Highly Selective Cascade Couplings for the Syntheses of Functionalized Piperidinones and Bispidines

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Supporting Information

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General. Unless otherwise noted, all reactions were conducted under N₂ atmosphere using standard air-free manipulation techniques. Solvents were purchased from Fisher Scientific Company or Aldrich and used without further purification. Commercial reagents were purchased either from Aldrich and used without further purification. Chiral substrates were prepared according to Deng’s or Evan’s procedures.

High performance liquid chromatography (HPLC) analysis was performed using Agilent Technology 1100 series instrument with YMC Pack Pro C18 (240 x 4.6 mm I.D., 5 μm particle size) column. Proton nuclear magnetic resonance (¹H NMR) spectra were measured on Bruker Avance-400 or 500 instrument (400 or 500 MHz). Carbon nuclear magnetic resonance (¹³C NMR) spectra were measured on Bruker Avance-400 or 500 instrument (100 or 125 MHz) with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS).

1. Procedure for the one-pot preparation of trans pyrrolidinones 1

(4R,5R)-1-allyl-5-nitro-4-(2,4,5-trifluorophenyl)piperidin-2-one (1a):

To a solution of nitro malonate 4a (100 g, 0.2983 mol) and allyl amine (22.14 g, 0.3878 mol) in iPrOH (500 mL) and water (100 mL) at 50°C was added 37 wt% HCHO (25.42 g, 0.3132 mol) dropwise over 1-2 h and the reaction solution was stirred for additional 2-3 h at 50°C. 5N NaOH (104.4 mL, 0.522 mol) was added in one portion at 50°C. The reaction solution was stirred additional 1-2 h at 50°C. Conc. HCl (54.2 mL, 0.6563 mol) was added dropwise over 30 min. between 50 – 60°C. The reaction solution was stirred at 55- 60°C for 2-3 h and then cooled to 45°C and 5% NaHCO₃ (ca. 100 mL) was added dropwise to pH = 7-8. Then, water (100 mL) was added over 30 min. The resulting slurry was stirred at 45°C for additional 1-2 h and cooled to ambient temperature slowly. After aging overnight, the slurry was filtered. The wet cake was displacement washed with 50% aq. iPrOH (150ml x 2), and suction dried at ambient temperature to give 72 g of off-white to yellowish solid. 76 % yield. The isolated crystalline trans pyrrolidinone 1a is stable at ambient temperature and no epimerization to its corresponding cis isomer was observed within a year.

¹H-NMR (500 MHz, CDCl₃): δ 7.04 (m, 1 H), 7.01 (m, 1 H), 5.76 (m, 1 H), 5.26 (m, 2 H), 5.07 (m, 1 H), 4.13 (dd, J = 6.2, 14.9 Hz, 1 H), 4.02 (m, 2 H), 3.91 (dd, J = 6.9, 13.2 Hz, 1H), 3.72 (dd, J = 5.1, 13.2 Hz, 1 H), 2.84 (dd, J = 6.2, 17.5 Hz, 1 H), 2.72 (dd, J = 9.8, 17.5 Hz, 1 H). ¹³C-NMR (125 MHz, CDCl₃): δ 166.7, 156.0 (ddd, J = 2.5, 10.0, 245.0 Hz), 150.1 (td, J = 13.6, 251.3 Hz), 147.3 (ddd, J = 3.8, 12.5, 246.3 Hz), 131.7, 121.6 (td, J = 5.0, 15.0 Hz), 119.6, 117.1 (ddd, J = 1.3, 6.3, 20.0 Hz), 106.9 (dd, J = 21.3, 27.5 Hz), 83.1 (d, J = 1.3 Hz), 49.4, 47.7, 36.7, 35.0. Anal calc’d for C₁₄H₁₃F₃N₂O₃: C, 53.51; H, 4.17; N, 8.91; Found: C, 53.59; H, 4.12; N, 8.90.

The title compound was prepared under similar conditions described above. $^{1}$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.19 (m, 2 H), 6.98 (m, 1 H), 6.86 (m, 2 H), 4.98 (ddd, $J = 5.2, 6.9, 8.3$ Hz, 1 H), 4.76 (d, $J = 14.4$ Hz, 1 H), 4.37 (d, $J = 14.4$ Hz, 1 H), 3.98 (m, 1 H), 3.80 (dd, $J = 6.5, 13.1$ Hz, 1 H), 3.78 (s, 3 H), 3.58 (dd, $J = 5.1, 13.1$ Hz, 1 H), 2.85 (dd, $J = 6.2, 17.6$ Hz, 1 H), 2.72 (dd, $J = 9.4, 17.6$ Hz, 1 H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 166.8, 159.6, 155.84 (ddd, $J = 3.2, 9.6, 245.9$ Hz), 150.0 (ddd, $J = 13.6, 14.4, 253.1$ Hz), 147.2 (ddd, $J = 4.0, 12.8, 247.5$ Hz), 129.9, 127.7, 121.5 (td, $J = 4.8, 16.0$ Hz), 117.0 (dd, $J = 5.6, 20.0$ Hz), 114.4, 106.7 (dd, $J = 20.8, 28.0$ Hz) 82.8, 55.4, 49.7, 47.4, 37.3, 34.9. HRMS calc’d for C$_{19}$H$_{17}$F$_3$N$_2$O$_3$ [M+H]$^+$ 395.1213, found 395.1221.

