Anellation and Ring Transformations of Push-pull-functionalized Deoxypyranosiduloses

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

Reaction of (*E*)-3-aminomethylene-α-D-*erythro*-hexopyranosid-2-ulose **5** with substituted 5-aminopyrazoles afforded the pyrano-anellated pyrazolo[1,5-*a*]pyrimidines **8**. The treatment of the corresponding (*E*)-2-aminomethylene-α-D-*erythro*-hexopyranosid-3-ulose **6** with 5-aminopyrazoles and (benzimidazol-2-yl)acetonitrile yielded in a ring transformation process the D-erythronoyl-pyrazolo[1,5-*a*]pyrimidine-3-carbonic acid derivatives **10** and D-erythronoyl-pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**12**), respectively.

Key words: Nucleoside Analogs, Push-pull Alkenes, Enaminones, Pyrazolo[1,5-*a*]pyrimidines, Pyrido[1,2-*a*]benzimidazole, Ring Transformations

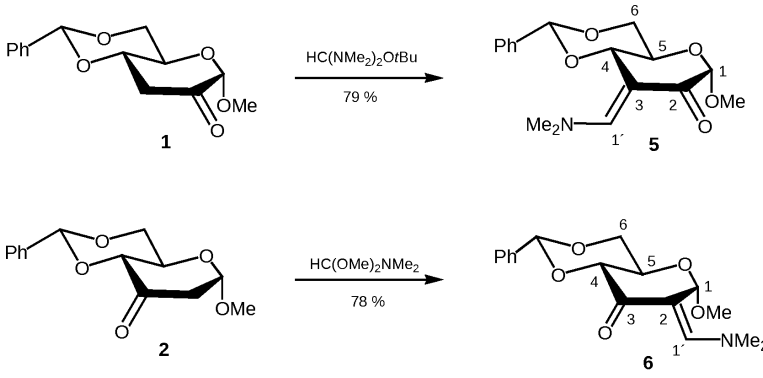
Introduction

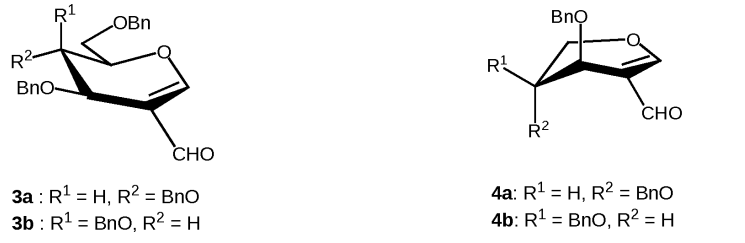
Anellated cyclic monosaccharide derivatives have attracted great interest in organic synthesis [1 – 3] because of their biological importance, for example as antibiotics and cancerostatics [4 – 7], or as inhibitors of different glycosidases [8, 9]. Furthermore, the natural products bengazol A and (–)-biopterin are representatives of biologically interesting acyclic *C*-nucleosides [10, 11]. Natural as well as synthetic acyclic nucleoside analogs [12 – 17] have shown antiviral activities against herpes virus [18], HIV and SIV (simian immunodeficiency virus) [19], and vaccinia [20]. The interesting properties of these compounds encouraged scientists to develop approaches to the synthesis of other anellated nucleoside analogs using the push-pull functionalization of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose (**1**) and methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**2**), respectively [21 – 26] (Scheme 1).

Acyclo-*C*-nucleoside analogs were prepared by ring transformation reactions of push-pull functionalized 2-formylglycals **3** and **4** with hydrazines, amidines, 2-aminobenzimidazole, 3-amino-2*H*-1,2,4-triazole, and 5(3)-amino-pyrazole-4-carboxylates [27 – 29]. The mechanism of this ring transformation involved the attack of the dinucleophiles at the formyl group and the anomeric position of glycals. Substitution of the ring oxygen atom resulted in the ring cleavage of the cyclic carbohydrates.

