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Stereoselective total synthesis of stagonolide-C

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ABSTRACT

The highly stereoselective synthesis of a biologically active stagonolide-C has been described. The pivotal functionalities are derived from Barbier allylation, an epoxidation by *m*-CPBA, a chiral-auxiliary mediated acetate aldol addition, a 1,3-*anti*-reduction, a Sharpless kinetic resolution, a Yamaguchi macrolactonization, and ring-closing metathesis.

1. Introduction

Nonenolides have been isolated as secondary metabolites of terrestrial and marine organisms, such as bacteria, fungi, and plants, and exhibit various biological activities including antibacterial, antifungal, phytotoxic, or enzyme-inhibitory effects.[1] Their scarcity coupled with the complexity of the natural material poses a great challenge for synthetic chemist. Stagonolide A, a new nonenolide, was first isolated and its chemical and biological characterization from the liquid culture filtrate of *Stagonospora cirsii* (a pathogen of *Cirsium arvense*) was carried out in 2007 by Berestetskiy et al.[2] In 2008, Evidente et al. reported the isolation of five new nonenolides from the same fungus, grown in solid culture.[3] Considering their origin and structural similarity, these five new nonenolides were named as stagonolides B–F, and 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* or *Sonchus arVensis*, whereas stagonolide A was highly toxic. Stagonolide C was isolated from the same fungus and was proposed as a potential mycoherbicide by causing necrotic lesions on leaves. Stagonolide A and stagonolide C **1** were weakly toxic to *Colpoda steinii*, a protozoan, when tested at 0.05 mg/mL, with the other stagonolides being nontoxic. All stagonolides shown in Figure 1 possess some common and interesting structural features; the olefinic moiety with a well-defined geometry as well as stereochemically pure hydroxyl appendages make them very challenging synthetic targets. The first total synthesis of **1** was reported by Mohapatra et al.[4] The target molecule was achieved by assembling the key fragments by using Sharpless epoxidation and intramolecular ring-closing metathesis to construct the macrolide *trans* double bond. Jana et al.[5] reported the synthesis by using a metal–enzyme combined DKR strategy, RCM. Qiao et al.[6] also achieved the total synthesis of the key fragment from L-glutamic acid and D-glucono-1,5-lactone, followed by Julia–Lythgoe olefination and Yamaguchi esterification. Recently Yadav et al.[7] reported a synthesis by using a Prins cyclization along with alkene rearrangement and ring-closing metathesis as the key steps. In continuation of our efforts[8] toward the total synthesis of biologically active natural products, we herein report the stereoselective total synthesis of stagonolide C **1** by employing a key inter-

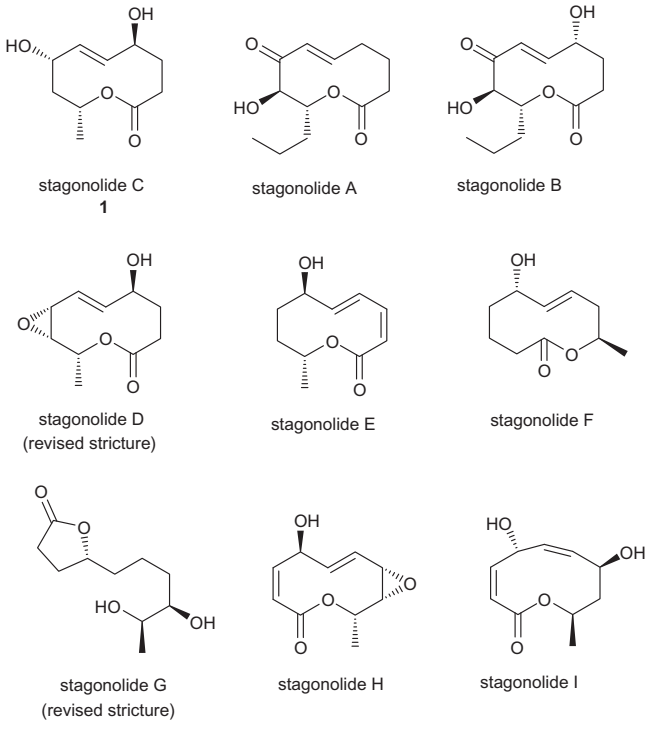

Figure 1. Naturally occurring stagonolides.

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mediate 1,3-*anti* diol by stereoselective epoxidation, chiral auxiliary mediated aldol reaction, Sharpless kinetic resolution, Yamaguchi macrolactonization, and RCM for the construction of the central nonenolide core with the required *E*-stereochemistry of the ring olefin.

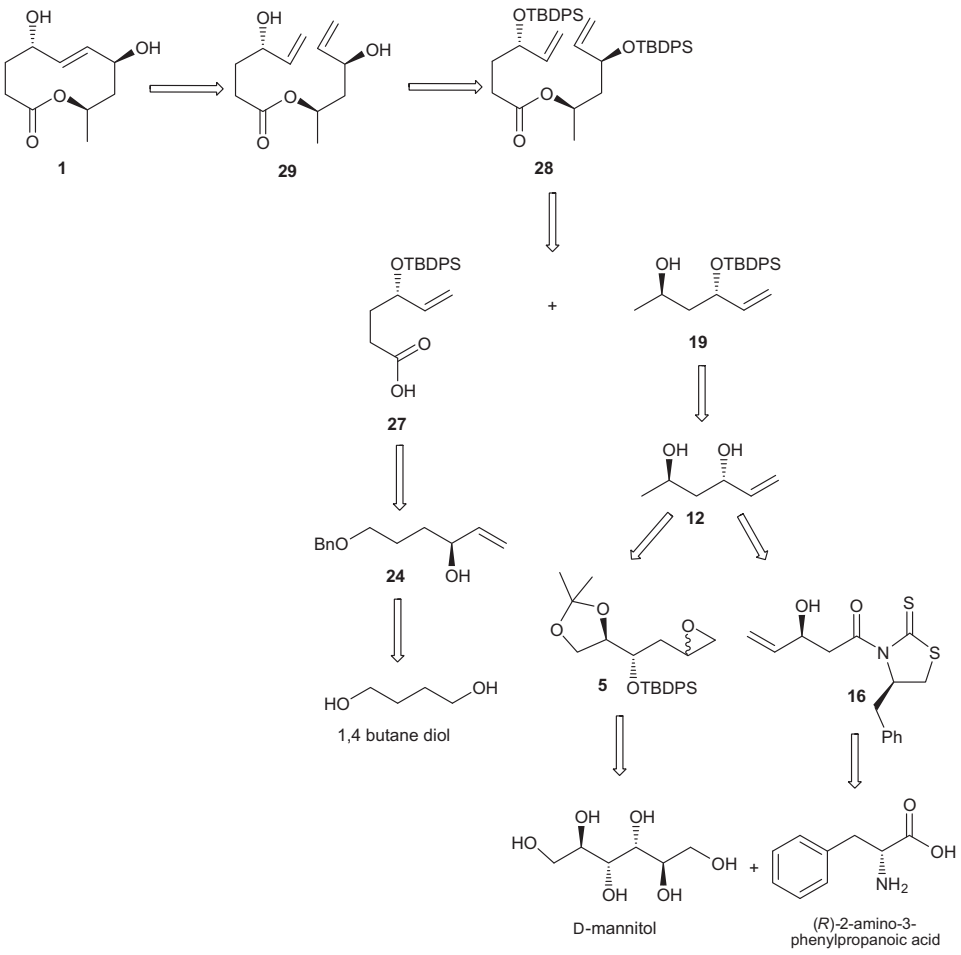
2. Results and discussion

Our synthetic approach for the synthesis of stagonolide-C **1** was envisioned through the retrosynthetic route depicted in Scheme 1. Accordingly we envisaged that stagonolide-C **1** could be accessed from ester **29** with two terminal olefin moieties by ring closing metathesis. Acid **27** and alcohol **19** were identified as the key coupling partners for compound **28**. Acid **27** can be prepared from benzylic ether **24** generated from 1,4-butanediol. Alcohol **19** with two stereocenters can be obtained from **12**. Key intermediate **12** was obtained from **5** by regioselective reductive opening of the epoxide ring, selective acetonide deprotection, and olefination. Compound **5** can be prepared by epoxidation, Barbier allylation of (*R*)-2,3-*O*-isopropylideneglyceraldehyde **2**, which in turn can be obtained from commercially available D-mannitol as the starting material in a chiron pool approach. The key segment **12** can also be achieved from acetate aldol adduct **16** by a 1,3-*anti*-selective reduction and a methyl Grignard reaction. Compound **16** can be obtained by an aldol reaction between acrolein **15** and the titanium enolate of *N*-acetyl-4-benzyl-thiazolidinethione **14**, which in turn can be prepared from D-phenylalanine (Scheme 1).

