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Synthesis of Novel Migrastatin and Dorrigocin A Analogues from D-Glucal

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Abstract: The synthesis of a range of analogues of the migrastatin macrolide core has been achieved from tri-*O*-acetyl-D-glucal in order to facilitate structure–activity studies. Efficient macrolactone formation was achieved in the presence of a reactive olefin, by increasing steric hindrance in the olefin environment. Acyclic analogues of migrastatin, structurally related to dorrigocin A, have also been prepared from D-glucal. The dorrigocin A analogues were prepared using the combination of the cross metathesis of ethyl 6-heptenoate with a glycal derivative and a subsequent allylic rearrangement–alkene isomerisation reaction (Perlin reaction). A synthetic route is thus provided that will enable dorrigocin A analogues to be prepared in parallel to migrastatin analogues in the search for novel anti-cancer and anti-arthritic therapeutics. Biological evaluation of one migrastatin and one dorrigocin A sugar derived analogue show that they inhibit proliferation and serum-induced migration of tumour and synovial cells at higher concentrations than evodiamine. Dorrigocin A analogues displayed similar potency to analogues of the migrastatin core.

Keywords: allylic rearrangement · cancer · carbohydrates · metathesis · natural products

Indroduction

Cell migration is involved in a number of physiological processes, including ovulation, embryonic development, tissue regeneration, and inflammation.[1] Cell migration is also observed in pathological conditions such as tumour angiogenesis, cancer cell invasion and metastasis and consequently inhibitors have significant potential as a novel therapy for cancer. Migrastatin **1**, a natural product derived from isomigrastatin, is an inhibitor of cell migration.[2,3] The first total chemical synthesis of **1** was achieved by Danishefsky and co-workers[4] and recently an alternative route has been described by Reymond and Cossy.[5] A semi-synthetic approach has been described to **1** from isomigrastatin by Shen and co-workers.[6] The preparation of migrastatin analogues, a diversion from the total synthesis of **1** by the Danishefsky group, led to the identification of simpler analogues such as **3**, based on the macrolide core, that are ~1000-fold more potent than migrastatin in cell migration assays in vitro.[7] The macrolactam **4a** and macroketone **4b** (Scheme 1), close structural analogues to **3**, block Rac activation. Rac is a small GTPase and controls levels of cellular cGMP. The Rac/cGMP pathway has recently been shown to be involved in platelet derived growth factor induced fibroblast cell migration and lamellipodia formation.[8] The migrastatin derivatives **4** nearly completely inhibit lung metastasis of highly metastatic mammary carcinoma cells in mouse models indicating promise for such macrocyclic compounds as anti-metastatic agents.[9] They also inhibit metastasis of breast cancer cells, prostate cancer cells, and colon cancer cells but not normal mammary-gland epithelial cells, fibroblasts, and leukocytes, indicating they are specific small-molecule inhibitors of tumour metastasis. More recently quinic acid based macrolides have been synthesized that inhibit murine 4T1 breast tumour cell migration.[10] In addition, dorrigocin A **2** also derived from isomigrastatin, and related to migrastatin by hydrolysis of the lactone and isomerisation of one alkene group, displays interesting biological properties, inhibiting the carboxymethyltransferase involved in Ras processing[11] and reversing the morphology of ras-transformed NIH/3T3 cells.[12] The synthesis of a fragment of 2,3-dihydrodorrigocin A has been achieved[13] but the biological evaluation of this fragment has not been described. As part of a goal in the

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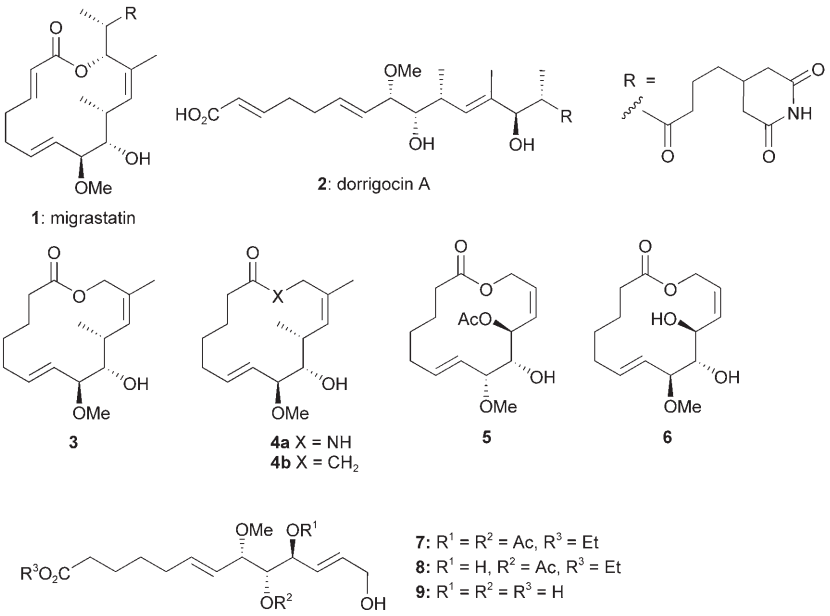
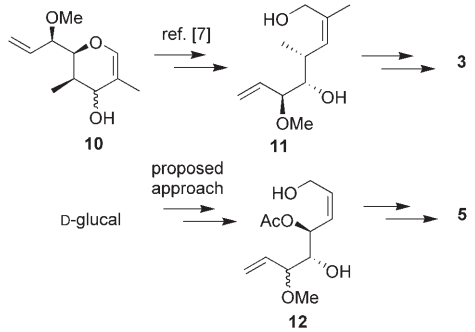
development of novel compounds that have potential in therapy of angiogenesis dependant disease and with a view to obtaining more information regarding the structure–activity of migrastatin analogues, we have developed a synthesis from D-glucal of novel analogues of the macrolide core structures. In addition the synthetic route has been adapted to facilitate the preparation of novel dorrigocin A analogues with a view to biological evaluation. Both analogues of the migrastatin core macrolide and dorrigocin A, derived from D-glucal, have been found have similar potency as inhibitors of migration of breast tumour cells and synoviocytes.



Scheme 1. Structures of migrastatin, dorrigocin A and analogues.

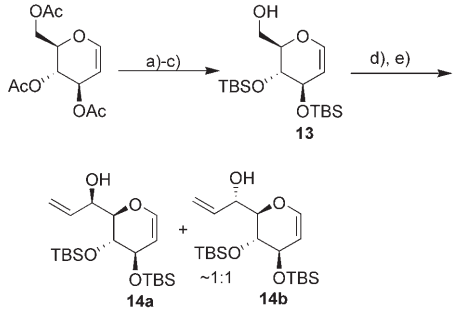
The Danishefsky approach to migrastatin and its macrolide core involved the synthesis of intermediate **10** and its conversion to **3** via **11** by a sequence of reactions that includes a water induced allylic rearrangement,[14] and ring-closing metathesis (RCM)[15] to form the macrocyclic ring.[16] We planned to explore the synthesis of the acyclic compound **12** from D-glucal and to then investigate its conversion into novel migrastatin analogues (Scheme 2).



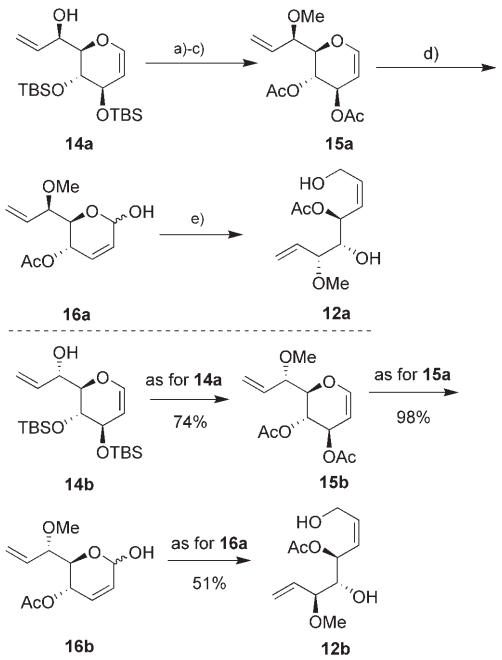
Scheme 2. Proposed synthesis of macrolide precursors from D-glucal.

The synthetic investigations began with easy accessible tri-*O*-acetyl-D-glucal. The acetate groups were first removed using potassium carbonate and methanol and then *tert*-butyldimethylsilyl (TBS)-protecting groups introduced to all free hydroxyl groups. The TBS-protecting group at *O*-6 was next selectively removed using HF/pyridine and **13** was obtained in 68% yield over three steps (Scheme 3). This alcohol **13** was converted to an aldehyde using the Swern oxidation and its subsequent reaction with vinyl magnesium bromide gave a ~1:1 mixture of diastereoisomers **14a** and **14b** in 78% yield over two steps. Other methods for the oxidation of alcohol **13** were investigated; the oxidation with TPAP/NMO was slow, whereas oxidation with PCC on scales above 2 g led to epimerisation at C-5 and a mixture of diastereoisomeric aldehydes. The oxidation with PCC did give the desired product in over 80% yield on a scale below 2 g. Attempts to purify the aldehyde precursor to **14a** and **14b** by chromatography led to a mixture of stereoisomers due to an epimerisation at C-5 and thus it was more advantageous to react the aldehyde from the Swern oxidation directly without purification. The diastereoisomers **14a** and **14b** were separated by using flash chromatography.

