SUPPORTING INFORMATION

C5'-Alkyl Substitution Effects on Digitoxigenin α-L-Glycoside Cancer Cytotoxicity

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Section A: 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 (SFM). 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 independent experimental runs (N = 6). All the dose-response curves were analyzed by Two-way ANOVA to compare digitoxin α-L-rhamnoside **4** and α-L-amicetoside **9** with its C5'-alkyl substituted digitoxin analogues **5** to **8** and **10** to **12** in the effect of concentrations to cytotoxicity and apoptosis activity. Two-way ANOVA with Bonferroni post test, nonlinear regression analysis 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 ≤ 3%.

Table S1-1. Cell death (%) and standard deviation (SD) as a function of drugs concentration.

Compound (α-L-rhamnosides)			**C5'-Me 4**	**C5'-Et 5**	**C5'-*n*Pr 6**	**C5'-*i*Pr 7**	**C5'-*i*Bu 8**
Drug Concentration	10 nM	% Cell Death	16.47	15.02	15.86	12.81	12.15
		SD	3.11	2.32	2.06	5.24	4.22
	25 nM	% Cell Death	24.53	24.93	20.15	19.33	14.36
		SD	5.25	6.68	3.35	4.36	2.60
	50 nM	% Cell Death	48.79	42.16	23.16	24.42	17.66
		SD	8.73	3.47	4.78	5.93	3.76
	75 nM	% Cell Death	78.16	71.83	34.10	37.08	24.50
		SD	6.86	5.24	7.61	7.29	4.84
	100 nM	% Cell Death	89.50	80.15	52.06	45.94	36.73
		SD	5.59	5.07	6.99	1.90	7.81
	250 nM	% Cell Death	100.0	98.51	84.94	73.97	68.62
		SD	0	1.86	8.57	3.15	6.14
	500 nM	% Cell Death	100.0	100.0	100.0	100.0	100.0
		SD	0	0	0	0	0

	1000 nM	% Cell Death	100.0	100.0	100.0	100.0	100.0
		SD	0	0	0	0	0
	10000 nM	% Cell Death	100.0	100.0	100.0	100.0	100.0
		SD	0	0	0	0	0

Table S1-2. P-values from Bonferroni post test of Two-way ANOVA analysis for selected comparisons of percent cell death in the effect of concentration.

Comparison	**Compound (nM)**								
	10	**25**	**50**	**75**	**100**	**250**	**500**	**1000**	**10000**
4 vs **5**	P>0.05	P>0.05	P>0.05	P>0.05	P<0.01	P>0.05	P>0.05	P>0.05	P>0.05
4 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
4 vs **7**	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
4 vs **8**	P>0.05	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P>0.05	P>0.05	P>0.05

Table S1-3. Non-linear-regression analysis of cytotoxicity dose-dependent experiment.

Compound	**C5'-Me 4**	**C5'-Et 5**	**C5'-*n*Pr 6**	**C5'-*i*Pr 7**	**C5'-*i*Bu 8**
IC_{50} (nM)	51.71	56.91	115.5	130.2	166.8
SE (nM)	1.036	1.035	1.052	1.057	1.052
R^2	0.9799	0.9843	0.9767	0.9809	0.9812

Table S1-4. Apoptotic cells (%) with standard deviation (SD) for each C5'-alkyl substituted digitoxin rhamnosides at 50 nM concentration and P-values from Bonferroni post test of One-way ANOVA analysis.

Compound (α-L-rhamnosides)	**C5'-Me 4**	**C5'-Et 5**	**C5'-*n*Pr 6**	**C5'-*i*Pr 7**	**C5'-*i*Bu 8**
% Apoptotic cell (Mean nM)	41.603	30.625	15.692	15.425	9.9487
SD	4.0938	6.1844	3.1165	2.7126	2.8321
Comparison		**4** vs **5**	**4** vs **6**	**4** vs **7**	**4** vs **8**
One-way ANOVA		P<0.001	P<0.001	P<0.001	P<0.001

Table S2-1. Cell death (%) and standard deviation (SD) as a function of drugs concentration.

Compound (α-L-amicetosides)			C5'-Me 9	C5'-Et 10	C5'-*i*Pr 11	C5'-*i*Bu 12
Drug Concentration	10 nM	% Cell Death	18.12	13.46	9.96	10.03
		SD	2.10	2.68	2.90	2.02
	25 nM	% Cell Death	22.09	19.43	12.07	12.41
		SD	1.60	2.76	2.71	1.83
	50 nM	% Cell Death	52.04	22.56	14.48	13.06
		SD	2.21	3.99	3.95	2.87
	75 nM	% Cell Death	77.04	39.69	16.05	15.00
		SD	3.17	4.46	3.87	2.64
	100 nM	% Cell Death	98.61	69.05	18.89	17.69
		SD	1.61	1.71	3.42	2.44
	250 nM	% Cell Death	100.0	87.87	22.73	21.86
		SD	0	3.46	2.90	2.32
	500 nM	% Cell Death	100.0	99.58	50.85	62.18
		SD	0	0.59	3.01	4.13
	1000 nM	% Cell Death	100.0	100.0	90.66	94.80
		SD	0	0	1.61	1.70
	10000 nM	% Cell Death	100.0	100.0	100.0	100.0
		SD	0	0	0	0

Table S2-2. P-values from Bonferroni post test of Two-way ANOVA analysis for selected comparisons of percent cell death in the effect of concentration.

Comparison	Compound (nM)								
	10	**25**	**50**	**75**	**100**	**250**	**500**	**1000**	**10000**
9 vs **10**	P<0.01	P>0.05	P<0.001	P<0.001	P<0.001	P<0.001	P>0.05	P>0.05	P>0.05
9 vs **11**	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>0.05
9 vs **12**	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.01	P>0.05

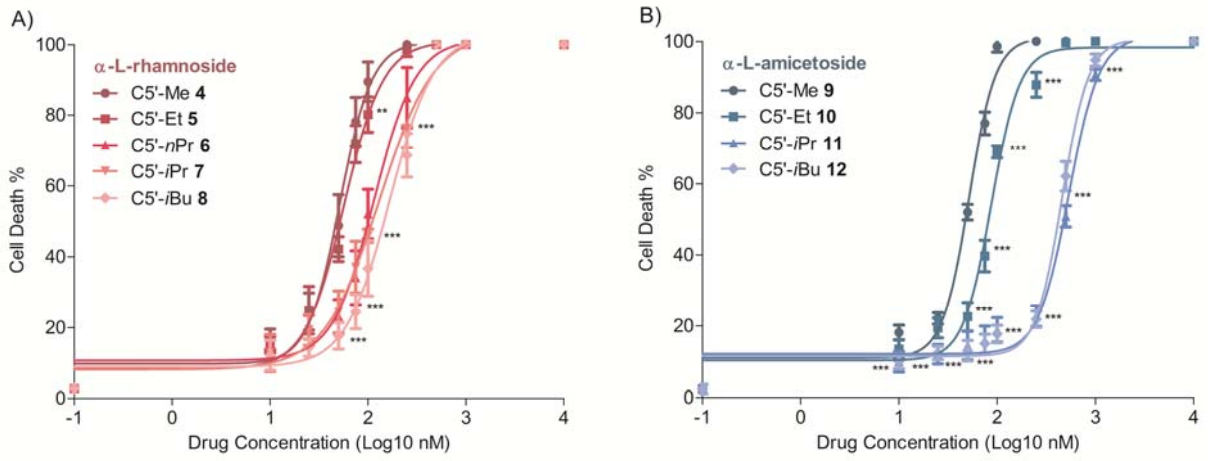
Table S2-3. Non-linear-regression analysis of cytotoxicity dose-dependent experiment.

Compound (α-L-amicetosides)	C5'-Me 9	C5'-Et 10	C5'-*i*Pr 11	C5'-*i*Bu 12
IC_{50} (nM)	51.73	87.35	533.1	458.1
SE (nM)	1.027	1.030	1.036	1.028
R^2	0.9848	0.9796	0.9790	0.9854

Table S2-4. Apoptotic cells (%) with standard deviation (SD) for each C5'-alkyl substituted digitoxin amicetosides at 50 nM concentration and P-values from Bonferroni post test of One-way ANOVA analysis.

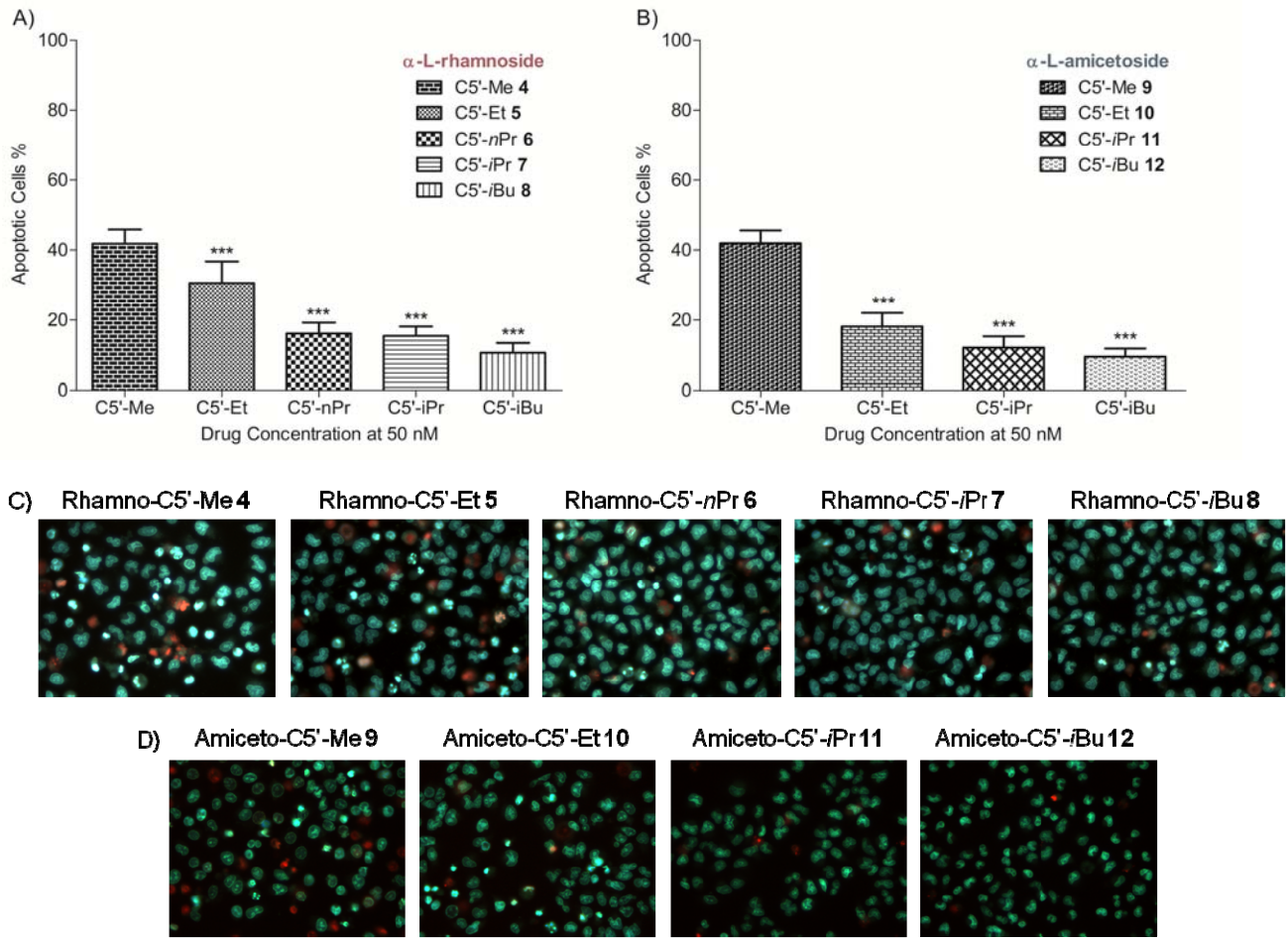
Compound (α-L-amicetosides)	**C5'-Me 9**	**C5'-Et 10**	**C5'-*i*Pr 11**	**C5'-*i*Bu 12**
% Apoptotic cell (Mean nM)	42.463	18.750	11.993	9.2821
SD	3.6968	3.8386	3.1854	2.3516
Comparison		**9** vs **10**	**9** vs **11**	**9** vs **12**
One-way ANOVA		P<0.001	P<0.001	P<0.001

Figure S3. Cytotoxicity as a function of drug concentration in the comparison of C5'-alkyl substitution.



The dose response curve of total cell death (apoptosis/necrosis) mediated by digitoxin analogues in a 12 h treatment at increasing concentrations (10 nM to 10 μM). All the data were analyzed by Two-way ANOVA (N = 6; *, P < 0.05; **, P < 0.01; ***, P < 0.001).

Figure S4. Apoptotic cell death as an effect of steric hindrance.



A & B) Apoptotic cell death (%) was compared for each C5'-alkyl substituted digitoxin rhamnosides and amicetosides at 50 nM concentration (One-way ANOVA; ***, $P < 0.001$). C & D) Hoechst 33342 stained apoptotic cell appear in blue and propidium iodide stained necrotic cell in red at 50 nM drug concentration.

Section B: MTT Colorimetric Assays.[1] 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. 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 α-L-rhamnoside **4** and α-L-amicetoside **9** with its C5'-alkyl substituted digitoxin analogues **5** to **8** and **10** to **12** in the effect of concentrations to cell survival. Two-way ANOVA with Bonferroni post test and nonlinear regression analysis were performed using GraphPad Prism version 5.03 for Windows, GraphPad Software, San Diego California USA. The cell survival at 10 μM was 0%.

Table S5. Dose-dependent experiment of C5'-alkyl substituted α-L-rhamnoside analogues **4** to **8** in 48 h treatment (SD = Standard Deviation).

Concentration (nM)			**0**	**1**	**10**	**25**	**50**	**100**	**500**	**1000**
Compound	**4**	Viability %	100	77.81	11.81	8.72	7.16	6.11	5.81	5.46
		SD	7.09	8.25	1.58	1.88	0.61	0.34	1.27	0.34
	5	Viability %	100	73.23	19.97	10.33	8.28	6.64	6.13	5.71
		SD	7.09	10.70	3.16	1.51	1.01	0.76	0.37	1.56
	6	Viability %	100	81.43	39.27	16.15	9.27	7.06	5.87	5.81
		SD	7.09	4.24	1.29	3.14	1.58	1.22	0.32	0.21
	7	Viability %	100	77.37	47.26	35.01	22.78	9.88	6.11	5.76
		SD	7.09	8.94	4.57	2.53	2.60	0.33	1.19	1.30
	8	Viability %	100	82.42	57.71	40.65	26.07	12.38	6.69	5.90
		SD	7.09	8.90	0.93	3.37	2.74	1.13	0.49	0.79

[1] (a) Mosmann, T. *J. Immunological Methods,* **1983**, *65,* 55-63. (b) Chanvorachote, P.; Nimmannit, U.; Stehlik, C.; Wang, L.; Jiang, B.-H.; Ongpipatanakul, B.; Rojanasakul, Y. *Cancer Res.,* **2006**, *66,* 6353-6360.

Table S6. Non-linear-regression analysis of MTT dose-dependent experiment for the comparison of C5'-alkyl substituted α-L-rhamnoside analogues **4** to **8** (SE = Standard Error).

Compound	**C5'-Me 4**	**C5'-Et 5**	**C5'-*n*Pr 6**	**C5'-*i*Pr 7**	**C5'-*i*Bu 8**
GI_{50} (nM)	2.097	2.141	4.876	6.322	13.42
SE (nM)	1.066	1.088	1.079	1.162	1.097
R^2	0.9868	0.9821	0.9879	0.9785	0.9798

Table S7. 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 h treatment.

Comparison	**Compound (nM)**							
	1	**10**	**25**	**50**	**100**	**500**	**1000**	**10000**
4 vs **5**	P>0.05	P<0.001	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
4 vs **6**	P>0.05	P<0.001	P<0.001	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
4 vs **7**	P>0.05	P<0.001	P<0.001	P<0.001	P>0.05	P>0.05	P>0.05	P>0.05
4 vs **8**	P>0.05	P<0.001	P<0.001	P<0.001	P<0.01	P>0.05	P>0.05	P>0.05

Table S8. Dose-dependent experiment of C5'-alkyl substituted α-L-amicetoside analogues **9** to **12** in 48 h treatment (SD = Standard Deviation).

Concentration (nM)			**0**	**1**	**10**	**25**	**50**	**100**	**500**	**1000**
Compound	**9**	Viability %	100	77.02	13.94	7.14	6.18	5.00	3.69	3.25
		SD	12.42	3.90	0.81	1.59	1.63	1.59	0.77	1.41
	10	Viability %	100	73.34	20.58	9.23	8.21	6.81	5.41	4.50
		SD	12.42	2.17	3.69	1.17	1.23	1.64	1.67	1.11
	11	Viability %	100	81.08	50.66	30.13	22.21	12.38	6.35	5.21
		SD	12.42	5.55	4.23	2.62	3.32	1.83	0.78	0.29
	12	Viability %	100	81.78	49.19	36.57	25.07	18.46	4.88	3.64
		SD	12.42	1.99	4.21	3.26	2.80	3.06	1.16	0.10

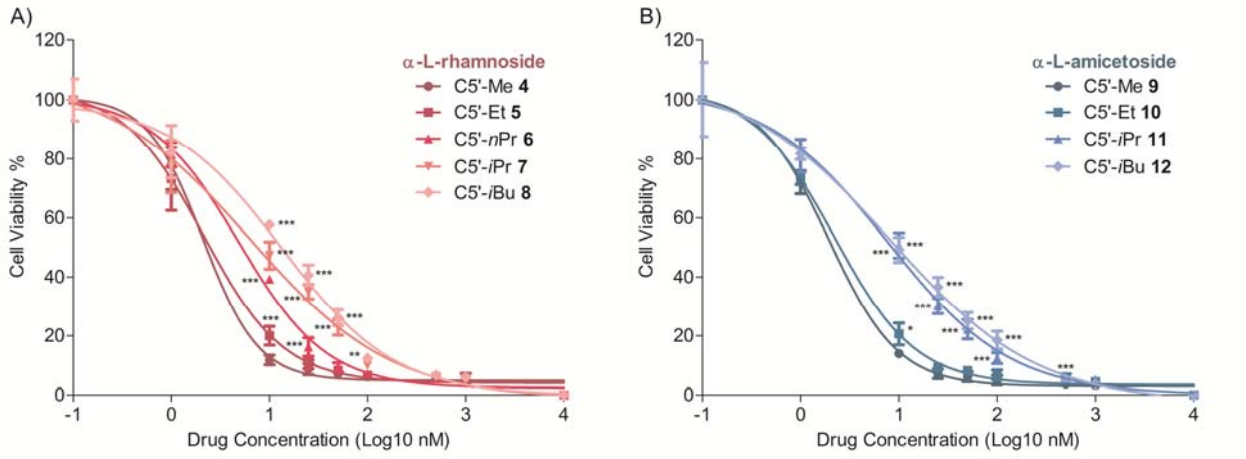
Table S9. Non-linear-regression analysis of MTT dose-dependent experiment for the comparison of C5'-alkyl substituted α-L-amicetoside analogues **9** to **12** (SE = Standard Error).

Compound	**C5'-Me 9**	**C5'-Et 10**	**C5'-*i*Pr 11**	**C5'-*i*Bu 12**
GI_{50} (nM)	1.927	2.191	7.659	8.267
SE (nM)	1.073	1.088	1.132	1.142
R^2	0.9838	0.9824	0.9776	0.9816

Table S10. 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 h treatment.

