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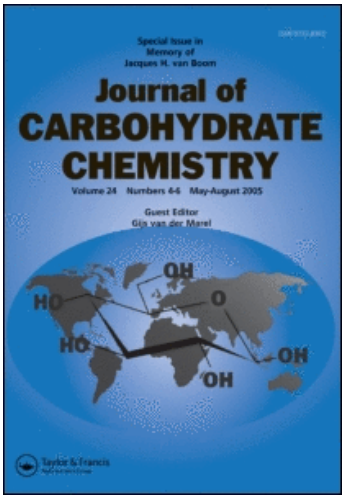

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Synthesis of (Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-α-d-altropyranosid-2-yl)thiophene Derivatives as Precursors of New Iso-*C*-nucleoside Analogues

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Synthesis of (Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)thiophene Derivatives as Precursors of New Iso-*C*-nucleoside Analogues

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ABSTRACT

Treatment of 2-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)ethanal (**3**) with malononitrile in the presence of aluminium oxide provided 2-cyano-4-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)crotononitrile (**4**). Starting from **4**, cyclization with sulphur and triethylamine yielded 2-amino-5-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)thiophene-3-carbonitrile (**5**). Further cyclization could be achieved with triethyl orthoformate/ammonia to furnish 4-amino-6-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)thieno[2.3-*d*]pyrimidine (**8**).

Key Words: Nucleoside analogues; Branched-chain sugars; Malononitrile; Thiopene; Thieno[2.3-*d*]pyrimidine.

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INTRODUCTION

The synthesis of *C*-nucleoside analogues in the last years has been carried out in a search for compounds having anticancer, antibacterial and antiviral activities.[1–4] Furthermore, iso-*C*-nucleosides in which the nucleobase is linked by a carbon-carbon bond to the sugar moiety at a carbon other than *C*-1 are a special type of *C*-nucleosides. These substances may have an increased chemical and enzymatic stability under physiological conditions.[5]

Several syntheses of iso-*C*-nucleosides have been reported.[4–6] Recently we described a method for the preparation of *C*-nucleosides on the basis of (α-D-glycopyranosyl) thiophene and thienopyrimidine derivatives[7] due to the wide spectrum of interesting biological properties of thiophene derivatives such as serine protease inhibitions,[8] dihydrofolate reductase inhibitions,[9] analgesic,[10,11] and anti-inflammatory[11] properties, among others. In the present paper we describe the synthesis of the corresponding iso-*C*-nucleosides, the (methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)thiophene and (methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)thieno[2.3-*d*]pyrimidine.

RESULTS AND DISCUSSION

Methyl 2,3-anhydro-4,6-benzylidene-α-D-allopyranoside **1** was reacted in two steps to furnish the known alkene derivative **2**.[12,13] Oxidation of **2** with osmium tetroxide and sodium periodate[14] afforded in two hours 2-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)ethanal **3** in 66% yield. The signals in the ^{1}H and ^{13}C NMR spectra found at $\delta = 9.66$ and 199.0, respectively, are typical of the aldehyde group in structure **3**.

Starting from **3**, the Knoevenagel reaction with excess malononitrile could be performed to yield the crotononitrile derivative **4** (Scheme 1). The reaction was catalyzed by aluminium oxide,[15,16] permitting complete transformation of the starting material in only one hour. After isolation of the product by column chromatography, the spectroscopic data of the product clearly verified the formation of compound **4**. In the IR spectrum both cyano groups appeared at 2242 cm^{-1} and the mass spectrum gave the corresponding molecular peak.

The degree of acidity of the methylene group at the neighbouring position to the dicyanomethylene moiety allowed the preparation of 2-amino-5-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)thiophene-3-carbonitrile (**5**) by treatment of **4** with elementary sulphur and triethylamine.[17] In the original procedure for the synthesis of such thiophenes, ethanol was used as solvent.[18] However, we carried out the reaction in *N,N*-dimethylformamide and isolated the thiophene-3-carbonitrile **5** as light yellow solid in 82% yield. As expected, in the IR spectrum of **5** only one CN band was found at a lower wave number 2204 cm^{-1} due to the conjugation of the cyano group with the thiophene ring and the amino group. In the ^{13}C NMR spectrum of **5** only one CN signal at $\delta = 115.2$ was present and in the ^{1}H NMR spectrum the signals of H-4 of the thiophene ring and amino group appeared at $\delta = 6.51$ and 4.71, respectively.

