SUPPORTING INFORMATION

Stereochemical Survey of Digitoxin Monosaccharides

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Section A: 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 % CO_2, 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 % CO_2, 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.

[1] Screening Services – NCI-60 DTP Human Tumor Cell Line Screen Home Page. http://dtp.nci.nih.gov/branches/btb/ivclsp.html (accessed October 15, 2010).

Growth inhibition of 50 % (GI_{50}) 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. GI_{50} (μM) for digitoxin monosaccharide analogues against 47 human cancer cell lines.

		Compound								
Cell Type	**Cell Line**	**1**	**2**	**3**	**4**	**6**	**7**	**8**	**9**	**10**
Leukemia	MOLT-4	0.00507	0.00463	0.00295	0.0353	< 0.010	0.00257	< 0.010	< 0.010	< 0.010
	RPMI-8226	0.0399	0.0455	0.0342	0.117	< 0.010	0.0235	< 0.010	< 0.010	0.0182
	SR	0.0155	0.0168	0.0157	0.0795	< 0.010	0.00225	< 0.010	> 100	> 100
Non-Small Cell Lung Cancer	A549/ATCC	0.0109	0.0113	0.00409	0.0306	< 0.010	0.00156	< 0.010	< 0.010	< 0.010
	EKVX	0.0120	0.0114	0.0144	0.0621	< 0.010	0.00513	< 0.010	< 0.010	< 0.010
	HOP-62	0.0184	0.0147	0.0117	0.0564	< 0.010	0.00855	< 0.010	< 0.010	< 0.010
	HOP-92	0.145	0.185	0.0360	0.128	< 0.010	0.0113	0.0195	0.0275	0.0268
	NCI-H226	0.0773	0.0670	0.0506	0.168	< 0.010	0.0193	0.0172	0.0103	0.0577
	NCI-H23	0.0176	0.0177	0.0142	0.0427	< 0.010	0.00413	< 0.010	< 0.010	< 0.010
	NCI-H322M	0.0332	0.0416	0.0183	0.106	< 0.010	0.00778	< 0.010	< 0.010	0.0122
	NCI-H460	0.0128	0.0102	0.00452	0.0351	< 0.010	0.00383	< 0.010	< 0.010	< 0.010
	NCI-H522	0.0085	0.00594	0.00677	0.0408	< 0.010	0.00938	< 0.010	< 0.010	< 0.010
Colon Cancer	COLO 205	0.0672	0.0612	0.125	0.348	< 0.010	0.0296	0.0191	< 0.010	0.0321
	HCT-15	0.0439	0.0403	0.0322	0.116	< 0.010	0.0205	< 0.010	< 0.010	0.0193
	HT29	0.0327	0.0343	0.0338	0.0970	< 0.010	0.0119	< 0.010	< 0.010	0.0122
	KM12	0.0479	0.0359	0.0421	0.228	< 0.010	0.0324	< 0.010	< 0.010	0.0314
	SW-620	0.0271	0.0261	0.0236	0.0526	< 0.010	0.0111	< 0.010	< 0.010	0.0112
CNS Cancer	SF-268	0.0240	0.0249	0.00744	0.0378	< 0.010	0.00428	< 0.010	< 0.010	< 0.010
	SF-295	0.0399	0.0401	0.0182	0.0716	< 0.010	0.0104	< 0.010	< 0.010	< 0.010
	SF-539	0.0232	0.0178	0.0135	0.0438	< 0.010	0.00780	< 0.010	< 0.010	0.0103
	SNB-19	0.0640	0.0575	0.0520	0.315	< 0.010	0.0375	0.0228	< 0.010	0.0278
	SNB-75	0.0362	0.0360	0.0255	0.0990	< 0.010	0.0149	< 0.010	< 0.010	0.0254
	U251	0.0372	0.0355	0.0300	0.105	< 0.010	0.0127	< 0.010	< 0.010	0.0181
Melanoma	LOX IMVI	0.0368	0.0318	0.0249	0.0606	< 0.010	0.0118	< 0.010	< 0.010	0.0114
	MALME-3M	0.0307	0.0358	0.0133	0.182	< 0.010	0.0183	0.0134	< 0.010	0.0138
	M14	0.0746	0.0858	0.0279	0.156	< 0.010	0.0193	0.0169	0.0119	0.0196
	SK-MEL-28	0.0784	0.0608	0.0465	0.186	< 0.010	0.0231	< 0.010	0.0183	0.0303
	SK-MEL-5	0.0371	0.0205	0.0121	0.0371	< 0.010	0.00544	< 0.010	< 0.010	< 0.010
	UACC-257	0.0603	0.0845	0.0427	0.157	< 0.010	0.0196	< 0.010	< 0.010	0.0217
	UACC-62	0.0427	0.0382	0.0368	0.168	< 0.010	0.0127	0.0105	< 0.010	0.0432
Ovarian Cancer	OVCAR-3	0.0364	0.0369	0.0173	0.0478	< 0.010	0.00494	< 0.010	< 0.010	< 0.010

	OVCAR-4	0.0282	0.0340	0.0256	0.191	< 0.010	0.0189	0.0115	< 0.010	0.0239
	OVCAR-8	0.0236	0.0436	0.0265	0.0767	< 0.010	0.00250	< 0.010	< 0.010	0.0104
	SK-OV-3	0.0481	0.0369	0.0343	0.194	< 0.010	0.0222	0.0132	< 0.010	0.0212
Renal Cancer	786-0	0.0285	0.0273	0.00993	0.0582	< 0.010	0.00621	< 0.010	< 0.010	0.0116
	A498	0.0337	0.0313	0.0248	0.131	< 0.010	0.0207	< 0.010	0.0146	0.0186
	ACHN	0.0106	0.00520	0.00296	0.0348	< 0.010	0.00431	< 0.010	< 0.010	< 0.010
	SN12C	0.0157	0.0112	0.00871	0.0409	< 0.010	0.00361	< 0.010	< 0.010	< 0.010
	TK-10	0.0270	0.0345	0.00501	0.0463	< 0.010	0.00375	< 0.010	< 0.010	< 0.010
	UO-31	0.0325	0.0338	0.0139	0.0570	< 0.010	0.00515	< 0.010	0.0136	0.0136
Prostate Cancer	PC-3	0.0291	0.0287	0.0147	0.101	< 0.010	0.00955	< 0.010	< 0.010	0.0106
	DU-145	0.0167	0.0137	0.00450	0.0305	< 0.010	0.00345	< 0.010	< 0.010	< 0.010
Breast Cancer	MCF7	0.0411	0.0328	0.0188	0.0793	< 0.010	0.00589	< 0.010	< 0.010	< 0.010
	MDA-MB-231	0.223	0.191	0.102	0.392	< 0.010	0.0339	0.0366	0.0318	0.146
	HS 578T	0.00961	0.00616	0.00281	0.0261	< 0.010	0.00457	< 0.010	< 0.010	< 0.010
	MDA-MB-435	0.0382	0.0488	0.0297	0.115	< 0.010	0.0277	< 0.010	< 0.010	0.0185
	T-47D	0.0429	0.0253	0.0326	0.409	< 0.010	0.0210	0.0360	< 0.010	0.0385

Figure S2. Carbohydrate survey of digitoxin monosaccharide analogues (**1** to **10**) against NCI panel cell lines. Reciprocal GI_{50} value is displayed for clarity.

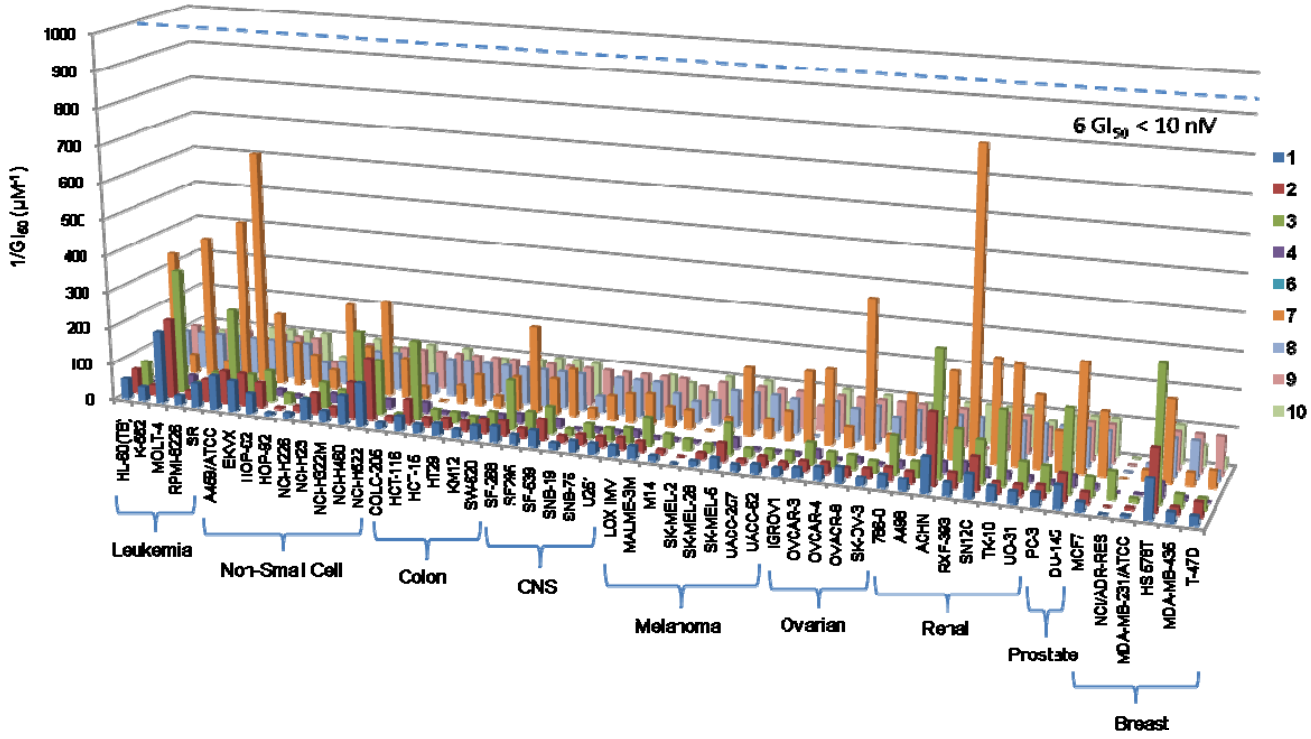
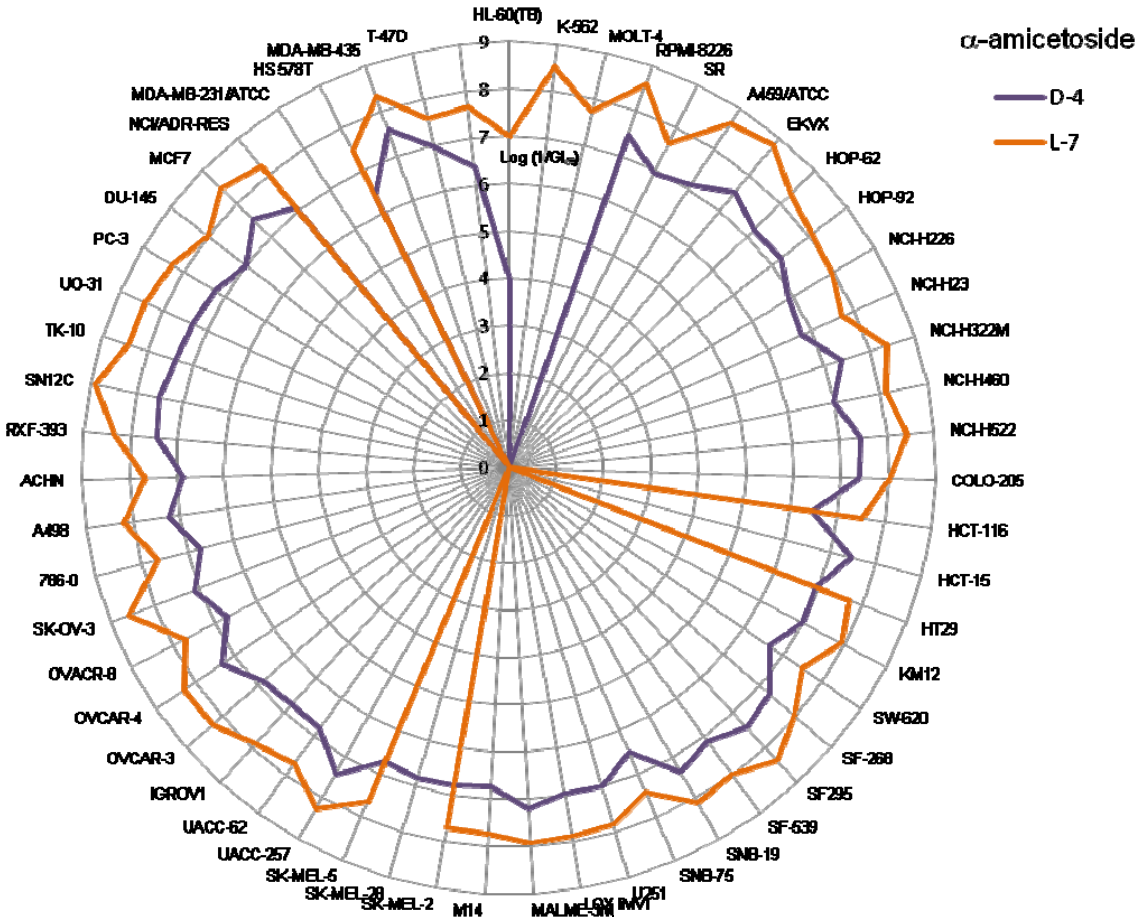


Figure S3. Pin-Wheel presentation of cytotoxicity against NCI-panel of 47 cancer cell lines as the effect of sugar-stereochemistry (i.e., α-L-amicetose **7** versus α-D-amicetose **4** digitoxin analogue).[a]



[a]NCI cancer cell lines is represented in each radius axis of the pin-wheel, and drug concentration is represented as Log ($1/GI_{50}$) in each circle. In general, α-L-amicetose **7** showed stronger potency in cancer cells growth inhibition than the relative α-D-amicetose **4** at least by a factor of 10.

