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Enantioselective synthesis of heliannuol E; structural consideration of natural molecule

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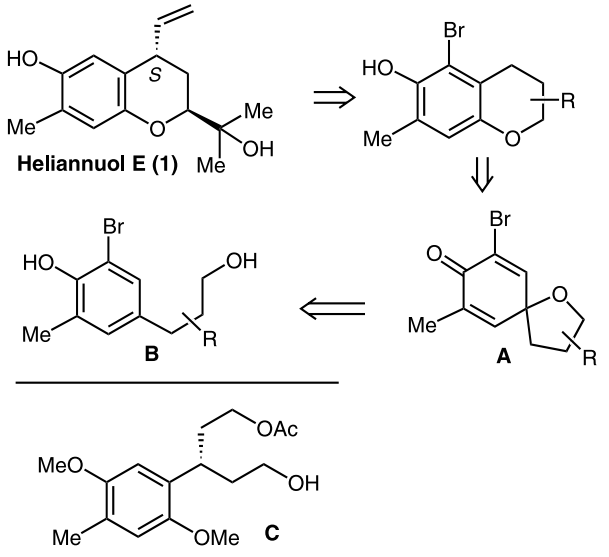
Abstract—Heliannuol E **1**, isolated from *Helianthus annuus* L. cv. SH-222, was successfully synthesized in both optically active forms, by novel ring-expansion reaction of the corresponding spirodienone derivatives **8** and **17**, which were produced from **7** and **16** under anodic oxidation conditions. The absolute structure of the natural product was determined to have *R*-configuration at the benzylic position.

In connection with heliannuol E **1**,[1] a plausible allelopathogenic substance of sunflowers,[2] we have accomplished a total synthesis of its racemic form.[3] The crucial construction of the chroman framework was successfully accomplished by using a novel ring-expansion reaction of the spirodienone derivatives **A**, generated electrochemically from the corresponding phenol **B** (Scheme 1).[4] As extended investigation, an optically active form of **1** would be included to contribute to structure–activity relationship studies, as well as to demonstrate our ring-expansion methodology as a new synthetic tool.

Previously, Shishido accomplished a total synthesis of (−)-**1**, and determined the absolute configuration of **1**, as depicted in Scheme 1.[5,6] The *S*-configuration of the benzylic position was derived from the acetate **C**, whose absolute configuration was spectroscopically determined by the PGME (phenylglycine methyl ester) method.[7]

According to Shishido's results, the synthesis was commenced with enzymatic separation of the diester **2**[3] to give monoester **3**, which on coupling with (*R*)-phenylethylamine gave amide **4** (Scheme 2). At this stage, its optical purity was 85% de. Further recrystallization provided a sample with 100% de, the stereochemistry of which was confirmed by X-ray single crystallographic analysis[8] to be **4** possessing *S*-configuration at the benzylic position. Compound **4** was successively reduced with $LiBH_4$, followed by



Scheme 1.

Keywords: heliannuol E; *Helianthus annuus* L. cv. SH-222; allelopathy; phenolic oxidation; ring expansion; spirodienone.

