Nucleoside Analogues from Push-Pull Functionalized Branched-Chain Pyranosides*

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The reaction of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**1**) with ethynylmagnesium bromide in tetrahydrofuran and subsequent trimethylsilylation yielded the methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-ethynyl-3-*O*-trimethylsilyl-α-D-*ribo*-hexopyranoside (**3**). Push-pull functionalization of **3** with N,N,N',N',N'',N''-hexamethylguanidinium chloride under basic conditions and following deprotection afforded the spiro{2,5-dihydro-3-dimethylamino-furan-2,8'-4',4'a,6',7',8',8'a-hexahydro-6'-methoxy-2'-phenyl-pyrano[3,2-*d*][1.3]dioxine}-5-ylidenemalononitrile (**9**). Furthermore, compound **1** reacted with N,N-dimethylformamide dimethylacetal to furnish methyl (*E*)-4,6-*O*-benzylidene-2-deoxy-2-dimethylaminomethylene-α-D-*erythro*-hexopyranosid-3-ulose (**10**). Treatment of **10** with methylhydrazine and amidines yielded (4*S*,5a*R*,8*R*,9a*S*)-2,5a,6,9a-tetrahydro-4-methoxy-2-methyl-8-phenyl-4*H*-[1,3]dioxino[4',5':5,6]-pyrano[4,3-*c*]pyrazole (**11a**) and (2*R*,4a*R*,6*S*,10b*S*)-4,4a,6,10b-tetrahydro-6-methoxy-2-phenyl-[1,3]dioxino[4',5':5,6]pyrano[4,3-*d*]pyrimidines **12**, respectively.

Key words: Deoxyuloses, Nucleoside Analogues, Pyrazoles, Pyrimidines, Enaminones

Introduction

Anellated carbohydrates constitute a class of nucleoside analogues in which the noncarbohydrate heterocycle is fused by one or two carbon atoms with the carbohydrate unit. Pyran rings are structural elements of numerous natural products [1 – 3]. It has been found that a great number of these compounds containing anellated pyrans exhibit biological activity, for example as cancerostatics or antibiotics [4 – 7]. Fused ring systems with at least one pyran moiety are also very interesting as potential inhibitors of glycosidases [8, 9]. Therefore, the development of new methods for the synthesis of anellated pyranose derivatives has become a topic of current interest in synthetic organic chemistry in the closer past [10 – 12].

In recent years, we have reported the preparation of *C*-branched monosaccharides with push-pull functionality which could be used as precursors for the synthesis of nucleoside derivatives [13, 14]. In this paper, we describe the synthesis of furan, pyrimidine and pyrazole nucleoside analogues starting from D-glucose.

Results and Discussion

The methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**1**) was synthesized in six steps originating from D-glucose [15]. In a Grignard reaction compound **1** was reacted with ethynylmagnesium bromide to yield the methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-ethynyl-α-D-*ribo*-hexopyranoside (**2**) [16 – 18]. The yield of the reaction could not be increased over 70% because of a side reaction of compound **1** with the Grignard reagent to form ethyne. Treatment of the branched-chain monosaccharide **2** with trimethylsilyl chloride in pyridine afforded the corresponding *O*-protected compound **3**.

In the ^{1}H NMR spectra of compound **2** the OH singlet at $\delta = 3.46$ and the 2'-H signal at $\delta = 2.45$ were found as significant changes compared with the ^{1}H NMR spectra of **1**. The ^{13}C NMR spectrum of **2** showed the signal for C-3 at $\delta = 65.9$ which is shifted upfield compared with the corresponding signal of

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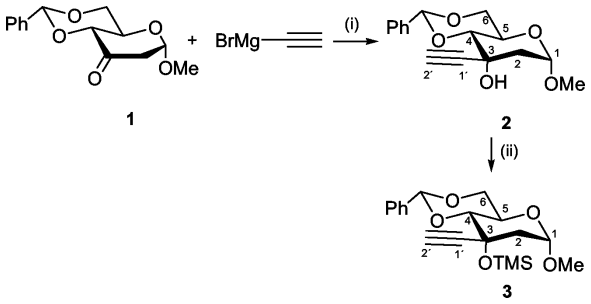


Scheme 1. Synthesis of methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-ethynyl-α-D-*ribo*-hexopyranosides **2** and **3**. (i) THF, 3 h, 22 °C; (ii) TMSCl, pyridine, 12 h, 22 °C.

