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Stereoselective synthesis of the polyketide chain of nagahamide A

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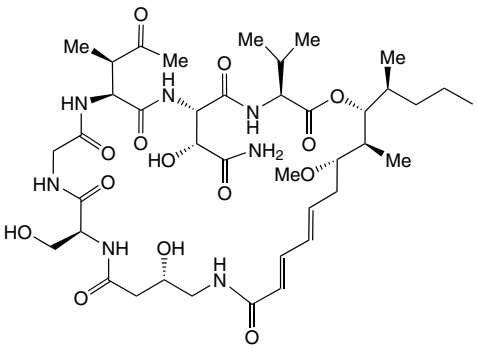
Abstract—A carbohydrate based approach for the enantioselective synthesis of the polyketide acid unit present in nagahamide A has been reported. Reductive ring opening of a chiral cyclopropane ketone group to enantioselectively install the methyl and propyl groups, is a salient feature of this synthesis.

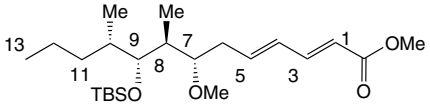
1. Introduction

Nagahamide A **1** was isolated from the marine sponge *Theonella swinhoei* and shown to posses antibacterial activity.[1] The structure of nagahamide A is characterized by a six amino acid peptide backbone joined together in a macrocyclic structure that incorporates a novel polyketide chain **2**. The polyketide ester **2** of nagahamide A **1** contains four contiguous stereogenic centres and a terminal *E*,*E*-dienoic ester group. Compound **2** is closely related to the naturally occurring YM 47522 **3**,[2] except for the stereochemical configuration of the terminal *E*,*Z*-dienoic acid group.[3]

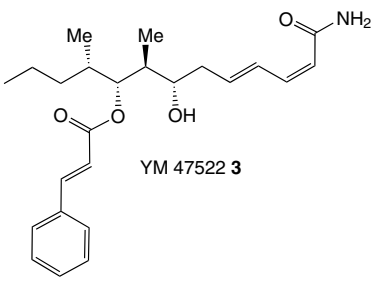
The off-template organo-metallic mediated C–C bond forming reactions at C-5 on sugar furanoses are well documented for their excellent stereocontrolled behaviour.[4] However, the off-template reduction of a double bond situated at C-5 to install, for instance, a methyl group, has never been very successful in terms of stereochemically, and invariably results in a mixture of diastereomers.[5] In our opinion, no attempts have been made to develop an appropriate strategy, by which enatioselectively an alkyl group at C-5 can be installed. Herein we report an organometallic mediated route via a regioselective ring opening reaction of a cyclopropyl[6] group to introduce methyl and alkyl groups simultaneously and which goes on to



Nagahamide A **1**



Polyketide chain **2**



YM 47522 **3**

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synthesise, for the first time, the polyketide side chain **2** of nagahamide A **1**.

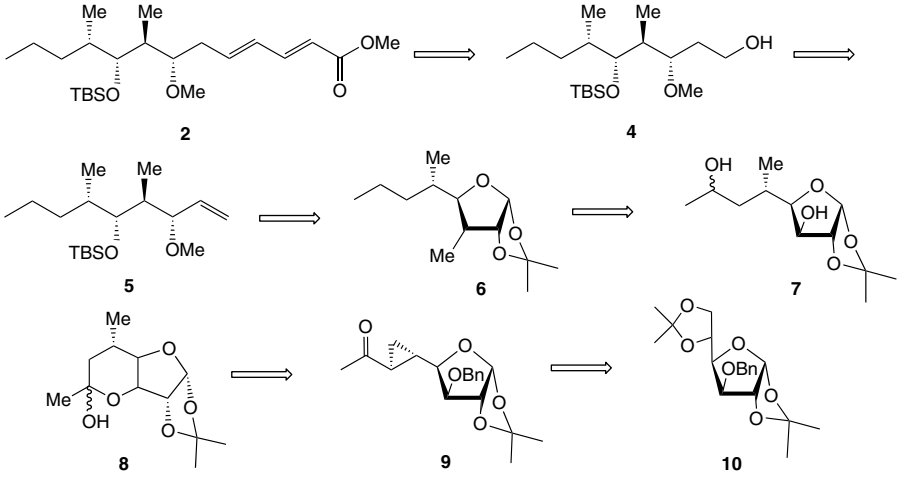
2. Results and discussion

In order to investigate the stereocontrolled cyclopropanation reaction, the 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose **10** was converted to the aldehyde[7] derivative **11** in two steps and then subjected to a reaction with acetonyltriphenylphosphorane to give a 60:40 mixture of *E*/*Z*-isomers [(*E*)-**12** and (*Z*)-**12**] of the unsaturated ketone derivative in a 60% yield; these were conveniently separated by silica gel chromatography. In the ^{1}H NMR spectrum of (*E*)-**12**, the olefinic protons appeared as a set of two double-doublets at 6.37 ppm ($J_{6,4} = 1.5$ Hz, $J_{6,5} = 16.2$ Hz) and 6.76 ppm ($J_{5,4} = 5.4$ Hz, $J_{5,6} = 16.2$ Hz), thereby confirming the *trans*-stereochemistry. On the other hand, the ^{1}H NMR spectrum of (*Z*)-**12** showed that the olefinic protons resonated as multiplets between 6.17 and 6.33 ppm. All the other protons resonated at their expected chemical shift values (see Scheme 1).

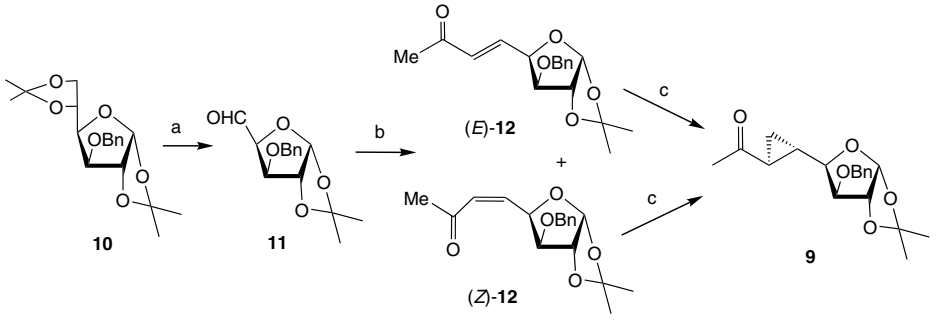
Major isomer (*E*)-**12** was treated with trimethylsulfoxonium iodide[8] in the presence of NaH to afford the cyclopropane derivative **9** (Scheme 2) in a 62% yield. The ^{1}H and ^{13}C NMR spectra clearly indicated the formation of a single product. Although its absolute stereochemistry could not be determined at this stage, we believe that the influence of the C-3 and C-4 substituents would allow the entry of a methylene group from the α-face. This contention was substantiated at a later stage.

