A Concise Total Synthesis of (−)-Quinocarcin via Aryne Annulation
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Table of Contents

Materials and Methods               S2
Experimental Procedures and Spectroscopic Data                     S3
Experimental Spectra                                                   S14
References                                                               S38
Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or ceric ammonium molybdate staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Analytical chiral supercritical fluid chromatography was performed with a Berger Analytix SFC (Thar Technologies) using a Chiralcel OD-H column (250 mm x 4.6 mm, 5 µm particle size, 2.0 mL/min flow rate). Preparatory reverse-phase HPLC was performed on a Waters HPLC with a Waters Delta-Pak column (100 mm x 2 mm, 15 µm particle size, 1.5 mL/min flow rate) equipped with a guard, employing a variable gradient of methanol and water. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me\(_4\)Si (\(\delta \) 0.0). Data for \(^1\)H NMR spectra are reported as follows: chemical shift (\(\delta \) ppm) (multiplicity, coupling constant (Hz), integration). Data for \(^{13}\)C NMR spectra are reported in terms of chemical shift relative to Me\(_4\)Si (\(\delta \) 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm\(^{-1}\)). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Optical rotations were measured on a Jasco P-1010 polarimeter using a 100 mm path-length cell.
**Experimental Procedures**

**Diazabicycle S-1.** A flame-dried 1 L round-bottomed flask equipped with a stir bar was charged with oxidopyrazinium bromide 13 (12.70 g, 45.2 mmol) and acetonitrile (250 mL). The suspension was cooled to −20 °C in a Thermo Scientific NESLAB CB-80 cold bath. N-methylmorpholine (14.9 mL, 136 mmol) was added via syringe and the mixture was stirred until all solids had dissolved (10 min). A solution of acrylamide 14 (14.57 g, 54.1 mmol) in acetonitrile (350 mL) was then added and the reaction was maintained at −20 °C for 100 h. The reaction was then diluted cold in EtOAc (400 mL) and washed with water (2 x 300 mL). The combined aqueous layers were extracted with EtOAc (2 x 200 mL) and the combined organic layers were washed with brine (400 mL), dried over MgSO₄, and concentrated under reduced pressure. The resulting crude orange-yellow solid was filtered through a plug of silica (CH₂Cl₂ → 75:25 EtOAc/hexanes) to remove orange baseline material. Solvent was removed under reduced pressure to afford an off-white solid. The crude solid was dissolved in a minimum amount of CH₂Cl₂ (240 mL), and to this solution was added hexanes (300 mL) while swirling until the first crystals were visible. The solution was then allowed to stand at 23 °C for 8 h. Filtration under vacuum provided diazabicycle S-1 (14.85 g, 70% yield) as a white solid. The mother liquor was concentrated and the residue was resubmitted to recrystallization to provide additional diazabicycle S-1 (2.75 g, 13% yield — 83% combined yield) as a white solid. 

**Notes:**
- Rᵢ = 0.38 (50:50 EtOAc/hexanes);
- ¹H NMR (500 MHz, CDCl₃) δ 7.53 (br s, 1H), 7.31–7.21 (comp m, 5H), 4.38 (d, J = 1.2 Hz, 1H), 4.32 (d, J = 1.2 Hz, 1H), 3.94 (d, J = 12.8 Hz, 1H), 3.89 (dd, J = 7.8, 4.6 Hz, 1H), 3.74 (d, J = 7.8 Hz, 1H), 3.68 (s, 1H), 3.59 (dd, J = 9.0, 3.9 Hz, 1H).
Hz, 1H), 3.57 (d, J = 12.8 Hz, 1H), 3.41 (s, 2H), 3.06 (ddd, J = 13.4, 7.8, 3.9 Hz, 1H), 2.15 (dd, J = 13.4, 9.0 Hz, 1H), 2.06 (dd, J = 13.9, 7.8 Hz, 1H), 1.91–1.84 (comp m, 3H), 1.82 (dd, J = 4.2, 3.7 Hz, 1H), 1.43–1.32 (comp m, 2H), 0.92 (s, 3H), 0.75 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 171.4, 171.3, 139.2, 138.2, 128.8, 128.5, 127.5, 94.0, 65.8, 63.4, 63.3, 53.3, 52.1, 49.2, 48.6, 47.9, 44.8, 38.5, 33.0, 31.3, 26.6, 20.8, 20.0; IR (Neat Film, NaCl) 3199, 2960, 1688, 1654, 1455, 1329, 1213, 1134, 853 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{25}\)H\(_{32}\)N\(_3\)O\(_4\)S [M+H\(^{+}\)]: 470.2108, found 470.2136; \([\alpha]\)\(^{22}\)D +100.72° (c 1.0, CHCl\(_3\)).