Both stereoisomers **14a** and **14b** were used separately for the synthesis of migrastatin analogues. Methylation of the free 6-OH group of **14a** to give **15a** was best effected using NaH and iodomethane in the presence of catalytic amounts of [18]crown-6 (Scheme 4). Other methylation reactions were less satisfactory and these included an investigation of Me_2SO_4 in the presence of alu-



Scheme 3. Synthesis of the diastereoisomers **14a** and **14b**. a) cat. K_2CO_3, MeOH; b) TBSCl, DMF; c) HF/pyridine, THF, 3 h (68% over three steps); d) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C → RT; e) 2 equiv vinyl-MgBr, THF, −78 °C (78% two steps).



Scheme 4. Synthesis of **12a** and **12b**. a) NaH, MeI, [18]crown-6, THF; b) TBAF, THF; c) Ac_2O, pyridine, CH_2Cl_2 (52%); c) H_2O/THF 10:1, 80°C, no light; d) $LiBH_4$, THF (68% over two steps).

mina, $CaCO_3$, Ag_2O and iodomethane, Me_3OBF_4 in the presence of 2,6-lutidine or NaH and iodomethane in absence of a crown ether. The silyl-protecting groups were exchanged for acetate protecting groups in two steps to give **15a**, which was obtained in 52% overall yield from **14a**. The allylic rearrangement of **15a** in the presence of water in THF at 80°C gave the lactol **16a**. Attempts to carry out similar allylic rearrangement reactions with the silylated product obtained from the methylation of **14a** were not successful and neither were attempts at acid-catalysed rearrangements of the diol intermediate obtained from desilylation of **14a** at room temperature. Reduction of the latent aldehyde of **16a** using lithium borohydride gave the desired acyclic intermediate **12a**. The moderate yield (68%) of the product obtained from this reduction reaction appears to arise from the tendency of the acetate group to migrate onto either of the two free OH groups of the product **12a**. It was therefore necessary to stop the reduction reaction after only 1 min to reduce acetate migration. A similar sequence of reactions from **14b** gave **12b** (47%) via **15b** and **16b**. The determination of the X-ray crystal structure of **16b** (Figure 1) provided the basis for the assignment of the absolute configuration at C-6 of the diastereoisomers **12a** and **12b** and other compounds described herein.

The regioselective acylation of **12a** using 6-heptenoyl chloride was next carried out and gave **17a**. Ring-closing metathesis (Scheme 5) of **17a** was not trivial and a number of attempts (varying the catalyst, concentration, solvent, temperature, and reaction time) to obtain the desired product in good yield were not successful. The reaction of **17a** with the Grubbs 2nd generation catalyst in toluene at 90°C

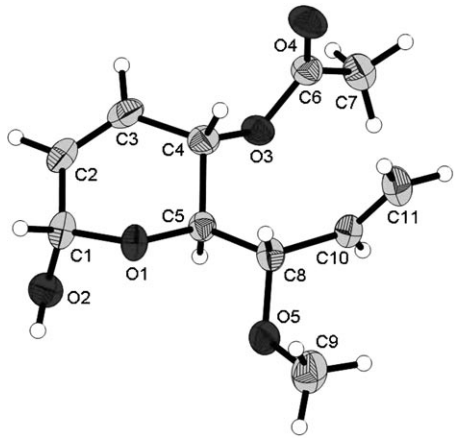
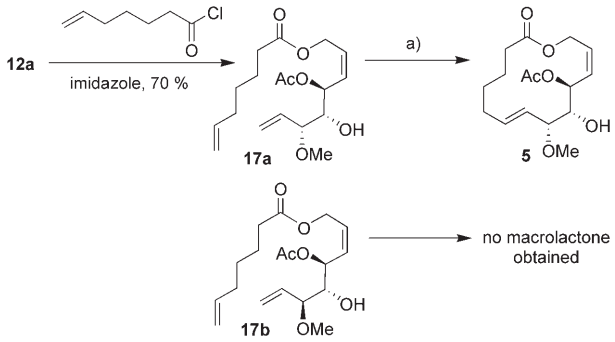


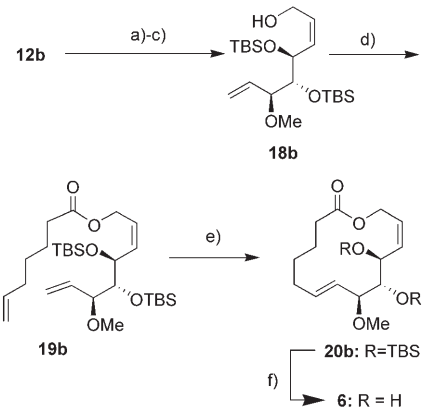
Figure 1. X-ray crystal structure of **16b**. Thermal ellipsoids are drawn on the 25% probability level

proved best and gave the desired product **5** after five minutes in 38% yield. Overall the migrastatin analogue **5** was obtained from D-glucal with an overall yield of 5% after 12 steps. Despite numerous attempts, RCM could not be achieved for **17b**, which had been prepared from **12b** by the same conditions as used for the preparation of **17a**. The only product which could be identified was a homodimer of **17b** and a number of other unidentified products were obtained.



Scheme 5. Synthesis of **5**. a) Grubbs-II (20%), toluene, 90°C, 5 min (38%).

A reason for the low yields of macrolactone from **17a** and no macrocyclisation from **17b** is possibly due to the presence of the *Z*-alkene group of **17a** and **17b**, which has the potential to undergo competing metathesis processes, consequently reducing the efficiency of the desired macrolactone formation. The di-*O*-TBS protected intermediate **18b** was thus synthesised (Scheme 6) from **12b**. It was envisaged that the increased steric bulk in the environment of the reactive alkene in **18b** would block undesired metathesis processes at this site and facilitate RCM to give the desired macrolactone. Steric effects that reduce the rates of metathesis processes have been described in the literature.[17] The acetate protecting group was thus removed from **12b**, then all three OH groups were converted to their TBS ethers using



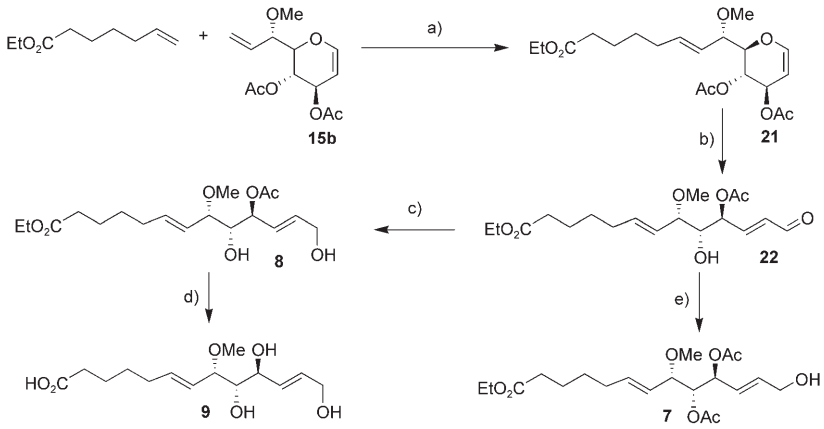
Scheme 6. Synthesis of **6**. a) NaOMe, MeOH, 0 °C; b) TBSOTf, CH_2Cl_2, 2,6-lutidine; c) AcOH/THF/H_2O 3:1:1 (59% over three steps); d) PPh_3, DIAD, 6-heptenoic acid, toluene (84%); e) Grubbs-II (30%), toluene, 80 °C, 30 min (97%); f) TBAF, THF (67%).

TBSOTf in the presence of 2,6-lutidine and the subsequent regioselective desilylation under acidic conditions provided **18b**. The attempted use of TBSCl and imidazole in the silylation reaction was not successful. The Mitsunobu reaction of **18b** with 6-heptenoic acid gave **19b** in 84% yield. Gratifyingly the RCM of **19b** gave **20b** in high yield (97%) using the Grubbs 2nd generation catalyst in toluene at 80 °C after 30 minutes. The TBS groups were finally removed from **20b** to give **6** (67%). Overall the macrolactone **6** was obtained in 16 steps in 6% yield from D-glucal.

