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Chemo-enzymatic asymmetric total synthesis of stagonolide-C

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ABSTRACT

Article history: Received 9 September 2009 Accepted 7 October 2009 Available online 26 November 2009 The naturally occurring phytotoxic noneolide stagonolide-C has been synthesized by a chemo-enzymatic approach. Two key intermediates have been synthesized by applying a metal–enzyme combined DKR (dynamic kinetic resolution) strategy, followed by RCM (ring-closing metathesis) to afford the target compound in an efficient way.

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1. Introduction

Naturally occurring 10-membered ring lactones (noneolides) from fungal metabolites present a wide variety of bioactive substances. Among them, modiolide A-B was isolated by Kobayashi and co-workers¹ and shown to have antibacterial and antifungal activities. Macrolides, particularly lactones with medium-sized rings (8-10-membered), have continued to attract the attention of both biologists and chemists during recent years,² due to the interesting biological properties and scarce availability of macrolides. A few examples, in particular of 10-membered-ring-containing macrolides that display potent biological activity, are putaminoxin and pinolidoxin.³ The nonenolide (5S,9R)-5-hydroxy-9-methyl-6-nonen-9-olide, a diastereomer of aspinolide, is one such example, and has been isolated from Stagonospora cirsii. S. 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.⁴ 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. When tested by a leaf disk puncture assay at a concentration of 1 mg/mL, these compounds showed no toxicity to C. arvense and Sonchus arvensis, whereas stagonolide was highly toxic. A further four nonenolides were isolated and characterized by spectroscopy. Three were new compounds which were named stagonolides G-I, and the fourth was identified as modiolide A, previously isolated from Paraphaeosphaeria sp., which is a fungus separated from the horse mussel (Scheme 1).

All of the noneolides shown in Scheme 1 possess interesting structural features, as they are compact, they contain a properly placed olefinic moiety with well-defined geometry and the presence of stereochemically pure hydroxy appendages makes them

* Corresponding author. E-mail address: snanda@chem.iitkgp.ernet.in (S. Nanda). very good synthetic targets. In this article we report the total synthesis of such a noneolide stagonolide-C. During the course of our study Mohapatra et al. reported the first asymmetric synthesis of stagonolide-C.⁵

2. Results and discussion

Retrosynthetic analysis of the target molecule stagonolide-C is shown in Scheme 2.

The internal double bond between C_5-C_6 was thought to be a crucial disconnection as it can be reconnected through a RCM reaction. The crucial ester linkage between C_1-C_9 is planned to be constructed by an esterification reaction of a properly substituted acid and alcohol. The required acid and the alcohol are constructed from a more easily available starting material. Two of the stereocenters in the parent molecule, for example, C_4 and C_9 are to be constructed by applying a metal–enzyme combined DKR strategy.⁶

2.1. Synthesis of the 4-methoxy-benzyloxy-hex-5-enoic acid fragment

The synthesis starts from 1,4-butane-diol. Selective monoprotection with TBS-Cl (tert-butyldimethyl silyl chloride) by the Mc-Dougals protocol⁷ yielded the mono TBS-protected ether **1** in 90%. Swern oxidation followed by addition of vinyl magnesium bromide at -78 °C afforded the alcohol 3 in 82% yield from aldehyde **2**. DKR of the secondary alcohol functionality in compound **3** was achieved by coupling enzyme-catalyzed transesterification reaction with a metal-catalyzed (ruthenium-based catalyst shown in Scheme 3) racemization method as reported by Kim et al.⁸ Isopropenyl acetate was used as the acyl donor in the DKR reaction. The DKR reaction is highly efficient for compound **3** as it yields the corresponding acetate 4 in 90% and with excellent enantioselection (ee = 99%).⁹ The acetate functionality was removed by treatment with K₂CO₃ in MeOH to yield enantiomerically pure 5 in 94%. The alcohol functionality in 5 was protected as its PMB ether by treating with PMB-imidate¹⁰ in the presence of a catalytic amount of



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Scheme 2. Retrosynthetic analysis of stagonolide-C.

HO

CSA (camphor sulfonic acid) to yield compound **6**. Compound **6** when treated with PPTS (pyridinium *para*-toluene sulfonate)/ MeOH led to removal of the TBS group¹¹ and afforded the compound **7** in 88% yield. Oxidation of the primary alcohol functionality with PDC (pyridinium dichromate) in DMF afforded the corresponding acid **8** in 72% yield (Scheme 3).¹² The same intermediate **8** was synthesized by Mohapatra et al. in eleven steps starting from 1,4-butane diol, whereas we have synthesized in eight steps starting from 1,4-butane diol in 29% overall yield.