Gratifyingly, compound (*Z*)-**12** also underwent cyclopropanation with the same reagents, as described above, to produce **9**, identical with the sample obtained above in a 67% yield. These results could be explained by the mechanism of the cyclopropanation reaction, which first involved a Michael type of 1,4-addition followed by cyclisation.

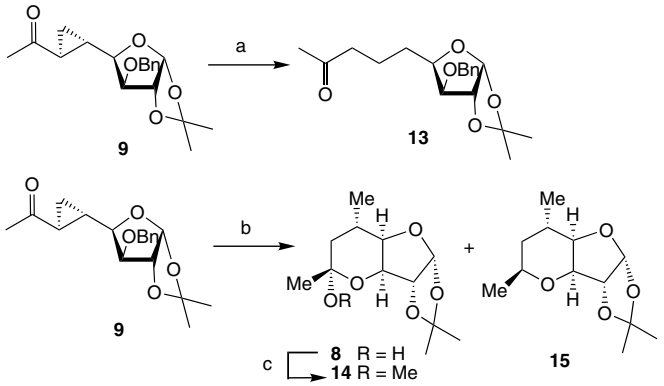
The radical ring opening reaction of **9** with *n*-Bu_3SnH[9] gave a linear product **13**, whose structure was confirmed by ^{1}H NMR, ^{13}C NMR and elemental analysis. On the other hand, reduction[10] of **9** with a 10% Pd/C at 200 psi at 60 °C predominantly gave compound **8** along with compound **15** as a minor product (Scheme 3). Compound **15,** whose structure was supported by spectroscopic and analytical data, seemed to have formed by the over reduction of **9**. It is gratifying to note that reduction of **9** at room temperature gave **8** as the only product in a 78% yield. Reaction of **8** with *p*-TSA in methanol gave the corresponding methyl ketal derivative **14**, which was prepared to support the structure of **8** using NMR experiments (Fig. 1).



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) Ref. 7; (b) $Ph_3P^+CH_2COCH_3Br^-$, Na_2CO_3, dioxane–H_2O (3:1), MeOH, 100 °C, 2 h, (60%); (c) NaH, $(CH_3)_3S^+OI^-$, DMSO, 10 °C, {62% from (*E*)-**12** and 67% from (*Z*)-**12**}.



Scheme 3. Reagents and conditions: (a) *n*-Bu_3SnH, cat. AIBN, toluene, reflux, 3 h, (82%); (b) 10% Pd/C, EtOAc, 200 psi, 60 °C, 20 h, **8** (65%) and **15** (20%); (c) MeOH, *p*-TSA (cat.), 0 °C, 2 h, (85%).

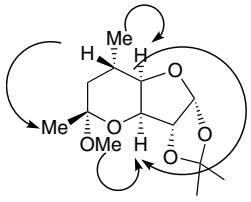
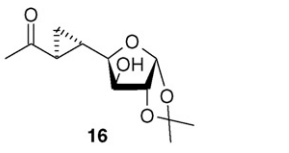


Figure 1. NOE studies on **14**.

The assignment of the absolute stereochemistry at the C-5 centre of cyclopropane derivative **9** was further determined based on single crystal X-ray crystallographic[11,12] studies of the debenzylated product **16**. The ORTEP diagram of **16** (Fig. 2) revealed that the cyclopropanation occurred from the α-face.

Our next concern involved the introduction of a methyl group at the C-3 centre for which compound **8** was reduced with $LiAlH_4$ to provide a (1:1) diastereomeric mixture (based on ^1H NMR and ^{13}C NMR spectra) of diol **7** (Scheme 4). It is pertinent to mention that the newly formed C-7 stereocentre of **7** was of no consequence, as it would finally be destroyed. Therefore, we decided to continue our synthetic strategy with a mixture. The less hindered secondary hydroxyl group of **7** was protected as its TBS ether **17** by using TBSCl and imidazole. In the ^1H NMR spectrum of **17**, the characteristic signals due to the TBS group were located in the up-field region. The ^{13}C NMR spectroscopy and elemental analysis were in full agreement with the assigned structure **17**. In order to install the methyl group at C-3, a conventional sequence of oxidation, Wittig reaction, and catalytic hydrogenation were adopted in order to obtain **19**. The removal of the TBS group followed by the Barton McCombie radical deoxygenation[13] gave **6**, whose structure was fully characterized by spectroscopy and elemental analysis. In the ^1H NMR spectrum of **6**, a characteristic triplet due to the H-2 proton was observed at 4.49 ppm ($J = 4.4$ Hz) indicating that the H-2 was *cis* to both H-1 and H-3. Due to the 1,2-isopropylidine group, the hydrogenation of the C_3-*exo*-methylene group was expected to occur from the β-face. The characteristic two doublets observed at 0.84 ppm ($J = 6.6$ Hz) and 1.01 ppm ($J = 6.6$ Hz) were attributed to methyl groups present at C-5 and C-3. Other resonances were in good agreement with the assigned structure **6**. The structure was further confirmed by its ^{13}C NMR spectroscopy and elemental analysis. The stereocentre at C-3 was further confirmed by NOE studies (Fig. 3). Strong NOEs were observed between the protons at C-1 (5.71 ppm) and C-2 (4.49 ppm), C-2 (4.49 ppm) and C-3 (1.82 ppm). No NOE was found between the protons at C-3 (1.82 ppm) and C-4 (3.69 ppm); a relevant NOE was observed between the methyl group at C-3 (1.01 ppm) with the proton at C-4 (3.69 ppm) suggesting the *anti* configuration. Treatment of **6** with 6 M HCl opened the isopropylidene ring and produced lactol **22** (Scheme 4).



