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

David G. Dennis, Mikiko Okumura, and David Sarlah*

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801, United States

Supporting Information

ABSTRACT: 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 of several investigations, all known approaches are based on annulations, relying on the union of properly prefunctionalized building blocks. Herein, we describe a conceptually different approach using a polynuclear arene as a starting template, ideally requiring only functional decorations to reach the desired target molecule. 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, the combination of site-selective arene and dearomative functionalization, provided the key anthracycline framework in five operations and enabled rapid and controlled access to (±)-idarubicinone.

The *Streptomyces*-produced type II polyketides doxorubicin (**1**)[1] and daunorubicin (**2**)[2] are among the most effective and most often used chemotherapeutics owing 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] 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.[6] Therefore, significant research efforts have been devoted to the identification of derivatives with improved pharmacological properties.[7] The successful result of one such medicinal chemistry campaign is idarubicin (**3**),[8] an FDA approved anticancer agent with superior therapeutic efficacy and reduced cardiotoxicity relative to daunorubicin (**2**).[9]

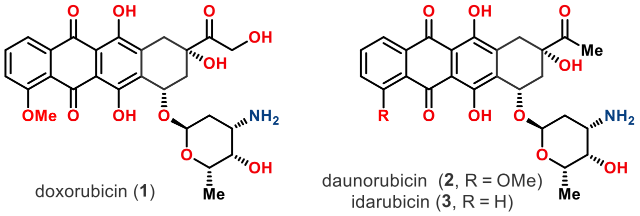

Figure 1. Structures of doxorubicin (**1**), daunorubicin (**2**), and idarubicin (**3**).

The need for tailored analogs has made anthracyclines the subject of rigorous investigation within the synthetic community.[10] 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 Figure 2a). The most commonly employed unifying disconnection is C-ring annulation, achieved through cycloadditions, cationic cyclizations, or anionic processes (Figure 2a, left inset).[11] Moreover, cycloadditions were also explored to forge other rings of the tetracyclic core of these molecules (Figure 2a, right insets).[12] Herein, we report a conceptually different, nonannulative approach to anthracyclinones, starting from a simple aromatic hydrocarbon via a global functionalization strategy (Figure 2b). Specifically, (±)-idarubicinone (**4**) was synthesized from tetracene (**5**), an ideal aromatic precursor containing the essential tetracyclic framework, through a manifold of arene functionalizations and a site-selective dearomative elaboration.

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 rings B and C within idarubicinone (**4**) (Figure 3). Thus, inspired by a similar transformation reported on anthracene, we achieved the first oxidation of **5** with catalytic amounts of cobalt(II) tetraphenylporphyrin (CoTPP, 5 mol %) and phenyliodine(III) sulfate as an oxidant,[13] delivering 5,12-tetracenequinone (**6**) in 77% yield. Although this transformation proceeded readily, the second oxidation to the corresponding 6,11-dihydroxy-5,12-tetracenequinone derivative **7** proved more challenging. Several oxidants known for direct arene oxidation, such as CAN, Frémy's salt, hypervalent iodine reagents, or oxidizing metal complexes,[14] 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 owing to the high oxidation potential of quinones. Therefore, we decided to evaluate C−H activation, anticipating that the quinone carbonyl groups would serve as weakly coordinating directing groups for the *peri*-(C-6) and (C-11) positions.[15] After examining several carbonyl-directed hydroxylation protocols, we developed a

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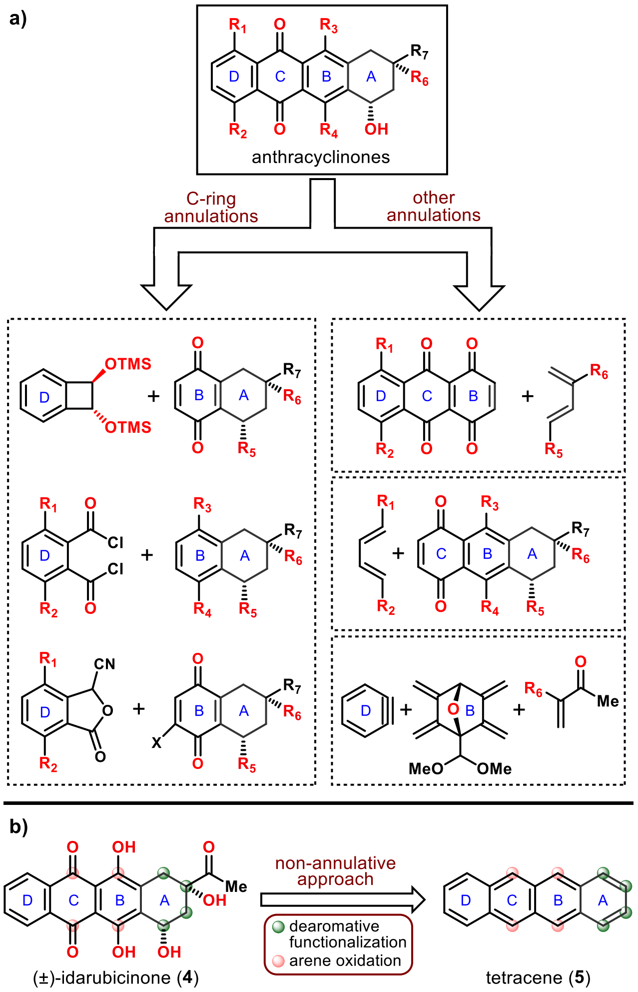

