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Stereoselective total synthesis of (+)-varitriol

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ABSTRACT

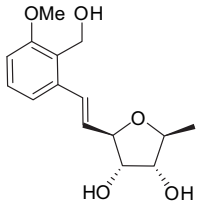
Stereoselective total synthesis of (+)-varitriol, an antitumor natural product, was accomplished by two versatile strategies starting from the commercially available D-(−)-ribose and ethyl (*S*)-lactate. The key steps involved in the synthesis of the target molecule are epoxidation, cyclization, dihydroxylation and Diels–Alder reaction.

1. Introduction

Marine fungi are an important source of marine natural products.[1] Amongst them, (+)-varitriol **1** isolated from the fungus *Emericella variecolor* has shown increased potency toward the renal, breast and CNS cancer cell lines.[2] The fascinating biological activities of (+)-**1** have attracted the attention of the synthetic community.

To date, several total syntheses of (+) and (−)-**1** have been completed. Jennings and Clemens[3a] reported the total synthesis of (−)-**1** using cross metathesis to link the carbohydrate and aromatic moieties. Subsequently, the Taylor group[3b] also achieved the synthesis of (−)-**1** by applying Horner–Wadsworth–Emmons (HWE) and Ramberg–Backlund reaction. Both these groups started their synthesis with D-(−)-ribose to construct the furanoside part, though, Jennings et al., emphasized the need for the use of expensive L-(+)-ribose for obtaining the natural (+)-varitriol. The first total synthesis of (+)-**1**, was reported by Shaw et al.,[3c] utilizing methyl α,D-mannopyranoside to construct the carbohydrate portion of the molecule which was later combined with the aromatic moiety by cross metathesis. Gracza et al.,[3d] reported the synthesis of (+)-**1** by applying Kocienski–Julia olefination of sulfonyl furan derivative with substituted benzaldehyde. A recent report by Ghosh and Pradhan,[3e] depicted the synthesis of both (+) and (−)-**1** and their epimers utilizing Heck reaction to couple the olefinic sugar moiety with the aromatic triflate. By the time this work is being submitted, some more reports for the synthesis of (+)-**1** have also appeared in literature.[3f,g] Furthermore, synthetic analogues of (+)-**1** were also reported by various approaches.[3h,i]

In the present investigation, we have made an attempt to install the required stereocenters from the commercially available D-(−)-ribose. We envisioned that the furanoside part of the natural (+)-**1** can be derived from D-(−)-ribose and the aromatic moiety from propargyl alcohol.



(+)-varitriol 1

2. Results and discussion

The synthesis of the furanoside part of (+)-**1** was initiated from D-(−)-ribose and the sequence of reactions are depicted in Scheme 1. 2,3-*O*-Isopropylidene-D-ribofuranose **2** (synthesized from D-(−)-ribose[4]) was treated with excess MeMgI to yield **3**,[5] which upon oxidative cleavage with $NaIO_4$ gave a lactol. Wittig olefination using carbethoxymethylene triphenylphosphorane resulted in α,β-unsaturated ester **4** with predominant *Z* selectivity[6] in 44% yield (*Z*/*E*, 2:1). Both the isomers were separable by silica gel column chromatography and the ester **4** was subjected to reduction with DIBAL-H to provide precursor **6** in 75% yield. Compound **6** was subjected to epoxidation with *m*-CPBA to furnish a mixture of

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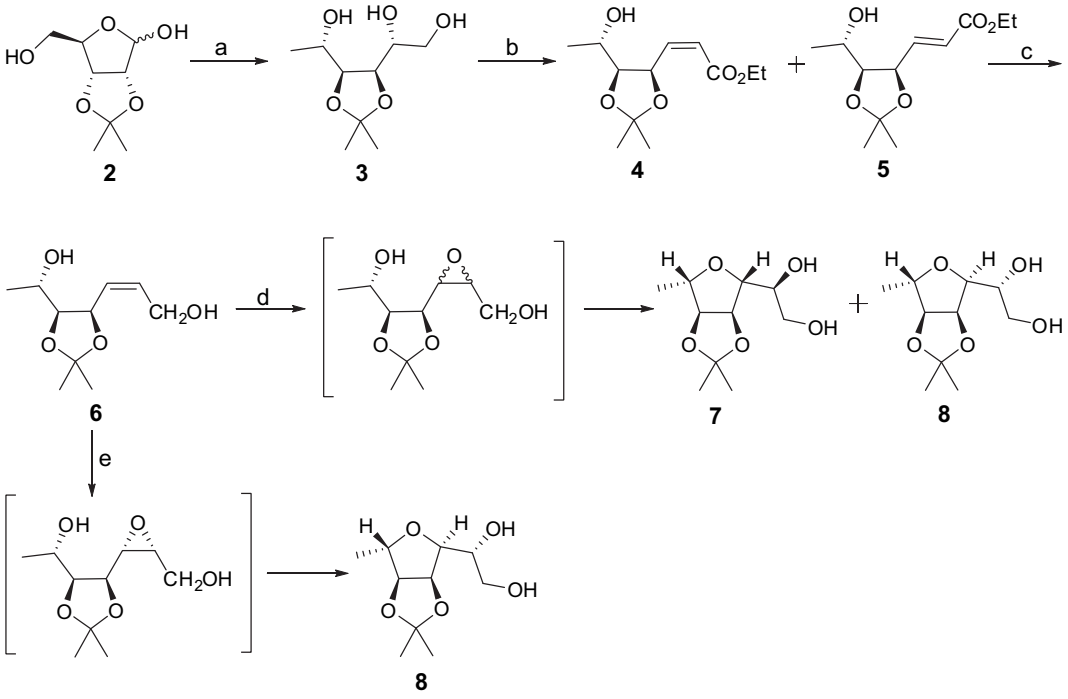
epoxide and cyclic diol. Although, pure epoxide could not be purified from this reaction mixture, it cyclized to form diols **7** and **8** during chromatography. These diols are obtained in 55% yield in the ratio of 1:1.[7] Subsequently, we also attempted to cyclize crude epoxide using CSA but no significant improvement in the yields of the diols could be noticed. Then, the allylic alcohol **6** was subjected to Sharpless epoxidation[8] to give a diol, which is identical in all respects to **8** formed by the reaction of *m*-CPBA. The stereochemistry of **8** having been established, the other isomer **7**, which is of the right stereochemical configuration for the synthesis of (+)-**1** was advanced further for cross metathesis reaction.

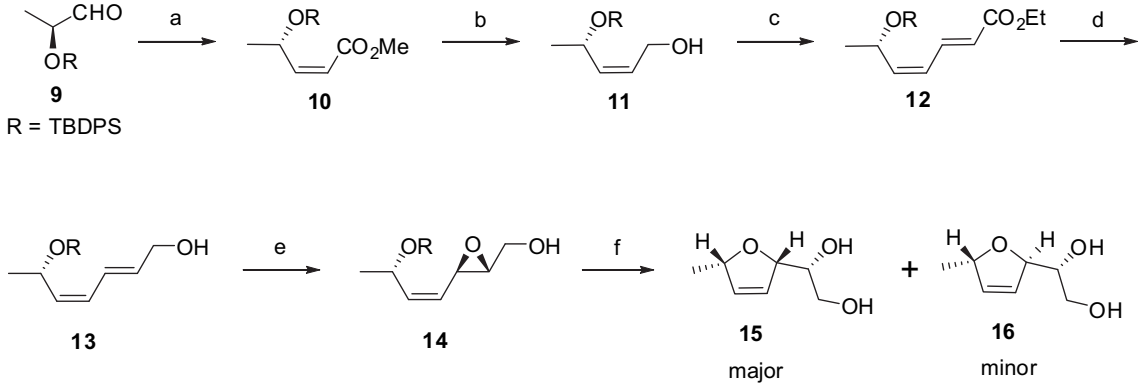
As depicted in Scheme 2, the protected lactaldehyde **9** (obtained from ethyl (*S*)-lactate[9]) was subjected to olefination reaction using Still–Gennari procedure[10] to afford the corresponding α, β-unsaturated ester **10** with prominent *Z*-stereochemistry in 77% yield. Compound **10** on reduction with DIBAL-H gave corresponding alcohol **11** (85%), which was later oxidized under Swern reaction conditions to give the corresponding aldehyde. Wittig olefination reaction with stabilized $Ph_3P{=}CHCO_2Et$ ylide afforded **12** (78%) with predominant trans-selectivity. DIBAL-H reduction of **12** followed by Sharpless epoxidation[11] gave **14** in 75% yield. Initially, we had proposed to synthesize the dihydrofuran[12] ring by opening the epoxide



Scheme 1. Reagents and conditions: (a) (i) CH_3MgI, Et_2O, 0 °C-rt, 3 h (71%); (b) (i) $NaIO_4$, THF/H_2O (9:1), 0 °C-rt, 3 h, (77%); (ii) $Ph_3P{=}CHCO_2Et$, cat. $PhCO_2H$, toluene, 90 °C, 4 h (65% of 4 and 5) (*Z*/*E*, 2:1); (c) DIBAL-H, CH_2Cl_2, 0 °C, 3 h (75%); (d) *m*-CPBA, CH_2Cl_2, 0 °C-rt, 24 h, silicagel, (27.5% of **7** and 27.5% of **8**); (e) (−)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −20 °C, 10 days (47%).

