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# ENANTIOSELECTIVE SYNTHESES OF HELIANNUOLS G AND H[#]

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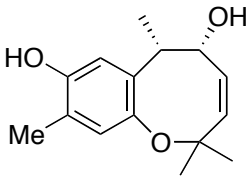
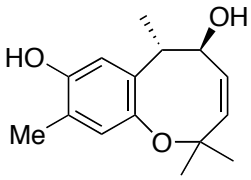
**Abstract** – Enantioselective total syntheses of the proposed structures for heliannuols G and H have been accomplished. However, their spectral properties were not identical with those of the natural products.

The heliannane type sesquiterpenes heliannuols G and H were isolated by Macías from a fresh leaf aqueous extract of *Helianthus annuus* L. SH-222 and YPP and exhibited phytotoxic allelopathic activity.[1] Because of their interesting structural features, an eight-membered oxygen-containing heterocycle fused to an aryl ring[2] and two contiguous tertiary stereogenic centers, we decided to try to synthesize these diastereomeric natural products in optically active form. We report here the first enantioselective total syntheses of the proposed structures for heliannuols G (**1**) and H (**2**), which are not identical with the natural products.




Heliannuol G (**1**)

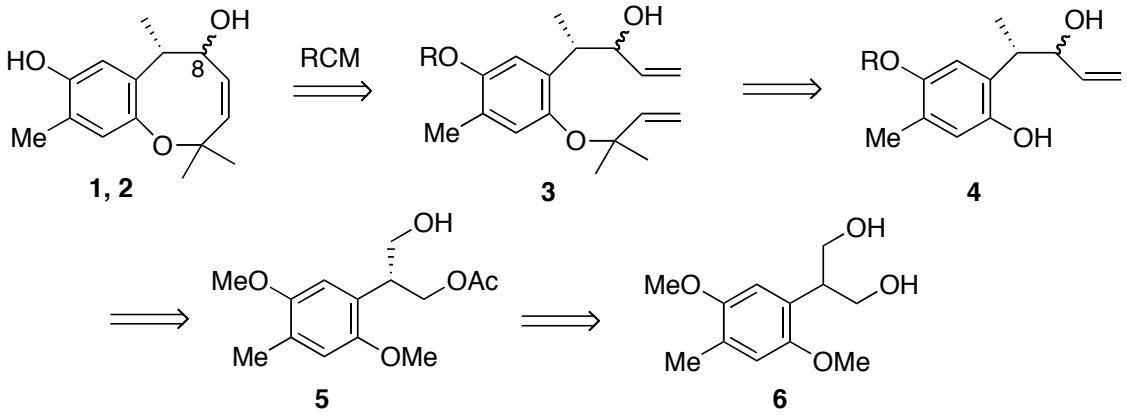



Heliannuol H (**2**)

**Figure 1**

[#]Dedicated to the memory of the late Professor Kenji Koga.

