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SYNTHESIS OF NOVEL OLIGOSACCHARIDES BASED ON 1,4-DIOXANYLOXY 3-OXASUGARS‡

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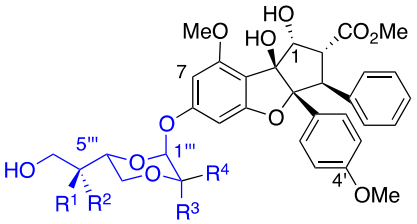
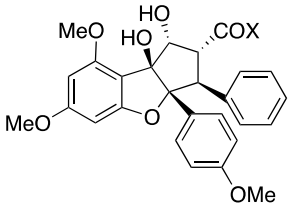
Abstract – The synthesis of a new family of di and tri-3-oxaoligosaccharides based on the 1,4-dioxanyloxy or 3-oxapseudosugar moiety is described. The approach involved the glycosylation of trichloroacetamidate donors with acceptor alcohols to provide 3-oxadi- and trisaccharides. In all cases, the glycosylation was highly stereoselective providing the 1α anomers exclusively.

INTRODUCTION

Uncommon sugars are frequently found in secondary metabolites and these moieties often play crucial roles in determining the biological activities of these compounds.[1] The potent anticancer metabolites silvestrol (**1**) and episilvestrol (**2**) (Figure 1) were isolated from several species of *Aglaia*[2,3] and contain a common cyclopenta[*b*]benzofuran with five contiguous stereogenic centres as well as a novel 1,4-dioxanyloxy or *3-oxapseudosugar*[4] substituent (highlighted). More recently, two other isomers, 2"'-episilvestrol (**3**) and 2"',5"'-diepisilvestrol (**4**) were isolated from *Aglaia folveolata* Pannell (Meliaceae).[5] Both silvestrol (**1**) and episilvestrol (**2**) have potency against lung, breast, and prostate cancer cell lines in vitro, with LC_{50} in the nanomolar range.[2,3]



1 silvestrol: R^1 = H; R^2 = OH; R^3 = OMe; R^4 = H
2 episilvestrol: R^1 = OH; R^2 = H; R^3 = OMe; R^4 = H
3 2"'-episilvestrol: R^1 = H; R^2 = OH; R^3 = H; R^4 = OMe
4 2"',5"'-diepisilvestrol: R^1 = OH; R^2 = H; R^3 = H; R^4 = OMe



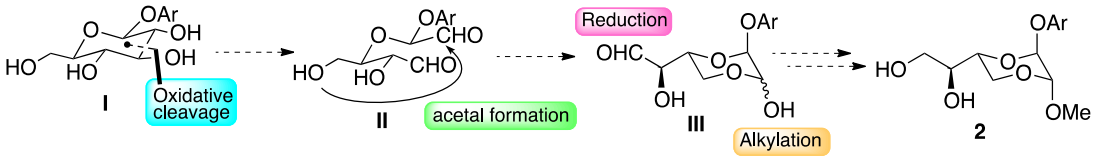
methyl rocaglate: X = OMe
rocagalmide: X = NMe_2

Figure 1

‡Dedicated to Professor Al Padwa

Silvestrol was also found to be active against the iv P388 murine leukemia model and possessed significant preclinical activity against B-cell malignancies with selectivity against B cell.[6] Interestingly, other *Aglaia* metabolites, containing only the parent cyclopenta[*b*]benzofuran core, such as aglafoline (methyl rocaglate) and rocaglamide (Figure 1), have been found to be significantly less active than **1**, suggesting that the presence of the novel dioxanyloxy group is critical to the activity of **1** and **2**. So far, two total syntheses of silvestrol (**1**) have been reported.[7,8]

We have suggested a biosynthetic origin of the dioxylanoxy 3-oxapseudosugar found in episilvestrol (**2**) which begins with a *O*-aryl-D-glucopyranoside **I** (Scheme 1).[4] Selective oxidative cleavage of the 2,3 diol in **I** gives the dialdehyde **II** which would rapidly undergo intramolecular acetal formation to give a stable acetal **III**. Reduction of the aldehyde and methylation of the acetal would then give the 1,4-dioxylanoxy group found in episilvestrol **2**. An inversion at C5''' would then give silvestrol (**1**).

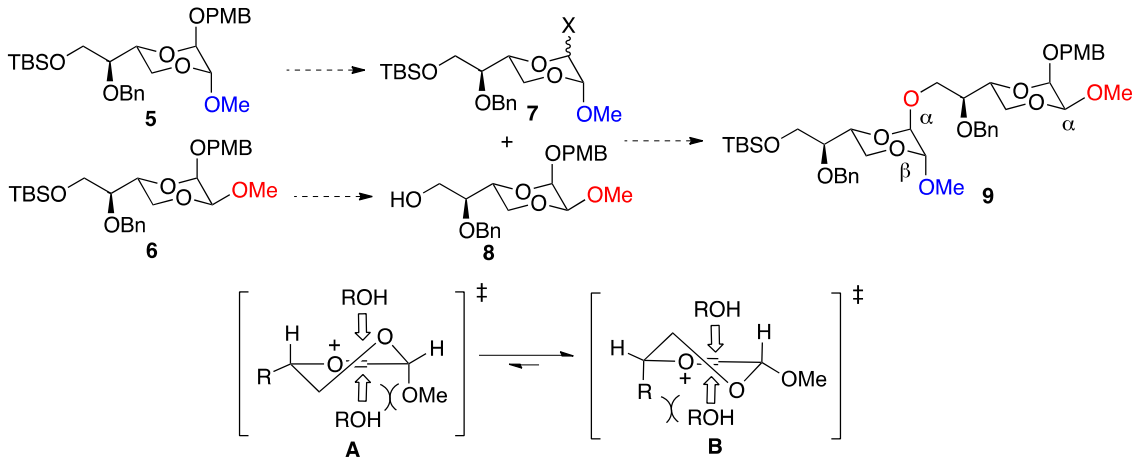


Scheme 1

Oligosaccharides are composed of two to ten monosaccharide residues linked together by glycoside bonds. They act as recognition sites for bacteria, viruses, toxins, antibodies and hormones and provide modulation of important biological processes such as cell-cell recognition and adhesion and viral or bacterial adhesion to host cells.[9] Oligosaccharide mimics of glycoproteins and glycolipids have been utilized to study the structural basis of protein-carbohydrate interactions. For example, C-linked oligosaccharides have been used to show the absence of any hydrogen bond involvement by the intersaccharidic oxygen in the binding area of immunoglobulin confirming the nature of binding is identical to *O*-linked oligosaccharides.[10] With the possibility of interesting biological applications in mind, we elected to investigate the synthesis of simple 1,6-linked-1,4-dioxylanoxy or 3-oxaoligosaccharides. Herein, we report the first stereoselective synthesis of di- and tri-3-oxasaccharides based on the 1,4-dioxanyloxy or 3-oxapseudosugar motif as found in episilvestrol (**2**).