The synthesis of dorrigocin A analogues was also achieved from **15b**. Firstly a cross-metathesis (CM)[16] of **15b** with ethyl 6-heptenoate (Scheme 7) gave (*E*)-alkene **21** in 55% yield. Whilst the water promoted allylic rearrangement of a glycal gives an unsaturated lactol (e.g. as for synthesis of **16a**) with the olefin having *Z* geometry, it is known that the olefin of the lactol can be isomerised to the corresponding *E* isomer giving an unsaturated aldehyde.[18] Thus allylic rearrangement and subsequent olefin isomerisation of the glycal **21** under Perlin conditions[19] gave the aldehyde **22** in high yield (94%). For **22** the ^{1}H NMR coupling constant between the relevant alkene protons was 15.8 Hz, supporting the stereochemical assignment. In general for compounds described herein, the olefin stereochemistry was determined on the basis of ^{1}H NMR coupling constants. The work-up of this reaction was important, and an extraction with dichloromethane after filtration proved to be essential to ensure the efficient isolation of **22**. The aldehyde group of **22** was reduced using sodium borohydride to give **8** and subsequent saponification of the ester groups of **8** gave the dorrigocin A analogue **9**. Alternatively the aldehyde **22** was acetylated and subsequent reduction of the aldehyde group of the product reduced gave **7**.

The compounds **5–8** were evaluated for their effects on proliferation and migration (acid phosphatase assay) of mouse breast tumour 4T1 cells and human K4 IM synoviocyte cells, that latter being relevant to primary rheumatoid arthritis synoviocyte responses.[20–21] Evodiamine was found to be a significantly more potent inhibitor of growth and migration of these cell types than the migrastatin or dorrigocin A analogues (full details are supplied in the Supporting Information) indicating the compounds described herein are not as potent as those synthesised by Danishefsky and coworkers, at least for the cell types studied herein.

In conclusion, syntheses of both migrastatin and dorrigocin A analogues from D-glucal have been successfully achieved, providing a basis for synthesis of sugar derived analogues and their subsequent biological investigation as inhibitors of the migration of diverse cell types. Ring closing metathesis in the presence of a reactive olefin that has potential to undergo competing metathesis reactions was achieved in the presence of bulky protecting groups. Preliminary biological evaluation has indicated that the compounds are less effective than evodiamine at inhibiting proliferation and serum-induced migration of 4T1 and K4 IM cells. A strategy has been devised that would enable dorrigocin A analogues to be prepared in parallel to migrastatin analogues in the search for novel anti-cancer and anti-arthritic therapeutics that act as cell migration inhibitors. The biological properties of the synthesized compounds are being investigated more widely and will be reported in due course as will the synthesis of further analogues.



Scheme 7. Synthesis of dorrigocin A analogues. a) CH_2Cl_2, Grubbs-II (55%); b) $HgSO_4$, H_2SO_4, dioxane (94%); c) $NaBH_4$, THF, 0 °C (65%); d) THF/H_2O/MeOH, LiOH (40%); e) i) Ac_2O, pyridine, CH_2Cl_2 (33%); ii) $NaBH_4$, THF, 0 °C (39%).

Experimental Section

General methods: NMR spectra were recorded with a Varian 300, 400, 500 or 600 MHz spectrometer. Chemical shifts are reported relative to internal Me_4Si in $CDCl_3$ (δ 0.0) or HOD for D_2O (δ 4.79) for ^1H and (δ 77.16) for ^{13}C. ^1H NMR signals were assigned with the aid of COSY. ^{13}C signals were assigned with the aid of DEPT-135, HSQC and HMBC. Mass spectra were recorded on a Micromass LCT KC420 or Micromass Quattro. TLC was performed on aluminium sheets precoated with silica gel 60 (HF254, E. Merck) and spots visualized by UV and charring with 1:20 H_2SO_4/EtOH. Flash column chromatography was generally employed and was carried out using silica gel 60 (0.040–0.630 mm, E. Merck) and employed a stepwise solvent polarity gradient correlated with the TLC mobility. Chromatography solvents used were EtOAc, CH_2Cl_2 (Riedel-deHaen), cyclohexane and MeOH (Sigma Aldrich). Anhydrous DMF and anhydrous toluene were used as purchased from Sigma-Aldrich. THF, CH_2Cl_2 and methanol were used as obtained from a Pure-Solv solvent purification system. Tri-*O*-acetyl-D-glucal was obtained from Sigma-Aldrich.

3,4-Di-*O*-(*tert*-butyldimethylsilyl)-D-glucal (13): K_2CO_3 (1.0 g, 7.24 mmol) was added to tri-*O*-acetyl-D-glucal (20.0 g, 73.5 mol) in methanol (120 mL) and the solution was stirred at room temperature for 4 h. The solvent was then removed under diminished pressure and any remaining methanol was removed by co-evaporation with $CHCl_3$ (3×40 mL) to afford a pale brown syrup. The syrup was dissolved in anhydrous DMF (100 mL) and imidazole (49.0 g, 720 mmol) was added. TBSCl (52.0 g, 345 mmol) in DMF (80 mL) was added to the solution via cannula under stirring. The resulting solution was stirred for 18 h at room temperature after which the reaction was poured into water (300 mL) and the product was extracted with Et_2O (4×500 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under diminished pressure. Removal of high boiling TBS impurities was achieved by Kugelrohr distillation at 150 °C for 1.5 h gave the tri-*O*-silylated D-glucal derivative as a pale orange oil (35.5 g, 99 %). R_f=0.70 (cyclohexane/EtOAc 95:5); $[\alpha]_D$=−29.0 (c = 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=6.32 (d, J=6.3 Hz, 1H), 4.69 (dd, J=5.8, 4.4 Hz, 1H), 3.99 (dtd, J=7.3, 3.6, 1.3 Hz, 1H), 3.94 (dd, J=11.2, 7.4 Hz, 1H), 3.89 (m, 1H), 3.80 (m, 1H), 3.76 (dd, J=11.2, 3.5 Hz, 1H), 0.90, 0.89 (2s, 27H), 0.10, 0.08, 0.06, 0.05 ppm (4s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=143.0, 101.4, 80.1, 70.2, 66.7, 61.8, 26.0, 25.9, 18.4, 18.0, −4.2, −4.3, −4.7 ppm; IR (thin film): $\tilde{\nu}$=2954, 2932, 2887, 2859, 1649, 1472, 1408, 1390, 1362, 1254, 1100, 1173, 1006, 963, 878, 838, 778, 669 cm^{-1}; HR-ESMS: m/z: calcd for $C_{24}H_{52}NaO_4Si_2$: 511.3071; found: 511.3076 $[M+Na]^+$.

A solution of 3,4,6-tri-*O*-*tert*-butyldimethylsilyl-D-glucal (35.5 g, 72.6 mmol) in anhydrous THF (540 mL) in a polypropylene bottle was cooled to 0 °C and HF/pyridine in THF (200 mL of stock solution prepared from 25 mL HF/pyridine, 50 mL anhydrous pyridine and 125 mL anhydrous THF) was added and the solution was allowed to attain room temperature. After 4 h, the reaction was quenched by the careful addition of saturated $NaHCO_3$ solution (800 mL) followed by addition of EtOAc (800 mL) and the resulting mixture was allowed to stir at room temperature for a further 10 minutes. The organic layer was removed and the aqueous layer extracted with EtOAc (3×500 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography of the residue (cyclohexane/EtOAc 100:0 to 97:3) afforded **13** (18.445 g, 68 %). R_f=0.28 (cyclohexane/EtOAc 90:10); m.p. 69–70 °C; $[\alpha]_D^{20}$=−59.8 (c=1.05 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=6.39 (d, J=6.3 Hz, 1H), 4.72 (ddd, J=6.2, 4.5, 0.9 Hz, 1H), 4.06–4.01 (m, 1H), 3.95 (t, J=3.8 Hz, 1H), 3.89 (dt, J=12.2, 5.8 Hz, 1H), 3.84–3.80 (m, 1H), 3.74 (ddd, J=12.6, 8.4, 4.7 Hz, 1H), 2.48 (dd, J=8.3, 5.2 Hz, 1H), 0.92 (2s, 9H), 0.91 (2s, 9H), 0.13, 0.12 ppm (3s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ= 143.7, 101.2, 78.6, 70.6, 66.6, 61.8, 25.81, 25.76, 18.04, 18.01, −4.3, −4.4, −4.7 ppm; IR (thin film): $\tilde{\nu}$=3460, 2954, 2929, 2895, 2858, 1649, 1473, 1254, 1111, 1065, 837, 777 cm^{-1}; HR-ESMS: m/z: calcd for $C_{18}H_{37}O_4Si_2$: 373.2230; found: 373.2248 $[M-H]^-$.

