A ring closing metathesis strategy for carbapyranosides of xylose and arabinose

Clayton E. Mattis and David R. Mootoo*

*Department of Chemistry, Hunter College and The Graduate Center
of the City University of New York, New York, NY 10016*

Abstract. The synthesis of β -carba- xylo and arabino pyranosides of cholestanol is described. The synthetic strategy, which is analogous to the Postema approach to C-glycosides, centers on the ring closing metathesis of an enol ether-alkene precursor to give a cyclic enol ether that is elaborated to a carba-pyranoside via hydroboration-oxidation on the olefin. The method, which is attractive for its modularity and stereoselectivity, may find wider applications to carba-hexopyranosides and other complex cycloalkyl ether frameworks.

Keywords: glycomimetic, carbasugar, cycloalkyl ether, arabinose, xylose, RCM

Chemical compounds studied in this article

Methyl 2,3-O-isopropylidene-beta-D-ribofuranoside (PubChem CID: 96666); Methyl alpha-D-arabinofuranoside; (PubChem CID: 11389582); cholestanol (PubChem CID: 6665); Methyl (triphenylphosphoranylidene)acetate (PubChem CID: 17453); Tebbe reagent (PubChem CID: 91617563); Grubbs catalyst 2nd generation (PubChem CID: 11147261); Dimethyl sulfide borane (PubChem CID: 9833925)

1. Introduction

Sugar residues comprise the structures of a variety of bioactive natural products and invariably, impact on potency and, or specificity.^{1,2,3,4} Thus, glycodiversification is a popular strategy in the development of carbohydrate-based therapeutics.^{5,6,7,8,9} In this context, nonhydrolyzable sugar analogues such as carbasugars, in which the ring oxygen is replaced with a “CH₂”, have attracted attention as potentially metabolically stable therapeutic agents and for mechanistic studies.¹⁰ The nuanced conformational properties of carbasugars relative

to their parent *O*-glycosides are of additional relevance to structure activity studies.¹¹ Consequently there is much interest in the synthesis and properties of carbasugars. While several methods have been developed for carbasugars in which the pseudo sugar ring is linked to relatively simple alcohol segments or to the primary alcohol oxygen of a sugar, structures with more complex alcohol segments are not as easily accessible because of the challenges associated with fabricating the pseudoglycosidic ether bond.^{10,12,13,14} We envisaged a RCM based approach to carbasugars that may address this issue and which has further appeal because of its modularity. This strategy is illustrated herein in the synthesis of β -carba- arabino and xylo pyranosides of cholestanol. We were drawn to these frameworks because of the existence of the parent sugars in several antitumor steroidal and triterpenoid saponins, of which OSW-1 1, is a notable example (Figure 1).^{15,16,17,18} β -Xylopyranosides also comprise the capsular polysaccharide of fungal pathogens associated with AIDS. Carbaxylosides thereof may be of interest to vaccine development in this area.¹⁹

Figure 1. OSW-1 and carbasugar analogues

Our approach builds on the C-glycoside synthesis from the Postema group, in which the pivotal reaction is the RCM on an enol ether – alkene **5** to give the C1-substituted glycal **4** (Scheme 1).²⁰ Stereoselective hydroboration-oxidation on **5** leads to the 1,2-*trans* / 2,3-*trans*

C-glycoside **3**. An attractive feature of this strategy is the modular assembly from “glycone” and “aglycone” precursors **6** and **7**. Through the use of C-branched sugar acids, this method has been applied to C-di- and higher order C-glycosides. An analogous strategy for carbasugars calls for a RCM on an enoether alkene **10** to give the cyclic enol ether **9**, which differs from **4**, the corresponding enol ether in the C-glycoside synthesis, in that the enol ether oxygen is exocyclic and not endocyclic. However, while RCM’s on enol ether – alkenes like **5** have been successful on a variety of highly substituted substrates, to the best of our knowledge, RCMs on variants like **10**, in which the ether oxygen is exocyclic to the eventual ring, have only been tested on silyl or simple alkyl enol ethers.^{21,22,23,24,25}

Scheme 1. RCM strategies to C- and carba- pyranosides

2. Results and discussion

Synthesis of “glycone” segments. The unsaturated acid precursor **15** for carba-arabinoses was obtained by hydrolysis of the known ester **14**, which in turn was prepared from 5-deoxy-5-iodo-D-ribo-furanoside **13**, via a known procedure (Scheme 2).²⁶ The carba-xyloside precursor **19**, which was previously prepared from L-tartaric, was prepared here via a more concise route, using a strategy similar to that used for **14**.²⁷ Thus, zinc mediated

reductive opening on the 5-deoxy-5-iodo-D-arabinofuranoside **16** afforded enal **17**.^{28,29} Treatment of **17** with methyl(triphenylphosphoranylidene)acetate provided **18** as a single *E*-isomer. Selective hydrogenation of the conjugated alkene followed by hydrolysis of the ester led to **19**.

