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Biomimetic Total Synthesis of (±)-Carbocyclinone-534 Reveals Its Biosynthetic Pathway

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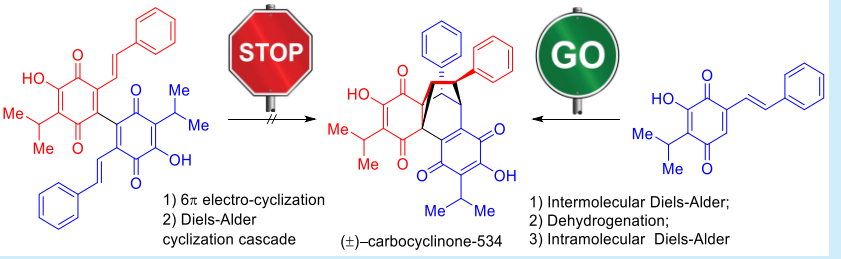

ABSTRACT: Carbocyclinone-534 is a new antibiotic produced after the metabolism of tapinarof. We identify a biomimetic total synthesis of carbocyclinone-534 in eight steps by taking advantage of an intermolecular Diels–Alder homodimerization/dehydrogenation/intramolecular Diels–Alder cycloaddition cascade. This synthetic sequence provides direct experimental evidence for revealing the biosynthetic pathway of carbocyclinone-534.

Nature has endowed the chemical world with a rich and diverse collection of cyclopropane-containing secondary metabolites.[1] Biosynthetically, some cyclopropanes are created through intramolecular Diels–Alder reaction (IMDA), for example, crispatene,[2] salvileucalin B,[3] mitrephorone A,[4] and staphirine.[5] A recent example is carbocyclinone-534 (**6**),[6] a new antibiotic produced after the metabolism of tapinarof (**1**), which is a topical nonsteroidal anti-inflammatory stilbene drug that has been approved in China to treat psoriasis and atopic dermatitis.[7] Recently, Crawford and co-workers isolated two stilbene dimers of tapinarof (**1**), duotap-520 (**4**) and carbocyclinone-534 (**6**), two metabolism products of tapinarof (**1**) produced by gammaproteobacterial *Photorhabdus*. Duotap-520 (**4**) showed activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE), and carbocyclinone-534 (**6**) exhibited growth inhibitory activity againsty mycobacteria.

Structurally, carbocyclinone-534 (**6**) is a racemic cyclopropane bridge-containing heptacyclic benzoquinone (6/3/6/5/6/6/6) with a carbon backbone containing six contiguous stereogenic carbon atoms, including two contiguous quaternary centers, in a highly sterically demanding cagelike core. The structure of carbocyclinone-534 (**6**) was further corroborated by X-ray crystallographic analysis. On the basis of their in vitro protein biochemical experiments and the racemic nature of carbocyclinone-534 (**6**) (Figure 1), Crawford and co-workers proposed that duotap-520 (**4**) was the heterocoupling product of tapinarof (**1**) and quinone **2**. Carbocyclinone-534 (**6**) might be synthesized from homocoupling product **3** through a spontaneous facile 6π-electrocyclization and Diels–Alder cyclization or from duotap-520 (**4**) through direct oxidation. Although it was not isolated, homodimerization product **3** was believed to be the putative intermediate for carbocyclinone-534 (**6**) synthesis. More interestingly, they found metal ions, Cu^{2+} and Mn^{2+}, for example, could assist the in vitro Plu1886-catalyzed divergent transformation of tapinarof (**1**) to duotap-520 (**4**) and carbocyclinone-534 (**6**), respectively. The novel structure of carbocyclinone-534 (**6**) and the interesting proposed biosynthetic pathway from a simple precursor attracted our attention. Herein, we report the biomimetic total synthesis of carbocyclinone-534 (**6**) and provide direct experimental evidence for revealing the biosynthetic pathway of carbocyclinone-534.

