OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

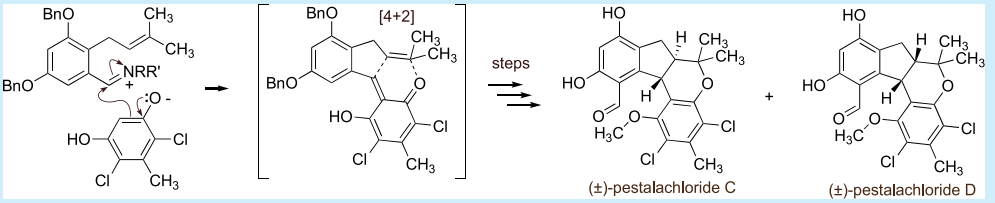
Total Synthesis of (±)-Pestalachloride C and (±)-Pestalachloride D through a Biomimetic Knoevenagel/Hetero-Diels−Alder Cascade

Vanessa Arredondo,[†] Daniel E. Roa,[†] Songyuan Yan,[†] Feng Liu-Smith,[‡] and David L. Van Vranken*,[†]

[†]Department of Chemistry, University of California, Irvine, 1102 Natural Sciences II, Irvine, California 92697, United States

[‡]Department of Medicine, School of Medicine, Chao Family Comprehensive Cancer Center, University of California Irvine, Irvine, California 92697, United States;

Supporting Information



ABSTRACT: A concise total synthesis of (±)-pestalachloride C and (±)-pestalachloride D was achieved through a Knoevenagel/hetero-Diels−Alder cascade reaction to test the nonenzymatic biosynthetic hypothesis of Shao, Wang, and co-workers. The cascade reaction generates a mixture of racemic indano[2,1-*c*]chromans like those found in the natural products.

Indano[2,1-*c*]chromans have unknowingly held the attention of humans for over two millennia (Figure 1).[1] The red extracts of sappanwood were mentioned in writings from as early as the second century. Crystals of the key constituent of these extracts, brazilin, were reported in 1808, but the indano[2,1-*c*]chroman structure was not deduced until 1901.[2] Plant-based indano[2,1-*c*]chromans, including (+)-brazilin,[3a] (+)-3′-*O*-methylbrazilin,[3] (+)-4′-*O*-methylbrazilin,[3] (+)-brazilane,[3b] caesalpiniaphenol E,[3b] (+)-hematoxylin (still used as a common cell stain), isohematoxylin,[4] and the protosappanins[5] are widely believed to arise from the C15 chalcone biosynthetic pathway.[6]

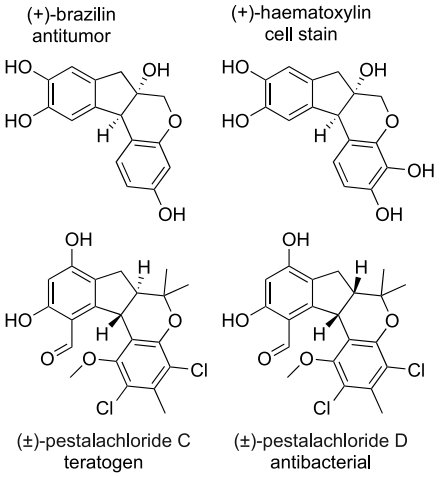


Figure 1. Naturally occurring indano[2,1-*c*]chromans.

In 2008, a new indano[2,1-*c*]chroman, (±)-pestalachloride C, was isolated from an endophytic plant fungus *Pestalotiopsis adusta* (L416).[7] The congested structure was distinct from that of other natural indano[2,1-*c*]chromans and is further distinguished by its occurrence in nature as a racemate.[8] Shao, Wang, and co-workers later isolated (±)-pestalachloride C, along with its epimer (±)-pestalachloride D, in a 3.6:1 ratio, from cultures of the marine fungus *Pestalotiopsis* sp., obtained from the soft coral *Sarcophyton* sp.[9] The *syn* isomer, pestalachloride D, exhibited no teratogenicity up to the assay limit of 50 μg/mL, whereas the *anti* isomer, pestalachloride C, exhibited teratogenic effects in zebrafish embryos at multiple stages, including egg coagulation, nonspontaneous movements, abnormal heartbeat, organ malformation, delayed hatching, and embryonic death.[9] A variety of selective teratogens such as retinoic acid, thalidomide, lenalidomide, pomalidomide, apremilast, vismodegib, and sodidegib have found use as drugs against cancer and other diseases.[10] A concise route to pestalachlorides C and D would facilitate assessment of their therapeutic potential.

