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Efficient metathesis route to the B-ring of eleutherobin and other medium-sized cyclic ethers

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Dedicated to Professor K. K. Balasubramanian on the occasion of his 65th birthday

Abstract—A short and efficient RCM route is reported for the synthesis of the B-ring of eleutherobin and other medium-sized cyclic ethers from readily available 1,2,5,6-diisopropylidene-D-glucose. This strategy is successfully extended to the synthesis of a few bicyclic ethers, which may find applications in the synthesis of novel bicyclic nucleosides.

1. Introduction

The success of the anti-cancer drug taxol® (paclitaxel) has stimulated an intensive search for other drugs that operate by the same mode of action.[1] Successful examples, isolated from natural sources, include discodermolide,[2] the epothilones,[3] laulimalide[4] and eleutherobin.[5] Among them, the latest discovery, eleutherobin **1**[6] was isolated from a marine soft-coral found in the Indian ocean and found to be closely related to sarcodictyins **4**, **5**,[7] valdivone **6**[8] and eleuthesides (Fig. 1).[9] Later, several related congeners of eleutherobin were isolated[10] from the Caribbean soft coral *Erythropodium caribaeorum*. Eleutherobin has been shown to possess potent cytotoxicity with an IC_{50} of 10.7 nM, which is comparable to taxol. As eleutherobin was only available in scarce amounts from natural sources, chemical syntheses have become important to study its biological properties further. These prompted synthetic chemists to develop new strategies[11] to synthesize eleutherobin and their sustained efforts have culminated in two total syntheses.[12–14]

In continuation of our interest in the development of simple and efficient routes to the syntheses of tubulin binding anti-cancer agents, we became interested in the synthesis of eleutherobin and its congeners.[15]

2. Results and discussion

A strategy for the synthesis of eleutherobin was designed based on the retrosynthetic analysis involving metathesis reaction as the key step and is shown in Scheme 1.

With the discovery of air stable Grubbs' first[16] and second generation catalysts,[17] the last decade has witnessed a meteoric rise in the utility of the ring closing metathesis reaction (RCM)[18] in the formation of several types of alkenes, carbo- and heterocycles. The reaction tolerates a wide range of functional groups and with these reliable and practical catalysts, the RCM reaction has been widely used in the synthesis of a number of cyclic natural and unnatural products. However, construction of medium-size rings by ring closing metathesis has often been hampered by entropic and thermodynamic instability factors.[19] Nevertheless, there are quite a few successful reports of constructing medium size rings by ring closing metathesis reaction.[20] Encouraged by these reports, we envisaged that a RCM reaction would be an ideal key reaction to construct these natural product skeletons. Eleutherobin possesses three double bonds, which could be formed as a result of a RCM reaction. However, only disconnection of the B-ring double bond will simplify the target molecule leading to precursor **C**, which then can be further disconnected to the bicyclic enone **8** and the epoxide **9** (Scheme 1).

From this retrosynthetic modus operandi, it is clear that the success of our synthetic route to eleutherobin depends on the construction of the B-ring with the strategically placed double bond. Furthermore, there are several natural products, which have nine-membered cyclic ethers as their

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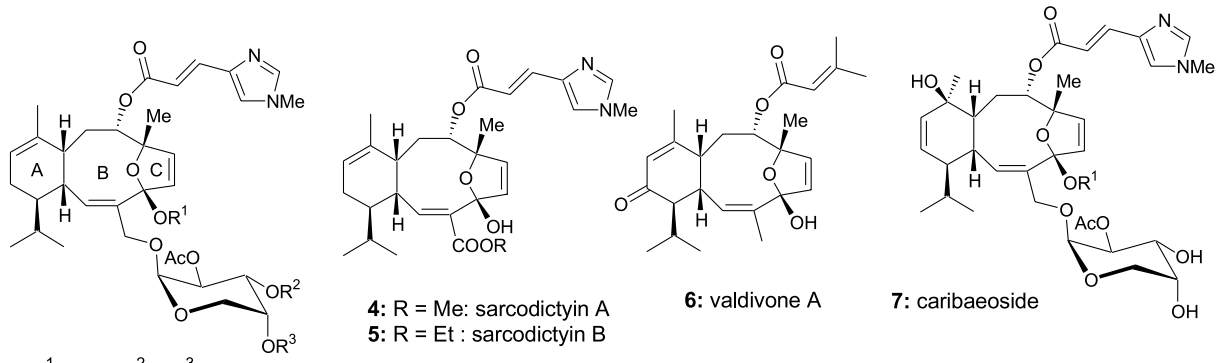
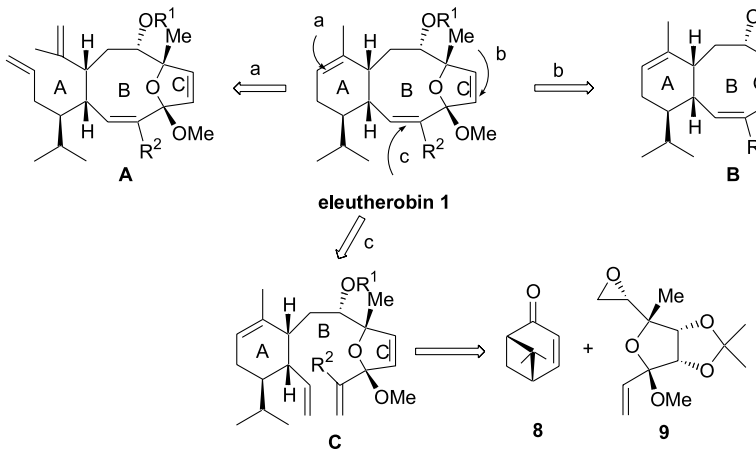


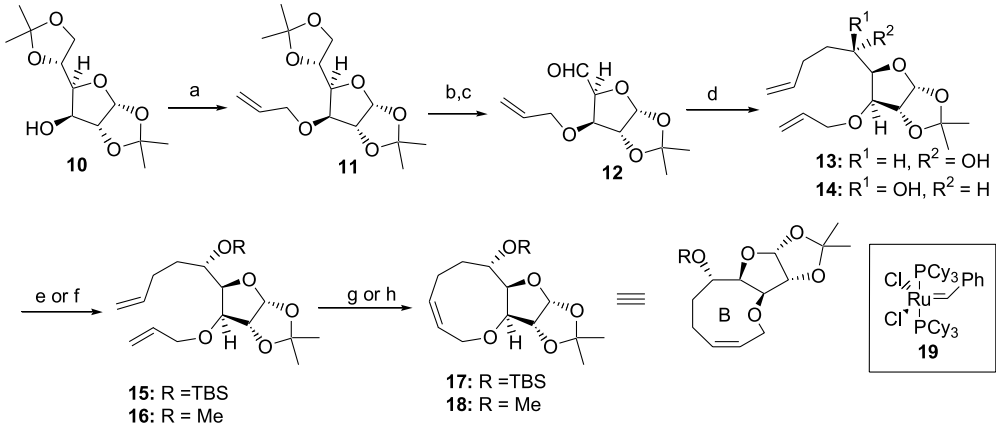
Figure 1.