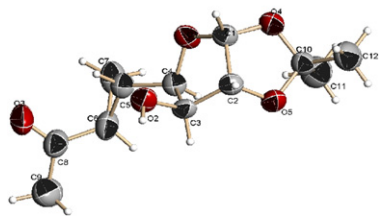
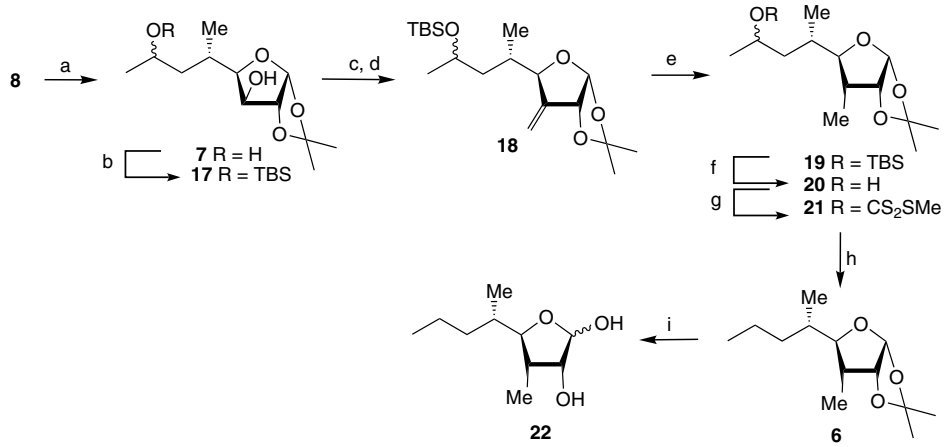


Figure 2. ORTEP diagram of **16**.

The Wittig reaction of **22** with $Ph_3P{=}CH_2$ gave the terminal olefinic product **23**. The characteristic signals due to the terminal olefin in the ^1H NMR spectrum of **23** supported the assigned structure. To assign the stereocentres at C-3, C-4, C-5 further, the diol **23** was protected as its acetonide derivative **24**. In the ^{13}C NMR of acetonide **24**, the appearance of the acetonide methyl groups C-7, C-8 at 19.6, 30.2, respectively, and the quaternary carbon C-6 at 97.9 clearly suggests the *syn* nature of the C-3 and C-5 hydroxyl groups.[14] Nuclear Overhauser effect (NOE) experiments allowed us to assign the absolute configuration further at C-3, C-4 and C-5. As shown in Figure 4, a relevant NOE was observed between the protons at C-3 (3.85 ppm) and C-5 (3.46 ppm). Strong NOEs were observed between the methyl group at C-4 (0.72 ppm) with the protons at C-3 and C-5. The axial acetonide methyl group C-7 (1.38 ppm) also had a strong NOE with the protons at C-3 and C-5. The above studies enabled us to assign the stereocentres at C-3, C-4 and C-5 as (*S*), (*S*) and (*R*), respectively. The higher reactivity of allylic hydroxyl group was exploited to selectively block with a methyl group using MeI–LiHMDS to give **25** (Scheme 5). In the ^1H NMR spectra of **25**, the resonance due to H-3 was clearly apparent as a triplet whereas the chemical shifts of all the other protons were comparable except for H-3 which showed an upfield shift of 0.56 ppm. The second hydroxyl group of **25** was first silylated and then treated with Me_2S–BH_3 to afford compound **4**.

Finally, compound **4** was oxidized with the Dess–Martin periodinane[15] and subjected to a Wittig reaction with



Scheme 4. Reagents and conditions: (a) lithium aluminium hydride, THF, 0 °C–rt, 1 h, (92%); (b) TBSCl, imidazole, CH_2Cl_2, 0 °C–rt, 0.5 h, (90%); (c) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, (97%); (d) $Ph_3P{=}CH_2$, THF, −15 °C, (75%); (e) 10% Pd/C, EtOAc, 2 h, (91%); (f) TBAF, THF, 0 °C, 0.5 h, (90%); (g) NaH, CS_2, CH_3I, 0 °C–rt, (75%); (h) *n*-Bu_3SnH, cat. AIBN, toluene, reflux, 3 h, (73%); (i) 6 M HCl, THF–H_2O (3:1), cat. H_2SO_4, 70 °C, 1 h, (70%).

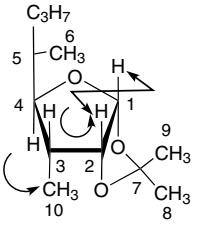


Figure 3. Some NOESY interactions for **6**.

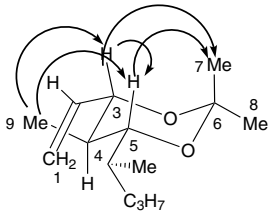


Figure 4. Some NOESY interactions for **24**.

$(EtO)_2P(O)CH_2$–CH=CH–COOMe[16] to give the polyketide side chain **2**. The structure of **2** was investigated by spectroscopic data. For example, its ^1H NMR spectrum revealed signals due to the olefin protons at δ 5.80 (d, $J_{2,3} = 15.2$ Hz), 7.28 (dd, $J_{3,2} = 15.2$ Hz, $J_{3,4} = 9.9$ Hz), 6.22 (dd, $J_{4,3} = 9.9$ Hz, $J_{4,5} = 15.1$ Hz) and 6.18 (dt, $J_{5,4} = 15.1$ Hz, $J_{5,6} = 7.4$ Hz) which were characteristic of the *E*,*E*-dienoic group.

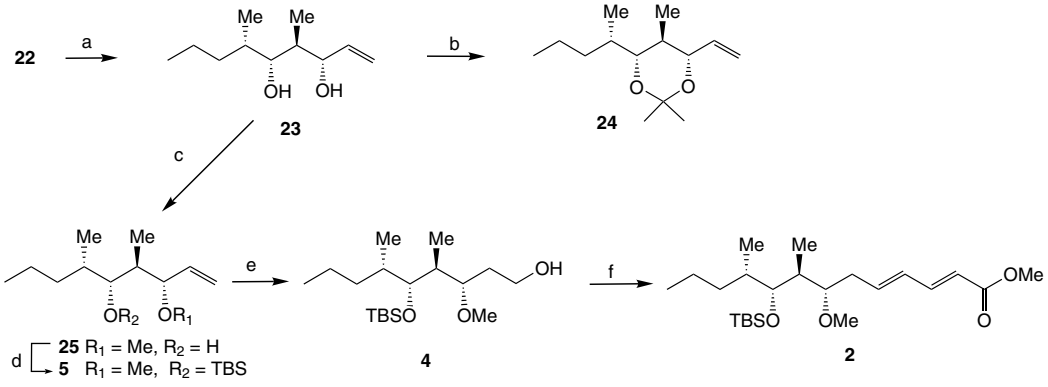
3. Conclusion

In conclusion, the first enantioselective synthesis of nagahamide A side chain **2** from D-glucose has been accomplished. Further work on peptide synthesis is in progress in our laboratory.

