Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

Bioinspired Total Synthesis of Delitschiapyrone A

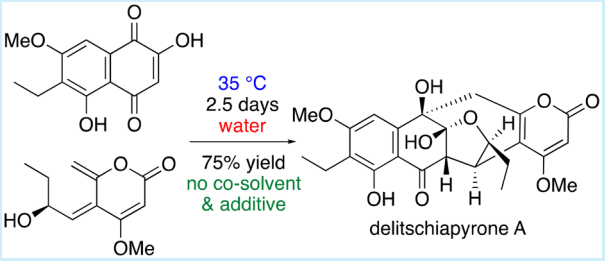
Kazuki Kurasawa,[†] Eunsang Kwon,*[,‡] Shigefumi Kuwahara,[†] and Masaru Enomoto*[,†]

[†]Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, 468-1 Aramaki Aza-Aoba, Aoba-ku, Sendai 980-8572, Japan

[‡]Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, 6-3 Aramaki Aza-Aoba, Aoba-ku, Sendai 980-8578, Japan

Supporting Information

ABSTRACT: A bioinspired seven-step total synthesis of delitschiapyrone A was accomplished in 32% overall yield from commercially available 4-bromo-3,5-dimethoxybenzoic acid. The key step of the synthesis is an exclusively regioselective and diastereoselective reaction cascade consisting of the Diels–Alder reaction, α-ketol rearrangement, and cyclic hemiacetalization, achieved by simply stirring a heterogeneous mixture of two Diels–Alder substrates (putative biosynthetic intermediates) and water at 35 °C, directly furnishing the pentacyclic natural product in 75% yield.



The Diels–Alder reaction has long been employed by organic chemists as an indispensable tool to obtain a cyclohexene structural motif by virtue of its wide range of applicability, as well as predictable stereoselectivity and regioselectivity; its power has especially been exerted in the total synthesis of natural products of high structural complexity.[1,2] In addition to organic chemists, it is well-known that nature also makes use of the Diels–Alder reaction for the biosynthesis of structurally diverse secondary metabolites, and the catalytic processes of some enzymes (so-called "Diels–Alderases") that promote this pericyclic reaction have gradually been elucidated at the molecular level.[3] Delitschiapyrone A (**1**) (see Figure 1), the

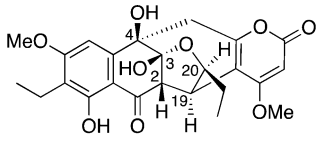
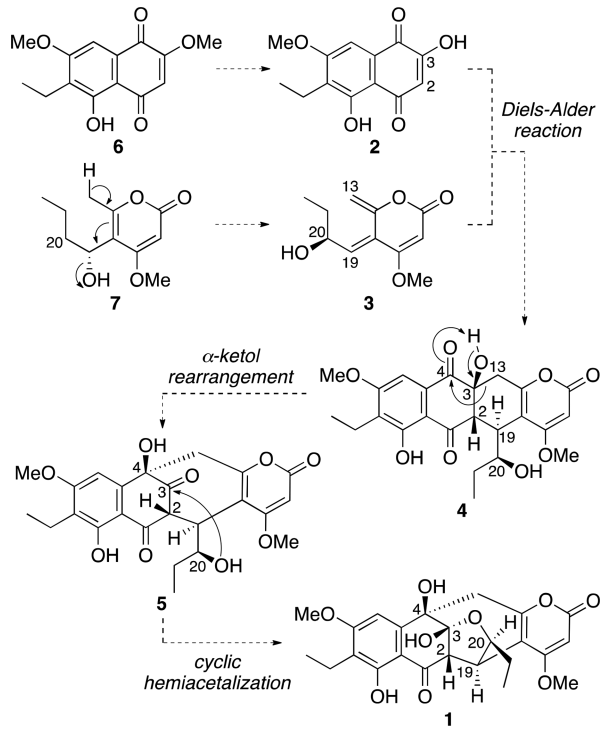


Figure 1. Structure of delitschiapyrone A (**1**).