Figure 2. (a) Selected annulation-based strategies to anthracyclinones. (b) This work: synthesis of (±)-idarubicinone (4) from tetracene (5) using a nonannulative approach.

one-pot procedure involving a modification of Ru-catalyzed sp^2 C−H oxygenation pioneered by Ackermann ($[Ru(cymene)Cl_2]_2$ and PIFA),[16] 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 phenol derivative, which underwent further oxidation to the hydroquinone stage in the presence of excess PIFA.[17]

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 ring A. We have recently reported a series of dearomatization strategies that employ visible-light-promoted *para*-cycloaddition between arenes and the arenophile *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD, **8**) and subsequent *in situ* manipulation of the resulting cycloadducts.[18] With polynuclear arenes, we consistently observed highly site-selective cycloadditions onto the terminal rings. Because tetracenequinone derivative **7** contains two such regions, rings A and D, amenable to cycloaddition with MTAD, another level of complexity to this process was introduced. However, based on previous studies, we know that the relevant mechanistic feature of this process is a photoinduced charge- and electron-transfer from the arene to the arenophile;[19] therefore, the HOMO of the arene should dictate the site-selectivity in polynuclear aromatic settings. Accordingly, computational studies (at the B3LYP/def2-TZVPPD level of theory) of **7** predicted a strong bias for the A ring, which has profoundly larger HOMO orbital coefficients, (see Figure 3, bottom inset for the corresponding HOMO surface). Indeed, this prediction correlated well with experiment, as we observed exclusive cycloaddition onto the A-ring to provide intermediate **9**. With this site-selective dearomatization, 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 (**7** → [**9**] → **10**) installed the boron moiety as a suitable handle for the introduction of the requisite acetyl group. Several hydroboration procedures were evaluated, but ultimately the cationic rhodium complex $[Rh(cod)_2BF_4]$ with 1,4-bis(diphenylphosphino)butane (dppb) and catecholborane provided the best outcome (for optimization details, see Table S1 in Supporting Information).[20] Although 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.[21] Importantly, following this protocol, we were able to prepare multigram quantities of boronic ester **10** in a single pass in 55% yield and an endo/exo 3:1 dr (see Figure 3, bottom inset for an X-ray diffraction structure of **10**).

Elaboration of organoborate **10** 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 reaction conditions failed,[22] 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,[23] which would provide rapid access to the C-9 acetyl group. Nevertheless, a major pitfall of this design was the presence of the quinone and its general incompatibility with organolithium reagents. Indeed, prospecting experiments involving boronic ester **10** 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 that involved *in situ* masking of the quinone. Thus, a tetrahydrofuran (THF) solution of boronic ester **10** was sonicated with Zn powder in the presence of trimethylsilyl chloride (TMSCl), resulting in the formation of a fully protected *bis*-hydroquinone.[24] This intermediate was exposed to a freshly prepared 1-lithioethyl vinyl ether to form the boronate complex **I-2**, which was immediately subjected to Zweifel olefination by addition of iodine and base.[25] 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 **11**. Remarkably, this one-pot operation involved several distinct transformations and was performed on a multigram scale in 72% yield.[26]

Although the arenophile-mediated dearomative hydroboration and subsequent Zweifel olefination introduced the desired methyl ketone, this sequence also installed a bridging urazole moiety, which had to be strategically transmuted to reveal the fully decorated A ring of idarubicinone (**4**). This task was

