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CARDIAC GLYCOSIDES: 5. STEREOSELECTIVE SYNTHESES OF DIGITOXIGENIN α-D, β-D, α-L, AND β-L-GLUCOSIDES

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Abstract--As part of a continuing study of cardiac glycosides,[1,2] stereoselective syntheses of the four possible glucosides of digitoxigenin were developed via the thermodynamically produced tetra-O-benzyl-D- and L-glucosyl α-trichloroacetaimidates 2α and **11**α, and the kinetically produced β-trichloroacetaimidates 2β and **11**β. A 58%:19% isolated yield ratio of α-D and β-D benzyl protected glycosides **6** and **3** could be obtained in 30 minutes reaction at -10°. Halide ion catalysis with a 2:1 excess of tetra-O-benzyl-α-D-glucopyranosyl bromide for 14 days in methylene chloride at room temperature gave a 39%:11% ratio of **6** and **3**, along with 43% of recovered digitoxigenin. Debenzylation of the D-glucosides required milder conditions (20% Pd/C, atmospheric pressure, 45 min - 1 hr) than the L-glucosides (40% Pd/C, 2 hr) but yields were typically 80% for both groups.

The Koenigs Knorr reaction[3] has been widely used to make β-D cardiac glycoside analogues, [1b,4] along with α-D (1',2'-cis) glycoside by-products. More recently, Wiesner and coworkers have used the 1-3 participation of a urethane group to add β-D-digitoxose (2'-deoxy) sugars to cardiac glycosides.[5] A variety of other methods have been used in modern oligosaccharide syntheses,[6,7] in particular the imidate[8] and halide ion catalysis[9] methods to selectively make 1',2'-cis glycosides. However, these approaches have not been applied to the syntheses of cardiac glycosides.

We report here the stereoselective syntheses of α (1',2'-cis) and β (1',2'-trans) D- and L-glucosides of digitoxigenin. With 5β-stereochemistry and concomitant steric bulk, digitoxigenin offers a challenging synthetic problem. We explored the methods of Schmidt and Michael (imidates catalyzed with $BF_3.Et_2O$ or p-toluene sulfonic acid)[8] and Lemieux (halide ion catalysis in the presence of tetraethylammonium bromide).[9] Best yields and shortest reaction times (Tables 2a, 2b, 5) were obtained with modified trichloroacetaimidate procedures. Halide ion catalysis produced lower yields but better stereoselectivity for making α-D **6** vs β-D **3**, 38.9%:10.9% vs 58%:19% for the imidate route. Reaction times were longer, 72 hours vs 30 min for the imidates. Selection of the catalyst was found to be crucial for maximal steric control in the imidate procedures and for avoiding 14β-OH dehydration. For synthesis of the β-D- and β-L glucosides **3** and **12** from 2α and **11**α, $BF_3.Et_2O$ was the best catalyst. For the α-L and α-D glucosides **6** and **15**, it was zinc triflate (zinc trifluromethanesulfonate)[10] from the triarylimidates **5** and **14**; and trimethylsilyl trifluoromethanesulfonate[11] from the trichloroacetaimidates 2β and **11**β.

RESULTS AND DISCUSSION

Stereochemical Assignments. The imidate routes found to give the most favorable yields and stereochemical control are shown in Schemes 1 and 2. ^{1}H-NMR of the C1'-anomeric protons could

unambigiously differentiate (Table 1) the β-imidates **5**, **2β**, **11β** and **14**, from the α-imidates **2α** and **11α**. Chemical shifts were consistant with those previously reported.[8] Excellent stereochemical contro] was observed in the imidate syntheses, i.e., no **14** in **11**, etc.

However, the glycosylation procedures (discussed below) gave mixtures of anomers. For example, reaction of β-imidate **5** with digitoxigenin and p-toluene sulfonic acid or pyridinium p-toluene sulfonate (PPTS) as catalyst (Table 2) gave a 10:1 mixture of digitoxigenin α-D-glucoside **6** and β-D-glucoside **3**. The anomers were then separated with flash chromatography, and characterized by ^{13}C NMR based on the chemical shifts for the C1' to C6' carbons of the sugars and C2 and C3 carbons of the steroid. Most important, the ^{13}C chemical shifts (Tables 3 and 4) are consistant with those reported by Kasai,[12,13] Tori,[14,15] and by Thomas.[16]

The ^{13}C chemical shifts for C3' and C5' are significantly affected by the γ-effect by changes in anomeric configuration (Table 3). The C1' signal was also shifted significantly downfield in perbenzylated digitoxigenin β-D and β-L glucosides **3** and **12** compared to digitoxigenin α-D and α-L glucosides **6** and **15**. It is important to note that the C1' signal of digitoxigenin glucosides should be upfield from the corresponding methyl glucosides because there is less deshielding from a steroid than from a methyl group.[12]

The ^{13}C chemical shifts of the steroid C1, C2, and C3 in the perbenzylated glucosides **12**, **15**, **3**, and **6** vs that of digitoxigenin (Table 4) are also consistant with those previously reported.[11-15] The glycosidation shifts were derived as $\delta A = \delta$ (glucoside)-δ (digitoxigenin) (Table 4). As can be seen, the signal for the steroid carbinol carbon (C3) is generally deshielded by about +7.0 ppm following β-D and β-L glycosidation. With α-glycosidation, the shift is smaller (+3 to 4 ppm).

