Synthesis of (±)-Idarubicinone via Global Functionalization of Tetracene

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I. General Procedures

All reactions were performed under a nitrogen atmosphere in oven- or heat-gun-dried glassware unless otherwise indicated. Dichloromethane (ACS grade) and tetrahydrofuran (HPLC grade) were dried for reactions using the MB-SPS solvent purification system containing activated alumina manufactured by MBRAUN. Tetracene is commercially available from several vendors. However, for this study it was prepared via reduction of more affordable tetracenequinone (TCI America) and purified using sublimation.\textsuperscript{1,2,3} [Rh(cod)\textsubscript{2}]BF\textsubscript{4} was prepared following known procedures\textsuperscript{4} from [Rh(cod)Cl]\textsubscript{2} purchased from Pressure Chemical. 1,4-Bis(diphenylphosphino)butane (dppb) was purchased from Oakwood Chemical. Pinacol hexahydrate was rendered anhydrous before use by azeotropic distillation with benzene followed by recrystallizing from benzene.\textsuperscript{5} N-Methyl-1,2,4-triazoline-3,5-dione (MTAD) was prepared based on literature procedures.\textsuperscript{6,7} The lights used for arene-arenophile cycloaddition were 4W LED corn bulbs (12V, cool white light, 6500K) which were wired to a suitable 12V power supply, then sealed into test tubes and capped with septa (see Photo S1). Catechol borane (HBcat) was prepared in two steps from catechol, boric acid, and borane dimethyl sulfide following literature procedures.\textsuperscript{8} Tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III) (Mn(dpm)\textsubscript{3}) was purchased from Strem Chemicals. Isopropoxy(phenyl)silane (Ph(iPrO)SiH\textsubscript{2}) was prepared from phenylsilane (PhSiH\textsubscript{3}) according to reported procedures.\textsuperscript{9} Reaction temperatures correspond to the external temperature of the reaction vessel unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Macherey-Nagel silica gel plates (SIL G-25 UV\textsubscript{254}). Plates were visualized by UV and visible light. Silicycle SiliaFlash® P60 (SiO\textsubscript{2}, 40–63 µm particle size, 230–400 mesh) was used for flash column chromatography.\textsuperscript{1}

\textsuperscript{1}H NMR spectra were obtained at 500 MHz and \textsuperscript{13}C NMR were obtained at 126 MHz. NMR spectra were recorded using a Bruker 500 MHz spectrometer and were referenced to residual chloroform (7.26 ppm, \textsuperscript{1}H; 77.16 ppm, \textsuperscript{13}C) or residual deuterated dimethylsulfoxide (2.50 ppm, \textsuperscript{1}H; 39.52 ppm, \textsuperscript{13}C). Chemical shifts are reported in parts per million (ppm) and multiplicities are as indicated: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants, J, are reported in Hertz (Hz). High resolution mass spectrometry (HRMS) data were collected by the University of Illinois Mass Spectrometry Laboratory using electrospray ionization (ESI) and a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z. Infrared (IR) spectra were measured neat on a Perkin-Elmer Spectrum Two FT-IR spectrometer. Peaks are reported in cm\textsuperscript{-1} with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad). Melting points were measured on a Buchi B-540 melting point apparatus and are uncorrected. The X-ray diffraction experiments were conducted using Bruker D8 Venture/Photon 100 diffractometer or Bruker APEX-II CCD diffractometer. Using Olex2,\textsuperscript{10} the structures were solved with ShelXT\textsuperscript{11} structure solution program using the intrinsic phasing solution method, and the XL refinement package using least squares minimization.
II. Experimental Section

Model Studies: Arenophile-Assisted Dearomative Hydroboration

Table S1: Optimization of dearomative hydroboration:

<table>
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<th>entry</th>
<th>catalyst</th>
<th>borane</th>
<th>solvent</th>
<th>ligand</th>
<th>additive</th>
<th>yield</th>
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<tr>
<td>1a</td>
<td>CuCl</td>
<td>B$_2$pin$_2$</td>
<td>THF</td>
<td>dppp</td>
<td>LiOrBu/MelOH</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2a</td>
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<td>B$_2$pin$_2$</td>
<td>Toluene</td>
<td>IMes</td>
<td>KOOrBu/MelOH</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>3a</td>
<td>CuCl</td>
<td>B$_2$pin$_2$</td>
<td>Toluene</td>
<td>IMes</td>
<td>KOOrBu/MelOH</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(COD)Cl]$_2$</td>
<td>HBcat</td>
<td>THF</td>
<td>dppp</td>
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<td>HBcat</td>
<td>THF</td>
<td>dppb</td>
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<td>HBpin</td>
<td>THF</td>
<td>dppp</td>
<td>-</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>7b</td>
<td>[Rh(COD)Cl]$_2$</td>
<td>HBcat</td>
<td>THF</td>
<td>dppb</td>
<td>AgBF$_4$</td>
<td>30%</td>
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<tr>
<td>8b</td>
<td>[Rh(COD)Cl]$_2$</td>
<td>HBcat</td>
<td>THF</td>
<td>dppb</td>
<td>AgOTf</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>9</td>
<td>[Rh(COD)$_2$]BF$_4$</td>
<td>HBcat</td>
<td>THF</td>
<td>dppb</td>
<td>-</td>
<td>52%</td>
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<tr>
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<td>[Rh(COD)$_2$]BF$_4$</td>
<td>HBcat</td>
<td>THF</td>
<td>dppb</td>
<td>-</td>
<td>73%</td>
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</table>