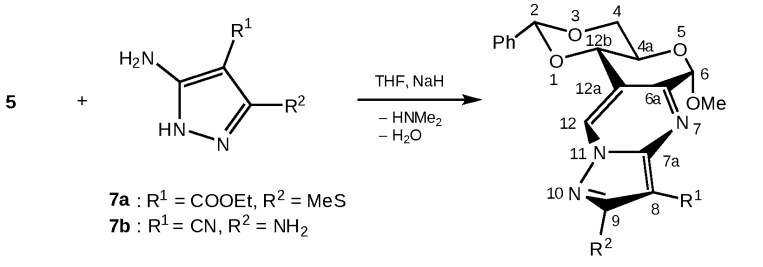
Bredereck *et al*. reported the reaction of ketones with acetals of amides [30]. In this way, ulose **1** was reacted with *N*,*N*-dimethylformamide dimethylacetal and bis(dimethylamino)*tert*-butoxymethane, respectively, in tetrahydrofuran to furnish the (*E*)-methyl 4,6-*O*-benzylidene-3-deoxy-3-dimethylaminomethylene-α-D-*erythro*-hexopyranosid-2-ulose (**5**) with an integrated push-pull alkene unit (Scheme 1). The reaction of compound **5** with hydrazine hydrate and amidines involved the substitution of the dimethylamino group, and the attack on the carbonyl group yielding a pyrano[3,4-*c*]pyrazole and the corresponding pyrimido anellated pyranosides, respectively [23].

Similarly, the treatment of 3-ulose **2** with *N*,*N*-dimethylformamide dimethylacetal afforded the (*E*)-methyl 4,6-*O*-benzylidene-2-deoxy-2-dimethylaminomethylene-α-D-*erythro*-hexopyranosid-3-ulose (**6**). Reaction of **6** with methylhydrazine and amidines yielded pyrano[4,3-*c*]pyrazole and pyrano[4,3-*d*]-pyrimidines, respectively [31]. On the other hand, the hexopyranosidulose **6** is comparable with the 2-formylglycals **3** and **4** because the displacement of the dimethylamino and methoxy group by binucleophiles should afford the same products in a ring transformation process.





Scheme 1. Push-pull-functionalized uloses **5**, **6** and 2-formylglycals **3**, **4**.



Scheme 2. Synthesis of pyranoanellated pyrazolo[1,5-*a*]pyrimidines **8a**, **b**.

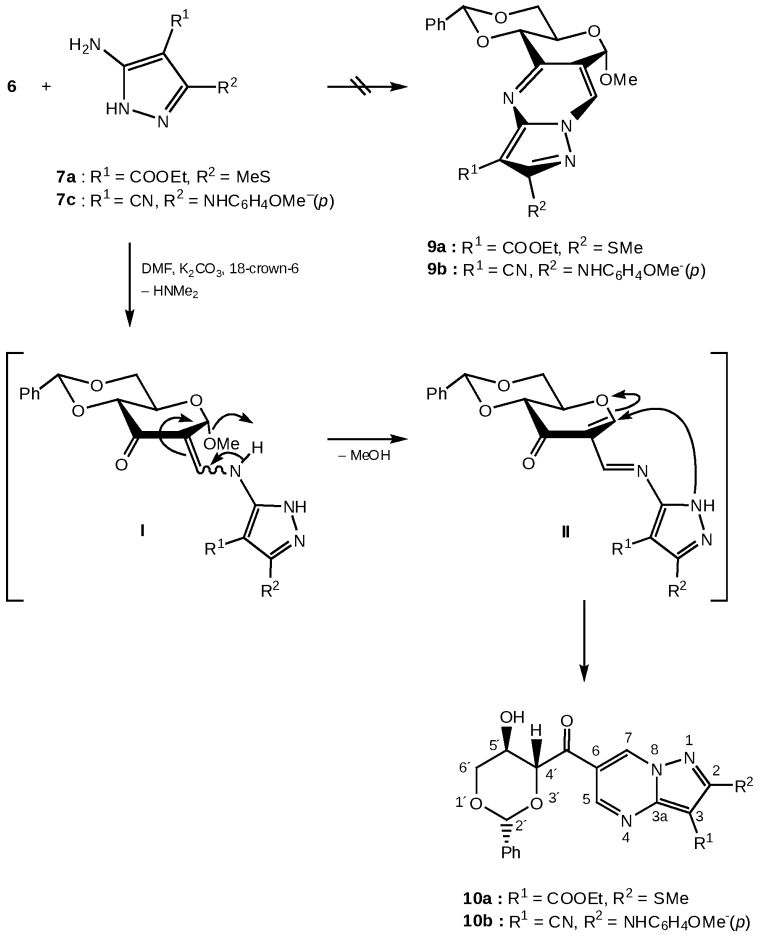
In this paper we report the reaction of the uloses **5** and **6** with aminopyrazoles and (benzimidazol-2-yl)acetonitrile which was carried out in order to synthesize new nucleoside analogs by anellation and ring transformation reactions, respectively.

