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Stereoselective total synthesis of (+)-sapinofuranone B

J.S. Yadav *,†, S.S. Mandal, J.S.S. Reddy, P. Srihari

Organic Division-I, Indian Institute of Chemical Technology, CSIR, Hyderabad 500607, Andhra Pradesh, India

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ABSTRACT

Two approaches for the total synthesis of (+)-sapinofuranone B have been described. The first strategy utilizes the methodology developed earlier in our group to get the chiral propargyl alcohol and the second strategy involves generation of *threo*-1,2-diol derivative by diastereoselective and enantioselective addition of [(*Z*)-γ-methoxymethoxyallyl]diisopinocampheylborane onto aldehyde and cross metathesis as the key steps.

1. Introduction

γ-Lactone motiff containing natural products are receiving significant attention due to their potent biological activities.[1] A decade back, Simpson and co-workers, while working for the production of xenovulene A **1** have isolated a novel metabolite sapinofuranone B **2** from fermentation extracts[2] (Fig. 1). During the same period, closely related lactones sapinofuranone A **3** and *ent*-sapinofuranone B **2a** were isolated from liquid cultures of *Saphaeropsis sapinae*.[3] Initially, the absolute structure of sapinofuranone B was established by spectroscopic studies and chemical correlation with the known L-factor **4** isolated from *Streptomyces griseus* and was later re-confirmed by its total synthesis.[2,4]

In continuation of our programme toward the total synthesis of biologically active lactone containing natural products,[5] we have recently communicated the total synthesis of sapinofuranone B.[6] Herein, we provide full details of the synthesis along with an alternative route for the total synthesis of sapinofuranone B starting from L-(+)-DET and *cis*-2-butene-1,4-diol.

2. Results and discussion

Retrosynthetically, **2** was envisioned to be obtained from **5** through one pot acetonide deprotection and lactonization. Compound **5** can be obtained from **6** via a Sonogashira coupling and reduction of triple bond to double bond. The ester **6** could be achieved from **7**, which in turn can be obtained from **8** through a ring opening reaction. The compound **8** can be easily accessible from commercially available L-(+)-DET (Scheme 1). Alternatively, compound **6** can also be synthesized from aldehyde **9**, which can be obtained from **10** in three steps. Compound **10** can be synthesized by cross metathesis between ethyl acrylate and compound **11**, which in turn can be prepared from **12**. Compound **12** can be obtained from an aldol type of reaction of suitably protected glyoxaldehyde **13** readily accessible from commercially available *cis*-2-butene-1,4-diol (Scheme 1).

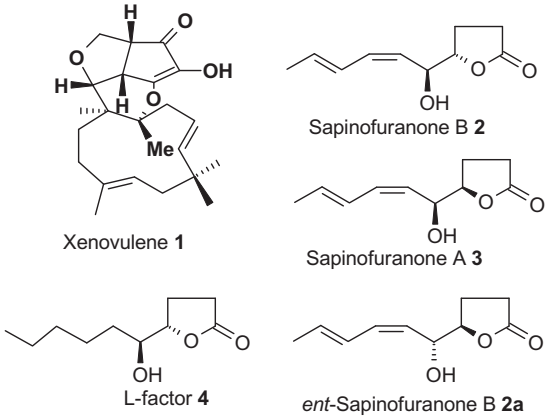

Fig. 1. Sapinofuranone B and related compounds.

Accordingly, the synthesis started with the known alcohol **14** synthesized earlier in our laboratory following known protocols.[7] The alcohol **14** was subjected to Swern oxidation to yield aldehyde **15**. Allylation with allyl bromide in presence of zinc provided the easily separable diastereomers **16** and **16a** in 9:1 ratio (Scheme 2). Based on the earlier report,[8] the major isomer was sought to be the desired product and we proceeded further. Compound **16** was protected using MOMCl in presence of Hünig's base to provide MOM ether **17**. TBS deprotection followed by treatment of the resulting alcohol with triphenylphosphine and carbon tetrachloride furnished chloro compound **8** in good yield. Hydroboration with

* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 27160387; e-mail address: yadavpub@iict.res.in (J.S. Yadav).
† King Saud University, Riyadh-11451, Saudi Arabia.

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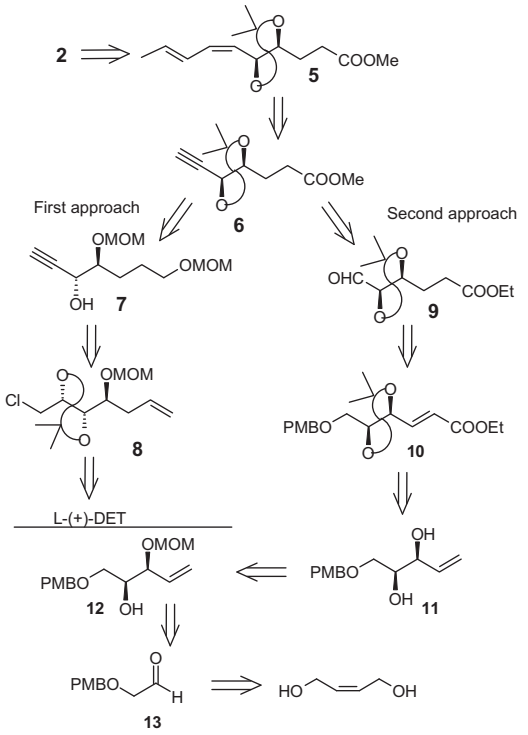
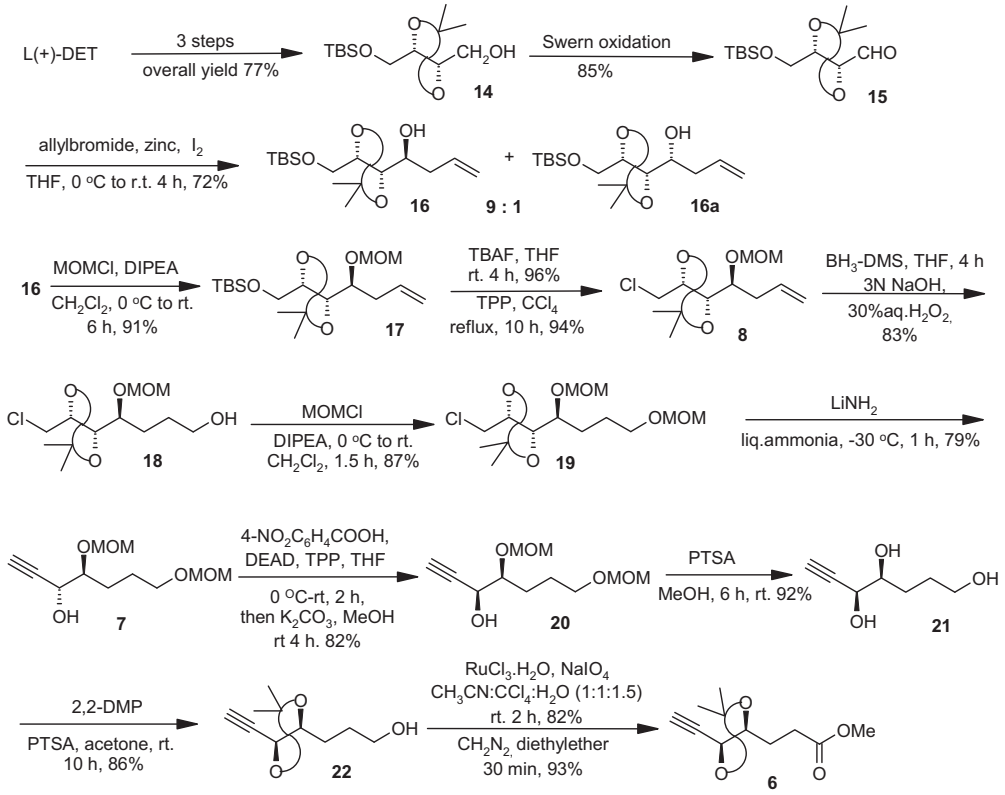


Scheme 1. Retrosynthesis.

