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REGULAR ARTICLE

Formal total synthesis of mandelalide A

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Abstract. In this article the formal total synthesis of mandelalide A has been described in details. The highly convergent and flexible strategy developed for mandelalide A involved the construction of key building blocks ***ent*-9** and **7**, and their assembly to the target compound. For the synthesis and coupling of these building blocks, the Brown's crotylation, Sharpless asymmetric dihydroxylation followed by *in situ* Williamson type etherification, modified Prins cyclization, Masamune-Roush olefination and Heck cyclization were employed, the latter being crucial for the highly stereoselective formation of the macrocycle of mandelalide A. Initially, Julia Kocienski olefination, ring-closing metathesis reaction were investigated for the synthesis of the aglycone of the proposed structure of the mandelalide A, and found to be unsuccessful.

Keywords. Cytotoxic; Heck cyclization; natural products; ring closing metathesis; total synthesis.

1. Introduction

Secondary metabolites produced by marine organisms are a rich source of lead molecules for cancer therapy and already many anticancer drugs have been developed based on marine natural products which are in clinical use.[1]

Mandelalides A-D are a new class of macrolides, isolated by Mc. Phail *et al*., from *Lissoclinum ascidian* from South Africa in 2012.[2] Initial bioassay results revealed that among the mandelalides A-D, mandelalide A (Figure 1) showed the most potent biological activity against human NCI- H460 lung cancer cells (IC_{50}, 12 nM) and mouse Neuro-2A neuroblastoma cells (IC_{50}, 29 nM). Very recently mandelalides E-L have been isolated by the same group and reported the structure-activity relationship studies.[3] Architecturally, mandelalide A is a 24-membered macrolide containing three olefinic bonds, two of which were in unusual *E*, *Z*-configured diene. The macrocycle is decorated with 9 chiral centres, a tri-substituted THF unit and tri-substituted THP moiety glycosylated with an unusual L-rhamnose derived pyranoside. The inimitable structural features and promising biological activities together with natural scarcity rendered mandelalide A, a fascinating synthetic target for natural product chemists to attempt its total synthesis. Pioneering efforts from the group led by Frustner resulted in the first total synthesis of the proposed structure of mandelalide A (**1**) and disclosed the incorrect structural assignment of the original molecule.[4a] Shortly thereafter Tao *et al.,* achieved the herculean task of structural revision and establishment of the absolute stereochemistry of mandelalide A, by synthesizing a series of its structural variants.[4b] Subsequently Frustner *et al.,* also synthesized the actual structure of mandelalide A and confirmed the structural revision made by Tao *et al.,*[4c] Recently, three more total syntheses from the groups of Altmann,[4d]

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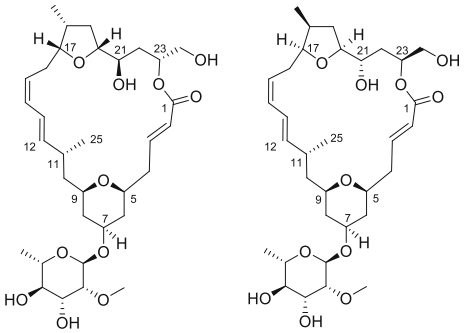


Figure 1. Proposed and revised structures of mandelalide A.

Smith,[4e] Carter[4f] and one synthetic study from the group of Sabitha[4g] were reported. Due to its high biological significance and formidable composition of structure, it led us to design and develop a divergent strategy for the synthesis of mandelalide A and we successfully achieved the synthesis of aglycone of the proposed structure of mandelalide A *via* intramolecular Heck cyclization as a key step.[5] In this article, we wish to report the synthetic study of the proposed structure of mandelalide A and the formal total synthesis of mandelalide A in detail.

2. Experimental

2.1 *General experimental methods*

All the reactions were performed in oven-dried glass apparatus under nitrogen or argon atmosphere under magnetic stirring. Standard methods were used to make anhydrous solvents. Unless otherwise noted, commercially available reagents were used without further purification. Glass columns packed with silica gel (60–120 or 100–200 mesh) were used for column chromatography. ^{1}H and ^{13}C NMR was recorded on 400 MHz, 500 MHz and 100 MHz, 125 MHz spectrometer, respectively, in $CDCl_3$ solvent using TMS as an internal standard. Chemical shifts are measured as ppm values relative to internal $CHCl_3$ δ 7.26 or TMS δ 0.0 for ^{1}H NMR and $CHCl_3$ δ 77 for ^{13}C NMR. In ^{1}H NMR multiplicity defined as: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublet; ddd = doublet of doublet of doublet; dt = doublet of triplet; m = multiplet; brs = broad singlet. Horiba sepa 300 polarimeter was used to record optical rotation using a 2 mL cell with a 10 mm path length. Alpha (Bruker) infrared spectrophotometer was used to record FTIR spectra. Either a TOF or a double focusing spectrometer was used to obtain high-resolution mass spectra (HRMS) $[ESI]^+$.

2.2 *(3R,4S)-6-(tert-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-3-methylhexan-1-ol* **(16)**

To a stirred solution of **11** (20 g, 54.50 mmol) in dry THF (150 mL) was added $BH_3{\cdot}SMe_2$ (6 mL, 60.0 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for another 12 h at the same temperature and then treated with aqueous NaOH (3 M solution, 100 mL), 30% H_2O_2 (50 mL). After stirring for 2 h at room temperature, the mixture was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed sequentially with saturated aqueous $Na_2S_2O_3$ (40 mL), brine (40 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave crude residue which was purified by column chromatography (SiO_2, 60–120 mesh, 12% EtOAc/hexane) to furnish **16** (17.6 g, 83%) as colourless oil. R_f = 0.5 (SiO_2, 20% EtOAc/hexane); $[\alpha]_D^{25}$ = −10.6 (*c* 0.3, $CHCl_3$); IR (Neat): ν_{max} 3391, 2927, 2855, 1612, 1513, 1462, 1301, 1248, 1173, 1059, 834, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.45 (ABq, J = 10.8 Hz, 2H), 3.79 (s, 3H), 3.73–3.67 (m, 3H), 3.64–3.59 (m, 1H), 3.49–3.45 (m, 1H), 1.99–1.94 (m, 1H), 1.72–1.67 (m, 2H), 1.62–1.55 (m, 1H), 1.53–1.48 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 130.8, 129.3, 113.7, 79.4, 71.5, 60.6, 59.8, 55.2, 35.5, 33.6, 32.6, 25.9, 18.3, 15.2, –5.30, –5.32. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{21}H_{38}O_4NaSi$ 405.2431, found 405.2439.

2.3 *tert-Butyl ((3S,4R,E)-8-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(4-methoxybenzyloxy)-4-methyloct-6-enyloxy)dimethylsilane* **(17)**

To a stirred solution of **16** (16 g, 41.88 mmol) in dry CH_2Cl_2 (150 mL) was added $NaHCO_3$ (3.52 g, 41.88 mmol) followed by Dess-Martin periodinane (26.6 g, 62.82 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 1 h at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and $Na_2S_2O_3$ (80 mL) and extracted with EtOAc (2 × 500 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure furnished crude aldehyde which was passed through a short pad of silica gel and used as such for the next reaction.

To a stirred solution of sulfone **12** (21.2 g, 62.82 mmol) in THF (100 mL) at −78 °C was added KHMDS (125.6 mL, 0.5 M in toluene, 62.82 mmol) under argon atmosphere. After stirring for 30 min, the crude aldehyde in THF (30 mL) was added to the reaction mixture at −78 °C *via* cannula. After being stirred for 3 h at −78 °C, the reaction was quenched with water (10 mL) and extracted with EtOAc (2 × 400 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 60–120 mesh, 7% EtOAc/hexane) afforded **17** (16.4 g, 81% yield over two steps) as a colourless oil. R_f = 0.5 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = −25.0 (*c* 3, $CHCl_3$); IR (Neat):

ν_{max} 2954, 2930, 2856, 1612, 1512, 1462, 1369, 1301, 1246, 1172, 1156,1062, 1037, 831, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.48 (dt, J = 15.1, 6.7 Hz, 1H), 5.38 (dt, J = 15.1, 6.7 Hz, 1H), 4.42 (ABq, J = 10.9 Hz, 2H), 4.14–4.07 (m, 1H), 4.03–3.97 (m, 1H), 3.80 (s, 3H), 3.72–3.65 (m, 2H), 3.59–3.53 (m, 1H), 3.41 (q, J = 4.2 Hz, 1H), 2.43–2.33 (m, 1H), 2.26–2.16 (m, 1H), 2.15–2.06 (m, 1H), 1.89–1.79 (m, 2H), 1.69–1.61 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 0.91–0.81 (m, 12H), 0.04 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 132.1, 131.1, 129.2, 126.2, 113.7, 108.8, 78.8, 75.6, 71.2, 68.8, 59.9, 55.2, 36.8, 36.2, 35.7, 33.2, 26.8, 25.9, 25.6, 18.2, 14.4, –5.28, –5.33. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{28}H_{48}O_5NaSi$ = 515.3163, found 515.3165.

2.4 *(3S,4R,E)-1-(tert-Butyldimethylsilyloxy)-8-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyloct-6-en-3-ol* **(10)**

To a stirred solution of **17** (15 g, 30.8 mmol) in $CHCl_3$: pH = 7 phosphate buffer (20:1, 100 ml) was added DDQ (13.8 g, 60.8 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (2 × 400 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 10% EtOAc/hexane) to afford **10** (10.74 g, 94% yield) as a clear oil. R_f = 0.3 (SiO_2, 15% EtOAc/hexane); $[\alpha]_D^{25}$ = −2.0 (*c* 0.7, $CHCl_3$); IR (Neat): ν_{max}3509 (br), 2931, 2858, 1462, 1370, 1253, 1156, 1064, 971, 835, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.56–5.48 (m, 1H), 5.43–5.36 (m, 1H), 4.11 (q, J = 6.6 Hz, 1H), 4.03–3.98 (m, 1H), 3.94–3.90 (m, 1H), 3.83–3.78 (m, 1H), 3.65–3.61 (m, 1H), 3.59–3.55 (m, 1H), 3.44 (brs, OH), 2.42–2.35 (m, 1H), 2.27–2.19 (m, 2H), 1.92–1.85 (m, 1H), 1.66–1.60 (m, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 0.9 (s, 9H), 0.86 (d, J = 6.9 Hz, 3H), 0.08 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.2, 126.1, 108.8, 75.7, 75.6, 68.8, 63.1, 38.8, 36.8, 35.5, 34.6, 26.8, 25.8, 25.6, 18.0, 15.1, –5.58, –5.56. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{20}H_{40}O_4NaSi$ = 395.2588, found 395.2591.

2.5 *(R)-1-((2R,4R,5R)-5-(2-(tert-Butyldimethylsilyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol* **(9)**

To a stirred solution of **10** (9 g, 24.2 mmol) in dry CH_2Cl_2 (70 mL) was added Et_3N (5.2 mL, 36.2 mmol) followed by MsCl (2.6 mL, 31.46 mmol) dropwise at 0 °C under nitrogen atmosphere and stirred for 1.5 h at rt. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (2 × 400 mL). The combined organic layers were washed with water (40 mL), brine (40 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided the mesylate compound which was used directly without further purification.

The above mesylate compound was added to a solution of AD-mix-β (67.6 g) and $MeSO_2NH_2$ (4.6 g, 48.4 mmol) in *t*-BuOH:water (1:1, 500 mL) at 0 °C. The reaction mixture was stirred for 72 h at this temperature before being quenched by slow addition of $Na_2S_2O_5$ (69.0 g, 363 mmol) and stirred for additional 0.5 h. Then the reaction mixture was diluted with water, and extracted with EtOAc (2 × 400 mL).The combined organic layers were washed with water (40 mL), brine (40 mL), dried over Na_2SO_4 and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 13% EtOAc/hexane) afforded **9** (7.4 g, 81% yield over two steps) as clear oil. R_f = 0.3 (SiO_2, 20% EtOAc/hexane); $[\alpha]_D^{25}$ = +22.2 (*c* 0.45, $CHCl_3$); IR (Neat): ν_{max} 3463 (br), 2955, 2859, 1461, 1370, 1253, 1095, 1063, 834, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ4.37–4.31 (m, 1H), 4.10 (dd, J = 8.0, 5.9 Hz, 1H), 4.02–3.96 (m, 1H), 3.79–3.66 (m, 3H), 3.62–3.54 (m, 2H), 2.64 (brs, OH), 2.37 (q, J = 7.3 Hz, 1H), 2.06 (dt, J = 14.3, 7.2 Hz, 1H), 1.72–1.53 (m, 4H), 1.41 (s, 3H), 1.37 (s, 3H), 1.35–1.29 (m, 1H), 0.95 (d, J = 7 Hz, 3H), 0.9 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.4, 81.8, 78.7, 73.5, 71.9, 69.8, 60.8, 37.8, 36.2, 35.7, 34.0, 26.9, 25.9, 25.7, 18.4, 14.9, –5.4. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{20}H_{40}O_5NaSi$ = 411.2537, found 411.2529.

2.6 *(2-((2R,3R,5R)-5-((R)-1-(Benzyloxy)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-methyltetrahydrofuran-2-yl)ethoxy)(tert-butyl)dimethylsilane* **(18)**

To a stirred solution of **9** (2 g, 5.15 mmol) in THF (20 mL) at 0 °C, was added sodium hydride portion wise (0.41 g, 60% dispersion in oil, 10.3 mmol) under nitrogen atmosphere. After being stirred for 15 min at 0 °C, was added BnBr (0.91 mL, 7.73 mmol) slowly followed by TBAI (0.19 g, 0.51 mmol). The reaction mixture was stirred for 12 h at room temperature and quenched carefully at 0 °C by slow addition of saturated aqueous NH_4Cl solution (10 mL). Then it was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated under *vacuo*. The residue was purified by column chromatography (SiO_2, 5% EtOAc/hexane) to afford **18** (2.26 g, 92% yield over two steps) as a colourless liquid. R_f = 0.6 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = +57.1 (*c* 0.35, $CHCl_3$); IR (Neat): ν_{max} 2955, 2928, 2856, 1457, 1376, 1253, 1219, 1094, 1069, 939, 834, 772, 697, 672 cm^{-1}; ^1H NMR (300 MHz): δ 7.39–7.25 (m, 5 H), 4.91 (d, J = 11.1 Hz, 1H), 4.59 (d, J = 11.1 Hz, 1H), 4.29–4.20 (m, 1H), 4.05–3.92 (m, 2H), 3.90–3.71 (m, 3H), 3.62–3.47 (m, 2H), 2.34 (p, J = 7.2 Hz, 1H), 2.06 (dt, J = 14.2, 7.0 Hz, 1H), 1.72–1.67 (m, 4H), 1.40 (s, 3H), 1.34 (s, 3H), 1.28–1.20 (m, 1H), 0.96 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (75 MHz): δ 138.9, 128.3, 128.0, 127.4, 108.3, 82.2, 79.9, 78.2, 73.9, 73.3, 69.9, 61.0, 36.6, 36.1, 35.4, 34.4, 27.0, 25.9, 25.80, 18.4, 15.3, –5.3. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{27}H_{46}O_5NaSi$ 501.3006, found 501.3012.

2.7 *2-((2R,3R,5R)-5-((R)-1-(Benzyloxy)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-methyltetrahydrofuran-2-yl)ethanol* **(19)**

TBAF (1 M in THF, 8.36 mL, 8.36 mmol) was added to a stirred solution of **18** (2 g, 4.18 mmol) in dry THF (15 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. It was quenched with saturated aqueous NH_4Cl (10 mL) solution and both the layers were separated. Aqueous layer was further extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under *vacuo*. The residue was purified by column chromatography (SiO_2, 27% EtOAc/hexane) to afford **19** (1.36 g, 90% yield) as a viscous liquid. $R_f = 0.2$ (SiO_2, 30% EtOAc/hexane); $[\alpha]_D^{25} = +60.4$ (c 0.7, $CHCl_3$); IR (Neat): ν_{max} 3611 (br), 2920, 2851, 2310, 1549, 1460, 1377, 1214, 1056, 939, 834, 772, 697, 672 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.37–7.31 (m, 5H), 4.81 (d, $J = 11.1$ Hz, 1H), 4.62 (d, $J = 11.1$ Hz, 1H), 4.26 (p, $J = 6.6$ Hz, 1H), 4.08–4.00 (m, 2H), 3.90 (dd, $J = 15.5$, 6.6 Hz, 1H), 3.90–3.70 (m, 2H), 3.67–3.61 (m, 1H), 3.50 (t, $J = 7.6$ Hz, 1H), 2.40–2.33 (m, 1H), 2.03 (dt, $J = 12.5$, 6.2 Hz, 1H), 1.77–1.64 (m, 4H), 1.62–1.55 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 1.32–1.27 (m, 1H), 0.96 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 128.3, 127.9, 127.6, 108.5, 82.3, 81.6, 79.4, 73.9, 73.1, 69.9, 61.9, 36.3, 36.2, 35.9, 33.2, 27.1, 25.8, 15.2. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{21}H_{32}O_5Na$ 387.2142, found 387.2149.

2.8 *(Z)-Methyl 4-((2R,3R,5R)-5-((R)-1-(tert-butyldiphenylsilyloxy)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-methyltetrahydrofuran-2-yl)but-2-enoate* **(20)**

To a stirred solution of **19** (1.1 g, 3.03 mmol) in dry CH_2Cl_2 (15 mL) was added $NaHCO_3$ (0.25 g, 3.03 mmol) followed by Dess-Martin periodinane (2.56 g, 6.06 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and saturated aqueous $Na_2S_2O_3$ (15 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4. Evaporation of the solvent under reduced pressure furnished crude aldehyde, which was passed through a short pad of silica gel and used as such for the next reaction.