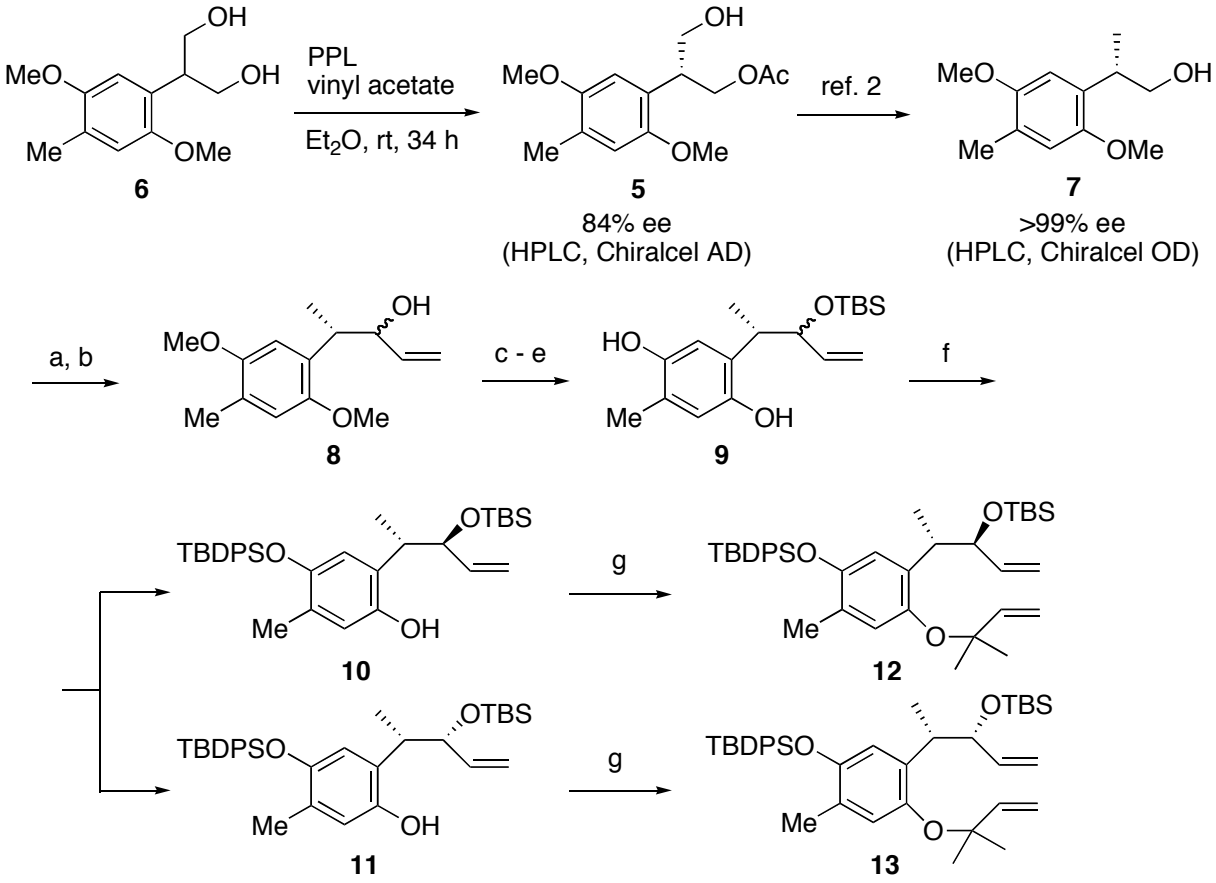
Our strategy is illustrated in Scheme 1. We thought that the heliannuols G and H might be derived from a ring closing metathesis (RCM)[2, 3] of the diene (**3**), which could be constructed by a palladium catalyzed dimethylallylation[4] of the phenol (**4**), a mixture of diastereoisomers at the future C8 position. This in turn would be synthesized from the optically active alcohol (**5**), which has already been prepared by lipase-mediated desymmetrization of the prochiral σ-symmetrical diol (**6**).[2] (Scheme 1)




**Scheme 1.** Retrosynthetic Analysis

PPL-Mediated desymmetrization of the prochiral diol (**6**) provided the optically active acetate [(*R*)-**5**][2] ($[\alpha]_D$ + 12.6° (*c* 1.01, $CHCl_3$)) in 34% yield. The major product of this reaction was the starting diol and the yield of **5** based on the consumed diol was quantitative. The enantiomeric excess (ee) was determined to be 84% by HPLC analysis on a Chiralcel AD column. Sequential tosylation, $NaBH_4$ reduction in hot DMSO and alkaline hydrolysis of **5** produced the alcohol (**7**)[2] in 55% overall yield. Fortunately, it was obtained as a crystalline compound and only one recrystallization was necessary to obtain it optically pure. Dess-Martin oxidation of the optically pure alcohol (**7**) provided the aldehyde which was immediately reacted with vinylmagnesium chloride to give an inseparable 4:1 diastereoisomeric mixture of the alcohol (**8**) in 77% yield for the 2 steps. At this point, a decrease in optical purity (*ca.* 80% ee by HPLC analysis on a Chiralcel OD column) was observed. Since separation of the diastereoisomers proved to be difficult at this stage, the mixture was treated with TBSOTf. The resulting silyl ether was sequentially oxidized with CAN and reduced with $Na_2S_2O_4$ to provide the hydroquinone (**9**) in good overall yield. The sterically less hindered phenolic hydroxyl group was protected successfully as the TBDPS ether to give a mixture of **10** and **11**. The two diastereomers were separated cleanly by preparative HPLC to provide the *anti*-(**10**) and *syn*-alkenylphenol (**11**) in 69% and 20% yields, respectively. Although the stereostructures of the products could not be determined at this stage, they were deduced in terms of the Felkin-Anh model for the addition of the Grignard reagent to the aldehyde. Confirmation was made by the conversion of the major *anti*-isomer into the final compound, whose structure was established by X-Ray crystallographic

