SUPPORTING INFORMATION

A Direct Comparison of the Anticancer Activities of Digitoxin *MeON*-Neoglycosides and *O*-Glycosides: Oligosaccharide Chain Length-Dependent Induction of Caspase-9-Mediated Apoptosis

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Growth Inhibition Assays.[1] The human tumor cell lines were grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. Cells are inoculated into 96 well microtiter plates in 100 µL at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37° C, 5 % CO2, 95 % air and 100 % relative humidity for 24 h prior to addition of experimental drugs. After 24 h, two plates of each cell line are fixed in situ with TCA, to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs are solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 µg/ml gentamicin. Additional four, 10-fold or ½ log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 µl of these different drug dilutions are added to the appropriate microtiter wells already containing 100 µl of medium, resulting in the required final drug concentrations. Following drug addition, the plates are incubated for an additional 48 h at 37°C, 5 % CO2, 95 % air, and 100 % relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed in situ by the gentle addition of 50 µl of cold 50 % (w/v) TCA (final concentration, 10 % TCA) and incubated for 60 minutes at 4°C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 µl) at 0.4 % (w/v) in 1 % acetic acid is added to each well, and plates are incubated for 10 minutes at room temperature. After staining, unbound dye is removed by washing five times with 1 % acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 µl of 80 % TCA (final concentration, 16 % TCA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

[(Ti-Tz)/(C-Tz)] x 100 for concentrations for which Ti>/=Tz

[(Ti-Tz)/Tz] x 100 for concentrations for which Ti<Tz.

Growth inhibition of 50 % (GI50) is calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation.

Table S1. $\mathbf{GI_{50}}$**s** (μM) for *O*-glycosides against 58 cell lines.

		Compound		
Cell Type	**Cell Line**	**1**	**2**	**3**
Leukemia	MOLT-4	0.0024	0.0046	0.0051
	HL-60(TB)	0.0036	0.0152	0.0182
	SR	0.0046	0.0168	0.0155
	CCRF-CEM	0.0047	0.0155	0.0177
	RPMI-8226	0.0179	0.0455	0.0399
	K-562	0.0254	0.0380	0.0267
Non-Small Cell Lung Cancer	NCI-H460	0.0038	0.0102	0.0128
	NCI-H522	0.0040	0.0059	0.0085
	A549/ATCC	0.0043	0.0113	0.0109
	EKVX	0.0048	0.0114	0.0120
	HOP-62	0.0078	0.0147	0.0184
	NCI-H23	0.0087	0.0177	0.0176
	NCI-H322M	0.0132	0.0416	0.0332
	NCI-H226	0.0333	0.0670	0.0773
	HOP-92	0.0598	0.1850	0.1450
Colon Cancer	HCT-116	0.0054	0.0147	0.0250
	SW-620	0.0075	0.0261	0.0271
	HT29	0.0149	0.0343	0.0327
	HCT-15	0.0222	0.0403	0.0439
	KM12	0.0264	0.0359	0.0479
	HCC-2998	0.0548	0.0841	0.0485
	COLO 205	0.0655	0.0612	0.0672
CNS Cancer	SF-268	0.0067	0.0249	0.0240
	SF-539	0.0068	0.0178	0.0232
	SNB-75	0.0123	0.0360	0.0362
	SF-295	0.0145	0.0401	0.0399
	U251	0.0166	0.0355	0.0372

	SNB-19	0.0439	0.0575	0.0640
Melanoma	SK-MEL-5	0.0055	0.0205	0.0371
	MALME-3M	0.0162	0.0358	0.0307
	LOX IMVI	0.0164	0.0318	0.0368
	UACC-62	0.0252	0.0382	0.0427
	UACC-257	0.0305	0.0845	0.0603
	M14	0.0393	0.0858	0.0746
	SK-MEL-28	0.0425	0.0608	0.0784
	NCI/ADR-RES	0.0115	0.0254	0.0236
Ovarian Cancer	OVCAR-5	0.0132	0.0307	0.0360
	OVCAR-4	0.0166	0.0340	0.0282
	OVCAR-8	0.0166	0.0436	0.0375
	OVCAR-3	0.0206	0.0369	0.0364
	IGROV1	0.0236	0.0566	0.0493
	SK-OV-3	0.0252	0.0369	0.0481
Renal Cancer	ACHN	0.0029	0.0052	0.0106
	SN12C	0.0044	0.0112	0.0157
	RXF 393	0.0045	0.0236	0.0301
	CAKI-1	0.0055	0.0293	0.0246
	UO-31	0.0071	0.0338	0.0325
	A498	0.0128	0.0313	0.0337
	786-0	0.0160	0.0273	0.0285
	TK-10	0.0199	0.0345	0.0270
Prostate Cancer	DU-145	0.0044	0.0137	0.0167
	PC-3	0.0119	0.0287	0.0291
Breast Cancer	HS 578T	0.0025	0.0062	0.0096
	BT-549	0.0029	0.0047	0.0112
	MCF7	0.0195	0.0328	0.0411
	T-47D	0.0229	0.0253	0.0429
	MDA-MB-435	0.0289	0.0488	0.0382
	MDA-MB-231	0.1040	0.1910	0.2230

Cytotoxicity Assays. All cell lines were maintained as previously reported.[2] Cells were harvested by trypsinization using 0.25% trypsin and 0.1% EDTA and then counted in a Cellometer Auto T4 cell counter (Nexcelom, inc), before dilution for assay plating. Cell plating, compound handling and assay set up were performed as previously reported[12] except the cells were plated in 50 μL volumes in 384 well clear bottom, tissue culture plates (Corning-Costar, Inc). Compounds were added from the 384-well compound stock plates at a 1:100 dilution (water) using a Biomek FX liquid handler equipped with a 384 channel head (Beckman Coulter, Inc.). Cell titer-glo reagent (15 μL) (Promega Corporation, Inc.) was added and incubated for 10 min at room temperature with gentle agitation to lyse the cells. Each plate was read for luminescence. The IC_{50} value for each compound represents four replicates of dose-response experiments conducted over six concentrations at two-fold serial dilutions. Within each experiment, percent inhibition values at each concentration were expressed as a percentage of the maximum luminescence signal observed for a 0 nM control. IC_{50} values were determined using XLFit 4.0 as previously reported.[2]

Table S2. IC_{50}s (μM) and standard errors for neoglycoside cytotoxicity against four cell lines.

Compound			**1**	**2**	**3**	**4**	**5**	**6**
Cell Line	SKOV-3	IC_{50}	0.05	0.07	0.097	0.98	5.92	0.86
		SE	0.02	0.03	0.004	0.03	0.09	0.03
	NCI-H460	IC_{50}	0.011	0.2	0.07	0.24	1.2	1.4
		SE	0.001	0.1	0.01	0.03	0.1	0.1
	NCI/ADR-RES	IC_{50}	0.037	0.05	0.069	4.2	1.1	3.2
		SE	0.003	0.01	0.006	0.4	0.1	0.2
	HT-29	IC_{50}	0.05	0.09	0.7	0.45	1.6	1.41
		SE	0.02	0.01	0.1	0.08	0.3	0.09

Apoptosis Assays. Sub-confluent (80%) densities of NCI-H460 cells were treated with different doses of drug for 12 h, and incubated with 10 µg/mL Hoechst 33342 nuclear stain for 30 min at 37°C. The percentage of cells having intensely condensed chromatin and/or fragmented nuclei was scored by fluorescence microscopy (Axiovert 100; Carl Zeiss) using Pixera software. Data from at least ten separate fields (~ 200 cells per field) were recorded and plotted. The data represent mean ± SD from three or more independent experiments; statistical significance for differences between data points was determined using the Student's t-test. Percent apoptotic cells in no treatment controls was < 1 %.

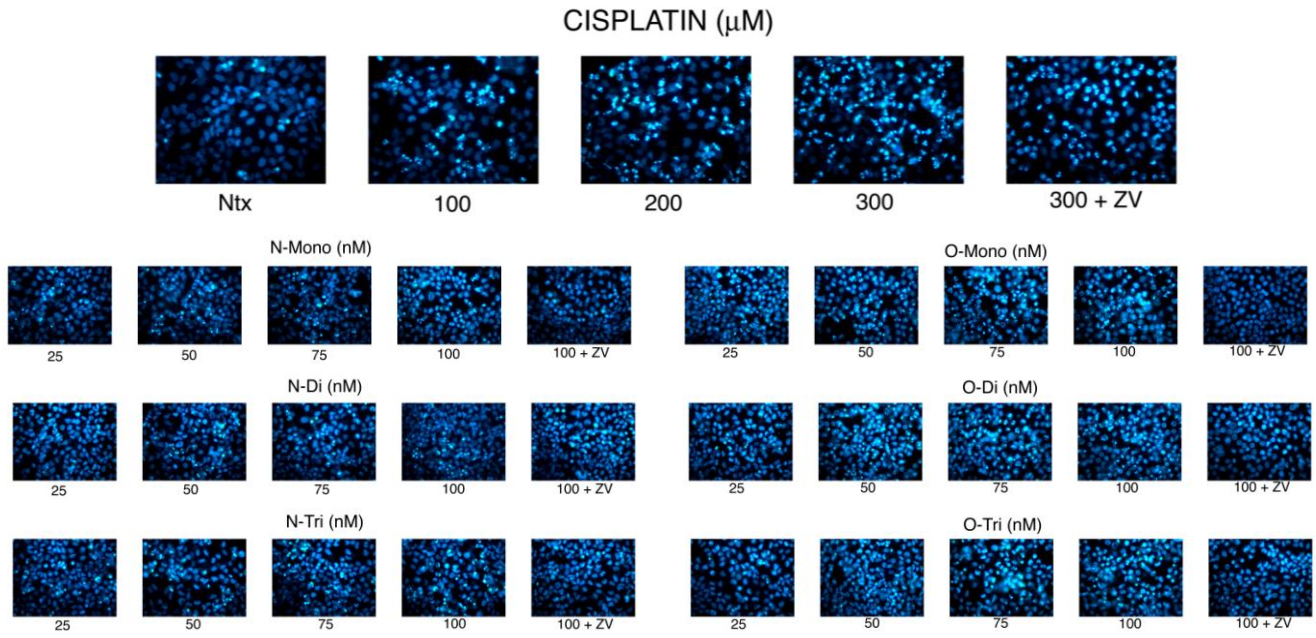


Figure S1. Fluorescence microscopy images from apoptosis assays.

Table S3. Percent apoptotic cells and standard deviation in NCI-H460 cells as a function of cisplatin concentration (nM).

Compound			Cisplatin
Drug Conc.	0 nM	% Apoptotic Cells	5.2
		SD	0.7
	100 nM	% Apoptotic Cells	28
		SD	2
	200 nM	% Apoptotic Cells	52
		SD	3
	300 nM	% Apoptotic Cells	76
		SD	9
	300 nM + ZV	% Apoptotic Cells	18
		SD	2

Table S4. Percent apoptotic cells and standard deviation in NCI-H460 cells as a function of drug concentration (nM).

Compound			1	2	3	4	5	6
Drug Conc.	25 nM	% Apoptotic Cells	21	5	3	5	4	2
		SD	2	1	0	1	1	1
	50 nM	% Apoptotic Cells	36	22	9	11	10	6
		SD	1	2	1	1	0	1
	75 nM	% Apoptotic Cells	54	40	20	19	17	11
		SD	3	2	1	2	2	1
	100 nM	% Apoptotic Cells	72	62	33	30	24	18
		SD	3	3	1	1	1	1
	100 nM + ZV	% Apoptotic Cells	3	2	2	2	1	1
		SD	0	0	0	0	0	0

Table S5. P-values from Student's t-test for selected comparisons of percent apoptotic cells.

Concentration	**Comparison**			
	4 vs **5**	**4** vs **6**	**1** vs **2**	**2** vs **3**
25 nM	0.19	0.05	0.003	0.001
50 nM	0.05	0.001	0.009	0.007
75 nM	0.06	0.03	0.01	0.002
100 nM	0.04	0.007	0.006	0.005

Caspase Assays. Caspase activity was determined by fluorometric assay using the enzyme substrate IETD-AMC for caspase-8 and LEHD-AMC for caspase-9, which are specifically cleaved by the respective enzymes at the aspartate residue to release the fluorescent group, AMC. Following treatment with drug (12 h), NCI-H460 cell extracts containing 50 μg of protein were incubated with 100 mM HEPES containing 10% sucrose, 10 mM dithiothreitol, 0.1% 3-((3-cholamidiopropyl)-1) propane sulfonate, and 50 μM caspase substrate in a total reaction volume of 0.25 ml. The reaction mixture was incubated for 60 min at 37 °C and quantified fluorometrically at the excitation and emission wavelengths of 380 and 460 nm, respectively. The data represent mean ± SD from three or more independent experiments.

Table S5. Caspase-8 activity and standard deviation in NCI-H460 cells as a function of drug concentration. Activity reported is normalized to a no-treatment control (defined as 1).

Compound			**1**	**4**
Drug Conc.	25 nM	Caspase act.	1.4	1.38
		SD	0.3	0.09
	50 nM	Caspase act.	1.6	1.5
		SD	0.1	0.3
	75 nM	Caspase act.	1.8	1.4
		SD	0.5	0.2
	100 nM	Caspase act.	1.9	1.7
		SD	0.3	0.4
	100 nM + ZV	Caspase act.	1.2	1.1
		SD	0.2	0.1

Table S6. Caspase-9 activity and standard deviation in NCI-H460 cells as a function of drug concentration. Activity reported is normalized to a no-treatment control (defined as 1).

Compound			**1**	**4**
Drug Conc.	25 nM	Caspase act.	4.1	2.3
		SD	0.3	0.2
	50 nM	Caspase act.	5.09	3.4
		SD	0.08	0.1
	75 nM	Caspase act.	7.3	3.7
		SD	0.4	0.3
	100 nM	Caspase act.	7.4	4.4
		SD	0.5	0.4
	100 nM + ZV	Caspase act.	1.19	1.09
		SD	0.08	0.2

Table S7. P-values from Student's t-test for selected comparisons of caspase-8 activity (Ntx = no treatment).

Concentration	**Comparison**	
	4 vs **Ntx**	**1** vs **Ntx**
25 nM	0.02	0.12
50 nM	0.08	0.02
75 nM	0.05	0.08
100 nM	0.10	0.03

Table S8. P-values from Student's t-test for selected comparisons of caspase-9 activity (Ntx = no treatment).

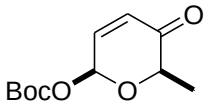
Concentration	**Comparison**	
	4 vs **Ntx**	**1** vs **Ntx**
25 nM	0.019	0.004
50 nM	0.001	0.0002
75 nM	0.007	0.002
100 nM	0.001	0.003

Section E: Synthetic Procedures

General methods.

Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon or nitrogen using oven-dried glassware and standard syringe/septa techniques. Ether, tetrahydrofuran, methylene chloride and methanol were dried by passing through activated alumina column with argon gas pressure. Hexanes refer to the petroleum fraction bp 40-60 ^{o}C. Commercial reagents were used without purification unless otherwise noted. Flash chromatography was performed using the indicated solvent system on silica gel standard grade 60 (230-400 mesh). R_f values are reported for analytical TLC using the specified solvents and 0.25 mm silica gel 60 F254 plates that were visualized by UV irradiation (254 nm) or by staining with $KMnO_4$ stain or anisaldehyde stain (465 mL of 95% EtOH, 17 mL conc. H_2SO_4, 5 mL acetic acid, and 13 mL anisaldehyde). Optical rotations were obtained using a digital polarimeter at sodium D line (589 nm) and were reported in concentration of g / 100 mL at 21 ^{o}C. ^{1}H and ^{13}C NMR spectra were recorded on 300, 400, or 600 MHz spectrometer. Chemical shifts are reported relative to $CHCl_3$ (δ 7.26 ppm) for ^{1}H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C. IR spectra were recorded on a FT-IR ppectrometer; thin film was formed in $CHCl_3$ solution. Melting points are uncorrected.

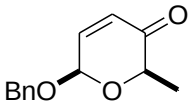
***Tert*-butyl (2S,6R)-5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (7):**



To a benzene solution (300 mL) of (5*R*)-1-Hydroxy-5-*tert*-butyl dimethylsilanyloxymethyl-5*H*-pyran 4-(1*H*)-one (18.5 g, 0.144 mol) and $(Boc)_2O$ (47.3 g, 0.22 mol) was added sodium acetate (13.2 g, 0.16 mol). After stirring at 80 °C for 2 hours, the mixture was cooled down to room temperature. The reaction was quenched by adding of 300 mL of saturated $NaHCO_3$ solution, extracted (3 x 300 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 7% EtOAc/hexanes to give two diastereomers of *tert*-butyl 5,6-dihydro-6-methyl-5-oxo-2H-pyran-2-yl carbonate (29.0 g, 0.127 mol, 88%) of **7α** and **7β** (**7α** : **7β** = 1:1.3). **7α**: *Rf* (20% Et_2O/hexanes) = 0.43; $[\alpha]_D^{21}$ –97.1 (c 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2986, 1752, 1703, 1633, 1278, 1258, 1159, 1090, 1058, 1029, 944 ; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 10.3, 3.8 Hz, 1H), 6.31 (d, *J* = 3.8 Hz, 1H), 6.17 (d, *J* = 10.3 Hz, 1H), 4.63 (q, *J* = 6.7 Hz, 1H), 1.50 (s, 9H), 1.39 (d, *J* = 6.7 Hz, 3H) ; ^{13}C NMR (67.5 MHz, CDCl3) δ 195.7, 151.8, 140.9, 128.4, 89.1, 83.5, 72.1, 27.6(3C), 15.2; CLHRMS Calcd for $[C_{11}H_{16}O_5Na]^+$: 251.0890, Found 251.0884.

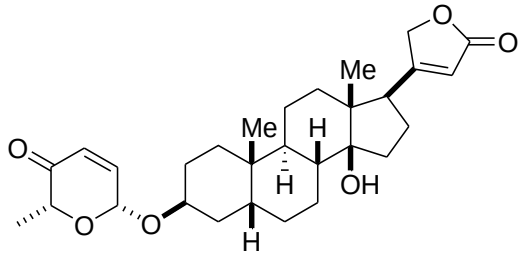
7β: *Rf* (20% EtOAc/hexanes) = 0.50; mp: 43-43.5 °C; $[\alpha]_D^{21}$ + 42.3 (c 1.3, $CHCl_3$); IR (thin film, cm^{-1}) 2986, 1752, 1703, 1633, 1278, 1258, 1159, 1090, 1058, 1029, 944; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 10.3, 2.6 Hz, 1H), 6.40 (dd, *J* = 2.6, 1.4 Hz, 1H), 6.20 (dd, *J* = 10.3, 1.2 Hz, 1H), 4.37 (q, *J* = 6.9 Hz, 1H), 1.51 (s, 9H), 1.49 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl3) δ 195.9, 151.7, 142.8, 128.3, 89.8, 83.7, 75.7, 27.6(3C), 18.6 ; CLHRMS Calcd for $[C_{11}H_{16}O_5Na]$+: 251.0890, Found 251.0883.

(2R,6R)-2-Methyl-6-(phenylmethoxy)-2*H*-pyran-3(6*H*)-one (8)



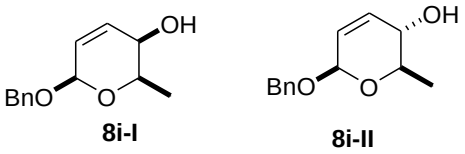
A CH_2Cl_2 (3 mL) solution of Boc pyranone **7β** (716 mg, 3.14 mmol) and benzyl alcohol (678 mg, 6.28 mmol) was cooled to 0 ^oC. A CH_2Cl_2 (2 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (81 mg, 2.5 mol%) and PPh_3 (82 mg, 10 mol%) was added to the reaction mixture at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 2 hours and was quenched with 10 mL of saturated $NaHCO_3$ solution, extracted (3 x 10 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 8% EtOAc/hexanes to give **8** (582 mg, 2.67 mmol, 85%) as a viscous oil: R_f (15% EtOAc/hexanes) = 0.23; $[\alpha]_D^{21}$ – 41.8 (*c* 1.20, $CHCl_3$); IR (thin film, cm^{-1}) 2933, 1698, 1453, 1373, 1163, 1057, 1023, 903, 800, 733, 697; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.92 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.14 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.40 (m, 1H), 4.95 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.24 (q, *J* = 6.9 Hz, 1H), 1.53 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 196.8, 146.4, 136.8, 128.5 (2C), 128.1(3C), 128.0, 94.3, 75.2, 70.1, 17.2; CLHRMS Calcd for $[C_{13}H_{14}O_3Na^+]$: 241.0835, Found 241.0843.

(2R,6R)-2-Methyl-6-(Digitoxigenoxy)-2*H*-pyran-3(6*H*)-one (9)



A CH_2Cl_2 /THF solution (8 mL, 4:1 V/V) of Boc pyranone **7β** (544 mg, 2.39 mmol) and digitoxigenin (1.34 g, 3.58 mmol) was cooled to 0 ^oC. A CH_2Cl_2 (1 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (72 mg, 2.5 mol%) and PPh_3 (73 mg, 10 mol%) was added to the reaction mixture at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 8 hours and was quenched with 20 mL of saturated $NaHCO_3$ solution, extracted (3 x 20 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 40% EtOAc/hexanes to give **9** (993 mg, 2.05 mmol, 86%) as a white solid: R_f (40% EtOAc/hexanes) = 0.17; mp: 211-212 ^oC; $[\alpha]_D^{21}$ + 17.6 (*c* 3.60, $CHCl_3$); IR (thin film, cm^{-1}) 3498, 2937, 2875, 1780, 1741, 1698, 1620, 1448, 1374, 1164, 1144, 1053, 1025, 958, 754; ^1H NMR (600 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 10.2, 1.8 Hz, 1H), 6.09 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.86 (m, 1H), 5.38 (dd, *J* = 2.4, 1.8 Hz, 1H), 4.98 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.79 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.16 (q, *J* = 6.6 Hz, 1H), 4.15 (m, 1H), 2.76 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.20-2.08 (m, 3H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.92-1.16 (m, 18H), 0.93 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.0, 174.6, 174.5, 147.8, 128.0, 117.6, 93.9, 85.5, 75.1, 73.5, 73.4, 50.9, 49.6, 41.8, 40.0, 36.4, 35.7, 35.2, 33.1, 30.1, 29.9, 26.9, 26.56, 26.53, 23.6, 21.3, 21.1, 16.9, 15.7; HRESIMS Calcd for $[C_{29}H_{40}O_6Na^+]$: 507.2717, Found 507.2717.

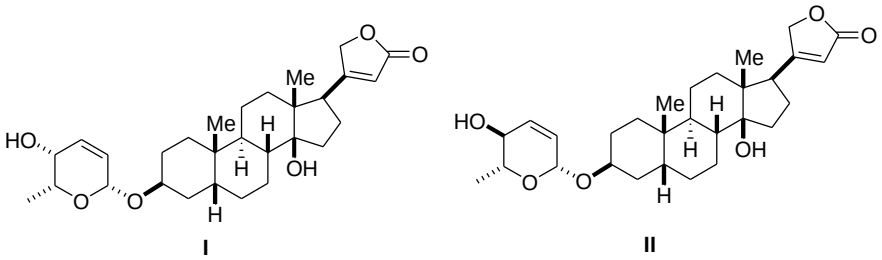
(2R,6R)-3,6-Dihydro-2-methyl-6-(phenylmethoxy)-2*H*-pyran-3-ol (8i)



8i-I **8i-II**

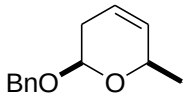
A CH_2Cl_2 (2 mL) solution of enone **8** (435 mg, 2.0 mmol) and $CeCl_3$ in MeOH solution (1.7 mL) was cooled to -78 ^oC. $NaBH_4$ (75 mg, 2.0 mmol) was added and the reaction mixture was stirred at -78^oC for 3 hours. The reaction mixture was diluted with Et_2O (5 mL) and was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 x 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% EtOAc/hexanes to give allylic alcohols **8i** (374 mg, 1.70 mmol, 85%) as a viscous oil (diastereometric ratio I:II = 1.5:1, inseparable by silica gel chromatography): R_f (40% EtOAc/hexanes) = 0.30; IR (thin film, cm^{-1}) 3397, 2978, 2933, 2869, 1498, 1455, 1378, 1053, 1010, 808, 738, 698; ^1H NMR (600 MHz, $CDCl_3$): **isomer I**: δ 7.35 (m, 5H), 6.16 (ddd, *J* = 10.2, 5.4, 1.2 Hz, 1H), 5.86 (d, *J* = 10.2 Hz, 1H), 5.14 (ddd, *J* = 1.8, 1.8, 1.2 Hz, 1H), 4.92 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 3.75 (qd, *J* = 6.0, 2.4 Hz, 1H), 3.68 (m, 1H), 2.0 (d, *J* = 10.2 Hz, 1H), 1.34 (d, *J* = 6.0 Hz, 3H); **isomer II**: δ 7.30 (m, 5H), 5.95 (ddd, *J* = 10.2, 2.4, 1.8 Hz, 1H), 5.79 (ddd, *J* = 10.2, 1.8, 1.2 Hz, 1H), 5.18 (ddd, *J* = 1.8, 1.8, 1.2 Hz, 1H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 3.90 (m, 1H), 3.64 (dq, *J* = 6.6, 6.0 Hz, 1H), 2.10 (d, *J* = 6.6 Hz, 1H), 1.38 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) **isomer I** : δ 137.5, 131.3, 130.6, 128.4 (2C), 127.9 (2C), 127.7, 97.0, 71.4, 69.9, 64.7, 16.6; **isomer II**: δ 137.7, 132.1, 128.7, 128.3 (2C), 127.9 (2C), 127.6, 95.5, 74.4, 69.2, 68.3, 17.8; CIHRMS Calcd for [$C_{13}H_{16}O_3Na^+$]: 243.0992, Found 243.0983.

(2R,6R)-3,6-Dihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3-ol (9i)



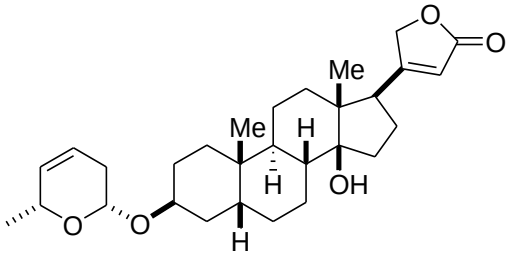
A CH_2Cl_2 (4 mL) solution of enone **9** (990 mg, 2.04 mmol) and $CeCl_3$ in MeOH solution (0.4 M, 4 mL) was cooled to -78 ^oC. $NaBH_4$ (77 mg, 2.04 mmol) was added and the reaction mixture was stirred at -78^oC for 3 hours. The reaction mixture was diluted with Et_2O (30 mL) and was quenched with 30 mL of saturated aqueous $NaHCO_3$, extracted (3 x 30 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 55% EtOAc/hexanes to give allylic alcohols **9i** (893 mg, 1.84 mmol, 90%) as a white solid (diastereometric ratio I:II = 1.5:1, inseparable by silica gel chromatography): R_f (60% EtOAc/hexanes) = 0.22; 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, $CDCl_3$): **isomer I**: δ 6.12 (ddd, *J* = 10.2, 4.8, 1.2 Hz, 1H), 5.86 (m, 1H), 5.80 (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), 4.12 (dd, *J* = 4.2, 1.8 Hz, 1H), 4.114(s, 1H), 3.70 (qd, *J* = 6.6, 2.4Hz, 1H), 3.64 (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), 0.94 (s, 3H), 0.87 (s, 3H); **isomer II**: δ 5.93 (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), 5.14 (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), 4.109 (s, 1H), 3.93 (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), 1.35 (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, $CDCl_3$) **isomer I** : δ 174.50, 174.46, 131.8, 130.9, 117.67, 96.1, 85.591, 73.43, 72.9, 71.4, 64.9, 50.90, 49.6, 41.9, 40.045, 36.4, 35.77, 35.19, 33.12, 30.20, 30.04, 26.9 (2C), 26.62, 23.64, 21.384, 21.151, 16.7, 15.8; **isomer II**: δ 174.52, 174.46, 131.7, 129.9, 117.66, 94.8, 85.598, 73.38, 73.4, 72.4, 68.7, 50.91, 49.6, 41.9, 40.052, 36.3, 35.76, 35.18, 33.13, 30.18, 30.06, 26.7 (2C), 26.66, 23.62, 21.380, 21.147, 18.4, 15.8; HRESIMS Calcd for [$C_{29}H_{42}O_6Na^+$]: 509.2879, Found 509.2880.