**Ester 12.** A flame-dried 500 mL round-bottomed flask equipped with a stir bar was charged with a 60% w/w suspension of NaH in mineral oil (1.32 g, 33.0 mmol). Methanol (200 mL) was slowly added with stirring at 23 °C under argon. **Warning:** vigorous gas evolution. The suspension was stirred until all solids had dissolved (15 min). A solution of diazabicycle S-1 (5.07 g, 10.8 mmol) in CH\(_2\)Cl\(_2\) (40 mL) was then added, and the reaction was maintained at 23 °C for 20 min. The reaction was quenched by the addition of saturated aqueous NH\(_4\)Cl (250 mL) and extracted into EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over MgSO\(_4\), and concentrated under reduced pressure. The residue was purified via flash chromatography over silica gel (25:75 \(\rightarrow\) 30:70 EtOAc/hexanes) to afford methyl ester 12 (2.75 g, 89% yield) as a white solid and sultam S-2 (1.74 g, 75% yield) as a white crystalline solid. \(R_f = 0.45\) (50:50 EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.35 (br s, 1H), 7.35–7.29 (comp m, 4H), 7.28–7.24 (m, 1H), 4.33 (d, J = 1.2 Hz, 1H), 4.19 (d, J = 1.2,
1H), 4.02 (s, 1H), 3.82 (d, J = 13.4 Hz, 1H), 3.74 (s, 3H), 3.73 (d, J = 13.4 Hz, 1H), 3.62 (d, J = 7.3 Hz, 1H), 3.02 (dd, J = 9.8, 5.6 Hz, 1H), 2.66 (ddd, J = 13.2, 7.3, 5.6 Hz, 1H), (dd, J = 13.2, 9.8 Hz, 1H); 13C NMR (125 MHz, CDCl₃) δ 173.6, 171.6, 141.3, 137.9, 128.7, 128.6, 127.6, 91.7, 63.3, 62.5, 52.6, 52.5, 48.4, 33.5; IR (Neat Film, NaCl) 3202, 2953, 1737, 1684, 1656, 1454, 1318, 1200, 850 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₆H₁₉N₂O₃ [M+H]⁺: 287.1396, found 287.1390; [α]ᵢ²⁶ D –23.66° (c 1.0, CHCl₃).

Analytical chiral SFC assay: Chiralcel OD-H column, 10:90 2-propanol:CO₂, 2.0 mL/min, λ = 254 nm, 40 °C isothermal method over 20 min. Racemic 12: tₕₙₚ = 11.31 min ((–)-12, 49.9%), tₙₚₙ = 11.89 min ((+)-12, 50.1%). Enantio-enriched 12: tₕₙₚ = 11.39 min ((–)-12, >99%) (the trace corresponding to (+)-12 was below the threshold of detection).

**Imide 16.** A flame-dried 500 mL 3-neck round-bottomed flask equipped with a stir bar and a reflux condenser was charged with benzyloxyacetic acid (8.76 g, 52.8 mmol) and CH₂Cl₂ (140 mL). To this solution was added oxalyl chloride (4.53 mL, 51.9 mmol) and N,N-dimethylformamide (0.205 mL, 2.65 mmol). **Warning:** vigorous gas evolution. The reaction was maintained at 23 °C until bubbling had ceased (45 min). A solution of ester 12 (5.00 g, 17.5 mmol), triethylamine (7.9 mL, 56.7 mmol), and 4-dimethylaminopyridine (0.325 g, 2.66 mmol) in CH₂Cl₂ (35 mL) was then added dropwise via syringe over 5 min. The reaction was heated to 40 °C and maintained for 30 h. After cooling to room temperature, the solution was diluted in CH₂Cl₂ (200 mL) and washed with saturated aqueous NH₄Cl (200 mL), water (200 mL), and brine (200 mL). The organic layer was dried over MgSO₄ and
concentrated under reduced pressure. The crude orange residue was purified via flash chromatography over silica gel (15:85 → 25:75 EtOAc/hexanes) to afford imide 16 (7.06 g, 93% yield) as a colorless oil. 