We chose to synthesize monomer tapinarof (**1**) and stilbene **11**, which could serve as precursors to heterodimer duotap-520 (**4**) and homodimer **3**, respectively (Scheme 1a). Aldehyde **8** could be readily prepared in 40% yield from commercially available 3,5-dihydroxylbenzoic acid through a four-step sequence developed by Gao and Zhang.[8] After Horner–Wadsworth–Emmons (HWE) olefination and subsequent demethylation with BBr_3, tapinarof (**1**) was synthesized in 68% yield (two steps).[9] Aldehyde **10** could be readily prepared in 34% yield from commercially available 1,2,4-trimethoxybenzene (**9**) through a four-step sequence developed by Majetich.[10]

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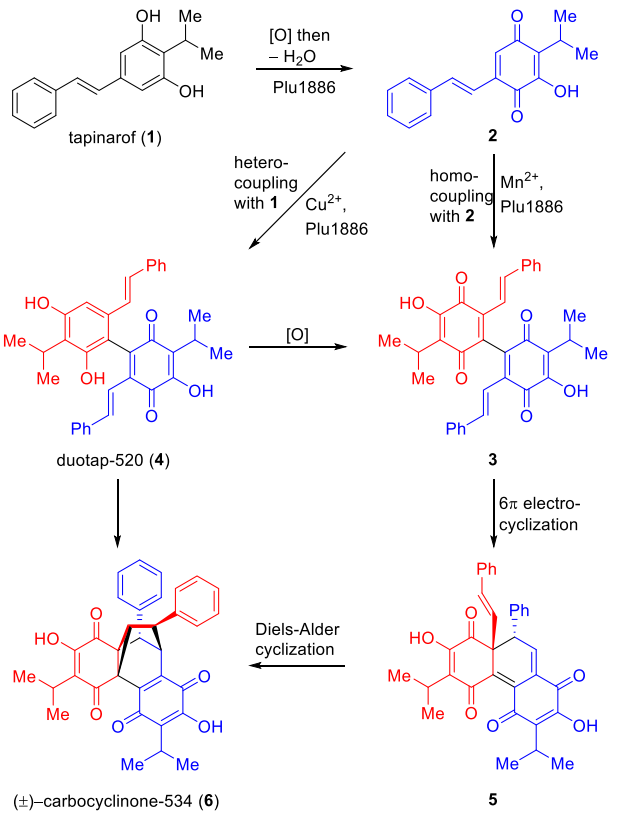
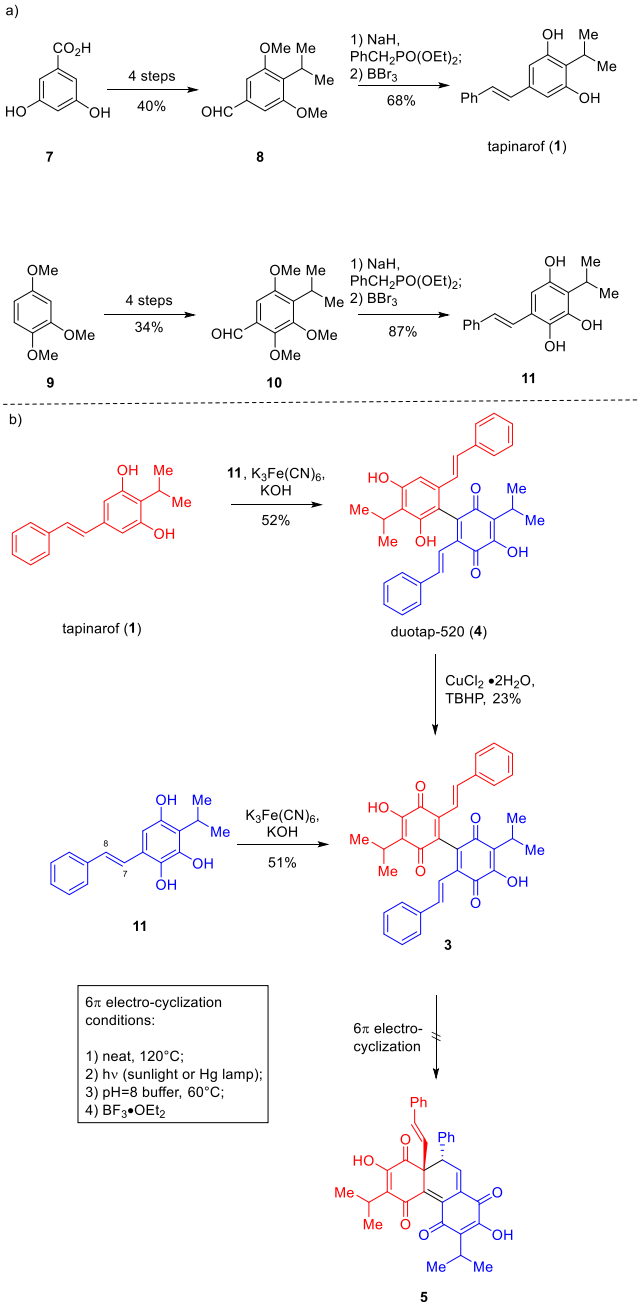