***Cis*-3,6-dihydro-6-methyl-2-(phenylmethoxy)-2*H*-pyran (8ii)**



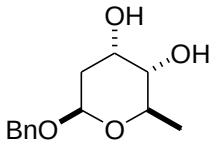
A flask was charged with dry *N*-methyl morpholine (NMM) 3.0 mL, triphenyl phosphine (1.45 g, 5.54 mmol) and was cooled to -30^{o}C under Ar atmosphere. Diethylazodicarboxylate (0.8 mL, 5.05 mmol) was added and the reaction was stirred for 5 minutes, allylic alcohol **8i** (370 mg, 1.68 mmol) was added in a 1M solution of NMM and the reaction mixture was stirred for 10 minutes, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (1.02 g, 5.05 mmol). The reaction was stirred at -30 ^{o}C for 2 hours and was monitored by TLC. Upon consumption of starting material, the reaction was warmed up to room temperature and stirred for another 2 hours. The reaction mixture was diluted with Et_2O (10 mL) and was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 x 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 2% Et_2O/hexanes to give product **8ii** (293 mg, 1.44 mmol, 84%) as a viscous oil: R_f (15% EtOAc/hexanes) = 0.48; $[\alpha]_D^{21}$ –128.5 (*c* 1.80, $CHCl_3$); IR (thin film, cm^{-1}) 2973, 2927, 1453, 1366, 1158, 1080, 1028, 880, 777, 733. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.69 (ddd, *J* = 10.2, 4.8, 2.4 Hz, 1H), 5.60 (ddd, *J* = 10.2, 1.2, 1.2 Hz, 1H), 4.95 (d, *J* = 12.0 Hz, 1H), 4.75 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.35 (m, 1H), 2.27 (dddd, *J* = 17.4, 8.4, 3.6, 2.4 Hz, 1H), 2.19 (dddd, *J* = 17.4, 6.6, 2.4, 1.2 Hz, 1H), 1.33 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.9, 130.9, 128.3 (2C), 127.9 (2C), 127.6, 122.5, 97.7, 70.6, 69.8, 30.9, 21.1; CLHRMS Calcd for [$C_{13}H_{16}O_2Na^+$]: 227.1042, Found 227.1045.

***Cis*-3,6-dihydro-6-methyl-2-(Digitoxigenoxy)-2*H*-pyran (9ii)**



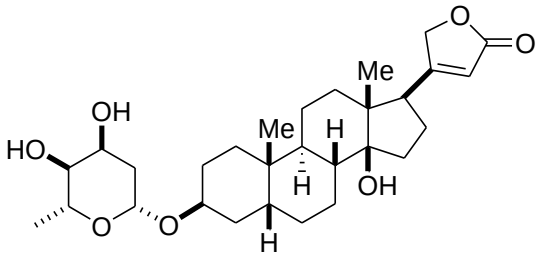
A flask was charged with dry *N*-methyl morpholine (NMM) 3.0 mL, triphenyl phosphine (1.75 g, 6.67 mmol) and was cooled to -30^{o}C under Ar atmosphere. Diethylazodicarboxylate (0.95 mL, 6.06 mmol) was added and the reaction was stirred for 5 minutes, allylic alcohol **9i** (985 mg, 2.02 mmol) was added in a 1M solution of NMM and the reaction mixture was stirred for 10 minutes, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (1.23 g, 6.06 mmol). The reaction was stirred at -30 ^{o}C for 6 hours and was monitored by TLC. Upon consumption of starting material, the reaction was warmed up to room temperature and stirred for another 1 hour. The reaction mixture was diluted with Et_2O (30 mL) and was quenched with 30 mL of saturated aqueous $NaHCO_3$, extracted (3 x 30 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 25% EtOAc/hexanes to give product **9ii** (760 mg, 1.61 mmol, 80%) as a white solid: R_f (30% EtOAc/hexanes) = 0.20; mp: 157-158 ^{o}C; $[\alpha]_D^{21}$ = -30.0 (*c* = 0.10, $CHCl_3$); IR (thin film, cm^{-1}) 3494, 2936, 2871, 1778, 1742, 1621, 1447, 1368, 1264, 1158, 1133, 1102, 1072, 1026, 974, 888, 781. ^{1}H NMR (600 MHz, $CDCl_3$) 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, 26.73, 26.65, 23.6, 21.4, 21.1, 21.03, 15.8; HRESIMS Calcd for [$C_{29}H_{42}O_5Na^+$]: 493.2929, Found 493.2924.

Phenylmethyl 2,6-dideoxy-β-D-ribo-hexopyranoside (10)



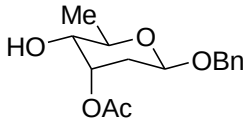
To a CH_2Cl_2 (3 mL) solution of olefin **8ii** (291 mg, 1.43 mmol) at 0 ^oC was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (0.67 mL). Crystalline OsO_4 (3.6 mg, 1 mol %) was added and the reaction was stirred for 3 hours. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 35% EtOAc/hexanes. Pure fractions were combined and concentrated to afford diol **10** as a viscous oil (313 mg, 1.31 mmol, 92%): R_f (50% EtOAc/hexanes) = 0.23; $[\alpha]_D^{21}$ – 85.9 (*c* 1.30, $CHCl_3$); IR (thin film, cm-1) 3426, 2883, 1496, 1454, 1364, 1164, 1137, 1072, 1007, 867, 731, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.90 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.57 (d, *J* = 12.0 Hz , 1H), 4.09 (m, 1H), 3.74 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.32 (m, 1H), 2.51(s, 1H), 2.35(s, 1H), 2.12 (ddd, *J* = 13.8, 3.6, 2.4 Hz, 1H), 1.78 (ddd, *J* = 13.8, 9.0, 3.0 Hz, 1H), 1.33(d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.7, 128.4 (2C) , 127.9 (2C), 127.7, 96.9, 73.0, 70.5, 69.5, 67.9, 37.7, 18.1; CLHRMS Calcd for $[C_{13}H_{18}O_4Na^+]$: 261.1097, Found 261.1087.

Digitoxigen 2,6-dideoxy-β-D-ribo-hexopyranoside (1)



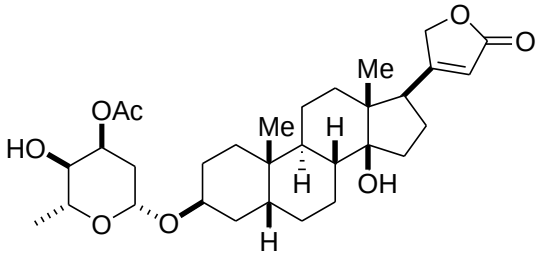
To a *t*-BuOH/acetone (4 mL) solution of olefin **9ii** (753 mg, 1.60 mmol) at 0 ^{o}C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (1.0 mL). Crystalline OsO_4 (4 mg, 1 mol %) was added and the reaction was stirred for 4 hours. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. 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 $CHCl_3/Et_2O$ to afford alcohol **1** as a white solid (868 mg, 1.72 mmol, 93%), > 99 % pure by LCMS. R_f (EtOAc) = 0.25; $[\alpha]_D^{21}$ –6.8 (*c* 0.65, MeOH); mp: 202-203 ^{o}C; IR (thin film, cm^{-1}) 3453, 2925, 2856, 1775, 1736, 1623, 1449, 1454, 1378, 1160, 1076, 1024, 951, 822; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (m, 1H), 4.98 (d, *J* = 18.0 Hz, 1H), 4.87 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.80 (d, *J* = 18.0 Hz, 1H), 4.13 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.03 (m, 1H), 3.71 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.34 (m, 1H), 2.77 (m, 1H), 2.33 (s, 1H), 2.20-2.00 (m, 4H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.90-1.10 (m, 19H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.56, 174.52, 117.7, 95.4, 85.6, 73.5, 73.1, 72.7, 69.2, 68.3, 50.9, 49.6, 41.9, 40.1, 38.3, 36.3, 35.8, 35.2, 33.2, 30.2, 29.9, 26.9, 26.7, 26.6, 23.6, 21.4, 21.2, 18.1, 15.8; HRESIMS Calcd for $[C_{29}H_{44}O_7Na^+]$: 527.2979, Found 527.2979.

Phenylmethyl 3-*O*-acetyl-2,6-dideoxy-*β*-D-ribo-hexopyranoside (11)



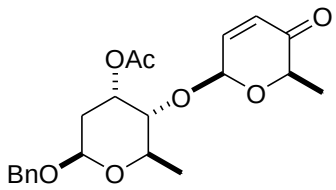
A round bottom flask containing a 0.5 M solution of diol **10** (300 mg, 1.26 mmol) in benzene (2.5 mL) was stirring at room temperature. To this solution were added trimethylorthoacetate (0.8 mL, 6.29 mmol) and a catalytic amount of *p*-toluenesulfonic acid (12 mg, 63 μmol). The reaction was allowed to stir until starting material is gone. The solvent was removed under reduced pressure and the residue was dissolved in 3 mL THF/H_2O (1:1,v/v) solution. Then *p*-toluenesulfonic acid (600 mg, 3.15 mmol) was added. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 30% EtOAc/hexanes. Pure fractions were combined and concentrated to afford compound **11** (335 mg, 1.20 mmol, 95%): R_f (50% EtOAc/hexanes) = 0.38; $[\alpha]_D^{21}$ –52.4 (*c* 1.40, $CHCl_3$); IR (thin film, cm-1) 3471, 2975, 2934, 1740, 1498, 1455, 1372, 1242, 1164, 1075, 1006, 698; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.29 (ddd, *J* = 3.6, 3.0, 3.0 Hz , 1H), 4.91 (d, *J* = 12.0 Hz ,1H), 4.83 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.57 (d, *J* = 12.0 Hz , 1H), 3.73 (dq, *J* = 9.0, 6.0 Hz , 1H), 3.46 (dd, *J* = 9.0, 3.0 Hz , 1H), 2.14 (ddd, *J* = 14.4, 3.6, 2.4 Hz , 1H), 2.10 (s, 3H), 1.87 (ddd, *J* = 14.4, 9.0, 3.0 Hz , 1H), 1.36 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.2, 137.5, 128.3(2C) , 127.8 (2C), 127.7, 97.0, 72.2, 71.0, 70.4, 70.3, 35.6, 21.1, 18.0; CLHRMS Calcd for [$C_{15}H_{20}O_5Na^+$]: 303.1203, Found 303.1201.

Digitoxigen 3-*O*-acetyl-2,6-dideoxy-*β*-D-ribo-hexopyranoside (12)



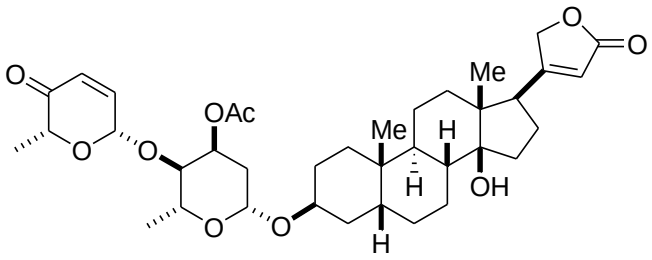
A round bottom flask containing a 0.5 M solution of diol **1** (620 mg, 1.23 mmol) in CH_2Cl_2 (3 mL) was stirring at room temperature. To this solution were added trimethylorthoacetate (0.47 mL, 3.69 mmol) and a catalytic amount of *p*-toluenesulfonic acid (12 mg, 61.5 μmol). The reaction was allowed to stir until starting material is gone. The solvent was removed under reduced pressure and the residue was dissolved in 6 mL THF/H_2O (1:1,v/v) solution. Then *p*-toluenesulfonic acid (120 mg, 0.62 mmol) was added. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction mixture was quenched with 10 mL of saturated aqueous $NaHCO_3$, extracted (3 x 10 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. It was purified by a silica gel column using 60% EtOAc/hexanes. Pure fractions were combined and concentrated to afford compound **12** (675 mg, 1.20 mmol, 98%) as a white solid: R_f (60% EtOAc/hexanes) = 0.14; $[\alpha]_D^{21}$ = + 1.7 (*c* = 1.15, $CHCl_3$); mp: 111-112 ^oC; IR (thin film, cm^{-1}) 3499, 2934, 2876, 1780, 1740, 1618, 1449, 1377, 1243, 1169, 1080, 1065, 1026, 1002, 948, 753, 666; ^1H NMR (600 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.28 (ddd, *J* = 3.6, 3.0, 3.0 Hz , 1H), 4.97 (d, *J* = 18.0 Hz ,1H), 4.80 (d, *J* = 18.0 Hz , 1H), 4.75 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.01 (m, 1H), 3.67 (dq, *J* = 9.0, 6.0 Hz , 1H), 3.43 (dd, *J* = 9.6, 2.4 Hz , 1H), 2.76 (m, 1H), 2.20-2.00 (m, 4H), 2.13 (s, 3H), 1.90-1.10 (m, 19H), 1.29 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.59, 174.51, 171.3, 117.6, 95.8, 85.6, 73.4, 73.1, 72.3, 71.4, 70.2, 50.9, 49.6, 41.8, 40.0, 36.3 (2C), 35.7, 35.2, 33.1, 30.1 (2C), 26.9, 26.64, 26.61, 23.6, 21.36, 21.2, 21.1, 18.1, 15.7; HRESIMS Calcd for [$C_{31}H_{46}O_8Na^+$]: 569.3085, Found 569.3085.

Phenylmethyl 3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2R,6R)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl]-β-D-ribo-hexopyranoside (11i)



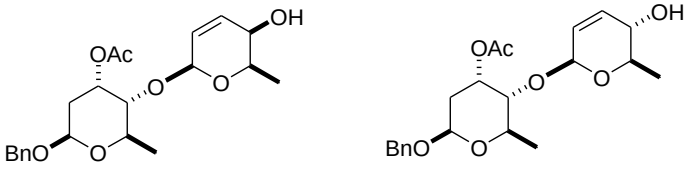
A CH_2Cl_2 (0.8 mL) solution of Boc pyranone **7** (337 mg, 1.48 mmol) and alcohol **11** (207 mg, 0.74 mmol) was cooled to 0 ^oC. A CH_2Cl_2 (0.4 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (19 mg, 2.5 mol%) and PPh_3 (20 mg, 10 mol%) was added to the reaction mixture at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 2 hours and was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 x 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 22% EtOAc/hexanes to give enone **11i** (228 mg, 0.58 mmol, 78%) as a viscous oil: R_f (30% EtOAc/hexanes) = 0.23; $[\alpha]_D^{21}$ +20.0 (*c* 0.55, $CHCl_3$); IR (thin film, cm^{-1}) 2931, 1739, 1698, 1454, 1373, 1256, 1242, 1155, 1050, 1004, 787, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.89 (dd, *J* = 10.2, 1.2 Hz, 1H), 6.13 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.44 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.42 (d, *J* = 1.2 Hz, 1H), 4.90 (d, *J* = 11.4 Hz, 1H), 4.83 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.16 (q, *J* = 6.6 Hz, 1H), 3.96 (dq, *J* = 9.0, 6.6 Hz, 1H), 3.55 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.19 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.06 (s, 3H), 1.85 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.40 (d, *J* = 6.6 Hz, 3H), 1.37 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 170.1, 146.3, 137.6, 128.8, 128.4 (2C), 127.8 (2C), 127.7, 97.1, 97.0, 79.4, 75.2, 70.5, 69.4, 69.3, 35.6, 21.2, 18.3, 16.3; CLHRMS Calcd for $[C_{21}H_{26}O_7Na^+]$: 413.1571, Found 413.1558.