biosynthesis of which was proposed to involve an intermolecular Diels–Alder reaction, is a cytotoxic natural product (IC_{50}: 12.3–35.5 μM against several cancer cell lines) that was isolated by Gunatilaka and co-workers from the fungus *Delitschia* sp. FL1581.[4] They determined its unique structure featuring an unprecedented 6/6/5/7/6 pentacyclic ring system with five contiguous stereocenters by X-ray crystallography, coupled with ECD spectral analysis, and deduced its biosynthetic pathway, as follows (see Scheme 1):

(1) two putative precursors—naphthoquinone **2** (dienophile) and α-pyrone derivative **3** (diene)—undergo the intermolecular Diels–Alder reaction to give cycloadduct **4**;

Scheme 1. Biosynthetic Pathway for 1 Proposed by Gunatilaka and Coworkers[4]



(2) the adduct **4** is transformed to 6/6/7/6 tetracyclic intermediate **5** via α-ketol rearrangement; and

Received: June 21, 2018

DOI: 10.1021/acs.orglett.8b01932
Org. Lett. XXXX, XXX, XXX–XXX

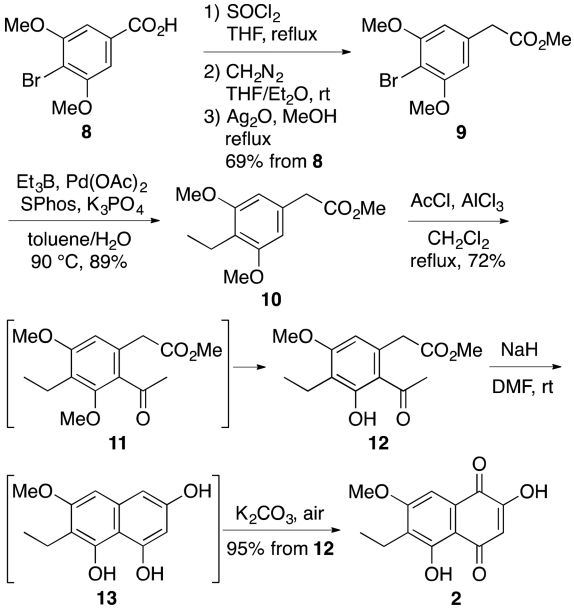
(3) cyclic hemiacetalization between the C20 hydroxyl and the C3 carbonyl in **5** delivers **1**.

In support of this proposal, they isolated two known compounds, **6** and **7**,[5,6] from the same fungal culture; the putative dienophile **2** is merely the 3-*O*-demethyl analogue of **6**, and the diene **3** would potentially be derivable from **7** via 1,4-conjugate elimination of water, followed by oxidation at the C20 position.

Inspection of the biosynthetic proposal led us to envisage that the transformation from **4** to **1** would probably proceed with exclusive stereoselection, regardless of whether it is an enzymatic or nonenzymatic process, since the attack of the C13 carbon to the C4 carbonyl in the α-ketol rearrangement of **4** would inevitably occur from the bottom face (*si* face) of the carbonyl group due to steric confinement imposed by the (2*S*,3*S*)-*cis*-decalin system, and the cyclization of the C20 hydroxyl of **5** onto the C3 carbonyl should occur also from the bottom face (*re* face) of the carbonyl, because of the presence of the rigid (2*R*,4*R*)-bicyclo[4.3.1]decane system in **5**. The intermolecular Diels–Alder reaction (**2**/**3** → **4**), on the other hand, has the possibility of affording eight isomers, including **4** (see p S41 in the Supporting Information (SI)), depending on its regio-, *endo*/*exo*-, and diastereofacial selectivities. In this article, we describe the first total synthesis of **1** in 32% overall yield from a commercially available benzoic acid derivative through only seven steps, which involve an efficient cascade sequence initiated by the Diels–Alder reaction between **2** and **3**.

Scheme 2 illustrates the preparation of the dienophile **2** from commercially available 4-bromo-3,5-dimethoxybenzoic acid (**8**).

