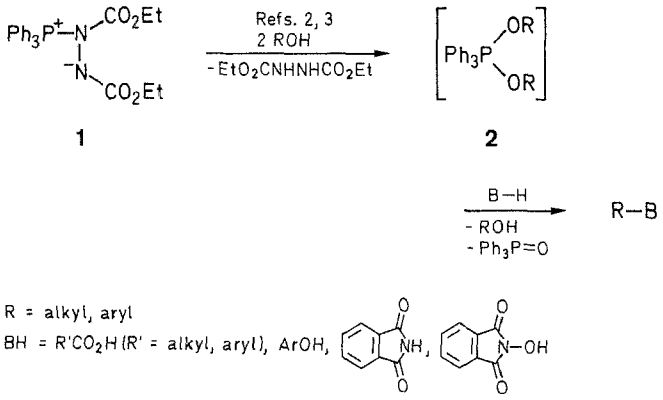
The Synthesis of "C–O–N" Analogues of Nucleosides via the Mitsunobu Reaction

Edward Grochowski,* Halszka Stepowska

Institute of Organic Chemistry, Polish Academy of Science, PL-01-224 Warsaw, Poland

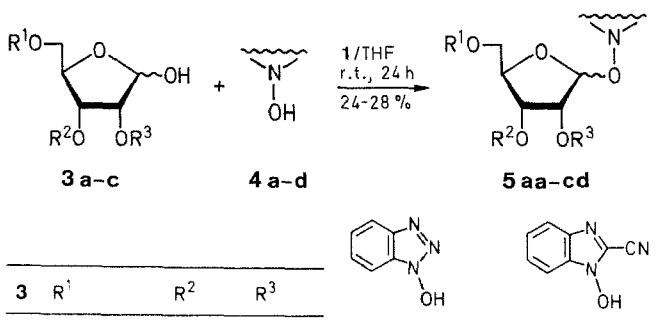
A number of *N–O-ribosides* **5** were prepared by the reaction of appropriate cyclic *N*-hydroxycompounds **4** with three of the representative ribofuranose derivatives **3** in the presence of triphenylphosphine and diethyl azodicarboxylate as coupling agents.

The reaction of triphenylphosphine with diethyl azodicarboxylate results in formation of very reactive 1 : 1 adduct **1**,[1] which is usually used for *in situ* hydroxy group activation in a wide variety nucleophilic displacement reactions (Mitsunobu Reaction).[2,3] In the carbohydrate field, this reaction has already been applied to glycoside bond formation.[4,5]

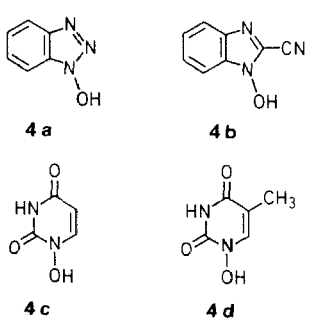


Previously,[6] we have described *O*-alkylation of cyclic *N*-hydroxycompounds (1-hydroxybenzotriazole and 1-hydroxybenzimidazole derivatives) with 2,3:3,5-di-*O*-isopropylidene-D-mannofuranose in the presence of betaine **1**. We have used this reaction as a model for the synthesis of "C–O–N" analogues of nucleosides. It should be mentioned that Mitsunobu's method has been ineffective in case of the reaction with peracetylated sugars.[7]

Now we report the application of this reaction to three representative ribofuranose derivatives **3** as alkylating agents for cyclic *N*-hydroxycompounds **4**. Under typical conditions, the reaction of 1-hydroxybenzotriazole **(4a)** or 1-hydroxy-2-cyanobenzimidazole **(4b)** with sugar **3** proceeds smoothly and affords the respective ribosides **5** in high yield (76–82%). Under the same conditions 1-hydroxyuracil **(4c)** and 1-hydroxythymine **(4d)** afforded respective "C–O–N" nucleoside analogues **5** in moderate yield (24–34%). (See the Table).