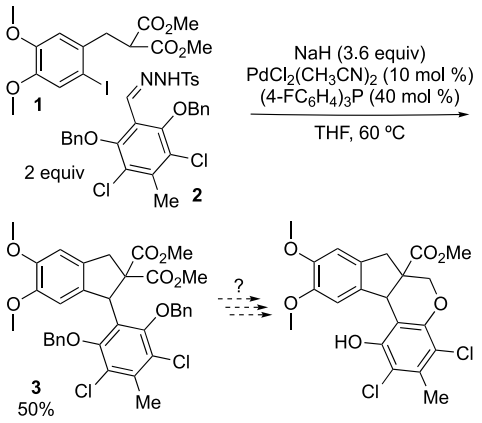
In 2014, our group developed a palladium-catalyzed carbene insertion reaction to construct 1-arylindanes that contain three of the four rings found in indano[2,1-*c*]chromans in high yield.[11] The palladium-catalyzed reaction creates a central point of disconnection to access these 1-arylindanes, and we envisioned utilizing the method to develop a convergent synthesis of indano[2,1-*c*]chromans. A model reaction involving a highly substituted aryl iodide and *N*-tosylhydrazone

Received: January 25, 2019

DOI: 10.1021/acs.orglett.9b00323
Org. Lett. XXXX, XXX, XXX−XXX

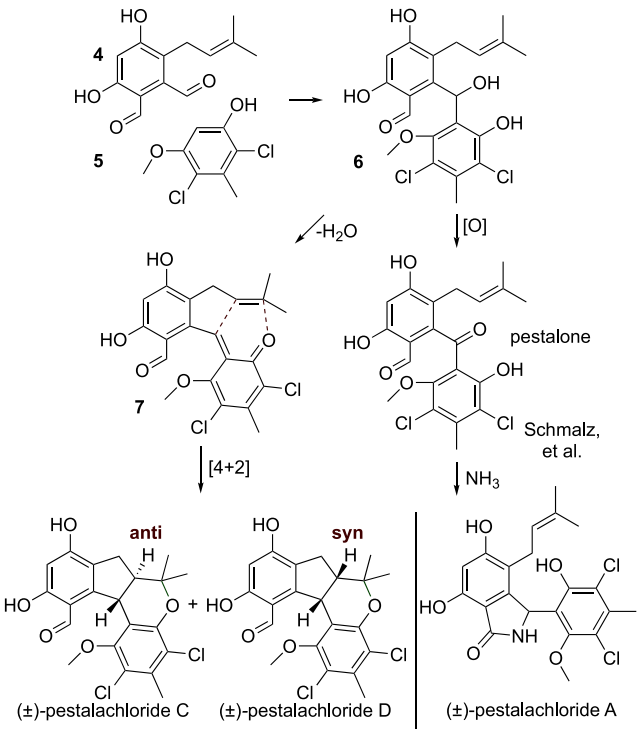
gave modest yields of the desired arylindane **3** even when 2 equiv of the *N*-tosylhydrazone were used (Scheme 1). Given the inefficiency of this chemistry we sought inspiration from nature.

Scheme 1. Palladium-Catalyzed Carbene Insertion To Construct 1-Arylindanes



The biosyntheses of pestalone and the pestalachlorides seem to be connected. Schmalz and co-workers demonstrated that pestalone[12] readily generated the lactam (±)-pestalachloride A in the presence of ammonia (Scheme 2).[13] In their isolation

Scheme 2. Shao, Wang, and Co-workers' Proposed Biosynthesis of Pestalachlorides and Pestalone



paper, Shao, Wang and co-workers proposed a compelling hypothesis for the biosynthesis of pestalone, (±)-pestalachloride C, and the new stereoisomeric natural product (±)-pestalachloride D (Scheme 2).[9]

The proposed biosynthesis involved a cascade reaction starting with condensation of the resorcinol **5** with the *o*-phthalaldehyde **4** to generate a benzhydrol **6** with two potential fates. Dehydration of the benzhydrol **6** produces a highly reactive quinone methide **7** which could undergo an inverse-electron-demand hetero-Diels–Alder cycloaddition to afford the *anti* isomer pestalachloride C or the *syn* isomer pestalachloride D (Figure 2). Alternatively, oxidation of the

