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Syntheses of heliannuols G and H; structure revision of the natural products

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Abstract—The structures of the natural heliannuols G and H were established by the enantiocontrolled syntheses of the dihydrobenzofurans predicted for the natural products employing the palladium-mediated cyclization and cross metathesis as the key steps.

The heliannuols G and H, heliannane sesquiterpenes isolated from the fresh leaf aqueous extracts of *Helianthus annuus* L. SH-222 and YPP by Macías et al.,[1] were found to have very interesting phytotoxic allelopathic activity. In our previous communication,[2] we reported the enantioselective synthesis of compounds **1** and **2** having the proposed structures for the heliannuols G and H; however, their ^{1}H NMR spectra were not identical with those of the natural products. Upon careful examination of the reported spectral data,[1] we noticed that the coupling constants of the olefinic protons for the natural heliannuols G and H were 15.7 and 15.5 Hz, respectively, strongly suggesting that the double bonds on the eight-membered heterocycle should be trans instead of cis. In addition, in reviewing the biogenetic hypothesis for heliannuol C,[3] we predicted that dihydrobenzofurans **3a** and **3b** should be the natural heliannuols G and H. Here we report the syntheses of **3a** and **3b**, thereby establishing the structures of the natural heliannuols G and H (Fig. 1).

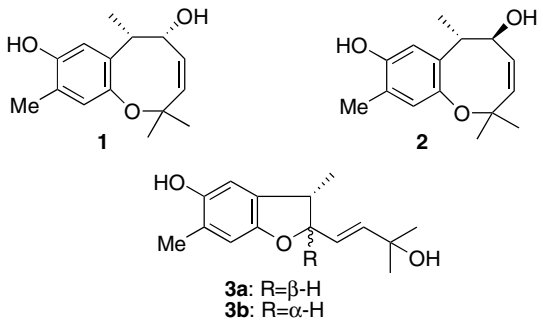

Figure 1.

We thought that dihydrobenzofurans **3a** and **3b** could be directly derived via the palladium-mediated cyclization[4] from the fully functionalized hydroquinone **4**, which in turn would be prepared from the optically pure alcohol **5** (route a). Alternatively, the target molecules could be prepared by the introduction of the isopropanol unit into the olefin part of **6**, which would also be assembled from **5** via the cyclization of the allyl alcohol or the acylated substrates **7**, employing cross metathesis[5] (route b) (Scheme 1).

First, we examined a direct and convenient synthetic route, that is, route a in Scheme 1. The alcohol (−)-**5**, prepared from the prochiral 2-(2,5-dimethoxy-4-methylphenyl)-propan-1,3-diol via desymmetrization using PPL,[2,6] was oxidized with Dess–Martin periodinane (DMP) to give alcohol **8** which was reacted with the dianion generated from 2-methyl-3-butyn-2-ol **9** with *n*-BuLi to provide acetylenic diol **10** as an inseparable mixture of diastereoisomers (dr = 4:1). Reduction with $LiAlH_4$ produced trans allylic diol **11**, which was exposed to acetylation conditions to give monoacetate **12** in a good overall yield. Attempted demethylation of the 1,4-dimethoxyphenyl moiety in **12** was examined

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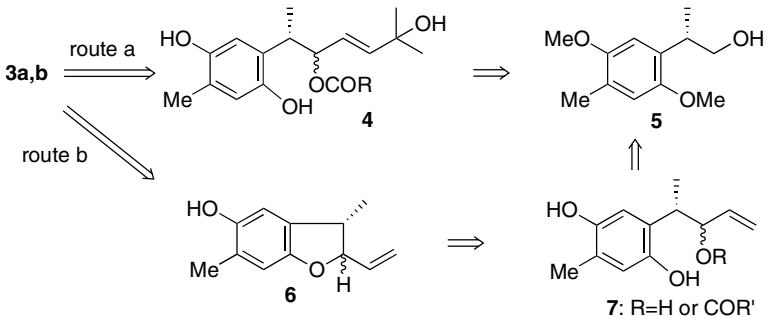
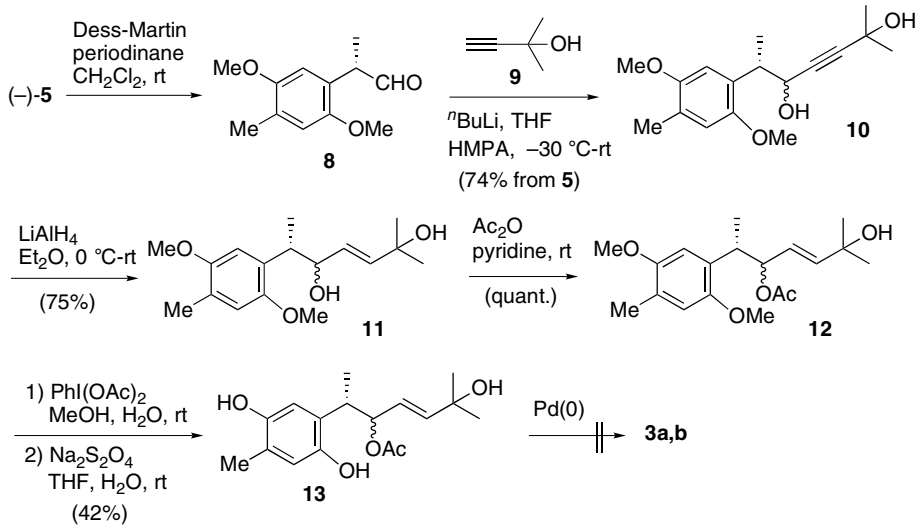


