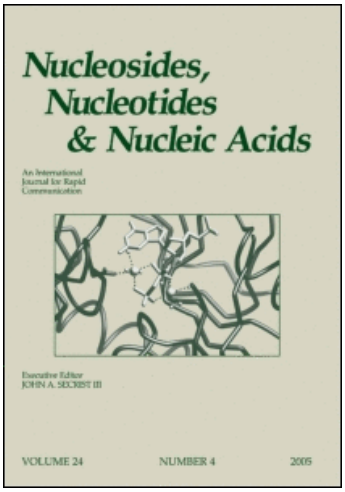

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Improved Synthesis of 2',3'-Dideoxycytidine (d2C) and Its Correlated Nucleoside Analogues

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IMPROVED SYNTHESIS OF 2',3'-DIDEOXYCYTIDINE (d2C) AND ITS CORRELATED NUCLEOSIDE ANALOGUES

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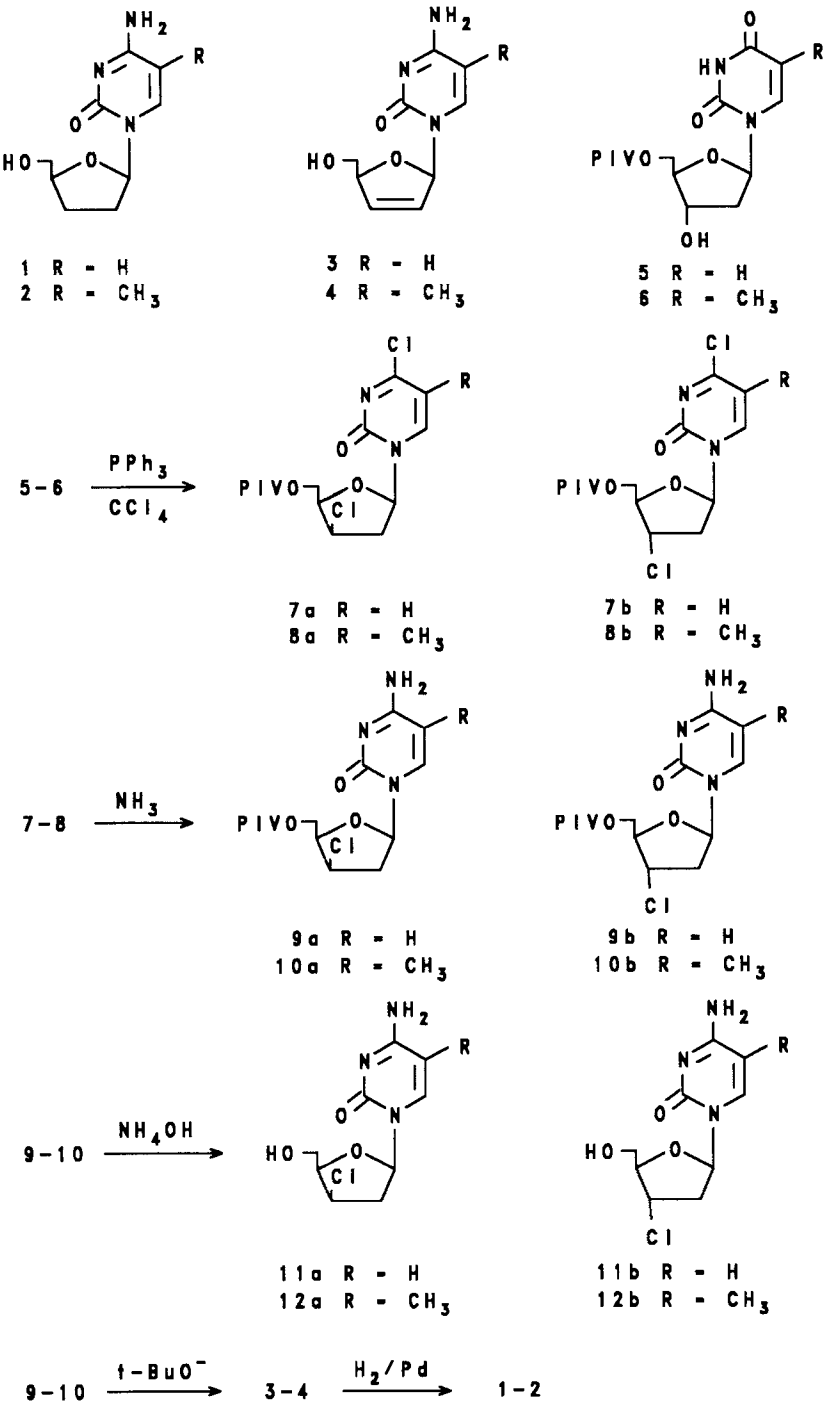
ABSTRACT. 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydrocytidine (d2C and d4C) have been synthesized in good yields from 2'-deoxyuridine via dichlorinated derivatives **7a-b**. The same synthetic strategy was used in the synthesis of $d2C^{Me}$ and $d4C^{Me}$ from thymidine. Following this method the evaluable 3'-chloro-2'-deoxycytidine derivatives **9 - 12** can easily be obtained.