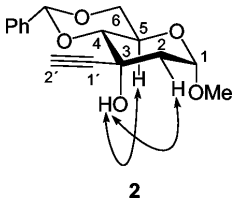


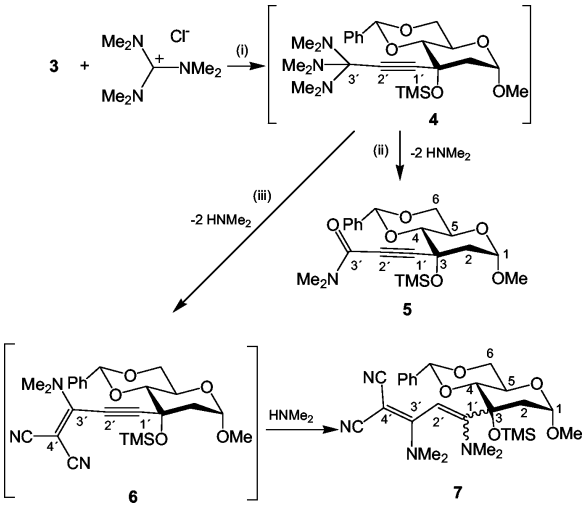
Fig. 1. NOE corelations of pyranoside **2**.

ulose **1** ($\delta = 196.9$). For the triple-bonded carbons C-1' and C-2', signals were found at $\delta = 83.9$ and $\delta = 71.9$, respectively.

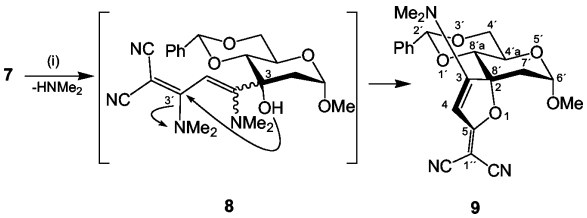
The elucidation of the configuration at C-3 was possible by NOE spectroscopy. Thus, the two-dimensional NOESY of **2** showed correlations of the OH hydrogen with the protons 5-H and 2eq-H which indicated an (*R*)-configuration at C-3 (Fig. 1).

Following procedures of Kantlehner *et al.* [19–21], the synthesis of a push-pull butadiene from compound **3** could be achieved by reaction of the terminal ethynyl carbon with N,N,N',N',N'',N''-hexamethylguanidinium chloride in tetrahydrofuran in the presence of NaH (Scheme 2). Hydrolysis of the intermediarily formed methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-[3-tris(dimethylamino)propynyl]-3-*O*-trimethylsilyl-α-D-*ribo*-hexopyranoside (**4**) afforded 3-(methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-trimethylsilyl-*a*-D-*ribo*-hexopyranosid-3-*C*-yl)propynic acid dimethylamide (**5**).

Contrary to these results, the *in situ* reaction of **4** with malononitrile gave 3-(*E*,*Z*)-2,4-bis(dimethylamino)-4-(methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-trimethylsilyl-α-D-*ribo*-hexopyranosid-3-*C*-yl)buta-1,3-diene-1,1-dicarbonitrile (**7**). The mechanism of the reaction could be described as follows: First an attack of malononitrile at the C-3' occurs with substitution of two dimethylamino groups to furnish the dicarbonitrile **6**. A subsequent Michael-like addition of



Scheme 2. Synthesis of compounds **5** and **7**. (i) NaH, THF, 3 h, 22 °C (**5**), 72 h, 55 °C (**7**); (ii) H_2O, 0 °C; (iii) malononitrile, THF, 24 h, 22 °C.



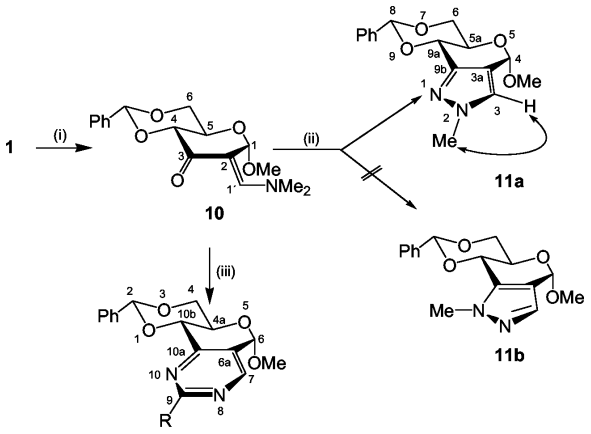
Scheme 3. Synthesis of compound **9**. (i) KF, DMF, 24 h, 90 °C.

dimethylamine at the triple bond yields the pyranosidic push-pull butadiene **7**.

The ^{13}C NMR spectrum of compound **7** showed the signals for C-1' and C-3' at $\delta = 170.2$ and $\delta = 169.2$, respectively. Furthermore, the signals of the dimethylamino groups at $\delta = 41.8$ and $\delta = 40.4$ were found. In a two-dimensional NOESY spectrum of **7** the proton H-2' showed correlations with the protons H-4 and both dimethylamino groups. Furthermore, correlations were found between the signals of both dimethylamino groups. From this result a twisted structure about the bonds of the butadiene chain can be concluded.

Deprotection of the trimethylsilyl substituted 3-OH group in compound **7** with potassium fluoride in DMF at -10 °C [22] caused an intramolecular substitution of the dimethylamino group at C-3' yielding the spiroanellated compound **9** (Scheme 3). Therefore, the isolation of the OH-group containing compound **8** was not possible.

