OL Organic Letters

pubs.acs.org/OrgLett Letter

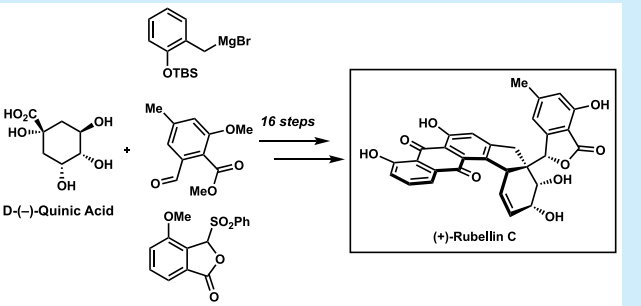
Total Synthesis of (+)-Rubellin C

Jackson A. Gartman and Uttam K. Tambar*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02127 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The rubellins are a family of stereochemically complex anthraquinoid heterodimers containing an unprecedented chemical scaffold. Although the rubellins have been known for over three decades, no total synthesis has been achieved since their discovery. Their topology is characterized by a 6−5−6 fused ring system, five neighboring stereocenters including a quaternary center all in a convoluted core, and an anthraquinone nucleus. The rubellin architecture has been shown to inhibit and reverse the aggregation of tau protein, a therapeutically relevant target for Alzheimer's disease. Herein, we describe the first stereoselective synthesis of a member of the family, (+)-rubellin C, in 16 steps. Strategic disconnections allow expedient construction of stereochemical and topological intricacy in a short sequence of borylative and transition metal-catalyzed steps.



Anthraquinone-based natural products have provided a variety of medicinally valuable entities, including FDA-approved therapies such as the chemotherapeutic anthracyclines, the chemotherapeutic and immunosuppressant mitoxantrone for multiple sclerosis, the laxative sennosides, and the anti-inflammatory diacerein for osteoarthritis.[1] A large number of naturally occurring anthraquinoids are characterized by homodimeric linkages.[2] Fewer family members are characterized by heterodimeric structures that contain anthraquinones linked by multiple bonds to other anthraquinone or xanthone partners; these natural products have inspired elegant syntheses to access their molecular architectures.[3]

The rubellins are a distinct class of anthraquinone dimers that were isolated in the 1980s in Italy from the phytopathogenic fungus *Mycosphaerella rubella* in enantiopure forms (Figure 1A).[4] Research surrounding the compounds lay dormant until the isolation of the rubellins in another fungus, *Ramularia collo-cygni*, the pathogen responsible for barley leaf disease in Europe.[5] The rubellins potently deaggregate and inhibit the formation of paired-helical filaments of tau protein, a biomarker and viable pharmacological target in tauopathies such as Alzheimer's disease.[6] This implicates the rubellin scaffold as a possible tool for neurodegenerative diseases.[7] Other isolated natural products with the core rubellin structure include the torrubiellins, uredinorubellins, melrubiellins, solanrubiellin, and caeruleoramularin.[8] Despite numerous biosynthetic and biological studies, none of the rubellin natural products have yet to be prepared through chemical synthesis, presumably due to substantial synthetic challenges presented by their intricate structures.

The rubellin core is beset with a myriad of synthetic challenges (Figure 1), including the quaternary center buried in an array of five contiguous stereocenters, the 6−5−6-fused ring system, and the assortment of oxidation levels. We were particularly interested in developing a synthetic approach to rubellin C (**1**) because of the exceptional challenge of accessing a Csp^3−Csp^3 hybridized "attached ring system",[9] where the quaternary C16 carbon in a ring is joined through a single carbon−carbon bond to C18 via a stereochemically defined lactone.

The challenge is enhanced further due to the presence of three neighboring stereocenters to the Csp^3−Csp^3 junction, burying the quaternary center in a fused ring system. Given the prevalence of the attached ring motif[9] and the inability to synthesize the rubellin ring system to date, we envisioned that a stereoselective approach to the core structure would have broad utility in complex molecule synthesis.

Our retrosynthesis of (+)-rubellin C (**1**) initially disconnects the central $C_{sp}{}^2$−$C_{sp}{}^3$ C5−C11 bond via a diastereoselective intramolecular Mizoroki−Heck reaction directed by the orientation of the quaternary center (Figure 1B).[10] The anthraquinone moiety could be introduced by a Hauser−Kraus annulation with a *p*-quinone monoketal intermediate (not shown) derived from selective aromatic oxidation of homoallylic lactone **4**. We reasoned that the key buried stereocenter at C16 and hydroxyl stereocenter at C18 could be accessed in a highly selective manner through phthalaldehyde

Received: June 27, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02127
Org. Lett. XXXX, XXX, XXX−XXX