Several pyrimidine 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydronucleoside analogues (d2N and d4N) have been recognized as potent and selective inhibitors of the replication of the human immunodeficiency virus (HIV)[1]. Among these, 3'-azido-3'-deoxythymidine[2] (AZT), 2',3'-dideoxycytidine[3] (d2C) and 3'-deoxy-2',3'-didehydrothymidine[4] (d4T) display a reasonably high chemotherapeutic activity.

2',3'-Dideoxynucleosides are generally synthesized following two principal routes; the first one[5] uses, as starting material, the intact nucleoside which is converted into the target compound by a number of transformations. In the other one[6], an appropriate protected form of d2- or d4sugar is coupled with the



different nucleobases to give generally a mixture of α and β anomers.

In this paper we describe an easy and profitable synthesis of d2- d4C (**1**, **3**) and d2- $d4C^{Me}$ (**2**, **4**) and of the 3'-chlorinated analogues **11-12** starting from 2'-deoxyuridine and thymidine respectively.

Some previous synthetic approaches for d2- d4C required the protection of the exocyclic amino group of the base, followed by deoxygenation of the appropriately derivatized sugar moiety. On the contrary, in alternative strategies, the deoxygenation of the sugar was followed by the introduction of the amino group on the base; this last step involved an additional reaction to activate the C-4 position of the pyrimidine ring to the nucleophilic displacement by ammonia.

In previous papers[7] we reported an easy and useful way to chlorinate the C-4 position of the pyrimidine base moiety using the adduct of triphenylphosphine (PPh_3) and CCl_4. As supported by many reports[8], this reagent is able to halogenate various substrates including nucleoside hydroxy functions[9]. In the present synthetic approach the use of such adduct affords the chlorination of both the C-4 and the C-3' positions in the same step, so that only one reaction is needed to activate the nucleobase and to functionalize the sugar moiety. As a starting product to obtain the dichlorinated derivatives **7-8**, we used the 5'-O-pivaloylderivatives **5-6** synthesized according to a previously reported procedure[10] in 90 and 94 % yield respectively. These products were allowed to react with a solution of PPh_3 (3.5 eq.) in CCl_4 or CCl_4/dimethylformamide (2:1, v/v), thus obtaining the following results. The reaction in dimethylformamide/CCl_4 (80 °C) led to the very rapid (15 min) and total chlorination of the 3'-position followed by a slower (3-5 hours) base halogenation, generally giving low yields (ca. 20%) of the dichlorinated products **7a** or **8a** with only the threo configuration[11]. On the other hand, when we performed the

TABLE 1

^{1}H NMR (270 MHz) Chemical shifts (J in Hz) of compounds **7-9**.