2.2. Synthesis of the (2*R*,4*S*)-4-methoxy-benzyloxy-hex-5-ene-2-ol fragment

The synthesis starts from the commercially available racemic 1,3-butane-diol. The primary alcohol functionality was selectively protected as its PMB ether by treatment with NaH and PMB–Br in the presence of a catalytic amount of TBAI (tetra-*n*-butyl ammonium iodide) to yield the compound **9** in 80% yield. Metal–enzyme-combined DKR reaction was applied to compound **9** in the

presence of isopropenyl acetate as an acyl donor to afford the corresponding acetate 10 in 92% yield with excellent enantioselection (ee = 98%).¹³ The acetate group in **10** was deprotected with $K_2CO_3/$ MeOH to afford enantiomerically pure 11 in 90% yield. The secondary hydroxyl group in 11 was protected as its TBDPS (tert-butyldiphenylsilyl) ether by treatment with imidazole/TBDPS-Cl to afford compound 12 in 95% yield. Removal of the PMB group was successfully achieved with DDQ¹⁴ to afford compound **13** in 86% yield. Oxidation under Swern condition¹⁵ afforded the aldehyde **14** in 92% yield. Vinylmagnesium bromide addition on compound 14 afforded the two diastereomers 15 and 16 in 1:1 ratio, which can be separated by silica gel chromatography. The anti-stereochemistry between the two hydroxyl functionalities was established by Rychnovsky's method.¹⁶ Thus, under treatment with TBAF (tetra*n*-butyl ammonium fluoride) compounds **15** and **16** afforded the respective diols 17 and 18. Reaction with 2,2-DMP (2,2-dimethoxypropane) in the presence of PPTS afforded the respective acetonides¹⁷ **19** and **20**. ¹³C NMR analysis of **19** and **20** established the relative stereochemistry of the two hydroxyl functionalities unam-

ЮH

OH



Scheme 3. Reagents and conditions: (a) NaH TBS-Cl, 90%; (b) (COCl)₂, DMSO, Et₃N, -78 °C, 88%; (c) CH₂=CH-MgBr, -78 °C, 82%; (d) CAL-B, isopropenyl acetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium(II), K₂CO₃, KOtBu 90%; (e) K₂CO₃, MeOH, 94%; (f) PMBO-(C=NH)-CCl₃, CSA, 85%; (g) PPTS, MeOH, 88%; (h) PDC, DMF, 72%.

biguously. The unwanted *syn*-diastereomer **16** was converted to the required *anti*-diastereomer **15** by Mitsunobu inversion followed by removal of the benzoate group under basic conditions. The secondary hydroxyl group in **15** was protected as its PMB ether by the treatment of PMB-imidate in the presence of catalytic CSA to afford compound **21** in 82% yield. Deprotection of TBDPS group was finally achieved by treatment with TBAF to afford the desired compound **22** in 90% yield.¹⁸ The same intermediate **22** was also synthesized by Mohapatra et al. in twelve steps starting from L-malic acid, whereas we have synthesized **22** from (±)-1,3-butanediol in ten steps in 28% overall yield (Scheme 4).

2.3. Coupling of fragment 8 and 22 for the total synthesis of stagonolide-C

After successful construction of both the required fragments **8** and **22**, the remaining task was to couple the two fragments followed by a RCM strategy. The coupling of the two fragments was successfully achieved by treating acid **8** with EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) to prepare the mixed anhydride, followed by the addition of alcohol **22** to afford the coupled ester **23** in 90% yield.¹⁹ The final RCM reaction seems to be crucial and problematic as depicted by Mohapatra et al. After numerous



Scheme 4. Reagents and conditions: (a) NaH, PMB–Br, TBAI (cat), 80%; (b) CAL-B, isopropenylacetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl ruthenium(II), K₂CO₃, KOtBu, 92%; (c) K₂CO₃, MeOH, 90%; (d) imidazole, TBDPS-CI, 95%; (e) DDQ, DCM/H₂O (19:1), 86%; (f) (COCl)₂, DMSO, Et₃N, -78 °C, 92%; (g) CH₂=CH–MgBr, -78 °C, 80%; (h) TPP (triphenylphosphine), DIAD (diisopropyl azodicarboxylate), PhCO₂H, NaOH, 90% in two steps; (i) TBAF, THF, 88%; (j) 2,2-DMP, PPTS, 86%; (k) PMBO-(C=NH)-CCl₃, CSA, 82%; (l) TBAF, THF, 90%.



