

Asymmetric Synthesis of Stagonolide-D and Stagonolide-G

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First asymmetric synthesis of the naturally occurring epoxy noneolide stagonolide-D has been reported in this article. Ring-closing metathesis (RCM) by Grubbs second generation catalyst, Sharpless asymmetric epoxidation (SAE), and *cis*-selective Horner–Wadsworth–Emmons (HWE) olefination by Ando method are the key reactions successfully employed to achieve the target molecule in a divergent approach. Structurally related small ring macrolide stagonolide-G has also been synthesized by employing RCM and a metal–enzyme combined dynamic kinetic resolution (DKR) strategy starting from (*S*)-ethyl lactate as a chiral pool.

Stagonospora cirsii, a pathogenic fungus isolated from *Cirsium arvense* (commonly called Canada thistle) and proposed as a potential mycoherbicide of this perennial noxious weed, it also produces phytotoxic secondary metabolites both in liquid and solid cultures. Stagonolide, being the main phytotoxic metabolite is a noneolide, and five new stagonolides B–F, were isolated from the fungus.[1] In the same year three more related stagonolides, named stagonolide G–I were also isolated from the same fungal pathogen.[2] *Cirsium arvense* is a tall herbaceous perennial plant growing 30–100 cm in length, forming extensive clonal colonies from an underground root system. The species is widely considered a weed even where it is native, for example being designated an "injurious weed" in the United Kingdom. In Canada, *Cirsium arvense* is classified as a primary noxious weed seed. In a preliminary study, it was found that *S. cirsii*, the fungus is capable of producing phytotoxins because culture filtrates have demonstrated phytotoxicity to the leaves and roots of *C. arvense*. Recently, with the purpose of finding new natural potential herbicides, the main phytotoxic metabolite produced by *S. cirsii* in liquid culture, named stagonolides, was isolated and characterized as a new noneolide.

Close structural inspection on stagonolides B–I reveals that one of the compound e.g., stagonolide-D is unique among others. As stagonolide-D possess stereochemically pure epoxy appendages at C_7 and C_8. And this kind of epoxy noneolides has not been synthesized yet. In this article we wish to report the first asymmetric synthesis of such an epoxy noneolide, stagonolide-D in a divergent approach. Retrosynthetic analysis of stagonolide-D reveals that RCM (ring-closing metathesis) reaction is a good option to make the C_5–C_6 internal double bond in the noneolide. The RCM precursor **1** was thought to be constructed by esterification reaction between carboxylic acid **2** and epoxy alcohol **3**. The hydroxy stereocenter in the carboxylic acid **2** (C_4 in stagonolide-D) was thought to be constructed by a metal–enzyme combined DKR reaction, whereas the stereochemically pure epoxy alcohol **3** that constitutes the epoxide appendage at C_7–C_8 in the target molecule is constructed by Sharpless asymmetric epoxidation from the required *Z*-allylic alcohol **4**. The *Z*-allylic alcohol **4** in turn can be easily accessed from (*S*)-ethyl lactate by adopting a *cis*-selective HWE olefination strategy (Scheme 1). The retrosynthesis of stagonolide-G was similar to that of stagonolide-D. The internal double bond between C_6–C_7 is thought to be constructed by RCM reaction. The RCM precursor **5** can be accessed by esterification reaction between the carboxylic acid **6** and alcohol **7**. The hydroxy stereocenter in the carboxylic acid **6** (C_4 in stagonolide-G) was planned to be created by metal–enzyme combined DKR reaction. The alcohol **7** that constitutes other two stereocenters in stagonolide-G (C_8 and C_9) was derived from (*S*)-ethyl lactate.

During the course of our study, the first asymmetric synthesis of stagonolide-G was recently reported by Srihari et al.[3,4] A revised structure of stagonolide-G was then reported by Angulo-Pachón et al.[5] The revised structure of stagonolide-G containing a γ-lactone moiety is anticipated to originate from the originally proposed 10-membered ring lactone by a spontaneous intramolecular *trans*-lactonization reaction as shown in Scheme 1.

Results and Discussion

Synthesis of Stagonolide-D. The synthesis started with natural (*S*)-ethyl lactate, which was protected as its PMB (*para*-methoxybenzyl) ether **9** by PMB-trichloroacetimidate.[6] Reduction of compound **9** with DIBAL-H (diisobutylaluminium hydride) in DCM (dichloromethane) at $-78\,^{\circ}C$ afforded the corresponding aldehyde **10** in 90% yield. *cis*-Selective HWE olefination by using Ando method[7] afforded the ester **11** in 88% yield ($Z{:}E = 15{:}1$). Reduction of compound **11** with DIBAL-H (2 equiv) produced the corresponding *Z*-allylic alcohol **4** in 87% yield. Sharpless asymmetric epoxidation[8] on compound **4** under standard condition yielded the epoxy alcohol **12** in 92%. Epoxy alcohol **12** is then oxidized to the corresponding aldehyde with DMP (Dess–Martin periodinane),[9] and the crude aldehyde was then subjected to one carbon extension with Wittig ylide (generated from methyl triphenylphosphonium iodide)[10] to afford the epoxy olefin **13** in 78% yield (in two steps). Deprotection of the PMB group in compound **13** was achieved by treatment of DDQ to yield the alcohol **3**. The crude alcohol **3** was esterified with carboxylic