Results and Discussion

Pyrazolo[1,5-*a*]pyrimidine-*C*-nucleosides have shown activities against various cancer cell lines and were used also for other biological tests [32]. In order to synthesize the corresponding pyranoanellated pyrazolo[1,5-*a*]pyrimidines **8** we utilized substituted 5(3)-amino-pyrazole-4-carbonic acid derivatives **7** [33 – 35] as binucleophiles in the reaction with the hexopyranosid-2-ulose **5** (Scheme 2). Sodium hydride was used as a base for abstracting the protons of the attacking nucleophile.

In the ^{13}C NMR spectra of compounds **8** the expected signals of the carboxylate and cyano groups, respectively, were visible. Furthermore, an upfield shift to δ = 138.2 and 138.4 for C-6a in **8a** and **8b**, respectively (the corresponding chemical shift of the C-2 in compound **5** is δ = 187.9), and the absence of signals for the dimethylamino group proved the cyclization through substitution of the dimethylamino group and condensation with the carbonyl group. The ^{1}H NMR spectra of **8a** and **8b** showed the signals for 12-H at δ = 8.74 and 8.53, respectively, typical for hydrogen bound to an sp^2 carbon atom.

Heterocyclization of ulose **6** with the substituted 5(3)-amino-pyrazole-4-carbonic acid derivatives **7** in

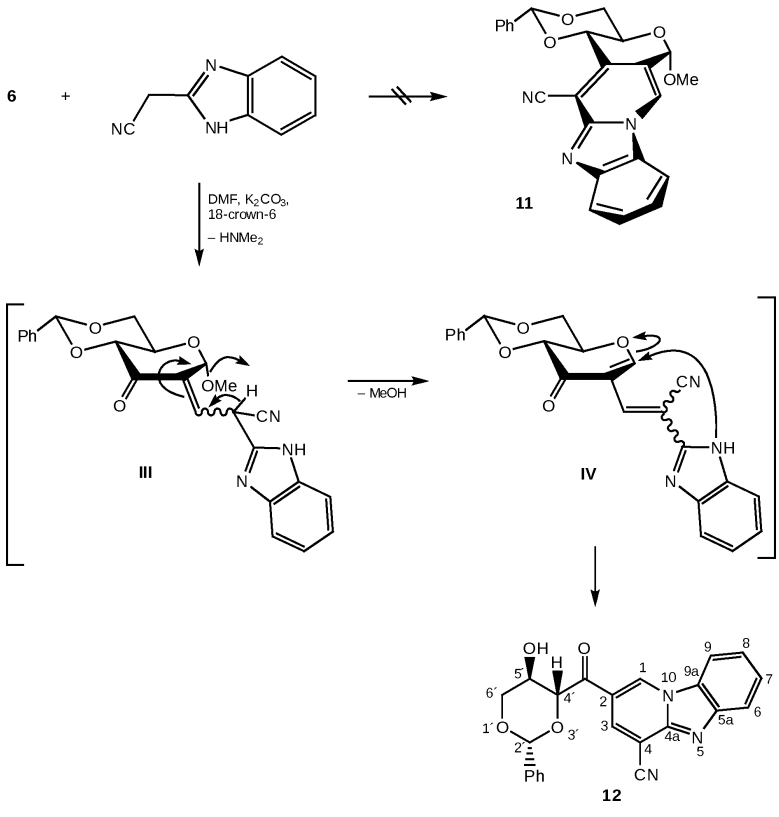


Scheme 3. Reaction of ulose **6** with aminopyrazoles **7**.

dimethylformamide at −15 °C in the presence of potassium carbonate/18-crown-6 yielded not the corresponding pyranoanellated pyrazolo[1,5-*a*]pyrimidines **9** but, in a ring transformation process, the pyrazolo [1,5-*a*]pyrimidines **10** with an open-chain monosaccharidic unit (Scheme 3). The first step of the reaction appears to be the attack of the exocyclic pyrazole amino group at C-1′ of **6** to yield the intermediate hexopyranosidulose **I** which reacts easily under elimination of methanol to furnish the glycal **II**. The endocyclic double bond of this unsaturated monosaccharide is push-pull-functionalized because of the substitution with the electron donating ring oxygen atom and the electron attracting imino function. Therefore, the intramolecular substitution of the ring oxygen by attack of the ring NH group of the pyrazole unit can yield the pyrazolo[1,5-*a*]pyrimidines **10**.