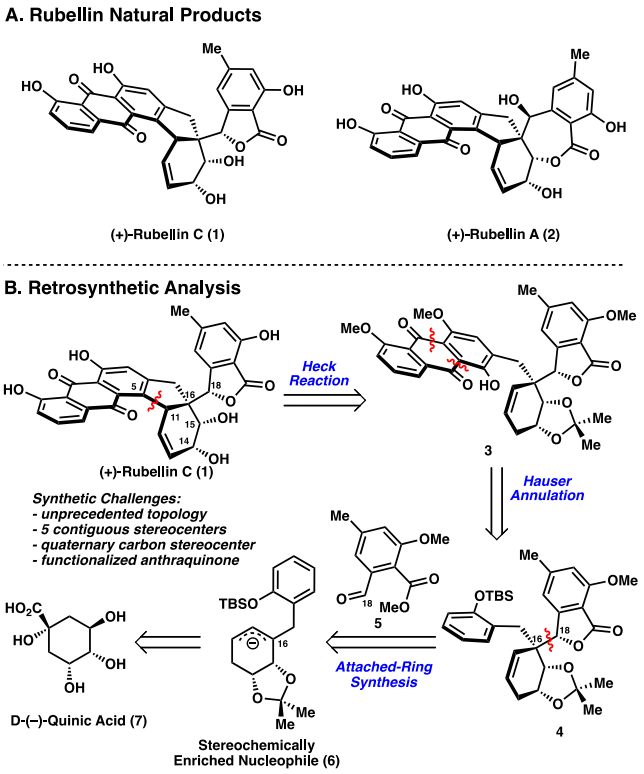


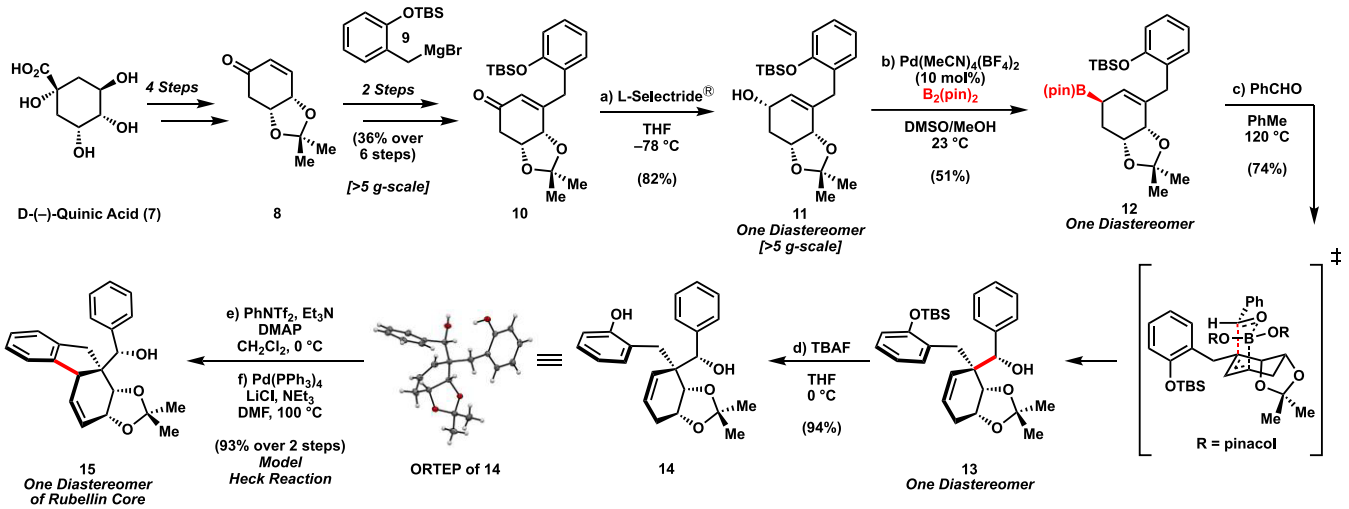
Figure 1. (A) Anthraquinone-based heterodimeric rubellin natural products. (B) Retrosynthetic analysis of (+)-rubellin C.

5 and properly designed synthon allyl anion **6**. Stereoselective access to the natural product would require this carbon−carbon bond-forming step to function precisely to produce the C16 and C18 stereocenters. A reasonable stereochemically defined allylic nucleophile corresponding to the allyl anion synthon would have to engage aldehyde **5** through the correct carbon (α- vs γ-addition), on the correct face, and with the correct orientation of the electrophilic partner, thus distinguishing between a total of eight possible isomers (constitutional and diastereomeric) of the coupled product. We proposed a sterically hindered allylboron allylation that would translate stereochemistry through a closed transition state.[11] The stereochemically enriched allylating reagent could be prepared from an abundant chiral pool starting material (**7**).