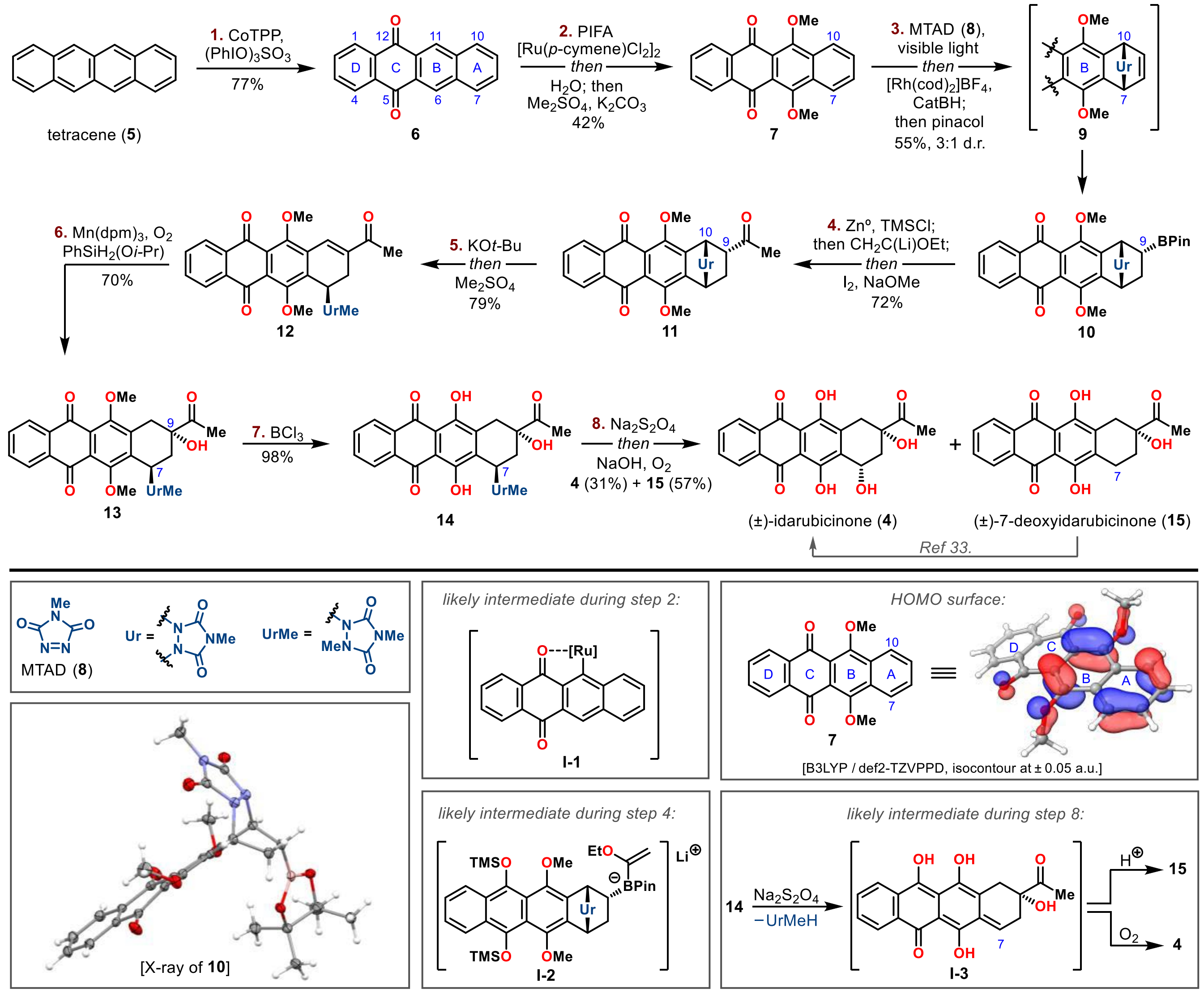

Figure 3. Synthesis of (±)-idarubicinone (**4**) from tetracene (**5**). Reagents and conditions: 1. CoTPP (5 mol %), $(PhIO)_3SO_3$, CH_2Cl_2, 25 °C, 2 h, 77%; 2. $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), PIFA, DCE, 100 °C, 12 h; then H_2O, 100 °C, 12 h; then Me_2SO_4, K_2CO_3, $(CH_3)_2CO$, 74 °C, 24 h, 42%; 3. MTAD (**8**), CH_2Cl_2, −50 °C, 36 h; then $[Rh(cod)_2]BF_4$ (10 mol %), dppb (10 mol %), HBcat, THF, −30 °C, 12 h; then pinacol, −78 to 25 °C, 12 h, 55% (3:1 dr); 4. Zn^0, TMSCl, THF, ultrasonication, 40 °C, 30 min; then $CH_2C(Li)OEt$, −78 to −25 °C, 30 min; then I_2, −78 to −25 °C, 30 min; then NaOMe, −78 to 25 °C, 4 h; then 1 M HCl, 25 °C, 2 h, 72%; 5. KO*t*-Bu, THF, −78 °C, 20 min; then Me_2SO_4, −78 to 0 °C, 1.5 h, 79%; 6. $Mn(dpm)_3$ (10 mol %), $PhSiH_2(Oi\text{-}Pr)$, O_2, *i*-PrOH/DCE 1:1, 0 to 25 °C, 2 h, 70%; 7. BCl_3, CH_2Cl_2, −78 °C, 1 h, 98%; 8. $Na_2S_2O_4$, H_2O/THF/MeOH 1:1:1, −20 °C, 20 min; then NaOH, −20 °C, 60 s; then O_2, −20 °C, 5 min, 31% of **4** and 57% of **15**.