Figure 1. Proposed biosynthetic pathway for carbocyclinone-534 and duotap-520.

By using a similar sequence, stilbene **11** was readily prepared from aldehyde **10** (87% yield for two steps). With both tapinarof (**1**) and stilbene **11** in hand, we investigated the oxidative phenolic homo- and heterocoupling reaction (Scheme 1b). Oxidative phenolic homocoupling reactions using different oxidants like thallium(III),[11] vanadium(V),[12] ruthenium(IV),[13] chromium(III),[14] and recently iron(III) salts,[15] O_2,[16] and electrochemistry[17] have been developed. By using the procedure of Hu and co-workers,[15e] we found by using $K_3Fe(CN)_6$ as the oxidant in the presence of KOH, resultant homocoupling product **3** could be obtained in 51% isolated yield and the low yield was mainly caused by the instability of dimerized quinone.

In contrast, like the presence of fierce competition of homocoupling of stilbene **11**, oxidative heterocoupling of tapinarof (**1**) with stilbene **11** is more challenging. By slow addition of stilbene **11** to a mixture of $K_3Fe(CN)_6$/KOH and excess tapinarof (**1**) in acetonitrile, the corresponding heterocoupling product duotap-520 (**4**) was obtained in 52% isolated yield without detection of homocoupling product **3**. Interestingly, duotap-520 (**4**) could be further oxidized to homodimer **3** with $CuCl_2{\cdot}2H_2O$,[18] although the yield is not satisfactory (23% yield). Then we turned to the 6π-electrocyclization/Diels–Alder cycloaddition cascade. The oxa or aza 6π-electrocyclization/Diels–Alder cascade is a general strategy in natural product biosynthesis and has been realized in a flask.[19] However, there was no precedent of all carbon 6π-electrocyclization for the quinone-containing substrate. We examined a variety of conditions (heat, *hv*, and Lewis acids) to promote the subsequent 6π-electrocyclization, and it turned out to be inaccessible in our hands (see the Supporting Information for more details).

Scheme 1. Syntheses of Monomeric Tapinarof (1), 11, and Duotap-520 (4)



In the optimization of homocoupling of stilbene **11**, we found that when there was no base in the system, the resultant quinone **2** after oxidation with $K_3Fe(CN)_6$ was spontaneously dimerized to form quinone **12** through intermolecular Diels–Alder reaction[20] (Scheme 2). The intermolecular Diels–Alder homodimerized product **12** was obtained as a single *endo* diastereomer, and the resultant quinone **2** and homocoupling product **3** were not detected. Notably, the intermolecular Diels–Alder reaction happened spontaneously with high regio- and diastereoselectivity: only the *endo* addition product was detected, and the structure of **12** was further corroborated by X-ray crystallographic analysis.[21] To gain more insight into the remarkable selectivities, DFT calculations were conducted at the SMD-(THF)-RI-PWPB95-D3-(BJ)/def2-QZVPP//SMD-(THF)-ωB97X-D/6-31G(d) level of theory. Scheme 2b shows