Absence of the typical signals of one of the dimethylamino groups in the ^{1}H and ^{13}C NMR spec-



Scheme 4. Synthesis of compounds **11** and **12**. (i) $HC(OMe)_2NMe_2$, toluene, 12 h, 100 °C; (ii) NH_2NHMe, MeOH, 5 h, 22 °C; (iii) $RC(NH_2)=NH_2^+X^-$ (**12a**: R = Me, X^- = Cl^-; **12b**: R = Ph, X^- = Cl^-; **12c**: R = MeS, X^- = HSO_4^-), K_2CO_3, 18-crown-6, DMF, 17 h, −15 °C.

tra indicated the ring closing reaction. Moreover, the downfield shift of the 4-H at $\delta = 5.33$ (compared with $\delta = 4.57$ in compound **7**) confirmed the cyclization.

Reaction of hexopyranosidulose **1** with dimethyformamide dimethylacetal [14, 23, 24] afforded methyl (*E*)-4,6-*O*-benzylidene-2-deoxy-2-dimethylaminomethylene-α-D-*erythro*-hexopyranosid-3-ulose (**10**) in 78% yield (Scheme 4). The specification of the *E*/*Z*-isomerism in compound **10** was achieved by a NOESY spectrum which showed cross peaks between the protons of the dimethylamino group and the anomeric proton. Therefore, the shown *E*-configuration can be assumed (Scheme 4).

The hexopyranosid-3-ulose **10** reacted with methylhydrazine in methanol at r. t. to furnish in a yield of 34% the pyrazoloanellated pyranoside **11a** (Scheme 4). In the ^{13}C NMR spectrum of compound **11a** no signals for a carbonyl carbon atom and for the dimethylamino group were detected, thus confirming the expected cyclization. Because the pyrano[4,3-*c*]pyrazole **11** could exist in two isomeric forms **11a** and **11b**, NOESY experiments were carried out. They showed cross peaks between the *N*-methyl protons and 3-H, which corroborated the structure **11a** for the isolated product.

Furthermore, we improved the reaction of **10** with amidinium salts in the presence of a base. Comparable reactions of α-aminomethyleneketones yielded pyrimidines in high yields [25 – 27]. The reaction of push-pull functionalized ulose **10** with acetamidinium hydrochloride in *N*,*N*-dimethylformamide using potassium carbonate/18-crown-6 as base afforded after chromatography compound **12a** in a yield of 53% (Scheme 4). The ^{13}C NMR spectrum of **12a** showed a strong upfield shift for C-10a at $\delta = 160.7$ (chemical shift of the corresponding C-3 in compound **10** at $\delta = 187.5$) and the absence of signals for the dimethylamino and carbonyl group. These observations approved the cyclization through substitution of the dimethylamino group and condensation with the carbonyl group. In the ^{13}C NMR spectrum of compound **12a** a signal of an *N*-methyl group was visible at $\delta = 26.2$. All other spectral data of this compound were also in accordance with the quite similar structure of **11a**.

In the same way, the treatment of **10** with benzamidinium chloride and methylisothiouronium sulfate in the presence of potassium carbonate/18-crown-6 under reflux yielded the corresponding [1,3]dioxino[4',5':5,6]pyrano[4,3-*d*]pyrimidines **12b** and **12c**, respectively.

Experimental Section

General procedures

Melting points were determined with a Boëtius melting point apparatus and are corrected. Optical rotations were measured with a Gyromat HP (Dr. Kernchen Ltd.) polarimeter. ^1H and ^{13}C NMR spectra were recorded with Bruker spectrometers AC 250 (250.1 MHz and 62.9 MHz, respectively) and ARX 300 (300.1 MHz and 75.5 MHz, respectively). The calibration of spectra was carried out by means of TMS ($\delta_H = 0$) or solvent peaks (δ_H ($CDCl_3$) = 7.25; δ_C ($CDCl_3$) = 77.0). For the assignment of ^1H and ^{13}C NMR signals, DEPT and two-dimensional ^1H,^1H COSY and NOESY as well as ^1H,^{13}C correlation spectra were recorded. 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 (0.063 – 0.20 mm, Merck). Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} foils (Merck) with detection by UV light and by charring with sulfuric acid. HPLC chromatography was carried out by a Merck SEPTECH apparatus and a column ($l = 250$ mm, $d = 25$ mm) filled with Lichrosorb Si 60, 7 μm (2 ml sample volume was used by a flow of 20 ml/min). Solvents and liquid reagents were purified and dried according to recommended procedures.

