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**De Novo Asymmetric Synthesis of Digitoxin Based
Carbohydrate Libraries**

Wenjun Xin

**Thesis submitted to the
Eberly College of Arts and Sciences
at West Virginia University
in partial fulfillment of the requirements
for the degree of**

**Master of Science
In
Organic Chemistry**

**George A. O'Doherty, Ph.D., Chair
Björn C. Söderberg, Ph.D.
Kung K. Wang, Ph.D.**

C. Eugene Bennett Department of Chemistry

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ABSTRACT

De Novo Asymmetric Synthesis of Digitoxin Based Carbohydrate Libraries

Wenjun Xin

The enantioselective syntheses of digitoxigen 2,6-dideoxy- β -L-ribo-hexopyranoside, its analogues and digitoxin monosaccharide analogues have been achieved. Key to this approach is the iterative application of the palladium-catalyzed glycosylation reaction, reductive 1,3-transposition and diastereoselective dihydroxylation. Anticancer tests showed that these analogues have even better anticancer activities.

DEDICATED TO

My mother Suzhen Ye and my father Dingyun Xin

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List of Abbreviations

Ac	Acetyl
Boc	<i>N</i> -tert-butoxycarbonyl
DBA	trans,trans-dibenzylideneacetone
DEAD	Diethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	<i>N, N</i> -Dimethylformamide
Et	Ethyl
EtOAc	Ethyl acetate
IR	Infrared
Me	Methyl
MHz	megahertz
mmol	millimole(s)
MS	Mass spectrum
NBS	<i>N</i> -Bromosuccinimide
NBSH	<i>o</i> -Nitrobenzenesulfonylhydrazide
NMR	Nuclear magnetic resonance
NMO	<i>N</i> -methylmorpholine
Ph	Phenyl
PMBz	<i>para</i> -Methoxybenzyl
PNBz	<i>p</i> -nitrobenzene

rt	room temperature
THF	tetrahydrofuran
TLC	Thin layer chromatography

Appendix

List of ^1H and ^{13}C NMR Spectra

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CHAPTER I

Asymmetric Synthesis of Digitoxin Sugar Analogues

1.1 Introduction

Digitoxin (**1**) (Figure 1) is a cardiac glycoside which can be extracted from the leaves of *Digitalis purpurea* (purple foxglove). It has long been used to slow the heart rate while increasing the contractility of the heart muscle (inotropic activity). It has been widely prescribed for congestive heart failure and cardiac arrhythmia for over 200 years. Oligosaccharides bearing deoxysugars have played a pivotal role in many pharmacologically important antibiotics, vaccines and antitumor agents.¹ Digitoxin has also been shown to possess potential anticancer activities.² The natural product digitoxin contains three D digitose sugars. Structurally, digitoxin is the combination of two natural products, the aglycon digitoxigenin (**2**)³ and the trisaccharide digoxose (**3**).⁴

Figure 1. Digitoxin, digitoxigenin and digoxose.

1.2 Previous approaches to digitoxin

There have been two syntheses of digitoxin from the aglycone, a carbohydrate approach by Wiesner (~20 steps from a protected 2-deoxy sugar) and a de novo approach by McDonald (20 steps from TMS-acetylene).⁵ There have been 8 syntheses of digitoxigenin.⁶

The first synthesis of digitoxin from digitoxigenin was accomplished by Wiesner's group (Scheme 1). The stereochemistry of the digitoxin glycoside bond was controlled by a 1,3-participation of PMBz ester (**4**). The PMBz ester (**4**) was derived from a 1,3-participation of *N*-methylurethane (**5**) which was derived from bromide (**6**) in 7 steps. In turn, bromide (**6**) was prepared from methyl α -D-glucoside.

Scheme 1. Retrosynthetic analysis of Wiesner's synthesis.

McDonald's synthesis (Scheme 2) achieved the product digitoxin by the acid catalyzed glycosylation of digitoxigenin and trisaccharide glycal (7). The trisaccharide glycal (7) was derived from 6-deoxy-D-ribofuranose (8) and alkynyl alcohol (9) through an acid catalyzed glycosylation. Furthermore, these two compounds were derived from alkynyl enone (10) in seven and five steps, respectively.

Scheme 2. Retrosynthetic analysis of McDonald's synthesis.

1.3 O'Doherty's synthesis of digitoxin

O'Doherty's group also prepared digitoxin via a de novo strategy, which could also be used to prepare various digitoxin analogues (Scheme 3).⁷ Due to the missing stereo-control element at the 2-position, it is particularly difficult to synthesize β-2-deoxy-glycosides. They successfully addressed the 2-deoxy-β-glycosides using a diastereoselective palladium-catalyzed glycosylation reaction. Digitoxin was derived

from digitoxin disaccharide (**11**), which was produced from a corresponding digitoxin monosaccharide. This digitoxin monosaccharide was prepared from digitoxigenin and Boc-pyranone (**13 β**) via a palladium-catalyzed glycosylation reaction. Boc-pyranone (**13 β**) was derived from the commercially available compound acylfuran (**14**). Comparing with the previous approaches, the O'Doherty's approach is a more efficient route in terms of number of steps and stereocontrol. In addition, this route is more amenable.

Scheme 3. Retrosynthetic analysis of O'Doherty's synthesis.

1.4 Total synthesis of digitoxigen 2,6- β -L-ribo-hexopyranoside and its analogues

1.4.1 Background

Previously, O'Doherty's group successfully synthesized and tested the natural compound digitoxin and its mono- and di-saccharide analogues as antitumor agents. The biological tests of these compounds from NCI (National Cancer Institute) showed that in

general the digitoxin monosaccharide is more active than digitoxin or the digitoxin disaccharide in cancer cell cytotoxicity (Figure 2).⁸ To further understand this phenomenon, we were interested in synthesizing several unnatural L-sugar digitoxin analogues (figure 3) with the particular goal of finding the most active anticancer agent.

Figure 2. Anticancer tests results of digitoxin mono-, di- and tri-saccharide.

Figure 3. The L-sugar digitoxin mono-, di- and tri-saccharide.