Section B: MTT Colorimetric Assays. The human lung epithelial cell line NCI-H460 was obtained from the American Type Culture Collection (Manassas,VA). The cells were cultured in RPMI 1640 medium (Invitrogen) supplemented with 10% fetal bovine serum and 2 mM L-glutamine and 100 units/ml penicillin/streptomycin. Cell cultures were maintained in a humidified atmosphere of 5% CO_2 at 37°C. Cells were passaged at preconfluent densities using a solution containing 0.25% trypsin and 0.5 mM EDTA (Invitrogen). Cells were seeded at a density of 10,000 cell/well in a 96 well plate for 12 hours with 10% FBS, 1% penicillin and streptomycin, and 1% L-glutamine resulting in 80% confluency. Each dose was prepared in 1% FBS medium by 1000X dilution of the drug which was prepared in Dimethyl Sulfoxide (DMSO) solution to ensure DMSO concentration less than 0.1%. Control experiments showed that 0.1% DMSO had no effect on cytotoxicity. The cell viability was measured by incubating the treated cell with 10 μL of 5mg/mL MTT solution in deionized water per well for 4 hrs, followed by solublizing the resulting formazan salt with DMSO for 45mins.[2] The plates were read by Gen5 Fluorescence Reader at 562 nm. Both time- and dose-dependent experiments were performed in 3 replicate wells of each compound or concentration with at least 3 experimental runs ($N = 9$). All the data were analyzed by Two-way ANOVA to compare digitoxin **1** with digitoxin monosaccharide analogues **3**, **6** and **7** in the effect of exposure time and concentrations. Two-way ANOVA with Bonferroni post test, non-linear regression analysis and Student t-test were performed using GraphPad Prism version 5.03 for Windows, GraphPad Software, San Diego California USA.

Table S4. Time-dependent experiment of digitoxin monosaccharide analogues at 50 nM concentration (SD = Standard Deviation).

Compound			**1**	**3**	**6**	**7**
Time (hour)	**0**	Viability %	99.03	97.55	97.01	97.43
		SD	2.60	4.93	0.98	1.91
	12	Viability %	82.71	73.40	67.79	61.64
		SD	3.01	6.99	6.22	5.23
	24	Viability %	45.84	25.22	20.45	19.34
		SD	3.61	3.95	1.71	1.13
	48	Viability %	18.33	11.34	9.40	9.32
		SD	3.32	0.2	2.04	1.88

[2] Mosmann, T. Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. *Journal of Immunological Methods,* **1983,** *65,* 55-63.

Table S5. P-values from Bonferroni post test of Two-way ANOVA analysis for selected comparisons of percent cell viability in the effect of time exposure.

Time (hour)	Comparison					
	1 vs **3**	**1** vs **6**	**1** vs **7**	**3** vs **6**	**3** vs **7**	**6** vs **7**
0	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
12	P<0.001	P<0.001	P<0.001	P<0.01	P<0.001	P<0.01
24	P<0.001	P<0.001	P<0.001	P<0.05	P<0.01	P>0.05
48	P<0.001	P<0.001	P<0.001	P>0.05	P>0.05	P>0.05

Table S6. Dose-dependent experiment of digitoxin monosaccharide analogues at 48 hr treatment (SD = Standard Deviation).

Concentration (nM)			**0**	**1**	**10**	**25**	**50**	**100**	**500**	**1000**
Compound	**1**	Viability %	100	75.65	57.32	37.69	18.33	10.72	7.92	6.16
		SD	10.43	2.54	4.67	3.77	3.32	0.96	0.32	1.17
	3	Viability %	100	73.59	43.46	21.55	11.34	9.22	7.07	6.91
		SD	10.43	14.31	6.90	1.84	0.20	0.81	0.46	1.98
	6	Viability %	100	71.77	22.78	11.42	9.40	8.64	7.51	7.28
		SD	10.43	15.89	2.26	1.33	2.04	1.86	0.50	2.15
	7	Viability %	100	77.03	18.56	12.99	9.32	8.68	7.61	6.62
		SD	10.43	10.91	2.42	1.72	1.88	0.10	2.20	1.40

Table S7. Non-linear-regression analysis of MTT dose-dependent experiment (SE = Standard Error)

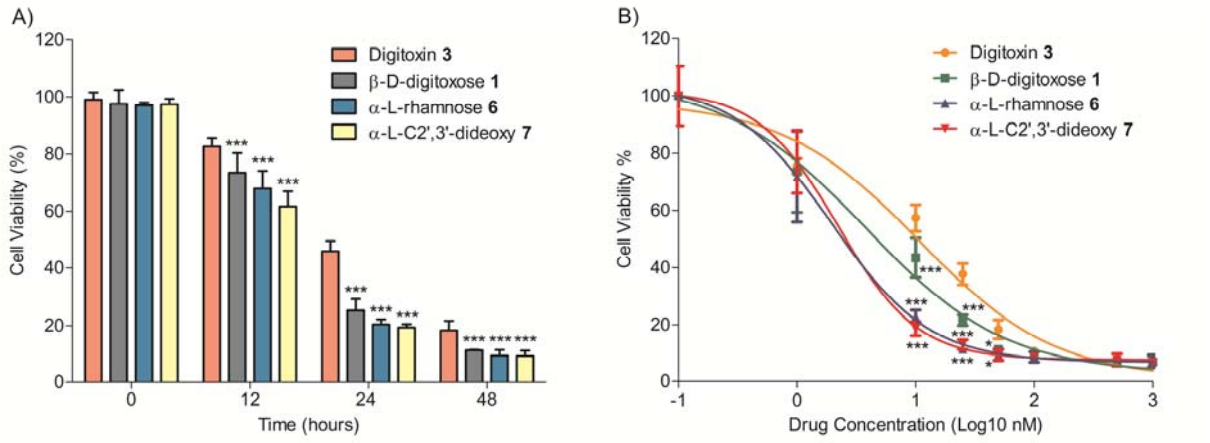
Compound	**1**	**3**	**6**	**7**
GI_{50} (nM)	10.70	3.76	1.967	2.210
SE (nM)	1.155	1.226	1.134	1.096
R^2	0.9586	0.9525	0.9631	0.9769

Table S8. P-values from Bonferroni post test of Two-way ANOVA analysis for selected comparisons of percent cell viability in the effect of concentration after 48 hr treatment.

Concentration (nM)	Comparison					
	1 vs **3**	**1** vs **6**	**1** vs **7**	**3** vs **6**	**3** vs **7**	**6** vs **7**
1	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
10	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P>0.05

25	P<0.001	P<0.001	P<0.001	P<0.01	P<0.01	P>0.05
50	P>0.05	P<0.01	P<0.01	P>0.05	P>0.05	P>0.05
100	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
500	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
1000	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05

Figure S9. A) Time-dependent experiment (50 nM). B) Dose-dependent experiment (48 h). Both time- and dose-dependent data were analyzed by Two-way ANOVA ($N = 9$; *, $P < 0.05$; ***, $P < 0.001$).



Section C: Apoptosis Assays. NCI-H460 cells were seeded at a density of 50,000 cell/well in 48 well plates for 12 hours with 10% FBS, 1% penicillin and streptomycin, and 1% L-glutamine resulting in 80% confluency. Cells were exposed for 12 hours to increasing concentration of each compound under serum free medium. All the stock solutions were prepared in the dilution with Serum-Free Medium (SFM) to have Dimethyl Sulfoxide (DMSO) concentration less than 0.1%. Control experiments showed that 0.1% DMSO had no effect on cytotoxicity. Apoptotic and necrotic cell death was determined by incubating cells with 10 μg/ml Hoechst 33342 nuclear stain and 20 μg/ml propidium iodide for 30 minutes at 37°C and scoring the percentage of cells having intensely condensed chromatin and/or fragmented nuclei by fluorescence microscopy (Leica DM IL) with Leica software. The apoptotic index was calculated as apoptotic nuclei / total nuclei * 100 (%). The experiment was performed in 2 replicate wells of each compound and concentration with at least 3 experimental runs (N = 6). All the dose-response curves were analyzed by Two-way ANOVA to compare digitoxin **1** with digitoxin monosaccharide analogues **3**, **6** and **7** in the effect of concentrations to apoptosis activity. Two-way ANOVA with Bonferroni post test, non-linear regression analysis and Student t-test were performed using GraphPad Prism version 5.03 for Windows, GraphPad Software, San Diego California USA. Percent of apoptotic cells in no treatment control was < 2%.

Table S10. Cell death (%) as a function of drug concentration (A = Digitoxigenin)

Compound			**1**	**3**	**6**	**7**	**A**
Drug Concentration	10 nM	% Cell Death	6.58	15.03	16.74	19.86	8.69
		SD	1.74	4.04	1.55	3.80	1.80
	25 nM	% Cell Death	9.38	30.36	30.29	24.55	7.64
		SD	3.44	5.34	6.85	7.48	2.38
	50 nM	% Cell Death	10.32	35.34	56.38	42.70	10.95
		SD	2.88	2.75	6.95	5.74	4.65
	75 nM	% Cell Death	13.71	48.30	63.58	71.20	12.49
		SD	3.77	3.98	5.71	4.49	2.67
	100 nM	% Cell Death	17.51	70.79	90.43	77.65	13.49
		SD	2.73	5.55	5.62	4.31	3.79
	250 nM	% Cell Death	36.83	83.94	100.0	89.13	13.97
		SD	4.34	6.59	0	7.16	3.04
	500 nM	% Cell Death	68.67	98.35	100.0	100.0	21.52
		SD	3.74	3.16	0	0	3.67

	1000 nM	% Cell Death	94.62	100.0	100.0	100.0	30.57
		SD	3.89	0	0	0	2.83
	10000 nM	% Cell Death	100	100.0	100.0	100.0	32.20
		SD	0	0	0	0	4.82

Table S11. P-values from Bonferroni post test of Two-way ANOVA analysis for selected comparisons of percent cell death in the effect of concentration (A = Digitoxigenin).

Comparison	**Concentration (nM)**								
	10	**25**	**50**	**75**	**100**	**250**	**500**	**1000**	**10000**
1 vs **3**	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P>0.05	P>0.05
1 vs **6**	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P>0.05	P>0.05
1 vs **7**	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.01	P<0.001	P>0.05	P>0.05
1 vs **A**	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P<0.001	P<0.001	P<0.001	P<0.001
3 vs **6**	P>0.05	P>0.05	P<0.001	P<0.001	P<0.001	P<0.001	P>0.05	P>0.05	P>0.05
3 vs **7**	P>0.05	P>0.05	P<0.01	P<0.001	P<0.05	P>0.05	P>0.05	P>0.05	P>0.05
3 vs **A**	P<0.05	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
6 vs **7**	P>0.05	P>0.05	P<0.001	P<0.01	P<0.001	P<0.001	P>0.05	P>0.05	P>0.05
6 vs **A**	P<0.01	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
7 vs **A**	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001

Table S12. Non-linear-regression analysis of Apoptosis dose-dependent experiment (A = Digitoxigenin, SE = Standard Error).

Compound	**1**	**3**	**6**	**7**	**A**
IC_{50} (nM)	357.0	74.83	46.72	55.68	322.90
SE (nM)	1.037	1.070	1.055	1.056	1.367
R^2	0.9885	0.9728	0.9738	0.9712	0.8514

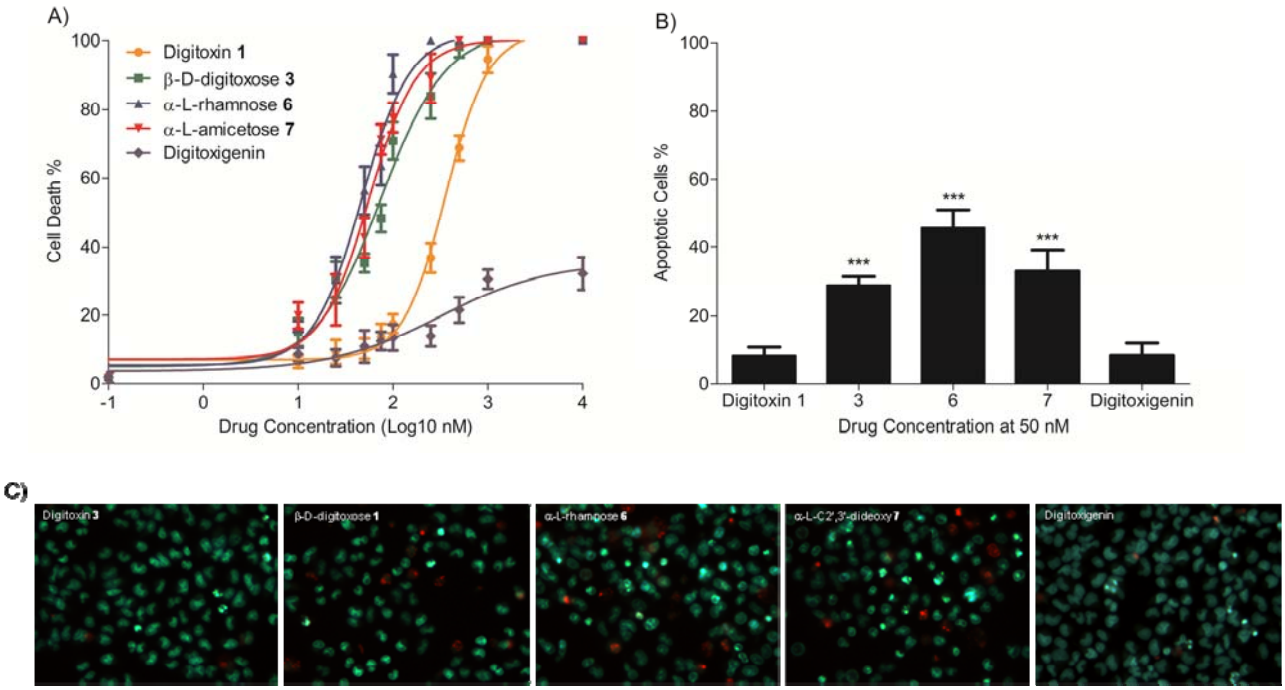
Table S13. Apoptotic cells (%) at 50 nM concentration (A = Digitoxigenin, SD = Standard Deviation)

Compound	**1**	**3**	**6**	**7**	**A**
% Apoptotic cell	8.36	28.83	45.81	33.04	8.46
SD	2.51	2.69	5.12	6.01	3.57

Table S14. P-values from Bonferroni post test of One-way ANOVA analysis for selected comparisons of percent apoptotic cell in the effect of drug at 50 nM concentration (A = Digitoxigenin).

Comparison	**1** vs **3**	**1** vs **6**	**1** vs **7**	**1** vs **A**	**3** vs **6**	**3** vs **7**	**3** vs **A**	**6** vs **7**	**6** vs **A**	**7** vs **A**
	P<0.001	P<0.001	P<0.001	P>0.05	P<0.001	P>0.05	P<0.001	P<0.001	P<0.001	P<0.001

Figure S15. A) The concentration-response curve of the apoptosis mediated total cell death by digitoxin analogues in 12 h treatment. B) Apoptotic cell death percentage was compared for each compound at 50 nM concentration (One-way ANOVA; ***, $P < 0.001$). C) Hoechst stained apoptotic cell appear in blue and propidium iodide stained necrotic cell in red at 50 nM for compound **1**, **3**, **6**, **7** and aglycone.

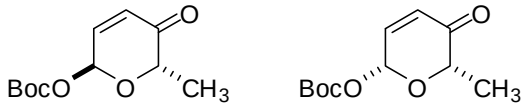


Section D: Synthetic Procedures

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 600 MHz and 400 MHz spectrometer. Chemical shifts are reported relative to $CDCl_3$ (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 spectrometer; thin film was formed in $CHCl_3$ solution. Melting points are uncorrected.

