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Total Synthesis of Russuphelol: A Case of Mistaken Chirality

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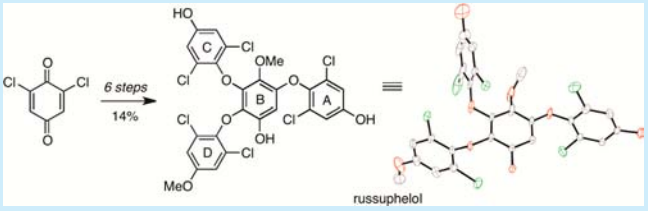
Supporting Information

ABSTRACT: The chlorohydroquinone tetramer, russuphelol, does not have stereocenters; however, it was reported as a chiral optically active substance with stable enantiomeric conformations. The natural product is synthesized in six steps and 14% overall yield. Synthetic material was used to experimentally investigate its chiral properties.



The genus *Russula* comprises many common, moderately large, often colorful mushrooms.[1] Individual *Russula* species can be delicious, such as the shrimp russula (*R. xerampilina*), sickening (*R. emetica*), or fatally toxic (*R. subnigricans*). Molecules with various biological activities have been isolated from *Russula* species. Investigations of the secondary metabolites of *R. subnigricans* resulted in the discovery of a family of chlorinated hydroquinone oligomers that have cytotoxic properties (Figure 1).[2] In 1995, Nozoe and co-workers isolated russuphelol (**1**), a tetracyclic member of this family, from the mushroom *Russula subnigricans*.[3]

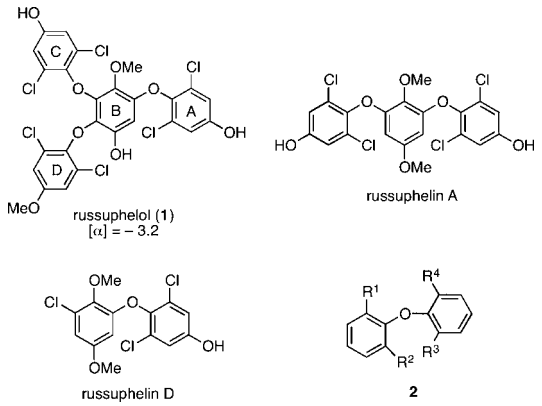


Figure 1. Russuphelol and congeners.

We became interested in russuphelol because it was reported to be a chiral molecule, and we have recently investigated conformationally chiral diphenyl ether natural products.[4] Specifically, the natural russuphelol sample was optically active ($[\alpha]_D = -3.2$) and had reported Cotton effects in the CD spectrum.[5]

Diphenyl ethers that are not part of a macrocyclic ring can possess stable single enantiomer conformations at room temperature.[6] Persistent chirality in simple diphenyl ethers of the type **2** (Figure 1) requires at least three substituents adjacent to the C–O–C linkage of the diphenyl ether to be non-hydrogen (e.g., R^1, R^2, $R^3 \neq H$) and at least one of the R^1–R^4 to be large (i.e., a fully substituted sp^3 carbon, such as a *tert*-butyl group).[7]

The molecular architecture of russuphelol contains four non-hydrogen substituents adjacent to the C–B diphenyl ether linkage and the B–D linkage; however, the substituents are oxygen and chlorine atoms and are not particularly large. In short, russuphelol does not fit the structure type of known chiral diphenyl ethers.

Nozoe and co-workers recognized the highly unusual optical activity for this type of diphenyl ether, and they interpreted it to indicate that an "asymmetric phase" resulted from the steric size of the B–C–D ring system. Nozoe's interpretation aroused our interest, as conformational chirality in such a system has not, to our knowledge, been previously observed.

The identification of molecular chirality in molecules that lack stereogenic sp^3-hybridized carbon atoms (i.e., stereocenters) is not trivial, and molecules that lack such stereocenters often have misunderstood chiral properties.[4,8] Chemical synthesis and derivatization is often the only way to determine if a molecule is chiral or achiral. We decided to prepare russuphelol to determine if it is a chiral molecule.

We envisioned russuphelol arising from quinone **3** (Scheme 1). This strategy would require selective methylation of the oxygen at C4′. Quinone **3** could be prepared from non-symmetric tricyclic bromoquinone **4**. Intermediate **4** would be constructed from dichloroquinone **5** and 2 equiv of phenol **6**.

