Biomimetic Synthesis

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Biomimetic Synthesis of (−)-Pycnanthuquinone C through the Diels–Alder Reaction of a Vinyl Quinone**

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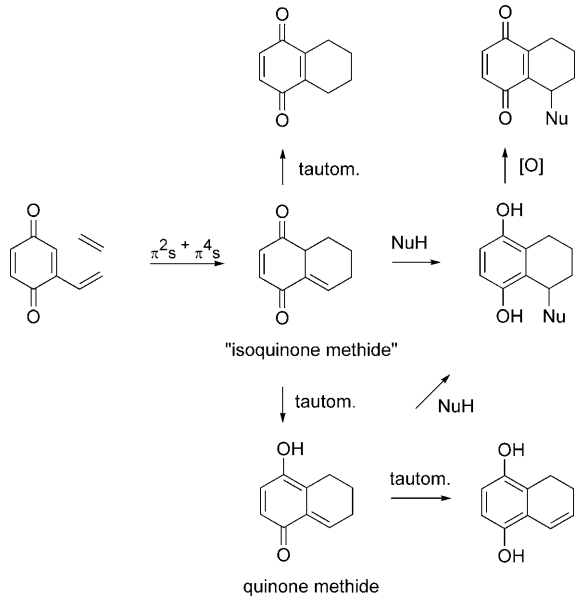
Dedicated to Rolf Huisgen on the occasion of his 90th birthday

Diels–Alder reactions of vinyl quinones may provide a rapid entry to highly functionalized bi- and polycyclic ring systems. They involve the inverse-electron-demand cycloaddition of a suitable dienophile to a vinyl quinone, which presumably generates an "isoquinone methide" (Scheme 1). This reactive



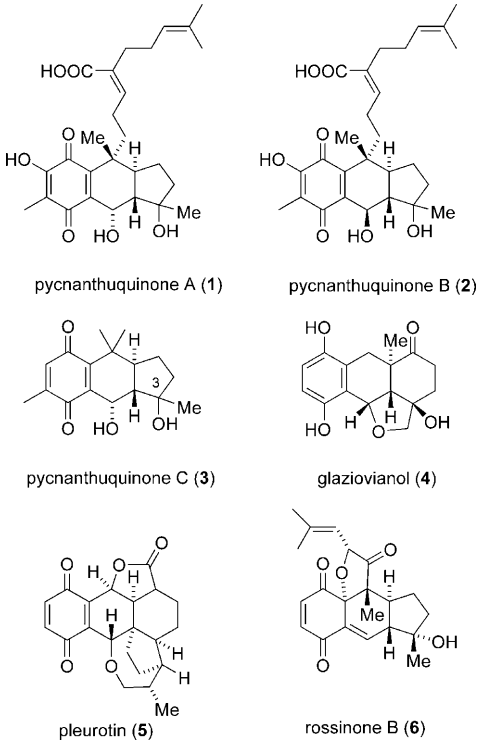
Scheme 1. Diels–Alder reactions of vinyl quinones and possible subsequent transformations.

intermediate could then tautomerize in several ways to yield quinone methides, bicyclic quinones, or hydroquinones. If the isoquinone methide or quinone methide is intercepted by a nucleophile, such as water, a functionalized tetraline hydroquinone may result. This may be oxidized readily to the functionalized tetraline quinone.

In comparison to classical Diels–Alder reactions involving quinones and electron-rich dienes, which have been extensively used in synthesis,[1] vinyl quinone Diels–Alder reactions (VQDA reactions) are largely unexplored. Many inter- and intramolecular versions as well as asymmetric variants and tandem reactions can be envisaged, which would lead to a wide variety of interesting ring systems. So far, VQDA reactions have been utilized in a total synthesis of (−)-halenaquinone[2] and in efficient approaches to complex heterocycles.[3] In addition, the self-dimerization of vinyl quinones has been studied in some detail.[4]

Given the abundance of quinones in nature, it is entirely possible that VQDA reactions bear some biosynthetic relevance. Indeed, many natural products can be identified that contain the corresponding retrons. These include the pycnanthuquinones (**1**–**3**),[5,6] glaziovianol (**4**),[7] pleurotin (**5**),[8] and, in a modified form, rossinone B (**6**).[9] In most of these, the retrosynthetic application of the reaction would lead to simple meroterpenoid quinones, which are common natural products themselves.