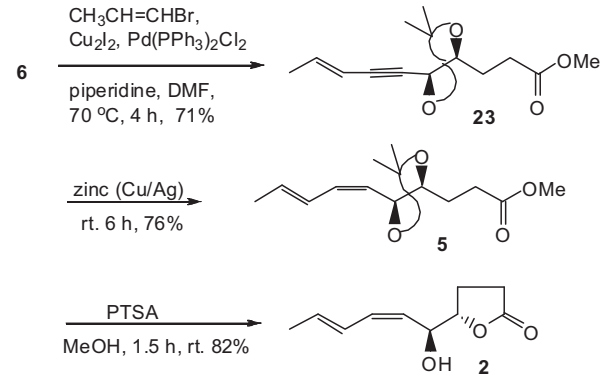
$BH_3 \cdot DMS$ yielded the terminal alcohol **18**,[9] which was protected as the corresponding MOM ether **19** using MOMCl, DIPEA in DCM. The chloro compound **19** was subjected to our previously reported protocol of base induced double eliminative acetonide opening reaction with $LiNH_2$ in liquid ammonia at −30 °C to give the chiral propargyl alcohol **7** in 79% yield.[10] Mitsunobu inversion[11] of alcohol **7** was achieved using DEAD, TPP and 4-nitro benzoic acid followed by hydrolysis of the resultant ester with K_2CO_3 in methanol to yield the alcohol **20** in 82% yield. Deprotection of MOM groups in compound **20** was achieved with catalytic amount of PTSA in MeOH to afford triol **21** in 92% yield. Triol **21** was subjected to 1,2-dihydroxyl protection with 2,2-dimethoxypropane and catalytic amount of PTSA in dry acetone to yield the corresponding acetonide **22**. The free primary alcohol **22** was then oxidized to acid using $RuCl_3 \cdot H_2O$ and $NaIO_4$[12] and further converted to its methyl ester **6** using diazomethane (Scheme 2).

Compound **6** was subjected to Sonogashira coupling[13] with *trans*-1-bromo-1-propene using Cu_2I_2, $Pd(Ph_3P)_2Cl_2$ and piperidine in dry DMF to afford the coupled product **23**. The compound **23** on reduction with Zn (preactivated with $AgNO_3$ and $Cu(OAc)_2 \cdot H_2O$ in MeOH)[14] afforded the diene **5** exclusively, which on treatment with catalytic amount of PTSA in MeOH underwent one pot acetonide deprotection and lactonization to afford the target molecule sapinofuranone B **2** in 82% yield (Scheme 3). The ^1H NMR and ^{13}C NMR spectral data of our synthetic compound were in good agreement with the data previously reported in literature.

The second strategy started with *cis*-2-butene-1,4-diol, which was protected as the corresponding di-*p*-methoxybenzyl ether **24**. Oxidative cleavage of **24** yielded PMB-protected glyoxaldehyde **13**.[15] The aldehyde **13** was treated with [*Z*-(methoxymethoxy)allyl] diisopinocampheylborane to yield product **25** with >95% ee in 65% yield.[16] Selective MOM deprotection with 6 N HCl in THF afforded diol **11**, which was treated with 2-methoxy-propene in presence of camphorsulphonic acid to give **26**. The olefin **26** was subjected to cross metathesis with ethyl acrylate in presence of Grubbs' second generation catalyst to yield α,β-unsaturated ester **10**.[17] Selective reduction of α,β-unsaturated double bond was achieved with $NiCl_2$ and $NaBH_4$ to yield product **27**.[18] DDQ assisted cleavage of PMB ether **27** provided alcohol **28**, which was subjected to Swern oxidation to yield aldehyde **9**. The aldehyde on Wittig reaction with 2-butene-1-triphenylphosphonium bromide in presence of



Scheme 2. Synthesis of intermediate **6**.



Scheme 3. Synthesis of sapinofuranone B.

LiHMDS provided inseparable mixture of diastereomers **5** and **5a** in 40:60 ratio. Exposure of this mixture to 6 N HCl yielded inseparable diastereomeric mixture of sapinofuranones B **2** and **2a** (Scheme 4).

Since the pure product was not separable from the mixture, we proceeded with aldehyde **9** to convert it into alkyne **6** using Bestman reagent.[19] The alkyne **6** was further utilized toward the enantiopure synthesis of sapinofuranone B **2** as mentioned earlier in the Scheme 3.

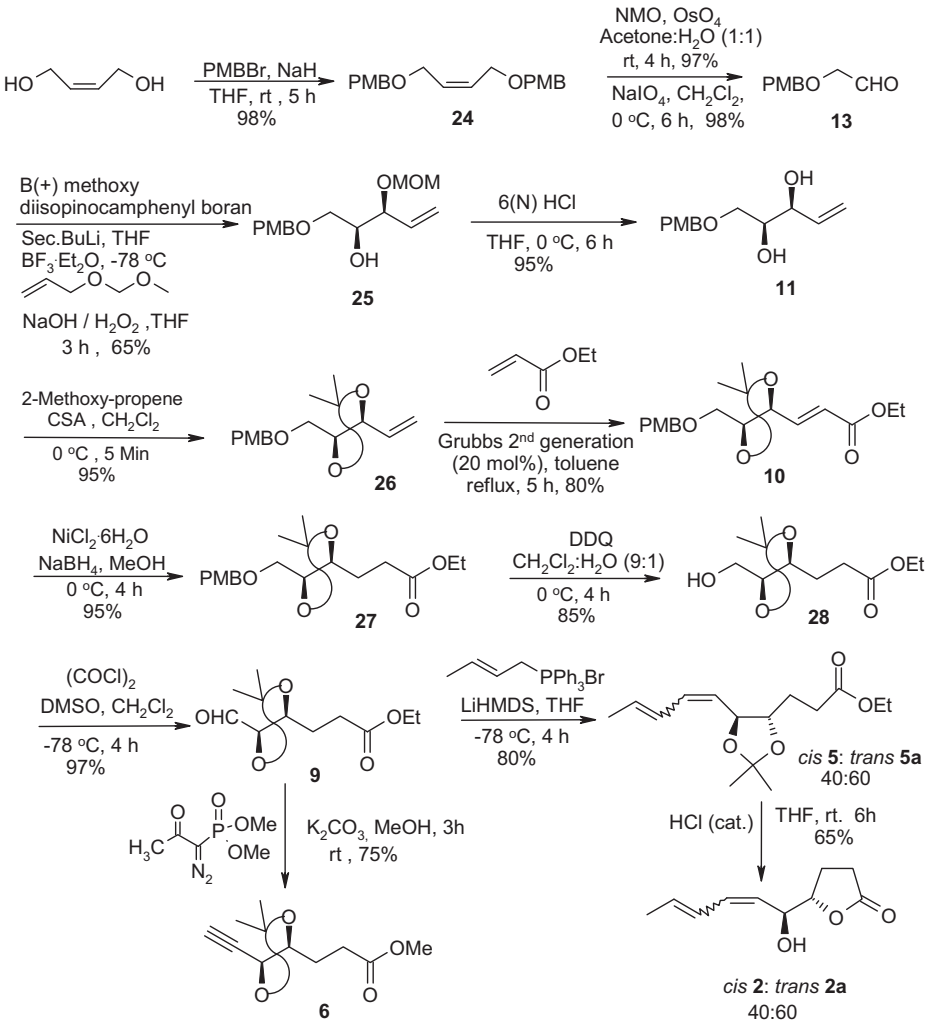
3. Conclusions

In conclusion, we have described the total synthesis of (+)-sapinofuranone B employing two different strategies involving a ring opening reaction to reveal an alkyne, Sonogashira coupling, cross metathesis and diastereoselective and enantioselective addition of [(*Z*)-γ-methoxymethoxyallyl]diisopinocampheylborane to aldehyde reaction as the key steps. The overall yields for the total synthesis are 11.5% (13 steps) and 9.9% (11 steps). The strategies utilized the commercially available L- (+)-DET and *cis*-2-butene-1,4-diol as the raw materials for the total synthesis. Synthesis of other related molecules are currently being investigated.

