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Asymmetric total syntheses of heliannuol E and *epi*-heliannuol E

Yongjiang Liu [b], Chong Huang [a], Bo Liu [a,c,*]

[a] Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China
[b] College of Chemical Engineering, Sichuan University, Chengdu 610065, China
[c] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China

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ABSTRACT

Asymmetric total syntheses of heliannuol E and *epi*-heliannuol E were achieved in 10 and 13 steps, respectively, from the commercially available starting materials. The syntheses feature an intramolecular attacking on the sulfate to form the dihydropyran ring of heliannuol E and an acyl transfer-secondary carbocation capture sequence to construct the dihydropyran ring of *epi*-heliannuol E.

Helianthus annuus is a rich source of bioactive natural products, from which Macias and co-workers have already isolated a number of sesquiterpenes, including structurally related heliannuols A–L[1] and heliespirones A–C (Fig. 1).[2] Most of these sesquiterpenes exhibit interesting allelopathic activity, which makes them alluring target molecules for synthetic chemists. Involved in such a synthetic endeavor, our group reported the first asymmetric total synthesis of *ent*-heliespirones A and C recently,[3] laying the foundation for enantioselective construction of other members in this heliannane family. Considering the structural similarity to heliespirones A and C, we selected heliannuol E and *epi*-heliannuol E as our further synthetic targets. While two racemic syntheses[4] have been developed, there are four enantioselective syntheses[5] of heliannuol E reported till now. The third generation enantioselective synthesis of heliannuol E by Shishido group counted only nine steps,[5d] superior to the former synthetic routes with approximate 20 overall synthetic steps[5a–c]; however, it is discounted by the required HPLC isolation and low selectivity. Accordingly, a new, concise, and efficient synthetic strategy is still worth exploring. Herein we would like to present our efforts on the asymmetric total synthesis of heliannuol E and the first asymmetric total synthesis of *epi*-heliannuol E.

Our asymmetric total synthesis of heliannuol E commenced with compound **1**, facilely prepared in seven steps from ethyl propiolate and prenyl bromide, according to our synthetic strategy toward *ent*-heliespirones A and C.[3] The treatment with sulfonyl chloride converted compound **1** to sulfate **2**,[6] by changing the secondary hydroxyl to a labile leaving group. Then compound **2** was subjected to CAN oxidation and subsequent reduction to form phenol **3**. Finally, a base-promoted intramolecular ring closure produced heliannuol E in good yield.[7] Notably, no trace amount of *epi*-heliannuol E could be detected (Scheme 1). The spectra of our synthetic heliannuol E were in accordance with those of other synthetic samples (see Supplementary data).

Total synthesis of *epi*-heliannuol E was initiated with compound **4**, another intermediate in our total synthesis of *ent*-heliespirones A and C, prepared in six steps from commercially available compounds.[8] The primary and secondary alcohols in compound **4** were selectively protected with acetyl anhydride in the presence of the tertiary alcohol to afford compound **5**, which was converted to phenol **6** after the routine treatment with an oxidation–reduction sequence. Based on our original design, in the presence of acid,

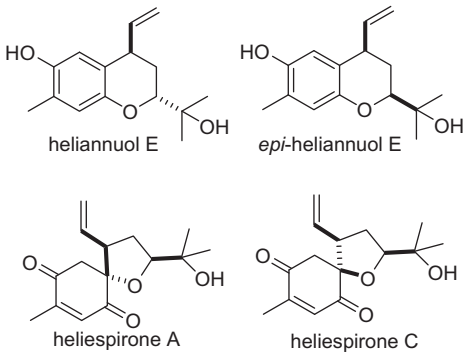

Figure 1. Structures of selected sesquiterpenes from *Helianthus annuus*.

* Corresponding author. Tel./fax: +86 28 8541 3712.
E-mail address: chembliu@scu.edu.cn (B. Liu).

