

Elaiolide: Synthesis of monomeric unit

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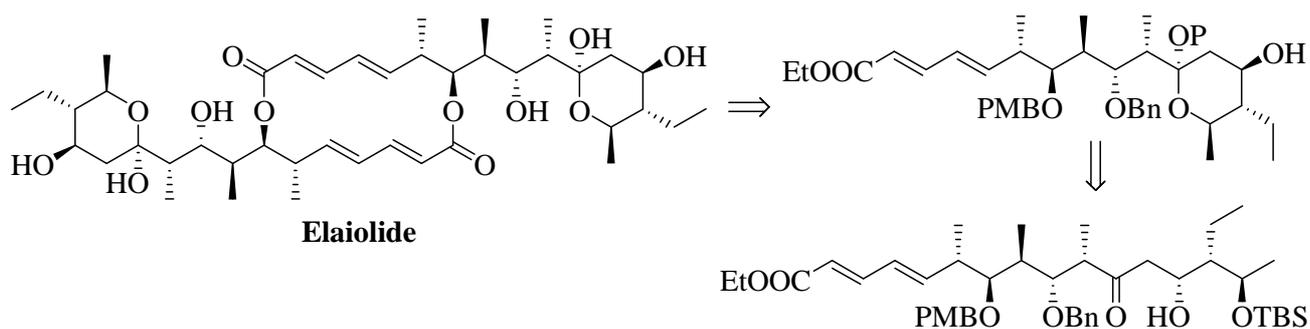


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Experimental Section

General Remarks: Unless otherwise mentioned, all reactions were carried out under an inert atmosphere of argon or nitrogen using standard syringe, septa and cannula techniques. All glassware was flame/oven-dried and cooled under an inert atmosphere of nitrogen unless otherwise stated. Solvents THF, Et₂O were distilled from Na-benzophenone ketyl, CH₂Cl₂, DMF, were distilled from CaH₂, under N₂ atmosphere. Column chromatography was performed using silica gel (60-120 mesh) and the column was usually eluted with ethyl acetate-petroleum ether. Analytical thin layer chromatography (TLC) was performed on precoated silica gel-60 F₂₅₄ (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light or by dipping the plates to H₂SO₄-β-naphthol or MeOH-anisaldehyde-H₂SO₄-acetic acid or and heating the plates at 120 °C. ¹H NMR spectra were recorded at 500, 400, 300, 200 MHz & ¹³C NMR spectra were recorded at 100, 75, 50 MHz in CDCl₃ using Tetramethylsilane as the reference standard. s, brs, d, dd, ddd, dt, t, q, quin, and m refer to singlet, broad singlet, doublet, doublet of doublet, doublet of doublet of doublet, doublet of triplet, triplet, quartet, quintet and multiplet respectively unless otherwise mentioned. Infrared spectra were recorded on Perkin-Elmer Infrared-683 spectrophotometer with NaCl optics. Spectra were calibrated against the polystyrene absorption at 1610cm⁻¹. Samples were scanned neat, KBr wafers or in chloroform as a thin film. The optical rotations were measured on JASCO DIP-360 Digital Polarimeter. Mass spectra were recorded on Micro Mass VG-7070H mass spectrometer for ESI and are given in mass units (m/z). High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

(2S,3R,4R,5S,6S)-3-(benzyloxy)-5-hydroxy-N-methoxy-7-(4-methoxybenzyloxy)-N-2,4,6-tetramethylheptanamide (9): AlMe₃ (9.7 mL, 2.0 M in toluene, 19.42 mmol) was added over a 10 min period to a stirred suspension of MeONHMe.HCl (1.89 g, 19.42 mmol) in DCM (50 mL) at 0 °C, and mixture was stirred for 1 h allowing the temperature to raise to room temperature. Then, a solution of *epi*-lactone **5** (2.0 g, 4.85 mmol) in DCM (40 mL + 5mL rinse) was cannulated into the suspension drop wise and stirred for 3 h. After the reaction was completed, p^H 8.0 phosphate buffer (20 mL) (1mL per mmol of AlMe₃) was added and the stirring was continued for 15 min. The reaction mixture was diluted with CHCl₃ (20 mL), filtered through a pad of celite and washed thoroughly with CHCl₃. The aqueous layer was extracted with CHCl₃ (3x 30 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated in *vacuo*. The residue obtained was purified by silica gel column