analysis. These compounds were treated independently with *i*-butyl-2-methyl-3-buten-2-yl carbonate in the presence of catalytic $Pd(Ph_3P)_4$ to give the desired dienes (**12**) and (**13**) in 84% and 72% yields, respectively. (Scheme 2)




**Scheme 2.** *Reagents and Conditions*: (a) Dess-Martin periodinane, $CH_2Cl_2$, rt, 30 min; (b) vinylmagnesium chloride, THF, 0 °C, 10 min, 77% (2 steps); (c) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, rt, 15 min, 83%; (d) $Ce(NH_4)_2(NO_3)_6$, MeCN, $H_2O$, rt, 20 min, 89%; (e) $Na_2S_2O_4$, THF, rt, 50 min, 98%; (f) TBDPSCl, imidazole, 4-DMAP, $CH_2Cl_2$, rt, 1.5 h, 69% for **10**, 20% for **11**; (g) *i*-$BuOCOOC(CH_3)_2CH{=}CH_2$, $Pd(Ph_3P)_4$, THF, rt, 84% for **12**, 72% for **13**.

The stage was now set to construct the oxygen-containing eight-membered heterocycle by the key RCM reaction[2] of the dienes (**12**) and (**13**). Treatment of the major diastereomer (**12**) with 60 mol% of (tricyclohexyl)phosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride (**15**) in refluxing $CH_2Cl_2$ provided the cyclized product (**14**) in 77% yield. Deprotection of **14** with HF•pyridine complex in pyridine at room temperature gave **2**[5] with the structure proposed for heliannuol H in 90% yield. The structure was confirmed by the X-Ray crystallographic analysis[6] as shown in Figure 2. We also examined the opposite sequence, namely deprotection followed by RCM. Interestingly, in the case of **16**, the RCM proceeded smoothly even at room temperature in the

presence of 10 mol% of **15** to give **2** in 84% yield for the 2 steps. For the minor isomer (**13**), however, sequential deprotection and RCM did not give the desired product (**1**) but instead a mixture of unidentified products. On the contrary, RCM followed by deprotection of the resulting **17** furnished **1** in 61% overall yield. However, the $^1$H-NMR spectra[7] of the compounds (**1**) and (**2**) thus prepared were not identical with those of the natural heliannuols G and H. (Scheme 3)