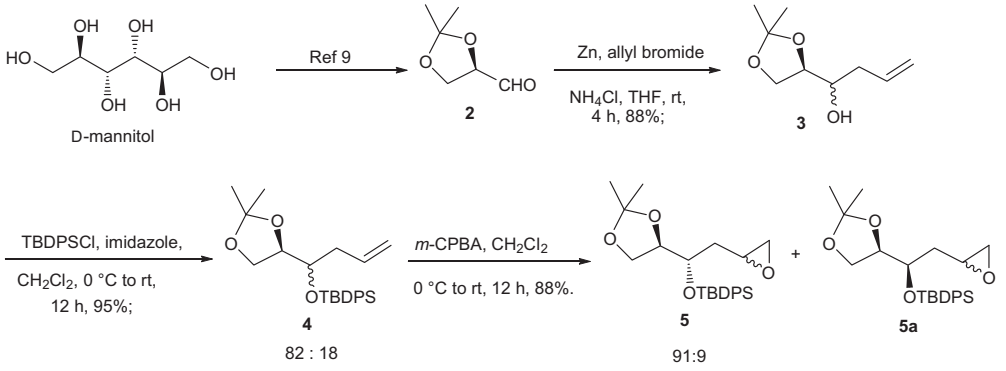
2.1. Synthesis of alcohol fragment 12 by using D-mannitol

The synthesis of the alcohol fragment began with commercial and inexpensive D-mannitol. This was easily converted into (*R*)-2,3-*O*-isopropylidene glyceraldehyde[9] **2** using a well-known procedure. Treatment of (*R*)-glyceraldehyde **2** with allyl bromide in the presence of zinc dust and aqueous ammonium chloride in THF at 0 °C to rt afforded the corresponding homoallyl alcohol[10] **3** as a major diastereomer in favor of the *anti*-isomer in 88% yield. The mixture of homo allylic alcohol **3** was then protected with a *tert*-butylphenylsilyl group by using TBDPSCl, and imidazole in DCM at rt for 12 h to afford an inseparable diastereomeric mixture of *anti* and *syn* (82:18 by LCMS) **4** in 95% yield.[11] The diastereomeric mixture **4**, upon treatment with *m*-CPBA in DCM at 0 °C to rt, produced the easily separable diastereomeric pair **5** and **5a** (Scheme 2). These pairs were separated by column chromatography to afford the required diastereomeric pair **5** in 72.2% yield. The diastereomeric ratio of **5** was confirmed by LCMS analysis (91:9). According to previous reports, the formation of the epoxide takes place *anti* to the alkoxy group at the homoallylic position. Studies with benzyl and *para*-methoxy benzyl groups produced the *anti* and *syn* products in a 2:1 ratio.[12] The *anti*, *syn* ratio mainly depends on the allylic 1,3 strain of the bulky TBDPS group and the homoallylic epoxy interaction with *m*-CPBA.[13]

The major diastereomeric pair **5** was used directly in further steps. The major 1,3-*anti*-epoxide **5** underwent regioselective reductive opening with DIBAL–H in DCM at −78 °C for 1 h to afford



Scheme 1. Retrosynthetic analysis of stagonolide-C.

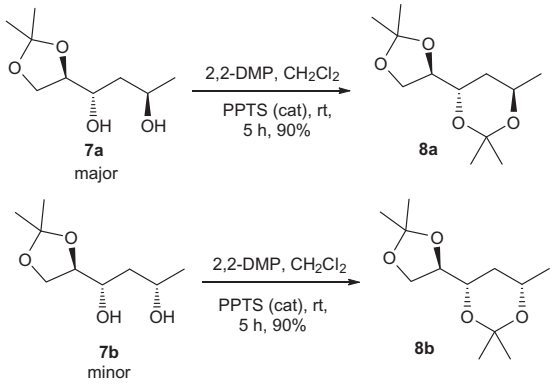


Scheme 2.

sec-alcohol **6** in 82% yield.[14] Subsequent silyl deprotection done by using TBAF in THF at rt furnished **7** as separable diastereomers. These diastereomers **7** were separated by flash column chromatography to afford the major diastereomer 1,3-*anti*-**7a** isolated in 82.8% yield along with minor **7b** 9.2% (Scheme 3).

In order to confirm the 1,3-*syn* and 1,3-*anti* relationships of **7a** and **7b**, they were separated and converted into acetonides by treatment with 2,2-DMP in the presence of cat. PPTS in DCM at rt for 5 h to obtain the respective 1,3-*anti*- and 1,3-*syn*-diols **8a** and **8b** both in 90% yield[15] (Scheme 4).

The *syn* and *anti* relative configuration of the hydroxy groups was confirmed based on Rychnovsky's analogy. The stereochemistry of *syn*- and *anti*-1,3-acetonide was confirmed by the ^{13}C NMR chemical shifts[16] of the six-membered acetonide. The ^{13}C NMR spectra of *syn*-1,3-diol acetonides **8b** show an axial methyl group around δ 29.7 and an equatorial methyl group around δ 19.5. ^{13}C NMR chemical shifts of ketal carbons follow a stereo regular pattern where the *syn*-diol acetonides resonate above δ 98.0, which was consistent with those found in the chair confirmation, and which is indicative of a 1,3-*syn*-diol disposition. Similarly the ^{13}C NMR spectrum of compound **8a** showed the ketal carbon at δ 100.0 and the acetonide methyl at δ 25.1 and 24.93, thus confirming it to be an *anti*-diol in a twist boat confirmation, which is indicative of a 1,3-*anti*-diol (Fig. 2). The major 1,3-*anti*-diol **7a** was protected with a *tert*-butylphenyl silyl group by using TBDPSCl and imidazole in DCM at rt for 12 h to afford compound **9** in 92% yield. After examining the deprotection of the acetonide under various reaction conditions (Table 1), we found that the deprotection of acetonide could be conducted successfully using PPTS in MeOH at 50 °C to afford diol **10** in 86% yield.[17] Direct conversion of diol **10** to olefin **11** under TPP, imidazole, and iodine in toluene refluxed for 2 days produced 10% of **11** along with a diiodo compound.

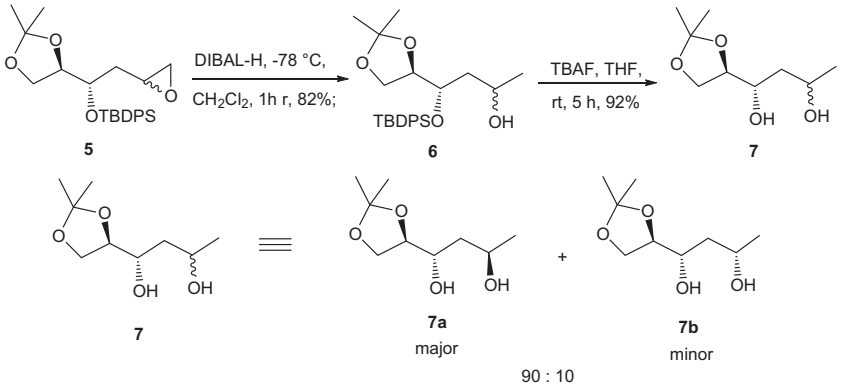


Scheme 4.

The mixture was treated with Zn in DMF and refluxed to afford olefin **11** in 85% yield.[18] Removal of both silyl groups with TBAF in THF at rt gave 1,3-diol **12** in 91% yield (Scheme 5), which proved to be identical to the literature,[19] when looking at the ^{1}H and ^{13}C NMR data and the specific rotation.

2.2. Synthesis of alcohol fragment 12 by using D-phenylalanine

The synthesis of **12** was also achieved by an alternative method according to Schemes 6–8. Our synthesis started from chiral auxiliary (*R*)-4-benzyl-thiazolidine-2-thione **13**, which was prepared from commercially available D-phenylalanine following the reported procedure.[20] Compound **13**, upon treatment with acetyl chloride in the presence of *n*-BuLi at −78 °C for 1 h, afforded N-acylated thiazolidinone **14** in 95% yield. Next, we started the synthesis of the key intermediate **16** with an aldol reaction between



Scheme 3.

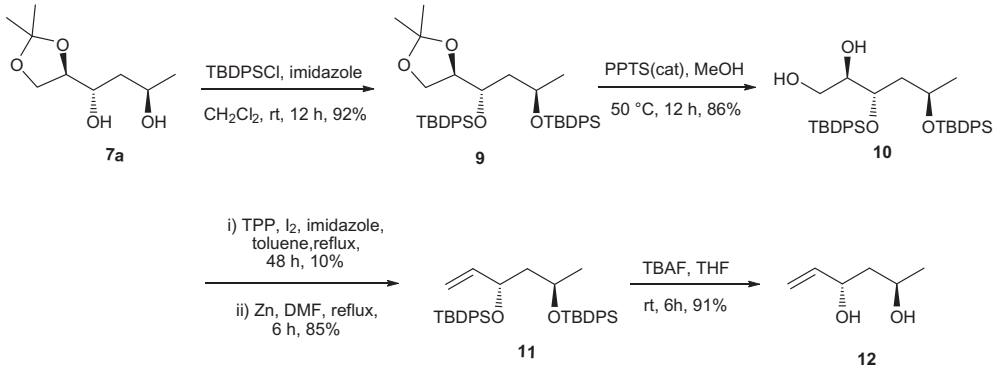
Table 1
Removal of the acetonide group in **9** under different conditions

S. No.	Reaction conditions	Yield[a] (%)
1	CSA (0.1 equiv)/MeOH/rt/12 h	No reaction
2	CSA (0.1 equiv)/MeOH/50 °C/12 h	60
3	*p*-TsOH (0.1 equiv)/MeOH/rt/6 h	Complex mixture
4	PPTS (0.1 equiv)/MeOH/rt/12 h	No reaction
5	PPTS (0.1 equiv)/MeOH/50 °C/12 h	86
6	80% aq AcOH (as solvent)/rt/12 h	55
7	80% aq AcOH (as solvent)/rt/36 h	40
8	50% aq CF_3CO_2H/CH_2Cl_2/rt/3 h	65

[a] Isolated yield after column chromatography purification.

acrolein **15** and the titanium enolate of *N*-acetyl-4-benzyl-thiazolidinethione **14**[8f,21] Consequently, the corresponding acetate aldol adducts **16** and **16a**[22] were obtained in 88% combined isolated yield with high diastereoselectivity (**16/16a** = *syn:anti* = 85:15). The more polar major *syn*-diastereomer **16** was easily separated by flash column chromatography in 74.8% isolated yield along with minor *anti*-diastereomer **16a** (13.2% isolated yield). The *syn*-aldol product **16** showed characteristic ^{1}H NMR chemical shift signals for the α-protons at δ 3.66 (dd, J = 17.3, 3.0 Hz, 1H) for the less shielded proton and at δ 3.32 (dd, J = 17.3, 8.6 Hz, 1H) for the more shielded proton along with other peaks in their respective positions, which confirmed the product formation. The less polar minor *anti*-aldol product **16a** showed characteristic ^{1}H NMR chemical shift signals for the corresponding α-protons at δ 3.62 (dd, J = 17.3, 8.6 Hz, 1H) for the less shielded proton and at δ 3.46–3.37 (m, 1H) for the more shielded proton (Scheme 6).