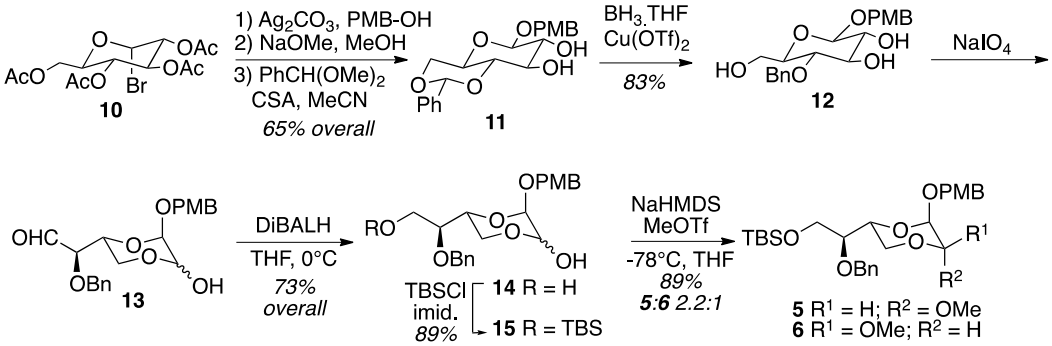
RESULTS AND DISCUSSION

We envisaged that 3-oxaoligosaccharides based on the 1,4-dioxylanoxy unit could be synthesized from the protected precursor **5**, utilized for our total synthesis of episilvestrol (**2**),[7] and the C2 epimer **6**[7b] (Scheme 2). Removal of the PMB protecting group in dioxane **5** and appropriate activation would give a glycosyl donor **7** whilst desilylation of dioxane **6** would provide the 2β[11] acceptor **8**.



Scheme 2

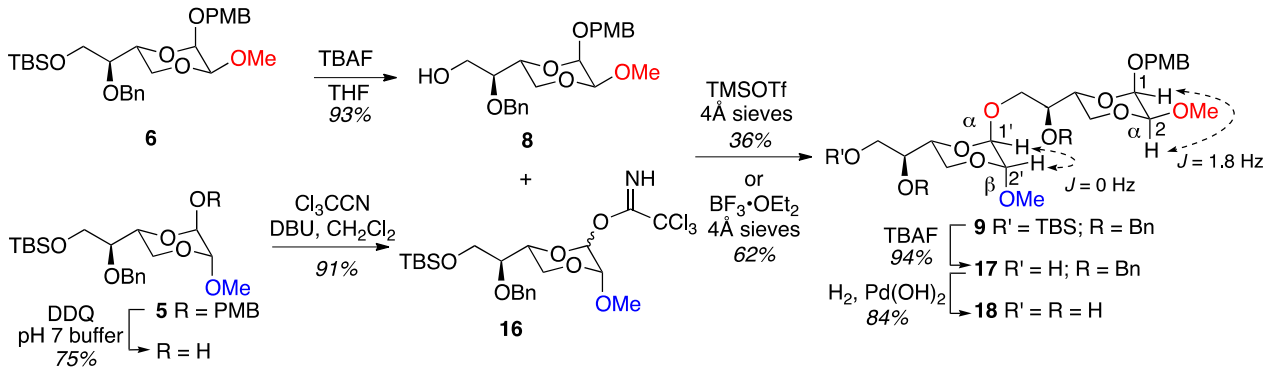
The stereochemistry of the glycosylation should follow from the analysis shown in Scheme 2 whereby the oxonium ion generated from **7** reacts with alcohols such as **8** on the same least hindered face in both half chair conformers **A** and **B**, however **A** may be the preferred conformation as the R group is in a psuedoequatorial orientation and the methoxy group is in the anomerically preferred axial position. This would afford a 1',2'-diaxial linked or 1'α, 2'β 3-oxadisaccharide **9** which could be then be converted into a glycosyl acceptor by silyl group removal.



Scheme 3

The synthesis of the donor and acceptor common intermediates **5** and **6** is shown in Scheme 3. The route follows our published synthesis of **5**[7b] and begins with Koenigs-Knorr glycosylation[12] of bromide **10** with PMB-OH followed by deacetylation and benzylidene formation to afford **11**. Selective benzylidene cleavage was achieved with BH_3•THF in the presence of $Cu(OTf)_2$[13] to give the alcohol **12** in 83% yield. The diol in compound **12** was then oxidatively cleaved with $NaIO_4$[14] to give 1,4-dioxane aldehyde **13** as a ~3:1 mixture of anomers. Reduction of **13** with DiBALH afforded the diol **14** which was selectively silylated to yield the TBS ether **15**. Methylation of the lactols **15** was achieved with NaHMDS followed by treatment with MeOTf[15] to afford the 2β ketal **5** and 2α ketal **6** in a 2.2:1 ratio in 89% overall yield. This ratio was lower than our reported procedure[7b] using nBuLi as base but supplied both methyl ketal anomers

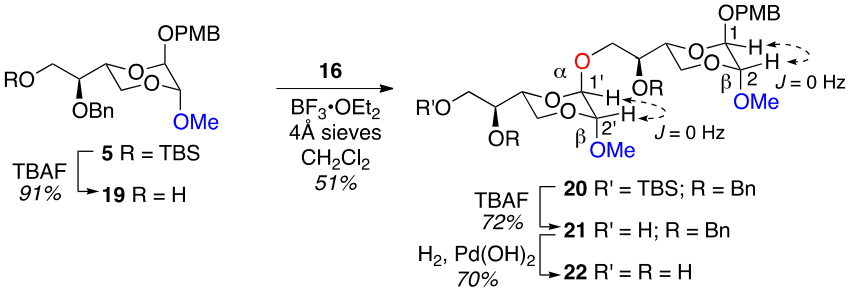
5 and **6** in high overall yield. The 2β isomer **5** displayed singlet at 4.29 ppm for H2 in its ^{1}H NMR spectrum while in the 2α methylketal **6**, the corresponding signal resonates as a doublet at 4.39 ppm (J = 1.8 Hz).