The title compound and its cis isomer were prepared by deprotection of 1a in the presence of catalytic amount of RhCl$_3$ in nPrOH at 95 °C followed by aqueous HCl treatment as shown in Scheme S1. The crystalline trans product could be prepared under similar isomerization conditions described above. $^{1}$H-NMR (400 MHz, $d_4$-MeOH): $\delta$ 7.38 (m, 1 H), 7.20 (m, 1 H), 5.31 (m, 1 H), 4.11 (m, 1 H), 4.02 (m, 2 H), 3.86 (dd, $J = 7.7, 12.9$ Hz, 1H), 2.70 (dd, $J = 7.2, 17.7$ Hz, 1 H), 2.64 (dd, $J = 9.6, 17.7$ Hz, 1 H). $^{13}$C-NMR (100 MHz, $d_4$-MeOH): $\delta$ 172.3, 157.5 (ddd, $J = 4.8, 16.1$ Hz), 124.2 (td, $J = 4.8, 16.1$ Hz), 118.2 (dd, $J = 5.6, 21.7$ Hz), 107.4 (dd, $J = 20.9, 28.9$ Hz), 84.2, 44.5, 37.8, 36.0. HRMS calc’d for C$_{11}$H$_{8}$F$_3$N$_2$O$_3$ [M+H]$^+$ 275.0638, found 275.0641.

2. General procedure for the one-pot preparation of cis pyrrolidinones 1

To a solution of nitro malonate 4 (3.0 mmol) and allyl amine (223 mg, 3.9 mmol) in i-PrOH (5 mL) and water (1 mL) at 50-55 °C was added a solution of 37 wt% HCHO (256 mg, 3.15 mmol) in water (1 mL) dropwise over 1.5 h and the reaction solution was stirred for additional 3 h at 55 °C. 5N NaOH (0.9 mL, 4.5 mmol) was added in one portion at 55 °C. The reaction solution was stirred additional 2 h at 55 °C. Conc. HCl (1.25 mL, 15 mmol) was added dropwise between 50 – 60 °C. The reaction solution was stirred at 55-
60 °C for 3-5 h and then cooled to ambient temperature. EtOAc (80 mL) was added and the organic phase was washed with water (10 mL) followed by brine (10 mL). Upon concentration, the residue was purified on silica gel column eluting with EtOAc/hexane to afford the desired cis pyrrolidinone 1.

**cis pyrrolidinone 1.**

\[ (4R,5S)-1\text{-allyl-4-(4-methoxyphenyl)-5-nitropiperidin-2-one} \]

\[ \text{1H-NMR (400 MHz, CDCl}_3\text{): } \delta 7.04 \text{ (d, } J = 6.8 \text{ Hz, 2 H), 6.88 \text{ (d, } J = 6.8 \text{ Hz, 2 H), 5.80 \text{ (m, 1 H), 5.28 \text{ (s, 1 H), 5.25 \text{ (dd, } J = 1.1, 6.3 \text{ Hz, 1 H),}} \]
\[ \quad 5.02 \text{ (dd, } J = 5.2, 9.9 \text{ Hz, 1 H), 4.17 \text{ (dd, } J = 6.1, 15.0 \text{ Hz, 1 H), 4.04 \text{ (dd, } J = 6.1, 15.0 \text{ Hz, 1 H), 3.84 \text{ (m, 1 H), 3.80 \text{ (s, 3 H), 3.73 \text{ (dd, } J = 6.3, 13.5 \text{ Hz, 1 H),}} \]
\[ \quad 3.66 \text{ (dd, } J = 5.1, 13.5 \text{ Hz, 1 H), 3.03 \text{ (dd, } J = 7.5, 17.9 \text{ Hz, 1 H), 2.90 \text{ (dd, } J = 6.4, 17.9 \text{ Hz, 1 H).} \]
\[ \text{13C-NMR (100 MHz, CDCl}_3\text{): } \delta 167.6, 159.8, 131.80, 128.6, 128.2, 119.2, 114.7, 82.5, 55.5, 49.5, 46.1, 40.6, 34.4. \]

HRMS calc’d for C\(_{15}\)H\(_{18}\)N\(_2\)O\(_4\) [M+H]+ 291.1339, found 291.1333.

**cis pyrrolidinone 1.**

\[ (4R,5S)-1\text{-allyl-4-(4-fluorophenyl)-5-nitropiperidin-2-one} \]

\[ \text{1H-NMR (500 MHz, CDCl}_3\text{): } \delta 7.11 \text{ (m, 2 H), 7.05 \text{ (m, 2H), 5.78 \text{ (m, 1 H), 5.28 \text{ (m, 1 H), 5.04 \text{ (m, 1 H), 4.18 \text{ (dd, } J = 6.1, 15.0 \text{ Hz, 1 H),}} \]
\[ \quad 4.03 \text{ (dd, } J = 6.4, 15.0 \text{ Hz, 1 H), 3.87 \text{ (m, 1 H), 3.74 \text{ (dd, } J = 6.0, 13.6 \text{ Hz, 1 H),}} \]
\[ \quad 3.69 \text{ (dd, } J = 5.3, 13.6 \text{ Hz, 1 H), 3.02 \text{ (dd, } J = 7.9, 17.9 \text{ Hz, 1 H), 2.91 \text{ (dd, } J = 6.4, 17.9 \text{ Hz, 1 H).} \]
\[ \text{13C-NMR (125 MHz, CDCl}_3\text{): } \delta 167.2, 162.8 (d, } J = 246.3 \text{ Hz), 132.1 \text{ (d, } J = 2.5 \text{ Hz), 131.7, 129.2 (d, } J = 7.5 \text{ Hz), 119.3, 116.3 \text{ (d, } J = 21.3 \text{ Hz), 82.3, 49.5, 46.2, 40.6, 34.1.} \]

HRMS calc’d for C\(_{14}\)H\(_{16}\)FN\(_2\)O\(_3\) [M+H]+ 279.1149, found 279.1149.

