Synthesis of Idarubicinone via Global Functionalization of Tetracene

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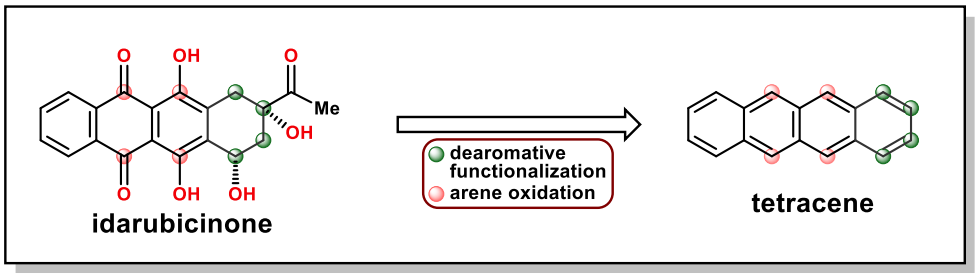

Anthracyclines are archetypal representatives of the tetracyclic type II polyketide natural products that are widely used in cancer chemotherapy. Although the synthesis of this class of compounds has been a subject to several investigations, all known approaches are based on annulations, relying on the 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]

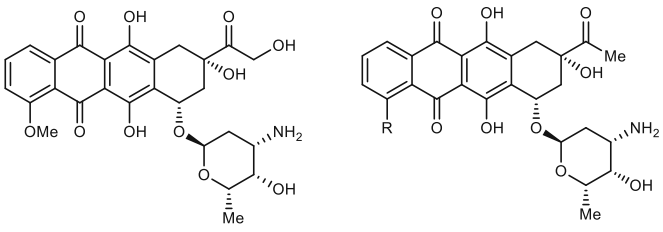

Figure 1. Clinically-relevant anthracyclines. Doxorubicin (**1**), daunorubicin (**2**), and idarubicin (**3**) are the most commonly used anthracyclines for chemotherapy.

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 decaketide, 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 processes[21] (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**).