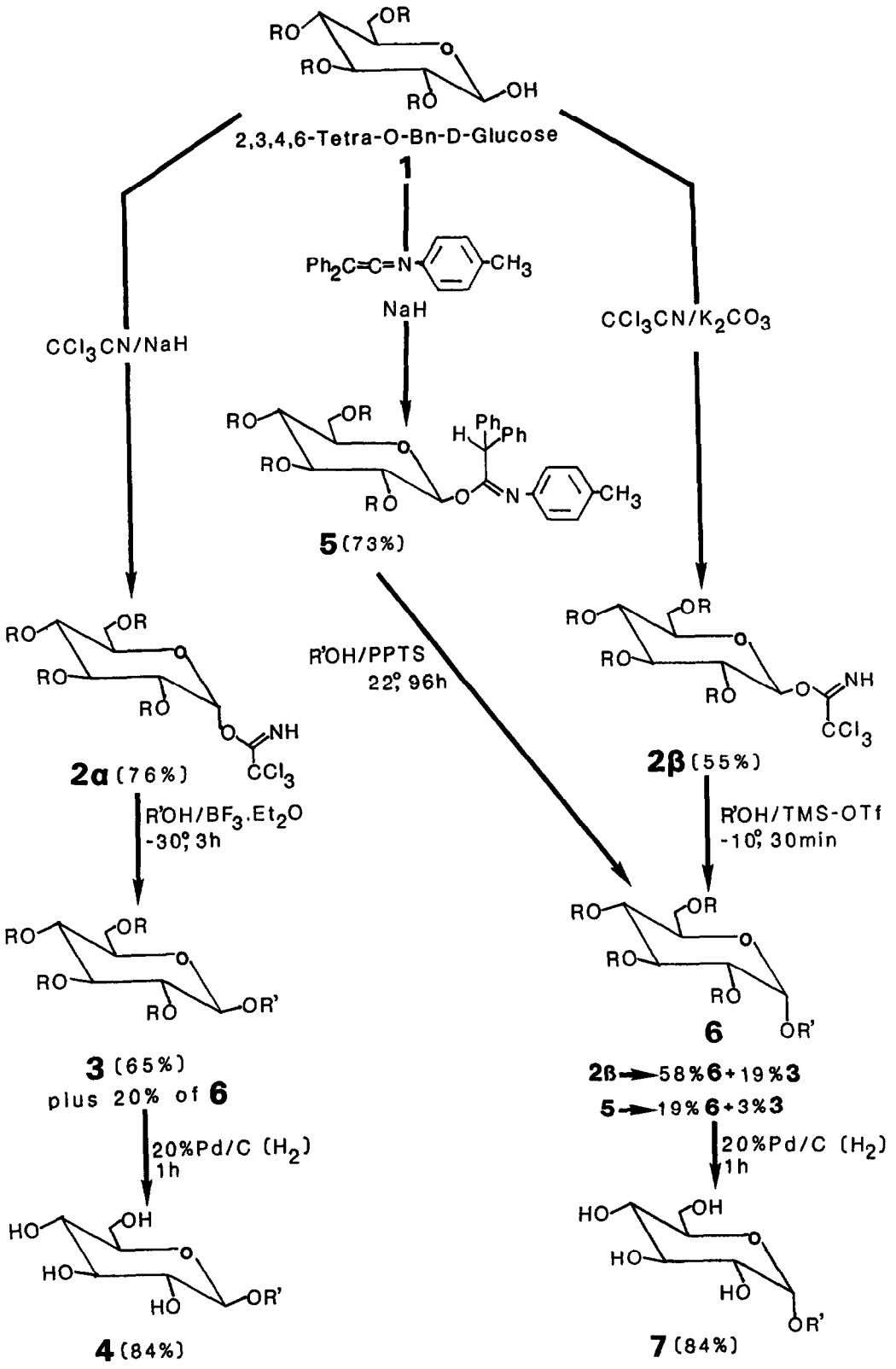
Synthesis. a. Imidate Formation: As reviewed by Neilson,[17] reaction of alcohols with ketenimines or nitriles containing electron withdrawing substituents on the α-carbon will directly produce imidates. Schmidt and Michel showed that tetrabenzyl-D-glucopyranose on reaction with aryl substituted ketenimines[18] (with NaH as a base) gave exclusively 1,2-trans-β-imidates. The same reaction with trichloroacetonitrile was initially thought to give exclusively 1,2-cis-α-imidates,[8a] but more recently, these authors have shown that 1,2-trans β-imidates can also be selectively produced.[8b] Using these methods as shown on Scheme 1, we made the imidates **2α** and **5** from tetrabenzyl-D-glucopyranose (**1**); and **11α** and **14** from tetrabenzyl-L-glucopyranose (**10**). The L-glucopyranoside **10** was prepared using conventional procedures from methyl α,β-L-glucopyranose **8**, benzylation to its tetrabenzyl analogue **9**, and acid hydrolysis. The D-glucopyranoside **1** was obtained commercially. Reaction of **1** or **10** with trichloroacetonitrile under kinetic conditions (anhydrous potassium carbonate, room temperature, 5-6 hr) gave imidates **2β** and **11β** in 55% total isolated yield.

The formation of the 1',2'-trans imidates **5** and **14** with diphenyl-ketene-p-tolylimine[8,18] and NaH was much slower than for the trichloroacetaimidates--typically 36 hours, and yields were much lower.

Table 1. O-Glycosylimidates

	Yield[a] (%)	^1H NMR (δ)[b] C1'H	NH	$J_{1',2'}$ (Hz)	IR (NaCl) C=N (cm^{-1})
2α	76	6.5	8.6	3.5	1670
2β	55	5.92	8.7	7.0	1670
5	73	6.11	5.2	7.0	1670
11α	85	6.5	8.67	3.5	1670
11β	56	6.10	8.68	7.5	1672
14	77	6.13	5.15	7.5	1672

[a] Isolated yields
[b] 80 MHz spectra in $CDCl_3$ with Me_4Si as internal standard


2,3,4,6-Tetra-O-Bn-D-Glucose
1
Ph2C=C=N-C6H4-CH3
NaH
CCl3CN/NaH
CCl3CN/K2CO3
5 (73%)
R'OH/PPTS
22°, 96h
2α (76%)
2β (55%)
R'OH/BF3.Et2O
-30°, 3h
R'OH/TMS-OTf
-10°, 30min
3 (65%)
plus 20% of 6
6
2β → 58% 6 + 19% 3
5 → 19% 6 + 3% 3
20%Pd/C (H2)
1h
4 (84%)
7 (84%)
R=PhCH2-
R'OH=Digitoxigenin

Scheme 1

Table 2a. Reactions, Reaction Conditions and Products for Scheme 1

Reactant	catalyst	Mole Ratio [Reactant]: [Digit]:[Cat]	Conditions hr		Product% 3:6	% Yield[a] 3+6
2α	---	1:5:--	22°	2	no reaction	--
2α	$BF_3.Et_2O$	1.3:1:1.3	-20°	0.5	-b-	5
2α	$BF_3.Et_2O$	1.3:1:0.1	-78°	3	3:1	78
2α	$BF_3.Et_2O$	1.3:1:0.3	-30°	3	3:1	85
2α	$ZnCl_2$	1.3:1:1.3	22°	24	-b-	10
2α	$SnCl_4$	1.3:1:1.3	0°	2	-b-	5
2β	TMs-OTf	1.0:1.3:0.43	-10°	0.5	1:3	77
5	(no catalyst)	1:2:--	22°	10	no reaction	--
5	$BF_3.Et_2O$	1.5:1:0.3	-20°	10	no reaction	--
5	p-TsOH	1.2:1:1	22°	96	1:10	18
5	PPTS	1.2:1:1	22°	96	1:10	21
5	Zn(OTf)2	1.5:1:1.5	22°	18	2:1	64

[a] Isolated yield.

[b] Most of the isolated product was a mixture with 14-ene-glucosides.