chromatography using 23% EtOAc/hexane to give the amide **9** (2.26 g) in 98.48% yield. $R_f = 0.25$ (30% EtOAc/hexane). $[\alpha]_D^{23} -8.2$ ($c = 1.9$, CHCl_3); IR (KBr): ν_{max} 3462, 2964, 2930, 1657, 1614, 1512, 1459, 1415, 1381, 1247, 1174, 1078, 1034, 993, 820, 755 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.40 – 7.27 (m, 5H, *Ar*), 7.24 (d, $J = 8.5$ Hz, 2H, OCH_2ArOMe), 6.85 (d, $J = 8.5$ Hz, 2H, OCH_2ArOMe), 4.65 (s, $J = 8.3$ Hz, 2H, OCH_2ArOMe), 4.42 (s, $J = 8.0$ Hz, 2H, OCH_2Ar), 3.93 – 3.83 (m, 2H, $-\text{OCH}_2\text{CH}(\text{CH}_3)$), 3.79 (s, 3H, $\text{OCH}_2\text{ArOCH}_3$), 3.63 – 3.53 (m, 4H, $-\text{NOCH}_3$, $-\text{CH}(\text{OH})-$), 3.49 (dd, $J = 8.7, 5.8$ Hz, 1H, $-\text{CHOBn}$), 3.40 – 3.23 (m, 1H, CH_3CHCO), 3.16 (s, 3H, $-\text{NCH}_3$), 1.93 – 1.78 (m, 1H, $-\text{CH}_2\text{CH}(\text{CH}_3)$), 1.74 (dd, $J = 6.1, 3.7$ Hz, 1H, $-(\text{CH}_3)\text{CHCHOBn}$), 1.29 (d, $J = 6.8$ Hz, 3H, $(\text{OBn})\text{CHCH}(\text{CH}_3)\text{CO}$), 1.05 (d, $J = 7.0$ Hz, 3H, $-\text{CH}(\text{CH}_3)\text{CH}-\text{OBn}$), 0.79 (d, $J = 6.8$ Hz, 3H, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}-$); ^{13}C NMR (75 MHz, CDCl_3): δ 176.30, 158.96, 137.82, 130.73, 129.13, 128.43, 127.99, 127.84, 113.57, 86.61, 76.50, 73.68, 72.88, 72.41, 61.41, 55.21, 38.67, 36.65, 36.54, 32.15, 14.07, 13.57, 10.68; ESI-MS (m/z): 474 $[\text{M}+\text{H}]^+$; HRMS: calculated for $\text{C}_{27}\text{H}_{40}\text{NO}_6$ $[\text{M}+\text{H}]^+$: 435.2855 found 435.2859.

(2S,3R,4S)-3-(benzyloxy)-N-methoxy-4-((4S,5S)-2-(4-methoxybenzyl)-5-methyl-1,3-dioxan-4-yl)-N,2-dimethylpentanamide (10): To a stirred solution of azeotropically dried Weinreb amide **9** (2.16 g, 4.56 mmol) in DCM (40 mL) at 0 °C was added DDQ (1.14 g, 5.02 mmol) at a time. The chocolate colored suspension was slowly warmed to RT and stirred for 2 h. Then the reaction mixture was quenched slowly by the addition of aq. Sat. NaHCO_3 solution (100 mL), stirred for 15 min, the layers were separated and aqueous layer was extracted with DCM (4x50 mL). The combined organic layers were given brine wash, dried over anhy. Na_2SO_4 , filtered, concentrated under reduced pressure and purification of resulted residue by column chromatography on silica gel using 20% EtOAc/hexane furnished PMB acetal **10** (1.87 g) in 87.0 % yield. $[\alpha]_D^{24} +54.9$ ($c = 1.35$, CHCl_3); IR (KBr): ν_{max} 2926, 2848, 1710, 1613, 1519, 1416, 1387, 1250, 1218, 1093, 1032, 829 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.42 – 7.23 (m, 7H, *Ar*), 6.87 (d, $J = 8.8$ Hz, 2H, *Ar*), 5.28 (s, 1H, $\text{MeOArCHO}-$), 4.59 (d, $J = 10.9$ Hz, 1H, ArCH_ACH_B), 4.34 (d, $J = 10.9$ Hz, 1H, ArCH_ACH_B), 4.07 (dd, $J = 11.1, 4.6$ Hz, 1H, $-\text{OCH}_A\text{H}_B\text{CH}(\text{CH}_3)$), 3.94 (dd, $J = 9.3, 3.1$ Hz, 1H, $\text{OCH}_A\text{H}_B\text{CH}(\text{CH}_3)$), 3.81 (s, 3H, ArOCH_3), 3.78 (dd, $J = 9.8, 1.3$ Hz, 1H, $-\text{CHOCHArOMe}$), 3.63 (s, 3H, $-\text{NOCH}_3$), 3.44 (t, $J = 11.1$ Hz, 1H, $-\text{CHOBn}$), 3.17 (s, 3H, $-\text{NCH}_3$), 3.10 (qd, $J = 7.0, 2.8$ Hz, 1H, $\text{CH}_3\text{CHCO}-$), 2.10 – 1.97 (m, 1H, $-\text{CH}_2\text{CH}(\text{CH}_3)$), 1.97 – 1.87 (m, 1H, $-(\text{CH}_3)\text{CHCHOBn}$), 1.21 (d, $J = 7.0$ Hz, 3H, $\text{CH}(\text{CH}_3)\text{CO}$), 0.99 (d, $J = 7.0$ Hz, 3H, $-\text{CH}(\text{CH}_3)\text{CH}-\text{OBn}$), 0.71 (d, $J = 6.7$ Hz, 3H, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}$); ^{13}C NMR (75 MHz, CDCl_3): δ 7.02, 159.70, 138.68, 131.58, 128.22, 128.18, 127.45, 127.30, 113.39, 100.66, 81.40, 79.81, 74.22, 73.23, 61.02, 55.24, 37.93, 37.31, 32.59, 30.50, 11.97, 10.41, 9.94; ESI-MS (m/z): 494 $[\text{M}+\text{Na}]^+$; HRMS: calculated for $\text{C}_{27}\text{H}_{38}\text{NO}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 435.2147 found 435.2146.

