030, 934, 875, 719, 603, 531 cm$^{-1}$; MS (ESI) m/z (%) 226.1 (42, M$^+$), 209.1 (100), 197.1 (64); MS (ESI negative mode) m/z (%) 306.6 (80, [M-H]), 304.4 (100, [M-H]$^-$), 80.9 (43, Br$^-$), 78.9 (44, Br$^-$); HRMS (ESI) m/z calcd for C$_{15}$H$_{16}$ON 226.1226, found 226.1225.

4-Methyl-3,3a,4,5-tetrahydro-[1,3]dioxolo[4',5':5,6]indenol[1,2-c]cyclopenta[b]pyrrole (1a)

Compound 1a was synthesized using a modified literature procedure.$[^3]$ Compound 11a (54 mg, 0.16 mmol) was dissolved in dry DCM (2 mL) under argon atmosphere and the solution was transferred to the
flask with a vacuum-dried (4 h, 140 °C) ZnBr$_2$ (179 mg, 0.78 mmol). The reaction mixture was stirred at room temperature for 16 h before being quenched with 1M solution of NaOH (3 mL) and vigorously stirred for an additional 5 min. The mixture was extracted between DCM (7 × 25 mL) and 1M solution of NaOH (15 mL). The water phase was neutralized with 1M HCl and extracted with DCM (3 × 25 mL). Combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure.

The extract was dissolved in dry MeOH (2.1 mL) and then formaldehyde (52 uL of 37% solution in water, 0.70 mmol) was added. The mixture was stirred for 3 h at room temperature and then NaBH$_3$CN (27 mg, 0.42 mmol) was added. After 19 h the mixture was extracted between DCM (3 × 25 mL) and 1M aqueous solution of NaHCO$_3$ (25 mL). Combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was loaded on a column in a small amount of DCM and purified by column chromatography on silica gel (95/4.5/0.5 DCM /MeOH/NH$_4$OH to provide the title compound as a dark orange oil (21 mg, 52%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 6.74 (s, 1H), 6.59 (s, 1H), 6.45 – 6.39 (m, 1H), 6.09 – 6.03 (m, 1H), 5.98 – 5.89 (m, 2H), 5.54 – 5.48 (m, 1H), 4.00 (dd, J = 13.7, 2.1 Hz, 1H), 3.12 (dd, J = 13.7, Hz, 1H), 2.87 – 2.59 (m, 3H), 2.47 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.3, 147.3, 145.4, 140.5, 139.6, 134.4, 132.3, 123.8, 105.2, 102.3, 101.1, 76.5, 71.1, 53.1, 42.2, 39.6; IR (KBr) ν 3037, 2929, 2898, 2848, 2777, 1705, 1601, 1464, 1309, 1165, 1153, 1038, 1030, 935, 872, 787, 721 cm$^{-1}$; MS (ESI) m/z (%) 254.1 (100, [M+H]$^+$), 225.1 (6), 223.1 (22), 197.1 (12); HRMS (ESI) m/z calcd for C$_{16}$H$_{16}$O$_2$N 254.1176, found 254.1179.

**9-Methoxy-4-methyl-3,3a,4,5-tetrahydrocyclopenta[b]indenol,2-c]pyrrole (1b)**

Compound 1b was synthesized using modified literature procedures.$^{[3,4]}$ Compound 11b (42 mg, 0.13 mmol) was dissolved in dry DCM (4 mL) under argon atmosphere and the solution was transferred to the flask with a vacuum-dried (4 h, 150 °C) ZnBr$_2$ (145 mg, 0.14 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 20 h before being quenched with 1M solution of NaOH (2 mL) and vigorously stirred for an additional 5 min. The mixture was extracted between DCM (4 × 25 mL) and 1M solution of NaOH (15 mL). Combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure.

