ORGANIC
LETTERS

2008
Vol. 10, No. 20
4505−4508

Synthesis of the Reported Structure of the Bisbenzoquinone Lanciaquinone, Isolated from *Maesa lanceolata*

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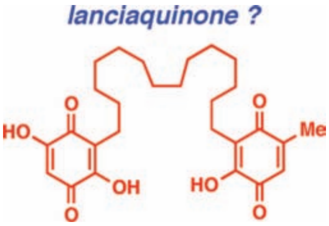
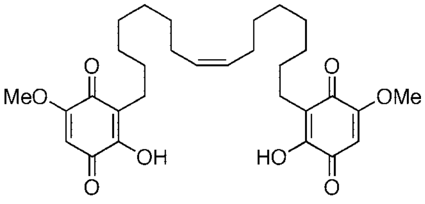
Received July 26, 2008

ABSTRACT

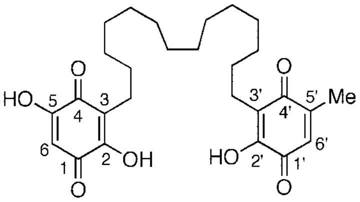


Lanciaquinone, isolated from *Maesa lanceolata*, was originally assigned as a bisbenzoquinone with a C_{14}-chain linking the two quinone rings. A synthesis of the reported structure, in which the key step is a double Claisen rearrangement, suggests that the structure of the natural product needs to be revised.

Quinones are ubiquitous in Nature and often participate in important biological redox processes such as in the electron transport pathways in photosynthesis that occur in the chloroplast of green plants.[1−3] Plants and trees of the Myrsinaceae family comprise 35 genera and over 1000 species and are a rich source of natural products, including, not surprisingly, quinones. One of the more unusual groups of compounds is the ardisiaquinones in which two benzoquinones are linked by a long hydrocarbon chain as in the symmetrical ardisiaquinone A **1**.[4,5] Recently, another bisbenzoquinone derivative, lanciaquinone, was isolated from a Myrsinaceae species, *Maesa lanceolata*, and assigned the unusual structure **2** in which the two quinones are linked by a C_{14}-alkyl chain (Figure 1).[6] In continuation of our interest in naturally occurring quinones,[7−9] we were intrigued by the structure of lanciaquinone **2**, even more so when we examined the data for the natural product. For example, the



1 ardisiaquinone A



2 lanciaquinone

Figure 1. Structures of the naturally occurring bisbenzoquinones, ardisiaquinone A and lanciaquinone.

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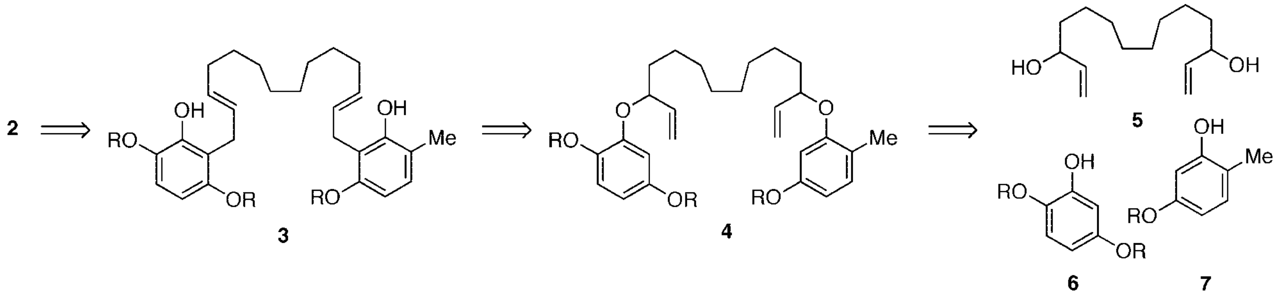
10.1021/ol801697g CCC: $40.75

Scheme 1. Retrosynthetic Analysis of Lanciaquinone **2** Revealing a Double Claisen Rearrangement, R = the Phenol Protecting Group