*Methyl 4,6-O-benzylidene-2-deoxy-3-C-ethynyl-α-*D*-ribo-hexopyranoside* (**2**)

Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose **1** (0.264 g, 1.0 mmol) was dissolved in abs. tetrahydrofuran (15 ml) and cooled to 0 °C. An ethynylmagnesium bromide solution in hexane (0.5 M, 4 ml) was added and the mixture was stirred for 5 h (TLC control). When the starting material had almost been consumed, the reaction mixture was diluted with ethyl acetate (50 ml) and water (20 ml). The now formed precipitate was filtered using a glass filter filled with celite. The filter material was washed three times with ethyl acetate. After separation of the organic layer the aqueous phase was washed with ethyl acetate (3 × 10 ml). The combined organic phases were dried with sodium sulfate and evaporated *in vacuo* and the remaining slightly yellow syrup was purified by column chromatography (toluene/ethyl acetate 2 : 1) yielding **2** as a colorless syrup. Yield 0.203 g (70%), colorless syrup. – $[\alpha]_D^{22} = +48.4$ (*c* 1.0, $CHCl_3$). – $R_f = 0.45$ (toluene/ethyl acetate 2 : 1). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.55-7.51$ (m, 2H, Ph), 7.37 – 7.33 (m, 3H, Ph), 5.66 (s, 1H, C*H*Ph), 4.77 (dd, 1H, $^3J_{1,2ax} = 4.3$ Hz, $^3J_{1,2eq} = 1.0$ Hz, 1-H), 4.32 (dd, 1H, $^2J_{6ax,6eq} = 10.0$ Hz, $^3J_{5,6eq} = 5.0$ Hz, 6eq-H), 4.16 (dt, 1H, $^3J_{5,6ax} = 10.0$ Hz, $^3J_{4,5} = 9.5$ Hz, $^3J_{5,6eq} = 5.0$ Hz, 5-H), 3.77 (t, 1H, $^2J_{6ax,6eq} = {}^3J_{5,6ax} = 10.0$ Hz, 6ax-H), 3.70 (d, 1H, $^3J_{4,5} = 9.5$ Hz, 4-H), 3.46 (s, 1H, OH), 3.39 (s, 3H, MeO), 2.45 (s, 1H, 2'-H), 2.37 (dd, 1H, $^2J_{2ax,2eq} = 15.0$ Hz, $^3J_{1,2eq} = 1.0$ Hz, 2eq-H), 2.20 (dd, 1H, $^2J_{2ax,2eq} = 15.0$ Hz, $^3J_{1,2ax} = 4.3$ Hz, 2ax-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 137.1$, 129.0, 128.2, 126.2 (Ph), 102.0 (*C*HPh), 97.8 (C-1), 83.9 (C-1'), 82.1 (C-4), 71.9 (C-2'), 68.9 (C-6), 65.9 (C-3), 59.1 (C-5), 55.5 (MeO), 41.4 (C-2). – MS (EI): m/z(%) = 290 (1) [M^+]. – $C_{16}H_{18}O_5$ (290.31): calcd. C 66.19, H 6.25; found C 65.50, H 6.43.

*Methyl 4,6-O-benzylidene-2-deoxy-3-C-ethynyl-3-O-trimethylsilyl-α-*D*-ribo-hexopyranoside* (**3**)

Compound **2** (0.29 g, 1.0 mmol) and trimethylsilyl chloride (0.12 ml, 1.0 mmol) in pyridine (10 ml) were stirred at 22 °C for 12 h. After completion of the reaction (monitored by TLC) the solvent was evaporated *in vacuo* and the residue was purified by column chromatography (toluene/ethyl acetate 2 : 1) to furnish a viscous compound **3**: Yield 0.260 g (72%), colorless syrup. – $[\alpha]_D^{22} = +42.2$ (*c* 1.0, $CHCl_3$). – $R_f = 0.7$ (toluene/ethyl acetate 2 : 1). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.54-7.51$ (m, 2H), 7.38 – 7.33 (m, 3H, Ph), 5.61 (s, 1H, C*H*Ph), 4.69 (br d, 1H, $^3J_{1,2ax} = 4.6$ Hz, 1-H), 4.30 – 4.20 (m, 2H, 5-H, 6eq-H), 3.70 (t, 1H, $^2J_{6ax,6eq} = {}^3J_{5,6ax} = 10.0$ Hz, 6ax-H), 3.58 (d, 1H, $^3J_{4,5} = 9.2$ Hz, 4-H), 3.31 (s, 3H, MeO), 2.45 (s, 1H, 2'-H), 2.30 (dd, 1H, $^2J_{2ax,2eq} = 14.6$ Hz, $^3J_{1,2eq} = 0.8$ Hz, 2eq-H), 2.10 (dd, 1H, $^2J_{2ax,2eq} = 14.6$ Hz, $^3J_{1,2ax} = 4.6$ Hz, 2ax-H), 0.18 (s, 9H, Me_3Si). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 137.7$, 128.8, 128.1, 126.3 (Ph), 101.8 (*C*HPh), 97.7 (C-1), 85.1 (C-1'), 83.0 (C-4), 72.8 (C-2'), 69.1 (C-6), 66.5 (C-3), 58.5 (C-5), 55.1 (MeO), 43.9 (C-2), 1.7 (Me_3Si). – MS (EI): m/z(%) = 362 (22) [M^+]. – $C_{19}H_{26}O_5Si$ (362.49): calcd. C 62.95, H 7.23; found C 62.49, H 7.12.