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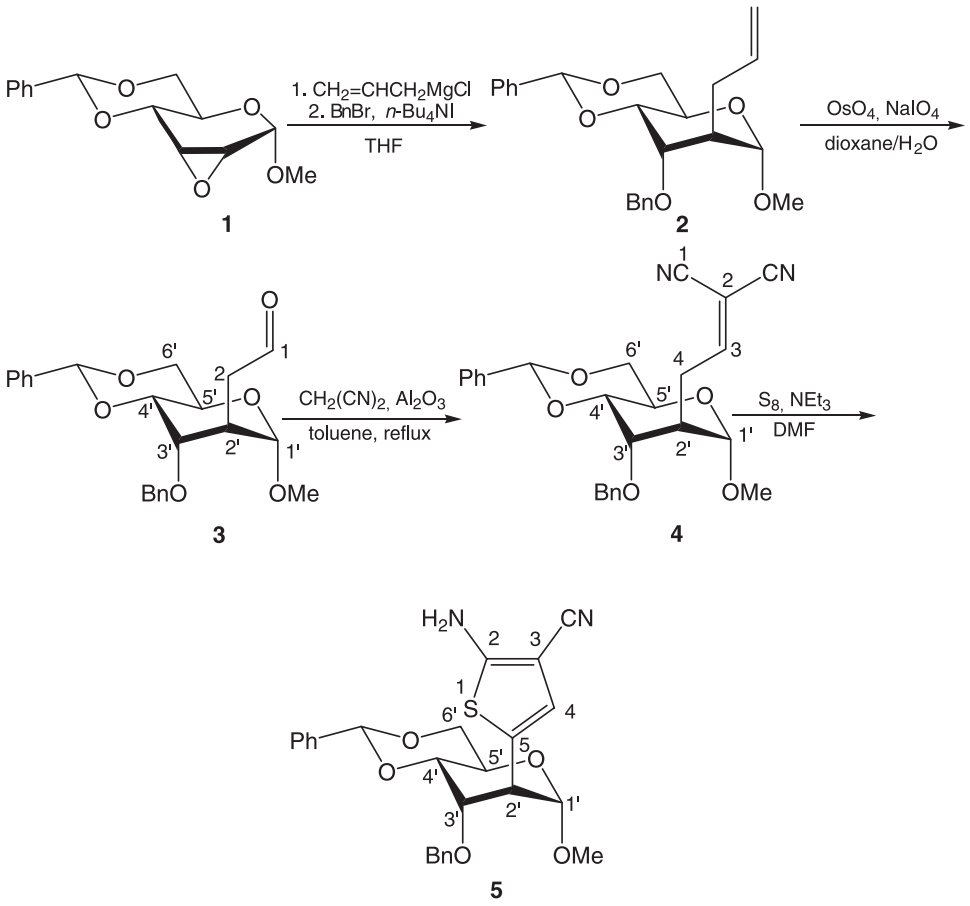

Scheme 1.

For further cyclization the enaminonitrile unit located in the thiophene ring of **5** could be used.[19] Treatment of thiophene **5** with triethyl orthoformate under reflux afforded a crude syrupy formimidic acid ester **6** which furnished, by reaction with a saturated ethanolic ammonia solution at room temperature, the 2-[aminomethylenamino]thiophene-3-carbonitrile **7** in 41% yield. On the other hand, **6** reacted with a saturated ethanolic ammonia solution under reflux gave the corresponding thieno[2.3-*d*] pyrimidine-4-amine **8** in 64% yield (Scheme 2).

In the IR and ^{13}C NMR spectra of compound **7** the expected CN peaks were displayed and in the ^{1}H NMR spectrum a broad singulet at $\delta = 7.83$ could be assigned to the aminomethylenamino group of the thiophene ring. The absence of CN peaks in the IR and in the ^{13}C NMR spectra of the (α-D-altropyranosid-2-yl)thieno[2.3-*d*] pyrimidine **8** proved the successful ring closure. Furthermore, in the ^{1}H NMR spectrum a defined singlet appeared at $\delta = 8.42$ belonging to H-2 of the thieno[2.3-*d*] pyrimidine ring.