Initially we developed a synthesis of the core structure of rubellin C to analyze our stereochemical hypotheses (Scheme 1). Our synthesis began with D-(−)-quinic acid **7**, which was elaborated to enone **8** in a few steps.[12] Benzylic Grignard reagent **9**, derived from *o*-cresol, was transformed into the cuprate and underwent 1,4-addition to enone **8** in the presence of trimethylsilyl chloride. The resulting silyl enol ether, obtained as one diastereomer, was converted to substituted enone **10** through Saegusa−Ito oxidation. To access the synthetic equivalent of synthon **5** (Figure 1), we chose to examine recently reported borylation chemistry from the Szabó group that would enable the stereospecific conversion of chiral allylic alcohols into allylboron reagents.[13] Selective reduction of the carbonyl center followed by allylic borylation would give our desired stereochemistry by inversion. A variety of reductants were screened, with L-Selectride (lithium tri*sec*-butylborohydride) giving the best chemo- and diastereoselectivity for addition into the convex face of bicyclic enone **10**. We utilized the aforementioned borylation to convert the resulting free allylic alcohol **11** to the bench-stable allyl nucleophile. Boronic acid pinacol ester **12** was formed in high diastereoselectivity using bis(pinacolato)diboron (B_2pin_2) and a palladium(II) tetrafluoroborate catalyst ($Pd(MeCN)_4(BF_4)_2$).

With the allyl nucleophile prepared, we then pursued the key allylative and Mizoroki−Heck transformations in our core system (Scheme 1). Thermal allylation of allyl pinacol boronic ester **12** with benzaldehyde furnished homoallylic alcohol **13** as a single isolable diastereomer. Presumably, the high stereocontrol was imparted through a closed Zimmerman−Traxler transition state on the convex side of the bicyclic system. This transformation installed the quaternary and hydroxyl stereocenters at C16 and C18 respectively in high yield and remarkably high diastereoselectivity. Removal of the *tert*-butyldimethylsilyl (TBS) protecting group with tetra-*n*-butylammonium fluoride (TBAF) generated free phenol **14**,

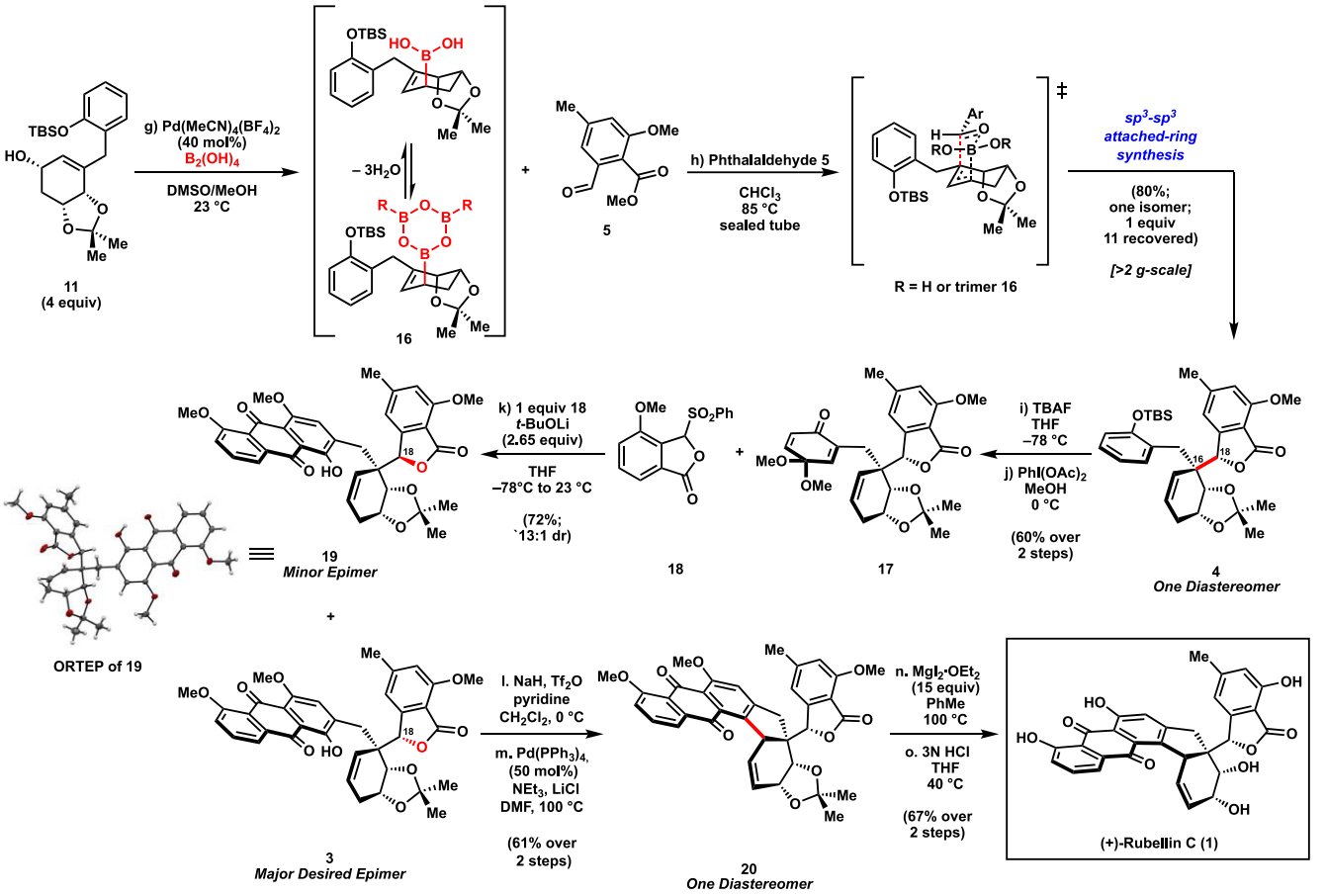
Scheme 1. Asymmetric Synthesis of Chiral Rubellin Core Structure[a]