4. Experimental section

4.1. General information

All the reagents employed were obtained commercially from M/s. Aldrich and used without further purifications unless otherwise stated. For anhydrous reactions, solvents were dried following known literature and removal of solvent was performed under reduced pressure using a rotary evaporator. All reactions requiring anhydrous conditions were carried out in oven-dried glassware under a nitrogen atmosphere. The ^{1}H NMR spectra were recorded at 300 or 400 MHz, and the ^{13}C NMR spectra were recorded at



Scheme 4. Synthesis of sapinofuranone B.

75 MHz/100 MHz at ambient temperature. Chemical shifts of the ^{1}H NMR spectra are expressed in parts per million relative to the solvent residual signal 7.26 in $CDCl_3$ or to tetramethylsilane (δ=0.00). Chemical shifts of the ^{13}C NMR spectra are expressed in ppm relative to the solvent signal 77.00 in $CDCl_3$ unless otherwise noted. One or more of the following methods were used for visualization: UV absorption by fluorescence quenching; iodine staining; anisaldehyde stain (ethanol (135 mL)/H_2SO_4 (5 mL)/AcOH (1.5 mL)/*p*-anisaldehyde 3.7 mL). Column chromatography was performed using 60–120 mesh silica gel. Ethyl acetate and hexane were the common eluents used unless specified. HPLC was carried on a Shimadzu LC-10AT vp quaternary gradient with UV–vis detection pump system.

*4.1.1. ((4S,5S)-5-((tert-Butyldimethylsilyloxy) methyl)-2,2-dimethyl-1,3-dioxolan-4-yl) methanol (**14**).* Sodium hydride [60% dispersion in mineral oil (1.77 g, 74 mmol) prewashed with hexane] was suspended in anhydrous THF (200 mL). The diol (12.0 g, 74.0 mmol) obtained after acetonide protection and ester reduction starting from L-(+)-DET was added to the mixture of slurry of sodium hydride (1.78 g, 74 mmol) at room temperature and stirred for 45 min at which time a large amount of an opaque white precipitate had formed. Then TBDMSCl (11.16 g, 74.0 mmol) dissolved in anhydrous THF (50 mL) was added and stirring was continued for 45 min at same temperature. The reaction mixture was poured into diethyl ether (100 mL) and washed with aqueous 10% K_2CO_3 solution (50 mL), brine solution (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The resulting oil was purified by flash column chromatography to give the title product **14** (18.4 g, 90% yield) as a colorless liquid. R_f (20% EtOAc/hexane): 0.5. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.90 (s, 9H), 1.37 (s, 3H), 1.38 (s, 3H), 2.31 (br s, 1H, OH), 3.59–3.70 (m, 3H), 3.80–3.97 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.5, 18.3, 25.8, 26.5, 26.7, 62.2, 64.1, 79.6, 82.3, 108.1. IR (neat): 674, 776, 838, 1003, 1082, 1219, 1258, 1375, 1466, 1534, 2932, 3458 cm^{-1}. MASS (LC–MS): *m*/*z* 299 [M+Na]$^+$. HRMS: calcd for $C_{13}H_{28}O_4SiNa$: 299.1654. Found 299.1650.

*4.1.2. (S)-1-((4S,5S)-5-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**16**).* To a solution of oxalyl chloride (9.40 mL, 108.7 mmol) in dry CH_2Cl_2 (130 mL) at −78 °C was added DMSO (15.4 mL, 217.4 mmol) over 10 min, and the mixture was stirred for 20 min. A solution of alcohol **14** (15 g, 54.3 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 10 min. After 1 h of stirring at −78 °C, Et_3N (45.3 mL, 326 mmol) was added dropwise at the same temperature, and resulting white slurry was stirred for further 20 min and allowed to warm to room temperature. The mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (1×50 mL). The organic layer was washed with water (2×25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure at low temperature to give aldehyde **15** (12.7 g, 85%). The aldehyde obtained was used as such in the next step without further purification.

To a solution of aldehyde **15** (12.20 g, 44.52 mmol), zinc (8.73 g, 133.5 mmol) and catalytic amount of iodine (50 mg) were added in anhydrous THF (150 mL). The mixture was stirred for 30 min at 0 °C, and then allyl bromide (7.6 mL, 89.0 mmol) was added dropwise for a period of 15 min. After 4 h of stirring at room temperature the reaction mixture was quenched with saturated NH_4Cl solution, filtered through a small pad of Celite and the residue was washed with ethyl acetate (2×40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure, which gave the diastereomeric mixture of allyl alcohols **16** and **16a** in 9:1 ratio. The crude diastereomeric mixture was purified by silica gel (100–200 mesh) column chromatography using hexane/ethyl acetate as eluent to afford allylic alcohol **16** (11.7 g, 72%) as colorless liquid. R_f (10% EtOAc/hexane): 0.4; $[\alpha]_D^{25}$ +8.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.91 (s, 9H), 1.35 (s, 3H), 1.37 (s, 3H), 2.14–2.23 (m, 1H), 2.40–2.49 (m, 1H), 2.90 (br s, 1H, −OH), 3.59–3.70 (m, 3H), 3.81–3.90 (m, 2H), 5.07–5.16 (m, 2H), 5.82–5.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.5, 18.3, 25.8, 26.8, 26.9, 37.8, 64.2, 71.5, 79.5, 81.6, 108.8, 117.5, 134.5. IR (neat): 774, 837, 1082, 1254, 1379, 1617, 2932, 3447 cm^{-1}. MASS (LC–MS): *m*/*z* 339 [M+Na]$^+$. HRMS: calcd for $C_{16}H_{32}O_4SiNa$: 339.1967. Found 339.1970.

*4.1.3. tert-Butyl(((4S,5S)-5-((S)-1-(methoxymethoxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)dimethylsilane (**17**).* To alcohol **16** (9.00 g, 28.5 mmol) in anhydrous CH_2Cl_2 (120.0 mL) at 0 °C were added *N*,*N*-diisopropylethylamine (29.7 mL, 170.8 mmol) and catalytic amount of DMAP and the mixture was stirred for 15 min. To the reaction mixture was added methyl chloromethyl ether (MOMCl) (8.6 mL, 113.9 mmol) dropwise over a period of 15 min, and the allowed to stir for 1 h at the same temperature and then warmed to room temperature and stirred further for 5 h. The reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The obtained crude product was purified by silica gel column chromatography to afford the MOM ether **17** (9.35 g, 91%) as colorless oil. R_f (10% EtOAc/hexane): 0.6. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.90 (s, 9H), 1.35 (s, 6H), 2.34–2.38 (m, 2H), 3.35 (s, 3H), 3.64–3.80 (m, 3H), 3.89–3.98 (m, 2H), 4.65 (s, 2H), 5.04–5.14 (m, 2H), 5.76–5.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.5, 18.3, 25.8, 26.8, 26.9, 37.8, 55.9, 64.2, 71.5, 79.5, 81.6, 96.2, 108.8, 117.5, 134.5. IR (neat): 775, 838, 917, 1086, 1253, 1375, 1466, 1638, 2932, 3418 cm^{-1}. MASS (LC–MS): *m*/*z* 383 [M+Na]$^+$. HRMS: calcd for $C_{18}H_{36}O_5SiNa$: 383.2229. Found 383.2224.