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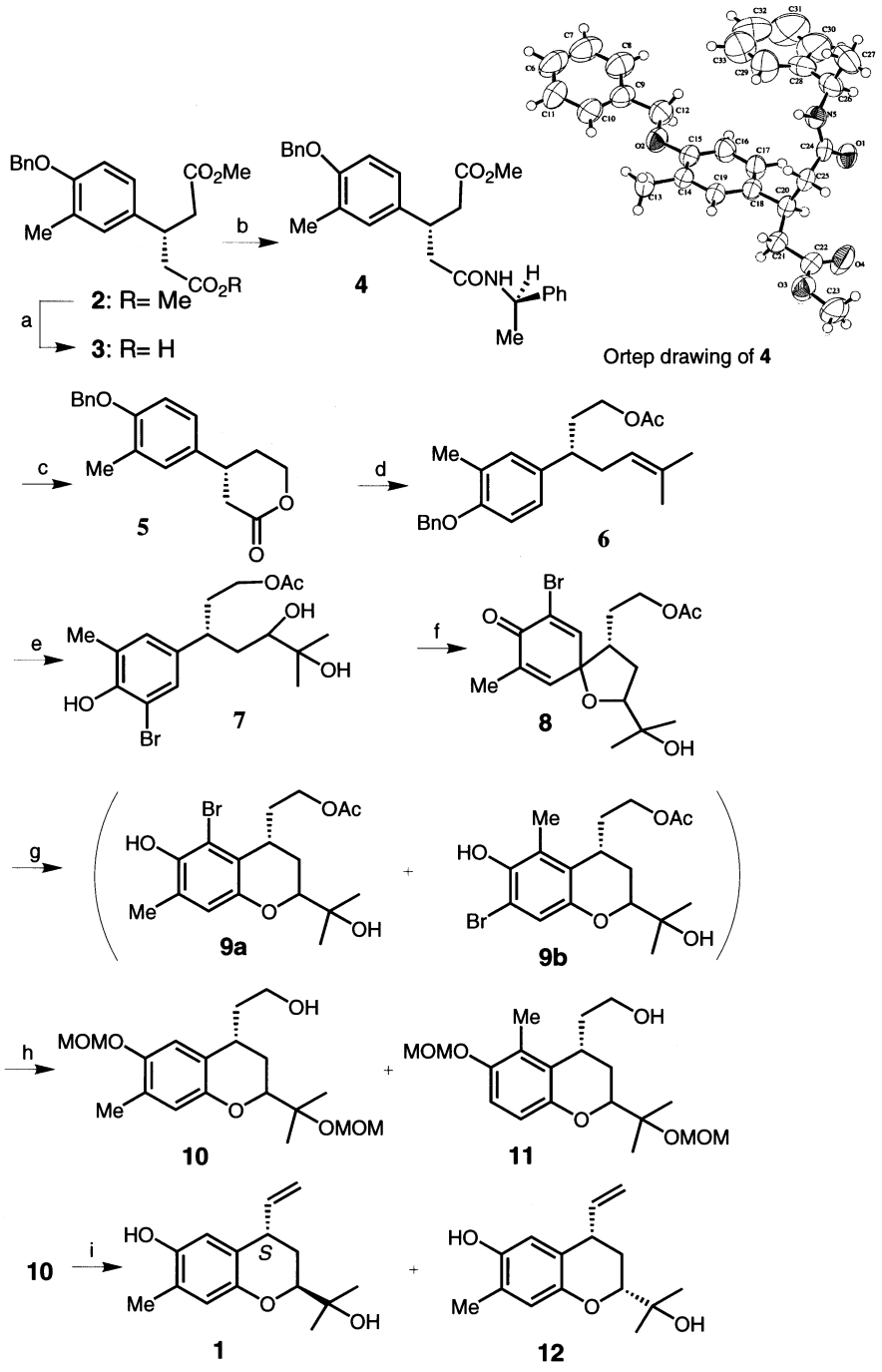
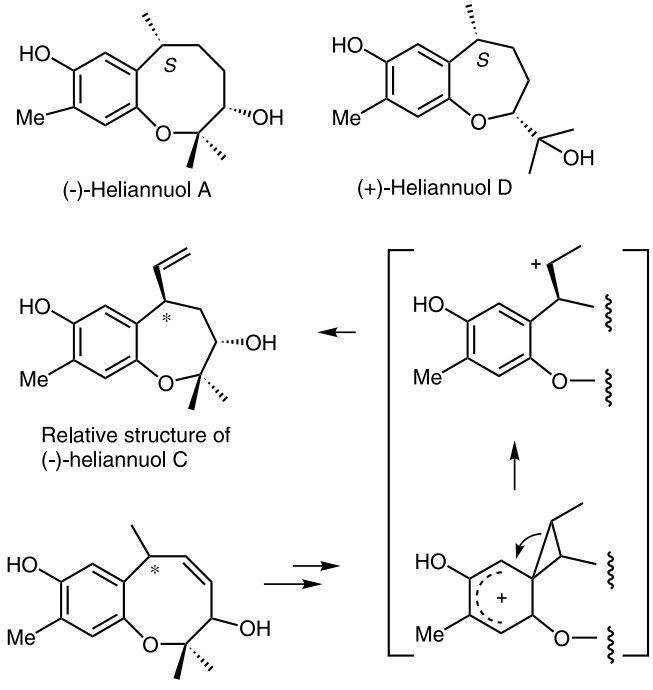