\[ R_f = 0.47 \text{ (30:70 EtOAc/hexanes)};^1H \text{ NMR (500 MHz, CDCl}_3\text{) } \delta 7.41–7.34 \text{ (comp m, 4H), 7.34–7.29 (comp m, 4H), 7.29–7.24 (comp m, 2H), 5.25 (d, } J = 1.2 \text{ Hz, 1H), 4.65 (s, 2H), 4.59 (d, } J = 1.2 \text{ Hz, 1H), 4.56 (d, } J = 16.8 \text{ Hz, 1H), 4.49 (d, } J = 16.8 \text{ Hz, 1H), 4.04 (s, 1H), 3.77 (d, } J = 4.9 \text{ Hz, 2H), 3.74 (s, 3H), 3.68 (d, } J = 7.1 \text{ Hz, 1H), 3.04 (dd, } J = 9.8, 6.0 \text{ Hz, 1H), 2.62 (ddd, } J = 13.4, 7.1, 6.0 \text{ Hz, 1H), 2.26 (dd, } J = 13.4, 9.8 \text{ Hz, 1H); } ^{13}\text{C NMR (125 MHz, CDCl}_3\text{) } \delta 175.9, 173.4, 172.1, 139.2, 137.4, 137.2, 128.8, 128.7, 128.6, 128.4, 128.3, 127.7, 99.8, 74.0, 72.9, 65.2, 64.7, 52.7, 52.7, 47.5, 32.7; \text{ IR (Neat Film, NaCl) 2952, 1736, 1634, 1454, 1200, 1117, 1028 cm}^{-1}; \text{ HRMS (FAB+) } m/z \text{ calc’d for } C_{25}H_{27}N_2O_5 [M+H]^+: 435.1920, \text{ found } 435.1930; [\alpha]^{21}D = -51.53^\circ (c 1.0, \text{ CHCl}_3).
69% yield) as a pale yellow oil. \( R_f = 0.70 \) (50:50 EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.18 (br s, 1H), 7.43 (d, \( J = 6.6 \) Hz, 2H), 7.39 (dd, \( J = 7.2, 6.6 \) Hz, 2H), 7.34, (tt, \( J = 7.2, 1.5 \) Hz, 1H), 7.29–7.22 (comp m, 5H), 6.01 (s, 1H), 4.76 (d, \( J = 1.2 \) Hz, 1H), 4.75 (d, \( J = 12.4 \) Hz, 1H), 4.71 (d, \( J = 12.4 \) Hz, 1H), 4.06 (s, 2H), 3.97 (d, \( J = 13.7 \) Hz, 1H), 3.69 (s, 3H), 3.65 (d, \( J = 9.0 \) Hz, 1H), 3.60 (d, \( J = 13.7 \) Hz, 1H), 3.56 (dd, \( J = 9.5, 4.2 \) Hz, 1H), 3.40 (s, 3H), 3.09 (dd, \( J = 9.5, 8.8 \) Hz, 1H), 2.33 (dt, \( J = 12.9, 9.8 \) Hz, 1H), 2.13 (ddd, \( J = 12.7, 8.3, 4.2 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 174.4, 173.2, 169.5, 137.4, 137.3, 136.8, 129.7, 128.8, 128.5, 128.3, 128.2, 127.8, 101.7, 73.7, 72.2, 70.0, 63.2, 56.4, 52.4, 52.0, 47.6, 33.1; IR (Neat Film, NaCl) 3316, 2951, 1737, 1696, 1512, 1454, 1436, 1201, 1174, 1028 cm\(^{-1}\); HRMS (ES+) \( m/z \) calc’d for C\(_{20}\)H\(_{31}\)N\(_2\)O\(_6\) [M+H]\(^+\): 467.2182, found 467.2188; \([\alpha]_{D}^{25}\) = \(-29.78^\circ\) (c 1.0, CHCl\(_3\)).