Since the key intermediate **7** formed from D-(−)-ribose for cross metathesis reaction is only to an extent of 27.5% in the mixture of diols (**7** and **8**), we also explored the synthesis of the furanoside moiety starting from ethyl (*S*)-lactate, a commercially available synthon, as shown below.

after deprotection of silyl ether, however, desilylation of **14** with TBAF gave a mixture of dihydrofurans **15** and **16** (75:25) along with small amounts of the uncyclized compound. Therefore, we treated the reaction mixture with CSA to ensure the complete cyclization and the major diol **15** was separated in 68% yield.



Scheme 2. Reagents and conditions: (a) $(F_3CCH_2O)_2POCH_2CO_2Me$, NaH, THF, −78 °C, 3 h (77%); (b) DIBAL-H, CH_2Cl_2, 0 °C, 2 h (85%); (c) (i) $(COCl)_2$ DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h (80%); (ii) $Ph_3P{=}CHCO_2Et$, benzene, rt, 6 h (78%); (d) DIBAL-H, CH_2Cl_2, 0 °C, 4 h (82%); (e) (−)-DET, $Ti(O^iPr)_4$, cumene hydroperoxide, CH_2Cl_2, −20 °C, 3 h (75%); (f) (i) TBAF, THF, 0 °C to rt, 24 h; (ii) cat. CSA, CH_2Cl_2, 6 h (68%).

Our next goal was the dihydroxylation[13] of the double bond of **15** to introduce hydroxyl groups with high diastereoselectivity for an efficient varitriol synthesis. Initially the diol **15** was protected with acetonide and dihydroxylation was carried out using OsO_4 in the presence of NMO to yield the secondary diol **19a** as an inseparable mixture. To explore the separation of this diol, it was again protected with acetonide but to our dismay the corresponding diols **20x** and **20y** were found to be formed in poor diastereoselectivity (70:30). Therefore, we attempted to improve the diastereoselectivity by changing the protective group of the diol **15** with TBS followed by dihydroxylation (**19b**) and acetonide protection, which gave **21** with maximum diastereoselectivity (95:5). This may be not only due to 2,5-*syn* hydrogens, but also due to bulkiness of TBS substituent, dictating the approach of OsO_4 from the more sterically accessible top face (Fig. 1). Due to clarity of proton interactions, the stereochemistry of the major diastereomer **20x** was assigned by the key NOE correlations (Fig. 2). The H-6 of CH_3 proton has shown NOE correlation with H-4, which is *syn* to H-3, whereas both H-3 and H-4 correlated with α-CH_3 of the acetonide ring. H-2 and H-5 protons correlated with each other and H-2 correlated with H-7. All these correlations confirmed stereochemistry of the compound **20x** (Scheme 3).

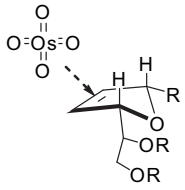


Fig. 1. Attack of OsO_4.

The diol, **7** or **22** (**7** obtained from D-(−)-ribose or **22** from ethyl (*S*)-lactate) was treated with TPP, imidazole and iodine in toluene at 50 °C to afford **23** in 75% yield (Scheme 4).[14] Since this compound showed exactly opposite sign of optical rotation compared with Jenning's molecule,[3a] we concluded that product **23** is of the right configuration required for the cross metathesis

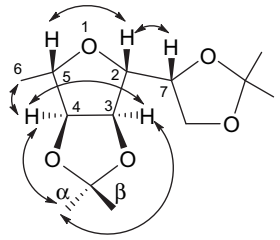
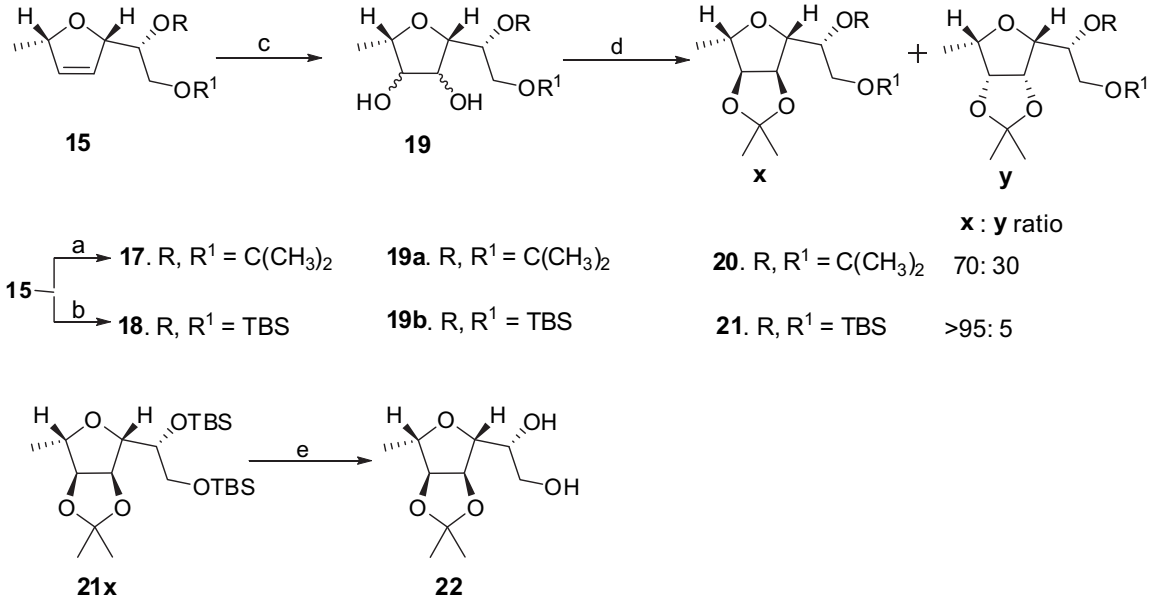


Fig. 2. NOESY correlations for compound **20x**

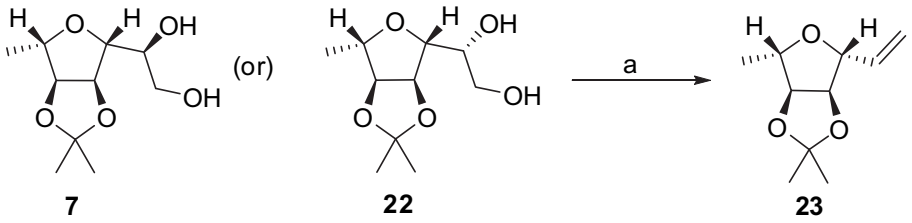
reaction in the next step. With the successful synthesis of furanoside moiety, we proceeded further with the synthesis of the aromatic part.