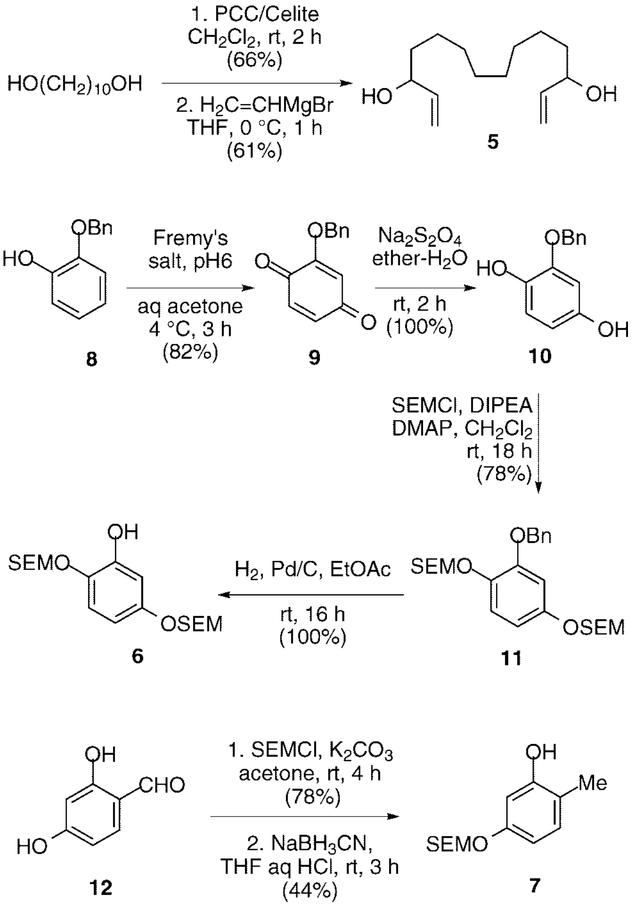


compound is reported to have an optical rotation, $[\alpha]_D = 29$ (c 0.5, $CHCl_3$); the ^1H NMR spectrum contains a four-proton triplet with two coupling constants ($J = 15.3$, 7.6 Hz) for the two benzylic CH_2 groups; and the ^{13}C NMR spectrum shows a very high field signal ($\delta = 8.90$) for the quinone methyl group. Since these data do not appear to be consistent with structure **2** and we have been unable to contact the original authors, we decided to resolve the issue by a synthesis of the reported structure of lanciaquinone.

Our retrosynthesis was based on the Claisen rearrangement−phenol oxidation strategy successfully used in our synthesis of other quinone natural products.[7,10−12] Thus, lanciaquinone **2** should be readily available by hydrogenation and oxidation of bisphenol **3**, obtained in a double Claisen rearrangement of the bisallyl ether **4**, itself obtained from the symmetrical diol **5** and the two phenols **6** and **7** (Scheme 1).[13−19]

Preliminary experiments had shown that the choice of phenol protecting group (R) was crucial, particularly in the 1,2,4-trihydroxybenzene derivative **6** where ester (acetate or benzoate) or silicon-based protecting groups tended to migrate from one oxygen to another. Ether-based protecting groups appeared the most satisfactory, and indeed we succeeded in preparing the trismethoxymethyl (MOM) protected target molecule, only to fail in the removal of the MOM groups due to degradation of the final product under the acidic conditions. We therefore elected to use an alternative ether, the 2-(trimethylsilylethoxy)methoxy (SEM) protecting group. The required building blocks were readily assembled as shown in Scheme 2. The known diol **5**[20] was readily obtained by oxidation of decane-1,10-diol followed by addition of vinylmagnesium bromide. Phenol **6** (R = SEM) was conveniently obtained from catechol monobenzyl ether **8** by oxidation to the quinone **9**, reduction to the