partially accomplished by treatment of ketone **11** with base followed by Me_2SO_4, initiating β-elimination of urazole at position C-10 with subsequent methylation of the urazole hydrazyl nitrogen, furnishing α,β-unsaturated ketone **12** 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 Supporting Information). Finally, subjecting olefin **12** to Mukaiyama hydration conditions[27] selectively introduced the tertiary alcohol at position C-9, as α-ketol product **13** was obtained in 70% yield as a single diastereoisomer. Notably, the use of recently reported silane, $PhSiH_2(Oi\text{-}Pr)$,[28] 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 **13** and idarubicinone (**4**) at this stage resided in two hydroquinone protecting groups and the urazole moiety instead of a hydroxy group at the C-7 position. Although deprotection of methyl ethers to hydroquinone proceeded without any difficulties using BCl_3 (**13** → **14**, 98% yield), the removal of the urazole proved to be an arduous task. Eventually, the inspiration for the direct urazole-to-hydroxy exchange was found in the Moore hypothesis for the biological mode of reactivity known as bioreductive alkylation.[29] 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. Moreover, this concept was demonstrated in solution with several anthracyclines, which formed the corresponding semiquinone intermediates upon subjection to specific reducing agents.[30] The direct translation of these findings to our system, for example the addition of sodium dithionite to precursor **14**, did not eliminate the urazole; however, after the addition of base (NaOH) we observed elimination and exclusive formation of 7-deoxyidarubicinone (**15**) under anaerobic conditions. This result was in accordance with the literature, since deoxygenated anthracyclinones were commonly observed upon reduction of anthracyclines.[31] Mechanistically, the reduction of quinone **14** to hydroquinone, followed by base-induced elimination of the urazole, likely formed the semiquinone methide **I-3**, which after protonation gave the deaminated product **15**. However, we noticed that in the presence of oxygen, this reactive intermediate underwent competitive oxidation,[32] delivering idarubicinone (**I-3** → **4**). Accordingly, short exposure of **14** to an aqueous solution of sodium dithionite and NaOH, followed by rapid saturation of reaction mixture with oxygen, provided (±)-idarubicinone (**4**) and (±)-7-deoxyidarubicinone (**15**) in 31% and 57% yield. Although extensive optimization of this protocol did not result in a higher ratio of desired anthracyclinone **4** to **15** (for details, see Table S3 in Supporting Information), this deoxygenated side-product could be readily converted to aglycone **4** in one or two steps using known protocols.[33]

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 the functionality of the 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 and 2% overall yield from tetracene (**5**).

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 critical to the overall synthetic design. In fact, polynuclear arenes are not commonly considered in synthetic planning for construction of stereochemically complex scaffolds. However, through the development and application of new methods, the present study provides a compelling case in which tetracene serves as an ideal template for imprinting of desired functionality. Thus, the range of available polynuclear arenes, as well as numerous functionalization opportunities, can be combined to render this global functionalization approach an appealing and complementary entry for the preparation of other type II polyketide-like compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b05370.

Experimental procedures and spectral data for all new compounds (PDF)

X-ray crystallographic data for $C_{19}H_{24}BN_3O_4$ (CIF)

X-ray crystallographic data for $C_{29}H_{30}BN_3O_8$ (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*sarlah@illinois.edu

ORCID

David Sarlah: 0000-0002-8736-8953

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Arcamone, F.; Cassinelli, G.; Fantini, G.; Grein, A.; Orezzi, P.; Pol, C.; Spalla, C. Adriamycin 14-Hydroxydaunomycin, a New Antitumor Antibiotic From S. peucetius var. caesius. *Biotechnol. Bioeng.* **1969**, *11*, 1101−1110.

(2) DiMarco, A.; Gaetani, M.; Orezzi, P.; Scarpinato, B.; Silvestrini, R.; Soldati, M.; Dasdia, T.; Valentini, L. Daunomycin, a New Antibiotic of the Rhodomycin Group. *Nature* **1964**, *201*, 706−707.

(3) Arcamone, F. *Doxorubicin, Anticancer Antibiotics*; Academic Press: New York, 1984. (b) Arcamone, F. Antitumor Anthracyclines: Recent Developments. *Med. Res. Rev.* **1984**, *4*, 153−188.

(4) Hortobagyi, G. N. Anthracyclines in the Treatment of Cancer. *Drugs* **1997**, *54*, 1−7.

(5) (a) Anthracycline Antibiotics in Cancer Therapy. In *Developments in Oncology*, 10th ed.; Muggia, F. M., Young, C. W., Carter, S. K., Eds.; The Hague: Martinus Nijhoff Publishers; 1982. (b) See also ref 5.

(6) (a) Cummings, J.; Anderson, L.; Willmott, N.; Smyth, J. F. The Molecular Pharmacology of Doxorubicin in vivo. *Eur. J. Cancer Clin. Oncol.* **1991**, *27*, 532−535. (b) Zucchi, R.; Danesi, R. Cardiac Toxicity of Antineoplastic Anthracyclines. *Curr. Med. Chem.: Anti-Cancer Agents* **2003**, *3*, 151−171.

(7) For example, see: Binaschi, M.; Bigioni, M.; Cipollone, A.; Rossi, C.; Goso, C.; Maggi, C. A.; Capranico, G.; Animati, F. Anthracyclines: Selected New Developments. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 113−130.

