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First enantioselective total synthesis of (−)-heliannuol C☆

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Abstract—The first, efficient total synthesis of (−)-heliannuol C (**1**) was accomplished enantioselectively, using a chemoenzymatic desymmetrization of the σ-symmetrical diol, a ring closing metathesis, a diastereoselective epoxidation, and a regioselective reductive cleavage of epoxide as the key reaction steps.

Heliannuol C (**1**) has been isolated from the aqueous leaf extracts of *Helianthus annuus* L. var. SH-222 and VYP by Macias.[1] Allelopathic activity bioassays of **1** suggested that this new type of sesquiterpene may be involved in the cultivar sunflower defense against dicotyledon species. Although the structure of **1** was determined mainly by NMR techniques, the absolute structure has never been established. A recent communication on the enantioselective synthesis[2] of heliannuol E (**2**)[3] suggested that the absolute structure of **1** would be (8*R*,10*S*) from the biogenetic parallelism. The promising biological profiles of this compound coupled with its intriguing structural features inspired us to develop an efficient and enantioselective strategy for the synthesis of the natural product. We report here the first, efficient total synthesis of (−)-heliannuol C, thereby establishing its absolute stereochemistry (Fig. 1).

heliannuol C (**1**) heliannuol E (**2**)

Figure 1.

We anticipated that heliannuol C (**1**) would be derived from **3** by regioselective cleavage[4] of the epoxide ring followed by dehydration to provide the C-8 vinyl functionality. Consideration of the molecular model of **4**, which can be prepared by ring-closing metathesis (RCM)[5] of **5**, suggested that the epoxidation would occur from the sterically less congested bottom face of the double bond to give **3** diastereoselectively.[4] The diene **5** might be obtained from the optically active alcohol **6**, previously prepared from the σ-symmetrical 3-aryl-1,5-pentanediol **7** by lipase mediated desymmetrization,[3] with the *R* configuration at the benzylic stereogenic center (Scheme 1).

Treatment of the prochiral diol **8** with immobilized lipase PS on diatomite[6] in the presence of vinyl acetate in Et_2O at room temperature for 13 h produced the monoacetate **9**, $[\alpha]_D^{26}$ +2.38 (*c* 0.29, $CHCl_3$), and the corresponding diacetate, which can be converted into **8** by basic hydrolysis (K_2CO_3 in aq. MeOH) in 24 and 76% yield, respectively. The enantiomeric excess of **9** was >99% as determined by HPLC on a Chiralcel OD column. The absolute configuration of the stereogenic center was elucidated by the following chemical conversion. Dehydration[7] of the primary alcohol moiety in **9** gave **10**, which was ozonized and reduced with $NaBH_4$ to provide the alcohol **11**. Tosylation, followed by reduction of the resulting **12** with $NaBH_4$ in hot DMSO, afforded the alcohol **13** after basic hydrolysis. Sequential oxidation of **13** with Dess–Martin periodinane and PDC provided the carboxylic acid **14**, whose spectral properties are identical with those of the known carboxylic acid **14**[4] having the *R* configuration, which, except for the sign of its optical rotation, has been prepared by our laboratory. Thus, the absolute configuration of **9** was established to be *S*[8] (Scheme 2).

Keywords: lipase; ring-closing metathesis; diastereoselective epoxidation; cleavage of epoxide; sesquiterpene.

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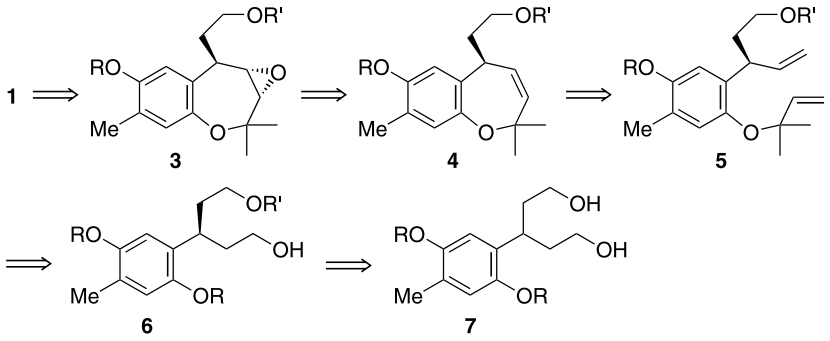
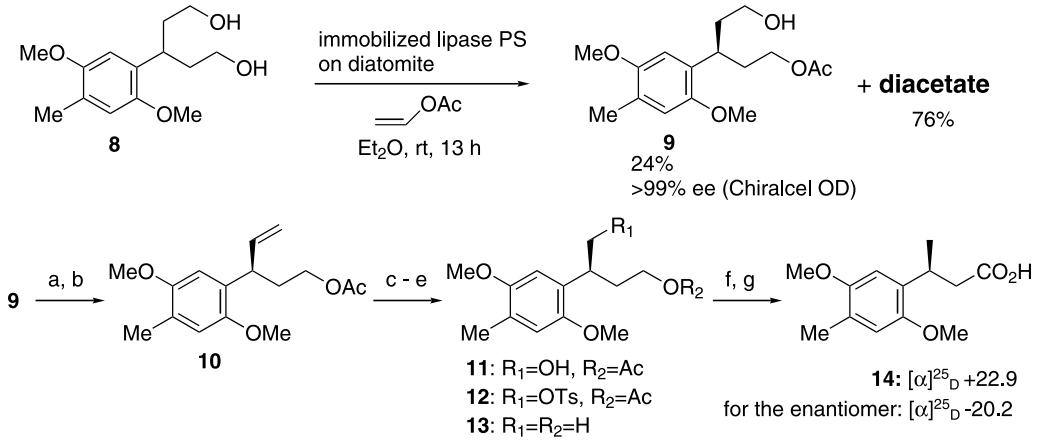