1.4.2 Retrosynthetic analysis

A similar approach was planned to synthesize these L-sugar digitoxin diastereomeric analogues (Scheme 4). The final product, L-sugar digitoxin trisaccharide could be derived from L-sugar digitoxin disaccharide through a palladium-catalyzed glycosylation reaction. The disaccharide could also be prepared from the L-sugar digitoxin monosaccharide via a palladium-catalyzed glycosylation reaction. The monosaccharide could be produced from the palladium-catalyzed glycosylation of digitoxigenin and L-Boc-pyranone (**18 β**). From previous work, it was known that the Boc-pyranone (**18 β**) could be derived from acylfuran.

Scheme 4. Retrosynthetic analysis of L-sugar digitoxin.

1.4.3 Synthesis of Boc-pyranones

According to the O'Doherty group's previous approach, acylfuran (**14**) could be enantioselectively reduced (Noyori (S,S), >95% ee)⁹ to furan alcohol (**19**) and converted into the L-sugar pyranone (**20**) and then diastereoselectively acylated into the α -Boc-pyranone (**18α**) and β -Boc-pyranone (**18β**).¹⁰ Alternatively, using the Noyori (R,R) catalyst would provide the enantiomeric furan alcohol (**21**) and similarly lead to the two D-sugar diastereomers (**13α**) and (**13β**). When the Boc-protection was performed at -78 °C, the α : β ratio is 3:1. When the Boc-protection was performed at elevated temperature ((Boc)₂O/NaOAc in benzene at 80 °C), a switch in the diastereoselectivity occurred (Scheme 5). The ratio of β -pyranone to α -pyranone at these higher temperatures could be as high as 1.3:1.

Scheme 5. Enantio- and diastereoselective pyranone synthesis.

1.4.4 Synthesis of digitoxigenin 2,6-dideoxy- β -L-ribo-hexopyranoside

Starting from β -Boc-pyranone (**18 β**), a palladium-catalyzed glycosylation reaction was performed between digitoxigenin (**2**) and Boc-pyranone (**18 β**) which gave pyranone (**23**) in 85% yield. Pyranone (**23**) was then reduced with NaBH₄ to obtain allylic alcohol (**24**) in 81% yield. The reductive rearrangement gave olefin (**25**) in 98% yield. The dihydroxylation of olefin (**25**) achieved the L-sugar digitoxin monosaccharide (**15**) in 93% yield (Scheme 6).

Scheme 6. Synthesis of digitoxigenin 2,6-dideoxy- β -L-ribo-hexopyranoside.

1.4.5 Synthesis of digitoxigenin 2,6-dideoxy- β -L-ribo-hexopyranoside analogues

From the L-sugar digitoxin monosaccharide **(15)**, digitoxigenin 2,6-dideoxy- β -L-glucopyranoside **(26)** was synthesized (Figure 4).

Figure 4. Digitoxin monosaccharide sugar analogues.

digitoxigen 2,6-dideoxy-β-L-gluco-hexopyranoside

(26)

digitoxigen 2,3-dideoxy-α-L-rhamno-hexopyranoside

(27)

digitoxigen α-L-rhamno-hexopyranoside

(28)

digitoxigen 2,3-dideoxy-2,3-dihydro-
α-L-rhamno-hexopyranoside

(29)

Mitsunobu reaction¹¹ of the L-sugar digitoxin monosaccharide (**15**) gave the C-3 inverted ester (**30**) in 85% yield. Hydrolysis of (**30**) with MeOH/Et₃N provided the diastereomeric monosaccharide digitoxigen 2,6-dideoxy-β-L-gluco-hexopyranoside (**26**) in good yield (Scheme 7).

Scheme 7. Synthesis of digitoxigen 2,6-dideoxy- β -L-gluco-hexopyranoside.

The palladium-catalyzed glycosylation reaction of digitoxigenin (**2**) and α -Boc-pyranone (**18a**) gave pyranone (**31**) in good yield. Then pyranone (**31**) was reduced with NaBH_4 to obtain analogue digitoxigen 2,3-dideoxy- α -L-rhamno-hexopyranoside (**27**) in 83% yield. Dihydroxylation of (**27**) gave the rhamno analogue (**28**). Reductive rearrangement of (**27**) gave C-2/C-3 dideoxy analogue (**29**) in 96% yield (Scheme 8).

Scheme 8. Synthesis of digitoxigen rhamno analogues.

1.4.6 Anticancer tests results of digitoxin monosaccharide sugar analogues

After having successfully synthesized several L-sugar digitoxin monosaccharide analogues, these compounds were sent for anticancer testing.¹² Tests results showed that these analogues have excellent anticancer activities. In fact, analogue **(28)** shows the best anticancer activity comparing with other analogues. For instance, **(28)** is 13.5 times more active than digitoxin in killing HT-29 cancer cell lines. Analogues **(15)**, **(26)**, **(29)** also

show much better activities comparing with digitoxin although the difference isn't as great (Figure 5).

Figure 5. Anticancer tests results of digitoxin monosaccharide sugar analogues.

WX-027: (15) WX-033: (26) WX-053: (27) WX-055: (29) WX-057: (28)

Dig: digitoxin (1)

1.4.7 Synthesis of digitoxigen 2,6-dideoxy- α -D-ribo-hexopyranoside analogues

Starting with Boc-pyraone (**13a**), a number of D-sugar digitoxin monosaccharide analogues have been achieved (Scheme 9). The palladium-catalyzed glycosylation reaction of digitoxigenin (**2**) and α -Boc-pyranone (**13a**) gave pyranone (**32**) in good yield. Then pyranone (**32**) was reduced with NaBH₄ to obtain the digitoxigen 2,3-dideoxy- α -D-rhamno-hexopyranoside (**33**) in 90% yield. Reductive rearrangement of (**33**) gave the dideoxy analogue (**34**) in 95% yield.

Scheme 9. Synthesis of digitoxigenin 2,6-dideoxy- α -D-ribo-hexopyranoside analogues.

1.4.8 Synthetic effort towards the L- β -glycoside of desacetoxy-oleandrin

Oleandrin (35) (Figure 6) is another cardiac glycoside which can be extracted from the leaves of one of the very poisonous plants oleander. The structures of digitoxin monosaccharide and β -oleandrin are very similar, with the addition of a C-16 acetoxy group and a C-3 methylated D-2-deoxy glucose sugar. We are interested in synthesizing an L-sugar β -desacetoxy-oleandrin from digitoxin monosaccharide and comparing their anticancer activities.