*4.1.4. (4R,5S)-4-(Chloromethyl)-5-((S)-1(methoxymethoxy) but-3-enyl)-2,2-dimethyl-1,3-dioxolane (**8**).* To a solution **17** (9.00 g, 24.9 mmol) in dry THF (100 mL) was added 1 (M) Bu_4NF solution in THF (24.9 mL) at 0 °C, and the resulting solution was allowed to stir at room temperature for 3 h. Saturated NH_4Cl solution (20 mL) was added, and the reaction mixture was stirred for 5 min and then diluted with water (50 mL) and extracted with EtOAc (100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by flash chromatography (elution with EtOAc/hexane) to yield corresponding alcohol (5.81 g, 96%) as colorless oil. R_f (30% EtOAc/hexane): 0.4. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 6H), 2.10 (br s 1H, OH), 2.31–2.51 (m, 2H), 3.45 (s, 3H), 3.60–3.85 (m, 4H), 3.96–4.09 (m, 1H), 4.62 (d, *J*=6.9 Hz, 1H), 4.70 (d, *J*=6.9 Hz, 1H), 5.04–5.20 (m, 2H), 5.72–5.84 (m, 1H); ^{13}C NMR (75 MHz $CDCl_3$): 26.8, 26.9, 37.8, 55.9, 62.2, 71.5, 79.5, 81.6, 96.2, 108.8, 117.5, 134.5. IR (neat): 852, 916, 1035, 1155, 1214, 1456, 1533, 1639, 2927, 3447 cm^{-1}. MASS (LC–MS): *m*/*z* 269 [M+Na]$^+$. HRMS: calcd for $C_{12}H_{22}O_5Na$: 269.1364. Found 269.1357.

To the solution of above alcohol (5.50 g, 22.5 mmol) in CCl_4 (75 mL) were added triphenylphosphine (11.81 g, 45.0 mmol) and sodium bicarbonate (catalytic amount) and the mixture was heated to reflux for 10 h. The reaction mixture was then cooled to room temperature and filtered. The solid residue was washed with EtOAc (2×30 mL) and the combined filtrates were washed with water (1×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography to obtain the pure product **8** (5.55 g, 94%) as colorless oil. R_f (10% EtOAc/hexane): 0.6. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 6H), 2.27–2.53 (m, 2H), 3.37 (s, 3H), 3.51–3.60 (m, 1H), 3.70–3.87 (m, 3H), 4.11–4.20 (m, 1H), 4.60 (d, *J*=6.8 Hz, 1H), 4.69 (d, *J*=6.8 Hz, 1H), 5.07–5.20 (m, 2H), 5.73–5.94 (m, 1H). IR (neat): 771, 842, 919, 1041, 1153, 1217, 1376, 1436, 1533, 1614, 2898, 2988, 3078 cm^{-1}. MASS (LC–MS): *m*/*z* 287

$[M+Na]^+$. HRMS: calcd for $C_{12}H_{21}ClO_4Na$: 287.1026. Found 287.1016.

*4.1.5. (S)-4-((4S,5R)-5-(Chloromethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(methoxymethoxy)butan-1-ol (**18**).* To the solution of compound **8** (5.20 g, 19.8 mmol) in dry THF (60 mL) was added $BH_3\cdot DMS$ (2.82 mL, 29.7 mmol) for over a period of 15 min maintaining the temperature at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for a period of 4 h. The solution was cooled to 0 °C and to this were added 3 N NaOH (until the mixture was basic, maintaining the temperature at 0 °C), H_2O_2 (9 mL, 30% solution in water), and the reaction mixture was further stirred for a period of 1 h and diluted with ethyl acetate (50 mL). The organic layers were separated and washed with brine (1×25 mL), dried over anhydrous Na_2SO_4 and evaporated to get the crude product. The product was purified by column chromatography to yield the alcohol **18** (4.61 g, 83%) as colorless liquid. R_f (40% EtOAc/hexane): 0.4. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.42 (s, 3H), 1.63–1.76 (m, 4H), 3.40 (s, 3H), 3.53–3.90 (m, 7H), 4.11–4.20 (m, 1H), 4.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.9, 27.0, 27.6, 45.4, 55.9, 62.4, 77.7, 78.6, 79.3, 96.2, 109.7. IR (neat): 772, 1028, 1362, 1427, 1638, 2967, 3418 cm^{-1}. MASS (LC–MS): *m*/*z* 305 $[M+Na]^+$. HRMS: calcd for $C_{12}H_{23}ClO_5Na$: 305.1131. Found 305.1135.

*4.1.6. (4S,5R)-4-((S)-2,4,9,11-Tetraoxadodecan-5-yl)-5-(chloromethyl)-2,2-dimethyl-1,3-dioxolane (**19**).* To alcohol **18** (4.50 g, 16.0 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 °C were added diisopropylethylamine (8.4 mL, 48.2 mmol) and catalytic amount of DMAP. After 15 min methyl chloromethyl ether (MOMCl) (2.41 mL, 32 mmol) was added dropwise over a period of 10 min, and stirring was continued for further 1.5 h. The reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (2×25 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The obtained crude product was purified by silica gel column chromatography to afford MOM ether **19** (4.56 g, 87%) as a colorless oil. R_f (10% EtOAc/hexane): 0.5; $[\alpha]_D^{25}$ −11.5 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.41 (s, 3H), 1.61–1.78 (m, 4H), 3.33 (s, 3H), 3.38 (s, 3H), 3.48–3.61 (m, 3H), 3.67–3.78 (m, 2H), 3.85 (t, *J*=6.8 Hz, 1H), 4.12–4.19 (m, 1H), 4.57 (s, 2H), 4.64 (d, *J*=6.8 Hz, 1H), 4.68 (d, *J*=6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 27.0, 27.1, 27.7, 45.5, 55.1, 55.9, 67.5, 77.63, 78.6, 79.6, 95.9, 96.0, 109.8. IR (neat): 1037, 1106, 1447, 1648, 2937 cm^{-1}. MASS (LC–MS): *m*/*z* 349 $[M+Na]^+$. HRMS: calcd for $C_{14}H_{27}ClO_6Na$: 349.1393. Found 349.1388.

*4.1.7. (3R,4S)-4,7-Bis(methoxymethoxy)hept-1-yn-3-ol (**7**).* To freshly distilled ammonia (40 mL) in a 100 mL two neck round bottom flask fitted with a cold finger condenser, was added catalytic amount of ferric nitrate, followed by the piece wise addition of lithium metal (375 mg, 53.6 mmol) at −33 °C and the resulting gray colored suspension was stirred for 30 min. To this reaction mixture was added chloride **19** (2.5 g, 7.6 mmol) in dry THF (15 mL) over a period of 10 min. After stirring the reaction mixture for 30 min, solid ammonium chloride (1.0 g) was added and ammonia was allowed to evaporate. The residue was partitioned between water and diethyl ether and the aqueous layer was extracted with (3×20 mL) diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to obtain a residue that was purified by silica gel column chromatography to yield acetylenic alcohol **7** (1.5 g, 79%) as a clear liquid. R_f (30% EtOAc/hexane): 0.5; $[\alpha]_D^{25}$ +18.7 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.54–1.84 (m, 4H), 2.39 (d, *J*=2.2 Hz, 1H), 3.33 (s, 3H), 3.46–3.60 (m, 5H), 4.10–4.27 (m, 2H), 4.56 (s, 2H), 4.68 (d, *J*=7.2, Hz, 1H), 4.73 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.8, 28.5, 55.1, 56.0, 65.1, 67.3, 74.1, 81.7, 84.6, 96.3, 97.8. IR (neat): 917, 1037, 1106, 1150, 1381, 1447, 1646, 2150, 2937, 3279, 3418 cm^{-1}. MASS (LC–MS): *m*/*z* 255 $[M+Na]^+$. HRMS: calcd for $C_{11}H_{20}O_5Na$: 255.1208. Found 255.1203.