Scheme 5. Reagents and conditions: (a) EEDQ, THF, 92%; (b) DDQ, DCM/H₂O (19:1), 85%; (c) Grubbs-II, DCM, 66%.

conditions were tried with Grubbs-I and Grubbs-II in different solvents, for example, DCM, benzene, and toluene, the final outcome was the same in all the cases. Either inseparable mixtures of various compounds were obtained or the starting material had decomposed during the course of the reaction. Finally deprotection of the PMB functionality was achieved by treating compound **23** with DDQ to afford the diol **24** in 85% yield. Compound **24** upon treatment with Grubbs-second generation catalyst afforded the target molecule Stagonolide-C (Scheme 5).

3. Conclusion

In conclusion we have described an efficient chemo-enzymatic asymmetric total synthesis of naturally occurring noneolide stagonilide-C. A metal-enzyme combined DKR strategy was successfully applied to access two advanced intermediates **8** and **22** in an efficient way. Coupling of these two intermediates followed by ring-closing metathesis with Grubbs-second generation catalyst afforded the target molecule. Synthetic studies directed towards several structurally related noneolides are currently in progress in our laboratory.

4. Experimental

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethylether were distilled from sodiumbenzophenone ketyl. Dichloromethane (DCM), dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Diisopropylether (DIPE) was refluxed over P2O5 and distilled prior to use. Vinyl acetate and isopropenyl acetate were freshly distilled prior to use. CAL-B (Candida antartica lipase-B, Novozym-435, immobilized on acrylic resin) was 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 CDCl₃ using TMS as the internal standard. Chemical shifts are shown in δ . ¹³C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as $\delta_{\rm H}$ and $\delta_{\rm C}$ for ¹H and ¹³C, respectively. Mass spectral analysis was performed in the Central Research Facility (CRF), IIT-Kharagpur. Optical rotations were measured on a JASCO P-1020 digital polarimeter. Chiral HPLC was performed using Chiral AS-H, OJ-H and OD-H column (0.46 × 25 cm, Daicel industries) with Shimadzu Prominence LC-20AT chromatograph coupled with UV–vis detector (254 nm). Eluting solvent used was a differing ratio of hexane and 2-propanol.

4.2. 4-(tert-Butyl-dimethyl-silanyloxy)-butan-1-ol 1

The mono TBS-protected ether was prepared as reported in the literature²⁰ and provided comparable spectral characteristic values.

4.3. 4-(tert-Butyl-dimethyl-silanyloxy)-butyraldehyde 2

Aldehyde **2** was prepared as reported in the literature²⁰ and provides comparable spectral characteristic values.

4.4. 6-(tert-Butyl-dimethyl-silanyloxy)-hex-1-en-3-ol 3

Aldehyde **2** (2.5 g, 11.26 mmol) was taken in 40 mL of anhydrous THF. Solution of vinylmagnesium bromide (1 M, 15 mL, 15 mmol) was added to it at -78 °C. The reaction mixture was kept at the same temperature for 1 h, after which time saturated NH₄Cl 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 (MgSO₄) and evaporated. Purification by silica gel chromatography (3:1, hexane/EtOAc) afforded the alcohol **3** in 82% yield.

 $\delta_{\rm H}$: 5.85 (m, 1H), 5.24 (dd, *J* = 16.2, 1.8 Hz, 1H), 5.07 (dd, *J* = 11.2 Hz, 1.8 Hz, 1H), 4.1 (m, 1H), 3.64 (t, *J* = 6.0 Hz, 2H), 1.6 (m, 4H), 0.9 (s, 9H), 0.05 (s, 6H).

 δ_{C} : 141.23, 114.51, 72.8, 63.36, 34.3, 28.71, 25.8, 18.72, -3.59, -4.56.

4.5. Acetic acid (S)-4-(*tert*-butyl-dimethyl-silanyloxy)-1-vinylbutyl ester 4

In a 50 mL round-bottomed flask attached to a grease-free highvacuum stopcock, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5tetraphenylcyclopentadienyl) ruthenium(II) [DKR catalyst, 84 mg, 0.136 mmol] was taken. The flask was successively charged with alcohol **3** (0.86 g, 3.4 mmol) in 10 mL dry toluene, Na₂CO₃ (3.4 mmol), CAL-B (25 mg) and KOtBu (0.17 mmol) followed by isopropenyl acetate (5 mmol). The reaction mixture was stirred at room temperature under argon atmosphere, after which it was filtered off and the solution was evaporated to afford the crude acetate **4**, which was subsequently purified by silica gel chromatography (10:1, hexane/EtOAc) to afford the pure acetate **4** in 90% yield. $\delta_{\rm H}$: 5.77 (m, 1H), 5.278 (d, *J* = 10.4 Hz, 1H), 5.25–5.14 (m, 2H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.05 (s, 3H), 1.7–1.5 (m, 4H), 0.9 (s, 9H), 0.06 (s, 6H). $\delta_{\rm C}$:170.33, 136.53, 116.62, 74.58, 62.68, 30.57, 28.33, 25.94, 21.22, 18.32, -5.22. $[\alpha]_{\rm D}^{29} = -2.7$ (*c* 1.0, MeOH).