Table 2b. Reactions, Reaction Conditions and Products for Scheme 2

Reactant	Catalyst	Mole Ratio [Reactant]: [Digit]:[Cat]	Conditions hr		Product 12:15	% Yield[a] 12+15
11α	$BF_3.Et_2O$	1.3:1 :0.3	-30°	3	3:1	88
11α	$BF_3.Et_2O$	1.3:1.1:0.1	-78°	3	3:1	75
11α	$BF_3.Et_2O$	1.3:1.0:0.1	0°	3	3:1	35[b]
11β	TMS-OTf	1.0:1.3:0.43	-10°	0.5	1:2.5	71
14	$BF_3.Et_2O$	1.5:1.0:0.3	-30°	5	no reactions[c]	--
14	p-TsOH	1.3:1.0:1.0	22°	96	1:10	20
14	PPTS	1.2:1.0:1.0	22°	96	1:10	25
14	Zn(oTf)2	1.5:1.0:1.5	22°	20	2:1.5	64

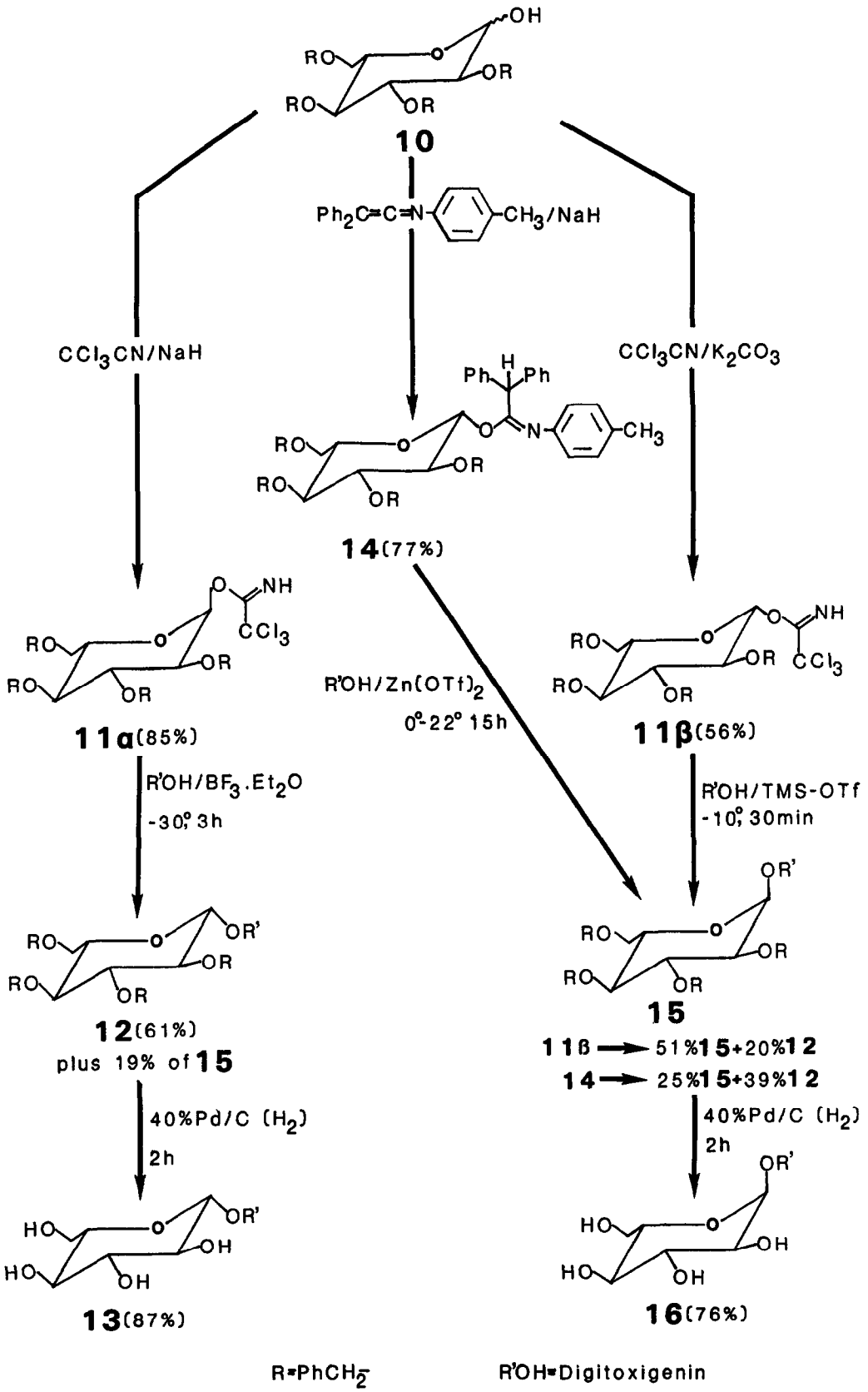
[a] Isolated yield.

[b] The product contained a mixture of 14-ene glycosides.

[c] Decomposition of the imidate.

Abbreviations:

PPTS - Pyridinium p-toluene sulfonate
TMS-OTf - Trimethylsilyl Trifluoromethane sulfonate
p-TsOH - p-Toluene Sulfonic Acid
$Zn(OTf)_2$ - Zinc Triflate
Digit - Digitoxigenin


10
$Ph_2C{=}C{=}N$ CH_3/NaH
CCl_3CN/NaH
CCl_3CN/K_2CO_3
14(77%)
11α(85%)
11β(56%)
R'OH/$Zn(OTf)_2$
0°-22° 15h
R'OH/$BF_3.Et_2O$
-30° 3h
R'OH/TMS-OTf
-10° 30min
12(61%)
plus 19% of 15
15
11β → 51%15+20%12
14 → 25%15+39%12
40%Pd/C (H_2)
2h
13(87%)
16(76%)
R=$PhCH_2$
R'OH=Digitoxigenin

Scheme 2

TABLE 3

^{13}C Chemical Shifts of D-Tetrabenzyl Glucopyranosides, L-Tetrabenzyl Glucopyranosides and Digitoxigenin[a]

	3	6	12	15	Digitoxigenin
C-1'	101.51	95.01	101.63	95.13	----
C-2'	78.05	90.49	78.07	73.46	----
C-3'	82.25	81.96	82.27	81.95	----
C-4'	75.66	75.57	75.64	75.48	----
C-5'	84.92	78.18	84.93	77.98	----
C-6'	69.13	68.95	69.25	68.70	----
C-1	30.46	30.06	30.25	29.70	29.62
C-2	29.85	29.61	24.49	23.64	27.85
C-3	73.86	70.54	73.99	70.39	66.75
C-4	35.19	35.20	32.09	33.13	33.28
C-5	36.46	36.64	36.64	36.14	35.97
C-6	26.54	26.56	26.53	26.57	26.47
C-7	21.16	21.21	21.21	21.19	21.14
C-8	41.83	41.79	41.85	41.85	41.73
C-9	35.79	35.74	35.78	35.72	35.46
C-10	35.19	35.20	35.19	35.22	35.37
C-11	21.37	21.28	21.33	21.28	21.32
C-12	40.05	40.03	40.05	40.06	39.99
C-13	49.61	49.63	49.63	49.62	49.60
C-14	85.54	85.34	85.53	85.50	85.45
C-15	33.15	33.08	33.14	33.19	33.06
C-16	26.90	26.92	26.92	26.91	26.88
C-17	50.94	51.03	50.94	50.95	50.94
C-18	15.75	15.74	15.77	15.77	15.76
C-19	23.70	23.62	23.75	21.39	23.70
C-20	174.60	174.78	174.66	174.65	174.94
C-21	73.42	73.44	73.49	73.46	73.54
C-22	117.66	117.50	117.64	117.64	117.52
C-23	174.60	174.78	174.66	174.53	174.90

[a] in p.p.m. downfield from Me_4Si in $CDCl_3$

Table 4. ^{13}C Glycosidation Shifts, Δ A in ppm

Δ A = δ (alchoholic glycoside) - δ (alcohol RH)

	C α(C3) (Δ δ A)	C β(C2) (Δ δ A)	C λ(C1) (Δ δ A)
3	73.86 (+7.11)	29.85 (+2.0)	30.46 (+0.84)
6	70.54 (+3.79)	29.61 (+1.76)	30.06 (+0.44)
12	73.99 (+7.24)	24.49 (-3.36)	30.25 (+0.63)
15	70.39 (+3.64)	23.64 (-4.21)	29.70 (+0.08)

b. Glycoside formation. The α-trichloroacetaimidates **2α** and **11α** react smoothly with digitoxigenin with $BF_3.Et_2O$ as a catalyst at -30° in 3 hr. Yields of the β-D and β-L glycosides **3** and **12** were 60-65% (isolated yields, Schemes 1 and 2), with an additional 20% of the α-D and α-L glycosides.