Scheme 1.

key substructure. A convenient access to the fully functionalized nine-membered B-ring of eleutherobin as well as other related natural products in enantiomerically enriched form still remains a challenge to synthetic chemists. Thus, in view of the importance of these medium-size cyclic ethers, we planned to synthesize a highly oxygenated nine-membered cyclic ether[21] starting from the readily available 1,2,5,6-diisopropylidene-D-glucose and the details are reported here.

Our synthesis, as depicted in Scheme 2, starts with the classical etherification of the secondary alcohol **10** to afford **11**. Under mild acidic conditions, the more exposed 5,6-*O*-isopropylidene group was selectively deprotected to give a diol which was subsequently cleaved by treating with silica



Scheme 2. Reagents & Conditions: (a) NaH, allylbromide, THF, TBAI (cat.), RT, 2 h, 93%. (b) 60% *aq*. AcOH, H_2O, 12 h, 90%. (c) Silica gel supp. $NaIO_4$, CH_2Cl_2, 30 min, 86%. (d) 4-Bromo-1-butene, Mg, THF, 0°C to RT, 12 h, 83%. (e) TBSCl, imid., DMF, 0°C to RT, 10 h, 84%, 77%. (f) NaH, MeI, 0°C to RT, 2 h, 77%. (g) **19** (10 mol%), CH_2Cl_2, 40°C, 2 h, (30% for R=TBS, 33% for R=Me). (h) **19** (10 mol%), $Ti(O/Pr)_4$ (7.5 mol%), CH_2Cl_2, 40°C, (83% for R=TBS, 63% for R=Me).

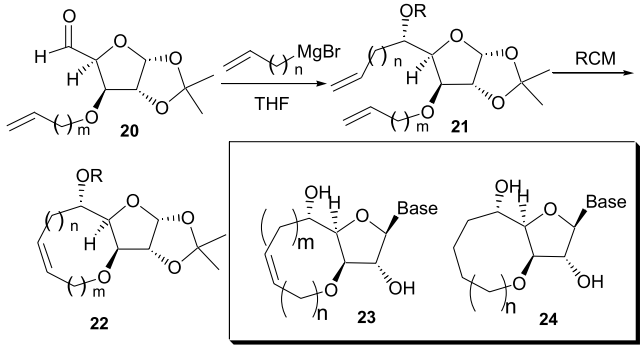
gel supported $NaIO_4$[22] to afford **12**. Addition of the Grignard reagent, derived from 4-bromo-1-butene and magnesium, to aldehyde **12** afforded two diastereomeric products **13** and **14** as a readily separable mixture in 3:2 ratio.[23] The stereochemistry of the major Grignard addition product was tentatively assigned as α-isomer as per the literature report.[23]

Moreover, the major isomer seems to be more polar than the other and this observation is consistent with all the Grignard reactions we have attempted on this system. All attempts to carry out this reaction at low temperature did not improve the ratio significantly. The major alcohol **13** was separated and subsequently protected as its TBS ether **15**, which sets the stage for the key RCM reaction. Unfortunately, when the RCM was carried out with Grubbs' first generation catalyst **19** under high dilution conditions (0.003 M solution with 10 mol% catalyst), only 30% of the desired cyclized product **17** was obtained, the remainder being unreacted starting material and presumably some cross-metathesis product. Assuming that the bulky TBDMS group would have provided a sterically crowed environment for the key RCM reaction, the major alcohol was protected as its methyl ether **16** and the key RCM reaction was subsequently attempted with Grubbs' first generation catalyst **19**. The observation of a similar result with the methyl ether suggested that the low yield could be presumably attributed to coordination of the metal center with the oxygen of the furanose ring as suggested by Fürstner.[24]

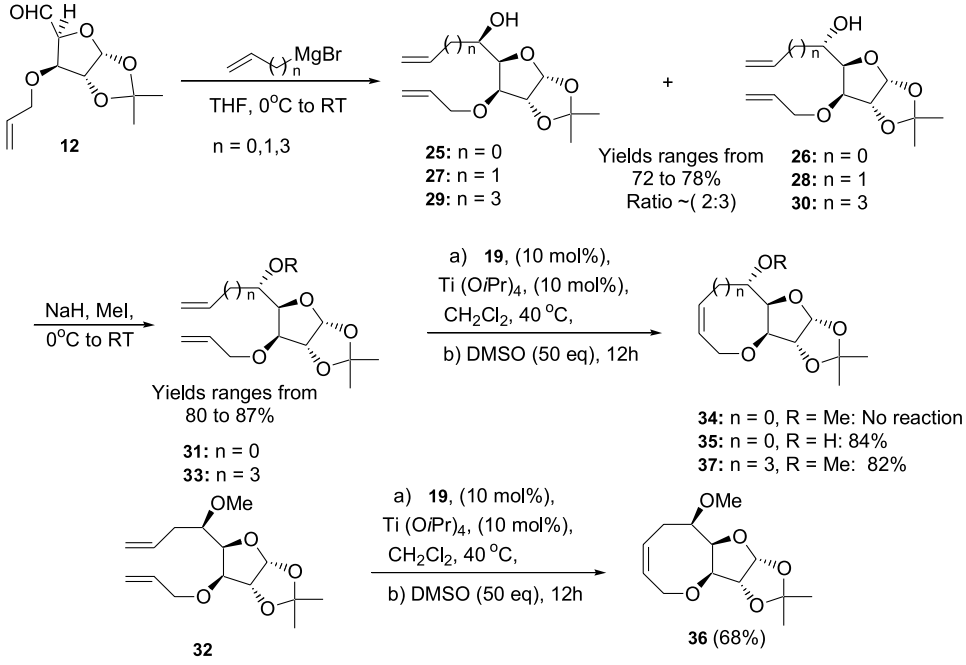
In order to destabilize this chelate structure, the RCM reaction of the dienes **15** and **16** was carried out with a catalytic amount of **19** in the presence of a sub-stoichiometric amount of $Ti(OiPr)_4$[24] and this modified protocol successfully led to the formation of the desired RCM products **17** and **18**, respectively, in high yields.