**Isoquinoline 9.** A flame-dried 500 mL 3-neck round-bottomed flask equipped with a stir bar and reflux condenser was charged with tetra-n-butylammonium difluorotriphenylsilicate (5.45 g, 10.1 mmol) and THF (120 mL). A solution of \( N \)-acyl enamine 11 (2.35 g, 5.04 mmol) in THF (50 mL) was added at 23 °C, followed by silylaryl triflate 17\(^{4}\) (3.31 g, 10.1 mmol). The reaction was heated to 40 °C and maintained for 15 h, then cooled to room temperature and concentrated under reduced pressure. The yellow residue was purified via flash chromatography over silica gel (15:85 \( \rightarrow \) 25:75 EtOAc/hexanes) to afford isoquinoline 9 (1.68 g, 60% yield) as a pale yellow oil. \( R_f = 0.65 \) (50:50 EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.06 (s, 1H), 7.55 (dd, \( J = 8.1, 7.8 \) Hz, 1H), 7.44 (d, \( J = 7.6 \) Hz, 2H), 7.34 (dd, \( J = 7.8, 7.1 \) Hz, 2H), 7.32–7.25 (comp m, 4H), 7.22 (dd, \( J = 7.6, 7.1 \) Hz, 2H), 7.15 (t, \( J = 7.3 \) Hz,
Tetrahydroisoquinolines 19a and 19b. A flame-dried 10 mL round-bottomed flask equipped with a stir bar was charged with 10% w/w palladium on carbon (0.019 g, 0.018 mmol) followed by a solution of isoquinoline 9 (0.100 g, 0.180 mmol) in THF (3.6 mL). The flask was purged with hydrogen and a hydrogen balloon was attached. The reaction was maintained at 23 °C for 6 h, then filtered through a plug of silica with 30:70 EtOAc/hexanes. Removal of the solvents under vacuum provided a 3.3:1 mixture of dihydroisoquinolines 18a and 18b (not shown) (0.082 g), which was carried on without further purification. A flame-dried 5 mL round-bottomed flask equipped with a stir bar was charged with dihydroisoquinolines 18a and 18b (0.082 g, 0.148 mmol) in methanol (2.9 mL), and the solution was cooled to 0 °C. Concentrated hydrochloric acid (0.018 mL, 0.216 mmol) was added via syringe followed by NaBH₄CN (0.046 g, 0.732 mmol) added in portions, allowing for bubbling to subside. The reaction was maintained at 0 °C for 15 min, and then quenched with saturated aqueous NaHCO₃ (1.5
mL) followed by CH$_2$Cl$_2$ (1.5 mL). The cloudy white mixture was vigorously stirred for 5 min, then 0.2
N NaOH was added dropwise until the mixture cleared (6 drops). The biphasic mixture was extracted
with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried over
MgSO$_4$, and concentrated under reduced pressure. The yellow residue was purified via flash
chromatography over silica gel (15:85 EtOAc/hexanes) to yield tetrahydroisoquinoline $^{19}$a (0.055 g,
55% yield over 2 steps) as a clear colorless oil and tetrahydroisoquinoline $^{19}$b (0.017 g, 17% yield over
2 steps) as a clear colorless oil.

**Tetrahydroisoquinoline $^{19}$a.** $R_f = 0.38$ (30:70 EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$
7.39 (d, $J = 7.3$ Hz, 2H), 7.36–7.29 (comp m, 4H), 7.29–7.23 (comp m, 3H), 7.21 (dd, $J = 7.3, 7.1$ Hz,
1H), 7.11 (t, $J = 7.8$ Hz, 1H), 6.72 (d, $J = 7.6$ Hz, 1H), 6.68 (d, $J = 8.3$ Hz, 1H), 4.66 (d, $J = 12.2$ Hz,
1H), 4.59 (d, $J = 12.2$ Hz, 1H), 4.47 (d, $J = 7.1$ Hz, 1H), 4.17 (dd, $J = 8.8, 2.2$ Hz, 1H), 3.99 (d, $J = 13.9$
Hz, 1H), 3.81 (d, $J = 13.9$ Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.63 (dd, $J = 8.3, 7.8$ Hz, 1H), 3.46–3.33
(comp m, 4H), 3.38 (s, 3H), 2.98 (ddd, $J = 11.2, 2.9, 2.7$ Hz, 1H), 2.65 (dd, $J = 14.7, 11.2$ Hz, 1H), 2.55
(dd, $J = 14.7, 2.7$ Hz, 1H), 2.35 (ddd, $J = 12.5, 7.1, 3.8$ Hz, 1H), 2.27 (ddd, $J = 12.7, 9.0, 8.8$ Hz, 1H);
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 176.1, 174.4, 157.1, 139.4, 139.1, 138.7, 129.3, 128.4, 128.3, 127.8,
127.5, 127.4, 127.1, 124.4, 121.8, 108.2, 75.2, 73.1, 72.0, 66.8, 59.1, 55.3, 53.6, 53.4, 52.3, 51.8, 45.0,
42.9, 34.5, 34.0; IR (Neat Film, NaCl) 2949, 1734, 1731, 1584, 1470, 1255, 1198, 1170, 1074 cm$^{-1}$;
HRMS (FAB+) $m/z$ calc’d for C$_{33}$H$_{39}$N$_2$O$_6$ [M+H]$^+$: 559.2803, found 559.2814; [$\alpha$]$^{23}_{D}$ = −52.71° (c 1.0,
CHCl$_3$).