Figure 6. Oleandrin, the L- β -glycoside of desacetoxy-oleandrin and digitoxigen 2,6-dideoxy- β -L-ribo-hexopyranoside.

The synthesis of digitoxigen 2,6-dideoxy- β -L-gluco-hexopyranoside (**26**) has already been achieved in good yield. Thus the synthesis of analogue (**36**) began with the direct methylation of (**26**)¹³ to selectively prepare the L- β -glycoside of desacetoxy-oleandrin (**36**) (Scheme 10).

Scheme 10. Synthetic effort towards the L- β -glycoside of desacetoxy-oleandrin.

However, this methylation reaction was not very selective. The highest yield was 25% by treating β -2,6-dideoxy-L-gluco-digitoxin-monosaccharide (**26**) with MeI and Ag₂O, which yielded a mixture of regioisomers.

1.4.9 Conclusion

A highly stereoselective route to anticancer compounds digitoxin and its analogues has been developed. This approach has been successfully applied to the synthesis of L-sugar digitoxin monosaccharide and several analogues. Anticancer tests showed that these analogues have excellent anticancer activities.

Chapter II

Experimental Section

General Methods and Materials.

^1H and ^{13}C NMR spectra were recorded on Jeol (270 MHz) and Varian VXR-600 (600 MHz) spectrometers. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl_3 (δ 7.26 ppm) for ^1H NMR and CDCl_3 (δ 77.0 ppm) for ^{13}C NMR. Infrared (IR) spectra were obtained on a Prospect MIDAC FT-IR spectrometer. Optical rotations were measured with a Jasco DIP-370 digital polarimeter in the solvent specified. Melting points were determined with Electrothermal Mel-Temp apparatus and are uncorrected. Flash column chromatography was performed on ICN reagent 60 (60-200 mesh) silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates (Whatman K6F 60Å, F_{254}) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. R_f values are obtained by elution in the stated solvent ratios (v/v). Ether, THF, methylene chloride and triethylamine were dried by passing through activated alumina (8 x 14 meshes) column with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Melting points are uncorrected. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven/flamed-dried glassware and standard syringe/septa techniques.

(S)-1-(2-Furyl)-ethanol (19**):**¹⁴

To a 25 ml flask was added furan ketone **14** (22.0 g, 7.27 mmol), CH₂Cl₂ (101.8 mL), formic acid/triethylamine (1:1, 110.6 mL) and Noyori asymmetric transfer hydrogenation catalyst (R)-Ru(η^6 -mesitylene)-(S,S)-TsDPEN (582 mg, 0.5 mol%). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 500 ml). The combined organic layers were washed with saturated NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 30% ether/hexanes to give furan alcohol **19** (21.3 g, 192 mmol, 96%): colorless oil; R_f (30% EtOAc/hexanes) = 0.41; $[\alpha]_D^{25} = +21$ ($c = 1.0$, CH₂Cl₂); IR (thin film, cm⁻¹) 3360, 2980, 2935, 1668, 1505, 1467, 1370, 1229, 1149, 1007, 877, 734; ¹H NMR (600 MHz CDCl₃) δ 7.30 (d, $J = 1.8$, 1H), 6.26 (dd, $J = 3.0, 1.8$ Hz, 1H), 6.15 (d, $J = 3.0$, 1H), 4.78 (dq, $J = 6.6, 6.6$ Hz, 1H), 3.11 (s, 1H), 1.46 (d, $J = 6.6$ Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 157.7, 141.6, 109.9, 104.9, 63.3, 21.1.

(2S)-6-Hydroxy-2-methyl-2H-Pyran-3 (6H)-one (20):¹⁴

Furan alcohol **19** (21.0 g, 189 mmol), THF (466 mL), and H₂O (155 mL) were added to a round bottom flask and cooled to 0 °C. Solid NaHCO₃ (33.4 g, 378 mmol), NaOAc•3H₂O (25.6 g, 189 mmol), and NBS (33.2 g, 189 mmol) were added to the solution and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated NaHCO₃ (400 mL), extracted (3 x 400 mL) with Et₂O, dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel chromatography eluting with 25% EtOAc/hexanes to give pyranone **20** (21.8 g, 172 mmol, 91%): R_f (60% EtOAc/hexanes) = 0.29; [α]_D²⁵ = +44 (c = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3381, 2988, 2942, 1692, 1447, 1373, 1232, 1021, 937; ¹H NMR (600 MHz, CDCl₃) major isomer δ 6.82 (dd, *J* = 10.2, 3.0 Hz, 1H), 5.96 (d, *J* = 10.2, 1H), 5.48 (d, *J* = 3.0 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) major isomer δ 197.6, 145.3, 126.6, 87.2, 74.8, 15.1.

(2S, 6S)-tert-butyl -5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (18):¹⁴

A benzene solution (288 mL) of pyronone alcohol **20** (15.1 g, 118 mmol) was added sodium acetate (10.7 g, 130 mmol) and (Boc)₂O (38.7 g, 117 mmol). The mixture was heated to 80 °C for 1 h. Then it was cooled down and quenched with 200 mL ice cold saturated NaHCO₃, extracted with Et₂O (3 x 500 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc/hexanes to give 22.0 g (96.8 mmol, 82%) of two diastereomers of Boc-protected pyranone **18a** and **18b** in 1:1.3: R_f(20% Et₂O/hexane) = 0.58; [α]²⁵_D = + 98 (c = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2984, 2942, 1752, 1703, 1371, 1273, 1254, 1153, 938, 838; ¹H NMR (600 MHz, CDCl₃) δ 6.78 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.22 (d, *J* = 3.6 Hz, 1H), 6.09 (d, *J* = 10.2 Hz, 1H), 4.53 (q, *J* = 6.6 Hz, 1H), 1.40 (s, 9H), 1.28 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 195.5, 151.7, 140.9, 128.2, 89.1, 83.3, 72.0, 27.5, 15.1; CIHRMS Calculated for [C₁₁H₁₆O₅Na⁺]: 251.0890, Found: 251.0883.

