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Enantioselective total synthesis of sagittacin E and related natural products†

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The first enantioselective total synthesis of eremophilane-type sesquiterpenoids, sagittacin E and related natural products, was achieved. This synthesis features an asymmetric desymmetrization by Shi asymmetric epoxidation, intramolecular aldol-type cyclization, allylic oxidation of a 1,4-diene compound, and stereoselective epoxidation.

The genus *Ligularia* is an important member of the family Compositae, which is a rich source of biologically active natural products. This genus produces mainly eremophilane-type sesquiterpenoids and pyrrolizidine alkaloids as secondary metabolites. Sagittacin E (**1**), isolated from *Ligularia sagitta* by Gao and co-workers in 2014, is a highly oxygenated eremophilane-type sesquiterpenoid that possesses mild cytotoxic activities against three human tumor cell lines, HL-60, SMMC-7721, and HeLa cells, and moderates antibacterial activities against *E. coli* and *E. carotovora* (Fig. 1).[1] Three structurally similar sesquiterpenoids **2–4** were isolated from *Ligularia sagitta*,[1,2] *Ligularia veitchana*,[2] and *Senecio nemorensis*.[3] Although the antibacterial activity of **3** against *E. coli* was reported, biological tests of **2** and **4** have not yet been performed. These four eremophilane-type natural products have very simple bicyclic skeletons, but highly oxygenated frameworks. Consequently, there are few total syntheses or synthetic studies on them to date. Very recently, Liu reported the efficient total synthesis of five eremophilane-type natural products in racemic form, including **3** and **4**, by using Robinson annulation and Suzuki coupling.[4]

We previously reported an asymmetric synthetic study of briarane-type diterpenoid pachyclavulide B using asymmetric epoxidation.[5] Our synthetic strategy featured desymmetrization of symmetric 1,4-cyclohexadiene derivatives by Shi asymmetric epoxidation. This desymmetrization technique is useful for the asymmetric total syntheses of natural products. Thus, we planned the asymmetric total synthesis of highly oxygenated eremophilane-type natural product sagittacin E and related compounds based on our developed desymmetrization reaction.

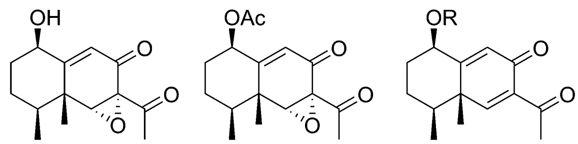

Fig. 1 Structures of sagittacin E (**1**) and related natural products **2–4**.

Herein, we describe the enantioselective total synthesis of eremophilane-type sesquiterpenoids, sagittacin E and structurally similar natural products, based on our asymmetric desymmetrization strategy.

Our synthetic strategy for the target natural products is outlined in Scheme 1. Sagittacin E (**1**) would easily be obtained by deacetylation of **2**. Likewise, **3** would be obtained by deacetylation of **4**. The acetyl sagittacin E (**2**) would be synthesized from the bicyclic diene **9** *via* allylic oxidation and stereoselective epoxidation. On the other hand, natural compound **4** would be derived from **9** only by allylic oxidation. The common intermediate **9** would be constructed by intramolecular aldol type condensation of nitrile **7** with a tethered aldehyde, followed by transformation of the nitrile group of the resulting bicyclic compound **8** to a methyl ketone. The precursor **7** would be synthesized in a multi-step operation from the optically active epoxide **6**, which would be obtained by asymmetric desymmetrization of 1,1,2,6-tetrasubstituted cyclohexadiene **5**.

Our synthetic project started with the construction of an asymmetric carbon *via* asymmetric desymmetrization with the Shi epoxidation protocol as shown in Scheme 2. Symmetric 1,4-diene derivative **12** having a quaternary carbon atom was synthesized from 2,6-dimethylbenzoic acid in a two-step procedure, *i.e.*, reductive methylation of **10** under Birch reduction conditions (78% yield),