Transamidation[23] of the β-hydroxy amide **16** with *N*,*O*-dimethylhydroxylamine hydrochloride and imidazole in CH_2Cl_2 for 12 h resulted in the corresponding Weinreb amide **17** in 92% yield. Grignard reaction of Weinreb amide **17** with methylmagnesium iodide in ether at 0 °C to rt for 1 h furnished β-hydroxy ketone **18** in 86% yield[24] (Scheme 7).



Scheme 5.

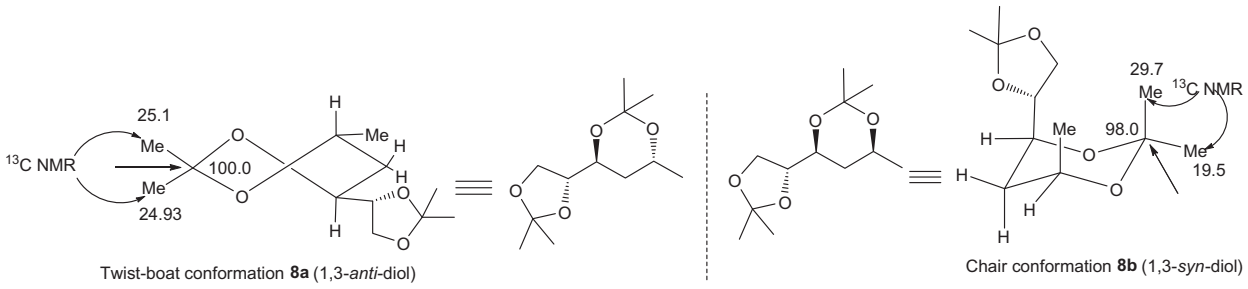
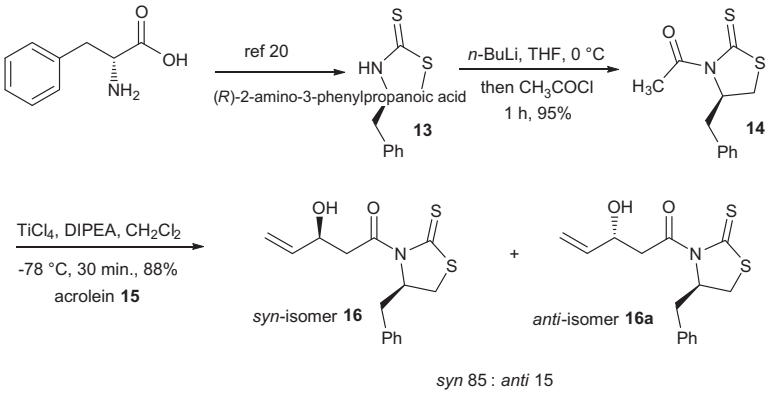
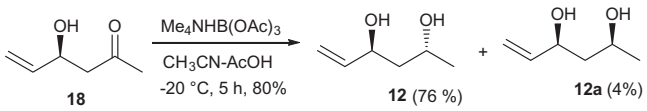


Figure 2. Characteristic conformations and ^{13}C NMR chemical shift values for 1,3-*syn*- and *anti*-diols.



Scheme 6.

The *anti*-selective reduction of β-hydroxy ketone **18** using tetramethylammonium triacetoxyborohydride[25] in the solvent system CH_3CN/AcOH (4:1) at −20 °C for 5 h afforded the corresponding 1,3-diols **12** and **12a** in 80% combined isolated yield with high diastereoselectivity (**12**/**12a** = *anti*:*syn* = 95:5) as a separable mixture, from which 76% of the major *anti*-diol **12** and minor *syn*-diol **12a** 4% was isolated by column chromatography (Scheme 8). The spectroscopic and specific rotation data of the compound were in full agreement with compound **12** prepared in the synthetic route as shown in Scheme 5. This is a new method for the synthesis of **12** which is an important intermediate.



Scheme 8.

Allylic alcohol **12** was selectively protected with a TBDPS group by using 1 equiv of TBDPSCl, imidazole in DCM at 0 °C for 5 h afforded the corresponding **19** and **20**, which were obtained in 90% combined isolated yield with high allylic selectivity[26] (**19**/**20** = 65: 35). The more polar major compound **19** was easily separated by flash column chromatography in 58.5% yield along with minor compound[5,27] **20** (31.5% yield). Compound **20** could be converted into its starting material **12** by simple desilylation using TBAF (Scheme 9).

2.3. Synthesis of the acid fragment

The other key fragment acid was synthesized by starting from 1,4-butane diol, which was protected with NaH and BnBr in the presence of a catalytic amount of TBAI in THF at rt for 5 h to give *mono*-benzyl ether **21** in 90% yield. The primary alcohol of **21** was oxidized with PCC in DCM at rt for 5 h to afford aldehyde **22** in 92% yield. Vinylation of aldehyde **22** using vinyl magnesium bromide in THF, at −78 °C for 1 h afforded *rac*-vinyl carbinol **23** in 88% yield. The *rac*-vinyl carbinol **23** upon Sharpless kinetic resolution[28] using (−)-DET, Ti(O*i*Pr)$_4$, and TBHP in DCM for 6 h afforded the enantiomerically enriched allylic alcohol **24** with 97% ee (determined by chiral HPLC) and 46% yield[29], which was separated from the epoxy product **24a** by column chromatography. Protection of alcohol **24** using TBDPSCl imidazole in DCM at 0 °C to rt for 8 h afforded TBDPS ether **25** in 95% yield. Subsequent removal of the benzyl group using DDQ in DCM–H_2O (19:1) at reflux for 4 h afforded primary alcohol **26** in 90% yield.[30] Oxidation of the primary alcohol **26** with PCC and NaOAc in dry CH_2Cl_2 at 0 °C to rt for 5 h furnished the aldehyde in 90% yield. Oxidation of the aldehyde using $NaClO_2$ and $NaH_2PO_4{\cdot}2H_2O$ in *t*-BuOH/H_2O (3:1) and a few drops of 2-methyl-2-butene at 0 °C to rt for 10 h (Pinnick's protocol) furnished acid **27** in 92% yield (Scheme 10).

2.4. Coupling of fragments 19 and 27 for the total synthesis of stagonolide-C

With the two key fragments **19** and **27** in hand our next task was to couple the two fragments and conduct the critical RCM reaction. Carboxylic acid **27** was coupled with alcohol **19** using Yamaguchi's protocol (2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP) to afford the dienoic ester **28** in 86% yield.[31] Finally deprotection of both TBDPS functionalities was achieved by treating compound **28** with HF/pyridine in pyridine and THF at rt for 8 h to afford diol **29** in 84% yield.[32] Compound **29** upon treatment with Grubbs 2nd generation catalyst in DCM at reflux for 24 h afforded target molecule stagonolide-C **1** in 68% yield (Scheme 11). The structural integrity of the synthetic stagonolide-C **1** with the correct stereochemistry at the three stereogenic centers was confirmed by comparison of its spectroscopic (^{1}H and ^{13}C NMR) data and specific rotation with literature data for the natural product {synthetic: $[\alpha]_D^{25} = +43.9$ (*c* 1.0, MeOH); Ref. 5: $[\alpha]_D^{29} = +44.4$ (*c* 1.0, MeOH)}.

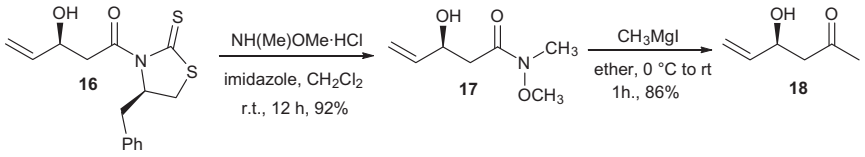
3. Conclusion

We have accomplished the total synthesis of stagonolide C **1** following a convergent approach involving a chiron pool synthesis. The main highlight of our synthetic strategy involves the Barbier allylation and subsequent epoxidation with *m*-CPBA. Chiral-auxiliary mediated acetate aldol addition, 1,3-*anti*-reduction, Sharpless kinetic resolution, Yamaguchi macrolactonization, and Grubbs' olefin metathesis reactions. This approach offers high stereoselectivity and readily available inexpensive starting material at low cost and simple experimental conditions, which makes it a useful and attractive process for the total synthesis of stagonolide C **1** for biological evaluation.

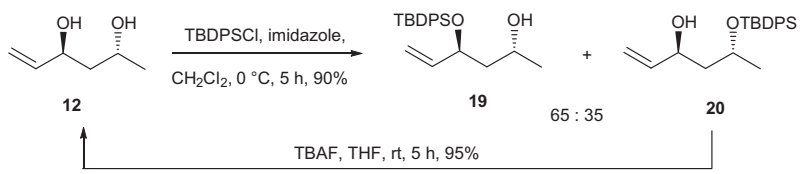
4. Experimental

4.1. General

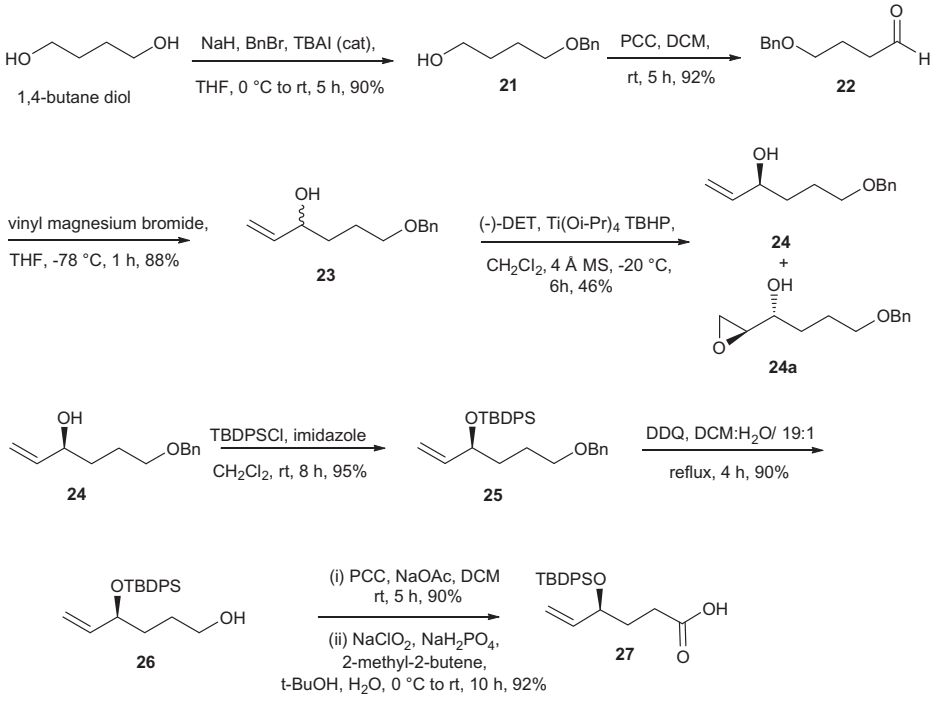
All solvents and reagents were used as received from suppliers. TLC was performed on Merck Kiesel gel 60, F_{254} plates with the