*4.1.8. (3S,4S)-4,7-Bis(methoxymethoxy)hept-1-yn-3-ol (**20**).* To a stirred solution of **7** (200 mg, 0.8 mmol), triphenylphosphine (528 mg, 2.0 mmol), and *p*-nitrobenzoic acid (345 mg, 2.0 mmol) in dry THF (10 mL) at 0 °C was added diethyl azodicarboxylate (348 mg, 2.0 mmol) via syringe. After half an hour, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (2×15 mL). The solvent was evaporated and the resulting residue was dissolved in MeOH (10 mL). To the reaction mixture K_2CO_3 (228 mg, 1.6 mmol) was added and the mixture was stirred further for additional 4 h at room temperature. The reaction mixture was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3×15 mL). Removal of solvent under reduced pressure followed by flash chromatography afforded **20** (164 mg, 82%) as a colorless liquid. R_f (30% EtOAc/hexane): 0.5. ^{1}H NMR ($CDCl_3$ 300 MHz): 1.61–1.88 (m, 4H), 2.40 (d, *J*=2.3 Hz, 1H), 3.24 (br s, 1H, OH), 3.33 (s, 3H), 3.42 (s, 3H), 3.52 (t, *J*=6.0 Hz, 2H), 3.57 (q, *J*=7.0 Hz, 1H), 4.27 (d, *J*=4.3 Hz, 1H), 4.57 (s, 2H), 4.68 (d, *J*=7.0 Hz, 1H), 4.79 (d, *J*=7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4, 27.7, 55.1, 55.8, 64.6, 67.4, 74.0, 82.1, 82.3, 96.2, 97.2. MASS (LC–MS): *m*/*z* 255 $[M+Na]^+$.

*4.1.9. (4S,5S)-Hept-6-yne-1,4,5-triol (**21**).* Compound **20** (200 mg, 1.0 mmol) and PTSA (catalytic amount) were dissolved in MeOH (3 mL) at room temperature. After stirring the mixture at room temperature for 5 h, solid K_2CO_3 was added and stirring was continued for further 30 min. The reaction mixture was filtered and washed with MeOH (2×3 mL). Combined organic filtrates were concentrated in vacuum to obtain a residue, which was purified by filter column to afford compound **21** (114 mg, 92%) as a sticky liquid. R_f (in EtOAc): 0.3. ^{1}H NMR (200 MHz, DMSO): δ 1.22–1.69 (m, 4H), 2.75 (d, *J*=2.1 Hz, 1H), 3.45 (br s, 3H, OH), 4.00–4.10 (m, 1H), 4.19–4.25 (m, 1H), 4.41 (d, *J*=5.0 Hz, 1H), 5.09 (d, *J*=6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.8, 28.5, 64.7, 66.9, 73.9, 81.6, 84.6. MASS (LC–MS): *m*/*z* 167 $[M+Na]^+$.

*4.1.10. 3-((4S,5S)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (**22**).* To a stirred solution of triol **21** (100 mg, 0.7 mmol) in dry acetone (5 mL) at 0 °C were added 2,2-dimethoxypropane (0.17 mL, 1.4 mmol) and freshly recrystallized *para*-toulenesulfonic acid (catalytic amount). The reaction mixture was warmed to room temperature, stirred for 10 h, neutralized with solid K_2CO_3 and filtered on Celite pad. The residue was washed with ethyl acetate, and the combined filtrates were concentrated. The obtained residue was then diluted with ethyl acetate, washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give crude product, which on purification by flash chromatography afforded **22** (110 mg, 86%) as colorless liquid. R_f (40% EtOAc/hexane): 0.45; $[\alpha]_D^{25}$ −10.0 (*c* 1.7, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.45 (s, 3H), 1.59–1.88 (m, 4H), 1.94 (br s, 1H, OH), 2.47 (d, *J*=2.2 Hz, 1H), 3.67 (t, *J*=5.9 Hz, 2H), 3.97–4.10 (m, 1H), 4.17 (dd, *J*=2.2, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 28.6, 28.9, 28.9, 62.3, 70.1, 74.8, 80.6, 81.3, 110.1. IR (neat): 758, 1048, 1421, 1638, 1717, 2926, 3425 cm^{-1}. MASS (LC–MS): *m*/*z* 207 $[M+Na]^+$.

*4.1.11. Methyl-3-((4S,5S)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl) propanoate (**6**).* To the solution of alcohol **22** (110 mg, 0.6 mmol) in CH_3CN (2 mL), CCl_4 (2 mL) and water (3 mL) were added $NaIO_4$ (513 mg, 2.4 mmol) and the mixture was vigorously stirred at room temperature. $RuCl_3\cdot H_2O$ (5.0 mg, 0.02 mmol) was added in one portion and after 2 h the reaction mixture was diluted with CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, evaporated under reduced pressure

to yield the crude product, which was purified by column chromatography to give the acid (97 mg, 82%) as sticky liquid. R_f (50% EtOAc/hexane): 0.5.

To a solution of *N*-methyl-*N*-nitrosotoluene-*P*-sulphonamide (1.07 g, 3.9 mmol) in 15 mL of diethyl ether was added a solution of 0.2 g of potassium hydroxide in 96% ethanol (5 mL) at 0 °C. After 5 min, the ethereal diazomethane solution was distilled off using a water bath. To pre-cooled solution (0 °C in ice bath) of carboxylic acid (200 mg, 0.79 mmol) in anhydrous diethyl ether (5 mL) was added, the ethereal solution of diazomethane in small portions until gas evolution ceased and the solution acquired a pale yellow color. The reaction mixture was washed with water (2×10 mL), brine (1×10 mL) and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography to yield product **6** (199 mg, 93%) as a colorless liquid. R_f (30% EtOAc/hexane): 0.7; $[\alpha]_D^{25}$ −17.7 (*c* 2.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.43 (s, 3H), 1.80–1.93 (m, 1H), 1.98–2.10 (m, 1H), 2.37–2.56 (m, 3H), 3.67 (s, 3H), 3.98–4.05 (m, 1H), 4.18 (dd, *J*=2.3, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$ 75 MHz): δ 26.1, 27.0, 27.2, 30.0, 51.9, 69.9, 74.9, 80.3, 80.4, 110.2, 173.2. IR (neat): 1078, 1461, 1647, 1742, 2385, 2922 cm^{-1}. MASS (LC–MS): *m*/*z* 235 $[M+Na]^+$. HRMS: calcd for $C_{11}H_{16}O_4Na$: 235.0946. Found 235.0943.

