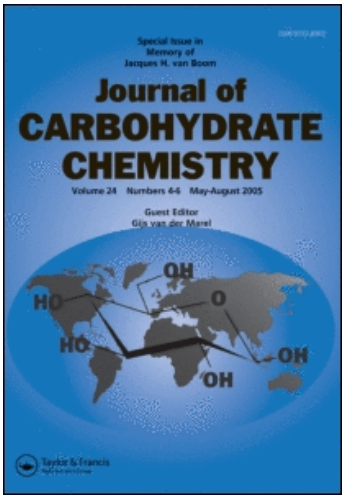

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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Online publication date: 12 November 2003

To cite this Article Methling, Karen , Kopf, Jürgen , Michalik, Manfred , Reinke, Helmut , Bürger, Christiane , Oberender, Heiderose and Peseke, Klaus(2003) 'Synthesis of Acyclic *C*-Nucleoside Analogues Using (*E*)-1,2-Dideoxy-1-dimethylamino-4,5:6,7-di-*O*-isopropylidene-d-*arabino*-hept-1-en-3-ulose ', Journal of Carbohydrate Chemistry, 22: 7, 537 — 548

To link to this Article: DOI: 10.1081/CAR-120026457

URL: http://dx.doi.org/10.1081/CAR-120026457

JOURNAL OF CARBOHYDRATE CHEMISTRY
Vol. 22, Nos. 7 & 8, pp. 537–548, 2003

Synthesis of Acyclic *C*-Nucleoside Analogues Using (*E*)-1,2-Dideoxy-1-dimethylamino-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-hept-1-en-3-ulose†

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ABSTRACT

1-Deoxy-3,4:5,6-di-*O*-isopropylidene-D-*arabino*-hex-2-ulose reacted with *N,N*-dimethylformamide dimethyl acetal and *tert*-butoxy[bis(dimethylamino)]methane, respectively, to furnish (*E*)-1,2-dideoxy-1-dimethylamino-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-hept-1-en-3-ulose. This push-pull activated heptenulose underwent ring closure reactions with various *N,N′*-nucleophiles like hydrazine hydrate, amidinium, guanidinium and isothiouronium salts in the presence of bases to yield pyrazole and pyrimidine derivatives, respectively, all of which derivatized with a di-*O*-isopropylidenated tetritol side chain. The isopropylidene groups were removed with

†This paper is dedicated to Professor Dr. Gérard Descotes on the occasion of his 70th birthday.

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DOI: 10.1081/CAR-120026457
0732-8303 (Print); 1532-2327 (Online)

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methanolic HCl in the pyrazole series, whereas aq TFA was used in the case of pyrimidine analogues.

Key Words: *C*-Nucleoside analogues; Heptenuloses; Push-pull alkenes; Tetritols; Pyrazoles; Pyrimidines.

INTRODUCTION

Naturally occurring *C*-nucleosides and their synthetic analogues show interesting antiviral and antibiotic properties.[1–4] Besides, owing to the C-C-linkage between the heterocycle and the ribofuranose/deoxyribofuranose, *C*-nucleosides are more stable towards chemical and enzymatic hydrolysis than their *N*-nucleoside counterparts. In acyclic *C*-nucleoside analogues, the furanose unit is replaced by a polyhydroxyalkyl ether or a polyhydroxyalkyl chain. Some of these compounds were isolated from natural sources and are of great interest because of their biological activities.[5–9] Therefore, the development of strategies for the synthesis of acyclic *C*-nucleoside analogues is of growing interest to organic chemists.[3,4,10] Cyclic monosaccharide derivatives with push–pull activated C-C-double bond are suitable compounds for cyclization reactions with *N*-nucleophiles furnishing nitrogen heterocycles anellated to the sugar ring[11–13] or *C*-nucleoside analogues.[14–17] Furthermore, ring transformations of such functionalized monosaccharides yielded new acyclic *C*-nucleoside analogues.[18–20]

In this paper we describe the synthesis of acyclic *C*-nucleoside analogues with pyrazole and pyrimidine rings as nucleobases, starting from the push–pull activated dimethylamino enulose **2**. The description also includes investigations of the antiviral potency of selected compounds against HSV-1.

RESULTS AND DISCUSSION

The starting material, 1-deoxy-3,4:5,6-di-*O*-isopropylidene-D-*arabino*-hex-2-ulose (**1**),[21] was synthesized from 2,3:4,5-di-*O*-isopropylidene-D-arabinose on the basis of D-mannitol in five steps.[22–25] Chain elongation to give the (*E*)-1,2-dideoxy-1-dimethylamino-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-hept-1-en-3-ulose (**2**) was achieved by the reaction of the ketone **1** with either *N,N*-dimethylformamide dimethyl acetal or *tert*-butoxy[bis(dimethylamino)]methane[26] (Scheme 1).[13,27] The dimethylamino enulose **2** was treated with hydrazine hydrate in EtOH under reflux to yield 3-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl]-1*H*-pyrazole (**3a**) in 96% yield (Scheme 1).

N-Acetylation of pyrazole **3a** with acetyl chloride under basic conditions yielded the 1-acetyl-5-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-1*H*-pyrazole (**4**, 95%).[28] In a ^{1}H,^{1}H-NOESY-spectrum, cross peaks were found between the protons of the acetyl group and the protons H-1′ and H-2′ confirming the position of the acetyl group.

