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Pericyclic Reactions of Prenylated Naphthoquinones: Biomimetic Syntheses of Mollugin and Microphyllaquinone

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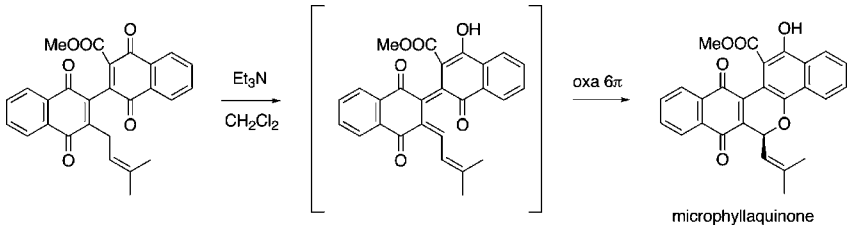
ABSTRACT



A total synthesis of the bioactive naphthohydroquinone mollugin and the related naphthoquinone dimer microphyllaquinone is described. Both syntheses exploit the propensity of prenylated quinones to undergo tautomerization/oxa 6π-electrocyclizations.

Natural products derived from prenylated naphthoquinones show significant biological activities (Figure 1).[1] In fact, plants that produce compounds of this class have long been recognized for their therapeutic benefits. For example, the Chinese medicinal plant *Rubia cordifolia* has yielded the achiral chromene mollugin (**3**) and the racemic dimer rubicordifolin (**4**), both of which show potential as antitumor compounds.[2] Rubioncolin A (**5**) and B (**6**) were isolated as racemates from the related *Rubia oncotricha*.[3] Firmianone A (**7**) was recently isolated as a single enantiomer from the tree *Firmia plantanifolia*, the root bark of which is used to treat rheumatism and asthma in Chinese herbal medicine.[4] Extracts from the roots of *Lippia microphylla*, commonly known as "alecrim-de-tabuleiro", are widely used as expectorants, astringents, and diuretics in Brazilian traditional medicine.[5] Phytochemical investigations have yielded the cytotoxic naphthoquinone dimers microphyllaquinone (**8**) and tecomaquinone I (**9**) as active ingredients.[6] Tecomaquinone I (**9**) has also been isolated from *Tectona grandis* (teak) and several other tree species.[7] Although **8** and **9** were found to be optically active, their absolute configurations remain unknown.

One of the distinct chemical features of prenylated naphthoquinones, and of allylic *para*-quinones in general, is their ability to tautomerize to vinyl *ortho*-quinone methides. These can undergo subsequent pericyclic reactions, such as electrocyclizations or cycloadditions. As shown in Scheme 1, tautomerization of **10** affords *ortho*-quinone methides **11** or **12**. The latter can undergo oxa 6π-electrocyclization to afford chromene **13**. This facile conversion has been utilized by Thomson in an elegant total synthesis of tecomaquinone I (**9**)[7] and was further investigated by Nicolaou et al. in the

(1) Singh, R.; Geetanjali; Chauhan, S. M. S. *Chem. Biodiversity* **2004**, *1*, 1241−1264.

(2) (a) Itokawa, H.; Ibraheim, Z. Z.; Qiao, Y. F.; Takeya, K. *Chem. Pharm. Bull.* **1993**, *41*, 1869−1872. (b) Lumb, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 2870−2871.

(3) Qiao, Y. F.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2896−2898.

(4) Bai, H. Y.; Li, S.; Yin, F.; Hu, L. H. *J. Nat. Prod.* **2005**, *68*, 1159−1163.

(5) Pascual, M. E.; Slowing, K.; Carretero, E.; Mata, D. S.; Villar, A. *J. Ethnopharmacol.* **2001**, *76*, 201−214.

(6) Santos, H. S.; Costa, S. M. O.; Pessoa, O. D. L.; Moraes, M. O.; Pessoa, C.; Fortier, S.; Silveira, E. R.; Lemos, T. L. G. *Z. Naturforsch., C: Biosci.* **2003**, *58*, 517−520.

(7) Khanna, R. N.; Sharma, P. K.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1821−1824.