Scheme 2. *Reagents and conditions*: (a) PLE/DMSO–buffer (95%); (b) (*R*)-phenyl ethylamine, BOP, Et_3N (quant.); (c) i. $LiBH_4/Et_2O$–EtOH, ii. CSA/PhH (83% in two steps); (d) i. DIBAL-H/PhMe, ii. *i*$PrPh_3PI$, *n*BuLi/THF (91% in two steps), iii. Ac_2O, pyr. (92%); (e) i. AD-mix-α (quant), ii. H_2, 10% Pd–C, iii. $C_5H_5NHBr_3$ (68%, 4:1 mixture); (f) CCE, 1.35–1.60 V, 2 F/mol, *n*Bu_4NClO_4 (supporting salt), platinum wire (cathode)-glassy carbon beaker (anode) (68%); (g) $BF_3{\cdot}OEt_2/CH_2Cl_2$ (61%); (h) i. H_2, 10% Pd–C, pyr./MeOH (96%), ii. MOMCl, *i*Pr_2NEt/CH_2Cl_2 (83%), iii. NaOMe/MeOH–THF (100%); (i) i. MsCl, pyr. (quant), ii. $NaBH_4$, *o*-$O_2NC_6H_4SeCN$, (iii) H_2O_2/THF (84% in two steps), (iv) 6 M aq. HCl/THF (50%).

acid-treatment to give lactone **5** in good overall yield. After successive DIBAL reduction, the Wittig reaction, and acetylation, the resulted **6** was submitted to asymmetric dihydroxylation by the Sharpless protocol to afford a diastereomeric 4:1 mixture of the corresponding diols. Without separation, the diols were submitted to hydrogenolysis, followed by bromination to afford the bromophenol **7**. The bromine substituent was

expected to control the oxidation potential to provide the desired **8** in good yield.[3] Anodic oxidation under the conditions as described in Scheme 2, produced the desired spiro compound **8** in 68% yield. A six-membered spiro derivative, cyclized with the *tert*-hydroxyl group, was not observed. The Lewis acid-promoted ring-expansion reaction of **8** afforded an inseparable mixture of the chroman-type product **9**. After removal of the bromine substituent, the *tert*-hydroxyl group and the phenol were protected as MOM ethers, followed by solvolysis to give alcohols **10** and **11** as a 3:1 chromatographically separable mixture. Compound **10** carrying the desired aromatic substitution, was manipulated in three steps to produce a vinyl group, which on acid-hydrolysis gave **1** and its epimer **12**. Although the former product showed the same spectroscopic data as those of the reported one, the optical rotation of the synthetic sample ($[\alpha]_D$ +79.7 (*c* 0.1, $CHCl_3$)) exhibited an opposite sign to the natural one ($[\alpha]_D$ −68.6 (*c* 0.1, $CHCl_3$)), although Shishido mentioned that (−)-**1** had the absolute structure as depicted in Scheme 2.[5] We carefully inspected the synthetic process, and confirmed that the following points would support our results. First of all, the stereochemistry of the benzylic position, which was enzymatically separated, was unambiguously confirmed by X-ray single crystallographic analysis of the phenylethylamide derivative **4**. From our extensive studies on phenolic oxidation, there was no serious epimerization at the benzylic positions even if carrying hydroxyl or alkyloxycarbonylamino groups.[9] If epimerization occurred, the optical purity of synthetic **1** would be decreased. However, over 92% ee was observed by HPLC examination using the chiral column.[10] The absolute configuration of heliannuols A and D carrying methyl substituents at the benzylic position have been determined to have *S*-configuration (Scheme 3).[11,12] However, according to the biosynthetic hypothesis of heliannuol C possessing a similar vinyl group to **1**,[2] there might be no need to have the same stereochemistry of its precursors carrying methyl groups: heliannuol C was produced by the ring contraction reaction with loss of the stereochemistry of the benzylic carbon of the precursor. Therefore, we undertook synthesis of (−)-**1** carrying *R*-configuration at the benzylic position, as follows.



Scheme 3. Natural heliannuols and biosynthetic hypothesis of heliannuol C.

The lactone **5** was converted into the corresponding thioacetal **13** (Scheme 4). Compound **13** was converted into TBS ether **14**, which on six-step manipulation gave **15**, an antipode of **6**. After asymmetric dihydroxylation and hydrogenolysis, the resultant phenol was selectively brominated to give the substrate **16** for electrolysis. Anodic oxidation under the same conditions as in the case of **7** provided the spiro derivative **17**, which was treated with $BF_3{\cdot}OEt_2$ to give a mixture of the expected chromans **18** in good yields. The conventional procedure enabled conversion of **18** into the chromatographically separable diols **19**, **20** (9:2). Finally, **19** was subjected to introduction of a vinyl group and deprotection to give (−)-**1** ($[\alpha]_D$ −77.1 (*c* 0.1, $CHCl_3$)) and **21**. The spectroscopic data were superimposable with those of the reported one.[1]

In conclusion, we have accomplished total synthesis of heliannuol E **1** in both optically active forms, by employing our novel ring-expansion reaction of the spiro derivatives **8** and **17**, produced by anodic oxidation of the corresponding phenols. Comparison of their optical rotations revealed that the natural (−)-heliannuol E should have the absolute structure as shown in Scheme 4.