*a.5 mol% alkoxide and 2.0 equiv MeOH. b.5 mol% additive c.10 mol% catalyst and ligand used.*

Synthesis of alcohol S4 and boronic ester S5:

Naphthalene S1 (113.3 mg, 0.88 mmol, 2.0 equiv.) and MTAD (8, 50.0 mg, 0.44 mmol, 1.0 equiv.) were added to a test tube, which was sealed with a septum and evacuated/purged with nitrogen gas three times. Then CH$_2$Cl$_2$ (4.4 mL, 0.10 M) was added, and the reaction was cooled to −50 ºC and irradiated with visible
light. Upon decolorization, the LED lights were turned off and THF was added (4.4 mL, 0.10 M) followed by a solution of [Rh(cod)2]BF4 (18.0 mg, 44 µmol, 10 mol%) and dppb (18.9 mg, 44 µmol, 10 mol%) in CH2Cl2 (0.5 mL). HBCat (95 µL, 0.88 mmol, 2.0 equiv.) was added in a dropwise fashion over two minutes, and the temperature was adjusted to –30 ºC for 12 h, resulting in the formation of S3. Catechol ester S3 could be oxidized with sodium perborate tetrahydrate to give the corresponding alcohol S4 by preparing a suspension of NaBO2•4H2O (680.3 mg, 4.4 mmol, 10 equiv.) in H2O (8.8 mL), and directly adding the entire reaction mixture to the suspension, followed by 12 h of vigorous stirring. The reaction was then extracted with EtOAc, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification via flash chromatography (SiO2, EtOAc:hexanes = 1:2) afforded the alcohol S4 as a white solid (84.2 mg, 0.32 mmol, 73%).

mp: 219.4 – 220.2 ºC;
Rf = 0.16 (EtOAc:hexanes, 1:2 v/v)

1H NMR (500 MHz, CDCl3): δ 7.35 – 7.43 (m, 3H), 7.29 – 7.33 (m, 1H), 5.25 – 5.28 (m, 2H), 4.59 – 4.64 (dt, J = 7.6, 2.7, 2.7, 1H), 2.80 – 2.86 (m, 4H), 1.96 (br, 1H), 1.49 (dt, J = 14.0, 2.7, 2.7 Hz, 1H)

13C NMR (126 MHz, CDCl3): δ 156.9, 156.6, 135.1, 130.9, 129.7, 129.2, 126.9, 123.5, 65.0, 58.3, 53.3, 36.5, 25.5

IR (ATR, cm⁻¹): 3402 (br), 2947 (w), 2931 (w), 1768 (m), 1701 (s), 1461 (w), 1396 (w), 1091 (w), 759 (m), 548 (m)


Alternatively, a solution of pinacol in THF (440 µL, 2 M, 2.0 equiv.) was added to the reaction mixture containing S3 at –30 ºC. and the solution was warmed to room temperature slowly over the course of 12 h. The mixture was diluted with saturated NaCl, extracted with EtOAc, combined organic phases dried over MgSO4, and concentrated under reduced pressure. Purification via flash chromatography (SiO2, Et2O:hexanes = 1:4) afforded the boronic ester S5 as a white solid (120 mg, 0.32 mmol, 72%), which was readily crystallized from Et2O.

mp: 148.7 – 150.0 ºC

Rf = 0.56 (EtOAc:hexanes, 1:2 v/v)

1H NMR (500 MHz, CDCl3): δ 7.23 – 7.32 (m, 4H), 5.43 (d, J = 2.8 Hz, 1H), 5.28 (dd, J = 3.1, 2.6 Hz, 1H), 2.83 (s, 3H), 2.47 (ddd, J = 13.3, 10.6, 3.1 Hz, 1H), 2.11 (ddd, J = 10.6, 4.9, 2.8 Hz, 1H), 1.82 (ddd, J = 13.3, 4.9, 2.6 Hz, 1H), 1.04 (s, 6H), 0.98 (s, 6H)

13C NMR (126 MHz, CDCl3): δ 157.1, 156.7, 135.3, 134.8, 128.7, 128.3, 124.3, 123.4, 84.1, 55.4, 54.2, 26.1, 25.3, 24.8, 24.6, 20.5
IR (ATR, cm\(^{-1}\)):
2978 (w), 1769 (w), 1710 (s), 1452 (m), 1372 (m), 1332 (m), 1141 (m)

HRMS (m/z): [M+H]\(^+\) calcd. for C\(_{19}\)H\(_{25}\)N\(_3\)O\(_4\)B, 370.1933; found, 370.1935.

Synthesis of tetracenequinone 6:

Tetracene (5) (200.0 mg, 876 \(\mu\)mol, 1.0 equiv.), cobalt tetraphenylporphyrin (CoTPP, 29.4 mg, 43.8 \(\mu\)mol, 5 mol%), and (PhIO)\(_3\)SO\(_3\) (1.62 g, 2.19 mmol, 2.5 equiv.) were combined in a round-bottom flask purged with nitrogen. Then CH\(_2\)Cl\(_2\) (30 mL, 0.03 M) was added and the flask was stirred at 25 \(^\circ\)C for 2 h. The resulting dark solution was filtered through a pad of silica gel using ethyl acetate as an eluent, and the solvent was removed in vacuo. The crude yellow-orange solid was purified via flash chromatography (SiO\(_2\), CH\(_2\)Cl\(_2\):hexanes = 7:3) to afford the title compound 6 as a yellow-orange solid (173.4 mg, 670 \(\mu\)mol, 77%). All spectroscopic data were consistent with those previously reported.\(^{12}\) This compound is commercially available from several vendors.