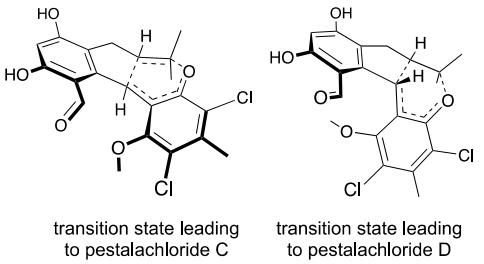
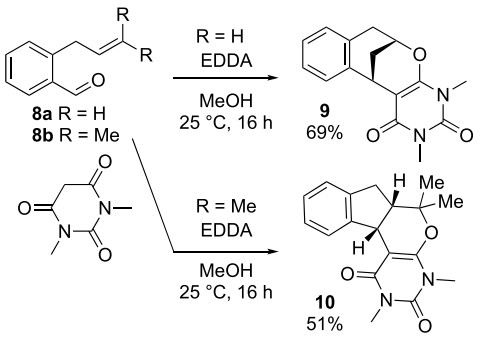


Figure 2. Depiction of transition states leading to pestalachlorides C and D.

benzhydrol **6** would directly generate pestalone and then (±)-pestalachloride A in the presence of ammonia. The involvement of aldiminium intermediates in the biosynthesis of (±)-pestalachloride A suggests a potential role for iminium intermediates in the formation of (±)-pestalachlorides C and D through a nonenzymatic biosynthetic process.

Shao and Wang's hypothesis is related to the Knoevenagel/hetero-Diels–Alder cascade reactions developed by Tietze and co-workers.[14] In 2001, Tietze and co-workers published a Knoevenagel/hetero-Diels–Alder cascade catalyzed by the diamine catalyst ethylenediammonium diacetate (10 mol % EDDA), presumably via an iminium ion. The reaction generates two types of fused barbituric acid derivatives: the allyl substrate **8a** afforded bridged tetralin **9**, whereas the prenyl-substituted substrate **8b** afforded the *cis*-fused indane **10** (Scheme 3).[15] Lee and co-workers have applied the Tietze

Scheme 3. Types of the Products Generated by the Tietze Knoevenagel/Hetero-Diels–Alder Cascade Reaction That Are Sensitive to the Structure of the Starting Materials



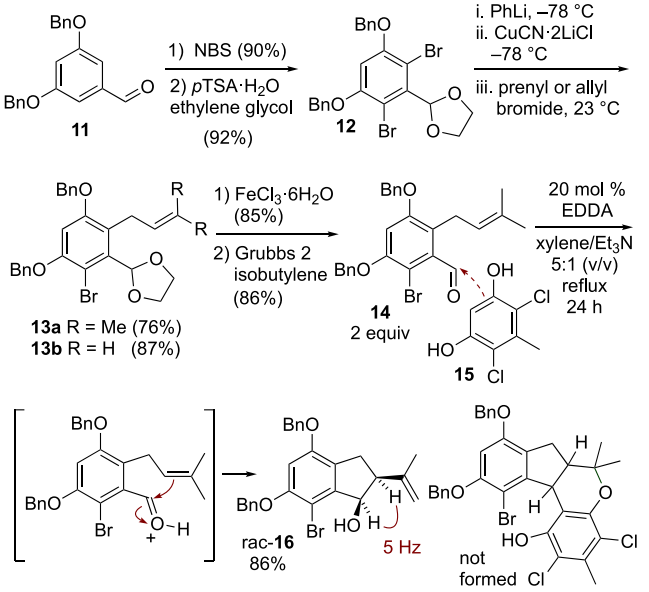
conditions to aromatic nucleophiles to generate cannabinoids and related ring systems.[16] The facile generation of tetracycles related to indano[2,1-*c*]chromans under organocatalytic conditions strongly supports Shao and Wang's proposed biosynthesis, but the stereoselectivity and sensitivity to substituents left us uncertain that it could be applied to a total synthesis of both the *syn* isomer pestalachloride D and the *anti* isomer pestalachloride C. Other workers have shown that quinone methide intermediates derived from benzylic alcohols can undergo intramolecular hetero-Diels–Alder reactions to

DOI: 10.1021/acs.orglett.9b00323
Org. Lett. XXXX, XXX, XXX–XXX

generate mixtures of *cis*-fused and *trans*-fused cyclopenta[*c*]-chromans.[17] Conflicted by the strong precedent and lingering questions, we set out to test the cascade reaction underlying the Shao and Wang biosynthetic hypothesis as an approach to pestalachlorides C and D.

