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Synthesis of new iso-*C*-nucleoside analogues from 2-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)ethanal

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In memory of Professor Dr. Christian Pedersen

Abstract—Treatment of 2-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)ethanal with malononitrile, cyanoacetamide and 2-cyano-*N*-(4-methoxyphenyl)acetamide, respectively, in the presence of aluminium oxide yielded 2-cyano-4-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)crotonic acid derivatives. Cyclization with sulfur and triethylamine was performed to synthesize the 2-amino-5-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thiophene-3-carbonic acid derivatives, which were treated with triethyl orthoformate/ammonia and triethyl orthoformate, respectively, to furnish 6-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thieno[2.3-*d*]pyrimidine derivatives. Deprotection in two steps afforded 2-amino-5-(1,6-anhydro-3-deoxy-β-D-altropyranos-3-yl)thiophene-3-carbonitrile and 6-(1,6-anhydro-3-deoxy-β-D-altropyranos-3-yl)thieno[2.3-*d*]pyrimidine derivatives, respectively.

Keywords: Nucleoside analogues; Iso-*C*-nucleosides; Branched-chain monosaccharides; Thiophenecarbonic acid derivatives; Thieno[2.3-*d*]-pyrimidines

1. Introduction

Representatives of 2-amino-thiophene-3-carboxylates have significant analgesic activity.[1] The corresponding 5-carboxamido-4-hydroxy-3-(β-D-ribofuranosyl)thiophene-2-carbonic acid derivatives were investigated as virucides and virostatic agents.[2] Furthermore, thieno[2,3-*d*]pyrimidine derivatives[3] showed interesting biological properties including antihypertensive,[4] antiallergenic,[5] antitumour,[6] antiviral,[6] anti-HIV-1[6] and analgesic[7] activities. A few examples of thieno[2,3-*d*]pyrimidine nucleosides are known.[8–11] In order to obtain potentially less toxic and more active compounds, which might also be less susceptible to resistance many synthetic strategies have been developed for the formation of *C*-nucleosides in the last years.[12] Furthermore, iso-*C*-nucleosides in which the nucleobase is linked by a carbon–carbon bond to the sugar moiety as a carbon other than C-1 are of growing interest.[13–15]

Gewald et al.[16] described the synthesis of thiophene derivatives with biological activity by the reaction of Knoevenagel compounds with elemental sulfur mostly in *N*,*N*-dimethylformamide using amines as bases. The reaction of 1,6-anhydro-2-(dicyanomethylene)-2,3-dideoxy-4-*S*-ethyl-4-thio-β-D-*erythro*-hexopyranose with

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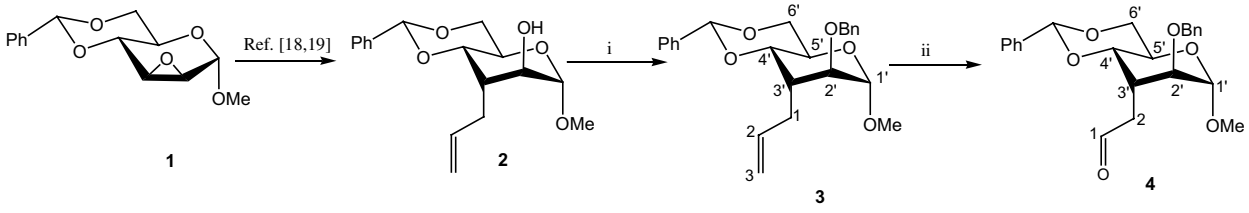
sulfur and triethylamine yielded the corresponding monosaccharidic anellated thiophene-3-carbonitrile.[17] Similarly, *C*-nucleosides and iso-*C*-nucleosides of 2-aminothiophene-3-carbonitriles with α-D-glycopyranosyl and α-D-altropyranosid-2-yl, respectively, units at C-5 were prepared.[18,19] These compounds were converted to 6-(α-D-glycopyranosyl and α-D-altropyranosid-2-yl, respectively)thieno[2,3-*d*]pyrimidines.

In the present paper we describe the synthesis of the hitherto unknown iso-*C*-nucleosides with a 3-deoxy-α-D-altropyranosid-3-yl unit in order to use these compounds later in various biological tests.

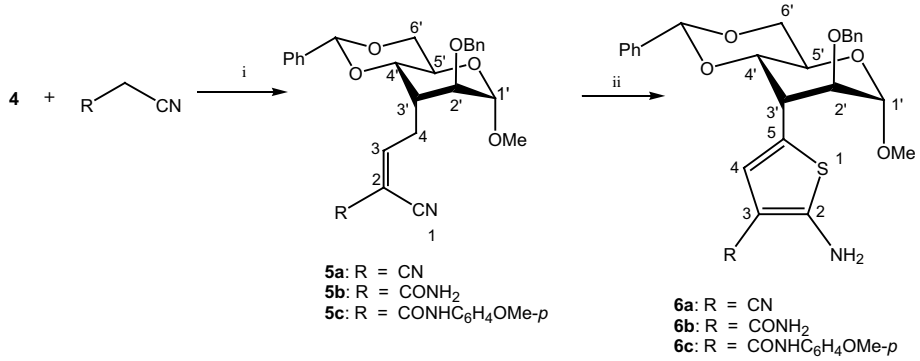
2. Results and discussion

4,6-*O*-Benzylidene-3-deoxy-3-(prop-2-enyl)-α-D-altropyranoside (**2**) was prepared in 80% yield by treatment of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) with allylmagnesium bromide (Scheme 1).[20,21] Benzylation of the 2-hydroxy group in THF with benzyl bromide and sodium hydride in the presence of tetrabutylammonium iodide[22,23] gave the branched-chain sugar **3**. Postema et al. have described the oxidation of similar unsaturated compounds with ozone in CH_2Cl_2 followed by reduction with Zn/acetic acid to give the corresponding aldehydes.[24] We decided for the oxidation with osmium tetroxide and sodium periodate in 1,4-dioxane/water (10:1)[25] and isolated the (pyranosid-3-yl)ethanal **4** in 75% yield. The branched-chain monosaccharidic aldehyde **4** was subsequently used as a versatile starting material for the preparation of iso-*C*-nucleosides.

Firstly, compound **4** was treated with malononitrile, cyanoacetamide and 2-cyano-*N*-(4-methoxyphenyl)acetamide, respectively, to give the corresponding products **5a**–**c** resulting from the Knoevenagel reaction (Scheme 2). These reactions were carried out by using an excess of the CH-acidic compounds and basic aluminium oxide in toluene.[26,27] The conversion of **5a** was complete after 1 h at room temperature providing **6a** in a yield of 90%. In order to drive the condensation of aldehyde **4** with cyanoacetamide and 2-cyano-*N*-(4-methoxyphenyl)acetamide to completion, it was required to heat the reaction mixtures to reflux for 24 h and 2 h, respectively. However, isolated yields were still lower than in the case of **5a**, because decomposition occurred under these reaction conditions. The structures **5a**–**c** were confirmed by the IR and NMR spectra. The appearance of cyano and carboxamide bands, respectively, in the IR spectra and the absence of the aldehyde signal and the occurrence of the typical cyano and carbonyl resonances in the ^{13}C NMR spectra clearly demonstrated the successful course of the Knoevenagel reaction. The values for the coupling constants $J_{H3\text{-}CN}$ and $J_{H3\text{-}C=O}$ (13 Hz and 6 Hz, respectively) determined from a coupled ^{13}C NMR spectrum confirmed the (*E*)-configuration of the structures **5b** and **5c**.



Scheme 1. Synthesis of 2-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)ethanal (**4**). Reagents and conditions: (i) BnBr, NaH, tetrabutylammonium iodide, THF, 22 °C; (ii) $NaIO_4$, OsO_4, dioxane/H_2O (10:1), 22 °C.