To a stirred suspension of $(CF_3CH_2O)_2P(O)CH_2COOMe$ (1.22 mL, 5.75 mmol) and 18-crown-6 (1.51 g, 5.75 mmol) in THF (10 mL) at −40 °C, KHMDS (0.5 M in toluene, 9.68 mL, 4.84 mmol) was added slowly. After 15 min stirring at the same temperature, the reaction mixture was cooled to −78 °C and stirred for another 30 min. Then a solution of the above aldehyde in dry THF (10 mL) was added dropwise *via* cannula. After being stirred at −78 °C for 1 h, the reaction was quenched by the careful addition of saturated aqueous $NaHCO_3$ (10 mL). Then it was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under *vacuo*. The residue was purified by column chromatography (SiO_2, 5% EtOAc/hexane) to afford **20** (1.05 g, 83% yield) as a viscous liquid. $R_f = 0.45$ (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25} = +44.00$ (c 0.25, $CHCl_3$); IR (Neat): ν_{max} 2935, 2843, 2322, 1720, 1648, 1456, 1367, 1334, 1227, 1175, 1134, 1074, 950, 844, 761, 700, 672, 616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.30 (m, 5H), 6.44 (dt, $J = 11.4$, 7.1 Hz, 1H), 5.87 (dt, $J = 11.4$, 1.8 Hz, 1H), 4.87 (d, $J = 11.2$ Hz, 1H), 4.56 (d, $J = 11.2$ Hz, 1H), 4.28–4.20 (m, 1H), 4.01 (dt, $J = 8.0$, 4.8 Hz, 2H), 3.93–3.87 (m, 1H), 3.71 (s, 3H), 3.60–3.55 (m, 1H), 3.5 (t, $J = 7.7$ Hz, 1H), 2.93–2.85 (m, 1H), 2.75–2.67 (m, 1H), 2.44–2.36 (m, 1H), 2.06–2.00 (m, 1H), 1.72–1.65 (m, 1H), 1.64–1.60 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 1.33–1.27 (m, 1H), 1.02 (d, $J = 6.86$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 148.3, 138.9, 128.3, 128.0, 127.5, 120.1, 108.4, 82.9, 80.9, 79.9, 73.9, 73.3, 69.9, 59.9, 36.3, 36.13, 35.9, 31.5, 27.1, 25.8, 14.8. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{24}H_{34}O_6Na$ 441.2252, found 441. 2250.

2.9 *(Z)-4-((2R,3R,5R)-5-((R)-1-(tert-Butyldiphenylsilyloxy)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-methyltetrahydrofuran-2-yl)but-2-en-1-ol* **(8)**

To a stirred solution of **20** (0.800 g, 1.91 mmol) in dry CH_2Cl_2 (10 mL), was added DIBAL-H (1.53 mL, 2.5 M in hexane, 3.82 mmol) dropwise at −78 °C and stirred for 30 min. The reaction was then quenched by slow addition of dry methanol and brought to room temperature. Saturated aqueous potassium-sodium tartrate (5 mL) solution was added to the reaction mixture and stirred for 2 h until two clear layers were separated. Reaction mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under *vacuo*. The residue was purified by column chromatography (SiO_2, 20% EtOAc/hexane) to afford **8** (0.68 g, 89% yield) as a colourless liquid. $R_f = 0.2$ (SiO_2, 25% EtOAc/hexane); $[\alpha]_D^{25} = +38.00$ (c 0.5, $CHCl_3$); IR (Neat): ν_{max} 3425, 2942, 2851, 2330, 1651, 1462, 1371, 1334, 1228, 1176, 1135, 1074, 950, 848, 762, 701, 672, 616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.27 (m, 5H), 5.78–5.70 (m, 1H), 5.66–5.59 (m, 1H), 4.80 (d, $J = 11.2$ Hz, 1H), 4.59 (d, $J = 11.2$ Hz, 1H), 4.27–4.18 (m, 2H), 4.06 (dd, $J = 12.6$, 6.2 Hz, 1H), 4.02 (dd, $J = 8.1$, 5.9 Hz, 1H), 3.90–3.87 (m, 2H), 3.64 (ddd, $J = 9.8$, 6.3, 2.7 Hz, 1H), 3.51 (t, $J = 7.4$ Hz, 1H), 2.40–2.27 (m, 2H), 2.14–2.08 (m, 1H), 2.06–1.99 (m, 1H), 1.76–1.64 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H), 1.36–1.31 (m, 1H), 0.99 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 130.2, 129.8, 128.3, 128.1, 127.6, 108.4, 81.4, 80.9, 78.8, 73.8, 73.4, 69.9, 58.3, 35.9, 35.6, 29.5, 27.0, 25.8, 15.0. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{23}H_{34}O_5Na$ 413.2307, found 413.2299.

2.10 *(4S,6R)-7-(tert-Butyldiphenylsilyloxy)-6-methyl hept-1-en-4-ol* **(21)**

Ozone was bubbled into a stirred solution of **14** (11.4 g, 33.64 mmol) in CH_2Cl_2 (800 mL) at −78 °C until a light blue colour persisted. After being stirred for 15 min Ar was bubbled through the solution until the blue colour was discharged. Dimethyl sulfide (24.8 mL, 841 mmol) was added at −78 °C, and the mixture was warmed slowly to room temperature and stirred for 40 min. The solvent was removed under *vacuo* and the residue was purified by flash column chromatography to afford aldehyde which was used directly in the next step.

To a stirred solution of (–)–Ipc_2BOMe (15.96 g, 50.46 mmol) in anhydrous diethyl ether (120 mL) at −78 °C was added allylmagnesium bromide (1 M in diethyl ether, 47 mL, 47 mmol), and the reaction mixture was stirred at room temperature for 1 h before being cooled to −78 °C. A solution of above aldehyde in diethyl ether (30 mL) was added dropwise to this suspension, and allowed to stir for 8 h at −78 °C. To this mixture were added a solution of 10% aqueous NaOH (50 mL) and 30% H_2O_2 (50 mL). After being stirred at room temperature for overnight, the resultant mixture was diluted with H_2O and extracted with EtOAc (3 × 500 mL). The combined organic extracts were washed with brine (100 mL) and dried over Na_2SO_4 and concentrated under *vacuo*. The residue was purified by column chromatography (SiO_2, 6% EtOAc/hexane) to afford **21** (9.4 g, 72% two steps) as oily liquid. $R_f = 0.4$ (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25} = +8.6$ (*c* 0.9, $CHCl_3$); IR (Neat): ν_{max} 3396, 2363, 1641, 1107, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.65 (m, 4H), 7.45–7.36 (m, 6H), 5.89–5.79 (m, 1H), 5.14–5.12 (m, 1H), 5.11–5.10 (m, 1H), 3.79–3.73 (m, 1H), 3.52–3.49 (m, 2H), 2.45 (brs, OH), 2.29–2.17 (m, 2H), 1.89 (q, $J = 6.7$ Hz, 1 H), 1.55–1.48 (m, 1H), 1.36 (dddd, $J = 14.2$, 7.6, 3.0 Hz, 1H), 1.06 (s, 9H), 0.89 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6, 135.0, 133.5, 129.6, 127.6, 117.6, 69.8, 69.0, 42.6, 41.7, 33.3, 26.8, 19.2, 17.2. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{24}H_{34}O_2SiNa$ 405.2225, found 405.2228.

2.11 *(4S,6R)-7-(tert-Butyldiphenylsilyloxy)-6-methyl hept-1-en-4-yl 3-(4-methoxybenzyloxy) propanoate***(13)**

To a stirred solution of alcohol **21** (8 g, 20.94 mmol) and acid **22** (8.2 g, 41.88 mmol) previously azeotrope with dry benzene, in dry CH_2Cl_2 (80 mL) was added DCC (8.6 g, 41.88 mmol) followed by DMAP (0.6 g, 4.18 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 12 h at room temperature before being quenched with H_2O (20 mL). Hexane (400 mL) was added and the white precipitate was filtered off and the residue was washed with hexane/CH_2Cl_2 (2:1, 300 mL). The combined filtrate and washings were washed with saturated aqueous $NaHCO_3$ (20 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. Purification of the residue by column chromatography (SiO_2, 6% EtOAc/hexane) afforded **13** (11.1 g, 93%) as a colour less oil. $R_f = 0.5$ (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25} = +15.6$ (*c* 0.4, $CHCl_3$); IR (Neat): ν_{max} 2957, 2932, 2858, 1732, 1612, 1427, 1247, 1181, 1108, 1036, 822, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68–7.64 (m, 4H), 7.45–7.36 (m, 6H), 7.24 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 5.80–5.65 (m, 1H), 5.11–5.02 (m, 3H), 4.45 (ABq, $J = 12.2$ Hz, 2H), 3.79 (s, 3H), 3.71 (t, $J = 6.5$ Hz, 2H), 3.50–3.44 (m, 2H), 2.57 (t, $J = 6.5$ Hz, 2H), 2.33–2.28 (m, 2H), 1.81–1.70 (m, 2H), 1.34–1.23 (m, 1H), 1.06 (s, 9H), 0.92 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 159.2, 135.6, 133.9, 133.6, 130.2, 129.5, 129.2, 127.6, 117.6, 113.7, 72.7, 71.3, 69.2, 65.5, 55.2, 39.5, 37.4, 35.4, 32.2, 26.9, 19.3, 16.3. HRMS (ESI): $[M + H]^+$ calcd. for $C_{35}H_{47}O_5Si$ 575.3187, found 575.3182.

2.12 *(2R,4S,6S)-2-((R)-3-(tert-Butyldiphenylsilyloxy) -2-methylpropyl)-6-(2-(4-methoxybenzyloxy)ethyl) tetrahydro-2H-pyran-4-ol* **(23)**

To a stirred solution of ester **13** (10 g, 17.42 mmol) in dry CH_2Cl_2 (80 mL) was added DIBAL-H (1 M in toluene, 35 mL, 34.8 mmol) dropwise *via* syringe at −78 °C under nitrogen atmosphere. After 45 min, the reaction was treated sequentially with pyridine (4.4 mL, 52.2 mmol) dropwise *via* syringe, a solution of DMAP (4.24 g, 34.84 mmol) in CH_2Cl_2 (15 mL) dropwise *via* cannula and acetic anhydride (9.8 mL, 104.4 mmol) dropwise *via* syringe. After being stirred for 14 h at −78 °C, the reaction mixture was then warmed to 0 °C and stirred for an additional 30 min and then the reaction was quenched at 0 °C with saturated aqueous NH_4Cl (40 mL) and saturated aqueous sodium potassium tartrate (30 mL). The mixture was stirred at room temperature vigorously for 30 min and extracted with EtOAc (2 × 400 mL). The combined organic extracts were washed with ice-cooled 1 M solution of sodium bisulfate (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (30 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude α-acetoxy ether which was used directly in the next reaction.

To a stirred solution of α-acetoxy ether in dry hexane (150 mL) at 0 °C acetic acid (5 mL, 217.5 mmol) was added followed by dropwise addition of $BF_3 \cdot OEt_2$ (0.3 mL, 1.74 mmol). Then the reaction mixture was stirred for 2 h before being quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under *vacuo*. The crude material was then dissolved in 50 mL methanol and potassium carbonate (4.8 g, 34.8 mmol). After being stirred for 3 h, methanol was evaporated under reduced pressure and water (10 mL) was added to the reaction mixture and extracted with EtOAc (2 × 400 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4 and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 25% EtOAc/hexane) afforded **23** (4.4 g, 45% over three steps) as a colour less oil. $R_f = 0.3$ (SiO_2, 30% EtOAc/hexane); $[\alpha]_D^{25} = -4.5$ (*c* 1.1, $CHCl_3$); IR (Neat): ν_{max} 3378, 2930, 2857, 1612, 1510, 1247, 1106, 819, 742, 702, 613 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ

7.68–7.65 (m, 4H), 7.44–7.35 (m, 6H), 7.24 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.39 (s, 2H), 3.78 (s, 3H), 3.77–3.72 (m, 1H), 3.58–3.49 (m, 3H), 3.46-3.39 (m, 2H), 3.35–3.29 (m, 1H), 1.97–1.84 (m, 3H), 1.82–1.70 (m, 1H), 1.66–1.60 (m, 2H), 1.27–1.20 (m, 2H), 1.16–1.07 (m, 1H), 1.06 (s, 9H), 0.95 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 135.6, 134.0, 133.9, 130.6, 129.5, 129.2, 127.5, 113.7, 73.0, 72.7, 72.3, 69.2, 68.3, 66.5, 55.2, 41.8, 41.3, 39.6, 36.2, 32.1, 26.9, 19.3, 16.6. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{35}H_{48}O_5NaSi$ 599.3163, found 599.3173.

2.13 *tert-Butyl((R)-3-((2R,4S,6S)-4-(tert-butyldimethylsilyloxy)-6-(2-(4-methoxybenzyloxy)ethyl)tetrahydro-2H-pyran-2-yl)-2-methylpropoxy)diphenylsilane* **(24)**

To a stirred solution of **23** (3.6 g, 6.26 mmol) in dry CH_2Cl_2 (30 mL) was added 2, 6-lutidine (2 mL, 18.78 mmol) followed by TBSOTf (1.6 mL, 6.88 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 1 h at room temperature, before being quenched with saturated aqueous $NaHCO_3$ (10 mL) solution and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with saturated aqueous $CuSO_4$ (20 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under *vacuo.* Purification of the residue by column chromatography (SiO_2, 5% EtOAc/hexane) afforded **24** (3.9 g, 93%) as a clear oil. R_f = 0.4 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25} = -7.7$ (c 1.75, $CHCl_3$); IR (Neat): ν_{max} 2931, 2857, 1612, 1512,1366, 1249, 1084, 834, 777, 702, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.65 (m, 4H), 7.43–7.35 (m, 6H), 7.24 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.39 (s, 2H), 3.79–3.70 (m, 2H), 3.79 (s, 3H), 3.59–3.49 (m, 3H), 3.47–3.39 (m, 1H), 3.37–3.30 (m, 1H), 2.00–1.92 (m, 1H), 1.81-1.69 (m, 3H), 1.66–1.59 (m, 2H), 1.25–1.15 (m, 3H), 1.06 (s, 9H), 0.96 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 135.6, 134.0, 133.9, 130.6, 129.4, 129.2, 127.5, 113.7, 73.0, 72.8, 72.2, 69.3, 68.9, 66.6, 55.2, 42.4, 41.9, 39.6, 36.3, 32.1, 26.9, 25.8, 19.3, 18.1, 16.5, –4.53, –4.51. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{41}H_{62}O_5NaSi_2$ 713.4028, found 713.4035.

2.14 *(R)-3-((2R,4S,6S)-4-(tert-Butyldimethylsilyloxy)-6-(2-(4-methoxybenzyloxy)ethyl)tetrahydro-2H-pyran-2-yl)-2-methylpropan-1-ol* **(25)**

To the stirred solution of **24** (3.6 g, 5.2 mmol) in THF (50 mL) and water (2 mL) was added 18-crown-6 (17.8 g, 67.6 mmol) followed by KOH (14.8 g, 250 mmol). The reaction mixture was stirred for 2 h at room temperature, before being quenched with water (10 mL) and extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under *vacuo.* The residue was purified by column chromatography (SiO_2, 15% EtOAc/hexane) to afford **25** (1.78 g, 82%) as a yellow liquid. R_f =0.3 (SiO_2, 20% EtOAc/hexane); $[\alpha]_D^{25} = +5.6$ (c 0.9, $CHCl_3$); IR (Neat): ν_{max} 3565, 2922, 2853, 1728, 1512, 1374, 1250, 1074, 837, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.42 (ABq, J = 11.6 Hz, 2H), 3.80 (s, 3H), 3.79–3.72 (m, 1H), 3.60–3.53 (m, 1H), 3.53–3.47 (m, 3H), 3.40–3.34 (m, 2H), 1.84–1.71 (m, 6H), 1.59–1.52 (m, 1H), 1.33 (ddd, J = 14.6, 5.9, 2.0 Hz, 1H), 1.24–1.17 (m, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 130.6, 129.3, 113.7, 74.8, 72.8, 72.7, 68.6, 68.3, 66.2, 55.2, 42.5, 41.5, 41.0, 36.1, 34.2, 25.8, 18.1, 17.9, –4.53, –4.55. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{25}H_{44}O_5NaSi$ 475.2850, found 475.2840.

To a stirred solution of **25** (1.6 g, 3.54 mmol) in dry CH_2Cl_2 (20 mL) was added $NaHCO_3$ (0.29 g, 3.54 mmol) and Dess Martin periodinane (2.4 g, 5.30 mmol) at 0 °C under N_2 atmosphere. After 2 h stirring at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with water (10 mL), brine (20 mL), dried over Na_2SO_4, concentrated under *vacuo* and the residue was purified by flash column chromatography to afford aldehyde **7** in quantitative yield and used directly in the next step.

2.15 *2-((2R,3R,5R)-5-((R)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-methoxybenzyloxy)ethyl)-3-methyltetrahydrofuran-2-yl)ethanol* **(30)**

To a stirred solution of compound **9** (3.0 g, 7.73 mmol) in THF (50 mL) was added NaH (0.59 g, 15.46 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 10 min, PMBBr (1.35 mL, 9.27 mmol) and TBAI (0.285 g, 0.77 mmol) were added sequentially to it and stirred for another 12 h at room temperature. Then the reaction mixture was quenched carefully with saturated NH_4Cl (20 mL) and extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under vacuo, which was passed through a short pad of silica gel and used as such for the next reaction.