Synthesis of tetracene derivative 7:

Tetracenequinone (6, 250.0 mg, 967 \(\mu\)mol, 1.0 equiv.), [Ru(p-cymene)Cl\(_2\)]\(_2\) (14.8 mg, 24.2 \(\mu\)mol, 2.5 mol%), and (bis(trifluoroacetoxy)iodo)benzene (PIFA, 1.04 g, 2.42 \(\mu\)mol, 2.5 equiv.) were combined in a vial and purged with nitrogen. Dichloroethane (DCE, 390 \(\mu\)L, 2.5 M) was added and the vial was heated to 100 \(^\circ\)C for 12 h. After cooling the resulting purple solution to room temperature, the reaction was charged with H\(_2\)O (349 \(\mu\)L, 19.36 mmol, 20 equiv.) and heated to 100 \(^\circ\)C for 12 h. After cooling the mixture to room temperature, the solvents were removed under reduced pressure, and potassium carbonate (K\(_2\)CO\(_3\), 2.68 g, 19.36 mmol, 20 equiv.) was added to the dark red gum. The mixture was purged with nitrogen for 30 min followed by the addition of acetone (4.8 mL), chloroform (4.8 mL) and dimethyl sulfate (1.8 mL, 19.36 mmol, 20 equiv.). The resulting mixture was then heated to 74 \(^\circ\)C for 24 h. After cooling, the orange solution was filtered, the insoluble residue was washed with CH\(_2\)Cl\(_2\), and the solvent was removed under reduced
pressure. The crude orange solid was purified via flash chromatography (SiO₂, CH₂Cl₂:hexanes = 7:3) to afford the title compound 7 as a yellow solid (118.6 mg, 407 μmol, 42%).

mp: 187–189 °C (lit.¹³ 188 °C)

R_f = 0.70 (CH₂Cl₂:hexanes, 7:1 v/v)

¹H NMR (500 MHz, CDCl₃): δ 8.40 – 8.42 (m, 2H), 8.25 – 8.27 (m, 2H), 7.73 – 7.75 (m, 4H), 4.13 (s, 6H)

¹³C NMR (126 MHz, CDCl₃): δ 182.9, 156.0, 135.1, 133.7, 132.9, 130.1, 126.9, 124.9, 120.9, 63.3

IR (ATR, cm⁻¹): 2935 (w), 2852 (w), 1666 (s), 1596 (m), 1400 (m), 1349 (s), 1272 (s), 1041 (m), 726 (s)

HRMS (m/z): [M+H]^+ calcd. for C₃₀H₁₅O₄, 319.0965; found, 319.0970.

Control experiment: Synthesis of tetracene derivative S₆:

Tetracenequinone (6) (250.0 mg, 967 μmol, 1.0 equiv.), [Ru(p-cymene)Cl₂]₂ (14.8 mg, 24.2 μmol, 2.5 mol%), and (bis(trifluoroacetoxy)iodo)benzene (PIFA, 1.04 g, 2.42 μmol, 2.5 equiv.) were combined in a vial and purged with nitrogen. Dichloroethane (DCE, 390 μL, 2.5 M) was added and the vial was heated to 100 °C for 12 h. After cooling the resulting purple solution to room temperature, water was added and resulting mixture was extracted with CH₂Cl₂ (3×30 mL). The combined organic layers were dried with MgSO₄ and the solvent was removed under reduced pressure. The crude orange solid was purified via flash chromatography (SiO₂, CH₂Cl₂:hexanes = 7:3) to afford the title compound S₆ as an orange solid (96.2 mg, 351 μmol, 36%).

mp: 312.6 – 313.6 °C (lit.¹⁴ 306 °C)

R_f = 0.33 (CH₂Cl₂:hexanes, 7:1 v/v)

¹H NMR (500 MHz, CDCl₃): δ 14.57 (s, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.39 (ddd, J = 13.5, 7.4, 3.4 Hz, 2H), 8.34 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.82 – 7.84 (m, 2H) 7.67 – 7.69 (m, 2H)

¹³C NMR (126 MHz, CDCl₃): δ 188.0, 182.7, 163.9, 136.5, 134.8, 134.6, 134.3, 131.4, 130.5, 129.1, 128.8, 127.9, 127.8, 127.2 (overlap of two peaks found by HSQC), 124.9, 121.9, 109.7

IR (ATR, cm⁻¹): 2917 (m), 1671 (m), 1615 (w), 1593 (m), 1457 (m), 1389 (m), 1282 (s) 752 (m), 715 (s)

HRMS (m/z): [M+H]^+ calcd. for C₁₈H₁₁O₃, 275.0703; found, 275.0701. These data are consistent with those reported in the literature.¹⁴,¹⁵
Synthesis of boronic ester 10 via dearomatative hydroboration:

\[ \text{Synthesis of boronic ester 10 via dearomatative hydroboration:} \]

