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# Annulations of isoquinoline and carboline ring systems: synthesis of 8-oxoprotoberberine derivatives

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## SUPPLEMENTARY INFORMATION

### Table of contents

**1. General** **S2**

**2. Synthetic procedures** **S2**

**2.1. General procedure for the synthesis of dienes** **S2**

**2.2. General procedure for the synthesis of cycloadducts** **S3**

**2.3. General procedure for the synthesis of oxoprotoberberines** **S4**

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## 1. General

The NMR spectra were recorded on a Bruker Avance III (500 MHz) spectrometer. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as the internal standard. Deuterochloroform was used as a solvent, unless otherwise stated. Mass spectral data were recorded using Agilent MSD TOF spectrometer coupled with Agilent 1200 HPLC. IR spectra were recorded on a IR Termo Scientific NICOLET iS10 (4950) spectrometer. Flash chromatography employed silica gel 60 (230-400 mesh) while thin layer chromatography was carried out using alumina plates with 0.25mm silica layer (Kieselgel 60 $F_{254}$, Merck). The solvents were purified by distillation before use.

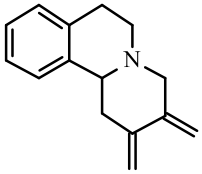
## 2. Synthetic procedures

### 2.1. General procedure for the synthesis of dienes

A mixture of iodoalkene (0.7 mmol), $Pd(OAc)_2$ (10 mol%), $PPh_3$ (20 mol%), $K_2CO_3$ (1.5 eq) in acetonitrile (10 mL) was refluxed under nitrogen atmosphere for 12h. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM, washed with water, dried ( $Na_2SO_4$) and filtered. The solvent was then evaporated under reduced pressure and the residue was purified by flash chromatography ($SiO_2$).

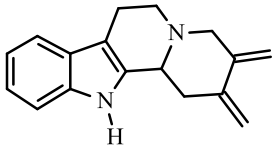
***Spectral data for selected dienes***

**Diene (4)**




Flash chromatography ($SiO_2$, 8:2 v/v petroleum ether-ether) afforded the product **4** (70%) as a light yellow amorphous solid.
**IR:** 2735, 1492, 1423, 1136, 1137, 732 $cm^{-1}$. **$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 7.21-7.10 (m, 4H), 5.16 (m, 2H), 4.85 (dt, 2H, *J*=14.5 and 2 Hz), 3.49 (d, 1H, *J*=13 Hz), 3.43 (d, 1H, *J*=10.5 Hz), 3,15 (m, 2H), 3.04 (m, 1H), 2.92 (dd, 1H, *J*=14 and 3 Hz), 2.77 (dt, 1H, *J*=16 and 3 Hz), 2.56 (dt, 1H, *J*=11 and 4 Hz), 2.37 (m, 1H). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 145.45, 144.09, 137.54, 134.42, 128.90, 126.19, 125.81, 125.29, 109.74, 109.36, 62.27, 62.07, 50.67, 40.00, 29.58. **HRMS (ESI):** calculated for **$C_{15}H_{17}N$** $(M+H)^+$ 212.14338, found 212.14299

**Diene (15)**



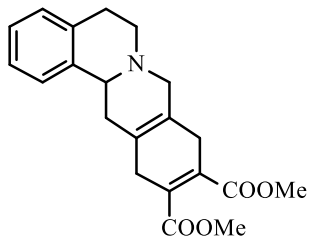
Flash chromatography ($SiO_2$, 7:3 v/v petroleum ether-ether) afforded the product **15** (48%) as a dark yellow amorphous solid.
**IR:** 3418, 3049, 2949, 1643, 898, 743 $cm^{-1}$.**$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 7.73 (brs, 1H), 7.48 (d, 1H, *J*=8 Hz), 7.31 (dt, 1H, *J*=8 and 1 Hz,), 7.15 (dt, 1H, *J*=7.5 and 1.5 Hz), 7.09 (dt, 1H, *J*= 7.5 and 1 Hz), 5.18 (s, 2H), 4.88 (s, 2H), 3.56 (d, 1H, *J*=12.5 Hz), 3.45 (dq, 1H, *J*=11.5 and 2.5 Hz), 3.15 (m, 2H), 3.02 (m, 1H), 2.78 (m, 2H), 2.66 (dt, 1H, *J*=11 and 4.5 Hz), 2.47 (m, 1H). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 144.40, 143.88, 136.09, 134.06, 127.24, 121.57, 119.51, 118.23, 110.76, 110.30, 110.08, 108.64, 61.38, 59.16, 52.35, 38.63, 21.62. **HRMS (ESI):** calculated for **$C_{17}H_{18}N_2$** $(M+H)^+$ 251.15428, found 251.15374

