Synthesis of Idarubicinone via Global Functionalization of Tetracene

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Submitted date: 30/04/2019 • Posted date: 02/05/2019

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Citation information: Dennis, David G.; Okumura, Mikiko; Sarlah, David (2019): Synthesis of Idarubicinone via Global Functionalization of Tetracene. ChemRxiv. Preprint.

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Synthesis of Idarubicinone via Global Functionalization of Tetracene

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Anthracyclines are archetypal representatives of the tetracyclic type II polyketide natural products that are widely used in cancer chemotherapy. Although the synthesis of this class of compounds has been a subject to several investigations, all known approaches are based on annulations, relying on the union of properly pre-functionalized building blocks. In a conceptually different construct aimed at the synthesis of these important molecules, a readily available tetranuclear compound could be used as a starting template, ideally requiring only functional decorations to reach the desired target molecule. Herein, we describe the realization of this concept, providing a non-annulative strategy to anthracyclines from a polynuclear arene. Specifically, tetracene was converted to idarubicinone, the aglycone of the FDA approved anthracycline idarubicin, through the judicious orchestration of Co- and Ru-catalyzed arene oxidation and arenophile-mediated dearomative hydroboration. Such a global functionalization strategy, a combination of site-selective arene and dearomative functionalization, provided the key anthracycline framework in five operations and enabled rapid and controlled access to idarubicinone. Finally, this design showcases the broader synthetic utility of long-underutilized simple polynuclear arenes as precursors for the synthesis of highly functionalized and stereochemically challenging products.

The *Streptomyces*-produced type II polyketides doxorubicin (**1**)¹ and daunorubicin (**2**)² are among the most effective and most often used chemotherapeutics due to their broad-spectrum of anticancer activity (Figure 1).³ For example, doxorubicin (**1**) is used for the treatment of breast and bladder cancers, childhood solid tumors, soft tissue sarcomas, and aggressive lymphomas.⁴ Similarly, daunorubicin (**2**) is primarily used as an antileukemic drug for multiple myeloma, acute myeloid leukemia, acute lymphocytic leukemia, and Kaposi's sarcoma.⁵ The antitumor activity of these agents is proposed to arise through several mechanisms, including the inhibition of DNA synthesis; DNA binding, cross-linking and alkylation; interference with DNA strand separation and helicase activity; topoisomerase-II-mediated DNA damage; and activation of apoptotic signaling pathways by reactive oxygen species.⁶ Although extremely effective, anthracyclines threaten patients with cumulative dose-dependent cardiotoxicity, severely limiting their long-term application as well as their use in patients with pre-existing cardiovascular risk.⁷ Therefore, significant research effort has been devoted to the identification of derivatives with improved pharmacological properties.⁸ The successful result of one such medicinal chemistry campaign is idarubicin (**3**),⁹ an FDA approved anticancer agent with superior therapeutic efficacy and reduced cardiotoxicity relative to daunorubicin (**2**).¹⁰

Figure 1. Clinically-relevant anthracyclines. Doxorubicin (**1**), daunorubicin (**2**), and idarubicin (**3**) are the most commonly used anthracyclines for chemotherapy.

Considering their clinical significance, the biosynthesis of anthracyclines has been a subject of intense research and proceeds through type II polyketide synthases.¹¹ The hallmark of this remarkable biosynthetic machinery is the minimal set of iteratively used enzymes that work in concert, attaching ketide units to a carrier protein that serves as an anchor for the growing polyketide chain (Fig. 2a). For the anthracyclines, nine iterative decarboxylative Claisen condensations of malonyl-CoA to a starter propionyl-CoA unit form a deca ketide, which undergoes a series of annulations, redox adjustments, glycosylation, and functionalizations to yield the final natural products.¹² Despite having well-characterized biosynthetic gene clusters, daunorubicin (**2**) is the only anthracycline commercially produced by fermentation. Other anthracycline-producing strains are less efficient or give a mixture of products that cannot easily be separated.¹³ Nevertheless, **2** has served as an important starting point for the synthesis of numerous analogs and derivatives intended to improve cancer treatment, including the natural products doxorubicin (**1**) and idarubicin (**3**). Moreover, the need for tailored analogs has made anthracyclines the subject of rigorous investigation within the synthetic community.^{14–18} Thus, many innovative pathways to the aglycon anthracyclines (anthracyclinones) have been established, all of which rely upon annulation to forge one of the rings (see Fig 2b). The most commonly employed unifying disconnection is C-ring annulation, achieved through cycloadditions,¹⁹ cationic cyclizations,²⁰ or anionic processes²¹ (Fig. 2b). Herein, we report a conceptually different, non-annulative approach to anthracyclinones, starting from a simple aromatic hydrocarbon *via* a global functionalization strategy (Fig. 2c). Specifically, idarubicinone (**4**) was synthesized from tetracene (**6**), an ideal aromatic precursor containing the essential tetracyclic framework. We envisioned that anthracyclinone **4** could be retrosynthetically traced back to **6** through a manifold of arene functionalizations (**6**→**5**) and a site-selective dearomative elaboration (**5**→**4**).