Scheme 2. Synthesis of "glycone" precursors

The feasibility of the key RCM reaction was tested using cholestanol **20** as a model steroidal segment (Scheme 3). Accordingly, DCC promoted esterification of **20** and alkenoic acids **15** and **19** produced esters **21** and **25** in 98 and 90% yields respectively. Next, olefination on **21** and **25** using the Tebbe and Takai reagents, afforded the respective enol ethers **22** and **26** in 70 and 66% yield.^{30,31} These materials were sensitive to acid and silica gel purification required the presence of triethylamine in the mobile phase. Treatment of **22** and **26** with 10 mole % Grubbs II catalyst in dichloromethane at 60 °C led to the cyclic enol ethers **23** and **27** in 75 and 80% yields respectively. Finally, a hydroboration – oxidation sequence on **23** and **27** afforded the β-carba- arabinoside and xyloside **24** and **28** respectively, as the only observed diastereomers, in 80 and 63% yields. The stereochemistry of **24** and **28** was

assigned from ^1H NMR analysis of their acetates **24-OAc** ($J_{1',2'} = 9.5$, $J_{2',3'} = 9.9$, $J_{3',4'} = 5.1$ Hz) and **28-OAc** ($J_{1',2'} = J_{2',3'} = J_{3',4'} = 9.5 - 9.6$ Hz, see supporting information for selected ^1H NMR assignments). NOEs between $\text{H}_{1'}$ - $\text{H}_{3'}$ and $\text{H}_{2'}$ - $\text{H}_{4'}$ supported the structure of **28-OAc**.

Scheme 3. Synthesis of carba-3 β -cholestan-3-yl pentopyranosides

3. Conclusion

In summary this RCM approach to cholestanol carba-pentopyranosides **24** and **28** illustrates a potentially general strategy for the synthesis of β -carba- arabino and xylo- pyranosides with complex aglycone segments. The methodology, which constitutes a synthesis of stereochemically complex cycloalkyl-ethers, is attractive for its modularity and stereoselectivity. The synthesis of carba-hexopyranosides is an obvious direction for future study and application to other groups of cycloalkyl ether frameworks is also envisaged.

4.1 Synthesis - General

Solvents were purified by standard procedures or used from commercial sources as appropriate. Petroleum ether refers to the fraction of petroleum ether boiling between 40 and 60 °C. Ether refers to diethyl ether. Unless otherwise stated thin layer chromatography (TLC)

was done on 0.25 mm thick precoated silica gel 60 (HF-254, Whatman) aluminium sheets and flash column chromatography (FCC) was performed using Kieselgel 60 (32-63 mesh, Scientific Adsorbents). Elution for FCC usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. Chromatograms were observed under UV (short and long wavelength) light, and/or were visualized by heating plates that were dipped in a solution of ammonium (VI) molybdate tetrahydrate (12.5 g) and cerium (IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulphuric acid (500 mL), or a solution of 20% sulfuric acid in ethanol. NMR spectra were recorded using Varian Unity Plus 500 and Bruker Ultra Shield Plus 600 MHz instruments, in CDCl_3 or C_6D_6 solutions with residual CHCl_3 or C_6H_6 as internal standard (δ_{H} 7.27, 7.16 and δ_{C} 77.2, 128.4 ppm). Optical rotations ($[\alpha]_{\text{D}}$) were recorded using a Jasco P-1020 polarimeter and are given in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ at 589 nm (sodium D-line). Chemical shifts are quoted in ppm relative to tetramethylsilane (δ_{H} 0.00) and coupling constants (J) are given in Hertz. First order approximations are employed throughout. High resolution mass spectrometry was performed on Ultima Micromass Q-TOF or Waters Micromass LCT Premier mass spectrometers.