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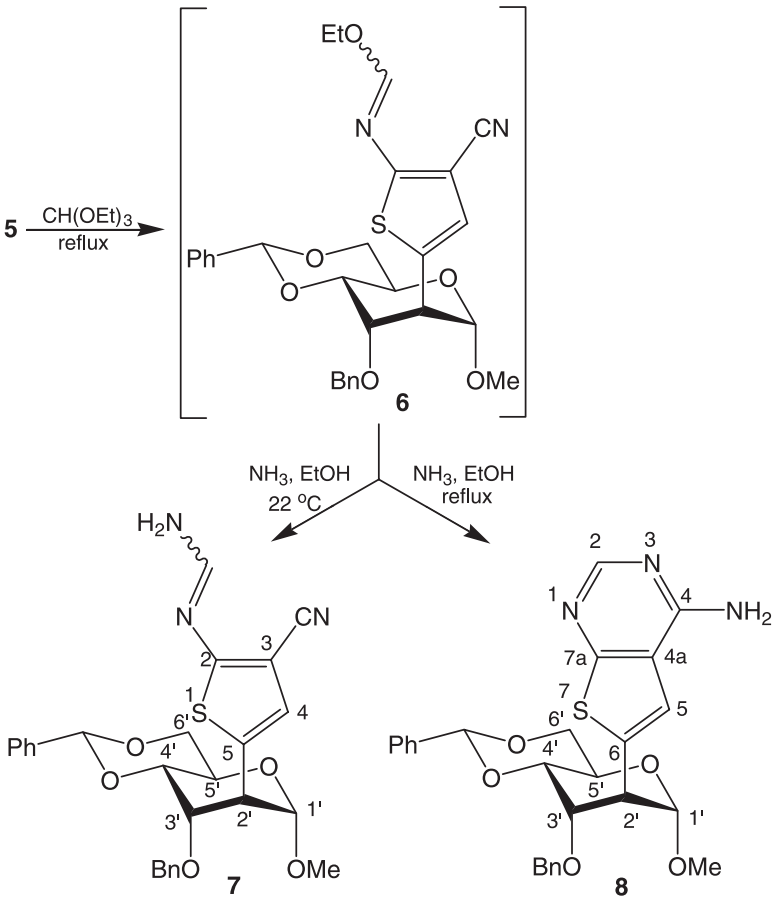

Scheme 2.

EXPERIMENTAL

General procedures. 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 ^{1}H 7.25; δ ^{13}C 77.0). 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 (230–400 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 sulphuric acid. Solvents and liquid reagents were purified and dried according to recommended procedures.

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2-(Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)ethanal (3). To methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-*C*-(prop-2-enyl)-α-D-altropyranoside (**2**) (1.98 g, 5 mmol) dissolved in dioxane/water 10:1 (50 mL), was added an OsO_4-solution (0.4 mg in dioxane, 0.4 mL), and the resulting reaction mixture was stirred at room temperature for 45 min. Then $NaIO_4$ (2.14 g), as a saturated solution in water was added, the mixture stirred for 2 h, filtered, and the solvent completely removed in vacuo. Compound **3** was obtained as a white solid after column chromatography (toluene/ethyl acetate 3:1): yield 1.31 g (66%); mp 95–97°C; $[\alpha]_D^{21}$ +45.7 (*c* 1.0, $CHCl_3$); R_f 0.35 (toluene/ethyl acetate 3:1). IR (KBr): 1717 cm^{-1} (CO). ^1H NMR (250.1 MHz, $CDCl_3$), δ 9.66 (t, 1H, $^3J_{1,2}$ = 1.2 Hz, H-1); 7.47–7.15 (m, 10H, ArH); 5.54 (s, 1H, C*H*-Ph); 4.82, 4.78 (q (AB), 2H, $^2J_{A,B}$ = 13.1 Hz, CH_2-Ph); 4.44 (m, 1H, H-5′); 4.41 (d, 1H, $^3J_{1',2'}$ = 0.5 Hz, H-1′); 4.31 (dd, 1H, $^2J_{6'a,6'b}$ = 10.3 Hz, $^3J_{5',6'a}$ = 5.4 Hz, H-6′a); 3.75–3.64 (m, 3H, H-3′, H-4′, H-6′b); 3.41 (s, 3H, OMe); 2.90 (m, 1H, H-2′); 2.66 (ddd, 1H, $^2J_{2a,2b}$ = 18.2, Hz, $^3J_{2a,2'}$ = 8.0 Hz, $^3J_{1,2a}$ = 1.2 Hz, H-2a); 2.47 (ddd, 1H, $^2J_{2a,2b}$ = 18.2, Hz, $^3J_{2b,2'}$ = 6.3 Hz, $^3J_{1,2b}$ = 1.2 Hz, H-2b). ^{13}C NMR (62.9 MHz, $CDCl_3$), δ 199.0 (C-1); 138.7, 137.5 (2 × *i*-Ph); 129.0 (*p*-Ph), 128.2, 128.1, 127.5, 126.2 (*o*-,*m*-Ph); 127.2 (p-Ph); 102.2 (*C*H-Ph); 101.4 (C-1′); 77.2 (C-4′); 74.4 (C-3′); 72.1 (*C*H_2-Ph); 69.4 (C-6′); 58.2 (C-5′); 55.7 (OMe); 44.7 (C-2); 37.5 (C-2′). MS (EI), *m/z*: 398 $[M]^+$.