**Tetrahydroisoquinoline $^{19}$b.** $R_f = 0.18$ (30:70 EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$
7.49 (d, $J = 7.6$ Hz, 2H), 7.38 (t, $J = 7.6$ Hz, 2H), 7.38–7.34 (comp m, 2H), 7.30 (t, $J = 7.3$ Hz, 1H),
7.19–7.14 (comp m, 3H), 7.12 (t, $J = 7.8$ Hz, 1H), 6.71 (d, $J = 7.8$ Hz, 1H), 6.65 (d, $J = 8.1$ Hz, 1H),
4.72 (d, $J = 12.2$ Hz, 1H), 4.68 (d, $J = 12.2$ Hz, 1H), 4.62 (dd, $J = 9.5, 2.2$ Hz, 1H), 4.03 (d, $J = 13.4$ Hz,
1H), 3.79 (d, J = 13.4 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.67–3.56 (comp m, 3H), 3.60 (d, J = 9.3 Hz, 1H), 3.39–3.32 (comp m, 2H), 3.38 (s, 3H), 3.30 (app dt, J = 8.1, 7.1 Hz, 1H), 2.60 (d, J = 7.6 Hz, 2H), 2.35–2.21 (comp m, 2H); 13C NMR (125 MHz, CDCl3) δ 176.2, 174.3, 156.6, 139.2, 138.2, 136.9, 129.8, 128.5, 128.3, 127.8, 127.6, 127.4, 121.6, 107.7, 72.8, 71.5, 69.4, 66.8, 59.2, 55.4, 52.3, 51.8, 47.4, 42.7, 34.1, 32.4; IR (Neat Film, NaCl) 2949, 1733, 1588, 1454, 1257, 1198, 1171, 1074 cm⁻¹; HRMS (FAB+) m/z calc’d for C31H39N2O6 [M+H]+: 559.2803, found 559.2825; [α]D²¹ –17.00° (c 0.5, CHCl₃).

**Lactam 20.** A flame-dried 20 mL scintillation vial equipped with a stir bar was charged with tetrahydroisoquinoline 19a (0.075 g, 0.135 mmol) in toluene (5.4 mL). The vial was sealed with a teflon cap and the reaction was heated to 110 °C for 24 h. The reaction was then cooled to room temperature and the solvent was removed under reduced pressure. Purification via flash chromatography over silica gel (25:75 EtOAc/hexanes) provided tetracyclic lactam 20 (0.071 g, 99% yield) as a pale yellow oil. Rf = 0.61 (50:50 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.34–7.22 (comp m, 9H), 7.21 (t, J = 8.0 Hz, 1H), 7.07 (dd, J = 7.6, 2.4 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 7.3 Hz, 1H), 5.64 (t, J = 2.2 Hz, 1H), 4.32 (d, J = 12.0 Hz, 1H), 4.29 (d, J = 12.0 Hz, 1H), 4.25 (dd, J = 9.5, 3.2 Hz, 1H), 3.79 (s, 3H), 3.76 (dd, J = 12.4, 2.2 Hz, 1H), 3.73 (s, 3H), 3.72 (br s, 1H), 3.68 (d, J = 6.4 Hz, 1H), 3.60 (br s, 1H), 3.48 (dd, J = 9.5, 2.0 Hz, 1H), 3.25 (app t, J = 8.1 Hz, 1H), 3.12 (app t, J = 13.4 Hz, 1H), 2.66 (app dt, J = 6.6, 6.6 Hz, 1H), 2.44 (dd, J = 14.2, 2.2 Hz, 1H), 2.21 (dd, J = 13.2, 9.5 Hz, 1H); 13C NMR (125 MHz, CDCl₃) δ 175.5, 170.8, 155.9, 138.7, 138.6, 138.3, 128.9, 128.6, 128.5, 128.1, 127.8, 127.6,
127.5, 123.2, 119.9, 108.9, 73.5, 70.9, 66.6, 65.2, 57.1, 55.5, 54.6, 52.4, 49.7, 41.2, 34.5, 32.4; IR (Neat
Film, NaCl) 2950, 1735, 1654, 1474, 1437, 1265, 1208, 1099, 1069 cm⁻¹; HRMS (FAB+) \textit{m/z} calc’d for
\(
\text{C}_{32}\text{H}_{35}\text{N}_2\text{O}_5\) [M+H]⁺: 527.2540, found 527.2543; \([\alpha]^{24}_D\) –85.60° (c 1.0, CHCl₃).