After successfully synthesising a model of the nine-membered B-ring of eleutherobin, we then examined the scope of utilizing this methodology to a diversity-oriented synthesis of various bicyclic ethers, which may find applications in the synthesis of novel bicyclic nucleosides (Scheme 3). Addition of Grignard reagents having terminal alkenes to the aldehyde **20**, followed by protection of the resultant alcohols should afford RCM precursors **21**. After the key RCM reaction, these bicyclic ethers could be used for the synthesis of several bicyclic nucleosides **23** and **24**.

Herein, we report the details of the synthesis of seven, eight and ten-membered cyclic ethers starting from the aldehyde **12**. The synthesis of five-seven fused bicyclic ether was started with the addition of vinyl magnesium bromide to aldehyde **12** at 0 °C in THF, and as expected, it afforded two diastereomeric products **25** and **26** as a readily separable mixture in 1:2 ratio. The major alcohol **26** was subsequently converted to its methyl ether **31** and unfortunately, when the RCM of diene **31** was carried out with Grubbs' catalyst **19** under high dilution conditions (0.003 M solution with 10% catalyst), in the presence of catalytic amount of $Ti(OiPr)_4$, only starting material was recovered. It has been reported that the protecting group in the allylic alcohol plays an



Scheme 3.



Scheme 4.

important role in the success of the RCM reaction[25] and so we attempted the RCM of the diene **26** (allylic alcohol) with Grubbs' catalyst **19** under our standard conditions. We were pleasantly surprised to see the formation of cyclised product **35** in 84% yield (Scheme 4).

The synthesis of five, eight-membered fused bicyclic ether was started with the addition of allyl magnesium bromide to aldehyde **12** at 0 °C in THF, and unfortunately it afforded **28** in 20% yield and the remainder being a complex mixture. Alternatively, a zinc mediated allylation was attempted with **12** and this protocol afforded two diastereomeric products **27** and **28** in 5:1 ratio. The alcohol **27** was subsequently converted to its methyl ether **32**, which was further subjected to RCM with Grubbs' catalyst **19** under our standard condition to give the cyclized product **36** in 68% yield. We also could successfully extend this method to synthesize the five, ten-membered fused bicyclic ether **37**. Addition of 5-bromo-1-pentene magnesium bromide in THF to aldehyde **12** afforded two diastereomeric products **29** and **30** in 1:1 ratio and the latter alcohol **30** was protected as its methyl ether **33**. Subsequently, RCM of the diene **33** was carried out with Grubbs' catalyst **19** in the presence of a catalytic amount of $Ti(OiPr)_4$ under high dilution conditions (0.003 M solution with 10% catalyst) to afford the desired product **37** in 82% yield. It is also very important to note that in this case, the RCM reaction exclusively provided the *cis* isomer.

3. Conclusion

In summary, we have successfully synthesized a model of the B-ring of eleutherobin utilizing the RCM reaction as the key step. The key factor involved in the success of this reaction was addition of $Ti(OiPr)_4$ which destabilised the possible formation of a chelated structure of ruthenium carbene with furanose oxygen. This methodology was then successfully extended to other medium-sized cyclic ethers through a common intermediate. This synthetic strategy has high potential in the synthesis of several related natural products and novel bicyclic nucleosides. Work is in progress in our laboratory to achieve this goal.

4. Experimental

4.1. General

Unless and otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and hexanes were freshly distilled from calcium hydride. DMF was distilled over calcium hydride and stored over Molecular Sieves 4 Å. Solvents for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried in oven at 100 °C for 12 h before use. Air and moisture sensitive reactions were performed under an argon/UHP nitrogen atmosphere. Column chromatography was performed using silica gel (100–200 mesh, Acme) with indicated solvents. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid and heat as developing agents. Optical rotation was recorded on Jasco DIP-370 digital polarimeter. IR spectra were recorded from Thermo Nicolet Avater 320 FT-IR and Nicolete Impact 400 machine. Mass spectra were obtained with Waters Micromass-Q-Tof micro™ (YA105) spectrometer. Elemental analysis was recorded on Thermo Finnigan Flash EA 1112. ^1H and ^{13}C NMR spectra were recorded either on Varian AS 400, Varian AS 500 or Varian ASM 300 instruments in $CDCl_3$ solutions. ^1H NMR data were reported in the order of chemical shift (δ in ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constant J in Hertz (Hz).

4.2. General procedure for Grignard reactions

A solution of the aldehyde (1 mmol) in dry THF (5 mL) was cooled to 0 °C under an argon atmosphere. The Grignard reagent (3 mmol) was added dropwise and stirred for 2 h at 0 °C then for 12 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo, and purified by silica gel chromatography (hexane/ethyl acetate) to give two diastereomeric alcohols.

4.3. General procedure for methylation of alcohol

To a suspension of sodium hydride (3 mmol, 60% dispersion in mineral oil) in dry THF (15 mL) was added a solution of alcohol (1 mmol) in THF (2 mL) dropwise at 0 °C and the mixture was stirred for 30 min. To this mixture iodomethane (2 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h and then for 1 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo, and purified by silica gel chromatography (hexane/ethyl acetate) afforded the corresponding product.

4.4. General procedure for ring closing metathesis reaction

Method A. A 1 mmol portion of diene was dissolved in 325 mL of dry dichloromethane under argon and the solution was degassed. To this mixture, a solution of Grubbs' catalyst (10 mol%) in CH_2Cl_2 (10 mL) was added dropwise and the reaction mixture was refluxed for 2–12 h. The reaction mixture was cooled to room temperature, concentrated in vacuo, and purified by a silica gel column chromatography (hexane/ethyl acetate) to give the product.

Method B. A solution of diene (1 mmol) and $Ti(OiPr)_4$ (10 mol%) in dry CH_2Cl_2 (325 mL) was stirred under reflux for 1 h. To this mixture, a solution of Grubbs' catalyst (10 mol%) in CH_2Cl_2 (10 mL) was added dropwise and the reaction mixture was refluxed for 2–12 h. The reaction mixture was cooled to room temperature and DMSO (50 equiv with respect to catalyst) was added and stirred for 6 h. Evaporation of the solvent and purification

by column chromatography yielded the corresponding product.