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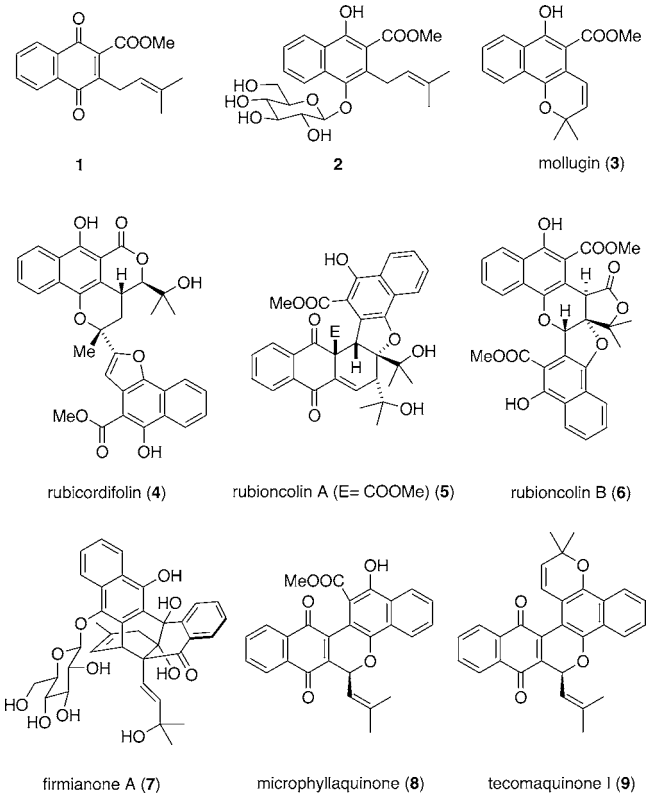


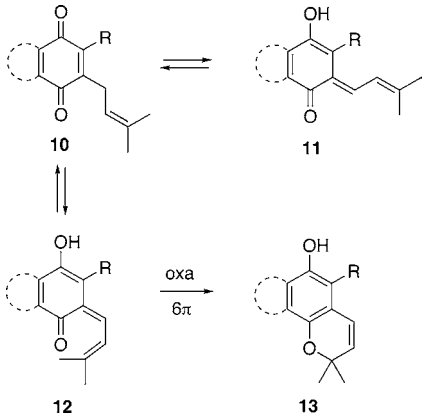
Figure 1. Natural products from prenylated naphthoquinones.

context of the xanthone-derived natural product 1-*O*-methyllateriflorone.[8]

We now wish to present the application of this reactivity to the total synthesis of mollugin (**3**)[9] and its extension to a concise synthesis of microphyllaquinone (**8**).

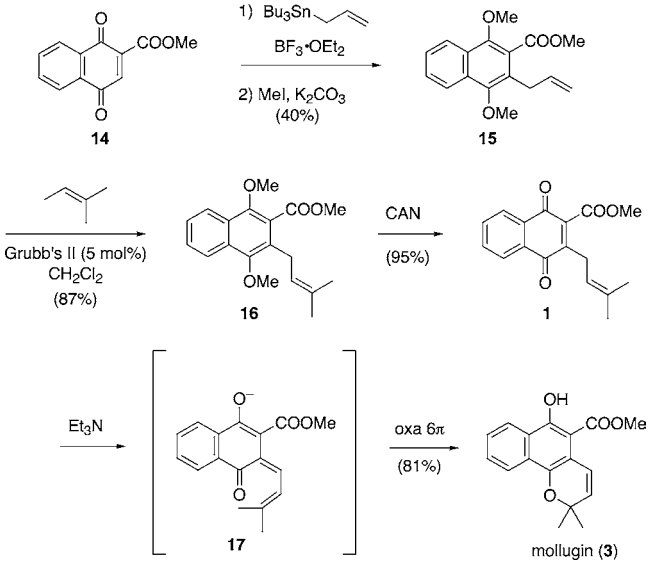
Our synthesis of mollugin begins with the readily available carbomethoxy naphthoquinone **14** (Scheme 2).[10] Sakurai-type allylation,[11] followed by tautomerization and methylation, gave naphthohydroquinone ether **15**. The prenyl moiety was then efficiently installed by Grubbs cross-metathesis with 2-methyl-2-butene, which afforded compound **16**.[12]

Scheme 1. Chromenes via Tautomerization/Oxa 6π-Electrocyclization



Oxidation of **16** with cerium ammonium nitrate (CAN) gave the natural product **1**.[13] Treatment of this material with triethylamine led to the clean formation of mollugin (**3**). This transformation is presumed to arise via 6π-electrocyclization of vinyl *ortho*-quinone methide **17** (Scheme 2).[9]

Scheme 2. Synthesis of Mollugin (**3**)



A variant of this chemistry was used in a synthesis of the more complex dimeric naphthoquinone microphyllaquinone (**8**). Retrosynthetically, **8** can be traced to the sterically congested *ortho*-quinone methide **18** via oxa 6π-electrocyclic ring opening (Scheme 3). This overcrowded alkene could in turn arise via tautomerization of the unsymmetrical naphthoquinone dimer **20**. Note that **20** could also undergo tautomerization to afford *ortho*-quinone methide **19**, an isomer of **18**, whose oxa 6π-electrocyclization would give chromene **21**. However, on the basis of simple electronic considerations, we speculated that the natural product **8** represented the most thermodynamically stable isomer of this series.