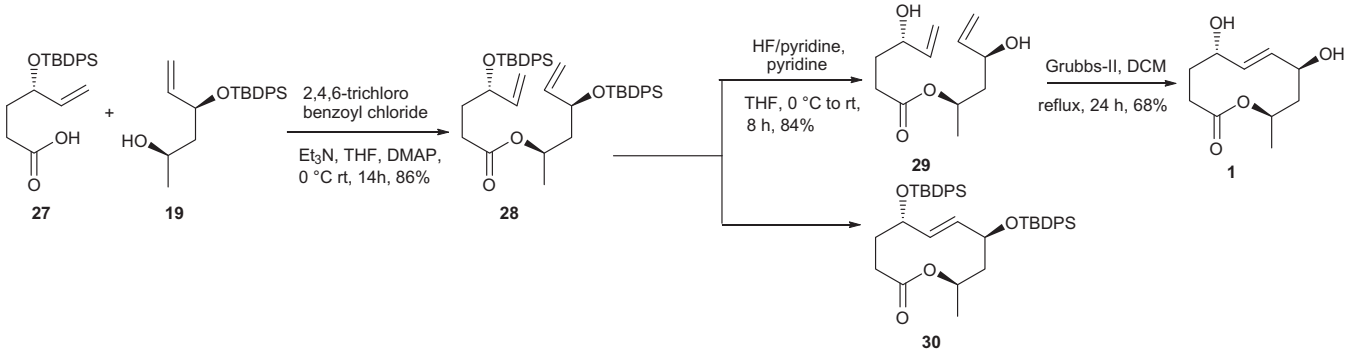
Scheme 7.



Scheme 9.



Scheme 10.



Scheme 11.

layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100–200 mesh) using a gradient of ethyl acetate and hexane as the mobile phase. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR spectroscopic data were collected at 300, 400, and 500 MHz, while ^{13}C NMR were recorded at 75, 100, and 125 MHz. ^{1}H NMR spectral data are given as chemical shifts in ppm followed by multiplicity (s—singlet; d—doublet; t—triplet; q—quartet; m—multiplet), number of protons, and coupling constants. ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with a JASCO digital polarimeter. HRMS spectroscopic data were collected using ORBITRAP high resolution mass spectrometer.

4.1.1. (*R*)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol 3

To a stirred solution of activated zinc (15.08 g, 230.6 mmol) in 100 mL of dry THF was added a solution of (*R*)-glyceraldehyde **2** (15 g, 115.3 mmol) in 150 mL of dry THF under nitrogen at 0 °C. After 30 min, allyl bromide (19.97 mL, 230.6 mmol) was added dropwise over 30 min at 0 °C. The reaction mixture was stirred for 4 h at room temperature. After completion of the reaction (monitored by TLC), the reaction was quenched by the slow addition of a saturated aqueous NH_4Cl solution (30 mL) at 0 °C over 30 min. After being stirred for 1 h, the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The crude product was partitioned between water and ethyl acetate (3 × 100 m). The combined organic layer was washed with brine (1 × 100 mL) dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 20% EtOAc in hexane) to afford **3** (17.46 g, 88%) as a colorless oil. $[\alpha]_D^{25} = +8.0$ (*c* 1.3, $CHCl_3$); IR (neat): ν_{max} 3460, 2988, 2895, 1375, 1215, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.92–5.78 (m, 1H), 5.19–5.09 (m, 2H), 4.05–3.98 (m, 2H), 3.97–3.89 (m, 1H), 3.82–3.72 (m, 1H), 2.37–2.15 (m, 2H), 2.08 (d, *J* = 3.4 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.9, 118.3, 117.9, 109.4, 109.0, 78.4, 78.0, 71.5, 70.3, 66.0, 65.1, 38.2, 37.5, 26.6, 26.5, 25.2, 25.2; MASS (ESIMS): *m*/*z* 195 $(M+Na)^+$; HRMS (ESIMS): *m*/*z* calcd for $C_9H_{16}O_3Na$ $(M+Na)^+$ 195.0997, found 195.0998.

4.1.2. (*R*)-*tert*-Butyl(1-(2,2-dimethyl-1,3-dioxolan-4-yl)but-3-enyloxy)diphenylsilane 4

To a stirred solution of alcohol **3** (10 g, 58.13 mmol) in anhydrous CH_2Cl_2 (150 mL) and imidazole (7.90 g, 116.3 mmol) at 0 °C was added TBDPSCl (18.12 mL, 69.76 mmol) dropwise and stirred

for 12 h at room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 8% EtOAc in hexane) to afford **4** (22.64 g, 95%) as a colorless syrupy liquid. $[\alpha]_D^{25} = +19.5$ (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} 3447, 3071, 2933, 2892, 2859, 1638, 1469, 1428, 1371, 1254, 1211, 1153, 1109, 1072, 997, 857, 821, 772, 740, 702, 610, 507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.61 (m, 4H), 7.55–7.28 (m, 6H), 5.80–5.63 (m, 1H), 4.99–4.84 (m, 2H), 4.02 (q, *J* = 6.3 Hz, 1H), 3.89–3.80 (m, 2H), 3.78–3.63 (m, 1H), 2.32–1.97 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.02, 135.97, 134.0, 133.8, 133.6, 129.71, 129.66, 127.6, 127.5, 127.4, 127.3, 117.5, 117.2, 77.8, 73.6, 72.9, 66.1, 65.3, 38.6, 37.5, 27.0, 26.5, 26.3, 25.4, 25.1, 19.4; MASS (ESIMS): *m*/*z* 433 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{25}H_{34}O_3NaSi$ $(M+Na)^+$ 433.2174, found 433.2176.

4.1.3. *tert*-Butyl((*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(oxiran-2-yl)ethoxy)diphenylsilane 5

To a stirred solution of *m*-CPBA (21 g, 121.9 mmol) in CH_2Cl_2 (150 mL) was added a solution of alkene **4** (20 g, 48.78 mmol) in CH_2Cl_2 (150 mL) and the mixture was stirred at room temperature overnight. After dilution with CH_2Cl_2 (200 mL), a saturated solution of $NaHSO_3$ (50 mL) was added to the reaction mixture and then it was washed with saturated $NaHCO_3$ (aq) solution (3 × 120 mL) and brine (1 × 150 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 15% EtOAc in hexane) to afford **5** (14.99 g, 72.2%) as a colorless syrup. $[\alpha]_D^{25} = +8.5$ (*c* 1.34, $CHCl_3$); IR (neat): ν_{max} 3448, 3049, 2932, 2891, 2858, 1636, 1470, 1427, 1373, 1257, 1213, 1109, 1073, 854, 823, 740, 703, 609, 506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74–7.64 (m, 4H), 7.47–7.33 (m, 6H), 4.26–4.08 (m, 1H), 3.99–3.85 (m, 2H), 3.76–3.58 (m, 1H), 3.07–2.91 (m, 1H), 2.67–2.56 (m, 1H), 2.27 (dd, *J* = 5.1, 2.6 Hz, 1H), 1.83–1.57 (m, 2H), 1.30 (s, 6H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.93, 135.89, 133.5, 133.4, 129.9, 129.8, 127.7, 127.60, 127.57, 127.5, 109.1, 78.3, 72.2, 66.7, 49.0, 47.4, 37.2, 27.0, 26.9, 26.4, 25.2, 19.4; MASS (ESIMS): *m*/*z* 427 $(M+H)^+$, 449 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{25}H_{34}O_4NaSi$ $(M+Na)^+$ 449.2124, found 449.2121.

4.1.4. (*S*)-4-(*tert*-Butyldiphenylsilyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)butan-2-ol 6

To a stirred solution of epoxide **5** (14 g, 32.86 mmol) in CH_2Cl_2 (150 mL) at −78 °C, a solution of DIBAL-H in toluene (1.0 M, 115.0 mL, 115.0 mmol) was added dropwise and stirred for 1.0 h at this temperature. The reaction was quenched by the addition of MeOH (20 mL), followed by a saturated aqueous sodium potassium tartrate solution (100 mL). It was warmed to 0 °C and stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and washed with brine (1 × 100 mL), dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 20% EtOAc in hexane) to afford **6** (11.53 g, 82%) as a colorless syrup. $[\alpha]_D^{25} = +13.3$ (*c* 0.64, $CHCl_3$); IR (neat): ν_{max} 3451, 2962, 2932, 2858, 2077, 1637, 1468, 1427, 1374, 1258, 1213, 1108, 1070, 740, 507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.81–7.59 (m, 4H), 7.44–7.33 (m, 6H), 4.22–4.03 (m, 1H), 3.92 (ddd, *J* = 12.0, 8.3, 6.7 Hz, 1H), 3.84–3.64 (m, 2H), 3.54 (ddd, *J* = 8.3, 6.7 Hz, 1H), 2.63 (d, *J* = 2.5 Hz, 1H), 1.63 (dd, *J* = 8.3, 4.5 Hz, 2H), 1.28 (s, 3H), 1.25 (s, 3H), 1.05 (s, 9H), 0.97 (d, *J* = 6.2 Hz, 2H), 0.94 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 133.4, 133.1, 130.0, 129.91, 129.86, 129.8, 127.7, 109.3, 78.6, 73.8, 67.7, 64.8, 43.9, 27.0, 26.3, 25.3, 23.8, 19.4; MASS (ESIMS): *m*/*z* 429 $(M+H)^+$, 451 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{25}H_{37}O_4Si$ $(M+H)^+$ 429.2461, found 429.2441.