Figure 2. Synthesis of anthracyclines. **a**, Doxorubicin (**1**) and daunorubicin (**2**) are assembled by Type II polyketide synthases that condense a propionyl-CoA starter unit with nine malonyl-CoA extender units in an iterative fashion to form the polyketide backbone of these natural products. Each malonyl-CoA unit contributes a 2-carbon ketide unit (marked bold) to the growing polyketide chain. **b**, Representative cycloaddition, cationic, and anionic synthetic approaches towards the aglycons of **1–3** using intermolecular C-ring annulation-based strategies. **c**, Synthesis of idarubicinone (**4**) through a non-annulative approach (this work). The anthracyclinone **4** was envisioned to derive from the simple polynuclear aromatic starting material tetracene (**6**) through a series of arene and dearomative functionalizations.

Following this global functionalization strategy, we commenced our studies by exploring functionalization reactions of tetracene (**5**), which would establish the proper oxidation states of the internal B and C rings within idarubicinone (**4**) (Figure 3). Thus, inspired by a similar transformation reported on anthracene,²² we achieved the

first oxidation of **5** with catalytic cobalt(II) tetraphenylporphyrin (CoTPP, 5 mol%) and phenyliodine(III) sulfate as an oxidant, delivering 5,12-tetracenequinone (**7**) in 77% yield. Although this transformation proceeded readily, the second oxidation to the corresponding 6,11-dihydroxy-5,12-tetracenequinone (**5**) proved more challenging. Several oxidants known for direct arene oxidation, such as CAN, Frémy's salt, hypervalent iodine reagents, or oxidizing metal complexes²³ were found to be unsuitable for this transformation. This setback was not surprising, as this type of *peri*-oxidation remains a largely unsolved synthetic challenge due to the high oxidation potential of quinones. Therefore, we decided to evaluate C–H activation, anticipating that the quinone's carbonyls, would serve as weakly coordinating directing groups for the *peri*-(C-6) and (C-11) positions.²⁴ After examining several carbonyl-directed hydroxylation protocols, developed a one-pot protocol involving a modification of Ru-catalyzed sp^2 C–H oxygenation pioneered by Ackermann ($[\text{Ru}(\text{cymene})\text{Cl}_2]_2$ and PIFA),²⁵ followed by sequential one-pot hydrolysis and methylation to give desired product **7**. Control experiments revealed that this functionalization likely proceeds through the *peri*-selective formation of ruthenacycle intermediate **I-1**, delivering trifluoroacetylphenol **I-2**, which underwent further oxidation to the hydroquinone stage in the presence of excess PIFA (see Supplementary Information for details). Finally, one-pot hydrolysis of trifluoroacetates and methylation of the resulting hydroquinone intermediate with Me_2SO_4 and base furnished the desired product **5**.

Figure 3. Two-fold oxidative functionalization of tetracene. Using Co- and Ru-catalyzed oxidations, tetracene was converted to the corresponding tetracenequinone derivative **5**. TPP = 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine. cymene = isopropylbenzene

With arene oxidation completed, which set the required oxidation state of the B and C rings, we turned our attention to the dearomative functionalization of the terminal A ring (Fig. 4). We have recently reported a series of dearomatization strategies based on visible-light-promoted *para*-cycloaddition between arenes and arenophile *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD) and subsequent *in situ* manipulation of the resulting cycloadducts.^{26–30} With polynuclear arenes, we consistently observed highly site-selective cycloadditions onto the terminal rings. Based upon these findings, the tetracenequinone derivative **5** contains two such regions, rings A and D, amenable to cycloaddition with MTAD. However, the salient mechanistic feature of this process is a photoinduced charge- and electron-transfer from the arene to the arenophile;^{26,31} therefore, the HOMO of the arene should dictate the regioselectivity in polynuclear aromatic settings. Accordingly, computational studies (at the B3LYP/def2-TZVPPD level of theory) of **5** predicted a strong bias for the A ring, which has profoundly larger HOMO orbital coefficients, (see Fig 4. for the corresponding HOMO surface). Indeed, this prediction correlated well with experiment, as we observed exclusive cycloaddition onto the desired A-ring. With this site-selective dearomatization, which provided the cycloadduct **I-3**, we explored several strategies to introduce the remaining two carbon atoms needed to complete

the idarubicinone framework. We found that the arenophile-based cycloaddition in combination with *in situ* Rh-catalyzed alkene hydroboration (**5**→[**I-3**]→**8**) installed the boron moiety as a suitable handle for the introduction of an attached methyl ketone. Several hydroboration procedures were evaluated, but ultimately the cationic rhodium complex [Rh(cod)₂BF₄] with 1,4-bis(diphenylphosphino)butane (dppb) and catecholborane provided the best outcome (for optimization details see Table S1 in Supplementary Information).³² While catecholborane was essential for the hydroboration step, the inherent instability of the resulting alkyl catechol boronic ester required immediate transesterification of catechol to pinacol to enable product isolation in higher yields. Importantly, using this protocol, we were able to prepare multigram quantities of organoborate **10** in a single pass in 55% yield and 3:1 dr (see Fig. 4 for an X-ray of **8**).

Figure 4. Synthesis of idarubicinone (4). Tetracyclic derivative **5** underwent MTAD-mediated dearomative hydroboration and Zweifel olefination to install appendant methyl ketone **9**. Four additional operations, including Mukayama hydration (**10**→**11**) and urazole to alcohol exchange via semiquinone methide **I-5** delivered target compound **4**. B3LYP/def2-TZVPPD level of theory was used for FMO calculations of **5** (isocontour at ± 0.05 a.u.). MTAD, *N*-methyl-1,2,4-triazoline-3,5-dione; cod, 1,5-cyclooctadiene; Cat, catechol; Pin, pinacol; dppb, bis(diphenylphosphino)butane (dppb); Ur, urazole; TMS, trimethylsilyl; dpm, tris(dipivaloylmethanato).

