Effect of the allylic substituents on ring closing metathesis: the total synthesis of stagonolide B and 4-*epi*-stagonolide B†

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The total syntheses of stagonolide B and its 4-epimer were carried out to probe into how the relative stereochemistry of allylic hydroxy groups and their protecting groups influence the efficiency of the ring closing metathesis.

Introduction

Since the first construction of a 10-membered lactone using ring closing metathesis (RCM) by Fürstner and Thomas in 1997,[1] the synthesis of numerous naturally occurring ten-membered ring lactones, generally referred as nonenolides, have been documented by employing the RCM construct.[2,3] Though RCM has become a multipurpose reaction in nonenolide synthesis, the outcome of the reaction is sensitive to multiple factors, such as the nature of the catalyst,[4] and the steric crowding around the newly forming ring-olefin.[5,6a] Sometimes, even the success of RCM is substrate-specific. In dealing with the synthesis of multiplolide A,[5] it was noticed that amongst the four similar substrates employed, only one of the substrates provided the desired 10-membered macrolactone. For example, RCM was found to be facile in constructing the macrolide **D** (a 1,4-*cis*-diol), whereas in the construction of the macrolide **C**, with a 1,4-*trans*-diol configuration, RCM led to oligomerization. A close examination of the available RCM-based nonenolide constructions with the 2-ene-1,4-diol unit revealed that they all dealt with RCM of the substrates leading to 1,4-*cis*-diol-configured nonenolides,[6] and reports dealing with the construction of nonenolides with a 1,4-*trans*-diol configuration are scarce.[7] Intrigued by this, we have selected the stagonolide B,[9] which presents such a 2*E*-ene-1,4-*trans*-diol unit as a representative natural product in order to explore its total synthesis, employing RCM as the key reaction.[8–10]

In 2007, Berestetskiy and co-workers described the isolation, and chemical and biological characterization of a new nonenolide produced by *Stagonospora cirsii* (a pathogen of *Cirsium arvense*) in liquid cultures, named stagonolide.[8] The relative and the absolute stereochemical structure of stagonolide was established by converting it to the known herbarumin I employing a $NaBH_4$ reduction of the keto group. Later, in 2008, Evidente *et al.* reported the isolation of five new nonenolides from the same fungus, grown in solid culture.[9] Considering their origin and structural similarity, these five new nonenolides were named as stagonolides B–F. The similarity in the spectral data of **1–6** with the previously reported natural products herbarumins was taken into account in assigning the connectivity of the free hydroxyl groups in stagonolides. Their relative orientations have been proposed as given in Fig. 1. Herein, we describe the first total synthesis of stagonolide B and its 4-epimer by employing RCM for the construction of the central nonenolide core with the required *E*-stereochemistry of the ring olefin.

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† Electronic supplementary information (ESI) available: X-Ray crystal structure data and co-ordinates of *epi*-**2**, ^1H and ^{13}C NMR spectra of **2** and *epi*-**2**, and the Moscher model for the determination of absolute stereochemistry of alcohol (*R*)-**10**. CCDC 743822. For crystallographic data in CIF or other electronic format, see DOI: 10.1039/b916198h

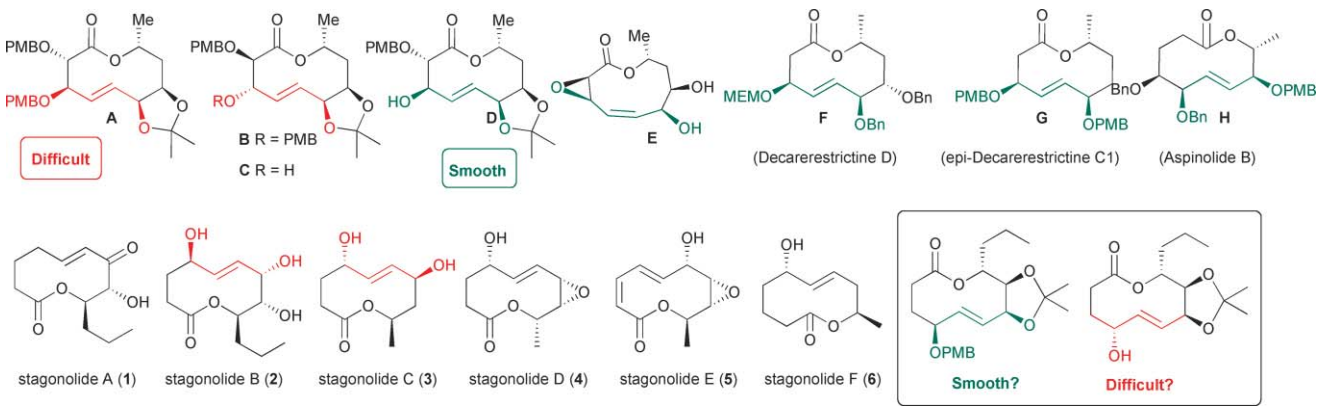


Fig. 1 The end results of RCM-mediated construction of selected nonenolides with a 2-ene-1,4-diol unit, and structures of recently isolated stagonolides A–F.

Results and discussion

The key retrosynthetic disconnections are given in Fig. 2. After the application of the RCM transformation, the enantiomeric acids (*R*)-**8** and (*S*)-**8**, and the alcohol **9** were identified as the key coupling partners for the synthesis of stagonolide B (**2**) and its 4-epimer *epi*-**2**. Easily available D-ribose has been selected as a starting point for the chiral pool synthesis of the known alcohol fragment **9**.[4,11] The synthesis of the enantiomeric acids **8** was planned through the enzymatic resolution of the TBS-protected hex-5-ene-1,4-diol **10**.[12] A PMB protection on the allylic –OH of the acid coupling partner was selected as a safe handle to change the steric nature of the adjacent functional groups that have been shown to influence the outcome of the RCM.[5,6a,7]

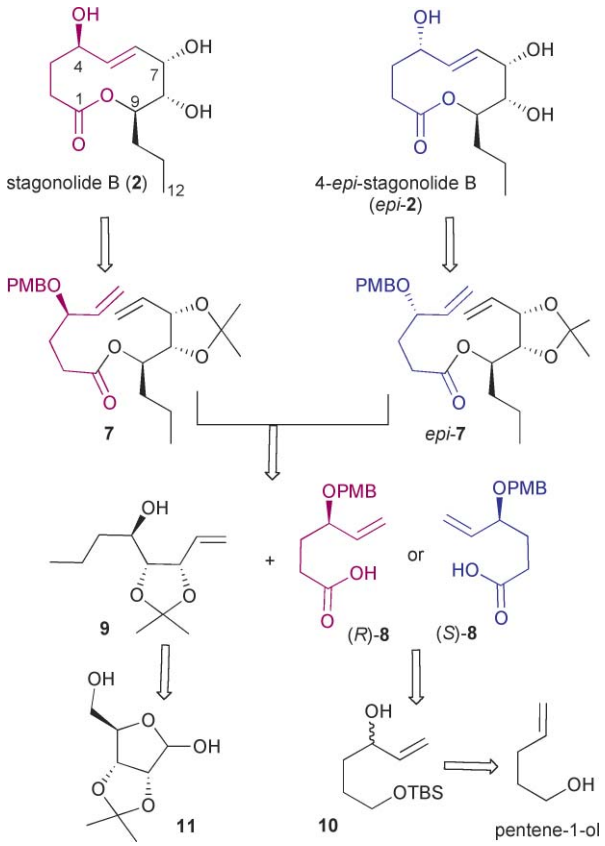


Fig. 2 Retrosynthetic analysis for stagonolide B.