To the stirred solution of above PMB protected compound in THF (50 mL), was added TBAF (1 M in THF, 15.46 mL, 15.46 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 2 h, before being quenched with saturated aqueous NH_4Cl (20 mL) solution and both the layers were separated. Aqueous layer was further extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under *vacuo.* The residue was purified by column chromatography (SiO_2, 30% EtOAc/hexane) to afford **30** (2.77 g, 91% yield over two steps) as a viscous liquid. R_f = 0.3 (SiO_2, 25% EtOAc/hexane); $[\alpha]_D^{25} = +42.0$ (c 0.4, $CHCl_3$); IR (Neat): ν_{max} 3727, 2921, 2852, 1730, 1612, 1513, 1462, 1374, 1247, 1057, 821, 772, 722, 667 cm^{-1}; ^{1} H NMR (400 MHz, $CDCl_3$) : δ 7.27 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.73 (d, J = 10.7 Hz, 1H), 4.54 (d, J = 10.7 Hz, 1H), 4.28–21 (m, 1H), 4.08–3.99 (m, 2H), 3.91–3.84 (m, 3H),

3.79 (s, 3H), 3.65–3.59 (m, 1H), 3.42 (t, J = 7.7 Hz, 1H), 2.36 (p, J = 7.3 Hz, 1H), 2.06–1.98 (m, 1H), 1.78–1.55 (m, 5H), 1.40 (s, 3H), 1.34 (s, 3H), 0.97 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 130. 8, 129.6, 113.8, 108.5, 82.4, 81.7, 79.0, 73.7, 73.1, 69.9, 62.0, 55.2, 36.3, 36.2 35.9, 33.2, 27.1, 25.8, 15.2. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{22}H_{34}O_6Na$ 417.2247, found 417.2248.

2.16 *(R)-4-((R)-2-(4-methoxybenzyloxy)-2-((2R,4R, 5R)-4-methyl-5-((Z)-penta-2,4-dienyl)tetrahydrofuran -2-yl)ethyl)-2,2-dimethyl-1,3-dioxolane* **(31)**

To a stirred solution of **30** (2.5 g, 6.34 mmol) in dry CH_2Cl_2 (20 mL) was added $NaHCO_3$ (0.52 g, 6.34 mmol) and Dess-Martin periodinane (4.0 g, 9.51 mmol) at 0 °C under nitrogen atmosphere. After 2 h stirring at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure furnished crude aldehyde, which was passed through a short pad of silica gel and used as such for the next reaction. To a stirred suspension of chromium (II) chloride (8.57 g, 69.74 mmol) in dry THF (20 mL) at 0 °C under Ar atmosphere was added a suspension of above aldehyde in dry THF (20 mL) with (1-Bromoallyl)trimethylsilane (7.37 g, 38.04 mmol) *via* cannula. The reaction mixture was warmed to rt and stirred for 12 h at that temperature, and the resultant deep purple suspension was quenched by the addition of P^H = 7 buffer and both the layers were separated. The aqueous layer was further extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under *vacuo.*

The crude residue was dissolved in THF (20 mL) and added to a stirred solution of KH (7.62 g, 30% wt suspension, 57.06 mmol) in THF (20 mL) *via* cannula at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to rt and stirred for 2 h. Then the reaction mixture was cautiously poured into ice cooled water (50 mL) and extracted with EtOAc (2 × 150 mL), washed with brine (20 mL), dried over Na_2SO_4 and concentrated under *vacuo.* The residue was purified by column chromatography (SiO_2, 12% EtOAc/hexane) to afford **31** (2.32 g, 88% yield over two steps) as a viscous liquid. R_f = 0.4 (SiO_2, 15% EtOAc/hexane); $[\alpha]_D^{25}$ = +27.6 (c 0.45, $CHCl_3$); IR (Neat): ν_{max} 2954, 2929, 2857, 1615, 1514, 1463, 1372, 1251, 1062, 1001, 834, 777, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.65 (dddd, J = 16.8, 11.1, 10.1, 1.1 Hz, 1H), 6.08 (t, J = 11.0 Hz, 1H), 5.56 (dd, J = 18.0, 7.4 Hz, 1H), 5.20 (dd, J = 16.9, 1.8 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.51 (d, J = 11.0 Hz, 1H), 4.25–4.19 (m, 1H), 4.0 (dd, J = 8.1, 5.8 Hz, 1H), 3.94–3.90 (m, 1H), 3.86 (dt, J = 9.3, 6.8 Hz, 1H), 3.80 (s, 3H), 3.56 (ddd, J = 10.2, 7.0, 2.6 Hz, 1H), 3.49 (t, J = 7.8 Hz, 1H), 2.38–2.31 (m, 3H), 2.07–2.01 (m, 1H), 1.67 (ddd, J = 13.9, 7.8, 2.6 Hz, 1H), 1.63–1.60 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.32–1.27 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 132.3, 131.2, 130.3, 129.7, 129.3, 117.3, 113.7, 108.3, 82.1, 81.3, 79.3, 73.6, 73.4, 70.0, 55.2, 36.5, 36.1, 35.5, 29.9, 27.1, 25.8, 15.1. HRMS (ESI): $[M + H]^+$ calcd. for $C_{25}H_{37}O_5$ 417.2649, found 417.2646.

2.17 *(2R,4R)-4-(4-methoxybenzyloxy)-4-((2R,4R,5R) -4-methyl-5-((Z)-penta-2,4-dienyl)tetrahydrofuran-2-yl)butane-1,2-diol* **(32)**

To a stirred solution of **31** (2.0 g, 4.80 mmol) in dry MeOH (20 mL), CSA (0.223 mg, 0.96 mmol) was added at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 8 h before being quenched with saturated aqueous $NaHCO_3$ (20 mL) solution and both the layers were separated. Aqueous layer was further extracted with EtOAc (2 × 150 mL), brine (20 mL) dried over Na_2SO_4 and concentrated under *vacuo.* The residue was purified by column chromatography (SiO_2, 39% EtOAc/hexane) to afford **32** (1.71 g, 95% yield over two steps) as a viscous liquid. R_f = 0.2 (SiO_2, 40% EtOAc/hexane); $[\alpha]_D^{25}$ = +23.1 (c 0.2, $CHCl_3$); IR (Neat): ν_{max} 3382, 2954, 2927, 2855, 1615, 1514, 1458, 1376, 1251, 1062, 834, 778, 671 cm^{-1};[1] H NMR (500 MHz, $CDCl_3$)δ 7.28 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.64 (dt, J = 16.8, 10.6 Hz, 1H), 6.08 (t, J = 10.6 Hz, 1H), 5.55 (dd, J = 16.7, 7.4 Hz, 1H), 5.21 (d, J = 16.8 Hz, 1H), 5.12 (d, J = 9.6 Hz, 1H), 4.77 (d, J = 11.2 Hz, 1H), 4.59 (d, J = 11.2 Hz, 1H), 4.00–3.92 (m, 2H), 3.91–3.85 (m, 1H), 3.79 (s, 3H), 3.63–3.55 (m, 2H), 3.44–3.39 (m, 1H), 2.41–2.29 (m, 3H), 2.07–2.00 (m, 1H), 1.66–1.58 (m, 2H), 1.45 (ddd, J = 14.3, 8.0, 2.6 Hz, 1H), 0.98 (d, J = 11.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 132.3, 130.7, 130.4, 129.9, 129.1, 117.4, 113.8, 81.7, 81.4, 78.6, 72.9, 69.1, 66.9, 55.2, 36.5, 35.4, 34.3, 29.8, 15.1. HRMS (ESI): $[M + H]^+$ calcd. for $C_{22}H_{33}O_5$ 377.2331, found 377.2330.

2.18 *(2R,4R)-1-(tert-Butyldimethylsilyloxy)-4-(4-met hoxybenzyloxy)-4-((2R,4R,5R)-4-methyl-5-((Z)-penta-2,4-dienyl)tetrahydrofuran-2-yl)butan-2-ol* **(29)**

To a stirred solution of **32** (1.5 g, 3.98 mmol) in CH_2Cl_2 (20 mL), imidazole (0.29 g, 4.38 mmol) and TBSCl (0.66 g, 4.38 mmol) were added sequentially at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 4 h before being quenched with saturated aqueous NH_4Cl (20 mL) solution and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by column chromatography (SiO_2, 8% EtOAc/hexane) to afford **29** (1.78 g, 94% yield over two steps) as clear oil. R_f = 0.4 (SiO_2, 15% EtOAc/hexane); $[\alpha]_D^{25}$ = +7.2 (c 2.22, $CHCl_3$). IR (neat): ν_{max} 2952, 2930, 2860, 1618,

1518, 1461, 1384, 1255, 1063, 831, 779, 674 cm^{-1};[1] H NMR (500 MHz, $CDCl_3$) : δ 7.24 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.65 (dddd, J = 16.9, 11.1,10.1, 1.1 Hz, 1H), 6.08 (t, J = 11.0 Hz, 1H), 5.56 (dd, J = 10.5, 7.5 Hz, 1H), 5.20 (dd, J = 16.9, 1.8 Hz, 1H), 5.11 (d, J = 10.1 Hz, 1H), 4.81 (d, J = 11.0 Hz, 1H), 4.57 (d, J = 11.0 Hz, 1H), 3.95–3.88 (m, 2H), 3.88–3.82 (m, 1H), 3.79 (s, 3H), 3.66 (dd, J = 12.5, 7.0 Hz, 1H), 3.55 (dd, J = 9.9, 4.2 Hz, 1H), 3.42 (dd, J = 9.9, 6.8 Hz, 1H), 2.71 (brs, 1H), 2.40–2.29 (m, 3H), 2.07–2.00 (m, 1H), 1.69–1.57 (m, 2H), 1.52–1.48 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 132.2, 131.2, 130.3, 129.8, 129.3, 117.3, 113.7, 82.2, 81.3, 79.2, 73.4, 68.7, 67.4, 55.2, 36.6, 35.5, 34.9, 29.9, 25.8, 18.3, 15.1, –5.3, –5.4. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{28}H_{46}O_5SiNa$ 513.3018, found 513.3013.

2.19 *tert-Butyl((2S,4S,6R)-2-(2-(4-methoxybenzyloxy)ethyl)-6-((R)-2-methylbut-3-enyl)tetrahydro-2H-pyran-4-yloxy)dimethylsilane* **(34)**

To a stirred solution of sulfone **33** (2.4 g, 10.62 mmol) in THF (30 mL) at −78 °C was added NaHMDS (7.0 mL, 1 M in THF, 7.08 mmol) under argon atmosphere. After being stirred for 30 min the crude aldehyde **7** in THF (20 mL) was added at −78 °C to the reaction mixture *via* cannula. The reaction mixture was slowly warmed to room temperature and stirred for 12 h before being quenched with water (10 mL) and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 4% EtOAc/hexane) afforded **34** (1.35 g, 82% over two steps) as yellow oil. R_f = 0.5(SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = −11.7 (c 0.45, $CHCl_3$); IR (Neat): ν_{max} 2928, 2856, 1513, 1462, 1360, 1248, 1076, 836, 775 cm^{-1};[1] H NMR (500 MHz, $CDCl_3$) : δ 7.25 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.79–5.70 (m, 1H), 4.98-4.88 (m, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.78–3.71 (m, 1H), 3.62–3.56 (m, 1H), 3.55–3.50 (m, 1H), 3.46–3.40 (m, 1H), 3.32–3.26 (m, 1H), 2.35 (q, J = 7.0 Hz, 1H), 1.82–1.71 (m, 3H), 1.66–1.60 (m, 1H), 1.3–1.14 (m, 4H), 0.99 (d, J = 6.5 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 144.6, 130.6, 129.2, 113.7, 112.1, 73.2, 72.7, 72.3, 68.9, 66.5, 55.2, 42.5, 41.88, 41.84, 36.2, 33.8, 25.8, 19.4, 18.1, –4.5. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{26}H_{44}O_4NaSi$ 471.2901, found 471.2913.

2.20 *2-((2S,4S,6R)-4-(tert-Butyldimethylsilyloxy)-6-((R)-2-methylbut-3-enyl)tetrahydro-2H-pyran-2-yl) ethanol* **(35)**

To a stirred solution of **34** (1.2 g, 2.68 mmol) in $CHCl_3$: pH = 7 phosphate buffer (20:1, 15 mL) was added DDQ (1.2 g, 5.36 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, before being quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 7% EtOAc/hexane) afforded **35** (0.8 g, 92%) as clear oil. R_f = 0.3(SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = −4.3 (c 1.6, $CHCl_3$); IR (Neat): ν_{max} 3398, 3077, 2928, 2856, 1464, 1374, 1253, 1075, 911, 839, 775 cm^{-1};[1] H NMR (500 MHz, $CDCl_3$): δ 5.70 (ddd, J = 17.3, 10.2, 7.6 Hz, 1H), 4.98–4.88 (m, 2H), 3.82–3.71 (m, 3H), 3.56–3.50 (m, 1H), 3.38–3.32 (m, 1H), 2.76 (brs, OH), 2.28 (q, J = 7.0 Hz, 1H), 1.84–1.60 (m, 5H), 1.35–1.15 (m, 3H), 1.0 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 112.5, 76.1, 73.9, 68.5, 61.5, 42.5, 41.7, 41.5, 37.7, 34.3, 25.8, 19.9, 18.1, –4.55, –4.57. HRMS (ESI): $[M + H]^+$ calcd. for $C_{18}H_{37}O_3Si$ 329.2506, found 329.2505.

2.21 *(E)-((2R,4R)-1-(tert-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-((2R,4R,5R)-4-methyl-5-((Z)-penta-2,4-dienyl)tetrahydrofuran-2-yl)butan-2-yl) 4-((2S,4R,6R)-4-(tert-butyldimethylsilyloxy) -6-((R)-2-methylbut-3-enyl)tetrahydro-2H-pyran-2-yl)but-2-enoate* **(26)**

To a stirred solution of **35** (0.7 g, 2.132 mmol) in dry CH_2Cl_2 (40 mL) was added $NaHCO_3$ (0.172 g, 2.132 mmol) and Dess Martin periodinane (1.36 g, 3.20 mmol) at 0 °C under N_2 atmosphere. After 2 h stirring at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (20 mL) brine (30 mL), dried over Na_2SO_4 and concentrated under *vacuo* gave the residue that was purified by flash column chromatography to afford aldehyde **28** which was used directly in the next step.

To a stirred solution of **29** (0.433 mg, 0.913 mmol) in dry CH_2Cl_2 (10 mL) was added diethyl phosphonoacetic acid (0.22 mL, 1.367 mmol) followed by DMAP (0.022 g, 0.182 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 10 min at 0 °C, and then EDCI (0.349 g, 1.822 mmol) was added to it. After 4 h of stirring at room temperature, the reaction mixture was quenched by the addition of water (5 mL) and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent under *vacuo* afforded crude ester compound which was passed through a short pad of silica and used as such for the next reaction.

To a mixture of phosphonate compound (0.433 g, 0.913 mmol) and LiCl (0.074 g, 1.826 mmol) in dry MeCN (10 mL) was added DBU (0.14 mL, 0.913 mmol) at 0 °C under argon atmosphere. After being stirred for 15 min at room temperature, the reaction mixture was again cooled to 0 °C and a solution of aldehyde **28** (0.300 g, 0.913 mmol) in MeCN (5 mL) was added drop wise *via* cannula. Then the reaction

mixture was stirred for 12 h at room temperature before being quenched by the addition of water (5 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under *vacuo*. The residue was purified by column chromatography (SiO_2, 60–120 mesh, 8% EtOAc/hexane) to afford **26** (0.61 g, 80% over two steps) as colourless oil. R_f = 0.45 (SiO_2, 15% EtOAc/hexane); $[\alpha]_D^{25}$ = +22.5 (*c* 0.4, $CHCl_3$); IR (Neat): ν_{max} 2963, 2930, 2856, 1714, 1614, 1586, 1461, 1248, 831, 779, 674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.99 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.63 (dt, *J* = 16.7, 10.2 Hz, 1H), 6.07 (t, *J* = 10.8 Hz, 1H), 5.89 (d, *J* = 15.7 Hz, 1H), 5.71 (ddd, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.58–5.51 (m, 1H), 5.27–5.16 (m, 2H), 5.09 (d, *J* = 10.2 Hz, 1H), 4.98–4.88 (m, 2H), 4.72 (d, *J* = 10.2 Hz, 1H), 4.40 (d, *J* = 10.2 Hz, 1H), 3.93–3.85 (m, 2H), 3.78 (s, 3H), 3.76–3.71 (m, 2H), 3.63 (ddd, *J* = 11.0, 5.0, 2.5 Hz, 1H), 3.43–3.34 (m, 2H), 3.32–3.26 (m, 1H), 2.47–2.40 (m, 1H), 2.38–2.28 (m, 4H), 2.09–1.98 (m, 2H), 1.84–1.73 (m, 3H), 1.69–1.59 (m, 2H), 1.34–1.12 (m, 4H), 1.00–0.96 (m, 6H), 0.88 (s, 9H), 0.86 (s, 9H), 0.05 (d, *J* = 1.8 Hz, 6H), 0.01 (d, *J*=3.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 159.0, 145.4, 144.4, 132.3, 131.1, 130.3, 129.9, 129.3, 123.2, 117.3, 115.1, 113.7, 112.4, 81.9, 81.3, 78.4, 74.1, 73.5, 71.4, 68.7, 64.9, 55.2, 42.4, 41.5, 41.4, 38.8, 36.4, 35.4, 34.0, 32.9, 29.9, 25.8, 19.9, 18.3, 18.1, 15.2, –4.5, –5.3. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{48}H_{80}O_8Si_2Na$ 863.5299, found 863.5291.

