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Towards the enantioselective synthesis of anti-HIV agents litseaverticillols C and K from D-glucose

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Abstract—The first enantioselective synthesis towards the litseaverticillols C and K has been achieved, from D-glucose, using the ring closing metathesis (RCM) and Wittig reactions as key steps.

1. Introduction

The litseaverticillols A–K belong to a novel class of monocyclic sesquiterpenoids with a new skeletal arrangement defined as 'litsean'.[1] These monocyclic terpenes, except litseaverticillol H, are subdivided into two classes: (i) first-generation litseaverticillols A–C and K and (ii) second-generation litseaverticillols D–G, I and J. The latter ones are the oxidative products of transformations at the C-10–C-11 olefinic regions of first-generation litseaverticillols whereas litseaverticillol H is obtained by two consecutive oxidations of litseaverticillol A. Litseaverticillols A–H are potent antivirals recently isolated by bioassay-guided fractionation of chloroform extracts of milled leaves and twigs of the perennial shrub or arbor *Litsea verticillata* Hance (Lauraceae),[2] which is found in Cuc Phuong National Park, Vietnam. Litseaverticillols I–K are not naturally occurring. These sesquiterpenoids showed inhibitory effects against the replication of human immunodeficiency virus (HIV) type-1 in HOG.R5 cells (a reporter cell line) with IC_{50} values ranging from 2 to 15 μg/mL. The growth of HOG.R5 cell was significantly affected at concentrations 2- to 3-fold higher than IC_{50} values; anti-HIV activity was present without apparent toxicity to host cells. Although the preliminary studies revealed unfavourable selectivity indices (SI), modulation of their intriguing structural features appears promising for development of these compounds as anti-HIV drugs.

2. Results and discussion

These structurally unique sesquiterpenoids, litseaverticillols A–K contain a cyclopentene ring with two stereogenic centres at C-1 and C-5, and an unsaturated branched chain appended to C-5. Litseaverticillols C (**3**) and K (**4**) are differentiated at stereocentres C-1 or C-5 and are geometric isomers of each other due to juxtaposition of substituents around the $\Delta^{6,7}$ double bond. Litseaverticillol C, 1β-hydroxy-(*E*)-litse-2,6,10-trien-4-one, (**3**) has the *E*-configuration at $\Delta^{6,7}$ as verified by a ROESY correlation between H-5 and H-14. The geometric isomer, 1β-hydroxy-(*Z*)-litse-2,6,10-trien-4-one, known as litseaverticillol K (**4**) possesses a *Z*-configuration (assigned through the observation of a ROE correlation between H-5 and H-8). Each of the litseaverticillols was obtained as a racemate through bioassay-guided fractionation; this suggests that these 'litseans' were all formed through non-enzymatic biosynthesis from achiral precursors without intervention of homochiral enzymes. Vassilikogiannakis and Stratakis[3] postulated a biomimetic sequence of the biosynthesis of litseaverticillols and suggested the revision of the structure of litseaverticillol E (Fig. 1).

Intrigued by their potential utility as chemotherapeutic agents, we embarked on the synthesis of enantiomerically pure litseaverticillols C and K sesquiterpenes. We wished to explore whether each enantiomer of litseaverticillol has different biological activity. Current preferences of the pharmaceutical industry and the regulatory agencies dictate development of single isomer drugs. An enantioselective total synthesis for litseaverticillols A and B has been reported by Kuwahara and co-workers.[4] We report herein the first enantioselective total synthesis of methyl ether analogue of (1*R*,5*R*)-litseaverticillol C (**3**), (1*R*,5*R*)-litseaverticillol K (**4**) and the cyclopentenone moiety inherent to all the litseaverticillols from commercially available D-glucose (Fig. 2).

Our retrosynthetic analysis of (1*R*,5*R*)-litseaverticillol C (**3**) using a chiral pool strategy is shown in Scheme 1. The

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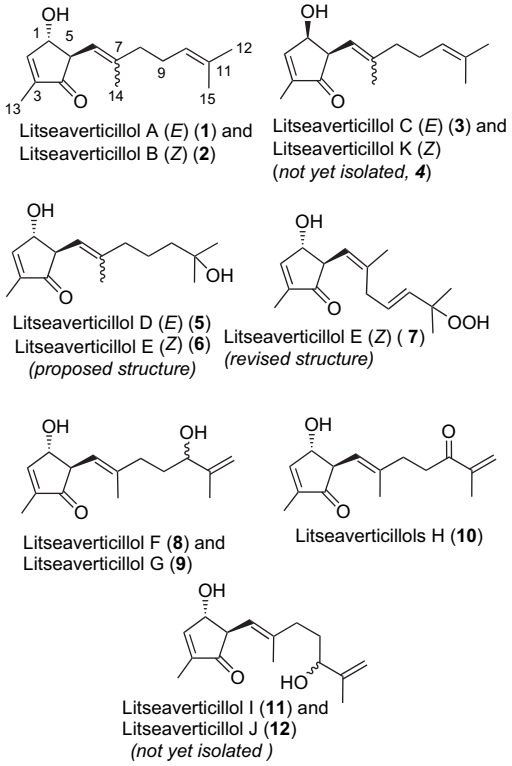


Figure 1. Litseaverticillols **1**–**12**.

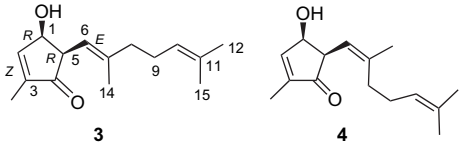
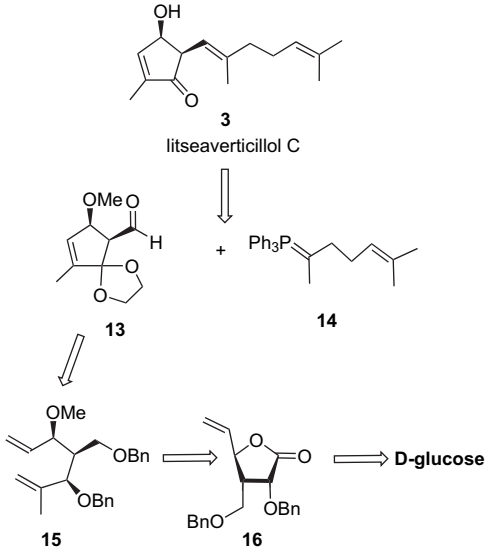


Figure 2. Litseaverticillols C and K.

salient feature of the synthesis was expected to be the RCM reaction of the functionalized diene (**15**) that was envisaged from 1,2:5,6-diisopropylidene-α-D-glucofuranose by simple synthetic transformations (Scheme 1).



Scheme 1. Retrosynthesis of litseaverticillol C.

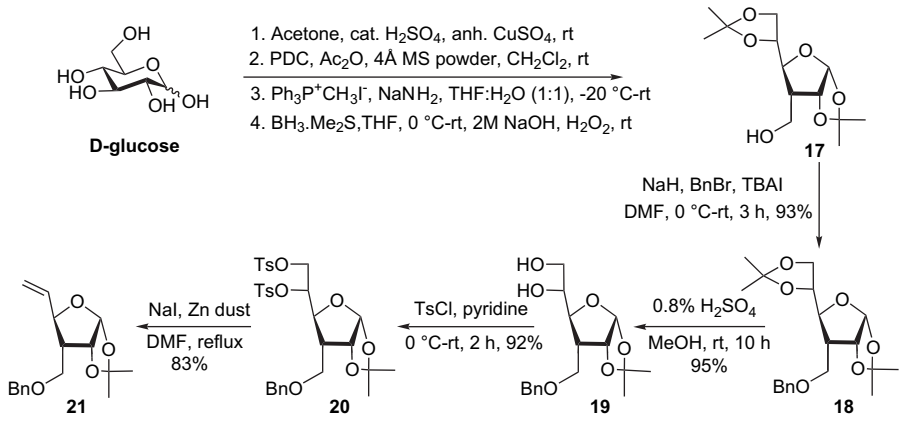
Our first goal was to install the crucial cyclopentene ring D-glucose was converted into the C-3-homologated compound **17** by standard procedures analogous to those reported in the literature[5,6] as shown in Scheme 2. The C-3-α-hydroxyl group in **17** was protected as the benzyl ether using phase-transfer conditions, and selective hydrolysis of the 5,6-acetonide in **18** using aqueous 0.8% H_2SO_4 in MeOH at room temperature afforded the diol **19**. Selective deoxygenation of the 5-hydroxyl group in **19** was investigated using several procedures; the most efficient one involved formation of the ditosylate **20**, followed by elimination of both tosylate groups using sodium iodide/Zn dust[7] to give the alkene **21** in 83% yield (Scheme 2).