4.6. (S)-6-(tert-Butyl-dimethyl-silanyloxy)-hex-1-en-3-ol 5

The pure acetate **4** (0.45 g, 1.5 mmol) was taken in MeOH followed by the addition of K_2CO_3 (0.213 g, 1.5 mol) and the solution was stirred at room temperature for 2 h. After this time, the MeOH was evaporated and the residue was taken in DCM, and washed successively with water and brine. The organic layer was dried (MgSO₄) and purified through silica gel chromatography (3:1, hexane/EtOAc) to yield the (*S*)-alcohol **5**.

 $[\alpha]_{\rm D}^{29} = -32.85$ (*c* 1.0, MeOH).

4.7. *tert*-Butyl-[(*S*)-4-(4-methoxy-benzyloxy)-hex-5-enyloxy]dimethyl-silane 6

A solution of 4-methoxybenzyl alcohol (2.2 g, 16 mmol) in 15 mL of ether was added to a suspension of 65% NaH (0.128 g, 3.2 mmol) in 20 mL of ether at room temperature. The resulting mixture was stirred at room temperature for 30 min and cooled to 0 °C. Trichloroacetonitrile (TCA, 1.926 mL, 19.2 mmol) was added to it and the reaction mixture was allowed to warm slowly to room temperature over 6 h. The solution was evaporated to an orange syrup, which was dissolved in anhydrous hexane (40 mL) containing a 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 (3.68 g, 13 mmol) was taken in cyclohexane (20 mL) and a solution of alcohol 5 (1.5 g, 6.52 mmol) in 10 mL of DCM was added. The resulting solution was cooled to 0 °C and CSA (0.151 g, 0.652 mmol) was added to it. The reaction mixture was stirred overnight at room temperature, and a white precipitate of trichloroacetamide developed slowly. The solution was filtered off, and washed with DCM. The filtrate was washed with NaHCO₃ solution, water and brine. Purification by means of silica gel chromatography 9:1 (hexane/EtOAc) yielded compound **6** in 85% yield. $\delta_{\rm H}$: 7.25 (d, *I* = 7.6 Hz, 2H), 6.86 (d, *I* = 7.6 Hz, 2H), 5.73 (m, 1H), 5.23–5.18 (m, 2H), 4.5 (d, J = 11.2 Hz, 1H), 4.28 (d, J = 11.2 Hz, 1H), 3.77 (s, 3H), 3.61 (m, 1H), 3.58 (t, J = 6.4 Hz, 2H), 1.65–1.54 (m, 4H), 0.917 (s, 9H), 0.049 (s, 6H). δ_C: 159.08, 139.21, 130.93, 129.32, 116.96, 113.76, 80.06, 69.71, 63.07, 55.27, 31.82, 28.72, 26.0, 18.37, -5.27. $[\alpha]_{D}^{29} = -18.5$ (c 1.0, MeOH). HRMS (+ESI) calcd for C₂₀H₃₄O₃SiNa (M+Na⁺): 373.2169; found, 373.2176.

4.8. (S)-4-(4-Methoxy-benzyloxy)-hex-5-en-1-ol 7

Compound **6** (1.5 g, 4.3 mmol) was dissolved in 25 mL of MeOH. Pyridinium *para*-toluene sulfonate (PPTS, 0.9 g, 4.3 mmol) was added to the reaction mixture and it was stirred at room temperature for 6 h. After completion of the reaction, the MeOH was evaporated and the crude reaction mixture was taken in DCM, washed with water, NaHO₃ solution and brine. The organic layer was dried (MgSO₄) and evaporated. The crude alcohol was purified by silica gel chromatography (3:1, hexane/EtOAc) to afford the compound **7** in 88% yield. $\delta_{\rm H}$: 7.25 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.75 (m, 1H), 5.24–5.19 (m, 2H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 3.77 (s, 3H), 3.75 (m, 1H), 3.59 (t, *J* = 6.0 Hz, 2H), 1.7–1.59 (m, 4H). $\delta_{\rm C}$: 159.19, 138.80, 130.48, 129.46, 117.19, 113.83, 80.10, 69.88, 62.76, 55.27, 32.27, 28.78. $[\alpha]_{\rm D}^{29} = -20.2$ (*c* 1.75, MeOH). HRMS (+ESI) calcd for $C_{14}H_{20}O_3Na$ (M+Na⁺): 259.1304; found, 259.1301.