(2S, 6S)-2-Digitoxigenoxy-6-methyl-2H-pyran-3(6H)-one (23):

A CH₂Cl₂/THF solution (19 mL, 4:1 V/V) of Boc-pyranone **18β** (1.29 g, 5.65 mmol) and digitoxigenin (3.17 g, 8.48 mmol) was cooled to 0 °C. A CH₂Cl₂ (2.5 mL) solution of Pd₂(DBA)₃•CHCl₃ (170 mg, 2.5 mol%) and PPh₃ (171 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 8 hours and was quenched with 20 mL of satd. aq NaHCO₃, extracted (3 x 50 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 40% EtOAc/hexanes to give **23** (2.32 g, 4.80 mmol, 85%) as a white solid: R_f (40% EtOAc/hexanes) = 0.17; mp: 211-212 °C; [α]_D²⁵ = + 5.28 (c = 1.0, CHCl₃); IR (thin film, cm⁻¹) 3505, 2938, 2875, 2376, 2311, 1780, 1741, 1698, 1620, 1448, 1374, 1164, 1144, 1053, 1028, 730; ¹H NMR (600 MHz, CDCl₃) δ 6.87 (dd, J = 10.4, 1.8 Hz, 1H), 6.12 (dd, J = 10.2, 1.2 Hz, 1H), 5.87 (m, 1H), 5.39 (dd, J = 2.4, 1.8 Hz, 1H), 4.99 (dd, J = 18.0, 1.8 Hz, 1H), 4.81 (dd, J = 18.0, 1.8 Hz, 1H), 4.18 (m, 2H), 2.78 (dd, J = 9.6, 6.0 Hz, 1H), 2.20-2.09 (m, 3H), 1.45 (d, J = 6.6 Hz, 3H), 1.92-1.16 (m, 18H), 0.95 (s, 3H), 0.88 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 197.0, 174.4, 174.3, 147.7, 128.2, 117.8, 93.9, 85.6, 75.2, 73.4, 73.3, 50.9, 49.6, 41.9, 40.0, 36.3, 35.8, 35.2, 33.2, 32.0, 30.0, 26.9, 26.4, 24.4, 23.7, 21.3, 21.2, 17.0, 15.8; ESIHRMS Calcd for [C₂₉H₄₀O₆Na⁺]: 507.2717, Found 507.2722.

(2S, 6S)-2-(Digitoxigenoxy)-2,5-dihydro-6-methyl-2H-pyran-5-ol (24**):**

A CH_2Cl_2 (9.4 mL) solution of enone **23** (2.32 g, 4.80 mmol) and CeCl_3 in MeOH solution (0.4 M, 9.4 mL) was cooled to $-78\text{ }^\circ\text{C}$. NaBH_4 (162 mg, 4.80 mmol) was added and the reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 3 h. The reaction mixture was diluted with ether (60 mL) and was quenched with 30 mL of satd. aq NaHCO_3 , extracted (3 x 60 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 55% EtOAc/hexanes to give allylic alcohols **24a/b** (1.89 g, 3.88 mmol, 81%) as a white solid (diastereometric ratio **24a**:**24b** = 1.5:1, inseparable by silica gel chromatography): R_f (60% EtOAc/hexanes) = 0.22; IR (thin film, cm^{-1}) 3449, 2934, 2871, 1779, 1737, 1619, 1448, 1380, 1320, 1169, 1136, 1051, 1026, 1006, 961, 751; ^1H NMR (600 MHz, CDCl_3) **24a** δ 6.12 (ddd, J = 10.2, 4.8, 1.2 Hz, 1H), 5.86 (m, 1H), 5.79 (d, J = 10.2 Hz, 1H), 5.07 (m, 1H), 4.97 (dd, J = 18.0, 1.2 Hz, 1H), 4.80 (dd, J = 18.0, 1.8 Hz, 1H), 4.12 (dd, J = 4.2, 1.8 Hz, 1H), 4.11 (s, 1H), 3.70 (qd, J = 6.6, 2.4 Hz, 1H), 3.60 (br, 1H), 2.77 (dd, J = 9.6, 6.0 Hz, 1H), 2.25-2.05 (m, 3H), 1.30 (d, J = 6.0 Hz, 3H), 1.80-1.05 (m, 18H), 0.93 (s, 3H), 0.86 (s, 3H); **24b** δ 5.91 (ddd, J = 10.2, 2.4, 2.4 Hz, 1H), 5.86 (m, 1H), 5.74 (ddd, J = 10.2, 1.2, 1.2 Hz, 1H), 5.13 (ddd, J = 1.8, 1.8, 1.8 Hz, 1H), 4.98 (dd, J = 18.0, 1.2 Hz, 1H), 4.80 (dd, J = 18.0, 1.2 Hz, 1H), 4.09 (m, 1H), 4.11 (s, 1H), 3.91 (br, 1H), 3.59 (dq, J = 6.6, 6.6 Hz, 1H), 2.77 (dd, J = 9.6, 6.0 Hz, 1H), 2.25-2.05 (m, 3H), 1.33 (d, J = 6.0 Hz,

3H), 1.80-1.05 (m, 18H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) **24a** δ 174.64, 174.60, 131.8, 131.0, 117.6, 96.0, 85.3, 74.3, 73.1, 71.4, 64.6, 50.9, 49.6, 41.8, 40.0, 36.4, 35.7, 35.1, 33.0, 32.1, 29.9, 26.9 (2C), 26.4, 23.6, 21.2, 21.1, 16.7, 15.7; **24b** δ 174.67, 174.60, 131.3, 129.8, 117.6, 94.8, 85.4, 73.4, 73.1, 72.3, 68.5, 50.9, 49.6, 41.8, 40.0, 36.3, 35.7, 35.1, 33.1, 32.0, 29.9, 26.8 (2C), 26.6, 23.6, 21.2, 21.1, 18.3, 15.7; ESIHRMS Calcd for $[\text{C}_{29}\text{H}_{42}\text{O}_6\text{Na}^+]$: 509.2879, Found 509.2879.