Comparison	Compound (nM)							
	1	**10**	**25**	**50**	**100**	**500**	**1000**	**10000**
9 vs **10**	P>0.05	P<0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
9 vs **11**	P<0.001	P<0.001	P<0.001	P<0.001	P<0.01	P>0.05	P>0.05	P>0.05
9 vs **12**	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P>0.05	P>0.05	P>0.05

Figure S11. Dose-response curve of cell viability in a 48 h treatment at increasing concentrations (1 nM to 10 μM) were performed to test the effect of C5'-alkyl substitution on rhamnoside and amicetoside analogues. All the data were analyzed by Two-way ANOVA ($N = 9$; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$).



Section C: NCI Growth Inhibition Assays.[2] 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.

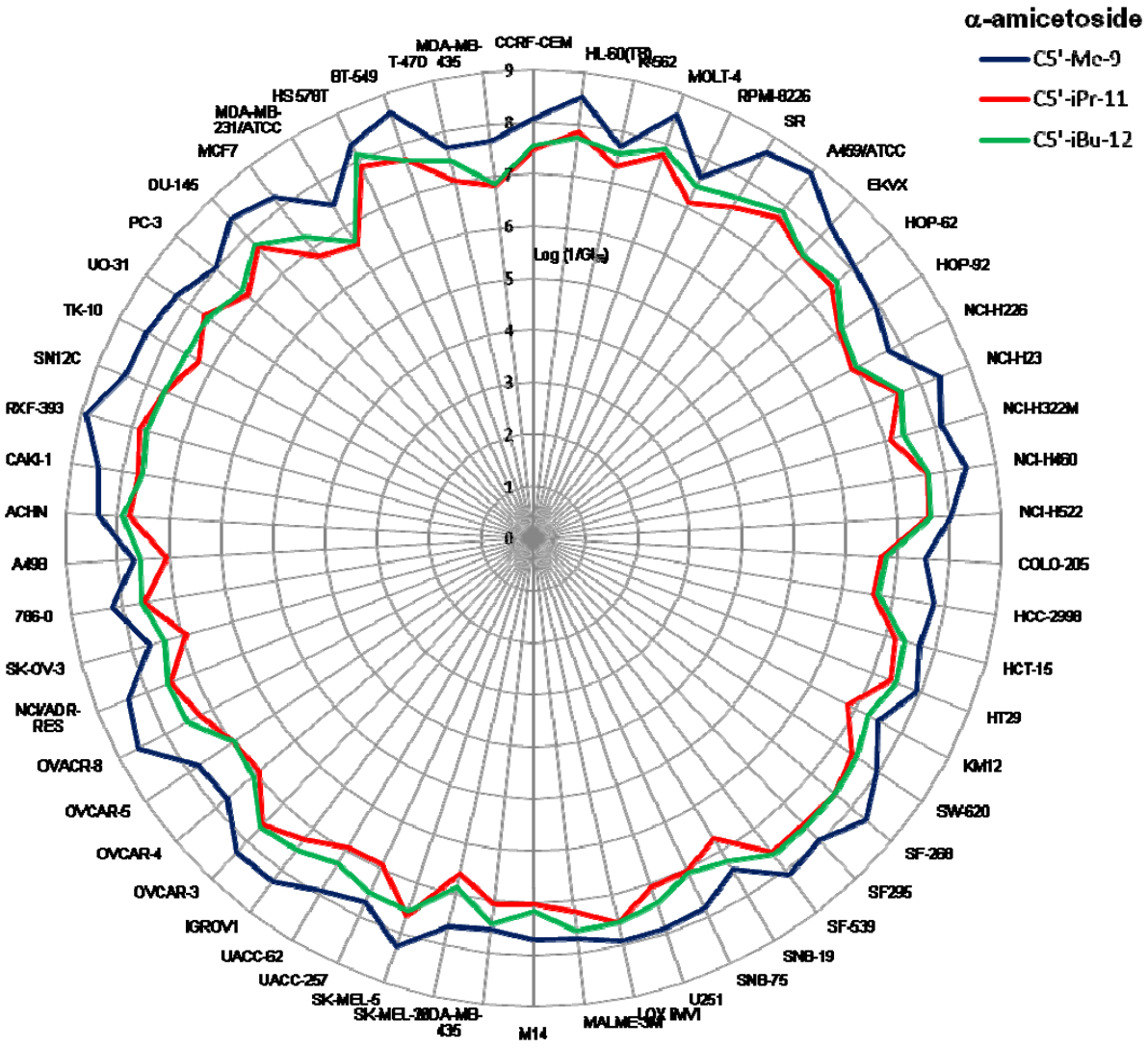
[2] Screening Services – NCI-60 DTP Human Tumor Cell Line Screen Home Page. http://dtp.nci.nih.gov/branches/btb/ivclsp.html (accessed October 15, 2010).

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 S12. GI_{50} (nM) for α-L-amicetose C5'-Me **9,** C5'-*i*Pr **11** and C5'-*i*Bu **12** against 60 cancer cell lines.

		Compound					Compound		
Cell Type	**Cell Line**	**C5'-Me 9**	**C5'- *i*Pr 11**	**C5'-*i*Bu 12**	**Cell Type**	**Cell Line**	**C5'-Me 9**	**C5'- *i*Pr 11**	**C5'-*i*Bu 12**
Leukemia	CCRF-CEM	8.49	33.1	28.5	Melanoma	LOX IMVI	11.8	26.9	27.2
	HL-60(TB)	2.96	14.3	18.3		MALME-3M	18.3	63.6	25.7
	K-562	19.5	47.0	26.9		M14	19.3	93.4	67.2
	MOLT-4	2.57	16.9	13.1		MDA-MB-435	27.7	82.8	35.1
	RPMI-8226	23.5	78.4	35.6		SK-MEL-2	**NA**	170.0	115.0
	SR	2.25	37.2	23.0		SK-MEL-28	23.1	252.0	133.0
Non-Small Cell Lung Cancer	A549/ATCC	1.56	17.7	13.4		SK-MEL-5	5.44	22.6	27.7
	EKVX	5.13	31.9	31.7		UACC-257	19.6	122.0	31.3
	HOP-62	8.55	31.1	23.1		UACC-62	12.7	119.0	50.5
	HOP-92	11.3	79.8	74.2	Ovarian Cancer	IGROV1	5.23	54.2	29.9
	NCI-H226	19.3	119.0	95.9		OVCAR-3	4.94	26.0	23.5
	NCI-H23	4.13	29.4	25.7		OVCAR-4	18.9	123.0	85.5
	NCI-H322M	7.78	77.4	42.5		OVCAR-5	17.4	107.0	113.0
	NCI-H460	3.83	21.7	20.9		OVCAR-8	2.50	56.2	29.6
	NCI-H522	9.38	26.0	23.6		NCI/ADR-RES	4.12	31.5	26.9
Colon Cancer	COLO 205	29.6	207.0	170.0		SK-OV-3	22.2	118.0	43.1
	HCC-2998	16.5	243.0	204.0	Renal Cancer	786-0	6.21	26.8	23.3
	HCT-116	**NA**	21.5	26.1		A498	20.7	90.1	27.0
	HCT-15	20.5	62.2	40.3		ACHN	4.31	17.0	12.2
	HT29	11.9	41.9	31.5		CAKI-1	3.32	20.8	24.4
	KM12	32.4	152.0	55.9		RXF 393	1.22	14.0	18.6
	SW-620	11.1	42.8	32.0		SN12C	3.61	23.7	23.7
CNS Cancer	SF-268	4.28	26.3	26.3		TK-10	3.75	53.8	28.6
	SF-295	10.4	28.6	24.9		UO-31	5.15	23.4	27.7
	SF-539	7.80	27.6	23.8	Breast Cancer	MCF7	5.89	161.0	52.8
	SNB-19	37.5	185.0	58.9		MDA-MB-231	33.9	259.0	225.0
	SNB-75	14.9	92.6	85.3		HS 578T	4.57	13.6	7.50
	U251	12.7	82.9	39.7		BT-549	2.41	20.7	22.5
Prostate Cancer	PC-3	9.55	61.9	46.3		T-47D	20.6	95.9	36.2
	DU-145	3.45	19.5	16.6		MDA-MB-435	21.0	150.0	149.0

Figure S13. Pin-Wheel presentation of cytotoxicity against NCI-panel of 58 cancer cell lines as an effect of C5'-alkyl substitution (*i.e.,* α-L-amicetose C5'-Me **9** versus C5'-*i*Pr **11** versus C5'-*i*Bu **12**).[a]



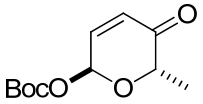
[a]NCI-cancer cell lines are presented in each radius axis of the pin-wheel, and drug concentration is presented in Log(1/GI_{50} M) in each circle. The result clearly showed that α-L-amicetose C5'-Me **9** inhibited growth of cancer cells with at least 10-fold stronger potency than C5'-*i*Pr **11** and C5'-*i*Bu **12**. Because there was no value provided from NCI for α-L-amicetose C5'-Me **9** in HCT-116 and SK-MEL-2 cell lines, these two cell lines were removed in order to clarify the presentation.

Section D: 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 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.

Section E: Synthetic Procedures

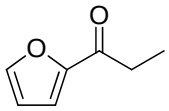
(2*S*, 6*S*)-*tert*-butyl -5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl carbonate (16a):[3]



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 **14a** (15 g, 0.136 mol) and CH_2Cl_2 (2 mL). After degassed (3 times) and addition of small quantity of $NaHCO_3$ to adjust the basicity, surfactant Cetyltrimethylammonium Bromide (5 g, 10 mol%) was added and stirred for 5 min. 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 **15a** were further dissolved in 228 mL 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 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 **α-16a** (15 g, 65.7 mmol, 48%) and **β-16a** (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(3), 15.1; ClHRMS: Calculated for [$C_{11}H_{16}O_5Na$+]: 251.0890, Found: 251.0883.

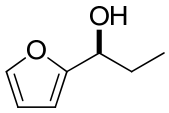
[3] Spectral data matches the previously reported compound **16a**, see: (a) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.,* **2007,** *72,* 2485-2493. (b) Guo, H.; O'Doherty, G. A. *J. Org. Chem.,* **2008,** *73,* 5211-5220.

1-(furan-2-yl)-propan-1-one (14b):



To 62 mL of furan **13** (0.86 mol) was dropped *n*-BuLi (100 mL, 0.24 mol) at 0 ^{o}C. Then let it warm up to room temperature and the resulting solution was stirred at room temperature for 3 h. Then 75 mL of anhydrous THF was added to dissolve the solid mixture at RT, which was then transferred to propionic acid (5.9 mL, 0.079 mol) in 50 mL of THF at 0 ^{o}C. Then resulting solution was stirred 30 min at 0 ^{o}C followed by warming and stirring at RT for 3 h. Then into the reaction mixture 300 mL of Et_2O was added to dilute the solution, followed by addition of 300 mL of distilled water at 0 ^{o}C. Into the flask, 200 mL of 2M NaOH and 200 mL sat. $NaHCO_3$ were added to wash the organic layer. The aqueous layer was extracted with Et_2O (300 ml x2). The pooled organic layer was washed with 200 mL saturated brine solution, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 2% EtOAc/hexane gave furan ketone **14b** (6.31 g, 64%) as light yellow oil; R_f = 0.83 (4:1 (v/v) Hexane/EtOAc); IR (thin film, cm^{-1}) 3131, 2980, 2939, 1672, 1569, 1469, 1394, 1158, 1010, 882, 758; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.16 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.51 (dd, *J* = 3.5, 1.8 Hz, 1H), 2.64 (q, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 190.1, 152.5, 146.0, 116.6, 112.0, 31.5, 7.9.

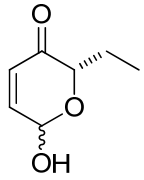
(*S*)-1-(furan-2-yl)-propan-1-ol (15b)[4]:



To a solution of aqueous HCO_2Na (17.7 g, 130 mL, 2.0 M) was added furan ketone **14b** (9.63 g, 0.078 mol) and CH_2Cl_2 (6 mL), followed by the addition of surfactant Cetyltrimethylammonium Bromide (2.83 g, 0.0078 mmol). The mixture was stirred for 5 min, then added Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η_6-mesitylene)-(*S,S*)-TsDPEN (0.047 g, 0.1 mol%). The resulting solution was stirred at room temperature under argon for 24 h. Then the mixture was added with 300 mL H_2O to dilute and extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with 40 mL saturated aqueous $NaHCO_3$, 40 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 8% EtOAc /hexane gave furan alcohol **15b** (6.4 g, 65%) as colorless oil; R_f = 0.42 (4:1 (v/v) Hexane/EtOAc); $[\alpha]_D^{25}$ = -13 (c = 0.8, $CHCl_3$); IR (thin film, cm^{-1}) 3371, 2966, 2935, 2877, 1507, 1461, 1151, 1009, 793, 733; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 1.8, 0.6 Hz 1H), 6.31 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.21 (d, *J* = 3.0 Hz, 1H), 4.56 (dd, *J* = 6.6, 6.6 Hz, 1H), 2.32 (s, 1 H), 1.85 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.9, 142.0, 110.2, 106.0, 69.3, 28.7, 10.0.

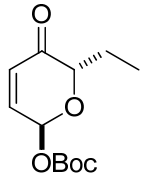
[4] Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori R. *Org. Lett.,* **2000**, *2*, 1749-1751.

(2*S*)-2-ethyl-6-hydroxy-2H-pyran-3(6H)-one (I):



To a solution of 3.06 g furan alcohol **15b** (24.3 mmol) in 82 mL THF-H_2O (3:1) was added 4.08 g $NaHCO_3$ (48.6 mmol), 3.30 g NaOAc•$3H_2O$ (24.3 mmol), and 4.32 g NBS (24.3 mmol) at 0 ^oC. The reaction mixture was kept stirring at this temperature for 1 h, then at 0 ^oC 80 mL saturated $NaHCO_3$ was added to quench the reaction. The reaction mixture was directly extracted with Et_2O (3 x 80 mL) and the organic layer was pooled, washed by 30 mL saturated brine, dried over Na_2SO_4 and then concentrated reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with 15% EtOAc/hexane afforded pyranone alcohol **I** (3.04 g, 88 %) as colorless oil; R_f = 0.44 (2:1 (v/v) hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 6.89 (dd, J = 10.2, 3.6 Hz, 1H), 6.08 (d, J = 10.2 Hz, 1H), 5.64 (m, 1H), 4.49 (dd, J = 7.6, 4.0 Hz, 1H), 3.87 (d, J = 5.2 Hz, 1H), 1.97-1.87 (m, 1H), 1.85-1.69 (m, 1H), 0.95 (dd, J = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 197.1, 144.9, 127.7, 87.7, 75.4, 23.1, 9.5.

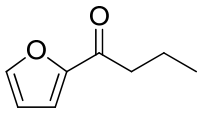
***tert*-butyl ((6*S*)-6-ethyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (16b):**



To a solution of 3.04 g pyranone alcohol **I** (21.4 mmol) in 10 mL CH_2Cl_2 was added 261.40 mg DMAP (2.14 mmol) at -78 ^oC. A pre-cooled solution of 5.60 g $(Boc)_2O$ (25.68 mmol) in 10 mL CH_2Cl_2 was added drop-wise into the reaction mixture via a cannula. The reaction mixture was stirred at -78 ^oC for 12 h. The reaction was quenched by 75 mL saturated $NaHCO_3$ and then extracted with Et_2O (150 mL x 3). The organic layers were pooled, then washed by 25 mL saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 5% EtOAc/hexane gave 4.61 g (89%) of two diastereomers of Boc-protected pyranone **α-16b** and **β-16b** in 1.8:1; **α-16b**: R_f = 0.69 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ = +62.9 (c = 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 2981, 2885, 1751, 1701, 1462, 1371, 1276, 1256, 1159, 1104, 1057, 1030, 940, 847; ^1H NMR (600 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.33 (d, *J* = 3.6 Hz, 1H), 6.16 (d, *J* = 10.2 Hz, 1H), 4.43 (dd, *J* = 7.2, 4.2 Hz, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.49 (s, 9H), 0.93 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.3, 151.8, 140.9, 128.9, 89.3, 83.4, 76.6, 27.6 (3), 22.8, 8.9; ESIHRMS Calcd for $[C_{12}H_{18}O_5 + Na]^+$: 65.10469, Found: 265.10500.

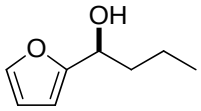
β-16b: R_f = 0.61 (4:1 (v/v) hexane/EtOAc); mp: 65-66 ^oC; $[\alpha]_D^{25}$ = -73.5 (c = 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 2983, 2877, 1740, 1684, 1461, 1397, 1292, 1254, 1160, 1053, 946, 846, 732; ^1H NMR (600 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.37 (dd, *J* = 3.0, 1.2 Hz, 1H), 6.20 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.14 (dd, *J* = 9.6, 4.8 Hz, 1H), 1.96-1.83 (m, 2H), 1.53 (s, 9H), 1.03 (dd, *J* = 7.8, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.7, 152.1, 142.4, 129.2, 90.0, 84.6, 83.8.0, 31.0, 27.9 (2), 18.9, 18.4; ESIHRMS Calcd for $[C_{12}H_{18}O_5 + Na]^+$: 265.10469, Found: 265.10508.

1-(furan-2-yl)-butan-1-one (14c):



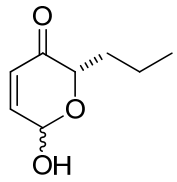
To 330 mL of furan **13** (4.54 mol) was dropped *n*BuLi (480 mL, 1.06 mol) at -0 ^{o}C. Then let it warm up to room temperature and the resulting solution was stirred at room temperature for 12 h. Then 400 mL of anhydrous THF was added to dissolve the solid mixture at RT, which was then transferred to butyric acid (48.3mL, 0.528 mol) in 50 mL of THF at -78 ^{o}C. Then resulting solution was stirred 30 min at -78 ^{o}C followed by warming and stirring at 0 ^{o}C for another 12 h. Then into the reaction mixture 30 ml of acetone was added to quench the reaction, followed by addition of EtOAc (600 ml). At 0 ^{o}C 400ml of sat. NH_4Cl was added to wash the organic layer. The aqueous layer was extracted with EtOAc (600 ml x 2). The pooled organic layer was washed with 50 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 5% Et_2O/hexane gave furan ketone **14c** (52.27 g, 72%) as light yellow oil; R_f = 0.69 (2:1 (v/v) Hexane/EtOAc); IR (thin film, cm^{-1}) 3132, 2964, 2876, 1674, 1568, 1467, 1394, 1159, 1020, 881, 760; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.10 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.45 (dd, *J* = 3.6, 1.8 Hz, 1H), 2.72 (dd, *J* = 7.8, 7.2 Hz, 2H), 1.68 (qdd, *J* = 7.8, 7.8, 7.2 Hz, 2H), 0.91(dd, *J* = 7.8, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.6, 152.9, 146.2, 116.8, 112.1, 40.4, 17.8, 13.8.

(*S*)-1-(furan-2-yl)butan-1-ol (15c):



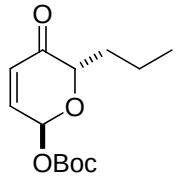
To a solution of aqueous HCO_2Na (672 mL, 2.0 M) was added furan ketone **14c** (52.27g, 1.344 mol) and CH_2Cl_2 (34 mL), followed by the addition of surfactant Cetyltrimethylammonium Bromide (13.6 g, 37.3 mmol). The mixture was stirred for 5 min, and added Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η_6-mesitylene)-(*S,S*)-TsDPEN (0.218 g, 0.1 mol%). The resulting solution was stirred at room temperature under argon for 24 h. Then the mixture was extracted with Et_2O (3 x 300 mL). The combined organic layer was washed with 50 mL saturated aqueous $NaHCO_3$, 50 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 10% Et_2O/hexane gave furan alcohol **15c** (42.16 g, 81%) as colorless oil; R_f = 0.59 (2:1 (v/v) Hexane/EtOAc); $[\alpha]_D^{25}$ = -26 (c = 1.5, CH_2Cl_2); IR (thin film, cm^{-1}) 3343, 2959, 2935, 2873, 1505, 1466, 1149, 1007, 732; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 1.8, 0.6 Hz 1H), 6.32 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.22 (d, *J* = 3.0, 1H), 4.68 (dd, *J* = 7.2, 6.6 Hz, 1H), 1.95 (s, 1 H), 1.83 (m, 2H), 1.50-1.41 (m, 1H), 1.39-1.31 (m, 1H), 0.94 (dd, *J* = 7.8, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.1, 142.0, 110.3, 105.9, 67.8, 37.8, 18.9, 14.0.