Elaboration of organoborate **8** to the full skeleton of idarubicinone required installation of a two-carbon fragment through a seemingly straightforward *B*-alkyl Suzuki coupling reaction. However, since several standard Pd- and Ni-catalyzed conditions failed, we decided to explore the C–C bond forming strategies involving the rich chemistry of boron 1,2-metalate rearrangements. Particularly, we were keen to explore Zweifel olefination with lithiated ethoxyvinyl ether,³⁵ which would provide rapid access to the appendant methyl ketone. Nevertheless, a major pitfall of this design was the presence of the quinone and its general incompatibility with organolithium reagents. Indeed, the prospecting experiments involving boronate **8** and 1-ethoxyvinyl lithium resulted in the addition of organolithium species to quinone, delivering a mixture of products without any traces of the desired olefinated

product. To address this chemoselectivity issue, we developed a one-pot process which involved *in situ* masking of the quinone. Thus, a THF solution of quinone boronate **8** was sonicated with Zn powder in the presence of TMSCl, resulting in the formation of a fully protected *bis*-hydroquinone.³⁶ This intermediate was exposed to a freshly prepared lithiated ethyl vinyl ether to form the boronate complex **I-4**, which was immediately subjected to Zweifel protocol by addition of iodine and base.³⁷ Concurrently with olefination, the excess iodine also oxidized the labile silylated hydroquinone back to the quinone, and workup of the reaction mixture with an aqueous HCl solution hydrolyzed the newly introduced vinyl ether to the corresponding methyl ketone **9**. Remarkably, this one-pot operation involved several distinct transformations and was performed on a multigram scale with 72% yield.

While the arenophile-mediated dearomative hydroboration and subsequent Zweifel olefination introduced the desired methyl ketone, this sequence also installed a bridged urazole moiety, which had to be strategically transmuted to reveal the fully decorated A ring of idarubicinone (**4**). This task was partially accomplished by treatment of ketone **9** with base followed by Me₂SO₄, initiating β-elimination of urazole at position C-10 with subsequent methylation of urazole hydrazyl nitrogen, furnishing α,β-unsaturated ketone **10** in 79% yield. The *N*-alkylation of the urazole motif proved necessary to prevent undesired side reactions during subsequent manipulations (for details see Table S2 in Supplementary Information). Finally, subjecting olefin **10** to Mukaiyama hydration conditions³⁸ selectively introduced the tertiary alcohol at position C-9, as α-ketol product **11** was obtained in 70% yield as a single diastereoisomer. Notably, the use of recently reported silane, PhSiH₂(OiPr),³⁹ was beneficial for high conversions of this hydrogen-atom transfer process.

This hydration achieved the proper oxidation state of the A-ring, and the only difference between intermediate **11** and idarubicinone (**4**) at this stage resided in two hydroquinone protecting groups and the urazole moiety instead of a hydroxy group at C-7 position. While deprotection of methyl ethers to hydroquinone proceeded without any difficulties using BCl₃ (**11**→**12**, 98% yield), the removal of the urazole proved to be an arduous task. Eventually, the inspiration for the direct urazole-to-hydroxy exchange arrived from an older hypothesis for the biological mode of reactivity known as bioreductive alkylation.⁴⁰ Thus, it was proposed that anthracyclines undergo *in vivo* quinone reduction and subsequent C-7 amino sugar elimination, producing a reactive species in the form of a phenylogous quinone methide.⁴¹ Moreover, this concept was demonstrated in a bulk solution with several anthracyclines, which formed the corresponding semiquinone intermediates upon subjection to specific reducing agents.^{42,43} The direct translation of these findings to our system—for example the addition of sodium dithionite to precursor **12**—did not eliminate the urazole; however, after the addition of base (NaOH) we observed elimination and exclusive formation of 7-deoxyidarubicinone (**13**) under anaerobic conditions. This result was in accordance with the literature, since deoxygenated anthracyclines were commonly observed upon reduction of anthracyclines. Mechanistically, the reduction of quinone **12** to hydroquinone, followed by base-induced elimination of the urazole, likely formed the semiquinone methide **I-5**, which after protonation gave deaminated product **13**. However, we noticed that in the presence of oxygen, this reactive intermediate underwent competitive oxidation,⁴⁴ delivering idarubicinone (**I-5**→**4**). Accordingly, short exposure of **12** to an aqueous solution of sodium dithionite and NaOH, followed by rapid saturation of reaction mixture with oxygen provided idarubicinone (**4**) and 7-deoxyidarubicinone (**13**) in 88% yield and 1:1.8 ratio. While extensive optimization of this protocol did not result in a higher ratio of desired anthracyclinone **4** to **13**, this deoxygenated side-product could be readily converted to aglycone **4** in one or two steps using known protocols.⁴⁵⁻⁴⁸

In summary, we have described a functionalization-based approach to idarubicinone (**4**) from tetracene (**5**). The salient feature of this strategy is a judicious orchestration of two arene functionalizations and dearomatization, introducing functionality of A, B, and C rings of the anthracyclinone skeleton. Specifically, Co- and Ru-catalyzed arene oxidations, site-selective arenophile-mediated dearomative hydroboration, and subsequent Zweifel olefination provided the fully decorated anthracyclinone framework. Moreover, adjustment of the A ring, including a formally redox neutral urazole-to-hydroxy exchange delivered idarubicinone (**4**) in 8 operations from tetracene (**6**).

