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Stereoselective Synthesis of (–)-Heliannuol E by α-Selective Propargyl Substitution

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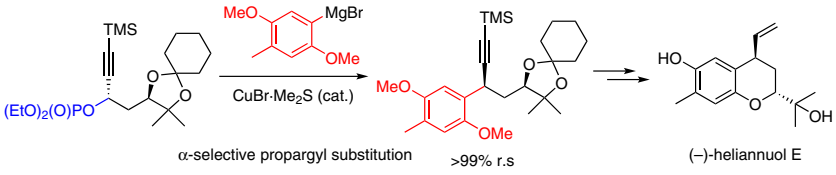

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Abstract This paper describes a stereoselective synthesis of (–)-heliannuol E through intramolecular cyclization of a phenol mesylate. The introduction of the aromatic group was achieved by α-selective propargyl substitution of a propargylic phosphate.

Key words heliannuol E, propargyl substitution, stereoselectivity, asymmetric synthesis, intramolecular cyclization

The common sunflower *Helianthus annuus* is a rich source of sesquiterpenoids such as heliannuols, which show allelopathy to suppress or eliminate competing plant species near native plants.[1,2] To date, 13 types of heliannuol have been isolated. Typically, they have a characteristic bicyclic structure consisting of an aromatic ring fused to a five- to eight-membered ring (Figure 1).[1] In 1999, Macias et al. isolated heliannuol E from an extract of *Helianthus annuus* L. cv. SH-222; this compound contains a fused six-membered ring.[3] Because of its unique structure, syntheses of heliannuol E have been reported by many chemists.[4]

The syntheses of optically active heliannuol E so far reported were carried out through enzyme-mediated optical resolution[4a,c,d] or by asymmetric synthesis with asymmetric auxiliaries[4f] or asymmetric catalysts.[4g–i] Syntheses by optical resolution required separation of the compounds, and the yields were low. In the asymmetric syntheses, the limited range of substrates is disadvantageous for the synthesis of derivatives for structure–activity relationship studies. In addition, the availability of auxiliaries or catalysts is a problem. Recently, we reported a copper-catalyzed α-selective propargyl substitution of the propargylic phosphate **14** with Grignard reagents (Scheme 1).[5] The reaction proceeds with high regio- and stereoselectivity, irrespective of steric and electronic effects of the nucleophile. Optically active propargylic phosphates can be easily synthesized by the reduction of alkynones with a commercially available ruthenium catalyst.[6] Considering these synthetic advantages, we carried out a stereoselective synthesis of heliannuol E (**5**).