(*S*)-6-hydroxy-2-propyl-2H-pyran-3(6H)-one (II):



To a solution of 3.67 g furan alcohol **15c** (26.2 mmol) in 106 mL THF-H_2O (3:1) was added 4.4 g $NaHCO_3$ (52.4 mmol), 3.56 g NaOAc•$3H_2O$ (26.2 mmol), and 4.66 g NBS (26.2 mmol) at 0 ^oC. The reaction mixture was kept stirring at this temperature for 1 h, then at 0 ^oC 60 mL saturated $NaHCO_3$ was added to quench the reaction. The reaction mixture was directly extracted with Et_2O (3 x 100 mL) and the organic layer was pooled, washed by 30 mL saturated brine, dried over Na_2SO_4 and then concentrated reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with 20% EtOAc/hexane afforded pyranone alcohol **II** (3.43 g, 84 %) as colorless oil; R_f = 0.41 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ = +12 (c = 1.6, CH_2Cl_2); IR (thin film, cm^{-1}) 3399, 2959, 2961, 2874, 1683, 1084, 1022, 968; ^1H NMR (600 MHz, $CDCl_3$) major isomer δ 6.88 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.07 (d, *J* = 10.2, 1H), 5.62 (s, 1H), 4.54 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.83 (s, 1H), 1.89-1.83 (m, 1H), 1.70-1.63 (m, 1H), 1.47-1.36 (m, 2H), 0.91 (dd, *J* = 7.8, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) major isomer δ 197.2, 144.9, 127.7, 87.7, 74.1, 31.8, 18.4, 13.9.

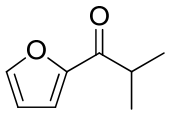
(2*S*,6*S*)-*t*-butyl-5,6-dihydro-6-propyl-5-oxo-2H-pyran-2-yl carbonate (16c):



To a solution of 4.0 g pyranone alcohol **II** (25.8 mmol) in 26 mL CH_2Cl_2 was added 315 mg DMAP (2.58 mmol) at -78 ^oC. A pre-cooled solution of 11.2 g $(Boc)_2O$ (51.6 mmol) in 15 mL CH_2Cl_2 was added drop-wise into the reaction mixture via a cannula. The reaction mixture was stirred at -78 ^oC for 12 h. The reaction was quenched by 150 mL saturated $NaHCO_3$ and then extracted with Et_2O (300 mL x 3). The organic layers were pooled, then washed by 50 mL saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 5% Et_2O/hexane gave 5.61 g (85%) of two diastereomers of Boc-protected pyranone **α-16c** and **β-16c** in 2.7:1; **α-16c**: R_f = 0.76 (3:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ = +55.2^o (c = 1.2, $CHCl_3$); IR (thin film, cm^{-1}) 2964, 2876, 1749, 1698, 1459, 1370, 1274, 1253, 1155, 1054, 936, 844; ^1H NMR (600 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.33 (d, *J* = 3.6 Hz, 1H), 6.19 (d, *J* = 10.2 Hz, 1H), 4.51 (dd, *J* = 8.4, 4.2 Hz, 1H), 1.92 (dddd, *J* = 14.4, 9.0, 7.8, 3.6 Hz, 1H), 1.70 (dddd, *J* = 14.4, 7.8, 7.8, 7.8 Hz, 1H), 1.51 (s, 9H), 1.48-1.40 (m, 2H), 0.91 (dd, *J* = 7.8, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 152.0, 141.0, 129.1, 89.4, 83.7, 75.6, 31.5, 27.9(3), 18.1, 13.8; ESIHRMS Calcd for $[C_{13}H_{20}O_5 + Na]^+$: 279.1203, Found: 279.1204.

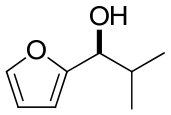
β-16c: R_f = 0.70 (3:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ = -77.8 (c = 1.3, $CHCl_3$); IR (thin film, cm^{-1}) 2963, 2875, 1743, 1683, 1468, 1370, 1284, 1252, 1158, 1058, 946, 847; ^1H NMR (600 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.36 (dd, *J* = 3.0, 1.2 Hz, 1H), 6.20 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.23 (dd, *J* = 10.2, 4.2 Hz, 1H), 1.94-1.87 (m, 1H), 1.79-1.73 (m, 1H), 1.52 (s, 9H), 1.56-1.51 (m, 1H), 1.49-1.41 (m, 1H), 0.95 (dd, *J* = 7.8, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 152.1, 142.0, 128.5, 89.6, 83.7, 79.7, 35.6, 27.9(3), 18.9, 13.8; ESIHRMS Calcd for $[C_{13}H_{20}O_5 + Na]^+$: 279.1203, Found: 279.1204.

1-(furan-2-yl)-2-methylpropan-1-one (14d):



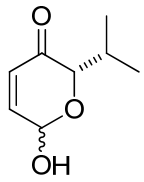
To 62 mL of furan **13** (0.86 mol) was dropped *n*-BuLi (100 mL, 0.24 mol) at 0 ^{o}C. Then let it warm up to room temperature and the resulting solution was stirred at room temperature for 3 h. Then 75 mL of anhydrous THF was added to dissolve the solid mixture at RT, which was then transferred to *iso*-butyric acid (8.8 mL, 0.079 mol) in 50 mL of THF at 0 ^{o}C. Then resulting solution was stirred 30 min at 0 ^{o}C followed by warming and stirring at RT for 3 h. Then into the reaction mixture 300 mL of Et_2O was added to dilute the solution, followed by addition of 300 mL of distilled water at 0 ^{o}C. Into the flask, 200 mL of 2M NaOH and 200 mL sat. $NaHCO_3$ was added to wash the organic layer. The aqueous layer was extracted with Et_2O (300 ml x2). The pooled organic layer was washed with 200 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 3% EtOAc/hexane gave furan ketone **14d** (7.4 g, 68%) as light yellow oil; R_f = 0.80 (4:1 (v/v) Hexane/EtOAc); IR (thin film, cm^{-1}) 3138, 2974, 2880, 1669, 1568, 1465, 1396, 1252, 1017, 884, 759; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (dd, J = 1.8, 0.6 Hz, 1H), 7.18 (d, J = 3.6 Hz, 1H), 6.53 (dd, J = 3.6, 1.8 Hz, 1H), 3.33 (hep, J = 6.6 Hz, 1H), 1.21 (d, J = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.7, 152.3, 146.3, 117.2, 112.2, 36.4, 18.9 (2).

(*S*)-1-(furan-2-yl)-2-methylpropan-1-ol (15d):



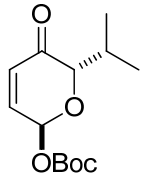
To a solution of aqueous HCO_2Na (6.8 g, 50 mL, 2.0 M) was added furan ketone **14d** (4.22 g, 0.031 mol) and CH_2Cl_2 (2 mL), followed by the addition of surfactant Cetyltrimethylammonium Bromide (1.12 g, 0.0031 mmol). The mixture was stirred for 5 min, then added Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η_6-mesitylene)-(*S,S*)-TsDPEN (0.019 g, 0.1 mol%). The resulting solution was stirred at room temperature under argon for 24 h. The mixture was added with 100 mL H_2O to dilute and extracted with EtOAc (3 x 70 mL). The combined organic layer was washed with 15 mL saturated aqueous $NaHCO_3$, 15 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 8% EtOAc /hexane gave furan alcohol **15d** (2.6 g, 61%) as colorless oil; R_f = 0.56 (4:1 (v/v) Hexane/EtOAc); $[\alpha]_D^{25}$ = -22.1 (c = 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 3387, 2961, 2873, 1505, 1469, 1150, 1007, 807, 730; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 1.8, 0.6 Hz 1H), 6.30 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.19 (d, *J* = 3.0, 1H), 4.33 (d, *J* = 7.2 Hz, 1H), 2.29 (s, 1H), 2.10 (hepd, *J* = 7.2, 6.6 Hz, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 141.7, 110.1, 106.5, 73.6, 33.5, 18.8, 18.4.

(2*S*)-6-hydroxy-2-isopropyl-2H-pyran-3(6H)-one (III):



To a solution of 1.93 g furan alcohol **15d** (13.8 mmol) in 44 mL THF-H_2O (3:1) was added 2.32 g $NaHCO_3$ (27.6 mmol), 1.87 g NaOAc•$3H_2O$ (13.8 mmol), and 2.45 g NBS (13.8 mmol) at 0 ^oC. The reaction mixture was kept stirring at this temperature for 1 h. Then at 0 ^oC 40 mL saturated $NaHCO_3$ solution was added to quench the reaction. The reaction mixture was directly extracted with Et_2O (3 x 40 mL) and the organic layer was pooled, washed by 15 mL saturated brine, dried over Na_2SO_4 and then concentrated reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with 15% EtOAc/hexane afforded pyranone alcohol **III** (1.87 g, 87 %) as colorless oil; R_f = 0.53 (2:1 (v/v) hexane/EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) major isomer δ 6.90 (dd, J = 10.2, 3.6 Hz, 1H), 6.09 (d, J = 10.2 Hz, 1H), 5.66 (d, J = 3.0 Hz, 1H), 4.40 (d, J = 3.0 Hz, 1H), 3.90 (dd, J = 3.6, 1.2 Hz, 1H), 2.43 (m, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) major isomer δ 197.1, 144.7, 128.2, 87.7, 78.5, 28.7, 19.2, 16.4.

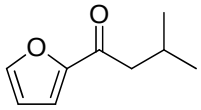
***tert*-butyl-((2*S*,6*S*)-6-isopropyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (16d):**



To a solution of 1.87 g pyranone alcohol **III** (12.0 mmol) in 5 mL CH_2Cl_2 was added 146.2 mg DMAP (1.20 mmol) at -78 ^oC. A pre-cooled solution of 5.24 g $(Boc)_2O$ (24.0 mmol) in 7 mL CH_2Cl_2 was added drop-wise into the reaction mixture via a cannula. The reaction mixture was stirred at -78 ^oC for 12 h. The reaction was quenched by 30 mL saturated $NaHCO_3$ and then extracted with Et_2O (50 mL x 3). The organic layers were pooled, then washed by 15 mL saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 5.5 % EtOAc/hexane gave 2.67 g (87%) of two diastereomers of Boc-protected pyranone **α-16d** and **β-16d** in 2.5:1; **α-16d**: R_f = 0.78 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ = +50.8 (c = 1.0, $CHCl_3$); IR (thin film, cm^{-1}) 2974, 2878, 1751, 1698, 1463, 1370, 1274, 1255, 1157, 1099, 1056, 943, 846, 736; ^1H NMR (600 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.35 (d, *J* = 3.6 Hz, 1H), 6.17 (d, *J* = 10.2 Hz, 1H), 4.34 (d, *J* = 3.0 Hz, 1H), 1.92 (dqq, *J* = 6.6, 6.6, 3.0 Hz, 1H), 1.50 (s, 9H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.6, 152.0, 141.0, 129.6, 89.6, 83.6, 79.9, 28.8, 27.9 (3), 18.8, 16.1; ESIHRMS Calcd for $[C_{13}H_{20}O_5 + Na]^+$: 279.12029, Found: 279.12069.

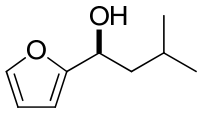
β-16d: R_f = 0.59 (4:1 (v/v) hexane/EtOAc); mp: 70.0 ^oC; $[\alpha]_D^{25}$ = -65.6 (c = 0.7, $CHCl_3$); IR (thin film, cm^{-1}) 2971, 2876, 1743, 1683, 1470, 1369, 1287, 1252, 1159, 1055, 944, 847; ^1H NMR (600 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.35 (dd, *J* = 2.4, 1.2 Hz, 1H), 6.19 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.88 (d, *J* = 7.2 Hz, 1H), 2.32 (dqq, *J* = 7.2, 6.6, 6.6 Hz, 1H), 1.53 (s, 9H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.5, 152.1, 142.4, 129.2, 90.1, 84.6, 83.8, 31.0, 27.9 (3), 18.9, 18.4; ESIHRMS Calcd for $[C_{13}H_{20}O_5 + Na]^+$: 279.12029, Found: 279.12060.

1-(furan-2-yl)-3-methylbutan-1-one (14e):



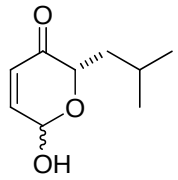
To 62 mL of furan **13** (0.86 mol) was dropped *n*-BuLi (100 mL, 0.24 mol) at 0 ^{o}C. Then let it warm up to room temperature and the resulting solution was stirred at room temperature for 3 h. Then 75 mL of anhydrous THF was added to dissolve the solid mixture at RT, which was then transferred to *iso*-valeric acid (8.8 mL, 0.079 mol) in 50 mL of THF at 0 ^{o}C. Then resulting solution was stirred 30 min at 0 ^{o}C followed by warming and stirring at RT for 3 h. Then into the reaction mixture 300 mL of Et_2O was added to dilute the solution, followed by addition of 300 mL of distilled water at 0 ^{o}C. Into the flask, 200 mL of 2M NaOH and 200 mL saturated $NaHCO_3$ were added to wash the organic layer. The aqueous layer was extracted with Et_2O (300 ml x2). The pooled organic layer was washed with 200 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 3% EtOAc/hexane gave furan ketone **14e** (8.4 g, 70%) as light yellow oil; R_f = 0.71 (5:1 (v/v) Hexane/EtOAc); IR (thin film, cm^{-1}) 3133, 2959, 2872, 1670, 1569, 1467, 1395, 1165, 1026 , 883, 757; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.14 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.49 (dd, *J* = 3.6, 1.8 Hz, 1H), 2.66 - 2.64 (m, 2H), 2.25 (hepd, *J* = 7.2, 1.8 Hz, 1H), 0.953 (d, *J* = 6.6 Hz, 3H), 0.949 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.0, 153.4, 146.4, 117.0, 112.3, 47.5, 25.5, 22.8 (2).

(*S*)-1-(furan-2-yl)-3-methylbutan-1-ol (15e):



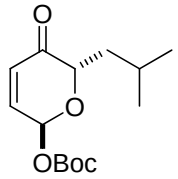
To a solution of aqueous HCO_2Na (9.7 g, 70 mL, 2.0 M) was added furan ketone **14e** (6.5 g, 0.042 mol) and CH_2Cl_2 (3 mL), followed by the addition of surfactant Cetyltrimethylammonium Bromide (1.56 g, 0.0042mmol). The mixture was stirred for 5 min, and added Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6-mesitylene)-(*S*,*S*)-TsDPEN (0.026 g, 0.1 mol%). The resulting solution was stirred at room temperature under argon for 24 h. Then the mixture was added with 100 mL H_2O to dilute and extracted with EtOAc (3 x 70 mL). The combined organic layer was washed with 15 mL saturated aqueous $NaHCO_3$, 15 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 8% EtOAc /hexane gave furan alcohol **15e** (5.3 g, 61%) as colorless oil; R_f = 0.54 (4:1 (v/v) Hexane/EtOAc); $[\alpha]_D^{25}$ = -22.1 (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3349, 2956, 2870, 1506, 1468, 1150, 1010, 806, 731; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 1.8, 0.6 Hz 1H), 6.32 (dd, *J* = 3.6, 1.8 Hz, 1H), 6.2 (d, *J* = 3.0, 1H), 4.74 (dd, *J* = 7.8, 5.4 Hz, 1H), 1.97 (s, 1H), 1.80-1.65 (m, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 142.0, 110.3, 105.9, 66.2, 44.7, 24.8, 23.2, 22.3.

(2*S*)-6-hydroxy-2-isobutyl-2H-pyran-3(6H)-one (IV):



To a solution of 5.00g furan alcohol **15e** (32.4 mmol) in 108 mL THF-H_2O (3:1) was added 5.44 g $NaHCO_3$ (64.8 mmol), 4.41 g NaOAc•$3H_2O$ (32.4 mmol), and 5.76 g NBS (32.4 mmol) at 0 ^oC. The reaction mixture was kept stirring at this temperature for 1 h. Then at 0 ^oC 100 mL saturated $NaHCO_3$ was added to quench the reaction. The reaction mixture was directly extracted with Et_2O (3 x 100 mL) and the organic layer was pooled, washed by 50 mL saturated brine, dried over Na_2SO_4 and then concentrated reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with 15% EtOAc/hexane afforded pyranone alcohol **IV** (4.35 g, 79 %) as colorless oil; R_f = 0.60 (2:1 (v/v) hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 6.87 (dd, J = 10.0, 3.6 Hz, 1H), 6.11 (d, J = 10.4 Hz, 1H), 5.61 (s, 1H), 4.58 (dd, J = 9.6, 3.2 Hz, 1H), 3.92 (s, 1H), 1.92-1.83 (m, 1H), 1.78-1.71 (m, 1H), 1.59-1.52 (m, 1H), 0.91 (d, J = 6.4, Hz, 3H), 0.89 (d, J = 6.8, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 197.7, 144.8, 127.6, 87.7, 72.9, 38.2, 24.3, 23.5, 21,5.

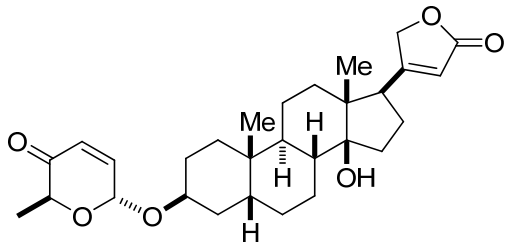
***tert*-butyl ((6*S*)-6-*iso*-butyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (16e):**



To a solution of 4.35 g pyranone alcohol **IV** (25.6 mmol) in 15 mL CH_2Cl_2 was added 313.8 mg DMAP (2.56 mmol) at -78 ^oC. A pre-cooled solution of 6.70 g $(Boc)_2O$ (30.7 mmol) in 15 mL CH_2Cl_2 was added drop-wise into the reaction mixture via a cannula. The reaction mixture was stirred at -78 ^oC for 12 h. The reaction was quenched by 100 mL saturated $NaHCO_3$ and then extracted with Et_2O (150 mL x 3). The organic layers were pooled, then washed by 40 mL saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. Flash chromatograph on silica gel eluting with 6.5 % EtOAc/hexane gave 5.33 g (77%) of two diastereomers of Boc-protected pyranone **α-16e** and **β-16e** in 2.5:1; **α-16e**: R_f = 0.68 (4:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25}$ = +32.5 (c = 0.9, $CHCl_3$); IR (thin film, cm^{-1}) 2959, 2877, 1751, 1701, 1470, 1370, 1275, 1252, 1156, 1104, 1055, 1029, 939, 844; ^1H NMR (600 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.25 (d, *J* = 3.6 Hz, 1H), 6.12 (d, *J* = 10.2 Hz, 1H), 4.47 (dd, *J* = 9.6, 3.0 Hz, 1H), 1.78 (m, 3H), 1.44 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 151.9, 140.7, 128.9, 89.2, 83.4, 74.0, 37.6, 27.7 (3), 24.1, 23.3, 21.3; ESIHRMS Calcd for $[C_{14}H_{22}O_5 + Na]^+$: 293.13594, Found: 293.13630.