*3-(Methyl 4,6-O-benzylidene-2-deoxy-3-O-trimethylsilyl-α-*D*-ribo-hexopyranosid-3-C-yl)propynic acid dimethylamide* (**5**)

To a solution of **3** (0.326 mg, 1 mmol) in abs. tetrahydrofuran (10 ml) was added sodium hydride (0.05 g, 2.1 mmol) at 22 °C. The resulting mixture was stirred under argon atmosphere. After 1 h of stirring N,N,N',N',N'',N''-hexamethylguanidinium chloride (0.215 g, 1.2 mmol) were added. The resulting solution was stirred for another 3 h and after completion of the reaction (monitored by TLC) the mixture was added to ice water (50 ml). The aqueous phase was extracted with ethyl acetate (3 × 50 ml) and the combined organic phases dried with sodium sulfate. Then the solvent was evaporated in *vacuo* and the residue was purified by column chromatography (toluene/ethyl acetate 4 : 1) to obtain **5** as a white solid. Yield 0.337 g (78%). – m. p. 194 °C. – $[\alpha]_D^{22} = +42.9$ (*c* 1.0, $CHCl_3$). – $R_f = 0.52$ (toluene/ethyl acetate 4 : 1). – IR (capillary): $\nu = 2226$ (C≡C), 1641.3 (C=O) (cm^{-1}). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.50-7.45$ (m, 2H, Ph), 7.37 – 7.30 (m, 3H, Ph), 5.60 (s, 1H, C*H*Ph), 4.70 (br d, 1H, $^3J_{1,2ax} = 4.7$ Hz, 1-H), 4.32 – 4.18 (m, 2H, 5-H, 6eq-H), 3.76 – 3.59 (m, 2H, 4-H, 6ax-H), 3.31 (s, 3H, MeO), 3.12 (s, 3H, Me_2N), 2.93 (s, 3H, Me_2N), 2.35 (dd, 1H, $^2J_{2ax,2eq} = 14.5$ Hz, $^3J_{1,2eq} = 0.8$ Hz, 2eq-H), 2.14 (dd, 1H, $^2J_{2ax,2eq} = 14.5$ Hz, $^3J_{1,2ax} = 4.7$ Hz, 2ax-H), 0.18 (s, 9H, Me_3Si). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 153.8$ (C-3'), 137.5, 128.8, 128.0, 126.1 (Ph), 101.7 *C*HPh, 97.5 (C-1), 91.3 (C-2'), 82.8 (C-4), 77.0 (C-1'), 69.1 (C-6), 67.0 (C-3), 58.3 (C-5), 55.1 (MeO), 43.0 (C-2), 38.1, 34.0 (Me_2N), 1.6 (Me_3Si). – MS (EI): m/z(%) = 433 (4) [M^+]. – $C_{22}H_{31}NO_6Si$ (433.57): calcd. C 60.94, H 7.21, N 3.23; found C 61.49, H 7.23, N 2.61.

*3-(E,Z)-2,4-Bis(dimethylamino)-4-(methyl-4,6-O-benzylidene-2-deoxy-3-O-trimethylsilyl-α-*D*-ribo-hexopyranosid-3-C-yl)buta-1,3-diene-1,1-dicarbonitrile* (**7**)

To a suspension of **3** (0.362 g, 1.0 mmol) and sodium hydride (0.05 g, 2.1 mmol) in abs. tetrahydrofuran (10 ml) was added N,N,N',N',N'',N''-hexamethylguanidinium chloride (0.215 g, 1.2 mmol) at 22 °C. The resulting mixture was stirred for 72 h at 55 °C. After cooling to 22 °C a suspension of malononitrile (0.066 g, 1.0 mmol) and sodium hydride (0.05 mg, 1.25 mmol) in abs. tetrahydrofuran (5 ml) were added. The resulting mixture was stirred for another 24 h

at 22 °C. After completing of the reaction (monitored by TLC) methanol was added, the solvent was evaporated *in vacuo*, and the residue was purified by column chromatography (ethyl acetate) to yield compound **7**. Yield 0.142 g (27%), Yellow solid; m. p. 227 °C. – $R_f = 0.2$ (ethyl acetate). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.49-7.47$ (m, 2H, Ph), 7.35 – 7.32 (m, 3H, Ph), 5.64 (s, 1H, C*H*Ph), 4.68 (br d, 1H, $^3J_{1,2ax} = 4.2$ Hz, 1-H), 4.57 (s, 1H, 2'-H), 4.40 – 4.34 (m, 2H, 5-H, 6eq-H), 4.25 (d, 1H, $^3J_{4,5} = 9.0$ Hz, 4-H), 3.73 (m, 1H, 6ax-H), 3.34 (s, 3H, MeO), 3.04 (s, 6H, Me_2N), 2.96 (s, 6H, Me_2N), 2.85 (dd, 1H, $^2J_{2ax,2eq} = 14.4$ Hz, $^3J_{1,2eq} = 0.6$ Hz, 2eq-H), 1.64 (dd, 1H, $^2J_{2ax,2eq} = 14.4$ Hz, $^3J_{1,2ax} = 4.6$ Hz, 2ax-H), 0.16 (s, 9H, Me_3Si). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 170.2$, 169.2 (C-1', C-3'), 137.1, 129.0, 128.2, 126.2 (Ph), 120.8 (2 CN), 102.1 (*C*HPh), 98.0 (C-1), 88.4 (C-2'), 80.0 (C-4), 76.5 (C-4'), 69.7 (C-6), 58.4 (C-5), 55.1 (MeO), 48.1 (C-3), 40.3 (C-2), 41.8 (Me_2N), 40.4 (Me_2N), 2.3 (Me_3Si). – MS (EI): $m/z\,(\%) = 526$ (69) [M^+]. – $C_{27}H_{38}N_4O_5Si$ (385.417): calcd. C 61.57, H 7.27, N 10.64; found C 61.48, H 7.30, N 10.14.