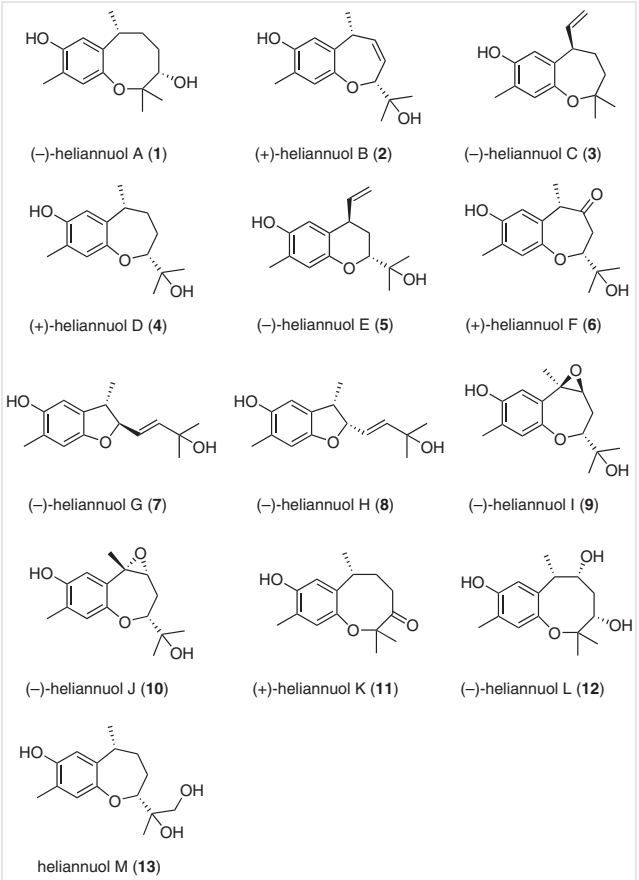

Figure 1 The heliannuol family

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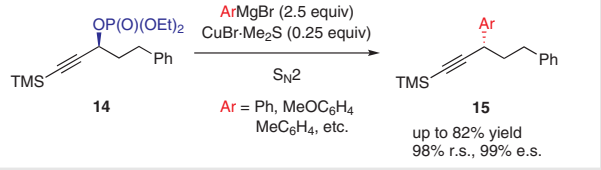
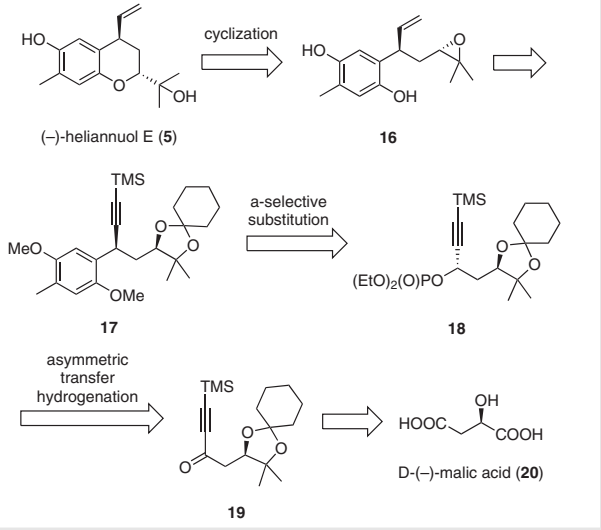


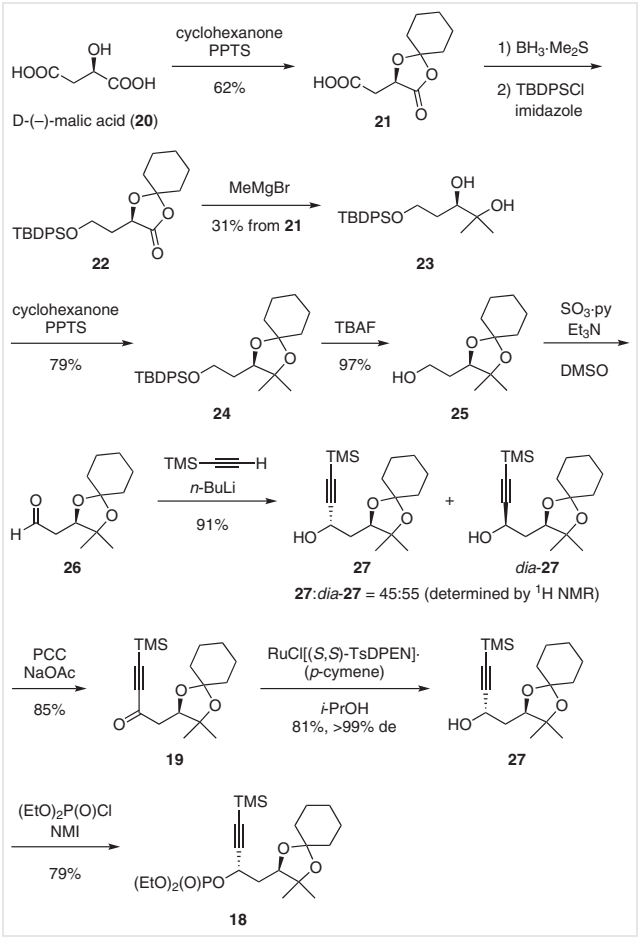
Scheme 1 α-Selective propargyl substitution

Our retrosynthetic analysis is shown in Scheme 2, where alkyne **17** is proposed to form (–)-heliannuol E (**5**) through an epoxidation and subsequent cyclization reaction. We surmised that the aromatic ring in **17** could be introduced through an α-selective propargyl substitution reaction between phosphate **18** and a Grignard reagent in the presence of a copper catalyst. Furthermore, D-malic acid (**20**) was envisaged as a starting compound for the synthesis of phosphate **18** via ketone **19**.



Scheme 2 Retrosynthetic analysis of (–)-heliannuol E (**5**)