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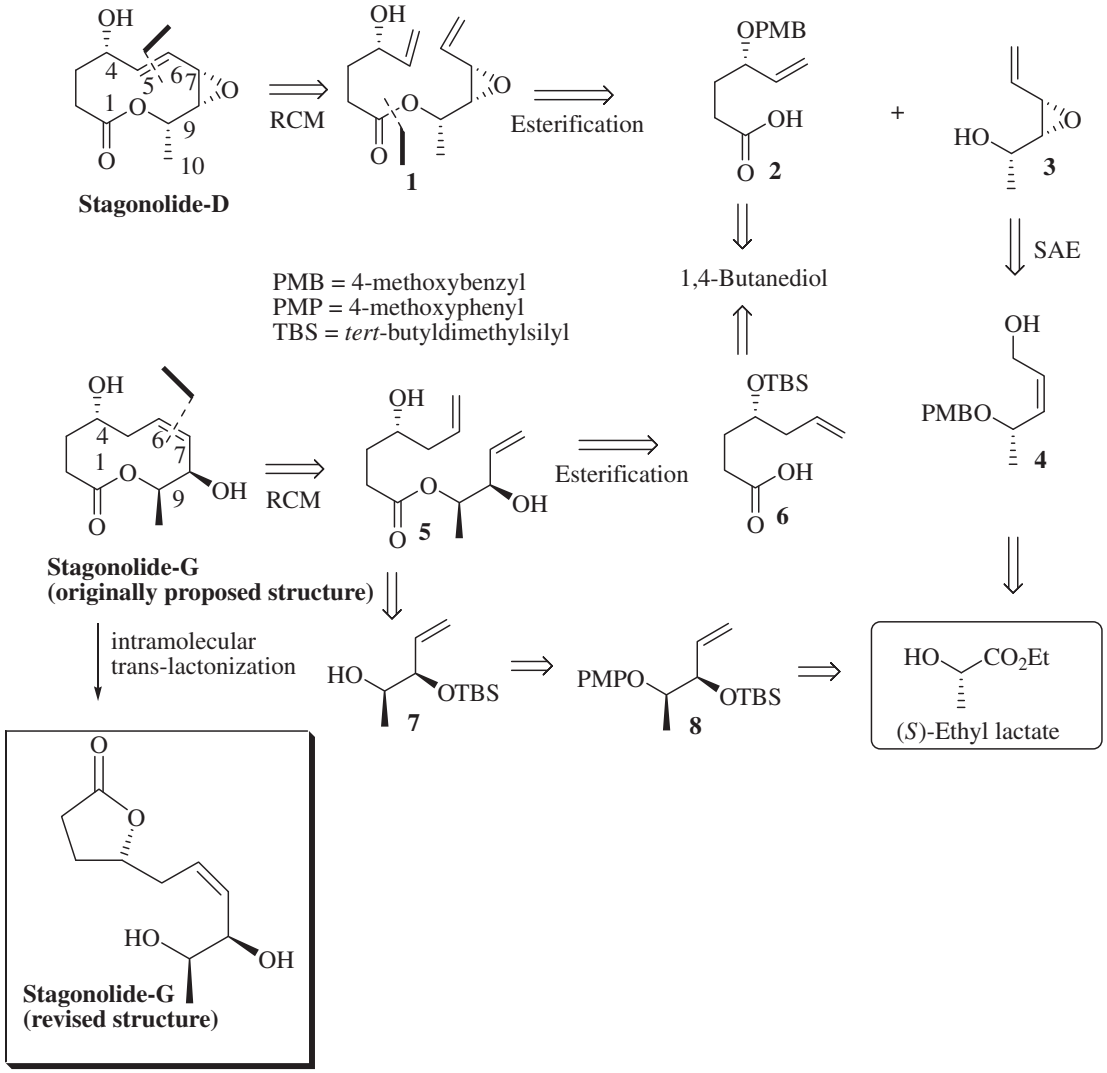
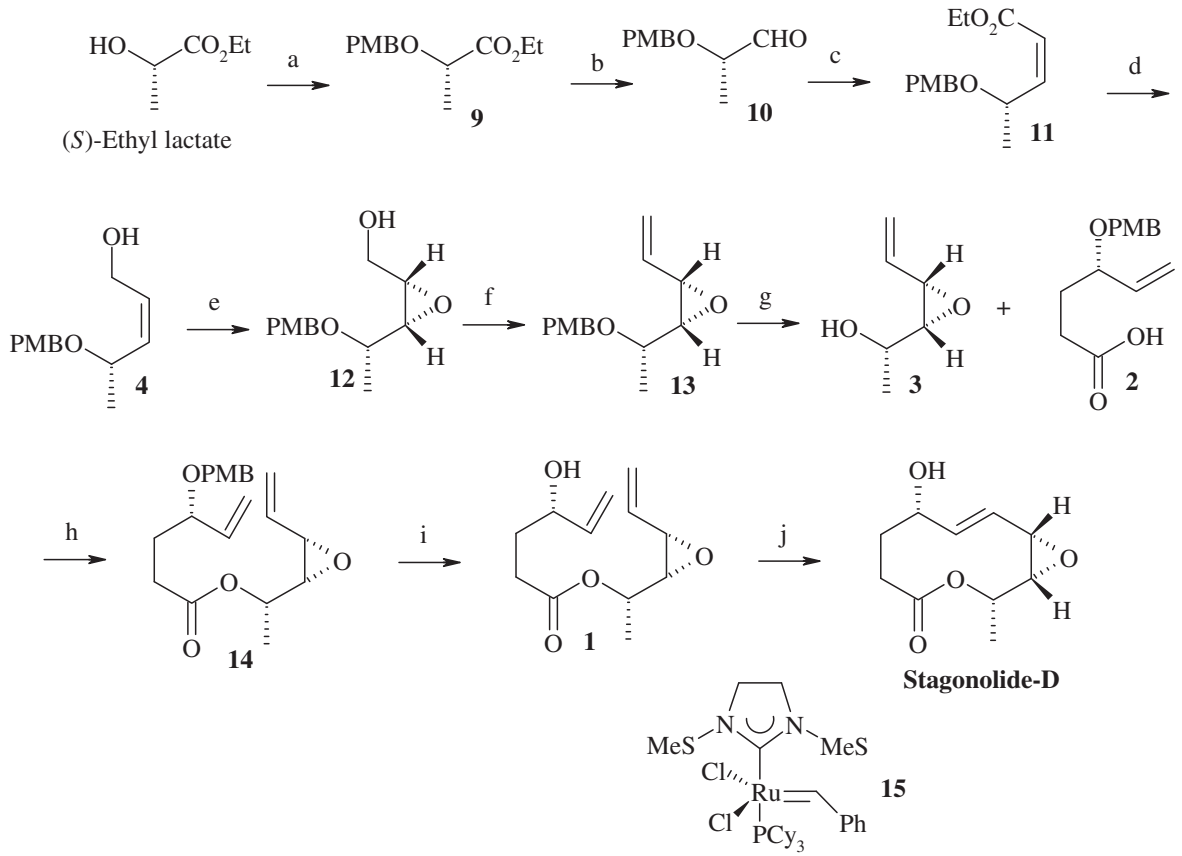


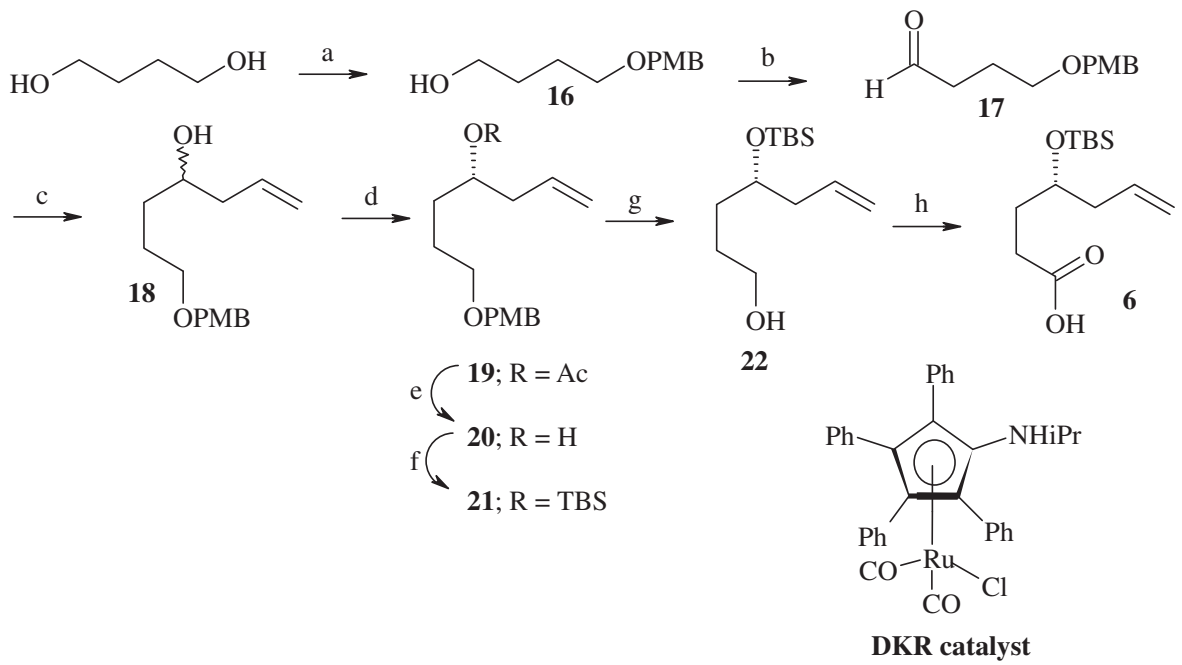
Scheme 1. Retrosynthetic analysis of stagonolide-D and stagonolide-G.