Importantly, by employing a simple polynuclear hydrocarbon aromatic starting material, the described work also presents a notable departure from previously reported syntheses of anthracyclines in which annulations were requisite to overall synthetic design. In fact, polynuclear arenes are not commonly considered in synthetic planning for construction of stereochemically complex scaffolds. However, through the development of new methodologies, the present study provides a compelling case in which tetracene serves as an ideal template for imprinting of desired functionality. Thus, given the availability of a range of polynuclear arenes, as well as numerous functionalization

opportunities, render this global functionalization approach an appealing and complementary entry for the preparation of other type II polyketide-like compounds.

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Acknowledgements

Financial support for this work was provided by the University of Illinois, the NIH/National Institute of General Medical Sciences (R01 GM122891), and the donors of the American Chemical Society Petroleum Research Fund (PRF#57175-DNII). D.S. is an Alfred P. Sloan Fellow. M.O. thanks the Honjo International Scholarship Foundation. Solvias AG is acknowledged for a generous gift of chiral ligands. We also thank Dr. D. Olson and Dr. L. Zhu for

NMR spectroscopic assistance, Dr. D. L. Gray and Dr. T. Woods for X-ray crystallographic analysis assistance, and F. Sun for mass spectrometric assistance.

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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. Anhydrous dichloromethane and tetrahydrofuran were purified using the MB-SPS solvent purification system containing activated alumina manufactured by MBRAUN. $[\text{Rh}(\text{cod})_2]\text{BF}_4$ was prepared following known procedure¹ from $[\text{Rh}(\text{cod})\text{Cl}]_2$. Pinacol hexahydrate was dried before use by azeotropic distillation with benzene followed by recrystallizing from benzene.² *N*-Methyl-1,2,4-triazoline-3,5-dione (MTAD) was prepared based on literature procedures.^{3,4} Catechol borane (HBcat) was prepared in two steps from catechol, boric acid, and borane dimethyl sulfide following literature procedures.⁵ Tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III) ($\text{Mn}(\text{dpm})_3$) was purchased from Strem Chemicals. Isopropoxy(phenyl)silane ($\text{Ph}(\text{iPrO})\text{SiH}_2$) was prepared from phenylsilane (PhSiH_3) according to reported procedure.⁶ 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 UV₂₅₄). Plates were visualized by UV and visible light. Silicycle SiliaFlash® P60 (SiO_2 , 40–63 μm particle size, 230–400 mesh) was used for flash column chromatography.

^1H NMR spectra were obtained at 500 MHz and ^{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, ^1H ; 77.0 ppm, ^{13}C) or residual deuterated dimethylsulfoxide (2.50 ppm, ^1H ; 35.92 ppm, ^{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^{-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 Olex2,⁷ the structures were solved with ShelXT⁸ 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 MTAD-mediated dearomative hydroboration:

S1 (2.0 eq)

+

MTAD
(S2, 1.0 eq)

→

S5

entry	catalyst	borane	solvent	ligand	additive	yield
1	CuCl	B ₂ pin ₂	THF	dppp	LiOtBu/MeOH	<5%
2	CuCl	B ₂ pin ₂	Toluene	IMes	KOtBu/MeOH	<5%
3	CuCl	B ₂ pin ₂	Toluene	IPr	KOtBu/MeOH	<5%
4	[Rh(COD)Cl] ₂	HBcat	THF	dppp	-	15%
5	[Rh(COD)Cl] ₂	HBcat	THF	dppb	-	25%
6	[Rh(COD)Cl] ₂	HBpin	THF	dppb	-	<5%
7	[Rh(COD)Cl] ₂	HBcat	THF	dppb	AgBF ₄	30%
8	[Rh(COD)Cl] ₂	HBcat	THF	dppb	AgOTf	<5%
9	[Rh(COD) ₂]BF ₄	HBcat	THF	dppb	-	52%
10 ^a	[Rh(COD) ₂]BF ₄	HBcat	THF	dppb	-	73%

Ur =

IMes, Ar = 1,3,5-Me-C₆H₂
IPr, Ar = 1,5-*i*Pr-C₆H₃

a. 10 mol% catalyst and ligand used.

Synthesis of alcohol **S5** and boronic ester **S6**:

Naphthalene (**S1**, 113.3 mg, 0.88 mmol, 2.0 equiv.) and MTAD (**S2**, 50.0 mg, 0.44 mmol, 1.0 equiv.) were added to the test tube, which was sealed with a septum and evacuated/purged with nitrogen gas three times. Then CH₂Cl₂ (4.4 mL, 0.10 M) was added, the reaction mixture was cooled to −50 °C, and irradiated with visible light. Upon decolorization, LED lights were turned off and THF (4.4 mL, 0.10 M) was added

followed by a solution of $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (18.0 mg, 44 μmol , 10 mol%) and dppb (18.9 mg, 44 μmol , 10 mol%) in CH_2Cl_2 (0.5 mL). HBcat (95 μL , 0.88 mmol, 2.0 equiv.) was added in a dropwise fashion, and the temperature was adjusted to $-30\text{ }^\circ\text{C}$ for 12 h, resulting in the formation of **S4**. Catechol ester **S4** could be oxidized with sodium perborate tetrahydrate to give the corresponding alcohol **S5** by preparing a suspension of $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (680.3 mg, 4.4 mmol, 10 equiv.) in H_2O (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 MgSO_4 , and concentrated under reduced pressure. Purification *via* flash chromatography (SiO_2 , EtOAc:hexanes = 1:2) afforded the alcohol **S5** as a white solid (84.2 mg, 0.32 mmol, 73%).