The extract was dissolved in dry MeOH (2.6 mL) and then formaldehyde (39 uL of 37% solution in water, 0.52 mmol) and ZnCl$_2$ (7 mg, 0.05 mmol) were added. The mixture was stirred for 1.5 h at room temperature before cooling to 0 °C and addition of NaBH$_3$CN (13 mg, 0.21 mmol). After 5 min at 0 °C, the reaction mixture was allowed to warm up to room temperature and stirred for an additional 4 h before
being extracted with DCM (5 × 25 mL) and water (15 mL). Combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (95/5 DCM /14% ammonia in methanol) to provide the title compound as an orange oil (23 mg, 74%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.13 (d, \(J = 8.2\) Hz, 1H), 6.77 (dd, \(J = 8.2, 2.5\) Hz, 1H), 6.67 (d, \(J = 2.5\) Hz, 1H), 6.46 – 6.42 (m, 1H), 6.11 – 6.05 (m, 1H), 5.56 – 5.51 (m, 1H), 3.97 (dd, \(J = 13.6, 2.1\) Hz, 1H), 3.78 (s, 3H), 3.10 (dd, \(J = 13.6, 1.3\) Hz, 1H), 2.85 – 2.75 (m, 2H), 2.63 – 2.55 (m, 1H), 2.45 (s, 3H);

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 157.7, 153.1, 148.6, 139.0, 134.5, 132.4, 123.6, 121.3, 112.5, 110.6, 76.8, 70.8, 55.7, 53.1, 42.3, 39.7; IR (KBr) \(\nu\) 3055, 2935, 2835, 1687, 1606, 1581, 1469, 1284, 1213, 1155, 1028, 870, 847, 789, 710 cm\(^{-1}\); MS (ESI) \(m/z\) (%) 240.1 ([M+H]⁺, 100); HRMS (ESI) \(m/z\) calcd for C\(_{16}\)H\(_{18}\)ON 240.1383, found 240.1384.
5. Synthesis of N-alkyl quarternary salts

3-(Benzo[d][1,3]dioxol-5-yl(triethylsilyl)methylene)-1,1-dimethyl-1,2,3,5,6,6a-hexahydro-cyclopenta[b]pyrrolo-1-ium (6c)

Compound 4a (58 mg, 0.16 mmol, Z/E ratio = 83/17) was dissolved in dry THF (2 mL) under argon atmosphere. Na₂CO₃ (103 mg, 0.93 mmol) and iodomethane (51 uL, 0.78 mmol) were added and the mixture was stirred at room temperature for 3 h before filtration followed by DCM wash. The unreacted iodomethane was removed and the mixture was concentrated on a rotary evaporator at 45 °C under reduced pressure. The crude product was crystallized from DCM/hexanes and the mother liquor was subjected to column chromatography (gradient elution 100 → 85/15 DCM/MeOH) to give a summary yield of 50% (40 mg, Z/E ratio = 78/22) of title compound 6c as a white crystalline solid. For the bioactivity testing and melting point measurement, the pure (Z)-6c obtained in a small amount from a different batch was used.

(Z)-6c: White crystalline solid, m.p. = 203.2 °C (from DCM/hexanes); ¹H NMR (400 MHz, CD₃OD) δ 6.85 (dd, J = 11.3, 7.9 Hz, 1H), 6.55 – 6.37 (m, 2H), 6.01 – 5.92 (m, 2H), 5.04 – 4.94 (m, 1H), 4.90 – 4.79 (m, 2H), 4.63 (dd, J = 14.3, 3.3 Hz, 1H), 3.29 (s, 3H), 2.94 (s, 3H), 2.76 – 2.58 (m, 2H), 2.27 – 2.16 (m, 1H), 2.05 – 1.90 (m, 1H), 0.97 (t, J = 7.9 Hz, 9H), 0.72 – 0.64 (m, 6H); ¹H NMR (600 MHz, CD₂Cl₂, mixture of rotamers, signals of both rotamers are listed) δ 6.82 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 7.4 Hz, 1H§), 6.46 (s, 1H), 6.46 (s, 1H§), 6.43 (dd, J = 7.9, 1.7 Hz, 1H), 6.40 (dd, J = 7.9, 1.7 Hz, 1H§), 5.98 (s, 2H), 5.97 – 5.95 (m, 2H§), 5.08 – 4.82 (m, 4H, 4H§), 3.64 – 3.61 (m, 3H, 3H§), 3.06 (s, 3H), 0.87 (m, 6H, 6H§) (§rotamer signals – the signals could not be assigned to the particular rotamer, one signal of the pair is always marked by §); ¹³C NMR (150 MHz, CD₂Cl₂) δ 148.9, 148.3, 146.70, 146.68, 146.65, 146.63, 138.3, 138.2, 137.46, 137.44, 133.80, 133.77, 132.1, 131.7, 120.0, 119.0, 109.7, 108.7, 107.6, 106.9, 101.69, 101.66, 86.72, 86.69, 75.9 (1C, 1C§), 52.3 (1C, 1C§), 45.0 (1C, 1C§), 37.5, 37.4, 23.9 (1C, 1C§), 7.8 (3C, 3C§), 3.9 (3C, 3C§) (§rotamer signals – the signals are in pairs but could not be assigned to the particular rotamer, lower intensity signal of the pair is always marked by §); IR (KBr) ν 3001, 2953, 2869, 1601, 1479, 1431, 1326, 1242, 1042, 1009, 934, 875, 836, 725 cm⁻¹; MS (ESI) m/z (%) 385.2 (25), 384.2 (100, [M]+), 339.2 (10); HRMS (ESI) m/z calcd for C₂₃H₂₄O₂NSi 384.2353, found 384.2353.