A 250 mL Schlenk flask containing tetracene derivative 7 (3.00 g, 9.42 mmol, 1.0 equiv.) and MTAD (8, 1.28 g, 11.3 mmol, 1.2 equiv.) was evacuated and refilled with nitrogen five times. CH\(_2\)Cl\(_2\) (100 mL) was added and the flask was immediately cooled to −50 °C and irradiated with visible light. After the pink and yellow solution had become yellow-orange (36–48 h, see Photo S1), the LED lights were turned off and the reaction was cooled to −78 °C. Then THF (100 mL) was added followed by a solution containing [Rh(cod)\(_2\)]BF\(_4\) (383.8 mg, 0.94 mmol, 10 mol%) and dppb (389.1 mg, 0.942 mmol, 10 mol%) in CH\(_2\)Cl\(_2\) (4 mL). HBcat (2.0 mL, 18.8 mmol, 2.0 equiv.) was added dropwise over two minutes and the flask was placed in a −30 °C cooling bath for 24 h. The reaction was cooled to −78 °C, ethanol (550 L, 9.42 mmol, 1.0 equiv) was added followed by a solution of pinacol (1.11 g, 9.42 mmol, 1.0 equiv.) in THF (4.7 mL). The reaction was warmed to room temperature slowly over 12 h. A solution of saturated sodium chloride (100 mL) was added and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) until no color remained in the aqueous layer. Combined organic phases were dried over MgSO\(_4\), concentrated under reduced pressure, and purified under an inert atmosphere by flash chromatography (SiO\(_2\), hexanes:CH\(_2\)Cl\(_2\):Et\(_2\)O = 2:1:1) to afford the title compound 10 as a yellow solid (2.9 g, 9.42 mmol, 55%, 3:1 dr). The two diastereomers were inseparable by chromatography and were used in the following reaction as a 3:1 mixture. The major diastereomer could be isolated by precipitation from diethyl ether.

**mp:** 126 – 128 °C [decomposition]

**R\(_f\):** 0.16 (hexanes:CH\(_2\)Cl\(_2\):Et\(_2\)O, 2:1:1 v/v/v)

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.14 – 8.20 (m, 2H), 7.73 – 7.76 (m, 2H), 5.91 (d, \(J = 2.8\) Hz, 1H), 5.81 (dd, \(J = 3.5, 2.6\) Hz, 1H), 4.04 (s, 3H), 4.02 (s, 3H) 2.89 (s, 3H), 2.51 (ddd, \(J = 13.5, 10.4, 3.5\) Hz, 1H), 2.19 (ddd, \(J = 10.4, 5.0, 2.8\) Hz, 1H), 1.79 (ddd, \(J = 13.5, 5.0, 2.6\) Hz, 1H), 1.01 (s, 6H), 0.98 (s, 6H)

\(^13\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 182.9, 182.6, 156.6, 156.1, 151.7, 150.9, 137.7, 137.4, 133.9, 133.955, 133.949, 133.91, 127.8, 127.6, 126.8, 126.7, 84.4, 64.0, 63.9, 49.5, 48.1, 25.5, 25.2, 24.6, 24.6, 19.9

IR (ATR, cm\(^{-1}\)): 2978 (w), 2944 (w), 1768 (m), 1707 (s), 1671 (s), 1593 (m), 1577 (m), 1312 (s)

HRMS (m/z): [M+H]^+ calcd. for C\(_{29}\)H\(_{31}\)N\(_3\)O\(_8\)B, 560.2199; found, 560.2216.

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Synthesis of ketone 11 via Zweifel Olefination:

To a flask containing boronic ester 10 (3.0 g, 5.36 mmol, 1.0 equiv.) was added solid zinc powder (701 mg, 10.7 mmol, 2.0 equiv), THF (17.9 mL, 0.3 M), freshly distilled TMSCl (1.4 mL, 10.7 mmol, 2.0 equiv) and the resulting mixture was sonicated at 40 ºC for 30 min resulting in a dark red solution. Separately, to a cold (−78 ºC) solution of freshly distilled ethyl vinyl ether (8.1 mL, 80.5 mmol, 15 equiv) in THF (107 mL, 0.05 M relative to ester 10) was added tBuLi (31.5 mL, 1.7 M in pentane, 53.6 mmol, 10 equiv.) dropwise over five minutes. After stirring at −78 ºC for 30 min, the flask was placed in an ice bath for 20 min, during which time yellow color dissipated, and then cooled again to −78 ºC. The solution of S7 was removed from the sonication bath, allowed to cool to room temperature, and added dropwise over five minutes to the
solution of ethoxyvinyl lithium at –78 ºC resulting in a red solution. After stirring at –78 ºC for 30 min, the cryogenic bath was removed while stirring continued until the reaction reached an internal temperature of –25 ºC (approximately 12 min at this scale). Then the flask was immediately cooled to –78 ºC and a solution of iodine (10.9 g, 42.9 mmol, 8.0 equiv.) in THF (10 mL) was added dropwise over five minutes resulting in a burgundy solution. The reaction was stirred at –78 ºC for 30 min before the cryogenic bath was removed for another 12 min. The flask was once again cooled to –78 ºC before a solution of sodium methoxide (17.1 g, 80.5 mmol, 15 equiv.) in methanol (22 mL) was added dropwise over five minutes, resulting in a deep red solution. After keeping the reaction at –78 ºC for 30 min, the cryogenic bath was removed and stirring continued for an additional 4 hours at room temperature. Then aqueous HCl was added (150 mL, 1 M) and the resulting yellow solution was allowed to stir until hydrolysis of the vinyl ether to the methyl ketone 11 was complete (approximately 2 hours, monitored by TLC). The layers were separated, and the aqueous layer was extracted repeatedly with CH$_2$Cl$_2$ until color in the aqueous phase no longer persisted. The organic layers were combined, dried with MgSO$_4$, and concentrated resulting in a black-brown oil. This oil was dissolved in ethyl acetate (250 mL), washed with a saturated solution of Na$_2$S$_2$O$_3$ (3x150 mL), washed with a saturated sodium chloride solution (150 mL), dried over MgSO$_4$, and concentrated to afford a brown-yellow oil. Purification by flash chromatography (SiO$_2$, hexanes:CH$_2$Cl$_2$:EtOAc = 2:1:1) afforded the title compound 11 as a yellow solid (1.22 g, 3.58 mmol, 72%).