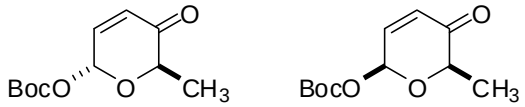
(2*S*, 6*S*)-*tert*-butyl -5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl carbonate (14a and 14b)[3]:



To a 500 mL Erlenmeyer flask of HCO_2Na (37.1 g, 0.545 mol) in deionized H_2O (272 ml) was added furan ketone **11** (15 g, 0.136 mol) and CH_2Cl_2 (2 mL). After degassed (3x) and addition of small quantity of $NaHCO_3$ to adjust the basicity, surfactant Cetyltrimethylammonium Bromide (5g, 10 mol%) was added and stirred for 5 mins. Followed by adding Noyori asymmetric catalyst (*R*)-Ru(η_6-mesitylene)-(*S,S*)-TsDPEN (85 mg, 0.1 mol%) and the resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude furan alcohol **12** was further dissolved in 228mL of THF/H_2O (3:1) and cooled to 0℃. Solid $NaHCO_3$ (23 g, 0.273 mol), $NaOAc•3H_2O$ (18.6 g, 0.136 mol), and NBS (24.2 g, 0.136 mol) were added to the solution and the mixture was stirred for 1 h at 0℃. The reaction was quenched with saturated $NaHCO_3$ (200 mL), extracted (3 x 300 mL) with Et_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture **13** was further dissolved in CH_2Cl_2 (200 mL) and the solution was cooled to -78℃. Catalytic amount of DMAP (1.22 g 7 mol%) was added to the reaction mixture, followed by adding $(Boc)_2O$ (59.5 g, 0.273 mol) in CH_2Cl_2 (70 ml) and allowed the resulting solution to stir for 12 h at -78 to -30℃. The reaction was quenched with saturated $NaHCO_3$, extracted with Et_2O (3x), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography with elution of 6% Et_2O/Hexane to give two diastereomers of Boc-protected pyranone **14a** (15 g, 65.7 mmol, 48%) and **14b** (5 g, 21.9 mmol, 16%) in 3:1. *Rf* (20% Et_2O/Hexane) = 0.58; $[\alpha]^{25}_D$ = + 98 (c = 1.0, CH_2Cl_2); IR (thin film, cm-1) 2984, 2942, 1752, 1703, 1371, 1273, 1254, 1153, 938, 838; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.22 (d, *J* = 3.6 Hz, 1H), 6.09 (d, *J* =10.2 Hz, 1H), 4.53 (q, *J* = 6.6 Hz, 1H), 1.40 (s, 9H), 1.28 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.5, 151.7, 140.9, 128.2, 89.1, 83.3, 72.0, 27.5, 15.1; ClHRMS: Calculated for [$C_{11}H_{16}O_5Na$+]: 251.0890, Found: 251.0883.

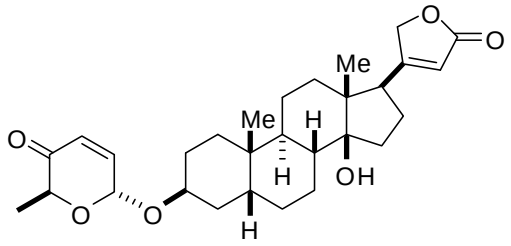
[3] Spectral data matches the previously reported compound 17a/b and 18a/b, see: (a) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.,* **2007,** *72,* 2485-2493. (b) Guo, H.; O'Doherty, G. A. *J. Org. Chem.,* **2008,** *73,* 5211-5220.

(2*R*, 6*R*)-*tert*-butyl -5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl carbonate (15a and 15b)[1]:



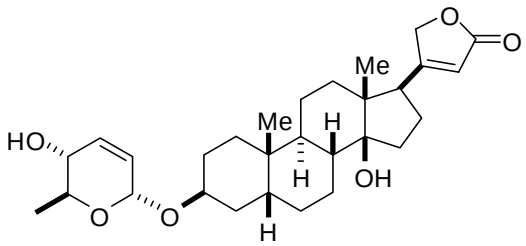
To a 500 mL Erlenmeyer flask of HCO_2Na (37.1 g, 0.545 mol) in deionized H_2O (272 ml) was added furan ketone **11** (15 g, 0.136 mol) and CH_2Cl_2 (2 mL). After degassed (3x) and addition of small quantity of $NaHCO_3$ to adjust the basicity, surfactant Cetyltrimethylammonium Bromide (5g, 10 mol%) was added and stirred for 5 mins. Followed by adding Noyori asymmetric catalyst (*R*)-Ru(η_6-mesitylene)-(*R,R*)-TsDPEN (85 mg, 0.1 mol%) and the resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude furan alcohol **(*ent*)-12** was further dissolved in 228mL of THF/H_2O (3:1) and cooled to 0℃. Solid $NaHCO_3$ (23 g, 0.273 mol), NaOAc•$3H_2O$ (18.6 g, 0.136 mol), and NBS (24.2 g, 0.136 mol) were added to the solution and the mixture was stirred for 1 h at 0℃. The reaction was quenched with saturated $NaHCO_3$ (200 mL), extracted (3 x 300 mL) with Et_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture **(*ent*)-13** was further dissolved in benzene solution (273 mL), followed by the addition of $(Boc)_2O$ (60 g, 0.275 mol) and NaOAc (11.3 g, 0.137 mol). After stirring at 80℃ for 4 h, the mixture was cooled down to room temperature and was quenched by adding 200 mL of satd. aq $NaHCO_3$, extracted with Et_2O (3x 300 mL), dried over with Na_2SO_4, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 7% EtOAc/hexanes to give two diastereomers of Boc-protected pyranone **15a** (8.8 g, 38.6 mmol, 28%) and **15b** (13.2 g, 57.8 mmol, 42.6%) in 1:1.5. **15a**: *Rf* (20% Et_2O/hexanes) = 0.43; $[\alpha]^{25}_D$ = -98 (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; CIHRMS Calcd for $[C_{11}H_{16}O_5Na]$+: 251.0890, Found 251.0884. **15b**: *Rf* (20% EtOAc/hexanes) = 0.50; mp: 43-43.5℃; $[\alpha]^{25}_D$ = +42.3 (c = 1.3, $CHCl_3$); IR (thin film, cm-1) 2986, 1752, 1703, 1633, 1278, 1258, 1159, 1090, 1058, 1029, 944; 1H NMR (270MHz, $CDCl_3$) 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 ; CIHRMS Calcd for $[C_{11}H_{16}O_5Na]$+: 251.0890, Found 251.0883.

(2S,6R)-2-Methyl-6-(Digitoxigenoxy)-2*H*-pyran-3(6*H*)-one (16a):



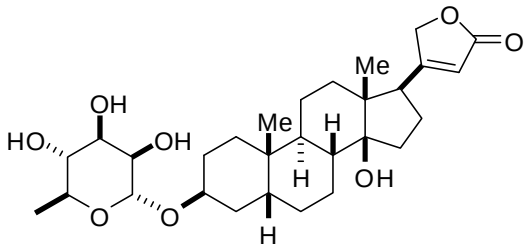
A CH_2Cl_2/THF solution (7 mL, 4:1 V/V) of Boc pyranone **14a** (884 mg, 3.87 mmol) and digitoxigenin (725 mg, 1.94 mmol) was cooled to 0℃. A CH_2Cl_2 (2 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (50.1 mg, 2.5 mol%) and PPh_3 (50.7 mg, 10 mol%) was added to the reaction mixture via dry cannula at 0℃. The resulting solution was stirred at 0℃ for 6 hours and was directly loaded and purified via silica gel flash chromatography with elution of 35% EtOAc/hexanes to obtain **16a** (766 mg, 1.58 mmol, 82%) as a yellow solid; *Rf* (60% EtOAc/hexanes) = 0.58; mp: 121-123 ℃; $[\alpha]^{25}_D$ = + 61.4 (c = 1.0, MeOH); IR (thin film, cm-1) 3481, 2939, 2253, 1738, 1698, 1620, 1448, 1374, 1319, 1237, 1157, 1102, 1079, 1024, 958, 905, 859, 645; ^{1}H NMR (600MHz, $CDCl_3$) δ 6.78 (dd, *J* = 10.4, 1.8 Hz, 1H), 5.99 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.80 (m, 1H), 5.21 (dd, *J* = 2.4, 1.8 Hz, 1H), 4.95 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.50 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.49 (q, *J* = 6.6 Hz, 1H), 4.04 (m, 1H), 2.73 (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 197.2, 174.9, 174.5, 144.4, 126.7, 117.3, 91.7, 85.1, 74.0, 73.4, 70.2, 50.8, 49.5, 41.5, 40.0, 36.3, 35.5, 35.0, 32.8, 30.3, 30.1, 26.8, 26.4, 26.3, 23.5, 21.1, 21.0, 20.8, 15.6; ESIHRMS Calcd for [$C_{29}H_{40}O_6Na^+$]: 507.27226, Found: 507.27172.

(2S,3R,6R)-3,6-Dihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-4,5-en-3-ol (8):



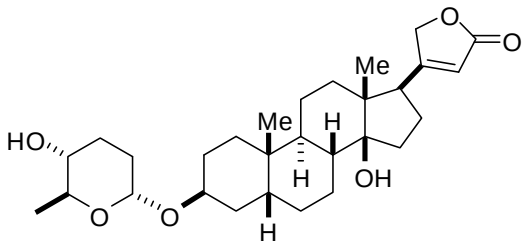
A CH_2Cl_2 (2.8 mL) solution of enone **16a** (678 mg, 1.40 mmol) in $CeCl_3 \cdot MeOH$ solution (0.4 M, 2.8 mL) was cooled to -78℃. $NaBH_4$ (58.2 mg, 1.54 mmol) was added and the resulting solution was stirred at -78℃ for 1 hour. The reaction mixture was diluted with Et_2O (20 mL) and was quenched with 20 mL of saturated aqueous $NaHCO_3$, extracted with Et_2O (3 x 20 mL), dried with 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 **8** (600 mg, 1.23 mmol, 88%) as a white solid; *Rf* (60% EtOAc/hexanes) = 0.22; mp: 155-156℃; IR (thin film, cm-1) 3448, 2933, 2871, 1780, 1741, 1618, 1446, 1378, 1320, 1180, 1135, 1049, 1024, 1004, 958, 751; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.90 (ddd, *J* = 10.2, 4.8, 1.2 Hz, 1H), 5.85 (m, 1H), 5.72 (d, *J* = 10.2 Hz, 1H), 5.07 (m, 1H), 4.98 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.11 (dd, *J* = 4.2, 1.8 Hz, 1H), 3.97 (s, 1H), 3.82 (dq, *J* = 6.6, 2.4Hz, 1H), 3.74 (br, 1H), 2.77 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.25-2.05 (m, 2H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.80-1.05 (m, 20H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.6, 132.8, 127.5, 117.6, 93.2, 85.5, 73.6, 73.4, 69.7, 67.9, 64.9, 50.9, 49.5, 41.8, 40.0, 36.4, 35.7, 35.1, 33.1, 30.7, 30.3, 26.7 (2C), 26.5, 23.6, 21.3, 21.1, 17.9, 15.7; HRESIMS Calcd for [$C_{29}H_{42}O_6Na^+$]: 509.2879, Found 509.28737.

(2S,3R,4R,5R,6R)-3,4,5,6-tetrahydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3,4,5-triol (6):



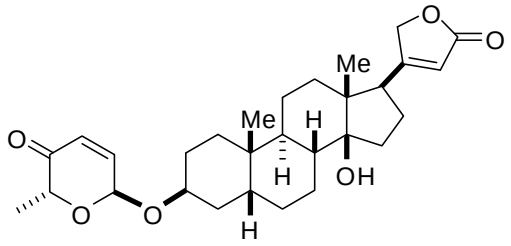
To a *t*-BuOH/acetone (7.5 mL, 1:1 (v/v), 0.5M) solution of allylic alcohol **8** (1.80 g, 3.70 mmol) at 0℃ was added a solution of *N*-methylmorpholine-*N*-oxide/water (50% w/v, 3.70 mL). Crystalline OsO_4 (9.4 mg, 1 mol %) was added and the reaction mixture was stirred for 4 hours. The reaction mixture was quenched with 20 mL of saturated $Na_2S_2O_3$ solution, extracted with EtOAc (3 x 30 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified via silica gel flash chromatography eluting with 90% EtOAc/Hexane. Pure fraction were combined, concentrated, and crystallized from CH_2Cl_2/hexanes to afford **6** as white solid (2.07 g, 3.55 mmol, 93%); R_f = 0.20 (EtOAc); mp: 160-162 ℃; $[\alpha]^{25}_D$ = -24 (*c* = 0.7, MeOH); IR (thin film, cm^{-1}) 3371, 2940, 2856, 1739, 1736, 1658; 1449, 1454, 1378, 1160, 1076, 1024, 951, 822; ^{1}H NMR (400MHz, CD_3OD) δ 5.90 (m, 1H), 5.04 (dd, *J* = 19.2, 2.0 Hz, 1H), 4.92 (dd, *J* = 19.2, 2.0 Hz, 1H), 4.77 (d, *J* = 2.0 Hz, 1H), 3.95 (br, 1H), 3.76 (dd, *J* = 2.8, 1.6 Hz, 1H), 3.69 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.66 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.37 (dd, *J* = 9.6, 9.6 Hz, 1H), 2.83 (m, 1H), 2.19 (m, 2H), 2.00-1.27 (m, 23H), 1.23 (d, *J* = 6.0 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 178.46, 177.25, 117.79, 99.85, 86.44, 75.36, 74.07, 73.58, 72.94, 72.51, 70.02, 52.11, 51.07, 42.69, 40.94, 38.18, 36.81, 36.39, 33.38, 31.62, 30.83, 28.06, 27.89, 27.51, 24.35, 22.58, 22.38, 17.98, 16.40; ESIHRMS Calcd. for [$C_{29}H_{44}O_8Na^+$]: 543.6446, found: 543.6446.