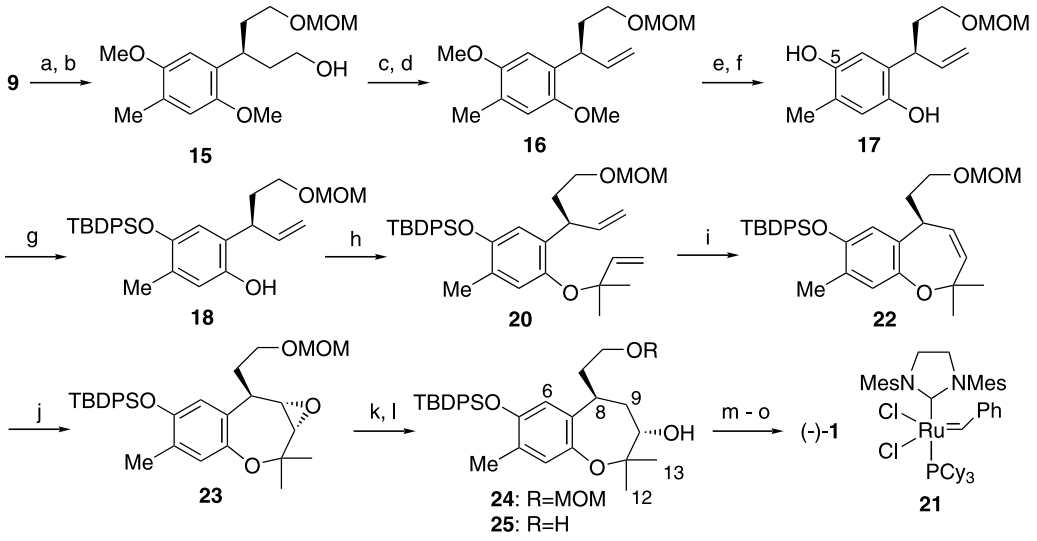
Scheme 1. Retrosynthetic analysis.



Scheme 2. *Reagents and conditions*: (a) *o*-nitrophenyl selenocyanate, *n*-Bu_3P, THF, rt, 50 min; (b) 35% H_2O_2, THF, rt, 10 h, 48% for the two steps; (c) O_3, MeOH then $NaBH_4$, MeOH, −78 to 0°C, 1.5 h, 50%; (d) TsCl, Et_3N, 4-DMAP, CH_2Cl_2, rt, 16 h; (e) $NaBH_4$, DMSO, 60°C then K_2CO_3, MeOH, H_2O, rt, 15 h, 54% for the two steps; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h; (g) PDC, DMF, rt, 19 h, 35% for the two steps.

For the synthesis of the natural heliannuol C, the acetoxyethyl moiety in **9** must be transformed to the vinyl group. Protection of the hydroxyl function as the methoxymethyl (MOM) ether followed by reduction with $LiAlH_4$ provided the alcohol **15**, which was dehydrated to give the alkene **16**. Sequential oxidation with CAN and reduction of the resulting quinone with $Na_2S_2O_4$ gave the hydroquinone **17**,[9] whose sterically less congested hydroxyl moiety (C-5) was selectively protected as the *t*-butyldiphenylsilyl ether to furnish **18** in 80% yield, accompanied by the bissilyl ether in 16% yield. With the desired phenolic compound **18** in hand, we next examined the key conversions in our strategy. The substrate diene **20** for the RCM was obtained in 85% yield as a single product by the reaction of **18** with *i*-butyl-2-methyl-3-buten-2-yl carbonate in the presence of tetrakis(triphenylphosphine)palladium in THF.[10] Treatment of **20** with 10 mol% of (tricyclohexyl)-phosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride **21** in CH_2Cl_2 at room temperature provided the desired seven-membered heterocycle **22** in 98% yield. Epoxidation of **22** with methyl(trifluoromethyl) dioxirane, generated in situ from methyl trifluoromethyl ketone and Oxone® in acetonitrile,[11] produced 78% yield of a 10:1 inseparable diastereomeric mixture of the epoxide **23**. Although the stereochemistry of the major diastereoisomer could not be determined at this stage, its confirmation was made in the next step. When a mixture of the epoxide was treated with $LiAlH_4$ in THF at 40°C, the reaction proceeded smoothly and regioselectively to give a chromatographically separable mixture of the alcohol **24** in 89% yield. The absolute configuration at C-10 of the major diastereoisomer was determined to be the requisite *S*[12] by the Kusumi–Mosher ester method,[13] and this result indicated that the epoxidation had occurred from the bottom face of the double bond in **22**, as we predicted. Removal of the MOM protecting group, dehydration of the resulting alcohol **25**, followed by desilylation produced (−)-heliannuol C (**1**), $[\alpha]_D^{25}$ −60 (*c* 0.29, MeOH) {lit.[1] $[\alpha]_D^{25}$ −38 (*c* 0.10, MeOH)}, the spectral data of which were in agreement with those reported for the natural heliannuol C (Scheme 3).