4.2 (4S, 5R)-4,5-O-isopropylidene-hept-6-enoic acid (15)

Methyl ester **14** (1.21 g, 5.65 mmol) was dissolved in 5:1 THF:H₂O (12 mL) and 3N NaOH (6 mL) was added. The mixture was stirred vigorously for 16 h, then brought to pH 5 by the addition of 1N HCl (15 mL), and extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated in *vacuo*. FCC of the residual oil afforded **15** (1.12 g, 98%): R_{f} = 0.4 (20% EtOAc: petroleum ether); ^1H NMR (600 MHz, CDCl_3) δ 1.38 (s, 3H), 1.49 (s, 3H), 1.76 (m, 2H), 2.46 (m, 1H), 2.55 (m, 1H), 4.19 (m, 1H),

4.57 (t, 1H, J = 6.9 Hz), 5.29 (d, 1H, J = 10.4 Hz), 5.37 (d, 1H, J = 17.2 Hz), 5.85 (m, 1H), 11.51 (bs, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 25.6, 25.8, 28.1, 30.6, 79.5, 108.6, 118.9, 133.6, 179.5; ESIHRMS ($\text{M}+\text{H}$) $^-$ calculated for $\text{C}_{10}\text{H}_{15}\text{O}_4$ 199.0970, found 199.0977.

4.3 (2S,3R)-2,3-bis(benzyloxy)pent-4-enal (**17**)

Activated zinc dust (5.14 g, 79.7 mmol) was added to a solution of **16** (3.62 g, 7.97 mmol) in EtOH (30 mL) 1,2-Dibromoethane (0.2 mL) was introduced and the mixture stirred for 2 h then filtered over a bed of Celite. The filtrate was concentrated in *vacuo* and the residue purified by FCC to give **17** (2.22 g, 94%) as a colorless oil: R_f = 0.6 (20% EtOAc: petroleum ether); ^1H NMR (500 MHz, CDCl_3) δ 3.76 (dd, 1H, J = 1.5, 4.5 Hz), 4.10 (dd, 1H, J = 4.5, 8.0 Hz), 4.48 (ABq, 2H, $\Delta\delta$ = 0.36 ppm, J = 12.0 Hz), 4.62 (ABq, 2H, $\Delta\delta$ = 0.11 ppm, J = 12.0 Hz), 5.29 (m, 2H), 5.87 (m, 1H), 7.19-7.29 (m, 10H), 9.6 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 70.7, 73.5, 79.9, 85.2, 119.9, 127.8, 127.9, 128.1, 128.2, 128.4, 128.5, 133.8, 137.1, 137.5, 202.6; ESILRMS ($\text{M}+\text{Na}$) $^+$ calculated for $\text{C}_{19}\text{H}_{20}\text{O}_3\text{Na}$ 319.1, found 319.1.

4.4 Methyl (4R, 5R, E)-4,5-bis(benzyloxy)hepta-2,6-dienoate (**18**)

A mixture of **17** (2.0 g, 6.76 mmol) and $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ (4.52 g, 13.52 mmol) in dry CH_3CN (40 mL) was heated at reflux for 2 h. After cooling to rt, the mixture was filtered and the filtrate concentrated under reduced pressure. FCC of the residue afforded **18** (2.38 g, 98%) as a colorless oil: R_f = 0.8 (20% EtOAc: petroleum ether); ^1H NMR (500 MHz, CDCl_3) δ 3.78 (s, 3H), 3.96 (dd, 1H, J = 5.5, 6.5 Hz), 4.14 (dt, 1H, J = 1.0, 5.5 Hz), 4.45 (app d, 1H, J = 12.0 Hz), 4.54 (app d, 1H, J = 12.0 Hz), 4.67 (app d, 2H, J = 12.0 Hz), 5.35 (m, 2H), 5.80

(m, 1H), 6.11 (dd, 1H, $J = 1.5, 16.0$ Hz), 6.96 (dd, 1H, $J = 6.0, 16.0$ Hz), 7.30-7.35 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 51.6, 70.7, 71.9, 79.9, 81.7, 119.6, 122.8, 127.6, 127.7, 128.3, 128.4, 134.3, 137.9, 138.2, 145.1, 166.5; ESILRMS ($\text{M}+\text{Na}$) $^+$ calculated for $\text{C}_{22}\text{H}_{24}\text{O}_4\text{Na}$ 375.2, found 375.2.

4.5 (4*R*,5*R*)-4,5-bis(benzyloxy)hept-6-enoic acid (**19**)