Scheme 4

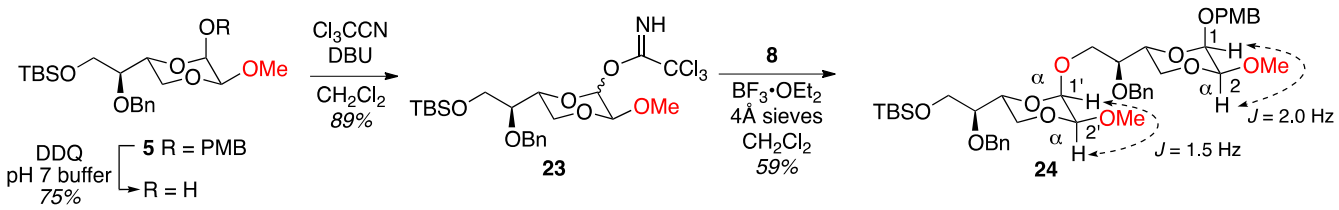
With the two glycosylation precursors in hand we next trialed several standard glycosylation methods. The procedure we utilized for the synthesis of both **1** and **2** involved a modified Mitsunobu coupling which was not applicable in this case.[7] Amongst the other glycosylation protocols available,[16] we found the trichloroacetamidate method pioneered by Schmidt[17] to be the most adaptable and the synthesis of the first example of a 1'α, 2α, 2'β oxadisaccharide **9** is shown in Scheme 4. Desilylation of **6** gave the glycosyl acceptor **8** in high yield whilst the glycosyl donor **16** was prepared from acetal **5** by oxidative deprotection of the PMB ether and conversion of the intermediate lactols into the trichloroacetamidate **16**.[18] Glycosylation of acceptor **8** with the donor **16** was achieved using TMSOTf as the promoter to afford disaccharide **9** as a single α'-anomer, in a low yield (36%) based on the donor **16**. When the reaction was conducted with BF_3•OEt_2 as the Lewis acid, the yield increased to 62%. The presence of powdered 4Å molecular sieves is critical for the success of the reaction. In the absence of sieves, considerable hydrolysis of the trichloroacetamidate was observed. Removal of the TBS group gave alcohol **17** followed by hydrogenolysis of the benzyl ethers provided triol **18**. Confirmation of the stereochemistry of the new glycosyl linkage arose from NMR analysis of **18**. The coupling constant for H1-H2 was 1.8 Hz, indicative of an *eq-ax* relationship whilst the coupling between H1'-H2' was closer to 0 Hz, showing these protons are in a *eq-eq* orientation. This result is in accord with our prediction that axial approach of the donor on the intermediate oxonium ion to form the 1'α-anomer is preferred.

The synthesis of the alternative 1'α, 2β, 2'β-isomer is shown in Scheme 5. The 2β isomer **5** was desilylated to give acceptor **19** in good yield. Glycosylation using the donor **16** then afforded the 1'α-anomer **20** in good yield as the only detectable diastereoisomer. Removal of the TBS group afforded the alcohol **21** and debenzylation then gave triol **22**. Again, ^{1}H NMR couplings supported the assigned 1'α, 2β, 2'β stereochemistry of the glycosylation product **20** ($^3J_{H1,H2} = {}^3J_{H1',H2'} = 0$ Hz).



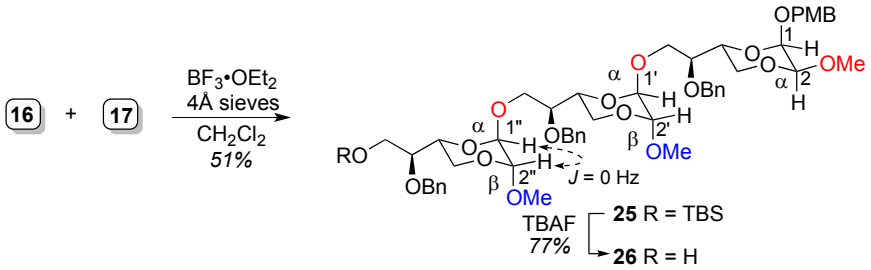
Scheme 5

To test the effect of the C2 stereochemistry on the glycosylation reaction, the 2α glycosyl donor was synthesized from compound **5** (Scheme 6). Removal of the PMB group gave the lactols as a mixture of anomers which were converted in the trichloroacetamidate **23** under the standard conditions. Glycosylation using the acceptor **8** afforded the 1'α, 2α, 2'α 3-oxadisaccharide **24**, again as the sole diastereoisomer. The coupling constants for H1-H2 and H1'-H2' were also consistent with the assigned stereochemistry.



Scheme 6

We next explored the synthesis of an example of a 3-oxatrisaccharide as shown in Scheme 7. Glycosylation of **17** with trichloroacetamidate **16** afforded the 3-oxatrisaccharide **25** as a single anomer. Removal of the TBS group gave the alcohol **26** in good yield. Again, the selectivity was high for the glycosylation reaction providing the 1"α anomer as confirmed by the H1"-H2" coupling constant of 0 Hz.



Scheme 7

CONCLUSION

The synthesis of a new family of oligosaccharides has been achieved based on the 1,4-dioxanyloxy or 3-oxasugar moiety. The glycosylation reactions were based on the Schmidt trichloroacetamidate method and were highly stereoselective with only the 1α isomers formed in all cases, regardless of the C2 stereochemistry. The stereochemical outcomes could easily be determined by ^{1}H NMR analysis. Examples of 3-oxadisaccharides and a trisaccharide were synthesized and this method could easily provide more

extended 3-oxaoligosaccharides. Studies directed towards the biological activities of these novel sugars are currently underway.