POSITION	7a	7b	8a	8b	9a	9b
H-5	6.38 d (7.1)	6.30 d (7.1)			5.89 d (7.5)	5.73 (7.4)
H-6	8.08 d (7.1)	7.94 d (7.1)	7.93 s	7.83 s	7.68 d (7.5)	7.62 d (7.4)
CH_3			2.11 s	2.14 s		
H-1'	5.94 dd (7.5,1.6)	6.03 dd (5.5,5.4)	5.95 dd (7.4,1.5)	6.15 dd (5.5,5.5)	6.09 dd (7.6,2.6)	6.20 dd (5.8,5.8)
H-2' a	3.01 ddd	2.90 ddd	3.02 ddd	2.98 ddd	2.99 ddd	2.81 ddd
b	2.57 ddd	2.49 ddd	2.53 ddd	2.50 ddd	2.40 ddd	2.52 ddd
H-3'	4.99 m	4.45 m	4.52 m	4.42 m	4.48 m	4.36 **
H-4'	4.44 m	4.39 m	4.42 m	4.26 m	4.31 m	4.25 m
H-5' a	4.48 dd	4.35 *	4.52 dd	4.40 *	4.35 *	4.36 *
b	4.29 dd		4.30 dd			
$(CH_3)_3$	1.13 s	1.13 s	1.14 s	1.13 s	1.13 s	1.22 s

s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, m = multiplet;* : AB part of an ABX system; ** : submerged by H_2-5' signal. The spectra were carried out in $CDCl_3$.

chlorination in CCl_4 (3-5 hours, reflux) very high yields of the mixture of the dichlorinated products **7a-b** (90 %) and **8a-b** (87 %) were obtained, observing detectable amounts of erythro products (**7b** 6 %, **8b** 30 %). The presence of erythro products can be related both to the different nucleophilicity of chlorine ion and formation rate of O^2,3'-anhydro intermediate[9] (precursor of the erythro forms) with varying solvent system. Analogously the different yields of the erythro products in uridine and thymidine derivatives can be explained as a

TABLE 1 (continued)

^{1}H NMR (270 MHz) Chemical shifts (J in Hz) of compounds **10-12**

POSITION	10a	10b	11a	11b	12a	12b
H-5			5.90 d (7.5)	5.89 d (7.4)		
H-6	7.52 s	7.29 s	7.92 d (7.5)	8.02 d (7.4)	7.76 s	7.86 s
CH_3	1.91 s	1.90 s			1.98 s	1.95 s
H-1'	6.14 dd (7.2,1.8)	6.21 dd (6.0,6.0)	6.04 dd (7.6,2.4)	6.26 dd (5.8,5.8)	6.07 dd (7.6,2.6)	6.27 dd (6.2,6.2)
H-2'a	3.01 ddd	2.74 ddd	3.06 ddd	2.59 m	3.07 ddd	2.59 m
b	2.38 ddd	2.44 ddd	2.39 ddd		2.36 ddd	
H-3'	4.51 m	4.33 **	4.67 m	4.52 m	4.67 m	4.53 m
H-4'	4.32 m	4.27 m	4.29 m	4.16 m	4.29 m	4.15 m
H-5'a	4.42 *	4.33 *	3.95 *	3.85 *	3.94 *	3.83 *
b						
$(CH_3)_3$	1.17 s	1.20 s				

s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, m = multiplet;* : AB part of an ABX system; ** : submerged by H_2-5' signal. The spectra were carried out in $CDCl_3$ for compounds 10 and in CD_3OD for 11-12.

consequence of the different reactivity, for the two bases, in the formation of O^2,3'-anhydro product in such conditions.