Conjugated ester **18** (1.20 g, 3.40 mmol) was dissolved in MeOH (30 mL) and CuCl (40 mg, 0.34 mmol) was added and the reaction mixture cooled to -78°C . NaBH_4 (646 mg, 17.1 mmol) was then added in one portion to the reaction. The brown slurry was stirred vigorously at -78°C until the color changed from brown to black over a period of 2 h. The reaction was then slowly warmed to rt, filtered and concentrated in *vacuo* to give a crude oil. FCC of the residual oil gave the dihydroderivative as a pale yellow oil (1.18 g, 99%): $R_f = 0.7$ (10% EtOAc: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.77 (m, 1H), 1.96 (m, 1H), 2.40 (m, 1H), 3.55 (m, 1H), 3.63 (s, 3H), 3.94 (t, 1H, $J = 6.7$ Hz), 4.43 (app d, 1H, $J = 12.0$ Hz), 4.55 (app d, 1H, $J = 11.4$ Hz), 4.67 (app d, 1H, $J = 12.0$ Hz), 4.78 (app d, 1H, $J = 12.0$ Hz), 5.36 (m, 2H), 5.85 (m, 1H), 7.29-7.36 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 26.2, 30.2, 51.5, 70.6, 73.3, 80.0, 82.6, 119.1, 127.5, 127.6, 127.7, 128.0, 128.3, 128.3, 128.4, 135.0, 138.5, 138.6, 174.1; ESILRMS ($\text{M}+\text{Na}$) $^+$ calculated for $\text{C}_{22}\text{H}_{26}\text{O}_4\text{Na}$ 377.2, found 377.2.

The material from the previous step (1.10 g, 3.11 mmol) was transformed to **19** (1.05 g, 99%) following the hydrolysis procedure that was used for **15**. For **19**: $R_f = 0.6$ (30% EtOAc: petroleum ether). ^1H NMR (500 MHz, CDCl_3) δ 1.67 (m, 1H), 1.86 (m, 1H), 2.33 (m, 2H), 3.48 (m, 1H), 3.85 (t, 1H, $J = 6.7$ Hz), 4.45 (ABq, 2H, $\Delta\delta = 0.36$ ppm, $J = 12.0$ Hz), 4.58

(ABq, 2H, $\Delta\delta = 0.23$ ppm, $J = 11.5$ Hz), 5.27 (m, 2H), 5.74 (m, 1H), 7.20-7.26 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ 23.6, 27.8, 68.3, 71.1, 77.6, 80.2, 117.0, 125.3, 125.4, 125.5, 125.8, 126.1, 132.5, 136.0, 136.1, 175.9; ESILRMS $(\text{M}-\text{H})^-$ calculated for $\text{C}_{21}\text{H}_{23}\text{O}_4$ 339.17, found 339.15.

4.6 **3 β -Cholestanyl (4*S*, 5*R*)-4,5-*O*-isopropylidene-hep-6-enoate (21)**

Cholesterol **21** (972 mg, 2.50 mmol) was added to a mixture of **15** (500 mg, 2.50 mmol), DCC (516 mg, 2.50 mmol) and DMAP (31 mg, 0.25 mmol) in DCM (10 mL). The reaction mixture was stirred for 1 h then diluted with ether and filtered. The filtrate was successively washed with 0.1 N aqueous HCl and brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. FCC of the residue gave ester **21** (1.40 g, 98%): $R_f = 0.7$ (10% EtOAc: petroleum ether); ^1H NMR (600 MHz, C_6D_6) δ 0.47 (t, 1H, $J = 11.8$ Hz), 0.65 (s, 3H, H-18), 0.68 (s, 3H, H-19), 0.78 – 0.95 (m, buried 5H), 0.93 (bd, 6H, $J = 6.5$ Hz, H-26, 27), 1.02 (d, 3H, $J = 6.4$ Hz), 1.15 – 1.63 (m, 22H), 1.28 (s, buried, 3H), 1.47 (s, buried, 3H), 1.68 (m, 1H), 1.74 (m, 1H), 1.86 (m, 2H), 1.98 (bd, 1H, $J = 12.8$ Hz), 2.45 (m, 1H), 2.55 (m, 1H), 4.01 (m, 1H), 4.33 (t, 1H, $J = 6.7$ Hz), 4.93 (m, 1H), 5.00 (d, 1H, $J = 10.4$ Hz), 5.18 (d, 1H, $J = 17.0$ Hz), 5.70 (m, 1H); ^{13}C NMR (150 MHz, C_6D_6) δ 12.1 (two peaks), 18.8, 21.3, 22.6, 22.8, 24.1, 24.3, 25.5, 26.6, 27.8, 28.2, 28.5, 28.7, 31.4, 32.0, 34.2, 34.3, 35.4, 35.5, 36.0, 36.5, 36.7, 39.7, 40.2, 42.7, 44.5, 54.1, 56.4, 56.5, 73.4, 77.3, 79.4, 108.2, 117.3, 134.7, 172.2; ESIHRMS $(\text{M}+\text{H})^+$ calculated for $\text{C}_{37}\text{H}_{63}\text{O}_4$ 571.4726, found 571.4717.