4. Experimental

4.1. General

All chemicals used in this study were purchased from Aldrich, Fluka, or Lancaster and used as received. All the moisture-sensitive reactions were performed under an



Scheme 5. Reagents and conditions: (a) $Ph_3P{=}CH_2$, THF, −78 °C–rt, 10 h, (71%); (b) DMP, *p*-TSA, acetone, rt, 3 h, (97%); (c) LiHMDS, CH_3I, THF, −78 to 0 °C, 1 h, (83%); (d) TBSOTf, lutidine, CH_2Cl_2, 0 °C–rt, 1 h, (80%); (e) H_3B–SMe_2, NaOAc, H_2O_2, 0 °C–rt, 6 h (60%); (f) (i) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt, 30 min, (85%); (ii) $(EtO)_2P(O)CH_2CH{=}CHCO_2Me$, LiHMDS, THF, −78 °C, 1 h, (82%).

inert atmosphere of either N_2 or Ar using dry solvents. The elemental analyses were recorded on Elmentar-Vario-EL (Heraeus Company Ltd, Germany). The NMR spectra were obtained on a Bruker 200, 400 or 500 Fourier transform spectrometer. The optical rotations were measured with a JASCO DIP 370 digital polarimeter. All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV, I_2 or anisaldehyde in ethanol as development reagents.

4.1.1. 3-*O*-Benzyl-5,6,8-trideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-oct-5*Z*-enofuranos-7-ulose (*Z*)-12 and 3-*O*-benzyl-5,6,8-trideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-oct-5*E*-enofuranos-7-ulose (*E*)-12. A solution of acetonyl-triphenylphophonium bromide (62.0 g, 155.5 mmol) and Na_2CO_3 (16.5 g, 155.5 mmol) in dioxane/H_2O (3:1, 120 mL) was heated at reflux for 45 min and then **11** (24.0 g, 91.5 mmol) in MeOH (30 mL) was added dropwise. After 2 h, the reaction mixture was concentrated, the residue dissolved in ethyl acetate, washed with saturated aqueous Na_2CO_3 solution, dried over Na_2SO_4 and concentrated. The residue was stirred with hexane (300 mL) and ethyl acetate (15 mL) for 1 h, filtered and the filtrate concentrated. The residue was purified on silica gel using ethyl acetate and light petroleum (1:9) to furnish (*Z*)-**12** (7.0 g, 24%), $[\alpha]_D^{25} = -37.2$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.50 (s, 3H), 2.20 (s, 3H), 3.35 (d, 1H, $J = 3.4$ Hz), 4.42 (d, 1H, $J = 11.7$ Hz), 4.56 (d, 1H, $J = 12.2$ Hz), 4.60 (d, 1H, $J = 3.9$ Hz), 5.44 (dd, 1H, $J = 3.4$, 5.4 Hz), 5.98 (d, 1H, $J = 3.9$ Hz), 6.17–6.33 (m, 2H), 7.23–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 26.5, 30.6, 71.8, 78.4, 82.8, 84.0, 104.8, 111.2, 127.1, 127.2, 127.3, 127.9, 137.2, 143.1, 197.7. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.90; H, 6.96. Found: C, 67.73; H, 6.76.

Further elution gave (*E*)-**12** (10.5 g, 36%), $[\alpha]_D^{25} = -63.7$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), 3.97 (d, 1H, $J = 3.4$ Hz), 4.46 (d, 1H, $J = 12.2$ Hz), 4.65 (d, 1H, $J = 12.2$ Hz), 4.66 (d, 1H, $J = 3.9$ Hz), 4.78 (ddd, 1H, $J = 1.6$, 3.4, 5.4 Hz), 5.99 (d, 1H, $J = 3.9$ Hz), 6.37 (dd, 1H, $J = 1.5$, 16.2 Hz), 6.76 (dd, 1H, $J = 5.4$, 16.2 Hz), 7.23–7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 26.7, 27.3, 72.0, 79.5, 82.6, 83.1, 104.9, 111.8, 127.6, 128.0, 128.4, 131.6, 136.9, 140.1, 197.2. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.90; H, 6.96. Found: C, 67.85; H, 6.68.

4.1.2. 3-*O*-Benzyl-5,6-*C*-methylene-5,6,8-trideoxy-1,2-*O*-isopropylidene-L-*glycero*-β-L-*iodo*-octos-7-ulofuranose 9. To a suspension of NaH (1.79 g, 60% dispersion in oil, 45.0 mmol), trimethyl sulfoxonium iodide (9.9 g, 45.0 mmol) in DMSO (50 mL) under argon at 10 °C was added (*E*)-**12** (13.0 g, 40.9 mmol) in DMSO (50 mL) over a period of 30 min. The reaction was quenched with ice-cold water and extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated. The residue was purified on silica gel using ethyl acetate and light petroleum (1.5:8.5) to afford **9** (8.41 g, 62%). Similarly, starting from (*Z*)-**12** and following the above procedure gave compound **9** in a 67% yield. $[\alpha]_D^{25} = +7.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (ddd, 1H, $J = 4.1$, 6.6, 9.3 Hz), 1.33 (s, 3H), 1.37 (dt, 1H, $J = 4.4$, 9.3 Hz), 1.47 (s, 3H), 1.90 (dt, 1H, $J = 4.4$, 8.3 Hz), 1.94–1.98 (m, 1H), 2.16 (s, 3H), 3.72 (dd, 1H, $J = 3.4$, 7.5 Hz), 3.85 (d, 1H, $J = 3.2$ Hz), 4.54 (d, 1H, $J = 11.9$ Hz), 4.63 (d, 1H, $J = 4.0$ Hz), 4.71 (d, 1H, $J = 11.9$ Hz), 5.92 (d, 1H, $J = 4.0$ Hz), 7.29–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.4, 21.2, 25.0, 25.7, 26.3, 29.6, 71.4, 81.7 (2C), 82.1, 104.3, 110.8, 127.3, 127.5, 128.1, 137.1, 206.0. Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.27. Found: C, 68.46; H, 7.10.

4.1.3. 5,6-*C*-Methylene-5,6,8-trideoxy-1,2-*O*-isopropylidene-L-*glycero*-β-L-*iodo*-octos-7-ulofuranose 16. Compound **9** (0.085 g, 0.26 mmol) in MeOH was hydrogenated using 10% Pd in charcoal at atmospheric pressure. After 4 h, the reaction mixture was filtered through a small Celite pad. The filtrate was concentrated and purified by column chromatography using ethyl acetate and light petroleum ether (1:3) to afford **16** as a crystalline solid (0.059 g, 95%), which was again recrystallised from CH_2Cl_2 and light petroleum ether. Mp. 135–136 °C; $[\alpha]_D^{25} = +49.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19–1.36 (m, 2H), 1.30 (s, 3H), 1.47 (s, 3H), 1.75 (m, 1H), 2.00 (m, 1H), 2.25 (s, 3H), 2.61 (br s, 1H), 3.86 (dd, 1H, $J = 2.6$, 6.3 Hz), 4.12 (d, 1H, $J = 2.6$ Hz), 4.52 (d, 1H, $J = 3.7$ Hz), 5.88 (d, 1H, $J = 3.7$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.09, 21.13, 24.77, 26.01, 26.61, 30.26, 75.91, 81.13, 85.10, 104.55, 111.13, 208.04. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.67; H, 7.56.