Digitoxigen 3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2R,6R)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl]-β-D-ribo-hexopyranoside (12i)



A CH_2Cl_2 (2 mL) solution of Boc pyranone **7** (560 mg, 2.45 mmol) and alcohol **12** (670 mg, 1.23 mmol) was cooled to 0 ^oC. A CH_2Cl_2 (0.5 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (63 mg, 2.5 mol%) and PPh_3 (64 mg, 10 mol%) was added to the reaction mixture at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 8 hours and was with 10 mL of saturated aqueous $NaHCO_3$, extracted (3 x 10 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 50% EtOAc/hexanes to give enone **12i** (643 mg, 0.98 mmol, 80%) as a white solid: R_f (60% EtOAc/hexanes) = 0.24; mp: 119-120 ^oC; $[\alpha]_D^{21}$ + 37.8 (*c* 1.40, $CHCl_3$); IR (thin film, cm^{-1}) 3495, 2937, 2876, 1780, 1743, 1700, 1621, 1448, 1374, 1244, 1154, 1096, 1068, 1051, 1027, 1004, 755, 695; ^1H NMR (600 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 10.2, 1.2 Hz, 1H), 6.11 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.86 (m, 1H), 5.41 (ddd, *J* = 3.6, 2.4, 2.4 Hz, 1H), 5.40 (dd, *J* = 1.2, 1.2 Hz, 1H), 4.97 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.79 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.76 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.15 (q, *J* = 6.6 Hz, 1H), 4.01 (m, 1H), 3.90 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.51 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.77 (m, 1H), 2.20-2.02 (m, 4H), 2.09 (s, 3H), 1.90-1.18 (m, 19H), 1.39 (d, *J* = 6.6 Hz, 3H), 1.31 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 174.5, 174.4, 170.2, 146.4, 128.8, 117.7, 97.0, 96.0, 85.6, 79.5, 75.2, 73.4, 73.1, 69.8, 69.0, 50.9, 49.6, 41.9, 40.1, 36.30, 36.26, 35.8, 35.2, 33.1, 30.15, 30.13, 26.9, 26.63, 26.60, 23.6, 21.4, 21.3, 21.1, 18.3, 16.3, 15.8; HRESIMS Calcd for [$C_{37}H_{52}O_{10}Na^+$]: 679.3458, Found 679.3453.

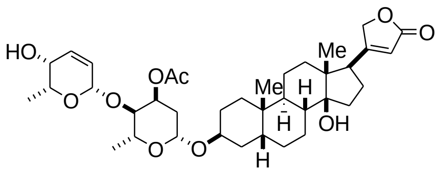
Phenylmethyl 3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2R,6R)-5,6-dihydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranoside (11ii)

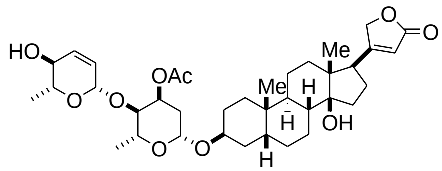


I **II**

A CH_2Cl_2 (0.6 mL) solution of enone **11i** (228 mg, 0.584 mmol) and $CeCl_3$ in MeOH solution (0.6 mL) was cooled to -78 ^oC. $NaBH_4$ (22 mg, 0.585 mmol) was added and the reaction mixture was stirred at -78^oC for 3 hours. The reaction mixture was diluted with Et_2O (5 mL) and was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 x 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 35% EtOAc/hexanes to give allylic alcohols **11ii** (211 mg, 0.538 mmol, 92%) as a viscous oil (diastereometric ratio I:II = 1.6:1, inseparable by silica gel chromatography): R_f (40% EtOAc/hexanes) = 0.15; IR (thin film, cm^{-1}) 3471, 2980, 2934, 2875, 1740, 1498, 1455, 1372, 1243, 1154, 1057, 1009, 736, 698; ^1H NMR (600 MHz, $CDCl_3$): **isomer I**: δ 7.28 (m, 5H), 6.17 (dd, *J* = 10.2, 5.4 Hz, 1H), 5.75 (d, *J* = 10.2 Hz, 1H), 5.57 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 5.15 (m, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.84 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 3.91 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.70 (dq, *J* = 1.8, 6.0 Hz, 1H), 3.60 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.47 (dd, *J* = 10.2, 3.6 Hz, 1H), 2.27 (d, *J* = 14.4 Hz, 1H), 2.10 (ddd, *J* = 14.4, 4.8, 2.4 Hz, 1H), 2.05 (s, 3H), 1.87 (ddd, *J* = 14.4, 9.6, 2.4 Hz, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H); **isomer II**: δ 7.34 (m, 5H), 5.96 (d, *J* = 10.2 Hz, 1H), 5.78 (d, *J* = 10.2 Hz, 1H), 5.42 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 5.18 (m, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.80 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 3.86 (m, 2H), 3.64 (dq, *J* = 6.6, 6.0 Hz, 1H), 3.45 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.16 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.06 (s, 3H), 1.83 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.63 (d, *J* = 7.8 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.29 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) **isomer I**: δ 170.3, 137.67, 131.8, 128.4, 128.2 (2C), 127.7 (3C), 98.3, 97.21, 78.2, 71.5, 70.51, 70.1, 69.3, 64.4, 35.9, 21.28, 18.1, 16.7; **isomer II** : δ 170.2, 137.65, 132.9, 129.3, 128.37 (2C), 127.8 (3C), 97.5, 97.16, 78.1, 74.5, 70.49, 69.8, 69.4, 68.5, 35.8, 21.25, 18.3, 18.2; CLHRMS Calcd for [$C_{21}H_{28}O_7Na^+$]: 415.1727, Found 415.1726.

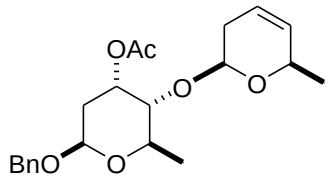
Digitoxigen 3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2R,6R)-5,6-dihydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl]-β-D-ribo-hexopyranoside (12ii)





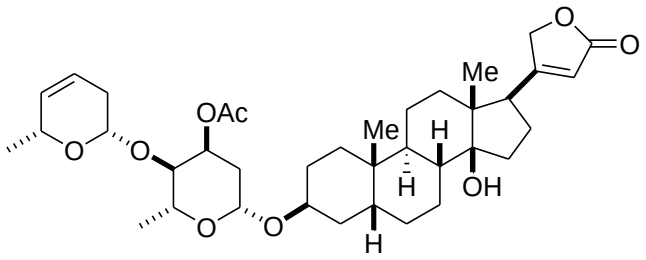
A CH_2Cl_2 (0.6 mL) solution of enone **12i** (764 mg, 1.16 mmol) and $CeCl_3$ in MeOH solution (0.4 M, 1.2 mL) was cooled to -78 ^oC. $NaBH_4$ (44 mg, 1.16 mmol) was added and the reaction mixture was stirred at -78^{o}C for 3 hours. The reaction mixture was diluted with Et_2O (10 mL) and was quenched with 10 mL of H_2O, extracted (3 x 10 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 70% EtOAc/hexanes to give allylic alcohols **12ii** (730 mg, 1.11 mmol, 95%) as a white solid (diastereometric ratio I:II = 1.5:1, inseparable by silica gel chromatography): R_f (80% EtOAc/hexanes) = 0.33; IR (thin film, cm^{-1}) 3483, 2935, 2878, 1781, 1739, 1620, 1448, 1378, 1245, 1170, 1153, 1058, 1026, 1004, 914, 863, 732; ^{1}H NMR (600 MHz, $CDCl_3$): **isomer I**: δ 6.14 (ddd, *J* = 9.6, 5.4, 1.2 Hz, 1H), 5.84 (m, 1H), 5.72 (dd, *J* = 9.6, 1.2 Hz, 1H), 5.52 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.11 (ddd, *J* = 1.8, 1.2, 1.2 Hz, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.74 (dd, *J* = 9.6, 1.8 Hz, 1H), 3.99 (m, 1H), 3.78 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.67 (qd, *J* = 6.6, 1.8 Hz, 1H), 3.57 (m, 1H), 3.42 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.75 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.20-1.94 (m, 4H), 2.05 (s, 3H), 1.89-1.10 (m, 19H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 3H), 0.84 (s, 3H); **isomer II**: δ 5.93 (ddd, *J* = 9.6, 1.8, 1.8 Hz, 1H), 5.84 (m, 1H), 5.75 (ddd, *J* = 9.6, 1.8, 1.8 Hz, 1H), 5.37 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.14 (ddd, *J* = 1.8, 1.2, 1.2 Hz, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.71 (dd, *J* = 9.6, 1.8 Hz, 1H), 3.99 (m, 1H), 3.84 (m, 1H), 3.83 (qd, *J* = 9.6, 6.0 Hz, 1H), 3.53 (dq, *J* = 6.0, 6.0 Hz, 1H), 3.40 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.75 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.20-1.94 (m, 4H), 2.07 (s, 3H), 1.89-1.10 (m, 19H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.25 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) **isomer I** : δ 174.6, 174.5, 170.3(2C), 131.7, 129.4, 117.6, 98.2, 95.89, 85.5, 78.1, 73.4, 73.0, 71.4, 70.4, 69.2, 69.0, 50.9, 49.6, 41.8, 40.0, 36.42, 36.2, 35.7, 35.1, 33.1, 30.1, 26.9, 26.63, 26.59, 23.6, 21.34, 21.33, 21.1, 18.1, 16.7, 15.7; **isomer II**: δ 174.6, 174.5, 170.3(2C), 133.1, 128.1, 117.6, 97.4, 95.85, 85.5, 78.0, 74.5, 73.4, 70.1, 69.2, 68.4, 64.4, 50.9, 49.6, 41.8, 40.0, 36.37, 36.2, 35.7, 35.1, 33.1, 30.1, 26.9, 26.63, 26.59, 23.6, 21.34, 21.30, 21.1, 18.3, 18.2, 15.7; HRESIMS Calcd for [$C_{37}H_{54}O_{10}Na^+$]: 681.3615, Found 681.3607.

Phenylmethyl 3-*O*-acetyl--2,6-dideoxy-4-*O*-[(2S,6R)-3,6-dihydro-6-methyl-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranoside (11iii)



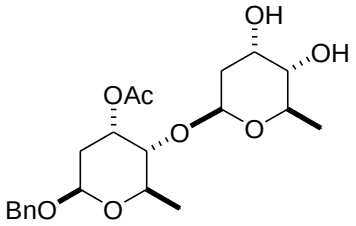
A flask was charged with dry *N*-methyl morpholine (NMM) 0.9 mL, triphenyl phosphine (465 mg, 1.78 mmol) and was cooled to -30^{o}C under Ar atmosphere. Diethylazodicarboxylate (0.25 mL, 1.61 mmol) was added and the reaction was stirred for 5 minutes, allylic alcohols **11ii** (195 mg, 0.50 mmol) was added in a 1M solution of NMM and the reaction mixture was stirred for 10 minutes, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (328 mg, 1.61 mmol). The reaction was stirred at -30 ^{o}C for 2 hours and was monitored by TLC. Upon consumption of starting material, the reaction was warmed up to room temperature and stirred for another 2 hours. The reaction mixture was diluted with Et_2O (10 mL) and was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 x 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 8% EtOAc/hexanes to give product **11iii** (156 mg, 0.41 mmol, 82%) as a viscous oil: R_f (15% EtOAc/hexanes) = 0.31; $[\alpha]_D^{21}$ +4.0 (*c* 0.5, $CHCl_3$); IR (thin film, cm^{-1}) 2974, 2927, 1742, 1453, 1367, 1243, 1156, 1090, 1065, 1044, 781, 698. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.63 (dddd, *J* = 9.6, 4.8, 2.4, 2.4 Hz, 1H), 5.55 (ddd, *J* = 10.2, 2.4, 1.2 Hz, 1H), 5.55 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.81 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.69 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.28 (m, 1H), 3.93 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.38 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.20 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.18 (ddd, *J* = 17.4, 7.2, 4.2 Hz, 1H), 2.13 (ddd, *J* = 17.4, 6.6, 3.0 Hz, 1H), 2.07(s, 3H), 1.84 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 137.7, 131.2, 128.4 (2C), 127.8 (2C), 127.7, 122.2, 100.3, 97.2, 79.2, 70.9, 70.5, 69.9, 69.4, 35.7, 30.9, 21.3, 20.8, 18.2; CLHRMS Calcd for $[C_{21}H_{28}O_6Na^+]$: 399.1778, Found 399.1773.

Digitoxigen 3-*O*-acetyl--2,6-dideoxy-4-*O*-[(2S,6R)-3,6-dihydro-6-methyl-2*H*-pyran-2-yl]-β-D-ribo-hexopyranoside (12iii)



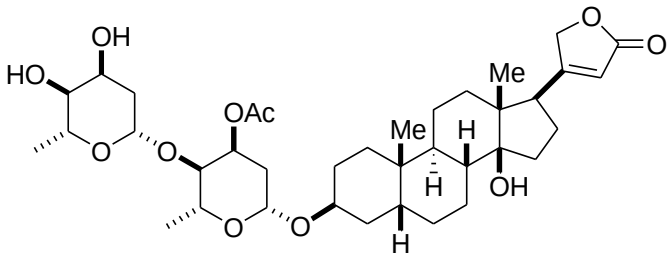
A flask was charged with dry *N*-methyl morpholine (NMM) 3.5 mL, triphenyl phosphine (951 mg, 3.63 mmol) and was cooled to -30 ^{o}C under Ar atmosphere. Diethylazodicarboxylate (0.52 mL, 3.30 mmol) was added and the reaction was stirred for 5 minutes, allylic alcohols **12ii** (725 mg, 1.10 mmol) was added in a 1M solution of NMM and the reaction mixture was stirred for 10 minutes, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (670 mg, 3.30 mmol). The reaction was stirred at -30 ^{o}C for 4 hours and was monitored by TLC. Upon consumption of starting material, the reaction was warmed up to room temperature and stirred for another 2 hours. The reaction mixture was diluted with Et_2O (20 mL) and was quenched with 10 mL of H_2O, extracted (3 x 10 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 85% Et_2O/hexanes to give product **12iii** (580 mg, 0.90 mmol, 82%) as a white solid: R_f (Et_2O) = 0.35; $[\alpha]_D^{21}$ +28.3 (*c* 1.20, $CHCl_3$); mp: 119-120 ^{o}C; IR (thin film, cm^{-1}) 3488, 2933, 2874, 1778, 1740, 1620, 1448, 1368, 1313, 1244, 1153, 1064, 1026, 1002, 973, 884, 784, 752, 684, 666. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.62 (dddd, *J* = 10.2, 5.4, 2.4, 2.4 Hz, 1H), 5.54 (dddd, *J* = 10.2, 4.8, 1.2 , 1.2 Hz, 1H), 5.39 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.98 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.74 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.66 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.26 (m, 1H), 4.01 (m, 1H), 3.87 (dq, *J* = 9.0, 6.6 Hz, 1H), 3.35 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.77 (m, 1H), 2.21-2.03 (m, 5H), 2.11 (s, 3H), 1.90-1.19 (m, 20H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.4, 173.4, 170.4, 131.2, 122.2, 117.7, 100.2, 96.0, 85.6, 79.3, 73.4, 73.0, 70.9, 70.2, 69.2, 50.9, 49.6, 41.9, 40.1, 36.4, 36.3, 35.8, 35.2, 33.1, 30.9, 30.173, 30.170, 26.9, 26.7, 26.6, 23.6, 22.6, 21.4, 21.2, 20.8, 18.2, 15.8; HRESIMS Calcd for [$C_{37}H_{54}O_9Na^+$]: 665.3666, Found 665.3658.