4.7 **(3*R*)-((5*S*,6*R*)-5,6-*O*-isopropylidene-octa-1,7-dien-2-yl)oxy)-cholestane (22)**

Tebbe reagent (5.71 mL, 0.5M in THF) was added under an argon atmosphere, at -78

$^{\circ}\text{C}$, to a mixture of **21** (200 g, 0.35 mmol), pyridine (0.10 mL) and 3:1 anhydrous toluene:THF (6 mL). The reaction mixture was warmed to rt, maintained at this temperature for 1 h, then poured into 1N aqueous NaOH at 0°C . The resulting suspension extracted with ether and the combined organic phase washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. FCC of the crude material over basic alumina afforded **22** (140 mg, 70% based on recovered starting material) as light yellow oil: $R_f = 0.7$ (basic alumina, 10% EtOAc: petroleum ether: 2% TEA); ^1H NMR (500 MHz, C_6D_6) δ 0.64 (dt, 1H, $J = 3.8$, 11.0 Hz), 0.78 (s, 3H), 0.82 (s, 3H), 0.85 – 1.10 (m, 5H), 1.06 (d, 6H, $J = 6.6$ Hz), 1.15 (d, 3H, $J = 6.6$ Hz), 1.20 – 1.80 (m, 19H), 1.42 (s, buried, 3H), 1.62 (s, buried, 3H), 1.74 (m, 2H), 1.90 (m, 2H), 2.01 (m, 2H), 2.13 (m, 2H), 2.43 (m, 1H), 2.64 (m, 1H), 4.08 (m, 1H), 4.17 (s, 1H), 4.23 (m, 1H), 4.25 (s, 1H), 4.51 (t, 1H, $J = 6.4$ Hz), 5.15 (d, 1H, $J = 10.4$ Hz), 5.32 (bd, 1H, $J = 16.6$ Hz), 5.92 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 12.7 (two peaks), 19.4, 21.9, 23.1, 23.4, 24.7, 24.9, 26.2, 28.3, 28.8, 28.9, 29.0, 29.3, 29.6, 32.8, 33.4, 34.8, 36.0, 36.2, 36.6, 37.0, 37.4, 40.3, 40.8, 43.3, 45.2, 54.9, 57.1 (two peaks), 75.8, 78.3, 80.3, 81.9, 108.6, 117.6, 135.9, 161.8; ESIHRMS ($\text{M}+\text{H}$) $^{+}$ calculated for $\text{C}_{38}\text{H}_{65}\text{O}_3$ 569.4934, found 569.4951.

4.8 (3R)-((1S,2R)-1,2-O-isopropylidene-cyclohex-3-ene-4-yl)oxy)-cholestane (23)

Nitrogen was bubbled through a solution of enol ether **22** (200 mg, 0.351 mmol) in anhydrous benzene (12 mL) for 30 min. Grubbs (II) catalyst (104 mg, 0.122 mmol) was then introduced the reaction mixture heated under nitrogen at 60°C for 1 h. Additional catalyst (52 mg, 0.061 mmol) was then added and heating continued for 1 h, at which time, the solvent was removed under reduced pressure. FCC of the residue provided **23** (150 mg, 78%) as a light brown oil: $R_f = 0.6$ (on alumina, 10% EtOAc: petroleum ether: 2% TEA); ^1H NMR

(500 MHz, C₆D₆) δ 0.66 (dt, 1H, J = 3.6, 11.5 Hz), 0.77 (s, 3H), 0.80 (s, 3H), 0.85-1.78 (m, 1H), 0.94-1.0 (m, 27H), 1.06 (d, buried, J = 6.8 Hz, 6H), 1.15, (d, 3H, buried J = 6.6 Hz), 1.55 (s, buried, 3H), 1.71 (s, buried, 3H), 1.91 (m, 1H), 1.97-2.15 (m, 5H), 2.54 (m, 1H), 4.08 (m, 1H), 4.20 (m, 1H), 4.81 (t, 1H, J = 5.1 Hz), 4.95 (d, 1H, J = 3.9 Hz); ¹³C NMR (125 MHz, C₆D₆) δ 12.7, 19.4, 21.9, 23.1, 23.4, 24.7, 24.9, 25.3, 26.6, 27.2, 28.5, 28.8, 29.0, 29.1, 29.3, 32.8, 34.8, 36.0, 36.2, 36.6, 37.0, 37.4, 40.3, 40.8, 43.3, 45.1, 54.9, 57.1 (two peaks), 73.4, 74.2, 75.3, 94.1, 108.7, 157.3.