We now report a concise total synthesis of pycnanthuquinone C (**3**) that strongly suggests that VQDA reactions occur in biosynthetic pathways. Pycnanthuquinone C is the simplest of the pycnanthuquinones, a family of natural products that



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have been isolated from very different biological sources. The more complex pycnanthuquinones A and B have been found in *Pycnanthus angolensis*, a West African tree used in traditional African medicine, in the search for compounds that have antihyperglycemic activity.[6] By contrast, no bioactivity has been reported for pycnanthuquinone C, which was isolated in minute quantities from the brown alga *Cystophora harveyi*.[7] Despite considerable efforts, the relative configuration of the pycnanthuquinones could not be elucidated with respect to the C3 carbon atom. Their absolute configuration has not thus far been established either.

Our total synthesis starts with a Heck cross-coupling reaction between bromohydroquinone **7** and the commercially available monoterpene alcohol (−)-linalool (**8**; Scheme 2). This reaction proceeded well under Jeffery conditions to afford alkenyl hydroquinone **9** in 81% yield.[10] Remarkably, only one Heck reaction involving an unprotected *ortho*-halohydroquinone appears to have been reported previously.[11] Reactions of this type provide an excellent entry into vinyl quinones. Since the absolute configuration of pycnanthuquinone C was not known at the outset of our study, we chose the more readily available enantiomer of linalool, which ultimately translated to the unnatural levorotatory enantiomer of pycnanthuquinone C.

Oxidation of hydroquinone **9** with manganese dioxide gave the sensitive vinyl quinone **10** and set the stage for the key reaction of the synthesis: Heating of a solution of **10** in a biphasic toluene/water mixture to 60 °C gave pycnanthuquinone C as a 5:4 mixture with its epimer **13** in 37% yield (Scheme 2). This reaction presumably involves a highly diastereoselective intramolecular VQDA reaction to afford the putative isoquinone methide **11**. The reactive intermediate **11** is then attacked by water in a nonstereoselective fashion to yield hydroquinone **12**, which is subsequently oxidized to (−)-**3** and its diastereomer **13** under the reaction conditions.

Synthetic (−)-pycnanthuquinone C (**3**) proved to be identical to the natural product in all respects with the notable exception of its optical rotation, which had the opposite sign and a higher absolute value. The relative (and thus absolute) configuration of its isomer **13** was elucidated by X-ray crystallography (Figure 1). This compound has not yet

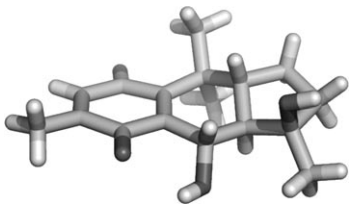
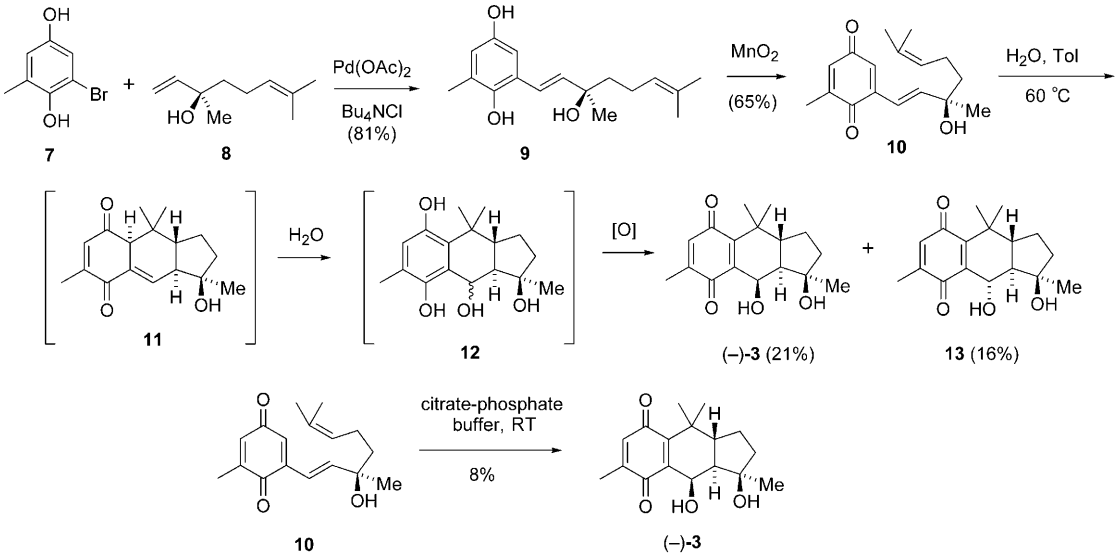


Figure 1. X-ray crystal structure of "pycnanthuquinone D" (**13**).