(8) For syntheses of idaroubicinone, see: (a) Di Marco, A.; Casazza, A. M.; Giuliani, F.; Pratesi, G.; Arcamone, F.; Bernadi, L.; Franchi, G.; Giradino, P.; Patelli, B.; Penco, S. Synthesis and Antitumor Activity of 4-Demethoxyadriamycin and 4-Demethoxy-4'-epiadriamycin. *Cancer Treat. Rep.* **1978**, *62*, 375−380. (b) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. A Convergent Synthesis of (+)-4-Demethoxydaunomycinone and (+)-Daunomycinone. *Tetrahedron* **1984**, *40*, 4625−4632. (c) Gupta, C. R.; Harland, P. A.; Stoodley, R. J. An Efficient Enantiocontrolled Synthesis of (+)-4-Demethoxydaunomycinone. *Tetrahedron* **1984**, *40*, 4657−4667. (d) Tanno, N.; Terashima, S. Asymmetric Synthesis of Optically Active Anthracyclinone Intermediate and 4-Demethoxyanthracyclinones by the Use of a Novel Chiral Reducing Agent. *Chem. Pharm. Bull.* **1983**, *31*, 821−836. (e) Tamura, Y.; Sasho, M.; Akai, S.; Kishimoto, H.; Sekihachi, J.; Kita, Y. A Highly Convergent Strategy for the Synthesis of 4-Demethoxydaunomycinone and Daunomycinone: A Novel Synthesis of C4-Acetoxylated Homophthalic Anhydrides. *Tetrahedron Lett.* **1986**, *27*, 195−198. (f) Krohn, K.; Rieger, H.; Broser, E.; Schiess, P.; Chen, S.; Strubin, T. Konvergente Synthese enantiomerenreiner Daunomycinon-Derivate. *Liebigs. Ann. Chem.* **1988**, *1988*, 943−948. (g) Carr, K.; Greener, N. A.; Mullah, K. B.; Somerville, F. M.; Sutherland, J. K. A Synthesis of (±)-Demethoxydaunomycinone. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1975−1980. (h) Achmatowicz, O.;

Szechner, B. New Chiral Pool Approach to Anthracyclinones. The Stereoselective Synthesis of Idarubicinone. *J. Org. Chem.* **2003**, *68*, 2398–2404. (i) Rho, Y. S.; Park, J.; Kim, G.; Kim, H.; Sin, H.; Suh, P. W.; Yoo, D. J. Facile Total Syntheses of Idarubicinone-7-β-D-glucuronide: Convenient Preparations of AB-Ring Synthon Using Some Carboxylic Acid Derivatives. *Synth. Commun.* **2004**, *34*, 1703–1722. (j) Gupta, R. C.; Jackson, D. A.; Stoodley, R. J.; Williams, D. J. Studies Related to Anthracyclines. Part 2. Synthesis of (±)-4-Demethoxydaunomycinone. *J. Chem. Soc., Perkin Trans. 1* **1985**, 525–533. (k) Cambie, R. C.; Larsen, D. S.; Rickard, C. E. F.; Rutledge, P. S.; Woodgate, P. D. Experiments Directed Towards the Synthesis of Anthracyclinones. X. A Synthesis of (±)-4-Demethoxydaunomycinone. *Aust. J. Chem.* **1986**, *39*, 487–502. (l) Carr, K.; Sutherland, J. K. A Simple Synthesis of Demethoxydaunomycinone. *J. Chem. Soc., Chem. Commun.* **1987**, 567–568. (m) Krohn, K.; Tolkiehn, K. Stereoselektive Synthese Des 4-Desmethoxydaunomycinons. *Tetrahedron Lett.* **1978**, *19*, 4023–4026. (n) Garland, R. B.; Palmer, J. R.; Schulz, J. A.; Sollman, P. B.; Pappo, R. A New Synthetic Route to 4-Demethoxydaunomycinone. *Tetrahedron Lett.* **1978**, *19*, 3669–3672. (o) Kende, A. A.; Curran, D. P.; Tsay, Y.; Mills, J. E. The Isobenzofuran Route to Anthracyclinones. *Tetrahedron Lett.* **1977**, *18*, 3537–3540. (p) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. Anthracyclines. Part 3. The Total Synthesis of 4-Demethoxydaunomycin. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2249–2255. (q) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. Total Synthesis of 4-Demethoxydaunomycin. *J. Chem. Soc., Chem. Commun.* **1982**, 158–160. (r) Allen, J. G.; Hentemann, M. F.; Danishefsky, S. J. A Powerful O-Quinone Dimethide Strategy for Intermolecular Diels−Alder Cycloadditions. *J. Am. Chem. Soc.* **2000**, *122*, 571–575. (s) Kimura, Y.; Suzuki, M.; Matsumoto, T.; Abe, R.; Terashima, S. A Simple and Efficient Synthesis of Optically Active (+)-4-Demethoxydaunomycinone. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 415–421.

(9) (a) Hollingshead, L. M.; Faulds, D. *Drugs* **1991**, *42*, 690. (b) Cersosimo, R. J. Idarubicin: an Anthracycline Antineoplastic Agent. *Clin. Pharm.* **1992**, *11*, 152–167.