4.1.5. 1-(2,2-Dimethyl-1,3-dioxolan-4-yl)butane-1,3-diols 7a and 7b

To an ice-cooled solution of **6** (11 g, 25.70 mmol) in dry THF (80 mL) was added a 1 M solution of TBAF in THF (51.4 mL, 51.4 mmol) and stirred for 5 h at room temperature. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 80 mL). The combined organic layer was washed with brine (1 × 80 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (100–200 mesh, 60% EtOAc–hexane) to give the more polar *anti*-diol **7a** (4.041 g, 82.8%) as a colorless oil and the minor *syn*-diol **7b** (0.449 g, 9.2%) as a colorless oil.

4.1.6. *anti*-Diol: (1*S*,3*R*)-1′-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)butane-1,3-diol 7a

$[\alpha]_D^{25} = -4.2$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3409, 2975, 2929, 1456, 1376, 1255, 1215, 1151, 1063, 971, 852, 514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.18 (dq, *J* = 12.4, 5.7 Hz, 1H), 4.07–3.91 (m, 4H), 2.76 (br s, –OH, 1H), 2.14 (br s, –OH, 1H), 1.63 (t, *J* = 5.7 Hz, 2H), 1.42 (s, 3H), 1.36 (s, 3H), 1.26 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.1, 78.3, 69.1, 65.6, 65.5, 40.2, 26.5, 25.2, 23.7; MASS (ESIMS): *m*/*z* 213 $(M+Na)^+$; HRMS (ESI): Calcd for $C_9H_{18}O_4Na$ $(M+Na)^+$ 213.1102, found 213.1110.

4.1.7. *syn*-Diol: (1*S*,3*S*)-1′-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)butane-1,3-diol 7b

$[\alpha]_D^{25} = +22.5$ (*c* 0.33, $CHCl_3$); IR (neat): ν_{max} 3417, 2980, 2930, 1455, 1377, 1255, 1215, 1153, 1064, 969, 849, 512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.23–3.90 (m, 5H), 3.11 (br s, –OH, 1H), 1.82–1.51 (m, 2H), 1.43 (s, 3H), 1.36 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.1, 78.4, 72.5, 68.9, 65.3, 40.5, 26.5, 25.2, 24.1; MASS (ESIMS): *m*/*z* 213 $(M+Na)^+$; HRMS (ESI): calcd for $C_9H_{18}O_4Na$ $(M+Na)^+$ 213.1102, found 213.1111.

4.1.8. (4*S*,6*R*)-4′-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2,6-trimethyl-1,3-dioxane 8a

To a solution of diol **7a** (0.1 g, 0.526 mmol) in dry CH_2Cl_2 (10 mL) was added 2,2-dimethoxy propane (0.077 mL, 0.63 mmol) and a catalytic amount of PPTS. The homogeneous solution was stirred for 4 h. Next, a saturated aq $NaHCO_3$ solution (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude residue was purified by column chromatography on silica gel (100–200 mesh, 5% EtOAc–hexane) to afford **8a** (0.109 g, 90%) as a colorless liquid. $[\alpha]_D^{25} = -37.6$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2986, 2935, 2891, 1453, 1376, 1223, 1180, 1131, 1073, 967, 933, 854, 520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.08–3.90 (m, 3H), 3.83–3.68 (m, 2H), 1.85 (ddd, *J* = 12.8, 9.0, 6.0 Hz, 1H), 1.64 (ddd, *J* = 12.8, 9.0, 6.0 Hz, 1H), 1.40 (s, 3H), 1.33 (s, 9H), 1.19 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.2, 100.0, 77.9, 67.8, 67.1, 62.5, 36.1, 26.6, 25.1, 24.93, 24.87, 21.5; MASS (ESIMS): *m*/*z* 253 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{12}H_{22}O_4Na$ $(M+Na)^+$ 253.1415, found 253.1411.

4.1.9. (4*S*,6*S*)-4′-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2,6-trimethyl-1,3-dioxane 8b

To a solution of diol **7b** (0.1 g, 0.526 mmol) in dry CH_2Cl_2 (10 mL) was added 2,2-dimethoxy propane (0.077 mL, 0.63 mmol) and a catalytic amount of PPTS. The homogeneous solution was stirred for 4 h. Next a saturated aq $NaHCO_3$ solution (2 mL) was

added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude residue was purified by column chromatography on silica gel (100–200 mesh, 5% EtOAc–hexane) to afford **8b** (0.109 g, 90%) as a colorless liquid. $[\alpha]_D^{25} = +3.4$ (*c* 3.1, $CHCl_3$); IR (neat): ν_{max} 3450, 2924, 2857, 1733, 1644, 1464, 1393, 1263, 1079, 407 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.05 (td, *J* = 7.9, 3.0 Hz, 1H), 4.02–3.94 (m, 1H), 3.90–3.83(m, 2H), 3.72 (ddd, *J* = 11.8, 7.9, 3.0 Hz, 1H), 1.73 (dt, *J* = 13.0, 3.0 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.27–1.20 (m, 1H), 1.12 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.8, 98.0, 78.0, 70.3, 66.8, 64.3, 35.4, 29.7, 26.4, 24.8, 21.8, 19.5; MASS (ESIMS): *m*/*z* 253 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{12}H_{22}O_4Na$ $(M+Na)^+$ 253.1415, found 253.1405.

4.1.10. (5*S*,7*R*)-5′-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2,7,10,10-pentamethyl-3,3,9,9-tetraphenyl-4,8-dioxa-3,9-disilaundecane 9

To a stirred solution of alcohol **7a** (3.7 g, 19.47 mmol) in anhydrous CH_2Cl_2 (80 mL) and imidazole (5.29 g, 77.89 mmol) at 0 °C was added TBDPSCl (12.66 mL, 48.68 mmol) dropwise and stirred for 8 h at room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with brine (1 × 80 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 5% EtOAc in hexane) to afford **9** (11.93 g, 92%) as a colorless syrup. $[\alpha]_D^{25} = +13.2$ (*c* 2.0, $CHCl_3$); IR (neat): ν_{max} 3453, 3068, 2932, 2893, 2858, 1634, 1466, 1427, 1376, 1256, 1212, 1108, 1072, 999, 857, 820, 738, 702, 610, 506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76–7.54 (m, 8H), 7.47–7.26 (m, 12H), 4.00–3.80 (m, 2H), 3.78–3.59 (m, 3H), 1.50–1.40 (m, 1H), 1.33 (s, 3H), 1.22 (s, 3H), 1.01 (s, 9H), 0.94 (s, 9H), 0.91–0.78 (m, 1H), 0.63 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.0, 135.9, 135.7, 134.7, 134.3, 129.6, 129.5, 129.4, 127.5, 127.4, 108.9, 78.9, 71.1, 67.1, 65.4, 45.4, 27.0, 26.9, 26.3, 25.2, 23.2, 19.3, 19.1; MASS (ESIMS): *m*/*z* 689 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{41}H_{54}O_4NaSi_2$ $(M+Na)^+$ 689.3458, found 689.3435.

4.1.11. (2*R*,3*S*,5*R*)-3,5-Bis(*tert*-butyldiphenylsilyloxy)hexane-1,2-diol 10

To a stirred solution of compound **9** (10 g, 15.01 mmol) in MeOH (60 mL) was added PPTS (0.377 g, 10 mol %) and then heated at 50 °C overnight. After completion of the reaction, a saturated aq. $NaHCO_3$ solution (10 mL) was added to the reaction mixture and then concentrated under reduced pressure and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with water (1 × 80 mL), brine (1 × 80 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by column chromatography on silica gel (15% EtOAc/hexane) to give **10** (8.08 g, 86%) as a colorless liquid. $[\alpha]_D^{25} = -3.1$ (*c* 1.05, $CHCl_3$); IR (neat): ν_{max} 3496, 3070, 2929, 2856, 1469, 1427, 1389, 1189, 1108, 1001, 822, 772, 738, 702, 611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.62 (m, 8H), 7.49–7.32 (m, 12H), 4.28–4.17 (m, 1H), 4.09–4.00 (m, 1H), 3.79 (dd, *J* = 6.0, 2.2 Hz, 2H), 3.65–3.57 (m, 1H), 3.44 (d, *J* = 2.2 Hz, 1H), 2.66 (d, *J* = 3.7 Hz, 1H), 1.74–1.66 (m, 2H), 1.58 (1.09, d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 135.8, 135.5, 134.0, 133.9, 133.3, 133.1, 129.8, 129.7, 127.8, 127.7, 127.5, 74.2, 69.2, 68.8, 64.7, 39.9, 27.0, 26.9, 22.6, 19.2, 19.1; MASS (ESIMS): *m*/*z* 650 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{38}H_{50}O_4NaSi_2$ $(M+Na)^+$ 649.3145, found 649.3172.

4.1.12. (5*R*,7*S*)-2,2,5,10,10-Pentamethyl-3,3,9,9-tetraphenyl-7-vinyl-4,8-dioxa-3,9-disilaundecane 11

To a refluxing solution of diol **10** (7.0 g, 11.18 mmol), imidazole (1.90 g, 28 mmol), and triphenylphosphine (11.73 g, 44.71 mmol) in dry toluene (100 mL) iodine (11.31 g, 44.71 mmol) was added portionwise through a condenser. The reaction mixture was then refluxed for 2 days. The reaction mixture was quenched with saturated sodium thiosulfate solution (50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL), water (1 × 50 mL), brine (1 × 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give **11** at 10% along with diiodo compound as a black liquid that was used in the next step without further purification. To a stirred solution of crude mixture of **11** and a diiodo compound in dry DMF (40 mL) at room temperature was added Zn dust (1.46 g, 22.34 mmol) and refluxed for 6 h. The mixture was then filtered through a Celite pad. The filtrate was then partitioned between water and ether (3 × 40 mL) The combined organic layer was washed with brine (1 × 40 mL) dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 10% EtOAc in hexane) to afford **11** (5.62 g, 85%) as a colorless liquid. $[\alpha]_D^{25} = +12.8$ (*c* 0.8, $CHCl_3$); IR (neat): ν_{max} 3070, 2930, 2856, 1469, 1426, 1377, 1260, 1106, 1046, 992, 925, 886, 820, 737, 697, 609; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72–7.54 (m, 8H), 7.49–7.26 (m, 12H), 5.51 (ddd, *J* = 17.3, 10.4, 7.3 Hz, 1H), 4.83–4.68 (m, 2H), 4.08–3.99 (m, 1H), 3.83–3.70 (m, 1H), 1.87–1.66 (m, 2H), 1.01 (s, 9H), 0.99 (s, 9H), 0.82 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.4, 135.91, 135.89, 135.81, 135.78, 134.8, 134.4, 134.3, 129.5, 129.4, 129.3, 127.41, 127.36, 127.3, 114.6, 72.9, 66.9, 48.1, 27.0, 23.3, 19.2, 19.1; MASS (ESIMS): *m*/*z* 615 $(M+Na)^+$.