Our synthesis of the requisite naphthoquinone dimer **20** begins with the known aryl bromide **22**, derived in three steps from 1-naphthol (Scheme 4).[14] Olefin cross-metathesis of **22** with 2-methyl-2-butene afforded prenylated naphthohydroquinone bromide **23** in good yield. Lithium−halogen exchange followed by transmetalation with 1 equiv of CuBr·

(8) Nicolaou, K. C.; Sasmal, P. K.; Xu, H. *J. Am. Chem. Soc.* **2004**, *126*, 5493−5501.

(9) For biosynthetic investigations into mollugin, see: Inoue, K.; Shiobara, Y.; Nayeshiro, H.; Inouye, H.; Wilson, G.; Zenk, M. H. *Phytochemistry* **1984**, *23*, 307−311.

(10) Barker, D.; Brimble, M. A.; Do, P.; Turner, P. *Tetrahedron* **2003**, *59*, 2441−2449.

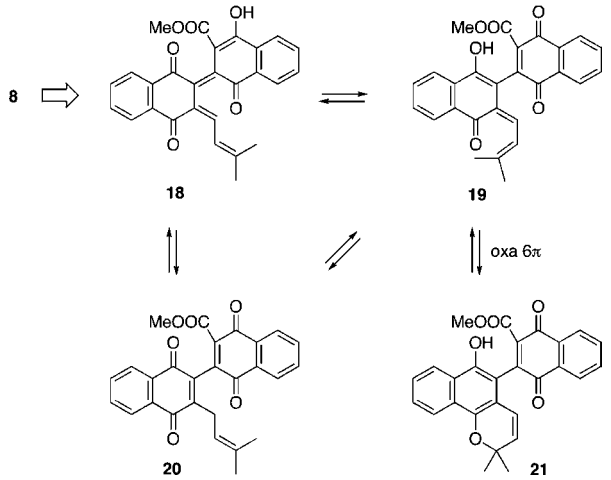
(11) Uno, H. *J. Org. Chem.* **1986**, *51*, 350−358.

(12) (a) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939−1942. (b) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943−1946.

(13) Heide, L.; Leistner, E. *J. Chem. Soc., Chem. Commun.* **1981**, 334−336.

(14) Kesteleyn, B.; De Kimpe, N.; Van Puyvelde, L. *J. Org. Chem.* **1999**, *64*, 1173−1179.

Scheme 3. Retrosynthetic Analysis of Microphyllaquinone (**8**)



Me_2S gave an organocopper(I) compound that we formulate as **24**. This reagent underwent efficient conjugate addition to carbomethoxy naphthoquinone **14** to afford naphthohydroquinone dimer **25** after tautomerization. It is noteworthy that organocopper reagent **24** remains homogeneous in tetrahydrofuran (THF) below −60 °C, which could be due to coordination of the copper(I) center with the prenyl side chain preventing polymerization.[15] Naphthohydroquinone dimer **25** was exhaustively oxidized with CAN to provide bisnaphthoquinone **20**. The relatively low yield of this reaction reflects difficulties encountered in isolation. Due to its sensitivity, **20** could only be purified by careful recrystallization.

The X-ray structure of **20** shows the two naphthoquinone moieties of this axially chiral compound in nearly perpendicular conformation (Figure 2). The dihedral angle between C2−C1−C11−C12 in **20** was found to be 86.2°.

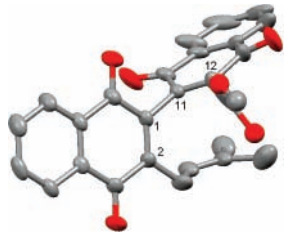
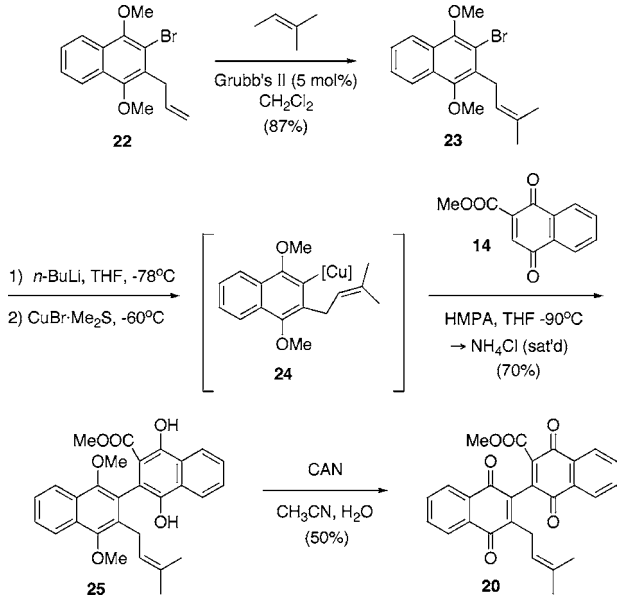