EXPERIMENTAL

General

Proton nuclear magnetic resonance spectra (^{1}H NMR, 400 MHz and 500 MHz) and proton decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR, 100 MHz and 125 MHz) were obtained in deuterochloroform with residual chloroform as internal standard. Chemical shifts are followed by multiplicity, coupling constant(s) (*J*, Hz), integration and assignments where possible. Optical rotations were recorded in a 10 cm microcell for a 1 mL solution and units are deg.cm^{2}g^{-1}. Flash chromatography was carried out on silica gel 60. Analytical thin layer chromatography (t.l.c.) was conducted on aluminium-backed 2mm thick silica gel 60 GF_{254} and chromatograms were visualized with 20% w/w phosphomolybdic acid in ethanol. High resolution mass spectra (HRMS) were obtained by ionizing samples *via* electron spray ionization (ESI). Anhydrous THF and CH_2Cl_2 were used from a solvent cartridge system. Dry methanol was distilled from magnesium methoxide. All other solvents were purified by standard methods. Petrol used refers to petroleum ether 40-60 ºC boiling range. All other commercially available reagents were used as received. The usual workup refers to extraction with particular solvent (3x), washing with water and brine, drying with $MgSO_4$ and concentrating under reduced pressure.

Methyl ketals 5 and 6

To a solution of the lactols **15**[7b] (623.6 mg, 1.23 mmol) in THF (16 mL) at –78 ºC, was added a solution of LiHMDS (1.0M, 1.6 mmol) drop wise followed by MeOTf (234 μL, 1.82 mmol). The solution was stirred for 20 mins at -78 ºC and sat. aq. $NaHCO_3$ and Et_2O were added. The usual workup with Et_2O and purification by flash chromatography with 10% EtOAc/petrol as eluent gave the 2β methyl ketal **5**[7b] (206 mg, 61%) as a colourless oil. ^{1}H NMR (500 MHz) δ 7.19-7.27 (m, 7H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.57 (ABq, *J* = 11.6 Hz, 2H), 4.55 (ABq, *J* = 11.2 Hz, 2H), 4.47 (s, 1H), 4.29 (s, 1H), 4.20-4.25 (m, 1H), 3.82 (dd, *J* = 11, 3.2 Hz, 1H), 3.77 (t, *J* = 11.2 Hz, 1H), 3.73 (s, 3H), 3.70 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.63 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.39-3.42 (m, 1H), 3.31 (s, 3H), 0.84 (s, 9H), 0.011 (s, 3H), 0.003 (s, 3H). Further elution gave the 2α methyl ketal **6**[7b] (96.6 mg, 28%) as a colourless oil. ^{1}H NMR (500 MHz) δ 7.28-7.34 (m, 7H), 6.83 (d, *J* = 9 Hz, 2H), 4.74 (ABq, *J* = 11.8 Hz, 2H), 4.65 (ABq, *J* = 12 Hz, 2H), 4.56 (d, *J* = 1.8 Hz, 1H), 4.39 (d, *J* = 1.8 Hz, 1H), 4.14-4.18 (m, 1H), 4.09 (dd, *J* = 12, 2.9 Hz, 1H), 3.78 (s, 3H), 3.75 (dd, *J* = 11, 4.1 Hz, 1H), 3.67 (dd, *J* = 11, 5.3 Hz, 1H), 3.66 (t, *J* = 10 Hz, 1H), 3.50 (s, 3H), 3.40-3.46 (m, 1H), 0.89 (s, 9H), 0.065 (s, 3H), 0.061 (s, 3H).

2α Acceptor 8

The methyl ketal **6** (305.8 mg, 0.605 mmol) was dissolved in THF (4 mL) and the solution was cooled to 0 ˚C. TBAF (560 mg, 1.78 mmol) was then added and the solution was stirred for 1.5 h. The reaction was quenched with 0.2M citric acid. The usual workup with CH_2Cl_2 and purification by flash chromatography (40% EtOAc/petrol) gave the glycosyl acceptor **8** (304 mg, 90%) as a pale yellow oil: $[\alpha]_D^{24}$ –42.8 (*c* 5.01, CH_2Cl_2); IR (film) υ_{max}: 3507, 2930, 1612, 1514, 1458, 1303, 1246, 1214, 1173, 1097, 1056; ^{1}H NMR (500 MHz) δ 7.28-7.34 (m, 7H), 6.85 (d, J = 8.4 Hz, 2H), 4.67 (ABq, *J* = 11.2 Hz, 2H), 4.59 (ABq, *J* = 12 Hz, 2H), 4.58 (s, 1H), 4.39 (d, *J* = 1.8 Hz, 1H), 4.14-4.19 (m, 1H), 4.13 (dd, *J* = 11.5, 2.9 Hz, 1H), 3.78 (s, 3H), 3.73-3.76 (m, 1H), 3.64-3.69 (m, 1H), 3.59 (t, *J* = 10 Hz, 1H), 3.50 (s, 3H), 3.39-3.42 (m, 1H); ^{13}C NMR (125 MHz) δ 159.4, 137.8, 130.0, 128.6, 128.0, 113.8, 99.2, 93.3, 78.7, 77.4, 77.2, 76.9, 72.5, 70.0, 67.3, 66.4, 56.9, 55.3; HRMS (ESI) calc. for $C_{22}H_{28}O_7$ $[M+Na]^+$: 427.1727; found 427.1727.

2β Donor 16

To a solution of the methyl ketal **5** (60 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) and pH buffer (0.4 mL) was added DDQ (50 mg) at 0 ºC and the reaction mixture stirred at rt for 17 h. The mixture was filtered through celite and the filtrate was concentrated. The crude residue was purified by flash chromatography with 15% EtOAc/petrol as eluent to give the mixture of lactols (34.6 mg, 75%) as a colourless oil. To a solution of lactols (29.6 mg, 0.07 mmol) in CH_2Cl_2 (0.4 mL), was added DBU (2.2 µL, 0.015 mmol) and trichloroacetonitrile (33.7 µL, 0.34 mmol) at 0 ˚C under argon. The solution was stirred at 0 ˚C over 3 h and most of the solvent was removed under reduced pressure. The residue was purified by flash chromatography (1% NEt_3, 10% EtOAc/petrol) to give the trichloroacetamidate **16** as a mixture of α and β isomers (20:1 by ^{1}H-NMR) (36.1 mg, 91%), as a pale yellow oil: $[\alpha]_D^{25}$ –45.8^o (*c* 0.80, CH_2Cl); IR (film) υ_{max}: 2929, 2857, 1671, 1463, 1257, 1173, 1069, 970, 925, 836, 798, 779, 735; ^{1}H NMR (500 MHz) δ 8.57 (s,1H, minor), 8.55 (s, 1H, major), 7.32-7.34 (m, 5H), 5.97 (s, 1H, major), 5.90 (d, *J* = 1.79 Hz, 1H, minor), 4.67 (ABq, *J* = 11.5 Hz, 4H, major and minor), 4.70 (d, *J* = 1.79 Hz, 1H, minor), 4.55 (s, 1H, major), 4.35-4.39 (m, 2H, major and minor), 4.01 (t, *J* = 11.5 Hz, 2H, major and minor), 3.66 (dd, *J* = 10.9 Hz, 5.4 Hz, 2H, major and minor), 3.71 (m, 2H, major and minor), 3.70 (dd, *J* = 10.5 Hz, 5.4 Hz, 2H, major and minor), 3.47 (s, 3H, minor), 0.87 (s, 18H, major and minor), 3.44 (s, 3H, major), 0.029 (d, 12H, major and minor); ^{13}C NMR (125 MHz) δ 128.4, 128.0, 127.8, 94.3, 93.7, 79.7, 73.2, 68.7, 62.5, 59.5, 26.1, 18.4, -5.0s; HRMS (ESI) calc. for $C_{22}H_{34}Cl_3N_1O_6Si$ $[M+Na]^+$: 564.11132; found 564.11132.