**cis pyrrolidinone 1.**

\[ (4R,5S)-1\text{-allyl-4-(4-methylphenyl)-5-nitropiperidin-2-one} \]

\[ \text{1H-NMR (500 MHz, CDCl}_3\text{): } \delta 7.16 \text{ (d, } J = 8.0, 2 \text{ H), 7.01 \text{ (d, } J = 8.0 \text{ Hz, 2 H), 5.80 \text{ (m, 1 H), 5.28 \text{ (s, 1 H), 5.25 \text{ (m 1 H), 5.03 \text{ (m, 1 H), 4.18 \text{ (dd, } J = 6.1, 15.0 \text{ Hz, 1 H),}} \]
\[ \quad 4.04 \text{ (dd, } J = 6.3, 15.0 \text{ Hz, 1 H), 3.85 \text{ (m, 1 H), 3.74 \text{ (dd, } J = 6.3 \text{ Hz, 13.5 Hz, 1 H), 3.66 \text{ (dd, } J = 5.1, 13.5 \text{ Hz, 1 H),}} \]
\[ \quad 3.05 \text{ (dd, } J = 7.6, 17.9 \text{ Hz, 1 H), 2.91 \text{ (dd, } J = 6.4, 17.9 \text{ Hz, 1 H), 2.34 \text{ (s, 3 H).} \]
\[ \text{13C-NMR (125 MHz, CDCl}_3\text{): } \delta 167.6, 138.6, 133.2, 131.8, 130.0, 127.4, 119.2, 82.4, 49.5, 46.2, 41.0, 34.2, 21.3.} \]

HRMS calc’d for C\(_{15}\)H\(_{19}\)N\(_2\)O\(_3\) [M+H]+ 275.1385, found 275.1385.

**cis pyrrolidinone 1.**

\[ (4R,5S)-1\text{-allyl-4-(4-chlorophenyl)-5-nitropiperidin-2-one} \]

\[ \text{1H-NMR (500 MHz, CDCl}_3\text{): } \delta 7.32 \text{ (d, } J = 8.5 \text{ Hz, 2 H), 7.07 \text{ (d, } J = 8.5 \text{ Hz, 2 H), 5.79 \text{ (m, 1 H), 5.28 \text{ (m, 1 H), 2.25 \text{ (m, 1 H), 5.04 \text{ (m, 1 H), 4.18 \text{ (dd, } J = 6.1, 14.9 \text{ Hz, 1 H),}} \]
\[ \quad 4.04 \text{ (dd, } J = 6.3, 14.9 \text{ Hz, 1 H), 3.86 \text{ (m, 1 H), 3.74 \text{ (dd, } J = 6.1, 13.6 \text{ Hz, 1 H), 3.69 \text{ (dd, } J = 5.2, 13.6 \text{ Hz, 1 H), 3.02}} \]
\[ \quad \text{ (dd, } J = 7.8, 17.8 \text{ Hz, 1 H), 2.91 \text{ (dd, } J = 6.3, 17.8 \text{ Hz, 1 H).} \]
\[ \text{13C-NMR (125 MHz, CDCl}_3\text{): } \delta 167.1, 134.8, 131.7, 129.6, 128.9, 119.4, 82.1, 49.5, 46.2, 40.7, 34.0.} \]

HRMS calc’d for C\(_{14}\)H\(_{16}\)ClN\(_2\)O\(_3\) [M+H]+ 295.0842, found 295.0844.
(4R,5S)-1-allyl-5-nitro-4-pyridin-3-ylpiperidin-2-one: \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.52 (m, 2 H), 7.55 (m, 1 H), 7.28 (m, 1 H), 5.70 (m, 1 H), 5.21 (m, 2 H), 5.01 (m, 1 H), 4.07 (m, 1 H), 3.99 (dd, \(J = 6.3, 14.9\) Hz, 1 H), 3.86 (m, 2 H), 3.67 (dd, \(J = 5.2, 13.1\) Hz, 1 H), 2.82 (dd, \(J = 6.1, 17.7\) Hz, 1 H), 2.68 (dd, \(J = 9.6, 17.7\) Hz, 1 H). \(^1\)\(^3\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 166.6, 149.7, 148.9, 134.6, 133.8, 131.5, 124.1, 119.3, 84.4, 49.2, 47.5, 40.3, 35.8. HRMS calc’d for C\(_{13}\)H\(_{16}\)N\(_3\)O\(_3\) [M+H]\(^+\) 262.1186, found 262.1190.