## 2.2. General procedure for the synthesis of cycloadducts

A mixture of diene (0.2 mmol) and DMAD (1.2eq, 0.24mmol) in toluene (5mL) was refluxed under nitrogen atmosphere for 12h. The solvent was then evaporated under reduced pressure and the residue was purified by flash chromatography ($SiO_2$).

***Spectral data for selected cycloadducts***

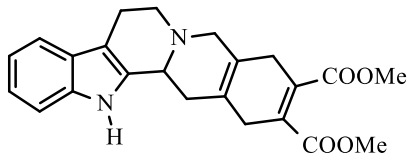
**Cycloadduct (9)**



Flash chromatography ($SiO_2$, 95:5 v/v ether-petroleum ether) afforded the product **9** (90%) as a dark orange amorphous solid.
**IR:** 1716, 1433, 1267, 1196, 1068, 736 $cm^{-1}$. **$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 7.16-7.10 (m, 4H), 3.78 (s, 6H), 3.58 (m, 1H), 3.25-2.91 (m, 8H), 2.73 (brd, 1H, *J*=16 Hz), 2.61-2.47 (m, 2H), 2.19 (brt, 1H, *J*=13 Hz). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 168.26, 168.08, 137.58, 134.24, 132.85, 131.79, 128.80, 126.09, 125.96, 125.18, 123.16, 122.86, 59.21,

58.05, 52.20, 50.84, 36.66, 32.25, 30.12, 29.34. **HRMS (ESI):** calculated for **$C_{21}H_{23}NO_4$** $(M+H)^+$ 354.16998, found 354.16918

**Cycloadduct (16)**



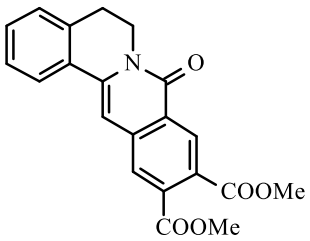

Flash chromatography ($SiO_2$, 8:2 v/v ether-petroleum ether) afforded the product **16 (**70%) as a brownish red amorphous solid.
**IR:** 2949, 1716, 1434, 1260, 1069, 738 $cm^{-1}$.**$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 7.74 (s, 1H), 7.50 (d, 1H, *J*=8 Hz), 7.32 (d, 1H, *J*=8 Hz), 7.16 (t, 1H, *J*=7.25 Hz), 7.11 (t, 1H, *J*=7 Hz), 3.80 (s, 3H), 3.79 (s, 3H), 3.62 (m, 1H), 3.28 (m, 1H), 3.20 (m, 1H,), 3.06-2.89 (m, 6H), 2.78 (m, 1H), 2.67 (dt, 1H, *J*=11 and 4 Hz), 2.32 (m, 2H). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 168.28, 168.07, 136.26, 134.14, 132.69, 131.88, 127.16, 123.70, 122.11, 121.64, 119.55, 118.25, 110.77, 108.70, 57.30, 55.80, 52.31, 52.30, 51.94, 34.87, 32.28, 30.30, 21.49. **HRMS (ESI):** calculated for **$C_{23}H_{24}N_2O_4$** $(M+H)^+$ 393.18088, found 393.17969

## 2.3. General procedure for the synthesis of oxoprotoberberines

A mixture of cycloadduct (0.1 mmol) and $MnO_2$ (10 mmol) in 1,4-dioxane (20 mL) was stirred at 70$^o$C (oil bath temperature) for 72h. Reaction mixture was diluted with AcOEt and filtered through celite. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($SiO_2$)

***Spectral data for selected oxoprotoberberines***

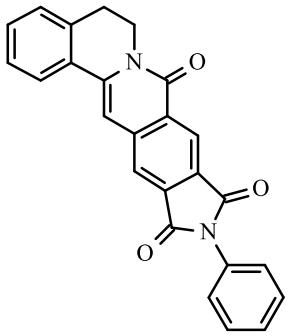
**Oxoprotoberberine (10)**




Flash chromatography ($SiO_2$, 9:1 v/v ether-petroleum ether) afforded the product **10** (45%) as a yellow amorphous solid.