Phenylmethyl 3-*O*-acetyl-4-*O*-[2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-2,6-dideoxy-*β*-D-ribo-hexopyranoside (13)



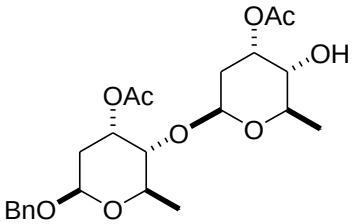
To a CH_2Cl_2 (3 mL) solution of olefin **12iii** (148 mg, 0.39 mmol) at 0 ^oC was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (0.11 mL). Crystalline OsO_4 (1.2 mg, 1 mol %) was added and the reaction was stirred for 3 hours. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 60% EtOAc/hexanes. Pure fractions were combined and concentrated to afford diol **13** (145 mg, 0.35 mmol, 90%): R_f (70% EtOAc/hexanes) = 0.18; $[\alpha]_D^{21}$ +1.6 (*c* 1.35, $CHCl_3$); IR (thin film, cm^{-1}) 3436, 2972, 2932, 2879, 1741, 1370, 1247, 1165, 1066, 1012, 868, 740, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.38 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.84 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.79 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.55 (d, *J* = 12.0 Hz , 1H), 4.05 (m, 1H), 3.88 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.67 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.35 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.24 (ddd, *J* = 9.0, 6.6, 3.6 Hz, 1H), 2.54 (s, 1H), 2.33(d, *J* = 5.4 Hz, 1H), 2.16 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.08 (ddd, *J* = 14.4, 3.0, 2.4 Hz, 1H), 2.06 (s, 3H), 1.82 (ddd, *J* = 14.4, 9.6, 3.0 Hz, 1H), 1.68 (ddd, *J* = 14.4, 9.6, 3.0 Hz, 1H), 1.31(d, *J* = 6.0 Hz, 3H), 1.22(d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 137.6, 128.3 (2C) , 127.8 (2C), 127.7, 98.6, 97.2, 79.4, 72.7, 70.5, 69.7, 69.3, 69.2, 68.0, 37.6, 35.6, 21.3, 18.2, 17.9; CLHRMS Calcd for $[C_{21}H_{30}O_8Na^+]$: 433.1833, Found 433.1826.

Digitoxigen 3-*O*-acetyl-4-*O*-[2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-2,6-dideoxy-*β*-D-ribo-hexopyranoside (14)



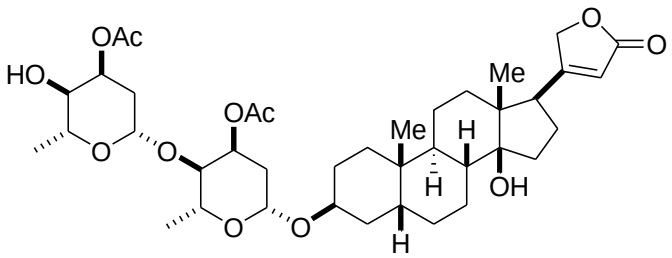
To a *t*-BuOH/acetone (1:1, 2 mL) solution of olefin **12iii** (530 mg, 0.824 mmol) at 0 ^{o}C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (0.8 mL). Crystalline OsO_4 (2.2 mg, 1 mol %) was added and the reaction was stirred for 8 hours. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using EtOAc. Pure fractions were combined and concentrated to afford alcohol **14** (507 mg, 0.75 mmol, 91%) as a white solid: R_f (EtOAc) = 0.33; $[\alpha]_D^{21}$ +23.5 (*c* 2.25, $CHCl_3$); IR (thin film, cm^{-1}) 3467, 2936, 1780, 1741, 1618, 1449, 1370, 1246, 1164, 1023, 752, 666; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.36 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.98 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.83 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.80 (d, *J* = 18.0, 1.2 Hz , 1H), 4.72 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.07 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 3.99 (m, 1H), 3.82 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.67 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.32 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.25 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.76 (m, 1H), 2.08 (s, 3H), 2.20-2.02(m, 5H), 1.90-1.20 (m, 20H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 174.6, 170.4, 117.6, 98.6, 95.9, 85.6, 79.5, 73.5, 73.0, 72.8, 70.0, 69.3, 69.1, 68.1, 50.9, 49.6, 41.8, 40.0, 37.6, 36.228, 36.223, 35.7, 35.1, 33.1, 30.1(2C), 26.9, 26.6, 26.6, 23.6, 21.4(2C), 21.1, 18.2, 18.0, 15.7; HRESIMS Calcd for $[C_{37}H_{56}O_{11}Na^+]$: 699.3720, Found 699.3712.

Phenylmethyl 3-*O*-acetyl-4-*O*-[3-*O*-acetyl-2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-2,6-dideoxy-*β*-D-ribo-hexopyranoside (15)



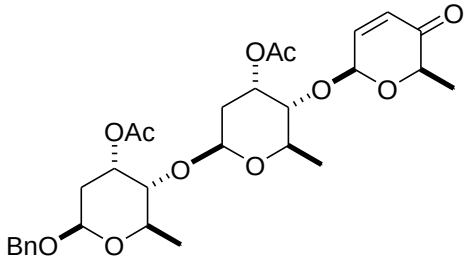
A round bottom flask containing a 0.5 M solution of diol **13** (140 mg, 0.34 mmol) in benzene (0.6 mL) was stirring at room temperature. To this solution were added trimethylorthoacetate (0.13 mL, 1.02 mmol) and a catalytic amount of *p*-toluenesulfonic acid (3.2 mg, 17 μmol). The reaction was allowed to stir until starting material is gone. The solvent was removed under reduced pressure and the residue was dissolved in 0.8 mL THF/H_2O (1:1,v/v) solution. Then *p*-toluenesulfonic acid (97 mg, 0.51 mmol) was added. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 45% EtOAc/hexanes. Pure fractions were combined and concentrated to afford compound **15** (143 mg, 0.32 mmol, 93%) as a white solid: R_f (80% EtOAc/hexanes) = 0.48; mp: 105-106 ^oC; $[\alpha]_D^{21}$ + 14.8 (*c* 1.15, $CHCl_3$); IR (thin film, cm^{-1}) 3475, 2972, 2932, 2879, 1741, 1370, 1243, 1165, 1068, 1009, 947, 870, 704; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.39 (ddd, *J* = 3.6, 3.0, 3.0 Hz , 1H), 5.25 (ddd, *J* = 3.6, 3.0, 2.4 Hz , 1H), 4.89 (d, *J* = 12.0 Hz ,1H), 4.79 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.74 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.55 (d, *J* = 12.0 Hz , 1H), 3.88 (dq, *J* = 9.0, 6.0 Hz , 1H), 3.65 (dq, *J* = 9.0, 6.0 Hz , 1H), 3.36 (dd, *J* = 9.0, 3.0 Hz , 1H), 3.35 (ddd, *J* = 9.0, 3.0, 3.0 Hz , 1H), 2.17 (ddd, *J* = 14.4, 3.6, 1.8 Hz , 1H), 2.13 (s, 3H), 2.08 (ddd, *J* = 14.4, 3.6, 2.4 Hz , 1H), 2.05 (s, 3H), 1.81 (ddd, *J* = 14.4, 9.6, 3.0 Hz , 1H), 1.78 (ddd, *J* = 14.4, 9.6, 3.0 Hz , 1H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 170.4, 137.8, 128.6 (2C) , 128.2 (2C), 127.9, 98.8, 97.4, 79.8, 72.2, 71.3, 70.7, 70.4, 69.7, 69.5, 36.1, 35.8, 21.5, 21.4, 18.4, 18.1; CLHRMS Calcd for $[C_{23}H_{32}O_9Na^+]$: 475.1938, Found 475.1926.

Digitoxigen 3-*O*-acetyl-4-*O*-[3-*O*-acetyl-2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-2,6-dideoxy-*β*-D-ribo-hexopyranoside (16)



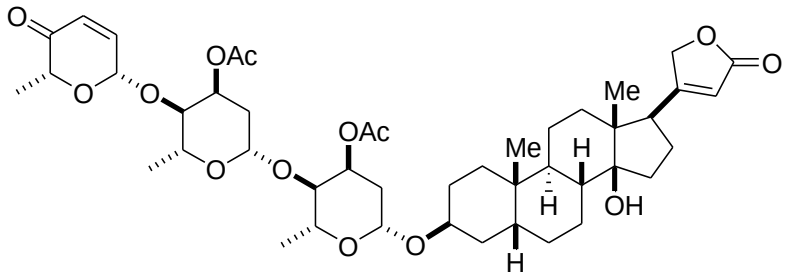
A round bottom flask containing a 0.5 M solution of alcohol **14** (391 mg, 0.578 mmol) in CH_2Cl_2 (2.5 mL) was stirring at room temperature. To this solution were added trimethylorthoacetate (0.22 mL, 1.73 mmol) and a catalytic amount of *p*-toluenesulfonic acid (5 mg, 29 μmol). The reaction was allowed to stir until starting material was gone. The solvent was removed under reduced pressure and the residue was dissolved in 3 mL THF/H_2O (1:1, v/v) solution. Then *p*-toluenesulfonic acid (55 mg, 0.29 mmol) was added. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 90% EtOAc/hexanes. Pure fractions were combined and concentrated to afford compound **16** (413 mg, 0.574 mmol, 99%) as a white solid: R_f (EtOAc) = 0.44; mp: 139-140 ^oC; $[\alpha]_D^{21}$ + 32.5 (*c* 1.10, $CHCl_3$); IR (thin film, cm^{-1}) 3460, 2972, 2937, 2876, 1780, 1740, 1619, 1449, 1371, 1318, 1244, 1167, 1066, 1024, 1004, 949, 868, 752; ^1H NMR (600 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.37 (ddd, *J* = 3.0, 3.0, 3.0 Hz , 1H), 5.25 (ddd, *J* = 3.0, 3.0, 3.0 Hz , 1H), 4.97 (dd, *J* = 18.0, 1.2 Hz ,1H), 4.79 (dd, *J* = 18.0, 1.2 Hz ,1H), 4.725 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.718 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.00 (m, 1H), 3.82 (dq, *J* = 9.0, 6.0 Hz , 1H), 3.64 (dq, *J* = 9.6, 6.0 Hz , 1H), 3.36 (ddd, *J* = 9.0, 6.0, 3.0 Hz , 1H), 3.32 (dd, *J* = 9.0, 3.0 Hz , 1H), 2.76 (m, 1H), 2.20-1.96 (m, 5H), 2.13 (s, 3H), 2.09 (s, 3H), 1.90-1.15 (m , 20H), 1.241 (d, *J* = 6.0 Hz, 3H), 1.240 (d, *J* = 6.0 Hz, 3H), 0.915 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 174.4, 171.2, 170.2, 117.7, 98.5, 95.9, 85.6, 79.5, 73.4, 73.0, 72.1, 71.1, 70.2, 69.8, 69.0, 50.9, 49.6, 41.8, 40.0, 36.2 (2C), 35.8, 35.7, 35.2, 33.1, 30.14, 30.12, 26.9, 26.63, 26.59, 23.6, 21.4, 21.3, 21.1 (2C), 18.2, 17.9, 15.7; HRESIMS Calcd for $[C_{39}H_{58}O_{12}Na^+]$:741.3826, Found 741.3819.

Phenylmethyl 3-*O*-acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2R,6R)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (15i)



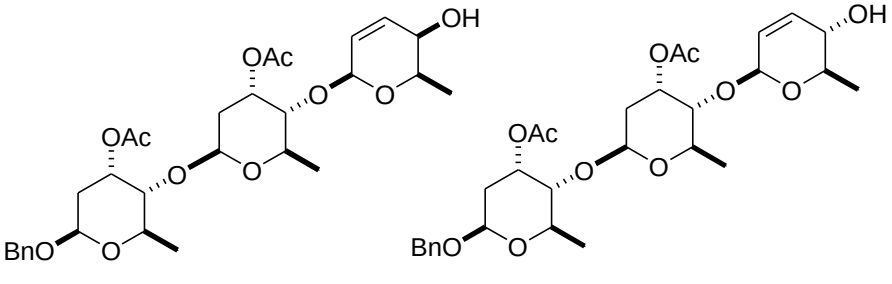
A CH_2Cl_2 (0.3 mL) solution of Boc pyranone **7** (228 mg, 0.62 mmol) and alcohol **15** (141 mg, 0.31 mmol) was cooled to 0 ^oC. A CH_2Cl_2 (0.2 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (16 mg, 2.5 mol%) and PPh_3 (16 mg, 10 mol%) was added to the reaction mixture at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 2 hours. The reaction mixture was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 x 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 33% EtOAc/hexanes to give enone **15i** (138 mg, 0.25 mmol, 79%) as a white solid: R_f (40% EtOAc/hexanes) = 0.18; mp: 95-96 ^oC; $[\alpha]_D^{21}$ +43.0 (*c* 0.3, $CHCl_3$); IR (thin film, cm^{-1})2980, 1740, 1702, 1454, 1372, 1243, 1158, 1055, 1006; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.87 (dd, *J* = 10.2, 1.2 Hz, 1H), 6.11 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.40 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.39 (m, 2H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.79 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.74 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.14 (q, *J* = 6.0 Hz, 1H), 3.88 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.86 (dq, *J* = 9.0, 6.0 Hz, 1H), 3. 45 (dd, *J* = 9.6, 3.0 Hz, 1H), 3. 34 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.15 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.11 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.81 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.76 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.26 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 170.1, 170.07, 146.2, 137.6, 128.7, 128.3 (2C), 127.8 (2C), 127.7, 98.7, 97.1, 97.07, 79.6, 79.2, 75.1, 70.5, 69.64, 69.60, 69.2, 69.0, 35.9, 35.7, 21.24, 21.20, 18.2, 18.0, 16.3; CLHRMS Calcd for $[C_{29}H_{38}O_{11}Na^+]$: 585.2306, Found 585.2299.