(2S, 6S)-2-(Digitoxigenoxy)-3,6-dihydro-6-methyl-2H-pyran (25):

A flask was charged with dry *N*-methyl morpholine (NMM) 5.76 mL, triphenyl phosphine (3.36 g, 12.8 mmol) and was cooled to -30 °C under Ar atmosphere. Diethylazodicarboxylate (1.83 mL, 11.7 mmol) was added and the reaction was stirred for 5 min, allylic alcohol **24a/b** (1.89 g, 3.88 mmol) was added in a 1 M solution of NMM and the reaction mixture was stirred for 10 min, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (2.36 g, 12.8 mmol). The reaction was stirred at -30 °C for 6h and was monitored by TLC, upon consumption of starting material, warm up to room temperature and stirred for another 1 h. The reaction mixture was diluted with ether (60 mL) and was quenched with 60 mL of satd. aq NaHCO₃, extracted (3 x 60 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexanes to give product **25** (1.80 g, 3.82 mmol, 98%) as a white solid: *R*_f (30% EtOAc/hexanes) = 0.20; mp: 157-158 °C; [α]_D²⁵ = +23.3 (*c* = 1.1, CHCl₃); IR (thin film, cm⁻¹) 3301, 2933, 2871, 1778, 1742, 1620, 1447, 1378, 1221, 1157, 1133, 1097, 1065, 1024, 974, 909, 782. ¹H NMR (600 MHz, CDCl₃) δ 5.86 (m, 1H), 5.66 (dddd, *J* = 10.2, 4.8, 2.4, 2.4 Hz, 1H), 5.55 (dddd, *J* = 10.2, 2.4, 1.2, 1.2 Hz, 1H), 4.99 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.70 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.06 (m, 1H), 4.29 (m, 1H), 2.76 (m, 1H), 2.24-2.04 (m, 4H), 1.90-1.08 (m, 19H), 1.24 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 3H), 0.86

(s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 174.6, 174.5, 131.1, 123.0, 117.6, 96.7, 85.6, 73.4, 72.1, 70.7, 50.9, 49.6, 41.9, 40.1, 36.3, 35.7, 35.2, 33.1, 31.6, 30.2, 29.8, 26.9, 26.7, 26.6, 23.6, 21.4, 21.1, 21.0, 15.8; ESIHRMS Calcd for $[\text{C}_{29}\text{H}_{42}\text{O}_5\text{Na}^+]$: 493.2929, Found 493.2930.

Digitoxigen 2,6-dideoxy- β -L-ribo-hexopyranoside (15):

To a *t*-BuOH/acetone (4 mL) solution of olefin **25** (1.80 g, 3.82 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide/water (2.4 mL). Crystalline OsO₄ (9.6 mg, 1 mol %) was added and the reaction was stirred for 4 h. The reaction was quenched with adding EtOAc and satd. NaHCO₃. The organic layer was separated and concentrated. It was purified by a silica gel column using 90% EtOAc/hexanes. Pure fractions were combined, concentrated, and crystallized from acetone/hexanes to afford alcohol **15** (2.07 g, 3.55 mmol, 93%) as a white solid: *R*_f (EtOAc) = 0.42; [α]_D²⁵ = +30.2 (*c* = 1.0, MeOH); mp: 188-189 °C; IR (thin film, cm⁻¹) 3440, 2934, 2856, 2193, 1736, 1619, 1448, 1380, 1160, 1134, 1065, 1026, 1002, 949, 906, 824; ¹H NMR (600 MHz, CDCl₃) δ 5.86 (m, 1H), 4.98 (d, *J* = 18.0 Hz, 1H), 4.86 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.80 (d, *J* = 18.0 Hz, 1H), 4.11 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.02 (m, 1H), 3.71 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.32 (m, 1H), 2.77 (m, 1H), 2.56 (s, 1H), 2.39 (s, 1H), 2.20-2.00 (m, 4H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.90-1.10 (m, 19H), 0.91 (s, 3H), 0.86 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 175.0, 174.9, 117.8, 95.6, 85.8, 73.8, 73.2, 72.9, 69.5, 68.5, 51.2, 49.8, 42.0, 40.2, 38.5, 36.5, 35.9, 35.4, 33.4, 32.3, 30.2, 27.1, 26.6, 24.6, 23.8, 21.5, 21.4, 18.4, 16.0; ESIHRMS Calcd for [C₂₉H₄₄O₇Na⁺]: 527.2979, Found 527.2985.

(2S, 6S)-2-methyl-3-hydroxy-6-Digitoxigenoxy-2H-pyran-4-nitrobenzoate (30):

A THF (0.6 mL) solution of diol **15** (50 mg, 0.1 mmol) at 0 °C was added PPh₃ (41 mg, 0.16 mmol) and *p*-nitrobenzoic acid (40 mg, 0.2 mmol), DEAD (27.5 mg, 0.16 mmol) in THF (0.2 mL) was added drop wise. The reaction mixture was warmed up to room temperature and stirred for 5 h. The reaction mixture was diluted with 5 mL EtOAc and quenched with 4 mL of satd. NaHCO₃, extracted with Et₂O (3 x 5 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 60% EtOAc/hexanes to afford **30** (56 mg, 0.85 mmol, 85%) as a white solid: *R*_f (EtOAc) = 0.75; [α]_D²⁵ = +8.68 (*c* = 0.5, CHCl₃); mp: 188-189 °C; IR (thin film, cm⁻¹) 3484, 2931, 2364, 2197, 2168, 2038, 1730, 1529, 1448, 1346, 1278, 1103, 1069, 1026, 989, 908; ¹H NMR (600 MHz, CDCl₃) δ 8.25 (m, 4H), 5.86 (m, 1H), 5.10 (m, 1H), 4.98 (d, *J* = 18.0 Hz, 1H), 4.80 (d, *J* = 18.0 Hz, 1H), 4.66 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.07 (m, 1H), 3.48 (m, 1H), 3.40 (dq, *J* = 9.0, 6.0 Hz, 1H), 2.77 (m, 1H), 2.39 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.20-2.05 (m, 4H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.90-1.10 (m, 19H), 0.93 (s, 1H), 0.91 (s, 3H), 0.86 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 174.5, 174.45, 131.1, 123.0, 117.7, 96.7 (2C), 85.6, 73.4, 73.1, 72.1, 70.7, 62.2 (2C), 51.0, 50.9, 49.6, 41.9, 40.1, 36.3, 35.7, 35.2, 33.2, 32.2, 31.6, 30.0, 26.9, 26.4, 24.3, 23.6, 21.3, 21.2, 21.1, 15.8, 14.4 (2C); ESIHRMS Calcd for [C₃₆H₄₇NO₁₀Na⁺]: 653.7591, Found 653.7591.