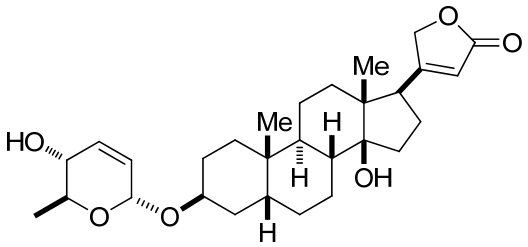
β-16e: R_f = 0.61 (4:1 (v/v) hexane/EtOAc); mp: 53-58 ^oC; $[\alpha]_D^{25}$ = -65.3 (c = 1.1, $CHCl_3$); IR (thin film, cm^{-1}) 2959, 2873, 1750, 1695, 1471, 1396, 1282, 1251, 1159, 1059, 938, 851, 791, 738; ^1H NMR (600 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.35 (d, *J* = 3.0 Hz, 1H), 6.19 (d, *J* = 10.8 Hz, 1H), 4.29 (dd, *J* = 11.4, 3.6 Hz, 1H), 1.90 (m, 2H), 1.82 (hepd, *J* = 6.6, 4.2 Hz, 1H), 1.50 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.5, 152.1, 141.7, 128.3, 89.4, 83.6, 78.2, 42.4, 27.8 (3), 24.3, 23.5, 21.3; ESIHRMS Calcd for $[C_{14}H_{22}O_5 + Na]^+$: 293.13594, Found: 293.13625.

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



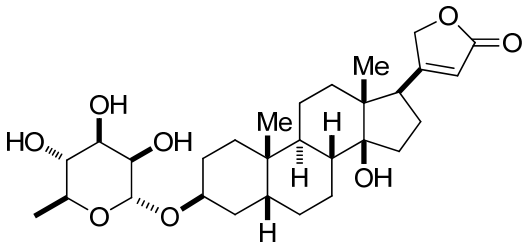
A CH_2Cl_2/THF solution (7 mL, 4:1 V/V) of Boc pyranone **16a** (884 mg, 3.87 mmol) and digitoxigenin (725 mg, 1.94 mmol) was cooled to 0℃. A CH_2Cl_2 (2 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (50.1 mg, 2.5 mol%) and PPh_3 (50.7 mg, 10 mol%) was added to the reaction mixture via dry cannula at 0℃. The 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 **17a** (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 (18a):



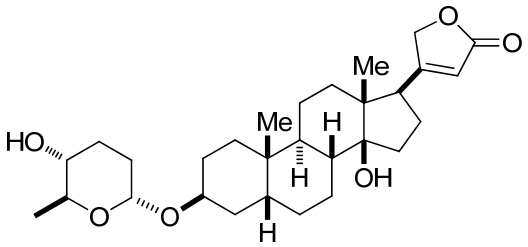
A CH_2Cl_2 (2.8 mL) solution of enone **17a** (678 mg, 1.40 mmol) in $CeCl_3 \cdot MeOH$ solution (0.4 M, 2.8 mL) was cooled to -78℃. $NaBH_4$ (58.2 mg, 1.54 mmol) was added and the resulting solution was stirred at -78℃ for 1 hour. The reaction mixture was diluted with Et_2O (20 mL) and was quenched 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 alcohol **22** (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 (4):



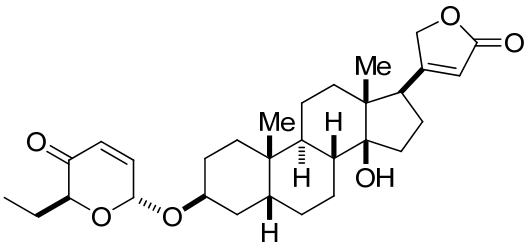
To a *t*-BuOH/acetone (7.5 mL, 1:1 (v/v), 0.5M) solution of allylic alcohol **18a** (1.80 g, 3.70 mmol) at 0℃ was added a solution of *N*-methylmorpholine-*N*-oxide/water (50% w/v, 3.70 mL). Crystalline OsO_4 (9.4 mg, 1 mol %) was added and the reaction mixture was stirred for 4 hours. The reaction mixture 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 **4** 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 (m, 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 (9):



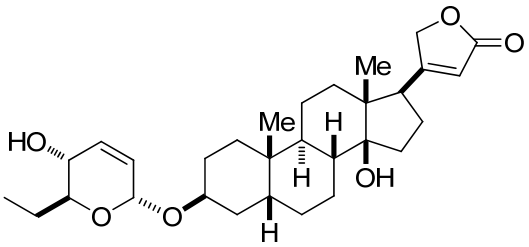
To a NMM (0.38 ml, 0.3M) solution of allylic alcohol **18a** (55 mg, 0.113 mmol) at 0℃ was added *o*-nitrobenzenesulfonyl hydrazine (NBSH) (123 mg, 0.566 mmol) and Et_3N (23 mg, 0.226 mmol). The resulting mixture was stirred and gradually raised to room temperature for 8 hrs. The reaction mixture was 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 **9** 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.

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



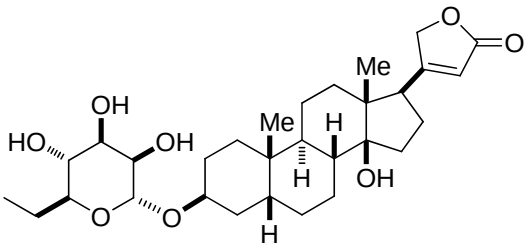
A CH_2Cl_2/THF solution (6 mL, 4:1 V/V) of Boc pyranone **16b** (647 mg, 2.67 mmol) and digitoxigenin (500 mg, 1.34 mmol) was cooled to 0℃. A CH_2Cl_2 (0.7 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (70.9 mg, 5.0 mol%) and PPh_3 (71.8 mg, 20 mol%) was added to the reaction mixture via dry cannula at 0℃. The resulting solution was stirred at 0℃ for 4 hours and was directly loaded and purified via silica gel flash chromatography with elution of 35% EtOAc/hexanes to obtain **17b** (600 mg, 1.20 mmol, 90%) as a yellow solid; *Rf* (60% EtOAc/hexanes) = 0.56; mp: 107-108℃; $[\alpha]^{25}_D$ = + 41.7 (c = 1.05, CH_2Cl_2); IR (thin film, cm-1) 3503, 2937, 2879, 1780, 1742, 1694, 1620, 1448, 1380, 1221, 1158, 1087, 1024, 902, 731; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 10.8, 3.6 Hz, 1H), 6.04 (dd, *J* = 10.8, 0.6 Hz, 1H), 5.85 (m, 1H), 5.27 (d, *J* = 3.6 Hz, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.35 (dd, *J* = 7.8, 3.6 Hz, 1H), 4.06 (m, 1H), 2.76 (m, 1H), 2.18 – 2.08 (m, 2H), 2.00 – 1.93 (m, 1H), 1.89 – 1.76 (m, 3H), 1.72 – 1.34 (m, 14H), 1.28 – 1.17 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.92 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.16, 174.62, 174.60, 144.50, 127.68, 117.95, 92.12, 85.79, 75.46, 74.33, 73.63, 51.12, 49.81, 42.09, 40.25, 36.69, 35.93, 35.44, 33.38, 30.64, 30.61, 27.12, 26.79, 26.65, 23.90, 23.10, 21.58, 21.39, 15.98, 9.73.; ESIHRMS Calcd for $[C_{30}H_{42}O_6Na^+]$: 521.28736, Found: 521.28774.

(2S,3R,6R)-3,6-Dihydro-2-Ethyl-6-(Digitoxigenoxy)-2*H*-pyran-4,5-en-3-ol (18b):



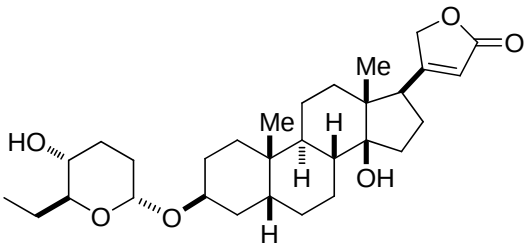
A CH_2Cl_2 (2.33 mL) solution of enone **17b** (580 mg, 1.16 mmol) in $CeCl_3 \cdot MeOH$ solution (0.4 M, 2.33 mL) was cooled to -78℃. $NaBH_4$ (48.4 mg, 1.28 mmol) was added and the resulting solution was stirred at -78℃ for 2 hour. The reaction mixture was diluted with Et_2O (20 mL) and was quenched 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 crystallized in CH_2Cl_2/Hexane to give allylic alcohols **18b** (450 mg, 0.90 mmol, 77%) as a white solid; *Rf* (60% EtOAc/hexanes) = 0.41; mp: 168-172 ℃; $[\alpha]^{25}_D$ = -18.0 (c = 1.00, CH_2Cl_2); IR (thin film, cm-1) 3440, 2940, 2870, 1785, 1740, 1450, 1380, 1175, 1135, 751; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.89 (d, *J* = 10.2 Hz, 1H), 5.85 (br, 1H), 5.71 (ddd, *J* = 10.2, 2.4 Hz, 1H), 5.01 (br, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.01 (dd, *J* = 2.4, 2.4 Hz, 1H), 3.87 (dd, *J* = 8.0 Hz, 1H), 3.51 (ddd, *J* = 9.0, 9.0, 2.6 Hz, 1H), 2.76 (m, 1H), 2.17 – 2.08 (m, 2H), 1.93 – 1.80 (m, 3H), 1.76 – 1.34 (m, 16H), 1.27 – 1.17 (m, 4H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.91 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.67, 174.66, 133.13, 127.87, 117.92, 92.76, 85.84, 73.63, 73.23, 72.96, 68.29, 51.15, 49.82, 42.10, 40.30, 36.66, 35.94, 35.45, 33.40, 30.67, 30.35, 27.11, 26.88, 26.83, 25.31, 23.87, 21.61, 21.39, 15.99, 10.17.HRESIMS Calcd for [$C_{30}H_{44}O_6Na^+$]: 523.30301, Found 523.30337.

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



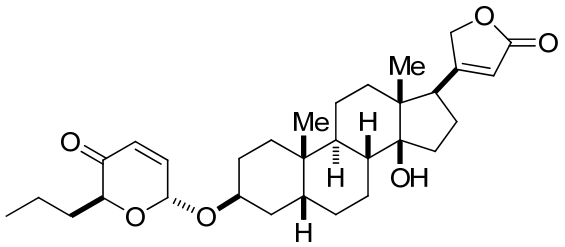
To a *t*-BuOH/acetone (2.4 mL, 1:1 (v/v), 0.1M) solution of allylic alcohol **18b** (120 mg, 0.240 mmol) at 0℃ was added a solution of *N*-methylmorpholine-*N*-oxide/water (50% w/v, 0.24 mL). Crystalline OsO_4 (3.0 mg, 5 mol %) was added and the reaction mixture was stirred for 4 hours. The reaction 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 80% EtOAc/Hexane (20% EtOAc/Hexane packing). Pure fraction were combined, concentrated, and crystallized from CH_2Cl_2/hexanes to afford **5** as white solid (95 mg, 0.18 mmol, 74%); R_f = 0.25 (EtOAc); mp: 215-217 ℃; $[\alpha]^{25}_D$ = -27.3 (*c* = 1.00, MeOH); IR (thin film, cm^{-1}) 3425, 2936, 2881, 1783, 1738, 1623; 1448, 1381, 1125, 1090, 1055, 1022, 969, 888, 730; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (m, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.87 (d, *J* = 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 3.95 (dd, *J* = 2.4, 2.4 Hz, 1H), 3.88 (br, 1H), 3.79 (m, 1H), 3.52 – 3.46 (m, 2H), 2.75 (m, 1H), 2.53 (d, *J* = 6.0 Hz, 1H), 2.31 (br, 1H), 2.26 (d, *J* = 5.4 Hz, 1H), 2.17 – 2.07 (m, 2H), 1.91 – 1.80 (m, 3H), 1.74 – 1.33 (m, 15H), 1.27 – 1.18 (m, 4H), 0.96 (dd, *J* = 11.6, 4.1 Hz, 3H), 0.91 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.72, 174.70, 117.93, 97.55, 85.82, 73.67, 72.89, 72.39, 72.34, 71.76, 71.73, 51.13, 49.82, 42.08, 40.26, 36.69, 35.93, 35.44, 33.39, 30.61, 29.56, 27.11, 26.77, 26.62, 24.60, 23.95, 21.61, 21.40, 15.99, 10.04. ESIHRMS Calcd. for [$C_{30}H_{46}O_8Na^+$]: 557.30849, found: 557.30881.

(2S,3R,6R)-3,6-dihydro-2-methyl-6-(Digitoxigenoxy)-2*H*-pyran-3-ol (10):



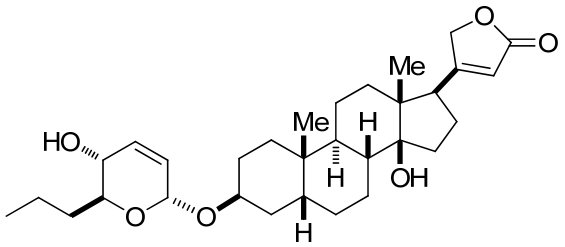
To a NMM (0.45 ml, 0.3M) solution of allylic alcohol **18b** (68 mg, 0.136 mmol) at 0℃ was added *o*-nitrobenzenesulfonyl hydrazine (NBSH) (236 mg, 1.09 mmol) and Et_3N (27.7 mg, 0.272 mmol). The resulting mixture was stirred and gradually raised to room temperature for 6 h. The reaction mixture was 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 **10** as white solid (62.5 g, 0.124 mmol, 92%); *Rf* (60% EtOAc/hexanes) = 0.23; mp: 135-137℃; $[\alpha]^{25}_D$ = -46.2 (*c* = 0.36, MeOH); IR (thin film, cm^{-1}) 3449, 2936, 2879, 1782, 1739, 1620, 1448, 1381, 1119, 1028, 992, 966; 914, 857, 732; ^1H NMR (600 MHz, $CDCl_3$) δ 5.85 (m, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.82 (d, *J* = 2.4 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 3.91 (br, 1H), 3.42 (ddd, *J* = 9.1, 2.4, 2.4 Hz, 1H), 3.32 (m, 1H), 2.76 (m, 1H), 2.17 – 2.07 (m, 2H), 1.89 – 1.34 (m, 23H), 1.27 – 1.14 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.92 (s, 3H), 0.86 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.66 (2C), 117.92, 93.92, 85.86, 74.74, 73.63, 70.65, 70.61, 51.16, 49.81, 42.12, 40.31, 36.67, 35.93, 35.46, 33.42, 30.74, 30.30, 29.84, 28.12, 27.11, 26.88, 26.82, 24.89, 23.96, 21.65, 21.42, 15.99, 10.00. ESIHRMS Calcd. for $[C_{30}H_{46}O_6Na^+]$: 525.31866, found: 525.31857.

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



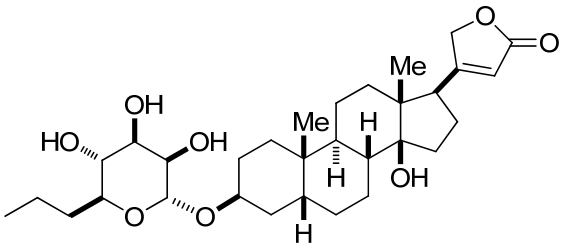
A CH_2Cl_2/THF solution (0.5 mL, 4:1 V/V) of Boc pyranone **16c** (137 mg, 0.534 mmol) and digitoxigenin (100 mg, 0.267 mmol) was cooled to 0℃. A CH_2Cl_2 (0.4 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (13.8 mg, 5.0 mol%) and PPh_3 (14.0 mg, 20 mol%) was added to the reaction mixture via dry cannula at 0℃. The resulting solution was stirred at 0℃ for 2 hours and was directly loaded and purified via silica gel flash chromatography with elution of 35% EtOAc/hexanes to obtain **17c** (120 mg, 0.234 mmol, 88%) as a yellow solid; *Rf* (50% EtOAc/hexanes) = 0.38; mp: 86-88℃; $[\alpha]^{25}_D$ = + 40.3 (c = 1.00, CH_2Cl_2); IR (thin film, cm-1) 3484, 2934, 2872, 1780, 1741, 1693, 1620, 1448, 1379, 1157, 1090, 1024, 912, 732; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.03 (d, *J* = 10.8 Hz, 1H), 5.84 (dd, *J* = 1.2, 1.2 Hz, 1H), 5.25 (d, *J* = 3.6 Hz, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.39 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.05 (m, 1H), 2.75 (m, 1H), 2.17 – 2.06 (m, 2H), 1.94 – 1.17 (m, 24H), 0.90 (s, 3H), 0.90 (t, *J* = 7.8 Hz, 3H), 0.84 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.29, 174.79, 174.69, 144.46, 127.56, 117.82, 91.93, 85.69, 74.15 (2C), 73.64, 51.10, 49.81, 41.99, 40.19, 36.65, 35.87, 35.41, 33.31, 31.86, 30.57, 30.49, 27.09, 26.75, 26.65, 23.85, 21.53, 21.36, 18.60, 15.95, 14.08.; ESIHRMS Calcd for $[C_{31}H_{44}O_6Na^+]$: 535.30301, Found: 535.30361.

(2S,3R,6R)-3,6-Dihydro-2-Propyl-6-(Digitoxigenoxy)-2*H*-pyran-4,5-en-3-ol (18c):



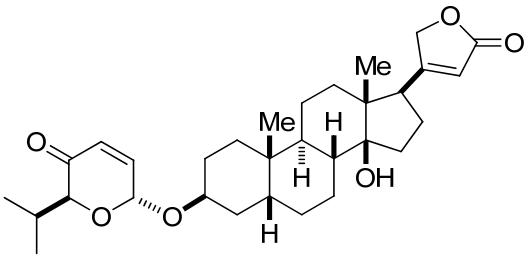
A CH_2Cl_2 (0.40 mL) solution of enone **17c** (100 mg, 0.195 mmol) in $CeCl_3 \cdot MeOH$ solution (0.4 M, 0.40 mL) was cooled to -78 ℃. $NaBH_4$ (7.4 mg, 0.195 mmol) was added and the resulting solution was stirred at -78 ℃ for 6 hour. The reaction mixture was diluted with Et_2O (20 mL) and was quenched 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 crystallized in CH_2Cl_2/Hexane to give allylic alcohols **18c** (83 mg, 0.161 mmol, 83%) as a white solid; *Rf* (50% EtOAc/hexanes) = 0.32; mp: 202-204 ℃; $[\alpha]^{25}_D$ = -9.8 (c = 0.50, $CHCl_3$); IR (thin film, cm-1) 3445, 2929, 2873, 1783, 1736, 1619, 1447, 1379, 1132, 1107, 1053, 1020, 1006, 908, 731; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 10.2, 1.2, 1.2 Hz, 1H), 5.85 (dd, *J* = 1.2, 1.2 Hz, 1H), 5.71 (ddd, *J* = 10.2, 3.0, 3.0 Hz, 1H), 5.00 (br, 1H), 4.98 (br, 1H), 4.78 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.00 (dd, *J* = 2.4, 2.4 Hz, 1H), 3.85 (d, *J* = 7.8 Hz, 1H), 3.58 (ddd, *J* = 9.6, 9.6, 2.4 Hz, 1H), 2.75 (m, 1H), 2.16 – 2.08 (m, 2H), 1.88 – 1.17 (m, 25H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 3H), 0.85 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.71, 174.68, 133.16, 117.89, 85.83, 73.65, 72.71, 71.69, 68.54, 51.15, 49.82, 42.08, 40.29, 36.63, 35.93, 35.45, 34.65, 33.39, 30.66, 30.54, 30.16, 29.91, 27.10, 26.93, 26.84, 23.86, 21.60, 21.39, 18.95, 15.99, 14.36.; HRESIMS Calcd for $[C_{31}H_{46}O_6H^+]$: 515.33672, Found 515.33713.