The synthesis begin with the preparation of the acids (*R*)- and (*S*)-**8** (Scheme 1). Readily available 4-pentene-1-ol was converted to the epoxide **13**. The one carbon extension of the epoxide[13] was carried out using trimethyl sulfonium iodide and *n*-BuLi in THF to afford the key allyl alcohol **10**. Alcohol **10**, upon treatment with *Amano PS*, afforded alcohol (*R*)-**10** [ee = 82%, corresponding acetate (*R*)-**14**] and acetate (*S*)-**14** (ee = 97%).[12] The enantiomeric excess was determined by GC analysis of the acetates and the absolute configuration of the alcohol (*R*)-**10** was established by using the Mosher ester method.[14] Protection of the hydroxyl group of (*R*)-**10** as its PMB ether, followed by silyl deprotection using TBAF, gave (*R*)-**16**. Oxidation of alcohol **16** to the aldehyde under Swern conditions, followed by further oxidation of intermediate aldehyde employing sodium hypochlorite under buffered conditions,[15] completed the synthesis of the acid fragment (*R*)-**8**. The acetate (*S*)-**14** was subjected to deacetylation and the resulting (*S*)-**10** was used for the synthesis of (*S*)-**8** employing the same sequence of reactions as used for its enantiomer synthesis.

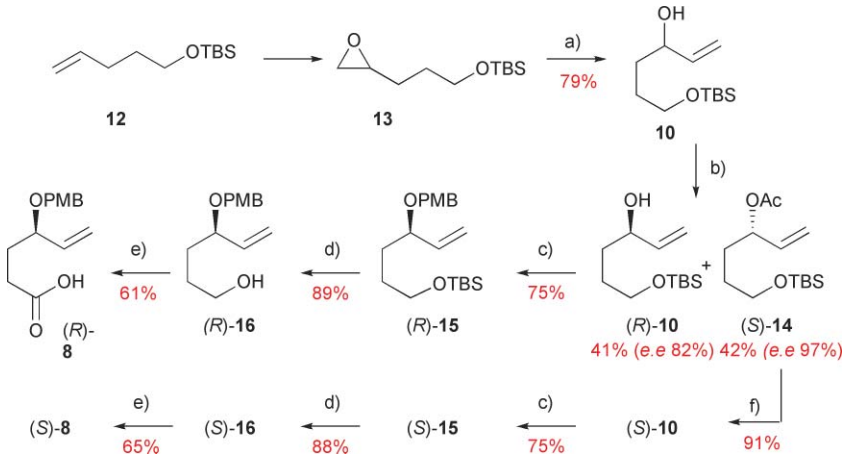
The alcohol fragment **9** was synthesized from D-ribose. The known ribose 2,3-acetonide **11** was prepared according to the reported procedure and subjected to one carbon Wittig homologation to afford the 1,2-diol **17**.[16] Selective 1°-OH tosylation of **17** followed by base treatment furnished the epoxide **19**.[17] Opening of the oxirane by using EtMgBr needed some experimentation, as the formation of the corresponding bromohydrin was the competing reaction. Under optimized conditions, we could isolate the requisite coupling partner **9** in 71% yield, with identical spectral and analytical data to that reported earlier.[4]

Our next concern was the execution of the key macrolide construction. The RCM precursor **7** was obtained by the coupling of acid (*R*)-**8** and alcohol **9** using the Yamaguchi reagent.[18] Various catalysts prescribed for the metathesis have been explored with this substrate **7**, the RCM of which turned out to be a difficult proposition. Anticipating this problem, we have opted for the PMB deprotection, which indeed was selected *a priori* as a safe handle.[5] The PMB deprotection was carried out with DDQ to afford the diene ester **20**. The attempted RCM of **20** was found to mainly yield the oligomeric products with both the 1st and 2nd generation catalysts of Grubbs' and Hoveyda–Grubbs' in solvents such as dichloromethane, benzene and toluene, either at rt or at reflux temperatures. Finally, when we switched to dichloroethane as a solvent,[3d,19] and employed 2nd gen. Grubbs'/Hoyeda–Grubbs' catalysts, we noticed the molecular ion peaks corresponding to the product in the LCMS.

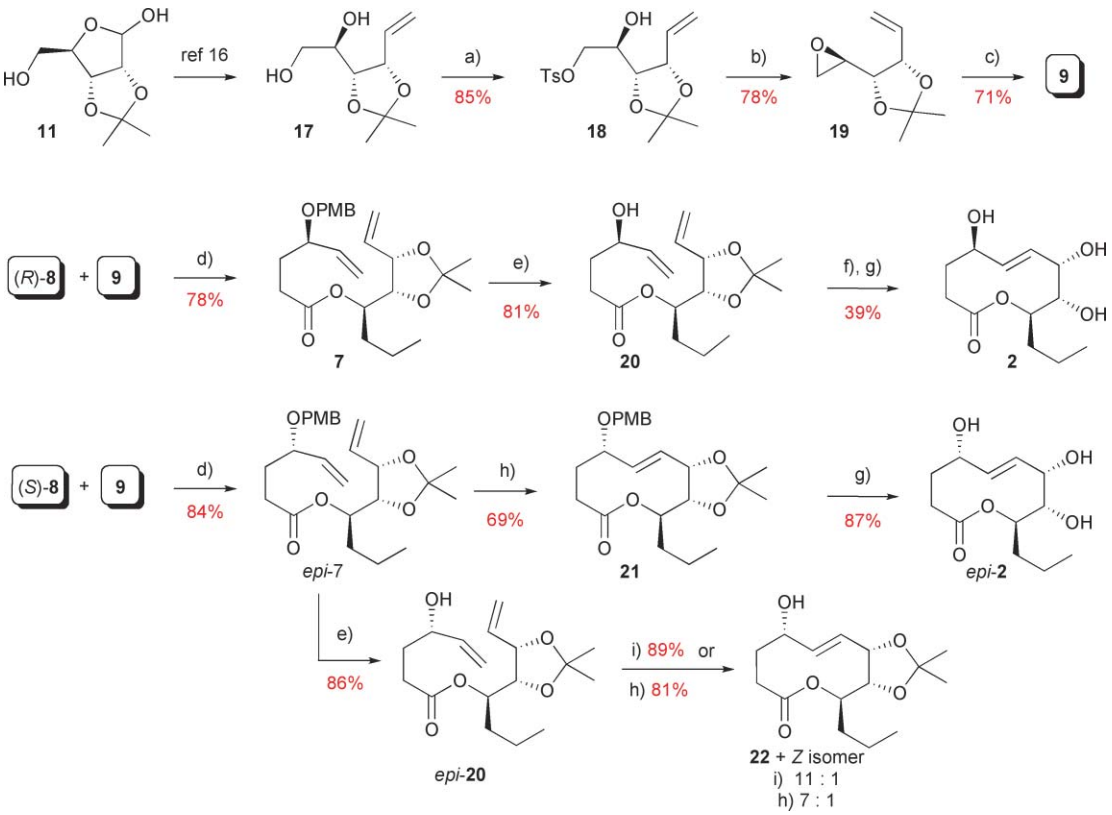
After examining the various reaction parameters, the RCM of **20** could be conducted successfully using 25 mol% of 2nd gen. Grubbs' catalyst in dichloroethane at reflux temperature. As the separation of the resulting lactone was found to be tedious, the crude RCM reaction mixture was advanced for the acetonide deprotection employing TFA at 0 °C for 1 h to afford the stagonolide B (**2**) in moderate yields. The analytical and spectral data of **2** were in agreement with the data reported for the natural product. The sign and magnitude of the specific rotation of synthetic stagonolide B confirmed the assigned absolute configuration of natural stagonolide B.[9]