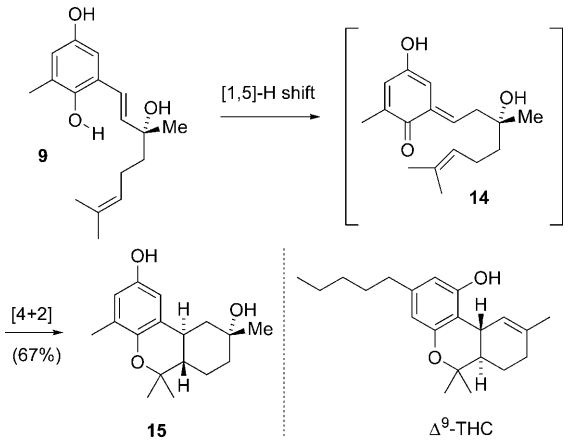
been isolated from natural sources but in light of our biosynthetic hypothesis, and given the joint isolation of pycnanthuquinone A and B, it seems likely that **13** exists in nature as well. It may well prove to be another case of "natural product anticipation" through total synthesis, in which case it should be called "pycnanthuquinone D".

The key VQDA reaction could also be carried out under more biomimetic conditions in a citrate–phosphate buffer at pH 5 and room temperature (Scheme 2). Although pycnanthuquinone C could be isolated, the yield was very low in this case.

Additionally, an interesting product was observed when a solution of vinyl hydroquinone **9** was concentrated on a rotary evaporator at elevated temperature: under such conditions, it isomerized to afford benzopyrane **15** as the only identifiable product (Scheme 3). This reaction presumably proceeds through intramolecular hydrogen shift, followed by a highly diastereoselective intramolecular cycloaddition of the resultant *ortho*-quinone methide **14**. Benzopyran **15**, whose



Scheme 2. Total synthesis of (−)-pycnanthuquinone C.



Scheme 3. Formation of "cannabinoid" **15** from vinyl hydroquinone **9**.

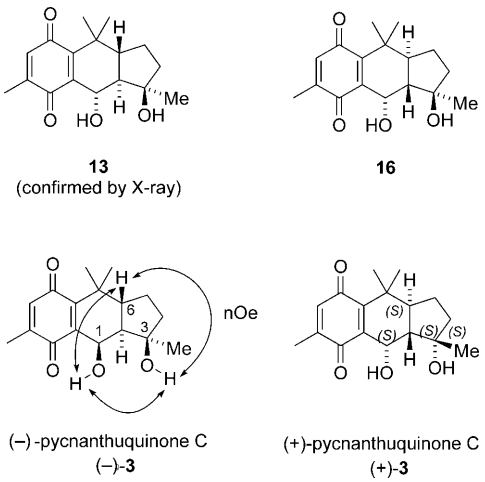


Figure 3. Elucidation of the relative (and absolute) configuration of pycnanthuquinone C.

structure was confirmed by X-ray crystallography (Figure 2), bears a strong resemblance to Δ^9-tetrahydrocannabinol (Δ^9-THC). Indeed domino reactions of this type have been used to synthesize cannabinoids, and our results could provide an asymmetric entry to this class of natural products.[12]

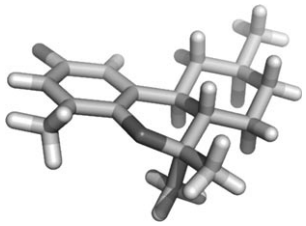


Figure 2. X-ray crystal structure of **15**.

Having developed a concise asymmetric synthesis of pycnanthuquinone C, we next turned our attention to the issue of the relative and absolute configuration of the natural product. Since the absolute configuration of (−)-linalool is known, we were able to determine the absolute configuration of our synthetic material at C3. In addition, we had established the structure of isomer **13** by X-ray crystallography, and the *trans* configuration of the hydrindane moiety could be gleaned from the literature.[5,6] This left us with two possible isomers, compounds **16** and (−)-**3** (Figure 3). Compounds (−)-**3** and **13** would arise as a pair from a highly diastereoselective Diels–Alder reaction and an unselective attack of water, whereas **16** and **13** would be formed through an unselective Diels–Alder reaction and a highly diastereoselective addition of water. Given the relative configuration of pycnanthuquinones A (**1**) and B (**2**), the latter seemed unlikely, but could not be ruled out.