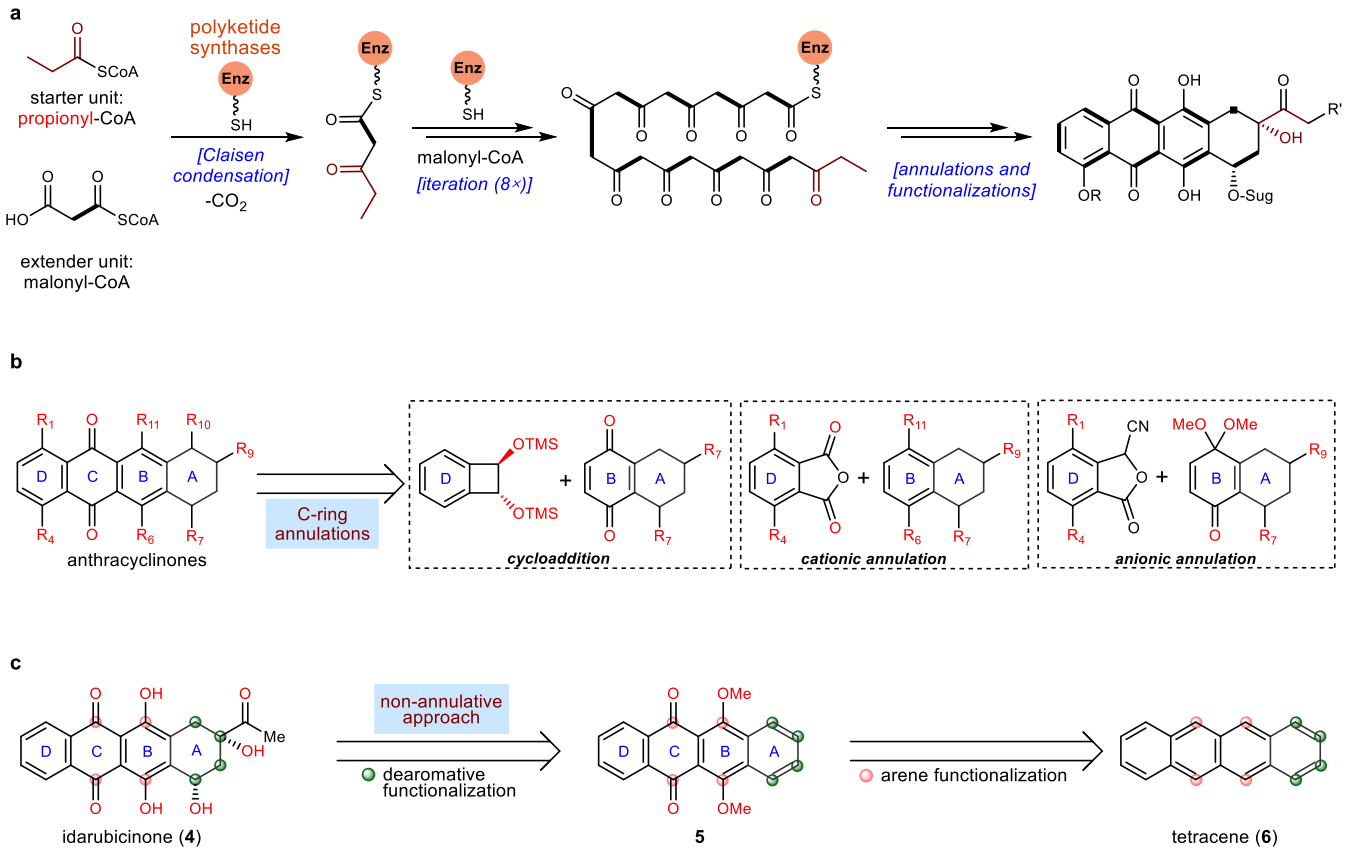

Figure 2. Synthesis of anthracyclines. a, Doxorubicin (**1**) and daunorubicin (**2**) are assembled by Type II polyketide synthases that condense a propionyl-CoA starter unit with nine malonyl-CoA extender units in an iterative fashion to form the polyketide backbone of these natural products. Each 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 complexes[23] 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 ($[Ru(cymene)Cl_2]_2$ 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 trifluoroacylphenol **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**.

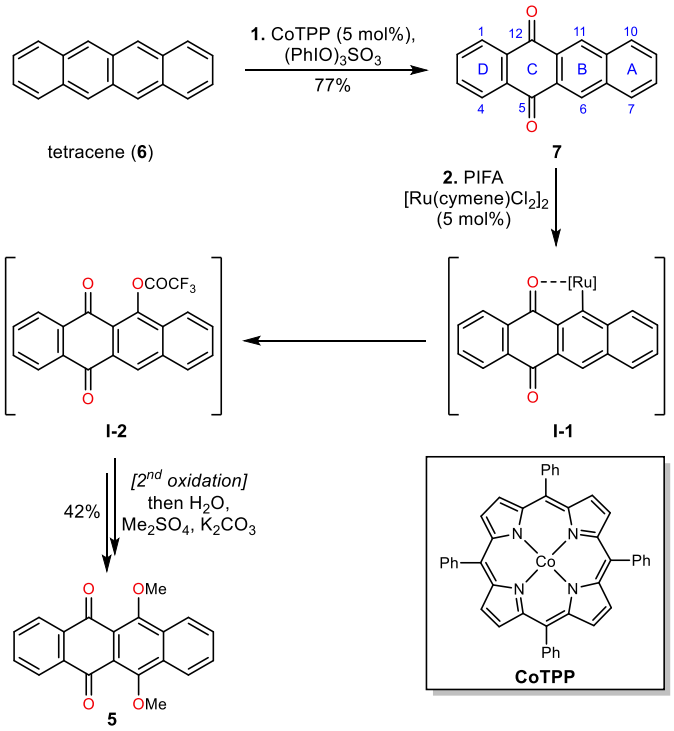

Figure 3. Two-fold oxidative functionalization of tetracene. Using Co- and Ru-catalyzed oxidations, tetracene was converted to the corresponding tetracenequinone derivative **5**. TPP = 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine. cymene = isopropylbenzene

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)$_2$BF$_4$] 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**).