The β-imidates **2β** and **11β** form the α-D and α-L glycosides **6** and **15** in satisfactory yield (50-58%) with trimethylsilyl trifluoromethanesulfonate[11] as the catalyst at -10°. As with the β-glycosides, a small amount of the anomeric glycoside is produced.

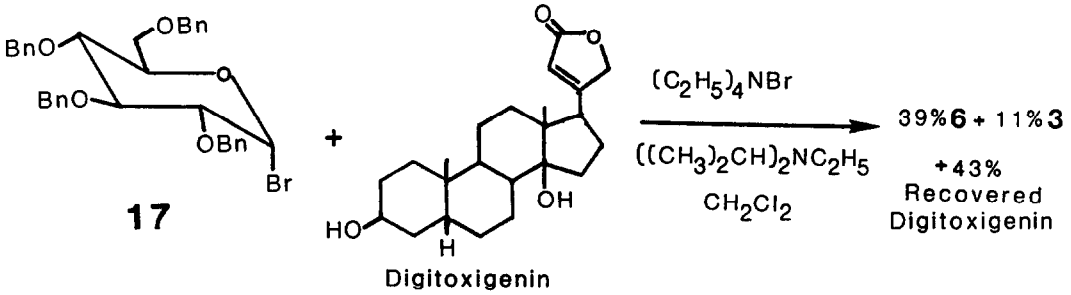
However, the choice of catalyst, catalyst stoichiometry, and temperature are crucial (Tables 2a and 2b). At room temperature, for example, 14β-dehydration is extensive. Schimidt and Michel[8a] report an alcohol:imidate:$BF_3.Et_2O$ stoichiometry of 1:1:1. This also results in extensive dehydration of the cardenolide 14β-OH. For these acid sensitive compounds, we found a 1:1:0.3 ratio to be optimal.

Reaction with digitoxigenin to produce the α-D and α-L glycosides **6** and **15** was slow even at room temperature. No further reaction could be observed (monitoring the reactions by tlc) even after 96 hours stirring.

As shown in Tables 2a and 2b, the triarylimidates **5** and **14** either produce 1) the desired α-glycosides in unacceptably low yield with high stereoselectiveity using p-toluene sulfonic acid or PPTS; or 2) the 'wrong' product (i.e. the β-glycosides) predominanting in moderate yield with zinc triflate. Use of $BF_3.Et_2O$ resulted in extensive decomposition of the triarylimidates, with recovery of nearly all the digitoxigenin starting material.

The difference of reaction rate of the trichloroacetaimidates **2α**, **2β**, **11α** and **11β** vs the triarylimidates **5** and **14** reflect several effects. The trichloroacetaimidates are inherently more reactive. Whereas **5** and **14** are stable at room temperature for a week or more (but the slightest acid will cause their decomposition), the trichloroimidates must be chromatographed very quickly and stored in a -20° freezer. Further, axial attack by the bulky cardenolide's secondary 3β-ol is naturally difficult, especially so with the added steric hindrance of the 2'-O-benzyl group.

c. Halide Ion Catalysis. 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl bromide (**17**) was prepared by stirring the corresponding O-p-nitrobenzoyl analogue[19] in methylene chloride saturated with HBr as previously reported by Ishikawa and Fletcher.[20] Following the procedure of Lemieux and coworkers,[9] 1.0 or 0.5 molar equivalents of digitoxigenin was stirred in methylene chloride at 20°, 40° or 60° (in a sealed tube) (Table 5) with one equivalent each of bromide **17**, tetraethylammonium bromide, and diisopropylethylamine. The reaction mixture was stirred in the dark for one hour with silver acetate, acetic acid and acetic anhydride, filtered, and extracted with methylene chloride. After the methylene chloride extract was washed several times with water to remove acetic acid, the solvent was removed and the crude product was chromatographed.



Scheme 3

TABLE 5. Yields of **6** and **3** From Halide Ion Catalysis

Ratio **17** to Digitoxigenin	1	1	1	1	1
	1	2	2	2	2
Temperature	20°	20°	40°	60°[a]	20°
Hours	72	72	24	24	14 days
α-Glucoside **6**	16.0%	23.1%	25.1%	13.3%	38.9%
β-Glucoside **3**	5.0%	8.1%	7.8%	6.9%	10.9%
Recovered Digitoxigenin	73.9%	61.5%	60.3%	76.0%	43.0%

[a] Sealed tube reaction.

Isolated yields of the α-D and β-D benzyl protected glycosides **6** and **3** are shown in Table 5. As can be seen in these data, greater stereoselectivity can be obtained with halide ion catalysis for making 1',2'-cis glycosides of the cardenolides--about 4:1 vs 3:1 for the trichloroacetaimidate approach. However, yields with the trichloroacetaimidate approach are better for these cardenolides, and reaction times much shorter. The versatility of the imidate approach is an additional factor. Trichloracetamidates can be used to synthesize all four possible digitoxigenin glycosides (Schemes 1 and 2), and in better yield.

d. Debenzylation. Debenzylation of the per-benzyl glycosides **3**, **6**, **12**, and **15** was achieved by catalytic hydrogenolysis over freshly prepared palladium on charcoal. Maximal yields for β-D **3** and α-D **6** were obtained using 20% Pd/C, hydrogenation in MeOH:EtOAc (3:1) at room temperature and atmospheric pressure for 45 min. -1 hr. Loss of the 20(22)-ene was negligible, based on UV analysis of the λ max 217 nm absorption in MeOH. Hydrogenolysis of the benzyl groups in the L-glycosides **12** and **15** required a higher percentage of palladium. We found that hydrogenolysis at room temperature with 20% Pd/C was not complete even after seven hours. However, when 40% Pd/C was used at room temperature and atmospheric pressure, hydrogenolysis was complete in 2 hours. Loss of the 20(22)-ene was again negligible.