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



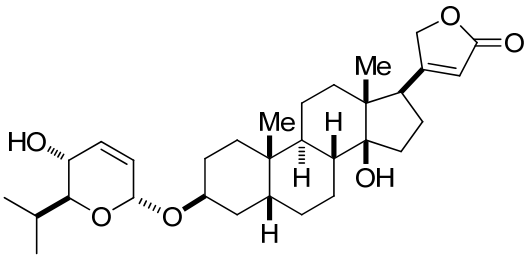
To a *t*-BuOH/acetone (1.60 mL, 1:1 (v/v), 0.1M) solution of allylic alcohol **18c** (83 mg, 0.161 mmol) at 0℃ was added a solution of *N*-methylmorpholine-*N*-oxide/water (50% w/v, 0.16 mL). Crystalline OsO_4 (2.0 mg, 5 mol %) was added and the reaction mixture was stirred for 6 hours. The resulting solution was directly loaded and purified via silica gel flash chromatography with elution of 75% EtOAc/Hexane (20% EtOAc/Hexane packing). Pure fraction were combined, concentrated, and crystallized from $CHCl_3$/Hexanes to afford **6** as white solid (65 mg, 0.11 mmol, 74%); *Rf* = 0.20 (EtOAc); mp: 144-145℃; $[\alpha]^{25}_D$ = -24.8 (*c* = 1.00, MeOH); IR (thin film, cm^{-1}) 3445, 2935, 2872, 1782, 1739, 1620; 1450, 1381, 1123, 1091, 1067, 1025, 968, 730; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.8, 1.8 Hz, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.86 (d, *J* = 1.8 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 3.94 (dd, *J* = 2.4, 2.4 Hz, 1H), 3.88 (br, 1H), 3.79 (d, *J* = 7.8 Hz, 1H), 3.57 (ddd, *J* = 9.6, 9.6, 2.4 Hz, 1H), 3.46 (dd, *J* = 9.0, 9.0 Hz, 1H), 2.75 (m, 1H), 2.50 (br, 1H), 2.27 (br, 1H), 2.23 (d, *J* = 4.8 Hz, 1H), 2.16 – 2.07 (m, 2H), 1.88 – 1.18 (m, 24H), 0.91 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.71, 174.68, 117.94, 97.40, 85.82, 73.66, 72.62, 72.35, 71.69, 71.57, 71.46, 51.13, 49.81, 42.07, 40.26, 36.68, 35.92, 35.44, 33.86, 33.39, 30.59, 29.45, 27.11, 26.77, 26.67, 23.95, 21.61, 21.40, 18.96, 15.99, 14.30. ESIHRMS Calcd. for [$C_{31}H_{48}O_8Na^+$]: 571.32614, found: 571.32473.

(2S,6R)-2-*iso*-propyl-6-(Digitoxigenoxy)-2*H*-pyran-3(6*H*)-one (17d):



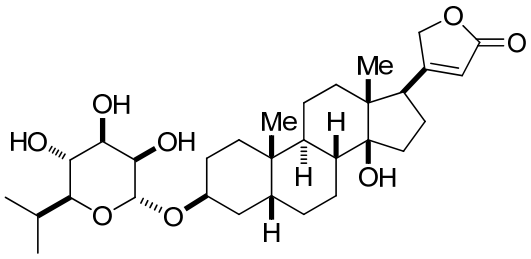
A CH_2Cl_2/THF solution (2.4 mL, 4:1 V/V) of Boc pyranone **16d** (340 mg, 1.340 mmol) and digitoxigenin (250 mg, 0.668 mmol) was cooled to 0℃. A CH_2Cl_2 (1.0 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (34.5 mg, 5.0 mol%) and PPh_3 (35.0 mg, 20 mol%) was added to the reaction mixture via dry cannula at 0℃. The resulting solution was stirred at 0℃ for 4 hours and was directly loaded and purified via silica gel flash chromatography with elution of 35% EtOAc/hexanes to obtain **17d** (322 mg, 0.628 mmol, 94%) as a yellow solid; *Rf* (50% EtOAc/hexanes) = 0.40; mp: 97-98℃; $[\alpha]^{25}_D$ = + 34.5 (c = 1.00, CH_2Cl_2); IR (thin film, cm-1) 3484, 2933, 2875, 1780, 1738, 1688, 1620, 1447, 1367, 1085, 1022, 1004, 908, 728; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 10.2, 3.6 Hz, 1H), 5.99 (d, *J* = 10.2 Hz, 1H), 5.80 (br, 1H), 5.25 (d, *J* = 3.6 Hz, 1H), 4.95 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.75 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.23 (d, *J* = 2.4 Hz, 1H), 4.00 (br, 1H), 2.72 (m, 1H), 2.39 (dhept, *J* = 6.6, 3.0 Hz, 1H), 2.13 – 2.03 (m, 2H), 1.84 – 1.31 (m, 16H), 1.23 – 1.15 (m, 4H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 3H), 0.81 (s, 3H), 0.79 (d, *J* = 7.2 Hz, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.27, 175.07, 174.74, 144.52, 127.87, 117.59, 91.93, 85.48, 78.35, 74.15, 73.64, 51.05, 49.78, 41.81, 40.06, 36.60, 35.75, 35.31, 33.15, 30.53, 30.46, 28.51, 27.01, 26.68, 26.45, 23.78, 21.43, 21.27, 19.19, 16.13, 15.88. ESIHRMS Calcd for $[C_{31}H_{44}O_6Na^+]$: 535.30301, Found: 535.30364.

(2S,3R,6R)-3,6-Dihydro-2-*iso*-propyl-6-(Digitoxigenoxy)-2*H*-pyran-4,5-en-3-ol (18d):



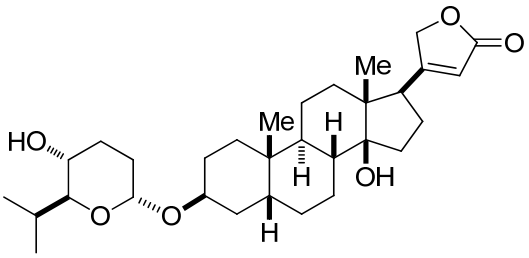
A CH_2Cl_2 (1.25 mL) solution of enone **17d** (322 mg, 0.628 mmol) in $CeCl_3 \cdot MeOH$ solution (0.4 M, 1.25 mL) was cooled to -78℃. $NaBH_4$ (28.5 mg, 0.753 mmol) was added and the resulting solution was stirred at -78℃ for 7 hour. The reaction mixture was diluted with Et_2O (20 mL) and was quenched 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 crystallized in CH_2Cl_2/Hexane to give allylic alcohols **18d** (274 mg, 0.532 mmol, 85%) as a white solid; *Rf* (50% EtOAc/hexanes) = 0.30; mp: 124-125℃; $[\alpha]^{25}_D$ = -12.0 (c = 1.00, CH_2Cl_2); IR (thin film, cm-1) 3448, 2934, 2879, 1782, 1738, 1618, 1472, 1447, 1380, 1136, 1083, 1026, 1000, 732; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 9.6, 1.8, 1.8 Hz, 1H), 5.85 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.70 (ddd, *J* = 10.2, 2.4, 2.4 Hz, 1H), 5.01 (br, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.05 (ddd, *J* = 9.0, 9.0, 1.2 Hz, 1H), 4.02 (dd, *J* = 3.0, 3.0 Hz, 1H), 3.47 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.75 (m, 1H), 2.17 – 2.08 (m, 2H), 2.05 (dhept, *J* = 6.6, 3.0 Hz, 1H), 1.88 – 1.81 (m, 2H), 1.74 – 1.31 (m, 15H), 1.27 – 1.17 (m, 4H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 3H), 0.85 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.68, 174.66, 133.48, 127.75, 117.91, 92.33, 85.83, 75.60, 73.64, 72.20, 65.69, 51.15, 49.82, 42.08, 40.29, 36.61, 35.92, 35.45, 33.39, 30.68, 29.97, 28.55, 27.10, 26.90, 26.83, 23.86, 21.62, 21.38, 20.05, 16.13, 15.99. HRESIMS Calcd for [$C_{31}H_{46}O_6Na^+$]: 537.31866, Found 537.31922.

(2S,3R,4R,5R,6R)-3,4,5,6-tetrahydro-2-*iso*-propyl-6-(Digitoxigenoxy)-2*H*-pyran-3,4,5-triol (7):



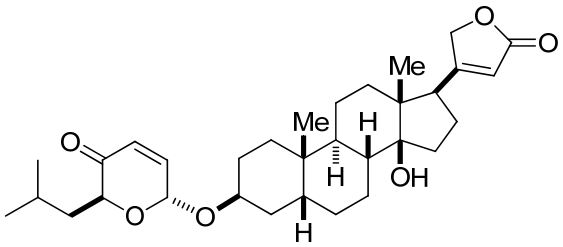
To a *t*-BuOH/acetone (2.40 mL, 1:1 (v/v), 0.2M) solution of allylic alcohol **18d** (250 mg, 0.486 mmol) at 0℃ was added a solution of *N*-methylmorpholine-*N*-oxide/water (50% w/v, 0.48 mL). Crystalline OsO_4 (6.2 mg, 5 mol %) was added and the reaction mixture was stirred for 6 hours. The resulting solution was directly loaded and purified via silica gel flash chromatography with elution of 65% EtOAc/Hexane (50% EtOAc/Hexane packing). Pure fraction were combined, concentrated, and crystallized from $CHCl_3$/Hexanes to afford **7** as white solid (215 mg, 0.392 mmol, 81%); *Rf* = 0.25 (EtOAc); mp: 234-236℃; $[\alpha]^{25}_D$ = -28.0 (*c* = 1.00, MeOH); IR (thin film, cm^{-1}) 3436, 2934, 2878, 1783, 1738, 1623; 1450, 1381, 1129, 1090, 1055, 1025, 986, 912, 731; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.8, 1.8 Hz, 1H), 4.96 (dd, *J* = 18.6, 1.8 Hz, 1H), 4.87 (d, *J* = 1.2 Hz, 1H), 4.78 (dd, *J* = 18.6, 1.8 Hz, 1H), 3.94 (dd, *J* = 2.4, 2.4 Hz, 1H), 3.86 (ddd, *J* = 3.0, 3.0, 1.2 Hz, 1H), 3.79 (ddd, *J* = 7.2, 7.2, 3.0 Hz, 1H), 3.63 (ddd, *J* = 9.6, 9.6, 3.0 Hz, 1H), 3.49 (dd, *J* = 9.6, 1.8 Hz, 1H), 2.75 (m, 1H), 2.43 (d, *J* = 7.2 Hz, 1H), 2.17 (d, *J* = 3.0 Hz, 1H), 2.15 – 2.07 (m, 4H), 1.88 – 1.80 (m, 2H), 1.73 – 1.33 (m, 14H), 1.26 – 1.17 (m, 4H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 3H), 0.85 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.69, 174.66, 117.94, 97.45, 85.82, 74.83, 73.65, 72.82, 71.73, 71.28, 69.79, 51.14, 49.82, 42.08, 40.27, 36.68, 35.92, 35.45, 33.40, 30.59, 29.38, 27.44, 27.11, 26.77, 26.65, 23.94, 21.62, 21.40, 20.09, 15.99, 15.12. ESIHRMS Calcd. for [$C_{31}H_{48}O_8Na^+$]: 571.32414, found: 571.32439.

(2S,3R,6R)-3,6-dihydro-2-*iso*-propyl-6-(Digitoxigenoxy)-2*H*-pyran-3-ol (11):



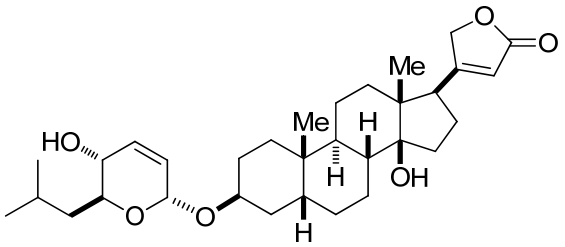
To a NMM (0.34 ml, 0.3M) solution of allylic alcohol **18d** (52 mg, 0.10 mmol) at 0℃ was added *o*-nitrobenzenesulfonyl hydrazine (NBSH) (174.0 mg, 0.80 mmol) and Et_3N (20.4 mg, 0.20 mmol). The resulting mixture was stirred and gradually raised to room temperature for 24 hrs. The reaction mixture was diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3 x 20 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified via silica gel flash chromatography eluting with 45% EtOAc/hexanes to give alcohol **11** as white solid (44.4 mg, 0.086 mmol, 85%); *Rf* (50% EtOAc/hexanes) = 0.25; mp: 156-158 ℃; $[\alpha]^{25}_D$ = -40.5 (*c* = 1.73, MeOH); IR (thin film, cm^{-1}) 3449, 2936, 2876, 1781, 1739, 1619, 1447, 1379, 1107, 1064, 1027, 992, 733; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 1.2, 1.2 Hz, 1H), 4.96 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.82 (d, *J* = 2.4 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.8 Hz, 1H), 3.90 (br, 1H), 3.49 (ddd, *J* = 9.6, 9.6, 4.8 Hz, 1H), 3.41 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.75 (m, 1H), 2.17 – 2.03 (m, 4H), 1.87 – 1.34 (m, 20H), 1.26 – 1.16 (m, 4H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 3H), 0.88 (d, *J* = 7.2 Hz, 3H), 0.85 (s, 3H). ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.80, 174.74, 117.85, 93.72, 85.84, 76.90, 73.66, 70.02, 67.94, 51.15, 49.82, 42.07, 40.28, 36.63, 35.90, 35.43, 33.37, 30.70, 30.14, 29.60, 28.38, 27.53, 27.09, 26.86, 26.82, 23.91, 21.64, 21.39, 20.04, 15.98, 15.31. ESIHRMS Calcd. for [$C_{31}H_{48}O_6Na^+$]: 539.33431, found: 539.33420.

(2S,6R)-2-*iso*-butyl-6-(Digitoxigenoxy)-2*H*-pyran-3(6*H*)-one (17e):



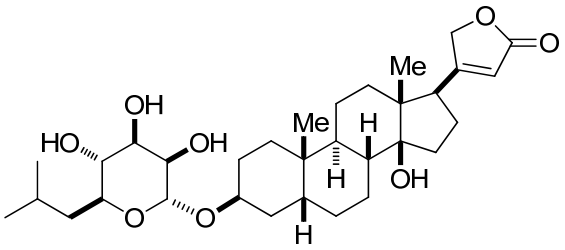
A CH_2Cl_2/THF solution (4.0 mL, 4:1 V/V) of Boc pyranone **16e** (725 mg, 2.68 mmol) and digitoxigenin (500 mg, 1.34 mmol) was cooled to 0℃. A CH_2Cl_2 (0.5 mL) solution of $Pd_2(dba)_3$•$CHCl_3$ (69.3 mg, 5.0 mol%) and PPh_3 (70.2 mg, 20 mol%) was added to the reaction mixture via dry cannula at 0℃. The resulting solution was stirred at 0℃ for 4 hours and was directly loaded and purified via silica gel flash chromatography with elution of 35% EtOAc/hexanes to obtain **17e** (690 mg, 1.31 mmol, 98%) as a yellow solid; *Rf* (60% EtOAc/hexanes) = 0.58; mp: 110-113℃; $[\alpha]^{25}_D$ = + 34.3 (c = 1.00, CH_2Cl_2); IR (thin film, cm-1) 3493, 2936, 2869, 1783, 1740, 1693, 1623, 1447, 1468, 1368, 1380, 1091, 1023, 907, 731; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.05 (d, *J* = 10.2 Hz, 1H), 5.85 (br, 1H), 5.25 (d, *J* = 3.0 Hz, 1H), 4.96 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.8 Hz, 1H), 4.45 (dd, *J* = 10.2, 3.0 Hz, 1H), 4.08 (dd, *J* = 2.4, 2.4 Hz, 1H), 2.76 (m, 1H), 2.17 – 2.08 (m, 2H), 1.90 – 1.75 (m, 5H), 1.71 – 1.34 (m, 14H), 1.29 – 1.18 (m, 4H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 3H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.86 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.59, 174.63, 174.60, 144.31, 127.59, 117.95, 91.49, 85.79, 73.63, 73.59, 72.87, 51.12, 49.81, 42.07, 40.25, 38.64, 36.65, 35.93, 35.46, 33.38, 30.58, 30.19, 27.11, 26.78, 26.76, 24.47, 23.87, 23.72, 21.71, 21.59, 21.40, 15.98. ESIHRMS Calcd for $[C_{32}H_{46}O_6Na^+]$: 549.31866, Found: 549.31889.

(2S,3R,6R)-3,6-Dihydro-2-*iso*-butyl-6-(Digitoxigenoxy)-2*H*-pyran-4,5-en-3-ol (18e):



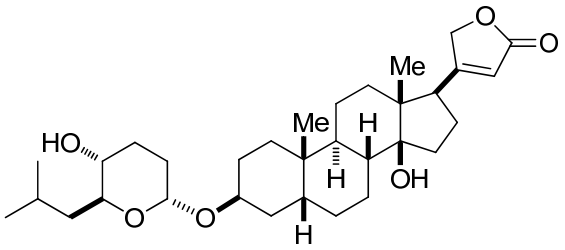
A CH_2Cl_2 (1.82 mL) solution of enone **17e** (480 mg, 0.911 mmol) in $CeCl_3 \cdot MeOH$ solution (0.4 M, 1.82 mL) was cooled to -78 ℃. $NaBH_4$ (38 mg, 1.00 mmol) was added and the resulting solution was stirred at -78 ℃ for 30 min. The reaction mixture was diluted with Et_2O (20 mL) and was quenched 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 crystallized in CH_2Cl_2/Hexane to give allylic alcohols **18e** (478 mg, 0.905 mmol, 99%) as a white solid; *Rf* (60% EtOAc/hexanes) = 0.55; mp: 131-135 ℃; $[\alpha]^{25}_D$ = -15.7 (c = 1.00, CH_2Cl_2); IR (thin film, cm-1) 3445, 2933, 2872, 1780, 1740, 1620, 1467, 1448, 1380, 1113, 1069, 1022, 910, 731; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 10.2, 1.2, 1.2 Hz, 1H), 5.85 (dd, *J* = 1.2, 1.2 Hz, 1H), 5.70 (ddd, *J* = 10.2, 2.4, 2.4 Hz, 1H), 5.01 (br, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.02 (dd, *J* = 3.0, 3.0 Hz, 1H), 3.81 (ddd, *J* = 8.4, 8.4, 1.8 Hz, 1H), 3.64 (ddd, *J* = 10.0, 10.0, 1.8 Hz, 1H), 2.76 (m, 1H), 2.17 – 2.08 (m, 2H), 1.89 – 1.81 (m, 3H), 1.75 – 1.34 (m, 17H), 1.28 – 1.18 (m, 4H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.85 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.66 (2C), 133.21, 127.78, 117.92, 91.97, 85.83, 73.63, 72.20, 70.12, 68.86, 51.15, 49.82, 42.09, 41.86, 40.29, 36.59, 35.94, 35.46, 33.40, 30.64, 29.74, 27.10, 26.98, 26.84, 24.40, 24.17, 23.85, 21.92, 21.62, 21.39, 15.99. HRESIMS Calcd for $[C_{32}H_{48}O_6Na^+]$: 551.33431, Found: 551.33461.