Reaction of **2** with 2-hydrazinoethanol furnished a mixture of the 1-(2-hydroxyethyl)]-3-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-1*H*-pyrazole (**3b**) and the corresponding regioisomer 1-(2-hydroxyethyl)-5-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-1*H*-pyrazole (44%) in a 32:1 ratio. The pure product **3b** could be

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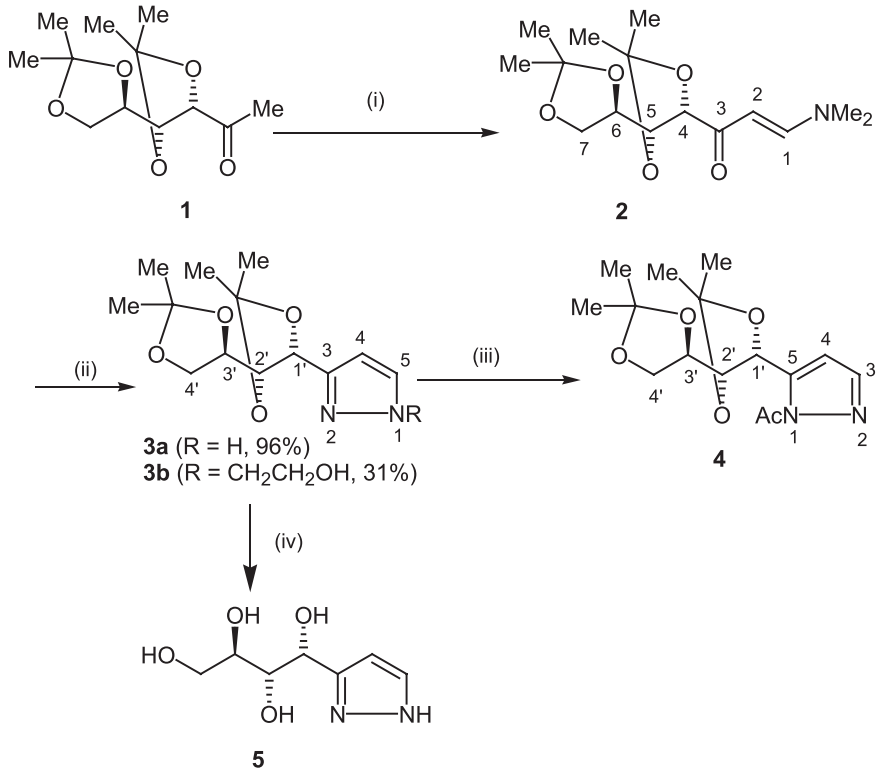

Scheme 1. (i) A: $HC(NMe_2)(OMe)_2$, toluene (82%); B: $HC(NMe_2)_2O$-*t*-Bu, THF (99%); (ii) $RNHNH_2$, EtOH; (iii) AcCl, 2,6-lutidine, CH_2Cl_2 (**3a**, 95%); (iv) 1. HCl, MeOH, 2. basic ion-exchange resin (**3a**, 98%).

obtained by HPLC in 31% yield. Cross peaks in the $^1H,^1H$-NOESY-spectrum were observed between H-5 of the pyrazole ring and the NCH_2-protons confirming the position of the hydroxyethyl group.

Deprotection of **3a** was carried out with HCl/MeOH at 0°C[29] and subsequent treatment of the resulting hydrochloride with basic ion-exchange at 65°C afforded the pyrazole **5** (98%) as colourless crystals.

The pyrimidine derivatives **6a–c** bearing various substituents at position 2 could be synthesized by cyclization reactions of the intermediate **2** with amidines and guanidine, respectively, liberated from the corresponding hydrochlorides upon treatment with NaOEt (Scheme 2). All analytical data were in accordance with the proposed structures **6a–c**. The structure of **6c** was further confirmed by X-ray crystallography. An ORTEP-drawing is shown in Figure 1 and displays the numbering scheme of the atoms. The crystal structure of **6c** is influenced by the formation of infinite chains of hydrogen bridges both along the a and the b axes. The dominating motif is that of the NH_2-group pointing to the nitrogen atoms in two different pyrimidine rings (symmetry codes $-$ x + 1.5, y $-$ 0.5, $-$ z + 0.25 and $-$ x + 1.5, y + 0.5, $-$ z + 0.25).

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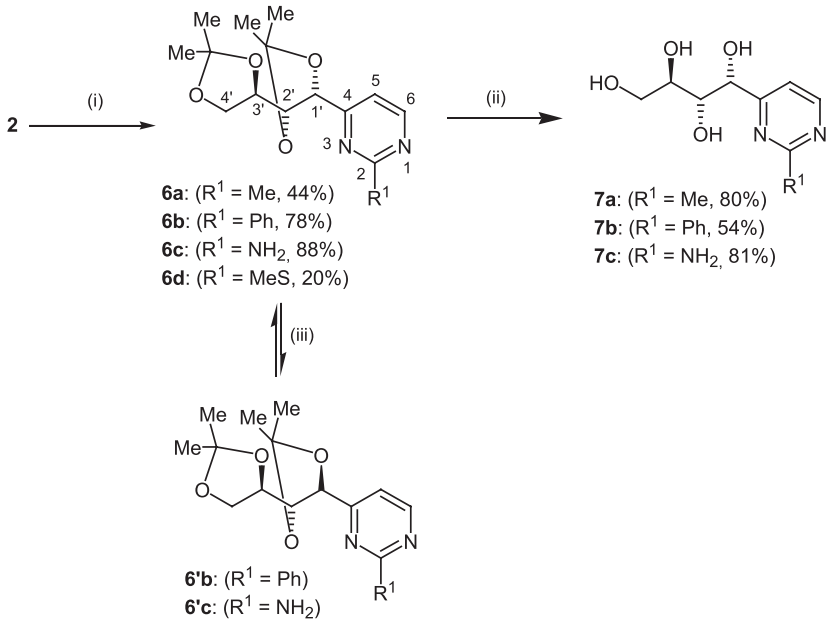

Scheme 2. (i) $R^1C(=NH_2^+)NH_2\ X^-$, NaOEt, EtOH or NaH/DMF (**6d**), $X^- = Cl^-$, $MeSO_4^-$; (ii) 1. CF_3COOH, THF, H_2O, 2. basic ion-exchange resin; (iii) NaOEt.