The presence of OH signals in the ^{1}H NMR spectra of **10a**,**b** as doublets at δ = 5.58 and 5.55, respectively, with coupling constants $^3J_{OH-5'}$ = 5.80 Hz confirmed the structure **10**. Furthermore, the absence of the signal for the anomeric methoxy group in the ^{13}C and ^{1}H NMR spectra confirmed the postulated reaction course. In addition, the carbonyl bands in the IR spectra and corresponding signals in the ^{13}C NMR spectra of compounds **10a**, **b** at δ = 191.9 and 191.6, respectively, proved that the carbonyl group of the hexopyranosidulose **6** was not involved in the cyclization reaction.

From the literature, nucleoside analogs with an imidazo[1,2-*a*]pyridine skeleton are known and show antiviral activity [36, 37]. Starting with compound **6** we tried to prepare the corresponding polycyclic *C*-nucleoside analog by reaction with (benzimidazol-2-yl)acetonitrile in *N*,*N*-dimethylformamide in the presence of potassium carbonate as a base. However, the expected anellation reaction of (benzimidazol-2-yl)-acetonitrile including condensation with the carbonyl



Scheme 4. Reaction of ulose **6** with (benzimidazol-2-yl)acetonitrile.

group of **6** and substitution of the dimethylamino group to furnish the polycyclic compound **11** did not take place. The signal of the carbonyl group was retained at δ = 191 in the ^{13}C NMR spectrum of the product. Therefore, we had to postulate a reaction course which could first afford the hexopyranosidulose **III** through substitution of the dimethylamino group (Scheme 4). This compound then could undergo elimination of methanol to yield the branched-chain glycal **IV** possessing a butadiene unit with push-pull functionality (butadiene with the electron donating ring oxygen atom and the electron attracting imino function). Intermediate **IV** was not isolable because of the immediately following intramolecular nucleophilic substitution by attack of the NH group at C-1 of the sugar ring resulting in a ring transformation reaction to afford the pyrido[1,2-*a*]benzimidazole-carbonitrile **12**.

Structure **12** was supported by the OH signal at δ = 5.6 ($^3J_{OH-5'}$ = 5.8 Hz) in the ^{1}H NMR spectrum. Furthermore, the couplings found over four bonds between 1-H and 3-H due to a typical *W*-coupling (1.2 Hz) confirmed the successful ring transformation.

Experimental Section

General

Solvents were distilled and if necessary dried using standard procedures. TLC was carried out on silica gel 60 GF_{254} (Merck) with detection by UV light (λ = 254 nm) and/or by charring with 10 % sulfuric acid in methanol. Silica gel 60 (63 – 200 mesh) (Merck) was used for column chromatography. Melting points were determined by using a Boetius melting point apparatus and are corrected. Specific rotations were determined with a Gyromat-HP instrument (Dr. Kernchen Ltd.). IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. ^{1}H NMR spectra (250.13 MHz and 300.13 MHz, respectively) and ^{13}C NMR spectra (62.9 MHz and 75.5 MHz, respectively) were recorded on Bruker instruments AC 250 and ARX 300, with $CDCl_3$ or [D_6]DMSO as solvent. The calibration of spectra was carried out on solvent signals [δ (^{1}H, $CDCl_3$) = 7.25; δ (^{13}C, $CDCl_3$) = 77.0; [D_6]DMSO: δ (^{1}H) = 2.50; δ (^{13}C) = 39.7]. The ^{1}H and ^{13}C NMR signals were assigned by DEPT and two-dimensional ^{1}H,^{1}H-COSY and ^{1}H,^{13}C correlation spectra. The mass spectra were recorded on an AMD 402/3 spectrometer (AMD Intectra GmbH). Elemental analyses were performed on a Leco CHNS-932 instrument.