Our synthesis began with the addition of 2 equiv of **6** to dichloroquinone **5** to form **7** (Scheme 2). Similar transformations have been reported in the literature but have required two sequential steps.[9] High-yielding bromination of the quinone B-ring was accomplished using pyridinium tribromide. Addition of phenol **8** to bromoquinone **4** proceeded smoothly to give quinone **3**. The structure of quinone **3** was confirmed by X-ray crystallographic analysis.[10]

Our first strategy for the conversion of **3** to russuphelol depended on a hydroquinone methylation. Quinone **3** was reduced to the corresponding hydroquinone (**9**). However,

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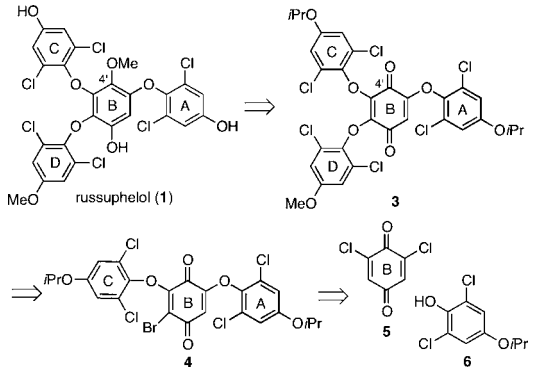
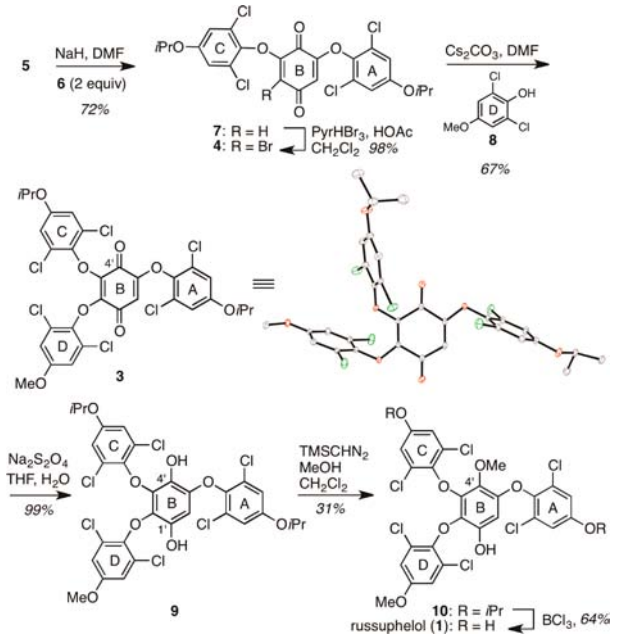
Scheme 1. Retrosynthetic Analysis of Russuphelol

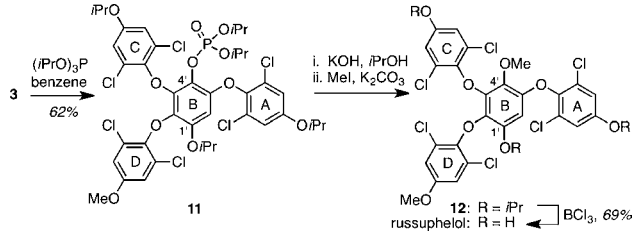


Scheme 2. First Synthesis of Russuphelol

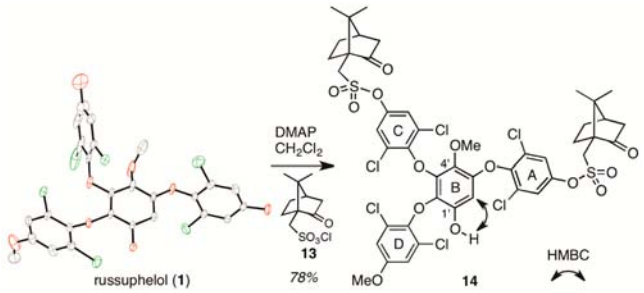


Quinones are known to undergo reductive alkylation with trialkyl phosphites to give monoalkylated hydroquinones.[14] We subjected **3** to triisopropyl phosphite, which delivered alkylation product **11** (Scheme 3). Presumably, the regioselectivity in this reaction results from an electronic preference for nucleophilic attack on the more electrophilic 4′-carbonyl, rather than the 1′-carbonyl. Intermediate phosphonate **11** could be hydrolyzed and methylated to give triisopropyl russuphelol (**12**). Removal of the isopropyl groups gave the natural product. The improved sequence was more efficient and enabled synthesis of 10 mg batches of russuphelol. Moreover, the material could be crystallized, and the structure was confirmed by X-ray crystallographic studies (Scheme 4).[15]

