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Note

Synthesis of D-erythrofuranosyl C-nucleosides of imidazole from 4(5)-(D-*arabino*-tetritol-1-yl)imidazole

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C-Nucleosides[1] have received considerable attention due to their significant antitumor and antiviral activities[2]. Some of them, such as pyrazofurin[3,4] and showdomycin[5], contain five-membered heterocyclic rings in the aglycon part. Many natural *N*-glycosylimidazoles have been described[6].

In this paper, we present the synthesis of the anomeric 4(5)-β- and -α-D-erythrofuranosylimidazoles, **2** and **3**, and their derivatives **4–10**, starting from the easily accessible 4(5)-(D-*arabino*-tetritol-1-yl)imidazole[7] (**1**).

As yet, only the synthesis of one anomeric *C*-D-erythrosylimidazole based on desulfurization of 4(5)-(D-erythrofuranosyl)imidazoline-2-thione has been reported[8].

RESULTS AND DISCUSSION

Refluxing of 4(5)-(D-*arabino*-tetritol-1-yl)imidazole[7] (**1**) with glacial acetic acid gave a mixture of 4(5)-β- and -α-D-erythrofuranosylimidazole (**2** and **3**). The mixture of **2** and **3** was acetylated conventionally to give the anomeric peracetates **4** and **5** in the ratio of ca. 3 : 1. After separation by flash-column chromatography, **4** and **5** were deacetylated with Amberlyst A-26 (HO^-) resin in methanol to give the free D-erythrofuranosyl C-nucleosides **2** and **3**, respectively. The anomers **4** and **5** were also selectively *N*-deacetylated using an aqueous solution of sodium hydrogencarbonate at room temperature to produce the di-*O*-acetylated nucleosides **6** and **7**. The free nucleosides **2** and **3** were separately tritylated to give the *N*-trityl derivatives **8** and **9**, from which only the β anomer **8** undergoes acetonation under standard conditions to yield the 2,3-*O*-isopropylidene derivative **10**. The reaction failed with the α anomer **9** probably for steric reasons.

The structures and configurations of compounds **2–10** were assigned as follows. Firstly, according to Hudson's rule[9], all our compounds to which the α-anomeric

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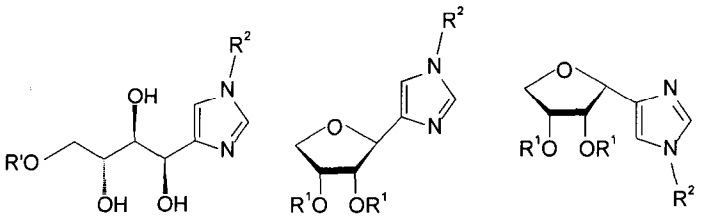

1 $R^1=R^2=H$
11 $R^1=H$ $R^2=Tr$
12 $R^1=Ts$ $R^2=Tr$

2 $R^1=R^2=H$
4 $R^1=R^2=Ac$
6 $R^1=Ac$ $R^2=H$
8 $R^1=H$ $R^2=Tr$
10 $R^1=\rangle CMe_2$ $R^2=Tr$

3 $R^1=R^2=H$
5 $R^1=R^2=Ac$
7 $R^1=Ac$ $R^2=H$
9 $R^1=H$ $R^2=Tr$

configuration is assigned show more positive optical rotation values than the respective β anomers. Secondly, in accord with the previous statements[10], all β anomers, except **8**, are less polar in TLC than the corresponding α anomers.

Conclusive configurational assignments for **2** and **3** are, however, based predominantly on ^1H and ^{13}C NMR spectroscopy. Thus, the H-1′ protons of the β anomers of *C*-ribofuranosyl compounds resonate at higher field than those of α anomers because of the shielding effects of the cis HO-2′ group[12]. On the basis of the above correlation, we propose for our *C*-erythrosyl compounds **2** and **3**, exhibiting H-1′ chemical shifts at 4.70 and 4.93 ppm, the configurations β and α, respectively (Table I).

A comparison of the $J_{1',2'}$ coupling constants of nucleosides can also be applied. β Anomers of D-ribofuranosyl C-nucleosides display in general a larger $J_{1',2'}$ coupling than the corresponding α anomers[15–18]. The same relation was observed for our anomers **2** and **3**, having $J_{1',2'}$ values of 6.6 and 4.8 Hz, respectively (Table I).

Furthermore, the $\Delta\delta$ value of the two methyl groups in the isopropylidene moiety of **10** ($\Delta\delta$ 0.19 ppm) indicates the β-anomeric configuration according to Imbach's rule[19].