Scheme 5 depicts the synthetic sequence developed for the synthesis of aromatic part. Initially, propargyl alcohol was protected as PMB ether **24**[15] and was converted to **25** in excellent yield by deprotonating acetylenic proton with *n*-BuLi followed by quenching with ethyl chloroformate.[16] The required 1-methoxy cyclohexa-1, 4-diene was prepared from anisole by Birch reduction,[17] which on treating with dienophile **25** in the presence of catalytic amount of dichloromaleic anhydride in a sealed tube at 180 °C for 7 h gave adduct **26** in 75% yield.[18] Deprotection of PMB group of **26** unexpectedly led to the formation of lactone **27**. To overcome this drawback, the ester **26** was initially subjected to reduction with DIBAL-H in CH_2Cl_2 to obtain primary alcohol **28**, which was protected as TBS ether to get **29** (90%). Next, the cleavage of the PMB ether was carried out using DDQ in CH_2Cl_2 and pH 7 buffer to furnish the alcohol **30** (72%), which on Dess–Martin periodinane[19] (DMP) oxidation followed by Wittig olefination with Ph_3PCH_3Br gave aromatic fragment **32** in 70% yield.

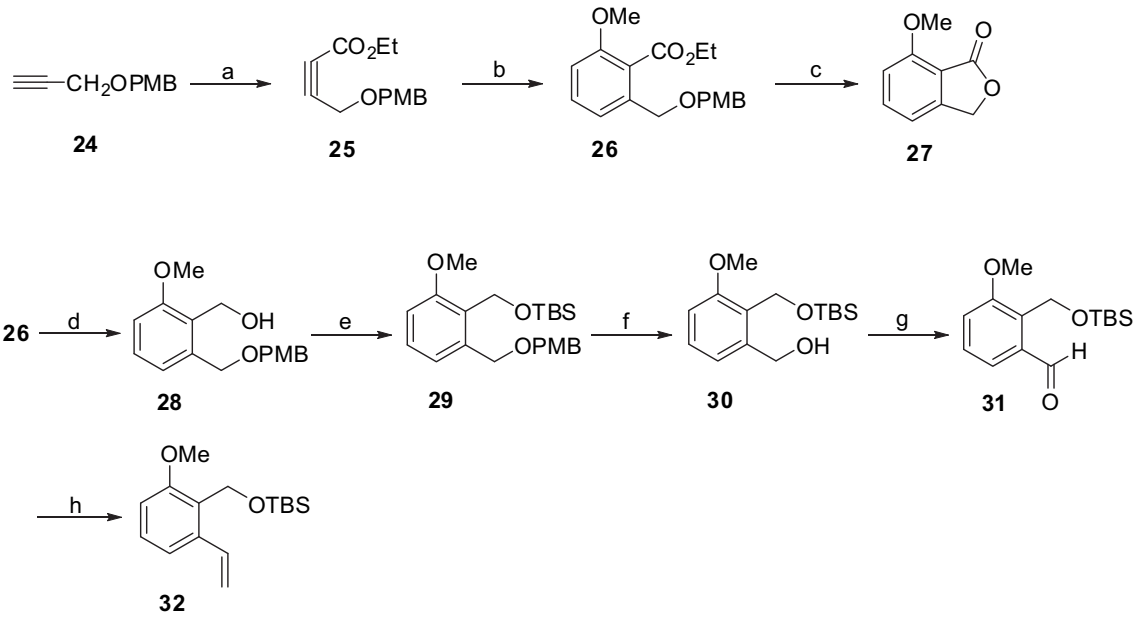
With the two fragments **23** and **32** in hand, merging of the two olefins was carried out with Grubbs cross metathesis[20] reaction. Treatment of **23** and **32** with the Grubbs second generation catalyst in CH_2Cl_2 provided the protected varitriol in 55% yield. Deprotection of TBS and acetonide groups with 1 N HCl in THF resulted in the target compound (+)-varitriol **1** in 70% yield (Scheme 6). All the analytical data were in close agreement with the reported values.[2a,3a]



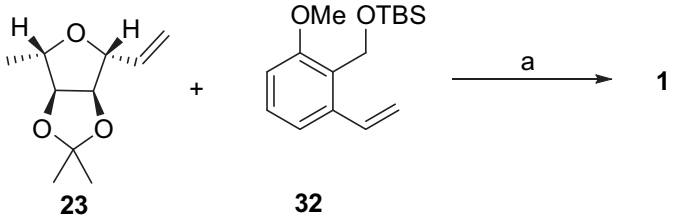
Scheme 3. Reagents and conditions: (a) 2,2 DMP, cat. CSA, CH_2Cl_2, 2 h (87%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C-rt, 12 h (72%); (c) OsO_4, NMO, acetone:water (4:1), 0 °C, 15 h (70%); (d) 2,2 DMP, cat. CSA, acetone, 6 h (85% of **21x**); (e) TBAF, THF, rt 12 h (68%).



Scheme 4. Reagents and conditions: (a) TPP, I_2, imidazole, toluene, 50 °C, 30 min (75%).



Scheme 5. Reagents and conditions: (a) *n*-BuLi, $ClCO_2Et$, THF, −78 °C-rt, 45 min (92%); (b) 1-methoxy cyclohexa-1,4-diene, dichloromaleic anhydride, neat, 180 °C, 7 h (75%); (c) DDQ, CH_2Cl_2/buffer pH=7 (18:2), 0 °C-rt, 3 h (75%); (d) DIBAL-H, CH_2Cl_2, 0 °C, 4 h (85%); (e) TBDMS/Cl, imidazole, DMAP, CH_2Cl_2, 0 °C-rt, 4 h (90%); (f) DDQ, CH_2Cl_2/buffer pH=7 (18:2), 0 °C-rt, 2 h (72%); (g) DMP, CH_2Cl_2, 0 °C-rt, 1 h (87%); (h) *n*-BuLi, Ph_3PCH_3Br, THF, 0 °C-rt, 2 h (70%).



Scheme 6. Reagents and conditions: (a) (i) Grubbs second generation catalyst, CH_2Cl_2, reflux, 18 h (55%); (ii) 1 M HCl, THF, rt, 3 h, (70%).

3. Conclusion

In summary, the stereoselective total synthesis of (+)-varitriol was accomplished by two different protocols starting from the commercially available D-(−)-ribose and ethyl (*S*)-lactate. The highly diastereocontrolled routes illustrate the utility of epoxidation, cyclization, dihydroxylation, and cross metathesis strategy for the natural (+)-varitriol. The synthesis of other potential analogues is in progress.

4. Experimental section

4.1. General

Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F_{254} to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate, hexane, dichloromethane, and acetone as the eluents. Optical rotation values were recorded on Horiba high sensitive polarimeter and IR spectra were recorded with a Perkin–Elmer FT-IR spectrophotometer. ^1H NMR spectra were recorded with 200, 300, 400, 500 MHz and ^{13}C NMR spectra were recorded with 75 MHz spectrometer using trimethylsilane as an internal standard in $CDCl_3$. Mass spectra were obtained on Finnigan MAT1020B or micromass VG 70–70H spectrometer operating at 70 eV using a direct inlet system. All high resolution mass spectra (HRMS) were recorded on QSTAR XL hybrid MS/MS system equipped with an ESI source (IICT, Hyderabad).

*4.1.1. (R)-1-((4R,5S)-5-((S)-1-Hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (**3**).* To a solution of MeMgI [prepared from Mg (5.3 g, 221.1 mmol) and MeI (13.8 mL, 221.1 mmol)] in anhydrous ether (110 mL) was added 2,3-*O*-isopropylidene-D-ribofuranose

2 (4.2 g, 22.1 mmol) in ether (15 mL) at 0 °C and reaction mixture was slowly warmed to rt and stirred for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (25 mL) and extracted with EtOAc (2×45 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography to afford **3** (3.23 g, 71%) as white solid; R_f (80% EtOAc/hexane) 0.4; mp 71–72 °C; $[\alpha]_D^{28}$+26.2 (*c* 0.01, $CHCl_3$); IR (KBr): *ν* 3320, 2933, 2930, 2873, 1375, 1247, 1221, 1073, 1044, 877 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 1.22–1.40 (9H, m, 3×CH_3), 2.13 (br s, OH), 2.96 (br s, OH), 3.59–3.74 (1H, m, CH_2OH), 3.75–4.15 (5H, m, CH_2OH, C*H*OH, CH_3CH (C*H*)$_2O_2C(CH_3)_2$), 4.47 (br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 20.5, 25.3, 27.8, 64.2, 65.8, 69.5, 77.2, 81.5, 108.6; ESI-MS: *m*/*z* 229 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 229.1207. $C_9H_{18}O_5Na$ requires 229.1202.