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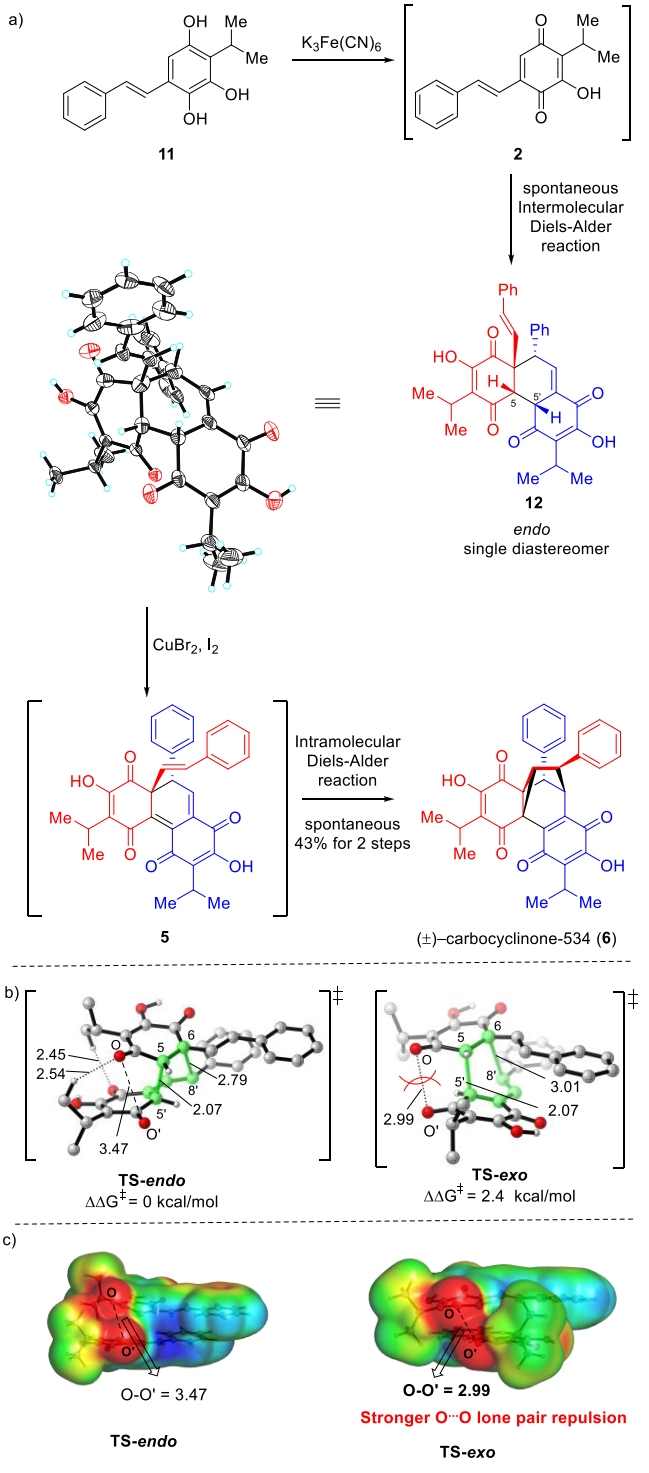
Scheme 2. (a) Total Synthesis of Carbocyclinone-534, (b) Calculated *endo* Transition Structures and Their Relative Gibbs Free Energies, and (c) Electrostatic Potential Map for TS-*endo* and TS-*exo*



the optimized transition states leading to *endo* and *exo* products for the intermolecular Diels–Alder homodimerization of **2** (computational details and full potential energy surfaces are provided in the Supporting Information). Both **TS**-*endo* and **TS**-*exo* are characterized by a concerted but asynchronous bond-forming process. **TS**-*endo* that gives the experimentally observed *endo* product **12** is favored by 2.4 kcal mol^{-1} over **TS**-*exo*, mostly due to a stronger O···O lone pair repulsion in **TS**-*exo* (Scheme 2c). Additionally, **TS**-*endo* is at least 4.2 kcal mol^{-1} more stable than transition sates (**TS′**-*exo* and **TS′**-*endo*) that lead to the other putative regioisomers, consistent with the experimental observation that *endo* product **12** is the single cycloadduct. Then we turned to the proposed bridged cyclopropane formation through intramolecular Diels–Alder reaction. As a prerequisite, we need to dehydrate the 5,5′-H to prepare diene **5** for subsequent Diels–Alder reaction. A series of dehydration conditions were screened, DBU/O_2,[22] $Pd(OAc)_2$, SeO_2,[23] DDQ, and $Sc(OTf)_3$[24] (see the Supporting Information for more details), and we found the dehydrogenation reaction happened effectively when $CuBr_2/I_2$[25] was used as the oxidant and the subsequent intramolecular Diels–Alder reaction happened spontaneously,[26] giving carbocyclinone-534 (**6**) as a single diastereomer (43% from **11**) without isolation of quinone **5**.