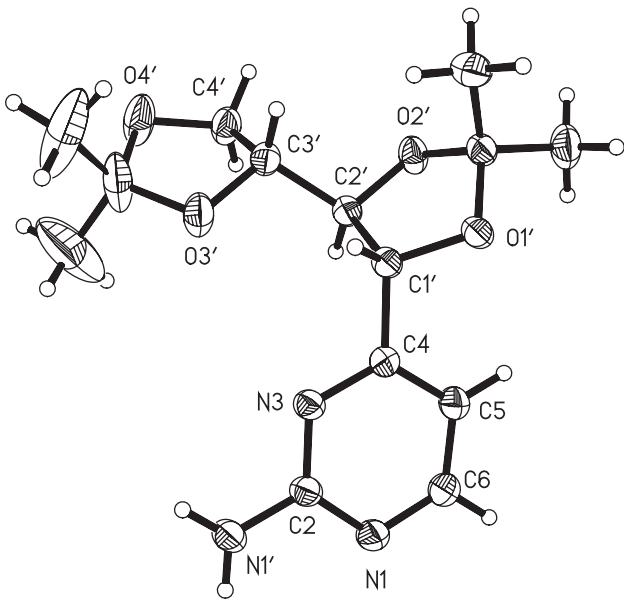

Figure 1. ORTEP drawing of **6c**, 30% probability of the thermal ellipsoids.

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Using an excess of NaOEt in the liberation of benzamidine from the corresponding hydrochloride during the cyclization of **2** to give **6b**, the side product **6′b** with a *ribo*-configurated tetrahydroxybutyl chain was isolated (6%) and characterized by ^{1}H NMR spectroscopy. Furthermore, the synthesis of **6c** in the presence of an excess of base afforded the *ribo*-configured compound **6′c** in 2% yield. The *ribo*-configurated compounds were formed by isomerization of **6b**,**c** catalyzed with NaOEt. It is necessary to avoid the use of excess of NaOMe and prolonged heating (ca $\sim$ 6 h) to minimize racemization of the pyrimidines to the isomeric compounds **6′b**,**c**. Treatment of **2** with *S*-methylisothiouronium sulfate in EtOH using NaOEt as a base gave the pyrimidine derivative **6d** in 15% yield. A slightly higher yield (20%) of pyrimidine **6d** was obtained by using NaH as the base in DMF.

The deprotected pyrimidine nucleoside analogues **7a–c** were obtained through reaction of the compounds **6a–c** with TFA acid in a mixture of THF and water.[30] The pyrimidine **7a** could be obtained after recrystallization from anhyd acetone (80%), whereas compounds **7b** and **7c** were purified by HPLC (RP18).

Biological Activity

Compounds **3a**, **4**, **5**, **6a–c** and **7a–c** were tested in vitro for their cytotoxicity and antiviral effects against HSV-1 (strain Mac Intyre) in a cell culture system with human embryonic fibroblasts (HF-cells) using acyclovir as a reference. The investigations of the cell morphology was controlled under the inverted microscope and compared to cell morphology of the reference cells. The compounds did not show any cytotoxicity nor any antiviral effects against HSV-1 in various concentration ranges. In comparison with acyclovir, it seems an acyclic ether side chain is essential for activity against HSV-1.

X-Ray Crystallography

A crystal of **6c** was measured on an Enraf-Nonius CAD4 4-circle-diffractometer with Cu-K_α radiation and a graphite monochromator using the CAD4 EXPRESS data collection software (Enraf-Nonius, 1994). The structure was solved with SHELXS-97 (G.M. Sheldrick, Universität Göttingen, 1990) and refined with the full matrix least squares methods of SHELXL-97 on F^2 (G.M. Sheldrick, Universität Göttingen, 1997). All non-hydrogen atoms were refined anisotropically and the hydrogens were put into theoretical positions and refined according to the riding model. CCDC 204493 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Further details of the crystal structure and the refinement calculations for **6c**: Molecular formula $C_{14}H_{21}N_3O_4$, formular weight 295.34, temperature 293(2) K, melting point 331 K, crystal system tetragonal, space group (H.-M.) $P4_12_12$, space group (Hall) P 4abw 2nw, cell dimensions a = 7.6235(3) Å, b = 7.6235(3) Å, c = 54.621(3) Å, $\alpha = \beta = \gamma = 90°$, cell volume: 3174.4(3) Å^3, Z = 8; F(000) = 1264, density (calcd.): 1.236 Mg/m^3, absorption coefficient μ = 0.758 mm^{-1}, crystal size 0.30 $\times$ 0.30 $\times$ 0.20 mm^3, Θ range for data collection 3.24 to 76.37°, index ranges $-9 \leq h \leq 0$, $0 \leq k \leq 9$, $-68 \leq l \leq 0$, reflections collected 3868, independent

reflections 3353 [R(int) = 0.0345], completeness to $\Theta = 76.37°$: 100.0 %, max./min. transmission 0.8632/ 0.8045, data/restraints/parameters 3353 / 0 / 216, Goodness-of-fit on F^2 1.084, final R indices: R1 = 0.0419, wR2 = 0.1202, observed reflections 3241, observation criterion $I > 2\sigma(I)$, R indices (all data): R1 = 0.0434, wR2 = 0.1216, absolute structure parameter: − 0.1(2), extinction coefficient 0.0346(14), largest diff. peak/ hole 0.229/− 0.238 e.$Å^{-3}$.