(10) For selected reviews on synthesis of anthracyclines, see: (a) Krohn, K. Building Blocks for the Total Synthesis of Anthracyclinones. *Prog. Chem. Org. Nat. Prod.* **1989**, *55*, 37–88. (b) Krohn, K. Synthesis of Anthracyclinones by Electrophilic and Nucleophilic Addition to Anthraquinones. *Tetrahedron* **1990**, *46*, 219–318. (c) Thomas, G. J. Synthesis of Anthracyclines Related to Daunomycin. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M.; Eds.; Springer-Verlag, 1990; pp 467–496. (d) Wheeler, D. M. S.; Wheeler, M. M. Stereoselective Syntheses of Doxorubicin and Related Compounds. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1994; Vol. *14*, pp 3–46. (e) Achmatowicz, O.; Szechner, B. Synthesis of Enantiomerically Pure Anthracyclinones. *Top. Curr. Chem.* **2007**, *282*, 143–186.

(11) For selected examples, see: (a) ref 8r. (b) Wong, C. M.; Popien, D.; Schwenk, R.; Raa, Te. Synthetic Studies of Hydronaphthacenic Antibiotics. I. The Synthesis of 4-Demethoxy-7-O-methyl Daunomycinone. *Can. J. Chem.* **1971**, *49*, 2712–2718. (c) Ishizumi, K.; Ohashi, N.; Tanno, N. Stereospecific Total Synthesis of 9-Aminoanthracyclines: (+)-9-Amino-9-deoxydaunomycin and Related Compounds. *J. Org. Chem.* **1987**, *52*, 4477–4485. (d) Ref 8b. (e) Hauser, F. M.; Prasanna, S. Total Syntheses of (±)-Duanomycinone. Regiospecific Preparations of (±)-7,9-Dideoxydaunomycinone and 6,11-Dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione. *J. Am. Chem. Soc.* **1981**, *103*, 6378–6386.

(12) For selected examples, see: (a) Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, R. N.; King, P. F.; Lyding, J. M.; Tsang, W.-C.; Vaya, J. An Efficient, Regiospecific Synthesis of (±)-Daunomycinone. *Tetrahedron* **1984**, *40*, 4569–4577. (b) Ref 8s. (c) Krohn, K.; Tolkiehn, K. Synthetische Anthracyclinone, XIV. Synthese neuer Derivate des Daunomycinons und des β-Rhodomycinons. *Chem. Ber.* **1980**, *113*, 2976–2993. (d) Dienes, Z.; Antonsson, T.; Vogel, P. Enantioselective Synthesis of (R)-(−)-2-Acetyl-2,5,12-trihydro-1,2,3,4-tetrahydro-6,11-naphthacenequinone via Diastereoselective Diels-Alder Cycloaddition. *Tetrahedron Lett.* **1993**, *34*, 1013–1016.

(13) (a) Geraskin, I. M.; Pavlova, O.; Neu, H. M.; Yusubov, M. S.; Nemykin, V. N.; Zhdankin, V. V. Comparative Reactivity of Hypervalent Iodine Oxidants in Metalloporphyrin-Catalyzed Oxygenation of Hydrocarbons: Iodosylbenzene Sulfate and 2-Iodylbenzoic Acid Ester as Safe and Convenient Alternatives to Iodosylbenzene. *Adv. Synth. Catal.* **2009**, *351*, 733–737. (b) Yusubov, M. S.; Nemykin, V. N.; Zhdankin, V. V. Transition Metal-Mediated Oxidations Utilizing Monomeric Iodosyl- and Iodylarene Species. *Tetrahedron* **2010**, *66*, 5745–5752.

(14) For selected comprehensive reviews on direct oxidation of arenes, see: (a) Dudfield, P. J. Synthesis of Quinones. In *Comprehensive Organic Synthesis*; Ley, S. V., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, pp 345–356. (b) Naruta, Y.; Maruyama, K. Recent Advances in the Synthesis of Quinonoid Compounds. In *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley: New York, 1988; Vol. 2, pp 241–402.

(15) For selected reviews on this topic, see: (a) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-Catalyzed C−H Activation: Examples and Concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900–2936. (b) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Transition Metal-Catalyzed Ketone-Directed or Mediated C−H Functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764–7786. (c) De Sarkar, S.; Liu, W.; Kozhushkov, S.; Ackermann, L. Weakly Coordinating Directing Groups for Ruthenium(II)-Catalyzed C−H Activation. *Adv. Synth. Catal.* **2014**, *356*, 1461–1479. (d) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C−H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788–802.