(2S,3R,6R)-3,6-dihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3-ol (7):



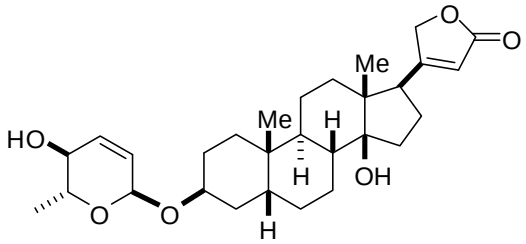
To a NMM (0.38 ml, 0.3M) solution of allylic alcohol **8** (55 mg, 0.113 mmol) at 0℃ was added *o*-nitrobenzenesulfonyl hydrazine (NBSH) (123 mg, 0.566 mmol) and Et_3N (23 mg, 0.226 mmol). The resulting mixture was stirred and gradually raised to room temperature for 8 hrs. The reaction mixture was diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3 x 20 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified via silica gel flash chromatography eluting with 50% EtOAc/hexanes to give alcohol **7** as white solid (50 g, 0.102 mmol, 90%); R_f(60% EtOAc/hexanes) = 0.20; mp: 172-173 ℃; $[\alpha]^{25}_D$ = -33.0 (*c* = 0.4, MeOH); IR (thin film, cm^{-1}) 3441, 2933, 2246, 1737, 1619, 1448; 1379, 1339, 1258, 1225, 1115, 1029, 990, 955; 906, 858, 824; ^{1}H NMR (600MHz, $CDCl_3$) δ 5.86 (m, 1H), 4.98 (dd, *J* = 18.2, 1.2 Hz, 1H), 4.81 (m, 1H), 4.80 (dd, *J* = 18.2, 1.2 Hz, 1H), 4.11 (dd, *J* = 4.2, 1.8 Hz, 1H), 3.90 (s, 1H), 3.63 (br, 1H), 3.25 (m, 1H), 2.77 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.25-2.05 (m, 3H), 1.48 (s, 1H), 1.20 (m, 6H), 1.80-1.05 (m, 19H), 0.92 (s,.3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 174.5, 117.6, 94.0, 85.5, 73.5, 72.3, 70.9, 69.6, 50.9, 49.6, 41.8, 40.0, 36.4, 35.7, 35.2, 33.1, 30.5, 30.2, 29.8, 27.7, 26.9, 26.7 (2C), 23.7, 21.4, 21.2, 17.9, 15.7; ESIHRMS Calcd. for [$C_{29}H_{44}O_6Na^+$]: 511.6458, found: 511.6458.

(2R,6S)-2-Methyl-6-(Digitoxigenoxy)-2*H*-pyran-3(6*H*)-one (17a):



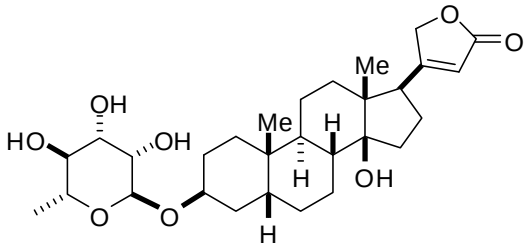
A CH_2Cl_2/THF solution (2.0 mL, 4:1 V/V) of Boc pyranone **15a** (316 mg, 3.87 mmol) and digitoxigenin (260 mg, 0.69 mmol) was cooled to 0℃. A CH_2Cl_2 (0.3 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (17 mg, 2.5 mol%) and PPh_3 (17 mg, 10 mol%) was added to the reaction mixture via dry cannula at 0℃. The resulting solution was stirred at 0℃ for 8 hours and was directly loaded and purified via silica gel flash chromatography with elution of 40% EtOAc/hexanes to obtain **17a** (296 mg, 0.61 mmol, 88%) as a yellow solid; mp: 153-154℃; *Rf* (55% EtOAc/hexanes) = 0.45; $[\alpha]^{25}_D$ = -27.0 (c = 1.0, MeOH); IR (thin film, cm-1) 3502, 2936, 2249, 1780, 1737, 1697, 1620, 1447, 1373, 1338, 1318, 1235, 1156, 1103, 1078, 1023, 958, 909, 824, 754; ^{1}H NMR (600MHz, $CDCl_3$) δ 6.80 (dd, *J* = 10.4, 1.8 Hz, 1H), 6.12 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.87 (m, 1H), 5.25 (dd, *J* = 2.4, 1.8 Hz, 1H), 4.99 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.58 (q, *J* = 6.6 Hz, 1H), 4.08 (m, 2H), 2.78 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.20-2.09 (m, 3H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.92-1.16 (m, 18H), 0.91 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.0, 174.4, 174.3, 147.7, 128.2, 117.8, 93.9, 85.6, 75.2, 73.4, 73.3, 50.9, 49.6, 41.9, 40.0, 36.3, 35.8, 35.2, 33.2, 32.0, 30.0, 26.9, 26.4, 24.4, 23.7, 21.3, 21.2, 17.0, 15.8; ESIHRMS Calcd for $[C_{29}H_{40}O_6Na^+]$: 507.2717, Found: 507.2722.

(2R,3S,6S)-3,6-Dihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-4,5-en-3-ol (5):



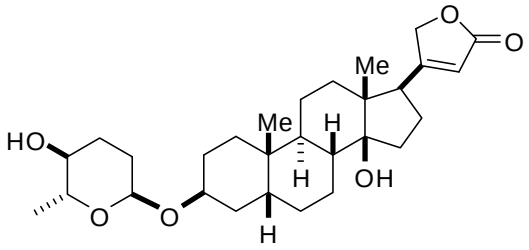
A CH_2Cl_2 (1.12 mL) solution of enone **17a** (270 mg, 0.55 mmol) in $CeCl_3 \cdot MeOH$ solution (0.4 M, 1.12 mL) was cooled to -78℃. $NaBH_4$ (20.8 mg, 0.55 mmol) was added and the resulting solution was stirred at -78℃ for 3 hour. The reaction mixture was diluted with Et_2O (10 mL) and was quenched with 10 mL of saturated aqueous $NaHCO_3$, extracted with Et_2O (3 x 20 mL), dried with 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 **5** (244 mg, 0.50 mmol, 90%) as a white solid; mp: 166-167℃; *Rf* (60% EtOAc/hexanes) = 0.20; IR (thin film, cm-1) 3327, 2939, 2871, 1738, 1741, 1618, 1448, 1378, 1320, 1180, 1135, 1049, 1024, 958, 750; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.90 (ddd, *J* = 10.2, 4.8, 1.2 Hz, 1H), 5.86 (m, 1H), 5.73 (d, *J* = 10.2 Hz, 1H), 5.01 (m, 1H), 4.97 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.81 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.00 (dd, *J* = 4.2, 1.8 Hz, 1H), 3.83 (s, 1H), 3.73 (dq, *J* = 6.6, 2.4Hz, 1H), 3.70 (br, 1H), 2.77 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.25-2.05 (m, 2H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.80-1.05 (m, 20H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.5, 174.4, 144.3, 127.0, 117.6, 91.6, 85.5, 73.6, 73.4, 70.3, 50.9, 49.6, 41.8, 40.0, 36.7, 35.6, 35.2, 33.1, 32.0, 30.1, 26.8 (2C), 26.5, 24.7, 23.7, 21.3, 21.1, 15.7, 15.2; HRESIMS Calcd for [$C_{29}H_{42}O_6Na^+$]: 509.2879, Found 509.2879.

(2R,3S,4S,5S,6S)-3,4,5,6-tetrahydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3,4,5-triol (18):



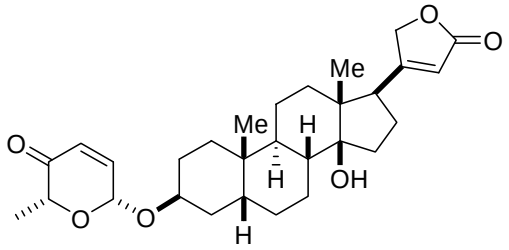
To a *t*-BuOH/acetone (330 *u*L, 1:1 (v/v), 0.5M) solution of allylic alcohol **5** (80 mg, 0.164 mmol) at 0℃ was added a solution of *N*- methylmorpholine -*N*-oxide/water (50% w/v, 170 *u*L). Crystalline OsO_4 (0.5 mg, 1 mol %) was added and the reaction mixture was stirred for 6 hours. The reaction mixture was quenched with 20 mL of saturated $Na_2S_2O_3$ solution, extracted with EtOAc (3 x 30 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified via silica gel flash chromatography eluting with 90% EtOAc/Hexane. Pure fraction were combined, concentrated, and crystallized from CH_2Cl_2/hexanes to afford **18** as white solid (68 mg, 0.130 mmol, 80%); mp: 262-265 ℃; R_f = 0.20 (EtOAc); $[\alpha]^{25}_D$ = +47.1 (*c* = 1.0, MeOH); IR (thin film, cm^{-1}) 3442, 2941, 2887, 2862, 1756, 1721, 1635; 1623, 1450, 1379, 1126, 1069, 1050, 1027, 980, 899; ^{1}H NMR (600MHz, CD_3OD) δ 5.90 (m, 1H), 5.04 (dd, *J* = 18.6, 1.2 Hz, 1H), 4.92 (dd, *J* = 18.6, 1.2 Hz, 1H), 4.76 (d, *J* = 1.8 Hz, 1H), 3.95 (m, 1H), 3.77 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.69 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.66 (dq, *J* = 8.4, 6.0 Hz, 1H), 3.37 (dd, *J* = 9.6, 9.6 Hz, 1H), 2.83 (m, 1H), 2.18 (m, 2H), 2.00-1.27 (m, 23H), 1.24 (d, *J* = 6.0 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.58, 177.40, 117.9, 100.1, 86.6, 75.5, 74.3, 73.9, 73.1, 72.7, 70.2, 52.3, 51.2, 42.9, 41.1, 38.6, 37.0, 36.5, 33.6, 33.3, 31.5, 28.2, 28.1, 25.4, 24.5, 22.7, 22.5, 18.1, 16.6; ESIHRMS Calcd. for [$C_{29}H_{44}O_8Na^+$]: 543.29284, found: 543.29278.

(2R,3S,6S)-3,6-dihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3-ol (4):



To a NMM (0.38 ml, 0.3M) solution of allylic alcohol **5** (65 mg, 0.134 mmol) at 0℃ was added *o*-nitrobenzenesulfonyl hydrazine (NBSH) (145 mg, 0.668 mmol) and Et_3N (27 mg, 0.267 mmol). The resulting mixture was stirred and gradually raised to room temperature for 24 hrs. The reaction mixture was diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3 x 30 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified via silica gel flash chromatography eluting with 50% EtOAc/hexanes to give alcohol **4** as white solid (60 mg, 0.123 mmol, 92%); mp: 188-190℃; R_f(60% EtOAc/hexanes) = 0.20; $[\alpha]^{25}_D$= -30.0 (*c* = 0.4, MeOH); IR (thin film, cm^{-1}) 3434, 2932, 2242, 1780, 1736, 1619; 1447, 1379, 1338, 1225, 1149, 1115, 1029, 989, 956; 908, 857, 824; ^{1}H NMR (600MHz, $CDCl_3$) δ 5.86 (m, 1H), 4.98 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.81 (m, 1H), 4.80 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.00 (dd, *J* = 4.2, 1.8 Hz, 1H), 3.92 (br, 1H), 3.63 (br, 1H), 3.25 (m, 1H), 2.77 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.25-2.05 (m, 2H), 1.48 (s, 1H), 1.20 (m, 6H), 1.80-1.05 (m, 20H), 0.93 (s,.3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.80, 174.75, 117.89, 94.05, 85.84, 73.66, 72.58, 70.78, 69.72, 51.12, 49.79, 42.09, 40.25, 36.89, 35.84, 35.42, 33.37, 32.36, 30.43, 30.34, 27.90, 27.07, 26.85, 24.37, 23.96, 21.54, 21.38, 18.11, 15.98; ESIHRMS Calcd. for $[C_{29}H_{44}O_6Na^+]$: 511.6458, found: 511.6458.

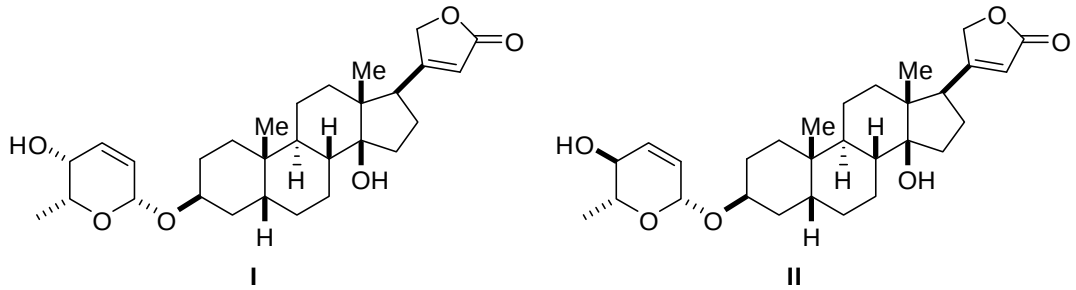
(2R,6R)-2-Methyl-6-(Digitoxigenoxy)-2*H*-pyran-3(6*H*)-one (17b)[4]:



A CH_2Cl_2/THF solution (8 mL, 4:1 V/V) of Boc pyranone **15b** (544 mg, 2.39 mmol) and digitoxigenin (1.34 g, 3.58 mmol) was cooled to 0 °C. 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 °C. The reaction mixture was stirred at 0 °C 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 **17b** (993 mg, 2.05 mmol, 86%) as a white solid: mp: 211-212 °C; R_f (40% EtOAc/hexanes) = 0.17; $[\alpha]^{21}_D$ = + 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; ^{1}H 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, 2H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.92-1.16 (m, 20H), 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.

[4] Spectral data for b-D-digitoxin analogues **17b**, **I**/**II**, **III**, and **3** see: (a) Zhou, M.; O'Doherty, G. A. *Org. Lett.,* **2006,** 8, 4339-4342. (b) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.,* **2007,** *72,* 2485-2493.

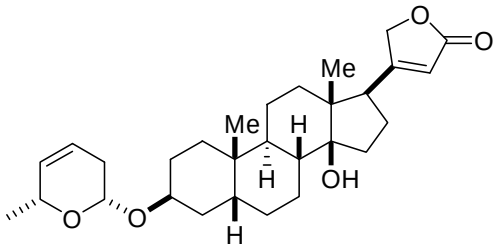
(2R,6R)-3,6-Dihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3-ol (1/II)[4]:



I II

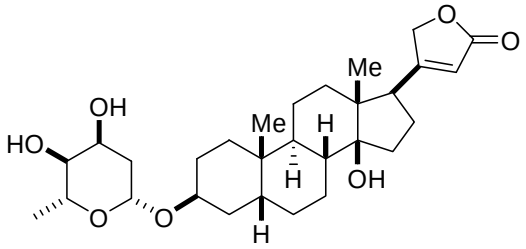
A CH_2Cl_2 (4 mL) solution of enone **17b** (990 mg, 2.04 mmol) and $CeCl_3$ in MeOH solution (0.4 M, 4 mL) was cooled to -78 ^oC. $NaBH_4$ (77 mg, 2.04 mmol) was added and the reaction mixture was stirred at -78^oC for 3 hours. The reaction mixture was diluted with Et_2O (30 mL) and was quenched with 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 **I/II** (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, 2H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.80-1.05 (m, 20H), 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, 2H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.80-1.05 (m, 20H), 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, 40.05, 36.4, 35.77, 35.19, 33.12, 30.20, 30.04, 26.9 (2C), 26.62, 23.64, 21.38, 21.15, 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-(Digitoxigenoxy)-2*H*-pyran (III)[4]:**



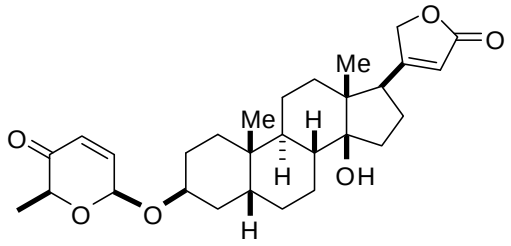
A flask was charged with dry *N*-methyl morpholine (NMM) 3.0 mL, triphenyl phosphine (1.75 g, 6.67 mmol) and was cooled to -30^{o}C under Ar atmosphere. Diethylazodicarboxylate (0.95 mL, 6.06 mmol) was added and the reaction was stirred for 5 minutes, allylic alcohol **I/II** (985 mg, 2.02 mmol) was 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 **III** (760 mg, 1.61 mmol, 80%) as a white solid: R_f (30% EtOAc/hexanes) = 0.20; mp: 157-158 ^{o}C; $[\alpha]^{21}_{D}$= -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, 20H), 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.