(2S,3R,4R,5R,6R)-3,4,5,6-tetrahydro-2-*iso*-butyl-6-(Digitoxigenoxy)-2*H*-pyran-3,4,5-triol (8):

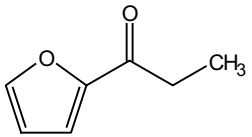


To a *t*-BuOH/acetone (3.80 mL, 1:1 (v/v), 0.1M) solution of allylic alcohol **18e** (200 mg, 0.379 mmol) at 0℃ was added a solution of *N*-methylmorpholine-*N*-oxide/water (50% w/v, 0.38 mL). Crystalline OsO_4 (4.8 mg, 5 mol %) was added and the reaction mixture was stirred for 5 hours. The resulting solution was directly loaded and purified via silica gel flash chromatography with elution of 75% EtOAc/Hexane (50% EtOAc/Hexane packing). Pure fraction were combined, concentrated, and crystallized from $CHCl_3$/Hexanes to afford **8** as white solid (175 mg, 0.311 mmol, 82%); *Rf* = 0.20 (EtOAc); mp: 151-155℃; $[\alpha]^{25}_D$ = -35.3 (*c* = 1.00, MeOH); IR (thin film, cm^{-1}) 3448, 2934, 2872, 1782, 1740, 1625; 1450, 1381, 1126, 1091, 1067, 1045, 1030, 980, 732; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (br, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.86 (br, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 3.97 (dd, *J* = 1.8, 1.8 Hz, 1H), 3.88 (br, 1H), 3.81 (m, 1H), 3.64 (ddd, *J* = 9.0, 9.0, 1.8 Hz, 1H), 3.43 (ddd, *J* = 9.0, 9.0, 1.8 Hz, 1H), 2.75 (m, 1H), 2.58 (d, *J* = 5.4 Hz, 1H), 2.32 – 2.30 (m, 2H), 2.16 – 2.07 (m, 2H), 1.88 – 1.80 (m, 3H), 1.72 – 1.66 (m, 3H), 1.61 – 1.34 (m, 13H), 1.25 – 1.18 (m, 4H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.85 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.72, 174.70, 117.93, 96.90, 85.81, 73.67, 72.99, 72.25, 71.63, 70.95, 69.86, 51.13, 49.81, 42.06, 41.10, 40.25, 36.67, 36.65, 35.92, 35.45, 33.38, 30.54, 29.11, 27.11, 26.76, 24.51, 24.16, 23.92, 21.85, 21.62, 21.40, 15.99. ESIHRMS Calcd. for [$C_{32}H_{50}O_8Na^+$]: 585.33979, found: 585.34016.

(2S,3R,6R)-3,6-dihydro-2-*iso*-butyl-6-(Digitoxigenoxy)-2*H*-pyran-3-ol (12):



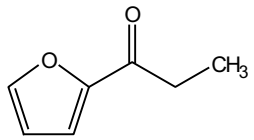
To a NMM (0.52 ml, 0.3M) solution of allylic alcohol **18e** (82 mg, 0.155 mmol) at 0℃ was added *o*-nitrobenzenesulfonyl hydrazine (NBSH) (270 mg, 1.25 mmol) and Et_3N (31.6 mg, 0.31 mmol). The resulting mixture was stirred and gradually raised to room temperature for 24 hrs. The reaction mixture was diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3 x 20 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified via silica gel flash chromatography eluting with 40% EtOAc/hexanes to give alcohol **12** as white solid (72.5 mg, 0.137 mmol, 88%); *Rf* (60% EtOAc/hexanes) = 0.50; mp: 188-189 ℃; $[\alpha]^{25}_D$ = -32.3 (*c* = 1.00, MeOH); IR (thin film, cm^{-1}) 3462, 2935, 2874, 1785, 1739, 1619, 1448, 1379, 1118, 1023, 995, 732; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (br, 1H), 4.96 (dd, *J* = 18.0, 1.2 Hz, 1H), 4.81 (d, *J* = 1.8 Hz, 1H), 4.78 (dd, *J* = 18.0, 1.2 Hz, 1H), 3.93 (br, 1H), 3.55 (ddd, *J* = 10.2, 10.2, 1.8 Hz, 1H), 3.26 (ddd, *J* = 9.0, 9.0, 5.5 Hz, 1H), 2.76 (m, 1H), 2.16 – 2.09 (m, 2H), 1.87 – 1.29 (m, 24H), 1.26 – 1.18 (m, 4H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.85 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.66, 174.64, 117.90, 93.18, 85.83, 73.62, 71.58, 71.34, 69.76, 51.15, 49.80, 42.09, 41.66, 40.28, 36.60, 35.91, 35.45, 33.40, 30.66, 30.16, 29.32, 27.96, 27.09, 26.94, 26.85, 24.40, 24.28, 23.91, 21.95, 21.65, 21.40, 15.97.; ESIHRMS Calcd. for [$C_{32}H_{50}O_6Na^+$]: 553.34996, found: 553.34985.



^{1}H NMR (270 MHz, $CDCl_3$)

14b

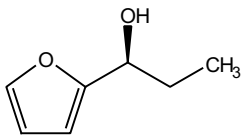
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2



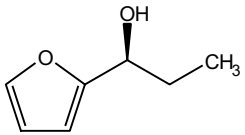
^{13}C NMR (67.5 MHz, $CDCl_3$)

14b

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

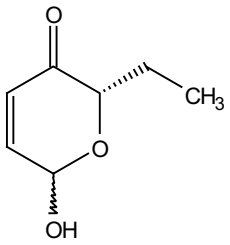


^{1}H NMR (600 MHz, $CDCl_3$)
15b



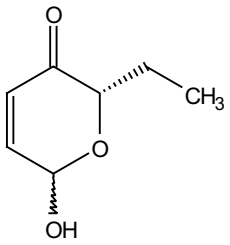
^{13}C NMR (150 MHz, $CDCl_3$)
15b

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



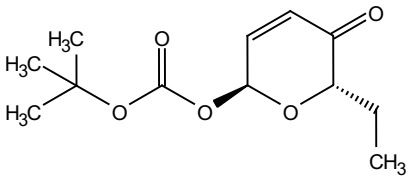
^{1}H NMR (400 MHz, $CDCl_3$)

I



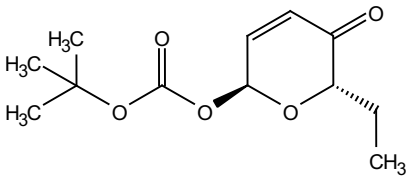
^{13}C NMR (100 MHz, $CDCl_3$)

I



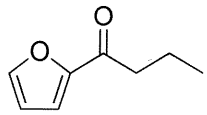
^{1}H NMR (600 MHz, $CDCl_3$)
16b

14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



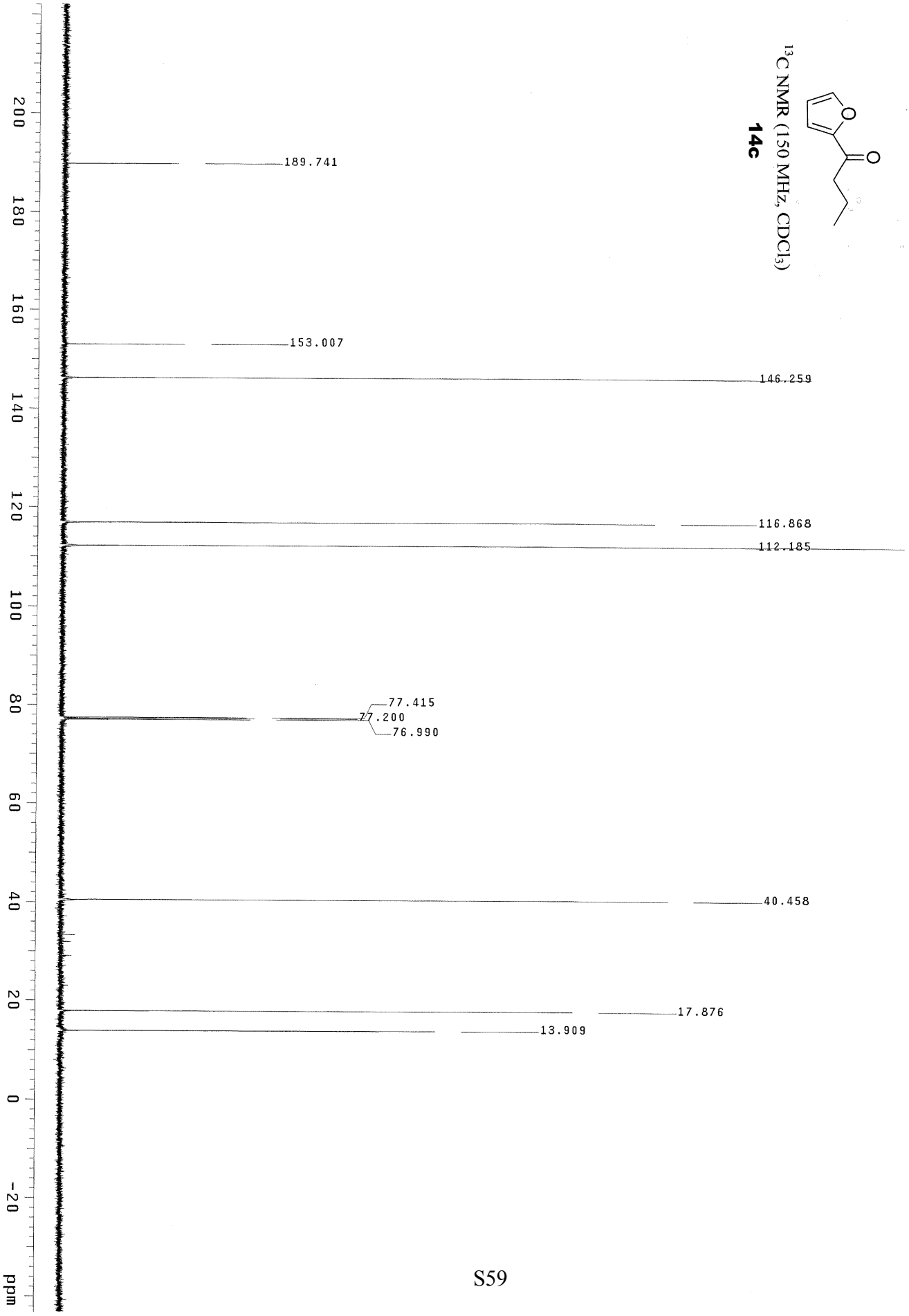
^{13}C NMR (150 MHz, $CDCl_3$)
16b

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3



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

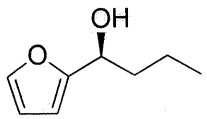
14c


^{13}C NMR (150 MHz, $CDCl_3$)
14c
189.741
153.007
146.259
116.868
112.185
77.415
77.200
76.990
40.458
17.876
13.909
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

STANDARD PROTON PARAMETERS

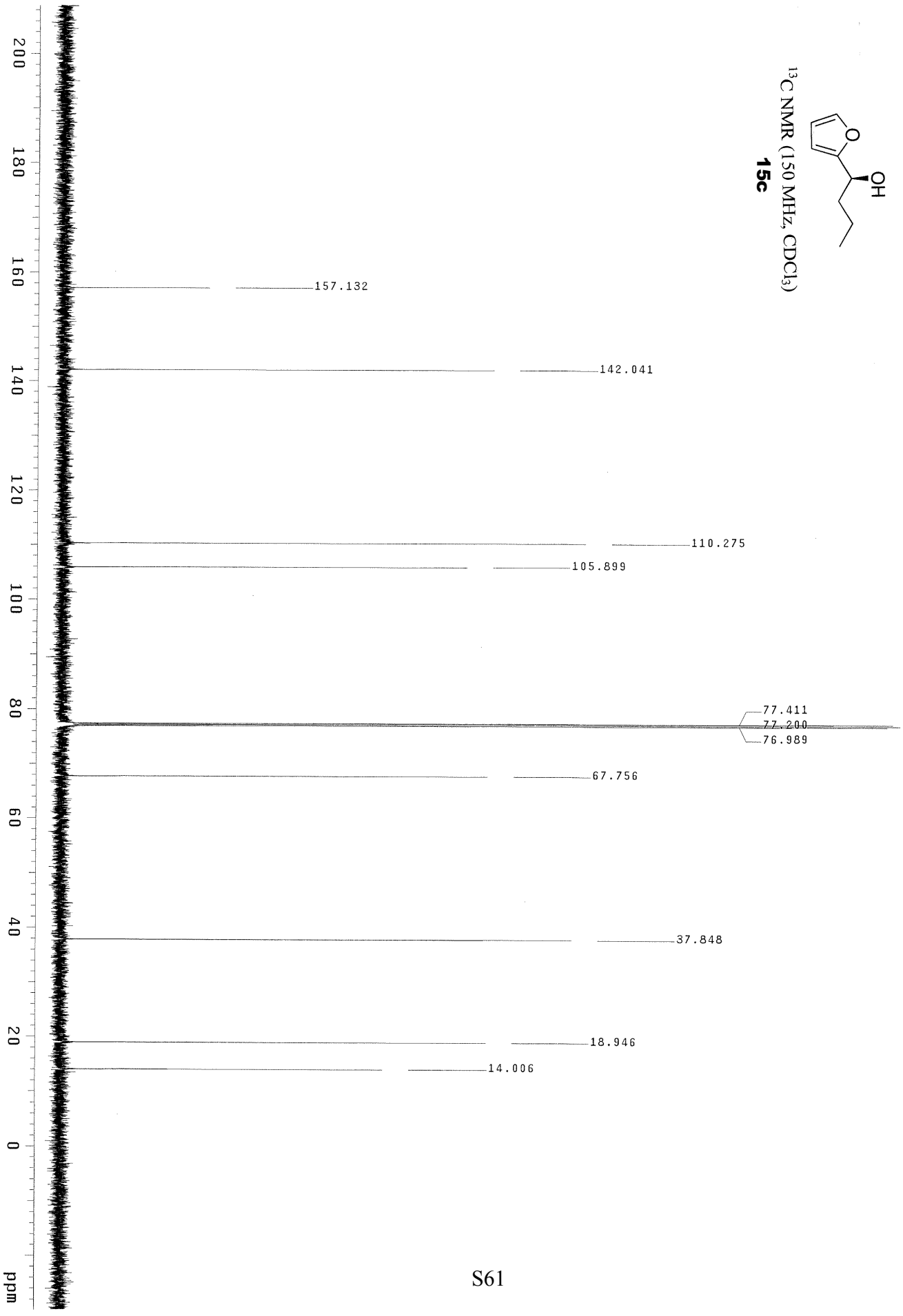
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory:

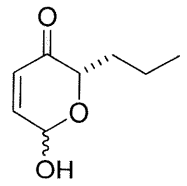
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 28.0 C / 301.1 K



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

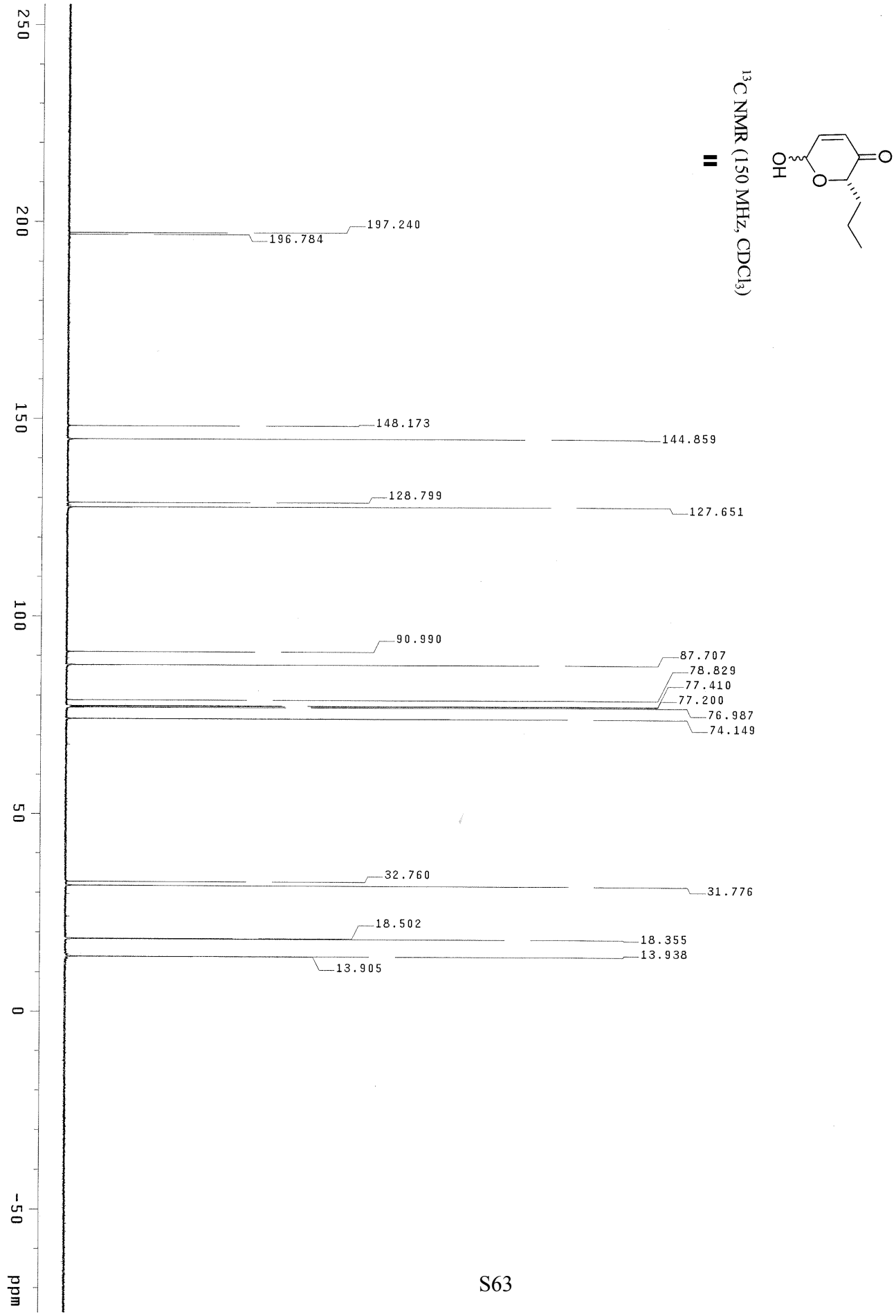
15c

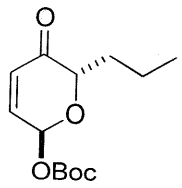

^{13}C NMR (150 MHz, $CDCl_3$)
15c
OH
157.132
142.041
110.275
105.899
77.411
77.200
76.989
67.756
37.848
18.946
14.006
200
180
160
140
120
100
80
60
40
20
0
ppm



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

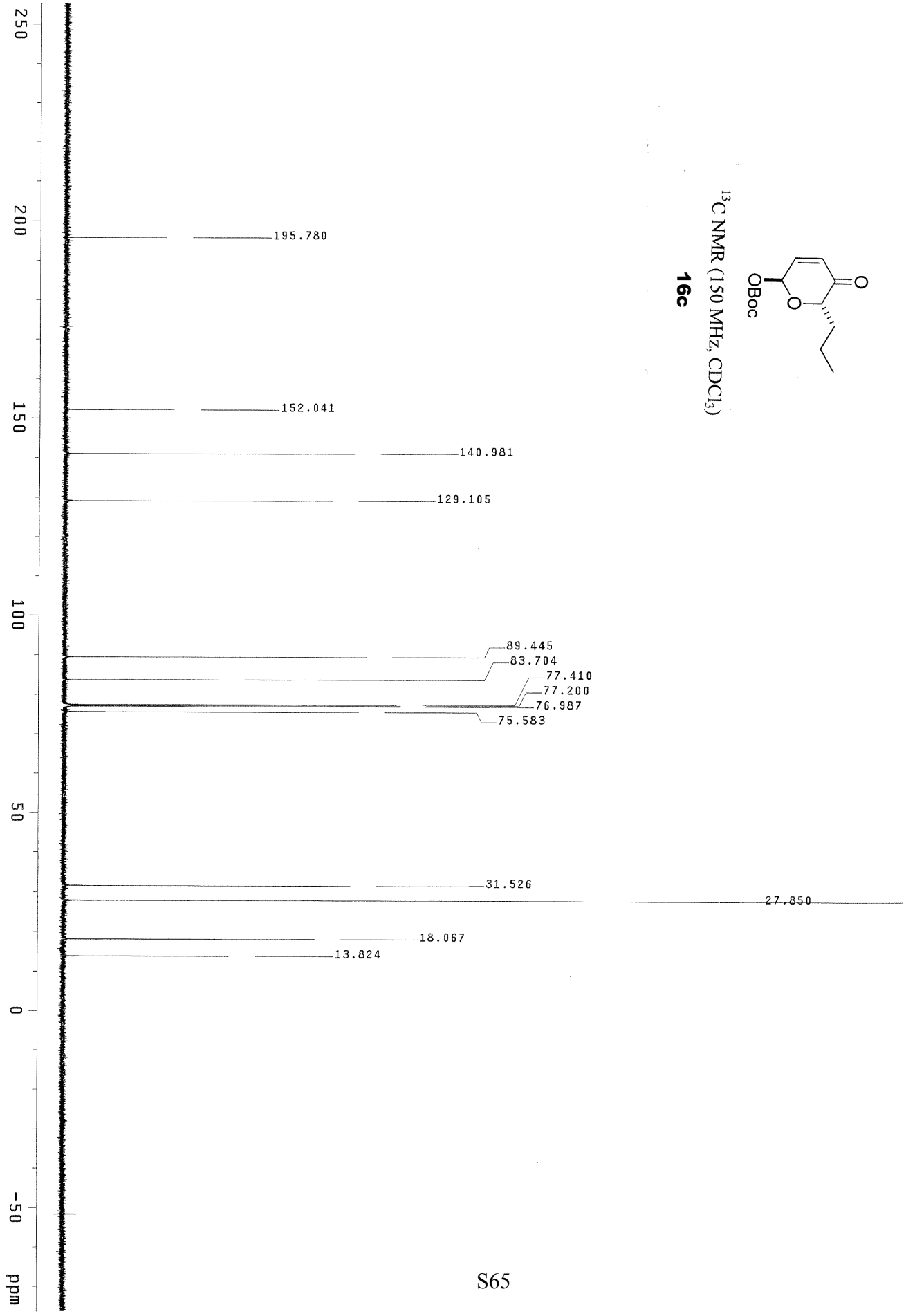
II


^{13}C NMR (150 MHz, CDCl$_3$)
OH
O
O
250
200
150
100
50
0
-50
ppm
197.240
196.784
148.173
144.859
128.799
127.651
90.990
87.707
78.829
77.410
77.200
76.987
74.149
32.760
31.776
18.502
18.355
13.938
13.905