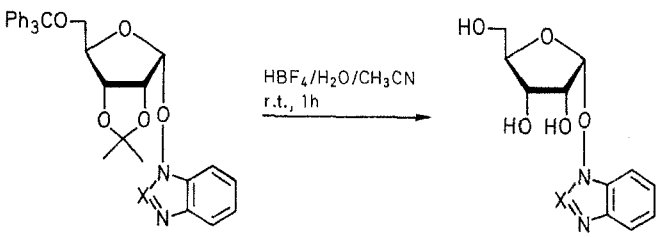


3	R^1	R^2	R^3
a	Ph_3C	Me_2C	
b	t-$BuMe_2Si$	PhCH	
c	$PhCH_2$	$PhCH_2$	$PhCH_2$

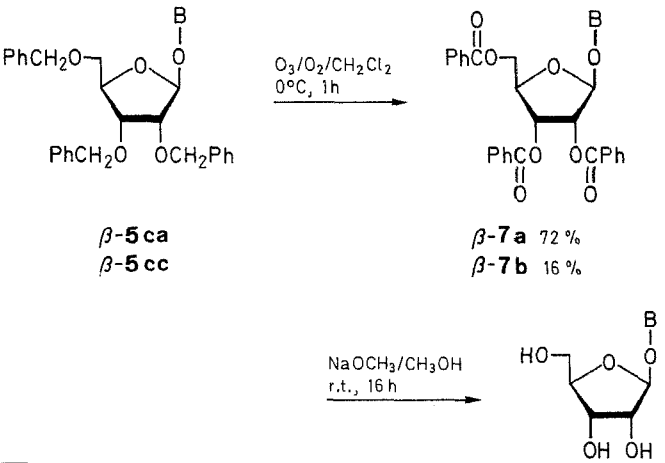


The configurations of anomers were assigned on the basis of $J_{1',2'}$ coupling constants for H-1':[8] ≈ 0 Hz for β-anomers and 3.5–6.6 Hz for α-anomers. Measurements of optical rotation support the assigned configurations. In cases of **3a** and **3b**, α-anomers were formed predominantly. The reaction of **3c** with all *N*-hydroxycompounds **4** afforded β-anomers with high selectivity. The cause for these reversed stereoselectivities is not clear.

The removal of the protecting groups of compounds **5aa** and **5ab** using tetrafluoroboric acid[9] afforded 1-(α-D-ribofuranosyloxy)benzotriazole **6a** and 1-(α-D-ribofuranosyloxy)-2-cyanobenzimidazole **6b** in 76 and 74% yield, respectively. Use of trifluoroacetic acid[10] afforded the same results.



In case of *N–O*-ribosides protected by benzyl groups **(5ca, cc, cd)**, catalytic and chemical hydrogenolysis failed, we therefore applied the oxidative technique.[11] Ozonization of β-**5ca** proceeded smoothly and afforded the respective acyl-protected riboside β-**7a** in high yield (72%). On the other hand, under the same conditions riboside β-**5cc** gave the respective acyl riboside β-**7b** in poor yield (16%). The removal of the protecting groups of compounds β-**7b** and β-**7a** using sodium methoxide afforded the "C–O–N" analogue of uridine β-**6c** in 78% yield and the benzotriazole *N–O*-riboside β-**6a** in 80% yield, respectively.