Treatment of olefin **21** with IR-120 (H^+) resin in methanol resulted in acidic hydrolysis to the corresponding methyl furanoside (**22**) as a mixture (α:β=20:80). Protection of the C-2-hydroxyl group as a benzyl ether using NaH and benzyl bromide in DMF provided compound **23**. Demethylation of **23** was performed using aqueous acetic acid under refluxing conditions to afford a mixture of lactols (α:β=50:50) **24**, which was oxidized to lactone **16** with PDC in DCM in 82% yield (Scheme 3).

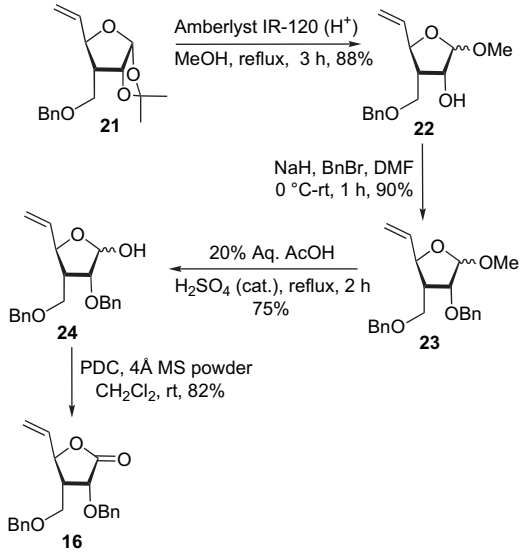
The lactone **16** was then treated with excess MeMgI in Et_2O to afford the dimethyl carbinol **25**; the allylic hydroxyl group of **25** was selectively protected as a methyl ether (**26**) using MeI and NaH at 0 °C. Mesylation of **26**, followed by base catalysed Hoffman elimination[8] with stoichiometric amount of *N*,*N*-dimethylaminopyridine (DMAP) at room temperature furnished the kinetically controlled less substituted *exo*-methylene compound **15**. The structure of the diene derivative **15** was confirmed by NMR, mass and elemental analyses (Scheme 4).

Having secured facile access to the key intermediate **15**, we now focused our attention on a ring closing metathesis reaction using Grubbs' first-generation catalyst (**A**). The initial reaction in refluxing benzene for two days was unsuccessful presumably due to steric hindrance. We turned to the second-generation catalyst (**B**), because of its superior stability and commercial availability.[9] The ring closing metathesis of diene using catalyst (**B**) in refluxing benzene proceeded smoothly to give the cyclopentene core **27** in excellent yield (Scheme 5).

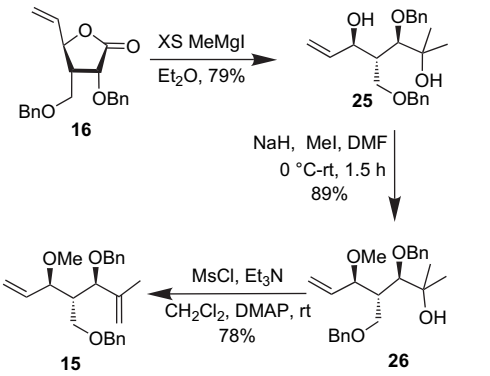
Dissolving metal reduction[10] of **27** removed the benzyl ethers to give the pivotal diol derivative (**28**). To introduce the side chain, it was deemed expedient to oxidize the secondary hydroxyl group to a keto moiety. Thus, the hydroxymethyl group of **28** was selectively protected as its TBDPS-ether (**29**) with TBDPS-Cl and imidazole. The free secondary hydroxyl group was oxidized to an α,β-unsaturated ketone (**30**) with the Dess–Martin periodinane (DMP). To successfully elaborate the side chain, the carbonyl group was protected as its ketal derivative (**31**) with ethylene glycol and *p*-TSA under reflux in benzene for 24 h[11] without any epimerization at the adjacent stereocentre and it is substantiated by its ^{13}C NMR data. At this juncture, it was necessary to first cleave the TBDPS-group with Bu_4NF in THF to afford the alcohol (**32**) (Scheme 6).



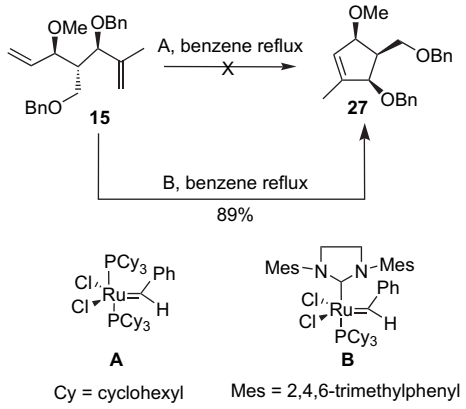
Scheme 2.



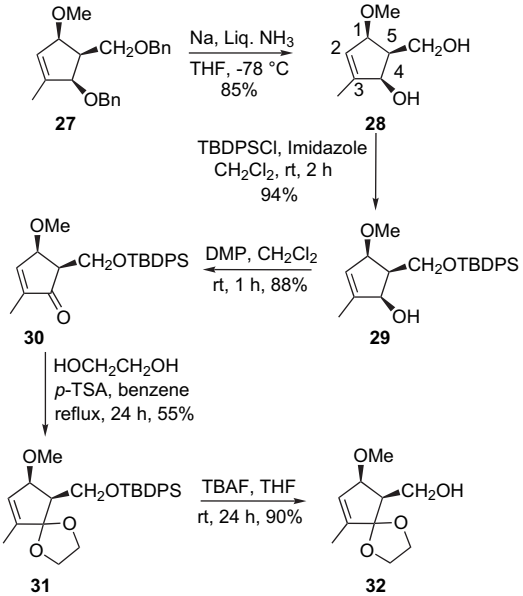
Scheme 3.



Scheme 4.



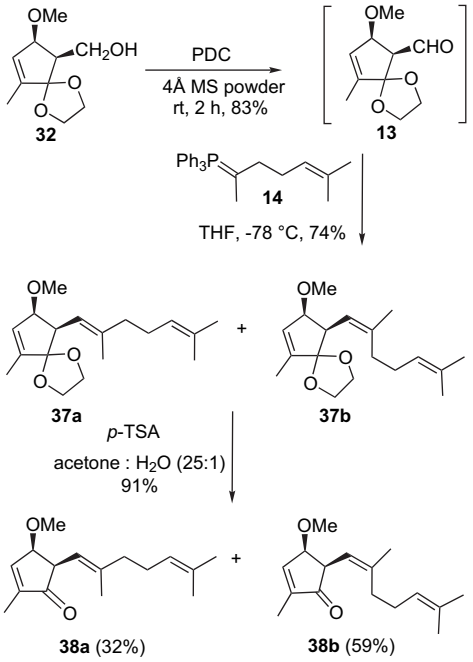
Scheme 5.