(E)-6c: ¹H NMR (400 MHz, CD₃OD) δ 6.87 – 6.81 (m, 1H), 6.47 – 6.37 (m, 2H), 5.99 – 5.93 (m, 2H), 5.19 – 5.11 (m, 1H), 4.91 – 4.85 (m, 1H), 4.64 (d, J = 15.1 Hz, 1H), 4.07 (d, J = 15.0 Hz, 1H), 3.14
(s, 3H), 3.04 – 2.97 (m, 1H), 2.84 (s, 3H), 2.73 – 2.59 (m, 1H), 2.41 – 2.30 (m, 1H), 2.19 – 2.09 (m, 1H), 0.95 – 0.87 (m, 9H), 0.76 – 0.68 (m, 6H);

9-Methoxy-4,4-dimethyl-3,3a,4,5-tetrahydrocyclopenta[b]inden[1,2-c]pyrrol-4-ium (13b)

Compound 1b (17 mg, 0.07 mmol) was dissolved in CHCl₃ (2.5 mL) and iodomethane (44 uL, 0.70 mmol) was added. The resulting mixture was stirred at room temperature for 96 h before the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (gradient elution 95/5 → 90/10 DCM /MeOH) to provide the title compound as an orange oil (15 mg, 57% isolated yield, 62% NMR yield).

$^1$H NMR (400 MHz, CDCl₃) δ 7.30 (d, $J = 8.4$ Hz, 1H), 7.02 – 6.98 (m, 1H), 6.88 (dd, $J = 8.4, 2.3$ Hz, 1H), 6.73 (d, $J = 2.2$ Hz, 1H), 6.24 – 6.19 (m, 1H), 5.46 – 5.41 (m, 1H), 4.77 (d, $J = 12.6$ Hz, 1H), 4.21 (d, $J = 6.2$ Hz, 1H), 4.05 (d, $J = 12.6$ Hz, 1H), 3.81 (s, 3H), 3.59 (s, 3H), 3.39 – 3.26 (m, 5H); $^{13}$C NMR (100 MHz, CDCl₃) δ 159.6, 147.1, 140.5, 136.7, 133.2, 132.4, 131.8, 123.8, 114.5, 110.9, 82.3, 75.4, 64.8, 56.4, 55.9, 51.0, 37.2; IR (KBr) ν 3452, 3003, 2962, 2835, 2040, 1606, 1581, 1470, 1435, 1296, 1219, 1146, 1024, 908, 820, 729, 606, 465 cm$^{-1}$; MS (ESI) m/z (%), 254.1 (100, [M]$^+$), 255.1 (10); HRMS (ESI) m/z calcd for C$_{17}$H$_{20}$ON 254.1539, found 254.1541; HRMS (ESI negative mode) m/z calcd for I 126.9050, found 126.9050.
6. Enantioselective synthesis