**mp**: 156 – 158 ºC [decomposition];

**Rf** = 0.12 (hexanes: CH$_2$Cl$_2$:EtOAc, 2:1:1v/v/v)

$^1$H NMR (500 MHz, CDCl$_3$): δ 8.14 – 8.16 (m, 2H), 7.74 – 7.76 (m, 2H), 6.15 (d, J = 3.0 Hz, 1H), 5.58 (dd, J = 3.5, 2.6 Hz, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 3.56 (ddd, J = 9.7, 4.5, 3.0 Hz, 1H), 2.92 (s, 3H), 2.44 (ddd, J = 13.7, 9.7, 3.5 Hz, 1H), 2.30 (s, 3H), 2.25 (ddd, J = 13.7, 4.5, 2.6 Hz, 1H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 203.2, 182.61, 182.58, 156.5, 156.4, 151.6, 151.0, 137.1, 134.07, 134.05, 133.89, 133.86, 133.81, 128.7, 128.1, 126.80, 126.78, 64.4, 64.2, 49.2, 48.0, 47.7, 28.6, 25.8, 25.0

**IR** (ATR, cm$^{-1}$): 2926 (w), 1714 (s), 1673 (m), 1592 (w), 1458 (m), 1312 (m), 1258 (m), 983 (w)

**HRMS** (m/z): [M+H]$^+$ calcd. for C$_{25}$H$_{22}$N$_3$O$_7$, 476.1453; found, 476.1481.
Synthesis of enone 12:

To a cold (−78 ºC) solution of 11 (500.0 mg, 1.05 mmol, 1.0 equiv.) in THF (10.5 mL) was added a solution of tBuOK (129.8 mg, 1.16 mmol, 1.1 equiv.) in THF (1.2 mL) dropwise over two minutes. This resulted in the yellow solution turning dark purple. After 20 minutes, dimethyl sulfate (502 μL, 5.26 mmol, 5.0 equiv.) was added and the reaction was warmed to 0 ºC and stirred at this temperature for 1.5 hours. The crude reaction mixture was concentrated under reduced pressure at 0 ºC and used without purification in the next step. To obtain an analytically pure sample, the residue was dry loaded on celite and immediately purified via flash chromatography (SiO$_2$, hexanes:CH$_2$Cl$_2$:EtOAc = 1:3:3) to deliver the title compound 12 as a yellow solid (407.3 mg, 0.831 mmol, 79%).

mp: 159 – 161 ºC [decomposition]

R$_f$ = 0.25 (hexanes: CH$_2$Cl$_2$:EtOAc, 1:3:3 v/v/v)

$^1$H NMR (500 MHz, CDCl$_3$): δ 8.19 – 8.21 (m, 2H), 7.92 (d, J = 3.0 Hz, 1H), 7.77 – 7.79 (m, 2H), 5.87 (dd, J = 9.5, 1.2 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.23 (dd, J = 19.3, 1.2 Hz, 1H), 3.05 (s, 2H), 2.75, (s, 3H), 2.61 (ddd, J = 19.3, 9.5, 3.0 Hz, 1H), 2.53 (s, 3H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 197.4, 182.6, 182.1, 156.7, 156.0, 155.3, 153.9, 138.7, 135.8, 134.2, 134.12, 134.05, 133.9, 133.4, 128.4, 127.9, 127.5, 127.0, 126.8, 63.7, 63.0, 48.1, 35.9, 26.1, 26.0, 25.9

IR (ATR, cm$^{-1}$): 2940 (w), 1772 (m), 1708 (s), 1667 (s), 1476 (m), 1457 (m), 1324 (s) 1239 (s), 1036 (m)

HRMS (m/z): [M+H]$^+$ calcd. for C$_{26}$H$_{24}$N$_3$O$_7$, 490.1609; found, 490.1613.
Table S2: The influence of N-substitution on Mukaiyama hydration:

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>R</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>CH₃</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>12a</td>
<td>H</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>12b</td>
<td>SEM</td>
<td>29%</td>
</tr>
<tr>
<td>4</td>
<td>12c</td>
<td>COPh</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>12d</td>
<td>MOM</td>
<td>53%</td>
</tr>
<tr>
<td>6</td>
<td>12e</td>
<td>Ac</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>12f</td>
<td>Boc</td>
<td>-</td>
</tr>
<tr>
<td>8ᵃ</td>
<td>12</td>
<td>CH₃</td>
<td>70%</td>
</tr>
</tbody>
</table>

ᵃ TBHP was not used, see below for optimized procedure.

Synthesis of α-ketol 13 via Mukaiyama hydration:

To a solution of enone 12 (500.0 mg, 1.02 mmol, 1.0 equiv.) in iPrOH (5 mL) and DCE (5 mL) at 0 °C was added Mn(dpm)₃ (61.8 mg, 0.102 mmol, 10 mol%) in a single portion. O₂ was then bubbled through the dark reaction mixture for 5 min. Then, Isopropoxy(phenyl)silane (640 µL, 3.064 mmol, 3.0 equiv.) was added in portions over the course of 1 hour at ambient temperature while oxygen continued to bubble through the reaction mixture. After the addition, the reaction was stirred for an additional hour. Celite (1g) was added to the mixture and solvent was removed in vacuo followed by purification via flash...
chromatography (SiO2, hexanes: CH2Cl2:EtOAc = 1:3:3) to provide the title compound 13 as a yellow solid (365.5 mg, 0.719 mmol, 70%).

mp: 129–130 °C [decomposition]