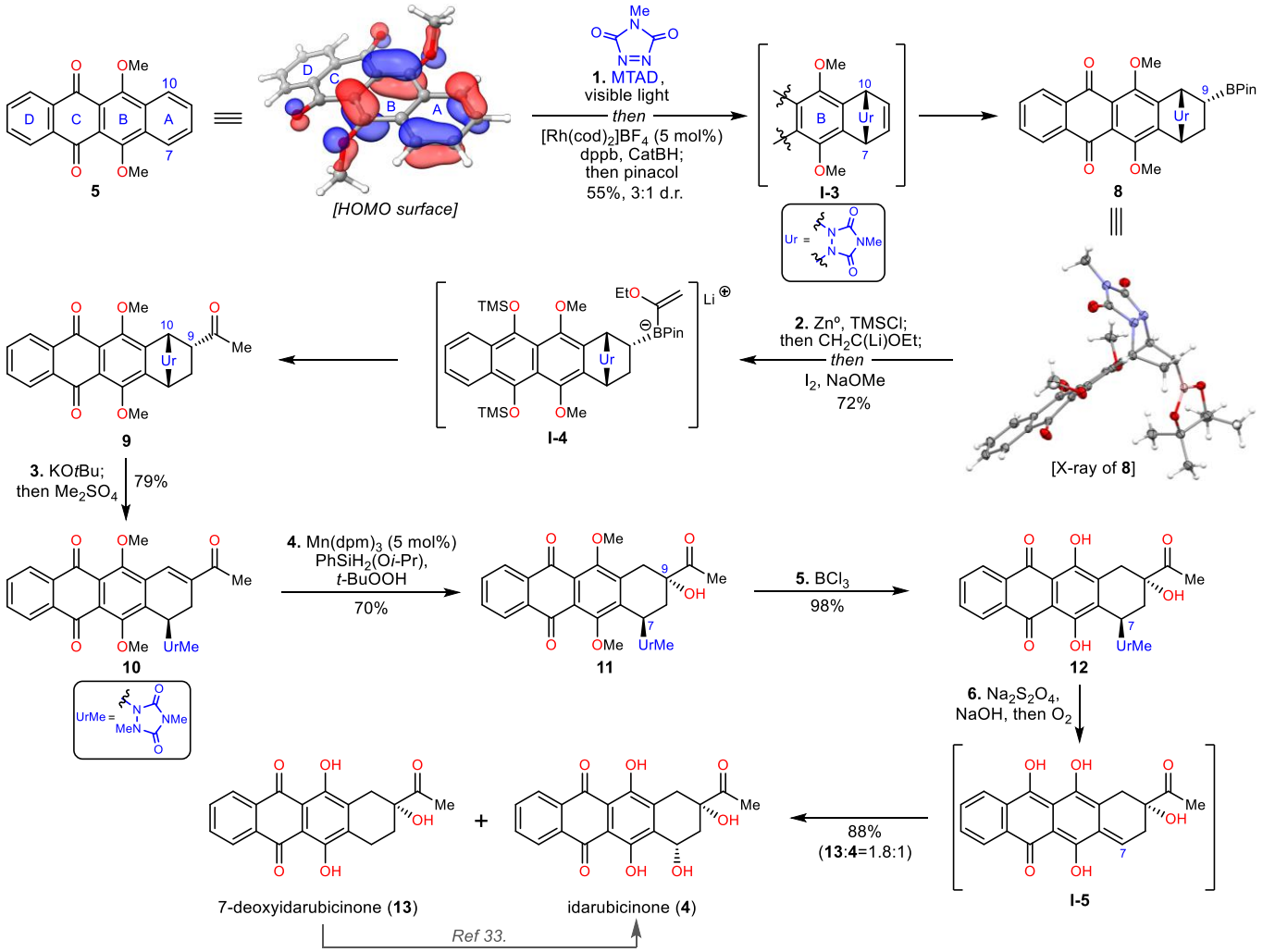

Figure 4. Synthesis of idarubicinone (4). Tetracyclic derivative **5** underwent MTAD-mediated dearomative hydroboration and and Zweifel olefination to install appendant methyl ketone **9**. Four additional operations, including Mukayama hydration (**10**→**11**) and urazole to alcohol exchange via semiquinone 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-ethoxyvinyllithium 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 Me_2SO_4, 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 conditions[38] 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, $PhSiH_2(OiPr)$,[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 BCl_3 (**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 anthracyclinones 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 anthracyclinones 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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