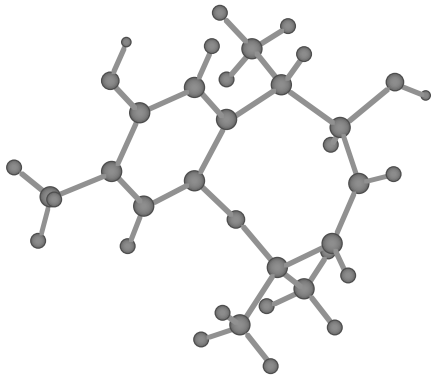
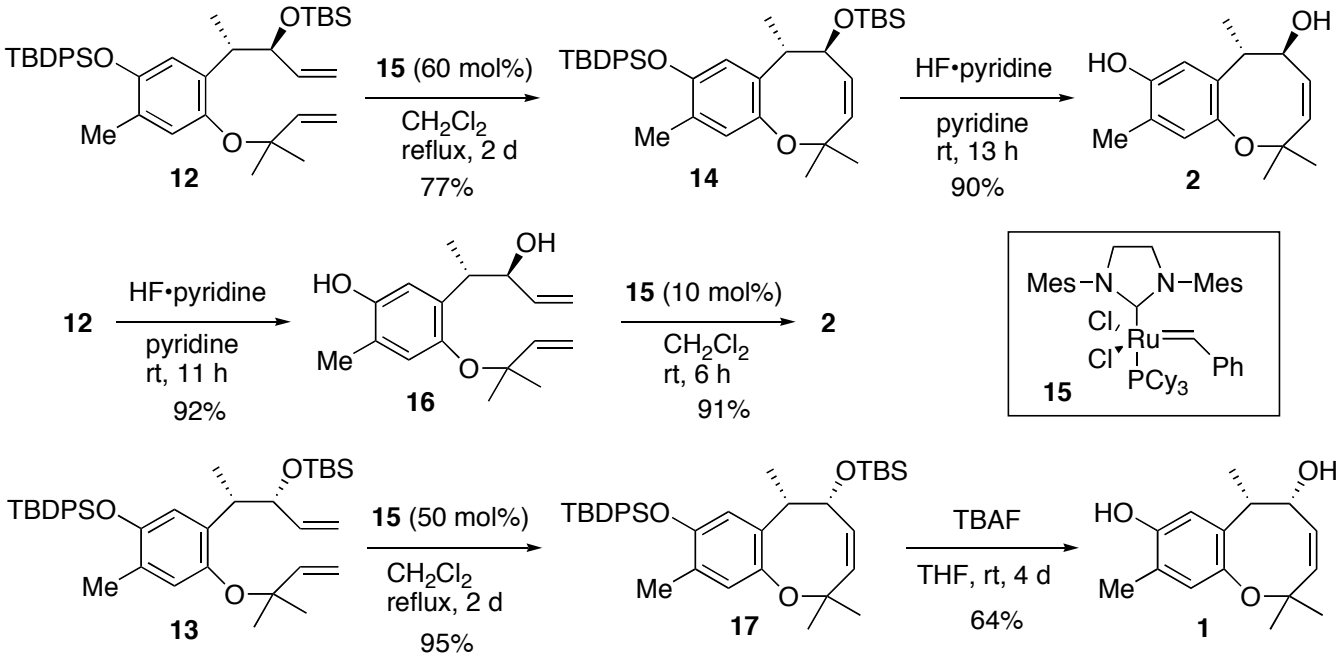


**Figure. 2.** The molecular structure of **2**.




**Scheme 3**

In summary, we have completed the first enantiocontrolled total syntheses of the compounds with the structures proposed for the natural heliannuols G and H. However, it was revealed by the present

synthesis that the initial structural assignments were incorrect. Determination of the real structures for the natural heliannuols G and H is now underway in our laboratories.

**ACKNOWLEDGEMENTS**

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5. The optical purity was determined to be 79% ee by the $^1$H-NMR spectrum of the corresponding di-MTPA ester of **2**.
6. Crystal data for **2**: $C_{15}H_{20}O_3$, $M$ = 248.32, orthorhombic, $a$=8.397(1)Å, $b$=10.458(2)Å, $c$=16.462(2)Å, $V$=1445.6(4)Å$^3$, $D_{calc}$=1.141 g/cm$^3$, $P2_12_12_1$ (#19), $Z$ = 4, $\mu$(MoKa)=0.78 cm$^{-1}$. No. of observed reflections, 13037, No. of variable parameters, 183. The final $R$=0.051 (all data), $R1$=0.044 (I>2.00s(I)), $wR(F^2)$=0.134 (all data).
7. **1**: $^1$H-NMR (400 MHz, $CDCl_3$, -40 ˚C) δ 1.35 (d, 3H, $J$=7.6 Hz), 1.35 (s, 3H), 1.69 (s, 3H), 2.20 (s, 3H), 3.04-3.06 (m, 1H), 4.30-4.36 (m, 1H), 5.40 (d, 1H, $J$=12.4 Hz), 5.77-5.82 (m, 1H), 6.62 (s, 1H), 6.77 (s, 1H). **2**: $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 3H, $J$=6.8 Hz), 1.36 (s, 3H), 1.58 (d, 3H, $J$=7.6 Hz), 1.86 (s, 1H, $D_2O$ exchangeable), 2.16 (s, 3H), 2.62 (dq, 1H, $J$=6.8, 9.2 Hz), 4.55 (s, 1H, $D_2O$ exchangeable), 5.19 (d, 1H, $J$=11.2 Hz), 5.35 (dd, 1H, $J$=7.6, 8.0 Hz), 5.54 (dd, 1H, $J$=7.6, 11.2 Hz), 6.48 (s, 1H), 6.68 (s, 1H).