1'α, 2α, 2'β'-L-3-Oxadisaccharide 9

BF_3•OEt_2 (130 µL, 0.0120 mmol, 0.15M in CH_2Cl_2) was added to a stirred solution of trichloroacetimidate

donor **16** (130 mg, 0.239 mmol), alcohol acceptor **8** (98.2 mg, 0.243 mmol) and freshly activated powdered 4Å molecular sieves (90 mg) in dry CH_2Cl_2 (5 mL) at -50 ˚C under a N_2 atmosphere. The mixture was stirred for 4 h, quenched with sat. aq. $NaHCO_3$ (2 mL) and filtered through a layer of celite. Usual workup with CH_2Cl_2 and purification by flash chromatography (20-30% EtOAc/petrol) afforded the disaccharide **9** (116 mg, 62%) as a colourless oil. $[\alpha]_D^{25}$ –60.7 (*c* 0.58, CH_2Cl_2); IR (film) υ_{max}: 2928, 1613, 1514, 1455, 1327, 1249, 12216, 1249, 1216, 1159, 1114, 1064; ^{1}H NMR (500 MHz) δ 7.28-7.35 (m, 12), 6.83 (d, *J* = 8.7 Hz, 2H), 4.71-4.74 (m, 3H), 4.56-4.60 (m, 5H), 4.38 (d, *J* = 4.38 Hz, 1H), 4.36 (s, 1H), 4.10-4.22 (m, 4H), 3.78-3.87 (m, 2H), 3.77 (s, 3H), 3.71 (dd, *J* = 10.9, 5.4 Hz, 1H), 3.65 (dd, *J* = 11.3, 3.3 Hz, 1H), 3.57-3.65 (m, 2H), 3.52 (m, 1H), 3.49 (s, 3H), 3.46 (m, 1H), 3.39 (s, 3H), 0.89 (s, 9H), 0.043 (s, 6H); ^{13}C NMR (125 MHz) δ 138.6, 138.1, 130.0, 128.5, 128.4, 128.1, 127.9, 127.7, 113.8, 99.3, 96.0, 95.7, 93.4, 80.1, 77.9, s72.8, 68.9, 67.4, 66.2, 66.1, 62.7, 60.1, 56.9, 55.3, 54.9, 29.8 , 26.0, 18.4; HRMS (ESI) calc. for $C_{42}H_{60}O_{12}Si$ $[M+Na]^+$: 807.3795; found 807.3795.

1'α, 2α, 2'β 3-Oxadisaccharide acceptor 17

TBAF (264 mg, 0.8 mmol) was added to a solution of the disaccharide **9** (220 mg, 0.28 mmol) in THF (2 mL) at 0 ˚C. The reaction was quenched with 0.2M citric acid after 4 h. The Usual workup with CH_2Cl_2 and purification by flash chromatography (50% EtOAc/petrol) yielded the 3-oxadisaccharide alcohol **17** (176 mg, 94%) as a pale yellow oil. $[\alpha]_D^{25}$ –78.3 (*c* 1.035, CH_2Cl_2); IR (film) υ_{max}: 2925, 1514, 1455, 1248, 1159, 1117, 1064; ^{1}H NMR (500 MHz) δ 7.28-7.35 (m, 12H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.72 (ABq, *J* = 11.5Hz, 2H), 4.54-4.62 (m, 6H), 4.38 (d, *J* = 4.38 Hz, 1H), 4.36 (s, 1H), 4.10-4.22 (m, 4H), 3.78-3.87 (m, 3H), 3.78 (s, 3H), 3.71 (dd, *J* = 10.9, 5.4 Hz, 1H), 3.66 (dd, *J* = 11.3, 3.3 Hz, 1H), 3.58-3.63 (m, 2H), 3.58-3.63 (m, 2H), 3.51-3.53 (m, 1H), 3.49 (s, 3H), 3.42-3.44 (m, 1H), 3.41 (s, 3H); ^{13}C NMR (125 MHz) δ 159.0, 138.1, 137.9, 130.1, 129.6, 128.7, 128.6, 128.2, 128.17, 128.11, 128.0, 113.9, 99.4, 95.9, 95.7, 93.7, 79.1, 77.7, 73.0, 72.4, 69.2, 67.2, 66.5, 66.3, 65.9, 60.6, 60.4, 57.0, 55.4, 55.0; HRMS (ESI) calc. for $C_{36}H_{46}O_{12}Si$ $[M+Na]^+$: 693.2881; found 693.2882.

1'α, 2α, 2'β Triol 18

To a solution of the oxadisaccharide **17** (58.2 mg, 0.0741 mmol) in MeOH (3 mL) was added $Pd(OH)_2$ (10.9 mg, 77.8 μmol) and the mixture was stirred under a H_2 atmosphere for 18 h. The mixture was filtered through celite, washed with EtOAc and concentrated to give the triol **18** as a pale yellow oil (42 mg, 84%). $[\alpha]_D^{25}$ –156.9 (*c* 0.2, CH_2Cl_2); IR (film) υ_{max}: 3465, 2930, 1612, 1515, 1457, 1249, 1159, 1115, 1060 cm^{-1}. ^{1}H NMR (500 MHz) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.70-4.65 (m, 3H), 4.51 (s, 1H), 4.41 (d, *J* = 1.8 Hz, 1H), 4.39 (s, 1H), 4.11-4.17 (m, 2H), 4.08 (dd, *J* = 11.6 Hz, 2.9 Hz, 1H), 3.91-3.95 (m,

3H), 3.89 (t, *J* = 11 Hz, 1H), 3.80 (s, 3H), 3.64-3.73 (m, 4H), 3.59 (dd, *J* = 10.7, 3.0 Hz, 1H), 3.53-3.56 (m, 2H), 3.51 (s, 3H), 3.43 (s, 3H); ^{13}C (125 MHz) δ 159.7, 129.8, 113.8, 99.1, 95.8, 93.8, 71.3, 70.5, 69.6, 68.7, 67.1, 66.2, 62.0, 56.9, 56.8, 55.3, 55.0, 54.9; HRMS (ESI) calc. for $C_{22}H_{34}O_{12}$ $[M+Na]^+$: 513.1943; found 513.1943.