![Chemical structures and reactions diagram]

- **2** to **SI7**: DPPA, DBU in THF, r.t., 69 h
- **SI7** to **NH2**: Na₂S, MeOH, r.t., 69 h
- **NH2** to **CAL-B** rac-14, 80%: EtOAc, 30 °C, 18 h
- **(S)-14** and **(R)-15, 50%**: CAL-B
- **Boc₂O** in THF, r.t., 3 h
- **(S)-16, 47% (from rac-14)** with 97% ee
- **boronic acid** and **Pd(PPh₃)₄**, **C₆H₅CO₂**: THF/H₂O, 70 °C, 16 h
- **(S)-9a, 92% (Z/E = 6:1)** with 96% ee
- **(R, S)-10a, 76%** with 97% ee
- **(S, R)-11a, 91%** with 97% ee
- **(S, R)-1a, 24%, 95% ee**
Table S5. Selected results from the optimisation of the reduction of azide SI7 to amine 14

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reductant (eq.)</th>
<th>Solvent</th>
<th>Conditions a)</th>
<th>Time (h)</th>
<th>Work-up</th>
<th>Yield after work-up b) (%)</th>
<th>Purification c)</th>
<th>Isolated yield (%)</th>
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<tr>
<td>1</td>
<td>PPh₃ (2.0)</td>
<td>THF/H₂O</td>
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<td>extraction</td>
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<td>CHR</td>
<td>62 d)</td>
</tr>
<tr>
<td>2</td>
<td>PPh₃ (2.0)</td>
<td>THF/H₂O</td>
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<td>extraction</td>
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<td>32 d)</td>
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<tr>
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<td>THF/H₂O</td>
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<td>90</td>
<td>--- e)</td>
<td>---</td>
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<td>basic ext. g), h)</td>
<td>40</td>
<td>CHR</td>
<td>15 d)</td>
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<tr>
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<td>PPh₃ (1.5)</td>
<td>Et₂O/H₂O</td>
<td>argon</td>
<td>24</td>
<td>extraction</td>
<td>82</td>
<td>PRC, CHR</td>
<td>82 i), 55 j)</td>
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<tr>
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<td>PPh₃ (1.1)</td>
<td>Et₂O/H₂O</td>
<td>argon</td>
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<td>drying k)</td>
<td>78</td>
<td>PRC, TLW, NEU h)</td>
<td>68 d)</td>
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<td>Et₂O/H₂O</td>
<td>argon</td>
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<td>drying k)</td>
<td>---</td>
<td>PRC, TLW, NEU j)</td>
<td>65 d)</td>
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<tr>
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<td>drying k)</td>
<td>71</td>
<td>---</td>
<td>---</td>
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<td>drying, k) evap. m)</td>
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<td>CHR</td>
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<td>CHR</td>
<td>72 n)</td>
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<td>CHR</td>
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<td>extraction</td>
<td>---</td>
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<td>0 p)</td>
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<tr>
<td>15</td>
<td>HS(CH₂)₂SH (4.0) q)</td>
<td>MeOH</td>
<td>argon</td>
<td>71</td>
<td>---</td>
<td>---</td>
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<td>96</td>
</tr>
<tr>
<td>16</td>
<td>HS(CH₂)₂SH (4.1) r)</td>
<td>MeOH</td>
<td>argon</td>
<td>25</td>
<td>filtration</td>
<td>---</td>
<td>CHR</td>
<td>92</td>
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</table>

a) Reactions were stirred at r.t. b) NMR yield. Mesitylene was used as an internal standard. c) CHR: column chromatography on neutralised SiO₂; PRC: precipitation with 1M HCl in ether; TLW: multiple washing with toluene; NEU: neutralisation. d) Isolated yield is determined by NMR standard (mesitylene) due to presence of PPh₃O byproduct. e) Crude containing PPh₃ and PPh₃O was allowed to react with Boc₂O without preceding resolution step to provide 74% of isolated yield of 16. f) 1M HCl in H₂O g) Et₂O wash h) 1M solution of Na₂CO₃ was added and resulting mixture was reextracted with Et₂O. i) Yield after precipitation. j) Yield after column chromatography. k) Anhydrous Na₂SO₄ was added and the mixture was filtered after 5 min. l) 1M solution of NaHCO₃ was used for neutralisation and resulting mixture was reextracted with Et₂O. m) 1 h at 400 mbar at 30°C. n) Starting material was regenerated. o) H₂S was generated from S₈, paraffin wax, Al₂O₃ (basic, Brock I) mixed in ratio 2/5/1. p) Starting material was regenerated. q) Et₃N (4 eq.) was added. r) Et₃N (4.1 eq.) was added.
5-Azido-1-iodocyclopent-1-ene (SI7)