4.1.4. 3-*O*-Benzyl-5,6,7,9-tetradeoxy-1,2-*O*-isopropylidene-α-D-*xylo*-nonos-8-ulofuranose 13. A solution of **9** (0.2 g, 0.6 mmol), tri-*n*-butyltin hydride (0.2 mL, 0.7 mmol) and AIBN (15 mg) in benzene (10 mL) under argon was heated at reflux for 3 h and concentrated. A saturated solution of KF and ether were introduced, stirred vigorously for 4 h and the ether layer separated, dried over Na_2SO_4 and concentrated. The residue was purified on silica gel using ethyl acetate and light petroleum (3:17) to obtain **13** (0.16 g, 82%). $[\alpha]_D^{25} = -56.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.48 (s, 3H), 1.58–1.70 (m, 4H), 1.12 (s, 3H), 2.42–2.48 (m, 2H), 3.76 (d, 1H, $J = 2.9$ Hz), 4.06–4.13 (m, 1H), 4.47 (d, 1H, $J = 12.2$ Hz), 4.59 (d, 1H, $J = 3.9$ Hz), 4.70 (d, 1H, $J = 12.2$ Hz), 5.88 (d, 1H, $J = 3.9$ Hz), 7.25–7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.4, 26.1, 26.6, 27.3, 29.7, 43.4, 71.6, 80.0, 82.2 (2C), 104.6, 111.1, 127.6, 127.8, 128.3, 137.5, 207.9. Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.83. Found: C, 67.98; H, 7.74.

4.1.5. 3,7-Anhydro-5-*C*-methyl-5,6,8-trideoxy-1,2-*O*-isopropylidene-L-*glycero*-β-L-*iodo*-octofuranose 15 and (7 *R*/*S*)-5,6,8-trideoxy-1,2-*O*-isopropylidene-5-*C*-methyl-β-L-*iodo*-octos-7-ulo-1,4-furano-3,7-pyranose 8. A solution of **9** (3.0 g, 9.0 mmol) in ethyl acetate (25 mL) was hydrogenated in the presence of 10% Pd/C (0.3 g) at 200 psi at 60 °C. After 20 h, the reaction mixture was filtered through a pad of Celite, concentrated and the residue purified on silica gel using ethyl acetate and light petroleum (1:9) to afford **15** (0.41 g, 20%), $[\alpha]_D^{25} = +11.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (d, 3H, $J = 7.6$ Hz), 1.12 (d, 3H, $J = 6.1$ Hz), 1.20–1.23 (m, 1H), 1.30 (s, 3H),

1.49 (s, 3H), 1.67–1.73 (m, 1H), 2.23–2.28 (m, 1H), 3.58–3.64 (m, 1H), 3.83 (s, 1H), 3.98 (d, 1H, $J = 1.6$ Hz), 4.45 (d, 1H, $J = 3.6$ Hz), 5.88 (d, 1H, $J = 3.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.6, 21.3, 25.6, 26.2, 27.0, 33.5, 65.7, 76.0, 77.5, 83.7, 104.4, 110.4. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.41; H, 8.60.

Further elution afforded **8** (1.43 g, 65%), ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (d, 3H, $J = 7.2$ Hz), 1.21 (s, 3H), 1.25 (s, 3H), 1.26 (dd, 1H, $J = 5.8$, 13.4 Hz), 1.49 (s, 3H), 1.65 (dd, 1H, $J = 5.2$, 13.4 Hz), 1.70–1.76 (m, 1H), 3.90 (t, 1H, $J = 3.4$ Hz), 4.05 (d, 1H, $J = 3.4$ Hz), 4.42 (d, 1H, $J = 3.9$ Hz), 5.78 (d, 1H, $J = 3.9$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.5, 22.6, 27.2, 28.0, 30.1, 36.4, 74.0, 79.8, 83.5, 96.0, 104.5, 111.0. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.87; H, 8.54.

4.1.6. (7*S*)-Methyl-5-*C*-methyl-5,6,8-trideoxy-1,2-*O*-isopropylidene-β-L-*iodo*-octos-7-ulo-1,4-furano-3,7-pyranose 14. A solution of **8** (0.2 g, 0.8 mmol) and *p*-TSA (15 mg) in MeOH (10 mL) was stirred at 0 °C for 2 h, neutralized with Et_3N and concentrated. The residue was partitioned between ethyl acetate and water, the organic layer dried (Na_2SO_4), concentrated and chromatographed on silica gel with ethyl acetate and light petroleum (1:19) to provide **14** (0.18 g, 85%). $[\alpha]_D^{25} = +122.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (d, 3H, $J = 7.5$ Hz), 1.29 (s, 3H), 1.33 (s, 3H), 1.41 (dd, 1H, $J = 6.0$, 13.9 Hz), 1.51 (s, 3H), 1.78 (dd, 1H, $J = 5.1$, 13.9 Hz), 1.93–2.00 (m, 1H), 3.22 (s, 3H), 3.94 (t, 1H, $J = 3.2$ Hz), 4.01 (d, 1H, $J = 3.2$ Hz), 4.56 (d, 1H, $J = 3.8$ Hz), 5.90 (d, 1H, $J = 3.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 23.1, 26.2, 26.7, 28.3, 36.9, 48.1, 72.8, 80.7, 84.4, 99.3, 105.0, 111.3. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.58. Found: C, 60.27; H, 8.65.