2β Acceptor 19

The methyl ketal **5** (78.6 mg, 0.155 mmol) was dissolved in THF (1 mL) and the solution was cooled to 0 ˚C. TBAF (143.5 mg, 0.46 mmol) was then added and the solution was stirred for 1.5 h. The reaction was quenched with 0.2M citric acid. The usual workup with CH_2Cl_2 and purification by flash chromatography (40% EtOAc/petrol) gave the glycosyl acceptor **19** (56.1 mg, 91%); $[\alpha]_D^{24}$ –124.9 (*c* 0.8750, CH_2Cl_2); IR (film) υ_{max}: 3503, 2924, 2837, 1612, 1586, 1514, 1454, 1400, 1303, 1246, 1211, 1196, 1175, 1175, 1154, 1108, 1027, 1058, 957, 892, 878, 851, 820, 738, 698; ^{1}H NMR (500 MHz) δ 7.28-7.34 (m, 7H), 6.85 (d, J = 8.4 Hz, 2H), 4.73 (ABq, *J* = 11.5 Hz, 2H), 4.66 (ABq, *J* = 11.5 Hz, 2H), 4.56 (s, 1H), 4.56 (s, 1H), 4.32-4.28 (m, 1H), 4.13 (dd, J = 11.5, 2.9 Hz, 1H), 3.79 (s, 3H), 3.73-3.76 (m, 1H), 3.84-3.69 (m, 1H), 3.59 (t, *J* = 10 Hz, 1H), 3.39 (s, 3H), 3.47-3.42 (m, 1H); ^{13}C NMR (125 MHz) δ 159.7, 138.0, 130.3, 129.4, 128.9, 128.4, 128.3, 114.2, 96.1, 94.3, 94. 3, 79.3, 72.7, 68.7, 66.0, 60.9, 60.8, 55.6, 55.2; HRMS (ESI) calc. for $C_{22}H_{28}O_7$ $[M+Na]^+$: 427.1727; found: 427.1727.

1'α, 2β, 2'β 3-Oxadisaccharide 20

$BF_3{\cdot}OEt_2$ (400 μL, 0.060 mmol, 0.15M in CH_2Cl_2) was added to a stirred solution of trichloroacetamidate donor **16** (57.2 mg, 0.12 mmol), alcohol acceptor **19** (56.3 mg, 0.13 mmol) and freshly activated powdered 4Å molecular sieves (90 mg) in dry CH_2Cl_2 (2 mL) at -60 ˚C under a Ar atmosphere. The mixture was stirred for 8 h, quenched with saturated $NaHCO_3$ (0.5 mL) and filtered through a layer of celite. Usual workup with CH_2Cl_2 and purification by flash chromatography (20-30% EtOAc/petrol) afforded the disaccharide **20** (41.4 mg, 51%) as a colourless oil. $[\alpha]_D^{25}$ –89.0 (*c*. 1.85, CH_2Cl_2); IR (film) $\upsilon_{max:}$ 2930, 1732, 1612, 1515, 1455, 1250, 1157, 1110, 1064; ^{1}H NMR (500 MHz) δ 7.26-7.35 (m, 12H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.75 (dd,*J* = 5.5Hz, 11.5 Hz, 2H), 4.73(s, 1H), 4.63 (s, 1H), 4.57 (dd, *J* = 5Hz, 11.5 Hz, 2H), 4.56 (s, 1H), 4.48 (d, *J* = 11.5 Hz), 4.36 (s, 2H), 4.33-4.27 (m, 1H), 4.22-4.18 (m, 1H), 3.78 (s, 3H), 3.71 (dd, *J* = 11.5, 4 Hz 1H), 3.68 (dd, *J* = 11.5, 2 Hz, 1H), 3.74-3.69 (m, 2H), 3.55-3.52 (m, 1H), 3.39 (s, 3H), 3.46-3.42 (m, 1H), 3.38 (s, 3H), 0.89 (s, 9H), 0.043 (s, 6H); ^{13}C NMR (125 MHz) δ 159.7, 158.7, 138.8, 130.2, 128.7, 128.6, 128.3, 128.1, 127.9, 114.2, 96.2, 96.1, 96.1, 95.9, 94.4, 80.3, 78.8, 77.6, 77.4, 77.1, 73.1, 72.8, 68.7, 66.2, 65.7, 65.2, 62.9, 60.8, 60.4, 55.2, 55.1, 26.2, 18.6, -5.1; HRMS (ESI) calc. for $C_{42}H_{60}O_{12}Si$ $[M+Na]^+$: 807.3746; found 807.3751.

1'α, 2β, 2'β 3-Oxadisaccharide acceptor 21

TBAF (50 mg, 0.19 mmol) was added to a solution of the disaccharide **20** (26 mg, 0.03 mmol) and THF (2 mL) at 0 ˚C. The reaction was quenched with 0.2M citric acid after 4 h. The Usual workup with CH_2Cl_2 and purification by flash chromatography (50% EtOAc/petrol) yielded the alcohol **21** (16 mg, 72%) as a pale yellow oil. $[\alpha]_D^{25}$ –75.2 (*c* 1.20, CH_2Cl_2); IR (film) υ_{max}: 3496, 2923, 1613, 1586, 1514, 1454, 1303, 1248, 1196, 1111, 1061; ^{1}H NMR (500 MHz): 7.34 (m, 12H), 6.86 (d, 8.5), 4.75 (dd, 4.5Hz, 12Hz, 2H), 4.61 (ABq, *J* = 11.5Hz, 2H), 4.59-4.55 (m, 4H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.38 (s, 1H), 4.36 (s, 1H), 4.30-4.23 (m, 2H), 3.89 (dd, *J* =5.5 Hz, 11.5 Hz, 1H), 3.82-3.69 (m, 5H), 3.82 (s, 3H), 3.65 (dd, J = 3, 11.5 Hz, 1H), 3.52-3.49 (m, 1H), 3.43-3.78 (m, 1H), 3.44 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (125 MHz) δ 159.7, 138.3, 138.1, 130.2, 128.8, 128.7, 128.4, 128.3, 128.2, 114.2, 96.2, 96.1, 95.9, 94.5, 79.3, 78.5, 77.6, 77.4, 77.1, 73.05, 72.6, 68.8, 66.2, 66.1, 65.8, 60.9, 60.7, 60.6, 55.6, 55.19, 55.17; $C_{36}H_{46}O_{12}$ $[M+Na]^+$: 693.2881; found 693.2883.