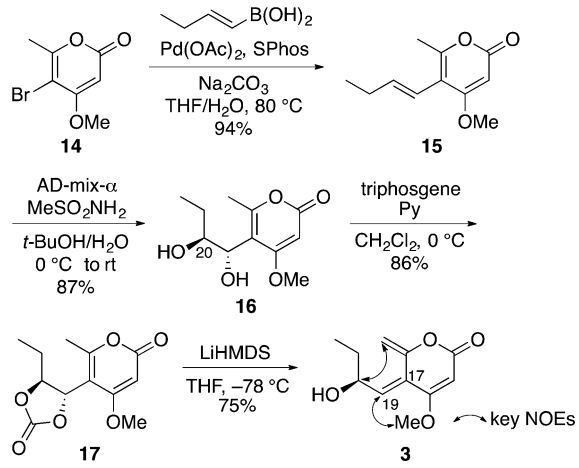
Scheme 2. Preparation of Dienophile Segment 2



One-carbon homologation of **8** by the standard Arndt–Eistert sequence gave **9**,[7] which was then subjected to the Suzuki–Miyaura coupling with triethylborane to afford **10**.[8] Treatment of **10** with AcCl (1.2 equiv) in CH_2Cl_2 at reflux in the presence of $AlCl_3$ (2.4 equiv) brought about its Friedel–Crafts acetylation to **11** and selective removal of the methoxy group *ortho* to the acetyl group, furnishing **12** in 72% yield.[9] Finally, the Dieckmann condensation of the keto ester **12**, followed by air oxidation of intermediate **13** in one pot, gave **2** in 42% overall yield from **8** via six operational steps.[10]

The preparation of the diene segment **3** (Scheme 3), which contains a previously unreported 5,6-dialkylidene-5,6-dihydro-

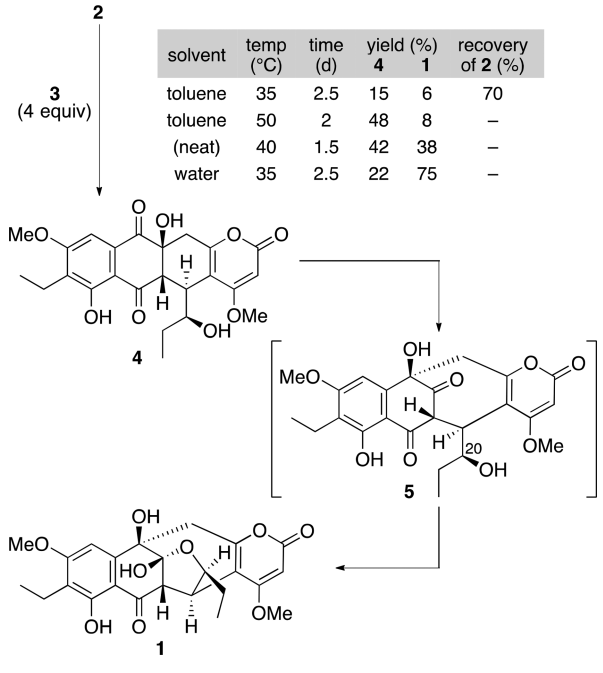
Scheme 3. Preparation of Diene Segment 3



2*H*-pyran-2-one unit, commenced with palladium-catalyzed cross-coupling of known bromide **14** with (*E*)-but-1-enylboronic acid to give **15** in 94% yield.[11] Subjecting **15** to the Sharpless asymmetric dihydroxylation conditions using AD-mix-α delivered diol **16**, whose enantiomeric excess was determined to be 99% by analyzing the ^{1}H NMR spectra of the corresponding (*R*)- and (*S*)-20-mono-MTPA esters. The diol **16** was converted to cyclic carbonate **17** and then exposed to LiHMDS in THF at −78 °C, which induced smooth 1,4-conjugate elimination to furnish **3** in 75% yield (53% overall yield from **14** in four steps) as a single geometrical isomer.[12] The *E*-geometry of its C17–C19 double bond was assigned by observing diagnostic NOE correlations, as depicted in Scheme 3.