(1*S*)-1-[(2*R*,3*R*,4*S*)-3,4-Bis-(*tert*-butyldimethylsilyloxy)-3,4-dihydro-2*H*-pyran-2-yl]-prop-2-en-1-ol (14a) and (1*R*)-1-[(2*R*,3*R*,4*S*)-3,4-bis-(*tert*-butyldimethylsilyloxy)-3,4-dihydro-2*H*-pyran-2-yl]-prop-2-en-1-ol (14b): A solution of oxalyl chloride (3.22 mL, 36.9 mmol) in dry CH_2Cl_2 (120 mL) was cooled to −78 °C and anhydrous DMSO (3.23 mL, 45.5 mmol) in dry CH_2Cl_2 (10 mL) was then added dropwise. After stirring at low temperature for 20 min, the solution was allowed to warm to −40 °C and the alcohol **13** (10.65 g, 28.43 mmol) in dry CH_2Cl_2 (45 mL) was added dropwise. The resulting white suspension was stirred for 20 min before triethylamine (12 mL, 86.1 mmol) was added dropwise and the mixture was stirred for a further 45 min at −40 °C, before it was allowed to attain room temperature. After 4 h, the mixture was poured onto cold water (100 mL) and saturated NH_4Cl solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (4×250 mL) and the combined organic layers were washed with water (150 mL) and twice with saturated $NaHCO_3$ solution (150 mL). Then the organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo to afford the crude aldehyde as a yellow solid (10.57 g).

The aldehyde (10.57 g, 28.4 mmol) was dissolved in anhydrous THF (100 mL) and the solution was cooled to −78 °C. Vinyl magnesium bromide (60 mL of a 1.0 M solution in THF) was added dropwise and the mixture was stirred at low temperature for 45 min, and for a further 2 h at room temperature. The mixture was then cooled to −20 °C and saturated NH_4Cl solution (60 mL) was added dropwise. The mixture allowed to attain room temperature and the aqueous layer then extracted with Et_2O (4×250 mL) and the combined organic layers washed with brine (70 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the residue (cyclohexane/Et_2O 100:0 to 97:3) gave **14a** (4.56 g, 40 %, R_f=0.40 cyclohexane/Et_2O 90:10) and **14b** (4.28 g, 38 %, R_f=0.25, cyclohexane/Et_2O 90:10). Analytical data for **14a**: $[\alpha]_D^{20}$=−57.7°(c=1.03 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=6.45 (d, J=6.3 Hz, 1H), 5.97 (ddd, J=16.0, 10.6, 4.9 Hz, 1H), 5.37 (d, J=17.2 Hz, 1H), 5.22 (d, J=10.6 Hz, 1H), 4.75 (brt, J = 5.1 Hz, 1H), 4.41 (brq, J = 6.7 Hz, 1H), 4.10 (brs, 1H), 3.93 (d, J=7.2 Hz, 1H), 3.89 (m, 1H), 3.51 (d, J=7.0 Hz, 1H), 0.91 (s, 18H), 0.14, 0.09 ppm (2s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=144.5, 137.8), 115.4, 99.6, 80.4, 71.4, 68.4, 65.1, 26.9, 25.8, 25.7, 18.0, −4.4, −4.68, −4.75, −4.77 ppm; IR (thin film): $\tilde{\nu}$=2931, 2858, 1643, 1471, 1408, 1362, 1254, 1092, 1041, 1003, 924, 879, 839, 777, 671 cm^{-1}; HR-ESMS: m/z: calcd for $C_{20}H_{39}O_4Si_2$: 399.2387; found: 399.2380 $[M-H]^-$. Analytical data for **14b**: $[\alpha]_D^{20}$=−54.9° (c=1.01 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=6.39 (d, J=6.3 Hz, 1H), 5.85 (ddd, J=17.4, 10.8, 6.9 Hz, 1H), 5.43 (dd, J=17.4, 1.5 Hz, 1H), 5.25 (dd, J=9.3, 1.5 Hz, 1H), 4.75 (m, 1H), 4.54 (brs, 1H), 3.97–3.94 (m, 1H), 3.89 (m, 1H), 3.80 (m, 1H), 3.07 (brs, 1H), 0.90, 0.88 (2s, 18H), 0.11, 0.10, 0.09 ppm (4s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=143.7, 137.2, 116.6, 101.2, 81.8, 70.3, 69.9, 66.4, 25.9, 25.8, 18.1, 18.0, −4.35, −4.36, −4.43, −4.8 ppm; IR (thin film): $\tilde{\nu}$=3460, 3068, 2954, 2931, 2895, 2858, 1649, 1471, 1408, 1390, 1362, 1254, 1090, 1063, 1005, 916, 883, 837, 777 cm^{-1}; HR-ESMS: m/z: calcd for $C_{20}H_{40}O_4Si_2Na$: 423.2363; found: 423.2381 $[M+Na]^+$.

(1*R*)-1-[(2*R*,3*R*,4*S*)-3,4-Diacetoxy)-3,4-dihydro-2*H*-pyran-2-yl]-prop-2-en-1-yl methyl ether (15b)

Alcohol 14b: (0.24 g, 0.60 mmol) in THF (6.0 mL) was cooled to 0 °C and NaH (35.2 mg of 60 % dispersion in mineral oil, 0.88 mmol) was added portionwise, followed by methyl iodide (195 μL, 3.13 mmol) and [18]crown-6 (16 mg, 0.06 mmol). The reaction mixture was allowed to attain room temperature and stirred for a further 2 h and cooled to 0 °C. Diethyl ether was added (10 mL) followed by saturated NH_4Cl solution (2 mL) and the mixture was allowed to attain room temperature once more. The aqueous layer was washed with Et_2O (3×10 mL), the combined organic layers were dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography of the residue (cyclohexane/Et_2O 100:0 to 90:10 gave methyl ether of **14b** as a colourless oil (0.20 g, 80 %); R_f=0.22 (CH_2Cl_2/cyclohexane 20:80); $[\alpha]_D^{20}$=−43.7 (c=3.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=6.37 (d, J=6.3 Hz, 1H), 5.83 (ddd, J=17.3, 10.5, 6.7 Hz, 1H), 5.36 (d, J=17.3 Hz, 1H), 5.31 (d, J=10.5 Hz, 1H), 4.73 (ddd, J=6.0, 4.3, 1.1 Hz, 1H), 4.13 (t, J=7.0 Hz, 1H), 3.94 (t, J=3.7 Hz, 1H), 3.91 (t, J=3.6 Hz, 1H), 3.75 (ddd, J=7.3,

3.9, 1.3 Hz, 1H), 3.29 (s, 3H), 0.89, 0.86 (2s, 18H), 0.09, 0.08, 0.06, 0.06 ppm (4s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 143.0), 135.1, 118.5, 101.6, 81.3, 77.9, 69.6, 67.4, 56.7, 26.0, 25.8, 18.2, 18.0, −4.1, −4.2, −4.2, −4.9 ppm; IR (thin film): $\tilde{\nu}$ = 3074, 2954, 2931, 2893, 2858, 1647, 1464, 1254, 1109, 1092, 1063, 835, 777 cm^{-1}; HR-ESMS: *m*/*z*: calcd for $C_{21}H_{42}NaO_4Si_2$: 437.2519; found: 437.2527 $[M+Na]^+$.

The oil (2.38 g, 5.74 mmol) obtained from the methylation of **14b** was dissolved in THF (70 mL) at 0 °C and TBAF (11.4 mL of 1.0 M solution in THF, 11.4 mmol) was added and the solution was allowed to attain room temperature and was stirred for a further 12 h. The mixture was then diluted with EtOAc (20 mL) and saturated NH_4Cl solution (20 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (3×50 mL), the combined organic layers were dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography of the residue (EtOAc/cyclohexane 1:1 to 1:0) gave a diol as a pale yellow oil (1.00 g, 94 %). R_f = 0.10 (EtOAc/cyclohexane 1:1); $[\alpha]_D^{20}$ = −24.8° (*c* = 1.04 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.30 (dd, *J* = 6.0, 1.7 Hz, 1H), 5.91 (ddd, *J* = 17.7, 10.0, 7.6 Hz, 1H), 5.37–5.33 (overlapping signals, 2H), 4.69 (dd, *J* = 6.0, 2.1 Hz, 1H), 4.25 (d, *J* = 7.3 Hz, 1H), 4.15 (br s, 1H), 4.05 (dd, *J* = 7.7, 2.4 Hz, 1H), 3.87 (dd, *J* = 10.1, 7.4 Hz, 1H), 3.77 (dd, *J* = 10.1, 2.5 Hz, 1H), 3.64 (br s, 1H), 3.35 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 143.2, 133.2, 118.6, 102.5, 80.0, 78.9, 70.4, 69.9, 57.4 ppm; HR-ESMS: *m*/*z*: calcd for $C_9H_{14}O_4Na$: 209.0790; found: 209.0800 $[M+Na]^+$.