The Shao and Wang biosynthetic hypothesis requires a regioselective Knoevenagel condensation with just one of the two aldehydes of *o*-phthalaldehyde **4**. To ensure condensation with the correct aldehyde, we opted to introduce the second formyl group at a later stage into the fully formed indane ring system (Scheme 4). We anticipated the need for a functional

Scheme 4. Premature Intramolecular Carbonyl Ene Process Competes with the Knoevenagel Reaction

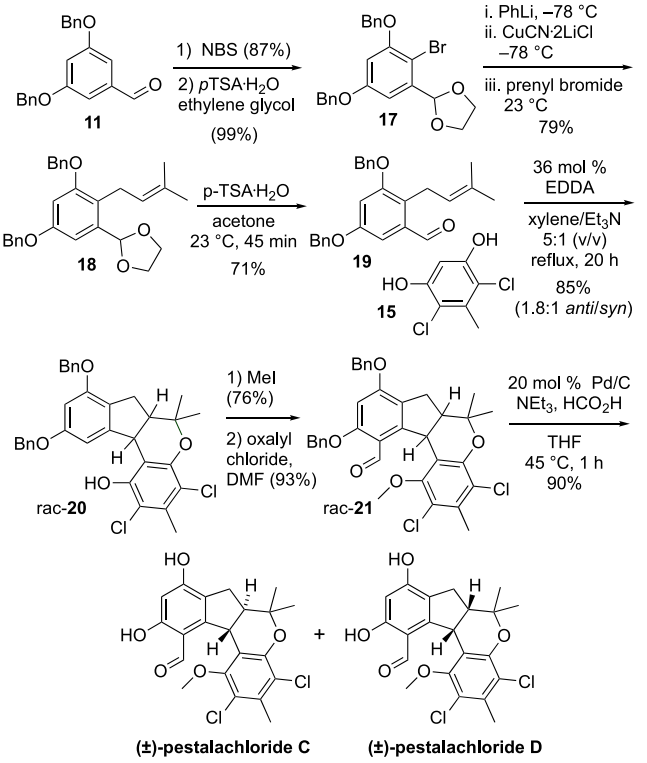


handle like bromine to allow installation of the aldehyde into a crowded position. To that end, we converted aldehyde **11** into an *o*,*o*′-dibromoaldehyde and masked the aldehyde to give acetal **12**. One of the two bromines was converted to the cyanocuprate through lithium−halogen exchange with 1.2 equiv of phenyllithium, and the cuprate was then coupled with prenyl bromide to afford acetal **13a**. The juxtaposition of aldehyde and prenyl group in **13a** is precarious. All attempts to deprotect the acetal led to complex mixtures arising from Prins reactions. We found it expedient to carry out the cuprate coupling with allyl bromide to afford allylbenzene derivative **13b**. After revealing the aldehyde, we gently converted the allyl group to a prenyl group using Grubbs metathesis.

4,6-Dichloroorcinol **15** was available through the regioselective chlorination of orcinol.[18] Sadly, we were unable to engage the dichloroorcinol in the Knoevenagel cascade due to the competing intramolecular carbonyl ene process. Under some conditions, the undesired indane **16** was formed stereoselectively in high yield. A *syn* orientation of the substituents on indane **16** has been tentatively assigned on the basis of the 5 Hz vicinal coupling constant[19] and is based on the preference for intramolecular carbonyl ene reactions to afford *syn*-cyclopentanols in saturated systems.[20]

We hypothesized that the *o*-bromo group of aldehyde **14** might be accelerating the undesired carbonyl ene reaction and set out to test the cascade on a less crowded substrate (Scheme 5). The desired monobromide **17** was prepared from aldehyde

Scheme 5. Synthesis of Oxygenated Benzaldehyde 19 and 4,6-Dichloroorcinol 15



11 by monobromination and protection of the aldehyde as an acetal. As before, aryl bromide **17** was converted to the cyanocuprate and coupled with prenyl bromide to afford dioxolane **18**.[13] This time, we were able to remove the acetal under mildly acidic conditions at incomplete conversion. The desired aldehyde **19** could be obtained in 71% yield.