Digitoxigen 3-*O*-acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2R,6R)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (16i)



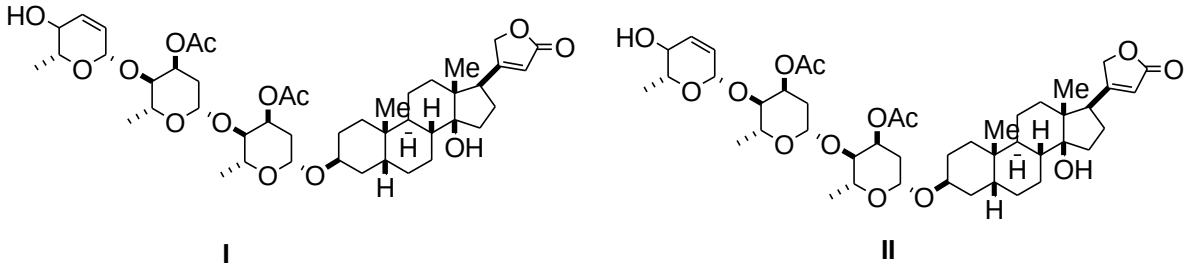
A CH_2Cl_2 (1.0 mL) solution of Boc pyranone **7** (418 mg, 1.83 mmol) and alcohol **16** (410 mg, 0.57 mmol) was cooled to 0 ^oC. A CH_2Cl_2 (0.3 mL) solution of $Pd_2(DBA)_3$•$CHCl_3$ (15 mg, 2.5 mol%) and PPh_3 (15 mg, 10 mol%) was added to the reaction mixture at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 8 hours and was quenched with 10 mL of saturated aqeous $NaHCO_3$, extracted (3 x 10 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 58% EtOAc/hexanes to give enone **16i** (425 mg, 0.513 mmol, 90%) as a white solid: R_f (60% EtOAc/hexanes) = 0.27; mp: 174-175 ^oC; $[\alpha]_D^{21}$ + 58.3 (*c* 1.40, $CHCl_3$); IR (thin film, cm^{-1}) 3524, 2980, 2938, 2876, 1780, 1744, 1702, 1622, 1449, 1372, 1243, 1156, 1094, 1056, 1026, 1004, 950, 756; ^1H NMR (600 MHz, $CDCl_3$) δ 6.87 (dd, *J* = 10.2, 1.8 Hz, 1H), 6.10 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.86 (m, 1H), 5.40-5.36 (m, 3H), 4.97 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.79 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.73 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.71 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.14 (q, *J* = 6.6 Hz, 1H), 3.99 (m, 1H), 3.86 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.81 (dq, *J* = 9.6, 6.0 Hz, 1H), 3. 44 (dd, *J* = 9.0, 3.0 Hz, 1H), 3. 31 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.76 (m, 1H), 2.20-2.00 (m, 5H), 2.09 (s, 3H), 2.08 (s, 3H), 1.90-1.15 (m, 20H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.25 (d, *J* = 6.6 Hz, 3H), 1.23 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 174.5, 174.4, 170.2, 170.1, 146.2, 128.7, 117.6, 98.7, 97.1, 95.9, 85.5, 79.6, 79.2, 75.1, 73.4, 73.0, 70.0, 69.7, 68.99, 68.97, 50.9, 49.6, 41.8, 40.0, 36.3, 36.2, 35.9, 35.7, 35.1, 33.1, 30.1(2C), 26.9, 26.62 26.59, 23.6, 21.4, 21.3, 21.2, 21.1, 18.2, 18.0, 16.3, 15.7; HRESIMS Calcd for $[C_{45}H_{64}O_{14}Na^+]$: 851.4194, Found 851.4183.

Phenylmethyl 3-*O*-acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2R,6R)-5,6-dihydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (15ii)



A CH_2Cl_2 (0.3 mL) solution of enone **15i** (138 mg, 0.245 mmol) and $CeCl_3$ in MeOH solution (0.3 mL) was cooled to -78 ^oC. $NaBH_4$ (10 mg, 0.25 mmol) was added and the reaction mixture was stirred at -78^oC for 3 hours. The reaction mixture was diluted with Et_2O (5 mL) and was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 x 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 50% EtOAc/hexanes to give allylic alcohols **15ii** (374 mg, 1.70 mmol, 85%) as a viscous oil (diastereometric ratio I:II = 1.4:1, inseparable in chromatography): R_f (60% EtOAc/hexanes) = 0.25; IR (thin film, cm^{-1}) 3478, 2972, 2932, 2874, 1742, 1371, 1243, 1156, 1059, 1010; ^{1}H NMR (600 MHz, $CDCl_3$): **isomer I**: δ 7.33 (m, 5H), 6.15 (dd, *J* = 10.2, 6.0, Hz, 1H), 5.72 (d, *J* = 9.6 Hz, 1H), 5.54 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 5.40 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.12 (m, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.788 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.75 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.551 (d, *J* = 12.0 Hz, 1H), 3.88 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.87 (m, 1H), 3.77 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.68 (qd, *J* = 6.0, 1.8 Hz, 1H), 3.58 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.39 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.34 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.16 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.08 (s, 3H), 2.069 (s, 3H), 2.02 (ddd, *J* = 14.4, 3.0, 2.4 Hz, 1H), 1.79 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.72 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.70 (s, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.25 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H); **isomer II**: δ 7.33 (m, 5H), 5.94 (ddd, *J* = 10.8, 1.8, 1.8 Hz, 1H), 5.86 (d, *J* = 10.2 Hz, 1H), 5.75 (ddd, *J* = 10.2, 1.8, 1.2 Hz, 1H), 5.39 (ddd, *J* = 3.6, 3.0, 3.0Hz, 1H), 5.38 (ddd, *J* = 3.0, 3.0, 2.4 Hz, 1H), 5.13 (m, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.783 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.71 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.548 (d, *J* = 12.0 Hz, 1H), 3.87 (m, 1H), 3.83 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.54 (dq, *J* = 6.6, 6.0 Hz, 1H), 3.35 (m, 2H), 2.32 (d, *J* = 11.4 Hz, 1H), 2.16 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.09 (s, 3H), 2.056 (s, 3H), 2.02 (ddd, *J* = 14.4, 3.0, 2.4 Hz, 1H), 1.81 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.76 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.23 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) **isomer I**: δ 170.1 (2C), 133.0 (2C), 131.7, 128.1 (2C), 127.7 (3C), 98.75 (2C), 98.24, 98.22, 79.5, 77.8, 71.4, 69.9, 69.7, 69.2, 69.1, 64.4, 36.0, 35.7, 21.30, 21.28, 18.18, 18.03, 17.9; **isomer II** : δ 170.3 (2C), 137.6 (2C), 129.2, 128.3 (2C), 127.8 (3C), 98.72, 97.6, 97.2 (2C), 79.6, 78.0, 74.5, 70.5, 70.2, 69.6, 69.3, 68.4, 35.9, 35.6, 21.28, 21.26, 18.17, 18.16, 16.7; CLHRMS Calcd for [$C_{29}H_{40}O_{11}Na^+$]: 587.2463, Found 587.2453.

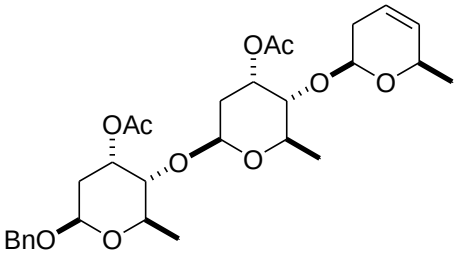
Digitoxigen 3-*O*-acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2R,6R)-5,6-dihydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (16ii)



I **II**

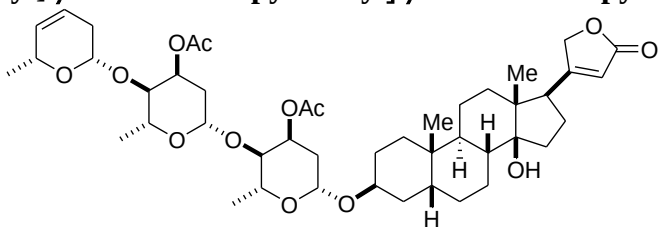
A CH_2Cl_2 (1.2 mL) solution of enone **16i** (405 mg, 0.488 mmol) and $CeCl_3$ in MeOH solution (0.4 M, 1.2 mL) was cooled to -78 ^oC. $NaBH_4$ (18.5 mg, 0.49 mmol) was added and the reaction mixture was stirred at -78^oC for 3 hours. The reaction mixture was diluted with Et_2O(20 mL) and was quenched with 10 mL of saturated aqueous $NaHCO_3$, extracted (3 x 10 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 85% EtOAc/hexanes to give allylic alcohols **16ii** (397 mg, 0.478 mmol, 98%) as a white solid (diastereometric ratio I:II = 1.7:1, inseparable in chromatography): R_f (90% EtOAc/hexanes) = 0.33; IR (thin film, cm^{-1}) 3480, 2972, 2934, 2876, 1780, 1742, 1621, 1449, 1372, 1316, 1244, 1155, 1060, 1025, 1008, 755, 668; ^1H NMR (600 MHz, $CDCl_3$): **isomer I**: δ 6.14 (ddd, *J* = 9.6, 5.4, 1.2 Hz, 1H), 5.84 (m, 1H), 5.70 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.51 (ddd, *J* = 3.6, 3.0, 3.0Hz, 1H), 5.36 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.10 (ddd, *J* = 1.2, 1.2, 1.2 Hz, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.710 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.706 (dd, *J* = 9.6, 1.8 Hz, 1H), 3.98 (m, 1H), 3.80 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.74 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.66 (qd, *J* = 6.0, 1.8 Hz, 1H), 3.57 (m, 1H), 3.37 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.30 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.75 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.20-1.96 (m, 5H), 2.073 (s, 3H), 2.05 (s, 3H), 1.90-1.12 (m, 20H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 3H), 0.85 (s, 3H); **isomer II**: δ 5.92 (ddd, *J* = 10.2, 2.4, 1.8 Hz, 1H), 5.84 (m, 1H), 5.74 (ddd, *J* = 10.2, 2.4, 1.8 Hz, 1H), 5.35 (m, 2H), 5.12 (ddd, *J* = 1.8, 1.8, 1.2 Hz, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.70 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.67 (dd, *J* = 9.6, 1.8 Hz, 1H), 3.98 (m, 1H), 3.84 (m, 1H), 3.79 (m, 2H), 3.52 (dq, *J* = 6.0, 6.0 Hz, 1H), 3.33 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.28 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.75 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.20-1.96 (m, 5H), 2.071 (s, 3H), 2.066 (s, 3H), 1.90-1.12 (m, 20H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) **isomer I** : δ 174.5, 174.4, 170.3 (2C), 131.7, 129.2, 117.6, 98.72, 98.2, 95.9, 85.6, 79.46, 77.8, 73.4, 73.0, 70.2, 69.06(2C), 69.04, 68.4, 50.9, 49.6, 41.8, 40.0, 36.28, 36.24, 36.0, 35.7, 35.1, 33.1, 30.1(2C), 26.9, 26.63, 26.59, 23.6, 21.35, 21.34, 21.30, 21.1, 18.21, 17.9, 16.7, 15.7; **isomer II**: δ 174.5, 174.4, 170.2 (2C), 132.9, 128.1, 98.70, 97.6, 95.9, 85.6, 79.53, 78.0, 74.5, 73.4, 71.4, 69.98, 69.94, 69.2, 68.4, 64.4, 50.9, 49.6, 41.8, 40.0, 36.25, 36.24, 35.9, 35.7, 35.1, 33.1, 30.1(2C), 26.9, 26.63, 26.59, 23.6, 21.35, 21.34, 21.27, 21.1, 18.19, 18.16, 18.0, 15.7; HRESIMS Calcd for [$C_{45}H_{66}O_{14}Na^+$]: 853.4350, Found 853.4339.

Phenylmethyl 3-*O*-acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2S,6R)-3,6-dihydro-6-methyl-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (15iii)



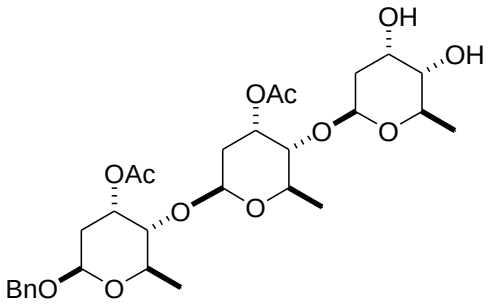
A flask was charged with dry *N*-methyl morpholine (NMM) 0.4 mL, triphenyl phosphine (191 mg, 0.73 mmol) and was cooled to -30^{o}C under Ar atmosphere. Diethylazodicarboxylate (0.1 mL, 0.66 mmol) was added and the reaction was stirred for 5 minutes, allylic alcohols **15ii** (125 mg, 0.22 mmol) was added in a 1M solution of NMM and the reaction mixture was stirred for 10 minutes, followed by addition of o-nitrobenzenesulfonyl hydrazide (NBSH) (135 mg, 0.66 mmol). The reaction was stirred at -30 ^{o}C for 4hours and was monitored by TLC, upon consumption of starting material, warm up to room temperature and stirred for another 2hours. The reaction mixture was diluted with Et_2O (10 mL) and was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 x 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% EtOAc/hexanes to give product **15iii** (97 mg, 0.18 mmol, 81%) as a white solid: R_f (50% EtOAc/hexanes) = 0.44; mp: 101-101.5 ^{o}C; $[\alpha]_D^{21}$ +38.0 (*c* 0.9, $CHCl_3$); IR (thin film, cm^{-1}) 2981, 2932, 2871, 1742, 1368, 1243, 1157, 1090, 1067, 1008, 704; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.62 (dddd, *J* = 10.2, 4.8, 2.4, 2.4 Hz, 1H), 5.53 (ddd, *J* = 9.6, 1.2, 1.2 Hz, 1H), 5.41 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.37 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.78 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.71 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.65 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.25 (m, 1H), 3.87 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.84 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.34 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.28 (dd, *J* = 9.6, 3.6Hz, 1H), 2.14 (m, 4H), 2.11 (s, 3H), 2.06 (s, 3H), 1.81 (dddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.74 (dddd, *J* = 14.4, 9.6, 3.0 Hz, 1H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 170.1, 137.6, 131.1, 128.3 (2C), 127.8 (2C), 127.7, 122.2, 100.3, 98.8, 97.2, 79.5, 78.9, 70.9, 70.5, 70.1, 69.7, 69.3, 69.2, 35.9, 35.7, 30.9, 21.33, 21.26, 20.8, 18.2, 18.0; CLHRMS Calcd for [$C_{29}H_{40}O_{10}Na^{+}$]: 571.2514, Found 571.2525.