*4.1.2. (Z)-Ethyl3-((4R,5S)-5-((S)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (**4**).* To a solution of triol **3** (3.1 g, 15 mmol) in THF/H_2O (9:1, 30 mL) was added $NaIO_4$ (3.86 g, 18 mmol) at 0 °C and stirred for 3 h at rt. The reaction mixture was quenched with saturated $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (2×15 mL). Combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to generate the lactol (2.01 g, 77%) as pale yellow liquid; R_f (25% EtOAc/hexane) 0.4, which was used as such for further reaction. To a solution of the lactol (2 g, 11.4 mmol) in toluene (20 mL) was added carbethoxymethylene triphenylphosphorane (6 g, 17.2 mmol) and catalytic benzoic acid. The mixture was stirred at 90 °C for 4 h. The reaction was allowed to reach rt and quenched with saturated aqueous solution of NaCl and $NaHCO_3$. The layers were partitioned and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic layers were filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give **4** (1.23 g, 44% yield) as pale yellow liquid; R_f (25% EtOAc/hexane) 0.6; $[\alpha]_D^{28}$ −104.7 (*c* 0.02, $CHCl_3$); IR (neat): *ν* 2981, 2935, 1741, 1377, 1208, 1167, 1076, 866 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.17 (3H, d, *J* 6.7 Hz, CH_3), 1.23 (3H, t, *J* 6.7 Hz, OCH_2CH_3), 1.32 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.87 (br s, OH), 3.62–3.73 (1H, m, CH_3CHOH), 4.08 (1H, dd, *J* 6.0, 7.5 Hz, C*H*O$C(CH_3)_2$), 4.13 (2H, q, *J* 6.7 Hz, OCH_2CH_3), 5.44–5.51 (1H, m, C*H*O$C(CH_3)_2$), 5.93 (1H, dd, *J* 1.5, 12.0 Hz, CH=C*H*CO_2Et), 6.21 (1H, dd, *J* 8.3, 11.3 Hz, C*H*=$CHCO_2$Et); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 14.0, 19.6, 25.3, 27.8, 61.0, 66.4, 74.6, 82.8, 109.1, 121.7, 146.5, 166.9; ESI-MS: *m*/*z* 245 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$, found 267.1259. $C_{12}H_{20}O_5Na$ requires 267.1255.

*4.1.3. (Z)-3-((4R,5S)-5-((S)-1-Hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (**6**).* To a solution of *cis* ester **4** (0.97 g, 3.9 mmol) in CH_2Cl_2 (10 mL) at 0 °C was slowly added DIBAL-H (7 mL, 20% solution in toluene, 9.9 mmol) and the mixture was stirred for 3 h at 0 °C. The reaction mixture was quenched with saturated aqueous sodium potassium tartrate (4 mL) and the stirring was continued for 1 h at rt. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by column chromatography resulting in allyl alcohol **6** (0.6 g, 75%) as colorless oil; R_f (50% EtOAc/hexane) 0.4; $[\alpha]_D^{28}$ +31.6 (*c* 0.012, $CHCl_3$); IR (neat): *ν* 3385, 2985, 2932, 1376, 1217, 1063, 1015, 872 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.26 (3H, d, *J* 6.0 Hz, CH_3CH), 1.35 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.68–3.80 (1H, m, CH_3CHOH), 3.84 (1H, dd, *J* 6.0, 9.0 Hz, C*H*O$C(CH_3)_2$), 3.97 (1H, dd, *J* 6.4, 12.2 Hz, CH_2OH), 4.22 (1H, dd, *J* 7.9, 11.8 Hz, CH_2OH), 5.05 (1H, dd, *J* 5.8, 9.6 Hz, C*H*O$C(CH_3)_2$), 5.62 (1H, t, *J* 10.7 Hz, olefin), 5.83–5.97 (1H, m, olefin); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 20.8, 25.7, 28.3, 57.2, 65.7, 73.7, 82.3, 109.0, 130.6, 131.5; ESI-MS: *m*/*z* 225 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 225.1111. $C_{10}H_{18}O_4Na$ requires 225.1102.

*4.1.4. (S)-1-((3aR,4R,6S,6aS)-2,2,6-Trimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethane-1,2-diol (**7**).* To a stirred solution of the allyl alcohol **6** (0.35 g, 1.73 mmol) in CH_2Cl_2 (15 mL) *m*-CPBA (1.06 g, 4.33 mmol, 70% purity) was added slowly at 0 °C. Then the reaction mixture was warmed to rt and stirred until the starting material disappeared. Later, the reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) solution and extracted with CH_2Cl_2 (2×5 mL). The layers were separated and the aqueous layer was again extracted with EtOAc (10 mL) and the combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to furnish the diol **7** (0.1 g, 27.5%) as pale yellow liquid; R_f (70% EtOAc/hexane) 0.5; $[\alpha]_D^{28}$ −31.2 (*c* 0.005, $CHCl_3$); IR (neat): *ν* 3416, 2981, 2932, 1378, 1212, 1075, 865 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.31 (3H, d, *J* 6.7 Hz, CH_3), 1.34 (3H, s, CH_3), 1.53 (3H, s, CH_3), 2.31 (br s, OH), 2.54 (br s, OH), 3.73–3.79 (3H, m, C*H*OH, CH_2OH), 3.91–3.96 (1H, m, furanoside), 3.96–4.06 (1H, m, furanoside), 4.25 (1H, dd, *J* 5.2, 6.7 Hz, furanoside), 4.70 (1H, dd, *J* 4.5, 6.7 Hz, furanoside); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 18.8, 25.4, 27.3, 64.6, 71.1, 80.8, 82.0, 85.5, 85.7, 114.8; ESI-MS: *m*/*z* 241 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 241.1157. $C_{10}H_{18}O_5Na$ requires 241.1152.

*4.1.5. (R)-1-((3aR,4S,6S,6aS)-2,2,6-Trimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethane-1,2-diol (**8**).* R_f (70% EtOAc/hexane) 0.4; $[\alpha]_D^{28}$ +9.54 (*c* 0.011, $CHCl_3$); IR (neat): *ν* 3515, 2976, 2937, 1378, 1211, 1111, 1059, 901 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.15 (3H, d, *J* 6.7 Hz, CH_3CH), 1.30 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.76 (br s, OH), 3.30 (br s, OH), 3.68–3.84 (2H, m, C*H*OH, CH_2OH), 3.90 (1H, dd, *J* 3.7, 6.0 Hz, CH_2OH), 4.03–4.10 (1H, m, furanoside), 4.29 (1H, q, *J* 6.7 Hz, furanoside), 4.48 (1H, d, *J* 6.0 Hz, furanoside), 4.76 (1H, dd, *J* 3.7, 6.0 Hz, furanoside); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 16.8, 24.5, 26.0, 63.4, 70.9, 78.8, 79.5, 81.0, 86.5, 112.6.

*4.1.6. (S,Z)-Methyl4-(tert-butyldiphenylsilyloxy)pent-2-enoate (**10**).* To a stirred suspension of NaH (1.13 g, 28.3 mmol) in dry THF (50 mL) at 0 °C under nitrogen was added bis-(2,2,2-trifluoroethyl) (methoxy-carbonylmethyl) phosphonate (6.91 g, 21.7 mmol) in dry THF (20 mL) very slowly and stirred for 30 min. Later, the reaction mixture was cooled to −78 °C and a solution of aldehyde **9** (5.9 g, 18.9 mmol) in dry THF (15 mL) was added drop wise. After stirring for 3 h at −78 °C the reaction mixture was quenched with saturated NH_4Cl solution (20 mL) and stirred at rt for 30 min. The two layers were separated and the aqueous layer was extracted with ether (2×35 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography to afford the ester **10** (5.35 g, 77%) as colorless liquid; R_f (5% EtOAc/hexane) 0.6; $[\alpha]_D^{28}$ +45.6 (*c* 0.011, $CHCl_3$); IR (neat): *ν* 3068, 2934, 2893, 2858, 1723, 1197, 1110, 1071, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.05 (9H, s, C(CH_3)$_3$), 1.23 (3H, d, *J* 5.8 Hz, CH_3), 3.50 (3H, s, OCH_3), 5.31–5.51 (2H, m, CH_3CH, olefin), 6.21 (1H, dd, *J* 8.0, 11.7 Hz, olefin), 7.21–7.40 (6H, m, ArH), 7.53–7.67 (4H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 19.1, 23.2, 26.9, 50.9, 66.6, 116.4, 127.3, 127.4, 129.5, 134.0, 134.1, 135.72, 137.76, 153.8, 165.8; ESI-MS: *m*/*z* 391 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 391.1711. $C_{22}H_{28}O_3NaSi$ requires 391.1705.