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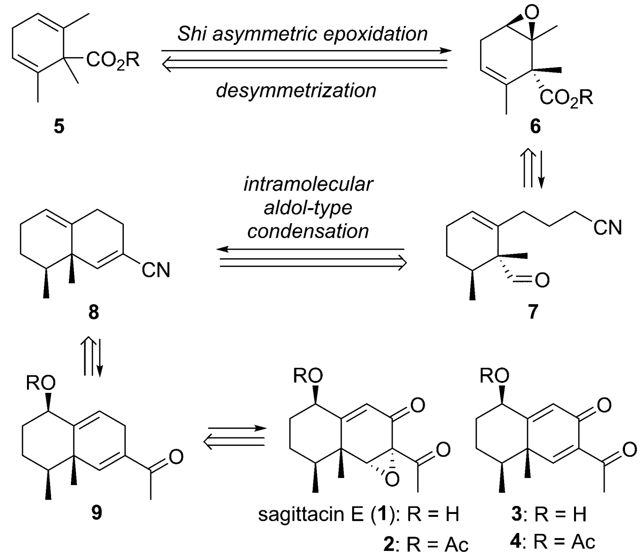
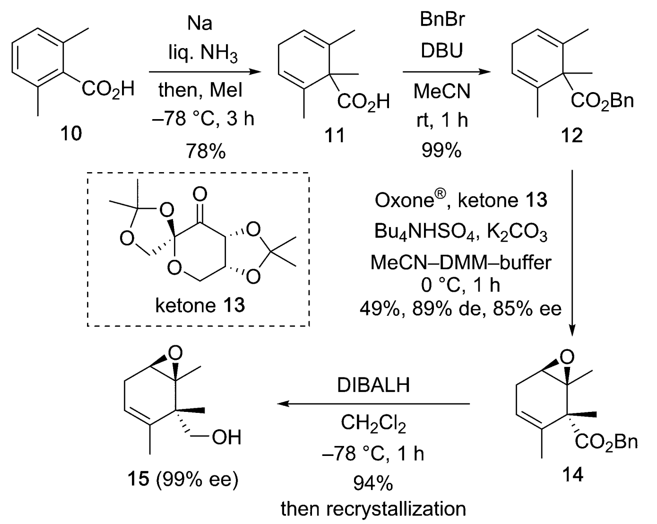


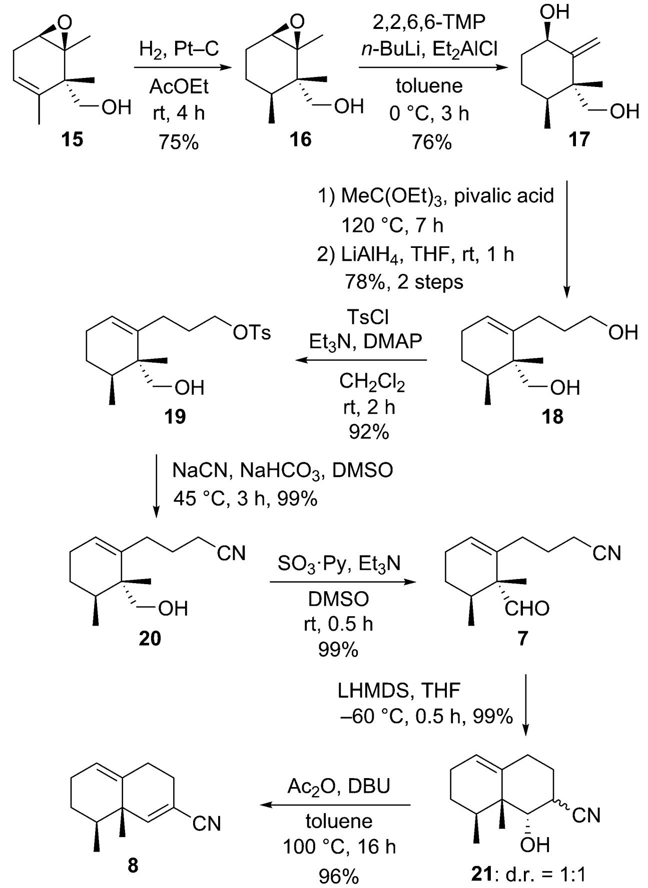
Scheme 1 Synthetic plan for sagittacin E (**1**) and related compounds.



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

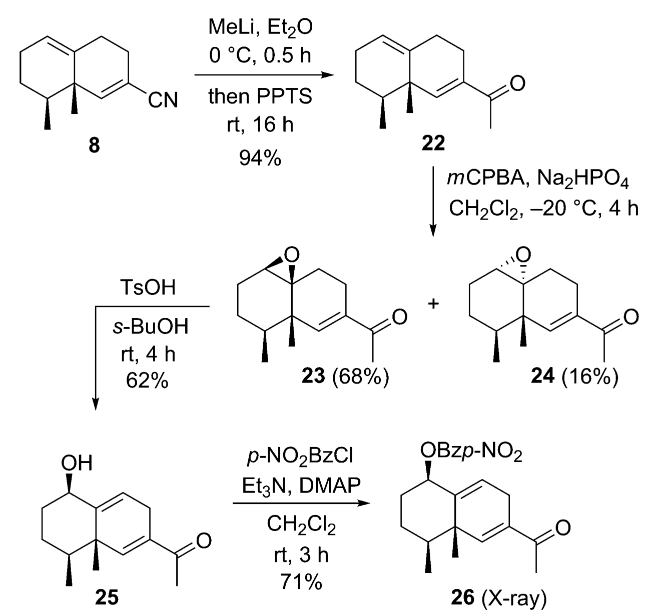


Scheme 3 Synthesis of the nitrile derivative **8**.