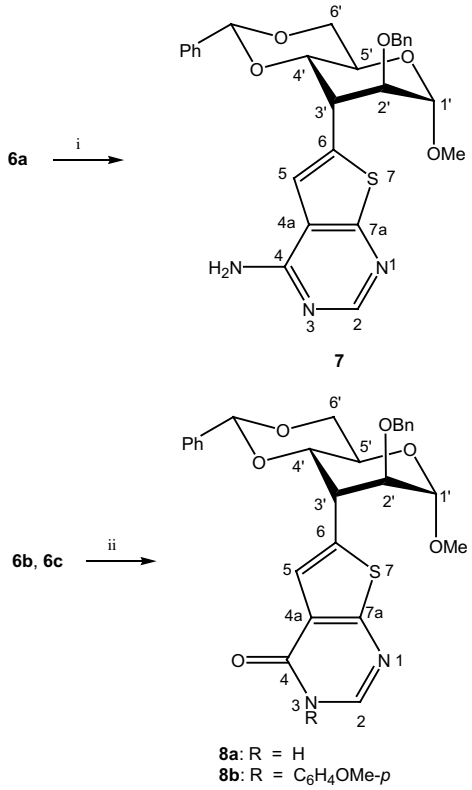
Scheme 2. Syntheses of 2-amino-5-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thiophene-3-carbonic acid derivatives **6**. Reagents and conditions: (i) Al_2O_3, toluene, 22 °C; (ii) S_8, Et_3N, DMF, 22 °C.

In order to prepare thiophene iso-*C*-nucleosides, compounds **5a**–**c** were treated according to this procedure with elemental sulfur in the presence of triethylamine in *N*,*N*-dimethylformamide to give the aminothiophene derivatives **6a**–**c** as light yellow solids in 85%, 45% and 65% yields, respectively (Scheme 2). The reaction of **5a** with elemental sulfur was completed in 15 min. For the generation of thiophene carbonic acid derivatives **6b** and **6c** a reaction time of 12 h was necessary. The structures of compounds **6a**–**c** were investigated by spectroscopic methods. In the IR spectra absorption bands for the amino groups were present. The DEPT spectra showed the absence of the former C-4 methylene group. Most characteristic in the ^{1}H NMR spectra of **6a**–**c** were the H-4 doublets at $\delta = 6.79$, 6.75 and 6.88, respectively, due to long-range couplings of H-4 of the thiophene ring with H-3′ in the sugar moiety probably caused by a 'W'-arrangement. The mass spectra of **6a**–**c** gave peaks corresponding to their molecular masses.

Starting from 1,2-enaminonitriles pyrimidine derivatives can be prepared.[28] In this manner **6a** was reacted with triethyl orthoformate under reflux. Without any further purification the syrupy formimidic acid ester obtained was converted into the corresponding 4-amino-6-(pyranosid-3-yl)thieno[2.3-*d*]pyrimidine **7** in 50% yield by treatment with a saturated ethanolic ammonia solution (Scheme 3). The mass spectrum of compound **7** showed the expected molecular peak and in the IR spectrum no absorption band for CN was visible anymore. In the ^{1}H NMR spectrum a new singlet at $\delta = 8.41$ appeared, which was assigned to the H-2 of the thieno[2.3-*d*]pyrimidine ring.

The 6-(pyranosid-3-yl)thieno[2.3-*d*]pyrimidin-4-ones **8a**,**b** could be obtained as white crystals in 56% and 65% yields, respectively, by reaction of the thiophenecarboxamides **6b** and **6c** with triethyl orthoformate in *N*,*N*-dimethylformamide (Scheme 3). The absence of an absorption band for NH_2 and the appearance of the carbonyl signals at different positions in the IR spectrum confirmed ring closure. In the ^{1}H NMR spectra of **8a,b** the characteristic singlets at $\delta = 7.99$ and 8.01, respectively, were in accordance with the expected value for H-2. Generally, two tautomeric forms can be formulated for compound **8a**. The NMR spectra showed the existence of only one compound in solution. However, we conclude from a carbonyl signal at 1668 cm^{-1} in the IR spectrum that compound **8a** predominantly exists as the oxo tautomer.

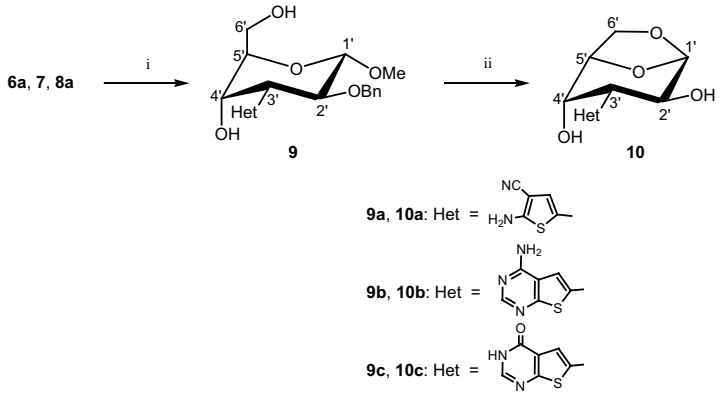
The deprotection of compounds **6a**, **7** and **8a** was carried out in two steps. In the first step the benzylidene group was completely removed by treatment with acetic acid/water at 70 °C. Compounds **9a**–**c** were obtained in medium yields due to the formation of elimination products, which were not completely characterized (Scheme 4). The value for the coupling constant $^3J_{2',3'}$ ($\sim$ 10.0 Hz) in comparison to compounds **6a**, **7** and **8a**



Scheme 3. Syntheses of 6-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thieno[2.3-*d*]pyrimidine derivatives **7**, **8**. Reagents and conditions: (i) (a) $(EtO)_3CH$, reflux (b) NH_3, EtOH, reflux; (ii) $(EtO)_3CH$, reflux.

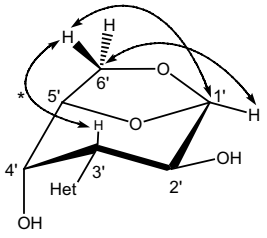
can only be explained by the fact that exists an axial–axial position of protons H-2′ and H-3′, which confirms also the preferred conformation $^1C_4$. This conformation was also verified by a correlation between H-1′ and H-6′a,b in the NOESY spectrum.

Iodotrimethylsilane (TMSI) is known as an useful reagent for the cleavage of benzylic and alkylic ethers.[29,30] According to this procedure the splitting of the 2-*O*-benzyl group was tried with iodotrimethysilane in chloroform at room temperature. After 24 h of reaction and followed by hydrolysis with methanol a new compound could be isolated in all cases. The NMR spectra showed that not only the benzyl, but also the glycosidic methyl group was cleaved under reacetalization. The cleavage of acetals in the presence of halotrimethylsilane and the introduction of halogenide at the anomeric carbon has already been reported.[31–33] In order to determine the structure of **10a**–**c** several measurements were made. The products were assigned as 1,6-anhydro-β-D-altropyranosides based on NOESY and HMBC experiments. In each case the NOESY spectra showed a characteristic correlation between the H-3′ and H-6′a protons and the HMBC spectra verified the connectivity through three bonds between H-1′ and C-6′ and between C-1′ and H-6′a, which are only possible in the postulated



Scheme 4. Deprotection of **6a**, **7**, **8a**. Reagents and conditions: (i) HOAc–H_2O 9:1, 70 °C; (ii) (a) TMSI, $CHCl_3$, 22 °C; (b) MeOH.