Under base-catalyzed conditions (Et_3N) aldehyde **19** and resorcinol **20** generated a complex mixture containing less than 6% of indano[2,1-*c*]chromans **20**. In the presence of EDDA, which promotes iminium ion formation, the reaction is much more efficient. With some optimization, the Knoevenagel/hetero-Diels−Alder cascade generated the indano[2,1-*c*]-chromans **20** in 85−90% yields in about 90% purity. The *anti* and *syn* isomers are formed in a 1.4−1.6:1 ratio, depending on the equivalents of 4,6-dichloroorcinol and reaction time. The ratio was 1.8:1 after chromatographic purification, probably due to slight chromatographic loss of the *syn* isomer. The inseparable mixture was carried on through the synthetic route. The success of this cascade reaction is consistent with a biosynthetic route that involves a nonenzymatic cascade reaction, although the solvents and temperatures are abiotic.

We were pessimistic that an aldehyde could be introduced at the more hindered position of the indane aromatic ring. Fortunately, Vilsmeier−Haack reaction of phenol **20** was found to introduce the formyl group at the desired position, but the resulting mixture of seven-membered ring hemiacetals and hydroxyaldehydes proved unwieldy. The fortuitous and surprising regioselectivity in the formylation was initially attributed to a directing effect from the phenolic hydroxyl group on the dichloroorcinol ring. We were surprised to find that *O*-methylation of the dichlorochroman phenol **20** was still followed by a highly regioselective Vilsmeier formylation at the hindered position to afford carbaldehyde **21**. Attempts to

DOI: 10.1021/acs.orglett.9b00323
Org. Lett. XXXX, XXX, XXX−XXX

cleave the benzyl ethers of carbaldehyde **21** under typical hydrogenolysis conditions with hydrogen gas were accompanied by concomitant reduction of the benzaldehyde moiety of **21** to a methyl group, but when formate was used as the reductant, deprotection proceeded cleanly to afford a mixture of (±)-pestalachloride C and (±)-pestalachloride D in a 1.6:1 ratio in 83−90% yield. The isomers were readily separable by reversed-phase HPLC.

Hydroxylated flavonoids are known to exert weak teratogenic effects, exhibit antimelanogenic activity, and inhibit proliferation of melanoma.[21] We tested (±)-pestalachlorides C and D against the A375 melanoma cell lines and found pestalachloride D to be slightly more potent with IC_{50}s of 12.4 ± 2.4 and 7.1 ± 0.6 μM, respectively.

The ready formation of pestalachlorides C and D through a Tietze cascade reaction, involving Knoevenagel reactions of dienophiles tethered to aldehydes followed by hetero Diels−Alder cycloaddition of a quinone methide intermediate, supports the Shao and Wang biosynthetic hypothesis for these racemic natural products. It adds to the growing list of related Knoevenagel/hetero-Diels−Alder cascade reactions that parallel biosynthetic pathways.[22,23] Late-stage introduction of the formyl group allows one to assemble (±)-pestalachlorides C and D in a facile and concise manner utilizing a Knoevenagel/hetero-Diels−Alder cascade cyclization reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00323.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: david.vv@uci.edu.

ORCID

Vanessa Arredondo: 0000-0001-6567-4549
Feng Liu-Smith: 0000-0003-3963-0651
David L. Van Vranken: 0000-0001-5964-7042

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the School of Physical Sciences. V.A. acknowledges support from a fellowship from the National Science Foundation. D.R. acknowledges support from the Allergan Summer Undergraduate Research Program. D.R. and S.Y. acknowledge support from the UCI University Research Opportunities Program.

■ REFERENCES

(1) Dapson, R.; Bain, C. Brazilwood, Sappanwood, Brazilin and the Red Dye Brazilein: From Textile Dyeing and Folk Medicine to Biological Staining and Musical Instruments. *Biotech. Histochem.* **2015**, *90*, 401.

(2) Gilbody, A. W.; Perkin, W. H.; Yates, J. CXLVI.—Brazilin and Hœmatoxylin. Part I. *J. Chem. Soc., Trans.* **1901**, *79*, 1396.