4.1.13. (2*R*,4*S*)-Hex-5-ene-2,4-diol 12

To a stirred solution of **11** (3.6 g, 6.08 mmol) in dry THF (50 mL) at 0 °C was added a 1 M solution of TBAF in THF (24.32 mL, 24.32 mmol) and stirred for 6 h at room temperature. The mixture was diluted with H_2O (25 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (1 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (100–200 mesh, 60% EtOAc–hexane) to afford **12** (0.642 g, 91%) as a colorless oil. $[\alpha]_D^{25} = -3.2$ (*c* 0.45, $CHCl_3$); IR (neat): ν_{max} 3336, 3084, 2962, 2922, 2852, 1459, 1420, 1376, 1299, 1218, 1120, 1080, 1042, 1018, 986, 923, 856.51, 827, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.89 (ddd, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.27 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.12 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.48–4.38 (m, 1H), 4.19–4.04 (m, 1H), 3.27 (br s, –OH, 2H), 1.77–1.56 (m, 2H), 1.22 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 114.5, 70.6, 65.3, 43.9, 23.7; MASS (ESIMS): *m*/*z* 139 $(M+Na)^+$; HRMS (ESI): Calcd for $C_6H_{12}O_2Na$ $(M+Na)^+$ 139.07295, found 139.07317.

Alternatively, to a stirred solution of $Me_4NHB(OAc)_3$ (4.58 g, 17.55 mmol) in dry CH_3CN (15 mL) and AcOH (5 mL) at −40 °C under nitrogen atmosphere was added slowly **18** (0.40 g, 3.51 mmol) in dry CH_3CN (5 mL) via cannula. Next, the clear reaction mixture was continued to stir at −20 °C for 5 h. After completion of the reaction, the reaction mixture was quenched with saturated aq. Rochelle's salt (10 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 55–60% EtOAc in hexane) to give major *anti*-diol **12** (0.308 g, 76%) as a colorless oil, and minor *syn*-diol **12a** (0.016 g, 4%) as a colorless oil.

4.1.14. *syn*-Diol:(2*S*,4*S*)-Hex-5-ene-2,4-diol 12a

^1H NMR (300 MHz, $CDCl_3$): δ 5.88 (ddd, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.25 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.10 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.45–4.31

(m, 1H), 4.20–3.99 (m, 1H), 2.96 (br s, –OH, 2H), 1.69–1.59 (m, 2H), 1.22 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6, 114.4, 73.7, 68.5, 44.6, 24.0; MASS (ESIMS): m/z 139 $(M+Na)^+$.

4.1.15. (*R*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)ethanone 14

To a stirred solution of **13** (2.75 g, 13.2 mmol) in dry THF (30 mL) at 0 °C under a nitrogen atmosphere was added slowly *n*-BuLi (6.3 mL, 15.7 mmol, 2.5 M) and stirred for 30 min at the same temperature. Next, acetyl chloride (1.24 g, 15.7 mmol) was slowly added at 0 °C and stirred for 1 h. After completion of the reaction, the reaction mixture was quenched with saturated aq. NH_4Cl (15 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (2 × 30 mL), brine (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 5% EtOAc in hexane) to afford **14** (3.13 g, 95%) as bright yellow crystals. $[\alpha]_D^{25} = -210.0$ (c 1.0, $CHCl_3$); IR (neat): ν_{max} 2925, 1701, 1362, 1215, 1018, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.21 (m, 5H, Ar-H), 5.37–5.29 (m, 1H), 3.36 (ddd, J = 11.3, 7.5, 0.9 Hz, 1H), 3.21 (dd, J = 13.2, 3.7 Hz, 1H), 3.02 (dd, J = 10.3, 0.9 Hz, 1H), 2.87 (d, J = 11.3 Hz, 1H), 2.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 170.6, 136.4, 129.3, 128.8, 127.1, 68.1, 36.6, 31.7, 27.0; MASS (LCMS): m/z 274 $(M+Na)^+$.

4.1.16. 1-(4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxypent-4-en-1-ones 16 and 16a

To a stirred solution of **14** (2.0 g, 7.96 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C under a nitrogen atmosphere was added dropwise $TiCl_4$ (1.04 mL, 9.56 mmol) and stirred for 5 min. Next, a solution of DIPEA (1.66 mL, 9.56 mmol) in dry CH_2Cl_2 (10 mL) was added *via* cannula. The reaction mixture was cooled to −78 °C and continued to stir for 30 min. Next a solution of acrolein **15** (0.44 g, 7.96 mmol) in dry CH_2Cl_2 (15 mL) was transferred via cannula to the reaction mixture, which was then stirred for 30 min at −78 °C, then slowly warmed to 0 °C, and stirred for another 30 min. After completion of the reaction, the reaction mixture was quenched with the addition of a half-saturated aq NH_4Cl (20 mL) while stirring and then allowed to return to room temperature and diluted with CH_2Cl_2 (60 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were washed with half-saturated aq NH_4Cl (2 × 40 mL), water (2 × 40 mL), brine (2 × 40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100–200 mesh, eluent: 15–20% EtOAc in hexane) to afford the more polar major *syn*-diastereomer **16** (1.830 g, 74.8%) as a yellow oil along with less polar minor *anti*-diastereomer **16a** (0.322 g, 13.2%) as a yellow oil.

4.1.17. (*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy pent-4-en-1-one

4.1.17.1. *Syn*-diastereomer 16. $[\alpha]_D^{25} = -166.4$ (c 0.8, $CHCl_3$); IR (neat): ν_{max} 3437, 3026, 2923, 1690, 1494, 1452, 1342, 1290, 1255, 1163, 1042, 998, 925, 772, 748, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.24 (m, 5H), 5.95 (ddd, J = 17.3, 10.5, 5.2 Hz, 1H), 5.44–5.30 (m, 2H), 5.17 (dt, J = 10.5, 1.4 Hz, 1H), 4.72–4.66 (m, 1H), 3.66 (dd, J = 17.3, 3.0 Hz, 1H), 3.41 (dd, J = 12.0, 7.5 Hz, 1H), 3.32 (dd, J = 17.3, 8.6 Hz, 1H), 3.23 (dd, J = 13.2, 3.7 Hz, 1H), 3.05 (dd, J = 13.2, 10.5 Hz, 1H), 2.90 (d, J = 12.0 Hz, 1H), 2.88–2.77 (br s, –OH, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3, 172.4, 138.7, 136.3, 129.3, 128.8, 127.2, 115.3, 68.6, 68.2, 45.4, 36.7, 32.0; MASS (ESIMS): m/z 308 $(M+H)^+$, 330 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{15}H_{17}NO_2NaS_2$ $(M+Na)^+$ 330.0602, found 330.0598.

4.1.18. (*R*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy pent-4-en-1-one

4.1.18.1. *Anti*-diastereomer 16a. $[\alpha]_D^{25} = -114.5$ (c 0.9, $CHCl_3$); IR (neat): ν_{max} 3458, 3026, 2924, 1690, 1494, 1453, 1342, 1291, 1257, 1163, 1137, 1042, 999, 925, 772, 748, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.23 (m, 5H), 5.94 (ddd, J = 17.3, 10.5, 5.7 Hz, 1H), 5.45–5.38 (m, 1H), 5.35 (d, J = 17.3, 1.9 Hz, 1H), 5.18 (d, J = 10.5, 1.9 Hz, 1H), 4.65–4.58 (m, 1H), 3.62 (dd, J = 17.3, 8.8 Hz, 1H), 3.46–3.37 (m, 2H), 3.22 (dd, J = 12.4, 2.8 Hz, 1H), 3.12 (br s, –OH, 1H), 3.04 (dd, J = 12.4, 10.5 Hz, 1H), 2.90 (d, J = 11.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 172.7, 138.7, 136.2, 129.3, 128.9, 127.2, 115.4, 69.1, 68.2, 45.1, 36.7, 31.9; MASS (ESIMS): m/z 308 $(M+H)^+$, 330 $(M+Na)^+$.

4.1.19. (*S*)-3-Hydroxy-*N*-methoxy-*N*-methylpent-4-enamide 17

To a stirred solution of **16** (1.6 g, 5.21 mmol) in dry CH_2Cl_2 (50 mL) at room temperature under a nitrogen atmosphere was added imidazole (1.77 g, 26.05 mmol) and Weinreb salt (1.51 g, 15.63 mmol) and continued to stir for 12 h at the same temperature. After completion of the reaction, the reaction mixture was quenched with saturated aq. NH_4Cl (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (1 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 35% EtOAc in hexane) to afford **17** (0.762 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = -28.9$ (c 0.55, $CHCl_3$); IR (neat): ν_{max} 3419, 2970, 2935, 1634, 1425, 1387, 1178, 1100, 1037, 994, 925, 780, 678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (ddd, J = 17.3, 10.5, 5.5 Hz, 1H), 5.32 (dt, J = 17.3, 1.4 Hz, 1H), 5.16 (dt, J = 10.5, 1.4 Hz, 1H), 4.60–4.54 (m, 1H), 3.79 (br s, –OH, 1H), 3.69 (s, 3H), 3.20 (s, 3H), 2.72 (d, J = 16.1 Hz, 1H), 2.60 (dd, J = 16.1, 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 139.1, 115.0, 68.8, 61.3, 38.0, 31.8; MASS (ESIMS): m/z 160 $(M+H)^+$, 182 $(M+Na)^+$; HRMS (ESI): Calcd for $C_7H_{14}O_3N$ $(M+H)^+$ 160.09682, found 160.09713.