4.4.1. (5*S*)-1,2-*O*-(-1-Methylethylidede)-3-*O*-allyl-5-*C*-buteyl-α-D-xylofuranose (13) and (5*R*)-1,2-*O*-(-1-methylethylidede)-3-*O*-allyl-5-*C*-buteyl-α-D-xylofuranose (14). Following the general procedure for Grignard reaction, a solution of aldehyde **12** (880 mg, 3.08 mmol) in THF was treated with 4-bromo-1-butenemagnesium bromide (9.32 mmol) to afford two diastereomeric products **13** (534 mg, 53%) and **14** (330 mg, 33%) as a readily separable mixture.

Compound **13**. Viscous colourless oil; R_f=0.6 (33%, EtOAc/hexane); $[\alpha]_D^{25}$ −53.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3443, 3075, 1641, 1077 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.97 (1H, d, *J*=3.9 Hz, anomeric C*H*), 5.93–5.78 (2H, m, 2×CH_2=C*H*), 5.34–5.22 (2H, m, CH_2=), 5.09–4.95 (2H, m, CH_2=), 4.58 (1H, d, *J*=3.9 Hz, C*H*), 4.22–4.15 (1H, m, C*H*), 4.05 (1H, dd, *J*=5.7, 3.3 Hz, C*H*), 4.01–3.94 (2H, m, CH_2), 3.92 (1H, d, *J*=3.3 Hz), 2.37–2.12 (2H, m, CH_2), 1.75–1.52 (2H, m, CH_2), 1.49 (3H, s, *Me*), 1.33 (3H, s, *Me*); δ_C (100 MHz, $CDCl_3$) 138.2, 133.2, 118.2, 114.7, 111.6, 104.7, 82.7, 82.6, 82.2, 70.7, 69.1, 32.1, 29.5, 26.7, 26.2. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.47; H, 8.42.

Compound **14**. Colourless oil; R_f=0.7 (33%, EtOAc/hexane); $[\alpha]_D^{25}$ −36.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3467, 3076, 1641, 1077 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.96 (1H, d, *J*=4.2 Hz, anomeric C*H*), 5.94–5.79 (2H, m, 2×CH_2=C*H*), 5.36–5.24 (2H, m, CH_2=), 5.10–4.96 (2H, m, CH_2=), 4.58 (1H, d, *J*=4.2 Hz, C*H*), 4.24–4.17 (1H, m, C*H*), 4.05–3.93 (4H, m, CH_2 and 2×C*H*), 2.38–2.12 (2H, m, CH_2), 1.90–1.53 (2H, m, CH_2), 1.49 (3H, s, *Me*), 1.33 (3H, s, *Me*); δ_C (100 MHz, $CDCl_3$) 138.5, 133.6, 118.6, 114.9, 111.7, 105.2, 82.5, 82.3, 82.0, 70.9, 69.3, 33.9, 29.9, 26.8, 26.4; HRMS (EI) calcd for $C_{15}H_{24}O_5Na$ *m*/*z* 307.1521, found *m*/*z* 307.1510.

4.4.2. (5*S*)-5-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-(1-methylethylidede)-3-*O*-allyl-5-*C*-buteyl-α-D-xylofuranose (15). A solution of the alcohol **13** (400 mg, 1.40 mmol) in dry DMF (0.8 mL) was treated with imidazole (286 mg, 4.21 mmol), TBSCl (253 mg, 1.68 mmol) and a catalytic amount of DMAP at 0 °C and this solution was stirred for 10 h at room temperature. The reaction mixture was extracted with ethyl acetate and washed with water and brine, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by silica gel chromatography (hexanes/ethyl acetate 20:1) to give **15** (480 mg, 87%) as a colourless oil. R_f=0.8 (20%, EtOAc/hexane); $[\alpha]_D^{25}$ −46.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3085, 1643, 1255, 1097 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.92 (1H, d, *J*=3.7 Hz, anomeric C*H*), 5.89–5.75 (2H, m, 2×CH_2=C*H*), 5.31–5.18 (2H, m, CH_2=), 5.06–4.93 (2H, m, CH_2=), 4.53 (1H, d, *J*=3.7 Hz, C*H*), 4.17–4.09 (1H, m, C*H*), 3.99–3.86 (3H, m, CH_2 and C*H*), 3.76 (1H, d, *J*=2.9 Hz, C*H*), 2.28–2.09 (2H, m, CH_2), 1.58–1.51 (2H, m, CH_2), 1.47 (3H, s, *Me*), 1.31 (3H, s, *Me*), 0.89 (9H, s, SiCMe_3), 0.11 (3H, s, Si*Me*), 0.08 (3H, s, Si*Me*); δ_C (75 MHz, $CDCl_3$) 138.8, 133.8, 117.9, 114.5, 111.4, 104.8, 83.9, 82.2, 82.1, 70.9, 70.8, 32.7, 29.5, 26.8, 26.5, 26.1, 18.5, −3.9, −4.7. Anal. Calcd for $C_{19}H_{34}O_5Si$: C, 63.28; H, 9.61. Found: C, 62.59; H, 9.28; HRMS (EI) calcd for $C_{19}H_{34}O_5SiNa$ *m*/*z* 421.2386, found *m*/*z* 421.2391.

4.4.3. (5*S*)-5-*O*-Methyl-1,2-*O*-(-1-methylethylidede)-3-*O*-allyl-5-*C*-buteyl-α-D-xylofuranose (16). Following the general procedure for methylation reaction, a solution of **13** (880 mg 3.08 mmol) in THF was treated with sodium hydride (370 mg, 9.26 mmol, 60% in dispersion in oil) and methyl iodide (0.38 mL, 6.12 mmol) in presence of catalytic amount of TBAI. The crude product was purified by silica gel chromatography (hexanes/ethyl acetate 20:1) to give **16** (740 mg, 80%) as a colourless oil. R_f=0.8 (33%, EtOAc/hexane); $[\alpha]_D^{25}$ −49.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3085, 1643, 1091 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.94 (1H, d, *J*=3.9 Hz, anomeric C*H*), 5.89–5.72 (2H, m, 2×CH_2=C*H*), 5.31–5.19 (2H, m, CH_2=), 5.05–4.94 (2H, m, CH_2=), 4.53 (1H, d, *J*=3.9 Hz, C*H*), 4.17–4.07 (2H, m, CH_2), 3.88 (1H, dd, *J*=12.6, 6.1 Hz, C*H*), 3.76 (1H, d, *J*=3.1 Hz, C*H*), 3.52–3.45 (1H, m, C*H*), 3.48 (3H, s, O*Me*), 2.25–2.14 (2H, m, CH_2), 1.52–1.47 (2H, m, CH_2), 1.49 (3H, s, *Me*), 1.30 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 138.3, 133.5, 118.1, 114.7, 111.4, 104.9, 83.9, 82.1, 81.8, 79.3, 70.7, 59.3, 30.2, 29.2, 26.6, 26.2. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 63.99; H, 8.73.