(4R,5S)-1-allyl-5-nitro-4-phenylpiperidin-2-one: \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.35 (m, 3 H), 7.13 (m, 2 H), 5.79 (m, 1 H), 5.28 (s, 1 H), 5.26 (m, 1 H), 5.07 (m, 1 H), 4.19 (dd, \(J = 6.1, 15.0\) Hz, 1 H), 4.05 (dd, \(J = 6.3, 15.0\) Hz, 1 H), 3.88 (m, 1 H), 3.75 (dd, \(J = 6.1, 13.5\) Hz, 1 H), 3.69 (dd, \(J = 5.1, 13.5\) Hz, 1 H), 3.08 (dd, \(J = 7.8, 17.9\) Hz, 1 H), 2.93 (dd, \(J = 6.4, 17.9\) Hz, 1 H). \(^1\)\(^3\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 167.3, 136.1, 131.6, 129.1, 128.5, 127.3, 119.0, 82.2, 49.3, 46.1, 41.0, 33.8. HRMS calc’d for C\(_{14}\)H\(_{17}\)N\(_2\)O\(_3\) [M+H]\(^+\) 261.1234, found 262.1235.

3. General procedure for the one-step preparation of bispidines 2

To a solution of nitro malonate 4 (1.5 mmol) in i-PrOH (7 mL) and water (1.5 mL) at ambient temperature was added t-BuCO\(_2\)H (77 mg, 0.75 mmol) followed by ally amine (214 mg, 3.75 mmol). Then, the reaction solution was heated to 55 °C and a solution of 37 wt% HCHO (268 mg, 3.3 mmol) in water (1 mL) was added dropwise over 2.5 h. After addition, the reaction solution was agitated at 55 °C for 5 – 10 h. EtOAc (80 mL) was added and the organic phase was washed with water (10 mL) followed by brine (10 mL). Upon concentration, the residue was purified on silica gel column eluting with EtOAc/hexane to afford the desired 2.

4. General procedure for the one-step preparation of bispidines 3

To a solution of nitro malonate 4 (1.5 mmol) in i-PrOH (7 mL) and water (1.5 mL) at ambient temperature was added MeSO\(_3\)H (72 mg, 0.75 mmol) followed by ally amine (214 mg, 3.75 mmol). Then, the reaction solution was heated to 55 °C and a solution of 37 wt% HCHO (487 mg, 6.0 mmol) in water (1 mL) was added dropwise over 2.5 h. After addition, the reaction solution was agitated at 55 °C for 5 – 10 h. EtOAc (80 mL) was added and the organic phase was washed with water (10 mL) followed by brine (10 mL). Upon concentration, the residue was purified on silica gel column eluting with EtOAc/hexane to afford the desired 3.
H), 5.72 (m, 1 H), 5.45 (dd, J = 0.7, 17.2 Hz, 1 H), 5.39 (d, J = 10.1 Hz, 1 H), 5.23 (m, 2 H), 4.40 (dd, J = 5.9, 14.7 Hz, 1 H), 4.29 (s, 1 H), 4.17 (dd, J = 1.6, 13.3 Hz, 1 H), 3.99 (dd, J = 6.8, 14.7 Hz, 1 H), 3.77 (d, J = 13.3 Hz, 1 H), 3.53 (dd, J = 1.3, 11.6 Hz, 1 H), 3.46 (s, 3 H), 3.37 (dd, J = 1.0, 10.4 Hz, 1 H), 3.24 (dd, J = 6.0, 13.6 Hz, 1 H), 3.10 (dd, J = 6.9, 13.6 Hz, 1 H), 2.94 (dd, J = 1.2, 10.3 Hz, 1 H), 2.86 (d, J = 11.5 Hz, 1 H). 13C-NMR (100 MHz, CDCl3): δ 168.1, 166.3, 156.8 (ddd, J = 3.2, 8.8, 248.2 Hz), 150.0 (td, J = 13.7, 253.8 Hz), 146.9 (ddd, J = 3.2, 12.0, 245.7 Hz), 133.0, 130.8, 120.5, 120.1, 118.0 (td, J = 5.3, 13.7 Hz), 117.4 (m), 106.0 (dd, J = 20.0, 30.0 Hz), 84.2, 65.7, 60.4, 60.0, 56.5, 52.7, 50.1, 49.9, 43.6. HRMS calc’d for C21H23F3N3O5 [M+H]+ 454.1584, found 454.1594.

(1R,5R,9R)-3,7-diallyl-5-nitro-9-(2,4,5-trifluorophenyl)-3,7-diaza-bicyclo[3.3.1]nonane-2,8-dione (2a)

1H-NMR (500 MHz, CDCl3): δ 6.99 (m, 1 H), 6.85 (m, 1 H), 5.80 (m, 2 H), 5.39 (d, J = 7.9 Hz, 1 H), 5.36 (dd, J = 1.1, 8.0 Hz, 1 H), 5.33 (s, 1 H), 5.28 (dd, J = 1.2, 17.1 Hz, 1 H), 4.45 (s, 1 H), 4.22 (dd, J = 1.1, 12.8 Hz, 1 H), 4.15 (m, 4 H), 4.05 (dd, J = 6.4, 15.0 Hz, 1 H), 3.71 (d, J = 2.3 Hz, 1 H), 3.70 (s, 1 H), 3.68 (s, 1 H). 13C-NMR (125 MHz, CDCl3): δ 163.7, 162.3, 156.4 (ddd, J = 2.8, 9.2, 248.6 Hz), 150.9 (td, J = 14.2, 255.3 Hz), 147.4 (ddd, J = 3.7, 12.6, 247.3 Hz), 131.2, 130.6, 121.5, 120.2, 117.5 (td, J = 4.9, 15.1 Hz), 116.4 (ddd, J = 1.5, 4.3, 20.3 Hz), 107.0 (dd, J = 17.0, 24.0 Hz), 84.2, 56.9, 52.8, 50.6, 50.1, 49.1, 39.3. HRMS calc’d for C19H19F3N3O4 [M+H]+ 410.1322, found 410.1311. Anal calc’d for C19H18F3N3O4: C, 55.75; H, 4.43; N, 10.26; Found: C, 55.67; H, 4.41; N, 10.22.