*Ethyl (2R,4aR,6S,12bS)-4a,12b-dihydro-6-methoxy -9-methylsulfanyl-2-phenyl-4H,6H-[1,3]-dioxino[4′,5′:5,6]pyrano-[3,4-d]pyrazolo[1,5-a]pyrimidine-8-carboxylate (**8a**)*

A solution of compound **5** (319 mg, 1.0 mmol) in abs. THF (30 mL) was cooled to 0 °C. At this temperature ethyl 5(3)-amino-3(5)-methylsulfanyl-1*H*-pyrazole-4-carboxylate (**7a**, 402 mg, 2.0 mmol) and NaH (60 %; 150 mg, 3.75 mmol) were added. The solution was allowed to warm to 22 °C and stirred until completion of the reaction (TLC-control). Then ice water (100 mL) was added, the aqueous phase was extracted with dichloromethane (3 × 40 mL) and dried with Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by column chromatography (toluene/ethyl acetate = 3 : 1) gave the pure compound **8a**. – Yield 180 mg (40 %, amorphous powder). – $[\alpha]_D^{21}$ = +42.6 (*c* = 1.0, $CHCl_3$). – R_f = 0.7 (toluene/ethyl acetate = 1 : 1). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.74 (s, 1 H, 12-H), 7.49 – 7.33 (5 H, Ph), 5.81 (s, 1 H, 2-H), 5.73 (s, 1 H, 6-H), 4.78 (d, 1 H, $^3J_{12b-4a}$ = 9.2 Hz, 12b-H), 4.44 – 4.23 (m, 4 H, 4a-H, 6-H, C*H*$_2$CH$_3$), 3.93 (t, 1 H, $^2J_{4ax-4eq}$ = $^3J_{4ax-4a}$ = 10.1 Hz, 4ax-H), 3.69 (s, 3 H, OMe), 2.57 (s, 3 H, SMe), 1.36 (t, 3 H, ^3J = 7.0 Hz, CH$_2$C*H*$_3$). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 162.7 (C=O), 160.4 (C-9), 149.0 (C-7a), 148.7 (C-12), 138.2 (C-6a), 136.7, 129.4, 128.4, 126.2 (Ph), 115.9 (C-12a), 102.3 (C-2), 100.4 (C-6), 94.3 (C-8), 73.4 (C-12b), 68.9 (C-4), 64.4 (C-4a), 60.5 (*C*H$_2$CH$_3$), 57.9 (O*C*H$_3$), 14.5 (SMe), 13.4 (CH$_2$*C*H$_3$). – MS (EI, 70 eV): *m/z* (%) = 457 (100) $[M]^+$. – $C_{22}H_{23}N_3O_6S$ (457.50): calcd. C 57.76, H 5.07, N 9.18, S 7.01; found C 57.66, H 5.01, N 9.07, S 6.74.

*(2R,4aR,6S,12bS)-9-Amino-4a,12b-dihydro-6-methoxy-2-phenyl-4H,6H-[1,3]dioxino[4′,5′:5,6]pyrano[3,4-d]pyrazolo[1,5-a]pyrimidine-8-carbonitrile (**8b**)*

Compound **5** (319 mg, 1.0 mmol) was reacted with 3,5-diamino-1*H*-pyrazole-4-carbonitrile (**7b**, 181 mg, 2.0 mmol) as described for the preparation of **8a**. After removal of the solvent the residue was purified by column chromatography (toluene/ethyl acetate = 1 : 1). – Yield 265 mg (70 %, colorless needles). – M. p. 303 °C. – $[\alpha]_D^{21}$ = +52.3 (*c* = 1.0, DMSO). – R_f = 0.4 (toluene/ethyl acetate = 1 : 1). – ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.53 (s, 1 H, 12-H), 7.55 – 7.38 (5 H, Ph), 6.90 (s, 2 H, NH$_2$), 5.95 (s, 1 H, 2-H), 5.84 (s, 1 H, 6-H), 4.98 (d, 1 H, $^3J_{12b-4a}$ = 8.9 Hz, 12b-H), 4.39 (dd, 1 H, $^2J_{4eq-4ax}$ = 8.9 Hz, $^3J_{4eq-4a}$ = 3.4 Hz, 4eq-H), 4.12 – 3.98 (m, 2 H, 4a-H, 4ax-H), 3.58 (s, 3 H, OMe). – ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 161.8 (C-9), 150.9 (C-7a), 147.1 (C-12), 138.4 (C-6a), 137.4, 129.3, 128.4, 126.5 (Ph), 116.1 (C-12a), 113.9 (CN), 101.3 (C-2), 93.3 (C-6), 72.5 (C-12b), 67.9 (C-4), 66.8 (C-8), 64.1 (C-4a), 56.8 (OCH$_3$). – MS (EI 70 eV): *m/z* (%) = 379 (36) $[M]^+$. – $C_{19}H_{17}N_5O_4$ (379.37): calcd. C 60.15, H 4.52, N 18.46; found C 60.59, H 5.02, N 17.89.