EXPERIMENTAL

General Methods. 2,3,4,6-Tetra-O-benzyl-D-glucopyranose and L-glucopyranose were purchased from Sigma Chemical Co. All reactions were carried out by using degassed solvents under a nitrogen atmosphere. ^1H NMR and ^{13}C NMR specra were recorded with Varian FT-80 spectrometer using $CDCl_3$ solutions with Me_4Si as an internal standard or as otherwise reported. IR spectra were recorded with a Beckman Model Acculab 7 by using a thin film of the neat liquid betwen NaCl plates or KBr pellets for solid samples. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Combustion analyses were obtained for MHW-Laboratories, Phoenix, AZ. Column chromatography utilized silica gel 60 (70-230 mesh). Flash chromatography, as we have previously reported,[1] utilized silica gel (230-400 mesh), supplied by E. Merck. We used thin-layer chromatography to monitor column fractions and to establish the homogeneity of products. It was performed on EM silica gel 60F-254 plates (0.25 mm thickness). Spots were located with 2% cerric sulfate (in 2N H_2SO_4) spray.

*2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl-1-O-trichloroacetaimidate (**2α**).*[8a] To a stirred suspension of NaH (0.5 g, 10 mmol) in CH_2Cl_2 (25 mL) was added a solution of **1** (5.4 g,10 mmol) in CH_2Cl_2 (25 mL) at room temperature. The suspension was stirred for 15 min then trichloroacetonitrile (3.5 mL) was slowly added. The resultant mixture was stirred for 2 hr at room temperature and filtered through celite. Evaporation of the filtrate gave a crude oil which was purified rapidly via flash chromatography over silica gel, elution with 15% Et_2O-Pet. ether (30-60°], to yield 5.5 g (76%) of **2** as an oil: IR (NaCl) 1670 (C=N), 3325 (NH) cm^{-1}; ^1H NMR δ 6.5 (1 H, d, $J_{1'2'}$=3.5 Hz, C1'H), 8.6 (1 H, s, -C=NH).

(3β,5β,14β,17β)-3-[(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)oxy]-14-hydroxycard-20(22)-enolide (**3**). To a stirred mixture of digitoxigenin (0.75 g, 2.0 mmol) and 4A molecular sieves in CH_2Cl_2 (80 mL) was added a solution of **2** (1.8 g, 2.63 mmol) in CH_2Cl_2 (20 mL) at -30°C. The solution was stirred for 10 min after which $BF_3.Et_2O$ (0.085 g, 0.073 mL, 0.6 mmol) in CH_2Cl_2 (1.0 mL) was slowly added. The resulting solution was allowed to stir at -30°C for 3 hr and then added to an ice water slurry (200 mL). The quenched reaction was extracted with CH_2Cl_2 (2 X 100 mL).

The combined extract was washed twice with 50 mL portions of 5% aqueous $NaHCO_3$ and once with 100 mL of H_2O, dried over $MgSO_4$, and concentrated to an oil. This crude oil was purified via column chromatography on silica gel (1:10 Et_2O/CH_2Cl_2) to yield 1.16 (65%) of **3** as an amorphous powder: ^1H NMR δ 7.25 (20 H, s, Ph), 5.85 (1 H, s, C22 H), 4.45 (d, $J_{1',2'}$=7 Hz, C1'H), 4.9 (2 H, qd, $J_{21,21'}$ = 18 Hz, $J_{21,22}$=2 Hz, C21 CH_2), 0.85 (3 H, s, C18 CH_3), 0.87 (3 H, s, C19 CH_3), 4.05 (1 H, bs, C3 H); ^{13}C NMR δ 101.51 (C1'), 84.92 (C5'), 82.25 (C3'), 75.66 (C4'), 69.13 (C6'), 73.86 (C3, genin).

In addition, 0.35 g (20%) α-D-anomer **6**, (spectral data identical to those reported for **6** below) and 0.1 g (0.26 mmol) of digitoxigenin were also recovered.

(3 β,5 β,14 β,17 β)-3-[(β-D-glucopyranosyl)oxy]-14-hydroxycard-20(22)-enolide (**4**). In 20 mL of EtOAc was dissolved 0.5 g (0.55 mmol) of **3**. The solution was hydrogenated over 20% Pd/C, freshly prepared by activating 0.7 g of charcoal with 8.0 mL of 5% $PdCl_2$ in 50 mL MeOH. The suspension of Pd/C was added to the solution of **3** at room temperature and atmospheric pressure. The theoretical amount of H_2 was absorbed in 1 hr. The catalyst was removed by filtration, washed with MeOH and the solvent evaporated to afford 0.293 g of crude **4**, which was purified on a short silica gel column (1.5:10 $MeOH/CH_2Cl_2$) to yield 0.25 g (83.7%) of pure **4**. The solid was recrystallized from $EtOH/E_2O$ to afford **4** as white powder: mp 228-233°C (lit[3] 238-242°C): IR (KBr) 3300 (OH), 2940 (CH), 1730 (α,β-unsat. C=O), 1615 (C=C) cm^{-1}; ^1H NMR (MeOH-d_4) δ 0.82 (3 H, s, C18 CH_3), 0.89 (3 H, s, C19 CH_3), 4.3 (1 H, d, $J_{1',2'}$ = 7.5 Hz, C1'H), 4.04 (1 H, m, C3 H), 4.9 (2 H, qd $J_{21,21'}$= 18.0 Hz, $J_{21,22}$=2.0 Hz, C21 CH_2); UV λmax (MeOH) 217 nm (log ε 4.22), $[\alpha]_D$ = -6.30 (c = .300); $[M]_D$ = -34.97, C = -106.5.

Anal. Calcd for $C_{29}H_{44}O_9 \cdot 1\ H_2O$: C, 62.91; H, 8.18. Found: C, 62.98; H, 7.95.

2,3,4,6-Tetra-o-benzyl- β-D-glucopyranosyl-1-0-trichloracetimidate **2β**[8]. To a stirred suspension of anhydrous potassium carbonate (3.0 g, 28 mmol) in CH_2Cl_2 (20 mL) was added to a solution of **1** (3.0 g, 5.55 mmol) in CH_2Cl_2 (10 mL) at room temperature. The suspension was stirred for 20 min then trichloroacetonitrile (3.0 mL) was slowly added. The resultant mixture was stirrered for 5 hr at room temperature and filtered through celite. Evaporation of the filterate gave a crude oil which was purified rapidly via flash chromatography over silica gel (15% Et_2O-n-hexane) to yield 2.10 g (55%) of **2β** as an oil: IR (NaCl) 1670 (C=N), 3325 (NH) cm^{-1}; ^1H NMR δ 5.92 (1 H, d, $J_{1,2}$=7.0 Hz, C1' H), 8.7 (S, 1 H, NH).