In summary, we have completed the first enantioselective total synthesis of the optically pure, natural enantiomer of (−)-heliannuol C. The key steps of the synthesis include the enantioselective construction of the two remote tertiary stereogenic centers by a combined use of the chemoenzymatic desymmetrization of



Scheme 3. *Reagents and conditions*: (a) MOMCl, *i*-Pr_2NEt, rt, 18 h, 95%; (b) $LiAlH_4$, THF, rt, 10 min, 96%; (c) *o*-nitrophenyl selenocyanate, *n*-Bu_3P, THF, rt, 15 min; (d) 35% H_2O_2, THF, rt, 3.5 h, 91% for the two steps; (e) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, H_2O, rt, 20 min; (f) $Na_2S_2O_4$, THF, H_2O, rt, 10 min, 95% for the two steps; (g) *t*-$BuPh_2SiCl$, imidazole, 4-DMAP, CH_2Cl_2, rt, 1 h, 80%; (h) *i*-$BuOCO_2C(Me)_2CH{=}CH_2$, $(Ph_3P)_4Pd$, THF, rt, 14 h, 85%; (i) **21**, CH_2Cl_2, rt, 16.5 h, 98%; (j) CH_3COCF_3, Oxone®, CH_3CN, rt, 2.5 h, 78%; (k) $LiAlH_4$, THF, 40°C, 20 min, 89%; (l) 6N-HCl, THF, rt, 3 h, 84%; (m) *o*-nitrophenyl selenocyanate, *n*-Bu_3P, THF, rt, 20 min; (n) 35% H_2O_2, THF, rt, 3.5 h, 88% for the two steps; (o) *n*-Bu_4NF, THF, rt, 15 min, quant.

the σ-symmetrical diol and a substrate controlled diastereoselective epoxidation of the double bond in the seven-membered heterocycle followed by regioselective hydride reduction of the epoxide. In addition, the absolute configurations were established to be (8*R*,10*S*) by the present total synthesis. The synthetic route developed here is not only general and efficient but also can be applied to the synthesis of the enantiomer and other related natural products.

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References

1. Macias, F. A.; Milinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R. *J. Org. Chem.* **1994**, *59*, 8261–8266.
2. The absolute structure of heliannuol E (**2**)[3] was revised to be (2*R*,4*R*) by an unambiguous total synthesis: Doi, F.; Ogamino, T.; Sugai, T.; Nishiyama, S. *Tetrahedron Lett.* **2003**, *44*, 4877–4880.
3. Sato, K.; Yoshimura, T.; Shindo, M.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 309–314.
4. Kishuku, H.; Shindo, M.; Shishido, K. *Chem. Commun.* **2003**, 350–351.
5. For a review, see: Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
6. In a previous report,[3] we used lipase AK to obtain the optically active monoacetate **9**. Further screening of enzymes revealed that the immobilized lipase PS on diatomite was the best choice for the desired transformation.
7. Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.
8. Our previous assignment[3] of the *R*-configuration for the (+)-monoacetate was incorrect and we herewith correct it to the opposite configuration.
9. Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807–1808.
10. Kaiho, T.; Yokoyama, T.; Mori, H.; Fujiwara, J.; Nobori, T.; Odaka, H.; Kamiya, J.; Maruyama, M.; Sugawara, T. JP 06128238, 1994; [*C.A.*, 1995, *123*, 55900].
11. Yang, D.; Wong, M. K.; Yip, Y. C. *J. Org. Chem.* **1995**, *60*, 3887–3889.
12. Selected $\Delta\delta$ values ($\Delta\delta = \delta_{(S)} - \delta_{(R)}$) for the MTPA ester of **24**: 9-C$\underline{H}_2$ (–0.106, –0.064), 8-C$\underline{H}$ (–0.032), 6-C$\underline{H}$ (–0.018), 12-C$\underline{H}_3$ (+0.093), 13-C$\underline{H}_3$ (+0.019).
13. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.