B	
β-5ca / β-7a / β-6a	
β-5cc / β-7b / β-6c	

Table. *N-O*-Ribosides **5** Prepared

Starting Materials	Product	Yield[a] (%)	Molecular Formula[b]	mp (°C)	$[\alpha]_D^{20}$ (*c*, solvent)	Ratio α/β[c]	^{1}H-NMR, δ, *J*(Hz) (only H-1′ for minor isomer)
3a/4a	**5aa**	82	$C_{33}H_{31}N_3O_5$ (549.5)	α 103–105	−11.1° (2, $CHCl_3$)	9	($CDCl_3$) 1.35, 1.65 (2s, 2 × 3H, $2CH_3$); 3.3–3.6 (dd, 2H, H-5′); 4.5–4.8 (m, 2H, H-3′, H-4′); 5.15 (t, 1H, $J_{2',3'}$ = 6.6, H-2′); 6.2 (d, 1H, $J_{1',2'}$ = 6, H-1′); 7.6 (m, 19H_{arom})
				β[d] –	–	1	($CDCl_3$) 5.90 (s)
3a/4b	**5ab**	78	$C_{35}H_{31}N_3O_5$ (573.5)	α 116–119	−17.8° (2, DMSO)	3	($CDCl_3$) 1.45, 1.60 (2s, 2 × 3H, $2CH_3$); 3.1–3.5 (m, 2H, H-5′); 4.2–4.7 (m, 2H, H-3′, H-4′); 5.1 (m, 1H, H-2′); 5.68 (d, 1H, $J_{1',2'}$ = 4, H-1′); 7.4 (m, 4H_{arom})
				β 131–135	−29.6° (0.9, DMSO)	1	($CDCl_3$) 5.80 (s)
3a/4c	**5ac**	24	$C_{31}H_{30}N_2O_7$ (542.4)	α 76–80	−1.6° (1.1, $CHCl_3$)	9	(DMSO-d_6) 1.4, 1.57 (2s, 2 × 3H, $2CH_3$); 3.21–3.48 (m, 2H, H-5′); 4.1–4.6 (m, 2H, H-3′, H-4′); 4.95 (t, 1H, $J_{2',3'}$ = 5.2, H-2′); 5.58 (d, 1H, $J_{5,6}$ = 8, H-5); 5.72 (d, 1H, $J_{1',2'}$ = 5.6, H-1′); 7.2–7.6 (m, 16H, 15H_{arom}, H-6)
				β[d] –	–	1	(DMSO-d_6) 5.77 (s)
3b/4c	**5bc**	31	$C_{22}H_{30}N_2O_7Si$ (462.4)	α oil	−2.2° (0.9, DMSO)	4	DMSO-d_6) 1.1–1.6 (m, 15H, $5CH_3$); 3.3–3.4 (m, 4H, H-5′, H-3′, H-4′); 5.1 (m, 1H, H-2′); 5.48 (d, 1H, $J_{1',2'}$ = 5.8, H-1′); 6.1 (d, 1H, $J_{5,6}$ = 8, H-5); 7.6 (m, 5H_{arom}); 8.1 (d, 1H, H-6)
				β[d] –	–	1	–
3c/4a	**5ca**	76	$C_{32}H_{31}N_3O_5$ (537.5)	α 111–114	+58.6° (2.8, $CHCl_3$)	1	(DMSO-d_6) 5.44 (d, $J_{1',2'}$ = 4.9)
				β 127–130	+32.0° (3.4, $CHCl_3$)	40	DMSO-d_6) 3.4–3.6 (m, 2H, H-5′); 3.9–4.1 (m, 2H, H-3′, H-4′); 4.6 (s, 6H, $3CH_2$); 4,7 (s, 1H, H-2′); 5.29 (s, 1H, H-1′); 7.4 (m, 19H_{arom})
3c/4c	**5cc**	32	$C_{30}H_{30}N_2O_7$ (530.4)	α[d] –	–	1	($CDCl_3$) 5.15 (d, $J_{1',2'}$ = 6.6)
				β 92–96	+41.7° (3.1, DMSO)	40	$CDCl_3$) 3.5–3.6 (m, 2H, H-5′); 4.0–4.1 (m, 2H, H-3′, H-4′); 4.6–4.7 (m, 7H, $3CH_2$, H-2′); 5.31 (s, 1H, H-1′); 5.48 (d, 1H, $J_{5,6}$ = 7.8, H-5); 7.4 (m, 15H_{arom}); 7.8 (d, 1H, H-6)
3c/4d	**5cd**	34	$C_{31}H_{32}N_2O_7$ (544.4)	α[d] –	–	1	(DMSO-d_6) 4.95 (d, $J_{1',2'}$ = 3.5)
				β 108–110	+40.5[c] (2, DMSO)	9	DMSO-d_6) 2.0 (s, 3H, CH_3); 3.3–3.5 (m, 2H, H-5′); 4.2 (m, 2H, H-3′, H-4′); 4.6 (s, 6H, $3CH_2$); 4.7 (s, 1H, H-2′); 5.20 (s, 1H, H-1′); 7.3 (m, 15H_{arom}); 7.72 (s, 1H, H-6)

[a] All the yields refer to isolated chromatographically pure mixture of anomers.

[b] Satisfactory microanalyses obtained: C ±0.36, H ±0.41, N ±0.37.

[c] The ratio of the anomers determined by ^{1}H-NMR spectroscopy.

[d] The anomer was not isolated in pure analytical form.

The NMR spectra were recorded on Jeol JNM-4H-100 and Bruker SM-100 spectrometers using TMS as internal standard. Optical rotations were measured with Perkin-Elmer 141 automatic polarimeter. All melting points are uncorrected. Column chromatography was carried out on silica gel (70–230 mesh, Merck). TLC was performed on silica gel 60F_{254} (Merck). Anhydrous reagents and solvents were used in all operations.