Alcohol 2 (265 mg, 1.26 mmol) was dissolved in dry THF (7.6 mL) under argon atmosphere. Diphenylphosphoryl azide (544 uL, 2.52 mmol) and DBU (396 uL, 2.65 mmol) were added and the resulting mixture was stirred at room temperature for 22 h before dilution with EtOAc (50 mL) and washing with 1M HCl (3 × 10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure at 30 °C (due to volatility of the compound). The crude product was purified by column chromatography on silica gel (9/1 hexanes/EtOAc) to give the title compound a brown oil (266 mg, 90%). The reaction was repeated several times with the yields in the range of 87-90%. The compound was stable for at least three weeks at -20 °C.

¹H NMR (400 MHz, CDCl₃) δ 6.42 – 6.36 (m, 1H), 4.33 – 4.25 (m, 1H), 2.57 – 2.42 (m, 1H), 2.42 – 2.27 (m, 2H), 2.09 – 1.94 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 144.5, 93.2, 73.5, 33.5, 30.0; IR (KBr) ν 2941, 2850, 2096, 1601, 1327, 1254, 1219, 1022, 818, 739, 557 cm⁻¹; MS (EI) m/z (%) 234.9 (36, [M]+), 207.9 (5), 192.9 (100, [M-N₃]+), 151.9 (7), 126.8 (17), 66.0 (66), 53.0 (35), 39.0 (16), 27.0 (13); HRMS (APCI) m/z calcld for C₇H₇NI, [M-N₂]⁺ 207.9618, found 207.9619.

2-Iodocyclopent-2-en-1-amine (rac-14)

Compound rac-14 was synthesized using a modified literature procedure.[⁵] Azide S₁⁷ (449 mg, 1.91 mmol) was dissolved in MeOH (5.7 mL) degassed by argon bubbling for 5 min, then Na₂S.9H₂O (1834 mg, 7.64 mmol) was added and the mixture was stirred at room temperature for 69 h before being diluted with EtOAc (20 mL) and filtered. The filtrate was extracted with water (20 mL) and then EtOAc (2 × 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure at room temperature. The crude product (loaded in a small amount of EtOAc) was purified by column chromatography on neutralized silica gel (gradient elution 97.5/2.3/0.2 → 95/4.5/0.5 DCM/MeOH/NH₄OH) was performed. The title compound was obtained as a brown oil (359 mg, 90%). The spectral data were in agreement with those already reported.[²]

2-Iodocyclopent-2-en-1-aminium chloride (SI8)

Compound rac-14 (96 mg, 0.39 mmol) was dissolved in ether and an excess of 1M HCl in dry ether was added to form a white precipitate. The suspension was left for 5 min to settle down and be decanted. The solid was washed with ether and
decantation was repeated. The ether residue was removed under reduced pressure to provide the title compound as a white powder in quantitative yield.

$^1$H NMR (400 MHz, D$_2$O) $\delta$ 6.63 (dt, $J$ = 4.0, 1.4 Hz, 1H), 4.42 – 4.35 (m, 1H), 2.61 – 2.40 (m, 3H), 2.04 – 1.92 (m, 1H); $^1$H NMR (400 MHz, (CD$_3$)$_2$SO) $\delta$ 8.39 (bs, 3H), 6.55 – 6.51 (m, 1H), 4.18 – 4.10 (m, 1H), 2.53 – 2.41 (m, 1H), 2.34 – 2.22 (m, 2H), 1.96 – 1.83 (m, 1H); $^{13}$C NMR (100 MHz, (CD$_3$)$_2$SO) $\delta$ 147.1, 90.6, 62.3, 32.9, 28.3; IR (KBr) ν 3450, 3371, 2978, 2910, 2856, 2706, 2619, 2036, 1603, 1508, 1379, 1325, 1134, 1026, 916, 849, 557, 418 cm$^{-1}$; MS (ESI) $m/z$ (%) 210.0 (100, [M+H]$^+$), 193.0 (94), 66.0 (29); HRMS (ESI) $m/z$ calcd for C$_5$H$_9$NI 209.9774, found 209.9775.

