FACILE SYNTHESIS OF PYRROLO[2,3-d]PYRIMIDINE AND PYRROLO[3,2-c]PYRIDINE 2',3'-DIDEOXYRIBONUCLEOSIDES VIA NUCLEOBASE ANION GLYCOSYLATION WITH 2,3-DIDEOXY-D-GLYCERO-PENTOFURANOSYL CHLORIDE

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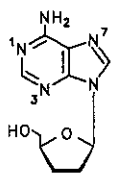
Abstract——A facile synthesis of pyrrolo[2,3-d]pyrimidine and pyrrolo[3,2-c]pyridine 2',3'-dideoxyribonucleosides employing a nucleobase anion and 2,3-dideoxy-D-glycero-pentofuranosyl chloride is described. The synthetic route allows large scale preparation of 2',3'-dideoxytubercidin, 3,7-dideaza-2',3'-dideoxyadenosine and related base-modified 2',3'-dideoxyribonucleosides not accessible by conventional glycosylation techniques.

Purine and pyrimidine 2',3'-dideoxy-β-D-ribofuranosides are potent inhibitors of human immunodeficiency virus (HIV).[1] AZT (a 3'-azido-2',3'-dideoxynucleoside) is currently used as chemotherapeutic agent for the treatment of AIDS.[2] Cytotoxic effects of common dideoxynucleosides have prompted us to search for structurally related compounds exhibiting a better selectivity index. Earlier we have reported on multi-step syntheses of base-modified 2',3'-dideoxyribonucleosides (2 and 3), isosteric to ddA (1), from corresponding 2'-deoxyribonucleosides.[3,4] We now present a short effective synthesis (3-4 steps instead of 7-8) by direct glycosylation of the nucleobase anions of 4a-c with the halogenose 5 allowing large-scale preparation of ddA derivatives.



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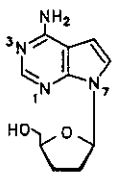

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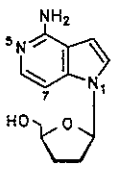

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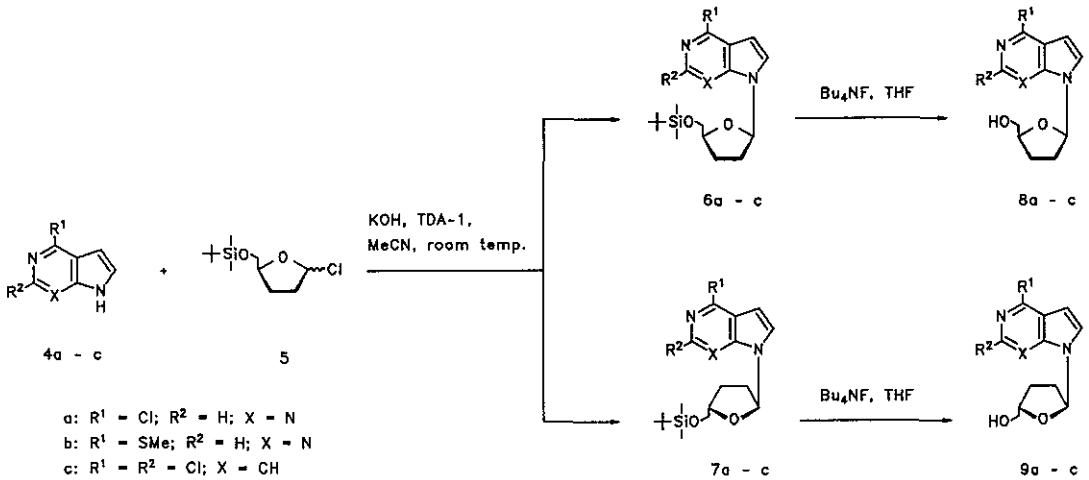
Glycosylation of the pyrrole moiety is not effective under conventional conditions[5] recently described for the synthesis of common 2',3'-dideoxyribonucleosides.[6,7] In 1983 our laboratory has developed the stereoselective synthesis of 2'-deoxy-β-D-ribonucleosides employing a nucleobase anion-generated with a strong base - and an α-configurated 2'-deoxyhalogenose.[8] We now use these conditions for the synthesis of pyrrolo[2,3-d]pyrimidine- and pyrrolo[3,2-c]pyridine 2',3'-dideoxy-D-ribonucleosides.