1,6-anhydrosugar structure. The mass spectra confirmed the proposed structures. In addition, the $^1H,^1H$ coupling constants and carbon chemical shifts determined for **10** were quite similar to the values reported for 1,6-anhydro-β-D-altropyranosides.[34–36]



Characteristic NOESY* and HMBC correlations

3. Experimental

TLC was carried out on silica gel 60 GF_{254} (Merck) with detection by UV light (λ = 254 nm) and/or by charring with 5% sulfuric acid in ethanol. 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 Polar LμP (IBZ Messtechnik). IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. ^1H NMR spectra (500.13 and 250.13 MHz, respectively) and ^{13}C NMR spectra (125.8 MHz, 75.5 MHz and 62.9 MHz, respectively) spectra were recorded on Bruker instruments AVANCE 500, ARX 300 and AC 250, respectively, with $CDCl_3$ or DMSO-d_6 as solvents. The calibration of spectra was carried out on TMS (internal, ^1H) and solvent (^{13}C) signals (δ $^1H_{TMS}$ = 0; δ $^{13}C_{CDCl_3}$ = 77.0). The ^1H and ^{13}C NMR signals were assigned by DEPT and two-dimensional $^1H,^1H$ COSY and $^1H,^{13}C$ correlation spectra. The mass spectra were recorded on an AMD 402/3 spectrometer (AMD Intectra GmbH). Elemental analysis were performed on a Leco CHNS-932 instrument. For chromatography Merck silica gel 60 (230–400 mesh) was used. Solvents and liquid reagents were purified and dried according to recommended procedures.

3.1. Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-3-(prop-2-enyl)-α-D-altropyranoside (3)

Sodium hydride (9.0 mmol) was added to a solution of methyl 4,6-*O*-benzylidene-3-deoxy-3-(prop-2-enyl)-α-D-altropyranoside (**2**, 1.58 g, 6.0 mmol) in tetrahydrofuran (50 mL). After stirring the mixture at room temperature for 30 min tetrabutylammonium iodide (0.185 g, 0.5 mmol) and benzyl bromide (0.72 mL, 6 mmol) were added. Stirring was continued for 3 h and then the solution was poured in water (30 mL) and extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The syrup obtained was purified by column chromatography (toluene/EtOAc 10:1) to yield 2.26 g (95%) of **3** as a white solid; TLC: toluene/EtOAc 10:1, R_f: 0.45; mp 44–46 °C; $[\alpha]_D^{22}$ +50.4 (*c* 0.5, $CHCl_3$); IR (KBr), *v* (cm^{-1}): 1641 (C=C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.51–7.27 (m, 10H, 2 × Ph); 5.81–5.65 (m, 1H, H-2); 5.59 (s, 1H, C*H*Ph); 5.10–4.98 (m, 2H, H-3); 4.66 (br s, 1H, $^3J_{1'2'} \sim 1.2$ Hz, H-1′); 4.55 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.27 (dd, 1H, $^2J_{6'ax,6'eq} \sim 10.0$ Hz, $^3J_{5',6'eq} \sim 4.9$ Hz, H-6′eq); 4.13 (dd, 1H, $^3J_{4',5'} \sim 10.0$ Hz, $^3J_{3',4'} \sim 5.2$ Hz, H-4′); 3.95 (dt, 1H, $^3J_{5',6'ax} \sim 10.0$ Hz, H-5′); 3.79 (t, 1H, H-6′ax); 3.61 (dd, 1H, $^3J_{2',3'} \sim 1.8$ Hz, H-2′); 3.35 (s, 3H, OMe); 2.53–2.46 (m, 2H, H-1); 2.41–2.31 (m, 1H, H-3′); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 137.9, 137.8 (2 × *ipso*-Ph); 137.1 (C-2); 128.9, 128.8, 128.4, 128.3, 127.8, 126.2 (*o*-, *m*-Ph); 116.7 (C-3); 101.9 (*C*HPh); 100.6 (C-1′); 76.3 (C-2′); 75.8 (C-4′); 71.7 (*C*H_2Ph); 69.6 (C-6′); 59.3 (C-5′); 55.1 (OMe); 39.2 (C-3′); 28.5 (C-1); MS,FAB$^+$ (*m*/*z*): 397 $[M+H]^+$; Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12. Found: C, 72.90; H, 7.24.

3.2. 2-(Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)ethanal (4)

Compound **3** (1.98 g, 5 mmol) was dissolved in 1,4-dioxane/water 10:1 (50 mL). An OsO_4-solution (0.4 mg in 1,4-dioxane, 0.4 mL) was added, and the resulting mixture was stirred by room temperature for 1 h. Then, $NaIO_4$ (3.2 g, 15 mmol) as a saturated solution in water was given to the mixture and stirring was continued for 12 h. After filtration the solvent was completely removed in vacuo. The residue was purified by column chromatography (toluene/EtOAc 10:1) to yield 1.49 g (75%) of **4** as a colourless syrup; TLC: toluene/EtOAc 10:1, R_f 0.30; $[\alpha]_D^{24}$ +52.7 (*c* 1.0, $CHCl_3$); IR (capillary), *v* (cm^{-1}): 1721 (CO); ^1H NMR (250 MHz, $CDCl_3$): δ 9.75 (s, 1H, H-1); 7.45–7.25 (m, 10H, 2 × Ph); 5.59 (s, 1H, C*H*Ph); 4.69 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.63 (br s, 1H, $^3J_{1',2'} \sim 1.2$ Hz, H-1′); 4.27 (dd, 1H, $^2J_{6'ax,6'eq} \sim 10.0$ Hz, $^3J_{5',6'eq} \sim 4.0$ Hz, H-6′eq); 4.16 (dd, 1H, $^3J_{4',5'} \sim 10.0$ Hz, $^3J_{3',4'} \sim 5.2$ Hz, H-4′); 3.89 (dt, 1H, $^3J_{5',6'ax} \sim 10.0$ Hz, H-5′); 3.80 (t, 1H, H-6′ax); 3.56 (dd, 1H, $^3J_{2',3'} \sim 2.1$ Hz, H-2′); 3.33 (s, 3H, OMe); 3.12–3.04 (m, 1H, H-3′); 2.98–2.93 (m, 2H, H-2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 201.4 (C-1); 137.8, 137.5 (2 × *ipso*-Ph); 129.1, 128.4, 128.3, 127.9, 127.8, 126.1 (*o*-, *m*-, *p*-Ph); 101.8 (*C*HPh); 100.5 (C-1′); 76.7 (C-2′); 75.1 (C-4′); 71.8 (*C*H_2Ph); 69.4 (C-6′); 59.6 (C-5′); 55.1 (OMe); 39.7 (C-2); 32.9 (C-3′); HRMS: Anal. Calcd for $C_{23}H_{26}O_6$ 398.17294; Found: $[M]^+$ *m*/*z* 398.17045.