Rf = 0.11 (hexanes: CH2Cl2:EtOAc, 1:3:3 v/v/v)

1H NMR (500 MHz, CDCl3): δ 8.13 – 8.17 (m, 2H), 7.71 – 7.74 (m, 2H), 5.76 (t, J = 9.0 Hz, 1H), 3.99 (s, 1H), 3.87 (s, 6H), 3.06 – 3.20 (m, 5H), 2.90 (s, 3H), 2.42, (s, 3H), 2.24 – 2.32 (m, 2H)

13C NMR (126 MHz, CDCl3): δ 209.8, 182.7, 182.3, 156.4, 155.5, 155.0, 154.7, 139.3, 135.71, 134.02, 133.97, 133.9 (overlap of two peaks found by HSQC), 126.8, 126.7, 126.5, 125.0, 77.4, 62.5, 62.0, 51.2, 34.6, 34.3, 32.9, 25.8, 24.3

IR (ATR, cm⁻¹): 3429 (br), 2927 (w), 2854 (w), 1764 (m), 1700 (s), 1672 (s), 1482 (m), 1259 (s), 1101 (m), 1036 (m)

HRMS (m/z): [M+H]+ calcd. for C26H26N3O8, 508.1714; found, 508.1712.

Preparation of α-ketol 14:

To a cold (−78 °C) solution of α-ketol 13 (545.7 mg, 1.07 mmol, 1.0 equiv.) in CH2Cl2 (10.7 mL, 0.1 M) was added BCl3 (10.7 mL, 1M in CH2Cl2, 10.7 mmol, 10 equiv.) dropwise over two minutes. Stirring was continued for one hour at which point 10 mL of methanol was added and the reaction mixture was allowed to warm to room temperature. The solution was concentrated under reduced pressure to give a red residue. Purification via flash chromatography (SiO2, CH2Cl2:EtOAc = 8:2, 1% AcOH) provided the title compound 14 as a red solid (505.9 mg, 1.05 mmol, 98%).

mp: 248.2 – 248.9 °C

Rf = 0.23 (CH2Cl2:EtOAc, 8:2 v/v, 1% AcOH)

1H NMR (500 MHz, DMSO-d6): δ 13.49 (s, 1H), 13.24 (s, 1H), 8.23 – 8.26 (m, 2H), 7.96 – 7.98 (m, 2H), 5.94 (s, 1H), 5.61 (dd, J = 10.1, 8.4 Hz, 1H), 3.09 (dd, J = 18.1, 2.8 Hz, 1H) 3.00 (d, J = 18.1 Hz, 1H) 2.97 (s, 3H), 2.85 (s, 3H), 2.36 (ddd, J = 13.2, 8.4, 2.8 Hz, 1H) 2.33 (s, 3H), 2.11 (dd, J = 13.2, 10.1 Hz, 1H)

13C NMR (126 MHz, DMSO-d6): δ 211.5, 186.7, 186.6, 155.9, 155.2, 155.0, 154.4, 138.5, 135.1, 153.1, 132.9, 132.8, 132.0, 126.7, 126.6, 111.2, 110.0, 76.2, 50.8, 34.51, 34.49, 31.4, 25.3, 24.5

IR (ATR, cm⁻¹): 3259 (br), 2926 (w), 1766 (m), 1704 (s), 1624 (m), 1586 (m), 1403 (s), 1246 (s), 1115 (m), 734 (m)
HRMS (m/z): [M+Na]⁺ calcd. for C_{24}H_{21}N_{3}O_{8}Na, 502.1221; found, 502.1233.

Table S3: Optimization of the final transformation of hydroquinone 14.

<table>
<thead>
<tr>
<th>Entry</th>
<th>THF:MeOH:H₂O</th>
<th>Na₂S₂O₄ (eq.)</th>
<th>NaOH (eq.)</th>
<th>time before O₂ quench</th>
<th>Temp (°C)</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1:1</td>
<td>2.5</td>
<td>-</td>
<td>15 min</td>
<td>-10</td>
<td>14 only°</td>
</tr>
<tr>
<td>2</td>
<td>1:1:1</td>
<td>2.5</td>
<td>10</td>
<td>60 s</td>
<td>-10</td>
<td>&gt;85% 15°</td>
</tr>
<tr>
<td>3</td>
<td>1:1:1</td>
<td>2.5</td>
<td>2.5</td>
<td>60 s</td>
<td>-10</td>
<td>14 + 15 only°</td>
</tr>
<tr>
<td>4</td>
<td>2:2:1</td>
<td>2.5</td>
<td>2.5</td>
<td>60 s</td>
<td>-10</td>
<td>14 + 15 only°</td>
</tr>
<tr>
<td>5</td>
<td>2:2:1</td>
<td>2.5</td>
<td>2.5</td>
<td>120 s</td>
<td>-10</td>
<td>14 + 15 only°</td>
</tr>
<tr>
<td>6</td>
<td>1:1:1</td>
<td>2.0</td>
<td>2.5</td>
<td>120 s</td>
<td>-20</td>
<td>14 + 15 only°</td>
</tr>
<tr>
<td>7</td>
<td>1:1:1</td>
<td>2.0</td>
<td>5.0</td>
<td>60 s</td>
<td>-20</td>
<td>&lt;5% 4*</td>
</tr>
<tr>
<td>8</td>
<td>1:1:1</td>
<td>2.0</td>
<td>10</td>
<td>60 s</td>
<td>-20</td>
<td>20% 4*</td>
</tr>
<tr>
<td>9</td>
<td>1:1:1</td>
<td>2.0</td>
<td>10</td>
<td>30 s</td>
<td>-20</td>
<td>10% 4*</td>
</tr>
<tr>
<td>10</td>
<td>1:1:1</td>
<td>2.0</td>
<td>10</td>
<td>45 s</td>
<td>-20</td>
<td>20% 4*</td>
</tr>
<tr>
<td>11</td>
<td>1:1:1</td>
<td>2.0</td>
<td>10</td>
<td>45s°</td>
<td>-20</td>
<td>14 +15 only°</td>
</tr>
<tr>
<td>12</td>
<td>1:1:1</td>
<td>1.2</td>
<td>10</td>
<td>45s°°°°°</td>
<td>-20</td>
<td>22% 4, 57% 15°</td>
</tr>
<tr>
<td>13</td>
<td>1:1:1</td>
<td>1.2</td>
<td>10</td>
<td>60s°°°°°°</td>
<td>-20</td>
<td>31% 4, 57% 15°</td>
</tr>
</tbody>
</table>