acid **2**, which was synthesized earlier in our laboratory by applying metal–enzyme combined DKR as a key step.[11] The ester **14** thus obtained was then subjected to RCM reaction with Grubbs first generation or second generation carbene complex. No ring-closing product was, however, obtained.[12] We envisioned that the presence of PMB group at C-4 position might cause some steric crowding and hence the two terminal vinyl groups cannot reach in close proximity to inhibit an efficient complexation with the metal catalyst, which is a prerequisite in RCM reaction. Hence the PMB group in compound **14** was deprotected by standard method[13] to afford the compound **1** in 80% yield. When compound **1** was subjected to RCM reaction with Grubbs second generation carbene complex **15** in benzene as solvent, the ring-closing product (stagonolide-D) was obtained in 60% yield (overall yield 17% from (*S*)-ethyl lactate) as a single *E*-isomer.[14] The *E*-geometry between C_5 and C_6 was confirmed by the ^{1}H NMR analysis ($J_{H_5,H_6} = 16.8$ Hz) of the final product. The similar precedence was observed by Fürstner et al., for the synthesis of amphidinolides.[14] The spectral characteristic values of our synthesized stagonolide-D and natural stagonolide-D are in perfect agreement (Scheme 2).

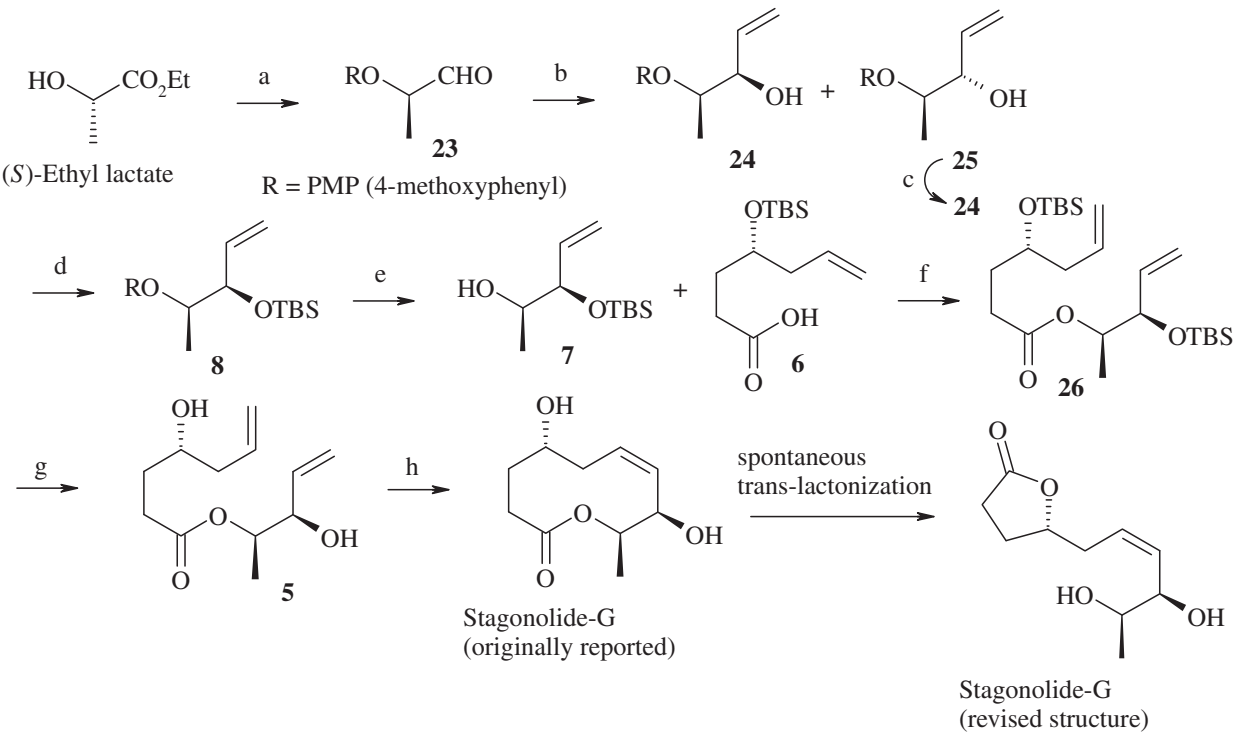
Synthesis of Stagonolide-G. At this onset we have decided to carry out the synthesis for the originally proposed structure of stagonolide-G by adopting the retrosynthetic strategy as outlined in Scheme 1. For the synthesis of the required acid fragment we have started from 1,4-butanediol. Selective monoprotection (as its PMB ether, **16**) and oxidation under Swern condition afforded the aldehyde **17** in 88% yield. Addition of allylmagnesium bromide on aldehyde **17** afforded the racemic alcohol **18** in 91% yield. DKR of secondary alcohol functionality in compound **18** was achieved by coupling enzyme-catalyzed transesterification reaction with metal-catalyzed (ruthenium-based catalyst shown in Scheme 3) racemization method.[15] Isopropenyl acetate was used as the acyl donor in the DKR reaction. The DKR reaction is highly efficient for compound **18** as it yields the corresponding acetate **19** in 92% yield with excellent enantioselection (ee = 98%).[16] The acetate functionality was removed by treatment with K_2CO_3 in MeOH to produce optically pure **20** in 94% yield. The free secondary hydroxy group in **20** was protected as its TBS ether by treatment with imidazole and TBS-Cl to afford the compound **21** in 88% yield. Removal of the PMB group



Scheme 2. Reagents and conditions: (a) PMBO (C=NH)CCl_3, CSA, cyclohexane:DCM (2:1), 12 h, 92%; (b) DIBAL-H (1 equiv), DCM, −78 °C, 90%; (c) $(PhO)_2POCH_2CO_2Et$, NaH, 0 °C, 88%; (d) DIBAL-H (2 equiv), DCM, −78 °C to rt, 87%; (e) Ti(O*i*-Pr)$_4$, (+)-DIPT, TBHP, DCM, −23 °C, 4 days, 92%; (f) DMP, LHMDS, $Ph_3P{=}CH_2$, 0 °C, 78%; (g) DDQ, DCM:H_2O (19:1); (h) EDCI, DMAP, 84%; (i) DDQ, DCM:H_2O (19:1), 80%; (j) **15** (10 mol %), C_6H_6, 60%.



Scheme 3. Reagents and conditions: a) NaH, PMB-Br, 82%; b) $(COCl)_2$, DMSO, Et_3N, −78 °C, 88%; c) $CH_2{=}CHCH_2MgBr$, THF, 91%; d) CAL-B, isopropenyl acetate, dicarbonylchloro[1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl]ruthenium(II), Na_2CO_3, KO*t*-Bu, 92%; e) K_2CO_3, MeOH, 94%; f) Imidazole, TBS-Cl, 88%; g) DDQ, DCM:H_2O (19:1), 89%; h) PDC, DMF, 74%.