tert-Butyl (S)-(2-iodocyclopent-2-en-1-yl)carbamate ((S)-16)

The title compound was prepared using a procedure reported earlier$^{[2]}$ with a reaction time of 18 h. The compound was isolated in 47% yield as a white amorphous solid.

Using this procedure the compound (R)-15 was formed as well. The compound was isolated in 50% yield as a white crystalline solid, m.p. = 177.8 °C (recrystallized from EtOAc).

The spectral data of both compounds were in agreement with those already reported.$^{[2]}$

**HPLC analysis:** The HPLC analysis was performed according to previously published$^{[2]}$; IA, heptane/i-PrOH = 80/20, flow rate = 1 mL/min, sample dissolved in i-PrOH, $\lambda$ = 190 nm, retention time: $t_R$ (minor) = 4.1 min, $t_R$ (major) = 4.5 min, 97% ee.
** tert-Butyl (S)-(2-iodocyclopent-2-en-1-yl)(3-(triethylsilyl)prop-2-yn-1-yl)carbamate ((S)-8)**

The title compound was prepared using the same procedure as for the preparation of compound rac-8 (83% yield), as a light yellow oil. The spectral data of the product (S)-8 were identical with those of the racemic compound rac-8 and in agreement with those already reported.\(^2\)

**HPLC analysis:** IC, heptane/i-PrOH = 100/0, flow rate = 1 mL/min, sample dissolved in heptane, λ = 200 nm, retention time: \(t_R\) (major) = 14.3 min, \(t_R\) (minor) = 20.9 min, 97% ee.
tert-Butyl (S,Z)-3-(benzo[d][1,3]dioxol-5-yl(triethylsilyl)methylene)-3,5,6,6a-tetrahydro-cyclopenta[b]pyrrole-1(2H)-carboxylate ((S)-9a)

The title compound was prepared using the same procedure as for the preparation of compound rac-9a (92% yield, E/Z = 86/14), as a colorless foam. The spectral data of the product (S)-9a were identical with those of the racemic compound rac-9 and in agreement with those already reported.¹²

**Specific rotation** $[\alpha]_{D}^{20} = +123.5^\circ$ (c 0.5, CHCl₃, 96% ee); **HLPC analysis:** IA, heptane/i-PrOH = 99.9/0.1, flow rate = 0.4 mL/min, sample dissolved in heptane, $\lambda = 266$ nm, retention time: $t_R$(minor) = 12.7 min, $t_R$(major) = 13.7 min, 96% ee.
**tert-Butyl 1-iodo-6-(triethylsilyl)-1,2,3,3a-tetrahydro-[1,3]dioxolo[4',5':5,6]indenono[1,2-c]cyclopenta[b]pyrrole-4(5H)-carboxylate ((R,S)-10a)**

The title compound was prepared using the same procedure as for the preparation of compound rac-10a (76% yield), as a light yellow solid. The spectral data of the product (R,S)-10a were identical with those of the racemic compound rac-10a and in agreement with those already reported. \(^{[2]}\)

**HLPC** analysis: IA, heptane/i-PrOH = 98/2, flow rate = 1 mL/min, sample dissolved in heptane, \(\lambda = 236\) nm, retention time: \(t_R(\text{major}) = 14.3\) min, \(t_R(\text{minor}) = 20.9\) min, 97% ee.

The title compound was prepared using the same procedure as for the preparation of compound rac-11a (91% yield), as an orange amorphous solid. The spectral data of the product (S,R)-11a were identical with those of the racemic compound rac-11.