4.1.7. 7-*O*-*tert*-Butyldimethylsilyl-5-*C*-methyl-5,6,8-tri-deoxy-1,2-*O*-isopropylidene-D/L-*glycero*-β-L-*iodo*-octofuranose 17. A stirred suspension of LAH (0.57 g, 15.2 mmol) and **8** (3.7 g, 15.2 mmol) in THF (20 mL) was stirred at rt for 1 h. After the usual workup, the crude product was purified on silica gel using ethyl acetate and light petroleum (3:7) to afford **7** (3.43 g, 92%), which was dissolved in dry CH_2Cl_2 (30 mL). Imidazole (1.89 g, 27.9 mmol) and *tert*-butyldimethylsilyl chloride (2.31 g, 15.3 mmol) were then added. After 0.5 h, the reaction mixture was washed with saturated NH_4Cl solution, water, dried (Na_2SO_4) and concentrated to afford **17** (4.51 g, 90%) and used as such for the next reaction. For analytic samples, a part of the residue was chromatographed on silica gel using ethyl acetate and light petroleum (1:9) to elute faster moving isomer, $[\alpha]_D^{25} = +13.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.90 (s, 9H), 1.04 (d, 3H, $J = 6.3$ Hz), 1.13 (d, 3H, $J = 5.9$ Hz), 1.26 (s, 3H), 1.30–1.38 (m, 2H), 1.41 (s, 3H), 1.49–1.61 (m, 1H), 1.87–1.97 (m, 1H), 2.98 (br d, 1H, $J = 5.4$ Hz), 3.72 (dd, 1H, $J = 2.9$, 9.8 Hz), 3.97–4.08 (m, 2H), 4.49 (d, 1H, $J = 4.0$ Hz), 5.83 (d, 1H, $J = 4.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.7, 18.1, 18.8, 22.3, 25.9, 26.0, 26.6, 27.7, 42.0, 67.5, 73.9, 85.2, 85.7, 104.3, 110.7. Anal. Calcd for $C_{18}H_{36}O_5Si$: C, 59.96; H, 10.06. Found: C, 60.25; H, 10.33.

Further elution gave slower moving isomer, $[\alpha]_D^{25} = +23.4$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09, 0.10 (2s, 6H), 0.90 (s, 9H), 1.12 (d, 3H, $J = 6.8$ Hz), 1.19 (d, 3H, $J = 5.9$ Hz), 1.30 (s, 3H), 1.32 (m, 2H), 1.50 (s, 3H), 1.54–1.67 (m, 1H), 1.92–2.02 (m, 1H), 3.49 (br s, 1H), 3.76 (dd, 1H, $J = 2.4$, 10.2 Hz), 4.03–4.20 (m, 1H), 4.52 (d, 1H, $J = 3.9$ Hz), 5.90 (d, 1H, $J = 3.9$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.7, −4.5, 17.5, 18.0, 24.7, 25.8, 26.0, 26.6, 28.3, 43.0, 66.4, 74.2, 84.9, 85.6, 104.2, 110.6. Anal. Calcd for $C_{18}H_{36}O_5Si$: C, 59.96; H, 10.06. Found: C, 59.83; H, 9.79.

4.1.8. 7-*O*-*tert*-Butyldimethylsilyl-3,5-*C*-dimethyl-3,5,6,8-tetradeoxy-1,2-*O*-isopropylidene-D/L-*glycero*-β-L-*talo*-octofuranose 19. Dry DMSO (2.6 mL, 36.7 mmol) and oxaloyl chloride (1.6 mL, 18.3 mmol) in CH_2Cl_2 (20 mL) at −78 °C under N_2 were stirred for 30 min and then **17** (4.4 g, 12.2 mmol) in CH_2Cl_2 (10 mL) was added. After 1 h, the reaction was quenched by Et_3N (7.7 mL) at −78 °C and worked up as usual. The residue (4.24 g, 97%) was dissolved in anhydrous THF (20 mL) and cooled to −78 °C. Methylenetriphenylphosphorane [prepared from PPh_3CH_3I (9.5 g) and *n*-BuLi (1.6 M, 15.0 mL)] were added. After 2 h stirring at rt, it was quenched by addition of saturated aqueous NH_4Cl solution. The two layers were separated, the organic layer dried over Na_2SO_4 and concentrated to form a residue which was purified on silica gel using ethyl acetate and light petroleum (1:19) to furnish the olefin **18** (3.16 g, 75%).

The above product (3.10 g, 8.7 mmol), 10% Pd/C (0.3 g) in EtOAc (20 mL) was stirred under hydrogen at normal temperature and pressure. After 2 h, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified on silica gel using ethyl acetate and light petroleum (1:19) to provide **19** (2.83 g, 91%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04, 0.05 (2s, 6H), 0.84 (d, 3H, $J = 7.3$ Hz), 0.88 (s, 9H), 1.01 (d, 3H, $J = 6.6$ Hz), 1.13 (d, 3H, $J = 6.3$), 1.31 (s, 3H), 1.40–1.60 (m, 2H), 1.49 (s, 3H), 1.76–1.90 (m, 2H), 3.76 (dd, 1H, $J = 2.2$, 10.2 Hz), 3.89–3.96 (m, 1H), 4.50 (t, 1H, $J = 3.9$ Hz), 5.71 (d, 1H, $J = 3.9$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.5, −3.9, 9.5 and 9.6, 14.1 and 14.4, 18.1, 24.2 and 24.4, 26.0, 26.4, 26.7, 29.4, 39.6, 44.6 and 44.7, 66.5 and 66.7, 83.1, 83.8, 104.5, 110.9. Anal. Calcd for $C_{19}H_{38}SiO_4$: C, 63.64; H, 10.68. Found: C, 63.48; H, 10.59.

4.1.9. 3,5-*C*-Dimethyl-3,5,6,7,8-pentadeoxy-1,2-*O*-isopropylidene-β-L-*talo*-octofuranose 6. A solution of **19** (2.70 g, 7.5 mmol) and 1 M solution of *n*-Bu_4NF (8.3 mL, 8.3 mmol) were stirred for 30 min and concentrated. The crude was extracted with ethyl acetate, washed with water, dried over Na_2SO_4, then concentrated. The residue was chromatographed on silica gel using ethyl acetate and light petroleum (3:7) to give **20** (1.65 g, 90%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (d, 3H, $J = 7.3$ Hz), 1.03 (d, 3H, $J = 6.8$ Hz), 1.18 (d, 3H, $J = 6.4$), 1.32 (s, 3H), 1.49 (s, 3H), 1.52–1.70 (m, 2H), 1.81–1.96 (m, 2H), 2.48 (br s, 1H), 3.83 (dd, 1H, $J = 2.0$, 10.2 Hz), 3.89–3.99 (m, 1H), 4.52 (t, 1H, $J = 3.9$ Hz), 5.72 (d, 1H, $J = 3.9$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.5 and 9.6, 13.4 and 13.5,

23.9, 26.4, 26.7, 29.8, 39.6, 44.4 and 44.6, 64.6, 83.0, 84.4, 104.4 and 104.5, 111.3.

The above product **20** (1.54 g, 6.3 mmol) in THF (10 mL) was added to NaH (0.3 g, 7.6 mmol) in THF (5 mL). The resulting solution was stirred at rt for 30 min, CS_2 (0.6 mL) and MeI (0.6 mL) were added. After usual work up, the residue was purified on silica gel by using ethyl acetate and light petroleum (1:9) to provide **21** (1.77 g, 75%).