Scheme 4. Reagents and conditions: a) (i) TPP, DIAD, 4-methoxyphenol, 84%, (ii) DIBAL-H, DCM, −78 °C, 88%; b) CH_2=CHMgBr, THF, −20 °C, 86%; c) TPP, DIAD, $PhCO_2H$, NaOH, 78%; d) 2,6-lutidine, TBS-OTf, 90%; e) CAN, pyridine, CH_3CN:H_2O (4:1), 80%; f) DIC (diisopropyl carbodiimide), DMAP, 84%; g) HF–pyridine, 66%; h) **15** (10 mol %), DCM, 62%.

was achieved by treatment with DDQ to produce the compound **22** in 89% yield. Finally oxidation of the primary hydroxy group was achieved by oxidation with PDC[17] to afford the corresponding carboxylic acid **6** in 74% yield (Scheme 3).

For the synthesis of the required alcohol fragment we have started from (*S*)-ethyl lactate. The free hydroxy group was protected as its PMP (*para*-methoxyphenyl) ether by Mitsunobu strategy[18] to afford the corresponding PMP-protected lactate. Reduction of this compound with DIBAL-H at −78 °C afforded the corresponding aldehyde **23** in 88% yield. Addition of vinylmagnesium bromide on **23** at −20 °C afforded two diastereomeric alcohols **24** and **25** (3:2) as separable mixture. The absolute configuration of **24** and **25** was confirmed by deprotecting the TBS and the PMP groups subsequently, which yielded known (2*R*,3*R*)-pent-4-ene-2,3-diol[19] (from **24**) and (2*R*,3*S*)-pent-4-ene-2,3-diol[20] (from **25**). The undesired diastereomer **25** was converted to **24** by Mitsunobu inversion and hydrolysis strategy. The free hydroxy group in **24** was protected as its TBS ether by treatment with 2,6-lutidine and TBSOTf to afford compound **8** in 90% yield. Deprotection of PMP group was achieved by treatment of **8** with CAN (ceric ammonium nitrate) in presence of pyridine[21] to afford compound **7** in 80% yield. Addition of pyridine is essential to make the reaction medium basic, otherwise deprotection of TBS group was observed under the reaction condition. Coupling with alcohol **7** and carboxylic acid **6** was achieved by treatment with DIC and DMAP to afford coupled ester **26** in 84% yield. Removal of TBS group in **26** was accomplished by treatment with HF–pyridine[22] to produce diol **5** in 66% yield. Ring-closing metathesis reaction of **5** with Grubbs-II catalyst **15** in dichloromethane afforded stagonolide-G in 62% yield (overall yield 15.6% from (*S*)-ethyl lactate). We would also like to mention that TLC analysis of the RCM reaction mixture shows one major spot (assumed 10-membered macrolide structure for stagonolide-G, the *Z*-isomer) along with one minor spot. We have separated the major spot and recorded its spectral value (^{1}H and ^{13}C NMR) which resembles with the natural stagonolide-G (*Z*-isomer). As the amount of the minor spot is so little we could not able to isolate it in pure form. We have observed a multiplet ranging from $\delta = 5.7$–5.6 for the olefinic protons (C_6 and C_7 in the originally proposed structure) in ^{1}H NMR spectrum. Careful analysis reveals that J_{1-2} (C_6–C_7) value is 11.2 Hz, which is consistent with the *Z*-geometry between C_6 and C_7 as reported in the literature.[2] Though we do not have any concrete logic to explain the *Z*-geometry between C_6 and C_7, but we are boosted by a similar report by Srihari et al.,[3] for their total synthesis of stagonolide-G (originally proposed structure). The spectral characteristic values of our synthesized stagonolide-G and natural stagonolide-G[2] are in good agreement (Scheme 4). But little discrepancy was observed in the chemical shift value (^{1}H and ^{13}C NMR) of NMR spectra between our synthesized product and the reported synthesized one.[2,3] In the mean time, Angulo-Pachón et al. reported the synthesis of stagonolide-G (originally proposed structure) and indicated the difference in NMR between the synthesized and natural stagonolide-G.[5] They also indicated that the 10-membered lactone stagonolide-G (originally proposed structure) was readily isomerized by acid treatment to the five-membered lactone, whose NMR was identical with the reported natural stagonolide-G. The structure of stagonolide-G was hence revised as shown in Scheme 4. The spectral value (both ^{1}H and ^{13}C NMR) of our synthetic stagonolide-G

perfectly matched with the reported value for the five-member ring lactone structure of stagonolide-G. It was anticipated that the RCM product (supposed to be the 10-membered lactone) underwent spontaneous intramolecular *trans*-lactonization to yield stagonolide-G (revised structure, 5-membered lactone) during the course of chromatographic separation or prolonged exposure in $CDCl_3$ solvent during NMR spectra recording.

Conclusion

In conclusion we have described efficient asymmetric synthesis of naturally occurring small ring macrolide, stagonolide-D and stagonolide-G by a divergent approach. The crucial reaction involved in our synthetic planning for stagonolide-D was ring-closing metathesis reaction of properly substituted vinyl epoxide, Sharpless asymmetric epoxidation and *cis*-selective HWE olefination by Ando protocol. Whereas in case of stagonolide-G the main reaction involved is ring-closing metathesis followed by spontaneous *trans*-lactonization of properly substituted ester which in turn can be easily accessed from (*S*)-ethyl lactate as a chiral pool. Synthetic studies directed toward similar structurally related small ring macrolides are currently in progress.

Experimental

General. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium diphenylketyl; dichloromethane (DCM), dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride. Diisopropyl ether (DIPE) was refluxed over P_2O_5 and distilled prior to use. CAL-B (*Candida antartica* lipase-B, Novozym-435, immobilized on acrylic resin) were obtained from Sigma and used as obtained. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic anisaldehyde and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on Bruker 400 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^{1}H and ^{13}C, respectively. Elemental analysis was performed by using Perkin-Elmer model 2400, series II CHN analyzer. Optical rotations were measured on a JASCO P-1020 digital polarimeter.

(*S*)-2-(4-Methoxybenzyloxy)propionic Acid Ethyl Ester (9). A solution of 4-methoxybenzyl alcohol (7.0 g, 51 mmol) in 75 mL of ether was added to a suspension of 65% NaH (0.305 g, 7.6 mmol) in 30 mL of ether at room temperature. The resulting mixture was stirred at room temperature for 30 min and cooled to 0 °C. Trichloroacetonitrile (TCA, 5.08 mL, 51 mmol) was added to it and the reaction mixture was allowed to warm slowly to room temperature during 6 h. The solution was evaporated to an orange syrup, which was dissolved in anhydrous hexane (80 mL) containing few drops of MeOH. This suspension was shaken vigorously and filtered through celite, and the filtrate was concentrated to afford the crude imidate. The crude imidate (15 g, 51 mmol) was taken in cyclohexane (80 mL) and a solution of alcohol (*S*)-ethyl lactate (3.0 g, 25.4 mmol) in 40 mL of DCM was added. The resulting solution was cooled to 0 °C and CSA (0.6 g, 2.54 mmol) was added to it. The reaction mixture was stirred overnight at room temperature, slowly developing a white precipitate of trichloroacetamide. The solution was filtered off, washed with DCM. The filtrate was washed with $NaHCO_3$ solution, water and brine. Purification by means of silica gel chromatography 9:1, hexane:EtOAc) yielded compound **9** in 92% yield. ^{1}H NMR: δ_H 7.30 (d, $J = 8.0$ Hz, 2H), 6.88 (d, $J = 8.2$ Hz, 2H), 4.62 (d, $J = 11.2$ Hz, 1H), 4.42 (d, $J = 11.2$ Hz, 1H), 4.2 (q, $J = 7.2$ Hz, 2H), 4.0 (q, $J = 7.2$ Hz, 1H), 3.8 (s, 3H), 1.38 (d, $J = 7.2$ Hz, 3H), 1.29 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR: δ_C 173.37, 159.41, 129.64, 129.4, 113.86, 73.77, 71.65, 60.79, 52.29, 18.70, 14.25. $[\alpha]_D^{29} = -64.39$ (*c* 1.0, $CHCl_3$).