4.9 β -carba-arabinoside (**24-OAc**)

BH₃.Me₂S (0.20 mL of a 90% solution in dimethyl sulfide) was added at 0 °C, under a nitrogen atmosphere to a solution of **23** (120 mg, 0.222 mmol) in THF (7 mL) and cooled to 0 °C. The mixture was warmed to rt, stirred for an additional 1 h at this temperature, then recooled to 0 °C and treated with a mixture of 3N NaOH (0.5 mL) and 30% aqueous H₂O₂ (0.5 mL) for 30 min. The mixture was then extracted with ether and the organic phase washed with saturated aqueous NaHCO₃ and brine, dried (Na₂SO₄), filtered and evaporated under reduced pressure. FCC of the residue provided **24** as a colorless oil (100 mg, 85%): R_f = 0.6 (20% EtOAc: petroleum ether); ¹H NMR (500 MHz, C₆D₆) δ 0.70 (bt, 1H, J = 11.0 Hz), 0.81 (s, 3H), 0.85 (s, 3H), 0.90-1.84 (m, 30H), 1.05 (d, buried, 6H, J = 6.4 Hz), 1.15 (d, buried, 3H, J = 6.2 Hz), 1.46 (s, buried, 3H), 1.63 (s, buried, 3H), 1.89 (m, 1H), 2.02 (m, 2H), 2.09 (m, 1H), 2.16 (m, 1H), 2.81 (s, 1H), 3.12 (dt, 1H, J = 4.0, 9.8 Hz), 3.38 (m, 1H), 3.93 (dd, 1H, J = 7.5, 9.8 Hz), 4.08 (m, 1H), 4.12 (dd, 1 H, J = 5.0, 7.5 Hz); ¹³C NMR (125 MHz, C₆D₆) δ 12.2, 12.3, 18.8, 21.4, 22.6, 22.8, 24.0, 24.2, 24.4, 24.7, 26.5, 28.2, 28.4, 28.5, 29.0, 30.0, 32.3, 35.3, 35.6, 35.7, 36.0, 36.5, 37.3, 39.7, 40.3, 42.7, 44.9, 54.6, 56.5, 56.6, 73.7,

77.0 (two peaks), 77.8, 80.8, 108.6.

A portion of the material from the previous step (40 mg, 0.07 mmol) was dissolved in ethyl acetate (2.0 mL) and treated with acetic anhydride (0.02 mL, 0.2 mmol) and DMAP (8 mg, 0.07 mmol) for 10 min. CH₃OH (0.1 mL) was then added to the reaction mixture, and the solvent evaporated *in vacuo*. FCC of the residue afforded **24-OAc** as a colorless oil (42 mg, 99%): R_f = 0.7 (15% EtOAc: petroleum ether); $[\alpha]_D^{20}$ -13 (c 0.1, CHCl₃); ¹H NMR (500 MHz, C₆D₆) δ 0.72 (bt, 1H, J = 11.0 Hz), 0.80 (s, 3H, CH₃-18/19), 0.84 (s, 3H, CH₃-18/19), 1.05 (d, buried, 6H, J = 6.5 Hz, CH₃-26,27), 1.13 (d, buried, 3H, J = 6.5 Hz, CH₃-21), 0.94-1.83 (m, 30H), 1.42 (s, buried 3H), 1.80 (s, buried, 3H), 1.85-2.08 (m, 3H), 2.02 (s, buried, 3H), 2.14 (m, 1H), 3.22 (dt, 1H, J = 4.0, 10.2 Hz, H1'), 3.37 (m, 1H, H3), 4.04 (m, 2H, H3', 4'), 5.64 (dd, 1H, J = 7.5, 10.2 Hz, H2'); ¹³C NMR (125 MHz, C₆D₆) δ 12.4 (two peaks), 19.0, 21.0, 21.6, 22.8, 23.1, 23.7, 24.4, 24.6, 26.5, 26.8, 28.2, 28.4, 28.7, 29.3, 30.0, 32.6, 35.7, 35.9 (two peaks), 36.2, 36.7, 37.5, 39.9, 40.5, 42.9, 45.3, 54.8, 56.7, 56.8, 74.1, 75.9, 77.0, 78.3, 79.2, 109.4, 169.3. ESIHRMS (M+Na)⁺ calculated for C₃₈H₆₄O₅Na 623.4651, found 623.4642.