The carbohydrate and pyrimidine substrates were prepared according to literature procedures: **3a**,[12] **3b**,[13] **3c**,[14] **4a**,[15] **4b**,[16], **4c**,[17] **4d**.[18]

*1-(5-O-triphenylmethyl-2,3-O-isopropylidene-*D*-ribofuranosyloxy)-cyanobenzimidazole* (**5ab**); *Typical Procedure for the Preparation of N–O-ribosides* (**5**):

5-*O*-Triphenylmethyl-2,3-*O*-isopropylidene-D-ribofuranose (**3a**; 0.648 g, 1.5 mmol), 1-hydroxycyanobenzimidazole (**4b**; 0.238 g, 1.5 mmol) and triphenylphosphine (0.398 g, 1.5 mmol) are dissolved in THF (25 mL) and treated with diethyl azodicarboxylate (0.3 mL; 1.6 mmol) at room temperature. A slightly exothermic effect is observed. The solution is left at room temperature for 12 h and then evaporated to dryness. The residue is chromatographed on silica gel with benzene/Et_2O 4:1 and 2:3 as eluent. The first main product is the **5ab** α-anomer followed by the β-anomer (Table).

1-(α-D-ribofuranosyloxy)cyanobenzimidazole (6b):

To a stirred solution of 1-(5-*O*-triphenylmethyl-2,3-*O*-isopropylidene-α-D-ribofuranosyloxy)cyanobenzimidazole (α-**5ab**; 0.573 g, 1 mmol) in CH_3CN (11 mL) a 35% aq. solution of HBF_4 (0.2 mL, ≈ 1 mmol) is added at room temperature. The reaction is monitored by analytical TLC (EtOAc/$CHCl_3$, 3:2). After ca. 1 h, Et_3N (0.14 mL, 1 mmol) is added, and the solvent is evaporated. The residue is subjected to preparative TLC on silica gel (EtOAc/$CHCl_3$, 3:2). The yield of α-**6b**: 0.215 g (74%) (0.195 g (67%) in the case of trifluoroacetic acid deprotection); mp 167–170°C; $[\alpha]_D^{20}$ −4° (*c* = 1.3, DMSO).

$C_{13}H_{13}N_3O_5$	calc.	C 53.61	H 4.49	N 14.42
(291.2)	found	53.28	5.00	14.61

^{1}H-NMR ($CDCl_3$): δ = 3.5 (m, 2H, H-5′, H-5″); 4.32–4.55 (m, 2H, H-3′, H-4′); 4.9 (m, 1H, H-2′); 5.62 (d, 1H, H-1′, $J_{1',2'}$ = 6.5 Hz); 7.4 (m, 4H_{arom}).

In the same way *1-(α-*D*-ribofuranosyloxy)benzotriazole* (**6a**) is obtained in a yield of 0.20 g (76%); mp 136–138°C; $[\alpha]_D^{20}$ +6.8° (*c* = 1.5, DMSO).

$C_{11}H_{13}N_3O_5$	calc.	C 49.44	H 4.89	N 15.72
(267.2)	found	48.97	4.91	15.56

^{1}H-NMR (DMSO-d_6): δ = 3.3–3.6 (m, 2H, H-5′, H-5″); 4.4–4.7 (m, 2H, H-3′, H-4′); 5.0 (m, 1H, H-2′); 5.72 (d, 1H, H-1′, $J_{1',2'}$ = 5.8 Hz); 7.3 (m, 4H_{arom}).

1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyloxy)benzotriazole (7a): Typical Procedure for the Oxidation of Compounds 5ca and 5cc with Ozone:

Into a solution of **5ca** (0.17 g, 0.3 mmol) in CH_2Cl_2 (50 mL) at 0°C gas from a laboratory generator, containing 2% ozone, is bubbled for 1 h until TLC (EtOAc/hexane 1:1) indicates completion of the reaction of the benzyl groups. The solution is then concentrated under reduced pressure, and the residue is purified by column chromatography (benzene/Et_2O, 4:1 and 2:3) to give **7a**; yield: 0.13 g (72%); mp 106–108°C; $[\alpha]_D^{20}$ = +46.3° (*c* = 2.7, $CHCl_3$).

$C_{32}H_{25}N_3O_8$ calc. C 66.32 H 4.34 N 7.25
(579.4) found 66.26 4.29 7.27

^{1}H-NMR ($CDCl_3$): δ = 4.72 (m, 2 H, H-5', H-5''); 4.9–5.1 (m, 2 H, H-3', H-4'); 6.18 (d, 1 H, H-2', $J_{2',3'}$ = 5 Hz); 6.40 (s, 1 H, H-1'); 7.3 (m, 15 H_{arom}).

In case of **5cc**, ozonization is carried out under the same conditions. The reaction affords *1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyloxy)uracil* (**7b**); yield: 92 mg (16%).