EXPERIMENTAL

General methods. Melting points were determined with a Boëtius melting point apparatus and are corrected. Optical rotations were measured with a Polar LμP (IBZ Meßtechnik) polarimeter. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 250 (250.1 MHz and 62.9 MHz, respectively) and a Bruker ARX 300 (300.1 MHz and 75.5 MHz, respectively). The calibration of spectra was carried out by means of solvent peaks ($CDCl_3$: δ_H 7.25; δ_C 77.0; DMSO-d_6: δ_H 2.50; δ_C 39.7 ; dioxane: δ_H 3.71; δ_C 67.6 for recording in D_2O). The ^{13}C NMR signals were assigned by DEPT and/or two-dimensional ^{1}H,^{13}C correlation spectra. Mass spectra were obtained with an AMD 402/3 spectrometer (AMD Intectra GmbH). Elemental analyses were performed with a Leco CHNS-932. Column chromatography was carried out on silica gel 60 (63–200 μm, Merck). Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} foils (Merck) with detection by UV-light and by charring with 10% methanolic sulphuric acid. HPLC separations were carried out under isocratic conditions (Lichrosorb Si 60, 7 μm, column: l = 250 mm, d = 25 mm, flow rate: 20 mL/min; Lichrosorb RP −18, 7 μm, column: l = 250 mm, d = 10 mm, flow rate: 15 mL/min). Products were detected with an UV-detector (Knauer) at 254 nm (toluene-ethyl acetate) and at 288 nm (H_2O-MeOH), respectively. Solvents and liquid reagents were purified and dried according to recommended procedures.

(*E*)-1,2-Dideoxy-1-dimethylamino-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-hept-1-en-3-ulose (2). Method A: Under an argon atmosphere, compound **1**[22] (244 mg, 1.00 mmol) and *tert*-butoxy[bis(dimethylamino)]methane (260 mg, 1.50 mmol) in anhyd THF (10 mL) were stirred under reflux for 2 h. After completion of the reaction (monitored by TLC; occasionally further addition of the reagent), the solvent was evaporated *in vacuo* and the residue purified by column chromatography (ethyl acetate) to yield 298 mg (99%) of **2** as a greenish syrup.

Method B: Under an argon atmosphere, compound **1** (244 mg, 1.00 mmol) was dissolved in anhyd toluene (10 mL). After addition of *N,N*-dimethylformamide dimethyl acetal (595 mg, 5.00 mmol) the solution was heated under reflux for 8 h. More *N,N*-dimethylformamide dimethyl acetal (119 mg, 1.00 mmol) was added and the reaction mixture was heated for another 16 h. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography to yield 244 mg (82%) of compound **2** as a greenish syrup; $[\alpha]_D^{22.4}$ + 29.3 (*c* 1.0, $CHCl_3$); R_f 0.22 (ethyl acetate); IR (capillary): 1648.7 cm^{-1} (C = O); ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.33, 1.37, 1.41, 1.44 (4s, 12H, 4 × CH_3), 2.83, 3.07 (2s, 6H, $N(CH_3)_2$), 3.96–4.12 (m, 2H, H-7a, H-7b), 4.23–4.33 (m, 3H, H-4, H-5, H-6), 5.43 (d, $J_{1,2}$ 12.6 Hz, 1H, H-2), 7.64 (d, 1H, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.3, 26.4, 27.1, 27.1 (4 × CH_3), 37.1, 44.8

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($N(CH_3)_2$), 65.7 (C-7), 76.4, 78.7 (C-4, C-6), 81.6 (C-5), 91.4 (C-2), 109.4, 110.5 ($2xC(CH_3)_2$), 153.7 (C-1), 194.7 (C-3). MS: *m/z* (FAB): 300 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.08; H, 8.19; N, 4.71.

3-(1,2:3,4-Di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-1*H*-pyrazole (3a). A solution of **2** (299 mg, 1.00 mmol) and hydrazine hydrate (175 mg, 3.5 mmol) in EtOH (7 mL) was heated under reflux for 2 h and then concentrated. After work-up, compound **3a** (257 mg, 96%) was isolated by column chromatography (1:1, toluene-ethyl acetate) as colourless needles; mp 60–63°C (toluene-ethyl acetate); $[\alpha]_D^{24.0}$ +3.4 (*c* 1.0, $CHCl_3$); R_f 0.33 (1:1, toluene-ethyl acetate); IR ($CHCl_3$): 3464 cm^{-1} (NH); ^1H NMR (300.1 MHz, $CDCl_3$): δ 1.31, 1.33, 1.45, 1.47 (4s, 12H, 4 × CH_3), 3.94 (dd, $J_{4'a,4'b}$ 8.6 Hz, $J_{3',4'a}$ 5.1 Hz, 1H, H-4′a), 4.07 (t, $J_{2',3'}$ 7.5 Hz, 1H, H-2′), 4.12 (dd, $J_{3',4'b}$ 6.3 Hz, 1H, H-4′b), 4.23 (m, 1H, H-3′), 5.06 (d, $J_{1',2'}$ 7.5 Hz, 1H, H-1′), 6.34 (d, $J_{4,5}$ 2.1 Hz, 1H, H-4), 6.90 (brs, 1H, NH), 7.52 (d, 1H, H-5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.2, 26.3, 26.7, 26.9 (4 × CH_3), 67.0 (C-4′), 75.3 (C-1′), 76.6 (C-3′), 81.4 (C-2′), 103.4 (C-4), 109.9, 110.1 (2 $C(CH_3)_2$), 134.4 (C-5), 146.3 (C-3). MS: *m/z* (EI): 268 $[M]^+$.

Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 57.94; H, 7.28; N 10.50.

1-(2-Hydroxyethyl)-3-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-1*H*-pyrazole (3b). Compound **2** (120 mg, 0.40 mmol) was dissolved under argon in anhyd EtOH (5 mL) and treated with 2-hydrazinoethanol (30 mg, 0.40 mmol). After heating under reflux for 2 h, the reaction mixture was treated with another portion of 2-hydrazinoethanol (30 mg, 0.40 mmol) and heated for another 2 h. The solvent was removed, and 55 mg (44%) of a mixture of compounds **3b** and the isomeric 1-(2-hydroxyethyl)-5-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-1*H*-pyrazole was isolated by column chromatography (ethyl acetate). Isolation of pure compound **3b** as a colourless syrup (39 mg, 31%) was carried out by HPLC (1:1, toluene-ethyl acetate); $[\alpha]_D^{25.0}$ +7.2 (*c* 1.0, $CHCl_3$); R_f 0.25 (ethyl acetate); R_f 0.09 (1:1, toluene-ethyl acetate); ^1H NMR (300.1 MHz, DMSO-d_6): δ 1.21, 1.23, 1.36, 1.37 (4s, 12H, 4 × CH_3), 3.70 (q, *J* 5.5 Hz, 2H, CH_2OH), 3.76 (dd, $J_{4'a,4'b}$ 8.3 Hz, $J_{3',4'a}$ 5.7 Hz, 1H, H-4′a), 4.00 (dd, $J_{3',4'b}$ 6.3 Hz, 1H, H-4′b), 4.11 (q, $J_{2',3'}$ 5.8 Hz, 1H, H-3′), 4.16 (q, 2H, NCH_2), 4.25 (dd, $J_{1',2'}$ 7.6 Hz, $J_{2',3'}$ 5.5 Hz, 1H, H-2′), 4.81 (t, 1H, OH), 4.84 (d, 1H, H-1′), 6.26 (d, $J_{4,5}$ 2.2 Hz, 1H, H-4), 7.64 (d, 1H, H-5); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 25.1, 26.2, 26.9, 26.9 (4 × CH_3), 53.7 (NCH_2), 61.8 (CH_2OH), 66.4 (C-4′), 75.4 (C-1′), 76.1 (C-3′), 81.0 (C-2′), 104.0 (C-4), 109.6, 109.8 ($2xC(CH_3)_2$), 131.0 (C-5), 150.6 (C-3). MS: *m/z* (EI): 312 $[M]^+$.

Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.25; H, 7.71; N, 8.98.

1-Acetyl-5-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-1*H*-pyrazole (4). Compound **3a** (40 mg, 0.15 mmol) was dissolved in anhyd CH_2Cl_2 (3 mL) and treated with acetyl chloride (17 mg, 0.22 mmol) and 2,6-lutidine (23 mg, 0.22 mmol). After a period of 2 and 4 days each, more acetyl chloride (17 mg, 0.22 mmol) and 2,6-lutidine (23 mg, 0.22 mmol) were added and the mixture was stirred at 22°C for 5 days. The solvent was evaporated in vacuo and 44 mg of **4** (95%) were isolated as a colourless syrup by column chromatography (5:1, toluene-ethyl acetate); $[\alpha]_D^{23.6}$ +14.6 (*c* 0.5,

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$CHCl_3$); R_f 0.34 (5:1, toluene-ethyl acetate); IR (KBr): 1740 cm^{-1} (C = O); ^1H NMR (300.1 MHz, $CDCl_3$): δ 1.26, 1.30, 1.42, 1.47 (4s, 12H, 4 × CH_3), 2.66 (s, 3H, CH_3C = O), 3.99 (dd, $J_{4'a,4'b}$ 8.6 Hz, $J_{3',4'a}$ 4.6 Hz, 1H, H-4′a), 4.10 (dd, $J_{3',4'b}$ 5.9 Hz, 1H, H-4′b), 4.23 (m, 1H, H-3′), 4.28 (t, $J_{2',3'}$ 6.9 Hz, 1H, H-2′), 4.99 (d, $J_{1',2'}$ 6.9 Hz, 1H, H-1′), 6.49 (d, $J_{3,4}$ 2.9 Hz, 1H, H-4), 8.19 (d, 1H, H-3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.7 (CH_3C = O), 25.2, 26.4, 26.8, 27.0 (4 × CH_3), 66.6 (C-4′), 75.3 (C-1′), 76.4 (C-3′), 80.7 (C-2′), 108.7 (C-4), 109.7, 110.5 (2x$C(CH_3)_2$), 129.9 (C-3), 155.8 (C-5), 169.5 (C = O). MS: *m*/*z* (EI): 310 $[M]^+$.

Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 58.20; H, 7.22; N, 9.10.