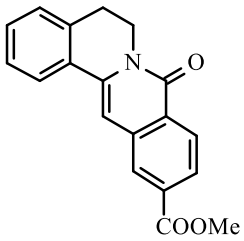
**IR:** 1729, 1712, 1645, 1620, 1293, 1161, 772 $cm^{-1}$. **$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 8.90 (s, 1H), 7.83 (d, 1H), 7.79 (s, 1H), 7.41 (m, 2H), 7.31 (m, 1H), 7.03 (s, 1H), 4.39 (t, 2H, *J*=6 Hz), 3.97 (s, 3H), 3.95(s, 3H), 3.05 (t, 2H, *J*=6 Hz). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 168.44, 166.55, 161.29, 140.59, 138.71, 136.43, 135.70, 130.54, 130.24, 129.47, 128.15, 127.70, 127.38, 126.70, 125.39, 125.15, 101.79, 52.95, 52.65, 39.86, 28.30. **HRMS (ESI):** calculated for **$C_{21}H_{17}NO_5$** $(M+H)^+$ 364.11795, found 364.11783

**Oxoprotoberberine (12a)**




The product **12a** is solidified upon work up of the reaction mixture as a yellow amorphous solid (66%)
**IR:** 1710, 1645, 1630, 1615 $cm^{-1}$. **$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 9.00 (s, 1H), 8.13 (s, 1H), 7.89 (m, 1H), 7.55-7.41 (m, 7H), 7.35 (m, 1H), 7.18 (s, 1H), 4.43 (t, 2H, *J*=6 Hz), 3.08 (t, 2H, *J*=6 Hz). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 166.53, 166.33, 161.56, 141.51, 141.26, 135.83, 134.13, 131.67, 130.64, 129.14, 128.27, 128.25, 128.14, 127.84, 127.52, 126.53, 125.57, 125.30, 122.28, 102.78, 40.01, 28.22. **HRMS (ESI):** calculated for **$C_{25}H_{16}N_2O_3$** $(M+H)^+$ 393.12337, found 393.12420

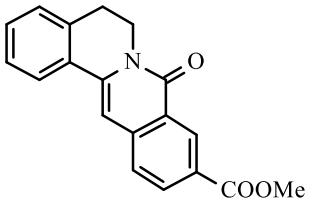
**Oxoprotoberberine (12b)**




Flash chromatography ($SiO_2$, 7:3 v/v ether-petroleum ether) afforded the product **12b** (45%) as a pale yellow amorphous solid.
**IR:** 1720, 1640, 1621, 1261, 1151, 1090, 754 $cm^{-1}$. **$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 8.49 (d, 1H, *J*=8.4 Hz), 8.30 (d, 1H, *J*=1.5 Hz), 8.05 (dd, 1H, *J*=8.4 and 1.5 Hz), 7.84 (m, 1H), 7.38 (m, 2H), 7,29 (m, 1H), 7.09 (s, 1H), 4.39 (t, 2H, *J*=6.1 Hz), 3.97 (s, 3H), 3.04 (t, 2H,

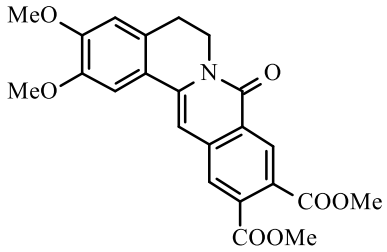
*J*=6.1 Hz). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 166.53, 161.67, 138.33, 136.30, 135.43, 133.40, 129.89, 129.64, 128.39, 128.36, 128.05, 127.58, 126.39, 125.11, 102.73, 52.49, 39.82, 28.46. **HRMS (ESI):** calculated for **$C_{19}H_{15}NO_3$** $(M+H)^+$ 306.11247, found 306.11175