Anal. Calcd for $C_{23}H_{26}O_6$ (398.45): C, 69.33; H, 6.58. Found: C, 69.18; H, 6.70.

2-Cyano-4-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)crotononitrile (4). To a solution of **3** (0.398 g, 1 mmol) in dried toluene (30 mL), were added malononitrile (0.165 g, 2.5 mmol) and Al_2O_3 (0.1 g), and the mixture was stirred under reflux for 1 h. After filtration the solvent was evaporated, the residue was purified by column chromatography (toluene/ethyl acetate 3:1) and recrystallized from ethanol to give **4** as white crystals: yield 0.388 g (87%); mp 148–150°C; $[\alpha]_D^{21}$ –56.7 (*c* 1.0, $CHCl_3$); R_f 0.45 (toluene/ethyl acetate 3:1). IR (KBr): 2242 cm^{-1} (CN). ^1H NMR (250.1 MHz, $CDCl_3$), δ 7.52–7.33 (m, 10H, ArH); 6.86 (t, 1H, $^3J_{3,4}$ = 7.8 Hz, H-3); 5.57 (s, 1H, C*H*-Ph); 4.89, 4.67 (2d, 2H, $^2J_{A,B}$ = 12.5 Hz, CH_2-Ph); 4.46–4.29 (m, 3H, H-1′, H-5′, H-6′a); 3.78–3.69 (m, 2H, H-4′, H-6′b); 3.58 (dd, 1H, $^3J_{3',4'}$ = 3.0 Hz, $^3J_{2',3'}$ = 2.0 Hz, H-3′); 3.41 (s, 3H, OMe); 2.63 (''t'', 2H, $^3J_{3,4}$ = $^3J_{2',4}$ = 7.8 Hz, H-4); 2.31 (dt, 1H, $^3J_{2',4}$ = 7.8 Hz, $^3J_{2',3'}$ = 2.0 Hz, H-2′). ^{13}C NMR (62.9 MHz, $CDCl_3$), δ 165.7 (C-3); 138.0, 137.4 (2 × *i*-Ph); 129.1 (*p*-Ph), 128.4, 128.3, 128.2, 126.2 (*o*-,*m*-Ph); 128.0 (*p*-Ph); 111.3, 110.1 (2 × CN); 102.3 (*C*H-Ph); 100.8 (C-1′); 91.7 (C-2); 76.9 (C-4′); 73.1 (*C*H_2-Ph); 72.6 (C-3′); 69.3 (C-6′); 58.3 (C-5′); 55.7 (OMe); 43.6 (C-2′); 33.6 (C-4). MS (CI), *m/z*: 447 $[M+1]^+$.

Anal. Calcd for $C_{26}H_{26}N_2O_5$ (446.50): C, 69.94; H, 5.87; N, 6.27. Found: C, 69.81; H, 5.64; N, 6.39.