Spiro{2,5-dihydro-3-dimethylamino-furan-2,8'-4',4'a,6',7',8',8'a-hexahydro-6'-methoxy-2'-phenyl-pyrano[3,2-d]-[1.3]dioxine}-5-ylidenemalononitrile (**9**)

Compound **7** (0.052 g, 0.1 mmol) was dissolved in abs. dimethylformamide (3 ml). After the addition of potassium fluoride (0.0083 g, 0.14 mmol) the mixture was stirred for 24 h at 90 °C. Removing of the solvent *in vacuo* yielded the row material which was purified by column chromatography (ethyl acetate). Yield 0.023 mg (78%), yellow syrup. – $[\alpha]_D^{22} = -31.3$ (*c* 0.9, $CHCl_3$). – $R_f = 0.5$ (ethyl acetate). – ^{1}H NMR (250 MHz, $CDCl_3$): $d = 7.35$ (br, 5H, Ph), 5.63 (s, 1H, 2'-H), 5.33 (s, 1H, 4-H), 4.86 (br d, 1H, $^3J_{6',7'} = 4.6$ Hz, 6'-H), 4.38 – 4.19 (m, 3H, 4'eq-H, 4'a-H, 8'a-H), 3.82 (t, 1H, $^2J_{4'ax,4'eq} = {}^3J_{4'ax,4'a} = 10.0$ Hz, 4'ax-H), 3.38 (s, 3H, MeO), 3.17 (s, 3H), 3.05 (s, 3H) (Me_2N), 2.83 (dd, 1H, $^2J_{7'ax,7'eq} = 15.2$ Hz, $^3J_{6',7'} = 4.6$ Hz), 2.03 (d, 1H, $^2J_{7'ax,7'eq} = 15.2$ Hz) (7'ax-H, 7'eq-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $d = 172.4$, 170.5 (C-3, C-5), 136.9, 129.0, 128.1, 126.0 (Ph), 117.7, 117.3 (2 CN), 101.6 (C-2'), 97.0 (C-6'), 91.8 (C-8'), 86.5 (C-4), 76.5 (C-8'a), 69.0 (C-4'), 60.0 (C-4'a), 55.4 (MeO), 38.9, 37.3 (Me_2N), 37.4 (C-7'). – MS (EI): $m/z\,(\%) = 409$ (100) [M^+] – HRMS $C_{22}H_{23}N_3O_5$ (409.44): calcd. 409.16377; found 409.16279.

Methyl (E)-4,6-O-benzylidene-2-deoxy-2-dimethylamino-methylene-α-D-*erythro-hexopyranosid-3-ulose* (**10**)

To a solution of **1** (0.264 g, 1.0 mmol) in abs. toluene (10 ml) was added *N*,*N*-dimethylformamide dimethylacetal (2.5 ml, 18.9 mmol). The resulting mixture was heated for 12 h at 100 °C. After completion of the reaction (monitored by TLC) compound **10** precipitated during cooling to 22 °C. The product was filtered and recrystallized from ethanol. Yield 170 mg (78%), yellow needles. – m. p. 148 – 152 °C. – $[\alpha]_D^{22} = +196.9$ (*c* = 1.0, $CHCl_3$). – $R_f = 0.1$ (toluene/ethyl acetate 1 : 2). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.61$ (s, 1H, 1'-H), 7.52 – 7.50 (m, 2H, Ph), 7.34 – 7.29 (m, 3H. Ph), 5.56 (s, 1H, 1-H), 5.60 (s, 1H, C*H*Ph), 4.32 (dd, 1H, $^2J_{6ax,6eq} = 10.1$ Hz, $^3J_{5,6eq} = 5.1$ Hz, 6eq-H), 4.24 (dt, 1H, $^3J_{4,5} = {}^3J_{5,6ax} = 10.1$ Hz, $^3J_{5,6eq} = 5.0$ Hz, 5-H), 4.02 (d, 1H, $^3J_{4,5} = 10.1$ Hz, 4-H), 3.77 (t, 1H, $^2J_{6ax,6eq} = {}^3J_{5,6ax} = 10.1$, 6ax-H), 3.38 (s, 3H, MeO), 3.11 (s, 6H, Me_2N). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 187.5$ (C-3), 151.9 (C-1'), 137.2, 129.0, 128.1, 126.6 (Ph), 102.5 (*C*HPh), 102.2 (C-2), 97.9 (C-1), 79.2 (C-4), 69.3 (C-6), 61.6 (C-5), 53.3 (MeO), 44.0 (br, NMe_2). – MS (EI): $m/z\,(\%) = 319$ (28) [M^+]. – $C_{17}H_{21}NO_5$ (319.14): calcd. C 63.94, H 6.63, N 4.39; found C 62.81, H 6.52, N 4.16.