2.22 *tert-Butyl-(2-((2R,3R,5R)-5-((R)-1-(tert-butyldimethylsilyloxy)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-methyltetrahydrofuran-2-yl)ethoxy)dimethylsilane* **(40)**

To a stirred solution of **9** (1.5 g, 3.86 mmol) in dry CH_2Cl_2 (15 mL) was added 2,6-lutidine (1.4 mL, 11.59 mmol) followed by TBSOTf (1.0 mL, 4.25 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for another 2 h at room temperature, before being quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with EtOAc (2 × 100 ml). The combined organic extracts were washed with saturated aqueous $CuSO_4$ (8 mL), water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under *vacuo.* Purification of the residue by column chromatography (SiO_2, 5% EtOAc/hexane) afforded **40** (1.8 g, 95%) as a clear oil. R_f = 0.5 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = +30.3 (*c* 0.6, $CHCl_3$); IR (Neat): ν_{max} 2954, 2931, 2858, 1466, 1374, 1251, 1092, 834, 776, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.29–4.23 (m, 1H), 4.04 (dd, *J* = 7.8, 5.9 Hz, 1H), 3.89–3.83 (m, 2H), 3.80–3.75 (m, 1H), 3.71–3.64 (m, 2H), 3.48 (t, *J* = 7.7 Hz, 1H), 2.26 (qt, *J* = 7.2 Hz, 1H), 1.97 (dt, *J* = 14.5, 7.2 Hz, 1H), 1.70–1.58 (m, 3H), 1.53–1.47 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 1.26–1.18 (m, 1H), 0.91 (d, *J* = 7 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.5, 81.6, 78.2, 72.5, 71.7, 70.0, 61.2, 37.0, 35.5, 35.3, 34.3, 27.1, 26.0, 25.8, 18.3, 18.2, 15.6, –4.0, –4.8, –5.3. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{26}H_{54}O_5NaSi_2$ 525.3402, found 525.3412.

2.23 *2-((2R,3R,5R)-5-((R)-1-(tert-Butyldimethylsilyloxy)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-methyltetrahydrofuran-2-yl)ethanol* **(39)**

To a stirred solution of **40** (1.5 g, 2.99 mmol) in dry THF (10 mL) in a polypropylene vial, was added HF-Py complex (70%, 0.4 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. Then the reaction mixture was cautiously poured into a saturated aqueous $NaHCO_3$solution and stirred for 30 min. Then both the layers were separated, aqueous layer was further extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (8 mL), water (5 mL), brine (5 mL) and dried over Na_2SO_4. Purification of the residue by column chromatography (SiO_2, 25% EtOAc/hexane) afforded **39** (1.0 g, 88% yield) as a colourless liquid. R_f = 0.2 (SiO_2, 30% EtOAc/hexane); $[\alpha]_D^{25}$ = +18.7 (*c* 0.65, $CHCl_3$); IR (Neat): ν_{max} 3444, 2955, 2857, 1471, 1370, 1249, 1214, 1058, 836, 777 cm^{-1}; ^{1} H NMR (300 MHz, $CDCl_3$) : δ 4.28–4.17 (m, 1H), 4.07–3.88 (m, 3H), 3.82–3.72 (m, 3H), 3.48 (t, *J* = 7.5 Hz, 1H), 2.39–2.27 (m, 1H), 2.00–1.90 (m, 1H), 1.78–1.50 (m, 4H), 1.38 (s, 3H), 1.32 (s, 3H), 1.31–1.27 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.6, 82.0, 81.2, 72.5, 70.7, 69.9, 61.8, 37.1, 35.6, 34.8, 33.0, 27.0, 25.9, 25.7, 18.1, 15.2, –4.1, –4.7. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{20}H_{40}O_5NaSi$ 411.2537, found 411.2542.

2.24 *tert-Butyl ((R)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((2R,4R,5R)-5-((Z)-3-iodoallyl)-4-methyltetrahydrofuran-2-yl)ethoxy)dimethylsilane* **(38)**

To a stirred solution of **39** (0.9 g, 2.32 mmol) in dry CH_2Cl_2 (10 mL) were added $NaHCO_3$ (0.18 g, 2.32 mmol) and Dess-Martin periodinane (1.5 g, 3.48 mmol) sequentially at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred for 2 h at room temperature before being quenched with saturated aqueous $NaHCO_3$ (8 mL) and saturated aqueous $Na_2S_2O_3$ (8 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent furnished crude aldehyde, which was passed through a short pad of silica gel and used as such for the next reaction.

To a suspension of iodomethyl triphenylphosphonium iodide (3.68 g, 6.96 mmol) in anhydrous THF (20 mL) was added NaHMDS (6.95 mL, 1.0 M in THF, 6.95 mmol) at 0 °C under argon atmosphere. Then the reaction mixture was stirred for another 15 min at 0 °C before being cooled to −78 °C and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (1.4 mL, 11.6 mmol) was added followed by the above aldehyde in dry THF (5 mL) *via* cannula. After 2 h stirring at −78 °C, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (3 mL) and stirred

for 1 h at rt and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under *vacuo.* Purification of the residue by column chromatography (SiO_2, 5% EtOAc/hexane) afforded **38** (0.97 g, 78% over two steps) as a viscous liquid. R_f = 0.6 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = +15.4 (*c* 1.2, $CHCl_3$); IR (Neat): ν_{max} 2954, 2929, 2857, 1463, 1372, 1251, 1062, 1001, 834, 777, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.32 (dd, *J* = 13.7, 6.5 Hz, 1H), 6.26 (dt, *J* = 7.5, 1.4 Hz, 1H), 4.28–4.22 (m, 1H), 4.04 (dd, *J* = 7.8, 5.9 Hz, 1H), 3.95–3.87 (m, 2H), 3.72 (dt, *J* = 12.8, 6.4 Hz, 1H), 3.50 (t, *J* = 7.6 Hz, 1H), 2.34 (q, *J* = 7.3 Hz, 1H), 2.25–2.21 (m, 2H), 1.98 (dt, *J* = 14.1, 7.3 Hz, 1H), 1.68 (ddd, *J* = 13.5, 8.8, 2.4 Hz, 1H), 1.52 (ddd, *J* = 13.7, 9.9, 3.8 Hz, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 1.31–1.27 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 108.6, 83.3, 81.9, 79.9, 72.5, 71.6, 70.0, 37.0, 36.9, 35.6, 35.3, 27.1, 26.0, 25.8, 18.2, 15.3, –4.0, –4.7. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{21}H_{39}O_4INaSi$ 533.1554, found 533.1563.

2.25 *(2R,4R)-4-(tert-Butyldimethylsilyloxy)-4-((2R,4R,5R)-5-((Z)-3-iodoallyl)-4-methyltetrahydrofuran-2-yl)butane-1,2-diol* **(S1)**

To a stirred solution of **38** (0.70 g, 1.37 mmol) in dry CH_3CN (8 mL) was added $CuCl_2{\cdot}H_2O$ (0.70 g, 4.12 mmol) at −5 °C portion wise. Then the reaction mixture was stirred for 2 h before being quenched with H_2O (3 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under *vacuo.* Purification of the residue by column chromatography (SiO_2, 35% EtOAc/hexane) afforded **S1** (0.72 g, 88%) as a clear oil. R_f = 0.2 (SiO_2, 40% EtOAc/hexane); $[\alpha]_D^{25}$ = +13.2 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} 3733, 3370, 2928, 2856, 2313, 1515, 1463, 1251, 1089, 835, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.32 (dd, *J* = 13.4, 6.1 Hz, 1H), 6.27 (dt, *J* = 7.5, 1.4 Hz, 1H), 3.99–3.94 (m, 2H), 3.93–3.88 (m, 2H), 3.60 (dd, *J* = 11.1, 3.5 Hz, 1H), 3.44 (dd, *J* = 11.1, 6.4 Hz, 1H), 2.37 (q, *J* = 7.3 Hz, 1H), 2.27–2.23 (m, 2H), 2.06–2.00 (m, 1H), 1.80–1.72 (m, 1H), 1.52 (dq, *J* = 14.6, 2.2 Hz, 1H), 1.29–1.23 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 83.6, 81.1, 80.1, 73.6, 69.1, 67.2, 36.9, 36.1, 35.9, 35.6, 25.9, 18.1, 15.4, –4.3, –4.9. HRMS (ESI): $[M + H]^+$ calcd. for $C_{18}H_{36}O_4ISi$ 471.1422, found 471.1416.

2.26 *(6R,8R)-8-((2R,4R,5R)-5-((Z)-3-Iodoallyl)-4-methyltetrahydrofuran-2-yl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecan-6-ol* **(41)**

To a stirred solution of **S1** (0.45 g, 0.95 mmol) in dry CH_2Cl_2 (5 mL) was added imidazole (0.1 g, 1.43 mmol) followed by TBSCl (0.21 g, 1.43 mmol) at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred for 3 h at rt before being quenched with saturated aqueous NH_4Cl (3 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under *vacuo.* Purification of the residue by column chromatography (SiO_2, 7% EtOAc/hexane) afforded **41** (0.52 g, 95%) as oily liquid. R_f = 0.2 (SiO_2, 10% EtOAc /hexane); $[\alpha]_D^{25}$ = +22.0 (*c* 1.4, $CHCl_3$); IR (Neat): ν_{max} 2953, 2928, 2856, 1465, 1367, 1252, 1094, 1002, 837, 776, 672 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.32 (dd, *J* = 13.5, 6.5 Hz, 1H), 6.25 (dt, *J* = 7.5, 1.2 Hz, 1H), 3.96–3.91 (m, 2H), 3.87–3.79 (m, 2H), 3.53 (dd, *J* = 9.7, 4.8 Hz, 1H), 3.47 (dd, *J* = 9.9, 6.7 Hz, 1H), 2.96 (brs, OH), 2.34 (q, *J* = 7.3, 1H), 2.26–2.21 (m, 2H), 2.05–1.97 (m, 1H), 1.56–1.50 (m, 1H), 1.30–1.23 (m, 2H), 0.98 (d, *J* = 7 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.1 (s, 3H), 0.06 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 83.3, 81.7, 80.0, 72.8, 68.6, 67.6, 36.9, 36.5, 35.66, 35.64, 25.9, 25.8, 18.26, 18.23, 15.4, –4.1, –4.9, –5.4. HRMS (ESI): $[M + H]^+$ calcd. for $C_{24}H_{50}IO_4Si_2$ 585.2290, found 585.2288.

2.27 *(6R,8R)-8-((2R,4R,5R)-5-((Z)-3-Iodoallyl)-4-methyltetrahydrofuran-2-yl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecan-6-yl 2-(diethoxyphosphoryl) acetate* **(37)**

To a stirred solution of **41** (0.45 g, 0.77 mmol) in dry CH_2Cl_2 (5 mL) was added diethyl phosphono acetic acid (0.4 mL, 2.31 mmol) followed by DMAP (0.019 g, 0.154 mmol) at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred for 10 min at 0 °C and EDCI (0.45 g, 2.31 mmol) was added to it. After being stirred for 4 h at room temperature, the reaction mixture was quenched by the addition of water and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under *vacuo.* Purification of the residue by column chromatography (SiO_2, 30% EtOAc/hexane) afforded **37** (0.55 g, 93%) as a yellow oil. R_f = 0.2 (SiO_2, 40% EtOAc/hexane); $[\alpha]_D^{25}$ = +24.8 (*c* 0.45, $CHCl_3$); IR (Neat): ν_{max} 2927, 2856, 1737, 1465, 1391, 1259, 1102, 1053, 1027, 970, 838, 778, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.31 (dd, *J* = 13.6, 6.5 Hz, 1H), 6.25 (dt, *J* = 7.3, 1.2 Hz, 1H), 5.07–5.01 (m, 1H), 4.20–4.14 (m, 4H), 3.94–3.88 (m, 1H), 3.80–3.71 (m, 2H), 3.65 (qd, *J* = 10.7, 4.7 Hz, 2H), 2.97 (s, 1H), 2.63 (d, *J* = 21.5 Hz, 2H), 2.25–2.21 (m, 2H), 2.05–1.97 (m, 1H), 1.79 (ddd, *J* = 14.3, 9.4, 2.6 Hz, 1H), 1.68 (ddd, *J* = 14.2, 9.2, 2.8 Hz, 1H), 1.34 (td, *J* = 7.0, 2.6 Hz, 6H), 1.30–1.27 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 138.9, 83.3, 81.6, 80.0, 73.3, 70.9, 64.3, 62.63, 62.60, 37.0, 35.4, 35.2, 34.9, 34.3, 33.8, 25.9, 25.8, 18.2, 18.17, 16.4, 15.4, –4.0, –4.9, –5.4. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{30}H_{60}INaO_8PSi_2$ 785.2501, found 785.2492.

2.28 *(E)-((6R,8R)-8-((2R,4R,5R)-5-((Z)-3-Iodoallyl)-4-methyltetrahydrofuran-2-yl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecan-6-yl) 4-((2S,4R,6R)-4-(4-methoxybenzyloxy)-6-((R)-2-methylbut-3-enyl)tetrahydro-2H-pyran-2-yl)but-2-enoate* **(36)**

To a mixture of compound **37** (0.28 g, 0.36 mmol) and LiCl (0.03 g, 0.609 mmol) in MeCN (3 mL) was added DBU (0.05 mL, 0.304 mmol) at 0 °C under argon atmosphere. After being stirred for 15 min at room temperature, the mixture was again cooled to 0 °C and a solution of aldehyde **28** (0.100 g, 0.304 mmol) in MeCN (3 mL) was added dropwise *via* cannula. Then the reaction mixture was stirred for 12 h at room temperature before being quenched by the addition of water and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 60–120 mesh, 3% EtOAc/hexane) afforded **36** (0.22 g, 78% over two steps) as a colorless oil. R_f = 0.5 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = +17.5 (*c* 0.4, $CHCl_3$); IR (Neat): ν_{max} 2927, 2856, 1722, 1464, 1370, 1254, 1174, 1076, 998, 837, 776, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.96 (dt, J = 15.4, 7.2 Hz, 1H), 6.32 (dd, J = 13.5, 7.0 Hz, 1H), 6.26 (dt, J = 7.3, 1.4 Hz, 1H), 5.87 (dt, J = 15.7, 1.0 Hz, 1H), 5.71 (ddd, J = 17.5, 10.3, 7.6 Hz, 1H), 5.04–4.99 (m, 1H), 4.97–4.88 (m, 2H), 3.95–3.90 (m, 1H), 3.79–3.67 (m, 5H), 3.39–3.33 (m, 1H), 3.32–3.26 (m, 1H), 2.47–2.40 (m, 1H), 2.37–2.29 (m, 3H), 2.26–2.22 (m, 2H), 2.04–1.98 (m, 1H), 1.88–1.74 (m, 2H), 1.70–1.60 (m, 3H), 1.34–1.20 (m, 4H), 0.99 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ 166.0, 145.3, 144.4, 138.9, 123.3, 112.4, 83.3, 81.7, 80.0, 74.1, 73.5, 71.7, 71.1, 68.7, 64.5, 42.4, 41.4, 41.3, 38.8, 37.0, 35.5, 35.2, 34.3, 34.0, 26.0, 25.8, 19.9, 18.2, 18.1, 18.0, 15.3, –4.0, –4.50, –4.53, –4.9, –5.3. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{44}H_{83}O_7INaSi_3$ 957.4389, found 957.4383.

2.29 *(1R,3R,4E,6Z,9R,10R,12R,13R,15R,18E,21S,23R)-13,23-bis((tert-Butyldimethylsilyl)oxy)-15-(((tert-butyldimethylsilyl)oxy)methyl)-3,10-dimethyl-16,25,26-trioxatricyclo[19.3.1.19,12]hexacosa-4,6,18-trien-17-one* **(42)**

To a stirred solution of vinyl iodide **36** (0.15 g, 0.134 mmol) which was previously azeotroped with benzene, in dry DMF (30 mL) was added Cs_2CO_3 (0.09 g, 0.273 mmol), Et_3N (0.045 mL, 0.192 mmol) and $Pd(OAc)_2$ (0.051 g, 0.241 mmol) sequentially at rt under argon atmosphere. Then the reaction mixture was stirred for 2 days at room temperature before being quenched by the addition of water and extracted with EtOAc (2 × 45 mL). The combined organic extracts were washed with brine (8 mL), dried over Na_2SO_4, and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 60–120 mesh, 3.5% EtOAc/hexane) afforded **42** (0.075 g, 60%) as a colourless oil. R_f = 0.35 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = −4.5 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} 2929, 2857, 1729, 1465, 1370, 1254, 1174, 1090, 838, 776, 621 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.0 (ddd, J = 15.5, 9.0, 4.7 Hz 1H), 6.32 (dd, J = 15.1, 10.6 Hz, 1H), 6.03 (t, J = 10.8 Hz, 1H), 5.93 (d, J = 15.7 Hz, 1H), 5.54 (dd, J = 15.1, 7.4 Hz, 1H), 5.37–5.29 (m, 1H), 5.02–4.97 (m, 1H), 3.94–3.88 (m, 1H), 3.81–3.66 (m, 5H), 3.45–3.88 (m, 1H), 3.36–3.29 (m, 1H), 2.56–2.48 (m, 1H), 2.44–2.36 (m, 2H), 2.35–2.28 (m, 2H), 2.05–1.93 (m, 2H), 1.89–1.81 (m, 1H), 1.78–1.68 (m, 2H), 1.65–1.59 (m, 2H), 1.42–1.28 (m, 3H), 1.22–1.13 (m, 1H), 1.01 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), –0.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 144.9, 140.9, 130.4, 127.3, 124.1, 123.3, 82.1, 81.2, 73.2, 72.5, 71.3, 68.8, 64.5, 43.2, 42.1, 40.8, 37.9, 35.9, 35.3, 34.2, 32.5, 30.7, 26.1, 25.8, 19.7, 18.22, 18.2, 18.1, 14.9, –3.9, –4.5, –5.27, –5.3, –5.4. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{44}H_{82}O_7NaSi_3$ 829.5260, found 829.5264.