4.10 Cholestanyl (4*R*,5*R*)-4,5-bis(benzyloxy)hept-6-enoate (**25**)

The reaction of acid **19** (1.0 g, 2.94 mmol) and **20** (1.14 g, 2.94 mmol) following the esterification procedure described for the synthesis of **21**, provided **25** (1.80 g, 90%) as a colorless oil: R_f = 0.8 (20% EtOAc: petroleum ether); ¹H NMR (500 MHz, CDCl₃) δ 0.36 (bt, 1H, J = 10.6 Hz), 0.53 (s, 3H), 0.56 (s, 3H), 0.62-0.1.60 (m, 27H), 0.81 (d, buried, 6H, J = 6.2 Hz), 0.90 (d, 3H, J = 6.0 Hz), 1.73-1.88 (m, 4H), 2.04 (m, 1H), 2.40 (m, 2H), 3.50 (m, 1H), 3.78 (t, 1H, J = 6.9 Hz), 4.30 (ABq, 2H, $\delta\Delta$ = 0.26 ppm, J = 12.0 Hz), 4.50 (ABq, 2H,

$\delta\Delta = 0.23$ ppm, $J = 11.5$ Hz), 4.79 (m, 1H), 5.00 (d, 1H, $J = 10.5$ Hz), 5.08 (d, 1H, $J = 17.0$ Hz), 5.65 (m, 1H), 6.97-7.10 (m, 6H), 7.22 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 12.3 (two peaks), 19.0, 21.5, 22.8, 23.0, 24.4, 24.5, 26.8, 28.0, 28.4, 28.7, 28.9, 31.2, 32.3, 34.6, 35.6, 35.7, 36.2, 36.7, 37.0, 39.9, 40.4, 42.9, 44.7, 54.4, 56.7 (two peaks), 70.8, 73.4, 73.5, 80.4, 82.9, 118.5, 127.6 (two peaks), 127.9, 128.1, 128.3, 128.5, 128.6, 135.5, 139.3, 139.6, 172.8; ESIHRMS ($\text{M}+\text{Na}$) $^+$ calculated for $\text{C}_{48}\text{H}_{70}\text{O}_4\text{Na}$ 733.5160, found 733.5172.

4.11 (3R)-((5R,6R)-5,6-bis(benzyloxy)octa-1,7-dien-2-yl)oxy)-3-cholestane (26)

A solution of titanium tetrachloride (0.09 mL, 2 M in CH_2Cl_2 , 0.176 mmol) was added to THF (3 mL) at 0 $^\circ\text{C}$. The mixture was stirred for 30 min at which point TMEDA (0.05 mL, 0.363 mmol) was added in one portion. The resulting yellow-brown suspension was allowed to warm to rt and stirred for 30 min. At this point, zinc dust (0.02 g, 0.03 mmol) and lead (II) chloride (0.3 mg, 1.0 μmol) were added in one portion, and stirring was continued at rt for 10 min. A solution of **25** (110 mg, 0.155 mmol) and dibromomethane (0.05 mL) in THF (1 mL) was then added via cannula to the reaction flask. The mixture was stirred at 60 $^\circ\text{C}$ for 1 h, cooled to 0 $^\circ\text{C}$, then quenched by addition of saturated aqueous K_2CO_3 (2 mL). The resulting mixture was warmed to rt and stirred at this temperature for 30 min, then diluted with ether (2 mL), stirred vigorously for an additional 15 min, and filtered through basic alumina using 3% triethylamine-ether as the eluent. The greenish-blue residue was triturated with diethyl ether (3 – 5 mL) and the combined ethereal extract was concentrated *in vacuo*. FCC over basic alumina afforded **26** as a yellow oil (72 mg, 66%): $R_f = 0.7$ (10% EtOAc: petroleum ether: 1% TEA); ^1H NMR (500 MHz, C_6D_6) δ 0.65 (bt, 1H, $J = 10.8$ Hz), 0.78 (s, 3H), 0.82 (s, 3H), 0.84-1.76 (m, 27H), 1.05 (d, buried, 6H, $J = 6.5$ Hz),

1.15 (d, 3H, $J = 6.5$ Hz), 1.98-2.05 (m 2H), 2.14 (m, 2H), 2.28 (m, 1H), 2.53 (m, 1H), 2.65 (m, 1H), 3.79 (m, 1H), 4.08 (m, 2H), 4.17 (s, 1H), 4.22 (s, 1H), 4.44 (app d, 1H, $J = 12.1$ Hz), 4.70 (m, 2H), 4.91 (app d, 1H, $J = 11.6$ Hz), 5.28 (d, 1H, $J = 10.5$ Hz), 5.36 (d, 1H, $J = 17.4$ Hz), 5.97 (m, 1H), 7.16- 7.36 (m, 6H, $J = 7.1$ Hz), 7.48 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 12.3, 12.4, 19.0, 21.6, 22.8, 23.0, 24.4, 24.6, 27.9, 28.4, 28.7, 29.0, 29.3, 32.4, 34.5, 35.7, 35.9, 36.2, 36.7, 37.1, 39.9, 40.5, 42.9, 45.0, 54.6, 56.7, 56.8, 70.8, 73.3, 75.4, 80.8, 81.5, 82.9, 118.2, 127.5, 127.6 (two peaks), 127.7, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 135.9, 139.4, 139.9, 161.8; ESILRMS $(\text{M}+\text{Na})^+$ calculated $\text{C}_{49}\text{H}_{72}\text{O}_3\text{Na}$ 731.55, found 731.54.