Digitoxigen 2,6-dideoxy-β-D-ribo-hexopyranoside (3)[4]:



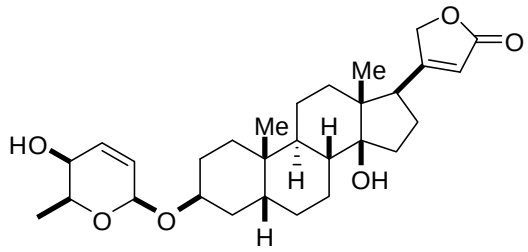
To a *t*-BuOH/acetone (4 mL) solution of olefin **III** (753 mg, 1.60 mmol) at 0 ^{o}C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (1.0 mL). Crystalline OsO_4 (4 mg, 1 mol %) was added and the reaction was stirred for 4 hours. The reaction was quenched by adding EtOAc 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 diol **3** as a white solid (868 mg, 1.72 mmol, 93%), > 99 % pure by LCMS. R_f(EtOAc) = 0.25; $[\alpha]^{21}_{D}$= –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, 21H), 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.

(2S,6S)-2-Methyl-6-(Digitoxigenoxy)-2*H*-pyran-3(6*H*)-one (16b):

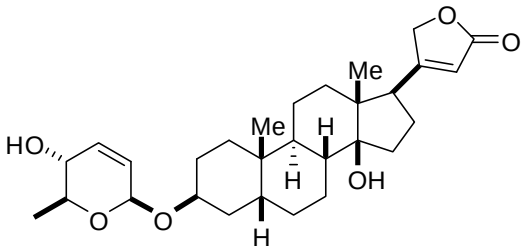


A CH_2Cl_2/THF solution (19 mL, 4:1 V/V) of Boc pyranone **14b** (1.29 g, 5.65 mmol) and digitoxigenin (3.17 g, 8.48 mmol) was cooled to 0℃. A CH_2Cl_2 (2.5 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (170 mg, 2.5 mol%) and PPh_3 (171 mg, 10 mol%) was added to the reaction mixture via dry cannula at 0℃. The resulting solution was stirred at 0℃ for 8 hours and was directly load16ed and purified via silica gel flash chromatography with elution of 40% EtOAc/hexanes to obtain **16b** (2.32 mg, 4.80 mmol, 85%) as a yellow solid; *Rf* (40% EtOAc/hexanes) = 0.17; mp: 177-180℃; $[\alpha]^{25}_D$ = + 5.28 (c = 1.0, $CHCl_3$); IR (thin film, cm-1) 3505, 2938, 2875, 2376, 2311, 1780, 1741, 1698, 1620, 1448, 1374, 1164, 1144, 1053, 1028, 730; ^{1}H NMR (600MHz, $CDCl_3$) δ 6.87 (dd, *J* = 10.4, 1.8 Hz, 1H), 6.12 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.87 (m, 1H), 5.39 (dd, *J* = 2.4, 1.8 Hz, 1H), 4.99 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.81 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.18 (m, 2H), 2.78 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.20-2.08 (m, 2H), 1.45 (d, *J* = 6.6 Hz, 3H), 1.92-1.16 (m, 20H), 0.95 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.0, 174.4, 174.3, 147.7, 128.2, 117.8, 93.9, 85.6, 75.2, 73.4, 73.3, 50.9, 49.6, 41.9, 40.0, 36.3, 35.8, 35.2 33.2, 32.0, 30.0, 26.9, 26.4, 24.4, 23.7, 21.3, 21.2, 17.0, 15.8; ESIHRMS Calcd for [$C_{29}H_{40}O_6Na^+$]: 507.272210, Found: 507.27206.

(2S,6S)-3,6-Dihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-4,5-en-3-ol (IV, V):



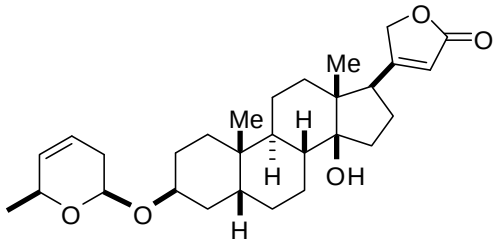
IV



V

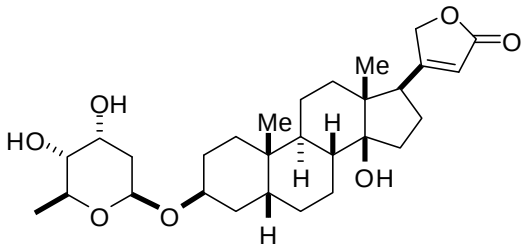
A CH_2Cl_2 (9.5 mL) solution of enone **16b** (2.32 g, 4.78 mmol) in $CeCl_3 \cdot MeOH$ solution (0.4 M, 9.5 mL) was cooled to -78℃. $NaBH_4$ (217 mg, 5.73 mmol) was added and the resulting solution was stirred at -78℃ for 2 hour. The reaction mixture was diluted with Et_2O (60 mL) and was quenched with 30 mL of saturated aqueous $NaHCO_3$, extracted with Et_2O (3 x 60 mL), dried with 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 **IV**/**V** (1.89 g, 3.88 mmol, 81%) as a white solid (diastereomeric ratio **IV:V** = 1.5:1, inseperable by silica gel chromatography); *Rf* (60% EtOAc/hexanes) = 0.22; IR (thin film, cm-1) 3449, 2934, 2871, 1779, 1737, 1619, 1448, 1380, 1320, 1169, 1136, 1051, 1026, 1006, 961, 751; ^{1}H NMR (600 MHz, $CDCl_3$): **isomer IV** δ 6.12 (ddd, *J* = 10.2, 4.8, 1.2 Hz, 1H), 5.86 (m, 1H), 5.79 (d, *J* = 10.2 Hz, 1H), 5.07 (m, 1H), 4.97 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.12 (dd, *J* = 4.2, 1.8 Hz, 1H), 4.11 (s, 1H), 3.70 (dq, *J* = 6.6, 2.4Hz, 1H), 3.60 (br, 1H), 2.77 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.25-2.05 (m, 2H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.80-1.05 (m, 20H), 0.93 (s, 3H), 0.86 (s, 3H); **isomer V** δ 5.91 (ddd, *J* = 10.2, 2.4, 2.4 Hz, 1H), 5.86 (m, 1H), 5.74 (ddd, *J* = 10.2, 1.2, 1.2 Hz, 1H), 5.13 (ddd, *J* = 1.8, 1.8, 1.8 Hz, 1H), 4.98 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.11 (s, 1H), 4.09 (m, 1H), 3.91 (br, 1H), 3.59 (dq *J* = 6.6, 6.6 Hz, 1H), 2.77 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.25-2.05 (m, 2H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.80-1.05 (m, 20H), 0.94 (s, 3H), 0.87 (s, 3H);^{13}C NMR (150 MHz, $CDCl_3$): δ 174.6, 132.8, 127.5, 117.6, 93.2, 85.5, 73.6, 73.4, 69.7, 67.9, 64.9, 50.9, 49.5, 41.8, 40.0, 36.4, 35.7, 35.1, 33.1, 30.7, 30.3, 26.7 (2C), 26.5, 23.6, 21.3, 21.1, 17.9, 15.7; HRESIMS Calcd for [$C_{29}H_{42}O_6Na^+$]: 509.287910, Found 509.28774.

(2S,6S)-6-Hydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3,4-ene (VI):



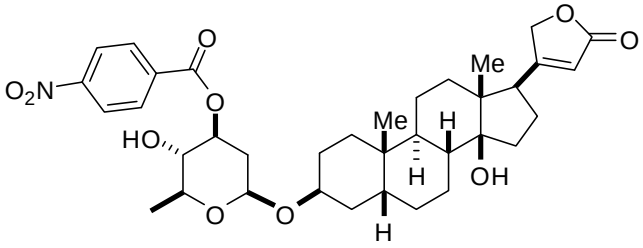
A flask was charged with dry *N*-methyl morpholine (NMM) (5.76 ml), PPh_3 (3.36 g, 12.8 mmol) and was cooled to -30 ℃ under Ar atmosphere. Diisopropylazodicarboxylate (2.30 ml, 11.7 mmol) was added and the reaction was stirred for 5 min, allylic alcohol **IV/V** (1.89 g, 3.88 mmol) was added in 1M solution of NMM, the resulting mixture was stirred for 10 min, followed by addition of *o*-nitrobenzenesulfonyl hydrazine (NBSH) (2.36 g, 12.8 mmol). The reaction was stirred at -30 ℃ for 6 hr and was monitored by TLC. Upon consumption of starting material, the reaction was warmed to room temperature and stirred for another 2 hr. The reaction mixture was diluted with ether (60 mL) and was quenched with saturated aq. $NaHCO_3$ (60 mL), extracted with ether (3 x 60 mL), dried over 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 **VI** (1.80 g, 3.82 mmol, 98%); *Rf* (30% EtOAc/hexanes) = 0.20; $[\alpha]^{25}_D$ = + 23.3 (c = 1.1, $CHCl_3$); IR (thin film, cm-1) 3301, 2933, 2871, 1778, 1742, 1620, 1447, 1378, 1221, 1157, 1133, 1097, 1065, 1024, 974, 909, 782; ^{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), 1.80-1.05 (m, 20H), 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, 36.4, 35.7, 35.2, 33.1, 31.6, 30.2, 29.8, 26.9, 26.7, 26.6, 23.6, 21.4, 21.1, 21.0, 15.8; HRESIMS Calcd for [$C_{29}H_{42}O_5Na^+$]: 493.292995, Found 493.29272.

(2S,6S)-3,4,6-Trihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3,4-diol (9)



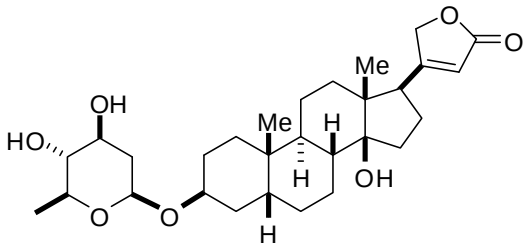
To a *t*-BuOH/acetone (8 mL, 1:1 (v/v), 0.5M) solution of olefin **VI** (1.80 g, 3.82 mmol) at 0℃ was added a solution of *N*-methylmorpholine-*N*-oxide/water (50% w/v, 4.0 mL). Crystalline OsO_4 (9.7 mg, 1 mol %) was added and the reaction mixture was stirred for 6 hours. The reaction mixture was quenched with 20 mL of saturated $Na_2S_2O_3$ solution, extracted with EtOAc (3 x 30 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified via silica gel flash chromatography eluting with 90% EtOAc/Hexane. Pure fraction were combined, concentrated, and crystallized from CH_2Cl_2/hexanes to afford **9** as white solid (1.54 g, 3.05 mmol, 80%); R_f = 0.20 (EtOAc); mp: 145-146 ℃; $[\alpha]^{25}_D$ = +30.2 (*c* = 1.0, MeOH); IR (thin film, cm^{-1}) 3440, 2934, 2856, 2193, 1736, 1619; 1448, 1380, 1160, 1134, 1065, 1026, 1002, 949, 906, 824; ^{1}H NMR (600MHz, $CDCl_3$) δ 5.86 (m, 1H), 4.98 (d, *J* = 18.2 Hz, 1H), 4.86 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.80 (d, *J* = 18.0 Hz, 1H), 4.11 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 4.02 (m, 1H), 3.71 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.32 (m, 1H), 2.77 (m, 1H), 2.56 (s, 1H), 2.39 (s, 1H), 2.20-2.00 (m, 4H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.90-1.10 (m, 20H), 0.91 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.0, 174.9, 117.8, 95.6, 85.8, 73.8, 73.2, 72.9, 69.5, 68.5, 51.2, 49.8, 42.0, 40.2, 38.5, 36.5, 35.9, 35.4, 33.4, 32.3, 30.2, 27.1, 26.6, 24.6, 23.8, 21.5, 21.4, 18.4, 16.0; ESIHRMS Calcd. for [$C_{29}H_{44}O_7Na^+$]: 527.298475, found: 527.29828.

(2S,3R,4S,6S)-3,6-Dihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-4-nitrobenzoate-3-ol (VII):

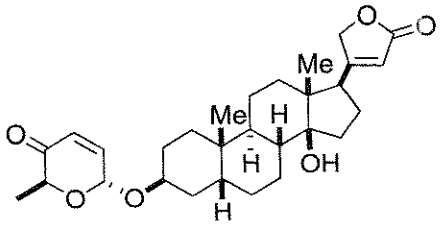


To a THF (0.6 ml) solution of diol **9** (50 mg, 0.1 mmol) at 0℃ was added PPh_3 (42 mg, 0.16 mmol) and *p*-nitrobenzoic acid (34 mg, 0.2 mmol), with drop-wise addition of Diisopropyl azodicarboxylate (33 mg, 0.16 mmol) in THF (0.2 ml). The resulting mixture was stirred for 5hr and gradually warmed to room temperature. The reaction mixture was diluted with EtOAc (5 ml) and quenched with saturated aq. $NaHCO_3$ (4 mL), extracted with ether (3 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 60% EtOAc/hexanes to give product **VII** (55 mg, 0.084 mmol, 85%); *Rf* (EtOAc) = 0.75; $[\alpha]^{25}_D$ = +8.68 (c = 0.5, $CHCl_3$); IR (thin film, cm-1) 3484, 2931, 2364, 2197, 2168, 2038, 1730, 1529, 1448, 1346, 1278, 1103, 1069, 1026, 989, 908; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (m, 4H), 5.86 (m, 1H), 5.10 (m, 1H), 4.98 (d, , *J* = 18.0 Hz 1H), 4.80 (d, *J* = 18.0 Hz, 1H), 4.66 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.07 (m, 1H), 3.48 (m, 1H), 3.40 (dq, *J* = 9.0, 6.0 Hz, 1H), 2.77 (m, 1H), 2.39 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.20-2.05 (m, 4H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.90-1.10 (m, 20H), 0.93 (s, 3H); 0.91 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.5, 174.45, 131.1, 123.0, 117.7, 96.7 (2C), 85.6, 73.4, 73.1, 72.1, 70.7, 62.2 (2C), 51.0, 50.9, 49.6, 41.9, 40.1, 36.3, 35.7, 35.2, 33.2, 32.2, 31.6, 30.0, 26.9, 26.4, 24.3, 23.6, 21.3, 21.2, 21.1, 15.8, 14.4 (2C); HRESIMS Calcd for [$C_{36}H_{47}NO_{10}Na^+$]: 653.7591, Found 653.7591.