2.30 *(1R,3R,4E,6Z,9R,10R,12R,13R,15R,18E,21S,23R)-13,23-Dihydroxy-15-(hydroxymethyl)-3,10-dimethyl-16,25,26-trioxatricyclo[19.3.1.19,12]hexacosa-4,6,18-trien-17-one* **(43)**

To a stirred solution of **42** (0.045 g, 0.055 mmol) in dry MeCN (8 mL) in a polypropylene vial, was added HF-Py complex (70%, 0.6 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for another 36 h. Then the reaction mixture was cautiously poured into saturated aqueous $NaHCO_3$ (8 mL) and stirred for 30 min. Then both the layers were separated, aqueous layer was further extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (8 mL), water (8 mL), brine (8 mL) and dried over Na_2SO_4. The solvent was evaporated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 6% MeOH/$CHCl_3$) afforded **43** (22 mg, 90% yield) as a colour less semi solid. R_f = 0.3 (SiO_2, 10% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ = −6.0 (*c* 0.6, EtOAc); IR (Neat): ν_{max} 3441, 3368, 3267, 2923, 2854, 1741, 1711, 1459, 1176, 1048, 953 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.06 (ddd, J = 15.1, 8.5, 5.5 Hz, 1H), 6.25 (dd, J = 15.2, 10.8 Hz, 1H), 6.02 (t, J = 10.8 Hz, 1H), 5.94 (d, J = 15.5 Hz, 1H), 5.63 (dd, J = 15.2, 7.5 Hz, 1H), 5.31–5.23 (m, 2H), 4.07–4.01 (m, 1H), 3.83–3.77 (m, 2H), 3.75–3.70 (m, 1H), 3.67 (dd, J = 11.9, 5.3 Hz, 1H), 3.49–3.42 (m, 2H), 3.37–3.31 (m, 1H), 2.52–2.41 (m, 3H), 2.40–2.28 (m, 2H), 2.18–2.11 (m, 1H), 2.09–2.03 (m, 1H), 1.94–1.85 (m, 1H), 1.82–1.52 (m, 5H), 1.36–1.28 (m, 2H), 1.17–1.09 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 146.4, 140.6, 130.2, 126.3, 123.6, 122.7, 82.4, 81.1, 73.3, 72.7, 72.2, 72.1, 68.2, 65.5, 42.6, 41.3, 40.4, 38.1, 36.8, 35.7, 33.9, 32.5, 30.9, 19.8, 14.5. HRMS (ESI): $[M+NH_4]^+$ calcd. for $C_{26}H_{44}O_7N$ 482.3112, found 487.3127.

2.31 *tert-Butyl((S)-1-((2S,4S,5S)-5-(2-(tert-butyldimethylsilyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)diphenylsilane* **(48)**

To a stirred solution of *ent*-**9** (1.5 g, 3.86 mmol) in CH_2Cl_2 (20 mL), imidazole (0.39 g, 5.79 mmol) and TBDPSCl (1.50 mL, 5.79 mmol) were added sequentially at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred for 24 h at room temperature before being quenched with saturated aqueous NH_4Cl (10 mL) solution and extracted with EtOAc. The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under *vacuo*. The residue was purified by column chromatography (SiO_2, 8% EtOAc/hexane) to afford **48** (2.27 g, 94% yield over two steps) as a clear oil. $R_f = 0.7$ (SiO_2, 20% EtOAc/hexane); $[\alpha]_D^{25} = -11.2$ (*c* 1.1, $CHCl_3$); IR (Neat): ν_{max} 2958, 2860, 1463, 1371, 1254, 1097, 1065, 831, 741, 702, 609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74–7.63 (m, 4H), 7.43–7.28 (m, 6H), 4.16 (ddd, $J = 12.9$, 7.9, 5.2 Hz, 1H), 4.03–3.99 (m, 1H), 3.84 (dd, $J = 7.6$, 5.8 Hz, 1H), 3.72–3.66 (m, 2H), 3.62–3.49 (m, 2H), 3.21 (t, $J = 7.8$ Hz, 1H), 2.18 (p, $J = 7.0$ Hz, 1H), 1.93 (dt, $J = 12.3$, 7.4, 1H), 1.78 (ddd, $J = 13.5$, 8.2, 3.9 Hz, 1H), 1.61–1.54 (m, 1H), 1.50 (dd, $J = 13.6$, 7.0 Hz, 1H), 1.31 (s, 3H), 1.36–1.27 (m, 1H), 1.26–1.22 (m, 1H), 1.21 (s, 3H), 1.06 (s, 9H), 0.89 (s, 9H), 0.81 (d, $J = 7.0$ Hz, 3H), 0.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.0, 135.9, 134.4, 134.2, 129.4, 127.3, 127.3, 108.4, 80.7, 78.1, 72.64, 72.5, 69.6, 61.0, 37.0, 35.3, 35.1, 34.1, 27.1, 26.9, 26.0, 25.7, 19.6, 18.3, 15.5, –5.3, –5.3. HRMS (ESI): $[M + H]^+$ calcd. for $C_{36}H_{59}O_5Si_2 = 627.3909$, found 627.3902.

2.32 *2-((2S,3S,5S)-5-((S)-1-(tert-Butyldiphenylsilyloxy)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-methyltetrahydrofuran-2-yl)ethanol* **(47)**

To a stirred solution of **48** (2 g, 3.18 mmol) in dry THF (15 mL) in a polypropylene vial, was added HF-Py complex (70%, 0.6 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. Then the reaction mixture was cautiously poured into saturated aqueous $NaHCO_3$ and stirred for 30 min. Then both the layers were separated, aqueous layer was further extracted with EtOAc (2×50 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (6 mL), water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 15% EtOAc/hexane) afforded compound **47** (1.45 g, 89% in three steps) as clear oil. $R_f = 0.3$ (SiO_2, 25% EtOAc in petroleum ether). $[\alpha]_D^{25} = -19.2$ (*c* 3.2, $CHCl_3$); IR (neat): ν_{max} 3457, 2955, 2926, 2855, 2749, 1456, 1378, 1243, 1191, 1084, 1021, 968, 823, 741, 703, 610 cm^{-1} ;^{1} H NMR (500 MHz, $CDCl_3$): δ 7.75–7.70 (m, 4H), 7.44–7.34 (m, 6H), 4.18–4.12 (m, 1H), 4.01 (ddd, $J = 8.1$, 5.3, 4.1 Hz, 1H), 3.83 (dd, $J = 7.6$, 5.8 Hz, 1H), 3.79–3.74 (m, 2H), 3.58–3.49 (m, 2H), 3.25 (t, $J = 7.7$ Hz, 1H), 2.21 (p, $J = 7.2$ Hz, 1H), 1.90 (ddd, $J = 12.4$, 7.8, 7.5 Hz, 1H), 1.78 (ddd, $J = 13.7$, 8.5, 3.9 Hz, 1H), 1.60 (ddd, $J = 13.8$, 8.0, 4.2 Hz, 1H), 1.55–1.49 (m, 1H), 1.48–1.42 (m, 1H), 1.37–1.32 (m, 1H), 1.31 (s, 3H), 1.21 (s, 3H), 1.04 (s, 9H), 0.81 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.0, 135.9, 134.2, 134.0, 129.5, 129.4, 127.4, 127.3, 108.5, 81.3, 80.4, 72.4, 72.3, 69.5, 61.4, 37.2, 35.5, 35.0, 32.9, 27.0, 27.0, 25.6, 19.6, 15.2. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{30}H_{44}O_5NaSi = 535.2854$, found 535.2855.

2.33 *tert-Butyl((S)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((2S,4S,5S)-5-((Z)-3-iodoallyl)-4-methyltetrahydrofuran-2-yl)ethoxy)diphenylsilane* **(49)**

To a stirred solution of **47** (1.3 g, 2.53 mmol) in dry CH_2Cl_2 (15 mL) were added $NaHCO_3$ (0.20 g, 2.53 mmol) and Dess-Martin periodinane (1.60 g, 3.79 mmol) sequentially at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred for 2 h at room temperature before being quenched with saturated aqueous $NaHCO_3$ (8 mL) and saturated aqueous $Na_2S_2O_3$ (8 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent furnished crude aldehyde, which was passed through a short pad of silica gel and used as such for the next reaction.

To a suspension of iodomethyl triphenylphosphonium iodide (4.01 g, 7.59 mmol) in anhydrous THF (25 mL) was added NaHMDS (7.59 mL, 1.0 M in THF, 7.59 mmol) at 0 °C under argon atmosphere. Then the reaction mixture was stirred for another 15 min at 0 °C before being cooled to −78 °C and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (1.52 mL, 12.65 mmol) was added followed by the addition of above aldehyde in dry THF (10 mL) *via* cannula. After 2 h stirring at −78 °C, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and stirred for 1 h at rt and extracted with EtOAc (2×60 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 5% EtOAc/hexane) afforded **49** (1.23 g, 77% over two steps) as a viscous liquid. $R_f = 0.6$ (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25} = -39.8$ (*c* 1.1, $CHCl_3$); IR (Neat): ν_{max} 2927, 2856, 2311, 1515, 1463, 1426, 1380, 1106, 1061, 821, 740, 702, 609 cm^{-1} ;^{1} H NMR (500 MHz, $CDCl_3$): δ 7.74–7.69 (m, 4H), 7.43–7.33 (m, 6H), 6.04 (dt, $J = 7.3$, 1.5 Hz, 1H), 5.75 (dt, $J = 7.3$, 5.5 Hz, 1H), 4.28–4.22 (m, 1H), 3.99–3.94 (m, 1H), 3.90 (dd, $J = 7.7$, 5.8 Hz, 1H), 3.69 (dt, $J = 8.8$, 6.8 Hz, 1H), 3.63 (ddd, $J = 10.9$, 6.7, 4.3 Hz, 1H), 3.31 (t, $J = 7.7$ Hz, 1H), 2.21–2.14 (m, 1H), 2.08–2.02 (m, 1H), 1.99–1.91(m, 2H), 1.74 (ddd, $J = 13.8$, 8.5, 3.6 Hz, 1H), 1.59 (ddd, $J = 12.8$, 8.4, 4.1 Hz, 1H), 1.32 (s, 3H), 1.23 (s, 3H), 1.25–1.21 (m, 1H), 1.03 (s, 9H), 0.89 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.1, 136.1, 136.0, 134.5, 134.0, 129.3, 129.2, 127.3, 127.2, 108.1, 82.6, 81.2, 79.7, 73.0, 72.5, 69.7, 37.3, 36.5, 35.5, 35.4, 27.1,

27.0, 25.7, 19.7, 15.3. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{31}H_{43}IO_4NaSi = 657.1882$, found 657.1875.

2.34 *(2S,4S)-4-(tert-Butyldiphenylsilyloxy)-4-((2S, 4S,5S)-5-((Z)-3-iodoallyl)-4-methyltetrahydrofuran-2-yl)butane-1,2-diol* **(50)**

To a stirred solution of **49** (1.0 g, 1.57 mmol) in dry CH_3CN (10 mL) was added $CuCl_2{\cdot}H_2O$ (0.80 g, 4.71 mmol) at −5 °C portion wise. Then the reaction mixture was stirred for 2 h before being quenched with H_2O (5 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under *vacuo.* The residue was purified by column chromatography (SiO_2, 29% EtOAc/hexane) to afford **50** (0.89 g, 95% yield over two steps) as a viscous liquid. R_f =0.2 (SiO_2, 30% EtOAc/hexane); $[\alpha]_D^{25} = -44.6$ (*c* 1.3, $CHCl_3$); IR (Neat): ν_{max} 3396, 2928, 2856, 1515, 1464, 1426, 1388, 1106, 821, 740, 701, 608 cm^{-1} ;[1] H NMR (400 MHz, $CDCl_3$): δ 7.73–7.67 (m, 4H), 7.45–7.35 (m, 6H), 6.09 (dt, J = 7.2, 1.5 Hz, 1H), 5.89–5.83 (m, 1H), 3.99–3.92 (m, 2H), 3.79–3.70 (m, 2H), 3.43 (dd, J = 11.0, 3.2 Hz, 1H), 3.28 (dd, J = 11.0, 6.4 Hz, 1H), 2.30 (brs, 2H), 2.27 (p, J = 7.1 Hz, 1H), 2.13–2.09 (m, 1H), 2.08–2.04 (m, 2H), 1.71 (ddd, J = 14.5, 10.4, 4.1 Hz, 1H), 1.44 (ddd, J = 14.2, 5.5, 1.8 Hz, 1H), 1.28–1.21 (m, 1H), 0.99 (s, 9H), 0.82 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138. 7, 136.1, 135.0, 133.8, 133.5, 129.7, 129.5, 127.6, 127.3, 83.1, 80.6, 80.1, 73.7, 69.0, 67.0, 36.4, 36.2, 35.7, 35.2, 27.0, 19.5, 15.5. HRMS (ESI): $[M + H]^+$ calcd. for $C_{28}H_{40}IO_4Si = 595.1744$, found 595.1742.

2.35 *(6S,8S)-8-((2S,4S,5S)-5-((Z)-3-Iodoallyl)-4-methyltetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10, 10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-ol* **(51)**

To a stirred solution of **50** (0.7 g, 1.17 mmol) in CH_2Cl_2 (10 mL), imidazole (0.12 g, 1.76 mmol) and TBDPSCl (0.45 mL, 1.76 mmol) were added sequentially at 0 °C. The reaction mixture was stirred for 4 h at room temperature before being quenched with saturated aqueous NH_4Cl (5 mL) solution and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated in *vacuo*. Purification of the residue by column chromatography (SiO_2, 9% EtOAc/hexane) afforded **51** (0.93 g, 95%) as clear oil. R_f = 0.45 (SiO_2, 15% EtOAc in petroleum ether). $[\alpha]_D^{25} = -35.9$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3395, 2925, 2855, 2311, 1514, 1465, 1427, 1108, 1107, 819, 740, 701, 609 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.75–7.69 (m, 4H), 7.65–7.62 (m, 4H), 7.45–7.32 (m, 12H), 6.01 (dt, J = 7.3, 1.5 Hz, 1H), 5.72 (dt, J = 7.3, 5.5 Hz, 1H), 4.04–3.98 (m, 1H), 3.92–3.86 (m, 1H), 3.80 (dd, J = 15.5, 7.2 Hz, 1H), 3.65 (ddd, J = 9.9, 6.4, 4.2 Hz, 1H), 3.47 (d, J = 5.3 Hz, 2H), 2.19 (p, J = 7.0 Hz, 1H), 2.09–2.02 (m, 1H), 2.00–1.92 (m, 2H), 1.61–1.56 (m, 2H), 1.17 (ddd, J = 14.9, 8.7, 6.7 Hz, 1H), 1.05 (s, 9H), 1.04 (s, 9H), 0.74 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.0, 136.1, 136.0, 135.5, 134.8, 133.8, 133.4, 129.7, 129.6, 129.4, 129.2, 127.7, 127.4, 127.2, 82.6, 81.0, 79.9, 73.6, 68.8, 68.3, 36.7, 36.4, 35.8, 35.3, 27.1, 26.8, 19.6, 19.2, 15.4. HRMS (ESI): $[M+H]^+$ calcd. for $C_{44}H_{58}IO_4Si_2 = 833.2920$, found 833.2917.

2.36 *(6S,8S)-8-((2S,4S,5S)-5-((Z)-3-Iodoallyl)-4-methyltetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10, 10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl 2-(diethoxyphosphoryl)acetate* **(46)**

To a stirred solution of **51** (0.7 g, 0.83 mmol) in dry CH_2Cl_2 (10 mL) was added diethyl phosphono acetic acid (0.4 mL, 2.50 mmol) followed by DMAP (0.020 g, 0.166 mmol) at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred for 10 min at 0 °C, and EDCI (0.479 g, 2.50 mmol) was added to it. After being stirred for 4 h at rt, the reaction mixture was quenched by the addition of water and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under *vacuo.* Purification of the residue by column chromatography (SiO_2, 35% EtOAc/hexane) afforded **46** (0.79 g, 95%) as yellow oil. R_f = 0.3 (SiO_2, 45% EtOAc/hexane); $[\alpha]_D^{25} = -40.3$ (*c* 0.6, $CHCl_3$); IR (Neat): ν_{max} 2928, 2857, 1737, 1693, 1515, 1466, 1428, 1391, 1266, 1108, 1027, 971, 820, 740, 702, 611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70–7.67 (m, 2H), 7.65–7.61 (m, 6H), 7.46–7.28 (m, 12H), 5.98 (dt, J = 7.5, 7.3 Hz, 1H), 5.60 (dt, J = 7.4, 5.3 Hz, 1H), 5.27–5.21 (m, 1H), 4.10–3.01 (m, 4H), 3.75 (ddd, J = 11.0, 7.2, 4.1 Hz, 1H), 3.68–3.62 (m, 2H), 3.59–3.62 (m, 2H), 2.71–2.69 (dd, J = 21.3, 4.0 Hz, 2H), 2.15 (p, J = 7.1 Hz, 1H), 2.06–2.00 (m, 1H), 1.97–1.90 (m, 2H), 1.82–1.77 (m, 1H), 1.68–1.62 (m, 2H), 1.23 (dt, J = 7.1, 2.1 Hz, 6H), 1.04 (s, 9H), 1.01 (s, 9H), 0.75 (d, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.00, 139.1, 136.2, 135.8, 135.6, 135.5, 134.8, 133.6, 133.3, 129.7, 129.3, 129.0, 127.7, 127.4, 127.0, 82.5, 80.9, 79.7, 72.7, 72.8, 72.5, 64.9, 62.6, 62.5, 60.4, 35.9, 35.2, 35.1, 27.2, 26.8, 19.6, 19.2, 16.3, 15.5. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{50}H_{68}INaO_8PSi_2 = 1033.3146$, found 1033.3135.