(3S,4R,5S)-4-(benzyloxy)-5-((4S,5S)-2-(4-methoxybenzyl)-5-methyl-1,3-dioxan-4-yl)-3-

methyl hexan-2-one (11): The above PMB acetal **10** (1.77 g, 3.75 mmol) was taken in Et₂O (30 mL) and cooled to -15 °C using ice-salt mixture. MeLi (15.0 mL, 1.0M solution in Et₂O) was added drop wise over a 15 min period and the reaction mixture was stirred for ½ h at -15 °C. Then, sat. aq. solution of. NH₄Cl (40 mL) was added slowly at 0 °C, the layers were separated, aqueous layer was extracted with Et₂O (3x30 mL), the combined organic layers were washed with brine, dried over anhy.Na₂SO₄ and filtered; the solvent was removed in *vacuo*. The resulting residue was purified on silica gel column by eluting with 15% EtOAc/hexane to furnish methyl ketone **11** (1.6 g) in quantitative yield. $[\alpha]_D^{24} +103.2$ ($c = 1.25$, CHCl₃); IR (KBr): ν_{\max} 2945, 2853, 1724, 1713, 1537, 1403, 1271, 1133, 1051, 829 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.39 (d, $J = 8.5$ Hz, 2H, *Ar*), 7.36 – 7.22 (m, 5H, *Ar*), 6.90 (d, $J = 8.5$ Hz, 2H, *Ar*), 5.32 (s, 1H, MeOArCHO-), 4.43 (ABq, $J = 11.2$ Hz, 2H, ArCH₂), 4.12 – 4.00 (m, 2H, -OCH₂CH(CH₃)), 3.81 (s, 3H, CH₃OAr), 3.77 (dd, $J = 10.2, 1.3$ Hz, 1H, -CHOCHArOMe), 3.45 (t, $J = 11.0$ Hz, 1H, -CHOBn), 2.71 (qd, $J = 6.7, 2.2$ Hz, 1H, CH₃CHCO-), 2.16 (s, 3H, -COCH₃), 2.12 – 2.00 (m, 1H, -CH₂CH(CH₃)), 1.94 (dd, $J = 15.0, 7.7$ Hz, 1H, -(CH₃)CHCHOBn), 1.18 (d, $J = 7.0$ Hz, 3H, -CH(CH₃)CO-), 0.96 (d, $J = 7.0$ Hz, 3H, -CH(CH₃)CH-OBn), 0.73 (d, $J = 6.7$ Hz, 3H, CH₂CH(CH₃)CH-); ¹³C NMR (75 MHz, CDCl₃): δ 11.66, 159.81, 138.49, 131.39, 128.31, 127.64, 127.53, 127.32, 113.53, 100.84, 81.37, 79.79, 73.96, 73.21, 55.26, 49.13, 36.98, 30.49, 28.95, 11.98, 9.86, 9.41; ESI-MS (m/z): 449 [M+Na]⁺; HRMS: calculated for C₂₆H₃₄O₅ Na [M+Na]⁺: 449.2303 found 449.2296.

(2S,3S,4R,5S,6R)-5-(benzyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethyloctane-1,7-diol (12):

DIBAL-*H* (6.0 mL, 25% Sol. in Toluene, 10.56 mmol) was added drop wise to the stirred solution of methyl ketone **11** (1.5 g, 3.52 mmol) in DCM (50 mL) at 0 °C and the reaction mixture was allowed to warm to RT. After 1 h, sat. aq. solution of sodium potassium tartarate (70 mL) was added carefully at 0 °C to quench the reaction. The resulted emulsion type mixture was stirred vigorously until clear separation of two layers was appeared (approx. 1 h). Then the layers were taken in separating funnel, DCM layer was separated, aqueous layer was extracted thoroughly with DCM (5x50 mL), the organic layers were washed with brine, dried over anhy. Na₂SO₄. The volatiles were removed in *vacuo*; resulted residue was purified by silica gel column chromatography using 25 % EtOAc/hexane to furnish pure diol **12** as a colorless liquid (1.347 g, 89.0 % yield). IR (KBr): ν_{\max} 3547, 2942, 2935, 2871, 1593, 1485, 1238, 1108 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.44 – 7.16 (m, 7H, *Ar*), 6.96 – 6.77 (m, 2H, *Ar*), 4.77 (d, $J = 11.7$ Hz, 1H, ArCH_ACH_BO), 4.53 (dd, $J = 11.3, 3.5$ Hz, 2H, MeOArCH₂), 4.44 (d, $J = 10.8$ Hz, 1H, ArCH_ACH_BO), 3.84 (dd, $J = 9.7, 1.7$ Hz, 1H, -CHOCH₂ArOMe), 3.81 – 3.73 (m, 4H, CH₃OAr, -

