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Chemoenzymatic total synthesis of stagonolide-E

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ABSTRACT

Asymmetric total synthesis of small ring macrolide stagonolide-E has been described in this communication. The main highlight of our synthetic strategy is the application of ME-DKR (metal enzyme combo dynamic kinetic resolution) reaction, asymmetric reduction with Noyori's BINAL-H reagent system, stereoselective cross metathesis, and RCM (ring closing metathesis) reaction at a late stage enables us to achieve the synthesis of the target molecule in an efficient way.

Naturally occurring 10-membered ring lactones from fungal metabolites present a wide variety of bioactive substances.[1] Macrolides, particularly lactones with medium-sized rings (8–10 membered), have continued to attract the attention of both biologists and chemists during current years, due to the interesting biological properties and scarce availability of macrolides.[2] *Stagonospora cirsii*, a fungal pathogen isolated from *Cirsium arvense* and proposed as a potential mycoherbicide of this perennial noxious weed, produces phytotoxic metabolites in liquid and solid cultures.[3] Recently, the main metabolite, stagonolide, with interesting phytotoxic properties, was isolated from a liquid culture and characterized as a new nonenolide. Five new nonenolides, named stagonolides B–F, were isolated and characterized using spectroscopic methods.[3] A further four nonenolides were isolated and characterized by spectroscopy. Three were new compounds and named stagonolides G–I, and the fourth was identified as modiolide A, pre-

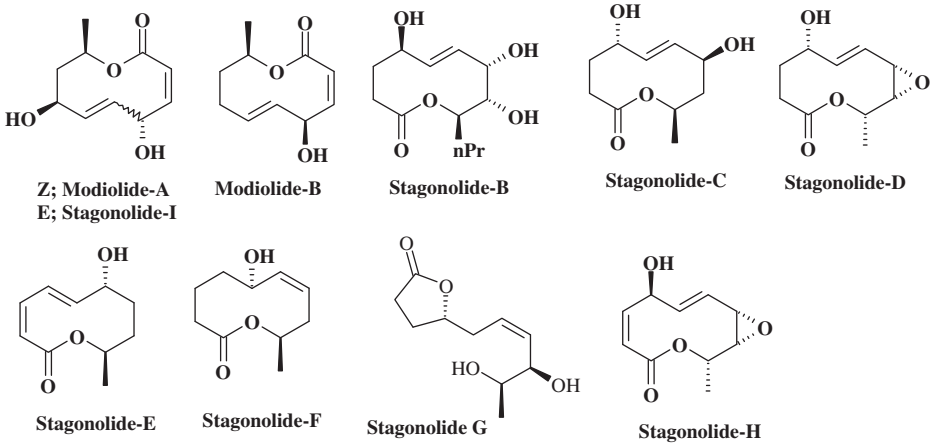

Figure 1. Naturally occurring stagonolides.

