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# A Diazo-Hooker Reaction Inspired by the Biosynthesis of Azamerone

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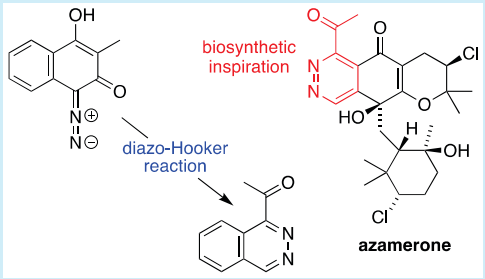
**ABSTRACT:** Motivated by the biosynthesis of azamerone, we report the rst example of a diazo-Hooker reaction, which involves the formation of a phthalazine ring system by the oxidative rearrangement of a diazoketone. Computational studies indicate that the diazo-Hooker reaction proceeds via an 8 -electro-cyclization followed by ring contraction and aromatization. The biosynthetic origin of the diazoketone functional group was also chemically mimicked using a related natural product, naphterpin, as a model system.






The Hooker reaction is one of the most remarkable transformations in the canon of organic synthesis. Under the original conditions of alkaline $KMnO_4$, a single methylene group is apparently deleted from the alkyl side chain of a 2-hydroxy-3-alkyl-1,4-naphthoquinone (Figure 1a).[1] In an elegant labeling experiment in which the aromatic ring was marked with a bromine substituent, Fieser showed that the Hooker reaction must proceed via oxidative cleavage of the naphthoquinone ring, followed by ring closure and loss of the C2 atom as carbon dioxide.[2] Fieser later reported an improved stepwise protocol for the Hooker reaction using alkaline $H_2O_2$ followed by $CuSO_4$ as the oxidants in place of $KMnO_4$.[3] Although the occurrence of a Hooker reaction in biosynthesis is unknown, we were intrigued by the possibility of a bioinspired, diazo variant of this rearrangement. We proposed that replacement of the C1 ketone of a naphthoquinone substrate with a diazo group could lead to the formation of a phthalazine product under oxidative conditions via a "diazo-Hooker reaction" (Figure 1b). This idea was inspired by the proposed biosynthesis of the unusual pyridazine[4] natural product azamerone (**1**)[5] from the related diazoketone,[6] A80915D (**2**)[7] (Figure 1c). Both **1** and **2** are members of the napyradiomycin family of meroterpenoids isolated from marine strains of *Streptomyces* bacteria.[8] In 2009, Winter et al. reported that 2-$^{13}$C-,9-$^{15}$N-labeled A80915D was converted into azamerone when fed back to their natural source, the marine sediment-derived *Streptomyces* sp. CNQ-766.[9] The position of the $^{13}$C label on the methyl ketone and the $^{15}$N label embedded within the pyridazine ring of the azamerone product implied a unique rearrangement mechanism involving oxidative cleavage of the aryl diazoketone, followed by cyclization and rearomatization. Herein, we propose that this biosynthetic transformation features a diazo-Hooker reaction, using synthetic and computational studies to support our hypothesis.

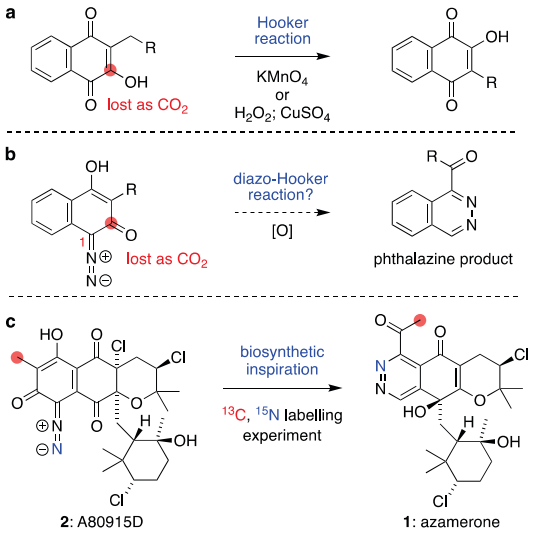



**Figure 1** (a) Hooker reaction. (b) Proposed diazo-Hooker reaction, inspired by (c) the biosynthesis of azamerone from A80915D.