Scheme 1. Retrosynthetic analysis for **3a**,**b**.

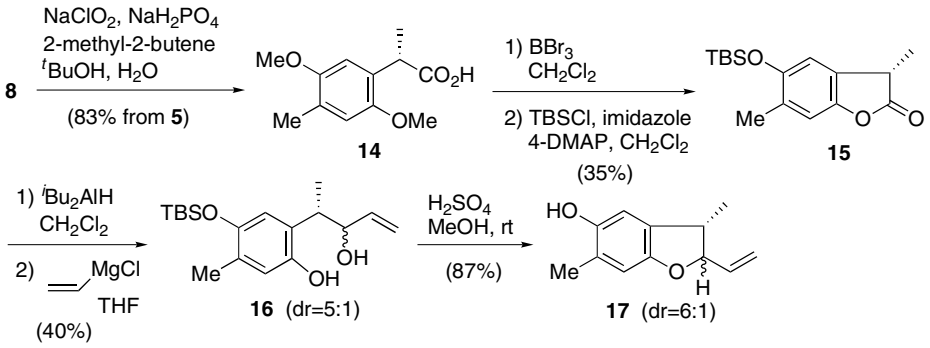
employing the procedure reported previously;[7] however, oxidation with cerium ammonium nitrate (CAN) did not furnish the benzoquinone but a complex mixture instead. After several attempts, oxidation using diacetoxyiodobenzene[8] gave the benzoquinone, which was then reduced with sodium hydrosulfite to give the requisite hydroquinone **13**, a substrate for the cyclization. Instead of the desired **3a** and **3b**, palladium-mediated cyclization[4] of **13** gave only recovered starting material or the formation of a mixture of unidentified products (Scheme 2).

Since the direct cyclization to the fully functionalized dihydrobenzofuran proved unsuccessful, we turned our attention to route b, proceeding with a stepwise assembly of the side chain. Aldehyde **8** was oxidized with sodium chlorite in the presence of 2-methyl-2-butene to provide carboxylic acid **14**, whose dimethyl ether was cleaved with boron tribromide to give the γ-lactone via simultaneous lactonization. The resulting phenolic hydroxyl group was protected as the *t*-butyldimethylsilyl (TBS) ether to give **15**, which was transformed into phenolic allyl alcohol **16** (dr = 5:1) by reduction with diisobutylaluminum hydride followed by treatment of the resulting hemiacetal with vinylmagnesium chloride. Upon exposure of **16** to acidic conditions, sulfuric acid in methanol[9] at room temperature, the cationic cyclization occurred to afford the benzofuran **17** (dr = 6:1) in 87% yield (Scheme 3).

Thus, although we successfully prepared the key compound for the synthesis of **3a** and **3b**, there were two drawbacks with the present route: (i) low overall yield and (ii) reproducibility of the cyclization step. To overcome these problems, we came up with another synthetic route, starting with treatment of aldehyde **8** with vinylmagnesium chloride in the presence of cerium trichloride[10] to produce a diastereomeric mixture (4:1) of allylic alcohol **19** without racemization. This was confirmed by HPLC analysis using a Chiralcel OD column. It should be noted that in the absence of cerium trichloride, partial racemization occurred. Mixed carbonate formation followed by sequential treatment with CAN and sodium hydrosulfite provided the hydroquinone **20**, which was reacted with catalytic tetrakis(triphenylphosphine)palladium[4] at room temperature for 3 h to give dihydrobenzofuran **17** in 83% yield. This product was identical to the material prepared in Scheme 3. Elaboration of the side chain was achieved by the cross metathesis[5] of **17** with 2-methyl-3-buten-2-ol (**21**) in the presence of 10 mol % of (tricyclohexyl)phosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]-ruthenium(IV) dichloride (**22**) in CH_2Cl_2 at room temperature to furnish the desired **3a**



Scheme 2. Attempted preparation of **3a** and **3b**.