Scheme 6.

The ylide (**14**) was prepared from diethyl malonate by a literature procedure.[12] Compound **32** was oxidized with PDC-4 Å molecular sieves at an ambient temperature to produce the aldehyde (**13**). Subsequent Wittig reaction between the aldehyde (**13**) and the ylide (**14**) at −78 °C gave a mixture of *E*- and *Z*-isomers (**37a/37b**) in 35:65. The separation of *E*/*Z*-isomers was not successful, however, the ^{1}H and ^{13}C NMR spectra were suggestive of these structures. Upon deketalisation of (**37a/37b**) with *p*-TSA in aqueous acetone, the *E*/*Z*-isomers of the keto derivatives (**38a/38b**) were obtained. Gratifyingly, both these isomers were separated by silica gel chromatography to afford optically pure *E*-**38a**

and *Z*-isomer (**38b**). The ^{1}H, ^{13}C NMR and analytical data confirmed the structures of both the isomers (Scheme 7).



Scheme 7.

The *E*- and *Z*-isomerism of two diastereomers **38a** and **38b** were confirmed by NOE spectrum. The NOESY experiment of **38a** showed correlation between H-5 and the methyl at C-14. Thus, **38a** was determined to be 1β-methoxy-(*E*)-litse-2,6,10-trien-4-one. Similarly the correlation between H-5 and H-8 confirmed the structure of **38a** as 1β-methoxy-(*Z*)-litse-2,6,10-trien-4-one (Fig. 3).

Finally, the hydrolysis of the methoxy group[13] at C-1 of **37a** would ensure the total synthesis of litseaverticillol C. However, the hydrolysis of methoxyl group under acidic conditions turned out to be a difficult proposition. Table 1 indicates various reagents and conditions that were explored to hydrolyse the methoxyl group of **38a** but to no avail. Under drastic conditions, **38b** was decomposed to an intractable mixture of products, while under mild reaction conditions **38a** remained intact (Scheme 8).

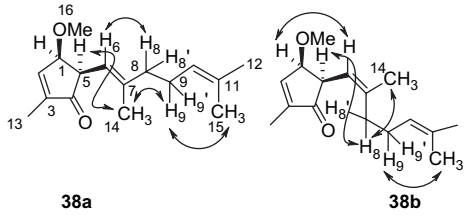
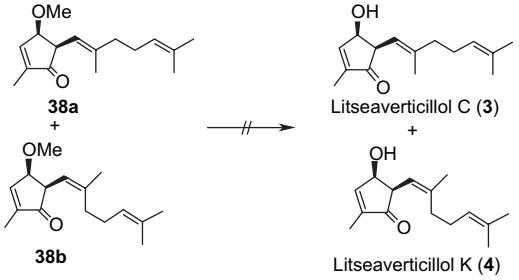


Figure 3. Selected NOESY correlations.

Table 1. Reagents and conditions attempted for the demethylation of **38a** and **38b**

S. no	Reagents and conditions	Result	References
1	TMSI, $CHCl_3$, 25 °C	No reaction	13a
2	BBr_3, CH_2Cl_2, −78 °C	Decomposition of starting material	13b
3	$AlCl_3$, CH_2Cl_2, 25 °C	Decomposition of starting material	13c
4	TMSCl, NaI, $CHCl_3$, 25 °C	No reaction	13d
5	$FeCl_3$, Ac_2O, CH_2Cl_2, 25 °C	No reaction	13e
6	NaI, AcCl, 25 °C	No reaction	13f



Scheme 8.

3. Conclusion

In conclusion, this article describes enantioselective studies towards the synthesis of litseaverticillols C (**3**) and K (**4**) from D-glucose.

4. Experimental

4.1. 3-Deoxy-3-*C*-benzyloxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (18)

Compound **17** (2.5 g, 9.1 mmol) in a dry THF and DMF mixture (2:1) (30 mL) was cooled to 0 °C and NaH (0.73 g, 18.3 mmol, 60% dispersion in oil) was added portion-wise and stirred at room temperature for 30 min. Benzyl bromide (1.6 mL, 13.7 mmol) was added at 0 °C followed by addition of cat. Bu_4NI (92 mg, 0.25 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with ice-cold water (20 mL) and the residue was partitioned between ethyl acetate (50 mL) and water (30 mL). The aqueous layer was again extracted with ethyl acetate (2×50 mL) and the combined organic layers were washed with brine (30 mL), dried (over Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel eluting with ethyl acetate and light petroleum (1:9) to afford **18** (3.1 g, 93%) as a light yellow coloured liquid. R_f (20% ethyl acetate/light petroleum) 0.45; $[\alpha]_D^{25}$ +64.5 (*c* 2.6, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3019, 2928, 1277 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.31 (3H, s, *Me*), 1.33 (3H, s, *Me*), 1.35 (3H, s, *Me*), 1.49 (3H, s, *Me*), 2.18 (1H, m, C*H*CH_2OBn), 3.69–3.77 (3H, m, C*H*CH_2O), 3.87 (1H, m, C*H*(O)CHO), 4.00–4.05 (2H, m, CHC*H*$_2$OBn), 4.54 (2H, ABq, *J* 12.0 Hz, OC*H*$_2$Ph), 4.76 (1H, t, *J* 4.0 Hz, C*H*CHOO), 5.74 (1H, d, *J* 3.6 Hz, OC*H*O), 7.26 (1H, m, *Ph*), 7.33 (4H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 25.2, 26.4, 26.8, 48.8, 65.9, 67.0, 73.1, 77.6, 79.5, 81.1, 105.0, 109.2, 111.7, 127.3, 127.4, 128.1, 138.3; MS: *m*/*z* 364. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 66.07; H, 7.85%.

4.2. 3-Deoxy-3-*C*-benzyloxymethyl-5,6-dihydroxy-1,2-*O*-isopropylidine-α-D-allofuranose (19)

Aqueous H_2SO_4 (0.8%, w/w, 20 mL) was added to a methanolic solution (60 mL) of compound **18** (3.2 g, 8.8 mmol).

The mixture was stirred at room temperature for 10 h, neutralized with K_2CO_3 and filtered. After removing methanol, the residue was partitioned between ethyl acetate (75 mL) and water (25 mL) and the aqueous layer was again extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by column chromatography on silica gel eluting with ethyl acetate and light petroleum (1:1) to give **19** (2.7 g, 95%) as a colourless viscous liquid. R_f (ethyl acetate) 0.55; $[\alpha]_D^{25}$ +31.0 (*c* 1.3, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3402, 3018, 2931, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.29 (3H, s, *Me*), 1.49 (3H, s, *Me*), 2.18 (1H, m, C*H*CH_2OBn), 2.42 (1H, br s, O*H*), 3.57 (1H, m, C*H*OH), 3.69 (2H, m, CH_2OH), 3.80 (1H, dd, *J* 3.7, 11.5 Hz, CHC$H_a$$H_b$OBn) 3.89 (1H, dd, *J* 3.7, 10.4 Hz, CHC$H_a$$H_b$OBn), 3.95 (1H, t, *J* 9.0 Hz, C*H*CHOH), 4.53 (1H, d, *J* 11.5 Hz, OC$H_a$$H_b$Ph), 4.62 (1H, d, *J* 11.5 Hz, OC$H_a$$H_b$Ph), 4.68 (1H, t, *J* 4.1 Hz, C*H*CHOO), 5.78 (1H, d, *J* 3.7 Hz, OC*H*O), 7.31–7.38 (5H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 26.3, 26.6, 49.1, 64.2, 67.5, 73.3, 73.8, 81.9, 82.6, 104.5, 112.2, 128.0, 128.2, 128.6, 136.6; MS: *m*/*z* 324. Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.86; H, 7.51%.