3.3. 2-Cyano-4-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)crotononitrile (5a)

To a solution of **4** (0.398 g, 1 mmol) in dried toluene (10 mL), malononitrile (0.165 g, 2.5 mmol) and Al_2O_3 (0.1 g, aluminium oxide 90, active basic, Merck) were added and the mixture was stirred at room temperature for 1 h. After filtration the solvent was evaporated and the residue was purified by column chromatography (toluene/EtOAc 10:1) to yield 0.400 g (90%) of **5a** as a colourless syrup; TLC: toluene/EtOAc 10:1, R_f 0.42; $[\alpha]_D^{25}$ +8.2 (*c* 1.0, $CHCl_3$); IR (capillary), *v* (cm^{-1}): 2235 (CN); ^1H NMR (250 MHz, $CDCl_3$): δ 7.43–7.31 (m, 10H, 2 × Ph); 7.03 (dd, 1H, $^3J_{3,4a} \sim 7.0$ Hz, $^3J_{3,4b} \sim 8.6$ Hz, H-3); 5.56 (s, 1H, C*H*Ph); 4.68 (br s, 1H, $^3J_{1',2'} \sim 1.2$ Hz, H-1′); 4.60 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.29 (dd, 1H, $^2J_{6'ax,6'eq} \sim 9.8$ Hz, $^3J_{5',6'eq} \sim 4.6$ Hz, H-6′eq); 4.17 (dd, 1H, $^3J_{4',5'} \sim 9.8$ Hz, $^3J_{3',4'} \sim 5.5$ Hz, H-4′); 3.93 (dt, 1H, $^3J_{5',6'ax} \sim 9.8$ Hz, H-5′); 3.80 (t, 1H, H-6′ax); 3.39 (s, 3H, OMe); 3.34 (dd, 1H, $^3J_{2',3'} \sim 2.1$ Hz, H-2′); 3.06–2.85 (m, 2H, H-4); 2.48–2.41 (m, 1H, H-3′); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.9 (C-3); 137.1, 136.9 (2 × *ipso*-Ph); 129.2, 128.6, 128.2, 127.9, 127.2, 125.9 (*o*-, *m*-, *p*-Ph); 112.0, 110.5 (2 × CN); 102.1 (*C*HPh); 99.4 (C-1′); 90.0 (C-2); 76.3 (C-2′); 75.2 (C-4′); 72.3 (*C*H_2Ph); 69.2 (C-6′); 59.2 (C-5′); 55.0 (OMe); 39.1 (C-3′); 29.9 (C-4); MS, EI (*m*/*z*): 446 $[M]^+$; Anal. Calcd for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87; N, 6.27. Found: C, 69.98; H, 5.98; N, 6.31.

3.4. (2*E*)-2-Cyano-4-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)crotonamide (5b)

To a solution of **4** (0.398 g, 1 mmol) in dried toluene (30 mL), cyanoacetamide (0.168 g, 2 mmol) and Al_2O_3 (0.1 g, aluminium oxide 90, active basic, Merck) were added and the mixture was stirred under reflux for 24 h. After filtration the solvent was evaporated and the residue purified by column chromatography (toluene/EtOAc 1:1) to yield 0.350 g (75%) of **5b** as a white solid; TLC: toluene/EtOAc 1:2, R_f 0.45; mp 62–64 °C; $[\alpha]_D^{23}$ +29.7 (*c* 1.0, $CHCl_3$); IR (KBr), *v* (cm^{-1}): 3194, 3343 (NH_2); 2222 (CN); 1696 (CO); ^1H NMR (250 MHz, $CDCl_3$): δ 7.61 (dd, 1H, $^3J_{3,4a} \sim 6.7$ Hz, $^3J_{3,4b} \sim 9.2$ Hz, H-3); 7.50–7.30 (m, 10H, 2 × Ph); 5.95 (br d, NH_2); 5.59 (s, 1H, C*H*Ph); 4.68 (br s, 1H, $^3J_{1',2'} \sim 1.2$ Hz, H-1′); 4.58 (s, 2H, CH_2Ph); 4.30 (dd, 1H, $^2J_{6'ax,6'eq} \sim 10.1$ Hz, $^3J_{5',6'eq} \sim 4.9$ Hz, H-6′eq); 4.19 (dd, 1H, $^3J_{4',5'} \sim 10.1$ Hz, $^3J_{3',4'} \sim 5.2$ Hz, H-4′); 4.01 (dt, 1H, $^3J_{5',6'ax} \sim 10.1$ Hz, H-5′); 3.81 (t, 1H, H-6′ax); 3.42–3.39 (m, 1H, H-2′); 3.40 (s, 3H, OMe); 3.11–2.89 (m, 2H, H-4); 2.62–2.54 (m, 1H, H-3′); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 161.1 (C-3); 160.9 (C-1); 137.4, 137.2 (2 × *ipso*-Ph); 129.1, 128.9, 128.2, 128.0, 127.9, 126.1 (*o*-, *m*-, *p*-Ph); 114.9 (CN); 110.8 (C-2); 101.9 (*C*HPh); 99.6 (C-1′); 76.6 (C-2′); 75.5 (C-4′); 72.1 (*C*H_2Ph); 69.3 (C-6′); 59.3 (C-5′); 55.0 (OMe); 38.9 (C-3′); 28.7 (C-4); MS, EI (*m*/*z*): 464 $[M]^+$; Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.23; H, 6.08; N, 6.03. Found: C, 67.75; H, 6.32; N, 5.88.

3.5. (2*E*)-2-Cyano-*N*-(4-methoxyphenyl)-4-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)crotonamide (5c)

To a solution of **4** (0.398 g, 1 mmol) in dried toluene (30 mL), 2-cyano-*N*-(4-methoxyphenyl)acetamide (0.376 g, 2 mmol) and Al_2O_3 (0.1 g, aluminium oxide 90, active basic, Merck) were added and the mixture was stirred under reflux for 2 h. After filtration the solvent was evaporated and the residue purified by column chromatography (toluene/EtOAc 7:1) to yield 0.400 g (70%) of **5c** as a white solid; TLC: toluene/EtOAc 7:1, R_f 0.38; mp 68–71 °C; $[\alpha]_D^{23}$ +35.8 (*c* 1.0, $CHCl_3$); IR (KBr), *v* (cm^{-1}): 3332 (NH); 2221 (CN); 1686 (CO); ^1H NMR (250 MHz, $CDCl_3$): δ 7.70 (dd, 1H, $^3J_{3,4a} \sim 6.4$ Hz, $^3J_{3,4b} \sim 8.9$ Hz, H-3); 7.65 (br s, NH); 7.47–7.41 (m, 2H, H_o-NHC_6H_4); 7.37–7.28 (m, 10H, 2 × Ph); 6.93–6.86 (m, 2H, H_m-NHC_6H_4); 5.59 (s, 1H, C*H*Ph); 4.69 (br s, 1H, $^3J_{1',2'} \sim 1.2$ Hz, H-1′); 4.59 (s, 2H, CH_2Ph); 4.31 (dd, 1H, $^2J_{6'ax,6'eq} \sim 10.1$ Hz, $^3J_{5',6'eq} \sim 4.9$ Hz, H-6′eq); 4.20 (dd, 1H,

$^3J_{4',5'} \sim 10.1$ Hz, $^3J_{3',4'} \sim 5.5$ Hz, H-4′); 4.02 (dt, 1H, $^3J_{5',6'ax} \sim 10.1$ Hz, H-5′); 3.82 (t, 1H, H-6′ax); 3.80 (s, 3H, *p*-OMe); 3.43–3.39 (m, 1H, H-2′); 3.42 (s, 3H, OMe); 3.11–2.92 (m, 2H, H-4); 2.64–2.59 (m, 1H, H-3′); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 160.5 (C-3); 157.1, 157.07 (C-1, C_p-NHC_6H_4); 137.3, 137.2 (2 × *ipso*-Ph); 129.7 (C_{ipso}-NHC_6H_4); 129.0, 128.6, 128.2, 128.1, 127.9, 126.1 (*o*-, *m*-, *p*-Ph); 122.3 (C_o-NHC_6H_4); 115.0 (CN); 114.2 (C_m-NHC_6H_4); 111.8 (C-2); 101.9 (*C*HPh); 99.6 (C-1′); 76.6 (C-2′); 75.5 (C-4′); 72.1 (*C*H_2Ph); 69.3 (C-6′); 59.4 (C-5′); 55.4 (*p*-OMe); 54.9 (OMe); 38.9 (C-3′); 28.7 (C-4); MS, EI (*m*/*z*): 570 $[M]^+$; Anal. Calcd for $C_{33}H_{34}N_2O_7$: C, 69.46; H, 6.01; N, 4.91. Found: C, 69.19; H, 6.06; N, 4.77.