mp: 219.4 – 220.2 $^\circ\text{C}$

R_f = 0.16 (EtOAc:hexanes, 1:2 v/v):

^1H NMR (500 MHz, CDCl_3): δ 7.35 – 7.43 (m, 3H), 7.29 – 7.33 (m, 1H), 5.25 – 5.28 (m, 2H), 4.59 – 4.64 (m, 1H), 2.80 – 2.86 (m, 4H), 1.96 (br, 1H), 1.49 (ddd, J = 14.0, 3.8, 1.8 Hz, 1H)

^{13}C NMR (126 MHz, CDCl_3): δ 156.86, 156.61, 135.08, 130.88, 129.71, 129.24, 126.89, 123.47, 65.04, 58.32, 53.26, 36.52, 25.54

IR (ATR, cm^{-1}): 2947 (w), 2931 (w), 1768 (m), 1701 (s), 1461 (s), 1396 (w), 1091 (w), 759 (m), 548 (m)

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_3\text{O}_3$, 260.1035; found, 260.1036.

Alternatively, a solution of pinacol in THF (440 μL , 2 M, 2.0 equiv.) was added to the reaction mixture containing **S4** at $-30\text{ }^\circ\text{C}$ 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 MgSO_4 , and concentrated under reduced pressure. Purification *via* flash chromatography (SiO_2 , Et_2O :hexanes = 1:4) afforded the boronic ester **S6** as a white solid (120 mg, 0.32 mmol, 72%), which was readily crystallized from Et_2O .

mp: 148.7 – 150.0 $^\circ\text{C}$

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

^1H NMR (500 MHz, CDCl_3): 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)

^{13}C NMR (126 MHz, CDCl_3): δ 157.08, 156.74, 135.29, 134.83, 128.72, 128.32, 124.27, 123.44, 84.05, 55.43, 54.22, 26.07, 25.29, 24.77, 24.64, 20.46

IR (ATR, cm^{-1}): 2978 (w), 1769 (w), 1710 (s), 1452 (m), 1372 (m), 1332 (m), 1141 (m)

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_4\text{B}$, 370.1938; found, 370.1935.

Synthesis of tetracenequinone **7**:

Tetracene (**6**, 200.0 mg, 876 μ mol, 1.0 equiv.), cobalt tetraphenylporphyrin (CoTPP, 29.4 mg, 43.8 μ mol, 5 mol%), and (PhIO)₃SO₃ (1.62 g, 2.19 mmol, 2.5 equiv.) were combined in a round-bottom flask and purged with nitrogen. Then CH₂Cl₂ (29.2 mL, 0.03 M) was added and the mixture was stirred at 25 °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 (SiO₂, CH₂Cl₂:hexanes = 7:3) to afford the title compound **7** as a yellow-orange solid (173.4 mg, 670 μ mol, 77%). All spectroscopic data were consistent with those previously reported for this compound.⁹

Synthesis of tetracene derivative **5**:

Tetracenequinone (**7**, 250.0 mg, 967 μ mol, 1.0 equiv.), [Ru(*p*-cymene)Cl₂]₂ (14.8 mg, 24.2 μ mol, 2.5 mol%), and [bis(trifluoroacetoxy)iodo]benzene (PIFA, 1.04 g, 2.42 μ mol, 2.5 equiv.) were combined in a vial and purged with nitrogen. Dichloroethane (DCE, 390 μ L, 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, the reaction was charged with H₂O (349 μ L, 19.36 mmol, 20 equiv.) and heated to 100 °C for 12 h. After cooling the mixture to room temperature, the solvents were removed under reduced pressure, and potassium carbonate (K₂CO₃, 2.68 g, 19.36 mmol, 20 equiv.) was added to the dark red gum. The mixture was purged with N₂ for 30 min followed by addition of acetone (4.8 mL), chloroform (4.8 mL), and dimethyl sulfate (1.85 mL, 19.36 mmol, 20 equiv.). The resulting reaction was then heated to 74 °C for 24 h. After cooling, the orange solution was filtered, the insoluble residue was washed with CH₂Cl₂, 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 as a yellow solid (118.6 mg, 407 μ mol, 42%).

mp: 187–189 °C (lit.¹⁰ 188 °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 182.92, 155.98, 135.06, 133.67, 132.93, 130.07, 126.89, 124.94, 120.94, 63.32
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 C₂₀H₁₅O₄, 319.0970; found, 319.0970.

Control experiment: Synthesis of tetracene derivative **S7**:

Tetracenequinone (**7**, 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, 1.04g, 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 the 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 **S7** as an orange solid (96.2 mg, 351 μmol, 36%).

mp: 312.6 – 313.6 °C (lit.¹¹ 306 °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 187.80, 182.52, 163.73, 136.34, 134.64, 134.43, 134.15, 131.22, 130.36, 128.93, 128.60, 127.84, 127.65, 127.03 (overlap of two peaks found by HSQC), 124.83, 121.79, 109.56;

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, 275.0701; found, 275.0708. These data are consistent with those reported in the literature.^{11,12}

Synthesis of boronic ester **8** via dearomative hydroboration:

A 250 mL Schlenk flask containing tetracene derivative **5** (3.00 g, 9.42 mmol, 1.0 equiv.) and MTAD (1.28 g, 11.3 mmol, 1.2 equiv.) was evacuated and refilled with nitrogen five times. CH₂Cl₂ (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 slowly added followed by a solution containing [Rh(cod)₂]BF₄ (383.8 mg, 0.94 mmol, 10 mol%) and dppb (389.1 mg, 0.942 mmol, 10 mol%) in CH₂Cl₂ (4 mL). HBcat (2.02 mL, 18.8 mmol, 2.0 equiv.) was added dropwise and the flask was placed in a -30 °C cooling bath for 24 h. The reaction was cooled to -78 °C, ethanol (550 µL, 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 (4.71 mL). The reaction was warmed to room temperature slowly over 12 h. A solution of saturated sodium chloride (100 mL) was added and aqueous layer extracted with CH₂Cl₂ until no color remained in the aqueous layer. Combined organic phases were dried over MgSO₄, concentrated under reduced pressure, and residue purified under an inert atmosphere by flash chromatography (SiO₂, hexanes:CH₂Cl₂:Et₂O = 2:1:1) to afford the title compound 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:CH₂Cl₂:Et₂O, 2:1:1 v/v/v)

¹H NMR (500 MHz, CDCl₃): δ 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)

¹³C NMR (126 MHz, CDCl₃): δ 182.89, 182.57, 156.58, 156.14, 151.74, 150.88, 137.74, 137.40, 133.97, 133.955, 133.949, 133.91, 127.81, 127.57, 126.79, 126.72, 84.36, 63.97, 63.92, 49.46, 48.09, 25.52, 25.21, 24.62, 24.57, 19.87

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 C₂₉H₃₁N₃O₈B, 560.2204; found, 560.2216.

Photo S1. Images of Experimental Setup for Dearomative Hydroboration: Dearomatization of dimethoxytetracenequinone **5** with MTAD at $-50\text{ }^{\circ}\text{C}$ after 5 minutes (left) and 48 hours (right).

Synthesis of ketone **9** via Zweifel Olefination:

To a flask containing boronic ester **8** (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 $40\text{ }^{\circ}\text{C}$ for 1.5 h, resulting in a dark red solution. Separately, to a cold ($-78\text{ }^{\circ}\text{C}$) solution of freshly distilled ethyl vinyl ether (8.14 mL, 80.5 mmol, 15 equiv) in THF (107 mL, 0.05 M relative to ester **8**) was added dropwise $t\text{BuLi}$ (31.5 mL, 1.7 M in pentane, 53.6 mmol, 10 equiv.). After stirring at $-78\text{ }^{\circ}\text{C}$ for 30 min, the flask was placed in an ice bath for 20 min, during which time the yellow color dissipated, and then cooled again to $-78\text{ }^{\circ}\text{C}$. The solution of **S8** was removed from the sonication bath, allowed to cool to room temperature, and was added dropwise to the solution of

ethoxyvinyl lithium at $-78\text{ }^{\circ}\text{C}$, resulting in a red solution. After stirring at $-78\text{ }^{\circ}\text{C}$ for 30 min, the cryogenic bath was removed while stirring continued until the reaction reached an internal temperature of $-25\text{ }^{\circ}\text{C}$ (approximately 12 min at this scale). Then, the flask was immediately cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of iodine (10.9 g, 42.9 mmol, 8.0 equiv.) in THF (10 mL) was added dropwise, resulting in a burgundy solution. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min before the cryogenic bath was removed for another 12 min. The flask was once again cooled to $-78\text{ }^{\circ}\text{C}$ before a solution of sodium methoxide (17.1 g, 80.5 mmol, 15 equiv.) in methanol (22 mL) was added dropwise, resulting in a dark red solution. After keeping the reaction at $-78\text{ }^{\circ}\text{C}$ 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 yellow solution was allowed to stir until hydrolysis of the vinyl ether to the methyl ketone **9** was complete (approximately 2 hours, monitored by TLC). The layers were separated, and the aqueous layer was extracted repeatedly with CH_2Cl_2 until color in the aqueous phase no longer persisted. The organic layers were combined and the solvent was removed under reduced pressure resulting in a black-brown oil. This oil was dissolved in ethyl acetate (100 mL), washed with a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (3 x 150 mL), 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_2Cl_2 :EtOAc = 2:1:1) afforded the title compound **9** as a yellow solid (1.22 g, 3.58 mmol, 72%).

mp: 156 – 158 $^{\circ}\text{C}$ [decomposition]

R_f = 0.12 (hexanes: CH_2Cl_2 :EtOAc, 2:1:1 v/v/v)

^1H 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 203.15, 182.61, 182.58, 156.48, 156.35, 151.62, 150.97, 137.16, 134.07, 134.05, 133.89, 133.86, 133.81, 128.72, 128.07, 126.80, 126.78, 64.36, 64.15, 49.17, 47.99, 47.68, 28.60, 25.77, 24.96

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

HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}_7$, 476.1458; found, 476.1481.