As reactive sugar component the anomeric halide 5 was used. The cold solution of 5, prepared in situ from the corresponding lactol[7] by Appel chlorination[9-11] was added portionwise to the anions of 4a-c, generated under solid-liquid phase-transfer conditions. The protected anomers 6a/7a and 6c/7c (1:1, each) were obtained in various amounts due to partial desilylation during work-up procedure. Therefore, upon large scale preparation the crude glycosylation mixture was deprotected first and then separated. The same procedure was followed in the case starting from 4b. Compounds 8a-c or 9a-c were obtained in 50-60% yield (8a/9a: 53%; 8b/9b: 57%; 8c/9c: 55%). Structural assignment was made by ^{13}C nmr (Table) and ^{1}H nmr spectroscopy.[12] Assignment of anomeric configuration of 8b/9b was made by ^{1}H-nmr NOE difference spectroscopy.[12] A 2-fold excess of the lactol[7] was used to generate the required amount of 5 neccessary to achieve complete conversion of the anions upon glycosylation reaction. According to the anomeric signal (^{1}H nmr) the lactol[7] was an 1 : 1 mixture giving anomeric halides upon Appel chlorination. Consequently the stereoselective glycosylation resulted in anomeric dideoxynucleosides. Further conversion of 8a,c provided 2',3'-dideoxynucleosides, such as 2',3'-dideoxytubercidin (2) or 3,7-dideaza-2',3'-dideoxyadenosine (3).[3,4]

Table. ^{13}C-Nmr Chemical Shifts of 2',3'-Dideoxyribonucleosides.[a)]

Compound	C-2[b)] C-6[c)]	C-4	C-4a C-3a	C-5 C-3	C-6 C-2	C-7a	C-7	SCH_3
6a	150.4	150.2	117.2	99.1	128.2			
6c	139.5	140.4	123.0	100.8	129.0	141.8	105.9	
7a	150.4	150.7	117.2	99.3	128.5			
7c	139.5	140.4	122.9	101.0	129.2	141.7	105.8	
8b	150.4	160.4	115.8	98.9	125.8	147.5		11.3
9a	150.4	150.7	117.2	99.3	128.6	150.7		
9b	150.5	160.5	115.8	99.9	126.0	147.6		11.3
9c	139.5	140.4	122.9	101.0	129.2	141.7	105.8	

	C-1'	C-2'	C-3'	C-4'	C-5'	C-Si	quat.C	CH_3-Si	
6a	84.2	31.7	25.6	81.0	64.5	25.7	18.0	-5.5	
6c	85.9	31.7	25.3	81.0	64.5	25.8	18.1	-5.5	
7a	84.8	31.4	26.2	80.4	65.1	25.8	17.9	-5.37;	-5.41
7c	86.3	31.2	25.9	80.2	65.0	25.8	18.0	-5.3;	-5.4
8b	83.8	31.9	26.2	81.2	63.2				
9a	84.7	31.3	26.4	81.0	63.4				
9b	84.3	31.4	26.7	80.8	63.6				
9c	86.1	31.2	26.1	80.7	63.3				

a) Spectra were measured in DMSO-d_6 rel. to TMS; b) Pyrrolo[2,3-d]pyrimidine numbering; c) Pyrrolo[3,2-c]pyridine numbering.

In conclusion, anion glycosylation of 4a-c under solid-liquid phase-transfer conditions with the halogenose 5 opens a direct access towards the synthesis of pyrrolo[2,3-d]pyrimidine and pyrrolo[3,2-c]pyridine 2',3'-dideoxyribonucleosides. Application of this technique for other modified nucleobases is under investigation.

EXPERIMENTAL

General Procedure

To a stirred suspension of powdered KOH (500 mg, 8.9 mmol) in anh. MeCN (25 ml, room temp., N_2) tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1, 20 µl, 0.06 mmol) was added. After 10 min, compounds 4a, 4b, or 4c (1.5 mmol) were added to the mixture and stirring was continued for another 10 min. Three portions (5 ml, each) of the freshly prepared, cold THF solution (15 ml) of 5-O-[(tert-butyl)dimethylsilyl]-2,3-dideoxy-D-glycero-pentofuranosyl chloride (5; 3 mmol) were added. Compound 5 was prepared from the corresponding lactol as described for the D-ribofuranosyl chloride.[10,11] The mixture was stirred for an additional 30 min. Insoluble material was filtered off. The filtrate was evaporated, and the resultant was applied to flash chromatography (silica gel 60, light petroleum-EtOAc, 9:1) which separated the protected anomers (6a/7a and 6c/7c; ratio: 1:1; yield: 40-50% of colorless oils) as well as the desilylated compounds (8a/9a and 8c/9c). The α-D-anomers were always faster migrating than the β-D-compounds (*data see Table and Notes*). Deprotection of 6a,c or 7a,c (1.25 mmol) was achieved with Bu_4NF (10 mmol, 1M solution in THF, 10 ml) at room temp. within 30 min. After removal of the solvent the residue was purified by silica gel chromatography (CH_2Cl_2-MeOH, 95:5) to give 8a,9a or 8c,9c as colorless solids (8a,8c [12]) or colorless oils (9a,9c) in 75-80% yield. Upon large scale preparation or in case of glycosylation of 4b the crude glycosylation mixture was directly deprotected and then purified to give 8a-c and 9a-c in 50-60% yield.