At the outset, to check the validity of our assumption, the diene *epi*-**7** was prepared by coupling the acid (*S*)-**8** and alcohol **9**. As expected, the RCM of the fully protected diene ester *epi*-**7** was facile with the 2nd gen. Grubbs' catalyst in toluene at 80 °C and gave **21** in 69% yield. The global deprotection of **21** by employing TFA gave the 4-*epi*-stagonolide B (*epi*-**2**) as a white solid and its structure was confirmed from the spectral, analytical and single crystal X-ray diffraction data (Scheme 2 and Fig. 3).

The difference in the outcome of the RCM reaction with respect to the relative stereochemistry of the allylic positions of dienes **7** and *epi*-**7** is particularly striking. This could be due to the conformational constraints during the formation of the ruthenacyclobutane.[4,7] Gennari and co-workers earlier reported a systematic investigation on the role of protecting groups and the stereochemistry of the allylic hydroxyl groups on the 10-membered carbocycle construction.[7,22] The RCM was



Scheme 1 *Reagents and conditions*: (a) $Me_3S^+I^-$, *n*-BuLi, THF, −78 °C→rt, 7 h; (b) *Amano PS*, benzene : petroleum ether (1 : 3), vinyl acetate, 40 °C, 96 h; (c) PMBCl, DMF, 60% NaH, 0→rt, 4 h; (d) TBAF, THF, rt, 4 h; (e) i. $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 1 h; ii. $NaClO_2$, NaH_2PO_4, DMSO, H_2O, 10 h; (f) K_2CO_3, MeOH, rt, 1 h.



Scheme 2 *Reagents and conditions*: (a) *p*-TsCl, TEA, DCM, 0 °C, 4 h; (b) MeOH, K_2CO_3, rt, 10 h; (c) EtMgBr, CuCN, Et_2O, 0 °C, 1 h; (d) 2,4,6-trichlorobenzoyl chloride, DMAP, ethyldiisopropylamine, 16 h; (e) DDQ, DCM–H_2O, 3 h; (f) 25 mol% 2nd gen. Grubbs' catalyst, 1,2-dichloroethane, reflux 24 h; (g) TFA, 0 °C, 1 h; (h) 10 mol% 2nd gen. Grubbs' catalyst, toluene, 80 °C, 6 h; (i) 10 mol% 2nd gen. Grubbs' catalyst, DCM, reflux, 6 h.

protecting group-specific. With PMP protection on both the allylic hydroxyl groups, 10-membered carbocycles with 2*E*-ene-1,4-*cis*- or *trans*-diol were obtained under forced RCM conditions, the former being obtained in good yields and the latter in poor yields. With both the MOM and methyl ether derivatives, the RCM led mainly to oligomerization.

The difficulties noticed with dienes such as **7** leading to a 10-membered macrocycle bearing allylic substituents with 1,4-*trans* configuration, might be because of the steric crowding, which persists on both faces during the formation of the ruthenacyclobutane.[7b,20,21] For the formation of a macrocycle with a 1,4-*cis* configuration (with *epi*-**7**), such a steric crowding is absent as both these allylic groups lie on the same face. A simple rotation around the C–C bond in the case of the former dienes also leads to the ruthenacyclobutane having both the allylic groups on the same face. This may provide a possible explanation for the competing

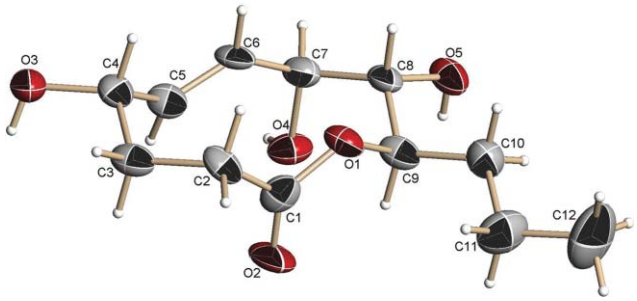


Fig. 3 The molecular structure of 4-*epi*-stagonolide B. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of an arbitrary radius.

di-/oligomerization reaction when the ring closure is sterically demanding.[22]

The feasibility of RCM with **20** (where one of the allylic hydroxy groups is free) could, to some extent, be explained by anticipating a co-operative O–H···Cl–Ru hydrogen bonding.[23c] The acceleration of RCM reaction rates with free allylic hydroxyl groups is well documented.[20] It has been shown recently that such acceleration by an allylic –OH group was also regio-[23a,b] and stereoselective.[23c] In this regard, diene *epi*-**20** bearing a free allylic –OH was prepared and subjected to ring closing metathesis using 2nd generation Grubbs' catalyst. The ring closure of *epi*-**20** was facile and even more productive when compared with the corresponding PMB-protected diene *epi*-**7**. The RCM of *epi*-**20** could be carried out smoothly in dichloromethane at reflux and *E*/*Z* noneolides **22** were obtained in an 11 : 1 ratio. Carrying out the reaction under conditions similar to those for *epi*-**7** (toluene, 80 °C) resulted in an increase of the *Z*-isomer (7 : 1 ratio). These results are indicative of the influence of the relative stereochemistry of the hydroxyl group on the RCM rate acceleration by the ruthenium catalyst. Though these limited examples provide clues as to where the RCM could be a difficult proposition, a more comprehensive examination is needed with a broad range of substrates varying the stereochemistry of other centers and also without any conformational rigidity such as an acetonide protecting group. Work in this direction is progressing in our lab.

Conclusions

The first total synthesis of stagonolide B (**2**) confirming its absolute stereochemistry has been documented. A combination of the chiral pool approach and enzymatic resolution has been adopted to synthesize the key coupling partners. The 4-*epi*-stagonolide B has also been synthesized to check the influence of the relative stereochemistry of allylic hydroxy groups and their protecting groups on the efficiency of the RCM and on the rate acceleration by the catalyst.