The correctness of our assignment was confirmed by ^{13}C NMR data. It has been found that the C-1′ signal of the α anomer always appears at higher field than that of the corresponding β anomer[10,13,14]. Our proposed anomeric configurations of **2** and **3** are in accord with this correlation, since the C-1′ chemical shifts of **2** and **3** are 79.03 and 77.88 ppm, respectively (Table II).

For the triacetates **4** and **5**, we assume the 1,4-disubstituted imidazole structures on the basis of the cross-ring coupling constants between the two aromatic protons ($J_{2,5} > 1.1$ Hz)[20,21].

The configurations of the anomeric *C*-erythrosyl compounds **2–10**, assigned mainly by their NMR spectra, were then confirmed independently by a stereospecific synthesis.

TABLE I

^{1}H NMR data [a] for **2–10**

Compound	H-1′	H-2′	H-3′	H-4′a	H-4′b	H-2	H-5	OAc	NAc	CMe_2	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'a}$	$J_{3',4'b}$	$J_{4'a,4'b}$	$J_{2,5}$
2 [b]	4.70	4.23	4.28	4.19	3.77	7.62	7.04				6.6	5.0	3.2	5.0	9.4	0.9
3 [b]	4.93	4.74	4.39	3.96	3.82	7.62	7.06				4.8	4.8	5.2	6.2	8.9	0.8
4 [c]	4.95	5.46	5.52	4.40	3.96	8.14	7.48	2.07 2.11	2.59		6.0	8.9	3.9	5.3	10.1	1.5
5 [c]	5.15	5.52	5.67	4.20	4.01	8.10	7.52	1.92 2.03	2.57		4.3	5.0	6.0	6.5	9.5	1.5
6 [c]	5.12	5.07	4.93	4.00	3.93	7.61	6.97	1.54 1.36			0	6.1	3.9	0	10.4	1.0
7 [c]	5.14	5.56	5.48	4.13	3.96	7.57	7.05	2.05 1.92			4.4	4.8	5.5	6.8	9.6	0
8 [c]	4.76	4.30	4.36	4.17	3.79	7.42	6.84				5.4	4.0	3.9	5.1	9.5	1.5
9 [c]	4.92	4.49	4.29	4.08	4.05	7.50	6.88				7.0	5.4	4.2	3.1	9.5	1.3
10 [c]	5.00	5.09	4.94	4.01	3.97		6.78			1.35 1.54	1.0	6.2	3.7	1.5	10.4	1.3

[a] Recorded at 27°C (300 MHz), δ in ppm, J in Hz, internal standard Me_4Si. [b] Solvent CD_3OD. [c] Solvent $CDCl_3$.

TABLE II

^{13}C NMR data [a] for **2** and **3** [b]

Compound	C-1′	C-2′	C-3′	C-4′	C-2	C-4	C-5
2	79.03	77.23	72.34	73.96	136.99	138.06	118.78
3	77.88	73.75	73.30	73.03	136.40	137.04	121.32

[a] Recorded at 30°C in CD_3OD at 100.6 MHz, δ in ppm, internal standard Me_4Si. [b] Chemical shifts were assigned using selective ^{1}H-decoupling techniques.

Thus, the starting material **1** was regioselectively tritylated to give the *N*-trityl derivative **11** in good yield. Tosylation of the primary OH group in **11** was carried out by means of *p*-toluenesulphonyl chloride in the presence of pyridine at −15°C to produce the tosylate **12**, which after addition of triethylamine, according to the Yoshimura procedure[22], underwent intramolecular S_N2 ring closure to give the α anomer of 4-(D-erythrofuranosyl)-1-triphenylmethylimidazole (**9**). This anomer was identical (NMR, $[\alpha]_D^{20}$) with that recognized as **9** using NMR spectroscopy. The β anomer **8** was not detected (TLC) in the mixture.

Finally, we conclude that the stereospecific synthesis of **9** presented above undoubtedly proved the configuration of this compound and confirmed our assignments made above on the basis of the physical data.

EXPERIMENTAL

General methods.—Evaporations were conducted in vacuo at < 40°C (bath). Melting points were determined with a Buchi SMP 20 apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. IR spectra were recorded with a Spectromom 2000 MOM spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded with Bruker AC 200 and MSL 300 spectrometers. UV spectra were recorded with a Specord UV-VIS instrument. TLC was conducted on Silica Gel HF_{254} (Merck) plates with *A*, 4:1 CH_2Cl_2—acetone; *B*, 4:1 $CHCl_3$–MeOH; *C*, 9:1 $CHCl_3$–EtOH; and detection with UV light and I_2 vapour. Column chromatography was performed in the flash mode on Silica Gel 60 (Merck; 230–400 mesh). Elemental analyses were carried out by the Microanalysis Service of the Technical University of Łódź.