(4S,5aR,8R,9aS)-2,5a,6,9a-Tetrahydro-4-methoxy-2-methyl-8-phenyl-4H-[1,3]dioxino[4',5':5,6]pyrano[4,3-c]pyrazole (**11a**)

To a solution of compound **10** (0.096 g, 0.3 mmol) in methanol (5 ml) was added methylhydrazine (0.014 g, 0.3 mmol). The mixture was stirred for 5 h at 22 °C. After completion of the reaction the solvent was removed *in vacuo* and the residue purified by column chromatography (toluene/ethyl acetate 1 : 1) to obtain **11a** as yellow syrup. Yield 0.039 g (43%). – $[\alpha]_D^{22} = +34.8$ (*c* = 1.0, $CHCl_3$). – $R_f = 0.4$ (toluene/ethyl acetate 1 : 1). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.55-7.52$ (m, 2H, Ph), 7.35 – 7.30 (m, 3H, Ph), 7.23 (s, 1H, 3-H), 5.74 (s, 1H, 8-H), 5.55 (s, 1H, 4-H), 4.76 (d, 1H, $^3J_{5a,9a} = 9.2$ Hz, 9a-H), 4.38 (dd, 1H, $^2J_{6ax,6eq} = 10.2$ Hz, $^3J_{5a,6eq} = 4.6$ Hz, 6eq-H), 4.13 (ddd, 1H, $^3J_{5a,6ax} = 10.4$, $^3J_{5a,9a} = 9.2$ Hz, $^3J_{5a,6eq} = 4.6$ Hz, 5a-H), 3.96 (t, 1H, $^2J_{6ax,6eq} = 10.2$, $^3J_{5a,6ax} = 10.4$ Hz, 6ax-H), 3.86 (s, 3H, MeN), 3.50 (s, 3H, MeO). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 146.3$ (C-9b), 137.3, 129.2, 128.2, 126.8 (Ph), 127.9 (C-3), 115.9 (C-3a), 102.5 (C-8), 96.0 (C-4), 75.1 (C-9a), 69.5 (C-6), 64.6 (C-5a), 55.6 (MeO), 39.2 (Me). – MS (EI): $m/z\,(\%) = 302$ (0.4) [M^+]. – $C_{16}H_{18}N_2O_4$ (302.33): calcd. C 63.56, H 6.00, N 9.27; found C 63.43, H 5.97, N 9.13.

(2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-9-methyl-2-phenyl[1,3]dioxino[4',5':5,6]pyrano[4,3-d]-pyrimidine (**12a**)

A suspension of potassium carbonate (0.260 g, 1.88 mmol), 18-crown-6 (0.450 g, 1.70 mmol) and acetamidinium chloride (0.060 g, 0.6 mmol) in abs. *N*,*N*-dimethylformamide (3 ml) was stirred at −15 °C for 20 min. Compound **10** (0.1 g, 0.3 mmol) was added to the solution. The reaction mixture was stirred for another 17 h

at −15 °C and then water (200 ml) was added to the solution. The resulting mixture was extracted with dichloromethane (4 × 40 ml) and the combined organic phases were dried over sodium sulfate. After filtration the solvent was evaporated *in vacuo*. The residue was dissolved in methanol and silica gel was added. After stirring for 10 min the solvent was removed under reduced pressure and the silica based residue was purified by column chromatography (toluene/ethyl acetate 1 : 1). Yield 0.015 g (53%), yellow crystals. – $[\alpha]_D^{25} = +64.7$ ($c = 0.8$, $CHCl_3$). – $R_f = 0.2$ (toluene/ethyl acetate 1 : 1). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.54$ (s, 1H, 7-H), 7.57 – 7.53 (m, 2H, Ph), 7.39 – 7.34 (m, 3H, Ph), 5.76 (s, 1H, 2-H), 5.54 (s, 1H, 6-H), 4.66 (d, 1H, $^3J_{4a,10b} = 9.5$ Hz, 10b-H), 4.43 (dd, 1H, $^2J_{4ax,4eq} = 10.4$ Hz, $^3J_{4eq,4a} = 4.9$ Hz, 4eq-H), 4.17 (ddd, 1H, $^3J_{4ax,4a} = 10.4$ Hz, $^3J_{4a,10b} = 9.5$ Hz, $^3J_{4eq,4a} = 4.9$ Hz, 4a-H), 3.94 (t, 1H, $^2J_{4ax,4eq} = {}^3J_{4ax,4a} = 10.4$ Hz, 4ax-H), 3.58 (s, 3H, MeO), 2.76 (s, 3H, Me). – ^{13}C NMR (250 MHz, $CDCl_3$): $\delta = 168.8$ (C-9), 160.7 (C-10a), 156.4 (C-7), 136.9, 129.3, 128.3, 126.7 (Ph), 124.2 (C-6a), 102.9 (C-2), 96.5 (C-6), 75.9 (C-10b), 69.3 (C-4), 63.0 (C-4a), 56.2 (MeO), 26.2 (Me). – MS (EI): $m/z\,(\%) = 314$ (14) [M^+]. – $C_{17}H_{18}N_2O_4$ (314.34): calcd. C 64.96, H 5.77, N 8.91; found C 64.61, H 5.67, N 8.01.