ACKNOWLEDGEMENTS

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12. ^{1}H Nmr spectra were recorded in DMSO-d_6, chemical shifts (δ) in ppm:

6a: δ = 8.64 (s, 2-H); 7.94 (d, J = 3.8 Hz, 6-H); 6.66 (d, J = 3.8 Hz, 5-H); 6.52 (dd, J = 3.5 and 6.9 Hz, 1'-H); 4.14 (m, 4'-H); 3.81 (dd, J = 3.8 and 11.2 Hz, 5'-H); 3.67 (dd, J = 4.5 and 11.2 Hz, 5'-H); 2.45 (m, 2'-H_a); 2.30 (m, 2'-H_b); 2.06 (m, 3'-H); 0.84 (s, tert-Bu); 0.00 - 0.01 (2xCH_3).

6c: δ = 7.85 (d, J = 3.4 Hz, 2-H); 7.81 (s, 7-H); 6.62 (d, J = 3.4 Hz, 3'-H); 6.33 (dd, J = 3.4 and 6.6 Hz, 1'-H); 4.15 (m, 4'-H); 3.67 (m, 5'-H); 2.35 (m, 2'-H); 2.02 (m, 3'-H); 0.82 (s, tert-Bu); -0.04 and -0.03 ($2CH_3$).

7a: δ = 8.66 (s, 2-H); 7.91 (d, J = 3.8 Hz, 6-H); 6.71 (d, J = 3.8 Hz, 5-H); 6.55 (m, 1'-H); 4.43 (m, 4'-H); 3.64 (m, 5'-H); 2.33 and 1.86 (2m, 2'-H and 3'-H); 0.88 (s, tert-Bu); 0.07 and 0.05 ($2CH_3$).

7c: δ = 7.78 (m, 7-H and 2-H); 6.65 (d, J = 3.3 Hz, 3-H); 6.38 (dd, J = 3.8 and 6.0 Hz, 1'-H); 4.33 (m, 4'-H); 3.63 (m, 5'-H); 2.21 and 1.86 (2m, 2'-H and 3'-H); 0.87 (s, tert-Bu), 0.06 and 0.05 (2s, $2CH_3$).

8a: mp 163°C (lit.[3], 163°C); 8c: mp 128°C (lit.[4], 128-129°C).

8b: δ = 8.62 (s, 2-H); 7.76 (d, J = 3.7, 6-H); 6.55 (d, J = 3.7, 5-H); 6.48 (dd, J = 6.8 and 4.2 Hz, 1'-H); 4.92 (t, J = 5.3 Hz, 5'-OH); 4.07 (m, 4'-H); 3.55 (m, 5'-H); 2.65 (s, SCH_3); 2.41 (m, 2'-H_α); 2.26 (m, 2'-H_β); 2.06 (m, 3'-H).

9a: δ = 8.67 (s, 2-H); 7.92 (d, J = 3.7 Hz, 6-H); 6.72 (d, J = 3.7 Hz, 5-H); 6.58 (dd, J = 4.6 and 6.8 Hz, 1'-H); 4.82 (t, J = 5.7 Hz, 5'-OH); 4.39 (m, 4'-H); 3.47 (m, 5'-H); 1.92 and 2.33 (2m, 2'-H and 3'-H).

9b: δ = 8.63 (s, 2-H); 7.66 (d, J = 3.7, 6-H); 6.53 (m, 5-H, 1'-H); 4.85 (t, J = 5.3 Hz, 5'-OH); 4.34 (m, 4'-H); 3.45 (m, 5'-H); 2.65 (s, SCH_3); 2.36 (m, 2'-H); 1.85 (m, 3'-H).

9c: δ = 7.81 (s, 7-H); 7.78 (d, J = 3.3 Hz, 2-H); 6.66 (d, J = 3.3 Hz, 1H, 3-H); 6.39 (dd, J = 4.2 Hz and 6.2 Hz, 1'-H); 4.81 (t, J = 5.7 Hz, 5'-OH); 4.29 (m, 4'-H); 3.45 (m, 5'-H); 1.80 - 2.47 (m, 2'-H and 3'-H).

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