Scheme 2. Synthesis of Building Blocks **5**, **6**, and **7**



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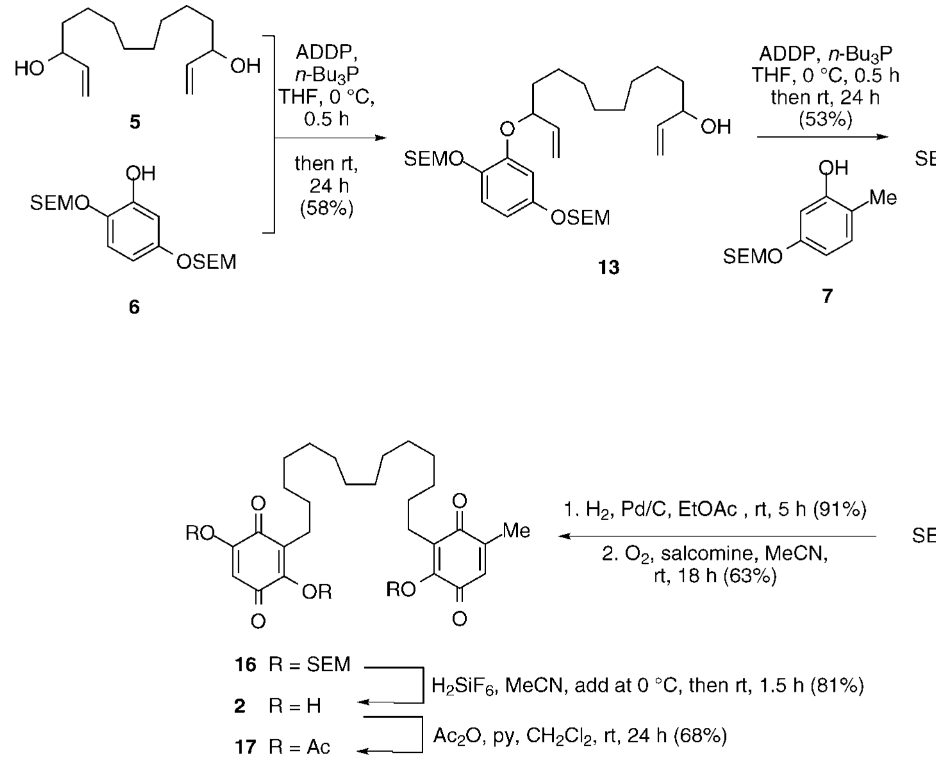
Scheme 3. Synthesis of the Reported Structure of Lanciaquinone **2**



hydroquinone **10**, protection with two SEM groups, and finally hydrogenolysis of the benzyl ether **11**. Phenol **7** (R = SEM) was obtained in two steps from 2,4-dihydroxybenzaldehyde by alkylation of the nonhydrogen-bonded phenol followed by reduction of the formyl group (Scheme 2).

With the three key building blocks in hand, the first coupling was carried out between the diol **5** and phenol **6** (0.62 equiv) under Mitsunobu conditions, although it was necessary to use a more reactive phosphine and azodicarbonyl dipiperidine (ADDP) as the azo compound to obtain good yields of the desired allyl ether **13**. Coupling of the remaining allyl alcohol **13** with phenol **7** proceeded under the same Mitsunobu conditions to give the Claisen precursor **14** (Scheme 3). Heating the bisallyl ether **14** to 200 °C in *m*-xylene in a microwave reactor for 2 h resulted in the desired double Claisen rearrangement to give the bisphenol **15** in acceptable yield. Thereafter, hydrogenation of the two double bonds and oxidation of the phenols to the quinones