\[ \text{N-Methyl amine 21.} \]

A flame-dried 1 dram vial equipped with a stir bar and a septum-bearing screw cap was charged with moist 20% w/w Pd(OH)₂ on carbon (±50% water) (0.062 g, 0.044 mmol) followed by a solution of lactam 20 (0.0435 g, 0.083 mmol) in MeOH (0.85 mL). The vial was purged with hydrogen and a hydrogen balloon was attached. The reaction was maintained at 23 °C for 20 h, at which point a 37% w/w aqueous solution of formaldehyde (0.310 mL, 4.14 mmol) was added via syringe. The reaction was maintained at 23 °C under hydrogen for an additional 20 h, and then filtered through a plug of Celite eluting with 10:90 MeOH/CH₂Cl₂. The solvent was removed under reduced pressure and the residue was purified via flash chromatography over silica (CH₂Cl₂ → 2:98 MeOH/CH₂Cl₂) to afford \textit{N}-methyl amine 21 (0.024 g, 80% yield) as a solid white foam. \textit{R}_{f} = 0.28
(10:90 MeOH/CH₂Cl₂); \(^1\text{H NMR}\) (500 MHz, CDCl₃) \(\delta\) 7.21 (t, \(J = 7.8\) Hz, 1H), 6.81 (d, \(J = 8.3\) Hz, 1H), 6.78 (d, \(J = 7.6\) Hz, 1H), 5.72 (dd, \(J = 5.6, 3.2\) Hz, 1H), 3.91 (ddd, \(J = 11.3, 6.2, 2.9\) Hz, 1H), 3.84 (s, 3H), 3.83 (app dt, \(J = 12.4, 2.4\) Hz, 1H), 3.76 (s, 3H), 3.66 (dd, \(J = 1.5, 1.2\) Hz, 1H), 3.60 (d, \(J = 6.4\) Hz, 1H), 3.55 (ddd, \(J = 11.0, 5.6, 3.4\) Hz, 1H), 3.31 (dd, \(J = 9.5, 6.6\) Hz, 1H), 3.03 (dd, \(J = 5.6, 4.6\) Hz, 1H), 2.96 (dd, \(J = 14.6, 12.7\) Hz, 1H), 2.66 (app dt, \(J = 13.2, 6.6\) Hz, 1H), 2.62 (dd, \(J = 14.6, 2.2\) Hz, 1H), 2.48 (s, 3H), 2.39 (dd, \(J = 13.2, 9.5\) Hz, 1H); \(^{13}\text{C NMR}\) (125 MHz, CDCl₃) \(\delta\) 174.9, 173.5, 156.1, 137.5, 128.8, 121.8, 120.1, 109.3, 67.4, 67.3, 66.4, 55.7, 55.4, 52.7, 52.0, 41.6, 37.3, 34.8, 32.2; IR (Neat Film,
NaCl) 3404, 2951, 1733, 1638, 1474, 1436, 1264, 1204, 1064, 915 cm\(^{-1}\); HRMS (EI+) \(m/z\) calc’d for C\(_{19}\)H\(_{24}\)N\(_2\)O\(_5\) [M]\(^+\): 360.1685, found 360.1701; [\(\alpha\)]\(_D\)\(^{22}\) = -104.64° (c 1.0, CHCl\(_3\)).