$\text{CH}(\text{OH})\text{CH}_3$), 3.69 (dd, $J = 7.6, 1.5$ Hz, 1H, $-\text{CHOBN}$), 3.57 (d, $J = 6.3$ Hz, 2H, $\text{HOCH}_2\text{CH}-$), 2.82 (s, 1H, 1°-OH), 2.01 – 1.88 (m, 2H, $2\text{CH}_3\text{CH}-\text{s}$), 1.71 (ddd, $J = 11.4, 6.8, 3.1$ Hz, 1H, $\text{HOCH}_2\text{CH}(\text{CH}_3)\text{CH}$), 1.63 (s, 1H, OH), 1.25 (d, $J = 6.1$ Hz, 3H, $-\text{CH}(\text{OH})\text{CH}_3$), 0.98 – 0.84 (m, 9H, 3CH_3 's); ^{13}C NMR (75 MHz, CDCl_3): δ 159.23, 138.72, 130.71, 129.24, 128.40, 127.52, 127.33, 113.86, 83.31, 81.54, 74.01, 73.34, 69.57, 66.75, 55.28, 42.72, 38.98, 38.63, 22.84, 14.56, 11.35, 11.10; ESI-MS (m/z): 451 $[\text{M}+\text{Na}]^+$; HRMS: calculated for $\text{C}_{25}\text{H}_{34}\text{O}_5$ Na $[\text{M}+\text{Na}]^+$: 435.2147 found 435.2146.

(2R,3R,4R,5R,6S)-5-(benzyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-7-oxooctanal (13):

DMSO (2 mL) was added to IBX (3.25 g, 11.6 mmol) at room temperature and the suspension was stirred for 15 min. Then THF (10 mL) was added, after 5 min of stirring, diol **12** (1.25 g, 2.90 mmol) in THF (13 mL + 5 mL rinse) was added drop wise through cannula and the reaction mixture was stirred for 2 h. After which time the reaction mixture was diluted with ether (15 mL), stirred for 15min, filtered through a pad of celite and washed thoroughly with ether. The filtrate was washed with ice-cold water (10 mL) and the aqueous layer was back extracted with ether (3x20 mL). The combined organic layers were washed with brine, dried over anhy. Na_2SO_4 , filtered, concentrated under reduced pressure. The crude residue obtained was chromatographed on silica gel column using 18% EtOAc/hexane to furnish pure keto-aldehyde **13** (1.07 g, 86 % yield). $R_f = 0.2$ (20% EtOAc/hexane). $[\alpha]_D^{24} +46.7$ ($c = 1.05$, CHCl_3); IR (KBr): ν_{max} 2961, 2947, 2853, 1734, 1724, 1571, 1466, 1251, 1093 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 9.74 (d, $J = 2.5$ Hz, 1H, $-\text{CHO}$), 7.39 – 7.22 (m, 5H, Ar), 7.18 (d, $J = 8.5$ Hz, 2H, Ar), 6.85 (d, $J = 8.6$ Hz, 2H, Ar), 4.49 – 4.33 (m, 3H, MeOArCH_2 , $\text{ArCH}_A\text{H}_B\text{O}-$), 4.25 (d, $J = 11.2$ Hz, 1H, $\text{ArCH}_A\text{H}_B\text{O}-$), 4.00 (dd, $J = 7.9, 1.8$ Hz, 1H, $-\text{CHOBN}$), 3.96 (dd, $J = 8.9, 3.0$ Hz, 1H, $-\text{CHOArOMe}$), 3.78 (s, 3H, CH_3OAr), 2.73 (qd, $J = 9.0, 2.6$ Hz, 2H, $-\text{CHCOCH}_3$, $-\text{CH}(\text{CH}_3)\text{CHO}$), 2.22 (s, 3H, $-\text{COCH}_3$), 1.90 – 1.76 (m, 1H, $\text{MeOArCH}_2\text{OCHCH}(\text{CH}_3)\text{CHOBN}$), 1.19 (d, $J = 7.1$ Hz, 3H, $-\text{CH}(\text{CH}_3)\text{COCH}_3$), 1.04 (d, $J = 7.0$ Hz, 3H, $-\text{CH}(\text{CH}_3)\text{CHO}$), 0.99 (d, $J = 7.1$ Hz, 3H, $-\text{CHCH}(\text{CH}_3)\text{CHOAr}$); ^{13}C NMR (75 MHz, CDCl_3): δ 211.41, 204.52, 159.16, 138.14, 130.43, 128.97, 128.36, 127.58, 127.36, 113.78, 80.61, 79.44, 73.36, 72.83, 55.24, 50.17, 49.32, 39.37, 28.80, 11.48, 11.11, 9.87; ESI-MS (m/z): 449 $[\text{M}+\text{Na}]^+$; HRMS: calculated for $\text{C}_{26}\text{H}_{34}\text{O}_5$ Na $[\text{M}+\text{Na}]^+$: 449.2298 found 449.2309.

(2E,4E,6S,7S,8S,9S)-ethyl-9-(benzyloxy)-7-(4-methoxybenzyloxy)-6,8-dimethyl-11-

oxododeca-2,4-dienoate (4): LiHMDS (5.63 mL, 1.0 M solution in THF, 5.63 mmol) was added drop wise to the stirred solution of phosphonate ester (1.46 g, 5.87 mmol) in THF (20 mL) at -78 °C. After $\frac{1}{2}$ hr, keto-aldehyde **13** (1.0 g, 2.35 mmol) in THF (10 mL) was added drop wise by cannula and the resulting yellow orange colored mixture was stirred at -78 °C for 3 h. After this

time the reaction mixture was quenched with aq. sat. NH_4Cl (10 mL) and extracted with EtOAc (3x 25 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated in *vacuo*. The residue was chromatographed over silica gel (15% EtOAc/hexane) to give keto-ester **4** (1.04 g) in 85% yield as pale yellow color oil. $R_f = 0.36$ (20% EtOAc/hexane).