Synthesis of enone **10**:

To a cold ($-78\text{ }^{\circ}\text{C}$) solution of **9** (500.0 mg, 1.05 mmol, 1.0 equiv.) in THF (10.5 mL) was added a solution of *t*BuOK (129.8 mg, 1.16 mmol, 1.1 equiv.) in THF (1.16 mL) dropwise. 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 $0\text{ }^{\circ}\text{C}$ for and stirred at this temperature for 1.5 hours. The crude reaction mixture was concentrated under reduced pressure at $0\text{ }^{\circ}\text{C}$ and used without purification in the next step. To obtain analytically pure sample, residue was dry loaded on celite and immediately purified *via* flash chromatography (SiO_2 , hexanes: CH_2Cl_2 :EtOAc = 1:3:3) to deliver the title compound **10** as a yellow solid (407.3 mg, 0.831 mmol, 79%).

mp: $159 - 161\text{ }^{\circ}\text{C}$ [decomposition]

R_f = 0.25 (hexanes: CH_2Cl_2 :EtOAc, 1:3:3 v/v/v):

^1H NMR (500 MHz, CDCl_3): δ 8.19 – 8.21 (m, 2H), 7.92 (d, $J = 3.0\text{ Hz}$, 1H), 7.77 – 7.79 (m, 2H), 5.87 (dd, $J = 9.5, 1.2\text{ Hz}$, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.23 (dd, $J = 19.3, 1.2\text{ Hz}$, 1H), 3.05 (s, 3H), 2.75, (s, 3H), 2.61 (ddd, $J = 19.3, 9.5, 3.0\text{ Hz}$, 1H), 2.53 (s, 3H)

^{13}C NMR (126 MHz, CDCl_3): δ 197.40, 182.62, 182.05, 156.69, 156.03, 155.33, 153.93, 138.70, 135.82, 134.21, 134.12, 134.05, 133.90, 133.37, 128.37, 127.85, 127.45, 126.96, 126.82, 63.66, 63.03, 48.06, 35.89, 26.12, 25.98, 25.85

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): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_7$, 490.1614; found, 490.1613.

Table S2: The influence of *N*-substitution on Mukaiyama hydration:

entry	compound	R	yield
1	10	CH ₃	56%
2	10a	H	18%
3	10b	SEM	29%
4	10c	COPh	50%
5	10d	MOM	53%
6	10e	Ac	—
7	10f	Boc	—
8 ^a	10	CH ₃	70%

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

Synthesis of α -ketol **11** via Mukaiyama hydration:

To a solution of enone **10** (500.0 mg, 1.02 mmol, 1.0 equiv.) in *i*PrOH (5 mL) and DCE (5 mL) at 0 °C was added Mn(dpm)₃ (61.8 mg, 0.102 mmol, 10 mol%) and oxygen was bubbled through the dark reaction mixture for 5 min. Then, isopropoxy(phenyl)silane (640 μ L, 3.064 mmol, 3.0 equiv.) was added in portions over the course of 1 h 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, solvent was removed *in vacuo*, and the residue was purified *via* flash chromatography (SiO₂, hexanes: CH₂Cl₂:EtOAc = 1:3:3) to provide the title compound **11** as a yellow solid (365.5 mg, 0.719 mmol, 70%).

mp: 129–130 °C [decomposition]

R_f = 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 209.83, 182.70, 182.32, 156.39, 155.54, 155.00, 154.70, 139.33, 135.71, 134.02, 133.97, 133.85 (overlap of two peaks found by HSQC), 126.80, 126.71, 126.48, 125.00, 77.36, 62.46, 62.00, 51.22, 34.59, 34.28, 32.92, 25.76, 24.28

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, 508.1720; found, 508.1712.

Preparation of α-ketol **12**:

To a cold (–78 °C) solution of α-ketol **11** (545.7 mg, 1.07 mmol, 1.0 equiv.) in CH₂Cl₂ (10.7 mL, 0.1 M) was dropwise added BCl₃ (10.7 mL, 1M in CH₂Cl₂, 10.7 mmol, 10 equiv.). Stirring was continued for additional hour at which point 10 mL of methanol was slowly added and the reaction mixture was allowed to warm to room temperature. The solution was concentrated under reduced pressure to give a red gummy residue. Purification *via* flash chromatography (SiO₂, CH₂Cl₂:EtOAc = 8:2, 1% AcOH) provided the title compound **12** as a red solid (505.9 mg, 1.05 mmol, 98%).

mp: 248.2 – 248.9 °C

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

¹H NMR (500 MHz, DMSO-*d*₆): 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 (t, J = 9.3 Hz, 1H), 2.97 – 3.11 (m, 5H), 2.85 (s, 3H), 2.33 – 2.38 (m, 4H), 2.11 (dd, J = 13.5, 9.3 Hz, 1H)

¹³C NMR (126 MHz, DMSO-*d*₆): δ 211.52, 186.69, 186.64, 155.87, 155.19, 154.96, 154.44, 138.50, 135.13, 153.08, 132.92, 132.80, 132.03, 126.67, 126.63, 111.16, 109.98, 76.21, 50.83, 34.51, 34.49, 31.38, 25.30, 24.48

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 C₂₄H₂₁N₃O₈Na, 502.1226; found, 502.1233.