Methyl (1S,5S,9S)-3,7-diallyl-9-(4-methylphenyl)-5-nitro-2-oxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate

Methyl (1R,5R,9R)-3,7-diallyl-9-(4-methylphenyl)-5-nitro-3,7-diaza-bicyclo[3.3.1]nonane-2,8-dione (2a): 1H-NMR (500 MHz, CDCl3): δ 7.08 (d, J = 8.4 Hz, 2 H), 7.06 (d, J = 8.4 Hz, 2 H), 5.76 (m, 1 H), 5.29 (m, 1 H), 4.56 (m, 1 H), 4.13 (dd, J = 2.1, 12.9 Hz, 1 H), 3.84 (dd, J = 7.0, 14.8 Hz, 1 H), 3.78 (s, 1 H), 3.64 (dd, J = 0.9, 12.9 Hz, 1 H), 3.47 (dd, J = 1.6, 11.2 Hz, 1 H), 3.33 (s, 3 H), 3.32 (dd, J = 1.6, 11.2 Hz, 1 H), 3.21 (dd, J = 1.3, 6.0, 13.5 Hz, 1 H), 3.06 (dd, J = 6.9, 13.5 Hz, 1 H), 2.99 (dd, J = 2.0, 10.3 Hz, 1 H), 2.86 (d, J = 11.2 Hz, 1 H), 2.29 (s, 3 H). 13C-NMR (125 MHz, CDCl3): δ 168.9, 166.6, 138.5, 133.3, 131.4, 129.7, 129.6, 129.3, 119.39, 119.37, 85.1, 65.1, 60.9, 59.9, 56.5, 54.1, 52.1, 49.6, 49.4, 21.0. HRMS calc’d for C22H28N3O5 [M+H]+ 414.2024, found 414.2012.

(1R,5R,9R)-3,7-diallyl-9-(4-methylphenyl)-5-nitro-3,7-diaza-bicyclo[3.3.1]nonane-2,8-dione
3.52 (dd, J = 1.7, 12.5 Hz, 1 H), 2.33 (s, 3 H). 13C-NMR (125 MHz, CDCl3): δ 164.7, 163.3, 139.2, 131.2, 131.0, 130.13, 130.09, 127.3, 120.5, 119.5, 85.4, 55.9, 52.7, 49.88, 49.87, 48.6, 45.4, 21.0. HRMS calc’d for C20H24N3O4 [M+H]+ 370.1761, found 370.1759. Anal calc’d for C20H23N3O4: C, 65.03; H, 6.28; N, 11.37; Found: C, 64.97; H, 6.32; N, 11.39.

**Methyl (1S,5S,9S)-3,7-diallyl-9-phenyl-5-nitro-2-oxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate:**

1H-NMR (500 MHz, CDCl3): δ 7.27 (m, 3 H), 7.21 (m, 2 H), 5.89 (m, 1 H), 5.74 (m, 1 H), 5.43 (dd, J = 1.3, 17.2 Hz, 1 H), 5.34 (dd, J = 0.9, 10.3 Hz, 1 H), 5.24 (m, 1 H), 5.21 (s, 1 H), 4.58 (m, 1 H), 4.15 (dd, J = 2.1, 13.0 Hz, 1 H), 3.85 (dd, J = 6.9, 14.9 Hz, 1 H), 3.81 (s, 1 H), 3.67 (d, J = 13.0 Hz, 1 H), 3.48 (dd, J = 1.5, 11.2 Hz, 1 H), 3.34 (dd, J = 1.4, 10.3 Hz, 1 H), 3.30 (s, 1 H), 3.22 (dd, J = 6.0, 13.5 Hz, 1 H), 3.07 (dd, J = 6.9, 13.5 Hz, 1 H), 2.99 (dd, J = 2.0, 10.3 Hz, 1 H), 2.88 (d, J = 11.2 Hz, 1 H). 13C-NMR (125 MHz, CDCl3): δ 169.1, 166.7, 133.4, 133.1, 131.5, 130.0, 128.9, 128.8, 119.7, 85.2, 65.4, 61.1, 60.1, 56.8, 54.7, 52.3, 49.8, 49.6. HRMS calc’d for C21H26N3O5 [M+H]+ 400.1867, found 400.1865. Anal calc’d for C21H25N3O5: C, 63.14; H, 6.31; N, 10.52; Found: C, 62.79; H, 6.30; N, 10.38.