Experimental

General methods

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. All anhydrous solvents were distilled prior to use: THF and diethyl ether from Na and benzophenone; MeOH, $(CH_2)_2Cl_2$ and CH_2Cl_2 from CaH_2. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem silica gel (60–120, 230–400 mesh). Optical rotations were determined on a Jasco DIP-370 digital polarimeter. Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectroscopy measurements were carried out on Bruker AC 200 MHz, Bruker DRX 400 MHz or Bruker DRX 500 MHz spectrometers, and TMS was used as the internal standard. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectroscopy (ESI, API-Q*Star* Pulsar) was carried out on a Finnigan MAT-1020 spectrometer. GC analyses were carried out on Agilent Technologies 7890 Model machine using HP-Chiral-20B (30 m × 0.32 mm × 0.25 μ) column. Elemental analysis data were obtained on a Thermo Finnigan Flash EA 1112 Series CHNS Analyser.

4-*O*-(*tert*-Butyldimethylsilyl)-hex-5-ene-1,4-diol (10)

A solution of trimethyl sulfonium iodide (7.5 g, 36.7 mmol) in THF (100 mL) was cooled to −78 °C and treated with *n*-BuLi (13.8 ml, 32.4 mmol) and stirred for 20 min. To this, a solution of **13** (2.0 g, 9.2 mmol) in THF (10 mL) was added slowly and stirred at −78 °C for 1 h and at rt for 6 h. The reaction mixture was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc. The combined organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (5% ethyl acetate in petroleum ether) gave **10** (1.67 g, 79%) as a colorless oil. IR ($CHCl_3$): 3370, 2930, 2858, 1472, 1256, 835 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.57–1.67 (m, 4H), 2.77 (br. s, 1H), 3.63 (br. t, J = 5.8 Hz, 2H), 4.11 (dd, J = 5.8, 11.0 Hz, 1H), 5.06 (ddd, J = 1.2, 1.7, 10.4 Hz, 1H), 5.21 (dt, J = 1.6, 17.2 Hz, 1H), 5.85 (ddd, J = 5.9, 10.4, 17.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.4 (q), 18.3 (s), 25.9 (q), 28.7 (t), 34.3 (t), 63.3 (t), 72.6 (d), 114.2 (t), 141.2 (d) ppm. ESI-MS *m*/*z*: 231.4 (42.8%, [M + H]$^+$), 253.4 (100%, [M + Na]$^+$), 269.4 (28.6%, [M + K]$^+$). Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37; Found: C, 62.41; H, 11.66%.

Amano PS-mediated resolution of (*RS*)-10

A suspension of (*RS*)-**10** (2.2 g, 9.5 mmol), *Amano PS* (600 mg) and vinyl acetate (4.4 mL, 47.8 mmol) in benzene–petroleum ether (50 mL, 1 : 2) was heated at 40 °C for 96 h. The contents were filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2→5% ethyl acetate in petroleum ether) to afford alcohol (*R*)-**10** (0.9 g, 41%) and acetate (*S*)-**14** (1.1 g, 42%) as colorless oils.

(4*R*)-4-*O*-(*tert*-Butyldimethylsilyl)-hex-5-ene-1,4-diol [(*R*)-10]

$[\alpha]_D^{25}$ = −1.9 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3370, 2930, 2858, 1472, 1256, 835 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.57–1.67 (m, 4H), 2.77 (br. s, 1H), 3.63 (t, J = 5.8 Hz, 2H), 4.11 (br. q, J = 5.7 Hz, 1H), 5.06 (ddd, J = 1.3, 1.6, 10.3 Hz, 1H), 5.21 (dt, J = 1.5, 17.2 Hz, 1H), 5.85 (ddd, J = 5.8, 10.3,

17.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: −5.4 (q), 18.3 (s), 25.9 (q), 28.7 (t), 34.3 (t), 63.3 (t), 72.6 (d), 114.2 (t), 141.2 (d) ppm. ESI-MS *m/z*: 231.4 (42.8%, $[M + H]^+$), 253.4 (100%, $[M + Na]^+$), 269.4 (28.6%, $[M + K]^+$). Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37; Found: C, 62.67; H, 11.53%.

(4*S*)-1-*O*-Acetyl-4-*O*-(*tert*-butyldimethylsilyl)-hex-5-ene-1,4-diol [(*S*)-14]

R_t = 25.47 (Flow rate: 1.1073 ml min^{-1}, 60 °C/10 min, 5 °C min^{-1} → 80 °C then 10 °C min^{-1} → 140 °C and 10 °C min^{-1} → 220 °C/5 min). $[\alpha]_D^{25}$ = −6.0 (*c* 1.0, $CHCl_3$); Lit.[12] $[\alpha]_D^{24}$ = −6.1 (*c* 1.28, $CHCl_3$). IR ($CHCl_3$): 2955, 2858, 1742, 1560, 1473, 1248, 1100, 835 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.87 (s, 9H), 1.44–1.72 (m, 4H), 2.05 (s, 3H), 3.60 (t, *J* = 6.2 Hz, 2H), 5.12–5.28 (m, 1H), 5.79 (ddd, *J* = 6.2, 10.4, 17.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.5 (q), 18.3 (s), 21.2 (q), 25.9 (q), 28.3 (t), 30.5 (t), 62.2 (t), 74.5 (d), 116.6 (t), 136.5 (d), 170.3 (s) ppm. ESI-MS *m/z*: 295.3 (100%, $[M + Na]^+$). Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36; Found: C, 61.64; H, 10.19%.

(*R*)-14

R_t = 25.40 (Flow rate: 1.1073 ml min^{-1}, 60 °C/10 min, 5 °C min^{-1} → 80 °C then 10 °C min^{-1} → 140 °C and 10 °C min^{-1} → 220 °C/5 min). $[\alpha]_D^{25}$ = +5.2 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36; Found: C, 61.84; H, 10.19%.

(4*S*)-4-*O*-(*tert*-Butyldimethylsily)-hex-5-ene-1,4-diol [(*S*)-10]

To a solution of (*S*)-**14** (2 g, 7.3 mmol) in methanol (20 mL) was added K_2CO_3 (2 g, 14.7 mmol) and reaction mixture stirred at rt for 1 h and filtered and the filtrate was concentrated under reduced presser. The residue was purified by silica gel column chromatography (2→5% ethyl acetate in petroleum ether) to afford alcohol (*S*)-**10** (1.5 g, 91%) as colorless oil. $[\alpha]_D^{25}$ = +1.8 (*c* 1, $CHCl_3$); Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37; Found: C, 62.70; H, 11.41%.