After purification of the dichlorinated products (**7**, **8**) or more conveniently, directly on the concentrated reaction mixture, the chlorine atom of the base was displaced by an amino group using a satured solution of ammonia in $CHCl_3$ thus obtaining the cytidine derivatives **9a-b** and **10a-b** in 93-98 % yields[12]. The successive treatment of **9a-b** with conc. aqueous

TABLE 2

^{13}C NMR (67.9 Mhz), Chemical shifts of compounds **7-9**.

POSITION	7a	7b	8a	8b	9a	9b
C-2	153.2 s	153.0 s	153.0 s	152.7 s	155.8 s	155.2 s
C-4	166.9 s	166.9 s	167.8 s	168.2 s	166.0 s	165.6 s
C-5	104.8 d	104.9 d	112.1 s	112.6 s	94.5 d	94.1 d
C-6	143.9 d	144.1 d	141.6 d	140.6 d	140.1 d	140.5 d
CH_3			15.6 q	15.7 q		
C-1'	87.6 d	88.5 d	87.0 d	87.4 d	85.7 d	86.4 d
C-2'	42.8 t	42.6 t	42.7 t	42.4 t	42.9 t	42.4 t
C-3'	57.3 d	53.9 d	57.1 d	53.8 d	57.4 d	53.7 d
C-4'	82.3 d	85.9 d	81.9 d	86.0 d	80.5 d	85.1 d
C-5'	63.0 t	63.0 t	62,6 t	62.6 t	63.5 t	62.7 t
C=O	178.0 s	177.9 s	177.8 s	177.8 s	177.8 s	177.8 s
$(CH_3)_3\underline{C}$	38.7 s	38.8 s	38.5 s	38.8 s	38.5 s	40.0 s
$(\underline{C}H_3)_3C$	27.0 q	27.0 q	26.9 q	27.1 q	27.9 q	27.1 q

s = singlet, d = doublet, t = triplet, q = quartet in the off resonance spectra. The spectra were carried out in $CDCl_3$.

ammonia furnished the 3'-chloro-2'-deoxycytidine derivatives **11a-b** (95 % for both) which were successively purified by silica gel chromatography. Alternatively, treating **9a-b** with t-BuO^-/t-BuOH we observed, for both the 3'-chloro isomers, the complete conversion into the 2',3'-unsatured product (d4C, **3**, 85 %). Analogous results were found for the same reactions on compounds **10a-b** thus obtaining the 3'-chloro-5-methyl-2'-deoxycytidine derivatives **12a-b** (94 % and 92 % respectively) or $d4C^{Me}$ (**4**, 87 %).

Finally hydrogenation of d4C and $d4C^{Me}$, at room temperature and atmospheric pressure over 10 % palladium on charcoal, gave the desired products d2C (**1**, 93 %) and $d2C^{Me}$ (**2**, 95 %). Starting

TABLE 2 (continued)

^{13}C NMR (67.9 Mhz), Chemical shifts of compounds **10-12**.

POSITION	10a	10b	11a	11b	12a	12b
C-2	155.8 s	155.4 s	158.5 s	158.5 s	158.5 s	158.6 s
C-4	165.7 s	165.7 s	168.1 s	168.1 s	167.8 s	167.8 s
C-5	101.3 s	101.7 s	95.6 d	96.3 d	103.9 s	104.7 s
C-6	137.8 d	137.3 d	142.5 d	142.9 d	140.0 d	140.4 d
CH_3	13.1 q	13.0 q			13.8 q	13.7 q
C-1'	85.4 d	86.0 d	87.7 d	89.9 d	87.4 d	89.9 d
C-2'	43.0 t	42.1 t	44.7 t	43.5 t	44.8 t	43.6 t
C-3'	57.5 d	54.3 d	59.6 d	56.0 d	59.7 d	56.1 d
C-4'	80.3 d	84.9 d	85.7 d	87.5 d	85.5 d	87.4 d
C-5'	63.1 t	62.9 t	62.9 t	61.9 t	63.0 t	62.0 t
C=O	177.9 s	177.7 s				
$(CH_3)_3\underline{C}$	38.6 s	38.7 s				
$(\underline{C}H_3)_3C$	27.0 q	27.1 q				

s = singlet, d = doublet, t = triplet, q = quartet in the off resonance spectra. The spectra were carried out in $CDCl_3$ for compounds 10 and in CD_3OD for 11-12.

from 2'-deoxyuridine and thymidine the overall yields obtained for d2C and $d2C^{Me}$ were 60 and 64 % respectively.