To the yellow oil (0.52 g, 2.79 mmol) in CH_2Cl_2 (7.7 mL) was added pyridine (1.13 mL, 14.0 mmol) and acetic anhydride (2.63 mL, 27.8 mmol) and the mixture was stirred overnight at room temperature. Ice (5 mL) was added and stirring continued and the mixture was allowed to attain room temperature and water (5 mL) and CH_2Cl_2 (10 mL) were then added. The organic layer was separated and the aqueous layer was washed with EtOAc (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent removed under diminished pressure to give **15b** as a yellow oil (0.75 g, 99 %). R_f = 0.60 (EtOAc/cyclohexane 1:1); $[\alpha]_D^{20}$ = −24.6 (*c* = 4.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.47 (d, *J* = 6.0 Hz, 1H), 5.81 (ddd, *J* = 18.2, 10.4, 7.9 Hz, 1H), 5.39–5.31 (m, 4H), 4.77 (m, 1H), 3.98 (dd, *J* = 8.4, 4.5 Hz, 1H), 3.75 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.26 (s, 3H), 2.06, 2.02 ppm (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 170.5, 169.2, 146.1, 134.0, 120.4, 98.9, 79.1, 77.7, 67.9, 67.4, 56.8, 21.0, 20.8 ppm; IR (thin film): $\tilde{\nu}$ = 3078, 2983, 2935, 2825, 1743, 1649, 1427, 1371, 1236, 1045, 958, 920, 822, 754 cm^{-1}; HR-ESMS: calcd for $C_{13}H_{18}NaO_6$: 293.1001; found: 293.0990 $[M+H]^+$.

(1*S*)-1-[(2*R*,3*R*,4*S*)-3,4-Diacetoxy-3,4-dihydro-2*H*-pyran-2-yl]-prop-2-en-1-yl methyl ether (15a): The reaction of alcohol **14a** (2.602 g, 6.5 mmol) in THF (50 mL) with NaH (360 mg of 60 % dispersion in mineral oil, 9.00 mmol), methyl iodide (2.0 mL, 32.1 mmol) and [18]crown-6 (100 mg, 0.38 mmol) as described for **14b** gave a methyl ether (2.30 g; R_f = 0.65, cyclohexane/Et_2O 9:1) as a colourless oil after chromatography (silica gel, cyclohexane/Et_2O 100:0 to 98:2). This oil (2.30 g, 5.546 mmol) was dissolved in THF (80 mL) and the mixture cooled to 0 °C. TBAF (15.5 mL of 1.0 M solution in THF, 15.5 mmol) was added and the mixture allowed to attain room temperature and was stirred for a further 20 h. EtOAc (50 mL) and saturated NH_4Cl solution (40 mL) were then added and the organic layer separated. The aqueous layer was washed with EtOAc (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent removed under diminished pressure. The residue was purified by chromatography (EtOAc/cyclohexane 1:1 to 1:0) to give the diol intermediate as a pale yellow oil (0.705 g, 58 % over two steps). R_f = 0.20 (EtOAc/cyclohexane 1:1); $[\alpha]_D^{20}$ = −11.7° (*c* = 1.01 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.29 (d, *J* = 5.3 Hz, 1H), 5.80 (ddd, *J* = 17.2, 10.5, 8.2 Hz, 1H), 5.37 (d, *J* = 10.2 Hz, 1H), 5.35 (dd, *J* = 17.2 Hz, 1H), 4.67 (d, *J* = 6.0 Hz, 1H), 4.20 (br d, *J* = 7.0 Hz, 1H), 3.97 (dd, *J* = 8.1, 3.7 Hz, 1H), 3.88 (dd, *J* = 9.8, 3.8 Hz, 1H), 3.59 (dd, *J* = 9.7, 7.2 Hz, 1H), 3.33 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 144.0, 133.4, 120.5, 102.5, 82.8, 78.1, 71.0, 69.6, 56.5 ppm; HR-ESMS: *m*/*z*: calcd for $C_9H_{14}O_4Na$: 209.0790; found: 209.0800 $[M+Na]^+$.

To the yellow oil (0.370 g, 1.99 mmol) in CH_2Cl_2 (8 mL) was added pyridine (1.1 mL, 13.6 mmol) and acetic anhydride (2.2 mL, 23.3 mmol) and the solution was stirred overnight at room temperature. Ice (5 mL) was then added and the stirred mixture was allowed to attain room temperature, and then diluted with water (5 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer was washed with EtOAc (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent removed under diminished pressure to give **15a** as a yellow oil (0.484 g, 90 %). R_f = 0.65 (EtOAc/cyclohexane 1:1); $[\alpha]_D^{20}$ = −29.2° (*c* = 1.03 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.39 (d, *J* = 6.1 Hz, 1H), 5.66 (dt, *J* = 17.5, 8.8 Hz, 1H), 5.30 (d, *J* = 10.3 Hz, 1H), 5.22–5.16 (overlapping signals, 3H), 4.76 (br t, *J* = 4.6 Hz, 1H), 4.04 (t, *J* = 6.2 Hz, 1H), 3.78 (t, *J* = 7.0 Hz, 1H), 3.22 (s, 3H), 1.99, 1.97 ppm (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 169.8, 169.0, 145.4, 133.7, 120.1, 98.2, 79.4, 76.4, 67.5, 66.3, 55.9, 20.7, 20.5 ppm; IR (thin film): $\tilde{\nu}$ = 3078, 2985, 2940, 2897, 2825, 1741, 1650, 1372, 1238, 1225, 1045, 1026, 959 cm^{-1}; HR-ESMS: *m*/*z*: calcd for $C_{13}H_{18}NaO_6$ 293.1001; found: 293.1004 $[M+Na]^+$.

(2*Z*,4*R*,5*R*,6*S*)-4-Acetoxy-6-methoxy-octa-2,7-diene-1,5-diol (12a): To water (10 mL), pre-heated to 80 °C in a flask from which light was excluded, was added **15a** (45 mg, 0.166 mmol) in THF (1 mL) and the mixture was stirred vigorously for 3 h. The mixture was cooled rapidly and the sample was freeze dried and gave **16a** as a white solid. This solid was dissolved in anhydrous THF (6 mL) at 0 °C and $LiBH_4$ (200 μL of 2.0 M solution in THF, 0.4 mmol) was added. After 60 s a solution of HCl (1.0 N) was added until no more effervescence was observed and the mixture was stirred for a further 20 min at 0 °C. The mixture was allowed to attain room temperature and the product then extracted with EtOAc (3× 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent was removed under diminished pressure. Chromatography (EtOAc/cyclohexane 1:9 to 1:0) gave **12a** (26 mg, 68 % over two steps) as a colourless oil. R_f = 0.15 (EtOAc/cyclohexane 1:1); $[\alpha]_D^{20}$ = −13.5° (*c* = 1.02 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.02 (dt, *J* = 10.0, 7.2 Hz, 1H), 5.75 (ddd, *J* = 17.6, 10.2, 8.1 Hz, 1H), 5.64 (dd, *J* = 9.8, 5.4 Hz, 1H), 5.60 (t, *J* = 10.2 Hz, 1H), 5.42 (d, *J* = 10.1 Hz, 1H), 5.30 (d, *J* = 17.3 Hz, 1H), 4.36 (dd, *J* = 12.8, 8.0 Hz, 1H), 4.09 (dd, *J* = 12.7, 6.5 Hz, 1H), 3.83 (t, *J* = 5.7 Hz, 1H), 3.52 (t, *J* = 7.1 Hz, 1H), 3.26 (s, 3H), 2.68, 2.46 (br s, 2H), 2.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 134.7, 134.1, 126.4, 121.3, 82.9, 73.3, 70.4, 58.2, 56.6, 21.3 ppm, IR (thin film): $\tilde{\nu}$ = 3420, 2983, 2929, 2826, 1734, 1373, 1241, 1078, 1026, 781 cm^{-1}; HR-ESMS: *m*/*z*: calcd for $C_{11}H_{18}O_5Na$: 253.1052; found: 253.1041 $[M+Na]^+$.

(2*Z*,4*R*,5*R*,6*R*)-4-Acetoxy-6-methoxy-octa-2,7-diene-1,5-diol (12b): Diacetate **15b** (913 mg, 3.378 mmol) in THF (5 mL) was added to a flask containing water (50 mL) at 80 °C, from which light had been excluded, and the mixture was stirred vigorously for 23 h. The mixture was then cooled rapidly and the water was removed by freeze drying to give **16b** as a white solid (761 mg, 98 %), which was used without further purification in the next step. IR (thin film): $\tilde{\nu}$ = 3419, 2983, 2933, 2902, 2827, 1739, 1691, 1427, 1371, 1238, 1182, 1128, 1082, 1036, 976, 935 cm^{-}; HR-ESMS: *m*/*z*: calcd for $C_{11}H_{15}O_5$: 227.0919; found: 227.0927 $[M-H]^-$.