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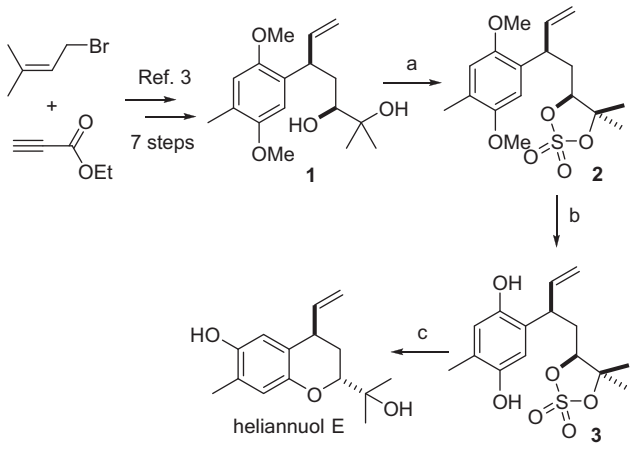
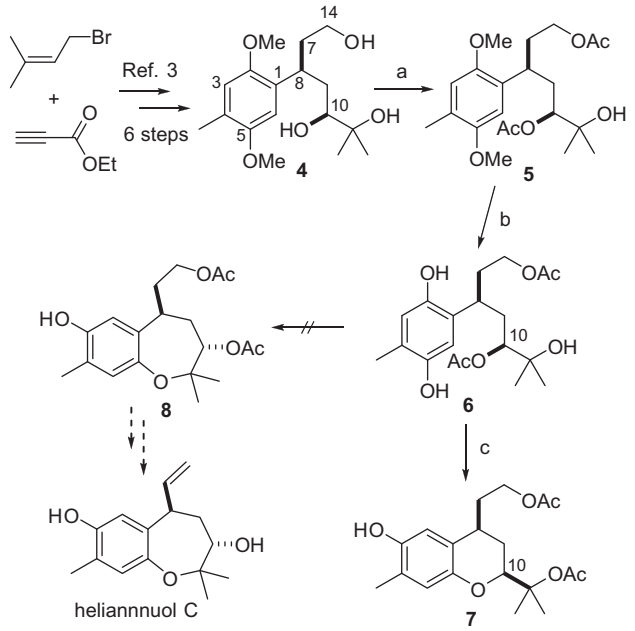


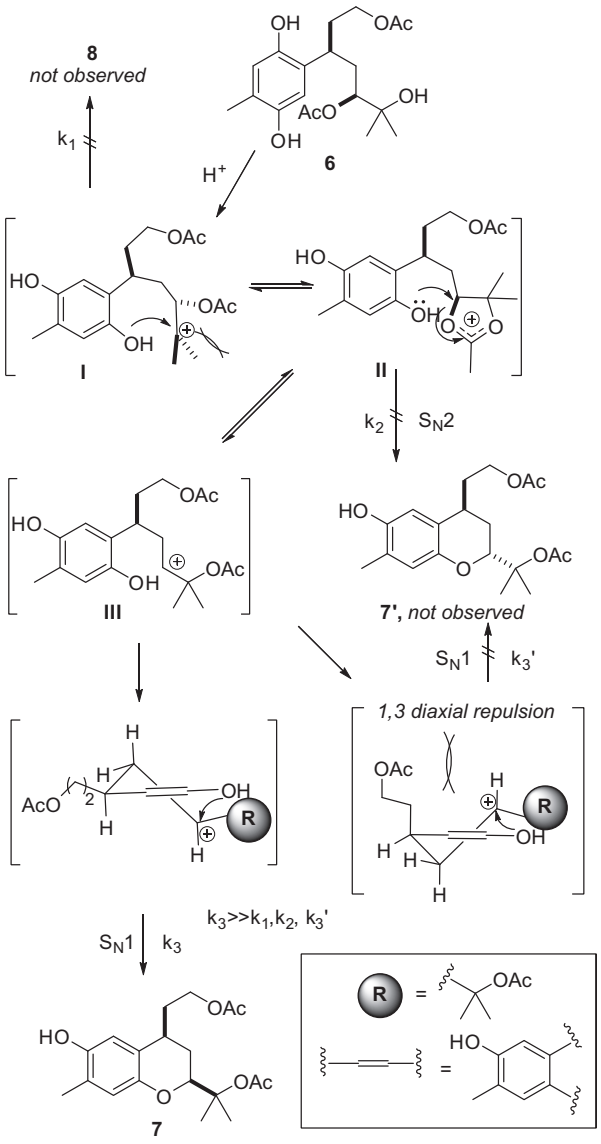
Scheme 1. *Reagents and conditions:* (a) SO_2Cl_2, triethylamine, DCM, 0 °C, 44%; (b) CAN, aqueous MeCN, −10 °C, then $Na_2S_2O_4$, THF/H_2O, rt, 85%; (c) K_2CO_3, DMF/MeCN, then 20% H_2SO_4 solution, ether/$CHCl_3$, 82%.