(2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2,9-diphenyl[1,3]dioxino[4',5':5,6]pyrano[4,3-d]pyrimidine (**12b**)

Compound **10** (0.032 g, 0.1 mmol) and benzamidinium chloride (0.04 g, 2.5 mmol) were converted as described for **12a**. Yield 0.024 g (66%), yellow powder. – m. p. 115 – 119 °C. – $[\alpha]_D^{24} = +94.4$ ($c = 0.9$, $CHCl_3$). – $R_f = 0.2$ (toluene/ethyl acetate 1 : 1). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.69$ (s, 1H, 7-H), 8.50 – 8.43 (m, 2H, Ph), 7.65 – 7.61 (m, 2H, Ph), 7.49 – 7.38 (m, 3H, Ph), 5.81 (s, 1H, 2-H), 5.59 (s, 1H, 6-H), 4.73 (d, 1H, $^3J_{4a,10b} = 9.5$ Hz, 10b-H), 4.47 (dd, 1H, $^2J_{4ax,4eq} = 10.3$ Hz, $^3J_{4eq,4a} = 4.9$ Hz, 4eq-H), 4.15 (ddd, 1H, $^3J_{4a,4ax} = 10.3$ Hz, $^3J_{4a,10b} = 9.5$ Hz, $^3J_{4a,4eq} = 4.9$ Hz, 4a-H), 3.98 (t, 1H, $^2J_{4ax,4eq} = {}^3J_{4ax,4a} = 10.3$ Hz, 4ax-H), 3.60 (s, 3H, MeO). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 164.8$ (C-9), 161.0 (C-10a), 156.6 (C-7), 137.1, 137.0, 131.0, 129.1, 128.6, 128.5, 128.3, 126.4 (Ph), 124.7 (C-6a), 102.4 (C-2), 96.5 (C-6), 76.0 (10b), 69.3 (C-4), 63.0 (C-4a), 56.2 (MeO). – MS (EI): $m/z\,(\%) = 376$ (22) [M^+]. – $C_{22}H_{20}N_2O_4$ (376.41): calcd. C 70.20, H 5.36, N 7.44; found C 70.16, H 5.30, N 7.39.

(2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-9-methylsulfanyl-2-phenyl[1,3]dioxino[4',5':5,6]pyrano–[4,3-d]pyrimidine (**12c**)

Following the procedure for **12a**, compound **10** (0.032 g, 0.1 mmol) and *S*-methylisothiouronium sulfate (0.04 g, 0.21 mmol) were allowed to react. Yield 0.011 g (31%), white needles. – m. p. 235 °C. – $[\alpha]_D^{23} = -19.6$ ($c = 1.0$, $CHCl_3$). – $R_f = 0.6$ (heptane/ethyl acetate 1 : 1). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.40$ (s, 1H, 7-H), 7.58 – 7.53 (m, 2H, Ph), 7.39 – 7.35 (m, 3H, Ph), 5.74 (s, 1H, 2-H), 5.51 (s, 1H, 6-H), 4.62 (d, 1H, $^3J_{4a,10b} = 9.5$ Hz, 10b-H), 4.43 (dd, 1H, $^2J_{4ax,4eq} = 10.3$ Hz, $^3J_{4eq,4a} = 4.9$ Hz, 4eq-H), 4.13 (ddd, 1H, $^3J_{4ax,4a} = 10.3$ Hz, $^3J_{4a,10b} = 9.5$ Hz, $^3J_{4eq,4a} = 4.9$ Hz, 4a-H), 3.93 (t, 1H, $^2J_{4ax,4eq} = {}^3J_{4ax,4a} = 10.3$ Hz, 4ax-H), 3.56 (s, 3H, MeO), 2.56 (s, 3H, MeS). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 173.5$ (C-9), 160.9 (C-10a), 156.4 (C-7), 136.9, 129.2, 128.2, 126.4 (Ph), 122.1 (C-6a), 102.4 (C-2), 96.6 (C-6), 75.8 (C-10b), 69.2 (C-4), 62.8 (C-4a), 56.1 (MeO), 14.2 (MeS). – MS (EI): $m/z\,(\%) = 346$ (0.5) [M^+]. – $C_{17}H_{18}N_2O_4S$ (346.40): calcd. C 58.94, H 5.24, N 8.09, S 9.26; found C 58.13, H 4.97, N 7.76, S 8.67.

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