4.9. (S)-4-(4-Methoxy-benzyloxy)-hex-5-enoic acid 8

Compound **7** (0.4 g, 1.7 mmol) was taken in anhydrous DMF (10 mL). Pyridinium dichromate (PDC, 3.2 g, 8.5 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 washing with an aq KHSO₄ solution. The organic solvent was dried (MgSO₄) and evaporated. The crude acid was purified by silica gel chromatography (1:1, hexane/EtOAc). $\delta_{\rm H}$: 7.24 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.73 (m, 1H), 5.25 (m, 2), 4.52 (d, *J* = 11.2 Hz, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 3.8 (s, 3H), 3.76 (m, 1H), 2.45 (t, *J* = 7.2 Hz, 2H), 1.94–1.8 (m, 4H). $\delta_{\rm C}$: 179.44, 159.06, 138.09, 130.35, 129.35, 117.70, 113.72, 78.76, 69.79, 55.18, 30.07, 30.01. [α]_D² = -19.9 (*c* 1.0, MeOH).

HRMS (+ESI) calcd for $C_{14}H_{18}O_4Na$ (M+Na⁺): 273.1097; found, 273.1091.

4.10. 4-(4-Methoxy-benzyloxy)-butan-2-ol 9

Butane-1,3-diol (10 g, 111 mmol) was taken in 200 mL of dry THF. Then, NaH (60% dispersion in mineral oil, 3.11 g, 111 mmol) was added to it portionwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Tetrabutylammonium iodide (TBAI, 5 mmol) was added to it followed by the addition of 4-methoxybenzylbromide. The reaction mixture was stirred for a further 2 h at room temperature. Water was added carefully to the reaction mixture to quench any excess of NaH. The reaction mixture was extracted with a large volume of EtOAc. The organic solution was washed with water and brine. Evaporation and purification by means of silica gel chromatography (2.5:1, hexane/EtOAc) afforded the compound **9** in 80% yield.

δ_H: 7.23 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.42 (s, 2H), 3.94 (m, 1H), 3.77 (s, 3H), 3.62 (m, 2H), 1.75–1.65 (m, 2H), 1.15 (d, J = 6.0 Hz, 3H).

 $δ_{\rm C}$: 159.20, 129.98, 129.24, 113.78, 72.86, 67.52, 55.20, 38.04, 23.27.

4.11. Acetic acid (*R*)-3-(4-methoxy-benzyloxy)-1-methyl-propyl ester 10

In a 100 mL round-bottomed flask attached to a grease free high vacuum stopcock, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium(II) [DKR catalyst, 142 mg, 0.228 mmol] was taken. The flask was successively charged with alcohol **9** (1.2 g, 5.7 mmol) in 20 mL of dry toluene, Na₂CO₃ (5.7 mmol), CAL-B (65 mg) and KOtBu (0.28 mmol) followed by isopropenyl acetate (5 mmol). The reaction mixture was stirred at room temperature under an argon atmosphere, after which the reaction mixture was filtered off and the solution was evaporated to afford the crude acetate **10**, which was subsequently purified by silica gel chromatography (7:1, hexane/EtOAc) to afford the pure acetate **10** in 92% yield. $\delta_{\rm H}$: 7.22 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.06 (m, 1H), 4.39 (s, 2H), 3.77 (s, 3H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.01 (s, 3H), 1.9–1.81 (m, 2H), 1.21 (d, *J* = 6.0 Hz, 3H). $\delta_{\rm C}$: 170.55, 159.20, 130.81, 129.27, 113.78, 72.65, 68.55, 66.25, 55.23, 36.06, 21.27, 20.22. [α]_D²⁹ = -6.45 (*c* 3.0, MeOH).

4.12. (R)-4-(4-Methoxy-benzyloxy)-butan-2-ol 11

The acetate group was deprotected as described earlier in Section 4.6. $[\alpha]_{D}^{29} = -24.4$ (*c* 0.5, MeOH).

4.13. *tert*-Butyl-[(*R*)-3-(4-methoxy-benzyloxy)-1-methyl-propoxy]-diphenyl-silane 12

Compound 11 (6.5 g, 27.5 mmol) was taken in 100 mL of anhydrous DCM. Imdidazole (3.75 g, 55 mmol) was added to it at room temperature. The reaction mixture was stirred for 15 min, after which time TBDPS-Cl (8 mL, 33 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 (MgSO₄) and evaporated to dryness to afford the crude silylated compound 12, which was purified by silica gel chromatography (15:1, hexane/EtOAc). *δ*_H: 7.7 (m, 4H), 7.5–7.4 (m, 6H), 7.22 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.32 (s, 2H), 4.06 (m, 1H), 3.80 (s, 3H), 3.51 (t, J = 6.6 Hz, 2H), 1.9–1.75 (m, 2H), 1.0 (s, 9H). δ_{C} : 159.13, 135.94, 135.62, 134.42, 134.05, 130.76, 129.53, 129.46, 127.66, 127.55, 127.45, 113.76, 72.52, 67.27, 66.94, 55.31, 39.80, 27.08, 23.78, 19.34. $[\alpha]_{D}^{29} = -22.1$ (c 1.2, MeOH).