**Methyl (1R,5R,9R)-3,7-diallyl-5-nitro-9-phenyl-3,7-diazabicyclo[3.3.1]-nonane-2,8-dione**

1H-NMR (500 MHz, CDCl3): δ 7.35 (m, 3 H), 7.06 (m, 2 H), 5.79 (m, 2 H), 5.30 (m, 4 H), 4.30 (m, 1 H), 4.18 (m, 2 H), 4.14 (dd, J = 6.1, 15.1 Hz, 1 H), 4.07 (dd, J = 6.1, 15.1 Hz, 1 H), 3.95 (dd, J = 7.0, 14.6 Hz, 1 H), 3.84 (d, J = 2.0 Hz, 1 H), 3.82 (d, J = 13.1 Hz, 1 H), 3.69 (d, J = 13.1 Hz, 1 H), 3.54 (dd, J = 1.8, 12.6 Hz, 1 H). 13C-NMR (125 MHz, CDCl3): δ 164.8, 163.4, 133.4, 131.4, 131.1, 129.7, 129.5, 127.8, 120.8, 119.8, 85.5, 56.2, 52.8, 50.9, 50.07, 48.8, 45.9. HRMS calc’d for C19H22ClN3O4 [M+H]+ 356.1605, found 356.1596.

**Methyl (1S,5S,9S)-3,7-diallyl-9-(4-chlorophenyl)-5-nitro-2-oxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate:**

1H-NMR (500 MHz, CDCl3): δ 7.25 (m, 2 H), 7.16 (m, 2 H), 5.88 (m, 1 H), 5.74 (m, 1 H), 5.43 (m, 1 H), 5.34 (dd, J = 1.1, 10.2 Hz, 1 H), 5.21 (m, 2 H), 4.53 (m, 1 H), 4.07 (dd, J = 2.1, 13.1 Hz, 1 H), 3.85 (6.9, 14.8 Hz, 1 H), 3.80 (s, 1 H), 3.67 (d, J = 13.1 Hz, 1 H), 3.49 (dd, J = 1.5, 11.3 Hz, 1 H), 3.37 (s, 3 H), 3.34 (dd, J = 1.5 Hz, 10.3 Hz, 1 H), 3.21 (m, 1 H), 3.07 (dd, J = 7.0, 13.5 Hz, 1 H), 2.97 (dd, J = 2.0, 10.3 Hz, 1 H), 2.85 (d, J = 11.3 Hz, 1 H). 13C-NMR (125 MHz, CDCl3): δ 168.8, 166.5, 135.0, 133.3, 131.2, 131.4, 131.3, 129.0, 119.9, 119.8, 85.1, 65.3, 61.0, 60.1, 56.6, 53.9, 52.5, 49.9, 49.5. HRMS calc’d for C21H25ClN3O5 [M+H]+ 434.1477, found 434.1477.
(1R,5R,9R)-3,7-diallyl-9-(4-chlorophenyl)-5-nitro-3,7-diazabicyclo[3.3.1]nonane-2,8-dione: ¹H-NMR (500 MHz, CDCl₃): δ 7.33 (m, 2 H), 7.00 (m, 2 H), 5.77 (m, 2 H), 5.30 (m, 4 H), 4.27 (m, 1 H), 4.15 (m, 2 H), 4.13 (m, 1 H), 4.06 (m, 1 H), 3.97 (dd, J = 7.0, 14.5 Hz, 1 H), 3.81 (d, J = 2.0 Hz, 1 H), 3.79 (d, J = 12.8 Hz, 1 H), 3.69 (d, J = 13.1 Hz, 1 H), 3.56 (dd, J = 1.8, 12.5 Hz, 1 H). ¹³C-NMR (125 MHz, CDCl₃): δ 164.5, 163.1, 135.7, 131.9, 131.3, 130.9, 129.9, 129.2, 121.0, 119.9, 85.2, 56.1, 52.7, 50.1, 50.0, 48.8, 45.3. HRMS calc’d for C₁₉H₂₁ClN₃O₄ [M+H]⁺ 390.1215, found 390.1213.

Methyl (1S,5S,9S)-3,7-diallyl-9-(4-methoxyphenyl)-5-nitro-2-oxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate: ¹H-NMR (500 MHz, CDCl₃): δ 7.12 (d, J = 8.9 Hz, 2 H), 6.78 (d, J = 8.9 Hz, 2 H), 5.88 (m, 1 H), 5.73 (m, 1 H), 5.43 (m, 1 H), 5.33 (m, 1 H), 5.23 (m, 1 H), 5.20 (s, 1 H), 4.57 (m, 1 H), 4.11 (dd, J = 1.9, 13.0 Hz, 1 H), 3.83 (dd, J = 7.0, 14.8 Hz, 1 H), 3.77 (s, 4 H), 3.65 (d, J = 13.0 Hz, 1 H), 3.47 (dd, J = 1.3, 11.2 Hz, 1 H), 3.34 (s, 3 H), 3.32 (d, J = 10.3 Hz, 1 H), 2.98 (dd, J = 1.5, 10.3 Hz, 1 H), 2.86 (d, J = 11.2 Hz, 1 H). ¹³C-NMR (125 MHz, CDCl₃): δ 169.1, 166.8, 159.9, 133.5, 131.6, 124.8, 119.6, 114.2, 85.3, 65.3, 61.1, 60.1, 56.8, 55.4, 54.0, 52.4, 49.8, 49.5. Anal calc’d for C₂₂H₂₇N₃O₆: C, 61.53; H, 6.34; N, 9.78; Found: C, 61.36; H, 6.32; N, 9.77.