(4*R*)-1-*O*-(4-Methoxybenzyl)-4-*O*-(*tert*-butyldimethylsilyl)-hex-5-ene-1,4-diol [(*R*)-15]

To a cooled solution of (*R*)-**10** (3.4 g, 14.7 mmol) in anhydrous DMF (35 mL), NaH (60% dispersion in mineral oil, 620 mg, 15.5 mmol) was added slowly and stirred for 5 min. Then PMB-Cl (2.2 mL, 16.2 mmol) was added and stirring continued at room temperature for 4 h. The reaction mixture was partitioned between water and EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (1→3% ethyl acetate in petroleum ether) afforded (*R*)-**15** (3.82 g, 75%) as a colorless oil. $[\alpha]_D^{25}$ = +13.4 (*c* 0.7, $CHCl_3$). IR ($CHCl_3$): 2954, 2857, 1613, 1514, 1250, 1097, 835 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.89 (s, 9H), 1.50–1.68 (m, 4H), 3.59 (br. t, *J* = 5.8 Hz, 2H), 3.67–3.77 (m, 1H), 3.79 (s, 3H), 4.28 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 5.19 (br. ddd, *J* = 0.8, 1.9, 16.2 Hz, 1H), 5.22 (br. ddd, *J* = 0.7, 1.9, 11.2 Hz, 1H), 5.65 (br. ddd, *J* = 7.6, 11.2, 16.2 Hz 1H), 6.86 (br. d, *J* = 8.6 Hz, 2H), 7.25 (br. d, *J* = 8.6 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: −5.35 (q), 18.3 (s), 25.9 (q), 28.6 (t), 31.8 (t), 55.1 (q), 63.0 (t), 69.6 (t), 80.0 (d), 113.7 (d), 116.9 (t), 129.2 (d), 130.8 (s), 139.2 (d), 159.0 (s) ppm. ESI-MS *m/z*: 351.0 (100%, $[M + H]^+$). Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.78; Found: C, 68.61; H, 9.88%.

(*S*)-15

$[\alpha]_D^{25}$ = −17.5 (*c* 1, $CHCl_3$); Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.78; Found: C, 68.19; H, 9.92%.

(4*R*)-1-*O*-(4-Methoxybenzyl)-hex-5-ene-1,4-diol [(*R*)-16]

To a cooled solution of **15** (3.0 g, 8.5 mmol) in dry THF (40 mL) was added tetrabutyl ammonium fluoride (2.68 g, 10.2 mmol) and stirred at rt for 4 h. The reaction mixture was partitioned in sat. ammonium chloride and ethyl acetate and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The purification of residue by silica gel column chromatography (25% ethyl acetate in petroleum ether) gave (*R*)-**16** (1.80 g, 89% yield) as a colorless oil. $[\alpha]_D^{25}$ = +19.4 (*c* 0.9, $CHCl_3$). IR ($CHCl_3$): 3020, 2928, 2855, 1612, 1514, 1215, 1035, 758 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.59–1.67 (m, 4H), 1.96 (br. s, 1H), 3.57–3.63 (m, 2H), 3.71–3.79 (m, 4H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 5.21 (br. ddd, *J* = 0.9, 1.8, 16.2 Hz, 1H), 5.23 (br. ddd, *J* = 0.7, 1.8, 11.3 Hz, 1H), 5.76–5.83 (m, 1H), 6.86 (br. d, *J* = 8.6 Hz, 2H), 7.25 (br. d, *J* = 8.6 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.8 (t), 32.3 (t), 55.2 (q), 62.8 (t), 69.8 (t), 80.1 (d), 113.8 (d), 117.2 (t), 129.4 (d), 130.4 (s), 138.7 (d), 159.1 (s) ppm. ESI-MS *m/z*: 237.4 (8.3%, $[M + H]^+$), 259.4 (100%, $[M + Na]^+$), 275.4 (20.8%, $[M + K]^+$). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; Found: C, 70.9; H, 8.69%.

(*S*)-16

$[\alpha]_D^{25}$ = −23.6 (*c* 1, $CHCl_3$); Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; Found: C, 71.02; H, 8.73%.

(4*R*)-4-(4-Methoxybenzyloxy)hex-5-enoic acid [(*R*)-8]

At −78 °C, a solution of DMSO (1.8 mL, 25.4 mmol) in CH_2Cl_2 (30 mL) was treated with oxalyl chloride (1.9 mL, 21.1 mmol) and stirred for 20 min. To this alcohol, (*R*)-**16** (2.0 g, 8.4 mmol) was added slowly and stirring was continued at −78 °C for another 1 h. To this, triethylamine (6 mL, 43 mmol) was added and the contents were allowed to warm to rt. The reaction mixture was poured into aqueous NH_4Cl (10 mL) and extracted with EtOAc. The combined organic layer was washed with water (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure and the resulting crude aldehyde was used directly for next step.

To a cooled solution of the above aldehyde (1.8 g) in DMSO (10 mL) and aq. $NaH_2PO_4 \cdot 2H_2O$ (0.8 g in 5 mL water), a solution of sodium chlorite (1.8 g, 19.8 mmol) in water (10 mL) was introduced slowly and the resulting mixture was stirred at rt for 10 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography (25→30% ethyl acetate in petroleum ether) to obtain acid (*R*)-**8** (1.28 g, 61%) as a colorless oil.

(*R*)-8

$[\alpha]_D^{25} = +23.2$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3076, 1710, 1612, 1514, 1422, 1249, 1035, 910, 734 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.81–1.94 (m, 2H), 2.43 (br. dd, $J = 7.1$ Hz, 2H), 3.73–3.83 (m, 4H), 4.27 (d, $J = 11.4$ Hz, 1H), 4.53 (d, $J = 11.4$ Hz, 1H), 5.26 (br. ddd, $J = 0.7$, 1.8, 10.9 Hz, 1H), 5.25 (br. ddd, $J = 0.9$, 1.8, 16.6 Hz, 1H), 5.65–5.82 (m, 1H), 6.6 (br. d, $J = 8.7$ Hz, 2H), 7.25 (br. d, $J = 8.7$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.1 (t), 30.1 (t), 55.2 (q), 69.8 (t), 78.8 (d), 113.7 (d), 117.8 (t), 129.4 (d), 130.3 (s), 138.1 (d), 159.1 (s), 179.2 (s) ppm. ESI-MS *m/z*: 273.2 (100%, $[M + Na]^+$), 289.2 (12.4%, $[M + K]^+$). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25; Found: C, 67.55; H, 7.32

(*S*)-8

$[\alpha]_D^{25} = -27.4$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25; Found: C, 67.83; H, 7.12%

1,2-Dideoxy-2,3-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-D-*ribo*-hex-1-enitol (18)

A solution of diol **17** (10.0 g, 53.2 mmol) in dry CH_2Cl_2 (150 mL) was cooled to 0 °C and treated with TsCl (10.25 g, 53.7 mmol) followed by TEA (22.3 mL, 161 mmol) and stirred at rt for 4 h. Then reaction mixture was partitioned between water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to afford **18** (15.46 g, 85%) as a pale yellow oil. $[\alpha]_D^{25} = +25.5$ (*c* 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.37 (s, 3H), 2.38 (br. s, 1H), 2.43 (s, 3H), 3.76–3.87 (m, 1H), 3.97 (dd, $J = 6.1$, 8.8 Hz, 1H), 4.05 (dd, $J = 6.6$, 10.3 Hz, 1H), 4.28 (dd, $J = 2.2$, 10.3 Hz, 1H), 4.66 (br. tt, $J = 1.2$, 6.3 Hz, 1H), 5.25 (dt, $J = 1.2$, 10.4 Hz, 1H), 5.40 (dt, $J = 1.4$, 17.2 Hz, 1H), 5.91 (ddd, $J = 6.6$, 10.4, 17.2 Hz, 1H), 7.33 (br. d, $J = 8.3$ Hz, 2H), 7.79 (br. d, $J = 8.3$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5 (q), 25.1 (q), 27.4 (q), 68.0 (d), 72.2 (t), 76.9 (d), 78.1 (d), 109.0 (s), 118.1 (t), 127.9 (d), 129.8 (d), 132.5 (s), 133.0 (d), 144.9 (s) ppm. Anal. Calcd for $C_{16}H_{22}O_6S$: C, 56.12; H, 6.48; Found: C, 55.89; H, 6.51%.