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The simplest possible diazo-Hooker reaction is presented in Figure 2. First, 2-methyl-1,3-dihydroxynaphthalene (**3**) was

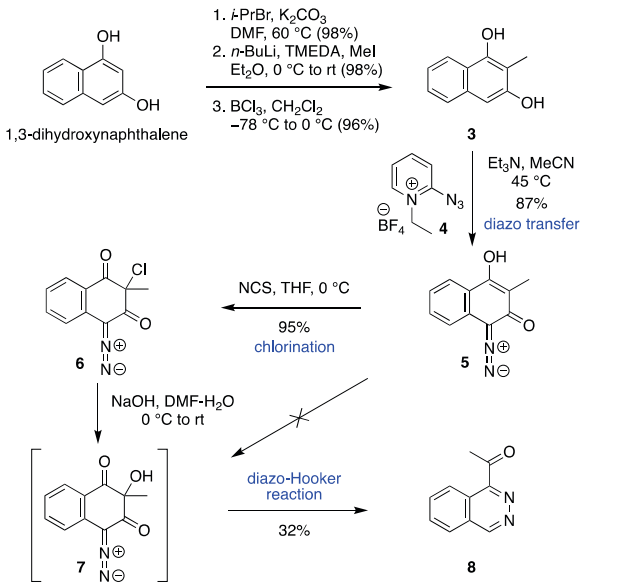


**Figure 2** Diazo-Hooker reaction.

synthesized in three steps from 1,3-dihydroxynaphthalene. The transfer of diazo from azidinium salt **4**[10] to **3** in the presence of $Et_3N$ then formed diazonaphthoquinone **5** in good yield.

Attempted oxidation of **5** using either Hooker s original conditions ($KMnO_4$) or Fieser s modi ed conditions ($H_2O_2$/$CuSO_4$), or an electrophilic oxidant such as *m*-CPBA or DMDO, led to either decomposition or loss of the diazo group. However, chlorination of **5** with NCS gave *α*-chloro-*β*-diketone **6** in high yield. Hydrolysis of **6** with NaOH in DMF/$H_2O$ then triggered the diazo-Hooker reaction to give phthalazine **8** in modest yield. The structure of **8** was assigned by NMR studies and comparison to literature data for the same compound previously synthesized using a Minisci reaction of phthalazine.[11] The intermediacy of *α*-hydroxy-*β*-diketone **7** in the rearrangement of **6** was indicated by its isolation in high yield when the reaction was stopped after 10 min. $S_N2$ substitutions at the tertiary position of cyclic *α*-chloro-*β*-dicarbonyl compounds with structures similar to that of **6** have been reported.[12] Further attempts to improve the yield of **8** and to broaden the scope of the diazo-Hooker reaction met with failure. Nevertheless, this remarkable rearrangement provides some supporting chemical evidence that favors the proposed biosynthesis of azamerone from a diazoketone precursor.

It is instructive to compare the mechanism of the newly discovered diazo-Hooker reaction with that of the canonical Hooker reaction of the simplest possible naphthoquinone substrate, phthiocol, under Fieser s optimized conditions (Figure 3a).[13] Initial oxidation of phthiocol by a hydroperoxide anion gives an epoxide, which opens to give *α*-hydroxy-*β*-diketone **9**. Nucleophilic attack of hydroxide at the C2 carbonyl of **9** gives **10**, which undergoes a retro-Dieckmann condensation to give **11**. Intramolecular aldol reaction of enolate **11** then forms the ring-contracted product, *α*-hydroxyketone **12**. This isolable intermediate (Fieser s intermediate) could alternatively arise via a benzilic acid