(1R,5R,9R)-3,7-diallyl-5-nitro-9-(4-methoxyphenyl)-3,7-diazabicyclo[3.3.1]nonane-2,8-dione: ¹H-NMR (500 MHz, CDCl₃): δ 6.97 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 5.78 (m, 2 H), 5.31 (m, 3 H), 5.26 (m, 1 H), 4.29 (dd, J = 6.2, 14.6 Hz, 1 H), 4.14 (m, 3 H), 4.05 (dd, J = 1.1, 9.1 Hz, 1 H), 3.95 (dd, J = 7.0, 14.6 Hz, 1 H), 3.81 (m, 2 H), 3.80 (s, 3 H), 3.68 (d, J = 13.1 Hz, 1 H), 3.52 (dd, J = 1.7, 12.5 Hz, 1 H). ¹³C-NMR (125 MHz, CDCl₃): δ 164.9, 163.5, 160.3, 131.4, 131.2, 129.0, 125.1, 120.7, 119.7, 115.0, 85.7, 56.0, 55.0, 50.9, 50.5, 48.8, 45.3. HRMS calc’d for C₂₀H₂₄N₃O₅ [M+H]⁺ 386.1711, found 386.1714. Anal calc’d for C₂₀H₂₃N₃O₅: C, 62.33; H, 6.01; N, 10.90; Found: C, 62.26; H, 6.58; N, 10.98.

Methyl (1S,5S,9S)-3,7-diallyl-9-(2,4-dimethoxyphenyl)-5-nitro-2-oxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate: ¹H-NMR (500 MHz, CDCl₃): δ 7.13 (d, J = 9.0 Hz, 1 H), 6.41 (m, 2 H), 5.87 (m, 1 H), 5.76 (m, 1 H), 5.42 (dd, J = 1.3, 17.1 Hz, 1 H), 5.33 (d, J = 17.1 Hz, 1 H), 5.23 (dd, J = 1.1, 9.1 Hz, 1 H), 5.21 (s, 1 H), 4.56 (s, 1 H), 4.48 (dd, J = 4.9, 14.7 Hz, 1 H), 4.32 (d, J = 13.0 Hz, 1 H), 3.80 (dd, J = 5.8, 14.0 Hz, 1 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.66 (d, J = 13.0 Hz, 1 H), 3.45 (dd, J = 1.2, 11.3 Hz, 1 H), 3.35 (s, 3 H), 3.30 (dd, J = 0.9, 10.2 Hz, 1 H), 3.23 (dd, J = 6.0, 13.5 Hz, 1 H), 3.09 (dd, J = 6.9, 13.5 Hz, 1 H), 3.03 (dd, J = 1.3, 10.2 Hz, 1 H), 2.92 (d, J =
11.3 Hz, 1 H). $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 169.1, 167.2, 160.7, 159.4, 133.4, 131.6, 129.1, 119.7, 119.6, 114.8, 104.8, 98.9, 84.8, 65.7, 60.9, 60.3, 56.7, 56.2, 55.4, 52.2, 50.5, 49.8, 43.8. HRMS calc’d for C$_{23}$H$_{30}$N$_3$O$_7$ [M+H]$^+$ 460.2078, found 460.2068.

(1R,5R,9R)-3,7-diallyl-5-nitro-9-(2,4-dimethoxyphenyl)-3,7-diazabicyclo[3.3.1]nonane-2,8-dione: $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 6.82 (d, $J = 9.2$ Hz, 1 H), 6.42 (m, 2 H), 5.78 (m, 2 H), 5.29 (m, 4 H), 4.04 (s, 1 H), 4.37 (d, $J = 13.0$ Hz, 1 H), 4.25 (dd, $J = 6.3$, 14.6 Hz, 1 H), 4.16 (m, 1 H), 4.14 (d, $J = 12.1$ Hz, 1 H), 4.07 (d, $J = 6.3$, 15.0 Hz, 1 H), 3.92 (dd, $J = 7.0$, 14.5 Hz, 1 H), 3.80 (s, 3 H), 3.72 (d, $J = 2.0$ Hz, 1 H), 3.71 (s, 3 H), 3.60 (d, $J = 12.9$ Hz, 1 H), 3.53 (s, 3 H), 3.45 (dd, $J = 1.5$, 12.7 Hz, 1 H). $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 165.4, 163.8, 161.4, 159.1, 131.7, 131.5, 128.7, 120.6, 119.6, 114.3, 105.1, 99.1, 85.5, 56.2, 55.6, 55.4, 53.3, 50.9, 49.8, 49.0, 40.9. HRMS calc’d for C$_{21}$H$_{26}$N$_3$O$_6$ [M+H]$^+$ 416.1816, found 416.1831.

Methyl (1S,5S,9S)-3,7-diallyl-5-nitro-2-oxo-9-pyridin-3-yl-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate: $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 8.54 (d, $J = 4.3$ Hz, 1 H), 8.47 (d, $J = 1.9$ Hz, 1 H), 7.58 (d, $J = 8.0$ Hz, 1 H), 7.23 (dd, $J = 4.8$, 8.0 Hz, 1 H), 5.91 (m, 1 H), 5.73 (m, 1 H), 5.44 (m, 1 H), 5.36 (m, 1 H), 5.24 (m, 2 H), 4.55 (dd, $J = 5.5$, 14.8 Hz, 1 H), 4.08 (dd, $J = 1.7$, 13.2 Hz, 1 H), 3.85 (dd, $J = 6.9$, 14.8 Hz, 1 H), 3.82 (s, 1 H), 3.74 (d, $J = 13.2$ Hz, 1 H), 3.53 (d, $J = 11.3$ Hz, 1 H), 3.37 (d, $J = 10.4$ Hz, 1 H), 3.34 (s, 3 H), 3.23 (dd, $J = 6.0$, 13.5 Hz, 1 H), 3.09 (dd, $J = 6.9$, 13.5 Hz, 1 H), 2.97 (dd, $J = 1.8$, 10.4 Hz, 1 H), 2.87 (d, $J = 11.4$ Hz, 1 H). $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 168.6, 166.4, 151.3, 150.2, 137.2, 133.2, 131.2, 129.3, 123.5, 120.0, 119.9, 84.9, 65.3, 60.8, 60.1, 56.6, 52.5, 52.1, 49.9, 49.5. HRMS calc’d for C$_{20}$H$_{25}$N$_4$O$_5$ [M+H]$^+$ 401.1820, found 401.1815.