1,2-Dideoxy-2,3-*O*-isopropylidene-4,5-anhydro-D-*ribo*-hex-1-enitol (19)

To a solution of **18** (8.52 g, 24.9 mmol) in methanol (75 mL), solid K_2CO_3 (10.32 g, 74.7 mmol) was added at rt and stirred for 10 h. The solids were removed by filtration. The filtrate was diluted with water and extracted with diethyl ether (3 × 75 mL). The combined organic extract was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to afford **19** (3.30 g, 78%) as a colorless oil. $[\alpha]_D^{25}$: +18.8 (*c* 1, $CHCl_3$). IR ($CHCl_3$): 2991, 2930, 1601, 1383, 1253, 1217, 1042, 872 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.50 (s, 3H), 2.66 (dd, $J = 2.5$, 5.0 Hz, 1H), 2.81 (dd, $J = 3.9$, 5.0 Hz, 1H), 2.94 (ddd, $J = 2.6$, 3.9, 7.2 Hz, 1H), 3.74 (dd, $J = 6.5$, 7.2 Hz, 1H), 4.72 (tt, $J = 1.0$, 6.7 Hz, 1H), 5.34 (ddd, $J = 1.0$, 1.6, 10.4 Hz, 1H), 5.46 (br. dt, $J = 1.4$, 17.1 Hz, 1H), 5.98 (ddd, $J = 6.8$, 10.4, 17.1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1 (q), 27.6 (q), 45.7 (d), 49.7 (d), 78.6 (d), 78.9 (d), 109. (s), 118.8 (t), 132.4 (d) ppm. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29 Found: C, 63.35; H, 8.18%.

(3*S*,4*R*,5*S*)-3,4-*O*-Isopropylidene-oct-1-ene-3,4,5-triol (9)

At 0 °C, a suspension of CuCN (1.64 g, 18.2 mmol) in dry ether (10 mL) was treated with a solution of EtMgBr [prepared from Mg (1.85 g, 76 mmol) and ethyl bromide (3.42 mL, 45.6 mmol)] in ether (30 mL) added slowly, and the contents were stirred at 0 °C for 20 min. To this, a solution of the epoxide **19** (2.59 g, 15.2 mmol) in ether (10 mL) was introduced and the mixture was stirred for another 1 h at 0 °C. The reaction mixture was quenched with cold water and extracted with ethyl acetate. The combined organic extract was dried (Na_2SO_4), concentrated and the resulting crude material was purified by column chromatography to afford alcohol **9** (2.1 g, 71%) as a colorless oil. $[\alpha]_D^{25} = +9.9$ (*c* 1.3, $CHCl_3$). IR ($CHCl_3$): 3437, 2987, 2959, 2936, 2874, 1458, 1428, 1381, 1253, 1217, 1168, 1099, 1067, 1033, 874 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, $J = 6.9$ Hz, 3H), 1.31–1.72 (m, 4H), 1.35 (s, 3H), 1.46 (s, 3H), 3.66 (br. t, $J = 8.5$ Hz, 1H), 3.96 (dd, $J = 6.5$, 8.2 Hz, 1H), 4.63 (br. t, $J = 6.9$ Hz, 1H), 5.30 (br. d, $J = 10.3$ Hz, 1H), 5.41 (br. d, $J = 17.2$ Hz, 1H), 6.03 (ddd, $J = 7.7$, 10.2, 17.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (q), 18.3 (t), 25.3 (q), 27.8 (q), 35.8 (t), 69.7 (d), 78.9 (d), 80.7 (d), 108.6 (s), 118.5 (t), 134.7 (d) ppm. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07 Found: C, 65.83; H, 9.84%.

Diene 7

To a solution of acid (*R*)-**8** (500 mg, 2.0 mmol) in dry THF (10 mL) were added 2,4,6-trichlorobenzoyl chloride (0.37 mL, 2.4 mmol) and *N*,*N*-diisopropylethylamine (2.0 mL, 11.5 mmol) and the contents were stirred for 2 h at ambient temperature. After completion of mixed anhydride formation as indicated by TLC, DMAP (500 mg, 4 mmol) and a solution of alcohol **9** (400 mg, 2.0 mmol) in THF (2 mL) were added and the reaction mixture was stirred for 16 h at rt. The reaction was quenched with water and extracted with ethyl acetate. The combined organic phase was washed with saturated $NaHCO_3$ solution, water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (8→10% EtOAc in petroleum ether) to afford the diene **7** (673 mg, 78%) as a light yellow oil. $[\alpha]_D^{25} = +9.6$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 2961, 2935, 2873, 1735, 1613, 1514, 1465, 1249, 910 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.3$ Hz, 3H), 1.20–1.34 (m, 2H), 1.36 (s, 3H), 1.48 (s, 3H), 1.55–1.67 (m, 2H), 1.79–1.91 (m, 2H), 2.32 (d, $J = 8.4$ Hz, 1H) 2.36 (dd, $J = 0.9$, 8.8 Hz, 1H) 3.70–3.80 (m, 4H), 4.16 (dd, $J = 6.5$, 7.4 Hz, 1H), 4.25 (d, $J = 11.3$ Hz, 1H), 4.52 (d, $J = 11.3$ Hz, 1H), 4.60 (ddt, $J = 0.9$, 6.4, 7.8 Hz, 1H), 4.91 (dt, $J = 4.0$, 7.4 Hz, 1H), 5.17–5.36 (m, 4H), 5.64–5.74 (m, 1H), 5.75–5.84 (m, 1H), 6.88 (br. d, $J = 8.6$ Hz, 2H), 7.24 (br. d, $J = 8.6$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (q), 17.9 (t), 25.2 (q), 27.5 (q), 30.3 (t), 33.3 (t), 55.2 (q), 69.8 (t), 71.6 (d), 78.4 (d), 78.8 (d), 79.0 (d), 108.7 (s), 113.7 (2C, d), 117.6 (t), 118.5 (t), 129.3 (d), 130.5 (s), 133.2 (d), 138.3 (d), 159.1 (s), 172.5 (s) ppm. ESI-MS *m/z*: 455.6 (100%, $[M + Na]^+$), 471.5 (18.5%, $[M + K]^+$). Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; Found: C, 69.31; H, 8.42%.