(16) (a) Thirunavukkarasu, V. S.; Ackermann, L. Ruthenium-Catalyzed C-H Bond Oxygenations with Weakly Coordinating Ketones. *Org. Lett.* **2012**, *14*, 6206–6209. For selected examples of Ru-catalyzed C−H hydroxylation, see: (b) Yang, F.; Ackermann, L. Ruthenium-Catalyzed C−H Oxygenation on Aryl Weinreb Amides. *Org. Lett.* **2013**, *15*, 718–720. (c) Yang, X.; Shan, G.; Rao, Y. Synthesis of 2-Aminophenols and Heterocycles by Ru-Catalyzed C−H Mono- and Dihydroxylation. *Org. Lett.* **2013**, *15*, 2334–2337. (d) Yang, Y.; Lin, Y.; Rao, Y. Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with Ester as an Effective Directing Group. *Org. Lett.* **2012**, *14*, 2874–2877. (e) Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. Ruthenium-Catalyzed Oxidative C(sp2)-H Bond Hydroxylation: Site-Selective C-O Bond Formation on Benzamides. *Org. Lett.* **2012**, *14*, 4210–4213. (f) Shan, G.; Han, X.; Lin, Y.; Yu, S.; Rao, Y. Broadening the Catalyst and Reaction Scope of Regio- and Chemoselective C-H Oxygenation: a Convenient and Scalable Approach to 2-Acylphenols by Intriguing Rh(II) and Ru(II) Catalysis. *Org. Biomol. Chem.* **2013**, *11*, 2318–2322. (g) Liu, W.; Ackermann, L. Ortho- and Para-Selective Ruthenium-Catalyzed C(sp2)−H Oxygenations of Phenol Derivatives. *Org. Lett.* **2013**, *15*, 3484–3486. (h) Yang, F.; Rauch, K.; Kettelhoit, K.; Ackermann, L. Aldehyde-Assisted Ruthenium(II)-Catalyzed C−H Oxygenations. *Angew. Chem., Int. Ed.* **2014**, *53*, 11285–11288.

(17) Control experiments confirmed the requirement of a specific Ru-catalysis for this transformation, as well as excess of PIFA for further oxidation. See Supporting Information.

(18) For selected examples, see: (a) Southgate, E. H.; Pospech, J.; Fu, J.; Holycross, D. R.; Sarlah, D. Dearomative Dihydroxylation with Arenophiles. *Nat. Chem.* **2016**, *8*, 922–928. (b) Okumura, M.; Nakamata Huynh, S. M.; Pospech, J.; Sarlah, D. Arenophile-mediated Dearomative Reduction. *Angew. Chem., Int. Ed.* **2016**, *55*, 15910–15914. (c) Okumura, M.; Shved, A. S.; Sarlah, D. Palladium-Catalyzed Dearomative *syn*-1,4-Carboamination. *J. Am. Chem. Soc.* **2017**, *139*, 17787–17790. (d) Hernandez, L. W.; Klöckner, U.; Pospech, J.; Hauss, L.; Sarlah, D. Nickel-Catalyzed Dearomative *trans*-1,2-Carboamination. *J. Am. Chem. Soc.* **2018**, *140*, 4503–4507. (e) Wertjes, W. C.; Okumura, M.; Sarlah, D. Palladium-Catalyzed Dearomative *syn*-1,4-Carboamination. *J. Am. Chem. Soc.* **2019**, *141*, 163–167.

DOI: 10.1021/jacs.9b05370
J. Am. Chem. Soc. 2019, 141, 10193–10198

(19) (a) Hamrock, S. J.; Sheridan, R. S. Para photoaddition of *N*-methyltriazolinedione to benzene. Synthesis of Energy-Rich Azo Compounds Comprising Benzene + Nitrogen. *J. Am. Chem. Soc.* **1989**, *111*, 9247. (b) Kjell, D. P.; Sheridan, R. S. Photochemical Cycloaddition of *N*-methyltriazolinedione to Naphthalene. *J. Am. Chem. Soc.* **1984**, *106*, 5368. (c) Kjell, D. P.; Sheridan, R. S. A Photochemical Diels−Alder Reaction of *N*-methyltriazolinedione. *J. Photochem.* **1985**, *28*, 205−214. (d) Hamrock, S. J.; Sheridan, R. S. Photochemical Diels−Alder Addition of *N*-methyltriazolinedione to Phenanthrene. *Tetrahedron Lett.* **1988**, *29*, 5509−5512.

(20) (a) Männig, D.; Nöth, H. Catalytic Hydroboration with Rhodium Complexes. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878−879. (b) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. Rhodium(I)-Catalyzed Hydroboration of Olefins. The Documentation of Regio- and Stereochemical Control in Cyclic and Acyclic Systems. *J. Am. Chem. Soc.* **1988**, *110*, 6917−6918. (c) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. Rhodium(I)- and Iridium(I)-Catalyzed Hydroboration Reactions: Scope and Synthetic Applications. *J. Am. Chem. Soc.* **1992**, *114*, 6671−6679.

(21) For an insightful perspective on stability of borates, see: Hall, D. G. *Structure, Properties, and Preparation of Boronic Acid Derivatives. Boronic Acids*; Wiley-VCH Verlag GmbH & Co. KGaA, 2011; pp 1−133.

(22) For recent reviews on the C(sp^2)−C(sp^3) bond formation, see: (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. The B-Alkyl Suzuki−Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd, Ni, Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417−1492. (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents to Construct C−C Bonds. *Chem. Rev.* **2015**, *115*, 9587−9652.

(23) (a) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. A Convenient Stereoselective Synthesis of Substituted Alkenes via Hydroboration-Iodination of Alkynes. *J. Am. Chem. Soc.* **1967**, *89*, 3652−3653. (b) For a recent review, see: Armstrong, R. J.; Aggarwal, V. K. 50 Years of Zweifel Olefination: a Transition-Metal-Free Coupling. *Synthesis* **2017**, *49*, 3323−3336.