Digitoxigen 3-*O*-acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2S,6R)-3,6-dihydro-6-methyl-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (16iii)



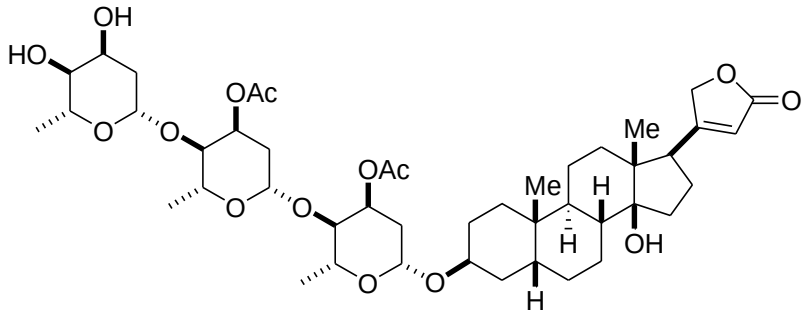
A flask was charged with dry *N*-methyl morpholine (NMM) 2.0 mL, triphenyl phosphine (411 mg, 1.57 mmol) and was cooled to -30 ^{o}C under Argon atmosphere. Diethylazodicarboxylate (0.22 mL, 1.42 mmol) was added and the reaction was stirred for 5 minutes, allylic alcohols **16ii** (395 mg, 0.475 mmol) was added in a 1 M solution of NMM and the reaction mixture was stirred for 10 minutes, followed by addition of o-nitrobenzenesulfonyl hydrazide (NBSH) (289 mg, 1.42 mmol). The reaction was stirred at -30 ^{o}C for 4 hours and was monitored by TLC, upon consumption of starting material, warm up to room temperature and stirred for another 1 hour. The reaction mixture was diluted with Et_2O (20 mL) and was quenched with 10 mL of H_2O, extracted (3 x 10 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 88% Et_2O/hexanes to give product **16iii** (345 mg, 0.42 mmol, 89%) as a white solid: R_f (Et_2O) = 0.33; mp: 144-145 ^{o}C; $[\alpha]_D^{21}$ +48.2 (*c* 1.50, $CHCl_3$); IR (thin film, cm^{-1}) 3516, 2967, 2935, 2871, 1782, 1742, 1621, 1449, 1369, 1316, 1243, 1155, 1091, 1064, 1047, 1026, 1005, 950, 882, 753; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.61 (dddd, *J* = 9.6, 4.8, 2.4, 2.4 Hz, 1H), 5.53 (dddd, *J* = 10.2, 2.4, 1.2, 1.2 Hz, 1H), 5.38 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.36 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.97 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.79 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.72 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.69 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.65 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.25 (m, 1H), 3.99 (m, 1H), 3.84 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.82 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.31 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.28 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.76 (m, 1H), 2.20-2.02 (m, 6H), 2.10 (s, 3H), 2.09 (s, 3H), 1.90-1.15 (m, 21H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.45, 174.41, 170.3, 170.2, 131.1, 122.2, 117.7, 100.3, 98.8, 95.9, 85.6, 79.5, 79.0, 73.4, 73.0, 70.9, 70.10, 70.06, 69.2, 69.1, 50.9, 49.6, 41.9, 40.1, 36.30, 36.25, 35.9, 35.8, 35.2, 33.1, 30.9, 30.2 (2C), 26.9, 26.65, 26.61, 23.6, 21.37, 21.35, 21.34, 21.1, 20.8, 18.2, 18.0, 15.8; HRESIMS Calcd for [$C_{45}H_{66}O_{13}Na^{+}$]: 837.4401, Found 837.4390.

Phenylmethyl 3-*O*-acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-4-*O*-[2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (15iv)



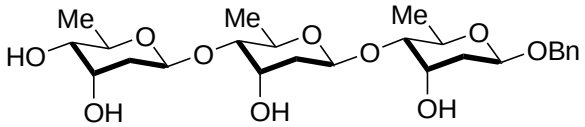
To a CH_2Cl_2 (0.6 mL) solution of olefin **15iii** (94 mg, 0.17 mmol) at 0 ^oC was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (80 μL). Crystalline OsO_4 (0.4 mg, 1 mol %) was added and the reaction was stirred for 3 hours. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 60% EtOAc/hexanes. Pure fractions were combined and concentrated to afford alcohol **15iv** (92 mg, 0.16 mmol, 92%) as a white solid: R_f (80% EtOAc/hexanes) = 0.25; mp: 167-167.5 ^oC; $[\alpha]_D^{21}$ +35.0 (*c* 1.45, $CHCl_3$); IR (thin film, cm^{-1}) 3455, 2972, 2932, 2880, 1741, 1370, 1244, 1162, 1065, 1011, 869, 704; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.39 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.34 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.81 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.78 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.70 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.54 (d, *J* = 12.0 Hz , 1H), 4.05 (m, 1H), 3.86 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.80 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.65 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.33 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.27 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.23 (ddd, *J* = 9.6, 6.0, 3.6 Hz, 1H), 2.47 (s, 1H), 2.25 (d, *J* = 6.6 Hz, 1H), 2.15 (ddd, *J* = 14.4, 3.6, 1.8 Hz, 1H), 2.09 (s, 3H), 2.08 (ddd, *J* = 14.4, 3.0, 1.8 Hz, 1H), 2.06 (ddd, *J* = 14.4, 3.0, 1.8 Hz, 1H), 2.05 (s, 3H), 1.80 (ddd, *J* = 14.4, 9.6, 2.4 Hz, 1H), 1.72 (ddd, *J* = 14.4, 9.6, 3.0 Hz, 1H), 1.66 (ddd, *J* = 13.8, 9.6, 3.0 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 170.2, 137.6, 128.3(2C) , 127.8 (2C), 127.7, 98.8, 98.7, 97.2, 79.5, 79.2, 72.7, 70.5, 69.9, 69.7, 69.3 (2C), 69.1, 68.0, 37.6, 35.9, 35.6, 21.3, 21.2, 18.2, 17.9 (2C); CIHRMS Calcd for $[C_{29}H_{42}O_{12}Na^+]$: 605.2568, Found 605.2580.

Digitoxigen 3-*O*-acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-4-*O*-[2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (16iv)



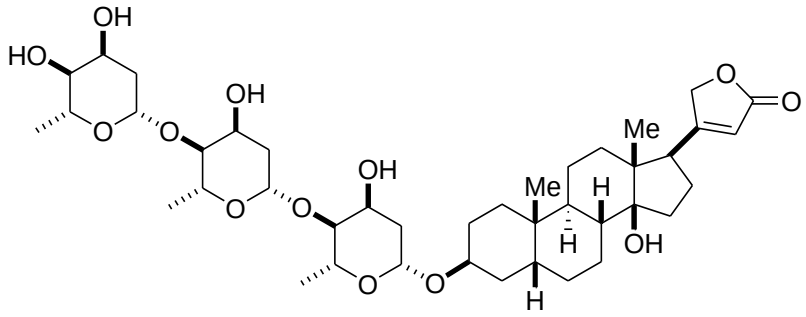
To a CH_2Cl_2 (0.8 mL) solution of olefin **16iii** (115 mg, 0.14 mmol) at 0 ^oC was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (100 μL). Crystalline OsO_4 (0.4 mg, 1 mol %) was added and the reaction was stirred for 4 hours. The reaction was concentrated and was purified by a silica gel column using EtOAc. Pure fractions were combined and concentrated to afford alcohol **16iv** (110 mg, 0.13 mmol, 91%) as a white solid: R_f (EtOAc) = 0.31; mp: 162-163 ^oC; $[\alpha]_D^{21}$ +47.2 (*c* 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3494, 2962, 2934, 2881, 1780, 1741, 1624, 1449, 1370, 1246, 1164, 1064, 1024, 948, 870, 753; ^1H NMR (600 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.37 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 5.33 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.98 (dd, *J* = 18.0, 1.8 Hz , 1H), 4.82 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.2 Hz , 1H), 4.71 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.67 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.08 (ddd, *J* = 3.0, 3.0, 3.0 Hz , 1H), 3.99 (m, 1H), 3.82 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.79 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.66 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.29 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.26 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.25 (ddd, *J* = 9.6, 6.0, 3.0 Hz, 1H), 2.76 (m, 1H), 2.20-2.01 (m, 6H), 2.09 (s, 6H), 1.90-1.18 (m, 21H), 1.22 (d, *J* = 6.0 Hz, 6H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 174.6, 170.33, 170.27, 117.6, 98.76, 98.71, 95.8, 85.6, 79.6, 79.2, 73.5, 73.0, 72.8, 70.02, 69.95, 69.3, 69.08, 69.05, 68.0, 50.9, 49.6, 41.8, 40.0, 37.7, 36.250, 36.245, 35.9, 35.7, 35.2, 33.1, 30.14, 30.12, 26.9, 26.63, 26.60, 23.6, 21.37, 21.34, 21.32, 21.1, 18.2, 17.97, 17.95, 15.8; HRESIMS Calcd for $[C_{45}H_{68}O_{15}Na^+]$: 871.4456, Found 871.4448.

Phenylmethyl 2,6-dideoxy-4-*O*-[[2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (17)



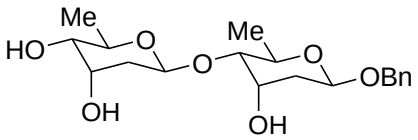
To a MeOH/H_2O (0.3 mL, 1:1, 1M) solution of alcohol **15iv** (14 mg, 24 μmol) at room temperature was added LiOH (2.5 mg, 60 μmol) and the reaction was stirred for 3 hours. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 75% EtOAc/hexanes. Pure fractions were combined and concentrated to afford **17** (11.5 mg, 23 μmol, 96%) as a white solid: R_f (80% EtOAc/hexanes) = 0.18; mp: 120-121 ^oC; $[\alpha]_D^{21}$ –13.3 (*c* 0.60, $CHCl_3$); IR (thin film, cm^{-1}) 3424, 2927, 2886, 1455, 1369, 1318, 1163, 1130, 1068, 1012, 869, 733, 699; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.91 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.90 (m, 2H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz , 1H), 4.25 (m, 2H), 4.12 (ddd, *J* = 3.6, 3.6, 2.4 Hz, 1H), 3.83 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.81(dq, *J* = 9.0, 6.0 Hz, 1H), 3.76 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.30 (m, 1H), 3.26 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.20 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.99 (s, 1H), 2.95 (s, 1H), 2.33 (s, 1H), 2.16 (ddd, *J* = 13.8, 3.6, 2.4 Hz, 1H), 2.14 (ddd, *J* = 14.4, 3.0, 2.4 Hz, 1H), 2.11 (ddd, *J* = 13.8, 3.0, 2.4 Hz, 1H), 2.03 (s, 1H), 1.78 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.74 (m, 2H), 1.28 (d, *J* = 6.6 Hz, 6H), 1.22 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8, 128.3 (2C) , 127.9 (2C), 127.6, 98.30, 98.26, 97.1, 82.6, 82.2, 72.7, 70.6, 69.5, 68.32, 68.26, 68.1, 66.4, 66.2, 37.8, 36.7, 36.6, 18.2 (2C), 18.1; CLHRMS Calcd for $[C_{25}H_{38}O_{10}Na^+]$: 521.2357, Found 521.2360.

Digitoxin (3)



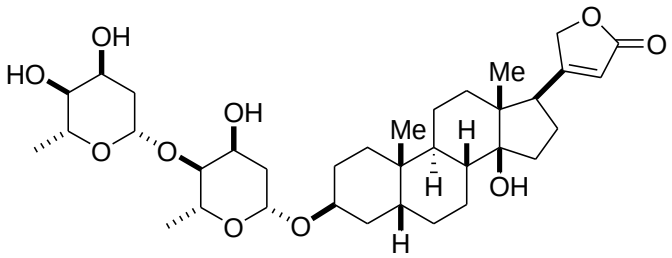
To a MeOH/H_2O (2 mL, 4:1) solution of diacetate **16iv** (20 mg, 23.5 μmol) at room temperature was added LiOH·H_2O (3 mg, 70 μmol) and the reaction was stirred for 2 hours. The reaction was quenched with adding 5 mL pH = 6.0 buffering solution. The mixture was extracted with CH_2Cl_2 (3×5 mL). The organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. It was purified by a silica gel column using 5% MeOH/EtOAc. Pure fractions were combined, concentrated, and crystallized from acetone/hexanes to afford digitoxin **3** (15 mg, 19.6 μmol, 83%) as a white crystal: R_f (EtOAc) = 0.20; mp: 253-254 °C; $[\alpha]_D^{21}$ +18.0 (*c* 0.20, $CHCl_3$); IR (thin film, cm^{-1}) 3466, 2926, 2856, 1777, 1736, 1449, 1378, 1368, 1163, 1128, 1068, 1013, 991, 869, 732; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (m, 1H), 4.98 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.91 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.89 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.86 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.25 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.24 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.13 (m, 1H), 4.02 (m, 1H), 3.83 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.78 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.76 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.31 (ddd, *J* = 9.6, 6.0, 3.0 Hz, 1H), 3.24 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.20 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.03 (s, 1H), 2.96 (s, 1H), 2.39 (s, 1H), 2.77 (m, 1H), 2.19-1.99 (m, 6H), 2.02 (s, 1H), 2.01 (s, 1H), 1.90-1.18 (m, 21H), 1.28 (d, *J* = 6.0 Hz, 3H), 1.223 (d, *J* = 6.0 Hz, 3H), 1.221 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.51, 174.48, 117.7, 98.3, 98.2, 95.4, 85.6, 82.6, 82.2, 73.4, 72.7 (2C) 72.5, 69.5, 68.3, 68.11, 68.08, 66.5, 66.4, 51.0, 49.6, 41.9, 40.1, 37.8, 37.2, 36.7, 36.2, 35.8, 35.2, 33.2, 30.2, 29.8, 26.9, 26.7, 26.5, 23.6, 21.4, 21.2, 18.16, 18.13, 15.8; HRESIMS Calcd for [$C_{41}H_{64}O_{13}Na^+$]: 787.4245, Found 787.4237.

Phenylmethyl 2,6-dideoxy-4-*O*-[2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (18)



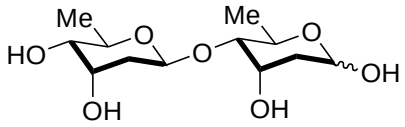
To a MeOH/H_2O (0.1 mL, 1:1, 1M) solution of diol **13** (6 mg, 14.6 μmol) at room temperature was added LiOH (0.35 mg, 14.6 μmol) and the reaction was stirred for 3 hours. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 65% EtOAc/hexanes. Pure fractions were combined and concentrated to afford triol **18** (5 mg, 13.6 μmol, 93%) as a white solid: R_f (80% EtOAc/hexanes) = 0.28; mp: 145-145.5 ^{o}C; $[\alpha]_D^{21}$ –44.0 (*c* 0.20, $CHCl_3$); IR (thin film, cm^{-1}) 3437, 2962, 2931, 2886, 1454, 1405, 1368, 1164, 1068, 1011, 868, 735, 698; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.92 (m, 1H), 4.91 (m, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.26 (dddd, *J* = 6.6, 3.6, 3.6, 1.8 Hz, 1H), 4.12 (dddd, *J* = 5.4, 4.2, 3.0, 2.4 Hz, 1H), 3.82 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.67 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.30 (ddd, *J* = 9.6, 6.6, 3.0 Hz, 1H), 3.26 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.96 (m, *J* = 2.4, 1.8, 1.2 Hz, 1H), 2.28 (d, *J* = 1.2 Hz, 1H), 2.17 (ddd, *J* = 14.4, 4.2, 2.4 Hz, 1H), 2.13 (ddd, *J* = 14.4, 3.0, 2.4 Hz, 1H), 1.96 (d, *J* = 6.6 Hz, 1H), 1.79 (m, 1H), 1.75 (m, 1H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.28(d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8, 128.4 (2C) , 127.9 (2C), 127.6, 98.3, 97.1, 82.7, 72.8, 70.6, 69.5, 68.3, 68.2, 66.3, 37.9, 36.6, 18.2, 18.1; CLHRMS Calcd for $[C_{19}H_{28}O_7Na^+]$: 391.1727, Found 391.1726.