*4.1.12. (Z)-1,4-Bis (4-methoxybenzyloxy) but-2-ene (**24**).* Sodium hydride (1.09 g, 45.45 mmol) was slowly added in portions to a solution of *cis* 2-butene-1,4-diol (1.0 g, 11.36 mmol) in anhydrous THF (40 mL) at 0 °C and stirred for 15 min. Then 4-methoxybenzyl bromide (4.1 g, 22.73 mmol) and catalytic amount TBAI were added at 0 °C and the reaction mixture was allowed to stir at room temperature for 4 h. After completion of the reaction, the reaction mixture was quenched by slow addition of water (5 mL) and extracted with EtOAc (50 mL). The organic layer was separated and washed with water (20 mL) and brine (10 mL). The organic solvent was evaporated and the crude product was purified by silica gel column chromatography using EtOAc/hexane (5%) as an eluent gave the PMB-protected diol **24** (3.68 g, 98%) as colorless liquid. R_f (10% EtOAc/hexane): 0.5; ^1H NMR ($CDCl_3$, 300 MHz): δ. 3.77 (s, 6H), 3.97 (d, 4H, *J*=4.7 Hz), 4.37 (s, 4H), 5.71 (t, 2H, *J*=4.7 Hz), 6.81 (d, 4H, *J*=8.5 Hz), 7.18 (d, 4H, *J*=8.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.2, 65.3, 71.8, 113.7, 129.3, 129.4, 130.1, 159.1. IR (KBr, neat) ν_{max}; 814, 1246, 1513, 1615, 1634, 2853, 2925, 2956 cm^{-1}; MS (ESI): *m*/*z*: 329 $(M+H)^+$. HRMS: calcd for $C_{20}H_{25}O_4$: 329.1310. Found 329.1378.

*4.1.13. 2-(4-Methoxybenzyloxy) acetaldehyde (**13**).* To the solution of alkene **24** (3.60 g, 109 mmol) in acetone/water (1:1, 40 mL) were added NMO (3.85 g 32.72 mmol) and OsO_4 (138.65 mg, 0.545 mmol, 2.5 wt % in isobutanol). The reaction mixture stirred for 4 h at room temperature and quenched with aqueous saturated $NaHSO_3$ solution (15 mL). The reaction was stirred for 30 min and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed by rotary evaporation. Silica gel column chromatography of the crude product using EtOAc/hexane (50%) as an eluent gave the diol (3.8 g, 97%) as white crystalline solid. R_f (40% EtOAc/hexane): 0.2; ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (br s, 2-OH), 3.52–3.64 (m, 6H), 3.79 (s, 6H), 4.45 (s, 4H), 6.86 (d, 4H, *J*=8.3 Hz), 7.22 (d, 4H, *J*=8.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.2, 71.0, 71.1, 73.1, 113.8, 129.4, 129.8, 159.3. IR (KBr, neat) ν_{max}; 814, 1033, 1094, 1250, 1513, 1610, 2901, 3285, 3439 cm^{-1}; MS (ESI): *m*/*z* 383 $(M+Na)^+$. HRMS: calcd for $C_{20}H_{26}O_6Na$: 383.1625. Found 383.1622.

A 100 mL round bottomed flask sealed with a rubber septum and a nitrogen line was charged with silica gel-supported $NaIO_4$ (8.50 g). To this was added. CH_2Cl_2 (40 mL) and cooled to 0 °C .To this heterogeneous mixture was added a solution of diol (3.77 g, 10.47 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred for 30 min at 0 °C after which it was allowed to warm to room temperature for 6 h and filtered through a glass frit. The silica gel was washed with $CHCl_3$ (3x15 mL). The filtrate was concentrated in vacuum to afford aldehyde **13** (1.85 g, 98%) as colorless oil. R_f (30% EtOAc/hexane): 0.6; ^1H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.97 (d, 2H, *J*=1.1 Hz), 4.52 (s, 2H), 6.84 (d, 2H, *J*=8.7 Hz), 7.23 (d, 2H, *J*=8.7 Hz), 9.67 (t, 1H, *J*=1.1 Hz).

*4.1.14. (2S,3S)-1-(4-Methoxybenzyloxy)-3-(methoxymethoxy) pent-4-en-2-ol (**25**).* To a stirred solution of methoxy methyl allyl ether (973 mg, 12.2 mmol,) in THF was added *sec*-BuLi in cyclohexane (1.3 M) at −78 °C over the period of 20 min. The reaction mixture was stirred for an additional 30 min at the same temperature and B (+) methoxy disopinocamphenyl borane (3.22 g, 12.2 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h, Boron trifluoride diethyl etherate (1.92 g, 13.52 mmol) was added dropwise followed by an immediate addition of aldehyde (1.83 g, 1 equiv) in THF (10 mL) at −78 °C. After stirring the reaction mixture for 5 h, the reaction mixture was allowed to warm to room temperature for 30 min. The reaction mixture was then quenched by addition of H_2O_2 (30%, aq)/$NaHCO_3$ (sat) (1:2) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with EtOAc (2×50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum. Silica gel column chromatography of the crude product using EtOAc/hexane (30%) as an eluent gave the corresponding alcohol **25** (1.86 g, 65%) as a colorless liquid. R_f (40% EtOAc/hexane): 0.5; $[\alpha]_D^{28}$ −12.6 (*c* 0.51, $CHCl_3$); ^1H NMR: (300 MHz, $CDCl_3$): δ 3.38 (s, 3H), 3.44–3.52 (m, 1H), 3.53–3.61 (m, 1H), 3.72–3.80 (m, 1H), 3.80 (s, 3H), 4.12 (t, 1H, *J*=6.8 Hz), 4.45 (d, 1H, *J*=11.5 Hz), 4.51 (d, 1H, *J*=11.5 Hz), 4.59 (d, 1H, *J*=6.6 Hz), 4.72 (d, 1H, *J*=6.6 Hz), 5.23–5.39 (m, 2H), 5.65–5.83 (m, 1H), 6.88 (d, 2H, *J*=8.7 Hz), 7.26 (d, 2H, *J*=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 55.6, 70.4, 72.7, 73.1, 78.1, 94.1, 113.7, 119.5, 129.4, 129.9, 134.3, 159.2. IR (KBr, neat): 1033, 1248, 1513, 1611, 1719, 2925, 3452 cm^{-1}; MS (ESI): *m*/*z* 305 $(M+Na)^+$. HRMS: calcd. for $C_{15}H_{22}O_5Na$: 305.1364. Found 305.1359.

4.1.15. (2S,3S)-1-(4-Methoxybenzyloxy) pent-4-ene-2,3-diol (11). To a solution of compound **25** (1.84 g, 6.52 mmol) in MeOH (18 mL) at 0 °C was added aqueous solution of 3 (N) HCl (5 mL). The reaction mixture was stirred at room temperature for 6 h and then quenched with solid $NaHCO_3$ and filtered. The filtrate was concentrated in vacuum. Silica gel column chromatography of the crude product using EtOAc/hexane (40%) as an eluent gave the diol **11** (1.47 g, 95%) as a colorless liquid. R_f (40% EtOAc/hexane): 0.2; $[\alpha]_D^{30}$ −9.2 (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.48–3.64 (m, 2H), 3.65–3.72 (m, 1H), 3.81 (s, 3H), 4.16 (t, 1H, *J*=5.8 Hz), 4.45 (d, 1H, *J*=11.5 Hz), 4.51 (d, 1H, *J*=11.5 Hz),5.22 (d, 1H, *J*=10.4 Hz), 5.34 (d, 1H, *J*=17.4 Hz), 5.78–5.94 (m, 1H), 6.88 (d, 2H, *J*=8.5 Hz), 7.25 (d, 2H, *J*=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 71.2, 72.7, 73.2, 73.4, 113.8, 117.1, 129.4, 129.6, 136.9, 159.3. IR (KBr, neat): 1036, 1248, 1372, 1731, 2924, 3445 cm^{-1}; MS (ESI): *m*/*z* 261 $(M+Na)^+$. HRMS: calcd for $C_{13}H_{18}O_4Na$: 261.1092. Found 261.1097.