To gain more insight into the possible biosynthetic pathway of carbocyclinone-534 (**6**) and duotap-520 (**4**), we performed some control experiments (Scheme 3). We found that the base is important for regulating the pathways of dimerization of triphenol **11** (see the Supporting Information for more details) (Scheme 3a): when there was no base, the resultant quinone **2** dimerized through intermolecular Diels–Alder reaction to render quinone **12**, while in the presence of KOH, the resultant quinone **2** dimerized through intermolecular Michael addition to render a triphenol, which was easily oxidized to afford homodimer **3**. Notably, although there were precedents for $FeCl_3$-catalyzed oxidative phenolic homocoupling reaction, the mechanism was not studied and unclear. Because quinone **2** is too active and cannot be isolated, we used quinone **11b** as a stable Michael addition acceptor, which was produced from stilbene **11** after double bond reduction and spontaneous oxidation in air. The heterocoupling of **11b** with tapinarof (**1**) was conducted in the presence of KOH without another oxidant, and the resultant triphenol product was further oxidized to afford heterodimer **4a** (54% yield). Homocoupling product **3a** was also readily obtained under the same condition from **11a** and **11b**. On the basis of the findings presented above, we propose the $K_3Fe(CN)_6$-catalyzed oxidative phenolic homocoupling reaction proceeds via a Michael addition/oxidation sequence. The application of this mechanism realized the oxidative phenolic heterocoupling reaction of quinone **11b** and tapinarof (**1**).

Under the oxidation of $CuCl_2{\cdot}2H_2O$/TBHP, tapinarof (**1**) could be converted to quinone **2**, which spontaneously dimerized to **12**, although the conversion and yield are quite low (12% yield) (Scheme 3b). Oxidation of triphenol **11** and the subsequent dehydrogenation of quinone **12** could be realized through air oxidization (1 day, 38% yield; 7 days, 88% yield). It is obvious that the second oxidation is more efficient (38% yield vs 12% yield). On the basis of the studies mentioned above, we modified the biosynthesis proposal of carbocyclinone-534 (**6**) (Scheme 3c). Tapinarof (**1**) could be transformed to triphenol **11** after oxidation, and then triphenol **11** dimerizes to generate homodimer **3** and heterodimer duotap-520 (**4**) when bases and oxidants are concurrently present, probably via an oxidation/Michael addition/oxidation sequence. However, when there was no base, the oxidation product quinone **2** spontaneously undergoes homodimerization through intermolecular Diels–Alder reaction to form compound **12**. Although in some cases 6π-electrocyclization is usually kinetically favored over an intramolecular Diels–Alder reaction,[27] obviously this intermo-