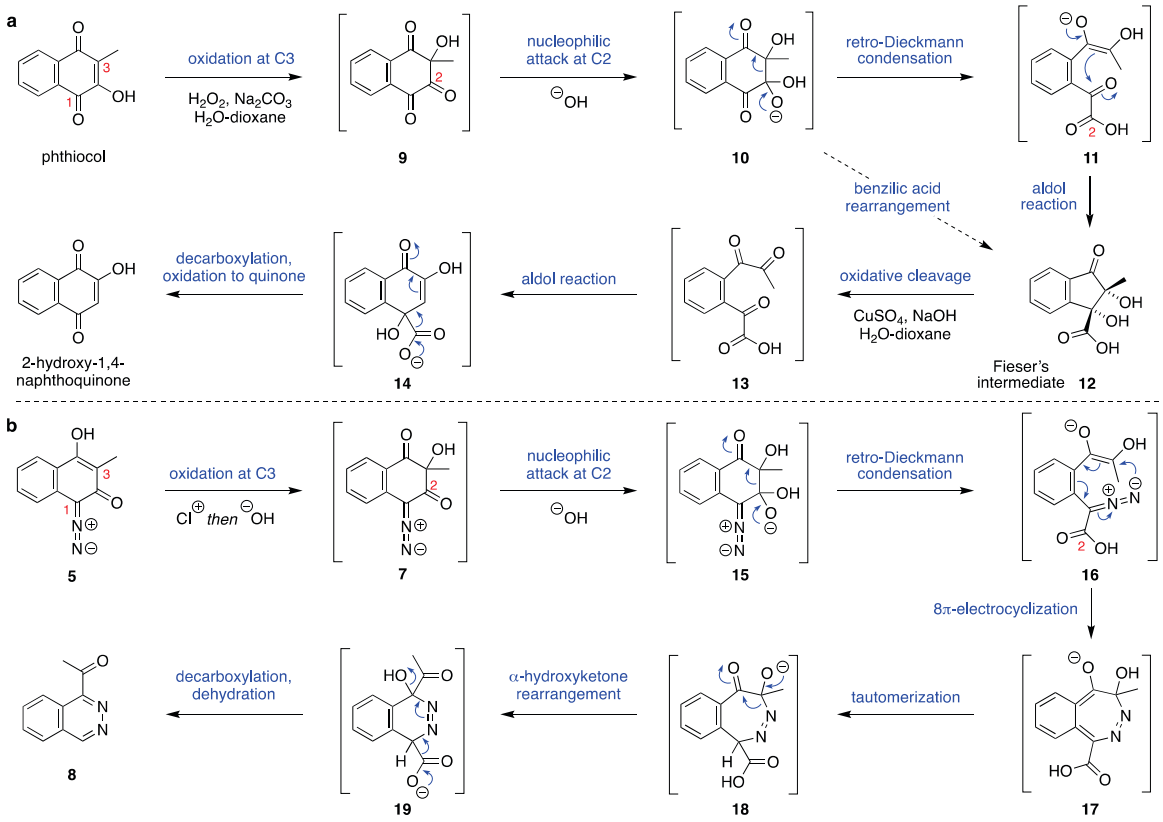


**Figure 3** Comparison of the mechanisms for (a) the Hooker reaction of phthiocol (under Fieser s modi ed conditions) and (b) the diazo-Hooker reaction.