After several unsuccessful attempts to prove the relative configuration of pycnanthuquinone C through chemical derivatization or interconversion, we focused our efforts on nOe measurements, which had reportedly given inconclusive results in the initial investigations.[5,6] However, with ample material at hand, we were able to observe nOe signals between the protons of both hydroxy groups and the methine hydrogen at C6 in anhydrous [D_6]DMSO. This is possible only if unnatural (−)-pycnanthuquinone C has the relative configuration indicated in Figure 3. Hence, the natural product (+)-pycnanthuquinone C has the all-*S* configuration.

Our total synthesis provides evidence that pycnanthuquinone C arises biosynthetically from its known congener **17** by means of epoxidation (→**18**), followed by formation of the vinyl quinone (→**19**), VQDA reaction, addition of water and aerobic reoxidation (Scheme 4). The fact that pycnanthuquinones A (**1**) and B (**2**) are diastereomers with respect to the secondary hydroxy group also supports this hypothesis, since an enzymatic hydroxylation would be expected to be highly diastereoselective.

A similar pathway could also occur in the biosynthesis of the meroterpenoid rossinone B (**6**). We propose that this natural product stems directly from rossinone A (**20**), which was isolated from the same natural source. Oxidation of **20** to **21**, followed by VQDA reaction, addition of water, and further oxidation would initially afford quinone **22**, which closely resembles the pycnanthuquinones. In this case, however, the VQDA sequence is followed by an intramolecular S_Ni' reaction that yields the tetracyclic framework of rossinone B.

In summary we have developed a three-step, protecting-group-free synthesis of (−)-pycnanthuquinone C that extends the reach of vinyl quinone Diels–Alder reactions. It also provides strong evidence for the formation of the pycnanthuquinone skeleton through a biosynthetic cycloaddition and has enabled the full elucidation of the stereochemistry of the natural product. The VQDA chemistry developed herein could be extended in a straightforward way towards the synthesis of pycnanthuquinones A and B as well as pleurotin.

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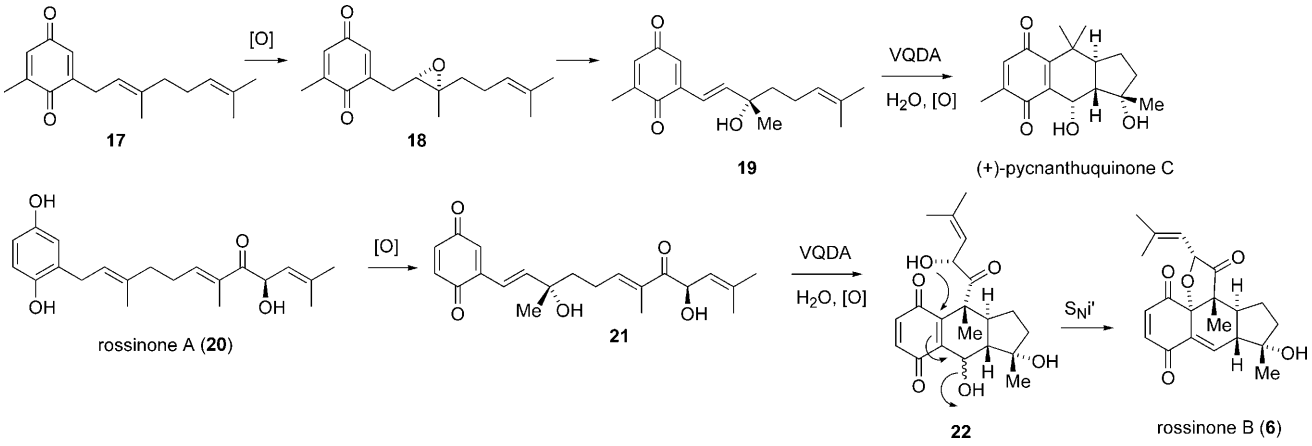

Scheme 4. Proposed biosynthesis of pycnanthuquinone C and rossinone B from known congeners.

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