3.6. 2-Amino-5-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thiophene-3-carbonitrile (6a)

Compound **5a** (0.446 g, 1 mmol) was dissolved in dry *N*,*N*-dimethylformamide (5 mL). To this solution, sulfur (0.048 g, 1.5 mmol) and triethylamine (0.21 mL) were added, and the whole mixture was stirred at room temperature for 15 min. Water (30 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 50 mL), the organic phase was washed with water (2 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (toluene/EtOAc 5:1) to yield 0.406 g (85%) of **6a** as a light yellow solid; TLC: toluene/EtOAc 5:1, R_f 0.38; mp 162–164 °C; $[\alpha]_D^{23}$ +91.2 (*c* 1.0, $CHCl_3$); IR (KBr), *v* (cm^{-1}): 3215, 3309 (NH_2); 2214 (CN); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50–7.30 (m, 10H, 2 × Ph); 6.79 (d, 1H, $^4J_{3',4} \sim 1.2$ Hz, H-4); 5.60 (s, 1H, C*H*Ph); 4.72 (s, 1H, H-1′); 4.65 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.61 (br s, NH_2); 4.27 (dd, 1H, $^2J_{6'ax,6'eq} \sim 10.0$ Hz, $^3J_{5',6'eq} \sim 5.2$ Hz, H-6′eq); 4.22 (dd, 1H, $^3J_{4',5'} \sim 10.0$ Hz, $^3J_{3',4'} \sim 5.4$ Hz, H-4′); 3.99 (dt, 1H, $^3J_{5',6'ax} \sim 10.0$ Hz, H-5′); 3.92 (dd, 1H, $^3J_{2',3'} \sim 2.1$ Hz, $^3J_{1',2'} \sim 1.0$ Hz, H-2′); 3.78 (t, 1H, H-6′ax); 3.68–3.62 (m, 1H, H-3′); 3.33 (s, 3H, OMe); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 162.2 (C-2); 137.3, 137.2 (2 × *ipso*-Ph); 129.1, 129.0, 128.6, 128.3, 127.9, 126.3 (*o*-, *m*-, *p*-Ph); 125.3 (C-4); 123.5 (C-5); 115.9 (CN); 102.2 (*C*HPh); 99.6 (C-1′); 87.1 (C-3); 78.2 (C-2′); 75.4 (C-4′); 72.4 (*C*H_2Ph); 69.3 (C-6′); 59.1 (C-5′); 54.9 (OMe); 41.3 (C-3′); MS, EI (*m*/*z*): 478 $[M]^+$; Anal. Calcd for $C_{26}H_{26}N_2O_5S$: C, 65.26; H, 5.48; N, 5.85; S, 6.70. Found: C, 65.21; H, 5.73; N, 5.61; S, 6.01.

3.7. 2-Amino-5-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thiophene-3-carboxamide (6b)

The reaction of **5b** (0.446 g, 1 mmol) with sulfur was carried out as described above for the preparation of **6a** (reaction time 12 h). Purification by column chromatography (EtOAc) gave 0.220 g (45%) of **6b** as a light yellow solid; TLC: EtOAc, R_f 0.48; mp 88–91 °C; $[\alpha]_D^{25}$ +92.6 (*c* 1.0, $CHCl_3$); IR (KBr), *v* (cm^{-1}): 3439, 3399, 3328 (NH_2); 1642 (CO); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50–7.30 (m, 10H, 2 × Ph); 6.75 (d, 1H, $^4J_{3',4} \sim 1.2$ Hz, H-4); 6.05 (br s, NH_2); 5.61 (s, 1H, C*H*Ph); 5.39 (br s, NH_2); 4.73 (s, 1H, H-1′); 4.66 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.28 (dd, 1H, $^2J_{6'ax,6'eq} \sim 9.8$ Hz, $^3J_{5',6'eq} \sim 5.2$ Hz, H-6′eq); 4.23 (dd, 1H, $^3J_{4',5'} \sim 9.8$ Hz, $^3J_{3',4'} \sim 5.8$ Hz, H-4′); 4.07 (dt, 1H, $^3J_{5',6'ax} \sim 9.8$ Hz, H-5′); 3.93 (dd, 1H, $^3J_{2',3'} \sim 2.1$ Hz, $^3J_{1',2'} \sim 0.9$ Hz, H-2′); 3.79 (t, 1H, H-6′ax); 3.71–3.66 (m, 1H, H-3′); 3.33 (s, 3H, OMe); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 167.8 ($CONH_2$); 161.8 (C-2); 137.8, 137.4 (2 × *ipso*-Ph); 129.0, 128.6, 128.2, 128.0, 127.8, 126.3 (*o*-, *m*-, *p*-Ph); 123.3 (C-4); 120.2 (C-5); 106.7 (C-3); 102.2 (*C*HPh); 99.7 (C-1′); 78.6 (C-2′); 75.6 (C-4′); 72.3 (*C*H_2Ph); 69.3 (C-6′); 59.1 (C-5′); 54.8 (OMe); 41.2 (C-3′); MS, EI (*m*/*z*): 496 $[M]^+$; Anal. Calcd for $C_{26}H_{28}N_2O_6S$: C, 62.89; H, 5.68; N, 5.64; S, 6.46. Found: C, 62.96; H, 5.98; N, 5.15; S, 5.92.

3.8. 2-Amino-*N*-(4-methoxyphenyl)-5-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thiophene-3-carboxamide (6c)

The reaction of **5c** (0.446 g, 1 mmol) with sulfur was carried out as described above for the preparation of **6a** (reaction time 12 h). Purification by column chromatography (toluene/EtOAc 4:1) gave 0.390 g (65%) of **6c** as a light yellow solid; TLC: toluene/EtOAc 4:1, R_f 0.30; mp 95–98 °C; $[\alpha]_D^{20}$ +92.9 (*c* = 0.5, $CHCl_3$); IR (KBr), *v* (cm^{-1}): 3436, 3322 (NH_2); 1633 (CO); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.57–7.43 (m, 2H, H_o-NHC_6H_4); 7.40–7.34 (m, 10H, 2 × Ph); 6.91–6.84 (m, 3H, H_m-NHC_6H_4, H-4); 6.03 (br s, NH_2); 5.63 (s, 1H, C*H*Ph); 4.76 (s, 1H, H-1′); 4.69 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.30 (dd, 1H, $^2J_{6'ax,6'eq} \sim 10.0$ Hz, $^3J_{5',6'eq} \sim 5.2$ Hz, H-6′eq); 4.27 (dd, 1H, $^3J_{4',5'} \sim 10.0$ Hz, $^3J_{3',4'} \sim 5{,}8$ Hz, H-4′); 4.12 (dt, 1H, $^3J_{5',6'ax} \sim 10.0$ Hz, H-5′); 3.96 (dd, 1H, $^3J_{2',3'} \sim 2.1$ Hz $^3J_{1',2'} \sim 0.9$ Hz, H-2′); 3.81 (t, 1H, H-6′ax); 3.80 (s, 3H, *p*-OMe); 3.76–3.69 (m, 1H, H-3′); 3.36 (s, 3H, OMe); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 163.9 ($CONH_2$); 161.2 (C-2); 156.3 (C_p-NHC_6H_4); 137.5, 137.4 (2 × *ipso*-Ph); 129.7 (C_{ipso}-NHC_6H_4); 129.1, 128.6, 128.3, 128.1, 127.9, 126.3 (*o*-, *m*-, *p*-Ph); 122.5 (C-4); 122.3 (C_o-NHC_6H_4); 120.7 (C-5); 114.2 (C_m-NHC_6H_4); 107.9 (C-3); 102.2 (*C*HPh); 99.7 (C-1′); 78.7 (C-2′); 75.7 (C-4′); 72.4 (*C*H_2Ph); 69.3 (C-6′); 59.2 (C-5′); 55.4 (*p*-OMe); 54.9 (OMe); 41.3 (C-3′); MS, EI (*m*/*z*): 602 $[M]^+$; Anal. Calcd for $C_{33}H_{34}N_2O_7S$: C, 65.76; H, 5.69; N, 4.65; S, 5.32. Found: C, 65.72; H, 5.96; N, 4.47; S, 5.01.