*4.1.7. (S,Z)-4-(tert-Butyldiphenylsilyloxy)pent-2-en-1-ol (**11**).* To a solution of ester **10** (4.5 g, 12.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C under nitrogen, was slowly added DIBAL-H (21.7 mL, 20% solution in toluene, 30.5 mmol) and the mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with saturated aqueous sodium potassium tartrate (10 mL) and later stirring was continued for 1 h at rt.

The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by column chromatography to give the alcohol **11** (3.53 g, 85%) as colorless oil; R_f (15% EtOAc/hexane) 0.4; $[\alpha]_D^{28}$ +20.6 (*c* 0.015, $CHCl_3$); IR (neat): ν 3345, 3069, 3018, 2962, 2932, 2858, 1108, 1080, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.04 (9H, s, $C(CH_3)_3$), 1.19 (3H, d, *J* 6.0 Hz, CH_3), 3.56–3.72 (2H, m, CH_3CH, CH_2OH), 4.45–4.57 (1H, m, CH_2OH), 5.23–5.34 (1H, m, olefin), 5.54 (1H, dd, *J* 9.8, 11.3 Hz, olefin), 7.29–7.45 (6H, m, ArH), 7.60–7.69 (4H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 24.7, 27.0, 58.3, 65.7, 96.2, 127.3, 127.4, 127.6, 129.7, 134.0, 134.1, 135.8, 136.0, 136.1; ESI-MS: *m*/*z* 363 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 363.1745. $C_{21}H_{28}O_2NaSi$ requires 363.1756.

*4.1.8. (S,2E,4Z)-Ethyl 6-(tert-butyldiphenylsilyloxy)hepta-2,4-dienoate (**12**).* To a stirred solution of oxalyl chloride (1.3 mL, 15 mmol) in CH_2Cl_2 (30 mL) at −78 °C under nitrogen DMSO (2.1 mL, 30 mmol) was added and stirred for 15 min followed by the addition of compound **11** (3.4 g, 10 mmol) in CH_2Cl_2 (10 mL). The contents were stirred for 1 h at −78 °C. The reaction mixture was quenched with Et_3N (8.4 mL, 60 mmol) and diluted with CH_2Cl_2 (20 mL) and then allowed the reaction mixture to come to rt. The reaction was then diluted with water (40 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was passed through a pad of silica gel to give the corresponding aldehyde (2.7 g, 80%), which was used as such for further reaction. To a solution of the aldehyde (2.65 g, 7.84 mmol) in benzene (25 mL) was added ethoxycarbonylmethylene triphenylphosphorane (3.27 g, 9.4 mmol) and the mixture was stirred at rt for 6 h and quenched with saturated aqueous solution of NaCl. The layers were partitioned and the aqueous phase was extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to give **12** (2.49 g, 78% yield) as pale yellow liquid; R_f (5% EtOAc/hexane) 0.5; $[\alpha]_D^{28}$ +59.6 (*c* 0.013, $CHCl_3$); IR (neat): ν 3068, 2965, 2933, 2895, 2859, 1715, 1266, 1180, 1136, 1110, 1084, 1041, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (9H, s, $C(CH_3)_3$), 1.22 (3H, d, *J* 5.8 Hz, CH_3), 1.26 (3H, t, *J* 6.5 Hz, OCH_2CH_3), 4.13 (2H, q, *J* 6.5 Hz, OCH_2CH_3), 4.71–4.80 (1H, m, CH_3CH), 5.67 (1H, d, *J* 15.3 Hz, $CH{=}CHCO_2Et$), 5.75–5.89 (2H, m, olefin), 7.04 (1H, dd, *J* 10.9, 15.3 Hz, $CH{=}CHCO_2Et$), 7.26–7.41 (6H, m, ArH), 7.56–7.68 (4H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 19.2, 24.6, 27.1, 59.9, 66.0, 96.2, 122.5, 124.6, 127.6, 127.6, 129.7, 133.5, 133.9, 135.7, 135.8, 138.5, 143.3, 165.9; ESI-MS: *m*/*z* 431 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 431.2016. $C_{25}H_{32}O_3NaSi$ requires 431.2018.

*4.1.9. (S,2E,4Z)-6-(tert-Butyldiphenylsilyloxy)hepta-2,4-dien-1-ol (**13**).* To a solution of unsaturated ester **12** (2.25 g, 5.51 mmol) in CH_2Cl_2 (20 mL) at 0 °C under nitrogen was slowly added DIBAL-H (9.8 mL, 20% solution in toluene, 13.7 mmol) and the mixture was stirred for 4 h at the same temperature. The reaction was quenched with saturated aqueous sodium potassium tartrate (5 mL) and the stirring was continued for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by column chromatography to give the allyl alcohol **13** (1.65 g, 82%) as colorless oil; R_f (30% EtOAc/hexane) 0.5; $[\alpha]_D^{28}$ +48.1 (*c* 0.01, $CHCl_3$); IR (neat): ν 3393, 3069, 2962, 2930, 2893, 2857, 1109, 1080, 989, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (9H, s, $C(CH_3)_3$), 1.20 (3H, d, *J* 6.0 Hz, CH_3CH), 3.96 (2H, d, *J* 5.2 Hz, CH_3CH, CH_2OH), 4.60–4.73 (1H, m, CH_2OH), 5.48 (1H, t, *J* 9.8 Hz, olefin), 5.55–5.66 (1H, m, $CH{=}CHCH_2OH$), 5.75 (1H, t, *J* 11.3 Hz, olefin), 5.85 (1H, dd, *J* 11.3, 15.1 Hz, $CH{=}CHCH_2OH$), 7.26–7.40 (6H, m, ArH), 7.58–7.69 (4H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 24.6, 27.0, 63.2, 65.9, 96.2, 126.2, 127.4, 127.6, 129.4, 129.5, 132.7, 134.1, 134.4, 135.9, 136.0, 136.1; ESI-MS: *m*/*z* 389 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 389.2638. $C_{23}H_{30}O_2NaSi$ requires 389.2634.

*4.1.10. ((2R,3R)-3-((S,Z)-3-(tert-Butyldiphenylsilyloxy)but-1-enyl)oxiran-2-yl)methanol (**14**).* Crushed and activated 4 Å molecular sieves were added to a stirred solution of CH_2Cl_2 (35 mL) under nitrogen. The flask was cooled to −20 °C, $Ti(O^iPr)_4$ (1.54 mL, 5.2 mmol) and (−)-DET (1 mL, 6.16 mmol) were added and stirred for 15 min. The allylic alcohol **13** (1.6 g, 4.37 mmol) in CH_2Cl_2 (5 mL) was added and stirred at the same temperature for 20 min and then cumene hydroperoxide (1.36 mL, 7.86 mmol) was added slowly. After the addition, the reaction was maintained at the same temperature with stirring for 3 h. Tartaric acid aqueous solution (15% w/v) was added at rt and stirring was continued until clear phases were reached (1 h). The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, concentrated, and diluted with Et_2O followed by the addition of precooled 10% (w/v) aqueous NaOH solution. The two-phase mixture was stirred vigorously for 15 min at 0 °C. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine and concentrated under reduced pressure. The crude product obtained was purified by silica gel column chromatography to furnish the epoxide **14** (1.25 g, 75%) as colorless oil; R_f (30% EtOAc/hexane) 0.4; $[\alpha]_D^{28}$ +39.4 (*c* 0.01, $CHCl_3$); IR (neat): ν 3428, 2962, 2931, 2894, 2858, 1109, 1080, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (9H, s, $C(CH_3)_3$), 1.24 (3H, d, *J* 6.0 Hz, CH_3CH), 2.67–2.73 (1H, m, epoxide), 3.07 (1H, dd, *J* 2.2, 9.0 Hz, epoxide), 3.19–3.32 (1H, m, CH_2OH), 3.60 (1H, d, *J* 12.8 Hz, CH_2OH), 4.58–4.70 (1H, m, CH_3CH), 4.87 (1H, dd, *J* 9.0, 11.3 Hz, olefin), 5.75 (1H, dd, *J* 9.0, 11.3 Hz, olefin), 7.28–7.44 (6H, m, ArH), 7.59–7.69 (4H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1, 24.5, 26.8, 51.1, 59.5, 61.0, 65.9, 124.7, 127.3, 127.6, 129.5, 129.6, 133.9, 135.7, 135.9, 140.9; ESI-MS: *m*/*z* 405 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 405.1857. $C_{23}H_{30}O_3NaSi$ requires 405.1861.