The final stage of our total synthesis of **1**, which involves the Diels–Alder assembly of the two segments, **2** and **3**, is shown in Scheme 4. To begin with, a solution of **2** and **3** (4 equiv) in

Scheme 4. Endgame of the Total Synthesis of 1



DOI: 10.1021/acs.orglett.8b01932
Org. Lett. XXXX, XXX, XXX–XXX

toluene was stirred at 35 °C under a nitrogen atmosphere. The Diels–Alder reaction proceeded, albeit sluggishly, and the desired cycloadduct **4**, the structure of which was determined by X-ray crystallography, was isolated in 15% yield after 2.5 days of stirring, with ca. 70% of the starting quinone **2** recovered. Interestingly, **4** was obtained as a single isomer, and none of the other regioisomers and stereoisomers were detected in the crude reaction mixture. Furthermore, close examination of the byproducts in this reaction revealed that our final synthetic target **1** was also produced (6% isolated yield), indicating that the three reactions (Diels–Alder reaction, α-ketol rearrangement, and cyclic hemiacetalization) could be effected as a cascade sequence.[13] When the reaction was conducted at 50 °C, the starting material **2** was consumed completely after 2 days, affording **4** in an improved yield of 48%, along with 8% of **1**, although heating the reaction mixture at reflux led to the formation of a complex mixture. Next, with the intention of increasing the reaction rate, the crystalline quinone **2** and the oily diene **3** were mixed under solvent-free (neat) conditions, and the resulting viscous suspension was stirred at 40 °C for 1.5 days, which provided **1** in 38% yield, together with a 42% yield of **4**. Finally, a much improved transformation of **2** into **1** was realized by adding water to the heterogeneous mixture of **2** and **3** and then stirring the mixture at 35 °C for 2.5 days, furnishing **1** in a satisfactory yield of 75%, along with the intermediary cycloadduct **4** in 22% yield.[14] The ^{1}H and ^{13}C NMR spectra of **1** were identical with those of natural delitschiapyrone A, and the specific rotation of **1** ($[\alpha]_D$ +124 (*c* 0.44, MeOH)) showed good agreement with that reported for the natural product ($[\alpha]_D$ +121 (*c* 0.12, MeOH)).[4] Water has been documented to promote various organic reactions, including the Diels–Alder reaction and α-ketol rearrangement.[15] The much more efficient conversion of **2**/**3** into **1** in the presence of water, rather than in toluene or under the neat conditions, seems to indicate that this reaction is one such example.

In the above-described cascade sequence, the desired final product **1** was obtained in 75% yield together with a 22% yield of the Diels–Alder adduct **4**, which means that the Diels–Alder process proceeded regioselectively and diastereoselectively in almost quantitative yield (75% plus 22%). The regioselectivity of this Diels–Alder reaction was rationalized by calculating the energies and coefficients of the frontier orbitals of **2** and **3**, which indicated that the LUMO of **2** would interact with the HOMO of **3** and that C2 and C3 of **2** would make bonds with C19 and C13 of **3**, respectively (see pp S55–S56 in the SI).[16] The diastereofacial selectivity of the cycloaddition was, on the other hand, interpreted by assuming a transition state (Figure 2a), based on the DFT-optimized structure of **3** at the B3LYP/6-31G(d) level of theory (Figure 2b). In this generally preferred *endo* transition state, the dienophile **2** approaches the diene **3**, which is in its preferred conformation to minimize 1,3-allylic strain,[17] from the sterically less-hindered upper face. An attractive electronic interaction between the hydrogen atom of the C20 hydroxyl of **3** (δ^+) and the oxygen atom of the C1 carbonyl of **2** (δ^-), which was suggested by the calculated electrostatic potentials of **2** and **3** (see p S56 in the SI), acts synergistically to enhance the diastereofacial selectivity and facilitate the intermolecular reaction.[18] It is worth mentioning that the attempted Diels–Alder reaction between **2** and (±)-20-*O*-acetyl-**3** gave a complex mixture, which shows the crucial role of the C20 hydroxyl of **3** in this Diels–Alder reaction.[19]