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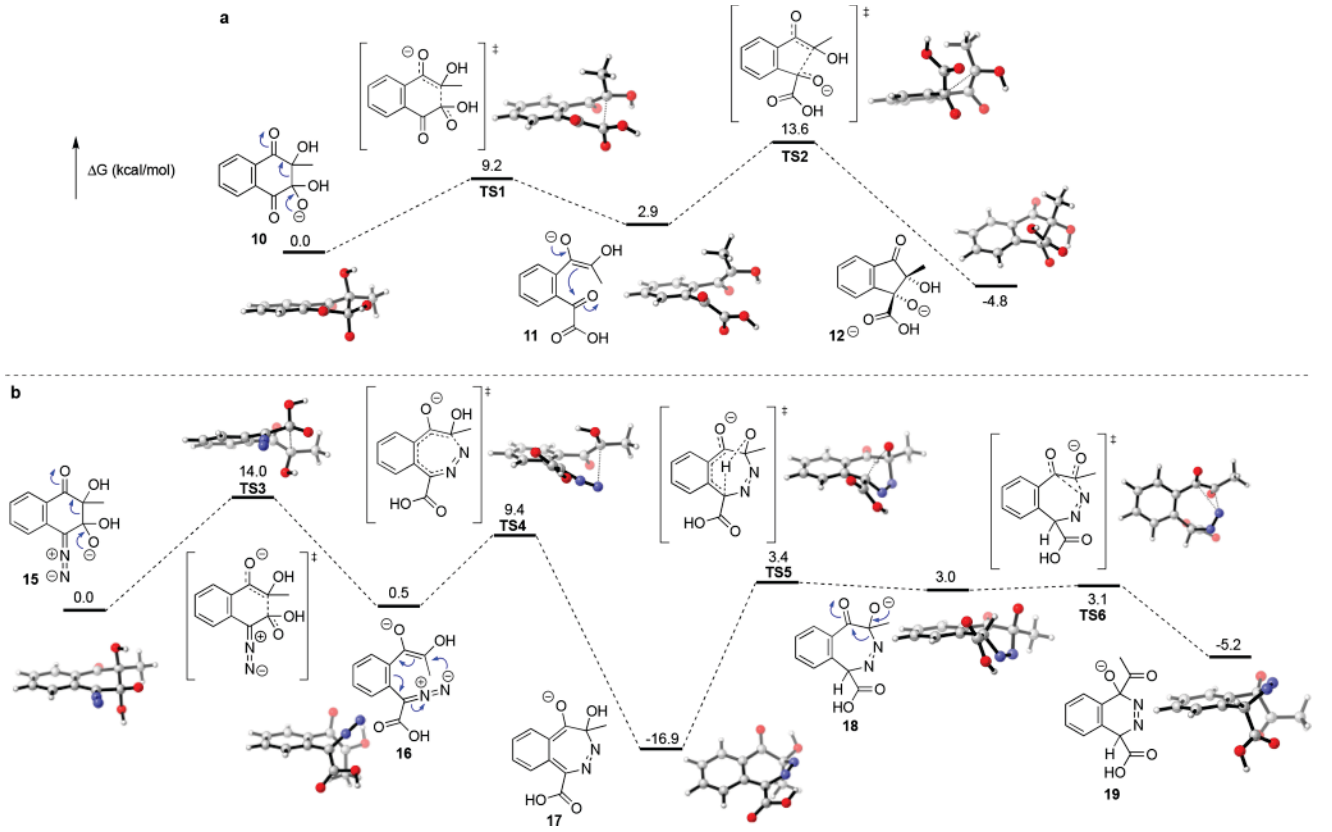


**Figure 4** Gibbs free energy diagrams for (a) the Hooker reaction and (b) the diazo-Hooker reaction. Energies are shown in kilocalories per mole, and bond lengths are given in angstroms.

rearrangement of **10**. Addition of a basic $CuSO_4$ solution to **12** then causes oxidative cleavage to give 1,2-diketone **13**, and then a second intramolecular aldol reaction to form **14**. Finally, decarboxylation of **14** and oxidation of the resultant hydroquinone give 2-hydroxy-1,4-naphthoquinone.

The mechanism of the diazo-Hooker reaction of **5**, the C1-diazoketone analogue of phthiocol, could share several features with the parent Hooker reaction (Figure 3b). First, C3 oxidation of **5** gives $\alpha$-hydroxy-$\beta$-diketone **7** via chlorination and subsequent $S_N2$ substitution of the intermediate $\alpha$-chloro-$\beta$-diketone with hydroxide. Nucleophilic attack by hydroxide at C2 then initiates a retro-Dieckmann condensation of **15** to give the diazocarboxylic acid **16**, which could undergo an 8 $\pi$-electrocyclization to give **17**. Several related 1,7-electrocyclic reactions of conjugated diazo compounds to give 1*H*-2,3-benzodiazepines have been reported.[14] Tautomerization of **17** to give ketol **18** could precede ring contraction via an $\alpha$-hydroxyketone rearrangement to give **19**. Finally, decarboxylation and dehydration form the aromatic phthalazine ring system of **8**. Alternatively, the phthalazine ring could arise from a more direct 6-endo-dig cyclization[15] of enolate **16** onto the nearby diazo group to give **19**.