(*S*)-2-(4-Methoxybenzyloxy)propionaldehyde (10). The ester **9** (4.0 g, 16.8 mmol) was dissolved in DCM (30 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane, 1.05 equiv) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 2 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (30 mL) and warmed to room temperature producing a white precipitate. The precipitate was filtered through a pad of Celite and washed with DCM (3 × 100 mL). The filtrate was then dried ($MgSO_4$) and concentrated in vacuo. The aldehyde **10** was used without further purification. ^{1}H NMR: δ_H 9.6 (s, 1H), 7.25 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 4.5 (s, 2H), 3.88 (m, 1H), 3.82 (s, 3H), 1.27 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR: δ_C 200.58, 159.54, 129.64, 129.48, 113.96, 79.11, 71.71, 55.29, 15.32. $[\alpha]_D^{29} = -34.5$ (*c* 1.0, $CHCl_3$).

Ethyl (*Z*)-(*S*)-4-(4-Methoxybenzyloxy)pent-2-enoate (11). To a solution of ethyl (diphenoxylphosphinoxy)acetate (3.6 g, 11.27 mmol) in dry THF (40 mL) was added NaH (0.63 g, 15.5 mmol) at 0 °C. After 15 min, aldehyde **10** (2.3 g, 11.27 mmol) in THF (10 mL) was added to the reaction mixture, and the reaction mixture was gradually warmed to room temperature. The reaction was quenched with saturated NH_4Cl, and the mixture was extracted with AcOEt (10 mL × 3). The combined extracts were washed with water (15 mL × 2) followed by brine, dried ($MgSO_4$), and concentrated. Finally it was purified by silica gel chromatography (hexane:EtOAc; 5:1) to afford the pure *Z*-olefin **11** in 88% yield. ^{1}H NMR: δ_H 7.24 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 6.20 (dd, $J = 12.0$, 8.4 Hz, 1H), 5.84 (d, $J = 12.0$ Hz, 1H), 5.14 (m, 1H), 4.44 (d, $J = 11.2$ Hz, 1H), 4.36 (d, $J = 11.2$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.82 (s, 3H), 1.31 (d, $J = 6.4$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR: δ_C 165.91, 159.17, 152.19, 130.55, 129.54, 120.23, 113.78, 71.3, 70.77, 60.25, 55.25, 20.45, 14.18. $[\alpha]_D^{29} = -46.75$ (*c* 1.2, $CHCl_3$).

(*Z*)-(*S*)-4-(4-Methoxybenzyloxy)pent-2-en-1-ol (4). The unsaturated ester **11** (1.4 g, 5.3 mmol) was dissolved in DCM (30 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane, 2.2 equiv) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 4 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (25 mL) and warmed to room temperature producing a white precipitate. The precipitate was filtered through a pad of Celite

and washed with DCM (3 × 100 mL). The filtrate was then dried ($MgSO_4$) and concentrated in vacuo. Purification was carried out by flash column chromatography eluting with ethyl acetate/hexane (1:3) to afford the allylic alcohol **4** in 87% yield. ^{1}H NMR: δ_H 7.25 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.74 (m, 1H), 5.51 (m, 1H), 4.47 (d, $J = 11.2$ Hz, 1H), 4.31 (d, $J = 11.2$ Hz, 1H), 4.26 (m, 1H), 4.18 (m, 1H), 4.08 (m, 1H), 3.79 (s, 3H), 1.25 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR: δ_C 159.17, 134.39, 130.66, 130.49, 129.55, 113.82, 69.92, 69.69, 58.68, 55.27, 21.45. $[\alpha]_D^{29} = -26.0$ (*c* 1.0, $CHCl_3$). Elemental analysis for $C_{13}H_{18}O_3$ Calcd: C, 70.24; H, 8.16%. Found: C, 70.26; H, 8.23%.

{(2*S*,3*R*)-3-[(*S*)-1-(4-Methoxybenzyloxy)ethyl]oxiranyl}-methanol (12). To a stirred solution of (+)-DIPT (0.75 mL, 3.53 mmol) in DCM (25 mL) at −23 °C containing 4 Å MS (0.3 g), sequentially Ti(O*i*-Pr)$_4$ (0.84 mL, 2.94 mmol) and anhydrous TBHP (*tert*-butyl hydroperoxide) (2.4 mL, 11.74 mmol) were added and stirred for 20 min. A solution of alcohol **4** (1.3 g, 5.87 mmol) in DCM (5 mL) was added and stirred for 72 h at −23 °C. The reaction mixture was quenched with 10% KOH solution (3 g in 30 mL brine), stirred for 3 h and filtered. The organic layers were dried over Na_2SO_4, evaporated and the residue obtained was purified by column chromatography (Silica gel, EtOAc/hexane, 2:3) to furnish epoxy alcohol **12** in 92% yield. ^{1}H NMR: δ_H 7.27 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 4.63 (d, $J = 11.6$ Hz, 1H), 4.52 (d, $J = 11.6$ Hz, 1H), 3.88 (m, 1H), 3.78 (s, 3H), 3.6 (m, 1H), 3.35 (m, 1H), 3.06 (m, 1H), 2.94 (m, 1H), 2.45 (br, 1H), 1.23 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR: δ_C 159.09, 130.41, 129.32, 113.77, 74.81, 71.05, 61.45, 58.89, 55.19, 54.77, 17.21. $[\alpha]_D^{29} = -6.8$ (*c* 0.8, $CHCl_3$). Elemental analysis for $C_{13}H_{18}O_4$ Calcd: C, 65.53; H, 7.61%. Found: C, 65.55; H, 7.55%.

(2*R*,3*S*)-2-[(*S*)-1-(4-Methoxybenzyloxy)ethyl]-3-vinyloxirane (13). Epoxyalcohol **12** (1.5 g, 6.3 mmol) was dissolved in DCM (25 mL). DMP (2.76 g, 6.5 mmol) was added to it, and the solution was stirred at room temperature for 3 h. After that time all the starting materials have consumed, ether was added to the reaction mixture. The reaction mixture was washed with saturated $Na_2S_2O_3$ solution and then brine. The organic layer was dried with $MgSO_4$ and concentrated to afford the crude aldehyde.