3.9. 4-Amino-6-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thieno[2.3-*d*]pyrimidine (7)

Compound **6a** (0.478 g, 1 mmol) was dissolved in triethyl orthoformate (10 mL) and the mixture heated under reflux for 1 h. After evaporation of the solvent under reduced pressure the residue was dissolved in a saturated solution of NH_3 in abs ethanol (10 mL) and the mixture again was heated under reflux for 2 h. Then the solvent was removed in vacuo and the residue purified by column chromatography (EtOAc) to yield 0.255 g (50%) of **7** as a white solid; TLC: EtOAc, R_f 0.32; mp 97–100 °C; $[\alpha]_D^{21}$ +83.1 (*c* 1.0, $CHCl_3$); IR (KBr), *v* (cm^{-1}): 3385, 3191 (NH_2); ^1H NMR (250 MHz, $CDCl_3$): δ 8.41 (s, 1H, H-2); 7.49–7.31 (m, 11H, 2 × Ph, H-5); 5.65 (s, 1H, C*H*Ph); 5.53 (br s, NH_2); 4.77 (s, 1H, H-1′); 4.70 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.38 (dd, 1H, $^2J_{6'ax,6'eq} \sim 10.0$ Hz, $^3J_{5',6'eq} \sim 5.2$ Hz, H-6′eq); 4.31 (dd, 1H, $^3J_{4',5'} \sim 10.0$ Hz, $^3J_{3',4'} \sim 5.8$ Hz, H-4′); 4.18 (dt, 1H, $^3J_{5',6'ax} \sim 10.0$ Hz, H-5′); 4.07 (dd, 1H, $^3J_{2',3'} \sim 2.1$ Hz, $^3J_{1',2'} \sim 1.2$ Hz, H-2′); 3.98–3.92 (m, 1H, H-3′); 3.83 (t, 1H, H-6′ax); 3.30 (s, 3H, OMe); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 167.4, 157.1 (C-4, C-7a); 153.3 (C-2); 137.6 (C-6); 137.2, 137.1 (2 × *ipso*-Ph); 129.1, 128.6, 128.3, 128.2, 127.9, 126.2 (*o*-, *m*-, *p*-Ph); 117.0 (C-5); 115.9 (C-4a); 102.4 (*C*HPh); 99.5 (C-1′); 78.7 (C-2′); 75.4 (C-4′); 72.4 (*C*H_2Ph); 69.3 (C-6′); 59.2 (C-5′); 54.8 (OMe); 42.0 (C-3′); MS, EI (*m*/*z*): 505 $[M]^+$; Anal. Calcd for $C_{27}H_{27}N_3O_5S$: C, 64.14; H, 5.38; N, 8.31; S, 6.34. Found: C, 64.18; H, 5.67; N, 7.97; S, 6.02.

3.10. 3,4-Dihydro-6-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thieno[2,3-*d*]pyrimidin-4-one (8a)

A solution of compound **6b** (0.478 g, 1 mmol) and triethyl orthoformate (300 μL, 3 mmol) in dry *N*,*N*-dimethylformamide (10 mL) was heated under reflux for 7 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (EtOAc) to yield 0.140 g (56%) of **8a** as a white solid; TLC: EtOAc, R_f 0.46; mp 109–112 °C; $[\alpha]_D^{25}$ +86.2 (*c* 1.0, $CHCl_3$); IR (KBr), *v* (cm^{-1}): 3168 (NH); 1668 (CO); ^1H NMR (250 MHz, $CDCl_3$): δ 12.2 (br s, NH); 7.99 (s, 1H, H-2); 7.57 (d, 1H, $^2J_{5,3'} \sim 1.2$ Hz, H-5); 7.52–7.34 (m, 10H, 2 × Ph); 5.66 (s, 1H, C*H*Ph); 4.77 (s, 1H, H-1′); 4.71 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.37 (dd, 1H, $^2J_{6'ax,6'eq} \sim 10.1$ Hz, $^3J_{5',6'eq} \sim 5.5$ Hz, H-6′eq); 4.32 (dd, 1H, $^3J_{4',5'} \sim 10.4$ Hz, $^3J_{3',4'} \sim 5.2$ Hz, H-4′); 4.16 (m, 1H, H-5′); 4.11 (br s, 1H, H-2′); 3.98–3.92 (m, 1H, H-3′); 3.84 (t, 1H, $^3J_{5',6'ax} \sim 10.1$ Hz, H-6′ax); 3.33 (s, 3H, OMe); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 165.3 (C-4); 159.5 (C-7a); 143.1 (C-2); 138.1 (C-6); 137.2, 137.1 (2 × *ipso*-Ph); 129.1, 128.7, 128.3, 128.2, 127.9, 126.9 (*o*-, *m*-, *p*-Ph); 124.0 (C-4a); 121.3 (C-5); 102.6 (*C*HPh); 99.7 (C-1′); 78.6 (C-2′); 75.4 (C-4′); 72.5 (*C*H_2Ph); 69.4 (C-6′); 59.3 (C-5′); 54.9 (OMe); 42.0 (C-3′); MS, EI (*m*/*z*): 506 $[M]^+$; Anal. Calcd for $C_{27}H_{26}N_2O_6S$: C, 64.02; H, 5.17; N, 5.53; S, 6.33. Found: C, 63.84; H, 5.44; N, 5.32; S, 6.03.

3.11. 3,4-Dihydro-3-(4-methoxyphenyl)-6-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranosid-3-yl)thieno[2,3-*d*]pyrimidin-4-one (8b)

The reaction of **6c** (0.446 g, 1 mmol) with triethyl orthoformate was carried out as described above for the preparation of **8a**. Purification by column chromatography (toluene/EtOAc 4:1) gave 0.200 g (65%) of **8b** as a white solid; TLC: toluene/EtOAc 4:1, R_f 0.35; mp 94–97 °C; $[\alpha]_D^{23}$ +139.9 (*c* 1.0, $CHCl_3$); IR (KBr), *v* (cm^{-1}): 1688 (CO); ^1H NMR (250 MHz, $CDCl_3$): δ 8.01 (s, 1H, H-2); 7.58 (d, 1H, $^2J_{3',5} \sim 1.2$ Hz, H-5); 7.52–7.49 (m, 2H, H_o-NHC_6H_4); 7.40–7.15 (m, 10H, 2 × Ph); 7.05–6.99 (m, 2H, H_m-NHC_6H_4); 5.65 (s, 1H, C*H*Ph); 4.77 (br s, 1H, $^3J_{1',2'} \sim 1.2$ Hz, H-1′); 4.71 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.36 (dd, 1H, $^2J_{6'ax,6'eq} \sim 10.1$ Hz, $^3J_{5',6'eq} \sim 5.2$ Hz, H-6′eq); 4.32 (dd, 1H, $^3J_{4',5'} \sim 10.1$ Hz, $^3J_{3',4'} \sim 5.8$ Hz, H-4′); 4.19 (dt, 1H, $^3J_{5',6'ax} \sim 10.1$ Hz, H-5′); 4.09 (dd, 1H, $^3J_{2',3'} \sim 2.1$ Hz, H-2′); 3.97–3.91 (m, 1H, H-3′); 3.86 (s, 3H, *p*-OMe); 3.83 (t, 1H, H-6′ax); 3.32 (s, 3H, OMe); ^{13}C NMR (62.9 MHz, $CDCl_3$): 163.2 (C-4); 159.9 (C-7a); 157.3 (C_p-NHC_6H_4); 145.9 (C-2); 138.1 (C-6); 137.2, 137.1 (2 × *ipso*-Ph); 129.9 (C_{ipso}-NHC_6H_4); 129.1, 128.9, 128.6, 128.3, 128.2, 127.9 (*o*-, *m*-, *p*-Ph); 125.3 (C-5); 123.9 (C-4a); 122.3 (C_o-NHC_6H_4); 114.7 (C_m-NHC_6H_4); 102.7 (*C*HPh); 99.6 (C-1′); 78.6 (C-2′); 75.4 (C-4′); 72.5 (*C*H_2Ph); 69.4 (C-6′); 59.2 (C-5′); 55.6 (*p*-OMe); 54.9 (OMe); 41.9 (C-3′); MS, CI (*m*/*z*): 613 $[M]^+$; Anal. Calcd for $C_{34}H_{32}N_2O_7S$: C, 66.65; H, 5.26; N, 4.57; S, 5.23. Found: C, 67.03; H, 5.48; N, 4.26; S, 4.84.