4.14. (R)-3-(tert-Butyl-diphenyl-silanyloxy)-butan-1-ol 13

Compound **12** (24.5 g, 55 mmol) was taken in 150 mL of DCM/ H₂O (19:1). DDQ (18.72 g, 82.5 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% NaHCO₃ solution, water and brine. The organic layer was dried (MgSO₄) and evaporated. Purification by silica gel chromatography (3:1, hexane/EtOAc) afforded the pure compound **13** in 86% yield. $\delta_{\rm H}$: 7.72–7.68 (m, 4H), 7.45–7.37 (m, 6H), 4.11 (m, 1H), 3.84 (m, 1H), 3.68 (m, 1H), 1.85 (m, 1H), 1.67 (m, 1H), 1.09 (d, *J* = 6.0 Hz, 3H), 1.06 (s, 9H). $\delta_{\rm C}$: 135.94, 135.88, 134.28, 133.79, 129.79, 129.69, 127.72, 127.57, 68.73, 59.98, 40.82, 27.03, 23.06, 19.20. [α]_D² = -2.6 (*c* 2.0, MeOH).

4.15. (R)-3-(tert-Butyl-diphenyl-silanyloxy)-butyraldehyde 14

Oxalvl chloride (3.62 mL, 41 mmol) was taken in anhydrous DCM (100 mL). Then DMSO (5.85 mL, 82.5 mmol) was added to the solution and kept at -78 °C. After 5 min alcohol 13 (9 g, 27.5 mmol) was added to it, and the solution was stirred at the same temperature for further 45 min. After this time Et₃N (23 mL, 165 mmol) was added slowly to the reaction mixture at the same temperature. The reaction mixture was allowed to attain room temperature. Water was added to the solution, and the mixture was extracted with DCM. The organic extract was washed with water, NaHCO₃ solution and brine. The organic layer was dried (MgSO₄) and evaporated. Purification by silica gel chromatography yielded the aldehyde 14 in 92% yield. $\delta_{\rm H}$: 9.76 (t, J = 2.0 Hz, 1H), 7.67 (m, 4H), 7.46–7.38 (m, 6H), 4.35 (m, 1H), 2.51 (m, 2H), 1.190 (d, J = 6.4 Hz, 3H), 1.08 (s, 9H). δ_{C} : 201.98, 135.75, 135.68, 133.95, 133.50, 129.79, 129.66, 127.68, 127.53, 65.61, 52.68, 26.85, 23.77, 19.11. $[\alpha]_D^{29} = -1.6$ (*c* 1.0, MeOH).

4.16. (3S,5R)-5-(tert-Butyl-diphenyl-silanyloxy)-hex-1-en-3-ol 15

Vinylmagnesium bromide addition onto aldehyde **14** was performed as described under Section 4.4 to yield two diastereomeric alcohols **15** (less polar by TLC) and **16** in a 1:1 ratio. They were separated by silica gel chromatography. δ_{H} : 7.74 (m, 4H), 7.41 (m, 6H), 5.84 (m, 1H), 5.26 (td, *J* = 16.0, 2.4 Hz, 1H), 5.08 (td, *J* = 10.4 Hz, 2.4 Hz, 1H), 4.45 (m, 1H), 4.18 (m, 1H), 1.7–1.6 (m, 2H), 1.05 (d, *J* = 6.0 Hz, 3H), 1.0 (s, 9H). δ_{C} : 141.30, 136.14, 136.10, 134.27, 133.74, 130.05, 129.80, 127.93, 127.80, 114.15, 69.81, 68.53, 45.12, 27.23, 23.05, 19.38.

4.17. (3*R*,5*R*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-hex-1-en-3-ol 16

 $δ_{\rm H}: 7.74 (m, 4H), 7.41 (m, 6H), 5.84 (m, 1H), 5.24 (td,$ *J*= 16.0, 2.4 Hz, 1H), 5.07 (td,*J*= 10.4 Hz, 2.4 Hz, 1H), 4.35 (m, 1H), 4.14 (m, 1H), 1.7–1.5 (m, 2H), 1.0 (s, 9H), 0.9 (d,*J* $= 6.0 Hz, 3H). <math>δ_{\rm C}:$ 141.01, 135.95, 135.48, 134.51, 133.76, 129.85, 129.69, 127.79, 127.58, 114.23.