2.37 *(E)-((6S,8S)-8-((2S,4S,5S)-5-((Z)-3-Iodoallyl)-4-methyltetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan -6-yl) 4-((2S,4R,6R)-4-(tert-butyldimethylsilyloxy)-6-((R)-2-methylbut-3-enyl)tetrahydro-2H-pyran-2-yl)but -2-enoate* **(45)**

To a mixture of compound **46** (0.369 g, 0.365 mmol) and LiCl (0.024 g, 0.608 mmol) in MeCN (6 mL) was added DBU (0.045 mL, 0304 mmol) at 0 °C under argon atmosphere. After being stirred for 15 min at room temperature, the mixture was again cooled to 0 °C and a solution of aldehyde **28** (0.100 g, 0.304 mmol) in MeCN (5 mL) was added dropwise

via cannula. Then the reaction mixture was stirred for 12 h at room temperature before being quenched by the addition of water and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 60–120 mesh, 6% EtOAc/hexane) afforded **45** (0.284 g, 79% two steps) as a colorless oil. R_f = 0.5 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = −19.4 (*c* 1, $CHCl_3$); IR (Neat): ν_{max} 2929, 2857, 1723, 1658, 1518, 1466, 1428, 1379, 1257, 1172, 1074, 999, 837, 776, 740, 610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.68–7.60 (m, 8H), 7.45–7.27 (m, 12H), 6.91 (dt, *J* = 15.7, 7.3 Hz, 1H), 5.96 (dt, *J* = 7.3, 1.3 Hz, 1H), 5.76 (dt, *J* = 15.6, 1.3 Hz, 1H), 5.69 (dd, *J* = 17.5, 10.2 Hz, 1H), 5.55 (dt, *J* = 7.3, 5.2 Hz, 1H), 5.29–5.23 (m, 1H), 4.93 (dt, *J* = 17.2, 1.3 Hz, 1H), 4.92–4.88 (m, 1H), 3.77–3.64 (m, 5H), 3.54 (ddd, *J* = 9.7, 6.4, 4.1 Hz, 1H), 3.40–3.34 (m, 1H), 3.33–3.27 (m, 1H), 2.47–2.40 (m, 1H), 2.36–2.29 (m, 2H), 2.11 (p, *J* = 6.8 Hz, 1H), 2.04–1.75 (m, 6H), 1.68–1.56 (m, 2H), 1.36–1.14 (m, 4H), 1.04 (s, 9H), 1.00 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.68 (d, *J* = 7.0 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 145.1, 144.4, 139.2, 136.2, 135.9, 135.6, 135.5, 135.0, 133.5, 133.4, 129.6, 129.2, 128.9, 127.6, 127.6, 127.4, 127.0, 123.9, 112.4, 82.4, 80.0, 79.7, 74.1, 73.6, 72.8, 71.4, 68.7, 65.3, 42.4, 41.4, 38.8, 36.3, 36.0, 35.2, 35.1, 34.0, 27.2, 26.8, 25.8, 20.1, 19.8, 19.2, 18.1, 15.5, –4.5, –4.5. HRMS (ESI): $[M+NH_4]^+$ calcd. for $C_{64}H_{95}O_7NISi_3$ = 1200.5461, found 1200.5455.

2.38 *(1R,3R,4E,6Z,9S,10S,12S,13S,15S,18E,21S,23R)-23-((tert-Butyldimethylsilyl)oxy)-13-((tert-butyldiphenylsilyl)oxy)-15-(((tert-butyldiphenylsilyl)oxy)methyl)-3,10-dimethyl-16,25,26-trioxatricyclo[19.3.1.19,12]hexacosa-4,6,18-trien-17-one* (44)

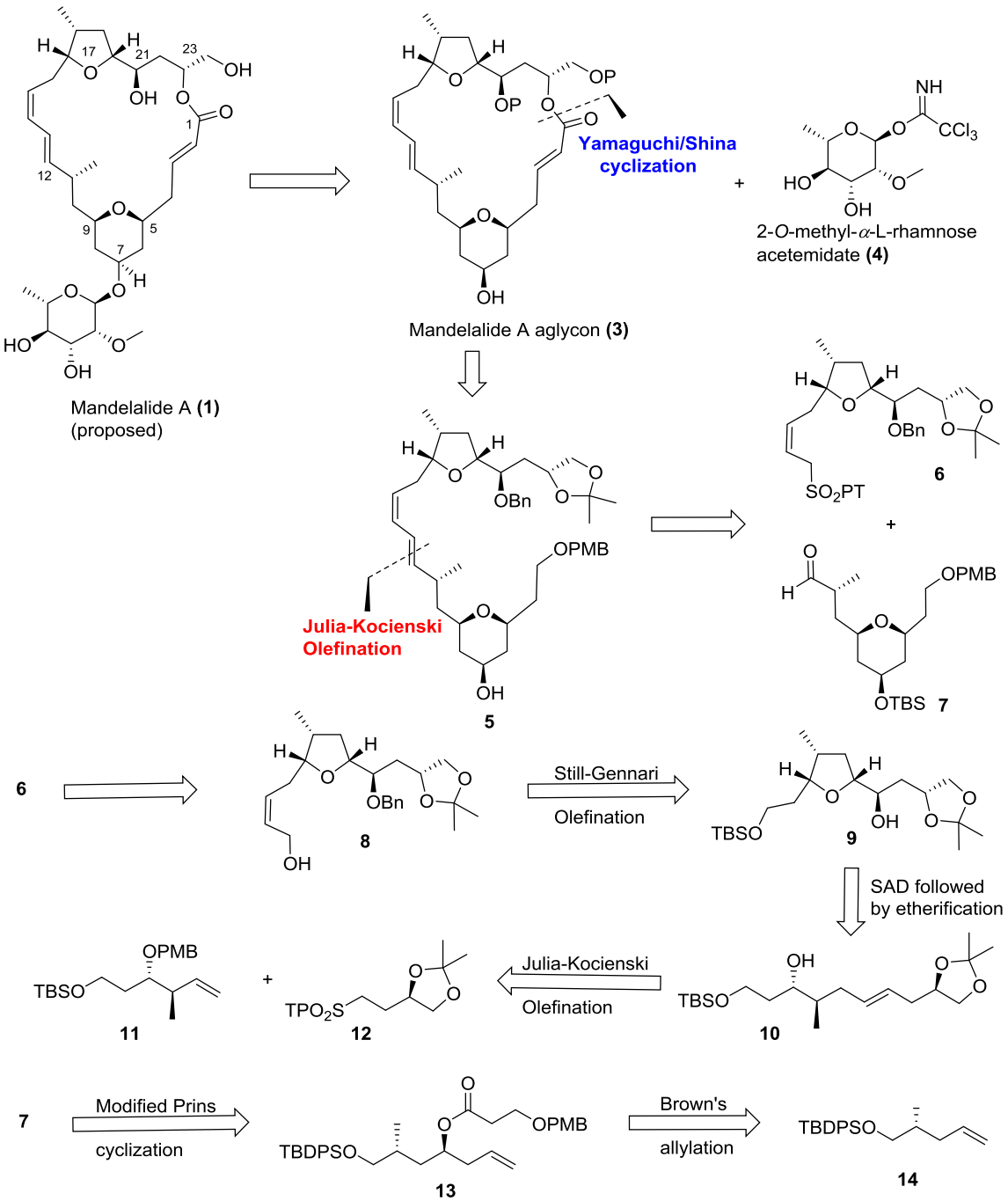
To a stirred solution of vinyl iodide **45** (0.1 g, 0.084 mmol) which was previously azeotroped with benzene, in dry DMF (20 mL) were added Cs_2CO_3 (0.046 g, 0.142 mmol), Et_3N (0.014 mL, 0.10 mmol) and $Pd(OAc)_2$ (0.028 g, 0.126 mmol) sequentially at rt under argon atmosphere. Then the reaction mixture was stirred for 24 h at room temperature before being quenched by the addition of water and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under *vacuo*. Purification of the residue by column chromatography (SiO_2, 60–120 mesh, 5% EtOAc/hexane) afforded **44** (0.059 g, 67%) as colourless oil. R_f = 0.35 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = +14.8 (*c* 0.15, CH_2Cl_2); IR (Neat): ν_{max} 2927, 2856, 1722, 1653, 1464, 1428, 1380, 1258, 1173, 1108, 1075, 833, 776, 739, 703, 611 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$): δ 7.66–7.60 (m, 8H), 7.43–7.26 (m, 12H), 6.89 (ddd, *J* = 15.6, 7.7, 6.0 Hz, 1H), 6.22 (dd, *J* = 15.1, 11.0 Hz, 1H), 5.94 (t, *J* = 10.8 Hz, 1H), 5.84 (dt, *J* = 15.8, 1.2 Hz, 1H), 5.53 (dd, *J* = 15.2, 8.1 Hz, 1H), 5.23–5.17 (m, 2H), 4.02 (ddd, *J* = 8.7, 5.6, 3.0 Hz, 1H), 3.79–3.69 (m, 2H), 3.63–3.60 (m, 2H), 3.55 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.40–3.35 (m, 1H), 3.31–3.26 (m, 1H), 2.40 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.37–2.30 (m, 1H), 2.18–2.11 (m, 2H), 2.00 (dt, *J* = 13.9, 7.2 Hz, 1H), 1.92 (ddd, *J* = 14.3, 8.3, 3.0 Hz, 1H), 1.83–1.71 (m, 4H), 1.65–1.60 (m, 1H), 1.38 (ddd, *J* = 13.1, 7.6, 5.5 Hz, 1H), 1.34–1.28 (m, 2H), 1.24–1.17 (m, 2H), 1.00 (s, 18H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 7.1 Hz, 3H) 0.87 (s, 9H), 0.06 (s, 6H) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ 165.7, 145.2, 140.1, 136.0, 135.9, 135.6, 135.6, 134.7, 134.0, 133.5, 133.4, 129.9, 129.5, 129.3, 127.6, 127.3, 127.3, 126.8, 124.3, 123.3, 81.2, 80.1, 73.8, 73.2, 72.7, 71.6, 68.8, 65.5, 43.0, 41.9, 41.8, 38.5, 35.7, 34.4, 34.1, 33.3, 30.2, 27.2, 26.7, 25.8, 20.2, 19.5, 19.2, 18.1, 15.2, −4.5. HRMS (ESI): $[M+NH_4]^+$ calcd. for $C_{64}H_{94}O_7NSi_3$ 1072.6332, found 1072.6339.

3. Results and Discussion

As mentioned above, we started working on the total synthesis of mandelalide A after its immediate isolation. Therefore initially we targeted the proposed structure of mandelalide A. Thus retrosynthetically, we envisioned that late-stage glycosylation of the macrocycle **3** with L-Rhamnose derived acetamide using regular protocols would construct the proposed structure of the natural product in its protected form (Scheme 1). Disconnection of macrocycle **3** led to the two key building blocks **6** and **7** with similar complexity, required for its construction using Julia-Kocienski olefination[6] followed by Yamaguchi/Shina macrolactonization. We realized that the compound **6** could be obtained from **9** using Still-Gennari olefination[7] which in turn could be obtained from **10** by means of Sharpless asymmetric dihydroxylation[8] with concomitant Williamson type etherification.[9] Compound **10** could be synthesized *via* coupling of **11** and **12** by means of Julia-Kocienski olefination. Compound **7** was expected to be synthesized from ester **13** using Prins cyclization.

As a manifestation of our synthetic strategy, the construction of building block **6** commenced (Scheme 2) from the known compound **11**, which was prepared from compound **15** in two steps according to the reported procedure.[10] Hydroboration of **11** with $BH_3{\cdot}SMe_2$ followed by oxidation with H_2O_2 furnished primary alcohol **16** in 83% yield. The primary alcohol **16** was subjected to DMP oxidation to provide an aldehyde, which on Julia-Kocienski olefination[6] with known sulfone **12**[11] afforded *E*-olefinic compound **17** in 81% yield over two steps.

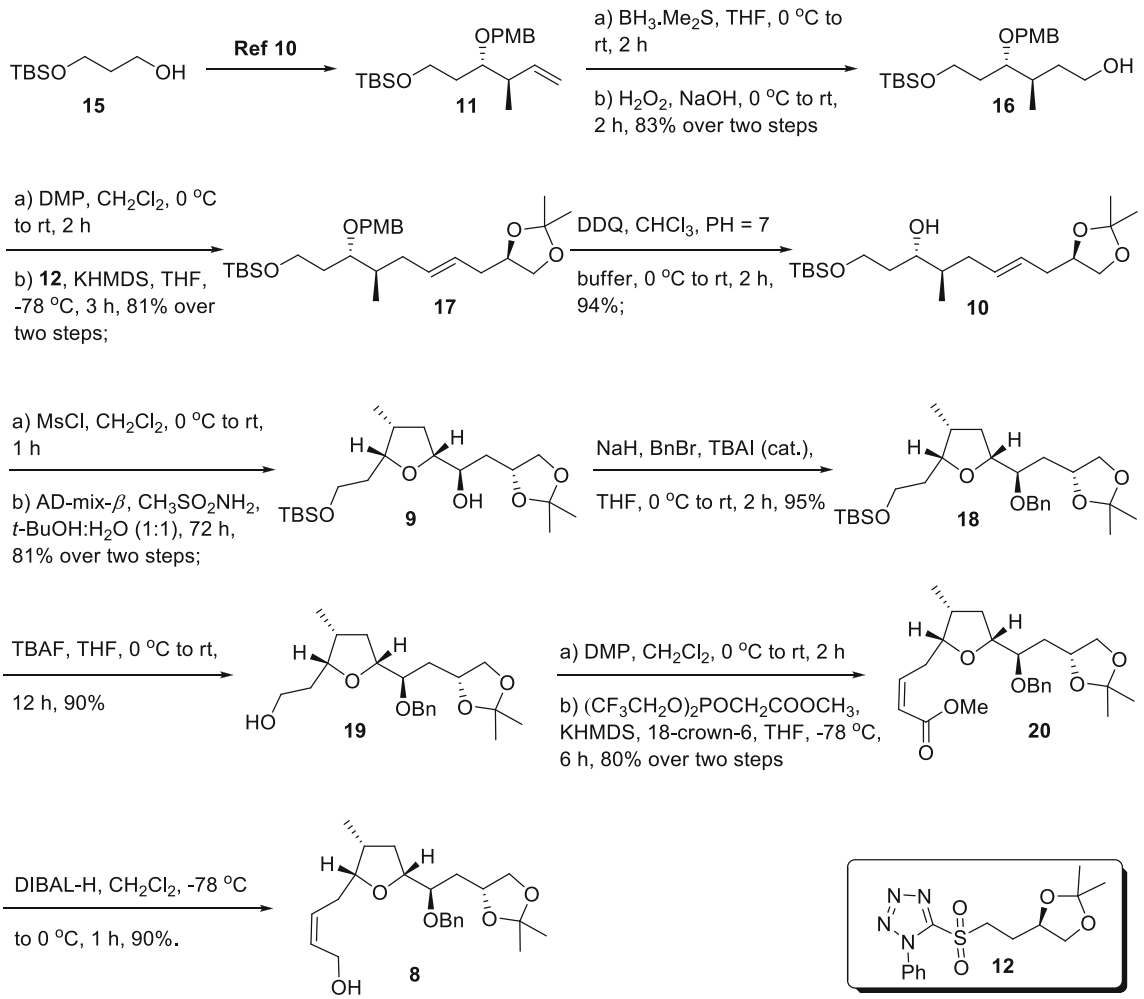
The oxidative deprotection of PMB ether with DDQ gave secondary alcohol **10** in 94% yield.[12] Mesylation of the free hydroxyl group in **10** followed by Sharpless asymmetric dihydroxylation using AD-mix-β



Scheme 1. Retrosynthetic analysis of the proposed structure of mandelalide A.

furnished diol, which underwent intramolecular cycloetherification and furnished the tetrahydrofuran ring **9** in 81% yield over two steps. Benzyl protection of the secondary hydroxyl of **9** with BnBr and NaH in the presence of catalytic amount of TBAI in THF gave compound **18** that was treated with TBAF in THF to furnish primary alcohol **19** in 85% yield over two steps. Oxidation of the primary alcohol **19** was carried out with DMP to give an aldehyde, which was subjected to Z-selective Still-Gennari olefination[7] to provide α,β-unsaturated ester **20** ($E{:}Z$ = 96:4) in 80% yield (over two steps). DIBAL-H mediated reduction of the α,β-unsaturated ester completed the synthesis of Z-allylic alcohol fragment **8** in 90% yield.