To **16b** (761 mg, 3.334 mmol) in anhydrous THF (30 mL) at 0 °C was added $LiBH_4$ (1.9 mL of a 2.0 M solution in THF, 3.8 mmol). After 60 s a solution of HCl (1.0 N) was added until no more effervescence was observed and the mixture was stirred for a further 20 min at 0 °C and then allowed to attain room temperature. The mixture was extracted with EtOAc (3×50 mL), the organic layers were combined, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography (EtOAc/cyclohexane 1:9 to 1:0) of the residue gave **12b** colourless oil (388 mg, 50 % over two steps). R_f = 0.15 (EtOAc/cyclohexane 1:1); $[\alpha]_D^{20}$ = +51.8° (*c* = 0.99 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.98 (ddd, *J* = 10.7, 7.7, 6.2 Hz, 1H), 5.70 (ddd, *J* = 17.2, 10.3, 8.2 Hz, 1H), 5.65 (t, *J* = 10.5 Hz, 1H), 5.52 (dd, *J* = 9.9, 4.9 Hz, 1H), 5.40 (d, *J* = 10.3 Hz, 1H), 5.31 (d, *J* = 17.1 Hz, 1H), 4.35 (dd, *J* = 13.1, 7.8 Hz, 1H), 4.06 (dd, *J* = 13.0, 6.2 Hz, 1H), 3.71 (dd, *J* = 6.5, 4.9 Hz, 1H), 3.44 (dd *J* = 8.1, 6.6 Hz, 1H), 3.30 (s, 3H), 2.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 170.5, 134.6, 134.0, 125.5, 120.6, 82.5, 74.1, 69.6, 58.3, 56.3, 21.2 ppm.

[(2*Z*,4*R*,5*R*,6*S*)-4-Acetoxy-5-hydroxy-6-methoxy-octa-2,7-diene-1-yl] hept-6-enoate (17a): To 6-heptenoic acid (35 μL, 0.257 mmol) in anhydrous CH_2Cl_2 was added oxalyl chloride (27 μL, 0.31 mmol) and one

drop of anhydrous DMF, and the resulting mixture was stirred for 2 h at room temperature. A mixture of the alcohol **12a** (53 mg, 0.23 mmol) and imidazole (22 mg, 0.32 mmol) in anhydrous CH_2Cl_2 was then added and the reaction was stirred overnight at room temperature. HCl (1 mL of a 0.1 M solution) was then added and stirring continued for a further 5 min and then CH_2Cl_2 (5 mL) and water (2 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3× 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography (EtOAc/cyclohexane 1:9 to 4:6) of the residue gave **17a** (50 mg, 70%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ=5.90–5.60 (m, 5H), 5.40 (dd, J=10.3, 5.1 Hz, 1H), 5.30 (dd, J=17.2, 6.5 Hz, 1H), 4.95 (m, 2H), 4.30 (dd, J=15.6, 7.7 Hz, 1H), 4.21 (dd, J=15.6, 7.7 Hz, 1H), 3.81 (m, 1H), 3.48 (q, J = 7.3 Hz, 1H), 3.26 (s, 3H), 2.31 (t, J=7.5 Hz, 1H), 2.29, (s, 3H), 2.30–2.25 (m, 2H), 1.65–1.55 (m, 2H), 1.45–1.30 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ=173.5, 169.6, 138.3, 134.4, 130.2, 126.9, 120.9, 114.6, 82.9, 73.6, 70.1, 56.3, 39.6, 34.0, 33.3, 28.3, 24.3, 21.0 ppm; HR-ESMS: m/z: calcd for $C_{18}H_{28}O_6Na$: 363.1784; found: 363.1799 $[M+Na]^+$.

(7*E*,9*S*,10*R*,11*R*,11*Z*)-11-Acetoxy-10-hydroxy-9-methoxy-oxacyclotetradeca-7,12-dien-2-one (5): To **17a** (17 mg, 0.05 mmol) in degassed and dried toluene (90 mL) at 90°C was added, via a cannula, Grubbs catalyst 2nd generation (9 mg, 0.011 mmol) in degassed and dried toluene (5 mL). Heating was continued for 5 min at 90°C and the solution was then filtered through a short column of silica, washing with EtOAc. The organic layer was removed under diminished pressure and **5** (6 mg, 38%) was obtained as a colourless oil after chromatography (EtOAc/cyclohexane 9:1 to 7:3) of the residue. ^{1}H NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ=5.81 (m, 2H), 5.61 (m, 2H), 5.51 (dd, J=16.1, 8.2 Hz, 1H), 4.78 (ddd, J=14.9, 4.7, 2.2 Hz, 1H), 4.59 (ddd, J=14.9, 5.3, 0.8 Hz, 1H), 3.95 (d, J=8.7 Hz, 1H), 3.69 (d, J=7.9 Hz, 1H), 3.32 (s, 3H), 2.43 (ddd, J=13.6, 8.7, 5.7 Hz, 1H), 2.25–2.15 (m, 2H), 2.15–2.05 (m, 1H), 2.06, (s, 3H), 1.85–1.70 (m, 2H), 1.55–1.45 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ=171.6, 168.1, 134.6, 128.6, 127.7, 125.5, 81.8, 74.1, 69.7, 61.2, 56.6, 34.2, 30.8, 26.7, 23.8, 22.0 ppm; HR-ESMS: m/z: calcd for $C_{16}H_{24}O_6Na$: 335.1471; found: 335.1487 $[M+Na]^+$.

(2*Z*,4*R*,5*R*,6R)-6-Methoxy-4,5-bis-(*tert*-butyldimethylsilyloxy)-octa-2,7-diene-1-ol (18b): To **12b** (405 mg, 1.76 mmol) in anhydrous methanol (10 mL) at 0°C was added sodium (76 mg, 3.3 mmol) and the mixture was then allowed to attain room temperature and after stirring for 2 h, the solution was evaporated and the residue was taken up in CH_2Cl_2 (40 mL) and *tert*-butyldimethylsilyl triflate (2.0 mL, 8.7 mmol) and 2,6-lutidine (2.0 mL, 17.2 mmol) were added. The mixture was stirred for 2 h at room temperature, satd. $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3×50 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography of the residue (EtOAc/cyclohexane 0:100 to 1:99) gave fully silylated compound as a colourless oil (851 mg, 91% over two steps). R_f=0.70 (EtOAc/cyclohexane 5:95); $[\alpha]_D^{20}$=+22.4° (c=0.99 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.68 (ddd, J=17.2, 10.4, 8.1 Hz, 1H), 5.51 (m, 2H), 5.26 (dd, J=10.5, 2.0 Hz, 1H), 5.21 (dd, J=17.2, 2.0 Hz, 1H), 4.40 (dd, J=7.0, 3.1 Hz, 1H), 4.22 (dd, J=12.9, 5.7 Hz, 1H), 4.06 (dd, J=12.9, 3.7 Hz, 1H), 3.62 (dd, J=6.6, 3.2 Hz, 1H), 3.41 (dd, J=8.0, 6.7 Hz, 1H), 3.22 (s, 3H), 0.90, 0.89, 0.87 (3s, 27H), 0.07, 0.06, 0.05, 0.02 ppm (4s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ=135.5, 130.5, 118.7, 84.2, 79.7, 69.5, 59.8, 56.2, 26.1, 26.0, 25.9 (3s), 18.4, 18.2 (2s), −4.2, −4.3, −4.7, −5.2 ppm; IR (thin film): $\tilde{\nu}$=2955, 2930, 2858, 1640, 1473, 1253, 1149, 1080, 836, 776 cm^{-1}; HR-ESMS: m/z: calcd for $C_{27}H_{58}O_4Si_3Na$: 553.3541; found: 553.3521 $[M+Na]^+$.

This intermediate (373 mg, 0.702 mmol) was dissolved in AcOH/THF/H_2O 3:1:1 (50 mL) and the mixture was stirred at room temperature for 42 h. Solid Na_2CO_3 was then added and the mixture extracted with Et_2O (3×60 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography of the residue (EtOAc/cyclohexane 0:100 to 5:95) gave **18b** as colourless oil (190 mg, 65%). R_f=0.40 (EtOAc/cyclohexane 30:70); $[\alpha]_D^{20}$=+10.2° (c=1.01 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ=5.72 (ddd, J=17.3, 10.4, 8.0 Hz, 1H), 5.68–5.60 (m, 2H), 5.27 (dd, J=10.4, 1.9 Hz, 1H), 5.22 (dd, J=17.3, 1.9 Hz, 1H), 4.55 (dd, J=8.4, 3.9 Hz, 1H), 4.12 (m, 2H), 3.66 (dd, J=5.9, 4.0 Hz, 1H), 3.48 (dd, J=8.0, 5.9 Hz, 1H), 3.23 (s, 3H), 0.90, 0.89, 0.87 (3s, 18H), 0.07, 0.06, 0.05, 0.02 ppm (4s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ=135.6, 132.6, 129.6, 118.7, 84.1, 79.1, 69.0, 59.4, 56.3, 26.9, 26.1, 25.9, 18.4, 18.2, −4.0, −4.2, −4.3, −4.7 ppm; IR (thin film): $\tilde{\nu}$=3369, 3079, 2954, 2930, 2888, 2857, 1472, 1253, 1148, 1075, 836, 777 cm^{-1}; ; HR-ESMS: m/z: calcd for $C_{21}H_{44}O_4Si_2Na$: 439.2676; found: 439.2671 $[M+Na]^+$.