$[\alpha]_D^{24} +29.3$ ($c = 0.95$, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.39 – 7.21 (m, 5H, Ar), 7.18 (d, $J = 8.5$ Hz, 1H, EtOOC-CH=CH-), 6.84 (d, $J = 8.5$ Hz, 2H, Ar), 6.28 – 6.09 (m, 2H, -CH=CH-CH(CH_3)), 5.78 (d, $J = 15.3$ Hz, 1H, EtOOC-CH=CH-), 4.46 (d, $J = 11.1$ Hz, 1H, - $\text{CH}_A\text{H}_B\text{ArOMe}$), 4.35 (dd, $J = 19.5, 11.1$ Hz, 2H, Ar CH_2O -), 4.20 (q, $J = 7.1$ Hz, 2H, - $\text{COOCH}_2\text{CH}_3$), 4.20 (d, $J = 11.1$ Hz, 1H, - $\text{CH}_A\text{H}_B\text{ArOMe}$), 3.88 (dd, $J = 8.6, 2.7$ Hz, 1H, - CHOBn), 3.79 (s, 3H, Ar OCH_3), 3.57 (dd, $J = 6.9, 1.8$ Hz, 1H, - CHOArOMe), 2.69 (qd, $J = 6.9, 2.2$ Hz, 1H, - HCOCH_3), 2.58 (dd, $J = 13.8, 6.9$ Hz, 1H, =CH-CH(CH_3 -), 2.21 (s, 3H, - COCH_3), 1.92 – 1.77 (m, 1H, MeOAr $\text{CH}_2\text{OCHCH}(\text{CH}_3)\text{CHOBn}$), 1.30 (t, $J = 7.1$ Hz, 3H, $\text{COOCH}_2\text{CH}_3$), 1.17 (d, $J = 7.0$ Hz, 3H, -CH(CH_3) COCH_3), 1.03 (d, $J = 6.8$ Hz, 3H, -CH(CH_3)CH=CH-), 0.94 (d, $J = 7.0$ Hz, 3H, -CHCH(CH_3) CHOAr). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 211.58, 167.19, 159.02, 147.14, 144.84, 138.31, 130.96, 128.96, 28.29, 128.12, 127.48, 127.29, 119.70, 113.70, 81.89, 80.82, 73.60, 72.60, 60.19, 55.24, 49.25, 41.53, 39.18, 28.79, 17.02, 14.28, 11.07, 9.81; ESI-MS (m/z): 545 $[\text{M}+\text{Na}]^+$; HRMS: calculated for $\text{C}_{32}\text{H}_{42}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 545.2874 found 545.2876.

(S)-2-hydroxybut-3-enyl 4-methylbenzenesulfonate (14): To a stirred solution of diol **8** (2.0 g, 0.02 mol) in DCM (30 mL) was added NEt_3 (9.5 mL, 0.07 mol) drop wise, followed by Bu_2SnO (0.56 g, 2.27 mmol) at 0 °C. After ½ hr, Ts-Cl (4.77 g, 0.02 mmol) in DCM (150 mL) was cannulated drop wise into the above solution over ½ hr period at 0 °C and stirring was continued at the same temperature for 7 h. After this time, the reaction mixture was diluted with DCM (70 mL), washed with water, aqueous layer was extracted with DCM (3x50 mL), and combined organic layers were given brine wash, dried over anhy. Na_2SO_4 , filtered, concentrated under reduced pressure, purified over silica gel (30% EtOAc/hexane) to furnish tosyl ether **14** (4.8 g, 87%) as yellow color oil. $R_f = 0.38$ (50% EtOAc/hexane). $[\alpha]_D^{24} +3.1$ ($c = 2.5$, CHCl_3); IR (KBr): ν_{max} 3453, 2926, 2855, 1647, 1598, 1358, 1178, 1096, 972, 817, 667 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.80 (d, $J = 8.3$ Hz, 2H, Ar), 7.36 (d, $J = 8.1$ Hz, 2H, Ar), 5.75 (ddd, $J = 17.0, 10.5, 5.5$ Hz, 1H, -CH=CH $_2$), 5.37 (d, $J = 17.2$ Hz, 1H, -CH=CH $_A\text{H}_B$), 5.24 (d, $J = 10.5$ Hz, 1H, -CH=CH $_A\text{H}_B$), 4.40 (tdd, $J = 5.5, 3.7, 1.8$ Hz, 1H, -CH(OH)CH=CH $_2$ -), 4.06 (dd, $J = 10.2, 3.4$ Hz, 1H, - $\text{OCH}_A\text{H}_B\text{CH}(\text{OH})$ -), 3.91 (dd, $J = 10.2, 7.4$ Hz, 1H, - $\text{OCH}_A\text{H}_B\text{CH}(\text{OH})$ -), 2.45 (s, 3H, CH_3ArSO_3 -); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 145.05, 134.56, 132.47, 129.88, 127.88, 117.97,

72.92, 70.29, 21.58. ESI-MS (m/z): 265 $[M+Na]^+$; HRMS: calculated for $C_{11}H_{14}O_4S Na$ $[M+Na]^+$: 265.0510 found 265.0505.