Digitoxigen 2,6-dideoxy- β -L-gluco-hexopyranoside (26**):**

A MeOH (0.2 mL) solution of **30** (28 mg, 42 μ mol) at room temperature was added Et₃N (12.6 mg, 126 μ mol) and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with 5 mL EtOAc and quenched with 4 mL of Satd. NaHCO₃, extracted (3x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. It was purified by a silica gel column using 90% EtOAc/hexanes. Pure fractions were combined, concentrated, and crystallized from acetone/hexanes to afford **26** (20.1 mg, 40 μ mol, 95%) as a white solid: R_f (EtOAc) = 0.42; $[\alpha]_D^{25} = +30.2$ ($c = 1.0$, MeOH); mp: 255-256 °C; IR (thin film, cm⁻¹) 3453, 2940, 2856, 2173, 1969, 1775, 1742, 1623, 1449, 1454, 1378, 1160, 1067, 1024, 951, 822; ¹H NMR (600 MHz, CDCl₃) δ 5.86 (m, 1H), 4.98 (dd, $J = 18.0, 1.8$ Hz, 1H), 4.80 (dd, $J = 18.0, 1.8$ Hz, 1H), 4.53 (dd, $J = 9.6, 1.8$ Hz, 1H), 4.02 (m, 1H), 3.58 (dq, $J = 9.0, 6.0$ Hz, 1H), 3.24 (m, 1H), 3.09 (m, 1H), 2.77 (m, 1H), 2.33 (s, 1H), 2.20-2.00 (m, 4H), 1.26 (d, $J = 6.0$ Hz, 3H), 1.90-1.10 (m, 21H), 0.92 (s, 3H), 0.86 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 174.65, 174.61, 117.6, 97.3, 85.4, 77.5, 73.5, 72.9, 71.8, 71.6, 50.9, 49.6, 41.8, 40.0, 39.5, 36.2, 35.7, 35.1, 33.1, 32.0, 29.9, 26.9, 26.4, 24.4, 23.6, 21.2, 21.1, 17.8, 15.8; ESIHRMS Calcd for [C₂₉H₄₄O₇Na⁺]: 527.2979, Found 527.2985.

(2R, 6S)-2-Digitoxigenoxy-6-methyl-2H-pyran-3(6H)-one (31):

A CH₂Cl₂/THF solution (1.5 mL, 4:1 V/V) of Boc-pyranone **18a** (316 mg, 1.39 mmol) and digitoxigenin (260 mg, 0.69 mmol) was cooled to 0 °C. A CH₂Cl₂ (0.24 mL) solution of Pd₂(DBA)₃•CHCl₃ (17 mg, 2.5 mol%) and PPh₃ (17 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 8 hours and was quenched with 4 mL of satd aq NaHCO₃, extracted (3 x 10 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 40% EtOAc/hexanes to give **31** (287 mg, 0.59 mmol, 86%) as a white solid: R_f (40% EtOAc/hexanes) = 0.17; mp: 145-146 °C ; [α]_D²⁵ = + 61.4 (c = 1.0, MeOH); IR (thin film, cm⁻¹) 3481, 2939, 2253, 1738, 1698, 1620, 1448, 1374, 1319, 1237, 1157, 1102, 1079, 1024, 958, 905, 859, 645; ¹H NMR (600 MHz, CDCl₃) δ 6.78 (dd, *J* = 10.4, 1.8 Hz, 1H), 5.99 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.80 (m, 1H), 5.21 (dd, *J* = 2.4, 1.8 Hz, 1H), 4.95 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.50 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.04 (m, 2H), 2.73 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.20-2.09 (m, 3H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.92-1.16 (m, 18H), 0.88 (s, 3H), 0.80 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 197.2, 174.9, 174.6, 144.4, 126.7, 117.3, 91.9, 85.2, 75.2, 74.1, 73.4, 50.9, 49.6, 41.5, 40.0, 36.3, 35.5, 35.0, 32.8, 30.3, 30.1, 26.8, 26.4, 26.3, 23.6, 21.2, 21.0, 15.6, 15.0; ESIHRMS Calcd for [C₂₉H₄₀O₆Na⁺]: 507.2717, Found 507.2722.

Digitoxigen 2,3-dideoxy- α -L-rhamno-hexopyranoside (27):

A CH_2Cl_2 (1.4 mL) solution of enone **31** (287 mg, 0.59 mmol) and CeCl_3 in MeOH solution (0.4 M, 1.4 mL) was cooled to -78°C . NaBH_4 (20 mg, 0.6 mmol) was added and the reaction mixture was stirred at -78°C for 3 h. The reaction mixture was diluted with ether (10 mL) and was quenched with 10 mL of satd. aq NaHCO_3 , extracted (3 x 10 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 55% EtOAc/hexanes to give allylic alcohol **27** (239 mg, 0.49 mmol, 83%) as a white solid: R_f (60% EtOAc/hexanes) = 0.22; mp: $193\text{--}194^\circ\text{C}$; IR (thin film, cm^{-1}) 3448, 2933, 2871, 1780, 1741, 1618, 1446, 1378, 1320, 1180, 1135, 1049, 1024, 1004, 958, 751; ^1H NMR (600 MHz, CDCl_3) δ 5.90 (ddd, $J = 10.2, 4.8, 1.2$ Hz, 1H), 5.85 (m, 1H), 5.72 (d, $J = 10.2$ Hz, 1H), 5.07 (m, 1H), 4.98 (dd, $J = 18.0, 1.2$ Hz, 1H), 4.80 (dd, $J = 18.0, 1.8$ Hz, 1H), 4.11 (dd, $J = 4.2, 1.8$ Hz, 1H), 3.97 (s, 1H), 3.82 (qd, $J = 6.6, 2.4$ Hz, 1H), 3.74 (br, 1H), 2.77 (dd, $J = 9.6, 6.0$ Hz, 1H), 2.25–2.05 (m, 3H), 1.29 (d, $J = 6.0$ Hz, 3H), 1.80–1.05 (m, 18H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 174.6, 132.8, 127.5, 117.6, 93.2, 85.5, 73.6, 73.4, 69.7, 67.9, 64.9, 50.90, 49.5, 41.8, 40.0, 36.4, 35.7, 35.1, 33.1, 30.7, 30.3, 26.7 (2C), 26.5, 23.6, 21.3, 21.1, 17.9, 15.7; ESIHRMS Calcd for $[\text{C}_{29}\text{H}_{42}\text{O}_6\text{Na}^+]$: 509.2879, Found 509.2879.