**Quinocarcin (1).** A flame-dried 15 mL round-bottomed flask equipped with a stir bar was charged with \(N\)-methyl amine 21 (36.4 mg, 0.101 mmol) in THF (2.7 mL). A solution of LiOH-H\(_2\)O (0.0423 g, 1.01 mmol) in H\(_2\)O (1.35 mL) was added via syringe and the mixture was vigorously stirred at 23 °C for 3 h. Ethyl acetate (4 mL) was added and the solution was neutralized to pH 7 with 2.0 N HCl (4 drops). The biphasic mixture was transferred to a 50 mL round-bottomed flask and the solvents were removed under reduced pressure. The resulting cloudy white residue was dried under high vacuum for 6 h, and then suspended in THF (7 mL) and cooled to -78 °C. Ammonia (14 mL) was condensed into the flask using a cold finger at -78 °C and lithium metal (0.0401 g, 5.78 mmol) was added. The mixture turned dark blue and was vigorously stirred for 2 min. The -78 °C cold bath was replaced with a -30 °C cold bath (MeCN/CO\(_2\)) and stirring was continued for 15 min. The reaction was quenched by the addition of methanol (5 mL) down the side of the cold finger and stirred for an additional 5 min. Solid NH\(_4\)Cl (0.960 g, 17.9 mmol) was added in portions, the cold bath was removed, and the ammonia was evaporated under a stream of argon at room temperature. Water (10 mL) was added and the mixture was neutralized to pH 7 with 1.0 N HCl (10 mL). The solvents were removed under reduced pressure, and the resulting solids were dissolved in a minimum amount of water (1 mL) and filtered through a 5 g Sep-Pak C\(_{18}\) plug (H\(_2\)O → 50:50 MeOH/H\(_2\)O) to remove salts. The crude residue was purified via semi-preparative reverse-phase HPLC (20:80 → 70:30 MeOH/H\(_2\)O, \(t_r\) = 33 min) to afford quinocarcin (1).
(0.0269 g, 81% yield over 2 steps) as a white solid. \(^1\)H NMR (500 MHz, CD\(_3\)OD) \(\delta\) 7.17 (t, \(J = 7.8\) Hz, 1H), 6.85 (d, \(J = 8.3\) Hz, 1H), 6.76 (d, \(J = 7.6\) Hz, 1H), 4.57 (d, \(J = 2.9\) Hz, 1H), 4.55 (dd, \(J = 7.3, 2.9\) Hz, 1H), 4.07 (br s, 2H), 3.82 (s, 3H), 3.68 (dd, \(J = 10.7, 2.9\) Hz, 1H), 3.43–3.33 (comp m, 2H), 3.39 (dd, \(J = 10.7, 7.3\) Hz, 1H), 2.79–2.74 (m, 1H), 2.77 (s, 3H), 2.64 (dd, \(J = 14.6, 2.4\) Hz, 1H), 2.64–2.60 (m, 1H), 2.46 (dd, \(J = 13.9, 10.5\) Hz, 1H); \(^1\)^C NMR (125 MHz, CD\(_3\)OD) \(\delta\) 179.5, 157.2, 137.6, 129.1, 124.0, 121.3, 110.0, 92.6, 73.2, 68.2, 66.9, 56.3, 55.9, 55.7, 42.8, 40.7, 32.9, 28.3; IR (Neat Film, NaCl) 3370, 2941, 1590, 1474, 1383, 1264, 1054 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{18}\)H\(_{23}\)N\(_2\)O\(_4\) [M+H]\(^+\): 331.1652, found 331.1669; [\(\alpha\)]\(_{D}^2\) -31.57° (c 0.28, H\(_2\)O). The analytical data for the synthetic sample matched those for the natural sample in all respects.\(^7\)
Figure 1.1. $^1$H NMR (500 MHz, CDCl$_3$) of diazabicycle S-1
Figure 1.2. Infrared spectrum (thin film/NaCl) of diazabicycle S-1.

Figure 1.3. $^{13}\text{C}$ NMR (125 MHz, CDCl$_3$) of diazabicycle S-1.
Figure 2.1. $^1$H NMR (500 MHz, CDCl$_3$) of methyl ester 12.
Figure 2.2. Infrared spectrum (thin film/NaCl) of methyl ester 12.