**Notes:**
a. yield determined by NMR using 1,1,2,2-tetrachloroethane b. isolated yield c. 0.10 mmol scale instead of 0.02 mmol d. gas dispersion tube used to quench with O₂ instead of a needle.

Preparation of idarubicinone (4) and 7-deoxyidarubicinone (15):

A flask charged with 14 (50.0 mg, 104 µmol, 1.0 equiv.) and sodium dithionite (Na₂S₂O₄) (32.2 mg, 85 wt%, 156 µmol, 1.5 equiv.) was purged with nitrogen for 10 min. Degassed THF (2.1 mL, 0.05 M), MeOH (2.1 mL, 0.05 M), and H₂O (2.1 mL, 0.05 M) were sequentially added, and the mixture was stirred at room temperature for 20 min at which time the light-red solution had darkened significantly. The flask was cooled to -20 °C and an aqueous solution of NaOH (41.7 mg, 1.0 M, 10 equiv.) was added, resulting in a deep blue
solution. After 60 s, the septum was removed, and a gas dispersion tube connected to a balloon of O$_2$ was submerged into the reaction mixture at –20 °C, causing the reaction mixture to rapidly turn from deep blue to vibrant purple as the entire balloon was allowed to discharge into the solution via the gas dispersion tube (see Photo S2 for detail). The reaction was then diluted with 1M aqueous HCl, extracted with EtOAc, and concentrated under reduced pressure. Purification via flash chromatography (SiO$_2$, hexanes:EtOAc = 8:2, 1% AcOH) provided idarubicinone (4) as a red solid (12.7 mg, 33 µmol, 31%) and 7-deoxyidarubicinone (15, 21.4 mg, 59.6 µmol, 57%) also as a red solid.

Idarubicinone (4)

mp: 176.5 – 177.8 (lit.$^{16}$ 176 – 178 °C)
R$_f$ = 0.42 (hexanes:EtOAc = 8:2 v/v, 1% AcOH)

$^1$H NMR (500 MHz, CDCl$_3$): 13.60 (s, 1H), 13.33 (s, 1H), 8.34 – 8.37 (m, 2H), 7.83 – 7.86 (m, 2H), 5.31 – 5.35 (m, 1H), 4.53 (s, 1H), 3.78 (d, J = 5.3 Hz, 1H), 3.20 (dd, J = 18.6, 2.1 Hz, 1H), 2.97 (d, J = 18.6 Hz, 1H), 2.43 (s, 3H), 2.36 (dt, J = 14.4, 2.1, 2.1 Hz, 1H) 2.19 (dd, J = 14.4, 4.9 Hz, 1H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 211.7, 187.1, 186.9, 156.4, 135.9, 135.0, 134.8, 134.7, 133.6, 133.5, 127.3, 127.2, 111.5, 111.1, 77.0, 61.9, 35.6, 33.4, 24.6

IR (ATR, cm$^{-1}$): 3416 (br), 2917 (s), 2849 (m), 1715 (m), 1626 (m), 1587 (s), 1411 (m), 1373 (m), 1342 (w), 1262 (m), 1236 (s), 1035 (w)

HRMS (m/z): [M-H]$^-$ calcd. for C$_{20}$H$_{15}$O$_7$, 367.0823; found, 367.0818

7-deoxyidarubicione (15)

mp: 210.9 – 211.6 °C (lit.$^{17}$ 210 – 211 °C)
R$_f$ = 0.64 (hexanes:EtOAc = 8:2 v/v, 1% AcOH)

$^1$H NMR (500 MHz, DMSO-$d_6$): δ 13.24 – 13.27 (m, 2H), 8.17 – 8.19 (m, 2H), 7.92 – 7.94 (m, 2H), 5.67 (s, 1H), 2.84 (d, J = 18.1 Hz, 1H) 2.68 – 2.77 (m, 3H), 2.30 (s, 3H), 1.90 – 1.97 (m, 1H), 1.73 (ddd, J = 13.2, 9.9, 6.8 Hz, 2H)

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ 212.9, 186.0, 186.0, 155.9, 155.3, 137.1, 136.1, 134.8 (overlap of two peaks found by HSQC), 132.8, 132.8, 126.5 (overlap of two peaks found by HSQC), 109.2, 109.1, 74.8, 31.6, 28.0, 24.4, 20.0

IR (ATR, cm$^{-1}$): 3490 (br), 1702 (m), 1620 (m), 1586 (s), 1408 (s), 1376 (m), 1351 (m), 1315 (w), 1270 (s), 1205 (w)

HRMS (m/z): [M+H]$^+$ calcd. for C$_{20}$H$_{17}$O$_8$, 353.1025; found, 353.1022. These data are consistent with those reported in the literature.$^{16,17}$
Photo S2. Images of experimental setup for the final transformation of hydroquinone 15: The reaction at different time points from left to right: a. before the addition of NaOH; b. 10 s after the addition of NaOH; c. 60 s after the addition of NaOH; d. after the addition of O₂; e. after the addition of 1M HCl.