Compound 20

A suspension of **7** (400 mg, 0.9 mmol) and DDQ (600 mg, 2.6 mmol) in CH_2Cl_2–H_2O (50 mL, 18 : 1) was stirred for 3 h at rt. The reaction mixture was quenched with aqueous $NaHCO_3$ solution and partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (25% EtOAc in petroleum ether) to afford **20** (233 mg, 81%) as a colourless oil. $[\alpha]_D^{25} = +29.4$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3453, 2962, 2875, 1732, 1645, 1382, 1217, 1066, 929 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.3$ Hz, 3H), 1.18–1.31 (m, 2H), 1.35 (br. s, 3H), 1.46 (br. s, 3H), 1.56–1.71 (m, 2H), 1.74–1.94 (m, 2H), 2.39 (br. dd, $J = 2.7$, 7.3 Hz, 1H), 2.35 (br. dd, $J = 1.5$, 7.3 Hz, 1H), 4.15 (d, $J = 6.6$ Hz, 1H), 4.19 (d, $J = 6.6$ Hz, 1H), 4.59 (ddt, $J = 1.0$, 6.6, 7.4 Hz, 1H), 4.91 (dt, $J = 4.0$, 7.3 Hz, 1H), 5.13 (dt, $J = 1.3$, 10.4 Hz, 1H), 5.21 (ddd, $J = 0.9$, 1.7,10.4 Hz, 1H), 5.25 (br. dt, $J = 1.4$, 7.2 Hz, 1H), 5.33 (br. ddd, $J = 1.1$, 1.7, 15.8 Hz, 1H), 5.70–5.92 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (q), 17.9 (t), 25.2 (q), 27.5 (q), 30.3 (t), 31.4 (t), 33.3 (t), 71.9 (d), 72.0 (d), 78.3 (d), 78.8 (d), 108.8 (s), 115.1 (t), 118.5 (t), 133.1 (d), 140.3 (d), 172.9 (s) ppm. ESI-MS *m/z*: 335.4 (100%, $[M + Na]^+$), 351.4 (13.2%, $[M + K]^+$). Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03; Found: C, 65.19; H, 9.29%.

Stagonolide B

To a solution of diene **20** (50 mg, 0.16 mmol) in dry dichloroethane (20 mL), 2nd gen. Grubbs' catalyst (35 mg, 0.04 mmol) was added and the mixture was degassed under an argon atmosphere thoroughly. The reaction mixture was refluxed for 24 h and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc in petroleum ether) giving impure macrolide (25 mg) as a colorless liquid. The above compound (25 mg) was suspended at 0 °C in TFA (2 mL) and stirred for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (70→100% EtOAc in petroleum ether) to obtain the **2** as a viscous liquid (15 mg, 39%). $[\alpha]_D^{25} = +27.1$ (*c* 0.9, $CHCl_3$); Lit.[9a] $[\alpha]_D^{25} = +20$ (*c* 0.1, $CHCl_3$). IR ($CHCl_3$): 3409, 2927, 1729, 1560 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.23–1.30 (m, 1H), 1.32–1.42 (m, 1H), 1.57 (ddq, $J = 4.9$, 9.8, 14.3 Hz, 1H), 1.64 (br. s, 1H, –OH), 1.82–1.92 (m, 2H), 2.07 (br. ddd, $J = 2.6$, 5.5, 14.3 Hz, 1H), 2.12 (br. dt, $J = 2.6$, 14.4 Hz, 1H), 2.24 (br. d, $J = 8.4$ Hz, 1H, C7–OH), 2.44 (br. s, 1H, –OH), 2.45 (br. dt, $J = 1.8$, 14.4 Hz, decouple at 1.9→t, $J = 13.4$, 1H), 3.57 (br. t, $J = 8.5$ Hz, decouple at 2.48→dd, $J = 2.6$, 9.9 Hz, 1H), 4.47–4.53 (br. s, decouple at 2.29→dt, $J = 2.6$, 4.6 Hz, 1H), 4.59–4.64 (br. s, 1H), 4.94 (dt, $J = 2.5$, 9.6 Hz, decouple at 1.90→t, $J = 9.5$ Hz, 1H), 5.63 (dt, $J = 2.7$, 16.1 Hz, 1H), 5.99 (dt, $J = 1.7$, 16.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (q), 18.0 (t), 27.8 (t), 31.6 (t), 33.6 (t), 68.6 (d), 70.2 (d), 73.6 (d), 73.6 (d), 127.1 (d), 127.2 (d), 176.5 (s). ESI-MS *m/z*: 267.2 (100%, $[M + Na]^+$). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25; Found: C, 59.22; H, 8.10%.

Diene *epi*-7

To a solution of acid (*S*)-**8** (240 mg, 0.96 mmol) in dry THF (5 mL), 2,4,6-trichlorobenzyl chloride (0.22 mL, 1.44 mmol) followed by *N*,*N*-diisopropylethylamine (0.83 mL, 4.79 mmol) were added and the mixture was stirred for 2 h at ambient temperature. After completion of mixed anhydride formation as indicated by TLC, a solution of alcohol **9** (192 mg, 0.96 mmol) in THF (2 mL) was introduced and the contents were stirred for 16 h at rt. The reaction mixture was quenched with cold water and extracted with ethyl acetate. The combined organic phase was washed with aq. $NaHCO_3$ solution and water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (8→10% EtOAc in petroleum ether) to procure *epi*-**7** (348 mg, 84%) as a light yellow oil. $[\alpha]_D^{25}$: –2.8 (*c* 1.4, $CHCl_3$). IR ($CHCl_3$): 2932, 2872, 1737, 1644, 1613, 1514, 1464, 1442, 1372, 1301, 1172, 1067, 1037, 928, 872, 821 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, $J = 7.2$ Hz, 3H), 1.23–1.36 (m, 2H), 1.36 (s, 3H), 1.48 (s, 3H), 1.56–1.71 (m, 2H), 1.77–1.96 (m, 2H), 2.19–2.48 (m, 2H), 3.70–3.79 (m, 1H), 3.79 (s, 3H), 4.16 (dd, $J = 6.6$, 7.4 Hz, 1H), 4.26 (d, $J = 11.4$ Hz, 1H), 4.52 (d, $J = 11.4$ Hz, 1H), 4.59 (ddt, $J = 1.0$, 6.7, 7.4 Hz, 1H), 4.91 (dt, $J = 4.0$, 7.4 Hz, 1H), 5.16–5.23 (m, 2H), 5.26–5.36 (m, 2H), 5.63–5.88 (m, 2H), 6.87 (br. d, $J = 8.6$ Hz, 2H), 7.24 (br. d, $J = 8.6$, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (q), 17.8 (t), 25.1 (q), 27.4 (q), 30.3 (t 2C), 33.3 (t), 55.2 (q), 69.7 (t), 71.6 (d), 78.3 (d), 78.7 (d), 79.0 (d), 108.7 (s), 113.7 (d), 117.6 (t), 118.3 (t), 129.2 (d), 130.5 (s), 133.2 (d), 138.3 (d), 159.1 (s), 172.4 (s) ppm. Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; Found: C, 69.31; H, 8.41%.