1'α, 2β, 2'β 3-oxodisaccharide triol 22

To a solution of disaccharide **21** (12.4 mg, 0.018 mmol) in distilled MeOH (1 mL) was added $Pd(OH)_2$ (2.5 mg, 0.018 mmol) and the mixture was stirred under a H_2 atmosphere for 18 h. The mixture was filtered through celite, washed with EtOAc and concentrated and the crude product was purified *via* flash chromatography (EtOAc:MeOH:H_2O 7:2:1) to afford the triol **22** (6.2 mg, 70%) as a colourless oil. $[\alpha]_D^{25}$ –103.9 (*c* 0.255, CH_2Cl_2); IR (film) υ_{max}: 3414, 2924, 2853, 2017, 1728, 1613, 1586, 1515, 1457, 1378, 1249, 1197, 1156, 1111, 1060; ^{1}H NMR (500 MHz) δ 7.29 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8 Hz, 2H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.56 (s, 1H), 4.53 (s, 1H), 4.51 (d, *J* = 12 Hz, 1H), 4.39 (s, 1H), 4.37 (s, 1H), 4.25-4.06 (m, 3H), 3.92-3.89 (m, 4H), 3.80 (s, 3H), 3.71-3.63 (m, 6H), 3.58-3.56 (m, 1H), 3.43 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (125 MHz) δ 160.4, 130.24, 114.3, 111.1, 96.1, 96.8, 111.1, 77.6, 77.0, 72.1, 71.2, 69.2, 67.4, 64.3, 63.5, 62.5, 60.04, 59.8, 55.6, 55.2; $C_{22}H_{34}O_{12}$ $[M+Na]^+$: 513.1942; found 513.1943.

2α Donor 23

To a solution of the methyl ketal **6** (120 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) and pH buffer (0.8 mL) was added DDQ (100 mg) at 0 ºC and the reaction mixture stirred at rt for 2h. The mixture was filtered through celite and the filtrate was concentrated. The crude residue was purified by flash chromatography with 15% EtOAc/petrol as eluent to give the mixture of lactols (72 mg, 75%) as a colourless oil. To a solution of the lactols (63.8 mg, 0.16 mmol) in CH_2Cl_2 (2 mL), was added DBU (5 µL, 0.03 mmol) and trichloroacetonitrile (81 µL, 0.81 mmol) at 0 ˚C under argon. The solution was stirred at 0 ˚C over 2.5 h and most of the solvent was removed under reduced pressure. The residue was purified by flash

chromatography (1% NEt_3, 10% EtOAc/petrol) to give the trichloroacetamidate **23** as a mixture of 1α and β anomers (10:1 - ^{1}H NMR), (77.6 mg, 89%) as a pale yellow oil. IR (film) υ_{max}: 2954, 2928, 2856, 1734, 1669, 1497, 1471, 1455, 1463, 1388, 1361, 1332, 1316, 1284, 1254, 1197, 1216, 1173, 1073, 1028; ^{1}H NMR (500 MHz) δ 8.55 (s, 1H, minor), 8.50 (s, 1H, major), 7.32-7.34 (m, 5H), 6.13(s, 1H, minor), 5.8 (d, *J* = 1.5 Hz, 1H, major), 4.67 (ABq, *J* = 12 Hz, 4H, major and minor), 4.59 (d, *J* = 1.5 Hz, 1H, minor), 4.55 (d, *J* = 1.5 Hz ,1H, major), 4.32-4.28 (m, 2H, minor), 4.18 (dd, *J* = 13 Hz, 4.5 Hz, 2H, major and minor), 4.06-4.03 (m, 12H, major), 3.92 (dd, *J* = 13 Hz, 4.5 Hz, 2H, major and minor), 3.80 (dd, *J* = 6 Hz, 11 Hz, 2H, major and minor), 3.74 (dd, *J* = 5.5 Hz, 11 Hz, 1H, major and minor), 3.68 (dd, *J* = 5.5 Hz, 11 Hz, 1H, major and minor), 3.54 (s, 3H, minor), 3.48 (s, 3H, major), 0.87 (s, 18H, major and minor), 3.44 (s, 3H, major), 0.02 & 0.03 (s, 12H, major and minor); ^{13}C NMR (100 MHz) δ 128.7, 128.9, 127.8, 96.0, 94.5, 77.6, 73.1, 70.5, 62.5, 55.8, 30.05, 26.3; HRMS (ESI) calc. for $C_{22}H_{34}Cl_3NO_6Si$ $[M+Na]^+$: 564.11132; found 564.11133.