[a]See the Supporting Information for reagents and conditions; L-Selectride = lithium tri-*sec*-butylborohydride, DMSO = dimethyl sulfoxide, TBAF = tetra-*n*-butylammonium fluoride, DMAP = 4-dimethylaminopyridine, DMF = dimethylformamide.

https://dx.doi.org/10.1021/acs.orglett.0c02127
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of (+)-Rubellin C[a]



[a]Reagents and conditions can be found in the Supporting Information; DMSO = dimethyl sulfoxide, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran, Tf_2O = trifluoromethanesulfonic anhydride, DMF = dimethylformamide.

whose X-ray crystal structure confirmed our stereochemical hypotheses in the preceding allylation, borylation, and reduction reactions. Triflation and subjection to palladium-catalyzed Mizoroki–Heck conditions gave one diastereomer of the final 6–5–6 fused system **15**.[14] The stereochemistry was confirmed by nuclear Overhauser effect (NOE) correlations to be the *cis*-ring junction as desired in the natural product scaffold.

After gaining supporting evidence for our stereochemical hypotheses in constructing the core structure of the natural product, we began the synthesis of the full rubellin C system with the allylation of phthalaldehyde **5**, which was accessible from commercial materials in seven steps.[15] Unfortunately, conventional allylation protocols utilized in complex molecule synthesis proved to be ineffective for the assembly of the buried quaternary carbon center in the rubellin C structure, presumptively due to steric congestion in the transition state (see the Supporting Information for details). For example, treatment of pinacol boronic ester **12** with phthalaldehyde **5** gave no yield of homoallylic lactone **4** under extreme thermal (>220 °C), ligand exchange, Lewis acidic, or Brønsted acidic conditions.[16] Conversion of allylic alcohol **11** to allyl metal reagents derived from metals known to proceed through Type I allylation reactions provided low reactivity with a mixture of isomers.[17]

We then examined a similar procedure for formation of allyl boronic acids instead of allyl boronic esters from allylic alcohol **11** utilizing tetrahydroxyboron $B_2(OH)_4$.[18] We hypothesized the higher allylative reactivity of allyl boronic acids, stemming from a lack of a hindered steric environment around the empty p-orbital of boron, would possibly allow for this congested key carbon–carbon bond-forming event. In addition, allyl boronic acids are thermally stable and thought to form trimeric allylic boroxines upon removal of water, containing only one oxygen per boron atom in a remarkably Lewis acidic system.[19] Use of $Pd(MeCN)_4(BF_4)_2$ with $B_2(OH)_4$ in a DMSO/MeOH mixture followed by extraction and treatment with Na_2SO_4 provided postulated allylating reagent **16** as either the boronic acid or allylboroxine, which allylated phthalaldehyde **5** to give homoallylic lactone **4** as one isolable diastereomer (Scheme 2). Notably, allylboron reagent **16** was the only reagent observed to undergo allylation with phthalaldehyde **5** to selectively afford the desired homoallylic lactone product. A large screening campaign was undertaken to optimize the yield of the boronic acid/allylation sequence. We realized in our studies that phthalaldehyde **5** could be used as a limiting reagent to produce 80% yield of lactone **4** based on limiting reagent with partial recovery of starting allylic alcohol **11**, demonstrating the powerful reactivity of allylboronic acids even in sterically crowded chemical environments. The requirement for excess allylic alcohol **11** may arise from the aggregated structure of the putative allylating species, boroxine **16**. Through the course of this transformation, we formed both the key quaternary and hydroxyl stereocenters in the Csp^3–

https://dx.doi.org/10.1021/acs.orglett.0c02127
Org. Lett. XXXX, XXX, XXX–XXX

Csp^3 attached-ring system with high control of stereo- and regioselectivity, forming one out of eight possible isomers.

Assembly of the core Csp^3–Csp^3 attached-ring system allowed us to pursue the late-stage Hauser–Kraus annulation and Mizoroki-Heck reaction (Scheme 2). Removal of the silyl group with TBAF provided the free phenol of **4**. Higher equivalents (>1.5) of TBAF epimerized the C18 lactone center, hinting toward its propensity to undergo stereochemical reconfiguration, possibly through either an addition to the C18 lactone center or deprotonation at the C18 position of the vinylogous ester. Oxidation of the free phenol with (diacetoxyiodo)benzene (PIDA) formed the *p*-quinone monoketal **17** in 60% yield over two steps.