DFT calculations were carried out to study the mechanism of the Hooker and diazo-Hooker reactions. Computations were conducted within *Gaussian 16*,[16] with preliminary conformational searches using Schrodinger[17] Maestro 10.6. The low-energy conformers that are within 5 kcal/mol of the global minimum were optimized with the B3LYP-D3[18] density functional with the 6-31G(d) basis set, using the SMD[19] solvation model of water. Vibrational frequency calculations were performed at the same level of theory to con rm the stationary point is an energy minimum or a transition state and to evaluate its zero-point vibrational energy (ZPVE) and thermal corrections at 298 K. Single-point energies were calculated using a larger basis set, 6-311+G(d,p), with the same solvation model. As shown in Figure 4a, the Hooker reaction proceeds via a stepwise mechanism. The ring opening of **10** requires a Gibbs free energy barrier of 9.2 kcal/mol (**TS1**) and leads to intermediate **11**. This is followed by an intramolecular aldol reaction via **TS2** to give **12**, with an overall barrier of 13.6 kcal/mol. The formation of the diastereomer of **12** has an overall barrier of 14.0 kcal/mol (Figure S1). Figure 4b shows the calculated Gibbs free energy diagram of the diazo-Hooker reaction. Ring opening of **15** via **TS3** followed by 8 $\pi$-electrocyclization of **16** via **TS4** leads to a stable seven-membered ring intermediate **17**. Tautomerization via **TS5** gives intermediate **18**, followed by $\alpha$-hydroxyketone rearrangement to form **19**. Our calculation suggests that the tautomerization step is the rate-determining step, and the overall barrier is 20.3 kcal/mol (**17** to **TS5**). The alternative, direct 6-endo-dig cyclization of **16** is unfavorable, with a high activation barrier of 42.1 kcal/mol (Figure S2). Further details of the DFT calculations are provided in the Supporting Information.

We can now propose a biosynthesis of azamerone (**1**) featuring a diazo-Hooker reaction of A80915D (**2**) to give pyridazine **20** (Figure 5). This diazo-Hooker reaction could be initiated by either direct oxidation of **2** at C7 or a stepwise chlorination/$S_N2$ hydrolysis mechanism. The involvement of a chlorination step in this biosynthetic diazo-Hooker reaction is attractive because halogenation, catalyzed by vanadium-dependent haloperoxidase (VHPO) enzymes,[20] is a common


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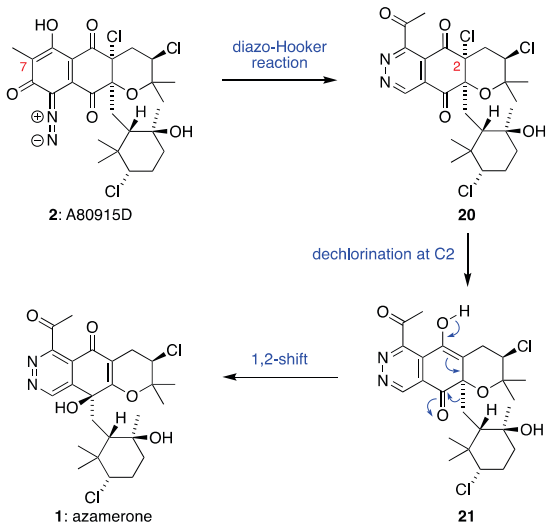