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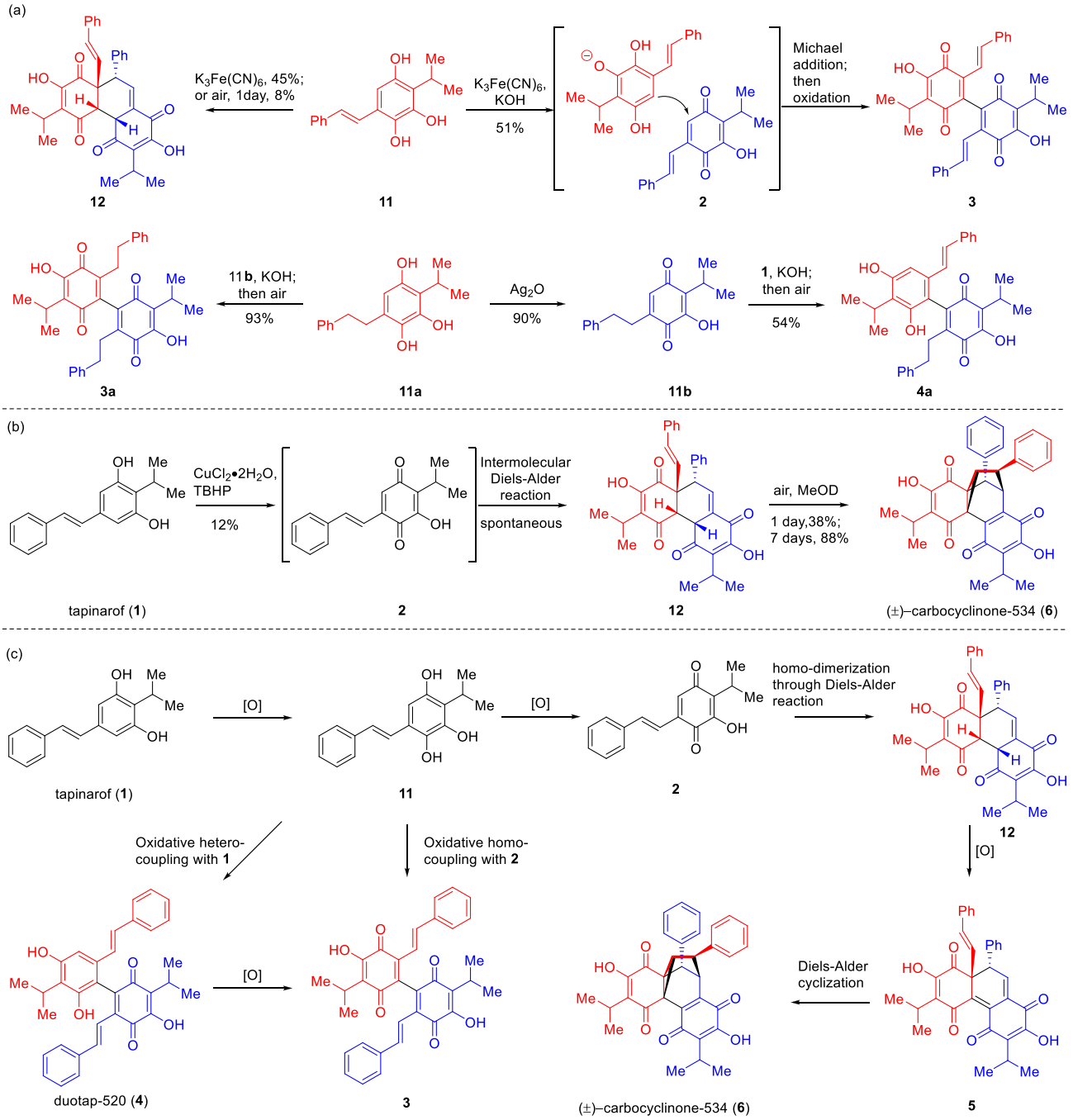
Scheme 3. Control Experiments and Our Proposed Biosynthetic Pathway for Duotap-520 and Carbocyclinone-534



lecular Diels–Alder homodimerization is much more favored than 6π-electrocyclization in this case under this specific condition. Compound **12** undergoes further oxidative dehydrogenation to render **5**, and then a spontaneous intramolecular Diels–Alder reaction affords carbocyclinone-534 (**6**). Basic conditions should play a key role throughout the regulation of different pathways. Notably, triphenol **11** has not been detected as a metabolite so far, probably due to its high efficiency of being oxidized under air.

In summary, the first biomimetic total synthesis of carbocyclinone-534 and duotap-520 was achieved in eight steps from commercially available 1,2,4-trimethoxybenzene. The key feature of this synthesis includes two cascade transformations: phenolic oxidation/intermolecular Diels–Alder homodimerization and dehydrogenation/intramolecular Diels–Alder cycloaddition. Our synthesis provided direct experimental evidence for revealing the biosynthetic pathway of carbocyclinone-534, and this oxidative phenolic heterocoupling reaction should have potential application in the synthesis of other biquinone skeleton-containing natural products such as popolophuanone E[28] and grifolinone C.[29]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02865.

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Experimental procedures, characterization data, and NMR spectral data of new compounds (PDF)

Accession Codes

CCDC 2014357 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, UK; fax: +44 1223 336033.

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Author Contributions

[§]C.Q. and X.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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