Digitoxigen α -L-rhamno-hexopyranoside (28**):**

To a *t*-BuOH/acetone (4 mL) solution of alcohol **27** (1.80 g, 3.82 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide/water (2.4 mL). Crystalline OsO₄ (9.6 mg, 1 mol %) was added and the reaction was stirred for 4 h. The reaction was quenched with adding EtOAc and satd. NaHCO₃. The organic layer was separated and concentrated. The crude product was purified by a silica gel column using 90% EtOAc/hexanes. Pure fractions were combined, concentrated, and crystallized from acetone/hexanes to afford triol **28** as a white solid (2.07 g, 3.55mmol, 93%): *R*_f (EtOAc) = 0.20; mp: 224-225 °C; [α]_D²⁵ = -24.0 (*c* = 0.7, MeOH); IR (thin film, cm⁻¹) 3453, 2925, 2856, 1775, 1736, 1623, 1449, 1454, 1378, 1160, 1076, 1024, 951, 822; ¹H NMR (600 MHz, CDCl₃) δ 5.87 (m, 1H), 4.98 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.87 (m, 1H), 4.80 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.12 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.06 (m, 1H), 3.71 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.44 (m, 1H), 2.77 (m, 1H), 2.58 (s, 1H), 2.36 (s, 1H) 2.20-2.00 (m, 4H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.90-1.10 (m, 19H), 0.93 (s, 3H), 0.87 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 174.48, 174.45, 117.8, 97.5, 85.6, 73.8, 73.4, 71.9, 71.6, 67.8, 50.9, 49.6, 41.9, 40.1, 38.3, 36.4, 35.7, 35.2, 33.2, 30.3, 29.5, 26.6, 26.5, 26.4, 23.7, 21.4, 21.2, 17.5, 15.8; ESIHRMS Calcd for [C₂₉H₄₄O₈Na⁺]: 543.6446, Found 543.6446.

Digitoxigen 2,3-dideoxy-2,3-dihydro- α -L-rhamno-hexopyranoside (29**):**

To a CH_2Cl_2 (0.35 mL) solution of allylic alcohol **27** (49 mg, 0.1 mmol) was added Et_3N (50.6 mg, 0.5 mmol), *o*-nitrobenzenesulfonyl hydrazide (NBSH) (101.5 mg, 0.5 mmol). The reaction was stirred at room temperature for 6 h. The reaction mixture was diluted with ether (5 mL) and was quenched with satd. aq NaHCO_3 , extracted (3 x 10 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc /hexanes to give product **29** (47 mg, 0.096 mmol, 96%) as a white solid: R_f (50% EtOAc /hexanes) = 0.20; mp: 180-181 °C; $[\alpha]_D^{25} = -33.0$ ($c = 0.4$, MeOH); IR (thin film, cm^{-1}) 3441, 2933, 2246, 1737, 1619, 1448, 1379, 1339, 1258, 1225, 1115, 1029, 990, 955, 906, 858, 824. ^1H NMR (600 MHz, CDCl_3) δ 5.86 (m, 1H), 4.98 (dd, $J = 18.0, 1.2$ Hz, 1H), 4.81 (m, 1H), 4.80 (dd, $J = 18.0, 1.8$ Hz, 1H), 4.11 (dd, $J = 4.2, 1.8$ Hz, 1H), 3.90 (s, 1H), 3.63 (br, 1H), 3.25 (m, 1H), 2.77 (dd, $J = 9.6, 6.0$ Hz, 1H), 2.25-2.05 (m, 3H), 1.48 (s, 1H), 1.20 (m, 6H), 1.80-1.05 (m, 19H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 174.6, 174.5, 117.6, 94.0, 85.5, 73.5, 72.3, 70.9, 69.6, 50.9, 49.6, 41.8, 40.0, 36.4, 35.7, 35.2, 33.1, 30.5, 30.2, 29.8, 27.7, 26.9, 26.7 (2C), 23.7, 21.4, 21.1, 17.9, 15.7; ESIHRMS Calcd for $[\text{C}_{29}\text{H}_{44}\text{O}_6\text{Na}]^+$: 511.6458, Found 511.6458.

(2S, 6R)-2-Digitoxigenoxy-6-methyl-2H-pyran-3(6H)-one (32):

A CH₂Cl₂/THF solution (3 mL, 4:1 V/V) of Boc-pyranone **13β** (200 mg, 0.87 mmol) and digitoxigenin (657 mg, 1.75 mmol) was cooled to 0 °C. A CH₂Cl₂ (0.36 mL) solution of Pd₂(DBA)₃•CHCl₃ (26.2 mg, 2.5 mol%) and PPh₃ (26.2 mg, 10 mol%) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 8 hours and was quenched with 5 mL of satd. aq NaHCO₃, extracted (3 x 10 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 40% EtOAc/hexanes to give **32** (337 mg, 0.69 mmol, 80%) as a white solid: R_f (55% EtOAc/hexanes) = 0.45; mp: 211-212 °C ; [α]_D²⁵ = -27.0 (c = 1.0, MeOH); IR (thin film, cm⁻¹) 3502, 2936, 2249, 1780, 1737, 1697, 1620, 1447, 1373, 1338, 1318, 1235, 1156, 1103, 1078, 1023, 958, 909, 824, 754; ¹H NMR (600 MHz, CDCl₃) δ 6.80 (dd, *J* = 10.4, 1.8 Hz, 1H), 6.12 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.87 (m, 1H), 5.25 (dd, *J* = 2.4, 1.8 Hz, 1H), 4.99 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.08 (m, 2H), 2.78 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.20-2.09 (m, 3H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.92-1.16 (m, 18H), 0.91 (s, 3H), 0.85 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 197.0, 174.4, 174.3, 147.7, 128.2, 117.8, 93.9, 85.6, 75.2, 73.4, 73.3, 50.9, 49.6, 41.9, 40.0, 36.3, 35.8, 35.2, 33.2, 32.0, 30.0, 26.9, 26.4, 24.4, 23.7, 21.3, 21.2, 17.0, 15.8; ESIHRMS Calcd for [C₂₉H₄₀O₆Na⁺]: 507.2717, Found 507.2722.