4.3. 3-Deoxy-3-*C*-benzyloxymethyl-5,6-di-*p*-toluenesulfonyl-oxy-1,2-*O*-isopropylidine-α-D-allofuranose (20)

To a solution of **19** (2.0 g, 6.2 mmol) in dry pyridine (20 mL) was added *p*-toluenesulfonyl chloride (4.7 g, 24.6 mmol) at 0 °C. The reaction mixture was stirred for 24 h at room temperature, diluted with ethyl acetate (60 mL) and washed sequentially with 1 N HCl (35 mL), saturated $NaHCO_3$ solution (50 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified on silica gel with ethyl acetate and light petroleum ether (1:4) to furnish **20** (3.6 g, 92%) as a white solid. R_f (40% ethyl acetate/light petroleum) 0.53; $[\alpha]_D^{25}$ +35.2 (*c* 1.0, $CHCl_3$); Mp=114–115 °C; ν_{max} (liquid film, $CHCl_3$) 3021, 2928, 1368, 1291, 1177, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.24 (3H, s, *Me*), 1.37 (3H, s, *Me*), 2.23 (1H, m, C*H*CH_2OBn), 2.38 (3H, s, *Me*-Ar), 2.39 (3H, s, *Me*-Ar), 3.51 (1H, t, *J* 8.8 Hz, C*H*OTs), 3.70 (1H, dd, *J* 6.2, 8.8 Hz, C$H_a$$H_b$OTs), 4.02–4.09 (2H, m, CH$_a$$H_bOTs, CHCH_a$$H_b$OBn), 4.19 (1H, dd, *J* 3.7, 11.0 Hz, CHCH$_a$$H_b$OBn), 4.45 (1H, d, *J* 12.4 Hz, OC$H_a$$H_b$Ph), 4.51 (1H, d, *J* 12.4 Hz, OCH$_a$$H_b$Ph), 4.56 (1H, m, CHC*H*OCH), 4.94 (1H, m, CHC*H*CHOO), 5.56 (1H, d, *J* 3.7 Hz, OC*H*O), 7.18 (2H, d, *J* 7.3 Hz, *Ar*), 7.24 (2H, d, *J* 7.8 Hz, *Ar*), 7.28–7.35 (5H, m, *Ph*), 7.59 (2H, d, *J* 7.8 Hz, *Ar*), 7.63 (2H, d, *J* 8.2 Hz, *Ar*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.4, 26.3, 26.6, 45.8, 66.5, 66.7, 73.1, 79.0, 79.8, 80.8, 104.8, 112.1, 127.4, 127.7, 127.8, 128.2, 129.5, 129.7, 132.4, 133.4, 137.9, 144.7; MS: *m*/*z* 632. Anal. Calcd for $C_{31}H_{36}O_{10}S_2$: C, 58.84; H, 5.73; S, 10.14. Found: C, 58.76; H, 5.71; S, 10.28%.

4.4. 3-Deoxy-3-*C*-benzyloxymethyl-1,2-*O*-isopropylidine-5-methylene-α-D-*ribo*-hexofuranose (21)

A heterogeneous mixture of the ditosylate (**20**) (2.5 g, 3.95 mmol), sodium iodide (5.9 g, 39.5 mmol) and zinc dust (2.6 g, 39.1 mmol) in DMF (25 mL) was refluxed for 4 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water (50 mL) and filtered. The filtrate was extracted with ethyl acetate (2×50 mL), washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After evaporation, the residue was chromatographed on silica gel eluting with ethyl acetate and light petroleum (1:9) to furnish **21** (0.95 g, 83%) as a colourless syrup. R_f (20% ethyl acetate/light petroleum) 0.55; $[\alpha]_D^{25}$ +37.4 (*c* 1.3, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3020, 2993, 2935, 1276, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.34 (3H, s, *Me*), 1.50 (3H, s, *Me*), 2.09 (1H, m, C*H*CH_2OBn), 3.44 (1H, dd, *J* 5.2, 9.1 Hz, C$H_a$$H_b$OBn), 3.75 (1H, t, *J* 9.1 Hz, CH$_a$$H_b$OBn), 4.18 (1H, dd, *J* 7.2, 10.3 Hz, C*H*CH=CH_2), 4.50 (2H, ABq, *J* 12.0 Hz, CH_2Ph), 4.73 (1H, t, *J* 4.1 Hz, CHC*H*O), 5.18 (1H, d, *J* 10.3 Hz, CH=C$H_a$$H_b$), 5.29 (1H, d, *J* 17.1 Hz, CH=CH$_a$$H_b$), 5.78 (1H, ddd, *J* 6.8, 10.3, 17.1 Hz, C*H*=CH_2), 5.83 (1H, d, *J* 3.7 Hz, OC*H*O), 7.25–7.33 (5H, m, *Ph*); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.2, 26.5, 50.0, 65.6, 73.0, 80.2, 80.4, 104.8, 111.4, 117.7, 127.2, 127.3, 128.1, 135.9, 138.1; MS: *m*/*z* 290. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.24; H, 7.74%.

4.5. Methyl-2-hydroxy-3-deoxy-3-*C*-benzyloxymethyl-5-methylene-α-D-*ribo*-hexofuranoside (22)

Activated Amberlyst IR-120 (H^+) resin (1.5 g) was added to a solution of **21** (1.0 g, 3.4 mmol) in dry methanol (20 mL) and the mixture was heated under reflux for 3 h. The reaction mixture was cooled to room temperature, filtered, concentrated and the residue was partitioned between ethyl acetate (30 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (2×25 mL), washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel by eluting with ethyl acetate and light petroleum (1:6) to give **22** in an anomeric mixture (α:β=20:80, 0.8 g, 88%), as a light yellow liquid. R_f (30% ethyl acetate/light petroleum) 0.52; ν_{max} (liquid film, $CHCl_3$) 3420, 3019, 2934, 1276, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.16–2.31 (1H, m, C*H*CH_2OBn), 3.33 (3H, s, O*Me*), 3.63–3.75 (2H, m, CH_2OBn), 4.20 (1H, m, C*H*CH=CH_2), 4.30–4.56 (3H, m, CH_2Ph, C*H*OH), 4.74 (1H, s, C*H*OMe), 5.09 (1H, d, *J* 10.1 Hz, CH=C$H_a$$H_b$), 5.14 (1H, d, *J* 17.0 Hz, CH=CH$_a$$H_b$), 5.74–5.85 (1H, m, C*H*=CH_2), 7.24–7.33 (5H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 47.0/47.7, 54.4/54.9, 66.1/67.2, 73.2/73.3, 76.8, 80.7/81.4, 108.2/109.2, 116.4/117.0, 127.6/127.3, 127.8/128.1, 128.4/128.5, 137.5/137.8, 139.3; MS: *m*/*z* 264. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.24; H, 7.56%.