III. References

IV. $^1$H- and $^{13}$C-NMR Spectra of Compounds

(Spectra are not transcribed, but include chemical shifts and multiplicities for both proton and carbon nuclei.)
$S_4$

(COSY, CDCl$_3$, 500 MHz)

$S_4$

(HSQC, CDCl$_3$, 500 MHz)
$^{13}$C NMR, CDCl$_3$, 126 MHz

(COSY, CDCl$_3$, 500 MHz)
S5
(HSQC, CDCl₃, 500 MHz)

S5
(HMBC, CDCl₃, 500 MHz)
10
($^1$H NMR, CDCl$_3$, 500 MHz)

10
($^{13}$C NMR, CDCl$_3$, 126 MHz)
10
(COSY, CDCl₃, 500 MHz)

10
(HSQC, CDCl₃, 500 MHz)
\[ ^{13}C \text{ NMR, CDCl}_3, 126 \text{ MHz} \]

(COSY, CDCl\textsubscript{3}, 500 MHz)
13
$^{1}H$ NMR, CDCl$_3$, 500 MHz

13
$^{13}C$ NMR, CDCl$_3$, 126 MHz
13 (COSY, CDCl₃, 500 MHz)

13 (HSQC, CDCl₃, 500 MHz)
(13C NMR, DMSO-d6, 126 MHz)

(COSY, DMSO-d6, 500 MHz)
**1H NMR, DMSO-\textit{d}_6, 500 MHz**

**13C NMR, DMSO-\textit{d}_6, 126 MHz**
(HMBC, DMSO-d$_6$, 126 MHz)

(\(^1\)H NMR, CDCl$_3$, 500 MHz)
$^{13}$C NMR, CDCl₃, 126 MHz

(COSY, CDCl₃, 500 MHz)
IV. Crystallographic Data

Crystallographic data for compound 10

Single crystals of compound 10 were obtained by slow recrystallization from diethyl ether. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100.2 K during data collection.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>CCDC 1910638</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{29}H_{30}BN_{3}O_{8}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>559.37</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.54178)</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁/n</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 9.4519(2) Å, α= 90°, b = 16.7889(3) Å, β= 101.6745(7)°, c = 16.9365(3) Å, γ = 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>2632.00(9) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.412 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.854 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>1176</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.169 x 0.063 x 0.060 mm³</td>
</tr>
</tbody>
</table>
Theta range for data collection 3.746 to 68.373°.
Index ranges -10<=h<=11, -19<=k<=20, -20<=l<=20
Reflections collected 29258
Independent reflections 4835 [R(int) = 0.0508]
Completeness to theta = 67.679° 100.0%
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.7531 and 0.7005
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 4835 / 242 / 454
Goodness-of-fit on F² 1.034
Final R indices [I>2sigma(I)] R1 = 0.0360, wR2 = 0.0775
R indices (all data) R1 = 0.0490, wR2 = 0.0833
Extinction coefficient n/a
Largest diff. peak and hole 0.277 and -0.222 e.Å⁻³

Crystallographic data for compound S5

Single crystals of compound S5 were obtained by slow recrystallization from diethyl ether. A suitable crystal was selected and diffraction data were collected on a Mo Bruker D8 Venture/Photon II diffractometer. The crystal was kept at 100.01 K during data collection.

Identification code dd62u_0m
Empirical formula \( \text{C}_{19}\text{H}_{24}\text{BN}_{3}\text{O}_{4} \)

Formula weight 369.22

Temperature/K 100.01

Radiation MoK\(\alpha\) (\(\lambda = 0.71073\))

Crystal system monoclinic

Space group \(P2_1/n\)

Unit cell dimensions
- \(a = 15.5798(3) \ \text{Å}\) \(\alpha = 90^\circ\)
- \(b = 13.7634(2) \ \text{Å}\) \(\beta = 100.2570(10) \ ^\circ\)
- \(c = 17.7218(3) \ \text{Å}\) \(\gamma = 90^\circ\)

Volume \(3739.37(11) \ \text{Å}^3\)

\(Z\) 8

Density (calculated) 1.312 Mg/m\(^3\)

Absorption coefficient 0.092 mm\(^{-1}\)

\(F(000)\) 1568.0

Crystal size \(0.499 \times 0.31 \times 0.292 \ \text{mm}^3\)

Theta range for data collection 4.672 to 56.566 \(^\circ\)

Index ranges \(-20 \leq h \leq 20, -18 \leq k \leq 18, -23 \leq l \leq 23\)

Reflections collected 121199

Independent reflections 9271 [\(R_{int} = 0.0356, R_{sigma} = 0.0141\)]

Completeness to theta = 28.283\(^\circ\) 99.9 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.7457 and 0.7106

Refinement method Full-matrix least-squares on \(F^2\)

Data / restraints / parameters 9271 / 64 / 545

Goodness-of-fit on \(F^2\) 1.066

Final R indices [\(I > 2\sigma(I)\)] \(R_1 = 0.0361, wR_2 = 0.0937\)

R indices (all data) \(R_1 = 0.0441, wR_2 = 0.1032\)

Extinction coefficient n/a

Largest diff. peak and hole 0.38 and -0.22 e.Å\(^{-3}\)