3-(D-*arabino*-Tetritol-1-yl)-1*H*-pyrazole (5). Compound **3a** (125 mg, 0.47 mmol) was dissolved in anhyd MeOH (5 mL) and treated with 5M HCl/MeOH (0.5 mL) at 0°C. After 15 min, more HCl in MeOH (0.5 mL) was added. After keeping the solution for another 15 min at 0°C, the solvent was evaporated in vacuo at 20°C. The residue was dissolved in H_2O (5 mL) and extracted with CH_2Cl_2 (3 mL × 3). The aqueous layer was concentrated, the residue was dissolved in anhyd MeOH (10 mL) and the solution refluxed in the presence of an ion-exchange resin (DOWEX, strongly basic) for 2 h. After the mixture was cooled the resin was filtered off and washed with anhyd MeOH (3 × 50 mL). The solvent was removed and the colourless solid was dried in vacuo to yield 86 mg of compound **5** (98%); mp 133.5–135.5°C (MeOH); $[\alpha]_D^{24.6}$ − 17.6 (*c* 1.0, H_2O); ^1H NMR (250.1 MHz, DMSO-d_6): δ 3.48 (m, 4H, H-2′, H-3′, H-4′), 4.88 (d, $J_{1',2'}$ 2.1 Hz, 1H, H-1′), 5.28 (brs, 5 H, 4 OH, NH), 6.22 (d, $J_{4,5}$ 2.0 Hz, 1H, H-4), 7.55 (d, 1H, H-5; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 63.6 (C-4′), 66.3 (C-1′), 71.5 (C-3′), 74.5 (C-2′), 103.1 (C-4), 133.3 (C-5), 150.4 (C-3). MS: *m*/*z* (FAB): 189 $[M + H]^+$.

Anal. Calcd for $C_7H_{12}N_2O_4$: C, 44.68; H, 6.43; N, 14.89. found: C, 44.77; H, 6.41; N, 14.79.

4-(1,2:3,4-Di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-2-methylpyrimidine (6a). Acetamidinium chloride (40 mg, 0.43 mmol) was suspended in anhyd EtOH (2 mL) under ultrasonic irradiation for 5 min and 1M of NaOEt/EtOH (0.43 mL) were added. The mixture was stirred for 5 min to obtain an ethanolic solution of acetamidine. Compound **2** (70 mg, 0.23 mmol) was dissolved in anhyd EtOH (3 mL) and the solution of acetamidine was added. After a period of 2 and 4 h each, more acetamidine (25 mg, 0.43 mmol) in anhyd EtOH (2.43 mL) was added and the reaction mixture was heated under reflux for 6 h. The solvent was removed *in vacuo*, and the residue was dissolved in H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water, dried and concentrated. The residue was purified by column chromatography (1:3, toluene-ethyl acetate) to yield 30 mg of **6a** (44%) as a colourless syrup; $[\alpha]_D^{24.5}$ − 9.1 (*c* 0.1, $CHCl_3$); R_f 0.35 (1:3, toluene-ethyl acetate); ^1H NMR (300.1 MHz, $CDCl_3$): δ 1.27, 1.33, 1.44, 1.51 (4s, 12H, 4 × CH_3), 2.70 (s, 3H, 2-CH_3), 4.11 (m, 2H, H-4′), 4.27 (dd, $J_{1',2'}$ 6.9 Hz, $J_{2',3'}$ 5.9 Hz, 1H, H-2′), 4.38 (q, $J_{3',4'} \sim$ 5.8 Hz, 1H, H-3′), 4.83 (d, 1H, H-1′), 7.31 (d, $J_{5,6}$ 5.1 Hz, 1H, H-5), 8.60 (d, 1H, H-6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.2 (CH_3), 25.9 (2-CH_3), 26.3, 26.8, 27.2 (3×CH_3), 66.1 (C-4′), 76.3 (C-3′), 80.2, 81.4 (C-1′, C-2′), 109.7, 111.2 (2×$C(CH_3)_2$), 115.5 (C-5), 157.1 (C-6), 167.8 (C-2), 168.2 (C-4). MS: *m*/*z* (EI): 294 $[M]^+$.

Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 60.99; H, 7.76; N, 9.13.

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4-(1,2:3,4-Di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-2-phenylpyrimidine (6b). Compound **2** (70 mg, 0.23 mmol) was reacted with benzamidinium chloride (67 mg, 0.43 mmol) as described for the preparation of **6a**. Column chromatography (10:1, toluene-ethyl acetate) yielded 64 mg of compound **6b** (78%) as colourless needles; mp 66–69°C (toluene-ethyl acetate); $[\alpha]_D^{24.5}$ − 13.6 (*c* 1.0, $CHCl_3$); R_f 0.33 (10:1, toluene-ethyl acetate); ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 1.30, 1.36, 1.49, 1.55 (4s, 12H, 4 × CH_3), 4.16 (dd, $J_{4'a,4'b}$ 8.5 Hz, 1H, H-4′a), 4.18 (dd, 1H, H-4′b), 4.45 (m, 2H, H-2′, H-3′), 4.97 (d, $J_{1',2'}$ 6.5 Hz, 1H, H-1′), 7.39 (d, $J_{5,6}$ 5.0 Hz, 1H, H-5), 7.44-7.53 (m, 3H, phenyl H-3, H-4, H-5), 8.40–8.50 (m, 2H, phenyl H-2, H-6), 8.79 (d, 1H, H-6); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 25.3, 26.3, 26.9, 27.2 (4 CH_3), 66.1 (C-4′), 76.4 (C-3′), 80.2 (C-1′), 81.3 (C-2′), 109.7, 111.2 (2 $C(CH_3)_2$), 116.4 (C-5), 128.2, 128.5 (phenyl C-2, C-3, C5, C-6), 130.8 (phenyl C-4), 137.3 (phenyl C-1), 157.6 (C-6), 164.2 (C-2), 168.3 (C-4). MS: *m/z* (FAB): 357 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.15; H, 6.63; N, 7.70.