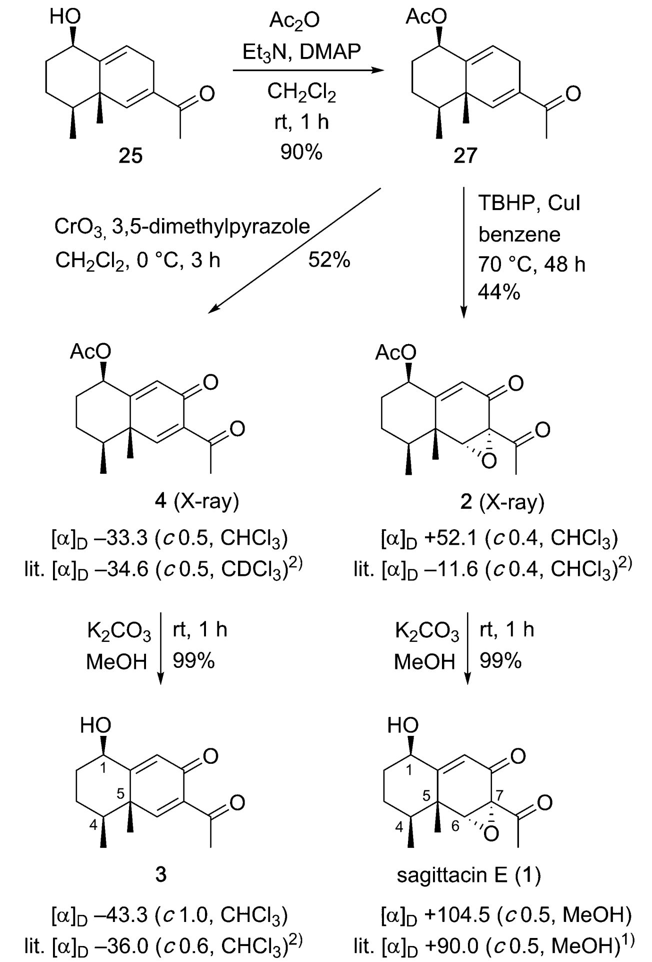
75% yield. The hydrogenation of **15** with platinum catalyst proceeded from the same side of the primary alcohol, thus the relative configuration of the two vicinal methyl groups was *syn*. Regioselective epoxide ring opening of **16** was achieved with DATMP (diethylaluminum 2,2,6,6-tetramethylpiperidine)[10] 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 monotoluenesulfonate **19** with sodium cyanide, to afford the nitrile **20** in 91% yield (2 steps). Parikh–Doering oxidation[11] 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 deacetoxylation *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-catalyzed[14] allylic oxidations failed, giving a complex mixture or recovered **27**, respectively, allylic oxidation using 3,5-dimethylpyrazole–chromium trioxide complex[15] in dichloromethane at 0 °C afforded the oxidized product **4**[16] in 52% yield. Alternatively, the combination of *tert*-butyl hydroperoxide and copper iodide[17] 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 ^{1}H and



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



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

^{13}C NMR spectra of the synthetic compounds **1–4** were identical with those of natural sagittasin 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**: $[\alpha]_D$ +104.5 (*c* 0.5, MeOH); natural product **1**: $[\alpha]_D$ +90.0 (*c* 0.5, MeOH)[1]]. Therefore, we determined the absolute configuration of naturally occurring sagittasin 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**: $[\alpha]_D$ −43.3(*c* 1.0, CHCl$_3$); natural product **3**: $[\alpha]_D$ −36.0 (*c* 0.6, CHCl$_3$)[2]] and [synthetic **4**: $[\alpha]_D$ −33.3 (*c* 0.5, CHCl$_3$); natural product **4**: $[\alpha]_D$ −34.6 (*c* 0.5, CDCl$_3$)[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**: $[\alpha]_D$ +52.1 (*c* 0.4, CHCl$_3$); natural product **2**: $[\alpha]_D$ −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 sagittasin 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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