(3) (a) Namikoshi, M.; Nakata, H.; Yamada, H.; Nagai, M.; Saitoh, T. Homoisoflavonoids and Related Compounds. II. Isolation and Absolute Configurations of 3,4-Dihydroxylated Homoisoflavans and Brazilins from *Caesalpinia Sappan* L. *Chem. Pharm. Bull.* **1987**, *35*, 2761. (b) Min, B. S.; Cuong, T. D.; Hung, T. M.; Min, B. K.; Shin, B. S.; Woo, M. H. Compounds from the Heartwood of *Caesalpinia Sappan* and Their Anti-Inflammatory Activity. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7436.

(4) Lin, L.-G.; Xie, H.; Li, H.-L.; Tong, L.-J.; Tang, C.-P.; Ke, C.-Q.; Liu, Q.-F.; Lin, L.-P.; Geng, M.-Y.; Jiang, H.; et al. Naturally Occurring Homoisoflavonoids Function as Potent Protein Tyrosine Kinase Inhibitors by C-Src-Based High-Throughput Screening. *J. Med. Chem.* **2008**, *51*, 4419.

(5) (a) Masuda, H.; Ohtani, K.; Mizutani, K.; Ogawa, S.; Kasai, R.; Tanaka, O. Chemical Study on *Haematoxylon Campechianum*: A Sweet Principle and New Dibenz[*b*,*d*]Oxocin Derivatives. *Chem. Pharm. Bull.* **1991**, *39*, 1382. (b) Nguyen, M. T. T.; Awale, S.; Tezuka, Y.; Tran, Q. L.; Kadota, S. Xanthine Oxidase Inhibitors from the Heartwood of Vietnamese *Caesalpinia Sappan*. *Chem. Pharm. Bull.* **2005**, *53*, 984.

(6) (a) Dewick, P. M. Biosynthesis of the 3-Benzylchroman-4-One Eucomin in *Eucomis bicolor*. *Phytochemistry* **1975**, *14*, 983. (b) Nagai, M.; Nagumo, S.; Eguchi, I.; Lee, S.; Suzuki, T. Sappanchalcone from *Caesalpinia Sappan* L., the Proposed Biosynthetic Precursor of Brazilin. *Yakugaku Zasshi* **1984**, *104*, 935. (c) Nagai, M.; Nagumo, S.; Lee, S.-M.; Eguchi, I.; Kawai, K.-I. Protosappanin A, a Novel Biphenyl Compound from Sappan Lignum. *Chem. Pharm. Bull.* **1986**, *34*, 1. (d) Lin, L.-G.; Liu, Q.-Y.; Ye, Y. Naturally Occurring Homoisoflavonoids and Their Pharmacological Activities. *Planta Med.* **2014**, *80*, 1053 and references cited therein .

(7) Li, E.; Jiang, L.; Guo, L.; Zhang, H.; Che, Y. Pestalachlorides A−C, Antifungal Metabolites from the Plant Endophytic Fungus *Pestalotiopsis Adusta*. *Bioorg. Med. Chem.* **2008**, *16*, 7894.

(8) Zask, A.; Ellestad, G. Biomimetic Syntheses of Racemic Natural Products. *Chirality* **2018**, *30*, 157 and references cited therein .

(9) Wei, M.-Y.; Li, D.; Shao, C.-L.; Deng, D.-S.; Wang, C.-Y. (±)-Pestalachloride D, an Antibacterial Racemate of Chlorinated Benzophenone Derivative from a Soft Coral-Derived Fungus *Pestalotiopsis* Sp. *Mar. Drugs* **2013**, *11*, 1050.

(10) Blagosklonny, M. V. Teratogens as Anticancer Drugs. *Cell Cycle* **2005**, *4*, 1518.

(11) Gutman, E. S.; Arredondo, V.; Van Vranken, D. L. Cyclization of η^3-Benzylpalladium Intermediates Derived from Carbene Insertion. *Org. Lett.* **2014**, *16*, 5498.

(12) Cueto, M.; Jensen, P. R.; Kauffman, C.; Fenical, W.; Lobkovsky, E.; Clardy, J. Pestalone, a New Antibiotic Produced by a Marine Fungus in Response to Bacterial Challenge. *J. Nat. Prod.* **2001**, *64*, 1444.

(13) Slavov, N.; Cvengroš, J.; Neudörfl, J.-M.; Schmalz, H.-G. Total Synthesis of the Marine Antibiotic Pestalone and Its Surprisingly Facile Conversion into Pestalalactone and Pestalachloride A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7588.