Figure 2. X-ray structure of **20**.

With **20** in hand, the stage was set to explore the key tautomerization/oxa 6π-electrocyclization cascade (Scheme 5). Although this reaction sequence could be achieved by simply heating **20** in methanol, basic conditions were found to be optimal. Thus, treatment of a cooled solution of **20**

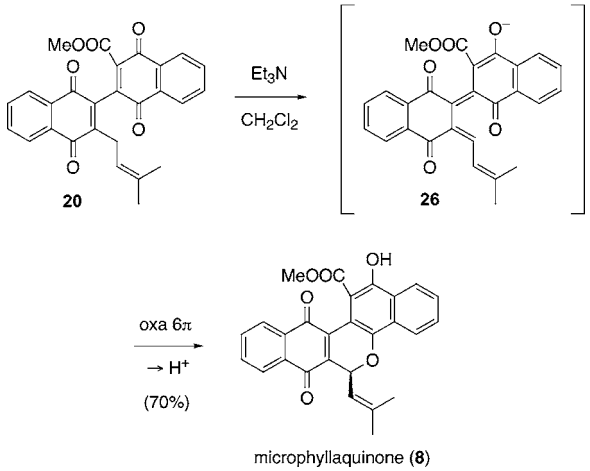
(15) Kamel, T.; Fujita, K.; Itami, K.; Yoshida, J.-I. *Org. Lett.* **2005**, *7*, 4725−4728.

Scheme 4. Preparation of Naphthoquinone Dimer **20**



with triethylamine gave microphyllaquinone (**8**) in good overall yield (Scheme 5). Presumably, this reaction involves deprotonation of **20** to afford *ortho*-quinone methide **26**, which then undergoes oxa 6π-electrocyclization to form the central pyran ring of the natural product.[16]

Scheme 5. Synthesis of Microphyllaquinone (**8**)



X-ray analysis of **8** shows that the central pyran ring adopts a puckered conformation (**8a**), placing the isobutenyl side chain in *pseudo*-axial position (Figure 3). Indeed, molecular mechanics calculations[17] suggest that **8a** is 4.8 kcal mol^{-1}

(16) Oxidation of naphthohydroquinone ether **25**, followed by treatment of the crude product with Et_3N, gave microphyllaquinone in 70% overall yield.

(17) These calculations were performed with Macromodel version 8.1 (Schroedinger LLC). Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskcamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

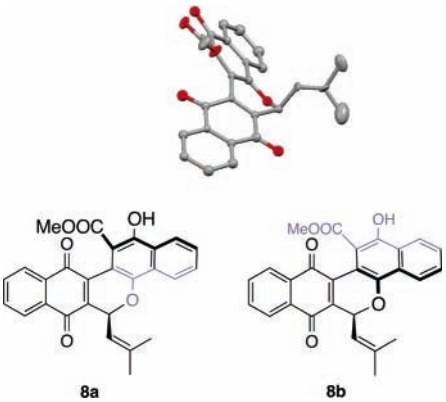


Figure 3. X-ray structure and conformational analysis of microphyllaquinone (**8**).

lower in energy than its atropisomer **8b**, wherein the isobutenyl chain would reside in a *pseudo*-equatorial position.

In summary, we have completed a concise, biomimetic synthesis of mollugin (**3**) and (±)-microphyllaquinone (**8**) featuring a tautomerization/oxa 6π-electrocyclization cascade as a key step. Current work is focused on an asymmetric variant of this sequence that hinges on chirality transfer from the axis of chirality in **20** to establish the stereocenter in **8**. Work toward the construction of enantiomerically enriched **20** is well underway and will be reported in due course.

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Supporting Information Available: Synthetic procedures and spectroscopic data for compounds **1**, **3**, **8**, **15**, **16**, **20**, **23**, and **25** and crystallographic data for **8** and **20** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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