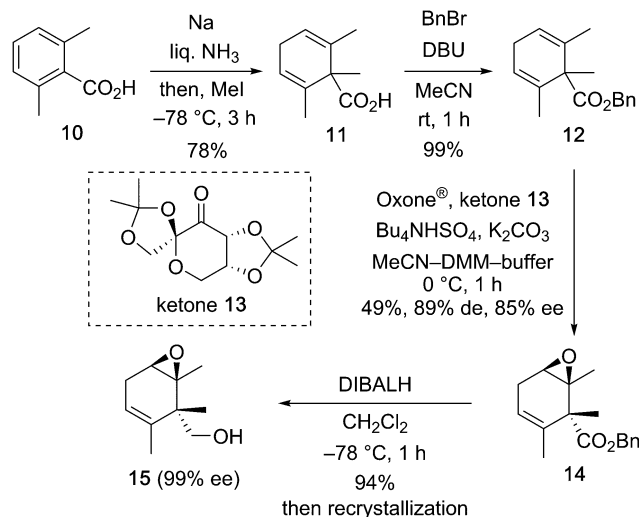


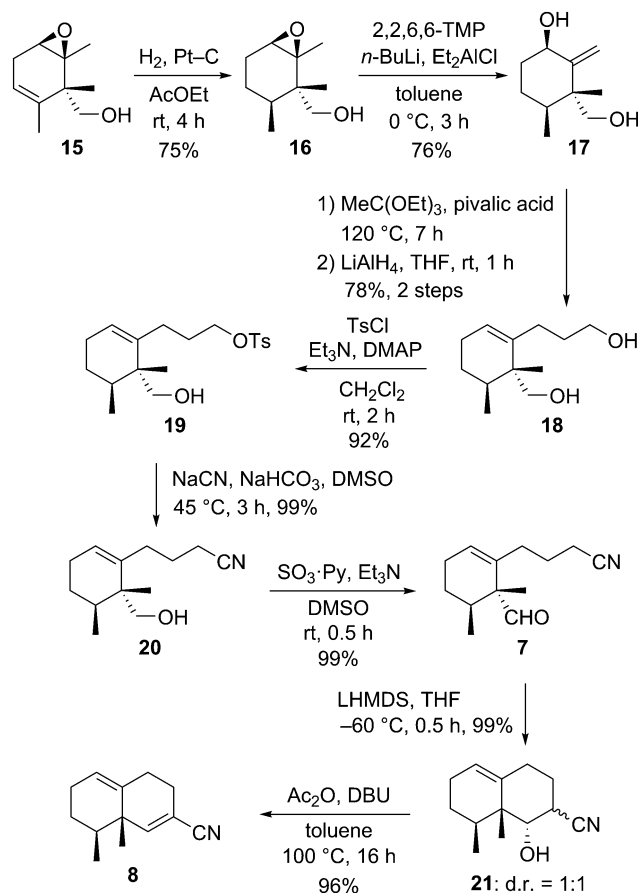
Scheme 1 Synthetic plan for sagittacin E (1) and related compounds.



Scheme 2 Asymmetric desymmetrization of the symmetric 1,4-diene derivative 12.

followed by esterification of the resulting symmetric diene derivative 11 (99% yield). Shi asymmetric epoxidation^{6,7} of 12 with Shi ketone 13 prepared from *D*-fructose, and Oxone[®] as the oxidant afforded the desymmetrized epoxide 14 in 49% yield, 89% de, and 85% ee.⁸ Reduction of the benzyl ester of 14 with DIBALH at -78 °C gave the alcohol 15 in 94% yield as a crystalline compound. After recrystallization, the primary alcohol 15 was obtained in enantiomerically pure form (99% ee).⁹

With the desymmetrization of the symmetric 1,4-diene derivative achieved by Shi asymmetric epoxidation, we focused our efforts on the construction of the eremophilane skeleton (Scheme 3). After many attempts to hydrogenate the double bond without opening the epoxide of 15, the use of platinum on carbon as a heterogeneous catalyst in AcOEt under hydrogen gave the best result to afford hydrogenated compound 16 in