4.1.20. (*S*)-4-Hydroxyhex-5-en-2-one 18

To a stirred solution of **17** (0.70 g, 4.40 mmol) in dry ether (20 mL) at 0 °C under a nitrogen atmosphere was slowly added a solution of methylmagnesium iodide (11 mL, 11 mmol, 1 M solution in ether). The reaction mixture was continued to stir for 1 h at room temperature. After completion of the reaction, the reaction mixture was quenched with saturated aq. NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (1 × 20 mL), brine (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 10% EtOAc in hexane) to yield β-hydroxy ketone **18** (0.431 g, 86%) as a colorless oil. $[\alpha]_D^{25} = -180.0$ (c 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (ddd, J = 17.3, 10.5, 6.0 Hz, 1H), 5.30 (dt, J = 17.3, 1.5 Hz, 1H), 5.15 (dt, J = 10.5, 1.5 Hz, 1H), 4.65–4.48 (m, 1H), 2.96 (br s, –OH, 1H), 2.72–2.65 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.0, 138.8, 115.1, 68.5, 49.5, 30.8; MASS (ESIMS): m/z 137 $(M+Na)^+$.

4.1.21. (2*R*,4*S*)-4-(*tert*-Butyldiphenylsilyloxy)hex-5-en-2-ol 19

To a stirred solution of diol **12** (0.50 g, 4.31 mmol) in anhydrous CH_2Cl_2 (20 mL) and imidazole (0.35 g, 5.17 mmol) at 0 °C was added TBDPSCl (1.12 mL, 3.45 mmol) dropwise and stirred for 5 h at the same temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (1 × 20 mL), brine (1 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatog-

raphy on silica gel (100–200 mesh, eluent: 8% EtOAc in hexane) to afford **19** (0.890 g, 58.5%) as a colorless syrup. $[\alpha]_D^{25} = -5.3$ (*c* 1.3, $CHCl_3$); IR (neat): ν_{max} 3497, 2924, 2854, 1463, 1427, 1216, 1109, 996, 924, 821, 771, 739, 702, 611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79–7.63 (m, 4H), 7.47–7.34 (m, 6H), 5.81 (ddd, *J* = 17.3, 10.5, 6.0 Hz, 1H), 5.23 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.06 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.54–4.38 (m, 1H), 4.24–4.07 (m, 1H), 3.02 (d, *J* = 2.8 Hz, 1H), 1.73 (ddd, *J* = 13.7, 9.6, 3.9 Hz, 1H), 1.65–1.54 (m, 1H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 136.0, 135.9, 133.3, 133.2, 129.9, 129.8, 127.7, 127.5, 115.0, 73.8, 64.6, 44.9, 27.0, 23.4, 19.2; MASS (ESIMS): *m*/*z* 355 $(M+H)^+$; HRMS (ESI): Calcd for $C_{22}H_{31}O_2Si$ $(M+H)^+$ 355.20878, found 355.20931.

4.1.22. (3*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)hex-1-en-3-ol 20

Compound **20** was obtained (0.480 g, 31.5%) as a colorless liquid. $[\alpha]_D^{25} = +5.0$ (*c* 1.4, $CHCl_3$); IR (neat): ν_{max} 3429, 2960, 2858, 1468, 1426, 1378, 1219, 1109, 994, 870, 821, 772, 703, 609, 505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.60 (m, 4H), 7.48–7.29 (m, 6H), 5.76 (ddd, *J* = 17.2, 10.4, 5.5 Hz, 1H), 5.17 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.04 (dt, *J* = 10.4, 1.6 Hz, 1H), 4.44–4.33 (m, 1H), 4.21–4.08 (m, 1H), 2.69 (d, *J* = 2.3 Hz, 1H), 1.75–1.50 (m, 2H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 135.93, 135.90, 134.0, 133.5, 129.9, 129.8, 127.8, 127.7, 127.6, 113.9, 69.5, 68.2, 45.1, 27.1, 23.0, 19.3; MASS (ESIMS): *m*/*z* 377 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{22}H_{30}O_2NaSi$ $(M+Na)^+$ 377.1912, found 377.1924.

4.1.23. 4-(Benzyloxy)butan-1-ol 21

To a suspension of NaH (4.44 g, 111.1 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (50 mL) was added dropwise a solution of 1,4-butane diol (10.00 g, 111.1 mmol)) in anhydrous THF (100 mL) at 0 °C and continued to stir for the next 30 min at room temperature. At 0 °C, benzyl bromide (13.19 mL, 111.1 mmol) was added and stirred for 4 h at room temperature with frequent monitoring of the progress of reaction by TLC. The reaction mixture was quenched by small crushed ice flakes until a clear solution (biphasic) had formed. The reaction mixture was then extracted with EtOAc (3 × 100 mL). The organic extracts were washed with water (1 × 100 mL), brine (1 × 100 mL), and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel (100–200 mesh, eluent: 20% EtOAc/hexane) afforded *mono*-protected alcohol **21** (17.9 g, 90%) as a colorless oil. IR (neat): ν_{max} 3685, 3019, 2946, 2868, 2400, 1519, 1423, 1099, 1045, 929, 848, 757, 669, 626, 413 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H), 4.49 (s, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 3.49 (t, *J* = 5.8 Hz, 2H), 2.24 (br s, –OH, 1H), 1.77–1.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 128.2, 127.5, 127.4, 77.2, 72.7, 70.0, 61.9, 29.6, 26.3; MASS (EIMS): *m*/*z* 180 $(M)^+$.

4.1.24. 4-(Benzyloxy)butanal 22

To stirred solution of alcohol **21** (10 g, 55.5 mmol) in dichloromethane (150 mL) at 0 °C were added pyridinium chlorochromate (17.96 g, 83.33 mmol) and Celite (17.96 g) and stirred at room temperature for 5 h. Diethyl ether (100 mL) was added and the reaction mixture was filtered through a small pad of Celite and silica gel. The filtered cake was washed thoroughly with ether (2 × 150 mL) and the filtrate was concentrated under reduced pressure. After flash column chromatography on silica gel (100–200 mesh, eluent: 8% EtOAc in hexane) aldehyde **22** (9.09 g, 92%) was obtained as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 9.76 (t, *J* = 1.5 Hz, 1H), 7.36–7.17 (m, 5H), 4.46 (s, 2H), 3.47 (q, *J* = 5.1 Hz, 2H), 2.53 (td, *J* = 7.0, 1.5 Hz, 2H), 1.92 (ddd, *J* = 13.0, 7.0, 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3, 138.2, 128.4, 127.6, 73.0, 69.0, 41.0, 22.6; MASS (EIMS): *m*/*z* 178 $(M)^+$.

4.1.25. 6-(Benzyloxy)hex-1-en-3-ol 23

To a stirred solution of aldehyde **22** (8.0 g, 44.94 mmol) taken in 100 mL of anhydrous THF, a solution of vinyl magnesium bromide (1 M solution in THF, 67.41 mL, 67.41 mmol) was added at −78 °C. The resulting mixture was stirred at −78 °C for 1 h, quenched by the addition of aq NH_4Cl solution, and then warmed to rt. The aqueous layer was separated and extracted with EtOAc (3 × 100 mL), and the combined organic layer was washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100–200 mesh, eluent: 15% EtOAc in hexane) to give **23** (8.147 g, 88%) as a colorless liquid, which was used without characterization.

4.1.26. (*S*)-6-(Benzyloxy)hex-1-en-3-ol 24

To a suspension of powered molecular sieves (4 Å, 800 mg) in dry CH_2Cl_2 (80 mL), $Ti(OiPr)_4$ (5.04 mL, 16.95 mmol) and (−)-DIPT (4.21 mL, 20.34 mmol) were added sequentially at −20 °C. After stirring for 30 min, allyl alcohol **23** (7 g, 33.9 mmol) in dry CH_2Cl_2 (80 mL) was added and stirring was continued for another 30 min at the same temperature. Then TBHP (4 M, 4.23 mL, 16.95 mmol) was added and after stirring for another 6 h at the same temperature, the reaction mixture was quenched by the addition of water (80 mL). It was then kept at room temperature and stirred for 30 min. After re-cooling to 0 °C, an aqueous solution of NaOH (30% w/v, 50 mL saturated with brine) was added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 80 mL). The combined organic extracts were washed with brine (1 × 80 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (100–200 mesh: eluent 15% EtOAc/hexane) to give **24** (3.22 g, 46%) as a colorless syrup. $[\alpha]_D^{25} = +2.5$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3416, 3073, 3030, 2929, 2859, 1487, 1451, 1363, 1273, 1205, 1099, 991, 920, 739, 697, 609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.43–7.23 (m, 5H), 5.87 (ddd, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.23 (d, *J* = 17.2, 1.3 Hz, 1H), 5.11 (d, *J* = 10.4, 1.3 Hz, 1H), 4.52 (s, 2H), 4.20–4.07 (m, 1H), 3.52 (t, *J* = 5.9 Hz, 2H), 2.37 (br s, –OH, 1H), 1.81–1.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 138.1, 128.3, 127.62, 127.57, 114.4, 72.9, 72.6, 70.3, 34.2, 25.7; MASS (ESIMS): *m*/*z* 229 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{13}H_{18}O_2Na$ $(M+Na)^+$ 229.1204, found 229.1205.

