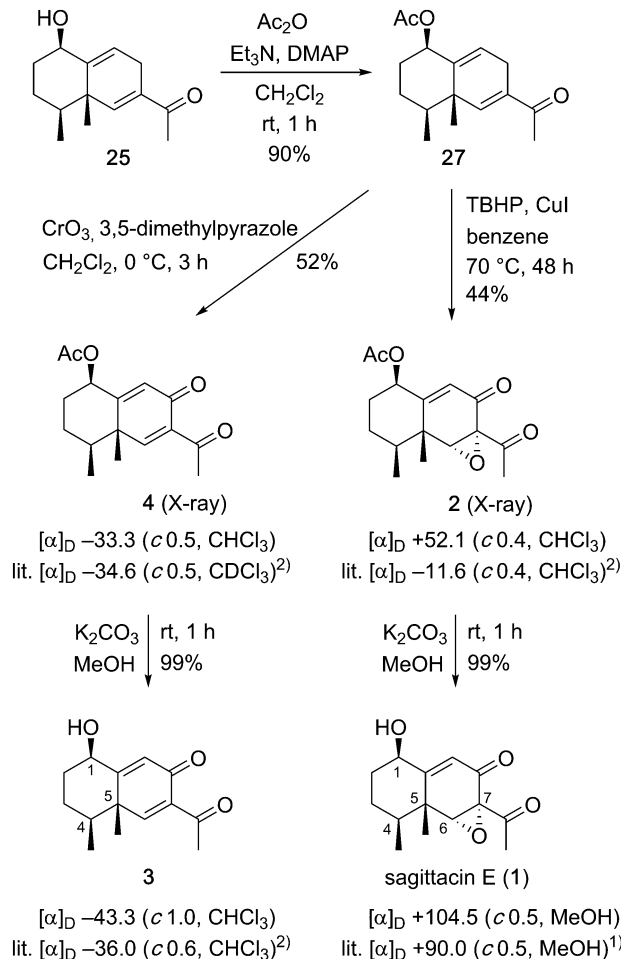


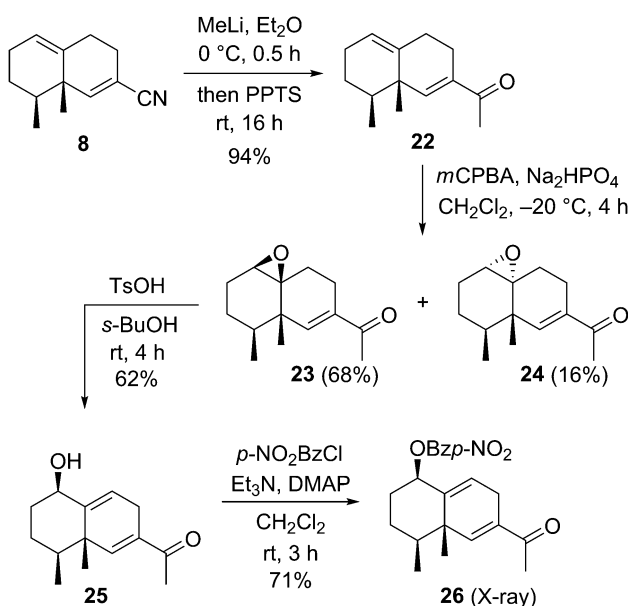
of the α proton of the cyano group with DBU, to afford the α,β -unsaturated nitrile derivative **8** in 96% yield.

After construction of the bicyclic framework, we transformed the nitrile to a methyl ketone group and performed the stereoselective introduction of the allyl alcohol unit on the bicyclic skeleton (Scheme 4). Nucleophilic addition of methyl lithium to the carbon atom of the nitrile group of **8**, followed by treatment with a Brønsted acid, afforded methyl ketone derivative **22** in 94% yield. Stereo- and chemoselective epoxidation of **22** with mCPBA gave the epoxide **23** and its diastereoisomer **24** in 68% and 16% yields, respectively. Many reaction conditions for transformation of the epoxide to the allyl alcohol *via* epoxide ring opening of **23** were attempted. As a result, use of *p*-toluenesulfonic acid as a Brønsted acid and *sec*-butyl alcohol as a solvent afforded the desired allyl alcohol **25** in 62% yield. The stereochemistry of **25** was confirmed by X-ray crystallographic analysis of *p*-nitrobenzoate derivative **26**,¹² prepared from **25** with *p*-nitrobenzoyl chloride and base. This result indicated that the stereoselective epoxidation of **22** occurred at the more electron-rich olefin from the same face as the two methyl groups.