Scheme 3. Synthesis of dihydrobenzofurans **17**.

and **3b** in 32% yield. To improve the yield, the phenolic hydroxyl moiety was protected as a TBS ether and compound **18** was subjected to the cross metathesis in refluxing CH_2Cl_2 producing **23** in 98% yield. Finally, desilylation with tetra-*n*-butylammonium fluoride afforded a mixture of **3a** and **3b** in 93% yield (Scheme 4). The diastereoisomers were separated by HPLC[11] affording **3a** {colorless oil; $[\alpha]_D$ −13.7 (*c* 0.4, $CHCl_3$); lit. $[\alpha]_D$ −6.2 (*c* 0.1, $CHCl_3$)} and **3b** {plate, mp 142–144 °C; $[\alpha]_D$ +166.3 (*c* 0.2, $CHCl_3$); lit. $[\alpha]_D$ −16.1 (*c* 0.2, $CHCl_3$)},[12] whose ^{1}H NMR data were identical with those of the natural heliannuols G and H. The structure of **3b** was confirmed by an X-ray crystallographic analysis[13] as shown in Figure 2.

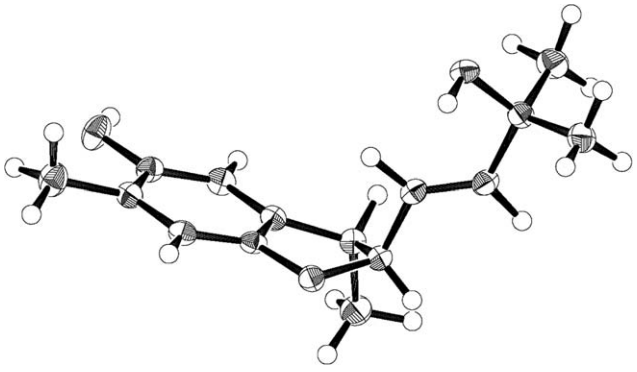


Figure 2. The molecular structure of **3b**.

In summary, we have completed the enantioselective syntheses of the predicted structures for the heliannuols G and H and established the real structures of the natural products. The key steps include palladium-mediated cyclization for the construction of the dihydrobenzofuran skeleton and highly efficient cross metathesis for assembling the dimethylallyl alcohol moiety. The synthetic route developed here is general and efficient and would be applicable to other related molecules. It should also be pointed out that the existence of the novel carbon framework of the heliannane sesquiterpenes in nature was clarified by the present work.

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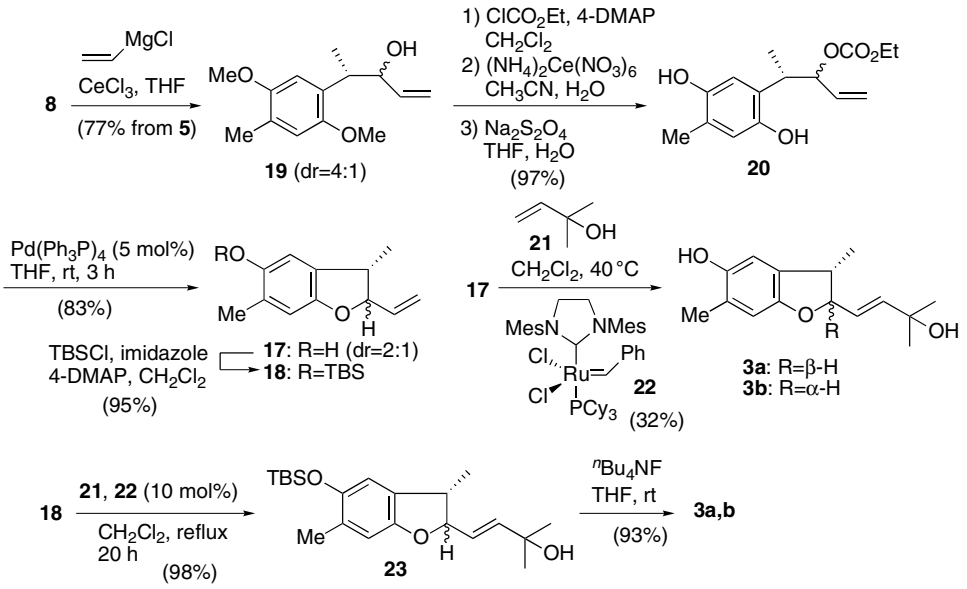

Scheme 4. Syntheses of heliannuols G (**3a**) and H (**3b**).

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11. *Conditions of HPLC separation*: Column, Mightysil Si 60 250-20 (5 μm); eluent, hexane/AcOEt = 7/3; flow rate 10 ml/min; detect, UV detection 254 nm; retention time for **3a** = 38.8 min, for **3b** = 35.6 min.
12. Because of the inaccessibility of the natural heliannuol H, the discrepancy of the optical rotations between the synthetic **3b** and the natural product[1] cannot be explained at this stage.
13. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 613441. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].