3.12. 2-Amino-5-(methyl 2-*O*-benzyl-3-deoxy-α-D-altropyranosid-3-yl)thiophene-3-carbonitrile (9a)

A solution of compound **6a** (0.480 g, 1 mmol) in acetic acid (5 mL) and water (0.5 mL) was heated at 70 °C for 2 h. Water (10 mL) and $NaHCO_3$ were added until neutralization of the solution. The mixture was extracted with EtOAc (3 × 50 mL), the organic phase was washed with water (2 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$/MeOH 10:1) to yield 0.187 g (48%) of **9a** as a white solid; TLC: $CHCl_3$/MeOH 10:1, R_f 0.49; mp 128–130 °C; $[\alpha]_D^{22}$ −33.0 (*c* 1.0, acetone); IR (KBr), *v* (cm^{-1}): 3208, 3304, 3408, 3428 (NH_2, OH); 2215 (CN); ^1H NMR (250 MHz, acetone-d_6): δ 7.31–7.16 (m, 5H, Ph); 6.56

(d, 1H, $^4J_{3',4} \sim 1.0$ Hz, H-4); 6.22 (br s, NH_2); 4.69 (d, 1H, $^3J_{1',2'} \sim 4.0$ Hz, H-1′); 4.52 (q(AB), 2H, $^2J_{A,B} \sim 11.5$ Hz, CH_2Ph); 4.24 (br s, OH); 4.03–3.95 (m, 1H, H-4′); 3.81–3.67 (m, 3H, H-5′, H-6′); 3.63 (dd, 1H, $^3J_{2',3'} \sim 10.0$ Hz, H-2′); 3.40 (s, 3H, OMe); 3.13 (ddd, 1H, $^3J_{3',4'} \sim 4.0$ Hz, H-3′); ^{13}C NMR (75.5 MHz, acetone-d_6): δ 164.5 (C-2); 139.0 (*ipso*-Ph); 128.3, 127.9, 127.6 (*o*-, *m*-, *p*-Ph); 124.9 (C-5); 124.5 (C-4); 116.1 (CN); 103.7 (C-1′); 84.6 (C-3); 78.7 (C-2′); 76.2 (C-5′); 72.7 (*C*H_2Ph); 68.6 (C-4′); 62.7 (C-6′); 54.7 (OMe); 44.3 (C-3′); MS, EI (*m*/*z*): 390 $[M]^+$; Anal. Calcd for $C_{19}H_{22}N_2O_5S$: C, 58.45; H, 5.68; N, 7.17; S, 8.21. Found: C, 58.61; H, 5.89; N, 6.46; S, 8.79.

3.13. 4-Amino-6-(methyl 2-*O*-benzyl-3-deoxy-α-D-altropyranosid-3-yl)thieno[2.3-*d*]pyrimidine (9b)

The deprotection of compound **7** (0.500 g, 1 mmol) was carried out as described above for the preparation of **9a** (reaction time 6 h). Purification by column chromatography (EtOAc/MeOH 10:1) gave 0.265 g (63%) of **9b** as a white solid; TLC: EtOAc/MeOH 10:1, R_f 0.31; mp 210–212 °C; $[\alpha]_D^{25}$ −1.4 (*c* 0.5, MeOH); IR (KBr), *v* (cm^{-1}): 3410, 3372, 3331, 3233 (NH_2, OH); ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.18 (s, 1H, H-2); 7.39 (d, 1H, $^2J_{5,3'} \sim 1.0$ Hz, H-5); 7.31 (br s, NH_2); 7.18–6.99 (m, 5H, Ph); 5.32 (d, 1H, $^3J_{4',OH\text{-}4'} \sim 5.5$ Hz, OH-4′); 4.86 (t, 1H, $^3J_{6',OH\text{-}6'} \sim 5.8$ Hz, OH-6′); 4.68 (d, 1H, $^3J_{1',2'} \sim 4.5$ Hz, H-1′); 4.46 (q(AB), 2H, $^2J_{A,B} \sim 11.6$ Hz, CH_2Ph); 3.93–3.85 (m, 1H, H-4′); 3.75–3.52 (m, 4H, H-2′, H-5′, H-6′); 3.37 (s, 3H, OMe); 3.37–3.32 (m, 1H, H-3′); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 166.5, 157.9 (C-4, C-7a); 153.5 (C-2); 138.5, 138.1 (C-6, *ipso*-Ph); 128.1, 127.6, 127.5 (*o*-, *m*-, *p*-Ph); 118.7 (C-5); 115.4 (C-4a); 103.1 (C-1′); 78.3 (C-2′); 76.7 (C-5′); 72.5 (*C*H_2Ph); 67.8 (C-4′); 61.6 (C-6′); 55.0 (OMe); 44.9 (C-3′); MS, EI (*m*/*z*): 417 $[M]^+$; Anal. Calcd for $C_{20}H_{23}N_3O_5S$: C, 57.54; H, 5.55; N, 10.07; S, 7.68. Found: C, 57.78; H, 5.69; N, 9.88; S, 7.96.

3.14. 3,4-Dihydro-6-(methyl 2-*O*-benzyl-3-deoxy-α-D-altropyranosid-3-yl)thieno[2,3-*d*]pyrimidin-4-one (9c)

The deprotection of compound **8a** (0.250 g, 0.5 mmol) was carried out as described above for the preparation of **9a** (reaction time 2 h). Purification by column chromatography (EtOAc/MeOH 10:1) gave 0.145 g (69%) of **9c** as a white solid; TLC: EtOAc/MeOH 10:1, R_f 0.48; mp 75–78 °C; $[\alpha]_D^{22}$ +0.8 (*c* 1.0, acetone); IR (KBr), *v* (cm^{-1}): 3415 (OH); 1669 (CO); ^{1}H NMR (250 MHz, acetone-d_6): δ 11.3 (br s, NH); 8.05 (s, 1H, H-2); 7.32 (d, 1H, $^4J_{3',5} \sim 1.0$ Hz, H-5); 7.24–7.11 (m, 5H, Ph); 4.77 (d, 1H, $^3J_{1',2'} \sim 4.0$ Hz, H-1′); 4.56 (q(AB), 2H, $^2J_{A,B} \sim 12.0$ Hz, CH_2Ph); 4.52–4.36 (br s, OH); 4.14 (t, 1H, $^3J_{3',4'} \sim {}^3J_{4',5'} \sim 4.0$ Hz, H-4′); 3.89–3.70 (m, 4H, H-2′, H-5′, H-6′); 3.46 (ddd, 1H, $^3J_{2',3'} \sim 10.0$ Hz, $^3J_{3',5} \sim 1.0$ Hz, H-3′); 3.43 (s, 3H, OMe); ^{13}C NMR (62.9 MHz, acetone-d_6): δ 164.9 (C-4); 157.7 (C-7a); 144.8 (C-2); 140.4, 139.1 (C-6, *ipso*-Ph); 128.5, 128.2, 127.8 (*o*-, *m*-, *p*-Ph); 124.9 (C-4a); 121.3 (C-5); 103.4 (C-1′); 79.1 (C-2′); 76.4 (C-5′); 72.9 (*C*H_2Ph); 68.9 (C-4′); 62.9 (C-6′); 54.9 (OMe); 45.2 (C-3′); MS, EI (*m*/*z*): 419 $[M+H]^+$; Anal. Calcd for $C_{20}H_{22}N_2O_6S$: C, 57.40; H, 5.30; N, 6.69; S, 7.66. Found: C, 57.77; H, 5.54; N, 5.93; S, 7.79.