4.4.4. *tert*-Butyl-(12,12-dimethyl-8,11,13,15-tetraoxa-tricyclo[7.6.0.010,14]pentadec-5-en-2-yloxy)-dimethylsilane (17). *Procedure A*. Following the general procedure for ring closing metathesis reaction (method A), from 200 mg (0.50 mmol) of **15** and 50 mg (0.060 mmol) of Grubb's catalyst, 55 mg (30%) of **17** was obtained as a colourless oil.

Procedure B. Following the general procedure for ring closing metathesis reaction (method B), from 200 mg (0.50 mmol) of **15**, 0.015 mL (0.050 mmol) of Ti(O*i*Pr)$_4$ and 41 mg (0.050 mmol) of Grubb's catalyst, 160 mg (86%) of **17** was obtained as a colourless oil. R_f=0.8 (20%, EtOAc/hexane); $[\alpha]_D^{25}$ −39.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2947, 1650, 1255, 1091 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.90 (1H, d, *J*=3.7 Hz, anomeric C*H*), 5.84 (1H, q, *J*=9.2 Hz, C*H*=), 5.52 (1H, dt, *J*=9.2, 5.1 Hz, C*H*=), 4.47 (1H, d, *J*=3.7 Hz, C*H*), 4.35 (1H, dd, *J*=14.2, 3.7 Hz, C*H*), 4.08 (1H, d, *J*=2.9 Hz, C*H*), 3.96–3.82 (3H, m, CH_2 and C*H*), 2.39–2.14 (2H, m, CH_2), 1.91–1.51 (2H, m, CH_2), 1.47 (3H, s, *Me*), 1.30 (3H, s, *Me*), 0.88 (9H, s, SiCMe_3), 0.09 (3H, s, Si*Me*) 0.08 (3H, s, Si*Me*); δ_C (125 MHz, $CDCl_3$); δ 135.9, 125.7, 111.3, 104.6, 86.4, 84.1, 81.1, 73.8, 66.2, 33.2, 29.8, 26.9, 26.5, 26.0, 18.4, −4.3, −4.8. Anal. Calcd for $C_{19}H_{34}O_5Si$: C, 61.58; H, 9.25. Found: C, 61.29; H, 9.16.

4.4.5. 2-Methoxy-12,12-dimethyl-8,11,13,15-tetraoxa-tricyclo[7.6.0.010,14]pentadec-5-ene (18). *Procedure A*. Following the general procedure (method A) for ring closing metathesis, from 170 mg (0.56 mmol) of **16** and 56 mg (0.080 mmol) of Grubb's catalyst, 52 mg (33%) of **18** was obtained as a colourless oil.

Procedure B. Following the general procedure B, from 150 mg (0.50 mmol) of **16**, 0.015 mL (0.050 mmol) of Ti(O*i*Pr)$_4$ and 41 mg (0.050 mmol) of Grubb's catalyst, 90 mg (66%) of **18** was obtained as a colourless oil. R_f=0.4 (20%, EtOAc/hexane); $[\alpha]_D^{25}$ −63.9 (*c* 1.0, $CHCl_3$); IR

(neat) ν_{max} 2940, 1657, 1466 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.89 (1H, d, J=3.8 Hz, anomeric C*H*), 5.83 (1H, q, J=9.2 Hz, C*H*=), 5.48 (1H, dt, J=9.2, 4.2 Hz, C*H*=), 4.43 (1H, d, J=3.8 Hz, C*H*), 4.31 (1H, dd, J=14.1, 3.8 Hz, C*H*), 4.06 (1H, d, J=3.1 Hz, C*H*), 4.01–3.51 (2H, m, CH_2), 3.37 (3H, s, O*Me*), 3.37–3.32 (1H, m, C*H*), 2.34–2.13 (2H, m, CH_2), 1.94–1.83 (1H, m, C*H*) 1.41 (3H, s, *Me*), 1.40–1.31 (1H, m, C*H*), 1.25 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 135.6, 125.6, 111.5, 104.8, 85.3, 83.4, 82.5, 80.5, 65.9, 57.5, 27.9, 26.8, 26.4, 26.0. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.30; H, 8.21.

4.4.6. (5*R*)-1,2-*O*-(-1-Methylethylidede)-3-*O*-allyl-5-*C*-vinyl-α-D-xylofuranose (25) and (5*S*)-1,2-*O*-(-1-methylethylidede)-3-*O*-allyl-5-*C*-vinyl-α-D-xylofuranose (26). Following the general procedure for Grignard reaction, a solution of aldehyde **12** (900 mg, 3.98 mmol) in THF was treated with vinylmagnesium bromide (12 mmol) to afford two diastereomeric products **25** (260 mg, 25%) and **26** (520 mg, 51%) as a readily separable mixture.

Compound **25**. Colourless oil; R_f=0.5 (25%, EtOAc/hexane); $[\alpha]_D^{25}$ −43.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3489, 3083, 1644, 1079, 1024 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.05–5.97 (1H, m, C*H*=), 5.99 (1H, d, J=3.6 Hz, anomeric C*H*), 5.93–5.86 (1H, m, C*H*=), 5.46–5.23 (4H, m, 2×CH_2=), 4.57 (1H, d, J=3.6 Hz, C*H*), 4.52 (1H, dd, J=5.2, 1.6 Hz, C*H*), 4.20–4.16 (1H, m, C*H*), 4.09 (1H, dd, J=6.4, 3.6 Hz, C*H*), 4.04 (1H, d, J=3.6 Hz, C*H*), 4.02–3.99 (1H, m, C*H*), 2.50 (1H, br s, O*H*), 1.49 (3H, s, *Me*), 1.32 (3H, s, *Me*); δ_C (100 MHz, $CDCl_3$) 137.7, 133.4, 118.4, 115.9, 111.7, 105.1, 82.7, 81.9, 81.4, 71.1, 70.6, 26.7, 26.2; LRMS (EI) $[M+Na]^+$279.0960; HRMS (EI) calcd for $C_{13}H_{20}O_5Na$ *m*/*z* 279.1208, found *m*/*z* 279.1207.