*4.1.11. (R)-1-((2S,5S)-5-Methyl-2,5-dihydrofuran-2-yl)ethane-1,2-diol (**15**).* To a stirred cold solution (0 °C) of the starting material **14** (4.25 g, 11.1 mmol) in THF (110 mL) under nitrogen, TBAF (27.8 mL, 1 M in THF, 27.8 mmol) was added slowly. The mixture was allowed to warm up to rt and was monitored by TLC (24 h). The reaction was quenched with saturated NH_4Cl solution (25 mL), extracted with EtOAc (2×25 mL), and concentrated under reduced pressure. The crude product was filtered through a short silica gel column and concentrated. To a solution of this product in CH_2Cl_2 (55 mL) camphorsufonic acid (1 g, 4.45 mmol) was added. The mixture was stirred at rt and monitored by TLC (6 h). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to afford the diol **15** (1 g, 68%) as yellow liquid; R_f (90% EtOAc/hexane) 0.5; $[\alpha]_D^{28}$ −5.8 (*c* 0.012, $CHCl_3$); IR (neat): ν 3387, 2971, 2927, 2868, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, d, *J* 6.7 Hz, CH_3CH), 1.85 (br s, OH), 2.79 (br s, OH), 3.57 (1H, dd, *J* 5.2, 9.8 Hz, CH_2OH), 3.61–3.76 (2H, m, CH_2OH, $CHOH$), 4.70–4.78 (1H, m, $CH{-}CHOH$), 4.84–4.95 (1H, m, CH_3CH), 5.80–5.92 (2H, m, olefin); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 63.4, 74.2, 82.2, 86.9, 126.5, 132.7; EIMS: *m*/*z* 144.

*4.1.12. (R)-2,2,3,3,8,8,9,9-Octamethyl-5-((2S,5S)-5-methyl-2,5-dihydrofuran-2-yl)-4,7-dioxa-3,8-disiladecane (**18**).* To a solution of

compound **15** (0.49 g, 3.4 mmol) in CH_2Cl_2 (5 mL) 2,6-lutidine (2.37 mL, 20.4 mmol) and TBSOTf (2.34 mL, 10.2 mmol) were added sequentially at 0 °C under nitrogen atmosphere. After stirring for 12 h at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (2×5 mL). The extracts were washed with saturated aqueous $CuSO_4$ solution (2×5 mL), water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography to furnish **18** (0.91 g, 72%) as pale yellow liquid; R_f (3% EtOAc/hexane) 0.5; $[\alpha]_D^{28}$ −27.08 (*c* 0.012, $CHCl_3$); IR (neat): *ν* 2942, 2866, 1463, 1143, 1069, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 0.07 (12H, d, *J* 6.0 Hz, 4×CH_3), 0.89 (18H, d, *J* 4.3 Hz, 2×C(CH_3)$_3$), 1.24 (3H, d, *J* 6.4 Hz, CH_3CH), 3.41–3.51 (1H, m, C*H*OTBS), 3.57 (1H, dd, *J* 5.8, 10.3 Hz, CH_2OTBS), 3.76 (1H, dd, *J* 3.3, 10.3 Hz, CH_2OTBS), 4.54–4.64 (1H, m, C*H*CHOTBS), 4.79–4.90 (1H, m, CH_3C*H*), 5.75 (1H, dd, *J* 1.5, 5.6 Hz, olefin), 5.88 (1H, dd, *J* 1.5, 6.0 Hz, olefin); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* −5.1, −4.4, −3.8, 22.7, 26.1, 26.2, 65.8, 77.8, 81.9, 86.4, 96.2, 128.4, 131.9; ESI-MS: *m*/*z* 395 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 395.2401. $C_{19}H_{40}O_3NaSi_2$ requires 395.2413.

*4.1.13. (3aR,4R,6S,6aS)-4-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2,6-trimethyltetrahydrofuro[3,4-d][1,3]dioxole (**20x**).* Prepared as described for **21x**. R_f (10% EtOAc/hexane) 0.4; $[\alpha]_D^{28}$ −2.1 (*c* 0.009, $CHCl_3$); IR (neat): *ν* 2985, 2934, 1376, 1254, 1213, 1157, 1077, 861 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 1.28 (3H, d, *J* 6.4 Hz, CH_3), 1.34 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.53(3H, s, CH_3), 3.82–3.88 (2H, m, CH_2O, furanoside), 3.97 (1H, qd, *J* 6.4, 4.7 Hz, furanoside), 4.07–4.13 (2H, m, C*H*O, CH_2O), 4.26 (1H, dd, *J* 6.9, 4.7 Hz, furanoside), 4.67 (1H, dd, *J* 6.9, 4.1 Hz, furanoside); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 19.0, 25.1, 25.4, 26.5, 27.6, 66.8, 75.9, 80.6, 82.3, 84.6, 86.0, 109.7, 114.6; ESI-MS: *m*/*z* 281 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 281.1366. $C_{13}H_{22}O_5Na$ requires 281.1364.

*4.1.14. (R)-2,2,3,3,8,8,9,9-Octamethyl-5-((3aR,4S,6S,6aS)-2,2,6-trimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4,7-dioxa-3,8-disiladecane (**21x**).* To a stirred solution of the olefin **18** (0.79 g, 2.12 mmol) in acetone/water (4:1, 10 mL) mixture, OsO_4 catalytic (0.15 mL) and NMO (0.637 g, 5.3 mmol) were added at 0 °C and stirred for 15 h at the same temperature. The reaction mixture was quenched with Na_2SO_3 (2.5 g) and the solvent was evaporated. The residue was diluted with EtOAc (10 mL) and filtered through a small pad of Celite. The aqueous layer was extracted with EtOAc (2×5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography to afford unseparable mixture of diols **19b** (0.6 g, 70%) as yellow liquid; R_f (50% EtOAc/hexane) 0.5. To a solution of the diol **19b** (0.6 g, 1.47 mmol) in acetone (5 mL) at rt was added 2,2-dimethoxypropane (0.27 mL, 2.21 mmol) followed by catalytic camphorsulfonic acid (0.07 g, 0.3 mmol). After 6 h of stirring, the reaction mixture was concentrated, quenched with $NaHCO_3$ (3 mL), extracted with CH_2Cl_2 (2×5 mL), and concentrated. The crude product was purified by column chromatography to give the pure compound **21x** (0.55 g, 85%) as yellow liquid; R_f (5% EtOAc/hexane) 0.4; $[\alpha]_D^{28}$ −12.5 (*c* 0.016, $CHCl_3$); IR (neat): *ν* 2932, 2859, 1254, 1086, 836, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 0.06 (12H, d, *J* 4.5 Hz, 4×CH_3), 0.88 (18H, d, *J* 4.5 Hz, 2×C(CH_3)$_3$), 1.27 (6H, t, *J* 6.0 Hz, 2×CH_3), 1.47 (3H, s, CH_3), 3.48–3.61 (2H, m, C*H*OTBS, CH_2OTBS), 3.72–3.83 (2H, m, CH_2OTBS, furanoside), 3.87(1H, dd, *J* 3.0, 4.5 Hz, furanoside), 4.05 (1H, t, *J* 6.7 Hz, furanoside), 4.69 (1H, dd, *J* 3.7, 6.7 Hz, furanoside); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* −5.49, −5.41, −4.58, −4.52, 18.1, 18.4, 25.6, 25.8, 25.9, 27.5, 29.6, 64.8, 72.8, 79.7, 80.1, 84.5, 85.9, 114.3; ESI-MS: *m*/*z* 447 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$, found 469.1267. $C_{22}H_{46}O_5NaSi_2$ requires 469.1262.