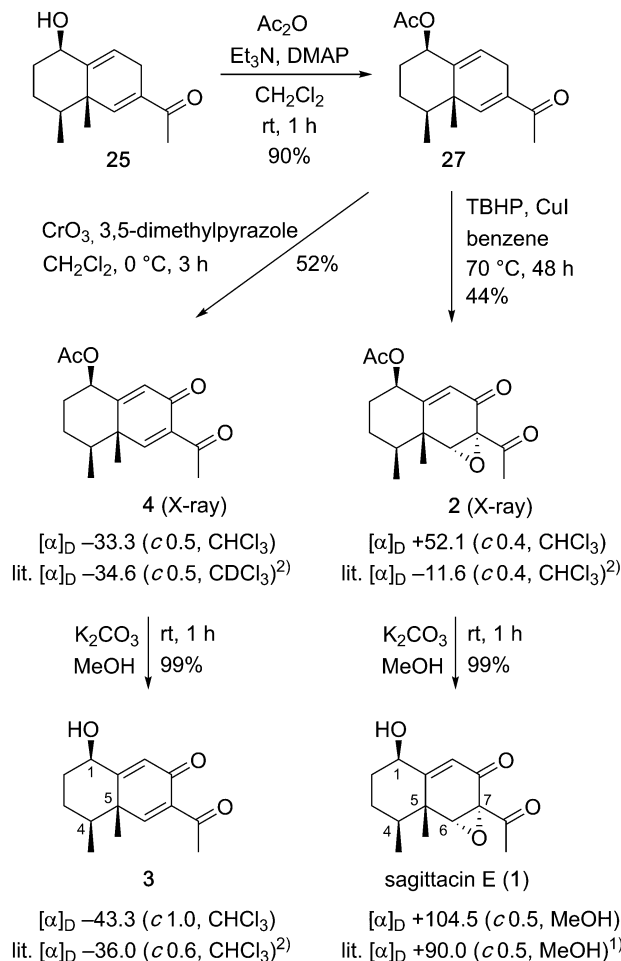
Scheme 3 Synthesis of the nitrile derivative 8.

75% yield. The hydrogenation of 15 with platinum catalyst proceeded from the same side of the primary alcohol, thus the relative configuration of the two vicinal methyl groups was *syn*. Regioselective epoxide ring opening of 16 was achieved with DATMP (diethylaluminum 2,2,6,6-tetramethylpiperidine)¹⁰ developed by Yamamoto as a strong base to produce the *exo*-methylene compound 17 in 76% yield. Extension of the side chain at the C1 position was carried out in two steps: Johnson–Claisen rearrangement of allyl alcohol 17, followed by reduction of the resulting ester compound, to give the diol 18 in 78% yield for 2 steps. Transformation of the primary alcohol of 18 to a cyano group took place as a two-step operation, selective toluenesulfonylation of the sterically less hindered primary alcohol group of diol 18, followed by nucleophilic substitution of the resulting monotosylate 19 with sodium cyanide, to afford the nitrile 20 in 91% yield (2 steps). Parikh–Doering oxidation¹¹ of 20 gave the aldehyde 7, the precursor of the planned aldol-type condensation to construct the bicyclic framework, in high yield. Treatment of 7 with LHMDS in THF at -60 °C furnished the bicyclic compound 21 as a separable mixture in a 1:1 ratio in quantitative yield. These compounds were diastereomers related to the cyano group at the C7 position. Dehydration of 21 was executed in a single operation composed of a two-step reaction, acetylation of the hydroxyl group with acetic anhydride, followed by deacetylation *via* deprotonation

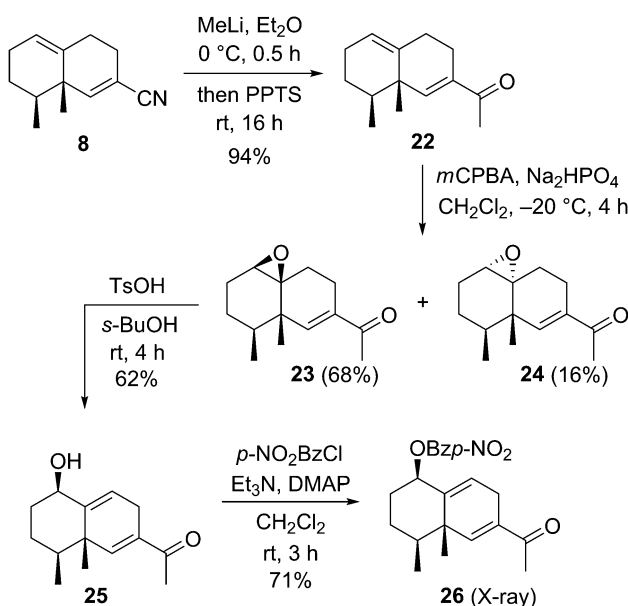
of the α proton of the cyano group with DBU, to afford the α,β -unsaturated nitrile derivative **8** in 96% yield.

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 1*R*,4*S*,5*R*,6*R* and 7*S* (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, CHCl₃); natural product **3**: $[\alpha]_{\text{D}} -36.0$ (*c* 0.6, CHCl₃)²] and [synthetic **4**: $[\alpha]_{\text{D}} -33.3$ (*c* 0.5, CHCl₃); natural product **4**: $[\alpha]_{\text{D}} -34.6$ (*c* 0.5, CDCl₃)²]. The absolute configurations of natural products **3** and **4** were determined as 1*R*,4*S* and 5*S*, 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, CHCl₃); natural product **2**: $[\alpha]_{\text{D}} -11.6$ (*c* 0.4, CHCl₃)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.

This work was supported by the Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Conflicts of interest

There are no conflicts to declare.

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