(3 β,5 β,14 β,17 β)-3-[(2,3,4,6-Tetra-O-benzyl- α-D-glucopyranosyl)oxy]-14-hydroxycard-20(22)-enolide (**6**) **a. From imidate 2β.** To a stirred mixture of digitoxigenin (1.5 g, 4.0 mmol) and 4Å molecular seives in CH_2Cl_2 (70 mL) was added a solution of **2β** (2.1 g, 3.06 mmol) in CH_2Cl_2 (20 mL) at -10°C. The solution was stirred for 15 min after which TMS-OTf (0.25 mL, 1.32 mmol) in CH_2Cl_2 (2 mL) was slowly added. The resulting solution was allowed to stir at-10°C for 15 min and at 0°C for an additional 15 min. The reaction mixture was added to ice H_2O (200 mL). The quenched reaction mixture was extracted with CH_2Cl_2 (2 X 100 mL). The combined extract was washed twice with 50 mL portions of 5% aqueous $NaHCO_3$ and once with 100 mL of H_2O, dried over $MgSO_4$, and concentrated to an oil. The crude oil was purified by flash chromatography on silica gel (10% Et_2O-CH_2Cl_2) to yield 1.03 g (58%) of **6** as amorphous powder. In addition 0.32 g (19%) of β-D anomer **3**. Spectral data were identical to those reported for **6** and **3** below. Digitoxigenin, (0.12 g (0.3 mmol), was also recovered. **b. By halide ion catalysis[9] from bromide 17.** In 40 ml of CH_2Cl_2 saturated with HBr was dissolved 0.69 g (1 mmol) of 1-O-(p-nitrobenzoyl)-2,3,4,6-tetra-O-benzyl-α-D-glucopyranose.[19] As previously reported,[20] the solution was kept at room temp for 2.5 h, the precipitated p-nitrobenzoic acid removed by filtration, and the solvent evaporated to afford 0.63 g of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide (**17**) as a light yellow oil. The product was then dissolved in CH_2Cl_2 along with 210 mg (1 mmol) of tetraethylammonium bromide, 129 mg (1 mmol) of diisopropylethylamine and 374 mg (1 mmol) or 187 mg (0.5 mmol) of digitoxigenin. The solution was then stirred at 20°, 40°, or 60° (in a sealed tube) for periods of up to 14 days (see Table 5). The reaction mixture was poured into a mixture of 1336 mg (8 mmol) of silver acetate, 240 mg (4 mmol) of acetic acid, and 204 mg (2 mmol) of acetic anhydride, and stirred in the dark for 1 h. The silver salts were filtered, washed with CH_2Cl_2, and the combined CH_2CH_2 solutions washed twice with 5 ml of water, and the water layer back-extracted twice with 5 ml of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over K_2CO_3, and solvent evaporated. To the residue was added 20 ml of dry benzene, and the solvent evaporated. The benzene addition was repeated twice to remove acetic acid. The resulting crude mixture was separated using flash chromatography (1:9 MeOH and CH_2Cl_2 followed by 3:10:87 MeOH, CH_2CN, and CH_2Cl_2) to afford α-D **6** β-D **3**, and recovered digitoxigenin in isolated yields shown in Table 5.

Diphenyl-ketene-p-tolylimine was prepared following the method of Stevens and Singhal[18] with little modification. However we found that substituting florosil for alumina gives better yields.

2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl-1-O-diphenyl-ketene-p-tolylimidate (**5**).[8a] To a stirred suspension of NaH (4.8 g, 0.2 mol) in CH_2Cl_2 (10 mL) was added a solution of **1** (2.7 g, 5 mmol) in CH_2Cl_2 (25 mL) at room temperature. The suspension was stirred for 20 min then a solution of diphenyl-ketene-p-tolylimine (1.4 g, 5 mmol) in CH_2Cl_2 (10 mL) was slowly added. The mixture was stirred for 35 h at room temperature and filtered through celite. Evaporation of filtrate gave an orange-brown oil which was purified on a short basic alumina column (1:20 EtOAc/n-hexane) to yield 3.0 g (73%) of **5** as a yellow oil : IR (NaCl) 1670 (C=N) cm^{-1}; ^1H NMR δ 6.11 (1 H, d, $J_{1,2}$=7 Hz, C1'H), 5.2 (1 H, s, Ph_2-CH-).

(3β,5β,14β,17β)-3-[(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)oxy]-14-hydroxycard-20(22)-enolide(**6**) from tolylimidate **5**. To a well stirred mixture of digitoxigenin (0.25 g, 0.66 mmol), 4Å molecular sieves and pyridinium-p-toluene sulfonate (0.17 g, 0.66 mmole) in CH_2Cl_2 (50 mL) at room temperature was added **5** (0.825 g, 1 mmol) in CH_2Cl_2 (20 mL). The resultant mixture was stirred for 96 hr at room temperature, and the solvent was evaporated to dryness. The residue was dissolved in Et_2O, filtered and the filtrate was washed with 100 mL of saturated aqueous NaCl, dried and evaporated to an oil. The crude oil was purified via flash chromatography on silica gel

(10% Et_2O-CH_2Cl_2) to yield 0.11 g (18.36%) of **6** as an oil: ^1H NMR: δ 7.25 (20 H, s, Ph), 5.8 (1H, s, C22 H), 4.5 (1 H, d, $J_{1',2'}$=3.0 Hz, C1' H), 4.8 (2H, qd, $J_{21,21'}$=18 Hz, $J_{21,22}$=1.5 Hz, C21 CH_2), 0.82 (3 H, s, C18 CH_3), 0.9 (3 H, s, C19 CH_3), 2.65 (1 H, d, J=8 Hz, C17 H); ^{13}C NMR δ 95.01 (C1'), 81.96 (C3') 80.49 (C2'), 78.18 (C5'), 75.57 (C4'), 68.95 (C6'), 70.54 (C3).

In addition, 13 mg (2.16%) of β-D-anomer **3** (spectral data identical to those reported for **3** above) and 0.16 g of digitoxigenin were also recovered.

(3β,5β,14β,17β)-3-(α-D-glucopyranosyl)oxy]-14-hydroxycard-20(22)-enolide (**7**). In 10 mL of EtOAc was dissolved 0.1 g (0.11 mmol) of **6**. The solution was hydrogenated over 20% Pd/C (freshly prepared by activating 0.2 g charcoal with 2.3 mL 5% $PdCl_2$ in 25 mL MeOH]. The activated charcoal was transferred with 50 mL MeOH to the solution of **6** at room temperature and atmospheric pressure. The theoretical amount of H_2 was absorbed in 45 min. The catalyst was removed by filtration, washed with MeOH and the solvent evaporated to afford 68 mg of crude **7**, which was purified on short silica gel column (1.5:10 MeOH/CH_2Cl_2) to yield 55 mg (84%) of pure **7**. The solid was recrystalized from MeOH/Et_2O to afford **7** as white powder: mp 230-233°, IR (KBr) 3300 (OH), 2945 (CH), 1750 α,β-unsat. C=O), 1615 (C=C) cm^{-1}; ^1H NMR (MeOH-d_4): δ 0.98 (6 H, s, C18 and C19 CH_3), 4.13 (1 H, d, $J_{1',2'}$=3.5 Hz, C1'H), 5.0 (2 H, qd, $J_{21,21'}$=18 Hz, $J_{21,22}$=1.5 Hz, (C21 CH_2), UV λmax (MeOH) 217 nM (log ε 4.18); $[\alpha]_D$ (MeOH) + 40.33 (c = .300); $[M]_D$ = + 233.72, C = 162.19.