The structures of the nucleosides were confirmed by spectroscopic data [^1H (table 1), ^{13}C (table 2) NMR, UV and FAB MS] which agreed, for known compounds, with the literature values[13].

EXPERIMENTAL

General procedure.

The ^1H and ^{13}C spectra were recorded with a Bruker WM 270 instrument. UV spectra were taken on a Perkin-Elmer lambda 7

spectrophotometer. FAB mass spectra (positive) were determined with a double-focusing mass spectrometer (ZAB 2SE). TLC were carried out on silica gel plates (Merck, 0.25 and 0.5 mm Kieselgel 60 F254). The products were visualized by UV light at 254 nm. Column chromatographies were performed on silica gel (Merck, Kieselgel 60, 0.063-0.200 mm). Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Optical rotation were measured with a Perkin-Elmer 141 polarimeter at 25 °C.

Reaction of Nucleosides 5 - 6 with PPh_3/CCl_4; General Procedure; Products 7a-b, 8a-b.

A mixture of **5** (1 mmol, 312 mg) or **6** (1 mmol, 326 mg) and triphenylphosphine (3.5 mmol, 917 mg) was suspended in dry CCl_4 (8 ml) and kept at reflux. The reaction was monitored by TLC (eluent $CHCl_3$/ethylacetate 6:4). After 2 h we observed the complete conversion of the starting product into the 3'-chloroderivatives (Rf 0.3-0.4) which gave, after additional 2-3 h, the dichlorinated products **7a** (Rf 0.6) and **7b** (Rf 0.7) or **8a** (Rf 0.75) and **8b** (Rf 0.85). The final suspension was filtered and the concentrated filtrate was applied to a silica gel column (70 cm x 1.5 cm i.d.). Elution of the column with $CHCl_3$/ethylacetate (8:2, v/v) afforded the pure products **7a** (293 mg) and **7b** (20 mg) or **8a** (205 mg) and **8b** (110 mg).

7a: UV ($CHCl_3$) λ_{max} 307 nm (5600); $[\alpha]_D$ = +129.2 (c = 0.42, $CHCl_3$) m.p.(n-hexane/CCl_4) 119-120 °C. **7b**: UV ($CHCl_3$) λ_{max} 307 nm (5600); $[\alpha]_D$ = +33.3 (c = 0.09, $CHCl_3$). **8a**: UV ($CHCl_3$) λ_{max} 317 nm (6400); $[\alpha]_D$ = +93.9 (c = 0.55, $CHCl_3$); m.p. (n-hexane/benzene) 120-121°C. **8b**: UV ($CHCl_3$) λ_{max} 317 nm (6400); $[\alpha]_D$ = +100.8 (c = 0.20, $CHCl_3$); m.p.(n-hexane/CCl_4) 132-134 °C; MS (FAB): **7a** and **7b** m/z 349 (MH^+, $2^{35}Cl$); **8a** and **8b** m/z 363 (MH^+,2 ^{35}Cl). The attempts to crystallize compound **7b** were unsuccessful.

Reaction of Nucleosides 7a-b and 8a-b with NH_3; General Procedure; Products 9a-b and 10a-b.