The above product **21**, *n*-Bu_3SnH (1.5 mL, 5.6 mmol) and AIBN (15 mg) in toluene (15 mL) under argon were heated at reflux for 3 h, concentrated and chromatographic purification on silica gel using ethyl acetate and light petroleum (3:97) afforded **6** (0.78 g, 73%). $[\alpha]_D^{25} = +46.7$ (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (d, 3H, $J = 6.6$ Hz), 0.90 (t, 3H, $J = 7.1$ Hz), 1.01 (d, 3H, $J = 6.6$ Hz), 1.31 (s, 3H), 1.33–1.45 (m, 4H), 1.49 (s, 3H), 1.55–1.61 (m, 1H), 1.79–1.84 (m, 1H), 3.69 (dd, 1H, $J = 2.2$, 10.2 Hz), 4.49 (t, 1H, $J = 4.4$ Hz), 5.71 (d, 1H, $J = 4.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.5, 13.2, 14.2, 20.5, 26.4, 26.7, 33.0, 36.8, 39.7, 83.1, 84.9, 104.5, 110.8. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.48; H, 10.64.

4.1.10. (3*S*,4*S*,5*R*,6*S*)-4,6-Dimethyl-non-1-ene-3,5-diol 23. Compound **6** (0.73 g, 3.2 mmol) and 6 M HCl (2 mL) in THF–H_2O (12:4 mL) were heated at 70 °C for 1 h. The reaction mixture was neutralized by addition of solid $NaHCO_3$, filtered and concentrated. The residue was partitioned between ethyl acetate and water, the organic layer separated, washed with water, dried over Na_2SO_4 and concentrated. The residue was purified on silica gel using ethyl acetate and light petroleum (1:3) to obtain **22** (0.42 g, 70%) which was dissolved in THF (10 mL) and $CH_2{=}PPh_3$ [prepared from PPh_3CH_3I (2.7 g) and *n*-BuLi (1.6 M, 4.0 mL)] at −78 °C was added. After 10 h of stirring at rt, it worked up as usual and the residue purified on silica gel using ethyl acetate and light petroleum (1:4) to furnish **23** (0.29 g, 71%). $[\alpha]_D^{25} = +7.7$ (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, 3H, $J = 6.6$ Hz), 0.85 (d, 3H, $J = 7.3$ Hz), 0.92 (t, 3H, $J = 6.6$ Hz), 1.30–1.38 (m, 4H), 1.65–1.75 (m, 2H), 3.35 (br s, 2H), 3.53 (dd, 1H, $J = 2.2$, 8.2 Hz), 4.08 (t, 1H, $J = 8.0$ Hz), 5.16–5.27 (m, 2H), 5.80–5.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0, 13.0, 14.3, 20.6, 34.7, 36.6, 41.0, 79.0 (2C), 116.5, 139.8. Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.98. Found: C, 70.77; H, 12.16.

4.1.11. (4*R*,5*S*,6*S*)-2,2,5-Trimethyl-4-((*S*)-pentan-2-yl)-6-vinyl-1,3-dioxane 24. Diol **23** (0.03 g, 0.16 mmol) in acetone (3 mL) was treated with 2,2′-dimethoxypropane (0.08 mL, 0.64 mmol) and a catalytic amount of *p*-TSA at room temperature. After 3 h, the reaction mixture was quenched with a drop of Et_3N. The solvent was evaporated in vacuo and purified by column chromatography using light petroleum ether and ethyl acetate (19:1) to give **24** (0.036 g, 97%) as a colorless liquid. $[\alpha]_D^{25} = +25.6$ (*c* 1.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.71 (d, 3H, $J = 6.7$ Hz), 0.83 (d, 3H, $J = 6.8$ Hz), 0.90 (t, 3H, $J = 6.6$ Hz), 1.31 (m, 4H), 1.38 (s, 3H), 1.44 (s, 3H), 1.65 (m, 2H), 3.46 (dd, 1H, $J = 2.2$, 10.2), 3.50 (dd, 1H, $J = 7.4$, 10.4), 5.20 (ddd, 1H, $J = 0.5$, 1.8, 10.1), 5.25 (ddd, 1H, $J = 0.8$, 1.8, 17.2), 5.69 (ddd, 1H, $J = 7.5$, 10.1, 17.2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.8, 12.5, 14.4, 19.6, 20.5, 30.2, 33.0, 35.1, 36.2, 75.8, 77.4, 97.9, 117.8, 137.7. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.38; H, 11.71.

4.1.12. (3*S*,4*S*,5*R*,6*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3-methoxy-4,6-dimethyl-non-1-ene 5. To a solution of **23** (0.2 g, 1.0 mmol) in dry THF (7 mL) at −78 °C, LiHMDS (1.06 M, 1.1 mL) was added. After 15 min, MeI (0.1 mL, 1.7 mmol) in THF (0.5 mL) was introduced and the reaction mixture warmed to 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to provide a residue which was purified on silica gel using ethyl acetate and light petroleum ether (1:19) to afford **25** (0.18 g, 83%). $[\alpha]_D^{25} = -20.7$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.72 (d, 3H, $J = 7.3$ Hz), 0.84 (d, 3H, $J = 6.6$ Hz), 0.91 (t, 3H, $J = 6.8$ Hz), 1.29–1.42 (m, 4H), 1.53–1.63 (m, 1H), 1.70–1.78 (m, 1H), 3.29 (s, 3H), 3.47 (dd, 1H, $J = 2.2$, 8.8 Hz), 3.52 (t, 1H, $J = 8.4$ Hz), 4.04 (br s, 1H), 5.20 (dd, 1H, $J = 1.8$, 17.1 Hz), 5.31 (dd, 1H, $J = 1.8$, 10.2 Hz), 5.54–5.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 14.6, 15.4, 21.1, 34.6, 38.6, 43.8, 56.2, 75.2, 79.5, 117.8, 137.5. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.07. Found: C, 71.82; H, 11.91.

The above product **25** (0.13 g, 0.6 mmol), 2,6-lutidine (0.3 mL) and TBSOTf (0.22 mL, 0.1 mmol) in CH_2Cl_2 (4 mL) were stirred at rt for 1 h, washed with water and concentrated. The residue was purified on silica gel using ethyl acetate and light petroleum (1:49) to furnish **5** (0.16 g, 80%). $[\alpha]_D^{25} = +3.9$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) data: δ 0.06 (s, 6H), 0.80 (d, 3H, $J = 7.3$ Hz), 0.86 (d, 3H, $J = 6.6$ Hz), 0.89–0.93 (m, 12H), 1.27–1.36 (m, 4H), 1.55–1.63 (m, 1H), 1.83–1.90 (m, 1H), 3.22 (s, 3H), 3.46 (t, 1H, $J = 7.6$ Hz), 3.80 (dd, 1H, $J = 2.2$, 5.8 Hz), 5.16–5.27 (m, 2H), 5.54–5.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.1, −3.8, 11.6, 14.4, 15.2, 18.6, 20.7, 26.2, 34.5, 38.4, 43.6, 56.0, 74.0, 84.8, 117.7, 137.3. Anal. Calcd for $C_{18}H_{38}SiO_2$: C, 68.72; H, 12.17. Found: C, 68.70; H, 11.92.