**Specific rotation** $[\alpha]_D^{20} = +416.5^\circ$ (c 0.6, CHCl$_3$, 97% ee); **HPLC** analysis: IA, heptane/i-PrOH = 98/2, flow rate = 1 mL/min, sample dissolved in i-PrOH, $\lambda = 200$ nm, retention time: $t_R$(major) = 14.3 min, $t_R$(minor) = 20.9 min, 97% ee.
4-Methyl-3,3a,4,5-tetrahydro-[1,3]dioxolo[4′,5′:5,6]indeno[1,2-c]cyclopenta[b]pyrrole

$((S,R)-1a)$

The title compound was prepared using the same procedure as for the preparation of compound rac-$1a$ (24% yield), as a dark orange oil. The spectral data of the product $(S,R)-1a$ were identical with those of the racemic compound rac-$1a$.

**Specific rotation**  $[\alpha]_{D}^{20} = +199.2^\circ$ (c 0.6, MeOH, 95% ee). **HPLC** analysis: ODH, heptane/i-PrOH = 99.5/0.5, flow rate = 1 mL/min, sample dissolved in $i$-PrOH, $\lambda = 229$ nm, retention time: $t_R$ (minor) = 10.6 min, $t_R$ (major) = 13.8 min, 95% ee.
7. Biological testing

**hAChE and hBuChE Inhibition Assay**

The inhibitory activities of prepared compounds and standards against human recombinant AChE (E.C.3.1.1.7) and human plasma BuChE (E.C. 3.1.1.8) were determined using modified Ellman’s method\[6\] and expressed as IC\(_{50}\) (the concentration of the compound that is required to reduce 50% of cholinesterase activity). Human recombinant AChE, phosphate buffer (PB, pH = 7.4), 5,5'-dithio-bis(2-nitrobenzoic) acid (Ellman’s reagent, DTNB), acetylthiocholine (ATCh), butyrylthiocholine (BuTCh), and other used compounds were purchased from Sigma-Aldrich (Prague, Czech Republic). Human plasma was used as a source of BuChE and was prepared from heparinized human blood. Blood was centrifuged for 20 minutes (4 °C, 2300 \( \times \) g) by Hettich Universal 320R centrifuge. The plasma was separated and stored at -80 °C. During the measurement, 96-well microplates from polystyrene (ThermoFisher Scientific, Waltham, MA, USA) were used. The solutions of the corresponding cholinesterase in PB were prepared up to the final activity 0.002 U/µL. The assay medium (100 µL) consisted of cholinesterase (10 µL), DTNB (20 µL of 0.01 M solution), and PB (40 µL of 0.1 M solution). The solutions of the tested compounds (10 µL of different concentrations) were pre-incubated for 5 minutes in the assay medium and then a solution of the substrate (20 µL of 0.01 M ATCh or BuTCh iodide solution) was added to initiate the reaction. The increase of absorbance was measured at 412 nm using Multimode microplate reader Synergy 2 (BioTek Inc., Winooski, VT, USA). For the calculation of the resulting measured activity (the percentage of inhibition I) following formula was used:

\[
I = \left(1 - \frac{\Delta A_t}{\Delta A_0}\right) \times 100
\]

where \(\Delta A_t\) indicates absorbance change provided by adequate enzyme exposed to the corresponding inhibitor and \(\Delta A_0\) indicates absorbance change when a solution of PB was added instead of a solution of inhibitor. Software Microsoft Excel (Redmont, WA, USA) and GraphPad Prism version 6.07 for Windows (GraphPad Software, San Diego, CA, USA) were used for the statistical data evaluation.
**IC$_{50}$ Determination**

IC$_{50}$ values were determined only for compounds with more than 50% inhibition in the 100 μM screening test.