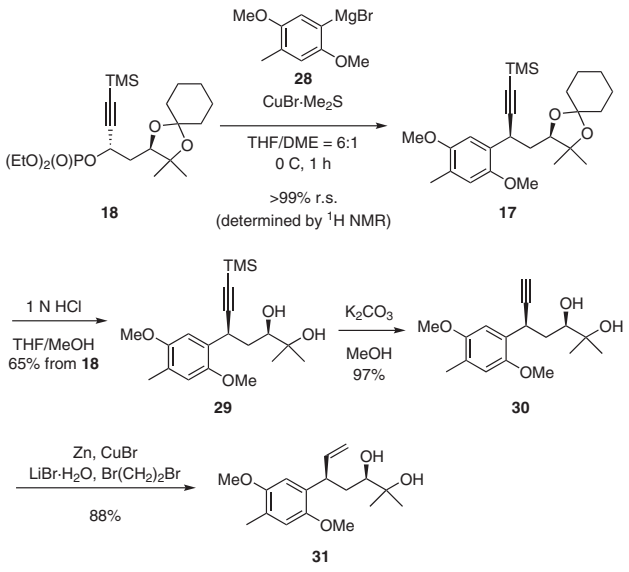
Protection of malic acid (**20**) with cyclohexanone in the presence of PPTS gave carboxylic acid **21** in 62% yield (Scheme 3).[7] After the reduction of **21** with $BH_3{\cdot}SMe_2$, the resulting alcohol was protected with TBDPSCl to give silyl ether **22**. Diol **23** was then obtained through a Grignard reaction with MeMgBr in 31% yield over three steps. Subsequently, **23** was protected with cyclohexanone in the presence of PPTS to give acetal **24** in 79% yield, which was deprotected by using TBAF to furnish alcohol **25** in 97% yield. Parikh–Doering oxidation of **25**, followed by the addition of (trimethylsilyl)ethyne afforded propargylic alcohols **27** and *dia*-**27** in 91% yield.[8] The stereoselectivity was determined by ^{1}H NMR spectroscopy (**27**/*dia*-**27** = 45:55). Oxidation of the mixture with PCC in the presence of NaOAc formed ketone **19**, which was converted into the optically active propargylic alcohol **27**[8] by ruthenium-catalyzed asymmetric transfer hydrogenation[6] in 81% yield and >99% de, as determined by ^{1}H NMR spectroscopy. Finally, the hydroxy group of **27** was protected with diethyl chlorophosphate to give phosphate **18** in 79% yield.



Scheme 3 Synthesis of phosphate **18**

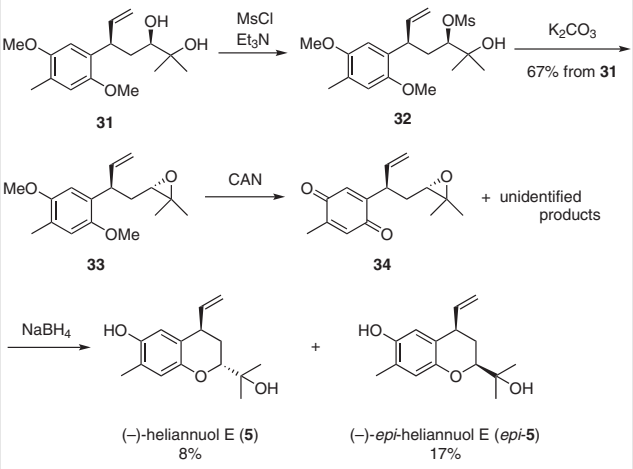
The α-selective propargylic substitution of **18** with Grignard reagent **28** and $CuBr{\cdot}SMe_2$ catalyst produced compound **17**, which was deprotected to give diol **29** in 65% yield (Scheme 4).[5] The regioselectivity of the propargyl substitution was >99%, as determined by ^{1}H NMR spectroscopy (see the Supporting Information).[5] After removal of the TMS group with K_2CO_3/MeOH, the resulting alkyne was reduced by using Zn[9] to form olefin **31** in 88% yield.

The final steps of the synthesis are summarized in Scheme 5. Mesylation of **31**, followed by the addition of K_2CO_3 to **32**, afforded epoxide **33** in 67% yield. Then, **33** was oxidized with CAN to produce quinone **34** as the major product, along with as other unidentified products, which could not be separated from **34** by column chromatography on silica gel. Subsequently, the addition of $NaBH_4$ to the mixture facilitated reduction to the phenol; this was followed by a cyclization reaction, to give (–)-heliannuol E (**5**) and (–)-*epi*-heliannuol E (*epi*-**5**) in yields of 8 and 17%, re-