**Figure 5** Proposed biosynthesis of azamerone from A80915D invoking a diazo-Hooker reaction.

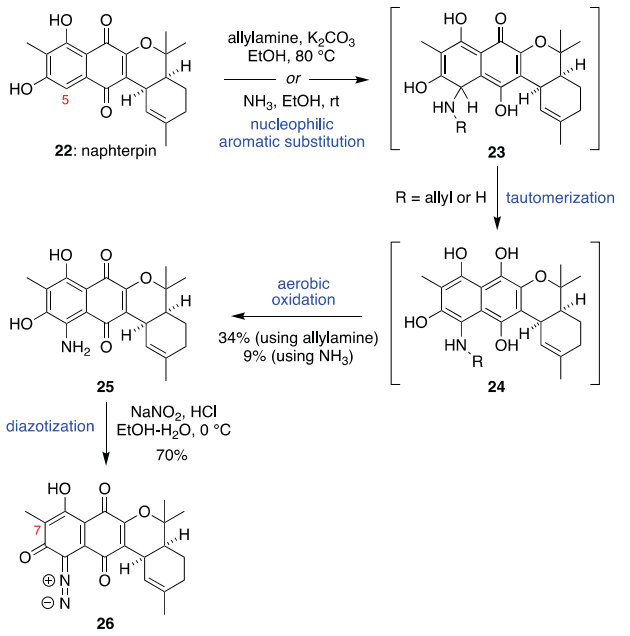


**Figure 6** Bioinspired amination/diazotization of naphterpin.

reaction in the biosynthesis of napyradiomycin natural products.[21] Indeed, the biosynthesis of **2** incorporates three separate, enzyme-catalyzed chlorination steps. Subsequent formation of azamerone then requires C2 dechlorination of **20**, followed by a 1,2-shift of the cyclohexyl side chain of **21** from C3 to C4.

While we have now demonstrated the feasibility of the diazo-Hooker reaction using both computational and experimental methods, the mechanistic origin of the diazoketone motif of A80915D is still unclear. However, previous $^{15}N$ labeling studies indicate that the two nitrogen atoms of A80915D are introduced separately, probably via diazotization of a primary aromatic amine.[9] Recently, a biosynthetic pathway to aromatic amines via enzyme-catalyzed nucleophilic amination of a hydroxyquinone was reported.[22] Furthermore, a diazo-forming enzyme that uses nitrite to oxidize a primary aromatic amine has been characterized in the biosynthesis of cremeomycin by *Streptomyces cremeus*.[23] We therefore attempted to chemically mimic these aromatic amination/diazotization reactions in the stepwise formation of a designed diazo-meroterpenoid **26**, using naphterpin (**22**)[24] as a readily available model system (Figure 6). Simple addition of $NH_3$ to a solution of **22** in EtOH at room temperature generated primary aromatic amine **25**, albeit in only 9 yield, via a redox-driven nucleophilic aromatic substitution.[25] The yield of this net C H amination was improved by replacing $NH_3$ with allylamine in $K_2CO_3$/EtOH at 80 °C, with deallylation also occurring under these conditions to give **25** in 34 yield. Use of methylamine gave the *N*-Me analogue of **25** in 60 yield. The mechanism of this amination presumably involves initial nucleophilic addition of the amine to C5 of **22** to give **23**, followed by tautomerization to hydroquinone **24** and then aerobic oxidation to give quinone **25**. Diazotization of **25** under standard conditions[26] then gave $\alpha$-diazo ketone **26** in good yield. Although an attempted diazo-Hooker reaction on this complex substrate was unsuccessful, the formation of a diazoketone via facile C H amination and diazotization perhaps gives some chemical insight into the biosynthetic origin into diazo-napyradiomycins such as A80915D.

In summary, we have discovered a diazo-Hooker reaction that mimics a key step in the biosynthesis of azamerone from A80915D. These chemical studies suggest that the unusual pyridazine ring system of azamerone arises from oxidative rearrangement of a diazoketone that could be initiated by a cryptic halogenation.[27] We also investigated the stepwise formation of a diazoketone natural product analogue of A80915D via redox-driven nucleophilic aromatic substitution with an amine followed by diazotization. The rst computational study of the parent Hooker reaction shows that the mechanism likely involves ring opening of the oxidized naphthoquinone ring followed by an intramolecular aldol reaction, rather than a benzilic acid rearrangement. Similar modeling of the diazo-Hooker reaction also supports a ring opening mechanism, with a subsequent cascade of 8 -electrocyclization, $\alpha$-hydroxyketone rearrangement, and aromatization giving the phthalazine product.

## ASSOCIATED CONTENT

### Supporting Information

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Experimental procedures and NMR spectra for all new compounds (PDF)

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## Notes

The authors declare no competing nancial interest.

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