3.15. 2-Amino-5-(1,6-anhydro-3-deoxy-β-D-altropyranos-3-yl)thiophene-3-carbonitrile (10a)

Compound **9a** (0.390 g, 1 mmol) was dissolved in chloroform (10 mL). To this solution trimethylsilyliodide (0.05 mL, 3.7 mmol) was added, and the whole mixture was stirred under argon at room temperature for 12 h. After disappearance of **9a**, MeOH (10 mL) was added and the mixture stirred for 4 h. The solution was concentrated under reduced pressure and the residue was purified by column chromatography ($CHCl_3$/MeOH 10:1) to yield 0.160 g (53%) of **10a** as a white solid; TLC: $CHCl_3$/MeOH 10:1, R_f 0.28; mp 78–81 °C; $[\alpha]_D^{21}$ −201.7 (*c* 1.0, acetone); IR (KBr), *v* (cm^{-1}): 3408, 3332, 3212 (NH_2, OH); 2203 (CN); ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.84 (br s, 2H, NH_2); 6.46 (s, 1H, H-4); 5.15 (s, 1H, H-1′); 5.14 (d, 1H, $^3J_{4',OH\text{-}4'} \sim 7.0$ Hz, OH-4′); 4.92 (d, 1H, $^3J_{2',OH\text{-}2'} \sim 7.0$ Hz, OH-2′); 4.38 (dd, 1H, $^3J_{5',6'b} \sim 5.5$ Hz, $^3J_{4',5'} \sim 2.5$ Hz, H-5′); 3.79 (d, 1H, $^2J_{6'a,6'b} \sim 7.5$ Hz, H-6′a); 3.61–3.56 (m, 1H, H-4′, H-6′b); 3.47 (ddd, 1H, $^3J_{1',2'} \sim 1.0$ Hz, $^3J_{2',3'} \sim 10.2$ Hz, H-2′); 2.86 (dd, 1H, $^3J_{3',4'} \sim 4.0$ Hz, H-3′); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 164.9 (C-2); 124.5 (C-5); 123.4 (C-4), 117.1 (CN); 102.3 (C-1′); 81.8 (C-3); 77.4 (C-5′); 70.5 (C-2′); 69.4 (C-4′); 65.4 (C-6′); 43.1 (C-3′); MS, EI (*m*/*z*): 268 $[M]^+$; Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.51; N, 10.44; S, 11.95. Found: C, 48.79; H, 4.59; N, 9.57; S, 12.27.

3.16. 4-Amino-6-(1,6-anhydro-3-deoxy-β-D-altropyranos-3-yl)thieno[2.3-*d*]pyrimidine (10b)

The reaction of compound **9b** (0.210 g, 0.5 mmol) with trimethylsilyliodide was carried out as described above for the preparation of **10a**. Purification by column chromatography (EtOAc/MeOH 5:1) gave 0.140 g (85%) of **10b** as a white solid; TLC: EtOAc/MeOH 5:1, R_f 0.22; mp 195–198 °C; $[\alpha]_D^{22}$ −104.5 (*c* 1.0, MeOH); IR (KBr), *v* (cm^{-1}): 3416, 3348, 3233 (NH_2, OH); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.18 (s, 1H, H-2); 7.34 (s, 1H, H-5); 7.29 (br s, 2H, NH_2); 5.23 (s, 1H, H-1′); 5.22 (d, 1H, $^3J_{4',OH\text{-}4'} \sim 6.0$ Hz, OH-4′); 5.08 (d, 1H, $^3J_{2',OH\text{-}2'} \sim 6.6$ Hz, OH-2′), 4.46 (dd, 1H, $^3J_{5',6'b} \sim 5.0$ Hz, $^3J_{4',5'} \sim 2.0$ Hz, H-5′); 3.89 (d, 1H, $^2J_{6'a,6'b} \sim 7.9$ Hz, H-6′a); 3.77–3.69 (m, 2H, H-2′, H-

4′); 3.64 (dd, 1H, H-6′b); 3.15 (dd, 1H, $^3J_{2',3'} \sim 10.1$ Hz, $^3J_{3',4'} \sim 3.5$ Hz, H-3′); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 166.3, 157.8 (C-4, C-7a); 153.2 (C-2); 138.9 (C-6); 118.2 (C-5); 115.5 (C-4a); 102.3 (C-1′); 77.5 (C-5′); 70.6, 69.4 (C-2′, C-4′); 65.6 (C-6′); 44.3 (C-3′); MS, FAB$^+$ (*m*/*z*): 295 [M]$^+$; HRMS: Anal. Calcd for $C_{12}H_{13}N_3O_4S$ 295.06268; Found: [M]$^+$ *m*/*z*: 295.06148.

3.17. 3,4-Dihydro-6-(1,6-anhydro-3-deoxy-β-D-altropyranos-3-yl)thieno[2,3-*d*]pyrimidin-4-one (10c)

The reaction of compound **9c** (0.210 g, 0.5 mmol) with trimethylsilyliodide was carried out as described above for the preparation of **10a**. Purification by column chromatography (EtOAc/MeOH 5:1) gave 0.115 g (74%) of **10c** as a white solid; TLC: EtOAc/MeOH 5:1, R_f 0.35; mp decomposition at 220 °C; $[\alpha]_D^{24}$ −72.3 (*c* 1.0, MeOH); IR (KBr), *v* (cm^{-1}): 3431 (NH, OH); 1686 (CO); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.3 (br s, NH); 8.03 (s, 1H, H-2); 7.21 (s, 1H, H-5); 5.23 (d, 1H, $^3J_{4',OH\text{-}4'} \sim 6.6$ Hz, OH-4′); 5.21 (s, 1H, H-1′); 5.09 (d, 1H, $^3J_{2',OH\text{-}2'} \sim 7.0$ Hz, OH-2′); 4.45 (dd, 1H, $^3J_{5',6'b} \sim 5.7$ Hz, $^3J_{4',5'} \sim 2.2$ Hz, H-5′); 3.91 (d, 1H, $^2J_{6'a,6'b} \sim 7.9$ Hz, H-6′a); 3.76–3.60 (m, 3H, H-2′, H-4′, H-6′b); 3.20 (dd, 1H, $^3J_{2',3'} \sim 10.1$ Hz, $^3J_{3',4'} \sim 3.8$ Hz, H-3′); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 163.8 (C-4); 157.3 (C-7a); 144.8 (C-2); 140.5 (C-6); 123.9 (C-4a); 120.2 (C-5); 102.2 (C-1′); 77.4 (C-5′); 70.7, 69.3 (C-2′, C-4′); 65.5 (C-6′); 43.7 (C-3′); MS, EI (*m*/*z*): 296 [M]$^+$; HRMS: Anal. Calcd for $C_{12}H_{12}N_2O_5S$ 296.04669; Found: [M]$^+$ *m*/*z* 296.04474.

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