4.1.13. (3*S*,4*S*,5*R*,6*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3-methoxy-4,6-dimethyl-nonan-1-ol 4. To a solution of **5** (0.11 g, 0.3 mmol) in anhydrous THF (3 mL) at 0 °C was added $H_3B{-}SMe_2$ (0.1 mL, 1.0 mmol). After stirring for 1 h, saturated NaOAc solution was introduced followed by the addition of 30% H_2O_2 (0.1 mL). The reaction mixture was further stirred at rt for 5 h, diluted with ethyl acetate, dried (Na_2SO_4) and concentrated. The crude was purified on silica gel using ethyl acetate and light petroleum (1:9) to provide **4** (70 mg, 60%). $[\alpha]_D^{25} = -23.9$ (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.05, 0.06 (2s, 6H), 0.82 (d, 3H, $J = 7.2$ Hz), 0.87 (d, 3H, $J = 6.8$ Hz), 0.91–0.93 (m, 12H), 1.17–1.20 (m, 1H), 1.34–1.39 (m, 3H), 1.60–1.65 (m, 1H), 1.66–1.71 (m, 3H), 2.06–2.10 (m, 1H), 3.34 (s, 3H), 3.48 (dd, 1H, $J = 2.4$, 7.6 Hz), 3.64 (dt, 1H, $J = 4.4$, 8.4 Hz), 3.78 (t, 2H, $J = 5.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ −3.7, −3.4, 11.0, 14.3 (2C), 18.6, 20.9, 26.4, 31.2, 36.2, 37.1, 38.6, 55.2, 61.7, 76.9, 82.5. Anal.

Calcd for $C_{18}H_{40}SiO_3$: C, 65.00; H, 12.12. Found: C, 64.73; H, 12.20.

4.1.14. (7*S*,8*S*,9*R*,10*S*)-9-(*tert*-Butyl-dimethyl-silanyloxy)-7-methoxy-8,10-dimethyl-trideca-2,4-dienoic acid methyl ester 2. A solution of **4** (45 mg, 0.14 mmol), pyridine (30 μL) and Dess–Martin periodinane (85 mg) in CH_2Cl_2 (2 mL) was stirred at rt for 30 min. A saturated solution of $NaHCO_3$ and $Na_2S_2O_3$ (1:1, 2 mL) was then added. The organic layer was separated while the aqueous layer was extracted with CH_2Cl_2. The combined organic extract was dried over Na_2SO_4, filtered and concentrated to give crude aldehyde (38 mg, 85%).

To a solution of methyl 4-(diethylphosphono)crotonate (60 mg) in anhydrous THF (2 mL) at −78 °C, LiHMDS (0.25 mL, 1.0 M) was added. After 1 h, this solution was transferred via cannula into the above prepared aldehyde (38 mg) in THF (2 mL) maintained at −78 °C. The reaction mixture was warmed to rt, stirred for 1 h and worked up as usual. The residue was purified on silica gel using ethyl acetate and light petroleum ether (1:9) to afford a terminal *E*,*E*-dienoic ester **2** (39 mg, 82%). $[\alpha]_D^{25} = -8.0$ (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01, 0.03 (2s, 6H), 0.81 (d, 3H, $J = 7.0$ Hz), 0.83 (d, 3H, $J = 6.5$ Hz), 0.89–0.91 (m, 12H), 1.14–1.20 (m, 1H), 1.28–1.40 (m, 3H), 1.60 (m, 1H), 1.99 (m, 1H), 2.23 (m, 1H), 2.41 (ddd, 1H, $J = 2.8$, 5.4, 14.7 Hz), 3.29 (s, 3H), 3.38 (ddd, 1H, $J = 2.8$, 5.4, 8.5 Hz), 3.58 (dd, 1H, $J = 2.3$, 6.5 Hz), 3.75 (s, 3H), 5.80 (d, 1H, $J = 15.2$ Hz), 6.18 (dt, 1H, $J = 7.4$, 15.1 Hz), 6.22 (dd, 1H, $J = 9.9$, 15.1 Hz), 7.28 (dd, 1H, $J = 9.9$, 15.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ −3.7, 11.2, 14.4, 14.7, 18.6, 20.9, 26.3, 33.6, 35.7, 37.6, 40.4, 51.3, 56.8, 76.2, 81.2, 119.2, 130.2, 141.1, 145.0, 167.4. Anal. Calcd for $C_{23}H_{44}SiO_4$: C, 66.94; H, 10.74. Found: C, 67.15; H, 10.51.

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11. *CCDC 290095, X-ray crystal data*: Single crystals of the complex were grown by slow evaporation of the solution in dichloromethane. A colourless needle of approximate size $0.2 \times 0.15 \times 0.16$ mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50 kV and 30 mA. Crystal to detector distance 6.05 cm, 512×512 pixels/frame, multiscan data acquisition. Total scans = 4, total frames = 2424, oscillation/frame −0.3°, exposure/frame = 20.0 s/frame, maximum detector swing angle = −30.0°, beam centre = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 1.56–25.00°, completeness to θ of 25.00° is 100%. SADABS correction applied, $C_{12}H_{18}O_5$, $M = 242.27$. Crystals belong to orthorhombic, space group $P2_1$, $a = 5.517(3)$, $b = 9.144(4)$, $c = 26.180(13)$ Å, $V = 1320.7(11)$ Å^3, $Z = 4$, $D_c = 1.218$ mg m^{-3}, μ(Mo-K_α) = 0.094 mm^{-1}, $T = 295(2)$ K, 6685 reflections measured, 2337 unique $[I > 2\sigma(I)]$, $R = 0.0472$, $wR2 = 0.1038$. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (SHELXTL)[12] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.
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16. Methyl-4-(diethylphosphono)crotonate was prepared from freshly distilled methyl 4-bromocrotonate (5 mL, 42.56 mmol) and triethylphosphite (8.85 mL, 51.07 mmol) at 120 °C for 3 h. The product was isolated by distillation at 130 °C under vacuo (0.4 mm); yield: 3.40 g (83%).