*4.1.16. (4S,5S)-4-(4-Methyoxybenzyloxy) methyl-2,2-dimethyl-5-vinyl-1,3-dioxolane (**26**).* To a solution of the diol **11** (1.46 g, 6.13 mmol), in CH_2Cl_2 (20 mL) at room temperature were added 2-methoxy-propene and followed by CSA (5 mg), and the mixture was stirred at room temperature for 5 min. Solid $NaHCO_3$ was added at 0 °C, and the mixture was again stirred for 10 min. The reaction mixture was filtered through a pad of neutral alumina and the filtrate was concentrated in vacuum. Silica gel chromatography using EtOAc/hexane (8%) as an eluent gave acetonide protected compound **26** (1.62 g, 95%) as a colorless liquid. R_f (20% EtOAc/hexane): 0.7; $[\alpha]_D^{30}$ −16.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 6H), 3.49–3.59 (m, 2H), 3.80 (s, 3H), 3.83–3.91 (m, 1H), 4.19 (t, 1H, *J*=7.9 Hz), 4.51 (s, 2H), 5.21 (d, 1H, *J*=10.4 Hz), 5.31 (d, 1H,

J=17.2 Hz), 5.75–5.90 (m, 1H), 6.85 (d, 2H, J=8.5 Hz), 7.24 (d, 2H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.9, 27.0, 55.3, 69.1, 73.2, 79.4, 80.0, 109.4, 113.7, 118.6, 129.3, 130.0, 135.4, 159.2. IR (KBr, neat): 822, 1082, 1248, 1379, 1514, 1613, 2931, 2986 cm^{-1}; MS (ESI): m/z 301 $(M+Na)^+$. HRMS: calcd for $C_{16}H_{22}O_4Na$: 301.1420. Found 301.1410.

*4.1.17. (E)-Ethyl 3-((4S,5S)-5-((4-methoxybenzyloxy) methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (**10**).* To a solution of compound **26** (1.60 g, 5.75 mmol) in anhydrous toluene was added ethyl acrylate (5.76 g, 57.55 mmol) at room temperature. The reaction mixture was degassed under an argon atmosphere during 20 min. Then to this solution was added Grubbs' second generation catalyst. The resultant mixture was refluxed under an argon atmosphere for 5 h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The resulting crude residue was purified by silica gel column chromatography using EtOAc/hexane (10%) as an eluent to give unsaturated ester compound **10** (1.62 g, 80%) as a colorless liquid. R_f (20% EtOAc/hexane): 0.5; $[\alpha]_D^{29}$ −22.6 (c 1.6, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, 3H, J=7.2 Hz), 1.41 (s, 3H), 1.42 (s, 3H), 3.50–3.62 (m, 2H), 3.79 (s, 3H), 3.82–3.91 (m, 1H), 4.18 (q, 2H, J=7.2 Hz), 4.34–4.43 (m, 1H), 4.45 (d, 1H, J=11.3 Hz), 4.52 (d, 1H, J=11.3 Hz), 6.04 (d, 1H, J=15.8 Hz), 6.82 (d, 2H, J=8.3 Hz), 6.83–6.89 (m, 1H), 7.20 (d, 2H, J=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 26.6, 26.9, 55.1, 60.5, 68.8, 73.2, 77.4, 79.5, 110.1, 113.7, 122.4, 129.3, 129.7, 143.9, 159.2, 165.9. IR (KBr, neat): 1035, 1175, 1248, 1370, 1514, 1721, 2927 cm^{-1}; MS (ESI): m/z 373 $(M+Na)^+$. HRMS: calcd for $C_{19}H_{20}O_6Na$: 373.1627. Found 373.1633.

*4.1.18. Ethyl-3-((4S,5S)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl) propanoate (**27**).* To a stirred solution of conjugated alkene **10** (1.0 g, 2.86 mmol) in MeOH at 0 °C was added a $NiCl_4 \cdot 6H_2O$ (149.4 mg, 0.628 mmol). The resultant mixture was stirred at 0 °C for 10 min and then was added $NaBH_4$ (217 mg, 5.7 mmol) in portions. The reaction mixture was stirred for another 3 h and quenched with water. The whole reaction mixture was concentrated to get the residue, which was extracted with EtOAc. The organic extract was washed with brine and dried over anhydrous Na_2SO_4 and evaporated. The crude reaction mixture was purified by silica gel column chromatography using EtOAc/hexane (10%) as an eluent to provide the corresponding saturated ester compound **27** (944 mg, 95%) as a clear oil. R_f (20% EtOAc/hexane): 0.5; $[\alpha]_D^{29}$ −13.2 (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, J=6.8 Hz), 1.34 (s, 3H), 1.36 (s, 3H) 1.61–1.74 (m, 1H), 1.78–1.93 (m, 1H), 2.28–2.42 (m, 2H), 3.27–3.35 (m, 1H), 3.36–3.43 (m, 1H), 3.44–3.55 (m, 1H), 3.73–3.78 (m, 1H), 3.79 (s, 3H), 4.11 (q, 2H, J=7.2 Hz), 4.42 (s, 2H), 6.82 (d, 2H, J=8.3 Hz), 7.21 (d, 2H, J=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$):δ 14.2, 26.9, 27.2, 28.1, 30.6, 55.2, 60.3, 70.1, 73.2, 77.4, 79.6, 108.9, 113.7, 129.3, 129.9, 159.2, 173.2. IR (KBr, neat): 819, 1035, 1084, 1174, 1248, 1370, 1514, 1613, 1734, 2934 cm^{-1}; MS (ESI): m/z 375 $(M+Na)^+$. HRMS: calcd for $C_{19}H_{29}O_6$: 353.1522. Found 353.1590.

*4.1.19. Ethyl 3-((4S,5S)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (**28**).* To a solution of compound **8** (0.92 g, 2.613 mmol) in CH_2Cl_2 (18 mL) at 0 °C was added DDQ (1.18 g, 5.23 mmol) in portion wise maintaining the solution at pH 7 using buffer solution (2 mL). The resultant mixture was stirred at room temperature for 3 h and then quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The crude reaction mixture was purified by silica gel column chromatography using EtOAc/hexane (25%) as an eluent to afford alcohol **28** (515.4 mg, 85%) as colorless oil. R_f (40% EtOAc/hexane): 0.5; $[\alpha]_D^{29}$ −17.6 (c 0.88, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 3H, J=7.3 Hz), 1.37 (s, 3H), 1.38 (s, 3H) 1.75–1.84 (m, 1H), 1.90–1.98 (m, 1H), 2.36–2.45 (m, 1H), 2.46–2.54 (m, 1H), 3.59 (dd, 1H, J=3.7, 12.0 Hz), 3.67–3.72 (m, 1H), 3.75 (dd, 1H, J=3.7, 12.0 Hz), 3.87 (dt, 1H, J=3.7, 8.3 Hz), 4.12 (q, 2H, J=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 27.0, 27.2, 27.9, 30.6, 60.5, 61.9, 76.1, 81.0, 108.9, 173.2. IR (KBr, neat) ν_{max} 1163, 1373, 1638, 1732, 2987, 3454 cm^{-1}; MS (ESI): m/z 255 $(M+Na)^+$. HRMS: calcd for $C_{11}H_{21}O_5$: 233.1310. Found 233.1384.