Compound **26**. Colourless oil; R_f=0.4 (25%, EtOAc/hexane); $[\alpha]_D^{25}$ −55.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3496, 3084, 1645, 1077, 1022 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.97 (1H, d, J=3.7 Hz, anomeric C*H*), 5.94–5.81 (2H, m, 2×CH_2=C*H*), 5.48–5.19 (4H, m, 2×CH_2=), 4.59 (1H, d, J=3.7 Hz, C*H*), 4.50 (1H, dd, J=7.3, 5.9 Hz, C*H*), 4.15 (1H, dd, J=12.8, 5.5 Hz, C*H*), 4.04 (1H, dd, J=6.9, 3.3 Hz, C*H*), 3.94 (1H, dd, J=12.5, 5.9 Hz, 1H), 3.86 (1H, d, J=3.3 Hz, C*H*), 2.97 (1H, br s, O*H*), 1.48 (3H, s, *Me*), 1.32 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 135.9, 133.6, 117.9, 117.1, 111.8, 104.9, 83.2, 82.3, 82.2, 71.0, 70.9, 26.8, 26.3. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.97; H, 7.97.

4.4.7. (5*S*)-5-*O*-Methyl-1,2-*O*-(-1-methylethylidede)-3-*O*-allyl-5-*C*-vinyl-α-D-xylofuranose (31). Following the general procedure for methylation reaction, a solution of **26** (740 mg, 2.88 mmol) in THF was treated with sodium hydride (460 mg, 8.66 mmol, 60% in dispersion in oil) and methyl iodide (0.36 mL, 2.54 mmol) in the presence of a catalytic amount of TBAI. The crude product was purified by silica gel chromatography (hexanes/ethyl acetate 20:1) to give **31** (680 mg, 87%) as a colourless oil. R_f=0.6 (20%, EtOAc/hexane); $[\alpha]_D^{25}$ −42.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3081, 1645, 1078 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.97 (1H, d, J=3.7 Hz, anomeric C*H*), 5.93–5.80 (1H, m, CH_2=C*H*), 5.75–5.63 (1H, m, CH_2=C*H*), 5.43–5.18 (4H, m, 2×CH_2=), 4.54 (1H, d, J=3.7 Hz, C*H*), 4.13–4.07 (2H, m, C*H*), 3.98–3.84 (2H, m, CH_2), 3.72 (1H, d, J=2.9 Hz, C*H*), 3.36 (3H, s, O*Me*), 1.48 (3H, s, *Me*), 1.31 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 133.9, 133.8, 119.6, 117.5, 111.7, 105.3, 82.5, 81.9, 81.5, 81.0, 70.9, 56.7, 26.8, 26.3. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 61.92; H, 8.17; HRMS (EI) calcd for $C_{14}H_{22}O_5Na$ *m*/*z* 293.1365, found *m*/*z* 293.1354.

4.4.8. 2,2-Dimethyl-3a,3b,5,8,8a,9a-hexahydro-1,3,4,9-tetraoxa-cyclopenta[*a*]azulen-8-ol (35). Following the general procedure B, from 120 mg (0.46 mmol) of **26**, 0.013 mL (0.046 mmol) of $Ti(OiPr)_4$ and 38 mg (0.046 mmol) of Grubb's catalyst, 90 mg (84%) of **35** was obtained as a colourless oil. R_f=0.3 (25%, EtOAc/hexane); $[\alpha]_D^{25}$ −18.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3483, 2929, 1652, 1087 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.96 (1H, d, J=3.6 Hz, anomeric C*H*), 5.59–5.56 (1H, m, CH_2=C*H*), 5.36–5.33 (1H, m, CH_2=C*H*), 4.89–4.85 (1H, m, C*H*), 4.58 (1H, d, J=3.6 Hz, C*H*), 4.51 (1H, dd, J=17.2, 2.4 Hz, C*H*), 4.44 (1H, dd, J=8.4, 4.8 Hz, C*H*), 4.15 (1H, dd, J=7.2, 2.4 Hz, C*H*), 4.05 (1H, d, J=3.6 Hz, C*H*), 2.44 (1H, br s, O*H*), 1.48 (3H, s, *Me*), 1.32 (3H, s, *Me*); δ_C (125 MHz, $CDCl_3$); δ 130.3, 126.0, 112.2, 105.2, 88.2, 85.9, 83.3, 72.3, 70.9, 27.3, 26.7; LRMS (EI) $[M+Na]^+$251.0827; HRMS (EI) calcd for $C_{11}H_{16}O_5Na$ *m*/*z* 251.0895, found *m*/*z* 251.0898.

4.4.9. (5*R*)-1,2-*O*-(-1-Methylethylidede)-3-*O*-allyl-5-*C*-allyl-α-D-xylofuranose (27) and (5*S*)-1,2-*O*-(-1-methylethylidede)-3-*O*-allyl-5-*C*-allyl-α-D-xylofuranose (28). A stirring solution of the aldehyde **12** (1.30 g, 5.75 mmol) and allyl bromide (1.47 mL, 17.25 mmol) was added a saturated aqueous solution of NH_4Cl/THF (5:1, 25 mol). The reaction mixture was cooled to 0 °C and zinc dust (2.25 g, 34.51 mmol) was slowly added to the reaction mixture and stirring was continued at 0 °C for 1 h. The reaction mixture was filtered and extracted with ethyl acetate, and the extracts were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo, and purified in a silica gel column chromatography afforded two diastereomeric products **27** (931 mg, 60%) and **28** (186 mg, 12%) as a readily separable mixture.