4.6. Methyl-2-*C*-benzyloxy-3-deoxy-3-*C*-benzyloxymethyl-5-methylene-*ribo*-hexofuranoside (23)

To a solution of compound **22** (1.0 g, 3.8 mmol) in dry DMF (20 mL) was added NaH (0.23 g, 5.7 mmol) portion-wise at 0 °C, and the mixture was stirred at room temperature for 30 min. Benzyl bromide (0.7 mL, 5.7 mmol) was added at 0 °C and stirring at room temperature was continued for another 30 min. The residue was partitioned between ethyl acetate (30 mL) and water (10 mL). The aqueous layer was again extracted with ethyl acetate (2×20 mL) and the combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue

was purified by column chromatography on silica gel by eluting with ethyl acetate and light petroleum (1:19) to afford **23** (1.2 g, 90%) as a light yellow coloured liquid. R_f (10% ethyl acetate/light petroleum) 0.57; ν_{max} (liquid film, $CHCl_3$) 3019, 2975, 1452, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.44–2.50 (1H, m, C*H*CH_2OBn), 3.33 (3H, s, O*Me*), 3.44 (1H, dd, *J* 5.5, 9.2 Hz, C*H*$_a$H$_b$OBn), 3.78 (1H, t, *J* 9.2 Hz, CH$_a$*H*$_b$OBn), 3.97 (1H, d, *J* 4.6 Hz, C*H*OBn), 4.24 (1H, t, *J* 8.6 Hz, C*H*CH=CH_2), 4.45 (1H, d, *J* 11.9 Hz, C*H*$_a$H$_b$Ph), 4.48 (1H, d, *J* 11.9 Hz, CH$_a$*H*$_b$Ph), 4.51 (1H, d, *J* 11.9 Hz, C*H*$_a$H$_b$Ph), 4.62 (1H, d, *J* 11.9 Hz, CH$_a$*H*$_b$Ph), 4.87 (1H, s, C*H*OMe), 5.11 (1H, d, *J* 9.6 Hz, CH=C*H*$_a$H$_b$), 5.19 (1H, d, *J* 17.4 Hz, CH=CH$_a$*H*$_b$), 5.79–5.85 (1H, m, C*H*=CH_2), 7.20–7.30 (10H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 47.3/45.2, 54.4/55.0, 65.9, 72.3/72.4, 72.8/73.1, 82.0/82.7, 106.1/106.4, 115.3/116.4, 127.4, 127.5, 127.6, 127.7/127.8, 128.2, 128.3, 137.8/138.0, 137.9/138.3, 139.4; MS: *m*/*z* 354. Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.46; H, 7.49%.

4.7. 3-Benzyloxy-4-benzyloxymethyl-5-vinyl-tetrahydrofuran-2-ol (24)

Compound **23** (1.4 g, 4.0 mmol) was dissolved in 20% aqueous acetic acid (35 mL) and concd H_2SO_4 (0.4 mL), and refluxed for 12 h. The reaction mixture was diluted with ethyl acetate and neutralized with $NaHCO_3$. It was then partitioned between ethyl acetate (50 mL) and water (20 mL). The aqueous layer was again extracted with ethyl acetate (2×20 mL) and the combined organic layers were washed with brine (35 mL), dried and concentrated. The residue was purified by column chromatography on silica gel eluting with ethyl acetate and light petroleum (1:9) to afford a yellow liquid **24** (1.0 g, 75%). R_f (20% ethyl acetate/light petroleum) 0.52; ν_{max} (liquid film, $CHCl_3$) 3395, 3019, 2934, 1276 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.21–2.26 (0.5H, m, C*H*CH_2OBn), 2.52–2.58 (0.5H, m, C*H*CH_2OBn), 3.16 (0.5H, br d, *J* 12.8 Hz, O*H*), 3.46 (0.5H, dd, *J* 5.5, 9.2 Hz, C*H*$_2$OBn), 3.54 (0.5H, dd, *J* 6.0, 9.2 Hz, C*H*$_2$OBn), 3.59 (0.5H, dd, *J* 3.7, 9.2 Hz, C*H*$_2$OBn), 3.79 (0.5H, t, *J* 9.2 Hz, C*H*$_2$OBn), 4.00 (0.5H, d, *J* 4.6 Hz, C*H*OBn), 4.07 (0.5H, dd, *J* 4.6, 7.8 Hz, C*H*OBn), 4.25 (0.5H, dd, *J* 7.8, 9.2 Hz, C*H*CH=CH_2), 4.39 (0.5H, t, *J* 7.0 Hz, C*H*CH=CH_2), 4.48 (1H, quintet, *J* 12.0 Hz, C*H*$_a$H$_b$Ph), 4.51–4.57 (2H, m, C*H*$_2$Ph), 4.64 (1H, dd, *J* 12.0, 19.7 Hz, CH$_a$*H*$_b$Ph), 4.75–4.78 (0.5H, m, O*H*), 5.11 (1H, t, *J* 11.0 Hz, C*H*OH), 5.21 (1H, ddt, *J* 1.3, 7.3, 17.0 Hz, CH=C*H*$_a$H$_b$), 5.34–5.37 (1H, m, CH=CH$_a$*H*$_b$), 5.78 (0.5H, ddd, *J* 7.0, 10.5, 17.0 Hz, C*H*=CH_2), 5.88 (0.5H, ddd, *J* 7.0, 10.5, 17.0 Hz, C*H*=CH_2), 7.23–7.33 (10H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 46.9/47.0, 65.9/66.0, 72.3, 73.2/73.6, 78.4/79.0, 83.0/83.4, 96.3/100.3, 116.3/116.8, 127.5/127.6, 127.8/127.9, 128.3, 128.5, 137.4/137.7, 138.1/138.3, 138.0/139.5; MS: *m*/*z* 340. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.94; H, 7.05%.

4.8. 3-Benzyloxy-4-benzyloxymethyl-5-vinyl-dihydro-furan-2-one (16)

To a mixture of **24** (0.5 g, 1.5 mmol) and 4 Å molecular sieves (750 mg) in dry CH_2Cl_2 (6.0 ml), PDC (0.9 g, 2.4 mmol) was added at room temperature. The mixture was stirred for 1 h at room temperature, filtered through a Celite pad and concentrated. The residue was chromatographed on silica gel using ethyl acetate and light petroleum (1:13) to give **16** (0.4 g, 82%) as a colourless oil. R_f (15% ethyl acetate/light petroleum) 0.55; $[\alpha]_D^{25}$ +48.6 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$): 1781, 1602, 1584, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.52 (1H, quintet, *J* 6.0 Hz, C*H*CH_2OBn), 3.50 (1H, dd, *J* 6.9, 9.2 Hz, C*H*$_a$H$_b$OBn), 3.76 (1H, dd, *J* 6.9, 9.2 Hz, CH$_a$*H*$_b$OBn), 4.15 (1H, d, *J* 6.9 Hz, C*H*CH=CH_2), 4.47 (1H, d, *J* 11.9 Hz, C*H*$_a$H$_b$Ph), 4.50 (1H, d, *J* 11.9 Hz, CH$_a$*H*$_b$Ph), 4.65 (1H, d, *J* 11.9 Hz, C*H*$_a$H$_b$Ph), 4.84 (1H, t, *J* 5.8 Hz, C*H*OBn), 4.90 (1H, d, *J* 11.9 Hz, CH$_a$*H*$_b$Ph), 5.24 (1H, d, *J* 10.6 Hz, CH=C*H*$_a$H$_b$), 5.33 (1H, d, *J* 17.0 Hz, CH=CH$_a$*H*$_b$), 5.83 (1H, m, C*H*=CH_2), 7.22–7.35 (10H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 45.8, 65.5, 72.3, 73.0, 73.4, 80.5, 117.9, 127.5, 127.7, 127.9, 128.0, 128.3, 128.4, 134.7, 136.9, 137.7, 173.4; MS: *m*/*z* 338. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.64; H, 6.56%.