1-Acetyl-4-(2,3-di-O-acetyl-α- and -β-D-erythrofuranosyl)imidazole (**5** *and* **4**).—A solution of 4(5)-(D-*arabino*-tetritol-1-yl)imidazole hydrochloride (**1** HCl; 1.0 g, 4.45 mmol) in glacial AcOH (100 mL) was boiled for 15 h under reflux and then evaporated in vacuo to dryness. To the syrupy residue were added Ac_2O (3 mL) and Et_3N (1 mL), and the mixture was stirred at room temperature for 48 h. After addition of ether (50 mL), the salts were filtered off and washed with ether (3 × 20 mL). The combined filtrate and washings were evaporated in vacuo. Column chromatography of the residue (solvent *A*) gave **4** (840 mg), R_f 0.45 (solvent *A*); and **5** (290 mg), R_f 0.35 (solvent *A*) (combined yield, 86%). Compound **4** had mp 76–78°C (from CH_2Cl_2–isopropyl ether); $[\alpha]_D^{20}$ −59° (*c* 0.55, $CHCl_3$); ν_{max}^{KBr} 2940, 1745, 1710, 1605, 1490, 1380, 1240, 1085, 1050 cm^{-1}; λ_{max}^{CHCl3} 226 nm (ε 5600). The ^1H NMR data are given in Table I. Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.48; H, 5.65; N, 9.32.

Compound **5** was a syrup; $[\alpha]_D^{20}$ −8° (*c* 0.32, $CHCl_3$); ν_{max} 2940, 1745, 1715, 1610, 1485, 1380, 1240, 1085, 1050 cm^{-1}; λ_{max}^{CHCl3} 227 nm (ε 6700). The ^1H NMR data are given in Table I. Anal. Found: C, 52.55; H, 5.20; N, 9.30.

4(5)-(2,3-Di-O-acetyl-β-D-erythrofuranosyl)imidazole (**6**).—A solution of **4** (127 mg, 0.43 mmol) and $NaHCO_3$ (36 mg, 0.43 mmol) in water (1.5 mL) was stirred at

room temperature for 24 h. The water was removed in vacuo and the residue dried by several additions and repeated evaporations of anhyd EtOH (3 × 10 mL). Column chromatography (solvent *C*) gave **6** (98 mg, 90%) as a syrup; R_f 0.55 (solvent *C*); $[\alpha]_D^{20}$ −73.5° (*c* 1.05, MeOH); ν_{max} 1745, 1605, 1490, 1240, 1085 cm^{-1}. The ^1H NMR data are given in Table I. Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.70; H, 5.42; N, 10.85.

*4(5)-(2,3-Di-*O*-acetyl-α-*D*-erythrofuranosyl)imidazole* (**7**).—This compound was prepared from **5** (132 mg, 0.446 mmol) as described for **6**, to yield **7** (95 mg, 84%) as a syrup; R_f 0.45 (solvent *C*); $[\alpha]_D^{20}$ +36.5° (*c* 0.85, MeOH); ν_{max} 1745, 1605, 1485, 1240, 1085 cm^{-1}. The ^1H-NMR data are given in Table I. Anal. Found: C, 51.85; H, 5.45; N, 10.9.

*4(5)-(β-*D*-Erythrofuranosyl)imidazole* (**2**).—A solution of **4** (180 mg, 0.61 mmol) in MeOH (10 mL) was stirred slowly with Amberlyst A-26 (HO^-) resin at room temperature for 24 h. The resin was collected and washed with MeOH (2 × 10 mL). The combined filtrate and washings were concentrated in vacuo to give **2** (74 mg, 71%) as a syrup; $[\alpha]_D^{20}$ −56.5° (*c* 1.33, MeOH); ν_{max} 1610, 1490, 1080 cm^{-1}. The ^1H and ^{13}C NMR data are given in Tables I and II. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.48; H, 5.82; N, 16.30.

*4(5)-(α-*D*-Erythrofuranosyl)imidazole* (**3**).—This compound was prepared from **5** (74 mg, 0.25 mmol) as described for **2**, to yield **3** (33 mg, 78%) as a syrup; $[\alpha]_D^{20}$ −7.5° (*c* 1.37, MeOH), ν_{max} 1610, 1490, 1080 cm^{-1}. The ^1H and ^{13}C NMR data are given in Tables I and II. Anal. Found: C, 49.38; H, 5.70; N, 16.35.