Anal. Calcd. for $C_{29}H_{44}O_9.1H_2O$:C, 62.91; H, 8.18. Found: C, 63.09; H, 8.24.

2,3,4,6-Tetra-O-benzyl-α,β-L-glucopyranoside (**10**). Methyl L-glucopyranose **8** was prepared from L-glucopyranose (5.0 g, 0.027 mol) following the method of Levene and Muskat[21] as a white crystalline solid, mp 106-107°. ^1H NMR (MeOH-d_4) δ 4.25 (1 H, d, $J_{1,2}$ = 8 Hz, C1'H), 3.51 (3 H, s, C1' OMe).

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.30, H, 7.27. Found: C, 43.19; H, 7.44.

The methyl α,β-L-glucopyranoside was benzylated following the method of Iwashige and Saeki[22] using NaH/benzyl chloride/DMSO at room temperature for 20 h. After usual work up the crude **9** was purified via column chromatography on silica gel (1:10 EtOAc-C_6H_6). The pure **9** was hydrolyzed with 80% HOAc-2N HCl[23] at 90°C for 10 h. After usual work up the crude **10** was purified via column chromatography on silica gel (2:10 EtOAc/C_6H_6). Recrystallization of crude **10** from MeOH gave 9.8 g (65% overall) of **10** as a white crystalline solid; mp 154-156°C (mixed anomers), ^1H NMR: δ 7.2 (20 H, s, 4 Ph), 5.1 (1 H, d, $J_{1',2'}$=4 Hz, C1'H), 1.6 (1 H, s, C1' OH).

Anal. Calcd. for $C_{34}H_{36}O_6$: C, 75.63; H, 6.71. Found: C, 75.72; H, 6.60.

2,3,4,6-Tetra-O-benzyl-α-L-glucopyranosyl-1-O-trichloroacetamidate (**11α**). To a stirred suspension of NaH (0.5 g, 10 mmol) and **10** (5.4 g, 10 mmol) in CH_2Cl_2 (50 mL) was added trichloroacetonitrile (3.5 mL) over a period of 5 min. The resultant mixture was stirred for 2 hr at room temperature and filtered through celite. Evaporation of filtrate gave a crude oil which was purified rapidly via flash chromatography over silica gel (15% Et_2O-n-hexane) to afford **11** as a homogenous oil, 5.8 g (85%): IR (NaCl) 1670 (C=N), 3325 (NH) cm^{-1}; ^1H NMR δ 6.5 (1 H, d, $J_{1',2'}$=3.5 Hz, C1'H), 8.67 (1 H, s, -C=NH).

(3β,5β,14β,17β)-3-[β-L-glucopyranosyl)oxy]-14-hydroxycard-20(22)-enolide (**12**). To a stirred mixture of **11** (1.8 g, 2.63 mmol), digitoxigenin (0.75 g, 2.0 mmol) and ca. 25 ml of molecular sives (4Å) in CH_2Cl_2 (100 mL) at -30°C, a solution of $BF_3.Et_2O$ (85 mg, 0.073 mL, 0.6 mmol) in CH_2Cl_2 (1.0 mL) was added slowly. The resultant solution was allowed to stir at -30°C for 3 h and then added to ice H_2O (200 mL). The quenched reaction was extracted with CH_2cl_2 (2 X 100 mL). The combined extract was washed twice with 50% aqueous $NaHCO_3$ and once with 100 mL of H_2O, dried over $MgSO_4$ and evaporated to an oil. The crude oil was purified via flash chromatography (CH_2Cl_2, 5% Et_2O-CH_2Cl_2, 7.5% Et_2O-CH_2Cl_2) to yield 1.10 g (61.2%) of **12** as an amorphous powder: ^1H NMR δ 7.25 (20 H, s, Ph), 5.85 (1 H, s, C22 H), 4.8 (qd,$J_{21,21'}$=17 Hz, $J_{21,22}$=2.0 Hz, 2 H, C21 CH_2), 4.02 (d, J=8 Hz, 1 H, C-3 H), 2.72 (d, J=7 Hz, 1 H, C17 H), 0.82 (s, 3 H, C18 CH_3), 0.9 (s, 3 H, C19 CH_3); ^{13}C NMR δ 101.63 (C1'), 69.25 (C6'), 73.99 (C3).

In addition, 0.34 g (19.26%) of α-L-anomer **15**, (spectral data identical to those reported for **15** below) and 1.11 g of digitoxigenin were also recovered.

(3β,5β,14β,17β)-3-[[β-L-glucopyranosyl)oxy]-14-hydroxycard-20(22)-enolide (**13**) In 40 mL of EtOAc was dissolved 1.0 g (0.11 mmol) of **12**. The solution was hydrogenated over 40% Pd/C (freshly prepared by activating 1.4 g charcoal with 32 mL of 5% $PdCl_2$ in 100 mL MeOH). The activated charcoal was transferred with 100 mL MeOH to the solution of **12** at room temperature and atmospheric pressure. The theoretical amount of H_2 was absorbed in 2 h. The catalyst was removed by filtration, washed with MeOH and the solvent was evaporated to afford 0.61 g of **13** which was purified by a short silica gel column (1.5:10 MeOH/CH_2Cl_2) to yield 0.523 g (87.5%) of pure **13**. The solid was recrystallized from EtOH/E_2O to afford **13** as white flakes: mp 234-235°C; IR (KBr) 3360 (OH), 1745 (α,β C=0), 1020 (C=C); ^1H NMR (MeOH-d_4) δ 5.82 (1 H, s, C11 H), 4.95 (2 H, qd $J_{21,21'}$=18 Hz, $J_{21,22}$=2 Hz, C-21 CH_2), 4.75 (s, OH) 4.0 (1 H, d, $J_{1',2'}$=8 Hz, C-1'H), 2.8 (d, J=8 Hz, C-17 H), 0.9 (s, 3 H, C18 CH_3), 0.98 (s, 3 H, C19 CH_3); UV λmax (MeOH) 217 nm (log ε 4.21); $[\alpha]_D$ = +16.33 (c = .300); $[M]_D$ = +90.66, C = +19.07.

Anal. Calcd. for $C_{29}H_{44}O_9$. $1H_2O$: C, 62.91; H, 8.18. Found: C, 63.07; H, 8.01.

2,3,4,6-Tetra-O-benzyl-β-L-glucopyranosyl-1-O-trichloroacetimidate (**11β**). To a stirred suspension of anhydrous potassium carbonate (3.0 g, 28 mmol) in CH_2Cl_2 (20 mL) was added to a solution of **10** (3.0 g, 5.55 mmol) in CH_2Cl_2 (10 mL) at room temperature. The suspension was stirred for zomin, then trichloroacetonitrile (3.0 mL) was slowly added. The resultant mixture was stirred for six hr at room temperature and filtered through celite. Evaporation of filtrate gave a crude oil which was purified rapidly via flash chromatography over silica gel (15% Et_2O-n-hexane) to yield 2.18 g (56%) of **11β** as an oil: IR (NaCl) 1672 (C=N), 3325 (NH) cm^{-1}; ^1H NMR: δ 6.10 (1 H, d, $J_{1,2}$ = 7.5 Hz), 8.68 (1 H, s, NH).