(2S,3R,4S,6S)-3,4,6-Trihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3,4-diol (10):

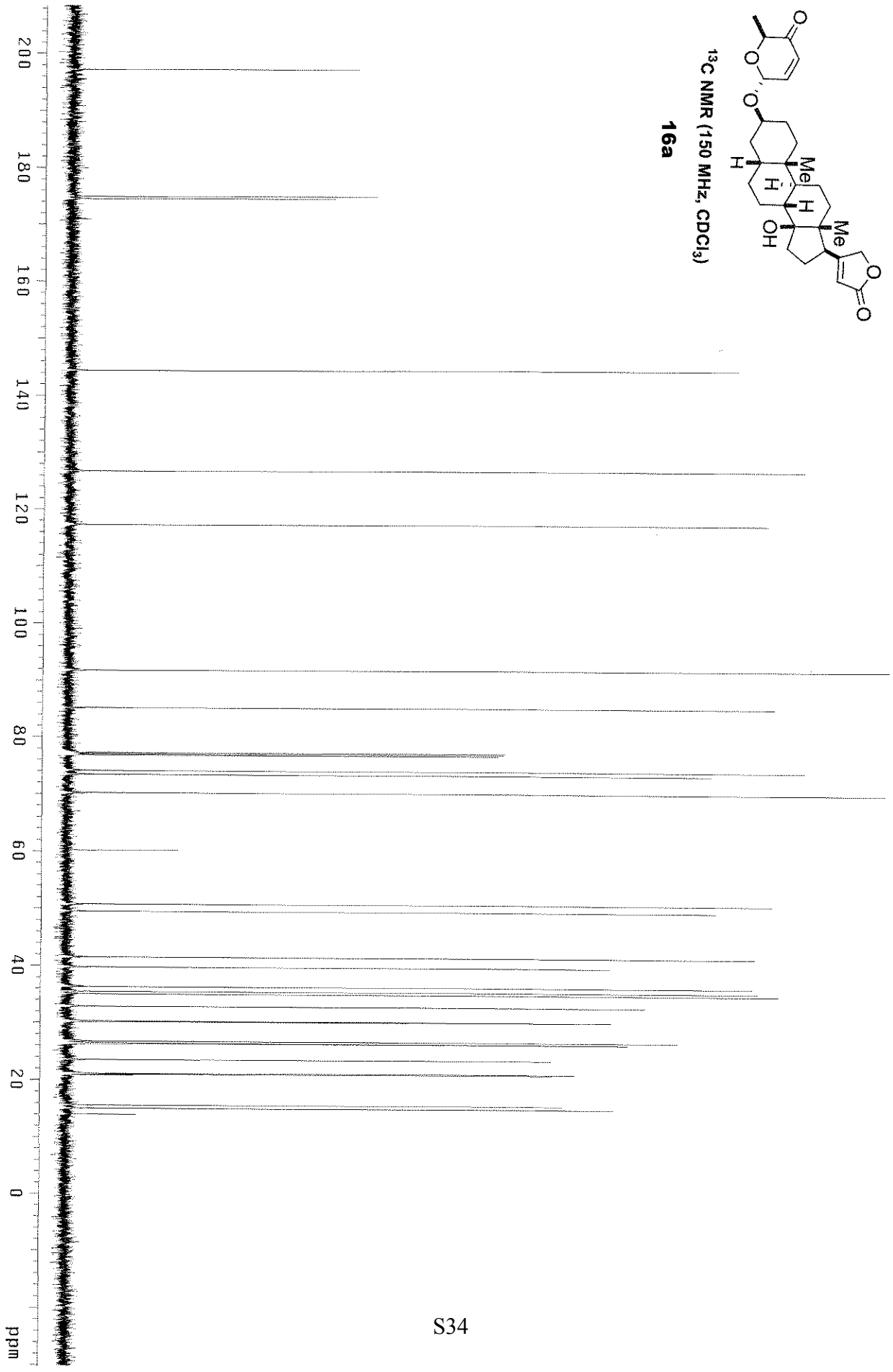


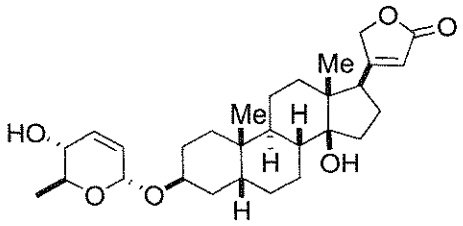
A MeOH (0.2 mL) solution of p-nitrobenzoate **VII** (28 mg, 42.8 μmol) at room temperature was added K_2CO_3 (6.0 mg, 43 μmol) and the reaction mixture was stirred for 2 hours. The reaction mixture was diluted with 5 ml Et_2O and quenched with 4 mL of saturated aq. $NaHCO_3$, extracted (3 x 5 mL) with Et_2O, dried over with Na_2SO_4, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 90%. Pure fraction were combined, concentrated, and crystallized from CH_2Cl_2/hexanes to afford **10** (20.1 mg, 40 μmol, 93%); *Rf* (EtOAc) = 0.42; $[\alpha]^{25}_D$ = +30.2 (c = 1.0, MeOH); IR (thin film, cm-1) 3453, 2940, 2856, 2173, 1969, 1775, 1742, 1623, 1449, 1454, 1378, 1160, 1067, 1024, 951, 822; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.86 (m, 1H), 4.98 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.80 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.53 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.02 (m, 1H), 3.58 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.24 (m, 1H), 3.09 (m, 1H), 2.77 (m, 1H), 2.33 (br, 1H), 2.20-2.00 (m, 4H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.90-1.10 (m, 21H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.65, 174.61, 117.6, 97.3, 85.4, 77.5, 73.5, 72.9, 71.8, 71.6, 50.9, 49.6, 41.8, 40.0, 39.5, 36.2, 35.7, 35.1, 33.1, 32.0, 29.9, 26.9, 26.4, 24.4, 23.6, 21.2, 21.1, 17.8, 15.8; ESIHRMS Calcd. for [$C_{29}H_{44}O_7Na^+$]: 527.29848, found: 527.29815.



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

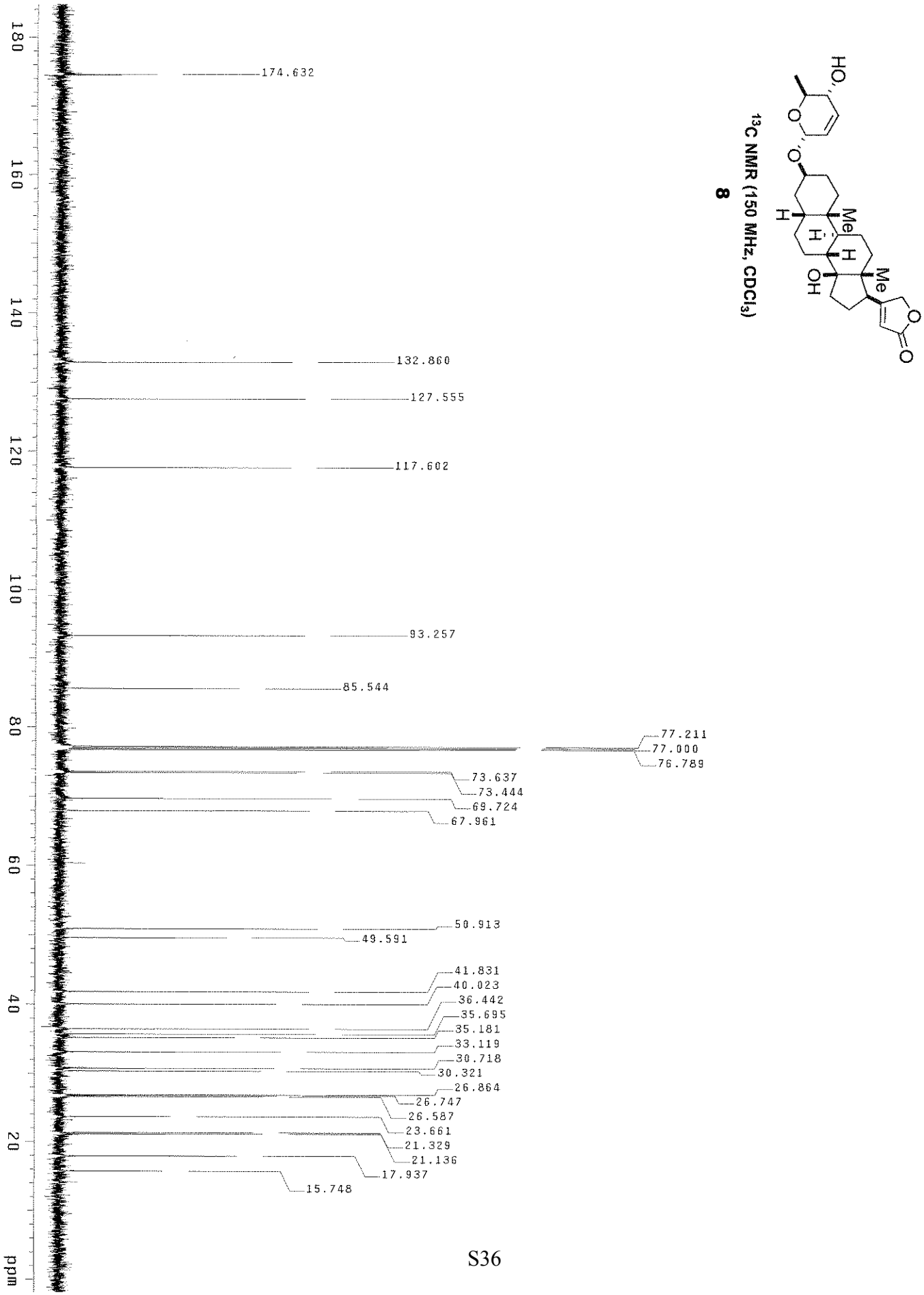
16a

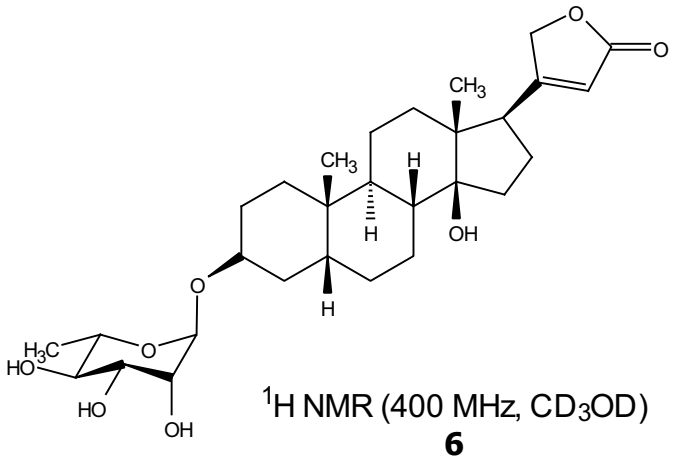

^{13}C NMR (150 MHz, CDCl$_3$)
16a
Me
H
H'
H
OH
Me
O
O
O
O
O
200
180
160
140
120
100
80
60
40
20
0
ppm



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

8

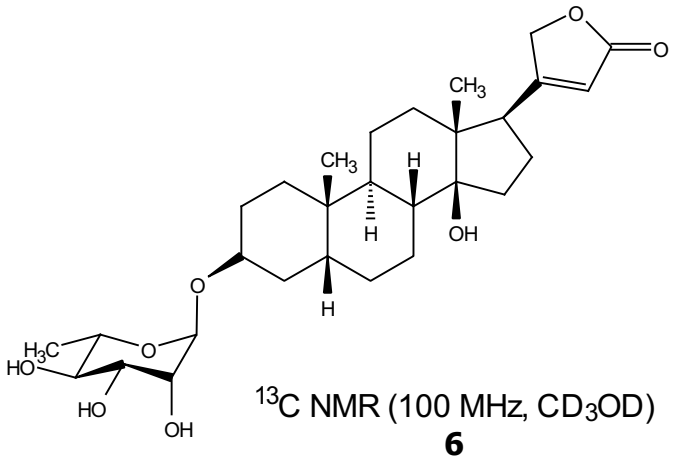

8
^{13}C NMR (150 MHz, CDCl$_3$)
174.632
132.860
127.555
117.602
93.257
85.544
77.211
77.000
76.789
73.637
73.444
69.724
67.961
50.913
49.591
41.831
40.023
36.442
35.695
35.181
33.119
30.718
30.321
26.864
26.747
26.587
23.661
21.329
21.136
17.937
15.748
ppm



^{1}H NMR (400 MHz, CD_3OD)

6

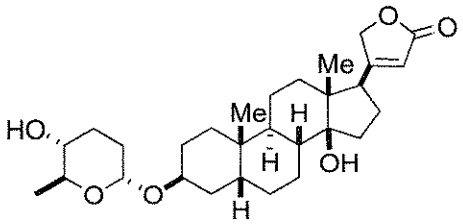
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2



^{13}C NMR (100 MHz, CD_3OD)