(S)-2-(tert-butyldiphenylsilyloxy) but-3-enyl 4-methylbenzenesulfonate (15): To a solution of tosyl ether **14** (2.2 g, 9.09 mmol) and imidazole (1.55g, 22.7 mmol) in DCM (25 mL) at 0 °C was added a solution TBDPSCI (2.6 mL, 10.0 mmol) in DCM (2.5 mL). The reaction mixture was warmed to room temperature where stirring was continued for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL), extracted with Et_2O (3x30 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica gel, 14% EtOAc/hexane) to afford 4.3 g of silyl tosyl ether **15** (quantitative yield) as a colorless oil. $R_f = 0.6$ (30% EtOAc/hexane). $[\alpha]_D^{23} -11.6$ ($c = 1.2$, $CHCl_3$); IR (KBr): ν_{max} 3070, 2932, 2858, 1472, 1427, 1365, 1150, 1111, 1030, 995, 960, 822, 701 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 7.67 – 7.52 (m, 6H, *Ar*), 7.46 – 7.22 (m, 8H, *Ar*), 5.70 (ddd, $J = 16.9, 10.5, 6.3$ Hz, 1H, $-CH=CH_2-$), 5.08 (d, $J = 8.1$ Hz, 1H, $-CH=CH_AH_B$), 5.03 (d, $J = 1.0$ Hz, 1H, $-CH=CH_AH_B$), 4.27 (q, $J = 6.0$ Hz, 1H, $-CH(OH)CH=CH_2-$), 3.89 (dd, $J = 9.7, 6.0$ Hz, 1H, $-OCH_AH_BCH(OH)-$), 3.82 (dd, $J = 9.7, 5.1$ Hz, 1H, $-OCH_AH_BCH(OH)-$), 2.42 (s, 3H, CH_3ArSO_3-), 1.03 (s, 9H, $-C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.57, 135.83, 134.72, 133.18, 132.79, 129.66, 127.88, 127.51, 117.61, 127.63, 127.42, 72.39, 71.92, 26.81, 26.49, 21.57, 19.22.; ESI-MS (m/z): 503 $[M+Na]^+$; HRMS: calculated for $C_{27}H_{36}NO_4SSi$ $[M+NH_4]^+$: 498.2129 found 498.2127.

(R)-(but-3-en-2-yloxy)(tert-butyl)diphenylsilane (7a): $NaBH_4$ (1.3 g, 0.03 mol) was added to the DMSO (25 mL) solution of TBDPS ether **15** (4.1g, 8.54 mmol) at 0 °C. The suspension was refluxed for 4 h at 60 °C. The reaction mixture was cooled to RT, diluted with Et_2O (100 mL), quenched with aq. sat. NH_4Cl (25 mL), extracted into Et_2O (3x70 mL), washed with brine, dried (Na_2SO_4), filtered and solvent was removed under reduced pressure. The residue remained was chromatographed over silica gel (4% EtOAc/hexane) to afford olefin **7a** (2.05 g) in 77% yield. $R_f = 0.8$ (20% EtOAc/hexane). $[\alpha]_D^{23} +1.0$ ($c = 0.65$, $CHCl_3$); IR (KBr): ν_{max} 2960, 2861, 1427, 1220, 1108, 823 773 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 7.74 – 7.62 (m, 4H, *Ar*), 7.47 – 7.30 (m, 6H, *Ar*), 5.86 (ddd, $J = 17.0, 10.4, 5.4$ Hz, 1H, $-CH=CH_2-$), 5.09 (d, $J = 17.2$ Hz, 1H, $-CH=CH_AH_B$), 4.95 (d, $J = 10.4$ Hz, 1H, $-CH=CH_AH_B$), 4.30 (quin., $J = 6.3$ Hz, 1H, $CH_3CH(OTBDPS)-$), 1.13 (d, $J = 6.3$ Hz, 3H, CH_3CH-), 1.07 (s, 9H, $-C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.44, 135.87, 134.55, 134.15, 129.48, 129.44, 127.42, 127.38, 112.69, 70.36, 26.97, 24.00, 19.24; ESI-MS (m/z): 333 $[M+Na]^+$; HRMS: calculated for $C_{20}H_{26}OSi Na$ $[M+Na]^+$: 333.1650 found 333.1660.