Compound **27**. Colourless oil; R_f=0.6 (25%, EtOAc/hexane); $[\alpha]_D^{25}$ −53.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3504, 3077, 1642, 1077, 1025 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.96–5.84 (2H, m, 2×CH_2=C*H*), 5.93 (1H, d, J=3.6 Hz, anomeric C*H*), 5.35–5.12 (4H, m, 2×CH_2=), 4.58 (1H, d, J=3.6 Hz, C*H*), 4.19 (1H, dd, J=12, 4.8 Hz, C*H*), 4.07–3.96 (4H, m, CH_2 and 2×C*H*), 2.54–2.29 (3H, m, CH_2 and OH), 1.48 (3H, s, *Me*), 1.32 (3H, s, *Me*); δ_C (100 MHz, $CDCl_3$); δ 134.3, 133.7, 118.0, 117.9, 111.5, 104.9, 82.1, 81.9, 81.7, 70.9, 68.2, 39.0, 26.7, 26.2. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.67; H, 8.88; HRMS (EI) calcd for $C_{14}H_{22}O_5Na$ *m*/*z* 293.1365, found *m*/*z* 293.1368.

Compound **28**. Colourless oil; R_f=0.5 (25%, EtOAc/hexane); $[\alpha]_D^{25}$ −63.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3510, 3076, 1642, 1077, 1018 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.98 (1H, d, J=3.6 Hz, anomeric C*H*), 5.95–5.81 (2H, m, 2×CH_2=C*H*), 5.34–5.09 (4H, m, 2×CH_2=), 4.58 (1H, d, J=3.6 Hz, C*H*), 4.19 (1H, dd, J=12.6, 5.1 Hz, C*H*), 4.09–3.95

(3H, m, CH_2 and C*H*), 3.92 (1H, d, J=3.3 Hz, C*H*), 2.29 (2H, t, J=6.3 Hz, CH_2), 1.49 (3H, s, *Me*), 1.33 (3H, s, *Me*); δ_C (125 MHz, $CDCl_3$) 134.5, 133.3, 118.3, 117.5, 111.8, 104.8, 82.9, 82.4, 81.8, 70.8, 69.6, 37.8, 26.8, 26.4; HRMS (EI) Calcd for $C_{14}H_{22}O_5Na$ *m/z* 293.1365, found *m/z* 293.1368.

4.4.10. (5*R*)-5-*O*-Methyl-1,2-*O*-(-1-methylethylidede)-3-*O*-allyl-5-*C*-allyl-α-D-xylofuranose (32). Following the general procedure for methylation reaction, a solution of **27** (700 mg, 2.58 mmol) in THF was treated with sodium hydride (310 mg, 7.76 mmol, 60% in dispersion in oil) and methyl iodide (0.32 mL, 5.17 mmol) in presence of catalytic amount of TBAI. The crude product was purified by silica gel chromatography (hexanes/ethyl acetate 20:1) to give **32** (680 mg, 92%) as a colourless oil. R_f=0.8 (25%, EtOAc/hexane); $[\alpha]_D^{25}$ −75.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3077, 1642, 1079, 1023 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.96–5.86 (3H, m, anomeric C*H* and 2×CH_2=C*H*), 5.33–5.10 (4H, m, 2×CH_2=), 4.55 (1H, d, J=3.6 Hz, C*H*), 4.15 (1H, dd, J=12.4, 6.4 Hz, C*H*), 4.05–4.00 (2H m, CH_2), 3.93 (1H, d, J=2.8 Hz, C*H*), 3.65–3.54 (1H, m, C*H*), 3.39 (3H, s, O*Me*), 2.64–2.60 (1H, m, C*H*), 2.35–2.29 (1H, m, C*H*), 1.46 (3H, s, *Me*), 1.31 (3H, s, *Me*); δ_C (125 MHz, $CDCl_3$); δ 134.1, 133.9, 117.6, 117.4, 111.7, 104.9, 82.2, 81.4, 80.5, 76.5, 71.1, 57.4, 34.9, 26.8, 26.4. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 64.04; H, 8.64; HRMS (EI) calcd for $C_{15}H_{24}O_5Na$ *m/z* 307.1521, found *m/z* 307.1518.

4.4.11. 9-Methoxy-2,2-dimethyl-3a,5,8,9,9a,10a-hexahydro-3b*H*-1,3,4,10-tetraoxa-cycloocta[*a*]pentalene (36). Following the general procedure for ring closing metathesis (method B), from 200 mg (0.70 mmol) of **32**, 0.020 mL (0.07 mmol) of Ti(O*i*Pr)$_4$ and 57 mg (0.07 mmol) of Grubb's catalyst, 122 mg (68%) of **36** was obtained as a colourless oil. R_f=0.40 (25%, EtOAc/hexane); $[\alpha]_D^{25}$ −81.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2929, 1656, 1138, 1097 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.95 (1H, d, J=3.9 Hz, anomeric C*H*), 5.87–5.76 (1H, m, C*H*=), 5.43–5.37 (1H, m, C*H*=), 4.62–4.59 (1H, m, C*H*), 4.55 (1H, dd, J=3.9, 1.5 Hz, C*H*), 4.34 (1H, t, J=2.7 Hz, C*H*), 4.03–3.94 (1H, m, C*H*), 3.86–3.85 (1H, m, C*H*), 3.49–3.41 (1H, m, C*H*), 3.41 (3H, s, O*Me*), 3.40–3.16 (1H, m, C*H*), 2.09–2.01 (1H, m, C*H*), 1.51 (3H, s, *Me*), 1.33 (3H, s, *Me*); δ_C (125 MHz, $CDCl_3$) 128.3, 127.7, 111.9, 104.5, 85.9, 85.1, 81.2, 72.2, 56.5, 29.7, 27.0, 26.9, 26.5; HRMS (EI) calcd for $C_{13}H_{20}O_5Na$ *m/z* 279.1208, found *m/z* 279.1209.

4.4.12. (5*R*)-1,2-*O*-(-1-Methylethylidede)-3-*O*-allyl-5-*C*-pentenyl-α-D-xylofuranose (29) and (5*S*)-1,2-*O*-(-1-methylethylidede)-3-*O*-allyl-5-*C*-pentenyl-α-D-xylofuranose (30). Following the general procedure for Grignard reaction, a solution of aldehyde **12** (280 mg, 1.23 mmol) in THF was treated with 5-bromo-1-pentenemagnesium bromide (9.32 mmol) afforded two diastereomeric products **29** (134 mg, 38%) and **30** (138 mg, 39%) as a readily separable mixture.