7a (1 mmol, 348 mg) or **7b** (0.1 mmol,35 mg) [**8a** (0.5 mmol, 181 mg) or **8b** (0.4 mmol, 145 mg)] was reacted with a saturated solution NH_3 in $CHCl_3$ (20 ml/mmol of nucleoside) at room temp. for 48 h. The final mixture was dried in vacuo and the product was purified on a silica gel column (30 cm x 1.5 cm i.d.) eluted

with increasing amounts of CH_3OH in $CHCl_3$. The fractions eluted with $CHCl_3/CH_3OH$ (9:1, v/v) afforded the product **9a** (322 mg) or **9b** (31 mg) [**10a** (168 mg) or **10b** (133 mg)]. More conveniently the reaction with ammonia could be performed directly on the dried final chlorination mixture (48 h, room temp.). The purification on silica gel column (eluted as above) allowed the recovery of the mixture of the 3'-chloro epimers **9a-b** (**10a-b**) which could be separated by TLC (silica gel, 0.5 mm, eluent acetone/H_2O, 10:0.1, v/v).

9a: UV (CH_3OH) λ_{max} 270 nm (7000); $[\alpha]_D$ = +77.5 (c = 0.22, $CHCl_3$); m.p. (benzene) 213-214 °C. **9b:** UV (CH_3OH) λ_{max} 269 nm (7000); $[\alpha]_D$ = +80.2 (c = 0.12, $CHCl_3$); m.p. (benzene) 172-174 °C. **10a:** UV (CH_3OH) λ_{max} 283 nm 9500), 240 (9700); $[\alpha]_D$ = +56.30 (c = 0.15, $CHCl_3$); m.p. (benzene) 111-112 °C. **10b:** UV (CH_3OH) λ_{max} 283 nm (9500), 240 (9700); $[\alpha]_D$ = +57.9 (c = 0.10, $CHCl_3$); m.p.(benzene) 92-94°C. MS(FAB): **9a** and **9b** m/z 330 (MH^+, ^{35}Cl); **10a** and **10b** m/z 344 (MH^+, ^{35}Cl).

Reaction of Nucleosides 9a-b and 10a-b with NH_4OH; General Procedure; Products 11a-b and 12a-b.

9a (1 mmol, 329 mg) or **9b** (0.3 mmol, 99 mg) [**10a** or **10b** (0.5 mmol, 171 mg)] was deacylated by treatment with concentrated aqueous ammonia (32%, 25 ml/mmol of nucleoside, 10 h, 50 °C, under stirring). The mixture was dried in vacuo and the nucleoside was purified on a silica gel column (30 x 1,5 cm i.d.). Elution of the column with increasing amounts of CH_3OH in $CHCl_3$ (from 5 to 20 %) afforded the product **11a** (232 mg) or **11b** (70 mg) [**12a** (122 mg) or **12b** (120 mg)].

11a: UV (CH_3OH) λ_{max} 271 nm (6800); $[\alpha]_D$ = +81.0 (c = 0.21, CH_3OH). **11b:** UV (CH_3OH) λ_{max} 271 nm (6800); $[\alpha]_D$ = +62.3 (c = 0.10, CH_3OH). **12a:** UV (CH_3OH)λ_{max} 277 nm (7300); $[\alpha]_D$ = +39.4 (c = 0.31,CH_3OH); m.p. ($CHCl_3/CH_3OH$) 194-195 °C. **12b:** UV (CH_3OH) λ_{max} 277 nm (7300); $[\alpha]_D$ = +45.4 (c = 0.12, CH_3OH). MS (FAB) **11a** and **11b** m/z 246 (MH^+, ^{35}Cl); **12a** and **12b** m/z 260 (MH^+, ^{35}Cl). The attempts to crystallize compounds **11a-b** and **12b** were unsuccessful.

Reaction of Nucleosides 9a-b and 10a-b with t-BuOK; General Procedure; Products 3 (d4C) and 4 ($d4C^{Me}$).