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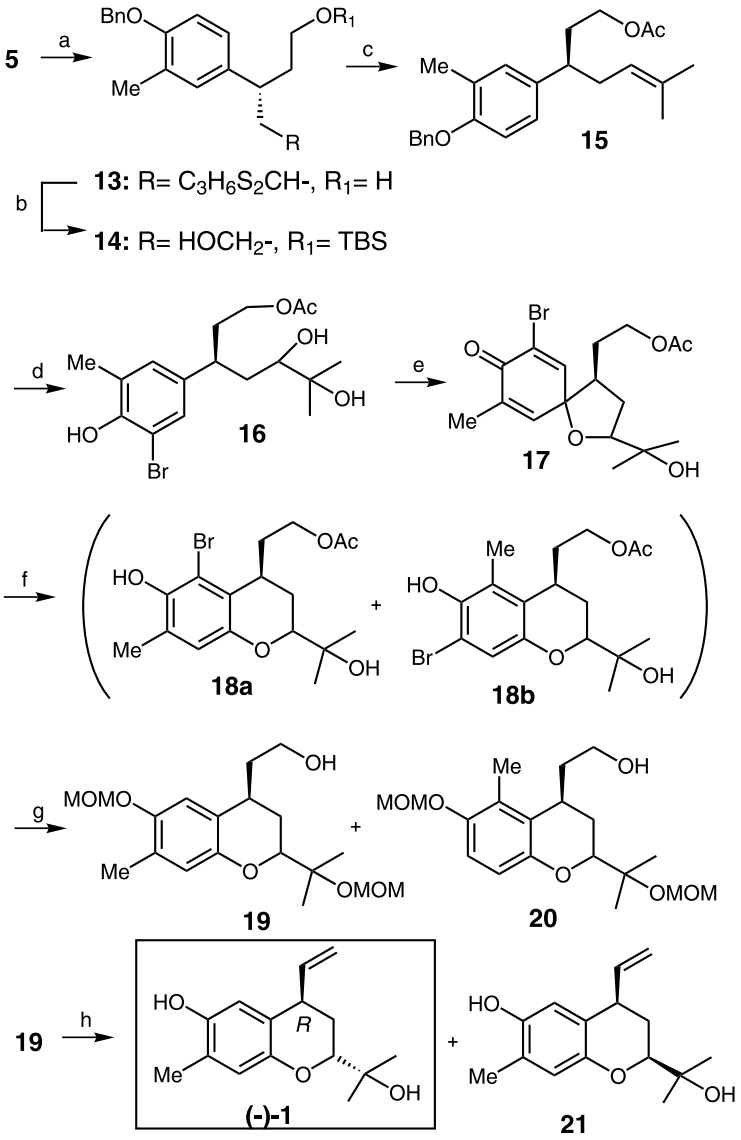

Scheme 4. *Reagents and conditions*: (a) i. DIBAL-H/PhMe, ii. 1,3-propanedithiol, $BF_3{\cdot}OEt_2$ (97% in two steps); (b) i. TBSCl, Imd/DMF (99%), ii. MeI, $NaHCO_3$/aq. MeCN, iii. $NaBH_4$/EtOH (78% in two steps); (c) i. Ac_2O, pyr. (86%), ii. TBAF/THF (98%), iii. $SO_3{\cdot}$pyr., DMSO, Et_3N/CH_2Cl_2, iv. K_2CO_3/MeOH (81% in two steps), v. *i*$PrPh_3PI$, *n*BuLi/THF (91%), vi. Ac_2O, pyr. (96%); (d) i. AD-mix-β (quant), ii. H_2, 10% Pd–C, iii. $C_5H_5NHBr_3$ (89%, 10:1 mixture); (e) CCE (58%); (f) $BF_3{\cdot}OEt_2/CH_2Cl_2$ (78%); (g) i. H_2, 10% Pd–C, pyr./MeOH (96%), ii. MOMCl, *i*Pr_2NEt/CH_2Cl_2 (74%), iii. NaOMe/MeOH–THF (100%); (h) i. MsCl, pyr. (66%), ii. $NaBH_4$, *o*-$O_2NC_6H_4SeCN$/EtOH, iii. H_2O_2/THF (77% in two steps), iv. 3 M aq. HCl/THF (100%).

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