2-Amino-5-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)thiophene-3-carbonitrile (5). Compound **4** (0.446 g, 1 mmol) was dissolved in dry DMF (5 mL). To this solution sulphur (0.048 g, 1.5 mmol) and triethylamine (0.21 mL) were added, and the entire mixture was stirred at room temperature for 2 h. Water (30 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic phase was washed with water (2 × 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromato-

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graphy (toluene/ethyl acetate 3:1) to give **5** as a light yellow solid: yield 0.392 g (82%); mp 158–160°C; $[\alpha]_D^{21}$ −65.3 (*c* 1.0, $CHCl_3$); R_f 0.40 (toluene/ethyl acetate 3:1). IR (KBr): 2204 cm^{-1} (CN). ^1H NMR (250.1 MHz, $CDCl_3$), δ 7.50–7.20 (m, 10H, ArH); 6.51 (d, 1H, $^4J_{2',4}$ = 0.9 Hz, H-4); 5.52 (s, 1H, C*H*-Ph); 4.89 (d, 1H, $^2J_{A,B}$ = 12.5 Hz, 1 × CH_2-Ph); 4.82 (br s, 1H, $^3J_{1',2'}$ = 0.6 Hz, H-1′); 4.74 (d, 1H, $^2J_{A,B}$ = 12.5 Hz, 1 × CH_2-Ph); 4.71 (br, 2H, NH_2); 4.48 (m, 1H, H-5′); 4.36 (dd, 1H, $^2J_{6'a,6'b}$ = 10.1 Hz, $^3J_{5',6'a}$ = 5.5 Hz, H-6′a); 3.92 (dd, 1H, $^3J_{4',5'}$ = 9.7 Hz, $^3J_{3',4'}$ = 3.0 Hz, H-4′); 3.84 (br ''t'', 1H, $^3J_{3',4'}$ = 3.0 Hz, $^3J_{2',3'}$ = 2.5 Hz, H-3′); 3.77 (''t'', 1H, $^2J_{6'a,6'b}$ = $^3J_{5',6'b}$ = 10.3 Hz, H-6′b); 3.43 (s, 3H, OMe); 3.39 (m, 1H, H-2′). ^{13}C NMR (62.9 MHz, $CDCl_3$), δ 161.3 (C-2); 138.4, 137.5 (2 × *i*-Ph); 129.0 (*p*-Ph); 128.3, 128.2, 127.8, 126.2, (*o*-, *m*-Ph); 127.6 (*p*-Ph), 126.0 (C-5); 123.5 (C-4); 115.2 (CN); 102.3 (*C*H-Ph); 100.8 (C-1′); 87.3 (C-3); 76.4 (C-4′); 75.9 (C-3′); 72.8 (*C*H_2-Ph); 69.4 (C-6′); 58.5 (C-5′); 55.7 (OMe); 45.5 (C-2′). MS (CI), *m/z*: 479 $[M+1]^+$.

Anal. Calcd for $C_{26}H_{26}N_2O_5S$ (478.56): C, 65.26; H, 5.48; N, 5.85; S, 6.70. Found: C, 65.56; H, 5.69; N, 5.76; S, 6.56.

5-(Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)-2-[aminomethylenamino]thiophene-3-carbonitrile (7). Compound **5** (0.478 g, 1 mmol) was dissolved in triethyl orthoformate (10 mL) and the reaction mixture was refluxed for 1 h. The solvent was then evaporated under reduced pressure and the residue dissolved in a saturated solution (10 mL) of NH_3 in ethanol. The mixture was then stirred for 1 h, and the solvent was evaporated. The residue was purified by column chromatography (toluene/ethyl acetate 1:1) to give **7** as a white solid: yield 0.207 g (41%); mp 113–115°C; $[\alpha]_D^{21}$ −75.8 (*c* 0.23, $CHCl_3$); R_f 0.41 (toluene/ethyl acetate 1:1). IR (KBr): 2215 cm^{-1} (CN). ^1H NMR (250.1 MHz, $CDCl_3$), δ 7.83 (br, 1H, C*H* = N); 7.50–7.15 (m, 10H, ArH); 6.71 (d, 1H, $^4J_{2',4}$ = 0.9 Hz, H-4); 5.53 (s, 1H, C*H*-Ph); 5.46 (br, NH_2); 4.89 (d, 1H, $^2J_{A,B}$ = 12.8 Hz, 1 × CH_2-Ph); 4.86 (s, 1H, H-1′); 4.76 (d, 1H, $^2J_{A,B}$ = 12.8 Hz, 1 × CH_2-Ph); 4.50 (m, 1H, H-5′); 4.37 (dd, 1H, $^2J_{6'a,6'b}$ = 10.2 Hz, $^3J_{5',6'a}$ = 5.5 Hz, H-6′a), 3.93 (dd, 1H, $^3J_{4',5'}$ = 9.5 Hz, $^3J_{3',4'}$ = 3.0 Hz, H-4′); 3.88 (br ''t'', 1H, $^3J_{3',4'}$ = 3.0 Hz, $^3J_{2',3'}$ = 2.5 Hz H-3′); 3.79 (''t'', 1H, $^2J_{6'a,6'b}$ = $^3J_{5',6'b}$ = 10.2 Hz, H-6′b); 3.48 (m, 1H, H-2′); 3.44 (s, 3H, OMe). ^{13}C NMR (62.9 MHz, $CDCl_3$), δ 164.8 (C-2); 153.8 (CH═N); 138.4, 137.5 (2 × *i*-Ph); 131.1 (C-5); 129.0 (*p*-Ph); 128.3, 128.2, 127.7, 126.2, (*o*-,*m*-Ph); 127.6 (*p*-Ph); 124.4 (C-4); 116.1 (CN); 102.3 (*C*H-Ph); 100.8 (C-1′); 96.9 (C-3); 76.3 (C-4′); 76.0 (C-3′); 72.8 (*C*H_2-Ph); 69.4 (C-6′); 58.5 (C-5′); 55.7 (OMe); 46.1 (C-2′). MS (CI), *m/z*: 506 $[M+1]^+$.