4.9. 3-Benzyloxy-4-benzyloxymethyl-2-methyl-hept-6-ene-2,5-diol (25)

A solution of **16** (0.80 g, 2.4 mmol) in dry ether (20 mL) was added drop-wise to a freshly prepared methyl magnesium iodide obtained from magnesium (0.2 g, 8.4 mmol) and methyl iodide (0.5 mL, 7.2 mmol) in Et_2O. The temperature was maintained below 40 °C throughout the addition. After stirring the reaction mixture for another 4 h, the reaction mixture was quenched with an ice-cooled saturated solution of ammonium chloride (20 mL). The aqueous reaction mixture was extracted with ether (3×40 mL). The combined ether extracts were dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel eluting with ethyl acetate and light petroleum (1:4) to afford **25** (0.69 g, 79%) as a colourless liquid. R_f (40% ethyl acetate/light petroleum) 0.43; $[\alpha]_D^{25}$ +44.0 (*c* 1.5, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3393, 3018, 2979, 2934, 1751, 1273 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.21 (3H, s, *Me*), 1.25 (3H, s, *Me*), 2.18 (1H, m, C*H*CH_2OBn), 3.37 (1H, m, O*H*), 3.41 (1H, dd, *J* 4.6, 9.2 Hz, C*H*$_a$H$_b$OBn), 3.63 (1H, d, *J* 4.6.0 Hz, CH$_a$*H*$_b$OBn), 3.75 (2H, br s, C*H*OH, C*H*OBn), 4.39 (1H, s, O*H*), 4.40 (1H, d, *J* 11.9 Hz, C*H*$_a$H$_b$Ph), 4.47 (1H, d, *J* 11.9 Hz, CH$_a$*H*$_b$Ph), 4.57 (1H, d, *J* 11.5 Hz, C*H*$_a$H$_b$Ph), 4.68 (1H, d, *J* 11.5 Hz, CH$_a$*H*$_b$Ph), 5.11 (1H, d, *J* 10.6 Hz, CH=C*H*$_a$H$_b$), 5.22 (1H, d, *J* 17.2 Hz, CH=CH$_a$*H*$_b$), 5.83 (1H, m, C*H*=CH_2), 7.22–7.32 (10H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 26.5, 27.1, 46.0, 70.1, 70.9, 73.1, 73.3, 75.4, 85.2, 115.8, 127.6, 128.3, 137.9, 138.1, 139.0; MS: *m*/*z* 370. Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.64; H, 7.98%.

4.10. 3-Benzyloxy-4-benzyloxymethyl-5-methoxy-2-methyl-hept-6-ene-2-ol (26)

To a suspension of NaH (60% dispersion in oil, 0.048 g, 1.2 mmol) in dry DMF (10 mL) was added a solution of **25** (0.40 g, 1.1 mmol) in DMF (5 mL) and the mixture was stirred at 0 °C for 30 min. Then methyl iodide (0.08 mL, 1.3 mmol) was added and the stirring was continued at room temperature for an additional 1 h. The reaction was quenched with water (10 mL) and the mixture was extracted with ethyl acetate (3×25 mL). The ethyl acetate layer was

washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel using ethyl acetate and light petroleum (3:17) to afford **26** (0.37 g, 89%) as oil. R_f (40% ethyl acetate/light petroleum) 0.56; $[\alpha]_D^{25}$ +23.4 (*c* 0.85, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3401, 3019, 2982, 2937, 1746, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.21 (3H, s, *Me*), 1.28 (3H, s, *Me*), 2.30 (1H, m, C*H*CH_2OBn), 3.22 (3H, s, O*Me*), 3.41 (1H, dd, *J* 6.7, 9.4 Hz, CH_aH_bOBn), 3.51 (1H, dd, *J* 4.3, 9.4 Hz, CH_aH_bOBn), 3.58 (1H, d, *J* 2.4 Hz, C*H*OBn), 3.90 (1H, t, *J* 7.8 Hz, C*H*OMe), 4.39 (1H, br s, O*H*), 4.48 (2H, ABq, *J* 12.1 Hz, CH_2Ph), 4.63 (2H, ABq, *J* 11.5 Hz, CH_2Ph), 5.19 (1H, dd, *J* 2.0, 11.8 Hz, CH=CH_aH_b), 5.27 (1H, m, CH=CH_aH_b), 5.70 (1H, ddd, *J* 8.2, 10.6, 17.0 Hz, C*H*=CH_2), 7.20–7.38 (10H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 27.1, 27.8, 44.7, 55.9, 69.6, 72.6, 73.1, 74.7, 80.8, 85.2, 118.4, 127.3, 127.4, 127.6, 128.1, 128.3, 136.3, 137.9, 138.8; MS: *m*/*z* 384. Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.82; H, 8.30%.

4.11. 2-Methyl-3-benzyloxy-4-benzyloxymethyl-5-methoxy-1,6-heptadiene (15)

To a solution of **26** (0.42 g, 1.1 mmol) in CH_2Cl_2 (20 mL) were added DMAP (0.54 g, 4.4 mmol), triethylamine (0.60 mL, 4.4 mmol) and MsCl (0.25 mL, 3.3 mmol), and the reaction mixture was stirred for 2 h at room temperature (monitored by TLC). After completion of the reaction, the mixture was partitioned between dichloromethane (30 mL) and water (10 mL). The organic layer was washed sequentially with dilute HCl (10 mL), saturated $NaHCO_3$ (15 mL), brine (10 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate and light petroleum (1:13) to afford **15** (0.31 g, 78%) as a colourless liquid. R_f (15% ethyl acetate/light petroleum) 0.65; $[\alpha]_D^{25}$ +25.0 (*c* 1.2, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3019, 2929, 1273 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.73 (3H, s, *Me*), 2.26 (1H, m, C*H*CH_2OBn), 3.26 (3H, s, O*Me*), 3.40 (1H, m, C*H*OBn), 3.43 (1H, dd, *J* 2.7, 4.7 Hz, C*H*OMe), 3.85 (1H, d, *J* 9.4 Hz, CH_aH_bOBn), 4.01 (1H, dd, *J* 3.9, 9.4 Hz, CH_aH_bOBn), 4.15 (1H, d, *J* 11.4 Hz, CH_aH_bPh), 4.36 (2H, s, CH_2Ph), 4.43 (1H, d, *J* 11.4 Hz, CH_aH_bPh), 4.95–5.18 (4H, m, CH_2=CH, CH_2=CCH_3), 5.84 (1H, ddd, *J* 8.2, 10.6, 17.0 Hz, C*H*=CH_2), 7.20–7.32 (10H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 17.1, 45.5, 56.3, 67.2, 70.0, 73.0, 81.6, 82.3, 115.0, 117.4, 127.2, 127.4, 127.9, 128.1, 128.2, 136.9, 138.7, 143.0; MS: *m*/*z* 366. Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.58; H, 8.29%.

4.12. 4-Methyl-3-benzyloxy-2-benzyloxymethyl-1-methoxy-4-cyclopentadiene (27)

A solution of compound **15** (5.0 g, 14.8 mmol) and the Grubbs' second-generation catalyst **B** (0.085 g, 7 mol %) in dry benzene (100 mL) was degassed under argon atmosphere. The reaction mixture was heated under reflux for two days. After completion of the reaction (monitored by TLC), the solvent was evaporated and the residue was purified by column chromatography on silica gel using ethyl acetate and light petroleum ether (1:11) to give **27** (4.1 g, 89%) as a light yellow coloured liquid. R_f (16% ethyl acetate/light petroleum) 0.55; $[\alpha]_D^{25}$ −46.2 (*c* 2.8, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3019, 2932, 1657, 1373, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.69 (3H, s, *Me*), 2.58 (1H, quintet, *J* 6.3 Hz, C*H*CH_2OBn), 3.28 (3H, s, O*Me*), 3.67–3.82 (2H, m, *J* 3.1 Hz, CH_2OBn), 4.07 (1H, m, C*H*OMe), 4.12 (1H, d, *J* 6.3 Hz, C*H*OBn), 4.49 (2H, s, CH_2Ph), 4.54 (1H, d, *J* 12.1 Hz, CH_aH_bPh), 4.65 (1H, d, *J* 12.1 Hz, CH_aH_bPh), 5.72 (1H, br s, C*H*=CCH_3), 7.18–7.32 (10H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.7, 46.9, 56.9, 66.5, 72.6, 73.2, 83.4, 84.0, 127.3, 127.6, 127.9, 128.0, 128.1, 138.5, 138.9, 145.6; MS: *m*/*z* 338. Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 77.94; H, 7.77%.

