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A Convenient Pathway to 2'-(tert-Butyloxycarbonyl)ribonucleosides

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Recently [1] we described the introduction of the tert-butyloxycarbonyl group (Boc) preferentially into the 2'-OH-position of the ribonucleosides cytidine, uridine, adenosine and guanosine. The corresponding derivatives are especially applicable for ribonucleotide synthesis.

The tert-butyloxycarbonyl group shows a much less carbonyl activity than other acyles [2, 3] and thus a higher base stability and resistance to migration of 2', 3'-acyles. It is absolutely stable in 5 % trichloro-acetic acid/dichloromethane at room temperature for more than 30 minutes, whereas 5'-O-dimethoxytrityles are eliminated in 1 minute [4].

On the other hand the Boc group can be acid-catalysed removed with 4N HCl/dioxane by cleavage of the tert-butyl-O -bond at 20 °C in 15 minutes. Phosphate and N-glycoside bonds are totally resistent under these conditions. The Boc group is therefore a most suitable protective group for 2'-OH-position in ribonucleotide synthesis.

In regard to cytidine, adenosine and guanosine the Boc group in 2'-OH-position is best introduced after sodium hydride activation [5, 6] of N-benzoyl-5'-O-(4,4'-dimethoxytrityl) derivatives [7, 8] (Bz = benzoyl, Dmtr = dimethoxytrityl) followed by reaction with pyrocarbonic acid-di-tert-butylester (Boc_2O).

In the case of less nucleophilic uridine [9], base protection demanding a higher expenditure of synthesis was not necessary. But the reaction of 5'-Dmtr-uridine with Boc_2O/NaH led to an unfavourable ratio of 2',3'-isomers in contrast to the corresponding N-benzoyl nucleosides [1].

Regioselective and in much higher total yield the introduction of the Boc group succeeds by using 3', 5' - diacetyl-uridine [10] as starting material (Scheme, Table 1 and 2).

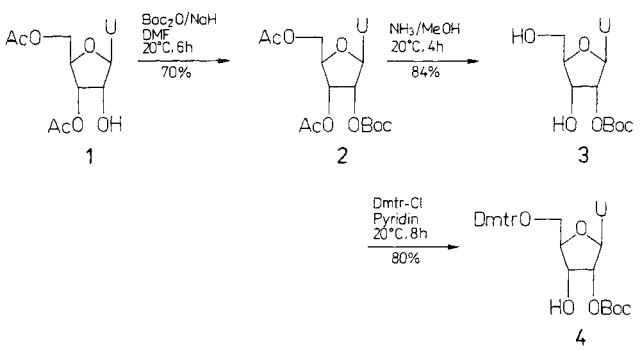

Table 1 2'-Boc-5'-Dmtr-nucleosides prepared

2'-Boc-5'-Dmtr-nucleoside [9]	yield[a] (%)	m. p. (°C)	molecular formula[b]
A^{Bz}	42	128 – 129	$C_{43}H_{43}N_5O_6$ (773.4)
G^{Bz}	12	164 – 166	$C_{43}H_{43}N_5O_{10}$ (789.7)
C^{Bz}	48	123 – 124	$C_{44}H_{45}N_3O_{11}$ (791.7)
U[c]	21 (47)[d]	115 – 116	$C_{35}H_{38}N_2O_{10}$ (646.4)

[a] Purification by column chromatography on silica gel 60 (0.063 – 0.20 mm) Merck using CH_2Cl_2 (linear MeOH gradient 0 – 2 %) as eluent, UV-detection at 254 nm.
[b] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.18, N ± 0.20.
[c] Identical with compound **4** (Scheme).
[d] See Scheme.

Experimental

2'-O-Boc-3',5'-O-diacetyl-uridine (**2**)

To a stirred solution of 3',5'-O-diacetyluridine [10] (**1**; 328 mg, 1 mmol) in dried DMF (8 ml) NaH (3.9 mmol, 55 – 60 % oil suspension) is added at – 20 °C. The resulting solution is stirred at – 20 °C for 1 h and then Boc_2O (786 mg, 3.6 mmol) in dried DMF (3 ml) is added dropwise within 45 minutes. The mixture is stirred at room temperature overnight and is evaporated at 0.13 kPa. The oily yellow residue is diluted in CH_2Cl_2 and washed with 5 % $NaHCO_3$ and H_2O. The collected organic phase is dried (Na_2SO_4) and evaporated under reduced pressure.

For analytical purposes a sample was purified by column chromatography (silica gel: Merck, 0.063 – 0.2 mm; eluent: CH_2Cl_2/MeOH, 99:1; analytical dates: see Table 2).

2'-O-Boc-uridine (**3**)

To **2** (1 mmol) a saturated solution of NH_3 in MeOH (5 ml) is added, stirred for 5 h at r.t. and evaporated under reduced

Table 2 Uridine derivatives prepared

uridine derivatives	yield[a)] (%)	m.p. (°C)	molecular formula[b)]	R_f[c)]	^{1}H-NMR[d)] (DMSO-d6/TMS)
2	70	59 – 61	$C_{18}H_{24}N_2O_{10}$ (428.53)	0.49	11.50 (s, 1H, NH), 7.70 (d, 1H, 6-H), 5.86 (d, 1H, 1'-H), 5.72 (d, 1H, 5-H), 5.44 – 5.22 (m, 2H, 2'-H, 4'-H), 4.35 – 4.15 (m, 3H, 3'-H, 5'-H), 2.04 (d, 6H, $2CH_3$), 1.42 (s, 9H, $3CH_3$)
3	84	80 – 84	$C_{14}H_{20}N_2O_8$ (344,46)	0.08	7.96 (d, 1H, 6-H), 5.90 (d, 1H, 1'-H), 5.81 (d, 1H, 5-H), 5.47 (d, 1H, 3'-OH), 5.30 (m, 1H, 2'-H), 5.15 (t, 1H, 5'-OH), 4.10 – 3.74 (m, 2H, 3'-H, 4'-H), 3.59 (m, 2H, 5'-H), 1.40 (s, 9H, $3CH_3$)

[a) b)] see table 1

[c)] The R_f values for all compounds are obtained on Merck silica gel 60 F_{254} using CH_2Cl_2/MeOH (95:5) as eluent, developer: H_2SO_4/MeOH (20:80), UV-detection at 254 nm.

[d)] Obtained on a Bruker WH 90/DS spectrometer.

pressure. The product is chromatographed over silica gel by eluting with CH_2Cl_2 (linear MeOH gradient 0 – 4 %) to give compound **3** as a solid.

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