*4.1.20. Ethyl-3-((4S,5R)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl) propanoate (**9**).* To a solution of oxalyl chloride (0.37 mL) in dry CH_2Cl_2 at −78 °C was slowly added a solution of DMSO (0.6 mL) in CH_2Cl_2. After stirring for 1 h at −78 °C, alcohol **28** (500 mg, 2.16 mmol) in dry CH_2Cl_2 (15 mL) was slowly added to the above solution. 45 min later triethylamine (7 mL) was introduced via a syringe. The reaction was then stirred at −78 °C for 10–15 min, and further at −50 °C for 20 min, prior to the addition of aqueous saturated NH_4Cl solution. The organic phase was separated and then washed with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and passed through a short pad of silica gel. The filtrate was concentrated to give the aldehyde (480 mg, 97%) as a pale yellow syrup, which was used as such for the next step without further purification. R_f (40% EtOAc/hexane): 0.7; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 3H, J=7.2 Hz), 1.37 (s, 3H), 1.38 (s, 3H), 1.71–2.13 (m, 2H), 2.29–2.58 (m, 2H), 3.52–3.92 (m, 2H), 4.12 (q, 2H, J=7.2 Hz), 9.71 (s, 1H).

*4.1.21. Methyl-3-((4S,5S)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl) propanoate (**6**).* To a stirred solution of aldehyde **9** (0.43 g, 1.88 mmol) and K_2CO_3 (0.52 g, 3.77 mmol) in 15 mL of dry methanol was added dimethyl-1-diazo-2-oxopropylphosphonate (376 mg, 2.26 mmol) and the reaction mixture was stirred for 4 h. The reaction mixture was diluted with Et_2O (25 mL), washed with an aqueous solution of 5%$NaHCO_3$ (10 mL) and dried over Na_2SO_4. Evaporation of the solvent yielded 300 mg (75%) of alkyne compound **6** as a slightly yellow oil. R_f (40% EtOAc/hexane): 0.8; $[\alpha]_D^{28}$ −17.7 (c 1.2, $CHCl_3$).

*4.1.22. Methyl-3-((4S,5S)-2,2-dimethyl-5-((E)-pent-3-en-1-ynyl)-1,3-dioxolan-4-yl)propanoate (**23**).* To a stirred solution of $Pd(PPh_3)_2Cl_2$ (99 mg, 0.14 mmol) and CuI (81 mg, 0.424 mmol) in piperidine were added solutions of *trans*-1-bromopropene (257 mg, 2.12 mmol) in piperidine and acetylene compound in DMF under argon atmosphere. The resultant mixture was stirred for 10 min at room temperature and then heated to 70 °C for 5 h. The reaction mixture was filtered through Celite and filtrate was concentrated in vacuum. Silica gel chromatography of the crude product using EtOAc/hexane (15%) as an eluent gave the conjugated ene compound **23** (267 mg, 75%) as a pale yellow liquid. R_f (40% EtOAc/hexane): 0.7; $[\alpha]_D^{29}$ −22.0 (c 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.45 (s, 3H), 1.79 (dd, 3H, J=1.5, 6.8 Hz), 1.84–2.12 (m, 2H), 2.42–2.58 (m, 2H), 3.69 (s, 3H), 4.00 (dt, 1H, J=4.5, 7.5 Hz), 4.35 (dd, 1H, J=1.9, 8.3 Hz), 5.51 (dqd, 1H, J=1.5, 2.3, 15.8 Hz), 6.11–6.23 (ddq, J=1.5, 6.8, 15.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6, 26.3, 27.0, 27.2, 30.1, 51.6, 70.7, 80.4, 83.1, 85.5, 109.7, 109.8, 141.1, 173.3. IR (KBr, neat): 757, 1074, 1214, 1373, 1645, 1738, 2852, 2923 cm^{-1}; MS (ESI): m/z 275 $(M+Na)^+$. HRMS: calcd for $C_{14}H_{20}O_4Na$: 275.1324. Found 275.1328.

*4.1.23. Methyl-3-((4S,5S)-2,2-dimethyl-5-((1Z,3E)-penta-1,3-dienyl)-1,3-dioxolan-yl)propanoate (**5**).* A solution of alkyne **23** (120 mg, 0.476 mmol) dissolved in MeOH (5 mL) was added to the suspension of activated Zn (300 mg) and stirred at room temperature for 5 h. The reaction mixture was heated to 40 °C until complete conversion of alkyne to alkene occurred (as judged by TLC). The metal was removed by filtration, washed with MeOH (5 mL) and

the combined solution was concentrated to 1/3 of the original volume. Ethyl acetate was added and the organic layer carefully washed with H_2O. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum. Silica gel chromatography of the crude product using EtOAc/hexane (20%) as an eluent gave the compound **5** (99 mg, 98%) as a light yellow liquid. R_f (40% EtOAc/hexane): 0.7; $[\alpha]_D^{29}$ −11.9 (*c* 0.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.41 (s, 3H), 1.79 (d, 3H, *J*=6.8 Hz), 1.82–2.08 (m, 2H), 2.34–2.58 (m, 2H), 3.61–3.71 (m, 4H), 4.50 (t, 1H, *J*=8.7 Hz), 5.20 (t, 1H, *J*=10.2 Hz), 5.73–5.89 (m, 1H), 6.19 (t, 1H, *J*=10.9 Hz), 6.26–6.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4, 26.8, 27.1, 27.2, 30.5, 51.6, 76.7, 79.9, 108.7, 123.9, 126.1, 133.3, 134.3, 173.6. IR (KBr, neat): 1166, 1372, 1440, 1635, 1734, 2928 cm^{-1}; MS (ESI): *m*/*z* 277 $(M+Na)^+$. HRMS: calcd for $C_{14}H_{22}O_4Na$: 277.1497. Found 277.1502.

Activation of zinc: A suspension of zinc (0.5 g) in H_2O (30 mL) was bubbled with argon for 5 min, and to this slurry was added $Cu(OAc)_2 \cdot H_2O$ (0.1 g). Stirring was continued for 15 min, before $AgNO_3$ (0.1 g) was added. The suspension was stirred further for 30 min. The metal was collected by suction and carefully washed with H_2O (2×10 mL), MeOH (2×10 mL) and Et_2O (2×10 mL), respectively. The ether moist zinc dust was transferred into MeOH/H_2O [1:1 (v/v), 4 mL] and was utilized immediately for the reaction.

*4.1.24. (S)-5-((S,2Z,4E)-1-hydroxyheha-2,4-dienyl)-dihydrofuran-2(3H)-one (**2**).* The ester compound **5** (62 mg, 0.24 mmol) was dissolved in THF (5 mL), and a catalytic amount of concentrated HCl was added at 0 °C. The reaction mixture was stirred at room temperature overnight and then quenched with solid $NaHCO_3$ and filtered. The filtrate was concentrated in vacuum. Silica gel chromatography of the crude product using EtOAc/hexane (40%) as an eluent gave the compound **2** (28.8 mg, 65%) as a colorless oil .R_f (50% EtOAc/hexane):0.3; $[\alpha]_D^{28}$ +20.1 (c 0.53, $CHCl_3$), [lit.[2] $[\alpha]_D^{25}$ +19.0 (*c* 0.77, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$): δ 1.80 (d, 3H, *J*=6.8 Hz), 1.94–2.37 (m, 2H), 2.45–2.69 (m, 2H), 4.46 (dd, 1H, *J*=6.8, 12.8 Hz), 4.57 (dd, 1H, *J*=5.8, 8.9 Hz), 5.30 (t, 1H, *J*=10.0 Hz), 5.80–5.90 (m, 1H), 6.19 (t, 1H, *J*=10.9 Hz), 6.28–6.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4, 23.7, 28.5, 70.0, 82.8, 123.9, 126.0, 133.8, 133.9, 177.1. IR (KBr, neat): 1039, 1184, 1460, 1767, 2854, 2924, 3383 cm^{-1}; MS (ESI): *m*/*z* 205 $(M+Na)^+$. HRMS: calcd for $C_{10}H_{14}O_3Na$: 205.0840. Found 205.0849.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.072.

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