Anal. Calcd for $C_{27}H_{27}N_3O_5S$ (505.58): C, 64.14; H, 5.38; N, 8.31; S, 6.34. Found: C, 64.28; H, 5.45; N, 8.38; S, 6.30.

4-Amino-6-(methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranosid-2-yl)thieno[2.3-d]pyrimidine (8). Compound **5** (0.478 g, 1 mmol) was dissolved in triethyl orthoformate (10 mL) and the reaction mixture was refluxed for 1 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in a saturated solution (10 mL) of NH_3 in ethanol. The mixture was stirred for 1 h and then heated until the product **7** disappeared (TLC control). The solvent was removed and the residue purified by column chromatography (ethyl acetate) to give **8** as a white solid: yield 0.323 g (64%); mp 100–102°C; $[\alpha]_D^{21}$ −85.3 (*c* 1.0, $CHCl_3$); R_f 0.33 (ethyl acetate). IR (KBr): 3230, 3196 cm^{-1} (NH_2). ^1H NMR (250.1 MHz, $CDCl_3$), δ 8.42

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(s, 1H, H-2); 7.48–7.27 (m, 10H, ArH); 6.97 (s, 1H, H-5); 5.67 (br d, 2H, NH_2); 5.49 (s, 1H, C*H*-Ph); 5.01 (s, 1H, H-1′); 4.93, 4.79 (q (AB), 2H, $^2J_{A,B}$ = 12.8 Hz, CH_2-Ph); 4.55 (m, 1H, H-5′); 4.38 (dd, 1H, $^2J_{6'a,6'b}$ = 10.3 Hz, $^3J_{5',6'a}$ = 5.5 Hz, H-6′a), 4.02 (br ''t'', 1H, H-3′); 3.95 (dd, 1H, $^3J_{4',5'}$ = 9.5 Hz, $^3J_{3',4'}$ = 3.1 Hz, H-4′); 3.78 (t, 1H, $^2J_{6'a,6'b}$ = $^3J_{5',6'b}$ = 10.3 Hz, H-6b′); 3.69 (br d, 1H, $^3J_{2',3'}$ = 2.5 Hz, H-2′); 3.47 (s, 3H, OMe). ^{13}C NMR (62.9 MHz, $CDCl_3$), δ 166.9, 157.2 (C-4, C-7a); 153.7 (C-2); 139.8, 116.9 (C-4a, C-6); 138.2, 137.4 (2 × *i*-Ph); 129.0 (*p*-Ph); 128.3, 128.2, 127.9, 126.1 (*o*-,*m*-Ph); 127.6 (*p*-Ph); 115.7 (C-5); 102.2 (*C*H-Ph); 100.7 (C-1′); 76.3 (C-4′); 76.0 (C-3′); 72.9 (*C*H_2-Ph); 69.4 (C-6′); 58.6 (C-5′); 55.8 (OMe); 46.4 (C-2′). MS (CI), *m/z*: 506 $[M+1]^+$.

Anal. Calcd for $C_{27}H_{27}N_3O_5S$ (505.58): C, 64.14; H, 5.38; N, 8.31; S, 6.34. Found: C, 63.92; H, 5.54; N, 8.15; S, 6.63.

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