After synthesizing the alcohol fragment **8**, we turned our attention to the synthesis of pyran fragment **7** from the known compound **14**[13] (Scheme 3). Ozonolysis of **14** furnished an aldehyde, which was subjected to Brown's allylation[14] with (–)-Ipc$_2$BOMe and allyl magnesium bromide at −78 °C to give the alcohol **21** in 72% yield

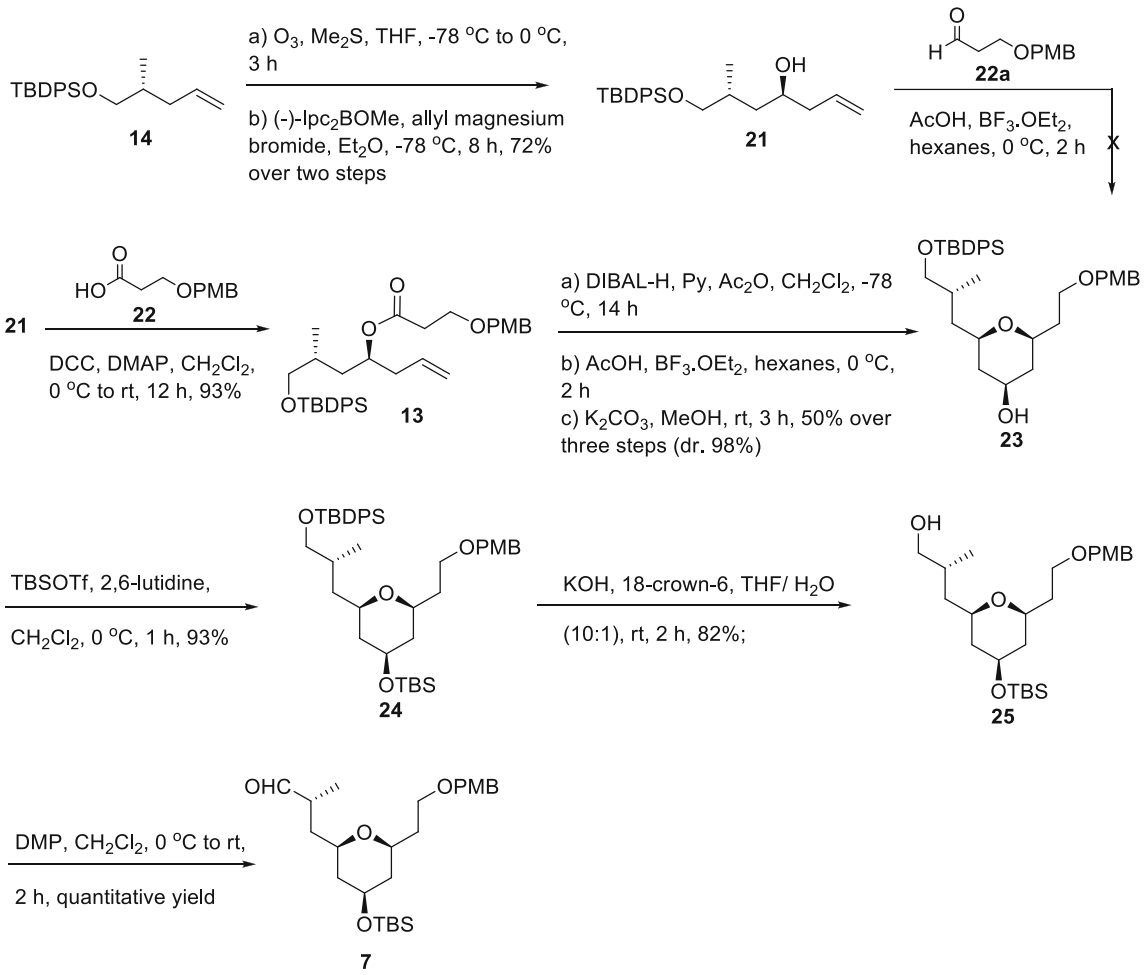


Scheme 2. Synthesis of alcohol fragment **8**.

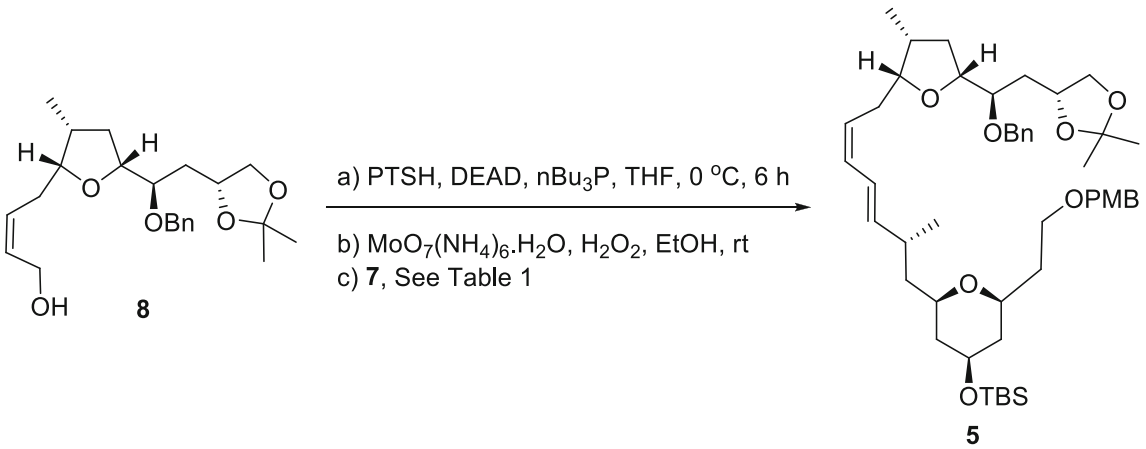
over two steps, with excellent diastereoselectivity (dr > 20:1). Prins cyclization[15] between aldehyde **22a** and the homoallylic alcohol **21** was unsuccessful to produce the desired product **23**. Therefore we planned to synthesize the tetrahydropyran unit *via* segment coupling Prins cyclization.[16] Accordingly, acylation of alcohol **21** with acid **22** was carried out under DCC-DMAP conditions to provide compound **13** in 93% yield. The controlled reduction of ester **13** with DIBAL-H gave a hemiacetal, which on acetyl protection followed by $BF_3{\cdot}OEt_2$ and acetic acid-mediated Prins cyclization in hexane at 0 °C and deprotection of the C4-OAc of resulting pyran ring afforded desired pyran alcohol **23** in 50% yield (over three steps). Protection of resulting hydroxyl group of **23** as its TBS ether and subsequent efficient removal of the TBDPS group under basic conditions furnished primary alcohol **25** in 77% yield over two steps. Finally, DMP oxidation of primary alcohol **25** furnished aldehyde **7** in quantitative yield.

After synthesizing these two key building blocks, we focused our attention to the stitching of these units *via* Julia-Kocienski olefination to accomplish the crucial coupled product **5** (Scheme 4). Accordingly, compound **8** was converted to sulfone under Mitsunobu conditions[17] followed by oxidation and then subjected to Julia-Kocienski olefination with aldehyde **7**, under assorted conditions as shown in Table 1, which were preceded abortive to furnish precursor for macrocyclization. Thus, this strategy was not pursued further for the synthesis of **3**.

The failure of Julia-Kocienski olefination forced us to devise an alternate strategy. We anticipated that the pre-installation of the α,β-unsaturated double bond at C2-C3 position followed by late-stage ring closing metathesis protocol might provide the desired macrocycle **3.** As depicted in Scheme 5, Masamune-Roush olefination[18] between **27** and **28** would give **26** that could be cyclized *via* a ring-closing metathesis reaction.[19] The phosphonate **27** would be obtained from **29**, which in turn could be obtained from **30** *via* oxidation followed by Nozaki-Hiyama reaction[20] and Peterson-type *syn* elimination.[21]



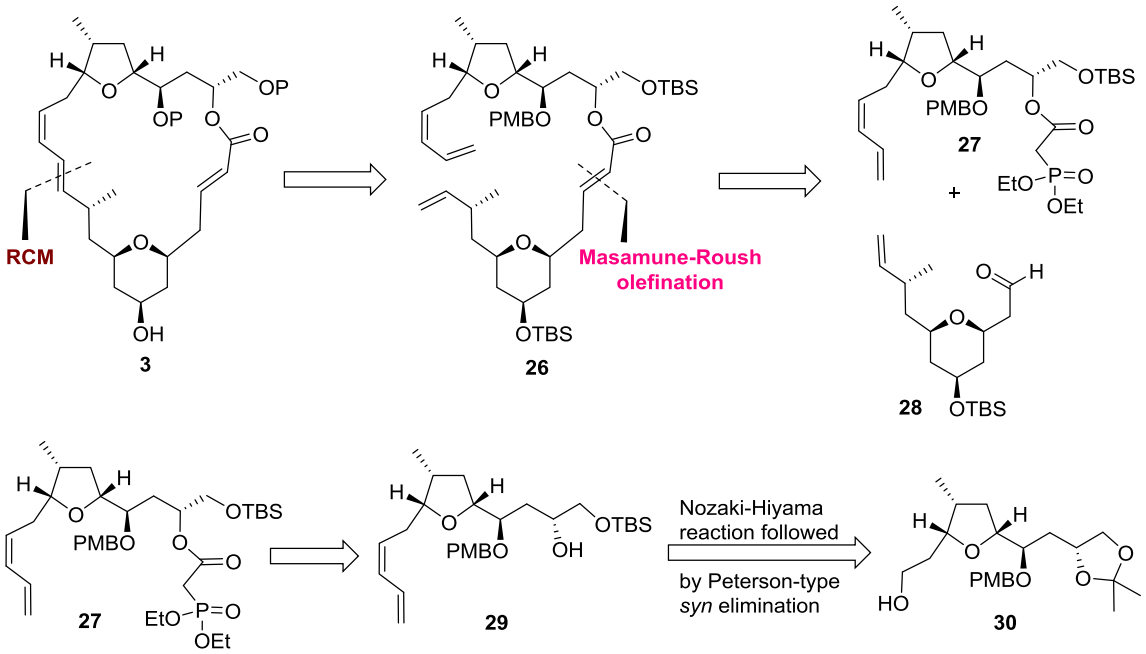
Scheme 3. Synthesis of pyran fragment **7**.



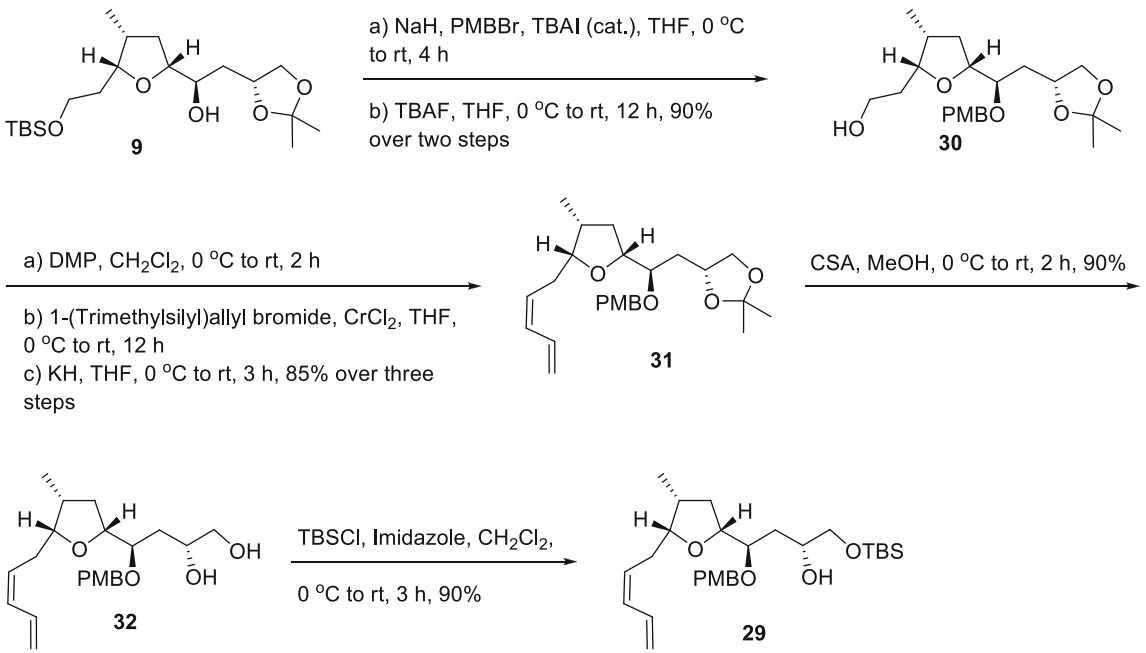
Scheme 4. Coupling of fragments **6** and **7** using Julia-Kocienski olefination.

Table 1. Screened conditions Julia-Kocienski olefination.

Entry	Conditions	Temperature	Time	Yield
1	KHMDS, THF	−78 °C	2.5 h	0%
2	*n*-BuLi, THF	−78 °C	1.5 h	0%
3	*t*-BuLi, THF	−78 °C	1.5 h	0%



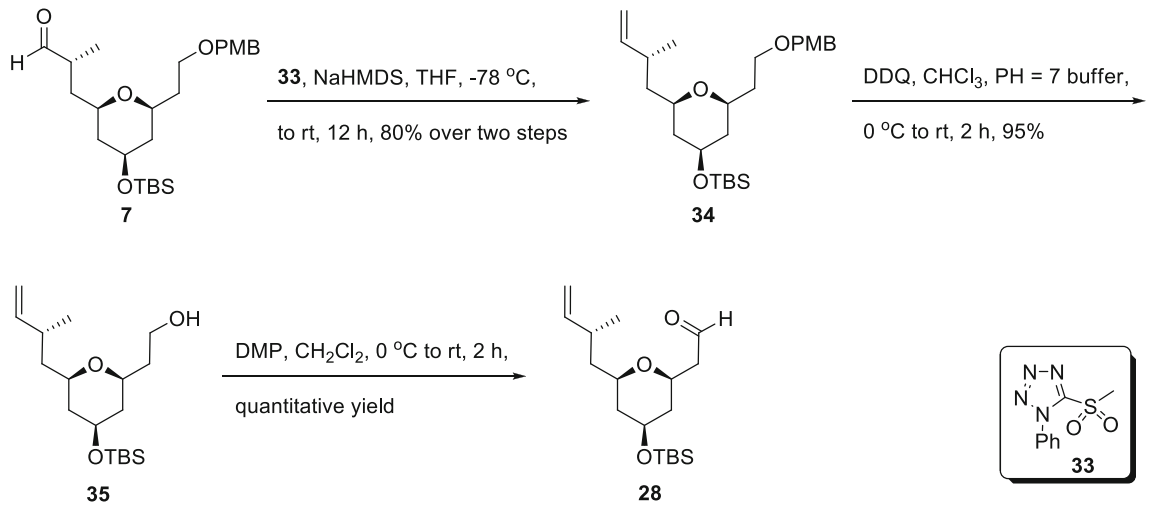
Scheme 5. Modified strategy for the construction of macrocycle **3**.



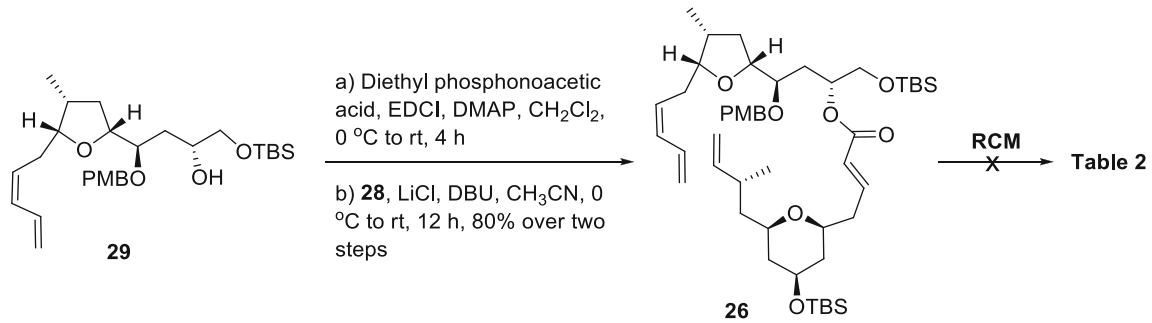
Scheme 6. Synthesis of diene fragment **29**.

As per the retrosynthetic plan the synthesis commenced from compound **9** (Scheme 6), which on PMB-protection as its PMB ether followed by TBS deprotection with TBAF in THF furnished primary alcohol **30** in 90% yield over two steps. Oxidation of **30** with DMP furnished an aldehyde, which was subjected to Nozaki-Hiyama reaction with allyl chromium reagent[22] generated in situ from allyl TMS bromide and chromium (II) chloride followed by Peterson–type *syn* elimination to furnish the required (*Z*)-diene compound **31** in 85% yield. Acetonide deprotection and chemoselective protection of primary alcohol as its TBS ether provided compound **29** in 90% yield.

The synthesis of the aldehyde **28** is depicted in Scheme 7. Olefination of aldehyde **7** *via* modified Julia reaction with known sulfone **33**[23] gave olefin compound **34** in 80% yield over two steps. Deprotection of PMB group afforded a primary alcohol **35** in 95% yield, which



Scheme 7. Synthesis of pyran aldehyde fragment **28**.



Scheme 8. Coupling of fragments for the synthesis of macrocycle **3**.

Table 2. Screened conditions for ring closing metathesis reaction.

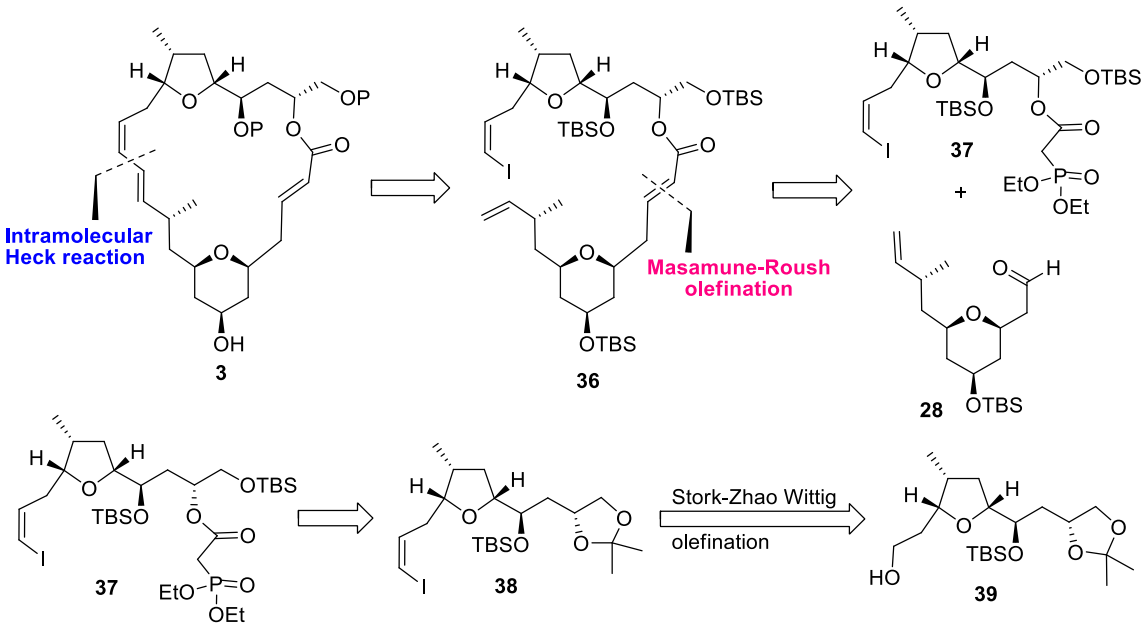
Entry	Catalyst	Conditions	Yield
1	Grubbs I (10%)	CH_2Cl_2, 12 h, rt	0%
2	Grubbs II (10%)	Toluene, 12 h, rt	0%
3	Hoveyda-Grubbs catalyst (10%)	Toluene, 12 h, rt	0%

on oxidation with DMP gave aldehyde **28** in quantitative yield.