4.13. 4-Methyl-3-hydroxy-2-hydroxymethyl-1-methoxy-4-cyclopentadiene (28)

A 100 mL flask, fitted with an ammonia condenser, was charged with anhydrous ammonia (~35 mL) at −78 °C under argon atmosphere, and sodium (0.6 g, 26.6 mmol) was added until the blue colour of the solution persisted. A sample of **27** (2.0 g, 12.6 mmol) in THF (20 mL) was added drop-wise over a period of 15 min at −78 °C. The solution was stirred for 45 min at this temperature and quenched with solid NH_4Cl (3–4 g, portion-wise addition) at −78 °C until the blue colour disappeared. Ammonia was allowed to evaporate and the residue was extracted with ethyl acetate (2×50 mL). The combined extracts were dried, concentrated and the residue was purified by column chromatography on silica gel using ethyl acetate and light petroleum (1:1) to produce **28** (0.79 g, 85%) as a viscous liquid. R_f (ethyl acetate) 0.45; $[\alpha]_D^{25}$ −57.1 (*c* 1.1, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3398, 3019, 2981, 2937, 2883, 1687, 1655, 1403 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.87 (3H, s, *Me*), 2.62 (1H, m, C*H*CH_2OH), 3.42 (3H, s, O*Me*), 3.94 (1H, dd, *J* 3.9, 12.1 Hz, C*H*OH), 4.04 (1H, dd, *J* 3.9, 12.1 Hz, C*H*OMe), 4.26 (1H, d, *J* 7.4 Hz, CH_aH_bOH), 4.39 (1H, d, *J* 7.4 Hz, CH_aH_bOH), 5.74 (1H, br s, C*H*=CCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.9, 46.3, 57.3, 59.8, 78.4, 84.8, 126.2, 148.2; MS: *m*/*z* 158. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.77; H, 8.83%.

4.14. 4-Methyl-3-hydroxy-2-*tert*-butyldiphenylsilyloxymethyl-1-methoxy-4-cyclopentadiene (29)

To a solution of diol (**28**) (0.10 g, 0.63 mmol) in CH_2Cl_2 (10 mL), TBDPS-Cl (0.2 mL, 0.70 mmol) and imidazole (0.064 g, 0.95 mmol) were added and stirred at room temperature for 4 h. The reaction mixture was poured into 10 mL of H_2O and extracted with CH_2Cl_2 (2×25 mL). The CH_2Cl_2 layer was washed with $NaHCO_3$ (15 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using ethyl acetate and light petroleum (1:13) to get compound **29** (0.24 g, 94%) as a colourless liquid. R_f (15% ethyl acetate/light petroleum) 0.51; $[\alpha]_D^{25}$ −18.4 (*c* 1.6, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3421, 3019, 2932, 2860, 1428, 1216, 1113 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (s, 9H, *t-Bu*), 1.88 (3H, s, *Me*), 2.36 (1H, d, *J* 8.0 Hz, O*H*), 2.48 (1H, quintet, *J* 6.6 Hz, C*H*CH_2OTBDPS), 3.19 (3H, s, O*Me*), 3.92 (1H, dd, *J* 6.6, 10.4 Hz, C*H*OMe), 4.01 (1H, d, *J* 8.0 Hz, C*H*OH), 4.06 (1H, br t, *J* 2.7 Hz, CH_aH_bOTBDPS), 4.35 (1H, t, *J* 6.6 Hz, CH_aH_bOTBDPS), 5.75 (1H, br s, C*H*=CCH_3), 7.34–7.43 (6H, m, *Ph*), 7.69 (4H, d,

J 6.6 Hz, *Ph*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.4, 19.2, 26.9, 49.2, 57.0, 60.6, 78.2, 83.3, 127.6, 127.7, 129.7, 133.5, 133.7, 135.6, 147.9; MS: *m*/*z* 397. Anal. Calcd for $C_{24}H_{32}O_3Si$: C, 72.68; H, 8.13. Found: C, 72.59; H, 8.12%.

4.15. (4*R*,5*R*)-5-*O*-*tert*-Butyldiphenylsilyloxymethyl-4-methoxy-2-methylcyclopent-2-enone (30)

To a solution of **29** (0.25 g, 0.63 mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (0.30 g, 0.69 mmol) at room temperature. After stirring for 1 h, the mixture was diluted with H_2O (10 mL), filtered, washed with Et_2O (10 mL). The aqueous phase was extracted with Et_2O (2×25 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography using ethyl acetate and light petroleum (1:15) as eluents to afford **30** (0.22 g, 88%) as a colourless oil. R_f (12% ethyl acetate/light petroleum) 0.48; $[\alpha]_D^{25}$ −33.5 (*c* 1, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3385, 3019, 2936, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.99 (9H, s, *t-Bu*), 1.80 (3H, m, *Me*), 2.78 (1H, m, C*H*CH_2OTBDPS), 3.46 (3H, s, O*Me*), 3.92 (1H, dd, *J* 3.4, 9.9 Hz, CH_aH_bOTBDPS), 4.02 (1H, dd, *J* 6.6, 9.9 Hz, CH_aH_bOTBDPS), 4.43 (1H, m, C*H*OMe), 7.30 (1H, m, C*H*=C(CO)CH_3), 7.34–7.42 (6H, m, *Ph*), 7.64–7.72 (4H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 10.1, 19.2, 26.7, 52.4, 58.3, 60.6, 78.6, 127.5, 127.6, 127.7, 127.8, 129.6, 133.5, 133.6, 133.7, 143.6, 154.3, 206.4; MS: *m*/*z* 395. Anal. Calcd for $C_{24}H_{30}O_3Si$: C, 73.05; H, 7.66. Found: C, 72.95; H, 7.53%.

4.16. 2-Methyl-5-*O*-*tert*-butyldiphenylsilyloxymethyl-4-methoxy-2-cyclopentadien-1-[1,3]dioxolane (31)

A solution of compound **30** (0.23 g, 0.58 mmol), ethylene glycol (0.65 mL, 11.6 mmol) and *p*-toluenesulfonic acid (10 mol %) in dry benzene (25 mL) was heated under reflux for 24 h using a Dean–Stark apparatus. The reaction mixture was washed subsequently with 5% aq $NaHCO_3$ (15 mL), water (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography using ethyl acetate and light petroleum (1:19) to afford **31** (0.14 g, 55%) as a colourless oil. R_f (12% ethyl acetate/light petroleum) 0.52; $[\alpha]_D^{25}$ −41.0 (*c* 1.6, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3018, 2937, 1654, 1371, 1274 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.05 (9H, br s, *t-Bu*), 1.71 (3H, m, *Me*), 2.53 (1H, quintet, *J* 6.6 Hz, C*H*CH_2OTBDPS), 3.29 (3H, s, O*Me*), 3.82–4.01 (6H, m, OCH_2CH_2O, CH_2OTBDPS), 4.14 (1H, br d, *J* 6.0 Hz, C*H*OMe), 5.89 (1H, br s, C*H*=CCH_3), 7.35–7.41 (6H, m, *Ph*), 7.70–7.75 (4H, m, *Ph*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.5, 19.2, 26.8, 53.3, 57.2, 59.4, 65.6, 66.6, 80.7, 117.2, 127.6, 129.3, 129.4, 133.9, 134.0, 135.5, 135.6, 146.0; MS: *m*/*z* 439. Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 71.10; H, 8.04%.