Digitoxigen 2,6-dideoxy-4-*O*-[2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranosid (2)



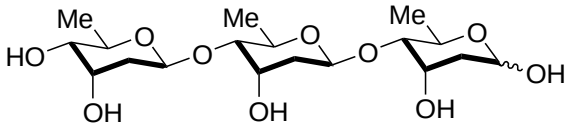
To a MeOH/H_2O (0.3 mL, 4:1, 1M) solution of alcohol **14** (17 mg, 25 μmol) at room temperature was added LiOH·H_2O (1.6 mg, 38 μmol) and the reaction was stirred for 3 hours. The reaction was quenched with 5 mL pH = 6.0 buffering solution. The mixture was extracted with CH_2Cl_2 (3×5 mL). The organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. It was purified by a silica gel column using EtOAc. Pure fractions were combined and concentrated, and further crystallized from $CHCl_3$/Et_2O to afford **2** (13 mg, 20.5 μmol, 82%) as a white solid: R_f (EtOAc) = 0.27; mp: 230-231 ^oC; $[\alpha]_D^{21}$ + 6.0 (*c* 0.40, $CHCl_3$); IR (thin film, cm^{-1}) 3450, 2933, 2876, 1778, 1740, 1621, 1449, 1380, 1165, 1132, 1067, 1013, 867, 754, 667; ^1H NMR (600 MHz, $CDCl_3$) δ 5.87 (m, 1H), 4.98 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.91 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.86 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.24 (ddd, *J* = 3.6, 3.0, 3.0Hz, 1H), 4.13 (ddd, *J* = 3.6, 3.0, 3.0Hz, 1H), 4.02 (m, 1H), 3.77 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.66 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.31 (m, 1H), 3.24 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.02 (s, 1H), 2.77 (m, 1H), 2.33 (s, 1H), 2.20-2.00 (m, 5H), 1.90-1.20 (m, 20H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 6.0 Hz, 3H), 0,92 (s, 3H), 0,87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.52, 174.48, 117.7, 98.2, 95.4, 85.6, 82.7, 73.4, 72.8, 72.6, 69.5, 68.2, 68.1, 66.5, 51.0, 49.6, 41.9, 40.1, 37.9, 37.2, 36.2, 35.8, 35.2, 33.2, 30.2, 29.8, 26.9, 26.7, 26.6, 23.6, 21.4, 21.2, 18.2, 18.1, 15.8; HRESIMS Calcd for [$C_{35}H_{54}O_{10}Na^+$]: 657.3615, Found 657.3608.

***O*-2,6-dideoxy-*β*-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-D-ribo-hexose (20)**



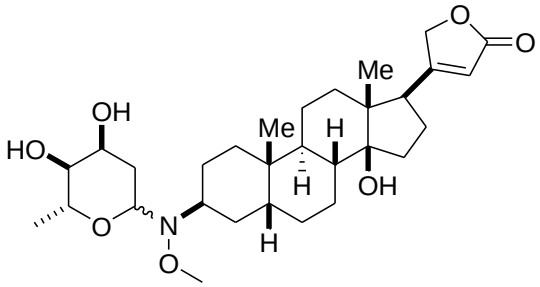
To an EtOH (2 mL) solution of **18** (15.6 mg, 42 μmol) under H_2 atmosphere at room temperature was added Pd/C (8 mg) and the reaction was stirred for 6 hours. The reaction mixture was filtered through a pad of celite using MeOH. The filtrate was concentrated and purified by a silica gel column using 1% MeOH/EtOAc. Pure fractions were combined and concentrated to afford digoxose **20** (11 mg, 39.5 μmol, 94%) as a white solid: R_f (10% MeOH/EtOAc) = 0.18; mp: 132-135 ^{o}C; $[\alpha]_D^{21}$ +56.7 (*c* 0.80, MeOH); IR (thin film, cm^{-1}) 3426, 2930, 1376, 1319, 1165, 1132, 1068, 1014, 992, 869, 729; ^{1}H NMR (600 MHz, $CD_3OD/CDCl_3$) **β**: δ 5.03 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.84 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.17 (ddd, *J* = 3.6, 3.0, 2.4 Hz, 1H), 3.98 (m, 1H), 3.78 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.69 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.15 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.13 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.04 (m, 2H), 1.61 (ddd, *J* = 13.8, 9.6, 3.0 Hz, 1H), 1.67 (m, 1H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.17 (d, *J* = 6.6 Hz, 3H); **α**: 5.01 (d, *J* = 3.0 Hz, 1H), 4.87 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.26 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.07 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.97 (m, 1H), 3.68 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.18 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.14 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.06 (m, 2H), 1.80 (ddd, *J* = 14.4, 3.0, 3.0 Hz, 1H), 1.68 (m, 1H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.16 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CD_3OD/CDCl_3$) **β**: δ 98.56, 91.4, 82.4, 72.46, 69.59, 68.0, 67.62, 66.3, 37.76, 37.69, 17.92, 17.86; **α**: δ 98.58, 91.5, 82.2, 72.44, 69.60, 67.6, 66.9, 61.6, 37.74, 34.3, 17.93, 17.7; CLHRMS Calcd for $[C_{12}H_{22}O_7Na^+]$: 301.1263, Found 301.1255.

***O*-2,6-dideoxy-*β*-D-ribo-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-*β*-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-D-ribo-hexose (21)**



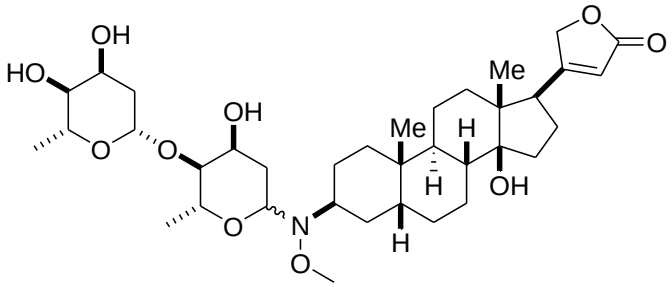
To an EtOH (0.3 mL) solution of **17** (11 mg, 22 μmol) under H_2 atmosphere at room temperature was added Pd/C (6 mg) and the reaction was stirred for 6 h. The reaction mixture was filtered through a pad of Celite using MeOH. The eluent was concentrated and purified by a silica gel column using 2% MeOH/EtOAc. Pure fractions were combined and concentrated to afford digoxose **21** (8 mg, 20 μmol, 92%) as a white solid: R_f (10% MeOH/EtOAc) = 0.29; mp: 210-212 ^{o}C; $[\alpha]_D^{21}$ +40.0 (*c* 0.35, MeOH); IR (thin film, cm^{-1}) 3425, 2929, 1376, 1319, 1231, 1165, 1133, 1067, 1013, 992, 869, 729; ^{1}H NMR (600 MHz, $CD_3OD/CDCl_3$) β: δ 5.04 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.845 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.841 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.18 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.17 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 3.98 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 3.78 (m, *2*H), 3.69 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.16 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.147 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.144 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.16 (m, 3H), 1.65 (m, 3H), 1.213 (d, *J* = 6.6 Hz, 3H), 1.175 (d, *J* = 6.6 Hz, 3H), 1.165 (d, *J* = 6.6 Hz, 3H); α: 5.01 (d, *J* = 3.0 Hz, 1H), 4.87 (dd, *J* = 10.2, 2.4 Hz, 1H), 4.848 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.26 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.06 (m, 2H), 3.77 (m, *2*H), 3.70 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.19 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.137 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.140 (m, 1H), 2.06 (m, 3H), 1.64 (m, 3H), 1.216 (d, *J* = 6.6 Hz, 3H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.160 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CD_3OD/CDCl_3$) β: δ 98.6, 98.5, 91.4, 82.4, 82.19, 82.17, 72.5, 69.64, 68.2, 67.6, 66.9, 66.15, 37.75 (2C), 36.61, 17.95 (2C), 17.75; α: δ 98.6, 98.5, 91.5, 82.21, 82.19, 82.17, 69.63, 68.0, 66.4, 66.18, 66.16, 61.50, 37.71, 36.62, 34.3, 17.95, 17.93, 17.90; CIHRMS Calcd for $[C_{18}H_{32}O_{10}Na^+]$: 431.1889, Found 431.1888.

Mono-*MeON*-digitoxoside (4).



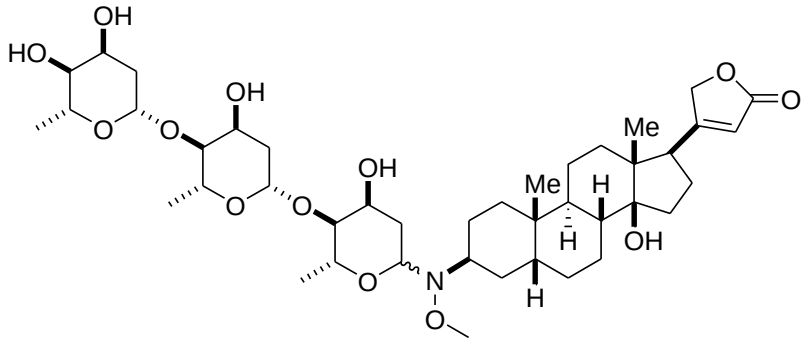
Aglycon **22** (16.7 mg, 41.3 μmol) and **19** (12.2 mg, 45.4 μmol) were added to a glass vial equipped with a stirring flea and then were dissolved in 9:1 MeOH/$CHCl_3$ (400 μL). AcOH was added (2.4 μL, 41.3 μmol) and the reaction mixture was stirred at 40 °C for 3 days. The crude reaction mixture was concentrated then purified via SiO_2 column chromatography eluting with 5 % MeOH/CH_2Cl_2 to provide 13.1 mg (59 % yield) of **4** as an oil (TLC Rf = 0.40 in 10 % MeOH/CH_2Cl_2), > 99 % pure by LCMS. Isomer ratio: 74:19:7, β-pyranose isomer predominant. ^{1}H NMR ($CDCl_3$, 400 MHz) β-pyranose: δ 5.88 (s, 1H), 5.01-4.79 (m, 2H), 4.59 (dd, 1H, *J* = 10.7, 1.7), 4.21 (m, 1H), 3.63-3.30 (m, 2H), 3.57 (s, 3H), 2.79 (m, 1H), 2.50-1.13 (m, 24H), 1.28 (d, 3H, *J* = 5.3), 0.94 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) β-pyranose: δ 174.08, 174.06, 117.3, 85.3, 83.1, 73.0, 72.9, 70.2, 67.9, 63.6, 62.2, 56.5, 50.5, 49.2, 41.6, 39.7, 36.3, 35.7, 35.2, 32.7, 30.3, 29.1, 26.7, 26.4, 23.5, 23.0, 20.8, 20.8, 20.7, 17.6, 15.4; HRESIMS calculated for [$C_{30}H_{47}NO_7Na^+$]: 556.32502, Found 556.32447.

Di-*MeON*-digitoxoside (5).



Aglycon **22** (12.3 mg, 30.5 μmol) and **20** (8.5 mg, 30.5 μmol) were added to a glass vial equipped with a stirring flea and then were dissolved in 9:1 MeOH/$CHCl_3$ (200 μL). AcOH was added (1.7 μL, 30.5 μmol) and the reaction mixture was stirred at 40 °C for 2.5 days. The crude reaction mixture was concentrated then purified via SiO_2 column chromatography eluting with 5 % MeOH/CH_2Cl_2 to provide 14.6 mg (72 % yield) of **5** as an oil (TLC Rf = 0.47 in 10 % MeOH/CH_2Cl_2). Isomer ratio: 100 % β-pyranose. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88 (s, 1H), 5.01-4.78 (m, 2H), 4.92 (dd, 1H, *J* = 9.8, 1.8), 4.58 (dd, 1H, *J* = 9.9, 1.6), 4.33 (m, 1H), 4.13 (m, 1H), 3.86-3.04 (m, 4H), 3.57 (3H), 2.80 (m, 1H), 2.26-1.11 (m, 26H), 1.29 (d, 3H, *J* = 6.3), 1.22 (d, 3H, *J* = 6.3), 0.93 (s, 3H), 0.87 (s, 3H); HRESIMS calculated for [$C_{36}H_{57}NO_{10}Na^+$]: 686.38802, Found 686.38747.

Tri-*MeON*-digitoxoside (6).



Aglycon **22** (6.9 mg, 17.1 μmol) and **21** (7.0 mg, 17.1 μmol) were added to a glass vial equipped with a stirring flea and then were dissolved in 9:1 MeOH/$CHCl_3$ (110 μL). AcOH was added (0.98 μL, 17.1 μmol) and the reaction mixture was stirred at 40 °C for 2.5 days. The crude reaction mixture was concentrated then purified via SiO_2 column chromatography eluting with 5 % MeOH/CH_2Cl_2 to provide 8.6 mg (63 % yield) of **6** as an oil (TLC Rf = 0.47 in 10 % MeOH/CH_2Cl_2). Isomer ratio: 100 % β-pyranose. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.87 (s, 1H), 5.03-4.78 (m, 2H), 4.91 (m, 2H), 4.58 (dd, 1H, *J* = 10.3, 1.9), 4.33 (m, 1H), 4.26 (m, 1H), 4.13 (m, 1H), 3.92-2.96 (m, 6H), 2.79 (m, 1H), 2.25-1.11 (m, 31H), 1.29 (d, 3H, *J* = 6.2), 1.23 (d, 3H, *J* = 6.3), 1.21 (d, 3H, *J* = 6.4), 0.93 (s, 3H), 0.87 (s, 3H). HRESIMS calculated for [$C_{42}H_{67}NO_{13}Na^+$]: 816.45101, Found 816.45046.

Section F: References

1. Screening Services—NCI-60 DTP Human Tumor Cell Line Screen Home Page. http://dtp.nci.nih.gov/branches/btb/ivclsp.html (accessed April 27, 2010).
2. Langenhan, J.M.; Engle, J.M.; Slevin, L.K.; Fay, L.R.; Lucker, R.W.; Smith, K.R.; Endo, M.M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 670-673.