4.18. (2R,4S)-Hex-5-ene-2,4-diol 17

Compound **15** (80 mg, 0.2 mmol) was taken in dry THF (4 mL). TBAF (1 M in THF, 0.307 mL) was added to it, and the reaction mixture was stirred for 3 h at room temperature. After this time, THF was evaporated, and water (20 mL) was added to it, the reaction mixture was extracted with EtOAc (2×25 mL), the organic layer was washed with dilute NaHCO₃ solution, brine and dried (MgSO₄). It was purified by flash chromatography (1:1; hexane/EtOAc) to afford the *anti* diol **17** in 85% yield. The spectral characteristic data (¹H and ¹³C NMR) were in perfect agreement with the literature values.²¹

4.19. (2R,4R)-Hex-5-ene-2,4-diol 18

The *syn*-diol **18** was obtained as described in Section 4.18 from compound **16**. The spectral characteristic data (¹H and ¹³C NMR) were in perfect agreement with the literature values.²¹

4.20. (4R,6S)-2,2,4-Trimethyl-6-vinyl-[1,3]dioxane 19

Anti diol **17** (40 mg, 0.34 mmol) was taken in 2 mL of dry DCM. 2,2-dimethoxypropane (DMP, 0.43 mmol, 106 μ L) was added to it followed by the addition of a catalytic amount of PPTS. The reaction mixture was stirred at room temperature overnight. The product was purified by flash chromatography (3:1, hexane/EtOAc) to afford the *anti* acetonide **19** in 80% yield. δ_{H} : 5.90 (ddd, *J* = 16.0. 9.6, 7.6 Hz, 1H), 5.4 (td, *J* = 16.0, 1.6 Hz, 1H), 5.16 (td, *J* = 9.6, 1.6 Hz, 1H), 4.46 (m, 1H), 4.17 (m, 1H), 1.55 (m, 2H), 1.52 (s, 3H), 1.46 9s, 3H), 1.24 (d, *J* = 6.0 Hz, 3H). δ_{C} : 140.67, 115.06, 100.18, 67.93, 62.53, 38.83, 25.72, 25.00, 21.79.

4.21. (4R,6R)-2,2,4-Trimethyl-6-vinyl-[1,3]dioxane 20

The *syn*-acetonide was prepared from the *syn*-diol **18** as described in Section 4.21. δ_{H} : 5.78 (ddd, J = 16.0, 9.6, 7.6 Hz, 1H), 5.35 (td, J = 16.0, 1.6 Hz, 1H), 5.15 (td, J = 9.6, 1.6 Hz, 1H), 4.35 (m, 1H), 4.08 (m, 1H), 1.5 (s, 3H), 1.45 (s, 3H), 1.24 (d, J = 6.0 Hz), δ_{C} : 138.83, 115.28, 98.59, 70.19, 64.86, 38.47, 30.29, 22.18, 19.82.

4.22. *tert*-Butyl-[(1*R*,3*S*)-3-(4-methoxy-benzyloxy)-1-methylpent-4-enyloxy]-diphenyl-silane 21

Secondary hydroxyl group in compound **15** was protected as its PMB ether as described in Section 4.7 to afford the compound **21** in 82% yield.

 $δ_{\rm H}: 7.67 (m, 4H), 7.5-7.32 (m, 6H), 7.25 (d,$ *J*= 8.4 Hz, 2H), 6.83 (d,*J*= 8.4 Hz, 2H), 5.61 (m, 1H), 5.25 (m, 2H), 4.37 (d,*J*= 11.8 Hz, 1H), 4.11 (q,*J*= 6.0 Hz, 1H), 4.03 (d,*J*= 11.8 Hz, 1H), 3.93 (m, 1H), 3.78 (s, 3H), 1.71 (t,*J*= 6.4 Hz, 2H), 1.06 (d,*J* $= 6.0 Hz, 3H), 1.03 (s, 9H). <math>δ_{\rm C}:$ 159.23, 139.54, 136.13, 135.11, 135.02, 134.67, 131.14, 129.70, 129.61, 129.48, 127.71, 127.59, 116.74, 113.91, 76.59, 70.02, 67.04, 55.48, 46.42, 27.27, 24.47, 19.49. $[α]_{\rm D}^{29} = +1.0$ (c 1.25, MeOH).

4.23. (2R,4S)-4-(4-Methoxy-benzyloxy)-hex-5-en-2-ol 22

Compound **21** was desilylated using TBAF as described in Section 4.18 to afford the alcohol **22** in 90% yield.

