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IMPROVED PROCEDURE FOR THE REGIOSPECIFIC SYNTHESIS OF 2'-DEOXYRIBONUCLEOSIDES

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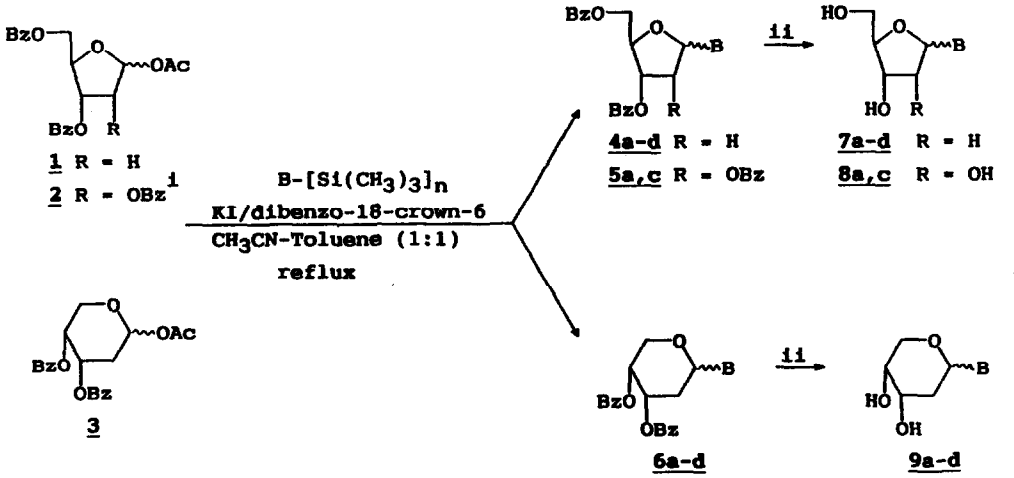
Summary: 2'-Deoxyribonucleosides are regiospecifically synthesized in high yields by catalyzing with KI-dibenzo-18-crown-6 PTC the condensation between unprotected silylated purines and pyrimidines and the appropriate easily available 2-deoxyribofuranosyl or pyranosyl sugar derivatives.

Antiviral[1] and anticancer[2] research, oligonucleotide synthesis and genetic engineering[3] are still lacking an efficient chemical method for the preparation of 2'-deoxyribonucleosides.

The synthesis of such starting materials must fulfill the following requirements: the 2-deoxy sugar derivative used in the condensation with nucleobases must be easily accessible and the coupling step has to be performed in high yields with regio and stereospecificity.



Scheme - a: B=Ad, b: B=Cy, c: B=Gu, d: B=Th, i: pure β anomer, ii: NH_3/MeOH

Up to now, two main procedures have been developped starting with 1α-chloro-2-deoxy-3,5-di-O-p.toluoyl D-ribose which is used in a phase

transfer glycosylation[4] under strongly alkaline conditions or in a "sodium salt glycosylation method[5]".

It is worth noting that these syntheses which are sometimes reported to be stereospecific or regiospecific[6-7] have been used only in the case of unnatural aglycons[8]. In this respect, much attention is being paid currently[9] to a practical chemical preparation of natural 2'-deoxyribonucleosides.

Protected nucleoside	Yield %	Free nucleoside	α:β	$t_{R\alpha}$: $t_{R\beta}$ (min)	HPLC conditions		UV (EtOH)
					Solvents v/v[a]	Flow rate (ml/min)	λ_{max}(nm)
4a	95	7a	62:38	4.91:5.96	A/B 5/95[b]	1.5	260
4b	77	7b	54:46	6.88:7.43	C 100[b]	1.1	269
4c	90	7c	68:32	5.97:6.71	A/B 2/98[b]	1.5	252
4d	70	7d	[d]	9.56	A/B 2/98[c]	1.0	268
5a	70	8a	32:68	9.10:9.75	A/B 2/98[c]	1	260
5c	61	8c	24:76	3.31:5.04	A/B 3/97[b]	1	252
6a	71	9a	44:56	7.23:8.96	A/B 6/94[c]	0.7	258
6b	71	9b	58:42	3.60:5.81	C 100[b]	1.5	268
6c	85	9c	46:54	7.41:8.91	A/B 4/96[c]	0.6	251
6d	72	9d	60:40	2.96:4.78	A/B 6/94[c]	1	266

Table - [a] Solvent A (acetonitrile), solvent B (ammonium acetate 0.05M pH 5.9), solvent C (water) [b] C_{18} Ultrabase (150 mm × 4.6, 5μ) [c] C_{18} Nucleosil (100 mm × 4.6, 5μ) [d] Unresolved (pure α and β references: t_R= 9.52 and 9.61).

As part of our continuing efforts directed towards the synthesis of nucleosides[10], we describe now a general and valuable regiospecific methodology which affords high yields of separable anomeric mixtures of N-9 purine and N-1 pyrimidine 2'-deoxyribonucleosides. According to this approach, the furanosyl derivative 1[11] (1 mmol), easily accessible from 2-deoxy D-ribose, is reacted with the unprotected silylated nucleobase (1 mmol) under phase transfer conditions using dibenzo-18-crown-6 (0.2 mmol) and potassium iodide (1 mmol) in an acetonitrile-toluene mixture (1/1, v/v) (10 ml) within 2 to 4 hrs at reflux (scheme). After the usual work-up, removal of the benzoyl groups by methanolic ammonia afforded the free nucleosides 7a-d as anomeric mixtures in quantitative yields. Comparison of our results in the 2'-deoxy purine nucleosides field for example (95% *vs* 61% for 4a[9d] and 90% *vs* 67% of mixture of regioisomers for 4c[12]) shows a very significant improved yield (Table).

As we are also interested in the synthesis of 2'-deoxyribopyranonucleo-

sides, preliminary experiments using the pyranosyl sugar 3[11] for condensation with nucleobases under Lewis acid conditions ($TiCl_4$ or $SnCl_4$) afforded the expected anomeric mixtures 6a-d together with unsaturated derivatives as by-products (up to 50%). In contrast, the above sugar 3, when reacted with nucleobases under the previous conditions, gave exclusively the nucleosides 6a-d in very good yields (Table).

All the unprotected nucleosides were characterized by analytical HPLC comparison with authentic samples[13] (Table).

The procedure described in this communication constitutes a powerful improvement at the laboratory scale for the chemical synthesis of 2'-deoxyribonucleosides and deserves the following comments:

- The starting pyranosyl and furanosyl sugars are easily prepared.
- Nucleobases bearing an exocyclic amino group do not need any protection.
- High yields and regiospecificity are observed in all cases and particularly for guanine nucleosides (85-90%) which are always the most challenging derivatives in the nucleoside area.

Extension to the *ribo* series proved also to be very successful starting from the pure anomer 2, as shown in the Scheme and the Table. As this new procedure provides separable 1:1 mixtures of the α- and β-anomers, it allows an easy access to the unnatural α-nucleosides as starting synthons for α-DNA[14] in satisfactory yield after chromatographic separation.

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11. Sugar precursors were synthesized as follows:

$$\underline{1}\ (70\%) \xleftarrow[iv]{i^{15},\ ii,iii,} \text{2-deoxy D-ribose} \xrightarrow{v^{16},\ vi} \underline{3}\ (50\%)$$

Reagents and conditions: i, HCl/MeOH, RT; ii, BzCl, pyridine, RT; iii, HCl conc., water, dioxan, 100°C, 1 hr; iv, Ac_2O, pyridine, RT; v, BzCl, pyridine, -10°C; vi, $Et_2O.BF_3$, Ac_2O, -20°C, 2 hrs.

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