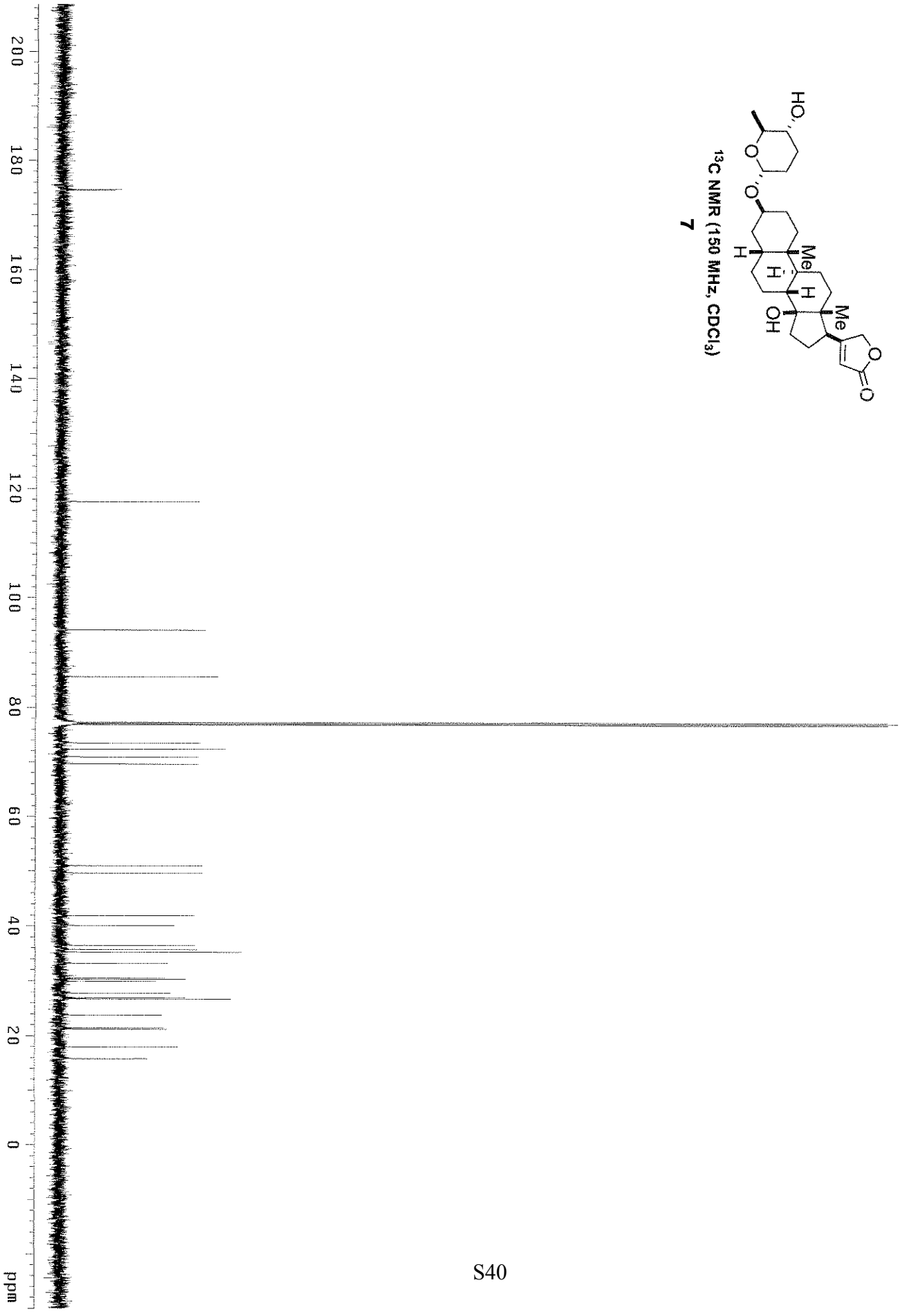
6

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20



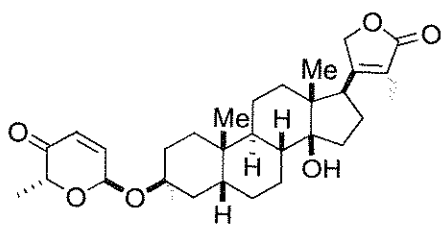
^{1}H NMR (600 MHz, $CDCl_3$)

7



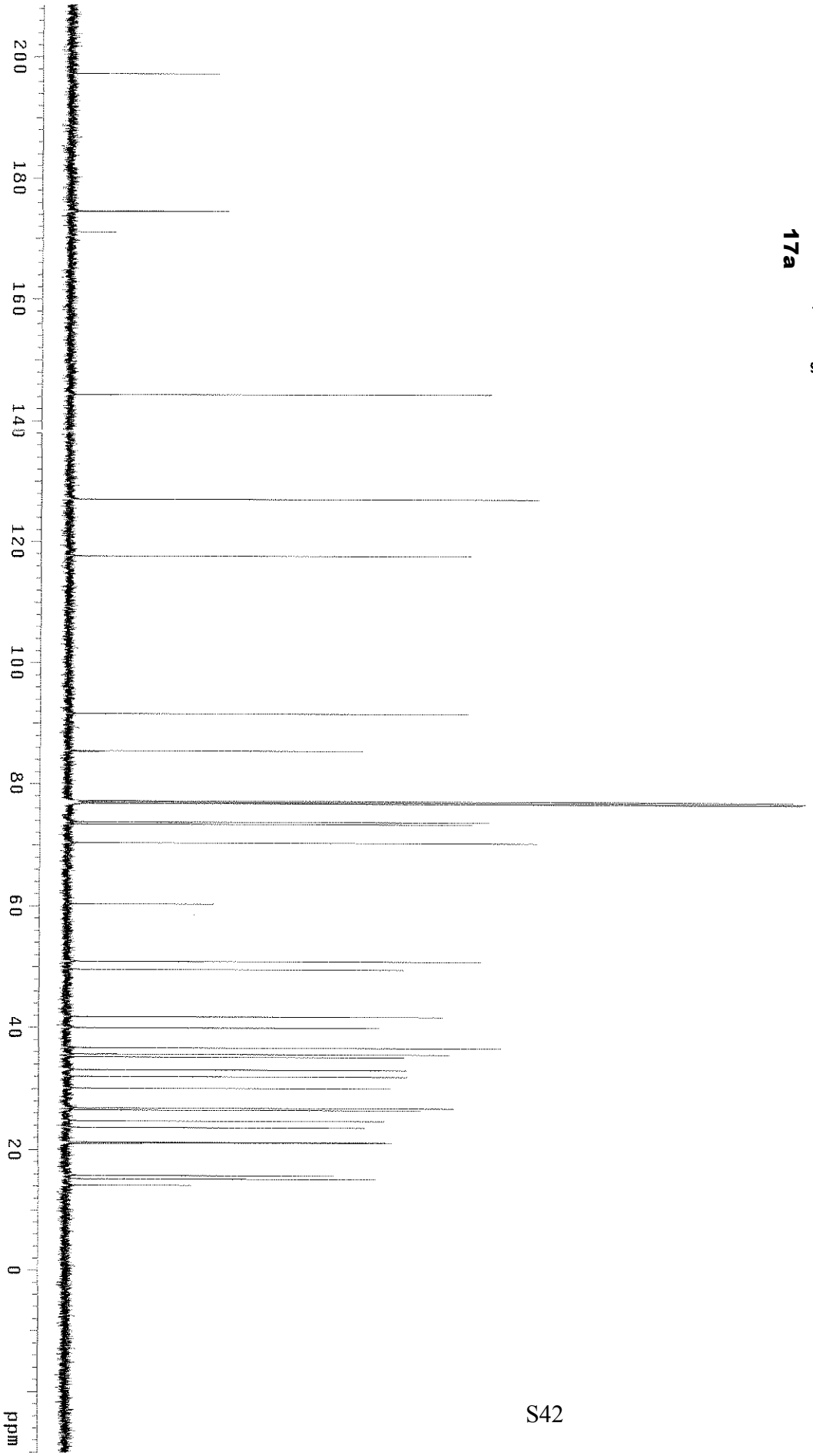
7

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



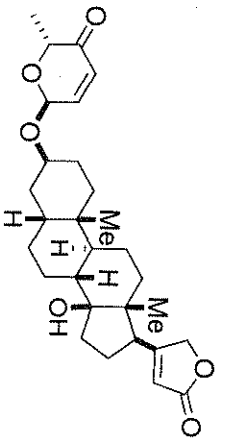
^{1}H NMR (600 MHz, $CDCl_3$)

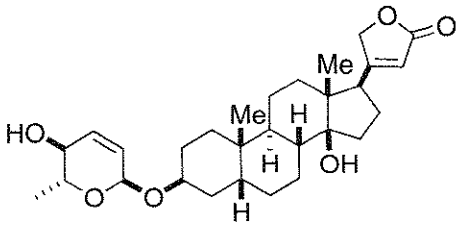
17a



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

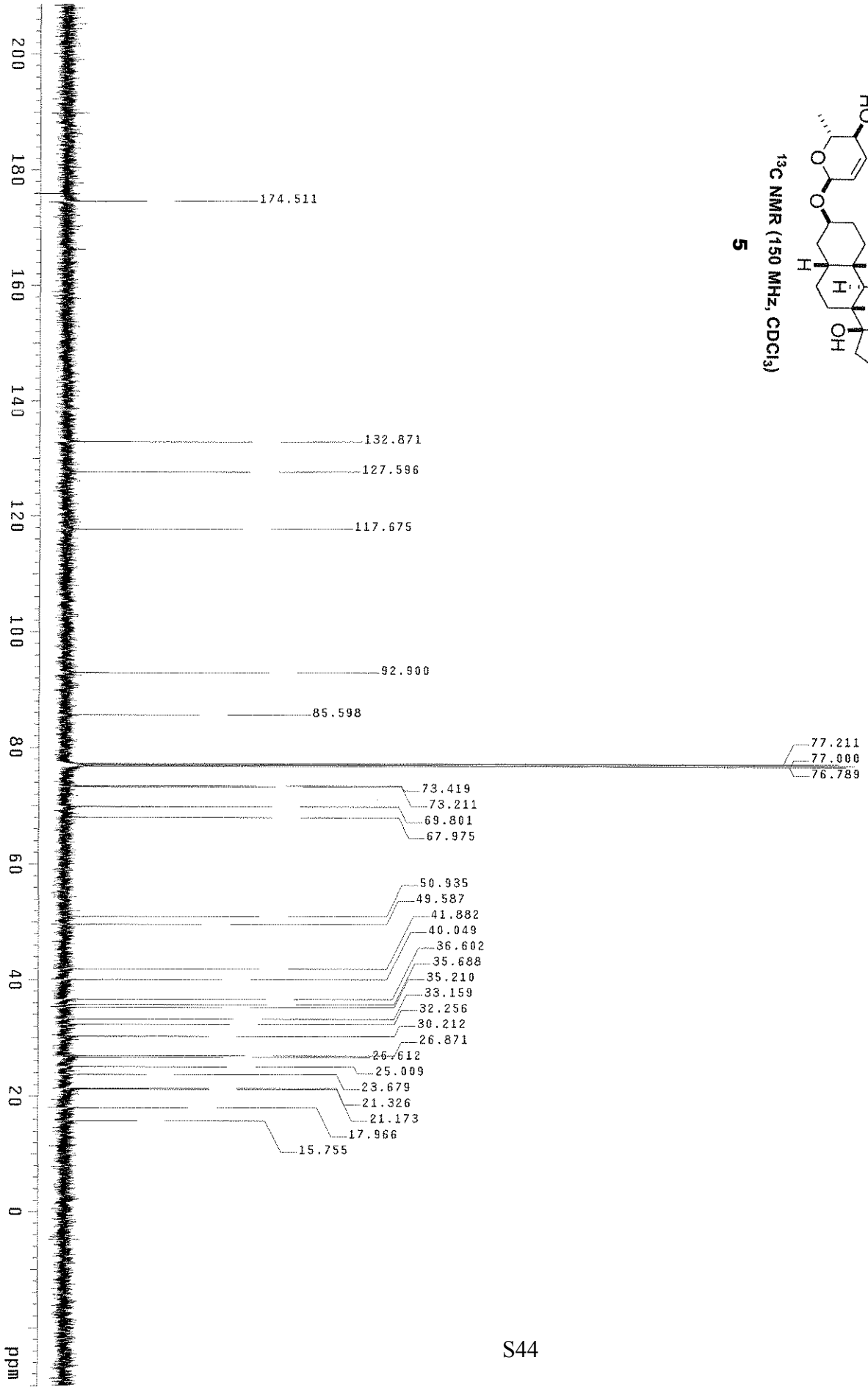
17a





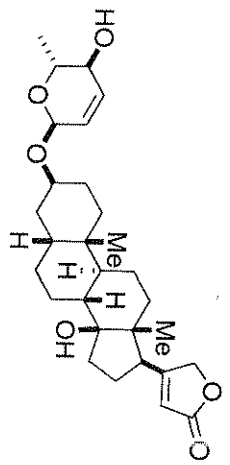
^{1}H NMR (600 MHz, $CDCl_3$)

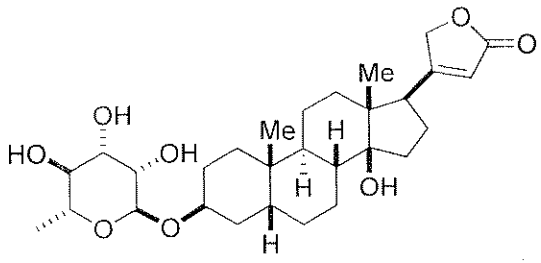
5



5

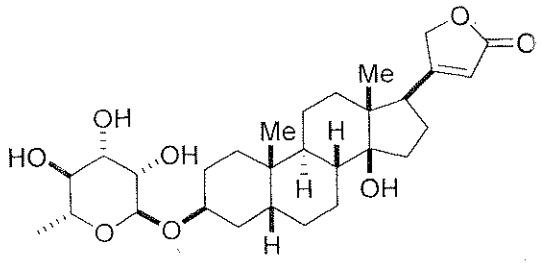
^{13}C NMR (150 MHz, $CDCl_3$)





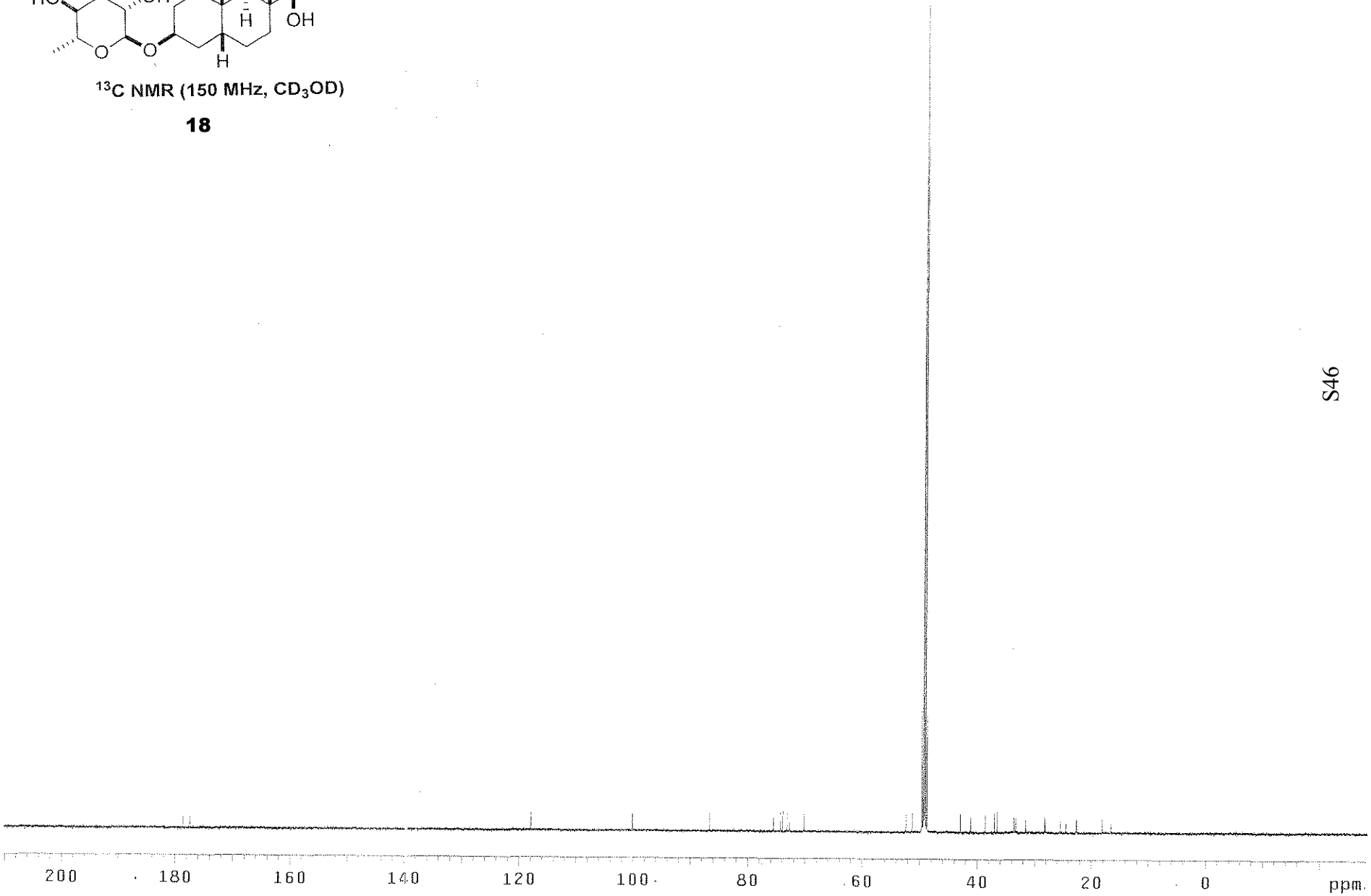
^{1}H NMR (600 MHz, CD_3OD)