(2S,3R)-3-(tert-butyldiphenylsilyloxy)-2-ethylbutan-1-ol (16): Olefin **7a** (1.9 g, 6.13 mmol) was dissolved in Et₂O (100 mL) and the solution was cooled to 0 °C. ethyl magnesium bromide (12.3 mL, 2.0 M sol in Et₂O, 0.02 mol) was added drop wise by syringe and the reaction mixture was allowed to warm to 25 °C over a period of 1 h, after which time Cp₂ZrCl₂ (89.5 mg, 0.30 mmol) was added. The suspension was stirred at 25 °C for 12 h. The solution was cooled to 0 °C, a gentle stream of O₂ gas (dried over P₂O₅) was bubbled through the reaction mixture for ½ h at 0 °C and for 1 h at 25 °C. The resultant suspension was diluted with Et₂O (100 mL), washed with 2 N NaOH (25 mL), NH₄Cl (15 mL) and NaHCO₃ (15 mL), dried (Na₂SO₄), filtered, concentrated and the resultant crude containing 9:1 mixture of diastereomers was purified by column chromatography (silica gel, 10% EtOAc/hexanes) to give pure alcohol **16** (1.5 g) in 70 % yield. R_f = 0.15(10% EtOAc/hexane). [α]_D²³ – 6.9 (*c* = 1.4, CHCl₃); IR (KBr): ν_{max} 3485, 2957, 2845, 1434, 1212, 1131, 859, 796 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.69 – 7.56 (m, 4H, *Ar*), 7.45 – 7.23 (m, 6H, *Ar*), 3.99 – 3.82 (m, 2H, -CH₂OH), 3.66 – 3.49 (m, 1H, CH₃CH(OTBDPS)CH-), 2.66 (brs, 1H, 1°-OH), 1.55 – 1.33 (m, 2H, CH₃CH₂-), 1.19 (qt, *J* = 8.6, 4.4 Hz, 1H, -CH(CH₃CH₂)-CH₂OH), 1.01 (d, *J* = 6.4 Hz, 3H, CH₃CH(OTBDPS)-), 0.98 (s, 9H, -C(CH₃)₃), 0.79 (t, *J* = 7.4 Hz, 3H, -CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 135.98, 135.91, 134.12, 132.95, 129.85, 129.60, 127.67, 127.43, 73.18, 62.42, 48.49, 27.00, 21.68, 21.37, 19.26, 12.03; ESI-MS (*m/z*): 357 [M+H]⁺; HRMS: calculated for C₂₂H₃₂O₂Si Na [M+Na]⁺: 379.2064 found 379.2068.

(2R,3R)-3-(tert-butyldiphenylsilyloxy)-2-ethylbutanal (6a): To a well stirred solution of alcohol **16** (0.5 g, 1.40 mmol) in CH₂Cl₂ (15 mL) at rt was added NaHCO₃(0.35 g, 4.21 mmol) and DMP (0.71 g, 1.68 mmol) and the mixture was stirred for 2 h at rt. The reaction mixture was diluted with Et₂O (20 mL), quenched with sat. sodium thiosulphate (10 mL) and stirred for 15 min. The layers were separated and aqueous layer was extracted with ether (3x25 mL). The combined organic layers were dried (Na₂SO₄), filtered, concentrated under reduced pressure and the residue was purified by chromatography (silica gel, 5% EtOAc/hexane) to afford aldehyde **6a** (0.47 g, 95%). R_f = 0.6 (10% EtOAc/hexane). [α]_D²³ –10.1 (*c* = 0.4, CHCl₃); IR (KBr): ν_{max} 2928, 2857, 1704, 1640, 1427, 1220, 1109, 911 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.63 (dd, *J* = 13.8, 3.3 Hz, 1H, -CHO), 7.60 (ddd, *J* = 7.5, 5.9, 1.6 Hz, 4H, *Ar*), 7.44 – 7.23 (m, 6H, *Ar*), 4.10 – 3.98 (m, 1H, CH₃CH(OTBDPS)-), 2.10 – 2.00 (m, 1H, -CH(CH₂CH₃)CHO), 1.75 – 1.57 (m, 1H, CH₃CH_AH_B-), 1.54 – 1.40 (m, 1H, CH₃CH_AH_B-), 1.02 (d, *J* = 6.4 Hz, 3H, CH₃CH(OTBDPS)-), 0.97 (s, 9H, -C(CH₃)₃), 0.77 (t, *J* = 7.5 Hz, 3H, -CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 205.09, 135.89(2C), 134.15, 133.31, 129.83, 129.62, 127.71, 127.47, 69.68,

61.14, 26.93, 21.72, 19.32, 18.90, 11.92; ESI-MS (m/z): 393 $[M+K]^+$; HRMS: calculated for $C_{22}H_{30}O_2Si Na [M+Na]^+$: 377.1912 found 377.1908.