**Oxoprotoberberine (12b')**



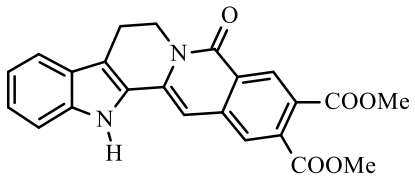

Flash chromatography ($SiO_2$, 7:3 v/v ether-petroleum ether) afforded the product **12b'** (43%) as a pale yellow amorphous solid.
**IR:** 1703, 1651, 1614, 1288, 1270, 766 $cm^{-1}$. **$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 9.11 (s, 1H), 8.24 (m, 1H, *J*=8.2 Hz), 7.85 (m, 1H), 7.62 (d, 1H, *J*=8.2 Hz), 7.40 (m, 2H), 7.33 (m, 1H), 7.04 (s, 1H), 4.39 (t, 2H, *J*=6.1 Hz,), 3.97 (s, 3H), 3.04 (t, 2H, *J*=6.1 Hz). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 166.57, 161.91, 139.89, 139.80, 135.71, 132.46, 130.46, 129.94, 129.79, 128.12, 127.93, 127.59, 126.40, 125.32, 124.46, 52.23, 39.73, 28.45. **HRMS (ESI):** calculated for **$C_{19}H_{15}NO_3$** $(M+H)^+$ 306.11247, found 306.11202

**Oxoprotoberberine (12c)**




Flash chromatography ($SiO_2$, 85:15 v/v ether–dichloromethane) afforded the product **12c** (50%) as a yellow amorphous solid.
**IR:**1709, 1563, 1514, 1273, 1241, 1118, 1046, 787 $cm^{-1}$. **$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 8.88 (s, 1H), 7.78 (s, 1H), 7.25 (s, 1H), 6.88 (s, 1H), 6.76 (s, 1H), 4.36 (t, 2H, *J*=6 Hz), 3.99 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 2.97 (t, 2H, *J*=6 Hz). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 168.51, 166.57, 161.36, 151.15, 148.66, 140.64, 138.88, 136.42, 130.59, 129.28, 126.83, 126.40, 124.65, 121.50, 110.50, 108.08, 100.42, 56.26, 56.09, 52.90, 52.60, 39.90, 27.84. **HRMS (ESI):** calculated for **$C_{23}H_{21}NO_7$** $(M+H)^+$ 424.13908, found 424.13949

**Oxocarboline (17)**




Flash chromatography ($SiO_2$, 75:25 v/v ether–petroleum ether) afforded the product **17** (23%) as a yellow amorphous solid.
**IR:** 3283, 1699,1621, 1606, 1439, 1299, 1284, 1148, 1231, 737 $cm^{-1}$. **$^1$H NMR (500 MHz, $CDCl_3$)** $\delta$ 8.77 (s, 1H ), 8.74 (s, 1H), 7.60 (d, 1H, *J*=7.5 Hz), 7.56 (s, 1H), 7.44 (d, 1H, *J*=8 Hz), 7.32 (t, 1H, *J*=7.5 Hz), 7.18 (t, 1H, *J*=7.5 Hz), 6.42 (s, 1H), 4.52 (t, 2H, *J*=7 Hz), 4.03 (s, 3H), 3.63 (s, 3H), 3.14 (t, 2H, *J*=7 Hz). **$^{13}$C NMR (125 MHz, $CDCl_3$)** $\delta$ 169.48, 165.88, 161.23, 138.72, 138.44, 136.92, 134.93, 130.73, 127.39, 126.01, 125.98, 125.53, 125.00, 124.97, 120.75, 119.58, 115.65, 111.84, 97.73, 53.16, 52.23, 41.00, 19.75. **HRMS (ESI):** calculated for **$C_{23}H_{18}N_2O_5$** $(M+H)^+$ 403.12885, found 403.12910