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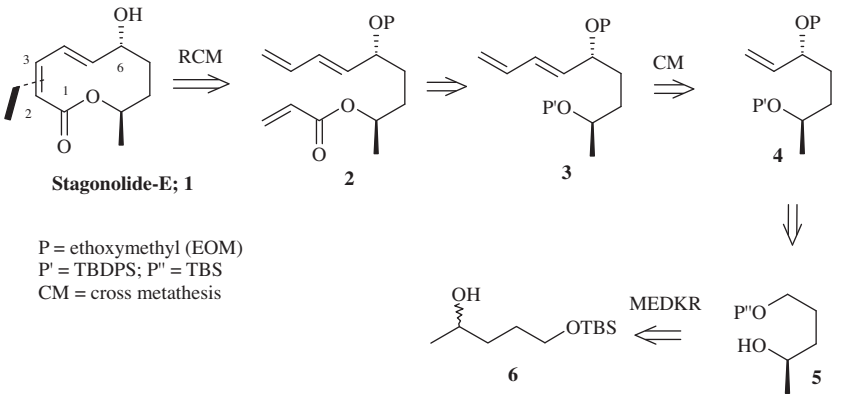
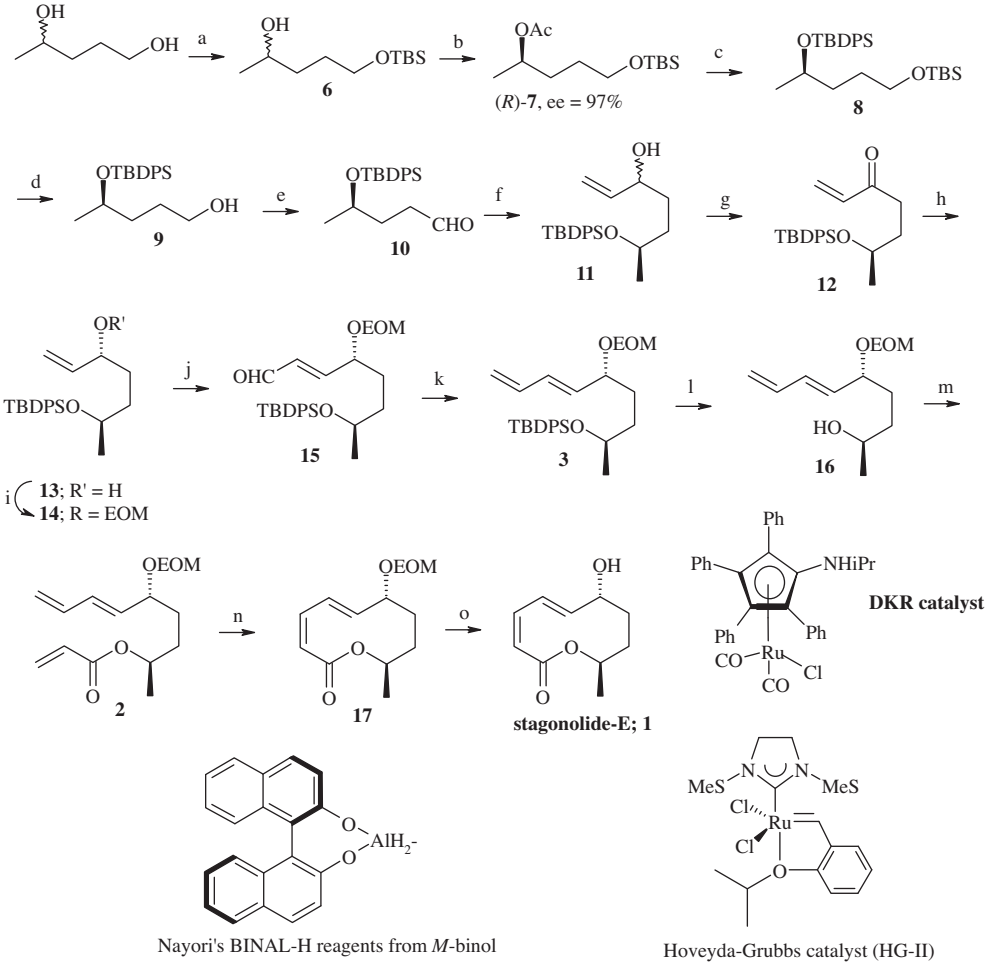


Scheme 1. Retrosynthetic analysis of stagonolide-E.



Scheme 2. Asymmetric synthesis of stagonolide-E. Reagents and conditions: (a) NaH, TBS-Cl, rt, 6 h, 92%; (b) CAL-B, isopropenylacetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium(II), K_2CO_3, KOtBu, 88%; (c) K_2CO_3, MeOH, 1 h; imidazole, TBDPS-Cl, 86%; (d) PPTS, MeOH, rt, 6 h, 85%; (e) DMP, DCM, rt, 2 h, 91%; (f) CH_2=CHMgBr, THF, −78 °C, 82%; (g) $(COCl)_2$, DMSO, Et_3N, −78 °C, 90%; (h) *M*-(+)-binapthol, $LiAlH_4$, −100 °C, 3 h, then add 12, −78 °C, 6 h, 85%; (i) EOM-Cl, DIPEA, rt, 12 h, 87%; (j) HG-II, acrolein, reflux, DCM, 6 h, 92%; (k) LHMDS, PH_3P^+MeI, 0 °C, 1 h, 80%; (l) TBAF, THF, rt, 3 h, 84%; (m) CH_2=CHCOCl, DIPEA, 6 h, rt, 80%; (n) G-II, DCM, reflux, 6 h, 62%; (o) 2.0 M HCl, THF, rt, 6 h, 88%.

viously isolated from *Paraphaeosphaeria* sp., a fungus separated from the horse mussel (Fig. 1).[4] In our continuous effort for the synthetic studies toward the small ring macrolides, we have already reported the total synthesis of stagonolide C,[5] stagonolide D & G,[6] chloriolide,[7] and achaetolide.[8] The main highlight of our previous synthetic strategy is chemoenzymatic kinetic resolution coupled with Mitsunobu inversion and chemoenzymatic dynamic kinetic resolution to access some valuable chiral secondary alcohol intermediates. These intermediates are then employed successively to gain access of more advanced intermediates, which has close resemblance of the target molecule. In the final step of the synthesis we often apply RCM reaction by Grubbs catalyst as well

as Yamaguchhi macrolactonization protocol. The success of our synthetic strategy depends on the optimization of Grubbs RCM method and Yamaguchhi macrolactonization protocol.