*Ethyl 6-(2,4-di-O-benzylidene-D-erythronoyl)-2-methylsulfanyl-pyrazolo[1,5-a]pyrimidine-3-carboxylate (**10a**)*

A solution of **6** (319 mg, 1.0 mmol) in DMF (5 mL) was cooled to −15 °C. While stirring under argon atmosphere potassium carbonate (830 mg, 6 mmol), 18-crown-6 (1.32 g, 5 mmol) and **7a** (402 mg, 2.0 mmol) were added. The suspension was stirred at −15 °C until complete conversion (TLC control). Then the reaction mixture was added to an ice/water mixture and the product precipitated from the solution. The solid was filtered and the aqueous phase extracted several times with dichloromethane. The organic phases were combined and dried with Na_2SO_4. After removal of the solvent the combined solids were purified by column chromatography (toluene/ethyl acetate = 1 : 1). For further purification the product was recrystallized from ethyl acetate. – Yield 112 mg (22 %, solid). – M. p. 211 – 213.5 °C. – $[\alpha]_D^{22}$ = −12.4° (*c* = 1.8, DMSO). – R_f = 0.3 (toluene/ethyl acetate = 1 : 1). – ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.97 (d, 1 H, $^4J_{7-5}$ = 2.1 Hz, 7-H), 9.20 (d, 1 H, $^4J_{5-7}$ = 2.1 Hz, 5-H), 7.49 – 7.37 (5 H, Ph), 5.87 (s, 1 H, 2′-H), 5.58 (d, 1 H, $^3J_{OH-5'}$ = 5.8 Hz, OH), 5.28 (d, 1 H, $^3J_{4'-5'}$ = 9.1 Hz, 4′-H), 4.31 (q, 2 H, $^3J_{CH_2CH_3}$ = 7.0 Hz, C*H*$_2$CH$_3$), 4.25 (dd, 1 H, $^2J_{6'ax-6'eq}$ = 10.7 Hz, $^3J_{5-6'eq}$ = 5.2 Hz, 6′eq-H), 3.94 (m, 1 H, 5′-H), 3.73 (t, 1 H, $^2J_{6'ax-6'eq}$ = $^3J_{5'-6'ax}$ = 10.7 Hz, 6′ax-H), 2.60 (s, 3 H, SMe), 1.32 (t, 3 H, $^3J_{CH_2CH_3}$ = 7.0 Hz, CH$_2$C*H*$_3$). – ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 191.9 (C=O), 162.4 (*C*OOEt), 161.9 (C-2), 149.2 (C-5), 137.8 (C-7), 129.3, 128.5, 126.6 (Ph), 118.5 (C-3a), 100.4 (C-2′), 80.7 (C-4′), 71.1 (C-6′), 62.1 (C-5′), 60.3 (*C*H$_2$CH$_3$), 14.8 (SMe), 13.4 (CH$_2$*C*H$_3$). – MS (EI, 70 eV): *m/z* (%) = 443 (1) $[M]^+$. – $C_{21}H_{21}N_3O_6S$ (443.47): calcd. C 56.87, H 4.77, N 9.48, S 7.23; found C 56.56, H 4.80, N 9.38, S 7.68.

*2-(p-Anisidino)-6-(2,4-di-O-benzylidene-D-erythronoyl) pyrazolo[1,5-a]pyrimidine-3-carbonitrile (**10b**)*