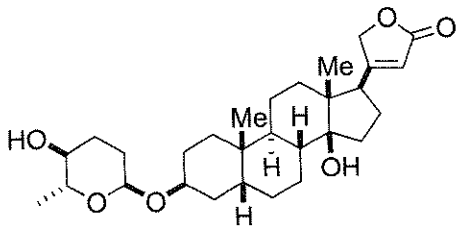
18



^{13}C NMR (150 MHz, CD_3OD)

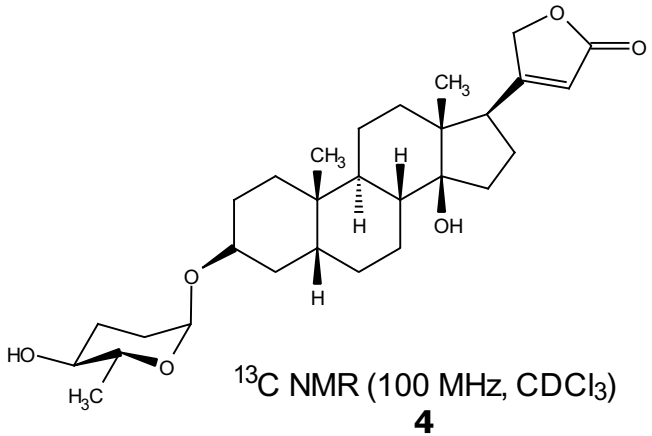
18





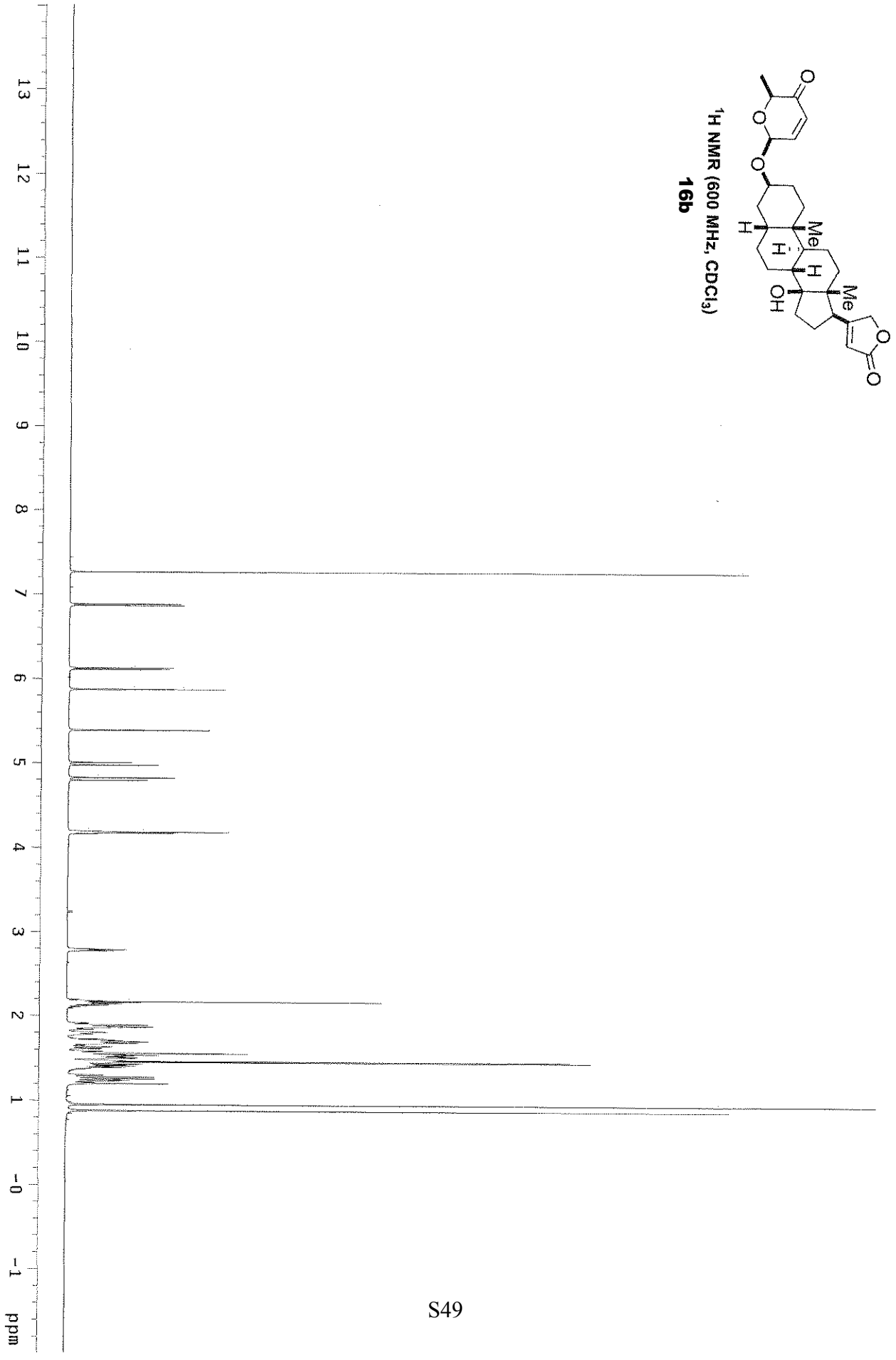
^{1}H NMR (600 MHz, $CDCl_3$)

4



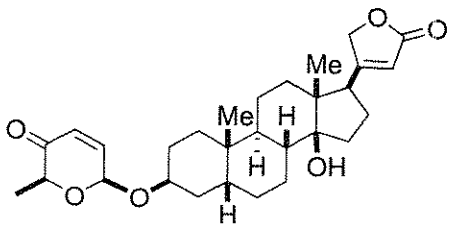
^{13}C NMR (100 MHz, $CDCl_3$)

4



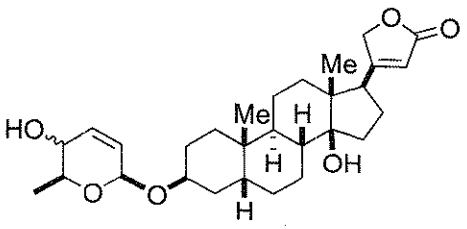
^{1}H NMR (600 MHz, $CDCl_3$)

16b



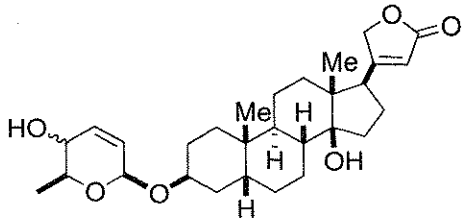
^{13}C NMR (150 MHz, $CDCl_3$)

16b



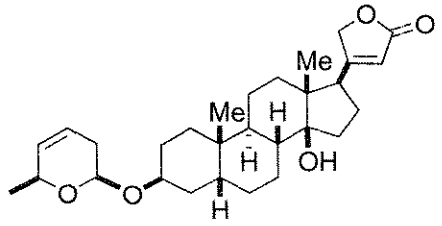
^{1}H NMR (600 MHz, $CDCl_3$)

IV/V



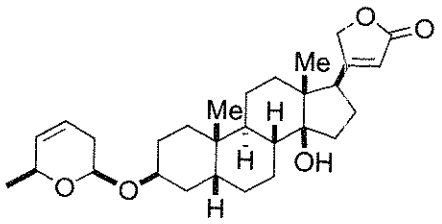
^{13}C NMR (150 MHz, $CDCl_3$)

IV/V



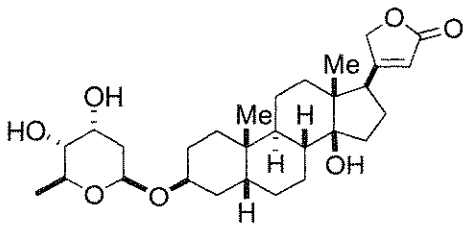
^{1}H NMR (600 MHz, $CDCl_3$)

VI



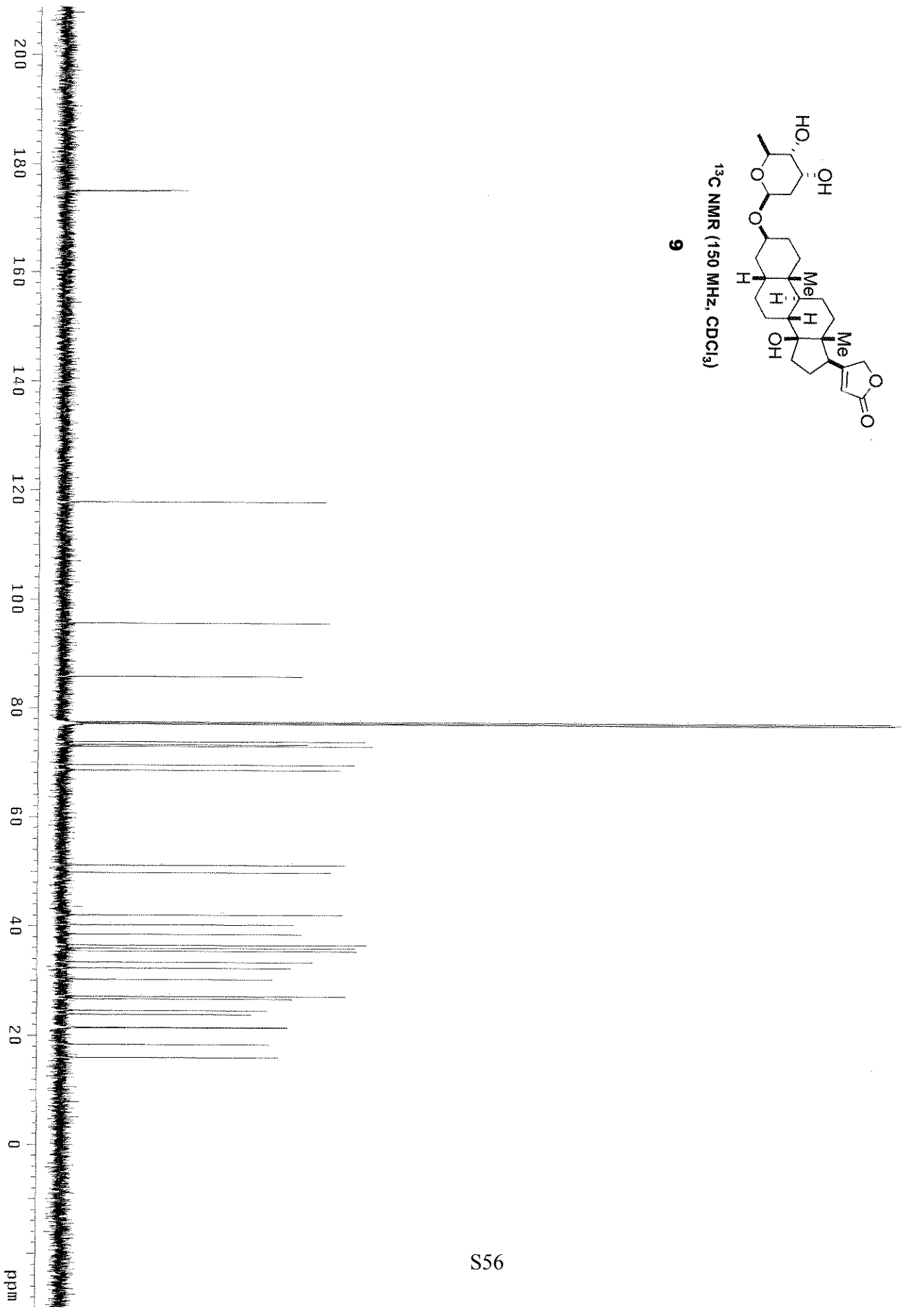
^{13}C NMR (150 MHz, $CDCl_3$)

VI



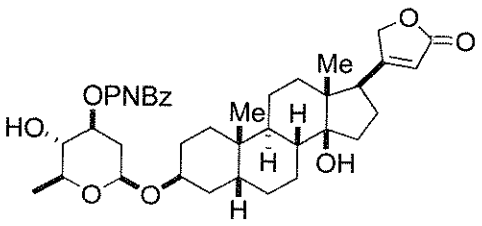
^{1}H NMR (600 MHz, $CDCl_3$)

9



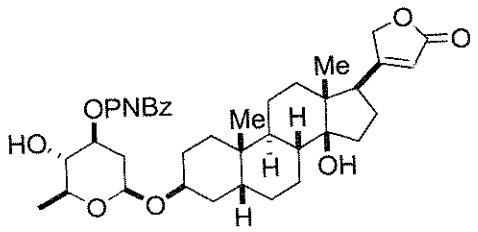
^{13}C NMR (150 MHz, $CDCl_3$)

9



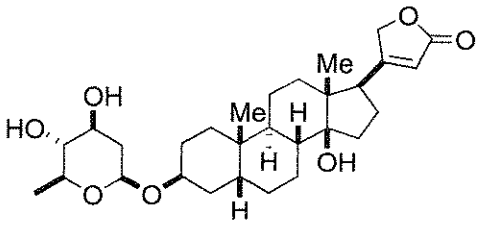
^{1}H NMR (600 MHz, $CDCl_3$)

VII



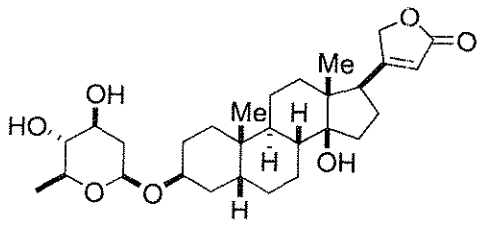
^{13}C NMR (150 MHz, $CDCl_3$)

VII



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

10



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

10