Compound 21

A solution of diene *epi*-**7** (70 mg, 0.16 mmol) and 2nd gen. Grubbs' catalyst (14 mg, 0.016 mmol) in dry toluene (20 ml) was degassed with argon thoroughly and heated at 80 °C for 6 h. The volatiles were removed and the residue was purified by flash chromatography to afford **21** (45 mg, 69%) as a colourless liquid. $[\alpha]_D^{25} = -9.0$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$): 3018, 2959, 2924, 2851, 1725, 1611, 1465, 1215, 1162, 1114, 1035, 820 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, $J = 7.2$, 3H), 1.21–1.34 (m, 2H), 1.39 (s, 3H), 1.51–1.68 (m, 2H), 1.55 (s, 3H), 1.71–1.76 (m, 1H), 1.94–2.08 (m, 2H), 2.26–2.36 (m, 1H), 3.79 (s, 3H), 3.81 (dd, $J = 4.6$, 8.5 Hz, 1H), 3.95 (dd, $J = 4.6$, 10.1 Hz, 1H), 4.27 (d, $J = 11.5$ Hz, 1H), 4.56 (d, $J = 11.5$ Hz, 1H), 4.71 (ddd, $J = 1.6$, 3.0, 4.6 Hz, 1H), 4.94 (ddd, $J = 2.6$, 8.3, 10.1 Hz, 1H), 5.66 (ddd, $J = 1.6$, 8.3, 15.9 Hz, 1H), 5.84 (dd, $J = 3.1$, 15.9 Hz, 1H), 6.85 (d, $J = 8.6$ Hz, 2H), 7.23 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (q), 17.8 (t), 26.3 (q), 28.4 (q), 31.2 (t), 31.8(t), 34.2 (t), 55.2 (q), 69.8 (t), 70.6 (d), 75.9 (d), 78.6 (d), 81.6 (d), 109.3 (s), 113.8 (d), 127.4 (d), 128.2 (d), 129.3 (d), 130.5 (s), 159.1 (s), 174.9 (s). ESI-MS *m/z*: 405.5 (10%, $[M + H]^+$), 427.5 (100%, $[M + Na]^+$. Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97; Found: C, 68.19; H, 8.01%.

4-*epi*-Stagonolide (*epi*-2)

A solution of compound **21** (21 mg, 0.05 mmol) and TFA (2 mL) was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (70→100% EtOAc in petroleum ether) to procure *epi*-**2** as a colorless solid (11 mg, 87%). MP: 185–187 °C. $[\alpha]_D^{25}$: +11.3 (*c* 0.3, CH_3OH). IR ($CHCl_3$): 3390, 2921, 1730, 1563 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 0.91 (t, $J = 7.4$ Hz, 3H),

1.22–1.36 (m, 2H), 1.43–1.51 (m, 1H), 1.76–1.85 (m, 2H), 1.89–1.94 (m, 1H), 2.03 (dt, $J = 2.2$, 13.5 Hz, 1H), 2.26 (ddd, $J = 2.4$, 6.3, 13.5 Hz, 1H), 3.50 (dd, $J = 2.5$, 9.7 Hz, 1H), 4.06 (br. ddd, $J =$ 4.7, 9.3, 10.8 Hz, 1H), 4.38 (br. dd, $J = 2.3$, 4.6 Hz, 1H), 5.13 (dt, $J = 2.7$, 9.6 Hz, 1H), 5.50 (ddd, $J = 2.3$, 9.3, 15.6 Hz, 1H), 5.77 (dd, $J = 2.2$, 15.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4 (q), 18.9 (t), 32.5 (t), 33.9 (t), 35.1 (t), 71.9 (d), 73.6 (d), 74.6 (d), 75.9 (d), 128.2 (d), 133.5 (d), 176.3 (s) ppm. ESI-MS *m/z*: 245.2 (100%, $[M + H]^+$). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25; Found: C, 58.85; H, 8.26%.

Diene *epi*-20

To a solution of *epi*-**7** (100 mg, 0.23 mmol) in CH_2Cl_2–H_2O (15 mL, 18 : 1) DDQ (157 mg, 0.69 mmol) was added and stirred for 3 h at rt. The reaction mixture was quenched with aqueous $NaHCO_3$ solution and partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (25% EtOAc in petroleum ether) to procure *epi*-**20** (60 mg, 86%) as a colorless oil. $[\alpha]_D^{25} = +30.5$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3453, 2961, 2864, 1732, 1643, 1388, 1215, 1061, 924 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, $J =$ 7.4 Hz, 3H), 1.23–1.34 (m, 2H), 1.35 (br. s, 3H), 1.47 (br. s, 3H), 1.58–1.71 (m, 2H), 1.74–1.89 (m, 2H), 2.35 (br. dd, $J = 2.7$, 7.4 Hz, 1H), 2.30–2.43 (m, 2H), 4.13 (br. dd, $J = 6.0$ Hz, 1H), 4.17 (dd, $J = 6.7$, 7.4 Hz, 1H), 4.59 (br. t, $J = 7.2$ Hz, 1H), 4.91 (dt, $J =$ 3.5, 7.6 Hz, 1H), 5.13 (br. dt, $J = 1.2$, 10.5 Hz, 1H), 5.18–5.26 (m, 2H), 5.32 (br. dt, $J = 1.2$, 17.0 Hz, 1H), 5.74–5.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q), 17.9 (t), 25.2 (q), 27.5 (q), 30.3 (t), 31.4 (t), 33.3 (t), 71.9 (d), 72.1 (d), 78.3 (d), 78.8 (d), 108.8 (s), 115.1 (t), 118.6 (t), 133.1 (d), 140.3 (d), 173.0 (s) ppm. ESI-MS *m/z*: 335.2 (100%, $[M + Na]^+$). Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03; Found: C, 65.24; H, 9.15%.

RCM of diene *epi*-20

To a degassed solution of diene *epi*-**20** (40 mg, 0.12 mmol) and 2nd gen. Grubbs' catalyst (11 mg, 0.012 mmol) in dry DCM (40 mL) was heated to reflux under argon atmosphere for 6 h and concentrated. The residue was purified by flash chromatography to furnish **22** (32 mg, 89%) as colourless semisolid. $[\alpha]_D^{25} = +55.1$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): 3467, 3020, 1732, 1542, 1452, 1349, 1216, 1046 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.9 (t, $J = 7.3$, 3H), 1.26–1.35 (m, 2H), 1.36 (s, 3H), 1.41–1.50 (m, 2H), 1.54 (s, 3H), 1.70–1.78 (m, 1H), 1.98–2.05 (m, 2H), 2.29–2.35 (m, 1H), 3.95 (dd, $J = 4.7$, 10.1 Hz, 1H), 4.13–4.20 (m, 1H), 4.68 (br. ddd, 1.9, 3.1, 4.7 Hz, 1H), 4.92 (ddd, $J = 2.7$, 8.9, 10.1 Hz, 1H), 5.64 (ddd, $J = 1.7$, 8.6, 15.9 Hz, 1H), 5.81 (dd, $J = 3.3$, 15.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (q), 17.8 (t), 26.2 (q), 28.4 (q), 31.2 (t), 33.6 (t), 34.1 (t), 70.8 (d), 75.6 (d), 75.7 (d), 78.6 (d), 109.3 (s), 126.7 (d), 128.1 (d), 175.0 (s) ppm. ESI-MS *m/z*: 307.1 (100% $[M + Na]^+$). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51; Found: C, 63.25; H, 8.39%.

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