A solution of t-BuOK [prepared from K (4 mmol, 156 mg) in t-BuOH (25 ml)] was added to a stirred solution of **9a** (1 mmol, 329 mg)

or **10a** (1 mmol,343 mg) in t-BuOH (5 ml) and the mixture kept at room temp. for 2 h. The reaction mixture was neutralized with NH_4Cl (4 mmol, 212 mg) and concentrated in vacuo. Column chromatography (40 x 1.5 cm i.d.) on silica gel, eluted with increasing amounts of CH_3OH in $CHCl_3$ (from 5 to 10 %), afforded **3** (176 mg) or **4** (194 mg) respectively. In the case of products **9b** (0.1 mmol, 33 mg) and **10b** (0.2 mmol, 68 mg) the elimination reaction required an additional 20 h at room temp., thus furnishing products **3** (17 mg) and **4** (38 mg) respectively.
3: UV (H_2O) λ_{max} 271 nm (8450); $[\alpha]_D$ = +61.7 (c = 0.3, ethanol) (lit. $[\alpha]_D$ = +52.0); m.p. (ethanol) 164-167 °C (lit. 168-169 °C). **4**: UV (H_2O) λ_{max} 277 nm (8500) $[\alpha]_D$ = +77.5 (c = 0.25, CH_3OH),(lit.$[\alpha]_D$ =+71.7); m.p. (ethanol) 162-165 °C (lit.165°C).

Reduction of Nucleosides 3 and 4 with H_2/Pd-C; Products 1 and 2
A solution of alkene **3** (0.5 mmol, 104 mg) or **4**, (0.5 mmol, 111 mg) in 6 ml of EtOH (98%) was hydrogenated over 100 mg of 10% palladium on charcoal at room temp. and atmospheric pressure. After 2 h the mixture was filtered and the filtrate was dried in vacuo. The mixture was purified on silica gel column (10 x 1 cm i.d.) eluted with increasing amounts of CH_3OH (from 5 to 20 %) in $CHCl_3$ thus furnishing pure **1** (96 mg) or **2** (106 mg).
1: UV (H_2O) λ_{max} 271 nm (9100);$[\alpha]_D$ = +86.3 (c = 0.17, H_2O), (lit. $[\alpha]_D$ = +81.0); m.p. (ethanol/benzene) 212-214 °C (lit. 215-217). **2**: UV (H_2O) λ_{max} 277 nm (8840); $[\alpha]_D$ = +81.9 (c = 0.10, CH_3OH). The attempts to crystallize **2** were unsuccessful.

Elemental analyses of compound 7-12

Comp.						Calc. %				Found %			
N°	C	H	Cl	N	O	C	H	Cl	N	C	H	Cl	N
1	9	13		3	3	51.17	6.20		19.90	51.26	6.29		19.84
2	10	15		3	3	53.32	6.71		18.66	53.60	6.86		18.88
3	9	11		3	3	51.67	5.30		20.09	51.80	5.35		20.13
4	10	13		3	3	53.80	5.87		18.83	53.73	5.99		18.88
7a	14	18	2	2	4	48.15	5.19	20.31	8.02	48.27	5.22	20.20	8.11
7b										48.32	5.37	20.17	8.23
8a	15	20	2	2	4	49.60	5.55	19.52	7.71	49.82	5.65	19.68	7.80
8b										49.77	5.59	19.58	7.73
9a	14	20	1	3	4	50.99	6.11	10.75	12.74	51.12	6.10	10.60	12.81
9b										51.20	6.21	10.64	12.61

10a	15	22	1	3	4	52.40	6.45	10.31	12.22	52.57	6.52	10.27	12.30
10b										52.65	6.47	10.11	12.33
11a	9	12	1	3	3	44.00	4.92	14.43	17.11	44.09	5.11	14.19	17.01
11b										44.13	5.07	14.26	16.96
12a	10	14	1	3	3	46.25	5.43	13.65	16.18	46.29	5.55	13.60	16.15
12b										46.41	5.64	13.40	16.31

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12. Attempts to achieve in the same step both the nucleophilic displacement of the chlorine atom on the base and the elimination reaction on the sugar using different solvents and higher temperature were unsuccessful.

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