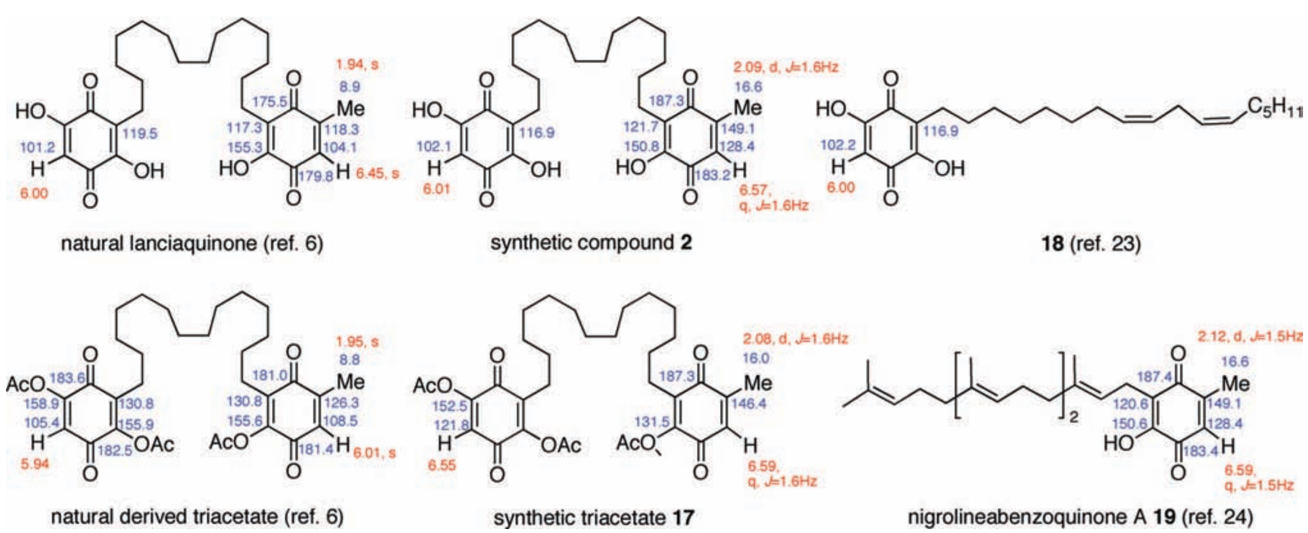

natural lanciaquinone (ref. 6)
synthetic compound **2**
18 (ref. 23)
natural derived triacetate (ref. 6)
synthetic triacetate **17**
nigrolineabenzoquinone A **19** (ref. 24)

Figure 2. Selected NMR spectroscopic data (^{1}H in red, ^{13}C in blue).

with oxygen in the presence of salcomine[21,22] gave the tris-SEM-protected target molecule **16** in good yield. Finally, deprotection of the SEM group with fluorosilicic acid gave the bisbenzoquinone **2**, readily converted into the triacetate **17** (Scheme 3).

The structure of the synthetic material **2**, and its triacetate **17**, were confirmed by detailed spectroscopic analysis. ^{1}H NMR data confirmed the presence of three hydroxy groups [$\delta_H = 7.68$ (2H) and $\delta_H = 6.85$ (1H) all exchangeable with D_2O], two CH [$\delta_H = 6.57$ (6′-H) and $\delta_H = 6.01$ (6-H)], two benzylic methylenes ($\delta_H = 2.44$), a methyl group ($\delta_H = 2.09$) (5′-Me) coupled to the 6′-H ($J = 1.6$ Hz), and a 24H methylene envelope ($\delta_H = 1.51-1.24$) in compound **2**. Analysis of the triacetate **17** confirmed the presence of three acetate groups and hence three hydroxy groups. Finally, HMQC and HMBC experiments, summarized in the Supporting Information, show the expected correlations.

The above data are consistent with structures **2** and **17**. However, there are significant differences between these NMR data and those reported for the natural product and its triacetate.[6] The comparative data are tabulated in the Supporting Information, and there are major differences in the ^{13}C NMR data, particularly in the quinone ring that bears the methyl group, as shown in Figure 2. Figure 2 also shows a comparison with two known quinone natural products **18**[23] and **19**,[24] the NMR data for which closely match those of our synthetic material **2**, providing further evidence for the correctness of compounds **2** and **17** obtained by synthesis. Hence, we conclude that the natural product lanciaquinone does not have structure **2**, and unfortunately, the inconsistencies (and possible typographical errors such as the optical rotation) in the data reported for the natural product[6] do not allow us to propose a credible alternative structure.

Acknowledgment. We thank the EPSRC for support of this work.

Supporting Information Available: Full experimental details and characterization data, copies of ^{1}H and ^{13}C NMR spectra, and detailed comparisons between NMR spectroscopic properties of synthetic materials and those reported for the natural product. This material is available free of charge via the Internet at http://pubs.acs.org.

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