4.17. 2-Methyl-5-hydroxymethyl-4-methoxy-2-cyclopentadien-1-[1,3]dioxolane (32)

Compound **31** (1 g, 5.0 mmol) and Bu_4NF (1 M solution in THF) (6.8 mL, 6.8 mmol) in THF (10 mL) were stirred together at room temperature for 24 h. The reaction mixture was partitioned between ethyl acetate (35 mL) and water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel eluting with ethyl acetate and light petroleum ether (1:1) to give **32** (0.41 g, 90%) as a syrup. R_f (ethyl acetate) 0.57; $[\alpha]_D^{25}$ −148.4 (*c* 1.3, $CHCl_3$); ν_{max} (liquid film, $CHCl_3$) 3394, 3019, 2976, 2932, 1684, 1406 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.72 (3H, br q, *J* 1.9 Hz, *Me*), 2.61 (1H, m, C*H*CH_2OH), 2.66 (1H, br s, O*H*), 3.40 (3H, d, *J* 2.3 Hz, O*Me*), 3.70 (1H, ddd, *J* 1.9, 6.2, 11.6 Hz, CH_aH_bOH), 3.82 (1H, ddd, *J* 1.9, 7.5, 11.6 Hz, CH_aH_bOH), 3.96–4.10 (4H, m, OCH_2CH_2O), 4.37 (1H, m, C*H*OMe), 5.91 (1H, m, C*H*=CCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.0, 51.8, 57.1, 59.6, 65.0, 66.3, 82.3, 117.2, 129.6, 143.9; MS: *m*/*z* 200. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.88; H, 8.15%.

4.18. 9-(2,6-Dimethyl-hepta-1,5-dienyl)-8-methoxy-6-methyl-1,4-dioxa-spiro[4,4]non-6-ene (37a and 37b)

To a mixture of **32** (0.035 g, 0.17 mmol) and 4 Å molecular sieves powder (0.2 g) in dry CH_2Cl_2 (5.0 mL) was added PDC (0.33 g, 0.87 mmol) at room temperature. The mixture was stirred for 2 h at room temperature, filtered and washed with ether (30 mL). The solvent was concentrated under reduced pressure to give **13** (0.029 g, 83%) as a colourless oil, which was used immediately for the next reaction.

To (6-methylhept-5-en-2-yl)triphenylphosphonium iodide (0.176 g, 0.35 mmol) suspended in dry THF (5 mL) at −78 °C under N_2 atmosphere was added *n*-BuLi (0.23 mL, 1.39 M, 0.32 mmol) in THF to form its ylide (**14**). After 30 min, aldehyde **13** (0.029 g, 0.15 mmol) in THF (1 mL) was added. After completion of reaction (monitored by TLC), saturated aq NH_4Cl (5 mL) was added, filtered and the filtrate was extracted with ethyl acetate (2×10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography using silica gel column chromatography eluting with ethyl acetate and light petroleum ether (1:24) to furnish a diastereomeric mixture of (**37a+37b**) in 35:65, confirmed from ^{1}H NMR (0.032 g, 74%), which were inseparable. R_f (8% ethyl acetate/light petroleum) 0.45; ν_{max} (liquid film, $CHCl_3$) 3019, 2971, 2855, 1464, 1378 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.61–1.65 (6H, m, 2×*Me*), 1.66–1.79 (6H, m, 2×*Me*), 2.03–2.16 (4H, m, CH_2=(CH_3)CH_2CH_2), 3.08 (0.65H, dd, *J* 6.2, 10.2 Hz, C*H*CH=CH_2), 3.18 (0.35H, dd, *J* 6.2, 9.3 Hz, C*H*CH=CH_2), 3.30 (3H, m, O*Me*), 3.85–4.12 (5H, m, C*H*OMe, OCH_2CH_2O), 5.11–5.34 (1H, m, C*H*=C$(CH_3)_2$), 5.35–5.63 (1H, m, C*H*=C$(CH_2)CH_3$), 5.87 (1H, m, C*H*=CCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.2/13.8, 16.4/17.6, 23.0/23.9, 25.7, 26.5/27.0, 32.4/40.0, 49.7/49.9, 57.2/57.3, 65.6/65.7, 65.9/66.0, 82.3/82.5, 118.0/118.2, 119.3/119.5, 124.2/124.4, 130.0/130.1, 131.3/131.5, 132.7, 144.9/145.0; MS: *m*/*z* 292. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.95; H, 9.54%.

4.19. (4*R*,5*R*,*E*)-5-(2,6-Dimethylhepta-1,5-dienyl)-4-methoxy-2-methylcyclopent-2-enone (38a)

Compounds **37a** and **37b** (30 mg, 0.034 mmol) and *p*-toluenesulfonic acid (cat.) were added to a mixture of acetone and

H_2O (25:1) (6 mL). After stirring at room temperature for 1 h, the reaction was quenched with water, concentrated and the residue was diluted with the mixture of ethyl acetate and water (2:1) (15 mL). The aqueous layer was extracted with ethyl acetate (2×10 mL), washed with brine (5 mL), dried (over Na_2SO_4) and concentrated. The residue was chromatographed on silica gel eluting with EtOAc–hexane (1:19). The first to be eluted was methylated litseaverticillol K (*Z*-isomer, **38b**) (15.0 mg, 59%) and further elution with ethyl acetate and petroleum ether (1:16) afforded the methylated litseaverticillol C (*E*-isomer, **38a**) (8.0 mg, 32%). R_f (8% ethyl acetate/light petroleum) 0.37; $[\alpha]_D^{25}$ +115.4 (*c* 0.3, $CHCl_3$); IR (liquid film, $CHCl_3$): 3014, 2966, 2925, 2856, 2827, 1710, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.59 (3H, s, *Me*), 1.66 (3H, s, *Me*), 1.79–1.82 (6H, m, *Me*), 2.05–2.15 (4H, m, CH_2=$(CH_3)CH_2CH_2$), 3.35 (3H, s, O*Me*), 3.49 (1H, dd, *J* 6.1, 9.3 Hz, C*H*CH=CH_2), 4.43 (1H, m, C*H*OMe), 5.04 (1H, br d, *J* 9.3 Hz, C*H*=$C(CH_3)_2$), 5.09 (1H, m, C*H*=$C(CH_2)CH_3$), 7.21 (1H, quintet, *J* 1.5 Hz, C*H*=C(CO)CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 10.2, 16.9, 17.7, 25.7, 26.4, 39.8, 49.9, 57.9, 79.2, 116.9, 124.1, 131.5, 140.6, 143.2, 154.1, 206.7; MS: *m*/*z* 248. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.29; H, 9.67%.

4.20. (4*R*,5*R*,*Z*)-5-(2,6-Dimethylhepta-1,5-dienyl)-4-methoxy-2-methylcyclopent-2-enone (38b)

R_f (8% ethyl acetate/light petroleum) 0.41; $[\alpha]_D^{25}$ +122.0 (*c* 0.3, $CHCl_3$); IR (liquid film, $CHCl_3$): 3010, 2969, 2922, 2853, 2821, 1715, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.64 (3H, s, *Me*), 1.70 (3H, s, *Me*), 1.79 (3H, d, *J* 1.5 Hz, *Me*), 1.80 (3H, t, *J* 1.7 Hz, *Me*), 2.12–2.25 (4H, m, CH_2=$(CH_3)CH_2CH_2$), 3.36 (3H, s, O*Me*), 3.48 (1H, dd, *J* 5.9, 9.5 Hz, C*H*CH=CH_2), 4.39 (1H, m, C*H*OMe), 5.04 (1H, dd, *J* 1.5, 9.7 Hz, C*H*=$C(CH_3)_2$), 5.18 (1H, m, C*H*=$C(CH_2)CH_3$), 7.21 (1H, m, C*H*=C(CO)CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 10.3, 17.7, 23.7, 25.7, 26.9, 32.7, 49.8, 57.8, 79.4, 117.3, 124.2, 131.8, 140.8, 143.3, 153.9, 206.6; MS: *m*/*z* 248.

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