(2S, 6R)-2-(Digitoxigenoxy)-2,5-dihydro-6-methyl-2H-pyran-5-ol (33):

A CH₂Cl₂ (1.12 mL) solution of enone **33** (270 mg, 0.55 mmol) and CeCl₃ in MeOH solution (0.4 M, 1.12 mL) was cooled to -78 °C. NaBH₄ (20.8 mg, 0.55 mmol) was added and the reaction mixture was stirred at -78 °C for 3 h. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of satd. aq NaHCO₃, extracted (3 x 10 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 55% EtOAc/hexanes to give allylic alcohol **33** (238 mg, 0.49 mmol, 90%) as a white solid: R_f (60% EtOAc/hexanes) = 0.20; mp: 198-199 °C; IR (thin film, cm⁻¹) 3327, 2939, 2871, 1738, 1741, 1618, 1448, 1378, 1320, 1180, 1135, 1049, 1024, 958, 750; ¹H NMR (600 MHz, CDCl₃) δ 5.90 (ddd, *J* = 10.2, 4.8, 1.2 Hz, 1H), 5.86 (m, 1H), 5.73 (d, *J* = 10.2 Hz, 1H), 5.01 (m, 1H), 4.97 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.81 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.00 (dd, *J* = 4.2, 1.8 Hz, 1H), 3.83 (s, 1H), 3.73 (qd, *J* = 6.6, 2.4 Hz, 1H), 3.70 (br, 1H), 2.77 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.25-2.05 (m, 3H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.80-1.05 (m, 18H), 0.93 (s, 3H), 0.87 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 174.5, 174.4, 144.3, 127.0, 117.6, 91.6, 85.5, 73.76, 73.4, 70.3, 50.9, 49.6, 41.8, 40.0, 36.7, 35.6, 35.2, 33.1, 32.0, 30.1, 26.8 (2C), 26.5, 24.7, 23.7, 21.25, 21.16, 15.7, 15.2; ESIHRMS Calcd for [C₂₉H₄₂O₆Na⁺]: 509.2879, Found 509.2879.

Digitoxigen 2,3-dideoxy-2,3-dihydro- α -D-rhamno-hexopyranoside (34**):**

To a CH_2Cl_2 (0.35 mL) solution of allylic alcohol **33** (50 mg, 0.1 mmol) was added Et_3N (50.6 mg, 0.5 mmol), *o*-nitrobenzenesulfonyl hydrazide (NBSH) (101.5 mg, 0.5 mmol). The reaction was stirred at room temperature for 6h. The reaction mixture was diluted with ether (5 mL) and was quenched with satd. aq NaHCO_3 , extracted (3 x 10 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc /hexanes to give product **29** (46.5 mg, 0.095 mmol, 95%) as a white solid: R_f (50% EtOAc /hexanes) = 0.20; mp: 180-181 $^\circ\text{C}$; $[\alpha]_D^{25} = -33.0$ ($c = 0.4$, MeOH); IR (thin film, cm^{-1}) 3434, 2932, 2242, 1780, 1736, 1619, 1447, 1379, 1338, 1225, 1149, 1115, 1029, 989, 956, 908, 857, 824; ^1H NMR (600 MHz, CDCl_3) δ 5.86 (m, 1H), 4.98 (dd, $J = 18.0, 1.2$ Hz, 1H), 4.81 (m, 1H), 4.80 (dd, $J = 18.0, 1.8$ Hz, 1H), 4.00 (dd, $J = 4.2, 1.8$ Hz, 1H), 3.92 (s, 1H), 3.63 (br, 1H), 3.25 (m, 1H), 2.77 (dd, $J = 9.6, 6.0$ Hz, 1H), 2.25-2.05 (m, 3H), 1.48 (s, 1H), 1.20 (m, 6H), 1.80-1.05 (m, 19H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 174.6, 174.5, 117.6, 93.9, 85.5, 73.5, 72.3, 70.7, 69.6, 50.9, 49.6, 41.9, 40.1, 36.7, 35.7, 35.2, 33.1, 32.0, 30.2, 30.1, 27.7, 26.9, 26.7 (2C), 23.7, 21.4, 21.1, 17.9, 15.8; ESIHRMS Calcd for $[\text{C}_{29}\text{H}_{44}\text{O}_6\text{Na}]^+$: 511.6458, Found 511.6458.

L- β -glycoside desacetoxy-oleandrin (36):

To a mixture of diol **25** (25 mg, 0.05 mmol) and silver (I) oxide (0.23 g, 1 mmol), was added 0.25 mL CH₃I. The reaction suspension was stirred at rt for 3 days. The reaction mixture was then passed through a celite pad with 20 mL Et₂O, concentrated under reduced pressure and purified using silica flash chromatography eluting with 50% EtOAc/hexanes to give product **36** (6.49 mg, 0.012 mmol, 25%) as a white solid: *R_f* (50% EtOAc/hexanes) = 0.20; mp: 185-186 °C; [α]_D²⁵ = +43.0 (*c* = 0.45, MeOH); IR (thin film, cm⁻¹) 3453, 2932, 2856, 2173, 1969, 1775, 1742, 1623, 1449, 1454, 1378, 1160, 1067, 1024, 951, 822, 731; ¹H NMR (600 MHz, CDCl₃) δ 5.86 (m, 1H), 4.98 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.53 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.02 (m, 1H), 3.58 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.40 (s, 3H), 3.24 (m, 1H), 3.09 (m, 1H), 2.77 (m, 1H), 2.33 (s, 1H), 2.20-2.00 (m, 4H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.90-1.10 (m, 21H), 0.92 (s, 3H), 0.86 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 174.5, 174.4, 117.7, 97.5, 85.6, 81.0, 73.4, 72.9, 71.8, 71.6, 56.2, 50.9, 49.6, 41.8, 40.0, 39.3, 36.2, 35.7, 35.2, 33.2, 32.0, 29.9, 26.9, 26.4, 24.4, 23.6, 21.2, 21.1, 17.8, 15.8; ESIHRMS Calcd for [C₃₀H₄₆O₇Na⁺]: 541.3141, Found 541.3141.

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Appendix

List of ^1H and ^{13}C NMR Spectra

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

¹³C NMR (150 MHz, CDCl₃)

$^1\text{H NMR}$ (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (150 MHz, CDCl_3)