Initial examination of the Hauser-Kraus annulation with typical bases such as lithium diisopropylamide (LDA) or the dimsyl anion with matching equivalents of *p*-quinone monoketal **17** and sulfone **18**, accessible in six steps from commercially available starting materials,[20] gave poor yields of the bright red anthraquinone solid **3** (see the Supporting Information for more details).[21] Use of lithium *tert*-butoxide (LTB) as a base gave an increase in yields; however, at higher base equivalents (>3) or upon heating, scrambling of the C18 stereocenter was observed to give undesired epimer **19** through either addition of the butoxide and opening of the ring system or through a deprotonation event to give an alkoxyfuran species that reprotonates on the opposite face. Careful examination of base equivalents led us to employ 2.65 equiv of LTB to achieve high yield of anthraquinone **3** with preservation of stereochemistry. The absolute stereochemistry of the undesired C18 epimer **19** formed in the Hauser–Kraus reaction with excess base was confirmed by X-ray crystallography, which also further established our stereochemical assignment of the allylation preceding this step.

To complete the synthesis, we attempted triflation, subsequent Mizoroki–Heck reaction, and deprotection of the near-complete rubellin system (Scheme 2). Treatment of anthraquinone **3** with excess sodium hydride in CH_2Cl_2 followed by addition of trifluoromethanesulfonic anhydride (Tf_2O) and pyridine supplied the triflate with minimal loss of stereochemical fidelity at the C18 center, which was immediately used in the subsequent Mizoroki–Heck reaction to deliver one diastereomer of the rubellin architecture **20**, with its stereochemistry confirmed by NOE correlations. Surprisingly, *O*-demethylation proved challenging; after vast screening of conditions, the mild nucleophilic iodide source magnesium iodide etherate suitably removed all of the methyl groups at higher temperatures.[22] Acidic hydrolysis of the acetonide produced one enantiomer of the natural product (+)-rubellin C (**1**), whose characterization data matched that described in the literature.[4] Our synthetic efforts therefore also confirm the absolute stereochemistry reported of natural (+)-rubellin C (**1**).

The first total synthesis of a member of the rubellin family of natural products has been accomplished with high stereoselectivity in 16 steps (longest linear sequence) from readily available D-(−)-quinic acid (**7**). The expedient construction of the core ring system relied on an efficient sequence of steps to install topological and stereochemical complexity, which may provide the means to explore structure–activity relationships. Exploration of these methods, the syntheses of the remaining rubellins, and biological studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02127.

Experimental procedures, spectroscopic data, crystallographic data, and NMR comparison for synthetic and previously isolated (+)-rubellin C (PDF)

Accession Codes

CCDC 2012492–2012493 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Uttam K. Tambar − *Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9038, United States;* orcid.org/0000-0001-5659-5355; Email: uttam.tambar@utsouthwestern.edu

Author

Jackson A. Gartman − *Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9038, United States;* orcid.org/0000-0002-3101-403X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02127

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the W. W. Caruth, Jr. Endowed Scholarship, Welch Foundation (I-1748), National Institutes of Health (R01GM102604), American Chemical Society Petroleum Research Fund (59177-ND1), Teva Pharmaceuticals Marc A. Goshko Memorial Grant (60011-TEV), and Sloan Research Fellowship. J.A.G. gratefully acknowledges an NIH Pharmacological Sciences Training Grant (GM007062). We thank Vincent Lynch (UT Austin) for X-ray crystal structural analysis, Hamid Baniasadi (UTSW) for high-resolution mass spectrometry assistance, and Jef De Brabander (UTSW), Joseph Ready (UTSW), Chuo Chen (UTSW), Tian Qin (UTSW), and Myles Smith (UTSW) for productive discussions. We also thank our diverse collection of lab members for creating an environment that supported the success of this project.

■ REFERENCES

(1) (a) Nadas, J.; Sun, D. Anthracyclines as effective anticancer drugs. *Expert Opin. Drug Discovery* **2006**, *1*, 549–568. (b) Scott, L. J.; Figgitt, D. P. Mitoxantrone: A Review of its Use in Multiple Sclerosis. *CNS Drugs* **2004**, *18*, 379–396. (c) Oshio, H.; Imai, S.; Fujioka, S.; Sugawara, T.; Miyamoto, M.; Tsukui, M. Investigation of Rhubarbs. III. New Purgative Constituents, Sennosides E and F. *Chem. Pharm. Bull.* **1974**, *22*, 823–831. (d) Fidelix, T. S. A.; Macedo, C. R.; Maxwell, L. J.; Trevisani, V. F. M. Diacerein for osteoarthritis. *Cochrane Database of Systematic Reviews* **2014**, *2*, 1–56.