BuChE inhibition at different concentrations of compound **6c** (IC$_{50} = 35.8 ± 1.7$ μM)

![BuChE inhibition curve for compound 6c](image)

BuChE inhibition at different concentrations of compound **13b** (IC$_{50} = 73.9 ± 1.0$ μM)

![BuChE inhibition curve for compound 13b](image)
8. Molecular docking methods

The molecular models of each derivative were built using the Molefacture module from the VMD software package.[7] Docking calculations were carried out using AutoDock Vina version 1.1.2 programme[8] and the UCSF Chimera graphical interface.[9] AutoDock Vina outputs correspond to the total Gibbs free energy of binding (in kcal/mol). Ligand parameterization for molecular-mechanical calculations was performed via the ParamChem server.[10] The energy minimization of ligand-AChE/BChE complexes was performed using the VMD software package and the NAMD simulation programme.[11] The results were visualized and figures produced using the UCSF Chimera programme.[9]

For molecular docking studies, hAChE (4bdt) and hBuChE (7amz) were used.

**Figure S1**: Active site of human acetylcholinesterase (hAChE; PDB id: 4bdt). The main residues are represented in sticks. The catalytic triad amino acids (Glu334, His447, Ser203) are in cyan. The acyl-binding pocket amino acids (Phe338, Phe295, Trp236, Phe297) are in green. The choline-binding pocket amino acids (Trp439, Tyr337, Trp86) are in yellow. Peripheral site residues (Tyr341, Asp74, Tyr72, Tyr124, Trp286) are in grey.
Figure S2: Acetylcholine (the natural substrate) docked into the active site of hAChE.

Binding of huprine W to hAChE (Figure S3) is characterised by the following features:

i) (7S,11S)-isomers of huprines, like huprine W, perfectly match the molecular surface of the active site gorge.\textsuperscript{12–14} Chloroquinolinium moiety of huprines is sandwiched between Trp86 and Tyr337 of the choline-binding pocket. Further, Phe338, Phe295, and Trp236 of the acyl-binding pocket extend an aromatic stacking pile.

ii) Additional interactions include those of the polarised chlorine substituent with Trp439.\textsuperscript{13}

iii) The delocalized positive charge of protonated huprines reinforces interactions with the π electrons of Trp86 and Tyr337.\textsuperscript{12}

iv) Further, there is a hydrogen bond between the protonated quinolinium nitrogen and the main chain carbonyl of His447 of the catalytic triad.\textsuperscript{13}

v) The aniline nitrogen of huprines is stabilized by a hydrogen bond network that involves two structural water molecules conserved among most cholinesterases.\textsuperscript{12}

vi) The hydroxyl group of huprines is hydrogen-bonded to both the catalytic Ser203 residue and Gly122 in the oxyanion hole.\textsuperscript{13}
Figure S3: Complex of huprine W with hAChE (PDB id: 4bdt). The (7S,11S)-isomer of huprine perfectly matches the molecular surface of the active site. Chloroquinolinium moiety of huprine is sandwiched between Trp86 and Tyr337 of the choline-binding pocket. Further, Phe338, Phe295, and Trp236 of the acyl-binding pocket extend an aromatic stacking pile. Additional interactions include those of the polarized chlorine substituent with Trp439. The delocalized positive charge of protonated huprines reinforces interactions with the π-electrons of Trp86 and Tyr337. Further, there is a hydrogen bond between the protonated quinolinium nitrogen and the main chain carbonyl of His447 of the catalytic triad. The aniline nitrogen of huprines is stabilized by a hydrogen bond network that involves two structural water molecules conserved among most cholinesterases. The hydroxyl group of huprines is hydrogen-bonded to both the catalytic Ser203 residue and Gly122 in the oxyanion hole.
9. References

[10] “CGenFF Home,” can be found under https://cgenff.umaryland.edu/, **2022**.
10. Copies of $^1$H and $^{13}$C NMR spectra

Data of compounds 1-5........................................................................................................SI - 43
Data of compounds 6-9.....................................................................................................SI - 55
Data of compounds 10-13.............................................................................................SI - 70
Data of compounds SI2-SI4.........................................................................................SI - 84
Data of compounds SI5-SI8.........................................................................................SI - 90
(Z)-4a
(Z)-4a
(Z)-4b
(Z)-4b
(Z)-6c
(E)-9a
(E)-9a
(Z)-9b
(Z)-9b
(E)-9b
(E)-9b
SI - 76

11b
12b
13b
SI3