Methyltriphenylphosphonium iodide (4.1 g, 10.16 mmol) was taken in dry THF (40 mL) at 0 °C. A solution of LHMDS (1 M in THF, 10.16 mL) was added to it at the same temperature. A yellow-orange color develops with time. After 15 min stirring at the same temperature the crude aldehyde (1.2 g, 5.08 mmol) was added to the reaction mixture. The solution kept at 0 °C for 1/2 h and then allowed to warm at room temperature. After that time, solution of NH_4Cl was added to the reaction mixture and it was extracted with ether. Evaporation of the organic solution and purification by means of flash chromatography the epoxy olefin **13** was obtained in 78% yield. ^{1}H NMR: δ_H 7.29 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.59 (m, 1H), 5.45 (m, 1H), 5.29 (d, $J = 10.0$ Hz, 1H), 4.68 (d, $J = 11.6$ Hz, 1H), 4.53 (d, $J = 11.6$ Hz, 1H), 3.79 (s, 3H), 3.33 (m, 1H), 3.13 (d, $J = 7.2$ Hz, 1H), 2.96 (dd, $J = 6.0$, 2.0 Hz, 1H), 1.25 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR: δ_C 159.10, 134.99, 130.49, 129.31, 119.59, 113.71, 75.07, 70.84, 63.31, 55.19, 54.82, 17.29. $[\alpha]_D^{29} = -11.2$ (*c* 0.5, $CHCl_3$). Elemental analysis for $C_{14}H_{18}O_3$ Calcd: C, 71.77; H, 7.74%. Found: C, 71.66; H, 7.70%.

(2*R*,3*S*)-1-Methyl-2,3-epoxypent-4-enyl (*S*)-4-(4-Methoxybenzyloxy)hex-5-enoate (14). The epoxy olefin **13** (0.15 g, 0.64 mmol) was taken in 5 mL of DCM:H_2O (19:1). DDQ (0.218 g, 0.96 mmol) was added to it in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered off, and the filtrate was washed with 5% $NaHCO_3$ solution, water and brine. The organic layer was dried ($MgSO_4$) and evaporated. Evaporation of the organic layer afforded the crude alcohol **3**, which was subsequently used for the next esterification reaction.

The crude alcohol **3** (73 mg, 0.64 mmol) was taken in dry DCM (2 mL). *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl, 185 mg, 0.96 mmol), DMAP (cat amount), and (*S*)-4-(4-methoxybenzyloxy)hex-5-enoic acid (**2**, 160 mg, 0.64 mmol) were sequentially added to the reaction mixture. The reaction mixture was kept at room temperature for 3 h. The ester was purified by flash chromatography. ^{1}H NMR: δ_H 7.26 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 5.67–5.5 (m, 3H), 5.48–5.19 (m, 3H), 4.82 (m, 1H), 4.52 (d, $J = 11.2$ Hz, 1H), 4.42 (d, $J = 11.2$ Hz, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.24 (m, 1H), 2.96 (dd, $J = 6.0$, 2.0 Hz, 1H), 2.46 (m, 2H), 1.8 (m, 2H), 1.22 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR: δ_C 172.69, 159.09, 138.29, 134.47, 130.56, 129.37, 120.07, 117.68, 113.75, 78.95, 70.0, 69.83, 61.2, 56.11, 55.26, 30.38, 30.09, 16.48. $[\alpha]_D^{29} = -2.6$ (*c* 2.0, $CHCl_3$). Elemental analysis for $C_{20}H_{26}O_5$ Calcd: C, 69.34; H, 7.57%. Found: C, 69.39; H, 7.51%.

(2*R*,3*S*)-1-Methyl-2,3-epoxypent-4-enyl (*S*)-4-Hydroxyhex-5-enoate (1). Ester **14** (58 mg, 0.16 mmol) was taken in 4 mL of DCM:H_2O (19:1). DDQ (55 mg, 0.24 mmol) was added to it in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered off, and the filtrate was washed with 5% $NaHCO_3$ solution, water and brine. The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (1:1, hexane:EtOAc) to afford the compound **1** in 80% yield. ^{1}H NMR: δ_H 5.9–5.81 (m, 1H), 5.6–5.5 (m, 2H), 5.4–5.2 (m, 2H), 5.12 (d, $J = 10.4$ Hz, 1H), 4.83 (m, 1H), 4.2 (m, 1H), 3.27 (dd, $J = 6.4$, 1.6 Hz, 1H), 2.98 (dd, $J = 5.2$, 1.6 Hz, 1H), 2.46 (t, $J = 7.2$ Hz, 2H), 1.8 (m, 2H), 1.21 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR: δ_C 173.08, 140.31, 134.39, 120.13, 115.16, 72.05, 70.29, 61.18, 56.22, 31.6, 30.28, 16.5. $[\alpha]_D^{29} = -44.5$ (*c* 0.5, $CHCl_3$). Elemental analysis for $C_{12}H_{18}O_4$ Calcd: C, 63.70; H, 8.02%. Found: C, 63.66; H, 8.13%.

(*E*)-(1*R*,2*S*,7*S*,10*S*)-7-Hydroxy-2-methyl-3,11-dioxabicyclo-[8.1.0]undec-8-en-4-one (Stagonolide-D). The compound **1** (30 mg, 0.081 mmol) was taken in anhydrous degassed C_6H_6 (80 mL). Grubbs second generation metathesis catalyst (7 mg, 0.008 mmol) was added to it and the solution was refluxed for 4 h. The solution was evaporated and the content of the flask was directly loaded on a silica gel column. Flash chromatography with hexane:EtOAc (3:1) afforded the pure stagonolide-D in 60% yield. ^{1}H NMR: δ_H 5.62 (dd, $J = 16.8$, 5.0 Hz, 1H), 5.5 (dd, $J = 16.8$, 8.4 Hz, 1H), 5.3 (m, 1H), 4.1 (m, 1H), 3.58 (dd, $J = 4.8$, 1.6 Hz, 1H), 3.01 (dd, $J = 4.8$, 2.0 Hz, 1H), 2.2–2.1 (m, 2H), 2.05 (m, 2H), 1.34 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR: δ_C 173.4, 134.22, 128.15, 75.2, 65.78, 58.3, 55.52, 35.0, 31.28,

16.3. $[\alpha]_D^{29} = -84.4$ (c 0.2, $CHCl_3$); Literature value, $[\alpha]_D^{25} = -82.0$ (c 0.2, $CHCl_3$); Elemental analysis for $C_{10}H_{14}O_4$ Calcd: C, 60.59; H, 7.12%. Found: C, 60.56; H, 7.19%.

7-(4-Methoxybenzyloxy)hept-1-en-4-ol (18). Aldehyde **17** (5 g, 24 mmol) was taken in 40 mL of anhydrous THF. Solution of allylmagnesium bromide (freshly prepared from allyl bromide and Mg metal, 36 mmol) was added to it at 0 °C. The reaction mixture was kept at the same temperature for 1 h, after that time saturated NH_4Cl solution was added to it. The solution was extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography (3:1, hexane:EtOAc) afforded the alcohol **18** in 91% yield. ^{1}H NMR: δ_H 7.24 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.93–5.72 (m, 1H), 5.14–5.07 (m, 2H), 4.44 (s, 2H), 3.7 (s, 3H), 3.62 (m, 1H), 3.48 (t, $J = 7.8$ Hz, 2H), 2.23 (m, 2H), 1.8–1.54 (m, 4H). ^{13}C NMR: δ_C 159.22, 135.12, 130.32, 129.35, 117.67, 113.83, 72.68, 70.6, 70.18, 55.28, 41.99, 34.1, 26.26. Elemental analysis for $C_{15}H_{22}O_3$ Calcd: C, 71.97; H, 8.86%. Found: C, 71.91; H, 8.88%.