Figure 2.3. $^{13}$C NMR (125 MHz, CDCl$_3$) of methyl ester 12.
Figure 2.4. Chiral SFC traces for racemic methyl ester 12.
Figure 2.5. Chiral SFC trace for enantioenriched methyl ester (-)-12 (>99% ee).
Figure 3.1. $^1$H NMR (500 MHz, CDCl$_3$) of imide 16.
Figure 3.2. Infrared spectrum (thin film/NaCl) of imide 16.

Figure 3.3. $^{13}$C NMR (125 MHz, CDCl$_3$) of imide 16.
Figure 4.1. $^1$H NMR (500 MHz, CDCl$_3$) of N-acyl enamine 11.
Figure 4.2. Infrared spectrum (thin film/NaCl) of N-acyl enamine 11.

Figure 4.3. $^{13}$C NMR (125 MHz, CDCl$_3$) of N-acyl enamine 11.
Figure 5.1. $^1$H NMR (500 MHz, CDCl$_3$) of isoquinoline 9.
Figure 5.2. Infrared spectrum (thin film/NaCl) of isoquinoline 9.

Figure 5.3. $^{13}$C NMR (125 MHz, CDCl$_3$) of isoquinoline 9.
Figure 6.1. $^1$H NMR (500 MHz, CDCl$_3$) of tetrahydroisoquinoline 19a.
Figure 6.2. Infrared spectrum (thin film/NaCl) of tetrahydroisoquinoline 19a.

Figure 6.3. $^{13}$C NMR (125 MHz, CDCl$_3$) of tetrahydroisoquinoline 19a.
Figure 7.1. $^1$H NMR (500 MHz, CDCl$_3$) of tetrahydroisoquinoline 19b.
Figure 7.2. Infrared spectrum (thin film/NaCl) of tetrahydroisoquinoline 19b.

Figure 7.3. $^{13}$C NMR (125 MHz, CDCl$_3$) of tetrahydroisoquinoline 19b.
Figure 8.1. $^1$H NMR (500 MHz, CDCl$_3$) of lactam 20.
Figure 8.2. Infrared spectrum (thin film/NaCl) of lactam 20.

Figure 8.3. $^{13}$C NMR (125 MHz, CDCl$_3$) of lactam 20.
Figure 9.1. $^1$H NMR (500 MHz, CDCl$_3$) of N-methyl amine 21.
**Figure 9.2.** Infrared spectrum (thin film/NaCl) of *N*-methyl amine 21.

**Figure 9.3.** $^{13}$C NMR (125 MHz, CDCl$_3$) of *N*-methyl amine 21.
Figure 10.1. $^1$H NMR (500 MHz, CD$_3$OD) of (–)-quinocarcin (1).
Figure 10.2. $^1$H NMR comparison of synthetic (above) and natural (below) (-)-quinocarcin (1) (500 MHz, CD$_2$OD).
Figure 10.3. Infrared spectrum (thin film/NaCl) of quinocarcin (1).

Figure 10.4. $^{13}$C NMR (125 MHz, CD$_3$OD) of quinocarcin (1).
Supplemental Table 1. Comparison of $^1$H NMR data for synthetic and natural quinocarcin.

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Supplemental Table 2. Comparison of $^{13}$C NMR data for synthetic and natural quinocarcin.$^8$

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$^a$ $^{13}$C NMR data measured at 125 MHz in CD$_3$OD.

$^b$ $^{13}$C NMR data measured at 100 MHz in CD$_3$OD.
References


(2) The specific experimental procedure for this dipolar cycloaddition is based on the previous synthesis of (−)-lemonomycin completed in our labs, see: Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* 2003, 125, 15000–15001.

(3) ¹H NMR analysis shows this crude material to be an 11:1 mixture of diastereomeric cycloadducts. The major diastereomer (S-1) is purified via subsequent recrystallization.


(5) The ratio of dihydroisoquinolines (i.e., 18a:18b) was determined by ¹H NMR.


(8) Fukuyama noted that the pH of the analytical solution had a dramatic effect on the chemical shifts in both the ¹H and ¹³C NMR spectra of quinocarcin, accounting for observed differences between natural and synthetic spectra. See: Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc.* 1988, 110, 5196–5198.