Table S3: Optimization of the final transformation of hydroquinone **12.**

Entry	THF:MeOH:H ₂ O	Na ₂ S ₂ O ₄ (eq.)	NaOH (eq.)	time before O ₂ quench	Temp (°C)	result
1	1:1:1	2.5	-	15 min	-10	12 only ^a
2	1:1:1	2.5	10	60s	-10	>85% 7 ^a
3	1:1:1	2.5	2.5	60s	-10	12 + 7 only ^a
4	2:2:1	2.5	2.5	60s	-10	12 + 7 only ^a
5	2:2:1	2.5	2.5	120s	-10	12 + 7 only ^a
6	1:1:1	2.0	2.5	120s	-20	12 + 7 only ^a
7	1:1:1	2.0	5.0	60s	-20	<5% 4 ^a
8	1:1:1	2.0	10	60s	-20	20% 4 ^a
9	1:1:1	2.0	10	30s	-20	10% 4 ^a
10	1:1:1	2.0	10	45s	-20	20% 4 ^a
11	1:1:1	2.0	10	45s ^c	-20	12 + 7 only ^a
12	1:1:1	1.2	10	45s ^{c,d}	-20	22% 4 , 57% 12 ^b
13	1:1:1	1.2	10	60s ^{c,d}	-20	31% 4 , 57% 12 ^b

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 (**13**):

A flask charged with **12** (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 (2.09 mL, 0.05 M), MeOH (2.09 mL, 0.05 M), and H₂O (2.09 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 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, a gas dispersion tube connected to a balloon of O₂ was submerged into the reaction mixture at –20 °C, causing the reaction mixture rapidly turned from deep blue to vibrant purple (see Photo S2 for details). The reaction was then diluted with 1M aqueous HCl, extracted with EtOAc, and concentrated under reduced pressure. Purification *via* flash chromatography (SiO₂, hexanes:EtOAc = 8:2, 1% AcOH) provided idarubicinone (**4**) as a red solid (12.7 mg, 33 μmol, 31%) and 7-deoxyidarubicinone (**13**, 21.4 mg, 59.6 μmol, 57%) also as a red solid.

Idarubicinone (**4**):

mp: 176.5 – 177.8 (lit.¹³ 176 – 178 °C)

R_f = 0.42 (hexanes:EtOAc = 8:2 v/v, 1% AcOH)

¹H NMR (500 MHz, CDCl₃): 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)

¹³C NMR (126 MHz, CDCl₃): δ 211.67, 187.06, 186.94, 156.64, 156.35, 135.88, 134.98, 134.75, 134.74, 133.62, 133.59, 127.28, 127.22, 111.54, 111.08, 76.96, 61.93, 35.59, 33.44, 24.62

IR (ATR, cm⁻¹): 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 C₂₀H₁₅O₇, 367.0816; found, 367.0818

7-deoxyidarubicinone (**13**):

mp: 210.9 – 211.6 °C (lit.¹⁴ 210 – 211 °C)

R_f = 0.64 (hexanes:EtOAc = 8:2 v/v, 1% AcOH)

¹H 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), 2.70 – 2.88 (m, 4H), 2.30 (s, 3H), 1.90 – 1.97 (m, 1H), 1.70 – 1.77 (m, 2H)

¹³C NMR (126 MHz, DMSO-*d*₆): δ 212.87, 186.01, 185.95, 155.89, 155.32, 137.08, 136.07, 134.81 (overlap of two peaks found by HSQC), 132.79, 132.78, 126.46 (overlap of two peaks found by HSQC), 109.18, 109.07, 74.82, 31.63, 28.01, 24.38, 19.93

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 C₂₀H₁₇O₆, 353.1025; found, 353.1022. These data are consistent with those reported in the literature.^{13,14}

Photo S2. Images of experimental setup for the final transformation of hydroquinone **12**: 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.

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

(HSQC, CDCl₃, 500 MHz)

(HMBC, CDCl₃, 500 MHz)

10
(HMBC, CDCl₃, 500 MHz)

IV. Crystallographic Data

Crystallographic data for compound **8**

Single crystals of compound **8** 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.

Identification code	CCDC 1910638	
Empirical formula	$\text{C}_{29}\text{H}_{30}\text{BN}_3\text{O}_8$	
Formula weight	559.37	
Temperature	100(2) K	
Radiation	$\text{CuK}\alpha$ ($\lambda = 1.54178$)	
Crystal system	Monoclinic	
Space group	$\text{P2}_1/\text{n}$	
Unit cell dimensions	$a = 9.4519(2) \text{ \AA}$	$\alpha = 90^\circ$.
	$b = 16.7889(3) \text{ \AA}$	$\beta = 101.6745(7)^\circ$.
	$c = 16.9365(3) \text{ \AA}$	$\gamma = 90^\circ$.
Volume	$2632.00(9) \text{ \AA}^3$	
Z	4	
Density (calculated)	1.412 Mg/m^3	
Absorption coefficient	0.854 mm^{-1}	
F(000)	1176	
Crystal size	$0.169 \times 0.063 \times 0.060 \text{ mm}^3$	
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 F ²
Data / restraints / parameters	4835 / 242 / 454
Goodness-of-fit on F ²	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 **S6**

Single crystals of compound **S6** 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	CCDC 1913279
Empirical formula	C ₁₉ H ₂₄ BN ₃ O ₄
Formula weight	369.22

Temperature/K	100.01
Radiation	MoK α ($\lambda = 0.71073$)
Crystal system	monoclinic
Space group	P2 ₁ /n
Unit cell dimensions	$a = 15.5798(3) \text{ \AA}$ $\alpha = 90^\circ$ $b = 13.7634(2) \text{ \AA}$ $\beta = 100.2570(10)^\circ$ $c = 17.7218(3) \text{ \AA}$ $\gamma = 90^\circ$
Volume	$3739.37(11) \text{ \AA}^3$
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°
Index ranges	$-20 \leq h \leq 20$, $-18 \leq k \leq 18$, $-23 \leq l \leq 23$
Reflections collected	121199
Independent reflections	9271 [$R_{\text{int}} = 0.0356$, $R_{\text{sigma}} = 0.0141$]
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 $-0.22 \text{ e.\AA}^{-3}$

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