(24) (a) Rasmussen, J. K.; Krepski, L. R.; Heilmann, S. M.; Smith, H. K., II; Tumey, M. L. A Convenient Synthesis of 1,2-Bis-[trimethylsiloxy]alkenes from α-Diketones. *Synthesis* **1983**, 457−459. (b) Boudjouk, P.; So, J. H. Organic Sonochemistry. Ultrasonic Acceleration of the Reaction of Dicarbonyls with Trimethylchlorosilane in the Presence of Zinc. *Synth. Commun.* **1986**, *16*, 775−778.

(25) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. Enantioselective Construction of Quaternary Stereogenic Centers from Tertiary Boronic Esters: Methodology and Applications. *Angew. Chem., Int. Ed.* **2011**, *50*, 3760−3763.

(26) For beneficial use of pot economy in organic synthesis, see: Hayashi, Y. Pot Economy and One-Pot Synthesis. *Chem. Sci.* **2016**, *7*, 866−880.

(27) Isayama, S.; Mukaiyama, T. A New Method for Preparation of Alcohols from Olefins with Molecular Oxygen and Phenylsilane by the Use of Bis(acetylacetonato)cobalt(II). *Chem. Lett.* **1989**, *18*, 1071−1074.

(28) Obradors, C. L.; Martinez, R. M.; Shenvi, R. A. Ph(*i*-PrO)SiH_2: An Exceptional Reductant for Metal-Catalyzed Hydrogen Atom Transfers. *J. Am. Chem. Soc.* **2016**, *138*, 4962−4971.

(29) (a) Moore, H. W. Bioactivation as a Model for Drug Design Bioreductive Alkylation. *Science* **1977**, *197*, 527−532. (b) Moore, H. W.; Czerniak, R. Naturally Occurring Quinones as Potential Bioreductive Alkylating Agents. *Med. Res. Rev.* **1981**, *1*, 249−280.

(30) (a) Gaudiano, G.; Frigerio, M.; Bravo, P.; Koch, T. H. Reduction of Daunomycin in Dimethyl Sulfoxide. Long-Lived Semiquinones and Quinone Methide and Formation of an Enolate at the 14-Position via the Quinone Methide. *J. Am. Chem. Soc.* **1992**, *114*, 3107−3113. (b) Gaudiano, G.; Frigerio, M.; Sangsurasak, C.; Bravo, P.; Koch, T. H. Reduction of Daunomycin and 11-Deoxydaunomycin with Sodium Dithionite in DMSO. Formation of Quinone Methide Sulfite Adducts and the First NMR Characterization of an Anthracycline Quinone Methide. *J. Am. Chem. Soc.* **1992**, *114*, 5546−5553. (c) Schweitzer, B. A.; Koch, T. H. Synthesis and Redox Chemistry of 5-Deoxydaunomycin. A Long-Lived Hydroquinone Tautomer. *J. Am. Chem. Soc.* **1993**, *115*, 5440−5445.

(31) (a) Kleyer, D. L.; Koch, T. H. Spectroscopic Observation of the Tautomer of 7-Deoxydaunomycinone from Elimination of Daunosamine from Daunomycin Hydroquinone. *J. Am. Chem. Soc.* **1983**, *105*, 2504−2505. (b) Bird, D. M.; Gaudiano, G.; Koch, T. H. Leucodaunomycins, New Intermediates in the Redox Chemistry of Daunomycin. *J. Am. Chem. Soc.* **1991**, *113*, 308−315. (c) Schweitzer, B. A.; Koch, T. H. Glycosidic Cleavage from Anaerobic Saponification of the Heptaacetate of Daunomycin Hydroquinone. *J. Am. Chem. Soc.* **1993**, *115*, 5446−5452. (d) See also ref 30.

(32) Gaudiano, G.; Koch, T. H. Reaction of the Quinonemethide from Reductive Glycosidic Cleavage of Daunomycin with Molecular Oxygen. Evidence for Semiquinonemethide Formation. *J. Am. Chem. Soc.* **1990**, *112* (25), 9423−9425.

(33) (a) Ref 8i. For similar hydroxylation at C-7 in other anthracyclinones, see: (b) Kende, A. S.; Tsay, Y.-G.; Mills, J. E. Total Synthesis of (±)-Daunomycinone and (±)-Carminomycinone. *J. Am. Chem. Soc.* **1976**, *98*, 1967−1969. (c) Wong, C. M.; Schwenk, R.; Popien, D.; Ho, T. L. The Total Synthesis of Daunomycinone. *Can. J. Chem.* **1973**, *51*, 466−467. (d) Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. Synthetic Approaches to Adriamycin. 2. Degradation of daunorubicin to a nonasymmetric tetracyclic ketone and refunctionalization of the A ring to adriamycin. *J. Org. Chem.* **1977**, *42*, 3653−3660. (e) Kimball, S. D.; Walt, D. R.; Johnson, F. Anthracyclines and Related Substances. 3. Regiospecific Total Synthesis of 11-Deoxydaunomycinone. *J. Am. Chem. Soc.* **1981**, *103*, 1561−1563.