2-Amino-4(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)pyrimidine (6c). Compound **2** (70 mg, 0.23 mmol) was reacted with guanidinium chloride (41 mg, 0.43 mmol) as described above for the preparation of compound **6a**. The product was isolated by column chromatography (1:3, toluene-ethyl acetate). Colourless plates of **6c** (60 mg, 88%) were obtained by recrystallization from $CHCl_3$/petroleum ether (40–60°C); mp 58–59°C; $[\alpha]_D^{24.9}$ −9.9 (*c* 1.0, $CHCl_3$); R_f 0.39 (1:3, toluene-ethyl acetate); IR ($CHCl_3$): 3529 cm^{-1}, 3424 (NH_2); ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 1.31, 1.33, 1.43, 1.49 (4s, 12H, 4 × CH_3), 4.07 (dd, $J_{4'a,4'b}$ 8.5 Hz, 1H, H-4′a), 4.10 (dd, 1H, H-4′b), 4.24 (dd, $J_{1',2'}$ 7.0 Hz, $J_{2',3'}$ 5.8 Hz, 1H, H-2′), 4.36 (q, $J_{3',4'}$ 5.8 Hz, 1H, H-3′), 4.66 (d, 1H, H-1′), 5.08 (brs, 2H, NH_2), 6.81 (d, $J_{5,6}$ 5.0 Hz, 1H, H-5), 8.26 (d, 1H, H-6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.3, 26.3, 26.8, 27.1 (4 × CH_3), 66.0 (C-4′), 76.3 (C-3′), 80.1 (C-1′), 81.0 (C-2′), 108.8 (C-5), 109.6, 111.0 (2×$C(CH_3)_2$), 158.7 (C-6), 162.7 (C-2), 169.2 (C-4). MS: *m/z* (FAB): 296 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{21}N_3O_4$: C, 56.94; H, 7.17; N, 14.23. Found: C, 56.85; H, 7.11; N, 13.93.

4-(1,2:3,4-Di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl]-2-methylsulfanylpyrimidine (6d). Method A: A mixture of compound **2** (70 mg, 0.23 mmol) in anhyd DMF (8 mL) containing *S*-methylisothiouronium sulfate (320 mg, 1.15 mmol) and NaH (60% suspension in mineral oil, 115 mg, 2.87 mmol) was stirred at 20°C for 48 h, and then poured onto ice water (75 mL). The mixture was extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic layers were washed with water (3 × 100 mL) and dried (Na_2SO_4). The solvent was evaporated and 15 mg (20%) of compound **6d** was isolated from the residue by column chromatography (4:1, toluene-ethylacetate) as a colourless syrup.

Method B: To a solution of **2** (70 mg, 0.23 mmol) in anhyd EtOH (5 mL), 1M ethanolic NaOEt (0.60 mL) was added, and the reaction mixture was heated under reflux. A suspension of *S*-methylisothiouronium sulfate (80 mg, 0.29 mmol) in anhyd EtOH (2 mL) was added slowly to the refluxing reaction mixture. After a period of 2 and 8 h each, NaOEt solution (0.30 mL) and *S*-methylisothiouronium sulfate (40 mg, 0.14 mmol) were added and the mixture was heated under reflux for 14 h. The solvent was evaporated to give **6d** (11 mg, 15%) isolated as described in method A;

$[\alpha]_D^{23.1}$ −10.6 (*c* 0.5, $CHCl_3$); R_f 0.52 (4:1, toluene-ethyl acetate); ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.30, 1.33, 1.44, 1.51 (4s, 12H, 4 × CH_3), 2.55 (s, 3H, SCH_3), 4.08 (dd, $J_{4'a,4'b}$ 8.5 Hz, 1H, H-4′a), 4.11 (dd, 1H, H-4′b), 4.31 (dd, $J_{1',2'}$ 6.6 Hz, $J_{2',3'}$ 5.7 Hz, 1H, H-2′), 4.38 (q, $J_{3',4'}$ 5.8 Hz, 1H, H-3′), 4.81 (d, 1H, H-1′), 7.15 (d, $J_{5,6}$ 5.1 Hz, 1H, H-5), 8.49 (d, 1H, H-6); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (SCH_3), 25.2, 26.4, 26.9, 27.2 (4 × CH_3), 66.1 (C-4′), 76.3 (C-3′), 80.0 (C-1′), 81.2 (C-2′), 109.7, 111.3 (2×$C(CH_3)_2$), 113.6 (C-5), 157.5 (C-6), 168.3 (C-4), 172.5 (C-2). MS: *m/z* (FAB): 327 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{22}N_2O_4S$: C, 55.20; H, 6.79; N, 8.58; S, 9.82. Found: C, 54.93; H, 6.91; N, 8.55; S, 9.83.