*4-(β-*D*-Erythrofuranosyl)-1-triphenylmethylimidazole* (**8**).—A solution of **2** (378 mg, 2.22 mmol), trityl chloride (618 mg, 2.22 mmol), and Et_3N (1.0 mL) in anhyd DMF (6 mL) was stirred at room temperature for 24 h. The resulting suspension was poured into ice–water, and the precipitate was filtered off and washed successively with water and ether. The crude product was purified by column chromatography (solvent *C*), and recrystallized from CH_2Cl_2–isopropyl ether to give **8** (789 mg, 86%); R_f 0.3 (solvent *C*); mp 198–200°C; $[\alpha]_D^{20}$ −42° (*c* 1.0, $CHCl_3$). The ^1H NMR data are given in Table I Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.35; H, 5.70; N, 6.85.

*4-(α-*D*-Erythrofuranosyl)-1-triphenylmethylimidazole* (**9**).—This compound was prepared from **3** (127 mg, 0.75 mmol) as described for **8**, to yield, after column chromatography (solvent *C*), **9** (126 mg, 41%); R_f 0.55 (solvent *C*); mp 157–160°C (from CH_2Cl_2–isopropyl ether); $[\alpha]_D^{20}$ +38° (*c* 1.0, $CHCl_3$). The ^1H NMR data are given in Table I. Anal. Found: C, 75.42; H, 5.65; N, 6.70.

*4-(2,3-*O*-Isopropylidene-β-*D*-erythrofuranosyl)-1-triphenylmethylimidazole* (**10**).—To a stirred suspension of **8** (92 mg, 0.223 mmol) in anhyd acetone (1 mL) was added a solution of anhyd $ZnCl_2$ (30 mg, 0.22 mmol) in anhyd acetone (0.14 mL). After 48 h stirring at room temperature, a solution of K_2CO_3 (31 mg, 0.223 mmol) in water (0.05 mL) was added, and the precipitate was filtered off and washed successively with 1:1 ether–acetone (5 mL) and CH_2Cl_2 (10 mL). The combined filtrates were evaporated and the residue was purified by column chromatography

(solvent *C*) to give **10** as a foam (35 mg, 35%); R_f 0.55 (solvent *C*); $[\alpha]_D^{20}$ −32.5° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 1372, 1363, 1120, 1095, 1075 cm^{-1}. The ^1H NMR data are given in Table I. Anal. Calcd for $C_{29}H_{28}N_2O_3$: C, 76.97; H, 6.24; N, 6.19. Found: C, 76.65; H, 6.11; N, 6.15.

*4-(*D-arabino-*tetritol-1-yl)-1-triphenylmethylimidazole* (**11**).—To a stirred solution of **1** HCl (1.8 g, 8 mmol) and Et_3N (3.5 mL) in anhyd DMF (9 mL) was added dropwise trityl chloride (2.45 g, 8.8 mmol) in anhyd DMF (30 mL). After 1.5 h at room temperature, the resulting suspension was poured into ice–water, and the precipitate was filtered off and washed with ether. The crude product was recrystallized from acetone to give **11** (3.1 g, 90%); mp 160–162°C; $[\alpha]_D^{20}$ −1.8° (*c* 0.9, MeOH); ν_{max}^{KBr} 3380, 3140, 2940, 1660, 1600, 1490, 1440, 1215, 1080, 1035, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.76–4.01 (m, 5 H, H-1′,2′,3′,4′a,4′b), 7.17 (s, 1 H, H-5), 7.38–7.52 (m, 16 H, 3 C_6H_5 and H-2). Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.38; H, 5.85; N, 6.20.

*4-(α-*D-*Erythrofuranosyl)-1-triphenylmethylimidazole* (**9**) *from* (**11**).—To a stirred suspension of **11** (0.863 g, 2 mmol) and anhyd pyridine (0.395 g, 5 mmol) in anhyd CH_2Cl_2 (10 mL) was added dropwise at −15°C a solution of tosyl chloride (0.381 g, 2 mmol) in anhyd CH_2Cl_2 (10 mL). The resulting suspension was stirred for 3 h at −15°C and then for an additional 24 h at room temperature. The mixture was poured into ice–water, and the solid material was filtered off and washed with CH_2Cl_2. The organic solution was dried over anhyd $MgSO_4$, filtered, and concentrated to 5 mL. After addition of Et_3N (2 mL), the mixture was kept for 2 days, evaporated to dryness, and purified by column chromatography (solvent *C*) to give **9** (175 mg, 21.2%); R_f 0.55 (solvent *C*); mp 156–158°C (from CH_2Cl_2–isopropyl ether); $[\alpha]_D^{20}$ +38° (*c* 1.0, $CHCl_3$). The ^1H NMR data were identical with those given in Table I for **9**. Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.60; H, 5.75; N, 6.75.

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