Compound **7b** is identical with the product previously prepared in 54% yield by the reaction of 2,3,5-tri-*O*-benzoylribofuranosyl chloride with 1-hydroxyuracil under high pressure.[19]

1-(β-D-Ribofuranosyloxy)benzotriazole (β-6a):

To a stirred solution of **7a** (0.145 g, 0.25 mmol) in anhydrous MeOH a solution of NaOMe, prepared by dissolving of sodium (46 mg, 2 mmol) in abs. MeOH (5 mL), is added dropwise at room temperature. The resulting solution is sealed and left at room temperature for 16 h. The stirred solution is neutralized by addition of Dowex 50 (H^+). The filtrate is evaporated to dryness giving *β*-**6a**; yield: 54 mg (80%) mp 114–116°C; $[\alpha]_D^{20}$ −16.5° (*c* = 1.4, DMSO).

$C_{11}H_{13}N_3O_5$ calc. C 49.44 H 4.89 N 15.72
(267.2) found 49.21 4.94 15.52

^{1}H-NMR (DMSO-d_6): δ = 3.4–3.6 (m, 2 H, H-5', H-5''); 4.3–4.5 (m, 2 H, H-3', H-4'); 5.2 (m, 1 H, H-2'); 5.9 (s, 1 H, H-1'); 7.4 (m, 4 H_{arom}).

Analogously *1-(β-D-ribofuranosyloxy)uracil* (**6c**) is obtained in a yield of 78%; mp 236°C (dec); $[\alpha]_D^{20}$ −7.5° (*c* = 2.4, DMSO).

$C_9H_{12}N_2O_7$ calc. C 41.55 H 4.64 N 10.76
(260.1) found 41.19 4.67 10.43

^{1}H-NMR (DMSO-d_6): δ = 3.9 (m, 2 H, H-5', H-5''); 4.1 (m, 1 H, H-4'); 5.3 (m, 2 H, H-2', H-3'); 5.4 (d, 1 H, H-5, $J_{5,6}$ = 8 Hz); 5.82 (s, 1 H, H-2'); 7.8 (d, 1 H, H-6); 11.3 (s, 1 H, NH).

^{13}C-NMR (DMSO-d_6): δ = 59.9 (C-5'); 68.7 (C-3'); 72.9 (C-4'); 76.6 (C-2'); 84.7 (C-1'); 99.7 (C-5); 110.5 (C-6); 143.5 (C-2); 161.0 (C-4).

Financial support from the Polish Academy of Sciences (grant CPBP 01.13) is gratefully acknowledged.

Received: 30 November 1987; revised: 18 April 1988

(1) Grochowski, E., Hilton, B.D., Kupper, R.J., Michejda, C.J. *J. Am. Chem. Soc.* **1982**, *104*, 6876.
(2) Varasi, M., Walker, K.A.M., Maddox, M.L. *J. Org. Chem.* **1987**, *52*, 4235.
(3) Mitsunobu, O. *Synthesis* **1981**, 1.
(4) Grynkiewicz, G. *Carbohydr. Res.* **1977**, *53*, C11.
(5) Szarek, W.A., Jarrell, H.C., Jones, J.K.N. *Carbohydr. Res.* **1977**, *57*, C13.
(6) Grochowski, E., Falent-Kwastowa, E. *J. Chem. Res. (S)* **1978**, 300.
(7) Grochowski, E, Falent-Kwastowa, E. *Pol. J. Chem.* **1980**, *54*, 2229.
(8) For a general review see: Townsed, L.B., in Zorbach, W.W., Tipson, R.S. (eds.) *Synthetic Procedures in Nucleic Acid Chemistry*, Vol II, Wiley-Interscience, New York, 1973, pp. 267–398.
(9) Angiebeaud, P., Defaye, J., Gadelle, A., Utille, J.P. *Synthesis* **1985**, 1123.
(10) Albert, R., Dax, K., Pleschko, R., Stülz, A.R. *Carbohydr. Res.* **1985**, *137*, 282.
(11) MacCoss, M., Cameron, D.J. *Carbohydr. Res.* **1978**, *60*, 206.
(12) Schmidt, R.R., Krag, J., Guillard, W. *Chem. Ber.* **1977**, *110*, 2433.
(13) Ogilvi, K. *Carbohydr. Res.* **1983**, *145*, 234.
(14) Barker, R., Fletcher, H.G. *J. Am. Chem. Soc.* **1964**, *86*, 4605.
(15) König, W., Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
(16) Konopski, L., Serafin, B. *Rocz. Chem.* **1977**, *51*, 1783.
(17) Klötzer, W. *Monatsh. Chem.* **1964**, *95*, 1734.
(18) Klötzer, W. *Monatsh. Chem.* **1965**, *96*, 1721.
(19) Grochowski, E., Stepowska, H., Sałański, P., Jurczak, J., in press.