*4.1.15. (R)-1-((3aR,4R,6S,6aS)-2,2,6-Trimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethane-1,2-diol (**22**).* To a solution of compound **21x** (0.51 g, 1.14 mmol) in dry THF (10 mL) under nitrogen, TBAF was added (4.1 mL, 1 M THF solution, 4.11 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred until the starting material disappeared. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography to get the diol **22** (0.169 g, 68%) as pale yellow liquid; R_f (80% EtOAc/Hexane) 0.5; $[\alpha]_D^{28}$ +4.38 (*c* 0.01, $CHCl_3$); IR (neat): *ν* 3420, 2981, 2932, 1377, 1211, 1074, 864 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.24 (3H, d, *J* 6.7 Hz, CH_3CH), 1.28 (3H, s, CH_3), 1.47 (3H, s, CH_3), 3.56 (1H, dd, *J* 6.7, 11.3 Hz, CH_2OH), 3.62–3.77 (3H, m, C*H*OH, CH_2OH, furanoside), 3.83–3.93 (1H, m, furanoside), 4.01 (br s, OH), 4.18 (1H, dd, *J* 4.5, 6.7 Hz, furanoside), 4.66 (1H, dd, *J* 4.5, 6.7 Hz, furanoside); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 18.8, 25.3, 27.3, 63.4, 71.9, 80.3, 81.7, 84.2, 85.8, 114.6; ESI-MS: *m*/*z* 241 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 241.1048. $C_{10}H_{18}O_5Na$ requires 241.1051.

*4.1.16. (3aS,4S,6R,6aR)-2,2,4-Trimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxole (**23**).* To a stirred solution of compound **22** (0.122 g, 0.55 mmol) in toluene (5 mL) was added TPP (0.44 g, 1.67 mmol) followed by imidazole (0.145 g, 2.23 mmol) at 50 °C. After 5 min iodine (0.497 g, 1.95 mmol) in toluene (5 mL) was added at the same temperature. After 30 min, the reaction mixture was cooled to rt and quenched with aqueous sodium hydroxide (0.156 g in 5 mL H_2O, 3.91 mmol). The mixture was stirred until virtually all the red deposits were dissolved. The aqueous layer was separated and extracted with EtOAc (10 mL). The organic layer was washed with saturated aqueous $Na_2S_2O_3$ (5 mL), $NaHCO_3$ (5 mL), water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by column chromatography to afford the pure olefin **23** (0.077 g, 75%) as colorless oil; R_f (15% EtOAc/hexane) 0.6; $[\alpha]_D^{28}$ +17.8 (*c* 0.009, $CHCl_3$); IR (neat): *ν* 2923, 2853, 1461,1375, 1247, 1158, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.29 (6H, d, *J* 6.2 Hz, CH_3CH, CH_3), 1.51 (3H, s, CH_3), 3.86–3.97 (1H, m, furanoside), 4.15–4.26 (2H, m, furanoside), 4.37 (1H, dd, *J* 5.0, 6.7 Hz, furanoside), 5.18 (1H, d, *J* 10.5 Hz, CH=CH_2), 5.34 (1H, d, *J* 17.1 Hz, CH=CH_2), 5.87 (1H, ddd, *J* 6.0, 10.5, 16.9 Hz, C*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 19.0, 25.5, 27.4, 80.1, 84.8, 85.4, 86.2, 114.8, 116.9, 136.1; EIMS: *m*/*z* 184 $[M]^+$.

*4.1.17. Ethyl 4-(4-methoxybenzyloxy)but-2-ynoate (**25**).* To a stirred solution of alkyne **24** (3.2 g, 18.18 mmol) in THF (60 mL) at −78 °C under N_2 atmosphere was added *n*-BuLi (1.6 M in hexane, 17 mL, 27.2 mmol) drop wise and stirred for 20 min. Then, ethyl chloroformate (5.2 mL, 54.5 mmol) was added and the solution was warmed to rt and stirred for 45 min and quenched with a saturated $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with Et_2O (2×15 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography afforded the pure alkynoate **25** (4.14 g, 92%) as pale yellow liquid; R_f (5% EtOAc/hexane) 0.4; IR (neat): *ν* 2939, 2840, 2236, 1713, 1513, 1250, 1090, 1057 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.33 (3H, t, *J* 6.8 Hz, CH_3), 3.79 (3H, s, OCH_3), 4.16–4.29 (4H, m, 2×OCH_2), 4.53 (2H, s, OCH_2Ph), 6.83 (2H, d, *J* 9.0 Hz, ArH), 7.24 (2H, d, *J* 8.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 13.8, 55.0, 56.1, 61.9, 71.5, 78.0, 83.1, 113.7, 128.6, 129.6, 152.9, 159.4; EIMS: *m*/*z* 248 $[M]^+$.

*4.1.18. Ethyl 2-methoxy-6-((4-methoxybenzyloxy)methyl)benzoate (**26**).* A neat solution of 1-methoxy cyclohexa-1,4-diene (3.19 g, 29.0 mmol), which is obtained by Birch reduction and alkynoate **25** (3.6 g, 14.5 mmol) and a catalytic amount of dichloromaleic anhydride (5 mg) were heated at 180 °C for 7 h in a sealed tube. Later, the reaction mixture was cooled to rt, diluted with EtOAc (35 mL) and washed with aqueous 10% $NaHCO_3$ solution followed by brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was

evaporated to give the crude product, which was purified by column chromatography to yield **26** (3.59 g, 75%) as pale yellow liquid; R_f (15% EtOAc/hexane) 0.4; IR (neat): ν 2937, 2841, 1724, 1588, 1512, 1467, 1250, 1112, 1066, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, J 7.5 Hz, CH_3), 3.79 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.32 (2H, q, J 7.5 Hz, OCH_2), 4.43 (2H, s, OCH_2), 4.57 (2H, s, OCH_2), 6.86 (3H, d, J 8.3 Hz, ArH), 7.02 (1H, d, J 7.5 Hz, ArH), 7.27 (2H, t, J 8.3 Hz, ArH), 7.33 (1H, d, J 7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 55.1, 55.9, 61.0, 69.4, 71.8, 110.6, 113.6, 120.3, 122.8, 129.3, 130.0, 130.3, 137.2, 156.5, 159.0, 167.5; ESI-MS: m/z 353 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 353.1362. $C_{19}H_{22}O_5Na$ requires 353.1364.

*4.1.19. (2-Methoxy-6-((4-methoxybenzyloxy)methyl)phenyl)methanol (**28**).* To a stirred solution of **26** (3.2 g, 9.69 mmol) in dry CH_2Cl_2 (30 mL) under nitrogen atmosphere DIBAL-H (17.2 mL, 20% solution in toluene, 24.2 mmol) was added drop wise at 0 °C and stirred for 4 h at the same temperature. The reaction mixture was quenched with saturated sodium potassium tartrate (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by silica gel chromatography to furnish **28** (2.37 g, 85%) as yellow liquid; R_f (25% EtOAc/hexane) 0.4; IR (neat): ν 3455, 3000, 2937, 2839, 1610, 1587, 1513, 1466, 1256, 1066, 1035, 1006 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.80 (br s, OH), 3.78 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.47 (2H, s, OCH_2), 4.55 (2H, s, OCH_2), 4.67 (2H, s, OCH_2), 6.77–6.90 (4H, m, ArH), 7.14–7.28 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.0, 55.5, 56.0, 70.6, 71.9, 110.8, 113.7, 122.1, 128.5, 128.4, 128.5, 129.4, 137.6, 157.8, 159.1; ESI-MS: m/z 311 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 311.1258. $C_{17}H_{20}O_4Na$ requires 311.1254.