(*R*)-1-[3-(4-Methoxybenzyloxy)propyl]but-3-enyl Acetate (19). In a 50 mL round bottom flask attached with a grease free high vacuum stopcock, dicarbonylchloro[1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl]ruthenium(II) (DKR catalyst, 84 mg, 0.136 mmol) was taken. The flask was successively charged with alcohol **18** (0.86 g, 3.6 mmol) in 10 mL dry toluene, Na_2CO_3 (3.4 mmol), CAL-B (25 mg), and KO*t*-Bu (0.17 mmol) followed by isopropenyl acetate (5 mmol). The reaction mixture was stirred at room temperature under argon atmosphere. After that time the reaction mixture was filtered off and the solution was evaporated to afford the crude acetate **19**, which was subsequently purified by silica gel chromatography (10:1, hexane:EtOAc) to afford the pure acetate in 92% yield. ^{1}H NMR: δ_H 7.23 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.82–5.62 (m, 1H), 5.1 (m, 2H), 4.91 (m, 1H), 4.39 (s, 2H), 3.76 (s, 3H), 3.4 (m, 2H), 2.28 (t, $J = 6.6$ Hz, 2H), 1.99 (s, 3H), 1.6 (m, 4H). ^{13}C NMR: δ_C 170.65, 159.16, 133.69, 130.59, 129.22, 117.67, 113.76, 72.99, 72.54, 69.57, 55.2, 38.69, 30.3, 25.64, 21.15. Elemental analysis for $C_{17}H_{24}O_4$ Calcd: C, 69.84; H, 8.27%. Found: C, 69.89; H, 7.21%. $[\alpha]_D^{29} = -3.74$ (c 2.0, $CHCl_3$).

(*S*)-4-(*tert*-Butyldimethylsiloxy)-7-(4-methoxybenzyloxy)-hept-1-ene (21). Compound **20** (1 g, 4 mmol) was taken in 30 mL of anhydrous DCM. Imidazole (816 mg, 12 mmol) was added to it at room temperature. The reaction mixture was stirred for 15 min. After that time TBS-Cl (1.2 g, 8 mmol) was added to it and the reaction mixture was stirred overnight. After completion of the reaction, water was added to the reaction mixture and the organic layer was washed with excess water and brine. The organic layer was dried ($MgSO_4$) and evaporated to dryness to afford the crude silylated compound **21**, which was purified by silica gel chromatography (15:1, hexane:EtOAc). ^{1}H NMR: δ_H 7.28 (d, $J = 8.6$ Hz, 2H), 6.90 (d, $J = 8.6$ Hz, 2H), 5.93–5.79 (m, 1H), 5.12–5.04 (m, 2H), 4.46 (s, 2H), 3.84 (m, 1H), 3.76 (s, 3H), 3.47 (t, $J = 6.4$ Hz, 2H), 2.27 (t, $J = 6.8$ Hz, 2H), 1.72–1.54 (m, 4H), 0.98 (s, 9H), 0.1 (s, 6H). ^{13}C NMR: δ_C 159.19, 135.25, 130.81, 129.2, 116.81, 113.76, 72.5, 71.81, 70.24, 55.13, 42.05, 33.37, 26.0, 25.72, 18.17, −4.29, −4.45. $[\alpha]_D^{29} = +2.13$ (c 1.0, $CHCl_3$).

(*S*)-4-(*tert*-Butyldimethylsiloxy)hept-6-en-1-ol (22). Compound **21** (600 mg, 1.7 mmol) was taken in 20 mL of DCM:H_2O (19:1). DDQ (561 mg, 2.5 mmol) was added to it in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered off, and the filtrate was washed with 5% $NaHCO_3$ solution, water and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography (3:1, hexane:EtOAc) afforded the pure compound **22** in 89% yield. ^{1}H NMR: δ_H 5.83–5.66 (m, 1H), 5.06–4.97 (m, 2H), 3.73 (m, 1H), 3.57 (m, 2H), 2.22 (m, 2H), 1.59–1.5 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR: δ_C 135.0, 116.84, 71.83, 62.86, 41.58, 33.08, 28.29, 25.84, 18.07, −4.49, −4.63. $[\alpha]_D^{29} = -3.96$ (c 1.75, $CHCl_3$).

(*S*)-4-(*tert*-Butyldimethylsiloxy)hept-6-enoic Acid (6). The compound **22** (700 mg, 2.9 mmol) was taken in anhydrous DMF (10 mL). Pyridinium dichromate (PDC, 5.4 g, 14.3 mmol) was added to the reaction mixture and the reaction mixture was stirred at room temperature till all the starting material has been consumed as indicated by TLC. Water was added to the reaction mixture, the water layer was extracted thrice with EtOAc (3 × 25 mL) followed by a washing with aq. $KHSO_4$ solution. The organic extract was dried ($MgSO_4$) and evaporated. The crude acid **6** was purified by silica gel chromatography (1:1, hexane:EtOAc). ^{1}H NMR: δ_H 5.89–5.68 (m, 1H), 5.09–5.01 (m, 2H), 3.77 (m, 1H), 2.41 (t, $J = 7.8$ Hz, 2H), 2.23 (t, $J = 6.2$ Hz, 2H), 1.85–1.68 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR: δ_C 180.18, 134.52, 117.25, 70.69, 41.78, 31.14, 29.85, 25.84, 18.06, −4.39, −4.70. $[\alpha]_D^{29} = -4.95$ (c 2.0, $CHCl_3$).

(*R*)-2-(4-Methoxyphenoxy)propionaldehyde (23). A solution of DIAD (diisopropyl azodicarboxylate) (5.4 mL, 27.56 mmol) in THF (20 mL) was added dropwise to a mixture of (*S*)-ethyl lactate (2.5 g, 21.2 mmol), 4-methoxyphenol (5.3 g, 42.37 mmol), and TPP (7.2 g, 27.56 mmol) in anhydrous THF (75 mL). The reaction mixture was stirred for overnight at room temperature. After evaporation of THF, a mixture of hexane:ether (1:1, 125 mL) was added to the viscous residue, the organic layer was washed with 1 M NaOH (50 mL), water and finally with brine. The organic extract was dried and evaporated to afford the PMP-protected lactate.

PMP-protected lactate (3 g, 13.4 mmol) was taken in anhydrous DCM (70 mL). DIBAL-H (13.4 mmol, 1 M in hexane) was added to the reaction mixture at −78 °C. The reaction mixture was kept at the same temperature for further 1 h. After that time a saturated solution of Na_2SO_4 was added to it, and the white gelatinous ppt was filtered off with a Celite pad. The organic layer was evaporated and purified by means of silica gel chromatography to afford the pure aldehyde in 88% yield. ^{1}H NMR: δ_H 9.72 (d, $J = 1.8$ Hz, 1H), 6.84 (s, 4H), 4.54 (dq, $J = 7.0$, 1.8 Hz, 1H), 3.76 (s, 3H), 1.45 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR: δ_C 202.97, 154.94, 151.63, 117.0, 115.13, 79.03, 55.91, 15.83. Elemental analysis for $C_{10}H_{12}O_3$ Calcd: C, 66.65; H, 6.71%. Found: C, 66.69; H, 6.65%. $[\alpha]_D^{29} = +0.38$ (c 1.0, $CHCl_3$).