(14) (a) Tietze, L. F.; Kettschau, G. Hetero Diels-Alder Reactions in Organic Chemistry. In *Stereoselective Heterocyclic Synthesis I*; Metz, P., Ed.; Springer: Berlin, 1997; 1−120. (b) Tietze, L. F.; Beifuss, U. Sequential Transformations in Organic Chemistry: A Synthetic Strategy with a Future. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Tietze, L. F. Domino Reactions in Organic Synthesis. *Chem. Rev.* **1996**, *96*, 115. (d) Tietze, L. F.; Lieb, M. E. Domino Reactions for Library Synthesis of Small Molecules in Combinatorial Chemistry. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363. (e) Tietze, L. F.; Modi, A. Multicomponent Domino Reactions for the Synthesis of Biologically Active Natural Products and Drugs. *Med. Res. Rev.* **2000**, *20*, 304. (f) Tietze, L. F.; Haunert, F. Domino Reaction in Organic Synthesis. An Approach to Efficiency, Elegance, Ecological Benefit, Economic Advantage and Preservation of Our Resources in Chemical Transformations. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, 2005; Chapter 4, pp 39−64.

DOI: 10.1021/acs.orglett.9b00323
Org. Lett. XXXX, XXX, XXX−XXX

(15) Tietze, L. F.; Ott, C.; Haunert, F. Efficient and Regioselective Synthesis of Bridged Ring Systems by Domino Knoevenagel - Hetero-Diels-Alder Reaction. *Can. J. Chem.* **2001**, *79*, 1511.
(16) (a) Lee, Y. R.; Xia, L. Efficient One-Pot Synthetic Approaches for Cannabinoid Analogues and Their Application to Biologically Interesting (−)-Hexahydrocannabinol and (+)-Hexahydrocannabinol. *Tetrahedron Lett.* **2008**, *49*, 3283. (b) Lee, Y. R.; Kim, Y. M.; Kim, S. H. Efficient One-Pot Synthesis of Benzopyranobenzopyrans and Naphthopyranobenzopyrans by Domino Aldol-Type Reaction/Hetero Diels−Alder Reaction of Resorcinols and Naphthols. *Tetrahedron* **2009**, *65*, 101.
(17) (a) Shrestha, K. S.; Honda, K.; Asami, M.; Inoue, S. Facile Synthesis of the Fused 6−6−5 Ring System Containing Chroman Ring from 2-(1-Hydroxy-5-Alkenyl)Phenol Derivatives via Intramolecular Inverse-Electron-Demand Diels−Alder Reaction. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 73. (b) Hug, R.; Hansen, H.-J.; Schmid, H. Thermische Cyclodehydratisierung von Salicylalkoholen; Eine Einfache Synthese von 4-Substituierten 2*H*-Chromenen. *Helv. Chim. Acta* **1972**, *55*, 1675.
(18) Kaiser, F.; Schmalz, H.-G. Synthetic Analogues of the Antibiotic Pestalone. *Tetrahedron* **2003**, *59*, 7345.
(19) (a) Agrawal, P. K.; Schneider, H.-J.; Malik, M. S.; Rastogi, S. N. ^{13}C NMR Shifts and Conformations of Substituted Indans. *Org. Magn. Reson.* **1983**, *21*, 146. (b) Guo, X.-X.; Sawano, T.; Nishimura, T.; Hayashi, T. Rhodium-Catalyzed Enantioselective Alkynylative Cyclization of Allenyl Aldehydes with Terminal Alkynes. *Tetrahedron: Asymmetry* **2010**, *21*, 1730. (c) Wu, A.; Cremer, D.; Auer, A. A.; Gauss, J. Extension of the Karplus Relationship for NMR Spin−Spin Coupling Constants to Nonplanar Ring Systems: Pseudorotation of Cyclopentane. *J. Phys. Chem. A* **2002**, *106*, 657.
(20) Grachan, M. L.; Tudge, M. T.; Jacobsen, E. N. Enantioselective Catalytic Carbonyl−Ene Cyclization Reactions. *Angew. Chem., Int. Ed.* **2008**, *47*, 1469.