 $δ_{\rm H}: 7.24 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.82 (m, 1H),$ 5.24 (m, 2H), 4.54 (d, J = 11.2 Hz, 1H), 4.29 (d, J = 11.2 Hz, 1H), 4.07
(m, 2H), 3.79 (s, 3H), 1.69 (m, 2H), 1.14 (d, J = 6.4 Hz, 3H). $δ_{\rm C}:$ 159.18, 138.11, 130.17, 129.40, 117.05, 113.81, 76.65, 69.94,
64.59, 55.20, 43.57, 23.27. $[α]_{\rm D}^{29} = -13.7$ (c 1.25, MeOH). HRMS
(+ESI) calcd for C₁₄H₂₀O₃Na (M+Na⁺): 259.1304; found, 259.1308.

4.24. (*S*)-4-(4-Methoxy-benzyloxy)-hex-5-enoic acid (1*R*,3*S*)-3-(4-methoxy-benzyloxy)-1-methyl-pent-4-enyl ester 23

The carboxylic acid 8 (222 mg, 0.889 mmol) was taken in 5 mL of anhydrous THF. Then. EEDO (2-ethoxy-1-ethoxycarbonyl-1.2dihydroquinoline, 330 mg, 1.3 mmol) was added to the reaction mixture and the solution was stirred for 30 min at room temperature. After this time alcohol 22 (140 mg, 0.59 mmol) was added to it and the solution was stirred for further 4 h at the same temperature. After completion of the reaction, the THF was evaporated and the crude mixture was directly purified using silica gel chromatography (3:1, hexane/EtOAc) to afford the ester 23 in 92% yield. $\delta_{\rm H}$: 7.25 (m, 4H), 6.86 (m, 4H), 5.71 (m, 2H), 5.25–5.15 (m, 4H), 5.10 (m, 1H), 4.51 (d, J = 11.2 Hz, 1H), 4.47 (J = 11.2 Hz, 1H), 4.27 (d, J = 11.2 Hz, 1H), 4.24 (d, J = 11.2 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.73 (m, 1H), 2.33-2.2 m, 2H), 1.88-1.65 (m, 4H), 1.18 (d, J = 6.4 Hz, 3H). δ_C : 172.77, 159.06, 159.02, 138.46, 138.34, 130.53, 130.32, 129.57, 129.28, 129.25, 117.55, 117.52, 117.04, 113.70, 79.14, 79.03, 69.86, 69.76, 67.64, 55.20, 55.17, 42.22, 30.49, 30.34, 20.52. $[\alpha]_{D}^{29} = -58.3$ (*c* 1.5, MeOH).

HRMS (+ESI) calcd for $C_{28}H_{36}O_6Na$ (M+Na⁺): 491.2404; found, 491.2409.

4.25. (*S*)-4-Hydroxy-hex-5-enoic acid (1*R*,3*S*)-3-hydroxy-1-methyl-pent-4-enylester 24

The PMB-ether groups in compound **23** were removed as described in Section 4.14 to afford the diol **24** in 85% yield. $\delta_{\rm H}$: 5.84 (m, 2H), 5.26–5.07 (m, 5H), 4.18 (m, 1H), 4.10 (m, 1H), 2.4–2.3 (m, 2H), 1.8–1.6 (m, 4H), 1.21 (d, *J* = 6.4 Hz, 3H). $\delta_{\rm C}$: 177.02, 140.54, 135.43, 117.47, 114.29, 80.45, 70.50, 65.24, 43.69, 28.65, 28.20, 20.54. [$\alpha_{\rm D}^{29}$ = –29.3 (*c* 0.5, MeOH). HRMS (+ESI) calcd for C₁₂H₂₀O₄Na (M+Na⁺): 251.1254; found, 251.1251.

4.26. (*E*)-(55,85,10*R*)-5,8-Dihydroxy-10-methyl-3,4,5,8,9,10-hexahydro-oxecin-2-one (stagonolide-C)

The diol **24** (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 (3:1) afforded the pure stagonolide-C in 65% yield. $\delta_{\rm H}$: 5.58 (dd, *J* = 15.6 Hz, 9.2 Hz, 1H), 5.42 (dd, *J* = 15.6 Hz, 9.2 Hz, 1H), 5.14 (m, 1H), 4.01 (m, 2H), 2.28 (m, 2H), 2.29 (m, 1H), 2.07–2.01 (m, 3H), 1.88 (dd, *J* = 13.2, 2.8 Hz, 1H), 1.77 (ddd, *J* = 13.2, 11.2, 2.8 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 3H). $\delta_{\rm C}$: 174.54 (qC), 135.81 (CH), 132.95 (CH), 74.42 (CH), 72.02 (CH), 67.75 (CH), 43.34 (CH₂), 34.39 (CH₂), 31.51 (CH₂), 21.35 (CH₃). [α]_D²⁹ = +44.4 (*c* 1.0, MeOH). HRMS (+ESI) calcd for C₁₀H₁₆O₄Na (M+Na⁺): 223.0941, found: 223.0944.

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