(2R,3R)-3-(tert-butyldimethylsilyloxy)-2-ethylbutanal (6b): To a well stirred solution of the above alcohol (0.64 g, 2.77 mmol) in CH_2Cl_2 (25 mL) at rt was added $NaHCO_3$ (0.7 g, 8.31 mmol) and DMP (1.41 g, 3.32 mmol) and the mixture was stirred for 2 h at rt. The reaction mixture was diluted with Et_2O (25 mL), quenched with saturated sodium thiosulphate (10 mL) and stirred for 15 min. The layers were separated and aqueous layer was extracted with ether (3x25 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated under atmospheric pressure at 20 °C and the residue obtained was purified by column chromatography (silica gel, 4% EtOAc/hexane) to afford aldehyde **6b** (0.59 g, 92%). $R_f = 0.65$ (10% EtOAc/hexane). $[\alpha]_D^{24} - 17.2$ ($c = 0.5$, $CHCl_3$); IR (neat): ν_{max} 2958, 2930, 2884, 2857, 1710, 1472, 1463, 1377, 1256, 1120, 986, 835, 775 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 9.66 (d, $J = 3.9$ Hz, 1H, -CHO), 4.11 – 3.96 (m, 1H, $CH_3CH(OTBS)-$), 2.06 (tt, $J = 6.0, 2.9$ Hz, 1H, - $CH(CH_2CH_3)CHO$), 1.70 (ddq, $J = 9.0, 7.1, 1.5$ Hz, 1H, $CH_3CH_AH_B-$), 1.51 (ddq, $J = 12.5, 7.5, 3.8$ Hz, 1H, $CH_3CH_AH_B-$), 1.19 (d, $J = 6.3$ Hz, 3H, $CH_3CH(OTBDPS)-$), 0.89 (t, $J = 7.3$, 3H, - CH_2CH_3), 0.85 (s, 9H, - $C(CH_3)_3$), 0.04 (s, 3H, -OSi(CH_3)), 0.04 (s, 3H, -OSi(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.59, 68.86, 61.05, 25.70, 22.27, 19.52, 17.93, 11.81, -5.03, -4.17; ESI-MS (m/z): 253 $[M+Na]^+$; HRMS: calculated for $C_{12}H_{27}O_2Si [M+H]^+$: 231.1775 found 231.1777.

(2E,4E,6S,7S,8S,9S,13R,14S,15R)-ethyl-9-(benzyloxy)-15-(tert-butyldimethylsilyloxy)-14-ethyl-13-hydroxy-7-(4-methoxybenzyloxy)-6,8-dimethyl-11-oxohexadeca-2,4-dienoate (3):

LiHMDS (0.29 mL, 1.0 M solution in THF, 0.29 mmol) was added drop wise to the stirring solution of keto-ester **4** (0.07 g, 0.14 mmol) in THF (2.0 mL) at -78 °C and stirring continued for ½ hr. After this time, aldehyde **6b** (0.07 g, 0.29 mmol) in THF (1 mL + 1 mL rinse) was cannulated drop wise into the above lithium enolate at -78 °C and stirring was continued for 3 h at the same temperature. Then the reaction mixture was quenched with aq. Sat. NH_4Cl (3 mL) at -78 °C and slowly warmed to RT. The layers were separated, aq. layer was back extracted into EtOAc (3x10 mL), combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, concentrated under reduced pressure. The residue obtained was purified over silica gel column (10% EtOAc/hexane) to furnish aldol adduct **3** (99.0 mg) in 92% yield as a colorless oil. $R_f = 0.45$ (20% EtOAc/hexane). $[\alpha]_D^{24} +10.9$ ($c = 0.4$, $CHCl_3$); IR (KBr): ν_{max} 2931, 2297, 1713, 1515, 1459, 1251, 1217, 1096, 955, 838, 672 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 7.37 – 6.97 (m, 8H, 7ArH's, - $CH=CH-COOEt$), 6.77 (dd, $J = 16.3, 9.5$ Hz, 2H, Ar), 6.21 – 5.95 (m, 2H, - $CH=CH-$

CH(CH₃)-), 5.69 (d, *J* = 15.4 Hz, 1H, EtOOC-CH=CH-), 4.57 (d, *J* = 18.6 Hz, 1H, ArCH_ACH_B), 4.42 – 4.22 (m, 3H, 2 MeOArCH₂-S, ArCH_ACH_B), 4.16 – 4.01 (m, 3H, CH₃CH₂OOC-,), 3.82 (dd, *J* = 10.9, 8.1 Hz, 1H, -CHOBn), 3.69 (m, 4H, CH₃OAr,), 3.52 – 3.42 (m, 1H, -CHOArOMe), 2.81 (dt, *J* = 17.5, 8.6 Hz, 1H, -COCH_AH_BCH(OH)-), 2.75 – 2.58 (m, 1H, -CHCOCH₃), 2.55 – 2.40 (m, 1H-COCH_AH_BCH(OH)-), 2.39 – 2.25 (m, 1H, =CH-CH(CH₃)-), 1.45-1.33 (m, 2H, CH₃CH₂), 1.26 – 1.14 (m, 6H, 2 CH₃-s), 1.14 – 1.05 (m, 4H, -CH(CH₂CH₃), CH₃), 0.93 (d, *J* = 6.8 Hz, 3H, CH₃CH(OTBS)-), 0.89 – 0.82 (m, 6H, 2 CH₃-s), 0.79 (s, 9H, -C(CH₃)₃), -0.01 (m, 6H, -OSi(CH₃)₂); ¹³C NMR ((75 MHz, CDCl₃): δ 12.58, 167.23, 158.98, 147.28, 144.91, 138.31, 130.96, 128.89, 128.26, 128.11, 127.41, 127.04, 119.65, 113.69, 81.95, 80.61, 73.69, 72.39, 69.94, 67.00, 60.20, 55.23, 49.65, 45.95, 41.53, 39.31, 30.93, 29.68, 25.75, 22.20, 17.37, 17.14, 14.29, 12.47, 11.03, 9.64, -5.23, -4.12; ESI-MS (*m/z*): 775 [M+Na]⁺; HRMS: calculated for C₄₄H₆₈O₈Na Si [M+Na]⁺: 775.4581 found 775.4579.