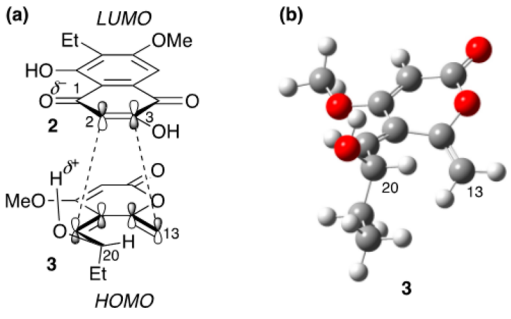


Figure 2. (a) Plausible transition state for the Diels–Alder reaction between **2** and **3**. (b) DFT-optimized structure of **3** at the B3LYP/6-31G(d) level of theory.

In summary, a biomimetic total synthesis of the cytotoxic fungal metabolite delitschiapyrone A (**1**) has been accomplished in an excellent overall yield of 32% from commercially available 4-bromo-3,5-dimethoxybenzoic acid (**8**) through seven steps. The notable features of the synthesis are (1) the dienophile segment **2** was prepared from **8** via a six-step sequence involving two one-pot processes (**10** → **12** and **12** → **2**); (2) the diene segment **3** was obtained as a single geometrical isomer by 1,4-conjugate elimination of the cyclic carbonate **16**; and (3) the Diels–Alder reaction of the juglone derivative **2** with the diene **3**, followed by concomitant α-ketol rearrangement and cyclic hemiacetalization, proceeded with exclusive regioselectivity and stereoselectivity, directly affording **1** in a good isolated yield of 75%. It is remarkable that the Diels–Alder-initiated reaction cascade was realized in a surprisingly efficient manner as a heterogeneous mixture with water (the solvent used by nature) at 35 °C (nearly ambient temperature), which would suggest the possibility that the final stage of the biosynthesis of delitschiapyrone A might occur nonenzymatically, even in nature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01932.

Experimental procedures, characterization data, NMR spectra for new compounds, and theoretical calculations (PDF)

Accession Codes

CCDC 1554823 contains 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, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ekwon@m.tohoku.ac.jp (E. Kwon).
*E-mail: masaru.enomoto.a2@tohoku.ac.jp (M. Enomoto).

ORCID

Masaru Enomoto: 0000-0001-6342-217X

Author Contributions

M.E. and S.K. designed the synthetic route and wrote the manuscript. K.K. conducted the synthetic experiments, with the aid of M.E. E.K. performed the X-ray crystallographic analysis, as well as computational studies, and wrote the manuscript.

DOI: 10.1021/acs.orglett.8b01932
Org. Lett. XXXX, XXX, XXX–XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by JSPS KAKENHI (Grant No. 16K07708), by JSPS Core-to-Core Program, A: Advanced Research Networks entitled "Establishment of International Agricultural Immunology Research-Core for a Quantum Improvement in Food Safety", and by the Platform Project for Supporting Drug Discovery and Life Science Research funded by the Japan Agency for Medical Research and Development (AMED). We thank Ms. Yuka Taguchi (Tohoku University) for her help with NMR and MS measurements.

■ REFERENCES

(1) Fringuelli, F.; Taticchi, A. *The Diels–Alder Reaction: Selected Practical Methods*; Wiley & Sons: West Sussex, U.K., 2002.

(2) (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (b) Stocking, E. M.; Williams, R. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115.

(3) (a) Zheng, Q.; Tian, Z.; Liu, W. *Curr. Opin. Chem. Biol.* **2016**, *31*, 95–102. (b) Hashimoto, T.; Kuzuyama, T. *Curr. Opin. Chem. Biol.* **2016**, *35*, 117–123.

(4) Luo, J.-G.; Wang, X.-B.; Xu, Y.-M.; U'Ren, J. M.; Arnold, A. E.; Kong, L.-Y.; Gunatilaka, A. A. L. *Org. Lett.* **2014**, *16*, 5944–5947.