4.12 (3R)-((1R,2R)-1,2-di-O-benzyl-cyclohex-3-ene-4-yl)oxy)-cholestane (27)

Treatment of **26** (65 mg, 0.092 mmol) following the RCM procedure described for the synthesis of **23** provided **27** (50 mg, 80%) as a light brown oil: $R_f = 0.8$ (20% EtOAc: petroleum ether: 1% TEA); ^1H NMR (500 MHz, C_6D_6) δ 0.45 (bt, 1H, $J = 10.5$ Hz), 0.58 (s, 3H), 0.63 (s, 3H), 0.64 – 1.60 (m, 25H), 0.84 (d, buried, 6H, $J = 6.5$ Hz), 0.95 (d, buried, 3H, $J = 6.5$ Hz), 1.66 - 1.83 (m, 4H), 1.93 (m, 3H), 2.10 (m, 1H), 2.34 (m, 1H), 3.68 (m, 1H), 3.93 (m, 1H), 4.27 (bt, 1H, $J = 4.2$ Hz), 4.40 (ABq, 2H, $\Delta\delta = 05$ ppm, $J = 12.0$ Hz), 4.56 (ABq, 2H, $\Delta\delta = 03$ ppm, $J = 12.0$ Hz), 4.86 (d, 1H, $J = 4.0$ Hz), 7.03 – 7.14 (m, 6H), 7.26 (d, 2H, $J = 7.5$ Hz), 7.32 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 12.3, 12.4, 19.0, 21.6, 22.8, 23.0, 24.3, 24.4, 24.6, 26.1, 28.1, 28.4, 28.7, 29.0, 32.4, 34.7, 35.7, 35.9, 36.2, 36.7, 37.1, 39.9, 40.5, 42.9, 44.9, 54.6, 56.7, 56.8, 71.1, 71.2, 75.1, 77.1, 77.5, 94.0, 126.9, 127.5, 127.6, 127.8, 127.9, 128.1, 128.3, 128.5, 128.9, 139.7, 140.1, 156.5; ESILRMS $(\text{M}+\text{Na})^+$ calculated $\text{C}_{47}\text{H}_{68}\text{O}_3\text{Na}$ 703.52, found 703.51

4.13 β -carba-xyloside (**28-OAc**)

Application of the hydroboration oxidation that was used for the synthesis of **24**, to **27** (50 mg, 0.073 mmol) and acetylation of the crude reaction product (following the procedure used for **24-OAc**), afforded β -carba-xyloside **28-OAc** as a colorless oil (43 mg, 80% over two steps): R_f = 0.8 (20% EtOAc: petroleum ether); ^1H NMR (500 MHz, CDCl_3) δ 0.51 (m, 1H), 0.57 (s, 3H, CH_3 -18/19), 0.68 (s, buried 3H, CH_3 -18/19), 0.80 (bd, buried, 6H, J = 6.8 Hz, CH_3 -26, 27), 0.65 – 1.75 (m, 31H), 0.82 (d, buried 3H, J = 6.8 Hz, CH_3 -21), 1.87 (m, 2H), 1.90 (s, 3H), 1.98 (m, 1H), 3.17 (m, 1H, H3), 3.23 (m, 1H, H1'), 3.33 (t, 1H, J = 9.0 Hz, H3'), 3.43 (m, 1H, H4'), 4.58 (m, 3H, $\text{PhCH} \times 3$), 4.80 (app d, 1H, J = 11.0 Hz, PhCH), 4.85 (t, 1H, J = 9.5 Hz, H2'), 7.19-7.25 (m, 10H, ArH); ^{13}C NMR (125 MHz, CDCl_3) δ 12.1, 12.3, 18.7, 21.2, 22.6, 22.8, 23.8, 24.2, 26.4, 27.5, 28.0, 28.3, 28.9, 29.4, 32.1, 35.4, 35.5, 35.7, 35.8, 36.2, 37.1, 39.5, 40.1, 42.6, 45.0, 54.4, 56.3, 56.5, 72.6, 75.1, 76.7, 77.0, 79.0, 80.9, 83.5, 127.5, 127.6, 127.7, 127.8 (two peaks), 128.0, 128.3, 128.4 (two peaks), 138.7, 138.8, 170.0; ESIHRMS ($\text{M}+\text{Na}$) $^+$ calculated $\text{C}_{49}\text{H}_{72}\text{O}_5\text{Na}$ 763.5307, found 763.5277.

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