(21) (a) Liu-Smith, F.; Meyskens, F. L. Molecular Mechanisms of Flavonoids in Melanin Synthesis and the Potential for the Prevention and Treatment of Melanoma. *Mol. Nutr. Food Res.* **2016**, *60*, 1264. (b) Veselinović, J. B.; Kocić, G. M.; Pavic, A.; Nikodinovic-Runic, J.; Senerovic, L.; Nikolić, G. M.; Veselinović, A. M. Selected 4-Phenyl Hydroxycoumarins: In Vitro Cytotoxicity, Teratogenic Effect on Zebrafish (*Danio rerio*) Embryos and Molecular Docking Study. *Chem. Biol. Interact.* **2015**, *231*, 10.
(22) (a) Yang, B.; Gao, G. Recent advances in the application of Diels-Alder reactions involving *o*-quinodimethanes, aza-*o*-quinone methides and *o*-quinone methides in natural product total synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7926. (b) Nielsen, C. D. -T.; Abas, H.; Spivey, A. C. Stereoselective Reactions of *ortho*-Quinone Methide and *ortho*-Quinone Methide Imines and Their Utility in Natural Product Synthesis. *Synthesis* **2018**, *50*, 4008. (c) Ai, W.-Y.; Liao, D.-H.; Lei, X.-G. Applications of *ortho*-Quinone Methides in the Synthesis of Natural Products. *Chin. J. Org. Chem.* **2015**, *35*, 1615. (d) Willis, J.; Bray, C. D. *ortho*-Quinone Methides in Natural Product Synthesis. *Chem. Eur. J.* **2012**, *18*, 9160. (e) Tietze, L. F.; Rackelmann, N. The Domino-Knoevenagel-hetero-Diels−Alder Reaction and Related Transformations. In *Multicomponent Reactions*; Zhu, J., Hugues, B., Eds.; Wiley-VCH: Weinheim, 2005; Chapter 5, pp 121−168.
(23) (a) Casiraghi, G.; Cornia, M.; Casnati, G.; Fava, G. G.; Belicchi, M. F. A one-step highly stereocontrolled synthesis of (−)- and (+)-hexahydrocannabinol and related compounds. *J. Chem. Soc., Chem. Commun.* **1986**, 271. (b) Lawrence, A. L.; Adlington, R. M.; Baldwin, J. E.; Lee, V.; Kershaw, J. A.; Thompson, A. L. A Short Biomimetic Synthesis of the Meroterpenoids Guajadial and Psidial A. *Org. Lett.* **2010**, *12*, 1676. (c) Newton, C. G.; Tran, D. N.; Wodrich, M. D.; Cramer, N. One-Step Multigram-Scale Biomimetic Synthesis of Psiguadial B. *Angew. Chem., Int. Ed.* **2017**, *56*, 13776. (d) Spence, J. T. J.; George, J. H. Structural Reassignment of Cytosporolides A−C via Biomimetic Synthetic Studies and Reinterpretation of NMR Data. *Org. Lett.* **2011**, *13*, 5318. (e) Spence, J. T. J.; George, J. H. Total Synthesis of Peniphenones A−D via Biomimetic Reactions of a Common *o*-Quinone Methide Intermediate. *Org. Lett.* **2015**, *17*, 5970. (f) Lam, H. C.; Phan, Q. D.; Sumby, C. J.; George, J. H. Biomimetic Synthesis of Hyperjapones F-I. *Aust. J. Chem.* **2018**, *71*, 649. (g) Dethe, D. H.; Kumar, V. B.; Maiti, R. Biomimetic Total Syntheses of Chromane Meroterpenoids, Guadials B and C, Guapsidial A and Psiguajadial D. *Org. Biomol. Chem.* **2018**, *16*, 4793. (h) Takao, K.; Noguchi, S.; Sakamoto, S.; Kimura, M.; Yoshida, K.; Tadano, K. Total Synthesis of (+)-Cytosporolide A via a Biomimetic Hetero-Diels−Alder Reaction. *J. Am. Chem. Soc.* **2015**, *137*, 15971. (i) Chapman, L. M.; Beck, J. C.; Lacker, C. R.; Wu, W.; Reisman, S. E. Evolution of a Strategy for the Enantioselective Total Synthesis of (+)-Psiguadial B. *J. Org. Chem.* **2018**, *83*, 6066.

DOI: 10.1021/acs.orglett.9b00323
Org. Lett. XXXX, XXX, XXX−XXX