(5) Sun, R.; Gao, Y.-X.; Shen, K.-Z.; Xu, Y.-B.; Wang, C.-R.; Liu, H.-Y.; Dong, J.-Y. *Phytochem. Lett.* **2011**, *4*, 101–105.

(6) Sparace, S. A.; Mudd, J. B.; Burke, B. A.; Aasen, A. J. *Phytochemistry* **1984**, *23*, 2693–2694.

(7) Pang, Y.-P.; Kozikowski, A. P. *J. Org. Chem.* **1991**, *56*, 4499–4508.

(8) Li, H.; Zhong, Y.-L.; Chen, C.; Ferraro, A. E.; Wang, D. *Org. Lett.* **2015**, *17*, 3616–3619.

(9) Intermediate **11** could be isolated in 52% yield (not optimized), when compound **10** was treated with AcCl (1.1 equiv) in CH_2Cl_2 at room temperature in the presence of $AlCl_3$ (2.2 equiv).

(10) (a) Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744–5745. (b) Husain, S. M.; Schätzle, M. A.; Röhr, C.; Lüdeke, S.; Müller, M. *Org. Lett.* **2012**, *14*, 3600–3603.

(11) (a) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466–468. (b) Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2667–2671. (c) Jolibois, A. E. R.; Lewis, W.; Moody, C. J. *Org. Lett.* **2014**, *16*, 1064–1067.

(12) This type of 1,4-elimination to provide a dienyl alcohol (e.g., **3**) from a cyclic carbonates (e.g., **17**) has, to our knowledge, never been reported so far. For 1,4-elimination, see: (a) Hill, R. K.; Bock, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 637–639. (b) Vogel, E.; Caravatti, G.; Franck, P.; Aristoff, P.; Moody, C.; Becker, A.-M.; Felix, D.; Eschenmoser, A. *Chem. Lett.* **1987**, *16*, 219–222. (c) Bickelhaupt, F. M. *Mass Spectrom. Rev.* **2001**, *20*, 347–361.

(13) As expected from the close proximity of the C20 hydroxyl to the C3 carbonyl, the α-ketol rearrangement product **5** was not obtained at all.

(14) The α-ketol rearrangement of **4** to **5**, which is intrinsically reversible, might have been promoted by the subsequent transformation of **5** into the stable cyclic hemiacetal **1**. For α-ketol rearrangement and its reversibility, see: Paquette, L. A.; Hofferberth, J. E. *Org. React.* **2003**, *62*, 477–567.

(15) For this type of water-promoted reactions (so-called "in-water" and "on-water" reactions), see: (a) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365–1372. (b) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279. (c) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103–8104. (d) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502. (e) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302–6337. (f) Nishimura, E.; Ohfune, Y.; Shinada, T. *Tetrahedron Lett.* **2015**, *56*, 539–541.

(16) For an example of Diels–Alder reaction of juglone (5-hydroxy-1,4-benzoquinone) with an unsymmetrical 1,3-diene having a substitution pattern analogous to that of **3**, see: Nechepurenko, I. V.; Shul'ts, E. E.; Tolstikov, G. A. *Russ. J. Org. Chem.* **2001**, *37*, 1276–1283.

(17) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006–5017.

(18) For analogous reactions, see: (a) Adam, W.; Gläser, J.; Peters, K.; Prein, M. *J. Am. Chem. Soc.* **1995**, *117*, 9190–9193. (b) Nicolaou, K. C.; Lim, Y. H.; Becker, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3444–3448. (c) Nicolaou, K. C.; Becker, J.; Lim, Y. H.; Lemire, A.; Neubauer, T.; Montero, A. *J. Am. Chem. Soc.* **2009**, *131*, 14812–14826.

(19) Judging from the phenolic OH proton region of the ^{1}H NMR spectrum, the crude reaction mixture seemed to contain at least four isomeric cycloadducts.

DOI: 10.1021/acs.orglett.8b01932
Org. Lett. XXXX, XXX, XXX–XXX