(2) (a) Altersolanols: Debbab, A.; Aly, A. H.; Edrada-Ebel, R.; Wray, V.; Mueller, W. E. G.; Totzke, F.; Zirrgiebel, U.; Schaechtele,

https://dx.doi.org/10.1021/acs.orglett.0c02127
Org. Lett. XXXX, XXX, XXX–XXX

C.; Kubbutat, M. H. G.; Lin, W. H.; Mosaddak, M.; Hakiki, A.; Proksch, P.; Ebel, R. Bioactive Metabolites from the Edophytic Fungus *Stremphylium globuliferum* Isolated from *Mentha pulegium*. *J. Nat. Prod.* **2009**, *72*, 626−631. (b) Alterporriols: Xia, G.; Li, J.; Li, H.; Long, Y.; Lin, S.; Lu, Y.; He, L.; Lin, Y.; Liu, L.; She, Z. Alterporriol-Type Dimers from the Mangrove Endophytic Fungus, Alternaria sp. (SK11), and Their MptpB Inhibitions. *Mar. Drugs* **2014**, *12*, 2953−2969. (c) Nigrodiquinones: Xu, W.-F.; Hou, X.-M.; Yang, K.-L.; Cao, F.; Yang, R.-Y.; Wang, C.-Y.; Shao, C.-L. Nigrodiquionone A, a Hydroanthraquinone Dimer Containing a Rare C-0-C-7' Linkage from a Zoanthid-Derivated *Nigrospora* sp. Fungus. *Mar. Drugs* **2016**, *14*, 51−58.

(3) (a) Nicolaou, K. C.; Lim, Y. H.; Piper, J. L.; Papageorgiou, C. D. Total Synthesis of 2,2'-*epi*-Cytoskyrin A, Rugulosin, and the Alleged Structure of Rugulin. *J. Am. Chem. Soc.* **2007**, *129*, 4001−4013. (b) Nicolaou, K. C.; Lim, Y. H.; Becker, J. Total Synthesis and Absolute Configuration of the Bisanthraquinone Antibiotic BE-43472B. *Angew. Chem., Int. Ed.* **2009**, *48*, 3444−3448. (c) Holmbo, S. D.; Pronin, S. V. A Concise Approach to Anthraquinone-Xanthone Heterodimers. *J. Am. Chem. Soc.* **2018**, *140*, 5065−5068.

(4) (a) Arnone, A.; Camarda, L.; Nasini, G.; Assante, G. Secondary Mould Metabolites. Part 15. Structure Elucidation of Rubellins A and B, two Novel Anthraquinone Metabolites from *Mycosphaerella rubella*. *J. Chem. Soc., Perkin Trans. 1* **1986**, 255−260. (b) Arnone, A.; Nasini, G.; Camarda, L.; Assante, G. Secondary Mould Metabolites. XXV. The Structure of Rubellins C and D, Two Novel Anthraquinone Metabolites from *Mycosphaerella rubella*. *Gazz. Chim. Ital.* **1989**, *119*, 35−39.

(5) Heiser, I.; Sachs, E.; Liebermann, B. Photodynamic oxygen activation by Rubellin D, a phytotoxin produced by *ramularia collo-cygni*. *Physiol. Mol. Plant Pathol.* **2003**, *62*, 29−36.

(6) Miethbauer, S.; Gaube, F.; Möllmann, U.; Dahse, H.-M.; Schmidtke, M.; Gareis, M.; Pickhardt, M.; Liebermann, B. Antimicrobial, Antiproliferative, Cytotoxic, and Tau Inhibitory Activity of Rubellins and Caeruleoramularin Produced by the Phytopathogenic Fungus *Ramularia collo-cygni*. *Planta Med.* **2009**, *75*, 1523−1525.

(7) Calcul, L.; Zhang, B.; Jinwal, U. K.; Dickey, C. A.; Baker, B. J. Natural Products as a rich source of tau-targeting drugs for Alzheimer's disease. *Future Med. Chem.* **2012**, *4*, 1751−1761.