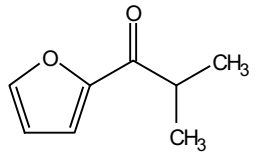
^{1}H NMR (600 MHz, $CDCl_3$)

16c



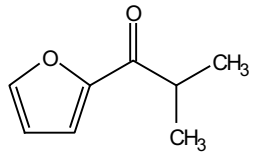
^{13}C NMR (150 MHz, $CDCl_3$)

16c



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

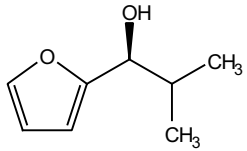
14d



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

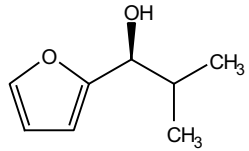
14d

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, $CDCl_3$)

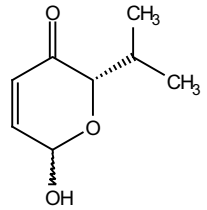
15d



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

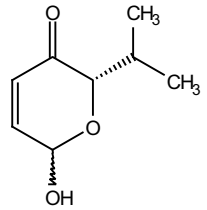
15d

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 (270 MHz, $CDCl_3$)

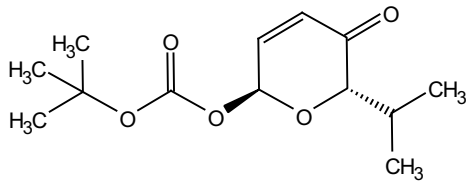
III



^{13}C NMR (67.5 MHz, $CDCl_3$)

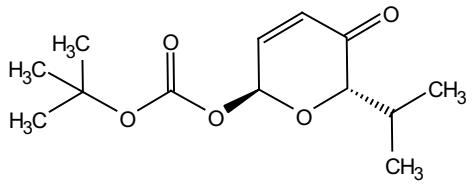
III

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, $CDCl_3$)

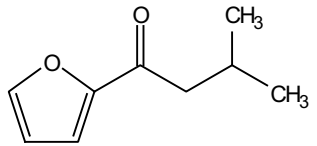
16d



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

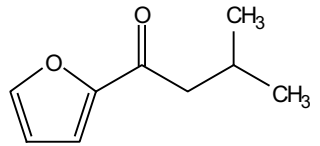
16d

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, $CDCl_3$)

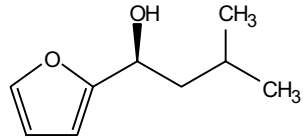
14e



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

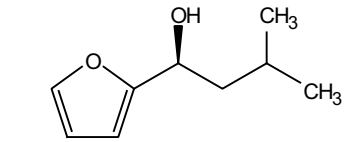
14e

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



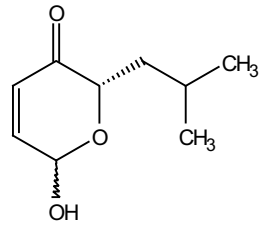
^{1}H NMR (600 MHz, $CDCl_3$)

15e



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

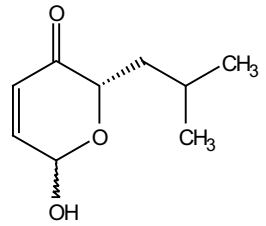
15e



^{1}H NMR (400 MHz, $CDCl_3$)

IV

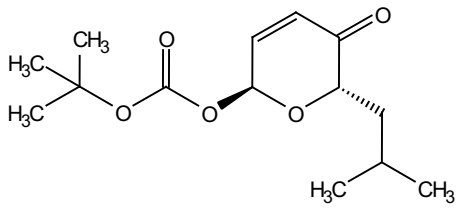
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2



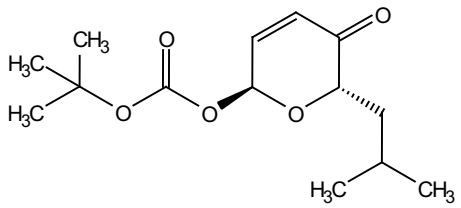
^{13}C NMR (100 MHz, $CDCl_3$)

IV

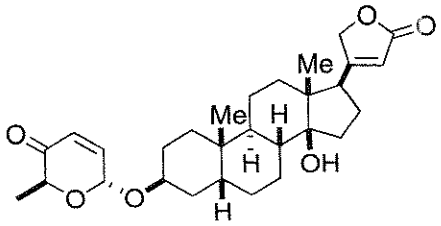
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20



^{1}H NMR (600 MHz, $CDCl_3$)
16e

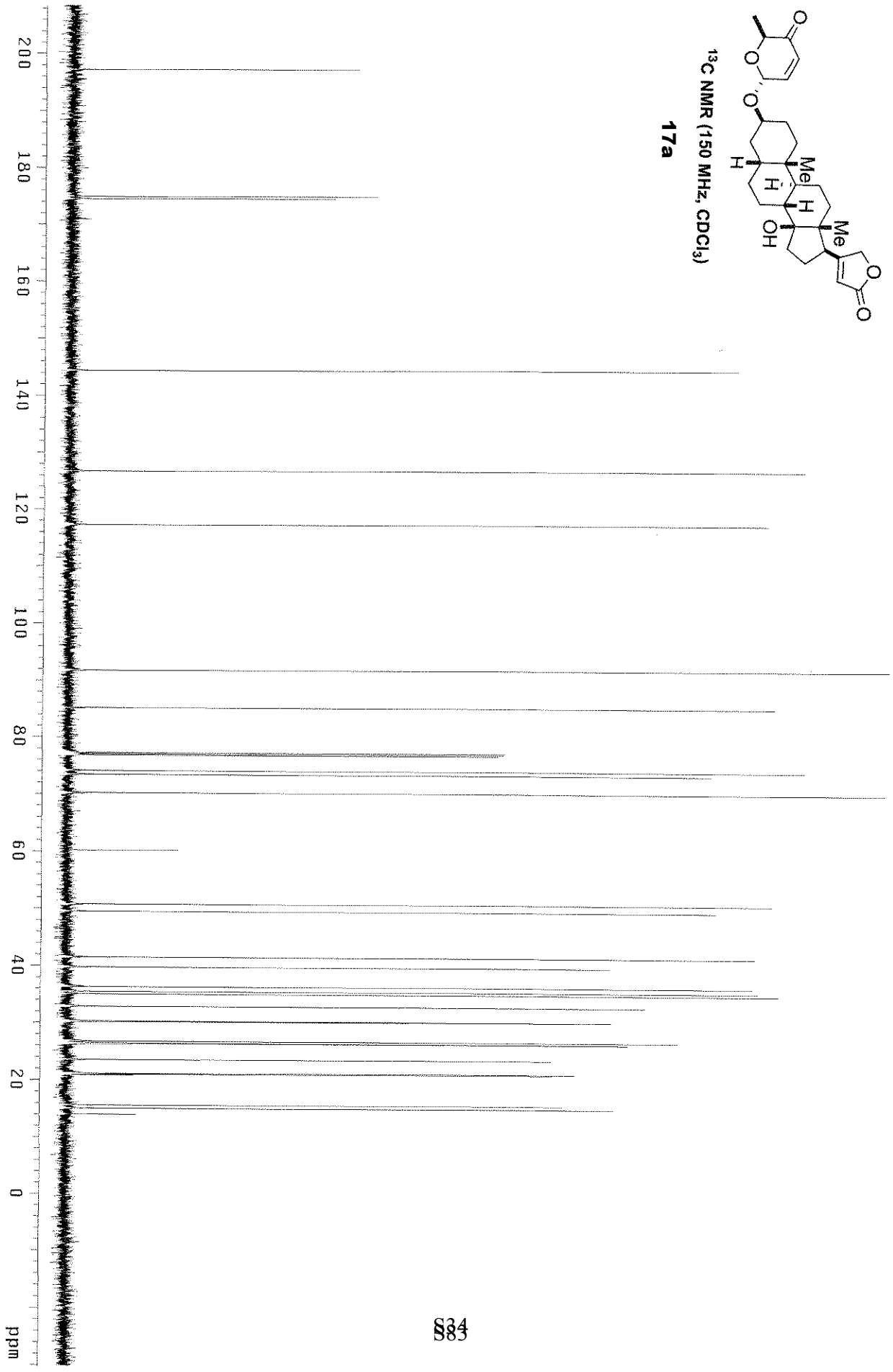


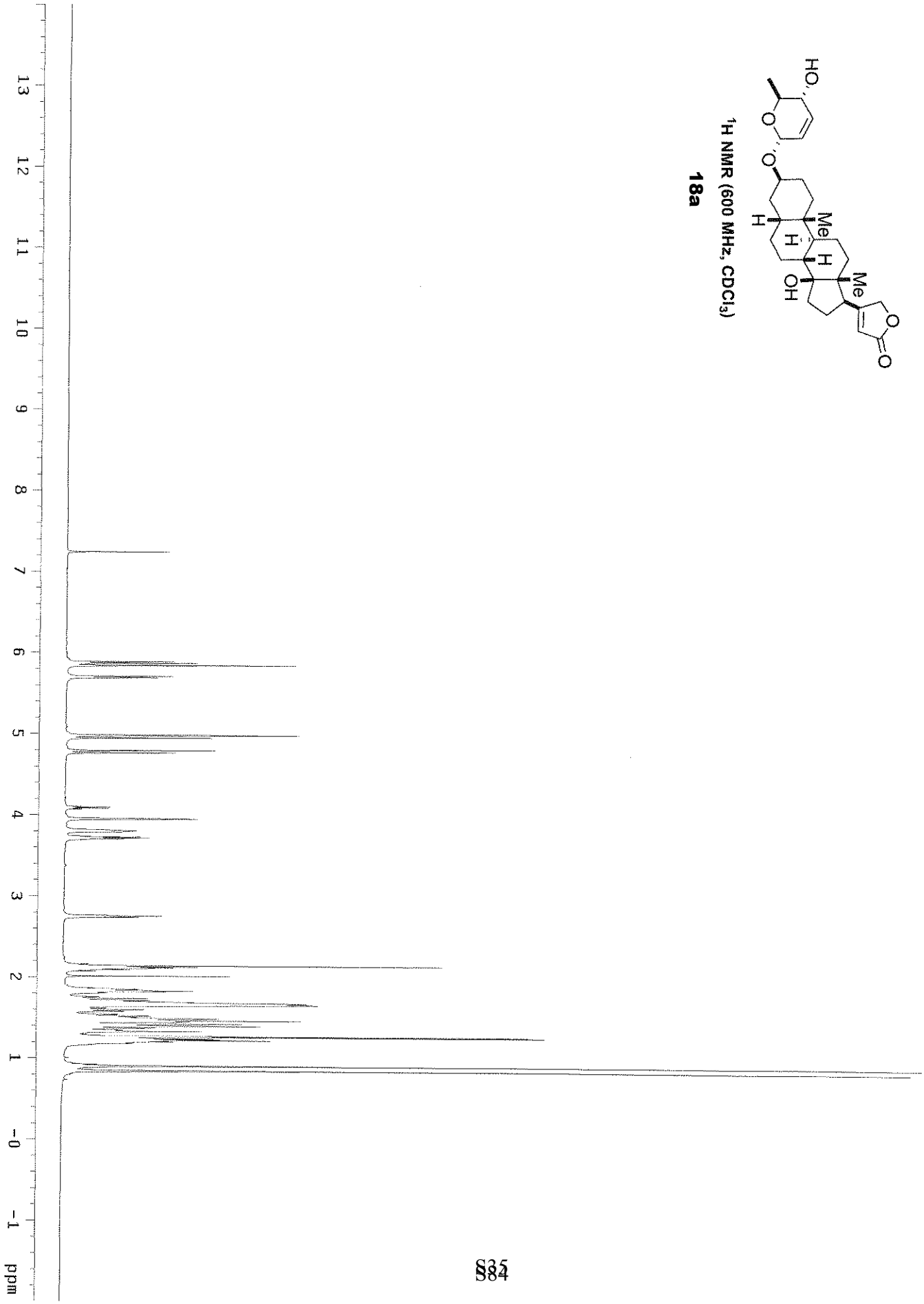
^{13}C NMR (150 MHz, $CDCl_3$)
16e



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

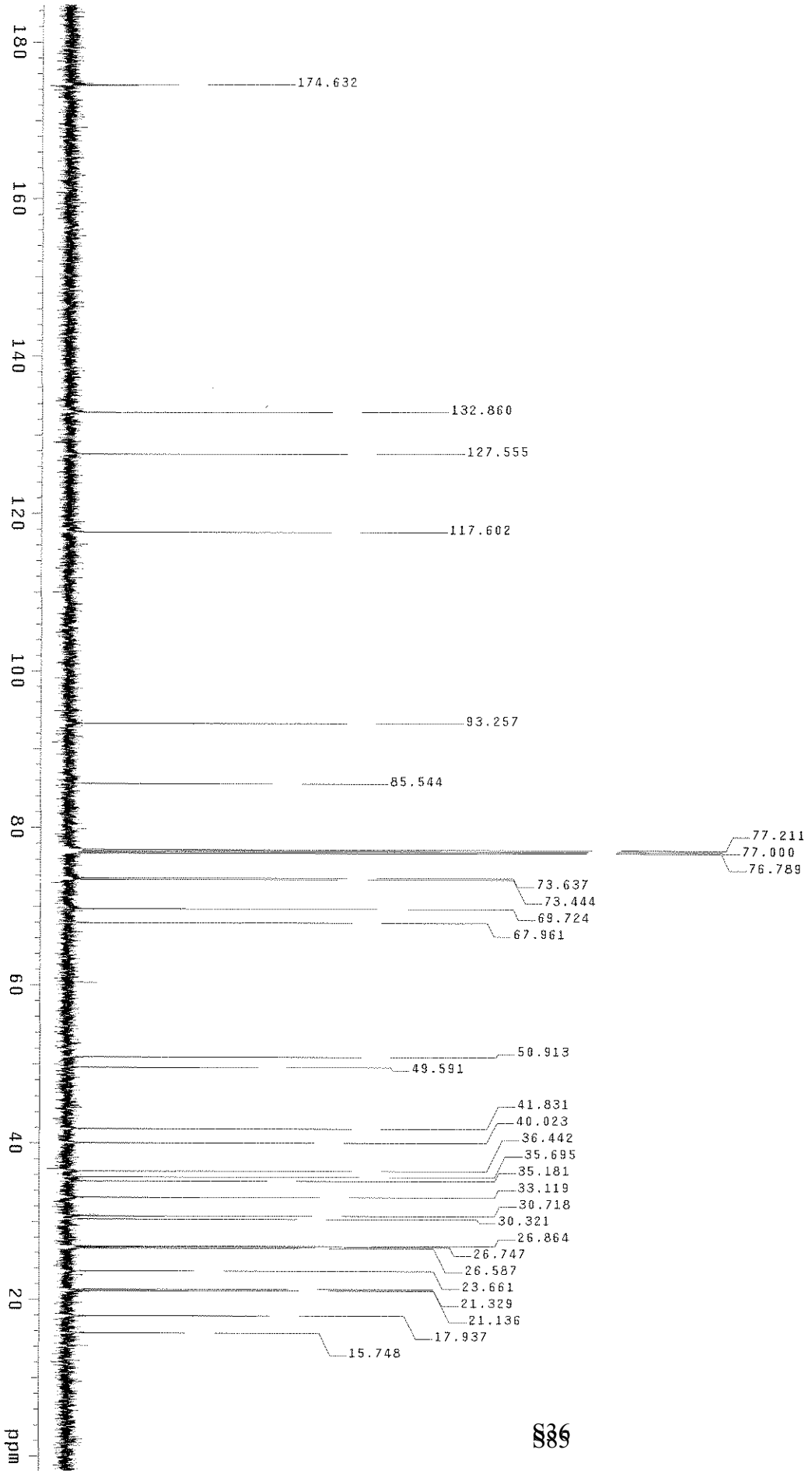
17a


^{13}C NMR (150 MHz, CDCl$_3$)
17a
Me
H
H'
OH
Me
O
O
O
O
O
200
180
160
140
120
100
80
60
40
20
0
ppm



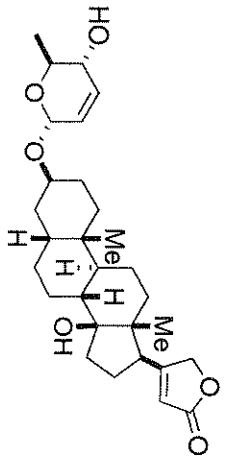
^{1}H NMR (600 MHz, $CDCl_3$)

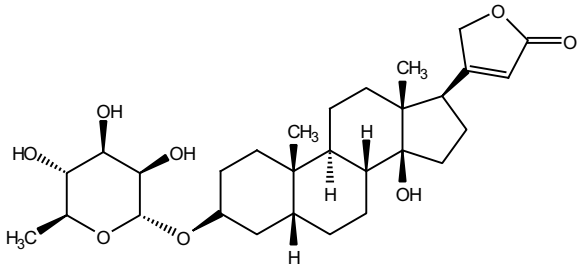
18a



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

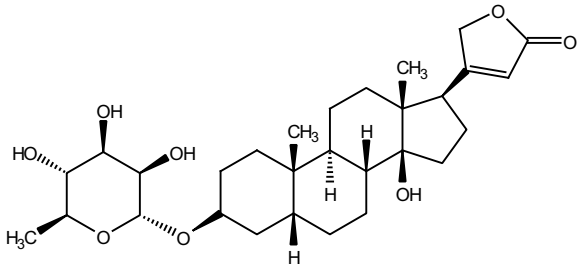
18a





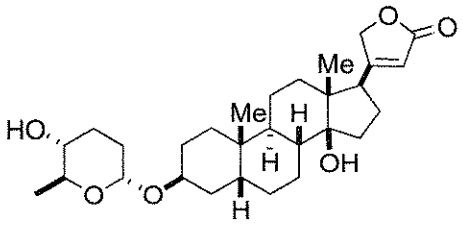
^{1}H NMR (400 MHz, CD_3OD)