(3*R*,4*R*)-4-(4-Methoxyphenoxy)pent-1-en-3-ol (24). Aldehyde **23** (500 mg, 2.8 mmol) was taken in 40 mL of anhydrous THF. Solution of vinylmagnesium bromide (1 M, 5.6 mL, 5.6 mmol) was added to it at −20 °C. The reaction mixture was kept at the same temperature for 1 h, after that time saturated NH_4Cl solution was added to it. The solution was

extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography (3:1, hexane:EtOAc) afforded the alcohol **24** and **25** in 86% yield (3:2), which are separated by silica gel chromatography. ^{1}H NMR: δ_H 6.85 (m, 4H), 5.90 (m, 1H), 5.42 (m, 1H), 5.29 (m, 1H), 4.36–4.24 (m, 2H), 3.78 (s, 3H), 1.23 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR: δ_C 154.46, 151.49, 136.24, 117.97, 116.99, 114.76, 78.07, 74.62, 55.71, 13.98. Elemental analysis for $C_{12}H_{16}O_3$ Calcd: C, 69.21; H, 7.74%. Found: C, 69.29; H, 7.71%. $[\alpha]_D^{29} = -0.36$ (*c* 1.0, MeOH).

(3*R*,4*R*)-4-Allyloxy-3-(*tert*-butyldimethylsiloxy)pent-1-ene (8). Alcohol **24** (200 mg, 0.96 mmol) was taken in dry DCM (2 mL). 2,6-Lutidine was (0.35 mL, 2 mmol) added to it at 0 °C and kept for 5 min at the same temperature. TBS-OTf (0.25 mL, 0.96 mmol) was added to the reaction mixture and the solution warmed to attain room temperature. The reaction mixture was kept for overnight, after that it was washed with $NaHCO_3$, brine and dried (Na_2SO_4). It was purified by flash chromatography (10:1; hexane:EtOAc) to afford compound **8** in 90% yield. ^{1}H NMR: δ_H 6.84 (m, 4H), 6.0–5.84 (m, 1H), 5.39–5.15 (m, 2H), 4.34 (m, 2H), 3.77 (s, 3H), 1.24 (d, $J =$ 6.4 Hz, 3H), 0.95 (s, 9H), 0.07 (s, 6H). ^{13}C NMR: δ_C 153.84, 138.49, 117.46, 117.16, 115.72, 114.63, 78.06, 75.63, 55.68, 25.93, 18.34, 14.43, −4.46, −4.65. $[\alpha]_D^{29} = -24.20$ (*c* 1.0, MeOH).

(2*R*,3*R*)-3-(*tert*-Butyldimethylsiloxy)pent-4-en-2-ol (7). Compound **8** (260 mg, 0.8 mmol) was dissolved in CH_3CN:H_2O (4:1, 10 mL), followed by addition of CAN (1.2 g, 2 mmol) and pyridine (1 mmol) at 0 °C. The solution was kept at the same temperature for 10 min. After that time it was extracted repeatedly with DCM. The organic layer was washed with water and brine. It was further purified by silica gel chromatography to afford the compound **7** in 80% yield. ^{1}H NMR: δ_H 5.86–5.69 (m, 1H), 5.23–5.14 (m, 2H), 3.96 (m, 1H), 3.70 (m, 1H), 1.07 (d, $J = 6.4$ Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H). ^{13}C NMR: δ_C 138.49, 137.30, 78.29, 70.84, 26.03, 18.51, 17.66, −4.08, −4.70. $[\alpha]_D^{29} = -4.95$ (*c* 1.0, MeOH).

(1*R*,2*R*)-2-(*tert*-Butyldimethylsiloxy)-1-methylbut-3-enyl (*S*)-4-(*tert*-Butyldimethylsiloxy)hept-6-enoate (26). The coupling between alcohol **7** and carboxylic acid **6** was performed as described in the section of compound **14** to afford the ester **26** in 84% yield. ^{1}H NMR: δ_H 5.85–5.65 (m, 2H), 5.26–5.03 (m, 4H), 4.91 (m, 1H), 4.11 (m, 1H), 3.71 (m, 1H), 2.32 (m, 2H), 2.28 (m, 2H), 1.78 (m, 2H), 1.09 (d, $J = 6.4$ Hz, 3H), 0.85 (s, 9H), 0.02 (s, 6H). ^{13}C NMR: δ_C 173.06, 136.75, 134.64, 117.08, 116.52, 74.41, 72.77, 70.85, 41.78, 31.50, 30.35, 25.83, 25.72, 18.03, 14.79, −4.41, −4.66. $[\alpha]_D^{29} = +3.47$ (*c* 2.0, MeOH).

(1*R*,2*R*)-2-Hydroxy-1-methylbut-3-enyl (*S*)-4-Hydroxyhept-6-enoate (5). The ester **26** (140 mg, 0.3 mmol) was taken in CH_3CN (4 mL). A solution of HF–pyridine (70% as HF, 0.7 mmol) was added to it and the solution was kept at room temperature for 24 h. After that time EtOAc was added to the solution and it was washed with $NaHCO_3$ and then brine. Purification by means of chromatography afforded the pure diol **5** in 66% yield. ^{1}H NMR: δ_H 5.78–5.72 (m, 1H), 5.67–5.60 (m, 1H), 5.09–4.85 (m, 5H), 4.22 (m, 1H), 3.76 (m, 1H), 2.27–2.14 (m, 4H), 1.74 (m, 2H), 1.12 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR: δ_C 172.78, 133.82, 129.62, 127.55, 117.35, 75.57, 72.55, 71.99, 40.89, 30.84, 29.86, 14.95. Elemental analysis for $C_{12}H_{20}O_4$ Calcd: C, 63.14; H, 8.83%. Found: C, 63.19; H, 8.89%.

(*S*)-5-[(*Z*)-(4*R*,5*R*)-4,5-Dihydroxyhex-2-enyl]dihydrofuran-2-one (Stagonolide-G). The diol **5** (40 mg, 0.175 mmol) was taken in anhydrous degassed DCM (100 mL). Grubbs second generation metathesis catalyst (15 mg, 0.0175 mmol) was added to it and the solution was refluxed for 6 h. The solution was evaporated and the content of the flask was directly loaded on a silica gel column. Flash chromatography with hexane:EtOAc (1:3) afforded the pure stagonolide-G in 62% yield. ^{1}H NMR: δ_H 5.65 (m, 2H), 4.84 (m, 1H), 4.11 (m, 1H), 3.68 (m, 1H), 2.37–2.14 (m, 4H), 1.79–1.72 (m, 2H), 1.10 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR: δ_C 178.0, 132.48, 127.89, 79.52, 72.4, 70.89, 33.85, 28.75, 27.5, 18.89. $[\alpha]_D^{29} = +96.2$ (*c* 0.1, $CHCl_3$); Literature value, $[\alpha]_D^{25} = +96.0$ (*c* 0.1, $CHCl_3$). Elemental analysis for $C_{10}H_{16}O_4$ Calcd: C, 59.98; H, 8.05%. Found: C, 59.93; H, 8.09%.

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Supporting Information

^{1}H NMR and ^{13}C NMR spectra of selected compounds. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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