Scheme 3. Second-Generation Synthesis of Russuphelol



Scheme 4. Derivitization of Russuphelol



methylation of **9** was not straightforward. Treatment of **9** with basic conditions led to oxidation back to quinone **3**. Presumably, the corresponding phenoxide is very electron-rich and undergoes oxidation with adventitious oxygen. Moreover, hydroquinone **9** is oxidized to quinone **3** on standing. Methylation of **9** with (trimethylsilyl)diazomethane was modestly selective;[11] at partial conversion, the desired compound (**10**) could be isolated along with the corresponding dimethyl hydroquinone.[12] Intermediate **10** was subjected to BCl_3 to remove the isopropyl protecting groups[13] and complete the synthesis of russuphelol. The ^1H and ^{13}C NMR chemical shifts of the synthetic material matched the chemical shifts reported for the natural sample.[12]

The methylation of **9** allowed us to complete the synthesis of russuphelol and verify the structure of the natural product. Moreover, intermediate **10** was a useful compound for our subsequent chirality investigations (vide infra). However, the overall chemical yield was only modest, and the chemical yields of **10** were highest at partial conversion. These factors caused the production of russuphelol to be operationally tedious, and a smoother transformation of quinone **3** to russuphelol was desired.

With russuphelol in hand, we turned our attention to determining if it is chiral. Distinguishing between chiral racemic and achiral molecules in the absence of sp^3-hybridized stereogenic carbon atoms is not trivial.[16] A convenient indicator of a slow racemization rate relative to the NMR time scale is the presence of chemical shift inequivalent geminal groups, but russuphelol lacks such structural features.[17] However, in isopropyl-containing russuphelol analogues such as **9**–**12**, if the molecules were chiral racemic compounds with stable enantiomeric conformations, then the methyl resonances of the isopropyl groups would be expected to have different chemical shifts. Inspection of the ^1H and ^{13}C NMR data for **9**–**12** revealed that each isopropyl group gave a single methyl resonance. Low-temperature ^1H NMR was performed in an attempt to induce decoalescence of the isopropyl methyl groups, which would allow determination of the racemization rate at low temperatures.[17] However, at temperatures as low as −100 °C no decoalescence was observed in **9**–**12**. These observations suggest that these molecules and, by analogy, russuphelol are achiral molecules, with racemization rates that are fast compared with the NMR time scale, even at cryogenic temperatures.

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It is possible that the chemical shift equivalence of the isopropyl methyl groups in **9**–**12** could be a result of accidental chemical shift equivalence, as the isopropyl groups are located on the periphery of the molecule. To further establish that russuphelol is achiral, we conjugated the natural product with enantiopure (1*S*,4*R*)-camphorsulfuryl chloride (**13**, Scheme 4).[18] If russuphelol was a racemic mixture of stable enantiomeric forms, two diastereomers should be observed, but if russuphelol is achiral, a single diastereomer would be formed. Addition of two equivalents of **13** to russuphelol gave (bis)sulfonylester derivative **14**. The structure of **14** was assigned based on the HMBC correlation indicated. Importantly, **14** was formed in good yield as a single diastereomer with a single set of ^{1}H and ^{13}C NMR signals. This further supports the assignment of russuphelol as an achiral molecule.

The observation that russuphelol is achiral indicates that the natural sample must have been contaminated with nonracemic impurities, which led to a false positive optical activity and Cotton effects. Maxima in the UV spectra occur between positive and negative Cotton effects.[19] If the Cotton effects reported for russuphelol are attributable to impurities, the UV spectrum of russuphelol should lack maxima at these wavelengths. The UV spectrum of pure synthetic russuphelol exhibited a single UV maximum at 286 nm and does not show other maxima at wavelengths between the reported Cotton effects.[5] Moreover, the synthetic sample was a white crystalline solid, rather than the reported pale brown powder. On the basis of these observations, we believe that the optical activity reported for the natural sample can be attributed to nonracemic impurities.

In summary, we report the first total synthesis of the chlorohydroquinone tetramer russuphelol. Our synthesis requires six steps from dichloroquinone (**5**) and proceeds in an overall yield of 14%. The structure of the natural product was verified by X-ray crystallography. The natural product was derivitized as the diisopropyl ether, which had chemical shift equivalent geminal methyl groups. Russuphelol was also derivitized as the (bis)camphorsulfonyl ester, which was formed as a single diastereomer. Furthermore, reported Cotton effects were not consistent with the UV spectrum acquired for pure synthetic russuphelol. Finally, the physical appearance reported for russuphelol suggested an impurity was present in the natural sample. We believe these results indicate that russuphelol is an achiral molecule that does not have stable single enantiomer conformations and is not optically active.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and depiction of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(5) Reported Cotton effects for natural russuphelol (see ref 3): (MeOH) λ_{ext} 347 nm ($\Delta\varepsilon$ −0.086), 311 (+0.063), 302 (−0.073), 273 (+0.11), 227 (−0.98).

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