Compound **6** (319 mg, 1.0 mmol) was reacted with 5(3)-amino-3(5)-(*p*-anisidino)-1*H*-pyrazol-4-carbonitrile (**7c**, 458 mg, 2.0 mmol) as described for the preparation of **10a**. After removal of the solvent the residue was purified by column chromatography (ethyl acetate/chloroform = 5 : 1). – Yield 87 mg (18 %, solid). – M. p. > 360 °C. – $[\alpha]_D^{24}$ = −24.5° (*c* = 0.8, DMSO). – R_f = 0.5 (ethyl acetate/chloroform = 5 : 1). – ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.76 (d, 1 H, $^4J_{7-5}$ = 2.1 Hz, 7-H), 9.61 (s, 1 H, NH), 9.41 (d, 1 H, $^4J_{5-7}$ = 2.1 Hz, 5-H), 7.62 (d, 2 H, Ar), 7.43 – 7.34 (5 H, Ph), 6.91 (d, 2 H, Ar), 5.81 (s, 1 H, 2′-H), 5.55 (d, 1 H, $^3J_{OH-5'}$ = 5.8 Hz, OH), 5.22 (d, 1 H, $^3J_{4'-5'}$ = 9.2 Hz, 4′-H), 4.22 (dd, 1 H, $^2J_{6'ax-6'eq}$ = 10.7 Hz, $^3J_{5'-6'eq'}$ = 5.2 Hz, 6′eq-H), 3.93 (m, 1 H, 5′-H), 3.73 (s, 4 H, OMe, 6′ax-H). – ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 191.6 (C=O), 158.9 (C-2), 155.3 (C-6), 152.1 (C-5), 139.8 (C-7), 137.9, 133.4, 129.6, 128.5, 126.6, 121.3, 114.4 (Ar, Ph), 118.8

(C-3a), 113.2 (CN), 100.5 (C-2′), 80.7 (C-4′), 71.1 (C-6′), 70.3 (C-3), 62.2 (C-5′), 55.6 (OMe). – MS (EI 70 eV): *m/z* (%) = 471 (30) $[M]^+$. – $C_{25}H_{21}N_5O_5$ (471.46): calcd. C 63.69, H 4.49, N 14.85; found C 63.45, H 4.31, N 14.01.

*2-(2,4-Di-O-benzylidene-D-erythronoyl)pyrido[1,2-a]-benzimidazole-4-carbonitrile (**12**)*

Compound **6** (319 mg, 1.0 mmol) was reacted with (benzimidazol-3-yl)acetonitrile (320 mg, 2 mmol) as described for the preparation of **10a**. After removal of the solvent the residue was purified by column chromatography (toluene/ethyl acetate = 1 : 2). – Yield 63 mg (16 %, yellow solid). – M. p. 226 °C. – $[\alpha]_D^{25} = -75.9$ (c = 1.5, $CHCl_3$). – R_f = 0.5 (toluene/ethyl acetate = 1 : 2). – ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 10.10 (s, 1 H, 1-H), 8.69 (d, 1 H, $^4J_{3-1}$ = 1.2 Hz, 3-H), 8.53 (d, 1 H, $^3J_{6-7}$ = 8.9 Hz, 6-H), 7.92 (d, 1 H, $^3J_{9-8}$ = 8.6 Hz, 9-H), 7.57 (m, 2 H, 7-H, 8-H), 7.45 – 7.30 (5 H, Ph), 5.87 (s, 1 H, 2′-H), 5.56 (d, 1 H, $^3J_{OH-5'}$ = 5.8 Hz, OH), 5.31 (d, 1 H, $^3J_{4'-5'}$ = 9.2 Hz, 4′-H), 4.26 (dd, 1 H, $^2J_{6'ax-6'eq}$ = 10.4 Hz, $^3J_{5'-6'eq}$ = 5.2 Hz, 6′eq-H), 3.97 (m, 1 H, 5′-H), 3.73 (t, 1 H, $^2J_{6'ax-6'eq} = {}^3J_{5'-6'ax}$ = 10.4 Hz, 6′ax-H). – ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 91.2 (C=O), 145.3 (C-4a), 144.7 (C-5a), 137.7 (*i*-Ph), 137.1 (C-7), 136.8 (C-1), 129.8 (C-3), 129.2, 128.4, 126.4 (Ph), 127.8 (C-7), 123.6 (C-2), 120.1 (C-6), 119.4 (C-9a), 115.2 (CN), 113.5 (C-9), 100.4 (C-4), 100.3 (C-2′), 80.2 (C-4′), 71.0 (C-6′), 61.9 (C-5′). – MS (EI 70 eV): *m/z* (%) = 399 (44) $[M]^+$. – $C_{23}H_{17}N_3O_4$ (399.40): calcd. C 69.17, H 4.29, N 10.52; found C 68.78, H 4.02, N 10.13.

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