Compound **29**. Semisolid; R_f=0.6 (33%, EtOAc/hexane); $[\alpha]_D^{25}$ −33.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3497, 3077, 1641, 1077 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.96 (1H, d, J=3.9 Hz, anomeric C*H*), 5.94–5.75 (2H, m, 2×CH_2=C*H*), 5.36–5.23 (2H, m, CH_2=), 5.06–4.93 (2H, m, CH_2=), 4.58 (1H, d, J=3.9 Hz, C*H*), 4.24–4.17 (1H, m, C*H*), 4.04–3.91 (3H, m, CH_2 and C*H*), 3.99 (1H, d, J=3.3 Hz, C*H*), 2.11–2.09 (2H, m, CH_2), 1.72–1.65 (2H, m, CH_2), 1.55–1.51 (2H, m, CH_2), 1.49 (3H, s, *Me*), 1.32 (3H, s, *Me*); δ_C (125 MHz, $CDCl_3$) 138.7, 133.4, 118.5, 114.6, 111.5 105.0, 82.5, 82.2, 81.9, 71.8, 69.7, 34.1, 33.7, 26.8, 26.2, 24.9; HRMS (EI) calcd for $C_{16}H_{26}O_5Na$ *m/z* 321.1678, found *m/z* 321.1678.

Compound **30**. Colourless oil; R_f=0.5 (33%, EtOAc/hexane); $[\alpha]_D^{25}$ −74.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3510, 3077, 1641, 1078 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.97 (1H, d, J=3.9 Hz, anomeric C*H*), 5.93–5.75 (2H, m, 2×CH_2=C*H*), 5.34–5.22 (2H, m, CH_2=), 5.05–4.93 (2H, m, CH_2=), 4.58 (1H, d, J=3.9 Hz, C*H*), 4.21–4.14 (1H, m, C*H*), 4.05–3.92 (3H, m, CH_2 and C*H*), 3.91 (1H, d, J=3.3 Hz C*H*), 2.44 (1H, br s, OH), 2.13–2.06 (2H, m, CH_2), 1.70–1.51 (4H, m, 2×CH_2), 1.49 (3H, s, *Me*), 1.33 (3H, s, *Me*); δ_C (125 MHz, $CDCl_3$) 138.7, 133.3, 118.3, 114.6, 111.8, 104.8, 82.8, 82.7, 82.4, 70.9, 69.7, 33.5, 32.4, 26.8, 26.3, 24.7; HRMS (EI) calcd for $C_{16}H_{26}O_5Na$ *m/z* 321.1678, found *m/z* 321.1678.

4.4.13. (5*S*)-5-*O*-Methyl-1,2-*O*-(-1-methylethylidede)-3-*O*-allyl-5-*C*-pentenyl-α-D-xylofuranose (33). Following the general procedure for methylation reaction, a solution of **30** (300 mg, 1.0 mmol) in THF was treated with sodium hydride (120 mg, 3.0 mmol, 60% in dispersion in oil) and methyl iodide (0.125 mL, 2.0 mmol) in the presence of catalytic amount of TBAI. The crude product purified by silica gel chromatography (hexanes/ethyl acetate 20:1) to give **33** (270 mg, 85%) as colourless oil. R_f=0.80 (25%, EtOAc/hexane); $[\alpha]_D^{25}$ −22.9 (*c* 1.0, $CHCl_3$); IR (neat) 3077, 1641, 1078, 1022 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.96 (1H, d, J=3.6 Hz, anomeric C*H*), 5.92–5.76 (2H, m, 2×CH_2=C*H*), 5.31–5.21 (2H, m, CH_2=), 5.04–4.95 (2H, m, CH_2=), 4.54 (1H, d, J=3.6 Hz, C*H*), 4.17–4.08 (2H, m, CH_2), 3.89 (1H, dd, J=13.2, 6 Hz, C*H*), 3.76 (1H, d, J=3.6 Hz, C*H*), 3.54–3.44 (1H, m, C*H*), 3.49 (3H, s, O*Me*), 2.10–2.05 (2H, m, CH_2), 1.64–1.35 (4H, m, 2×CH_2), 1.49 (3H, s, *Me*), 1.32 (3H, s, *Me*); δ_C (125 MHz, $CDCl_3$) 138.7, 133.6, 118.1, 114.6, 111.5, 105.0, 83.8, 82.2, 81.5, 79.3, 70.7, 59.2, 33.7, 30.3, 26.7, 26.3, 24.3; HRMS (EI) calcd for $C_{17}H_{28}O_5Na$ *m/z* 335.1834, found *m/z* 335.1822.

4.4.14. 11-Methoxy-2,2-dimethyl-3a,5,8,9,10,11,11a,12a-octahydro-3b*H*-1,3,4,12-tetraoxa-cyclodeca[*a*]pentalene (37). Following the general procedure for ring closing metathesis reaction (method B), from 120 mg (0.38 mmol) of **33**, 0.011 mL (0.038 mmol) of Ti(O*i*Pr)$_4$ and 31 mg (0.038 mmol) of Grubb's catalyst, 90 mg (82%) of **37** was obtained as a colourless oil. R_f=0.70 (25%, EtOAc/hexane); $[\alpha]_D^{25}$ −121.9 (*c* 1.0, $CHCl_3$); IR (neat) 2983, 1649, 1078 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.99 (1H, d, J=3.9 Hz, anomeric C*H*), 5.69–5.60 (2H, m, 2×C*H*=), 4.46 (1H, d, J=3.9 Hz, C*H*), 4.39–4.32 (1H, m, C*H*), 4.13 (1H, dd, J=9.3, 3.0 Hz, C*H*), 3.91 (1H, d, J=3.3 Hz, C*H*), 3.83 (1H, dd, J=6.0, 3.0 Hz, C*H*), 3.78–3.51 (1H, m, C*H*), 3.49 (3H, s, O*Me*), 2.81–2.70 (1H, m, C*H*), 2.02–1.98 (1H, m, C*H*), 1.81–1.51 (4H, m, 2×CH_2), 1.48 (3H, s, *Me*), 1.32 (3H, s, *Me*); δ_C (125 MHz, $CDCl_3$) 137.9, 125.9,

111.6, 105.7, 83.9, 81.8, 80.4, 78.9, 77.6, 63.8, 58.6, 28.9, 27.1, 26.8, 26.4; LRMS (EI) $[M+Na]^+$307.1321; HRMS (EI) calcd for $C_{15}H_{24}O_5Na$ *m/z* 307.1521, found *m/z* 307.1512.

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