(8) On rubellins: (a) Miethbauer, S.; Heiser, I.; Liebermann, B. The Phytopathogenic Fungus *Ramularia collo-cygni* Produces Biologically Active Rubellins on Infected Barley Leaves. *J. Phytopathol.* **2003**, *151*, 665−668. Heiser, I.; Hess, M.; Schmidtke, K.-U.; Vogler, U.; Miethbauer, S.; Liebermann, B. Fatty Acid Peroxidation by Rubellin B, C, and D, Phytotoxins Produced by *Ramularia collo-cygni*. *Physiol. Mol. Plant Pathol.* **2004**, *64*, 135−143. (c) Miethbauer, S.; Haase, S.; Schmidtke, K.-U.; Günther, W.; Heiser, I.; Liebermann, B. Biosynthesis of photodynamically active rubellins and structure elucidation of the new anthraquinone derivatives produced by *Ramularia collo-cygni*. *Phytochemistry* **2006**, *67*, 1206−1213. On related family members: (d) Miethbauer, S.; Günther, W.; Schmidtke, K.-U.; Heiser, I.; Gräfe, S.; Gitter, B.; Liebermann, B. Uredinorubellins and Caeruleoramularin, Photodynamically Active Anthraquinone Derivatives Produced by Two Species of the Genus *Ramularia*. *J. Nat. Prod.* **2008**, *71*, 1371−1375. (e) Isaka, M.; Palasarn, S.; Tobwor, P.; Boonruangprapa, T.; Tasanathai, K. Bioactive Anthraquinone Dimers from the Leafhopper Pathogenic Fungus *Torrubiella* sp. BCC 28517. *J. Antibiot.* **2012**, *65*, 571−574. (f) Pérez Hemphill, C. F.; Daletos, G.; Hamacher, A.; Kassack, M. U.; Lin, W.; Mandi, A.; Kurtan, T.; Proksch, P. Absolute Configuration and Anti-Tumor Activity of Torrubiellin B. *Tetrahedron Lett.* **2015**, *56*, 4430−4433. (g) Zhang, C.-H.; Yao, D.-L.; Li, C.-S.; Luo, J.; Jin, M.; Zheng, M.-S.; Lin, Z.-H.; Jin, T.-F.; Li, G. Cytotoxic Anthraquinone Dimers from *Melandrium firmum*. *Arch. Pharmacal Res.* **2015**, *38*, 1033−1037. (h) Chen, H.; Du, K.; Sun, Y.-J.; Hao, Z.-Y.; Zhang, Y.-L.; Bai, J.; Wang, Q.-H.; Hu, H.-Y.; Feng, W.-S. Solanrubiellin A, a hydroanthraquinone dimer with antibacterial and cytotoxic activity from *Solanum lyratum*. *Nat. Prod. Res.* **2019**, *8*, 1−6.

(9) (a) Overman, L. E.; Pennington, L. D. A new strategy for synthesis of attached rings. *Can. J. Chem.* **2000**, *78*, 732−738. (b) Ley, S. V.; Abad-Somovilla, A.; Anderson, J. C.; Ayats, C.; Bänteli, R.; Beckmann, E.; Boyer, A.; Brasca, M. G.; Brice, A.; Broughton, H. B.; Burke, B. J.; Cleator, E.; Craig, D.; Denholm, A. A.; Denton, R. M.; Durand-Reville, T.; Gobbi, L. B.; Göbel, M.; Gray, B. L.; Grossmann, R. B.; Gutteridge, C. E.; Hahn, N.; Harding, S. L.; Jennens, D. C.; Jennens, L.; Lovell, P. J.; Lovell, H. J.; de la Puente, M. L.; Kolb, H. C.; Koot, W.-J.; Maslen, S. L.; McCusker, C. F.; Mattes, A.; Pape, A. R.; Pinto, A.; Santafianos, D.; Scott, J. S.; Smith, S. C.; Somers, A. Q.; Spilling, C. D.; Stelzer, F.; Toogood, P. L.; Turner, R. M.; Veitch, G. E.; Wood, A.; Zumbrunn, C. The Synthesis of Azadirachtin: A Potent Insect Antifeedant. *Chem. - Eur. J.* **2008**, *14*, 10683−10704. (c) Schnermann, M. J.; Overman, L. E. A Concise Synthesis of (−)-Aplyviolene Facilitated by a Strategic Tertiary Radical Conjugate Addition. *Angew. Chem., Int. Ed.* **2012**, *51*, 9576−9580. (d) Daub, M. E.; Prudhomme, J.; Roch, K. L.; Vanderwal, C. D. Synthesis and Potent Antimalarial Activity of Kalihinol B. *J. Am. Chem. Soc.* **2015**, *137*, 4912−4915. (e) Huffman, B. J. Electronic complementarity permits hindered butenolide heterodimerization and discovery of novel cGAS/STING pathway antagonists. *Nat. Chem.* **2020**, *12*, 310−317.

(10) (a) Abelman, M. M.; Oh, T.; Overman, L. E. Intramolecular Alkene Arylations for Rapid Assembly of Polycyclic Systems Containing Quaternary Centers. *J. Org. Chem.* **1987**, *52*, 4130. (b) Zhang, Y.; O'Connor, B.; Negishi, E. Palladium-Catalyzed Procedures for [3 + 2] Annulation via Intramolecular Alkenylpalladation and Arylpalladation. *J. Org. Chem.* **1988**, *53*, 5588−5590.

(11) Lachance, H.; Hall, D. G.; Denmark, S. E. Allylboration of Carbonyl Compounds. *Organic Reactions*; Wiley, 2012; Vol. *73*, pp 1−575.