(1R,5R,9R)-3,7-diallyl-5-nitro-9-(4-fluorophenyl)-3,7-diazabicyclo[3.3.1]nonane-2,8-dione: $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 8.62 (dd, $J = 1.5$, 4.8 Hz, 1 H), 8.38 (d, $J = 2.4$ Hz, 1 H), 7.40 (m, 1 H), 7.31 (dd, $J = 4.8$, 7.9 Hz, 1 H), 5.77 (m, 2 H), 5.32 (m, 4 H), 4.29 (m, 1 H), 4.2 (s, 1 H), 4.16 (dd, $J = 1.4$, 13.1 Hz, 1 H), 4.08 (m, 2 H), 3.97 (dd, $J = 7.0$, 14.6 Hz, 1 H), 3.85 (dd, $J = 1.0$, 12.9 Hz, 1 H), 3.81 (d, $J = 2.1$ Hz, 1 H), 3.73 (d, $J = 13.1$ Hz, 1 H), 3.65 (dd, $J = 1.7$, 13.1 Hz, 1 H). $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 164.2, 162.7, 150.9, 149.4, 135.4, 131.2, 130.8, 129.5, 124.3, 121.1, 120.0, 84.9, 65.3, 52.5, 50.1, 50.0, 48.9, 43.9. HRMS calc’d for C$_{18}$H$_{23}$N$_4$O$_4$ [M+H]$^+$ 357.1557, found 357.1551.

Methyl (1S,5S,9S)-3,7-diallyl-9-(4-fluorophenyl)-5-nitro-2-oxo-3,7-diazabicyclo[3.3.1]nonane-1-carboxylate: $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.20 (dd, $J = 8.4$, 11.9 Hz, 2 H), 6.96 (t, $J = 8.5$ Hz, 2 H),
5.88 (m, 1 H), 5.73 (m 1 H), 5.43 (dd, J = 1.3, 17.3 Hz, 1 H), 5.34 (dd, J = 0.9, 10.2 Hz, 1 H), 5.23 (m, 1 H), 5.21 (s, 1 H), 4.54 (dd, J = 5.5, 14.8 Hz, 1 H), 4.09 (dd, J = 2.0, 13.1 Hz, 1 H), 3.85 (dd, J = 7.0, 14.8 Hz, 1 H), 3.81 (s, 1 H), 3.67 (d, J = 13.1 Hz, 1 H), 3.48 (dd, J = 1.3, 11.3 Hz, 1 H), 3.34 (s, 3 H), 3.33 (dd, J = 1.1, 10.2 Hz, 1 H), 3.21 (dd, J = 6.1, 13.5 Hz, 1 H), 3.08 (dd, J = 7.0, 13.5 Hz, 1 H), 2.98 (dd, J = 1.8, 10.4 Hz, 1 H), 2.86 (d, J = 11.3 Hz, 1 H). 

13C-NMR (125 MHz, CDCl3): δ 168.9, 166.5, 162.9 (d, J = 247.3 Hz), 133.2, 131.8 (d, J = 7.4 Hz), 131.3, 128.8 (d, J = 3.4 Hz), 119.8, 115.8 (d, J = 21.3 Hz), 85.1, 65.2, 60.9, 60.1, 56.7, 53.8, 52.4, 49.8, 49.4. HRMS calc’d for C21H25FN3O5 [M+H]+ 418.1773, found 418.1780.

**NO**

(1R,5R,9R)-3,7-diallyl-9-(4-fluorophenyl)-5-nitro-3,7-diazabicyclo-[3.3.1]nonane-2,8-dione: 1H-NMR (500 MHz, CDCl3): δ 7.05 (d, J = 6.6 Hz, 4 H), 5.78 (m, 2 H), 5.31 (m, 4 H), 4.28 (m, 1 H), 4.16 (m, 2H), 4.12 (m, 1 H), 4.07 (m, 1 H), 3.96 (dd, J = 7.0, 14.5 Hz, 1 H), 3.82 (d, J = 2.0 Hz, 1 H), 3.80 (m, 1 H), 3.69 (d, J = 13.1 Hz, 1 H), 3.56 (d, J = 1.7, 12.7 Hz, 1 H). 13C-NMR (125 MHz, CDCl3): δ 164.5, 163.2 (d, J = 249.9 Hz), 163.1, 131.3, 130.9, 129.6 (d, J = 8.3 Hz), 129.2 (d, J = 3.3 Hz), 120.9, 119.8, 116.7 (d, J = 21.7 Hz), 85.4, 56.1, 52.8, 50.1, 49.9, 48.8, 45.2. HRMS calc’d for C19H21FN3O4 [M+H]+ 374.1511, found 374.1509.