(3β,5β,14β,17β)-3-[[2,3,4,6-Tetra-O-benzyl-α-L-glucopyranosyl)oxy]-14-hydroxycard-20(22)-

enolide (15). To a stirred mixture of digitoxigenin (1.5 g, 4.0 mmol) and 4Å molecular seives in CH_2Cl_2 (70 mL) was added a solution of **11β** (2.1 g, 3.06 mmol) in CH_2Cl_2 (20 mL) at -10°C. The solution was stirred for 15 min after which TMS-OTf (0.25 mL, 1.32 mmol) in CH_2Cl_2 (2 mL) was slowly added. The resulting solution was allowed to stir at -10°C for 15 min and at 0°C for additional 20 min. The reaction mixture was added to ice-H_2O-5% aqueous $NaHCO_3$ (1:1, 200 mL). The quenched reaction mixture was extracted with CH_2Cl_2 (2 X 100 mL). The combined extract was washed twice with 50 mL portions of H_2O, dried over $MgSO_4$, and concentrated to an oil. The crude oil was purified by flash chromatography on silica gel (10% Et_2O-CH_2Cl_2) to yield 0.906 g (51%) of **15** as oil. In addition 0.35 g (20%) of β-D anomer **12** was isolated. Spectral data were identical to those reported for **15** and **12** below. Digitoxigenin (0.15 g) was also recovered.

2,3,4,6-Tetra-O-benzyl-β-L-glucopyranosyl-1-O-diphenyl-ketene-p-tolylimidate **(14).** To a stirred suspension of NaH (1.2 g, 0.05 mol) in CH_2Cl_2 (10 mL) was added a solution of **10** (1.36 g, 2.5 mmol) in CH_2Cl_2 (20 mL) at room temperature. The suspension was stirred for 20 min then a solution of diphenyl-ketene-p-tolylimine (1.06 g, 3.75 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred for 20 h at room temperature and filtered through celite. Evaporation of filtrate gave a reddish brown oil which was purified on a short basic alumina column (1:20 C_6H_6/n-hexane) to yield 1.6 g (77%) of pure **14** as a homogenous oil: IR (NaCl) 1672 (C=N) cm^{-1}; ^1H NMR δ 6.13 (1 H, d, $J_{1',2'}$= 7.5 Hz C1'H), 5.15 (1 H, s, Ph_2-CH-).

(3β,5β,14β,17β)-3-[(2,3,4,6-Tetra-O-benzyl-α-L-glucopyranosyl)oxy]-14-hydroxycard-20(22)-enolide (15). (i) Catalysis with pyridinium-p-toluenesulfonate: A mixture of digitoxigenin (0.675 g, 1.8 mmol), 10 ml of molecular sieves (4Å) and pyridinium-p-toluene sulfonate (0.5 g, 2.0 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature. After 15 min a solution of **14** (1.6 g, 1.0 mmol) was added in CH_2Cl_2 (10 mL) dropwise and the mixture was stirred for 96 h. The reaction mixture was diluted with Et_2O (100 ml), washed with 100 mL of 50% aqueous NaCl, dried and evaporated to an oil. The crude oil was purified via flash chromatography on silica gel (10% Et_2O-CH_2Cl_2) to yield 0.257 g (15.6%) of **15** as amorphous powder: ^1H NMR δ 7.2 (20 H, s, Ph), 5.84 (s, 1 H, C22 H), 4.1 (d, J=8 Hz, 1 H, C17 H), 4.52 (d, $J_{1',2'}$ = 4 Hz, 1 H, C1'H), 4.9 (2 H, qd $J_{21,21'}$=18 Hz, $J_{21,22}$=2.5 Hz, C21 CH_2), 0.8 (s, 3 H, C18 CH_3), 0.89 (3 H, s, C19 CH_3) 2.72 (d, J=8 Hz, 1 H, C-17 H), 4.0 (d, J=8 Hz, 1 H, C3 H); ^{13}C NMR δ 95.13 (C1'), 73.46 (C2'), 81.95 (C3'), 75.48 (C-4'), 70.39 (C6).

In addition, 0.3 g of digitoxigenin was also recovered.

(ii) catalysis by zinc triflate: To a well stirred mixture of digitoxigenin (0.75 g, 2.0 mmol), 4Å molecular sieves and zinc triflate[17a] (1.1 g, 3.0 mmol) in CH_2Cl_2 (80 mL) at 0°C was added **14** (2.4 g, 3.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 2 h at 0°C then 15 hr at room temperature, and neutralized with triethylamine. After insoluble materials were removed by filtration, the filtrate was evaporated and the residue was purified via flash chromatography on silica gel (CH_2Cl_2, 5% Et_2O-CH_2Cl_2, 7.5% Et_2O-CH_2Cl_2) to yield 0.441 g (25%) of **15** as an amorphous powder.

In addition, 0.7 g (39%) of β-L-anomer **12** (spectral data identical to those reported for **12** above) and 0.2 g of digitoxigenin were also recovered.

(3β,5β,14β,17β)-3-[(α-L-glucopyranosyl)oxy]-14-hydroxycard-20(22)-enolide **(16).** In 20 mL of EtOAc was dissolved 390 mg (0.43 mmol) of **15**. The solution was hydrogenated over 40% Pd/C (freshly prepared by activating 0.6 g charcoal with 15.0 mL 5% $PdCl_2$ in 50 mL MeOH). The activated charcoal was transferred with 50 mL MeOH to the solution of **15** at room temperature and atmospheric pressure. The theoretical amount of H_2 was absorbed in 2 hr. The catalyst was removed by filtration, washed with MeOH and the solvent was evaporated to afford 0.220 g of **16** which was purified by short silica gel column (1.5:10 MeOH/CH_2Cl_2) to yield 0.178 g (76.39%) of pure **16**. The solid was recrystallized from EtOH/Et_2O to afford **16** as white flakes: mp 208-211°C; IR (KBr) 3360 (OH), 1740 (α,β unsatd. C=O), 1020 (C=C)CM^{-1}; ^1H NMR (MeOH-d_4) δ 5.82 (1 H, s, C22 H), 4.75 (1 H, s,), 4.3 (1 H, d, $J_{1',2'}$=4.0 Hz, C1'H), 2.8 (1 h, d, J-8 Hz, C17 H), 0.98 (s, 3 H, C19 CH_3), 0.9 (s, 3 H, C18 CH_3), 4.95 (2 H, qd, $J_{21,21}$=18.0 Hz, $J_{21,22}$=2.0 Hz, C 21 CH); UV max (MeOH) 217 nm (log ε 4.2); $[\alpha]_D$ =-24.33 (c = .300); $[M]_D$ = 134.97, C = -206.50.

Anal Calcd. for $C_{29}H_{44}O_9.1\ H_2O$: C, 62.91; H, 8.18. Found: C, 62.94; H, 8.01.

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