2-Methyl-4-(D-*arabino*-tetritol-1-yl)pyrimidine (7a). To a solution of **6a** (50 mg, 0.17 mmol) in THF (1 mL) and H_2O (2 mL), was added TFA (10 μL, 0.13 mmol) and the mixture was stirred for 8 h at 70°C. More TFA (10 μL, 0.13 mmol) was added and the solution was stirred for another 8 h at 70°C. After cooling to 22°C, the solution was treated with ion-exchange resin (DOWEX, strongly basic) for 30 min at 65°C. At 22°C, the resin was filtered off and washed with H_2O (3 × 5 mL). Removal of the solvent followed by recrystallization from anhyd acetone gave **7a** (29 mg, 80%) as a colourless solid; mp 220–221.5°C (decomposition); $[\alpha]_D^{24.0}$ −77.6 (*c* 0.5, H_2O); R_f 0.29 (RP18, H_2O); ^1H NMR (250.1 MHz, D_2O): δ 2.68 (s, 3H, 2-CH_3), 3.64–3.74, 3.84–3.92 (2m, 4H, H-2′, H-3′, H-4′), 5.02 (brs, 1H, H-1′), 7.54 (d, $J_{5,6}$ 5.3 Hz, 1H, H-5), 8.67 (d, 1H, H-6); ^{13}C NMR (62.9 MHz, D_2O): δ 27.0 (2-CH_3), 65.9 (C-4′), 73.9, 74.9, 76.2 (C-1′, C-2′, C-3′), 119.1 (C-5), 160.0 (C-6), 169.6 (C-2), 174.0 (C-4). MS: *m/z* (FAB): 215 $[M + H]^+$.

Anal. Calcd for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.69; H, 6.53; N, 13.00.

2-Phenyl-4-(D-*arabino*-tetritol-1-yl)pyrimidine (7b). Compound **6b** (61 mg, 0.17 mmol) was deprotected as described for the preparation of compound **7a**. The resin was washed with H_2O/ MeOH (1:1, v/v; 3 × 5 mL). The obtained white solid was purified by RP-HPLC (1.5:1, H_2O-MeOH) to yield **7b** (42 mg, 54%) as colourless needles; mp 180–182°C (H_2O-MeOH); $[\alpha]_D^{22.4}$ −74.0 (*c* 0.36, MeOH); R_f 0.35 (RP18 1.5:1, H_2O-MeOH); ^1H NMR (250.1 MHz, DMSO-d_6): δ 3.48 (dd, $J_{4'a,4'b}$ 11.8 Hz, $J_{3',4'a}$ 6.5 Hz, 1H, H-4′a), 3.66 (m, 2H, H-3′, H-4′b), 3.82 (dd, $J_{2',3'}$ 8.6 Hz, 1H, H-2′), 4.96 (dd, $J_{1',2'}$ 1.6 Hz, 1H, H-1′), 5.91 (brs, 4H, 4 OH), 7.50–7.56 (m, 3H, phenyl H−3+ H−4+ H−5), 7.59 (dd, $J_{1',5}$ 0.7 Hz, $J_{5,6}$ 5.2 Hz, 1H, H-5), 8.35–8.44 (m, 2H, phenyl H−2+ H−6), 8.85 (d, 1H, H-6); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 63.5 (C-4′), 71.2 (C-3′), 72.3 (C-1′), 73.9 (C-2′), 117.3 (C-5), 127.7, 128.6 (phenyl H−2+ H−3+ H−5 + H−6), 130.6 (*p*-Ph), 137.5 (*i*-Ph), 157.1 (C-6), 162.2 (C-2), 173.6 (C-4). MS: *m/z* (FAB): 277 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86, H, 5.84; N, 10.14. Found: C, 60.23; H, 5.63; N, 9.95.

2-Amino-4-(D-*arabino*-tetritol-1-yl)pyrimidine (7c). Compound **6c** (118 mg, 0.40 mmol) was dissolved in a mixture of THF (2 mL) and H_2O (4 mL) and treated with TFA (88 mg, 0.78 mmol). After stirring for 8 h at 65°C, excess of TFA (30 μL, 0.39 mmol) was added. The solution was stirred for 16 h at 65°C. After cooling to 22°C ion-exchange resin (DOWEX, strongly basic) was added and the mixture was stirred for 1 h at 65°C. At 22°C the resin was filtered off and washed with H_2O (3 ×

7 mL). The solvent was removed in vacuo to afford **7c** as a white solid which was purified by RP-HPLC (H_2O) to yield **7c** (70 mg, 81%) as colourless needles; mp 113–115°C (H_2O); $[\alpha]_D^{23.6}$ − 80.7 (*c* 0.5, H_2O); R_f 0.51 (RP18, H_2O); ^{1}H NMR (250.1 MHz, D_2O): δ 3.65–3.75 (m, 1H, H-4′a), 3.80–3.93 (m, 3H, H-2′, H-3′, H-4′b), 4.86 (d, $J_{1',2'}$ 1.5 Hz, 1H, H-1′), 6.96 (d, $J_{5,6}$ 5.3 Hz, 1H, H-5), 8.31 (d, 1H, H-6); ^{13}C NMR (62.9 MHz, D_2O): δ 65.8 (C-4′), 73.8, 74.7, 76.1 (C-1′, C-2′, C-3′), 111.6 (C-5), 161.5 (C-6), 164.9 (C-2), 174.9 (C-4). MS: *m/z* (FAB): 216 $[M + H]^+$.

Anal. Calcd for $C_8H_{13}N_3O_4 \cdot H_2O$: C, 41.28; H, 6.37; N, 17.74. Found: C, 41.20; H, 6.48; N, 18.02.

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Received March 3, 2003
Accepted July 25, 2003

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