[(2*Z*,4*R*,5*R*,6*R*)-6-Methoxy-4,5-bis-(*tert*-butyldimethylsilyloxy)-octa-2,7-diene-1-yl] hept-6-enoate (19b): To **18b** (70 mg, 0.168 mmol), 6-heptenoic acid (45 μL, 0.33 mmol), and triphenylphosphine (120 mg, 0.458 mmol) in toluene (4 mL), diisopropyl azodicarboxylate (105 μL, 0.533 mmol) was added dropwise and the resulting mixture stirred at room temperature for 2 h. Satd. NH_4Cl was added and the mixture extracted with EtOAc (3×15 mL). The organic layers were combined, washed with brine, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography (EtOAc/cyclohexane 0:100 to 2:98) gave **19b** as a yellow oil (74 mg, 84%). R_f=0.45 (EtOAc/cyclohexane 5:95); $[\alpha]_D^{20}$=+15.8° (c=0.98 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ=5.79 (ddt, J=17.0, 10.3, 6.7 Hz, 1H), 5.75–5.65 (m, 2H), 5.54 (dt, J=11.3, 6.2 Hz, 1H), 5.28 (dd, J=10.6, 1.6 Hz, 1H), 5.21 (dd, J=17.2, 1.8 Hz, 1H), 5.00 (dq, J=17.2, 1.7 Hz, 1H), 4.95 (dq, J=10.2, 1.5 Hz, 1H), 4.65 (dd, J=12.9, 7.8 Hz, 1H), 4.53 (dd, J=12.9, 6.1 Hz, 1H), 4.45 (dd, J=9.3, 3.2 Hz, 1H), 3.67 (dd, J=6.5, 3.2 Hz, 1H), 3.38 (dd, J=8.0, 6.6 Hz, 1H), 3.22 (s, 3H), 2.31 (t, J=7.4 Hz, 2H), 2.06 (m, 2H), 1.64 (m, 2H), 1.42 (m, 2H), 0.90, 0.87 (2s, 18H), 0.07, 0.06, 0.04, 0.01 ppm (4s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ=173.4, 138.4, 135.3, 134.1, 124.4, 119.0, 114.7, 84.2, 79.5, 69.1, 60.9, 56.2, 34.1, 33.4, 28.3, 26.1, 25.9, 24.4, 18.4, 18.2, −4.2, −4.4, −4.8 ppm; IR (thin film): $\tilde{\nu}$=3079, 2953, 2930, 2857, 1778, 1739, 1472, 1250, 1098, 836, 777 cm^{-1}; HR-ESMS: m/z: calcd for $C_{28}H_{54}O_5Si_2Na$: 549.3408; found: 549.3392 $[M+Na]^+$.

(7*E*,9*R*,10*R*,11*R*,12*Z*)-9-Methoxy-10,11-bis-(*tert*-butyldimethylsilyloxy)-oxacyclotetradeca-7,12-dien-2-one (20b): Ester **19b** (12 mg, 0.023 mmol) was dissolved in dried and degassed toluene (40 mL) and the mixture heated to 80°C. Grubbs catalyst 2nd generation (6.0 mg 0.007 mmol) was dissolved in toluene and added to the mixture via a cannula and heating was continued for 30 min. The mixture was then filtered through a short column of silica and the solvent removed under diminished pressure. Chromatography (EtOAc/cyclohexane 0:100 to 2:98) gave **20b** as a colourless oil (11 mg, 97%). R_f=0.55 (EtOAc/cyclohexane 10:90); $[\alpha]_D$=−20.2° (c=0.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ=5.96 (dd, J=11.5, 9.9 Hz, 1H), 5.65–5.60 (m, 2H), 5.31 (dd, J=15.6, 8.9 Hz, 1H), 4.65 (dd, J=9.8, 1.6 Hz, 1H), 4.60 (dd, J=13.1, 4.6 Hz, 1H), 4.49 (dd, J=13.1, 9.4 Hz, 1H), 3.78 (dd, J=7.4, 2.1 Hz, 1H), 3.19 (s and m, 4H), 2.42–2.37 (m, 2H), 2.20–2.15 (m, 1H), 2.05–2.00 (m, 1H), 1.80–1.75 (m, 2H), 1.50–1.45 (m, 1H), 1.45–1.40 (m, 1H), 0.90, 0.86 (2s, 18H), 0.09, 0.08, 0.04, 0.02 ppm (4s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.5, 135.0, 134.4, 125.7, 122.7, 85.4, 79.2, 68.0, 61.3, 55.8, 34.7, 29.1, 26.6, 26.0, 25.9, 22.6, 18.4, 18.3, −4.2, −4.3, −4.4, −4.7 ppm; IR (thin film): $\tilde{\nu}$=2955, 2928, 2855, 1738, 1653, 1472, 1252, 1147, 1072, 835, 775 cm^{-1}; HR-ESMS: m/z: calcd for $C_{26}H_{50}O_5Si_2Na$: 521.3095; found: 521.3094 $[M+Na]^+$.

(7*E*,9*R*,10*S*,11*R*,12*Z*)-10,11-Dihydroxy-9-methoxy-oxacyclotetradeca-7,12-dien-2-one (6): To **20b** (11.0 mg, 0.022 mmol) in THF (1.5 mL), TBAF (120 μL of a 1.0 M solution in THF, 0.12 mmol) was added, and the resulting mixture was stirred at room temperature for 24 h. Solid NH_4Cl was added and the mixture extracted with EtOAc (3×15 mL). The organic layers were combined, washed with brine, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography (EtOAc/cyclohexane 25:75 → 40:60) gave **6** as a colourless oil (4.0 mg, 67%). R_f=0.20 (EtOAc/cyclohexane 70:30); $[\alpha]_D^{20}$=−34° (c=0.25 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ=6.04 (t, J=10.3 Hz, 1H), 5.90–5.85 (m, 1H), 5.82 (dd, J=15.3, 7.8 Hz, 1H), 5.24 (dd, J=15.5, 8.7 Hz, 1H), 4.65 (dd, J=13.1, 8.7 Hz, 1H), 4.55–4.50 (m, 2H), 3.79 (dd, J=8.6, 3.7 Hz, 1H), 3.40 (t, J = 8.6 Hz, 1H), 3.30 (s, 3H), 2.74 and 2.66 (2brs, 2H), 2.44 (ddd, J=15.0, 6.9, 4.5 Hz, 2H), 2.31 (ddd, J=14.7, 10.0, 4.3 Hz, 2H), 2.11 (m, 1H), 1.85–1.75 (m, 1H), 1.70–1.60 (m, 1H), 1.55–1.50 (m, 1H), 1.35–1.25 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C,

TMS): δ = 173.0, 137.5, 132.4, 126.8, 125.9, 83.8, 75.0, 66.5, 60.3, 56.0, 34.5, 30.3, 27.8, 22.6 ppm; HR-ESMS: *m/z*: calcd for $C_{14}H_{22}O_5Na$: 293.1365; found: 293.1379 $[M+Na]^+$.

Ethyl [(2*R*,3*R*,4*S*)-3,4-diacetoxy-3,4-dihydro-pyran-2-yl]-(6*E*,8*R*)-8-methoxy-6-octenoate (21): To **15b** (504 mg, 1.865 mmol) and ethyl 6-heptenoate (1.20 mL, 6.84 mmol) was added, via a cannula, the Grubbs′ catalyst 2nd generation (79 mg, 0.093 mmol) which had been dissolved in degassed and dried CH_2Cl_2 (15 mL) and the mixture was heated at reflux for 48 h. The organic layer was removed under diminished pressure and chromatography (EtOAc/cyclohexane 1:9 to 2:8) of the residue gave **21** as a colourless oil (412 mg, 55 %). R_f = 0.20 (EtOAc/cyclohexane 25:75); $[\alpha]_D^{20}$ = −30.7° (*c* = 0.95 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.46 (d, *J* = 6.1 Hz, 1H), 5.73 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.56 (ddt, *J* = 15.5, 8.4, 1.3 Hz, 1H), 5.33–5.30 (m, 2H), 4.75 (dd, *J* = 6.1, 3.4 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.95 (dd, *J* = 8.4, 4.7 Hz, 1H), 3.69 (dd, *J* = 8.4, 4.7 Hz, 1H), 3.21 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.10 (m, 2H), 2.05, 2.01 (2s, 6H), 1.61 (m, 2H), 1.42 (m, 2H), 1.22 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.5, 170.4 and 169.2, 145.9, 136.6, 125.7, 98.5, 78.5, 78.0, 68.1, 67.5, 60.1, 56.4, 34.0, 31.9, 28.4, 24.3, 21.0, 20.8, 14.2 ppm; HR-ESMS: *m/z*: calcd for $C_{20}H_{30}O_8Na$: 421.1838; found: 421.1834 $[M+Na]^+$.