With the desired allyl alcohol in hand, we were on track to achieve our goal for the synthesis of the eremophilane-type target molecules (Scheme 5). After acetylation of **25**, many conditions for allylic oxidation of the resulting **27** were examined. Although manganese acetate-catalyzed,¹³ or palladium-catalyzed¹⁴ allylic oxidations failed, giving a complex mixture or recovered **27**, respectively, allylic oxidation using 3,5-dimethylpyrazole–chromium trioxide complex¹⁵ in dichloromethane at 0 °C afforded the oxidized product **4**¹⁶ in 52% yield. Alternatively, the combination of *tert*-butyl hydroperoxide and copper iodide¹⁷ caused sequential allylic oxidation and stereoselective epoxidation of **27** to give the epoxide **2** in 44% yield. Finally, removal of the acetoxy group of the resulting oxidized products **4** and **2** quantitatively produced the corresponding alcohols **3** and **1**, respectively. Both ¹H and



Scheme 5 Asymmetric synthesis of sagittacin E (**1**) and related natural products.



Scheme 4 Synthesis of the allyl alcohol **25** and its benzoate **26**.

¹³C NMR spectra of the synthetic compounds **1–4** were identical with those of natural sagittacin E (**1**) and related natural products **2–4**.^{1,2} The optical rotation of the synthetic **1** had the same rotation as that reported for the natural product [synthetic **1**: $[\alpha]_{\text{D}} +104.5$ (c 0.5, MeOH); natural product **1**: $[\alpha]_{\text{D}} +90.0$ (c 0.5, MeOH)¹]. Therefore, we determined the absolute configuration of naturally occurring sagittacin E as *1R,4S,5R,6R* and *7S* (natural product numbering). Optical rotations of synthetic alcohol **3** and its acetate **4** also had the same rotations as those reported [synthetic **3**: $[\alpha]_{\text{D}} -43.3$ (c 1.0, CHCl_3); natural product **3**: $[\alpha]_{\text{D}} -36.0$ (c 0.6, CHCl_3)²] and [synthetic **4**: $[\alpha]_{\text{D}} -33.3$ (c 0.5, CHCl_3); natural product **4**: $[\alpha]_{\text{D}} -34.6$ (c 0.5, CDCl_3)²]. The absolute configurations of natural products **3** and **4** were determined as *1R,4S* and *5S*, respectively. However, interestingly, the optical rotation of the synthetic epoxide **2** was different from the reported value of the natural product [synthetic **2**: $[\alpha]_{\text{D}} +52.1$ (c 0.4, CHCl_3); natural product **2**: $[\alpha]_{\text{D}} -11.6$ (c 0.4, CHCl_3)²]. Fortunately, we were able to obtain a single crystal of **2** by recrystallization from hexane. The stereochemistry of **2** was confirmed by the X-ray crystallographic analysis of **2**¹⁸ to be the same configuration as that of sagittacin E (**1**). Since natural product **2** was isolated along with **3** and **4**,² the optical rotation value of our synthetic sample **2** must be the correct value for natural product **2**.

The first enantioselective total synthesis of (+)-sagittacin E and three related natural products was achieved. This synthesis features an asymmetric desymmetrization of a symmetric 1,4-cyclohexadiene derivative having a quaternary carbon by Shi asymmetric epoxidation, intramolecular aldol-type cyclization of a nitrile compound to construct the bicyclic skeleton, allylic oxidation of a 1,4-diene compound, and stereoselective epoxidation.

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Conflicts of interest

There are no conflicts to declare.

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