Scheme 2. *Reagents and conditions:* (a) Ac_2O, DMAP, TEA, DCM, 0 °C, 95%; (b) CAN, aqueous MeCN, −10 °C, then $Na_2S_2O_4$, THF/H_2O, rt, 90%; (c) *p*-TsOH, toluene, rt, 86%.

the tertiary alcohol had been anticipated to give a tertiary carbocation, which might be subsequently captured by phenol to produce compound **8**,[9] an intermediate toward heliannuol C. However, compound **7** was actually obtained instead under acidic conditions with the C10 chirality retained (Scheme 2), the stereochemistry of which was deduced from that of the final known compound, *epi*-heliannuol E.

The plausible mechanism for the transformation from compound **6** to **7** is depicted in Scheme 3. Firstly, the tertiary carbocation **I** could be generated when compound **6** was treated with *para*-toluenesulfonic acid; then a secondary carbocation **III** could be produced in quick equilibrium with intermediate **I** via intermediate **II** through acetyl transfer. Interestingly, the intramolecular S_N1 capture of secondary carbocation by phenol (k_3) might be the most facile process, compared to the transition states of other process (k_1, k_2, k_3'), since compound **7** was achieved as the only

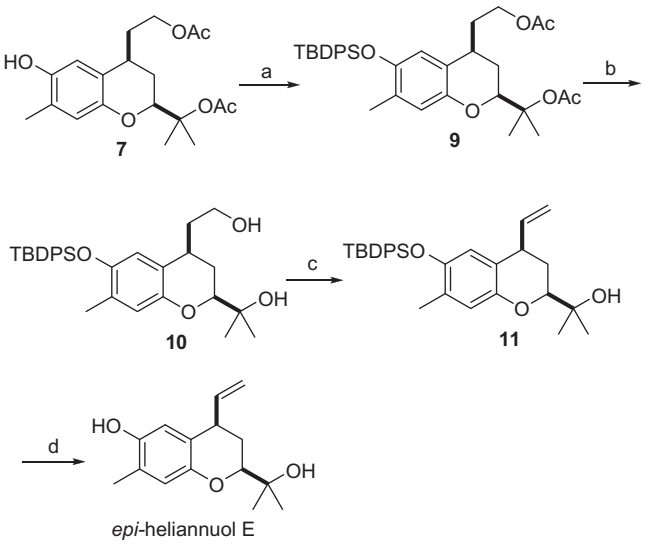


Scheme 3. Plausible mechanism for the formation of compound **7**.

isolable product and the formation of its epimer, that is, compound **7′** was not observed.

To prevent the decomposition of compound **7** in the course of direct conversion of its primary hydroxyl to terminal double bond with organoselenium and peroxide, the free phenol group was protected as the *tert*-butyldiphenylsilyl ether, affording compound **9**, the acetates of which were cleaved to give diol **10** with diisobutylaluminum hydride.[10] Subsequently, the primary alcohol was transformed to terminal alkene **11** with organoselenium methodology.[3,11] Removing the silyl protective group of compound **11** smoothly converted it to *epi*-heliannuol E (Scheme 4),[12] whose characterization data were well consistent with those reported before (see Supplementary data).

In summary, we have accomplished asymmetric total synthesis of heliannuol E and *epi*-heliannuol E concisely, in 10 and 13 steps, respectively, from the commercially available starting materials. Our syntheses feature an intramolecular attacking on the sulfate to form the dihydropyran ring of heliannuol E and an acyl transfer-secondary carbocation capture sequence to construct the dihydropyran ring of *epi*-heliannuol E. Total synthesis of other members in this family is underway in our laboratory.



Scheme 4. *Reagents and conditions:* (a) TBDPSCl, DMAP, imidazole, DCM, rt, 90%; (b) DIBAL-H, DCM, 0 °C, 72%; (c) $^{n}Bu_3P$, *o*-NO_2PhSeCN, THF, 0 °C, then 30% H_2O_2; (d) TBAF, THF, 0 °C, 63% for two steps.

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Supplementary data

Supplementary data associated (characterization data for new compounds) with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.131.

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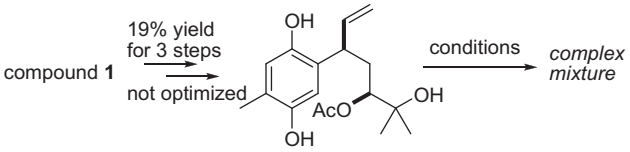

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