(12) (a) Li, M.; Li, Y.; Ludwik, K. A.; Sandusky, Z. M.; Lannigan, D. A.; O'Doherty, G. A. Stereoselective Synthesis and Evaluation of C6"-Substituted 5a-Carbasugar Analogues of SL0101 as Inhibitors of RSK1/2. *Org. Lett.* **2017**, *19*, 2410−2413. (b) Wang, Z. X.; Miller, S. M.; Anderson, O. P.; Shi, Y. A Class of C_2 and Pseudo C_2 Symmetric Ketone Catalysts for Asymmetric Epoxidation. Conformation Effect on Catalysis. *J. Org. Chem.* **1999**, *64*, 6443−6458.

(13) Selander, N.; Paasch, J. R.; Szabó, K. J. Palladium-Catalyzed Allylic C-OH Functionalization for Efficient Synthesis of Functionalized Allylsilanes. *J. Am. Chem. Soc.* **2011**, *133*, 409−411.

(14) Liang, S.; Paquette, L. A. Palladium-Catalyzed Intramolecular Cyclization of Vinyl and Aryl Triflates. Associated Regioselectivity of the β-Hydride Elimination Step. *Acta Chem. Scand.* **1992**, *46*, 597−605.

(15) Mamidyala, S. K.; Cooper, A. Probing the reactivity of *o*-phthalaldehydic acid/methyl ester: synthesis of *N*-isoindolinones and 3-arylaminophthalides. *Chem. Commun.* **2013**, *49*, 8407−8409.

(16) Batey, A. R.; Thadani, A. N.; Smil, D. V. Potassium Allyl- and Crotyltrifluoroborates: Stable and Efficient Agents for Allylation and Crotylation. *Tetrahedron Lett.* **1999**, *40*, 4289−4292. (b) Lou, S.; Moquist, P. N.; Schaus, S. E. Asymmetric Allylboration of Ketones Catalyzed by Chiral Diols. *J. Am. Chem. Soc.* **2006**, *128*, 12660−12661. (c) Chen, J. L.-Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. Highly Diastereo- and Enantioselective Allylboration of Aldehydes using α-Substituted Allyl/Crotyl Pinacol Boronic Esters via in Situ Generated Borinic Esters. *J. Am. Chem. Soc.* **2013**, *135*, 5316−5319.

(17) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. Enantioselective Iridium-Catalyzed carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level via Transfer Hydrogenative Coupling of Ally acetate: Departure from Chirally Modified Allyl Metal Reagents in Carbonyl Addition. *J. Am. Chem. Soc.* **2008**, *130*, 14891−14899. (b) Fandrick, K. R.; Fandrick, D. R.; Gao, J. J.; Reeves, J. T.; Tan, Z.; Li, W.; Song, J. J.; Lu, B.; Yee, N. K.; Senanayake, C. H. Mild and General Zinc-Alkoxide-Catalyzed Allylations of Ketones with Allyl Pinacol Boronates. *Org. Lett.* **2010**, *12*, 3748−3751. (c) Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. Highly Diastereoselective Synthesis of Homoallylic Alcohols Bearing Adjacent Quaternary Centers Using

https://dx.doi.org/10.1021/acs.orglett.0c02127
Org. Lett. XXXX, XXX, XXX−XXX

Substituted Allylic Zinc Reagents. *J. Am. Chem. Soc.* **2007**, *129*, 5376−5377. (d) Harvey, N. L.; Krysiak, J.; Chamni, S.; Cho, S. W.; Sieber, S. A.; Romo, D. Synthesis of (±)-Spongiolactone Enabling Discovery of a More Potent Derivative. *Chem. - Eur. J.* **2015**, *21*, 1425−1428.

(18) Wang, D.; Szabó, K. J. Copper-Catalyzed, Stereoselective Cross-Coupling of Cyclic Allyl Boronic Acids with α-Diazoketones. *Org. Lett.* **2017**, *19*, 1622−1625.

(19) Raducan, M.; Alam, R.; Szabó, K. J. Palladium-Catalyzed Synthesis and Isolation of Functionalized Allylboronic Acids: Selective, Direct Allylboration of Ketones. *Angew. Chem., Int. Ed.* **2012**, *51*, 13050−13053.

(20) Bates, M. A.; Sammes, P. G.; Thomson, G. A. Synthesis of the *C*-Glycoside Fragment of Nogalamycin and some Nogalamycin Precursors. *J. Chem. Soc., Perkin Trans. 1* **1988**, *1*, 3037−3045.

(21) Mal, D.; Pahari, P. Recent Advances in the Hauser Annulation. *Chem. Rev.* **2007**, *107*, 1892−1918.

(22) Woo, C. M.; Gholap, S. L.; Lu, L.; Kaneko, M.; Li, Z.; Ravikumar, P. C.; Herzon, S. B. Development of Enantioselective Synthetic Routes to (−)-Kinamycin F and (−)-Lomaiviticin Aglycon. *J. Am. Chem. Soc.* **2012**, *134*, 17262−17273.

https://dx.doi.org/10.1021/acs.orglett.0c02127
Org. Lett. XXXX, XXX, XXX−XXX