In this letter we wish to report a short and efficient asymmetric synthesis of stagonolide-E by chemoenzymatic approach. The first stereoselective synthesis of the parent molecule has been reported by Sabitha et al.,[9] which involves Yamaguchi macrolactonization at the penultimate stage.

The retrosynthetic scheme for the target molecule is depicted in Scheme 1. We envisioned that the C2–C3 bond can be connected through RCM reaction of a properly substituted olefinic species **2**, which can be accessed from a conjugated olefinic compound **3**. Cross metathesis could be serving as a good option for the synthesis of conjugated olefinic species from precursor **4**. Compound **4** can be easily accessed from racemic **6** by adopting ME-DKR reaction and asymmetric reduction of carbonyl functionality by Noyori's BINAL-H reagent.

We have started our synthetic journey from the known pentane 1,4-diol. Monosilylation with TBS-Cl by McDougal's protocol[10] afforded the monosilylated compound **6** in a 92% yield. Metal-enzyme combined DKR[11] of compound **6** with CAL-B (*Candida antartica* lipase) and Ru-based racemization catalyst (DKR catalyst) in the presence of isopropenyl acetate afforded acetate **7** in an 88% yield (ee = 97%; determined by chiral HPLC of the corresponding benzoate derivative; Chiralcel OJ-H). Deprotection of the acetate functionality with K_2CO_3–MeOH afforded (*R*)-**6**, which was subsequently protected as its TBDPS ether by treatment with imidazole and TBDPS-Cl to afford compound **8** in an 86% yield (in two steps). Selective deprotection of TBS group in **8** was achieved by treatment with PPTS in methanol yielded alcohol **9** (85% yield). Oxidation of compound **9** with DMP furnished the aldehyde **10** in a 91% yield. Vinylmagnesium bromide addition of aldehyde **10** at −78 °C afforded alcohol **11** as inseparable diastereomeric mixtures in an 82% yield. Oxidation of the alcohol functionality under Swern condition[12] afforded the ketone **12** in a 90% yield. Asymmetric ketone reduction with Noyori's BINAL-H reagent[13] (*M*-binapthol and $LiAlH_4$, attack from the *Si* face of the ketone occurs) afforded alcohol **13** in an 85% yield, which on protection with EOM-Cl (ethoxy methyl chloride)[14] and DIPEA (diisopropyl ethyl amine) afforded compound **14** in an 87% yield. Compound **14** on cross metathesis (CM) with acrolein in the presence of Hoveyda–Grubbs metathesis catalyst[15] (HG-II, 5 mol %) afforded the unsaturated aldehyde **15** in a 92% yield (exclusively *E* isomer). Wittig olefination of **15** with methyltriphenylphosphonium iodide in the presence of LHMDS afforded conjugated olefin **3** in an 80% yield. Deprotection of TBDPS group in compound **3** is achieved by TBAF to afford compound **16** in an 84% yield. Compound **16** on treatment with acryloyl chloride in the presence of DIPEA afforded the RCM precursor acrylic ester **2** in an 80% yield. Ring closing metathesis reaction of compound **2** with G-II catalyst[16] in refluxing DCM afforded compound **17** as a major product in a 62% yield. Finally deprotection of EOM group is achieved with 2 M HCl in THF to afford stagonolide-E (**1**, yield = 88%; overall yield = 9.9% from 1,4-pentanediol; Scheme 2). The spectral data (^1H and ^{13}C NMR value) of our synthesized stagonolide-E matches perfectly with the natural stagonolide-E.

In conclusion an efficient asymmetric synthesis of the target molecule stagonolide-E has been accomplished in a linear way. The main highlights of our synthetic strategy involves application ME-DKR reaction, stereoselective reduction of carbonyl functionality with Noyori's BINAL-H reagent system, cross metathesis reaction with Hoveyda–Grubbs catalyst and finally RCM reaction with Grubbs second generation catalyst afforded the target molecule (overall yield = 9.9%).

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.059.

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