*4.1.20. tert-Butyl(2-methoxy-6-((4-methoxybenzyloxy)methyl)benzyloxy)dimethylsilane (**29**).* To a stirred solution of **28** (2.1 g, 7.29 mmol) in dry CH_2Cl_2 (20 mL) under N_2 atmosphere were added imidazole (1.18 g, 18.2 mmol) followed by catalytic amount of DMAP (10 mg) and TBDMSCl (1.31 g, 8.75 mmol) at 0 °C. The resulting mixture was stirred for 4 h at rt. The reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by silica gel column chromatography to afford the TBS ether **29** (2.63 g, 90%) as pale yellow liquid; R_f (5% EtOAc/hexane) 0.5; IR (neat): ν 2952, 2892, 2855, 1513, 1466, 1252, 1068, 839, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.0 (6H, s, 2×CH_3), 0.85 (9H, s, C(CH_3)$_3$), 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.47 (2H, s, OCH_2), 4.63 (2H, s, OCH_2), 4.75 (2H, s, OCH_2), 6.76 (1H, d, J 8.3 Hz, ArH), 6.82 (2H, d, J 6.9 Hz, ArH), 7.06 (1H, d, J 7.7 Hz, ArH), 7.16–7.29 (3H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3, 18.3, 25.9, 55.1, 55.5, 55.6, 69.1, 72.0, 110.0, 113.7, 120.7, 126.9, 128.5, 129.2, 130.4, 139.5, 157.1, 159.0; ESI-MS: m/z 425 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 425.2112. $C_{23}H_{34}O_4NaSi$ requires 425.2124.

*4.1.21. (2-((tert-Butyldimethylsilyloxy)methyl)-3-methoxyphenyl) methanol (**30**).* To a stirred solution of **29** (1.8 g, 4.47 mmol) in CH_2Cl_2/buffer solution (pH=7) [prepared from NaH_2PO_4 and Na_2HPO_4] (18:2 mL) was added DDQ (1.52 g, 6.71 mmol) at 0 °C. The reaction mixture was warmed to rt and stirring was continued for 2 h. The mixture was quenched with saturated $NaHCO_3$ (10 mL) and filtered through a small pad of Celite. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography to afford the alcohol **30** (0.9 g, 72%) as pale yellow liquid; R_f (15% EtOAc/hexane) 0.5; IR (neat): ν 3438, 2932, 2890, 2856, 1588, 1466, 1257, 1041, 838, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.09 (6H, s, 2×CH_3), 0.89 (9H, s, C(CH_3)$_3$), 3.49 (1H, t, J 5.8 Hz, CH_2OH), 3.83 (3H, s, OCH_3), 4.61 (2H, d, J 5.8 Hz, OCH_2), 4.90 (2H, s, OCH_2), 6.81 (1H, d, J 7.8 Hz, ArH), 6.95 (1H, d, J 7.8 Hz, ArH), 7.23 (1H, t, J 7.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2, 26.0, 55.5, 56.4, 64.3, 96.2, 110.3, 122.3, 126.9, 129.2, 142.9, 156.9; ESI-MS: m/z 305 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 305.1556. $C_{15}H_{26}O_3NaSi$ requires 305.1548.

*4.1.22. 2-((tert-Butyldimethylsilyloxy)methyl)-3-methoxybenzaldehyde (**31**).* To a solution of compound **30** (0.2 g, 0.7 mmol) in dry CH_2Cl_2 (4 mL) under nitrogen at 0 °C, was added Dess–Martin periodinane (0.451 g, 1.06 mmol), the solution was warmed to rt and stirred for 1 h. Later the reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) and saturated $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 mL) and washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by the column chromatography to furnish the aldehyde **31** (0.172 g, 87%) as colorless liquid; R_f (7% EtOAc/hexane) 0.5; IR (neat): ν 2936, 2890, 2855, 1693, 1586, 1465, 1257, 1064, 838, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.04 (6H, s, 2×CH_3), 0.86 (9H, s, C(CH_3)$_3$), 3.87 (3H, s, OCH_3), 5.09 (2H, s, OCH_2), 7.07 (1H, d, J 7.1 Hz, ArH), 7.35 (1H, t, J 7.7 Hz, ArH), 7.50 (1H, d, J 7.7 Hz, ArH), 10.50 (1H, s, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3, 18.2, 25.7, 54.6, 55.9, 115.6, 120.0, 128.7, 131.6, 136.2, 156.7, 192.6; ESI-MS: m/z 319 $[M+K]^+$.

*4.1.23. tert-Butyl(2-methoxy-6-vinylbenzyloxy)dimethylsilane (**32**).* To a stirred solution of Ph_3PCH_3Br (0.516 g, 1.4 mmol) in THF (7 mL) under nitrogen, n-BuLi (1.6 M in hexane, 0.67 mL, 1.07 mmol) was added at 0 °C, brought to rt and stirred for 30 min. Then the reaction mixture was cooled to 0 °C, aldehyde **31** (0.15 g, 0.53 mmol) in THF (2 mL) was added, warmed to rt and stirred for 2 h. The reaction mixture was quenched with water (5 mL) and extracted with ether (2×5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by column chromatography to afford the olefin **32** (0.1 g, 70%) as colorless liquid; R_f (5% EtOAc/hexane) 0.4; IR (neat): ν 2953, 2891, 2855, 1575, 1468, 1256, 1067, 838, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.11 (6H, s, 2×CH_3), 0.95 (9H, s, C(CH_3)$_3$), 3.88 (3H, s, OCH_3), 4.87 (2H, s, OCH_2), 5.37 (1H, dd, J 1.4, 10.9 Hz, olefin), 5.72 (1H, dd, J 1.4, 17.5 Hz, olefin), 6.80 (1H, d, J 8.0 Hz, ArH), 7.14–7.27 (3H, m, olefin, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2, 18.4, 25.9, 55.5, 55.9, 109.8, 115.9, 118.3, 126.3, 128.5, 135.0, 139.6, 157.3; ESI-MS: m/z 301 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 301.1592. $C_{16}H_{26}O_2NaSi$ requires 301.1599.

*4.1.24. (+)-Varitriol (**1**).* To oven-dried 25 mL two necked round-bottom flask fitted with a reflux condenser was added Grubbs second generation catalyst (10 mg, 0.01 mmol) under argon atmosphere followed by dry degassed CH_2Cl_2 (1 mL). The compound **23** (25 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was added followed by **32** (50 mg, 0.18 mmol) in CH_2Cl_2 (2 mL). The solution was refluxed for 18 h and later the reaction mixture was cooled slowly to rt. The organic solvent was evaporated under reduced pressure and purified by column chromatography to give the protected varitriol (32 mg, 55%) as pale yellow oil; R_f (20% EtOAc/hexane) 0.5. Later a solution of protected varitriol (23 mg, 0.05 mmol) in THF (3 mL) was stirred with 1 M HCl (3 mL) for 3 h at rt. The reaction mixture was quenched with Na_2CO_3 and the resulting mixture was extracted with EtOAc (3×5 mL). The extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product obtained was purified by column chromatography to result in natural (+)-varitriol **1** (10 mg, 70%) as colorless oil; R_f (30% acetone/dichloromethane) 0.3; $[\alpha]_D^{28}$ +18.1 (*c* 0.005, MeOH); [lit.[2a] $[\alpha]_D^{25}$ +18.5 (*c* 2.30, MeOH)]; IR (neat): ν 3353, 2922, 1576, 1361, 1256, 1086 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 1.27 (3H, d, J

5.7 Hz, C*H*$_3$CH), 3.62 (1H, t, *J* 4.8 Hz, OH), 3.70 (1H, q, *J* 5.7 Hz, C*H*OH), 3.80–3.85 (4H, m, OCH$_3$, C*H*CH$_3$), 3.91 (1H, q, *J* 3.8 Hz, C*H*OH), 4.03 (1H, d, *J* 4.8 Hz, OH), 4.24 (1H, br s, OH), 4.29 (1H, t, *J* 4.8 Hz, C*H*–CH=CH–Ar), 4.71 (2H, d, *J* 4.8 Hz, C*H*$_2$OH), 6.20 (1H, dd, *J* 6.7, 15.4 Hz, olefin), 6.89 (1H, d, *J* 7.7 Hz, ArH), 7.09–7.15 (2H, m, olefin, ArH), 7.22 (1H, t, *J* 7.7 Hz, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ 19.4, 55.3, 56.0, 76.4, 77.1, 80.0, 85.2, 110.6, 119.2, 127.9, 129.3, 129.4, 132.4, 138.9, 158.8; ESI-MS: *m*/*z* 303 [M+Na]$^+$; HRMS (ESI): [M+Na]$^+$, found 303.1212. $C_{15}H_{20}O_5Na$ requires 303.1208.

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