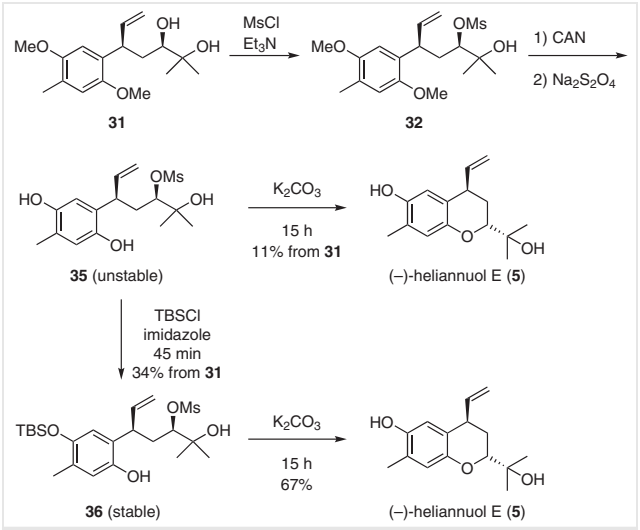
Scheme 4 Synthesis of olefin **31**

spectively. The ^{1}H NMR and ^{13}C NMR spectra of **5** and *epi*-**5** were consistent with those previously reported.[3,4a,b,f,h] No seven-membered-ring product was formed in the cyclization reaction of **34**. We proposed that *epi*-**5** was produced via a cation generated by ring-opening of the epoxide.



Scheme 5 Attempted synthesis of (–)-heliannuol E (**5**) via epoxide **33**

Next, we examined the cyclization of mesylate **35** without the formation of epoxide **33** (Scheme 6). Mesylation of diol **31** followed by oxidation with CAN and subsequent reduction with $Na_2S_2O_4$ resulted in **35**, which was unstable[9] and was therefore immediately used for the next reaction. K_2CO_3 was added, and the mixture was allowed to react for 15 hours to give **5** as the sole product in 11% yield. Because the cyclization was slow, the yield was reduced due to the decomposition of **35** over time. Therefore, the hydroxy group was protected to form the stable silyl ether **36** in 34% yield over four steps.[10,11] Finally, cyclization of **36** in the presence of K_2CO_3 resulted in the formation of **5** as the sole product in 67% yield. In this reaction, the TBS group was removed after the cyclization, as monitored by TLC, and the yield of **5** was thereby improved (23% yield from **31**).



Scheme 6 Synthesis of (–)-heliannuol E (**5**)

In conclusion, we have successfully synthesized (–)-heliannuol E (**5**) through an α-selective propargyl substitution as the key step. Propargylic phosphate **18** was synthesized from D-malic acid (**20**) and subjected to copper-catalyzed α-selective propargyl substitution to produce alkyne **17** efficiently and with high selectivity. In the final steps of the synthesis, cyclization of silyl ether **36** led to the formation of **5** as the sole product. This synthesis was achieved in a total of 20 steps, with a yield of 1.5% from **20**. By using the present method, various heliannuol E derivatives could be synthesized by changing the Grignard reagents.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1719844.

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(11) The reaction of **35** with TBSCl resulted only in production of compound **36**, and the disilyl ether was not formed. The regioisomer was not formed because of steric hindrance.

(12) **(–)-Heliannuol E** (**5**) K_2CO_3 (73.9 mg, 0.535 mmol) was added to an ice-cold solution of olefin **36** (58.3 mg, 0.127 mmol) in MeOH (10 mL). The mixture was stirred at 0 °C for 1 h, then heated and stirred at 45 °C for 15 h. The mixture was then diluted with 3 N aq HCl to pH 5–6 and extracted with Et_2O (×3). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by recycling HPLC [LC-Forte/R equipped with YMC-Pack SIL-60, hexane–EtOAc (4:1), 25 mL/min] to give a colorless oil; yield: 22.7 mg (67%); R_f = 0.33 (hexane–EtOAc, 3:1); $[\alpha]_D^{26}$ –69 (*c* 0.33, $CHCl_3$) [Lit.[3] –68.6 (*c* 0.1, $CHCl_3$)]. IR (neat): 3379, 1635, 1196 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 3 H), 1.30 (s, 3 H), 1.82–1.97 (m, 2 H), 2.20 (s, 3 H), 2.33–2.38 (br s, 1 H), 3.43–3.52 (m, 1 H), 3.74 (dd, *J* = 10.4, 3.6 Hz, 1 H), 4.35 (s, 1 H), 4.91 (dd, *J* = 16.8, 1.6 Hz, 1 H), 5.11 (dd, *J* = 10.4, 1.6 Hz, 1 H), 6.08 (ddd, *J* = 16.8, 10.4, 6.4 Hz, 1 H), 6.49 (s, 1 H), 6.66 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 24.3, 26.0, 27.6, 38.0, 72.1, 77.6, 115.9, 116.0, 118.6, 120.7, 124.2, 142.2, 147.5, 148.3. HRMS (FD): *m/z* $[M]^+$ calcd for $C_{15}H_{20}O_3$: 248.14124; found: 248.14106.