1'α, 2α, 2'α 3-Oxadisaccharide 24

$BF_3{\cdot}OEt_2$ (40 μL, 4 μmol, 0.15M in CH_2Cl_2) was added to a stirred solution of trichloroacetimidate donor **23** (45 mg, 80 μmol), alcohol acceptor **7** (35 mg, 90 μmol) and freshly activated powdered 4Å molecular sieves (50 mg) in dry CH_2Cl_2 (2 mL) at 60 ˚C under an Ar atmosphere. The mixture was stirred for 8 h, quenched with saturated $NaHCO_3$ (0.5 mL) and filtered through a layer of celite. The usual workup with CH_2Cl_2 and purification by flash chromatography (50% EtOAc/petrol) afforded the 3-oxadisaccharide **21** (36 mg, 59%) as a colourless oil. $[\alpha]_D^{23}$ –61.6 (*c* 0.21, CH_2Cl_2); IR (film) υ_{max}: 2927, 2855, 1613, 1586, 1514, 1497, 1454, 1388, 1359, 1328, 1303, 1248, 1215, 1172, 1099, 1060, 1028; ^{1}H NMR (500 MHz) δ 7.34-7.27 (m, 12H), 6.85 (d, *J* = 9 Hz, 2H), 4.8 (d, *J* = 11.5 Hz, 1H), 4.72 (dd, *J* = 12 Hz, 6.5 Hz, 1H), 4.65 (d, *J* = 2 Hz, 1H), 4.59 (d, *J* = 1.5 Hz, 1H), 4.62-4.54 (m, 3H), 4.41 (d, *J* = 1.5 Hz, 1H). 4.38 (d, *J* = 2 Hz, 1H), 4.13 -4.05 (m, 4H), 3.78 (s, 3H), 3.79-3.61 (m, 8H), 3.51 (s, 3H), 3.48 (s, 3H), 3.48-3.45 (m, 1H), 0.90 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz) δ 159.6,138.9, 138.7, 130.2, 129.8, 128.6, 128.4, 128.0, 128.0, 127.9, 114.1, 99.6, 99.6, 95.3, 93.6, 77.8, 76.9, 73.5, 73.3, 69.1, 68.1, 67.3, 67.1, 66.0, 63.5, 57.1, 55.6, 26.2, 18.6, -5.0; HRMS (ESI) calc. for $C_{42}H_{60}O_{12}Si$ $[M+Na]^+$: 807.3746; found 807.3747.

1'α, 1"α, 2α, 2'β, 2'β 3-Oxatrisaccharide 25

A 0.15M solution of $BF_3{\bullet}OEt_2$ in CH_2Cl_2 (34 μL, 0.005 mmol) was added to a stirred solution of donor **16** (20 mg, 0.03 mmol), alcohol acceptor **17** (24 mg, 0.04 mmol) and freshly activated powdered 4Å molecular sieves (90 mg) in dry CH_2Cl_2 (1 mL) at -60 ˚C under Ar atmosphere. The mixture was stirred for 8 h, quenched with saturated $NaHCO_3$ (2 mL) and filtered through a layer of celite. Usual workup with CH_2Cl_2

and purification by flash chromatography (20-30% EtOAc/petrol) afforded the 3-oxatrisaccharide **26** (16 mg, 51%) as a colourless oil. $[\alpha]_D^{27}$ –53.6 (c 0.36, CH_2Cl_2); IR (film) υ_{max}: 2929, 2326, 2342, 1722, 1514, 1455, 1251, 1158, 1115, 1066; ^{1}H NMR (500 MHz) δ 7.33-7.27 (m, 17H), 6.84 (d, ^{19}2H), 4.75-4.68 (m, 3H), 4.67 (s, 1H), 4.61 (s, 2H), 4.59-4.55 (s, 6H), 4.53 (s, 2H), 4.38 (d, *J* = 1.5 Hz, 1H), 4.37 (s, 1H) , 4.36 (s, 1H), 4.22-4.1 (m, 4H), 3.9-3.77 (m, 4H), 3.76 (s, 3H), 3.74-3.6 (m, 5H), 3.59-3.52 (m, 3H), 3.49 (s, 3H), 3.84 (s, 6H), 0.89 (s, 9H), 0.043 (s, 6H); ^{13}C NMR (125 MHz) δ 159, 137.5, 129.8, 127.4, 117.0, 114.0, 112.1, 85.6, 82.6, 70.4, 65.7, 55.3 54.9, 29.8, 26.0, 18.4, -5.0; HRMS (ESI) calc. for $C_{56}H_{78}O_{17}Si$ $[M+Na]^+$: 1073.4905; found 1073.4902.

1'α, 1"α, 2β, 2'β, 2"β 3-Oxatrisaccharide alcohol 26

TBAF (8 mg, 20.0 μmol) was added to a solution of the trisaccharide **25** (7.6 mg, 7.0 μmol) in THF (1 mL) at 0 ˚C and the solution was stirred for 5 h. The reaction was quenched with 0.2M citric acid and the usual workup with CH_2Cl_2 followed by purification by flash chromatography (50% EtOAc/petrol) afforded trisaccharide alcohol **26** (5.1 mg, 77%); $[\alpha]_D^{25}$ –103.4 (*c* 0.73, CH_2Cl_2); IR (film) υ_{max}: 2927, 1514, 1158, 1117, 1064 cm^{-1}. ^{1}H NMR (500 MHz) δ 7.28-7.35 (m, 17H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.69-4.74 (m, 3H), 4.50-4.61 (m, 8H), 4.38 (d, *J* = 1.8 Hz, 1H), 4.36 (s, 1H), 4.31 (s, 1H), 4.12-4.24 (m, 4H), 3.78-3.87 (m, 3H), 3.76 (s, 3H), 3.50-3.75 (m, 11H), 3.49 (s, 3H), 3.39 (s, 3H), 3.34 (s, 3H), 2.17 (s, 1H); ^{13}C NMR (125 MHz) δ 159.0, 130.0, 129.6, 128.6, 128.2, 128.0, 127.9, 120.6, 118.9, 113.8, 112.0, 109.0, 99.5, 99.4, 96.0, 95.8, 93.5, 85.4, 79.1, 78.4, 77.9, 77.4, 76.8, 72.9, 72.4, 69.8, 69.0, 67.3, 66.3, 66.1, 65.8, 60.5, 60.4, 60.3, 57.9, 54.9; HRMS (ESI) calc. for $C_{50}H_{64}O_{17}$ $[M+Na]^+$: 959.4045; found 959.4035.

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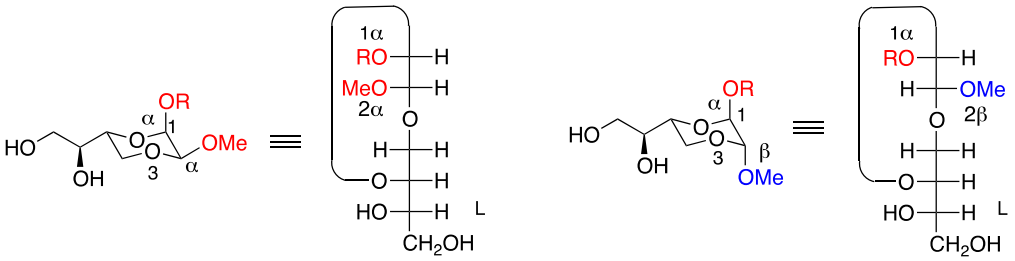

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