4.1.27. (*S*)-(6-(Benzyloxy)hex-1-en-3-yloxy)(*tert*-butyl)diphenyl silane 25

To a stirred solution of alcohol **24** (2.0 g, 9.7 mmol) in anhydrous CH_2Cl_2 (50 mL) and imidazole (1.32 g, 19.41 mmol) at 0 °C was added TBDPSCl (3.03 mL, 11.65 mmol) dropwise and stirred for 8 h at room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (1 × 50 mL), brine (1 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography using silica gel (100–200 mesh, 2% EtOAc/hexane) afforded **25** (4.09 g, 95%) as a colorless syrup $[\alpha]_D^{25} = +16.5$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3448, 3069, 2932, 2857, 1642, 1455, 1426, 1392, 1361, 1199, 1108, 1031, 923, 821, 737, 701, 612, 507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.56 (m, 4H), 7.41–7.16 (m, 11H), 5.75 (ddd, *J* = 16.9, 10.4, 6.3 Hz, 1H), 5.01–4.90 (m, 2H), 4.38 (s, 2H), 4.16 (q, *J* = 5.2 Hz, 1H), 3.38–3.22 (m, 2H), 1.66–1.41 (m, 4H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6, 138.7, 136.0, 135.6, 134.4, 134.1, 129.6, 128.2, 127.5, 127.4, 114.6, 74.3, 72.6, 70.2, 34.1, 27.3, 24.7, 19.5; MASS (ESIMS): *m*/*z* 467 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{29}H_{36}O_2NaSi$ $(M+Na)^+$ 467.2382, found 467.2398.

4.1.28. (*S*)-4-(*tert*-Butyldiphenylsilyloxy)hex-5-en-1-ol 26

To a stirred solution of **25** (3.0 g, 6.75 mmol) in CH_2Cl_2–water (19:1, 40 mL), DDQ (6.135 g, 27.02 mmol) was added and stirred at reflux for 4 h. Saturated aq. $NaHCO_3$ solution (30 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with water (1 × 40 mL), brine 1 × 40 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by column chromatography on silica gel (20% EtOAc/hexane) and afforded **26** (2.15 g, 90%) as a colorless syrupy liquid. $[\alpha]_D^{25} = +17.5$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3686, 3020, 2400, 2362, 1731, 1519, 1427, 1111, 1026, 929, 848, 755, 669, 627, 502 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.68–7.59 (m, 4H), 7.43–7.28 (m, 6H), 5.77 (ddd, *J* = 16.9, 10.4, 5.8 Hz, 1H), 5.06–4.93 (m, 2H), 4.20 (q, *J* = 5.8 Hz, 1H), 3.45 (t, *J* = 5.0 Hz, 2H), 1.56–1.42 (m, 4H), 1.37 (br s, –OH, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.3, 136.0, 135.9, 134.2, 133.9, 129.6, 129.5, 127.5, 127.4, 114.6, 74.1, 62.9, 33.7, 27.5, 27.0, 19.3; MASS (ESIMS): *m*/*z* 377 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{22}H_{30}O_2NaSi$ $(M+Na)^+$ 377.1912, found 377.1911.

4.1.29. (*S*)-4-(*tert*-Butyldiphenylsilyloxy)hex-5-enoic acid 27

To a stirred solution of alcohol **26** (1.5 g, 4.23 mmol) in CH_2Cl_2 (50 mL) and NaOAc (1.051 g, 12.71 mmol) at 0 °C were added PCC (1.370 g, 6.34 mmol) and celite (1.370 g) and stirred at room temperature for 5 h. Diethyl ether (50 mL) was added and the reaction mixture was filtered through a small pad of Celite and silica gel. The filtered cake was washed thoroughly with ether (2 × 50 mL) and the filtrate was concentrated under reduced pressure to give the crude aldehyde (1.34 g, 90%). The crude aldehyde was dissolved in *t*-BuOH–H_2O (40 mL, 3:1), cooled to 0 °C, and after 10 min, treated with 2-methyl-2-butene followed by an aq solution of $NaClO_2$ (0.688 g, 8.46 mmol) and $NaH_2PO_4{\cdot}H_2O$ (1.17 g, 8.46 mmol) in H_2O (10 mL). After 10 h, the reaction mixture was quenched with $KHSO_4$ (15 mL) and H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with brine (1 × 40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. After flash column chromatography on silica gel (100–200 mesh, eluent: 30% EtOAc in hexane), **27** (1.36 g, 92%) was obtained as a colorless liquid $[\alpha]_D^{25} = +14.5$ (*c* 0.6, $CHCl_3$); IR (neat): ν_{max} 3450, 3065, 2934, 2859, 1709, 1647, 1463, 1423, 1265, 1109, 1075, 1031, 927, 822, 742, 701,504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74–7.62 (m, 4H), 7.49–7.31 (m, 6H), 5.76 (ddd, *J* = 16.8, 10.4, 6.1 Hz, 1H), 5.11–4.97 (m, 2H), 4.28 (q, *J* = 5.5 Hz, 1H), 2.37 (dd, *J* = 13.8, 7.6 Hz, 2H), 1.81 (dd, *J* = 13.8, 8.3 Hz, 2H), 1.28 (s, 1H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.7, 139.6, 135.9, 135.8, 133.9, 133.8, 129.7, 129.5, 127.5, 127.4, 115.3, 73.2, 31.8, 28.9, 27.0, 19.3; MASS (ESIMS): *m*/*z* 391 $(M+H)^+$.

4.1.30. (*S*)-((2*R*,4*S*)-4′-(*tert*-Butyldiphenylsilyloxy)hex-5-en-2-yl) 4-(*tert*-butyldiphenylsilyloxy)hex-5-enoate 28

To a stirred solution of acid **27** (800 mg, 2.05 mmol) in dry THF (20 mL) were added 2,4,6-trichlorobenzoyl chloride (0.38 mL, 2.46 mmol) and Et_3N (1.43 mL, 10.25 mmol) and the contents were stirred at ambient temperature. After completion of the mixed anhydride formation as indicated by TLC, DMAP (500 mg, 4.1 mmol) and a solution of alcohol **19** (725 mg, 2.05 mmol) in THF (10 mL) were added and the reaction mixture was stirred for 14 h at rt. The reaction was quenched with water and extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with saturated $NaHCO_3$ (1 × 20 mL) and brine (1 × 20 mL) solution, dried (Na_2SO_4), and evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (100–200 mesh: eluent 20% EtOAc/hexane) and afforded **28** (1.241 g, 86%) as a colorless syrupy liquid. $[\alpha]_D^{25} = -48.3$ (*c* 0.33, $CHCl_3$); IR (neat): ν_{max} 3071, 2932, 2892, 2857, 1734, 1637, 1467, 1426, 1364, 1256, 1109, 1077, 997, 926, 820, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72–7.55 (m, 8H), 7.48–7.27 (m, 12H), 5.83–5.64 (m, 2H), 5.04–4.75 (m, 5H), 4.21 (q, *J* = 5.6 Hz, 1H), 4.09 (q, *J* = 6.6 Hz, 1H), 2.22–2.09 (m, 2H), 1.83–1.58 (m, 4H), 1.06 (s, 9H), 1.04 (s, 9H), 1.00 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 140.2, 139.7, 135.94, 135.89, 135.8, 134.1, 134.0, 133.8, 129.6, 129.5, 129.43, 129.37, 127.5, 127.45, 127.36, 127.3, 115.1, 115.0, 73.5, 72.4, 67.8, 44.1, 32.1, 27.0, 26.9, 20.2, 19.2; MASS (ESIMS): *m*/*z* 723 $(M+H_2O)^+$; HRMS (ESI): Calcd for $C_{44}H_{56}O_4NaSi_2$ $(M+Na)^+$ 727.36093, found 727.36088.

4.1.31. (*S*)-((2*R*,4*S*)-4′-Hydroxyhex-5-en-2-yl) 4-hydroxyhex-5-enoate 29

To a stirred solution of **28** (0.8 g, 1.13 mmol) in dry THF (20 mL) at 0 °C was added pyridine (0.726 mL, 9.08 mmol) and 70% HF-pyridine solution (0.063 mL, 4.54 mmol) under N_2 at room temperature. The resulting solution mixture was allowed to stir for 8 h. The reaction mixture was quenched with satd $NaHCO_3$ and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with water (1 × 15 mL), brine (1 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography using silica gel (100–200 mesh, 40% EtOAc/hexane) afforded **29** (0.217 g, 84%) as a colorless oil. $[\alpha]_D^{25} = -28.8$ (*c* 0.5, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 5.98–5.75 (m, 2H), 5.33–5.02 (m, 5H), 4.24–4.12 (m, 1H), 4.11–4.03 (m, 1H), 2.53–2.32 (m, 2H), 1.99–1.51 (m, 4H), 1.29 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 140.57, 140.59, 114.9, 114.3, 71.8, 68.5, 68.1, 43.8, 31.8, 30.6, 20.8; MASS (ESIMS): *m*/*z* 251$(M+Na)^+$; HRMS (ESI): Calcd for $C_{12}H_{20}O_4Na$ $(M+Na)^+$ 251.1259, found 251.1251.

4.1.32. Stagonolide C 1

To a solution of **29** (80 mg, 0.350 mmol) in dry dichloromethane (150 mL) was added second generation Grubbs catalyst (30 mg, 0.0350 mmol) and the mixture was degassed under N_2 thoroughly. The reaction mixture was refluxed for 24 h, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (5% MeOH/$CHCl_3$) to afford stagonolide C **1** (48 mg, 68%) as a colorless liquid. $[\alpha]_D^{25} = +43.9$ (*c* 1.0, MeOH); Lit.[5] $[\alpha]_D^{29} = +44.4$ (*c* 1.0, MeOH); ^1H NMR (500 MHz, $CDCl_3$): δ 5.60 (dd, *J* = 15.6, 9.3 Hz, 1H), 5.44 (dd, *J* = 15.6, 9.3 Hz, 1H), 5.15 (dq, *J* = 11.0, 6.5 Hz, 1H), 4.18–4.05 (m, 2H), 2.36–2.25 (m, 1H), 2.09–1.98 (m, 3H), 1.89 (dd, *J* = 13.7, 2.6 Hz, 1H), 1.78 (ddd, *J* = 13.7, 11.0, 2.6 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 135.8, 133.0, 74.4, 72.0, 67.7, 43.3, 34.4, 31.5, 21.3; MASS (ESIMS): *m*/*z* 223 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{10}H_{16}O_4Na$ $(M+Na)^+$ 223.09408, found 223.09409.

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