(6*E*,8*S*,9*R*,10*S*,11*E*)-10-Acetoxy-9-hydroxy-8-methoxy-13-oxo-trideca-6,11-dienoic acid ethyl ester (22): To a solution of **21** (92 mg, 0.23 mmol) in dioxane (2 mL) was added H_2SO_4 (3 mL, 0.5 mM), and $HgSO_4$ (10 mg, 0.034 mmol) and stirring continued for 15 h. The mixture was then filtered through Celite, washing with CH_2Cl_2. The product was extracted into CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with brine, dried ($MgSO_4$) and the solvent removed under diminished pressure to afford **22** as a colourless oil (77 mg, 94 %). R_f = 0.25 (EtOAc/cyclohexane 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.59 (d, *J* = 7.9 Hz, 1H), 6.93 (dd, *J* = 15.8, 6.4 Hz, 1H), 6.21 (dd, *J* = 15.8, 7.8 Hz, 1H), 5.76 (dt, *J* = 15.4, 6.8 Hz, 1H), 5.55 (t, *J* = 5.3 Hz, 1H), 5.37 (dd, *J* = 15.8, 8.2 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.72 (m, 1H), 3.48 (dd, *J* = 8.2, 5.7 Hz, 1H), 3.27 (s, 3H), 2.92 (br s, 1H), 2.33 (m, 2H), 2.14–2.12 (2s, 6H), 2.12 (m, 2H), 1.65 (m, 2H), 1.45 (m, 2H), 1.25 ppm (t, *J* = 7.2 Hz, 3H); HR-ESMS: *m/z*: calcd for $C_{18}H_{28}O_7Na$: 379.1733; found: 379.1723 $[M+Na]^+$.

Ethyl (6*E*,8*R*,9*R*,10*R*,11*E*)-9,10-Diacetoxy-13-hydroxy-8-methoxy-trideca-6,11-dienoate (7): To **22** (77 mg, 0.22 mmol) in dry CH_2Cl_2 (10 mL) was added pyridine (51 mg, 0.64 mmol) and acetic anhydride (120 μL, 1.27 mmol) and the mixture left to stand overnight. Water was added and the product extracted into CH_2Cl_2 (3 × 30 mL). The organic layers were then combined, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography (EtOAc/cyclohexane 1:1) of the residue gave the acetylated aldehyde intermediate as a colourless oil (28 mg, 33 %). R_f = 0.40 (EtOAc/cyclohexane 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.56 (d, *J* = 7.8 Hz, 1H), 6.76 (dd, *J* = 15.8, 5.7 Hz, 1H), 6.23 (dd, *J* = 15.8, 7.2 Hz, 1H), 5.76 (dt, *J* = 15.4, 7.2 Hz, 1H), 5.70 (t, *J* = 5.9 Hz, 1H), 5.27 (dd, *J* = 15.5, 8.0 Hz, 1H), 5.20 (t, *J* = 4.9 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.71 (dd, *J* = 8.2, 5.1 Hz, 1H), 3.24 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.09–2.07 (2s, 6H), 2.10–2.05 (m, 2H), 1.63 (m, 2H), 1.43 (m, 2H), 1.24 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 192.8, 173.5, 170.0, 169.3, 149.3, 137.0, 133.6, 125.1, 80.5, 74.4, 71.3, 60.2, 56.5, 34.0, 31.9, 28.4, 24.4, 20.7, 14.2 ppm; HR-ESMS: *m/z*: calcd for $C_{20}H_{30}O_8Na$: 421.1838; found: 421.1851 $[M+Na]^+$.

To a solution of this aldehyde (28 mg, 0.07 mmol) in THF (5 mL) at 0 °C was added $NaBH_4$ (6 mg, 0.16 mmol) and the mixture stirred for 4 h. HCl (0.2 N) was then added and the mixture extracted with EtOAc (3 × 10 mL). The organic layers were then combined, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography (EtOAc/cyclohexane 70:30) gave **7** as a colourless oil (11 mg, 39 %). $[\alpha]_D^{20}$ = + 27.7° (*c* = 0.55 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.92 (dt, $J_{2\text{-}3}$ = 15.6, 5.0 Hz, 1H), 5.76–5.66 (m, 2H), 5.43 (dd, *J* = 7.8, 5.0 Hz, 1H), 5.28 (dd, *J* = 15.3, 8.2 Hz, 1H), 5.13 (t, *J* = 5.6 Hz, 1H), 4.16 (br d, *J* = 5.0 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.62–3.57 (m, 1H), 3.21 (s, 3H), 2.30 (t, *J* = 7.3 Hz, 2H), 2.09–2.03 (2s, 6H), 2.10–2.05 (m, 2H), 1.63 (m, 2H), 1.40 (m, 2H), 1.24 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9), 170.5, 169.8, 136.9, 135.6, 125.8, 124.8, 80.8, 74.8, 72.6, 62.8, 60.5, 56.6, 34.3, 32.1, 28.7, 24.6, 21.3, 21.2, 14.4 ppm; IR (thin film): $\tilde{\nu}$ = 3428, 2931, 1736, 1642, 1372, 1226, 1025 cm^{-1}; HR-ESMS: *m/z*: calcd for $C_{20}H_{32}O_8Na$: 423.1995; found: 423.1996 $[M+Na]^+$.

Ethyl (6*E*,8*S*,9*R*,10*S*,11*E*)-10-Acetoxy-9,13-dihydroxy-8-methoxy-trideca-6,11-dienoate (8): To **22** (183 mg, 0.51 mmol) in THF (20 mL) at 0 °C was added $NaBH_4$ (39 mg, 1.03 mmol) and the mixture was stirred for 8 min. HCl (0.2 N) was then added and the mixture extracted with EtOAc (3 × 30 mL). The organic layers were then combined, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography (EtOAc/cyclohexane 25:75) of the residue gave **8** as a colorless oil (119 mg, 65 %). R_f = 0.20 (EtOAc/cyclohexane 25:75); $[\alpha]_D^{20}$ = + 17.8° (*c* = 1.95 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.95–5.85 (m, 2H), 5.76 (m, 1H), 5.35–5.30 (m, 2H), 4.18 (d, *J* = 4.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.67 (m, 1H), 3.39 (t, *J* = 7.8 Hz, 1H), 3.25 (s, 3H), 2.32 (m, 2H), 2.12 (s, 3H), 2.12–2.07 (m, 2H), 1.66 (m, 2H), 1.44 (m, 2H), 1.26 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.9, 170.2, 137.7, 135.1, 126.3, 125.0, 82.6, 75.1, 74.1, 63.0, 60.5, 56.1, 34.3, 32.2, 28.7, 24.6, 21.5, 14.5 ppm; IR (thin film): $\tilde{\nu}$ = 3428, 2933, 1733, 1647, 1373, 1240, 1024 cm^{-1}; HR-ESMS: *m/z*: calcd for $C_{18}H_{30}O_7Na$: 381.1889; found: 381.1877 $[M+Na]^+$.

(6*E*,8*R*,9*R*,10*R*,11*E*)-9,10,13-Trihydroxy-8-methoxy-trideca-6,11-dienoic acid (9): To **8** (26 mg, 0.073 mmol) in THF/water/methanol 4:1:1 (3 mL) was added dropwise LiOH (3 mL of 1.0 M solution in water). After 1 h HCl (0.2 M) was added and the solvent removed. The residue was dissolved in brine and then extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed under diminished pressure. Chromatography (MeOH/$CHCl_3$ 0:1 to 1:1) of the residue gave **9** as a colourless oil (8 mg, 40 %). R_f = 0.30 (MeOH/$CHCl_3$ 2:8); $[\alpha]_D^{20}$ = + 5.0° (*c* = 0.35 in CH_3OH); ^{1}H NMR (300 MHz, CD_3OD): δ = 5.85–5.70 (m, 3H), 5.45 (dd, *J* = 15.5, 8.5 Hz, 1H), 4.15–4.10 (m, 2H), 3.65 (dd, *J* = 8.3, 5.0 Hz, 1H), 3.60–3.55 (m, 1H), 3.39 (t, *J* = 5.4, 5.4 Hz, 1H), 3.26 (s, 3H), 2.40 (t, *J* = 7.3 Hz, 2H), 2.17 (m, 2H), 1.64 (m, 2H), 1.49 ppm (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 137.2, 132.9, 131.5, 128.5, 83.6, 78.1, 73.0, 63.3, 56.4, 33.2, 30.0, 26.2 ppm; HR-ESMS: *m/z*: calcd for $C_{14}H_{23}O_6$: 287.1495; found: 287.1482 $[M-H]^-$.

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