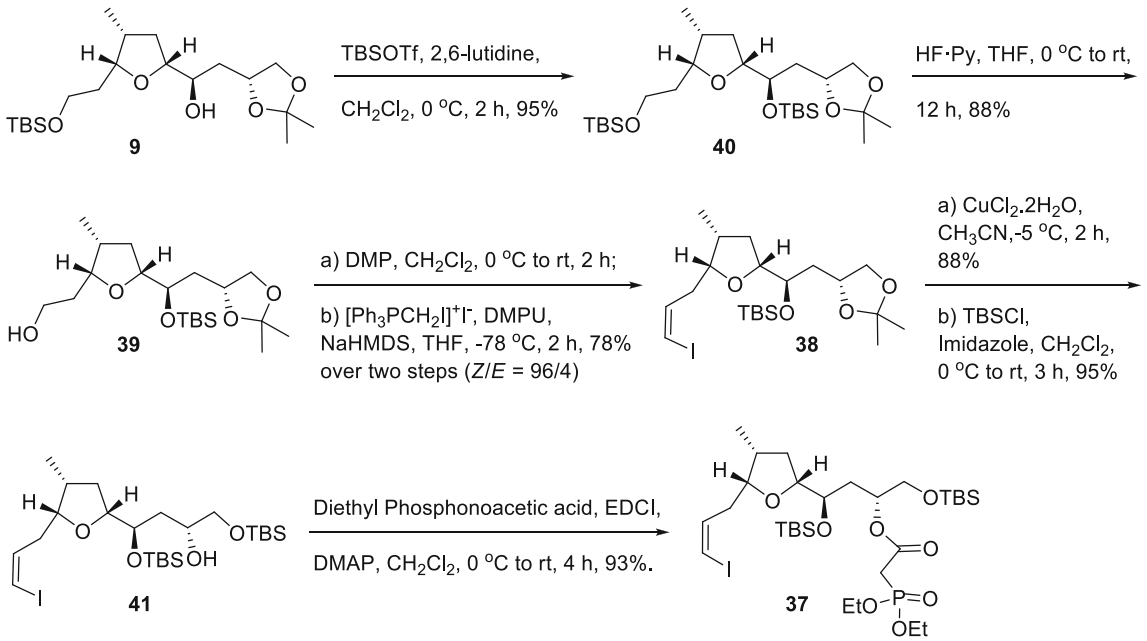
With the two key fragments in hand, we focused our attention on the stereocontrolled union of these fragments (Scheme 8) to reach the desired macrocycle. To this end, **29** was acylated with diethyl phosphonoacetic acid to give a phosphonate intermediate which underwent Masamune-Roush[18] smoothly with the aldehyde **28** and furnished ring-closing metathesis precursor **26** in 80% yield. Now the stage was set for the crucial macrocyclization, but miserably the ring-closing metathesis reaction under a variety of conditions, as shown in Table 2 had failed to provide the desired cyclised product.

Having professed the difficulties in synthesizing the macrocycle **3** with either of the two sequences (as shown in Scheme 1 and 5), we decided at this juncture to follow the sequence depicted in Scheme 9. We realized that a compound **36** would give the desired aglycone *via* intramolecular Heck cyclization[5] and the compound **36** would be accessed from **37** and **28** *via* Masamune-Roush olefination. The phosphonate **37** could be obtained from **38**, *via* protecting group manipulation followed by acylation with diethyl phosphonoacetic acid. The vinyl iodide compound **38** would be obtained from **39** *via* oxidation followed by Stork-Zhao Wittig olefination.[24]

Thus the synthesis of phosphonate **37** commenced from compound **9** (Scheme 10), which on TBS protection followed by selective removal of primary TBS furnished compound **39** in 84% yield over two steps. DMP-oxidation of the primary alcohol **39** gave an



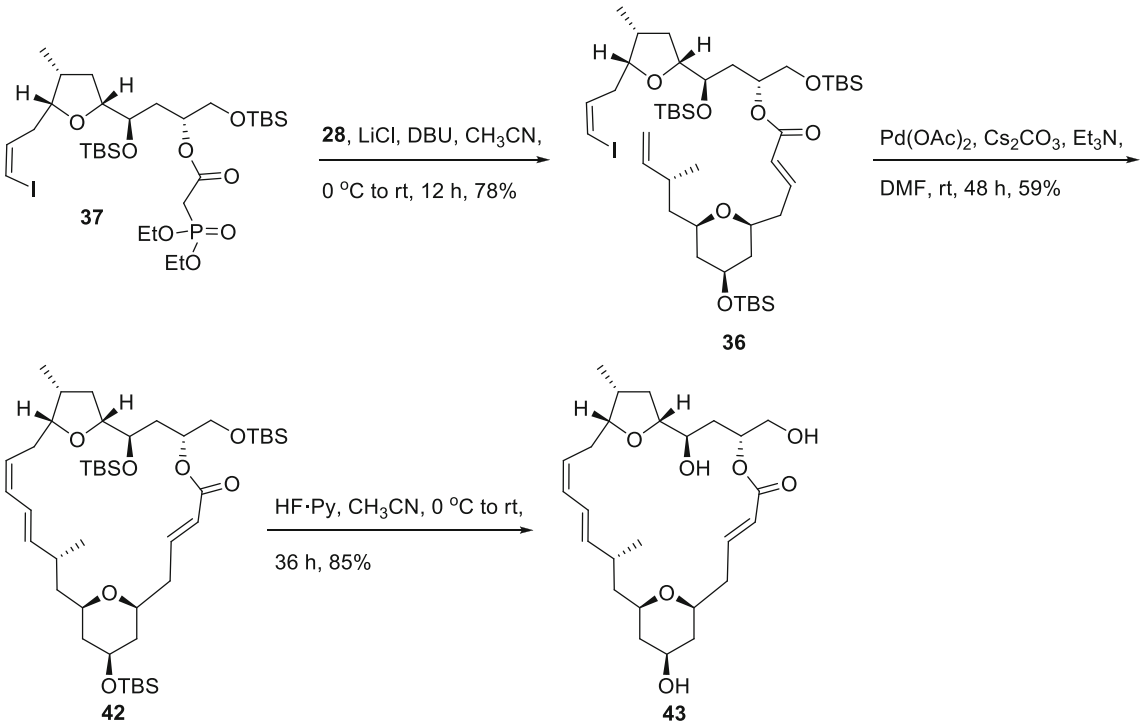
Scheme 9. Retrosynthetic analysis for construction of macrocycle **3** using intramolecular Heck cyclization.



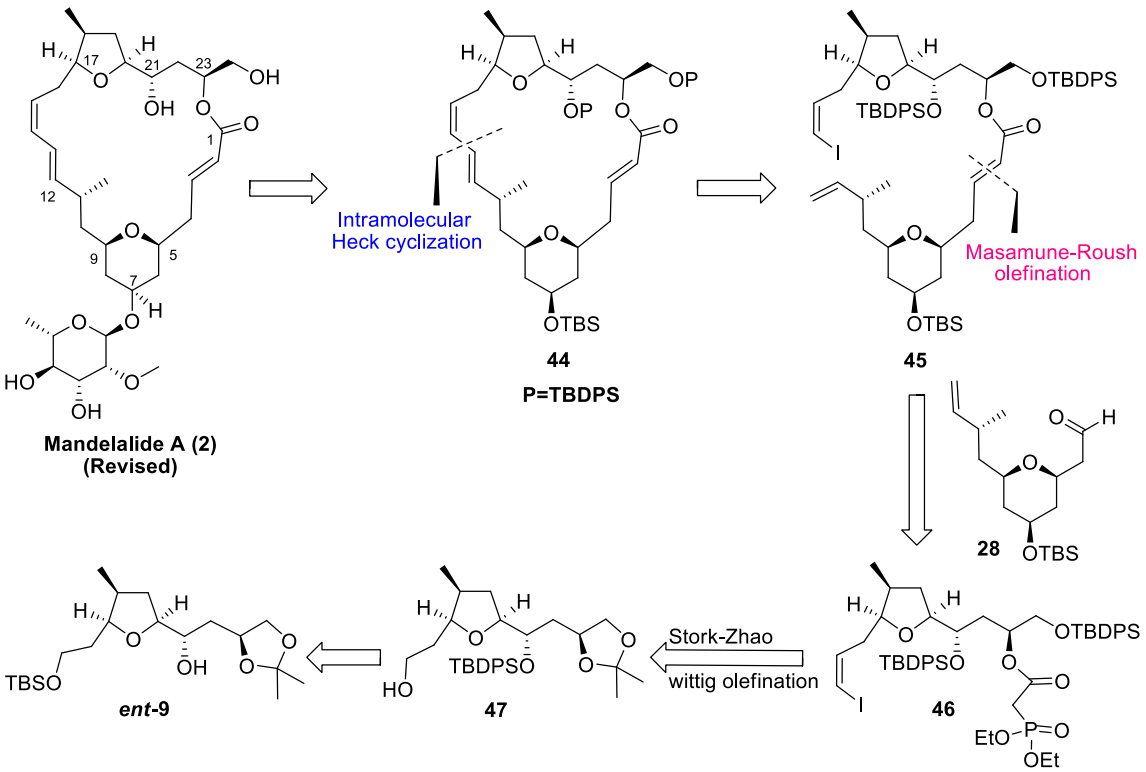
Scheme 10. Synthesis of phosphonate **37**.

aldehyde which on Stork-Zhao-Wittig[24] afforded the Z-vinyl iodide **38** in 78% yield (Z/E = 96/4) over two steps. The deprotection of acetonide in presence of TBS was a difficult task. Under acidic conditions, TBS deprotection along with acetonide deprotection occurred. Finally, $CuCl_2 \cdot 2H_2O$ in CH_3CN at $-5\,^{\circ}C$ deprotected the acetonide without affecting TBS group in 88% yield.[25] Chemoselective protection of primary alcohol as its TBS ether followed by esterification with diethyl phosphonoacetic acid completed the synthesis of phosphonate fragment **37** in 93% yield.

Now to synthesize the aglycone of the mandelalide A (**1**) *via* intramolecular Heck cyclization, Masamune-Roush olefination reaction between **37** and **28** was carried out to give compound **36** in 78% yield (Scheme 11).[18] Now the stage was set to carry out the intramolecular Heck cyclization[5] by using $Pd(OAc)_2$ in the presence of Cs_2CO_3 to give fully protected aglycone **42** in 59% yield which on global deprotection using HF·Py resulted in the aglycone of the proposed structure of mandelalide A **43** in 85% yield[5].

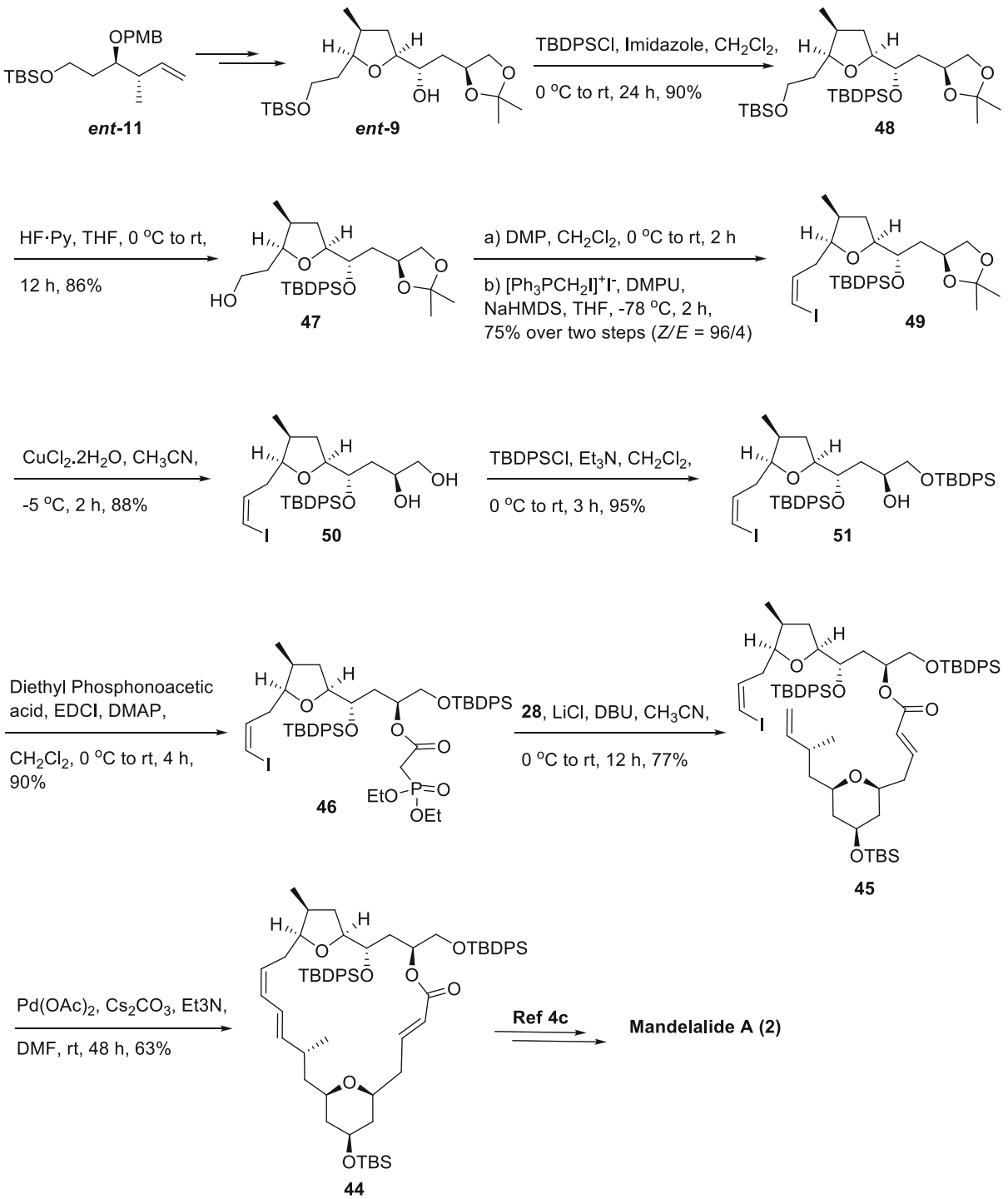


Scheme 11. Synthesis of proposed mandelalide A aglycone.



Scheme 12. Final strategy for the construction of precise mandelalide A (**2**).

Now at this stage, the structure of mandelalide was revised to **2** (Figure 1) and we had decided to synthesize the actual structure of mandelalide A. However to synthesize the revised structure of mandelalide A, we had to synthesize the aglycone with orthogonal protecting groups at C24-OH, C23-OH and C7-OH. Thus, mandelalide A could be synthesized from aglycone **44** *via* the selective deprotection of TBS at C7-OH followed



Scheme 13. Formal total synthesis of mandelalide A (**2**).

by glycosidation. Fully protected aglycone **44** could be obtained from compound **45** *via* intramolecular Heck cyclization, which in turn could be obtained from **46** and **29** *via* Masamune-Roush olefination. Finally, compound **46** would be obtained from *ent*-**9** *via* compound **47**.

Thus our synthesis started with the *ent*-**9** compound, which was synthesized from *ent*-**11** following the same sort of reactions as described in Scheme 2. TBDPS protection of the secondary alcohol of *ent*-**9** gave compound **48** in 90% yield, which on treatment with HF · Py in THF at 0 °C furnished primary alcohol **47** in 86% yield. Oxidation of the primary alcohol **47** was carried out with DMP to give an aldehyde, which on reaction with the ylide generated from $[Ph_3PCH_2I]^+I^-$ with KHMDS gave *Z*-vinyl iodide **49** in 75% yield ($Z/E = 96/4$) over

two steps. Acetonide deprotection with $CuCl_2 \cdot 2H_2O$ at −5 °C gave diol **50** in 88% yield. Selectively primary alcohol was protected as TBDPS ether to give compound **51** followed by acylation of secondary alcohol with diethyl phosphonoacetic acid under EDCI/DMP conditions afforded the phosphonate **46** in 90% yield. Now the coupling reaction between aldehyde **28** and phosphonate **46** was accomplished by Masamune-Roush olefination[18] in presence of DBU and LiCl faithfully delivered compound **45** in 77% yield, which on intramolecular Heck cyclization[5] afforded compound **44**[4c] in 63% yield, whose spectral and analytical data were in good agreement with the literature report.

4. Conclusions

In summary, a formal total synthesis of mandelalide A (**2**) has been achieved in 31 total steps (17 longest linear sequences from compound **15**) with 10.2% overall yield by utilizing intramolecular Heck cyclization as a key step. The other key reactions utilized in the synthesis are Julia-Kocienski olefination, asymmetric dihydroxylation followed by *in situ* cycloetherification and Masamune-Roush olefination reactions. The strategy developed here is highly flexible for the synthesis of analogues of nanomolar cytotoxic agent mandelalide A, that could be potentially useful in the field of non-small cell lung cancer (NSCLC). The Julia-Kocienski olefination and the ring closing metathesis were also investigated for the union of the building blocks and stereoselective formation of macrocycle **3** and found unsuccessful as a means to construct the mandelalide A.

Supplementary Information (SI)

^1H and ^{13}C NMR spectra of all new compounds are available in Supplementary Information at www.ias.ac.in/chemsci.

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