4



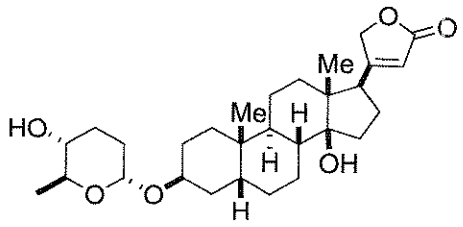
^{13}C NMR (100 MHz, CD_3OD)

4



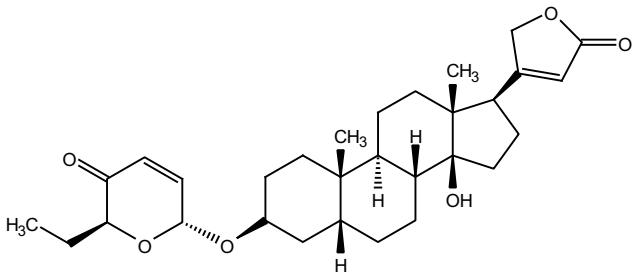
^{1}H NMR (600 MHz, $CDCl_3$)

9



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

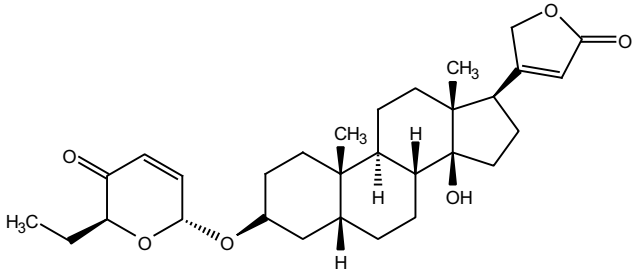
9



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

17b

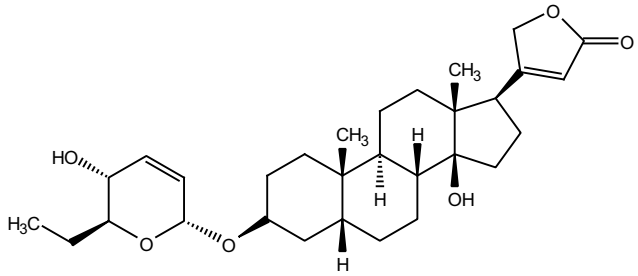
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



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

17b

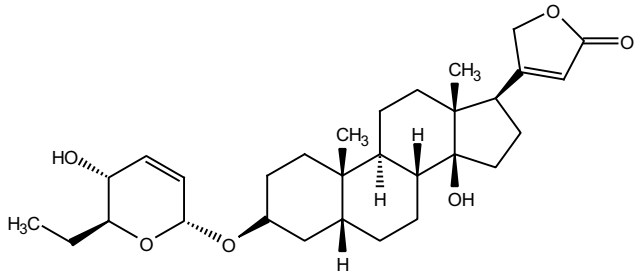
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20



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

18b

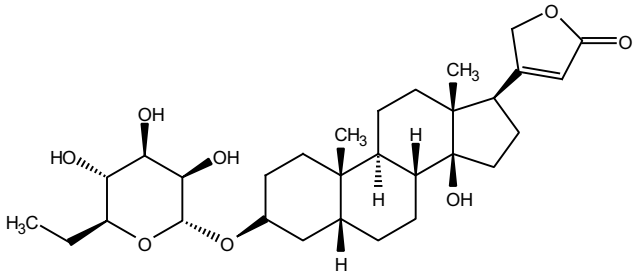
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



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

18b

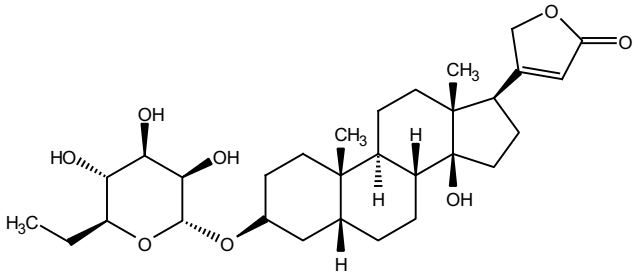
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20



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

5

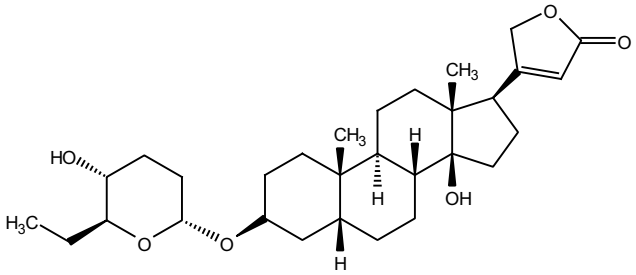
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



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

5

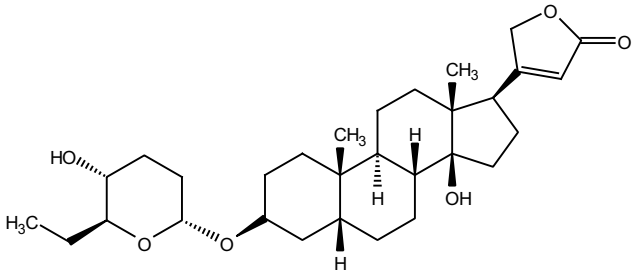
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20



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

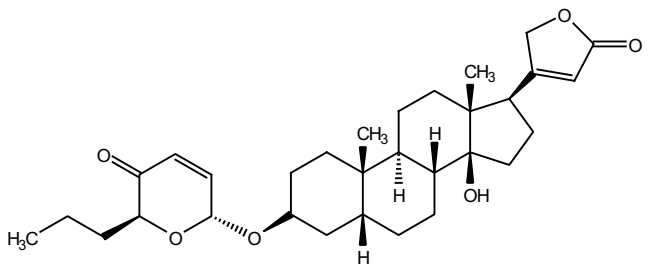
10

13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



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

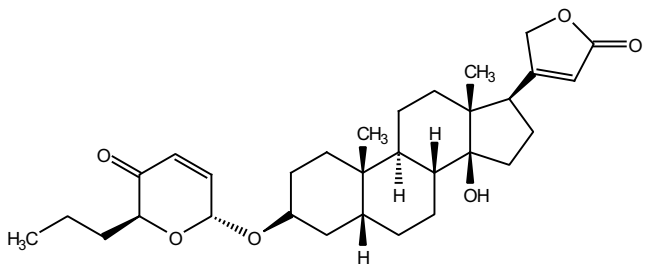
10



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

17c

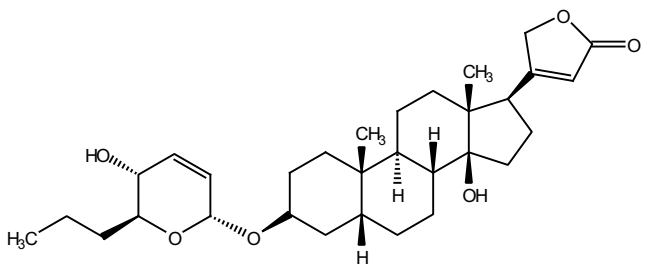
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



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

17c

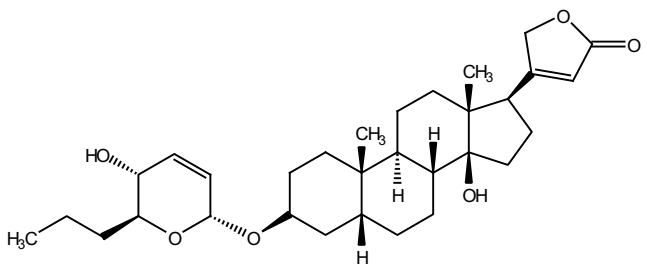
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3



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

18c

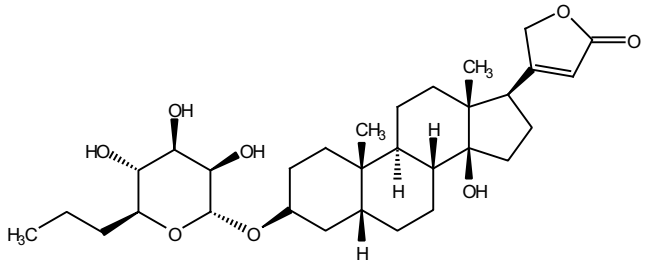
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



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

18c

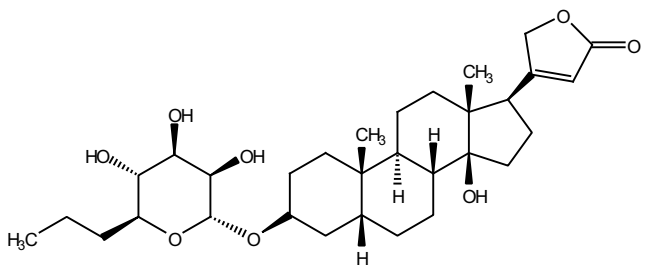
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20



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

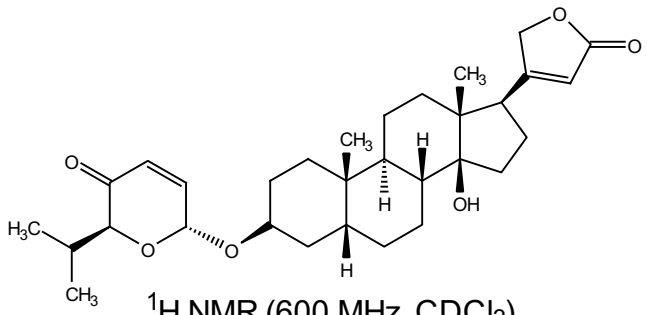
6

13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



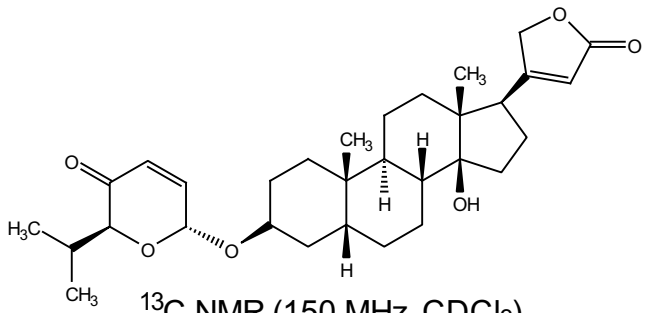
^{13}C NMR (150 MHz, $CDCl_3$)

6



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

17d



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

17d

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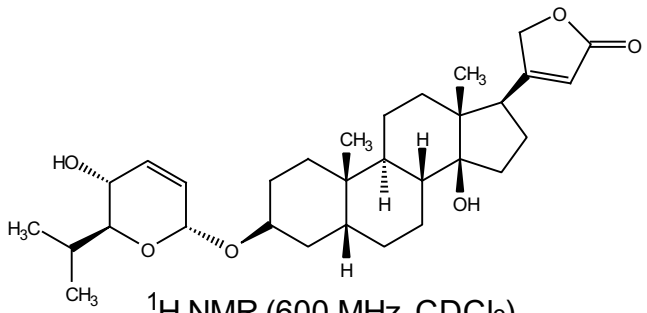
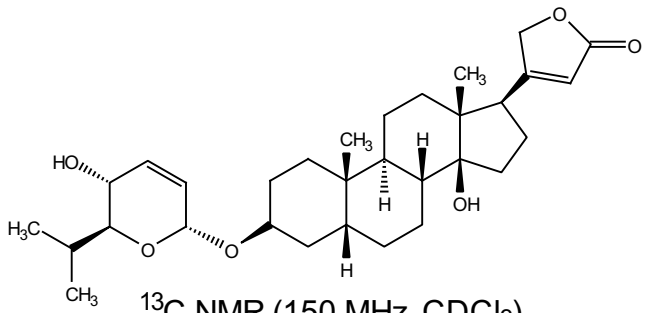


^{1}H NMR (600 MHz, $CDCl_3$)

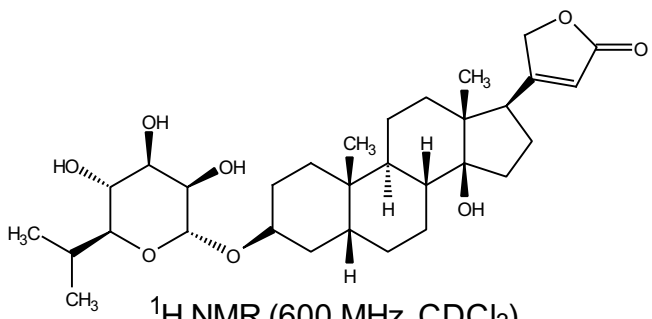
18d



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

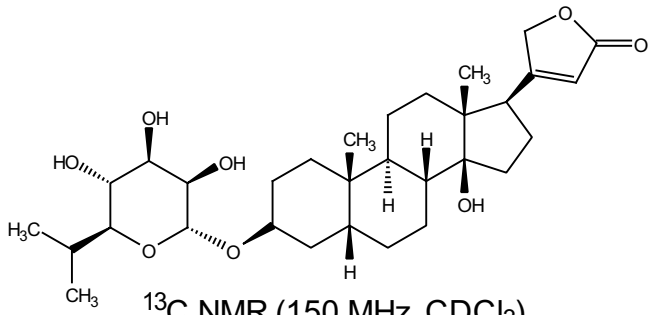
18d

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



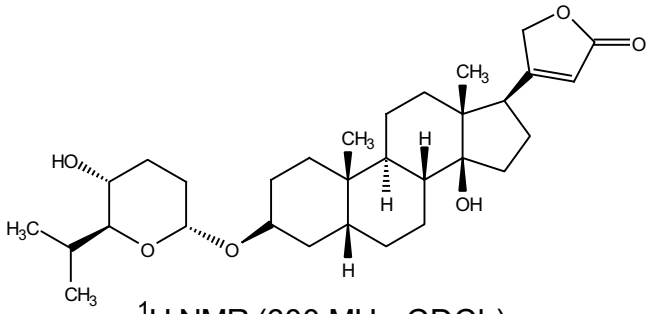
^{1}H NMR (600 MHz, $CDCl_3$)

7



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

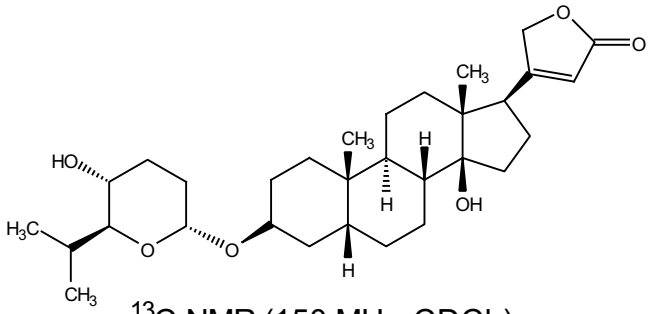
7



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

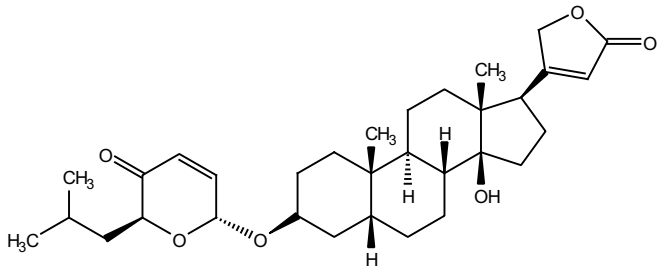
11

13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



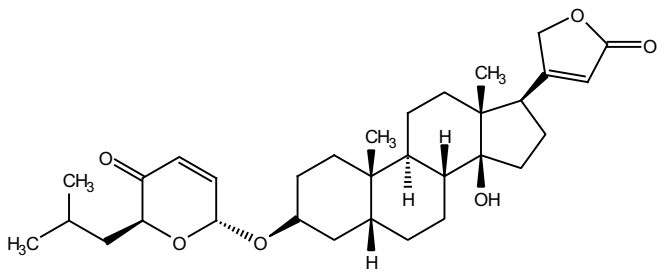
^{13}C NMR (150 MHz, $CDCl_3$)

11



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

17e



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

17e

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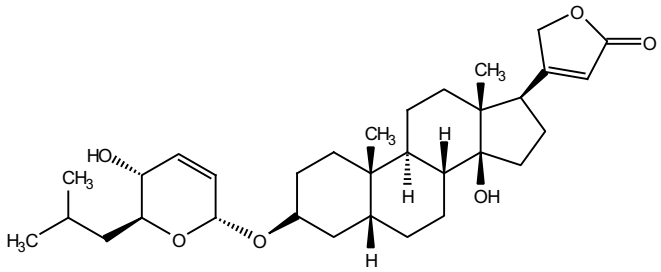
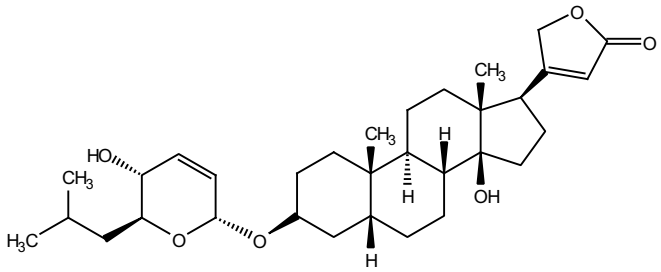


^{1}H NMR (600 MHz, $CDCl_3$)

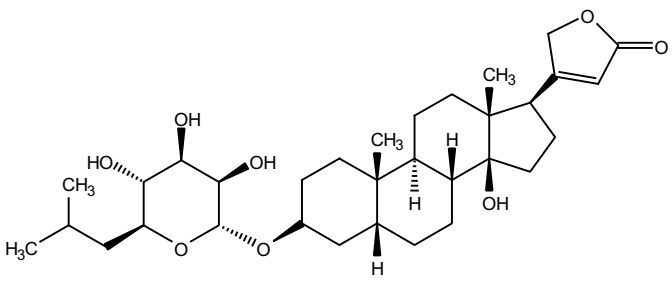
18e

13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



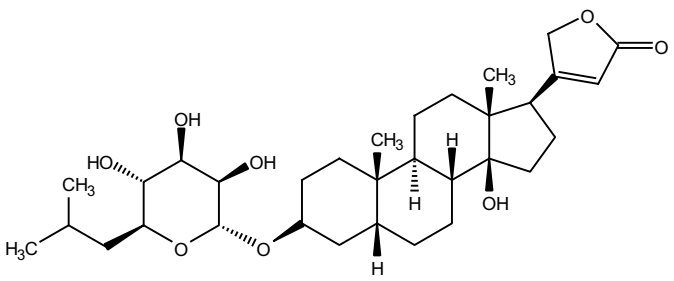
^{13}C NMR (150 MHz, $CDCl_3$)

18e



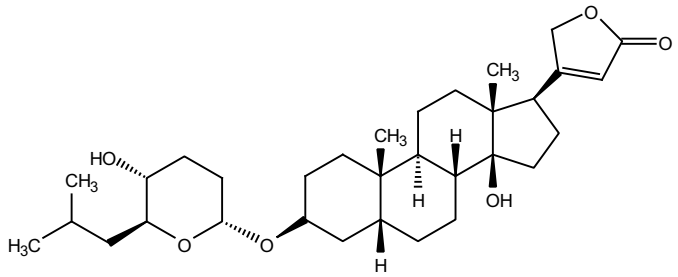
^{1}H NMR (600 MHz, $CDCl_3$)

8



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

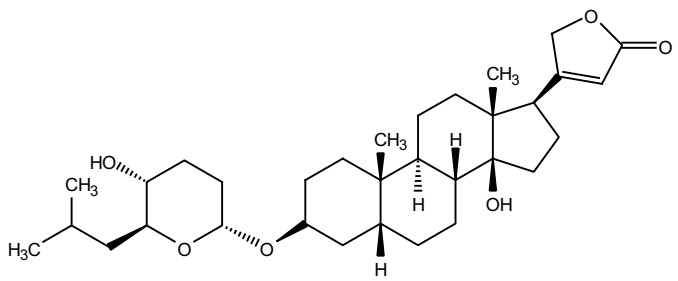
8



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

12

13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1



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

12