Synthesis of a Pseudodisaccharide α-C-Glycosidically Linked to an 8-Alkylated Guanine

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Received: 25 February 2013; in revised form: 21 March 2013 / Accepted: 21 March 2013 / Published: 2 April 2013

Abstract: The synthesis of stable guanofosfocin analogues has attracted considerable attention in the past 15 years. Several guanofosfocin analogues mimicking the three constitutional elements of mannose, ribose, and guanine were designed and synthesized. Interest in ether-linked pseudodisaccharides and 8-alkylated guanines is increasing, due to their potential applications in life science. In this article, a novel guanofosfocin analogue 6, an ether-linked pseudodisaccharide connected α-C-glycosidically to an 8-alkylated guanine, was synthesized in a 10-longest linear step sequence from known diol 13, resulting in an overall yield of 26%. The key steps involve the ring-opening of cyclic sulfate 8 by alkoxide generated from 7 and a reductive cyclization of 4-N-acyl-2,4-diamino-5-nitrosopyrimidine 19 to form compound 6.

Keywords: guanofosfocin; 8-alkylated guanine; ether-linked pseudodisaccharide; analogues; α-C-glycoside; nitrosopyrimidine

1. Introduction

Stable carbohydrate mimics are used widely to study the biological functions of oligo- and polysaccharides [1–3]. Well-known examples include C-glycosides [4], carbasugars [5] and thiooligosaccharides [6].
Guanofosfocin B (1, Figure 1) is one of the three guanofosfocins which were isolated in 1996 by Nippon Roche [7] from the fermentation broth of *Streptomyces* sp. AB 2570 and *Trichoderma* sp. FD 5372. Guanofosfocins are of interest as strong inhibitors of chitin synthases (IC$_{50}$: 1–10 nM). Detailed investigations of their biological activity were, however, hampered by their rapid decomposition. The instability, not surprising considering the two activated acetal moieties found in 1, was addressed by several groups by synthesizing stable open chain analogues of 1 while potentially retaining the promising biological properties. Sugimura *et al.* designed several analogues such as 2 (Figure 1) that maintained the alkoxy substituent attached to the C(8) of guanine [8–10]. Later on, they replaced the mannosyl moiety by a carba-mannosyl unit, and synthesized analogue 3 (Figure 1) [11]. Vasella *et al.* aimed at C-mannosides, replacing the anomeric oxygen by a methylene group, and prepared analogues 4 [12] and 5 [13] (Figure 1). We also considered the guanofosfocin analogue 6 of interest, in analogy to other, stable ether-linked pseudo-disaccharides [14–16] and report a synthesis of this ether-linked pseudo-disaccharide containing an 8-alkylated guanine.

**Figure 1.** Compounds prepared on the way to stable analogues of guanofosfocins.

2. Results and Discussion

The structure of 6 is characterized by an ether-linked pseudo-disaccharide with the $\alpha$-C-mannopyranosyl unit linked to C(8) of a guanine via a methylene group. Accordingly, we had to incorporate a methylene group between the guanyl and mannosyl moieties and install the ether bond between the secondary C(3)-OH group of mannose and the C(6)-OH group of an allofuranose. Retrosynthetically (Scheme 1), the ether bond could be formed by ring-opening cyclic sulfate 8 by the alkoxy anion corresponding to alcohol 7 [17], and the 8-substituted guanine could be formed by regioselective 4-N-acylation of 2,4-diamino-5-nitrosopyrimidine 9, followed by reductive cyclization, using a procedure developed by Vasella *et al.* [18].
Our synthesis started with the preparation of the protected α-allofuranose-diol 13, following known procedures as outlined in Scheme 2 [19–22]. The secondary alcohol 7 was synthesized from commercially available methyl α-D-mannoside in 36% overall yield using the three-step sequence reported by Vasella et al. [13]. Epoxide formation from vicinal diol 13 under Mitsunobu conditions [23] yielded 66% of 14. With epoxide 14 in hand, we carried out the oxirane ring-opening by the secondary alkoxide of 7 to get the pseudo-disaccharide 15 in 39% yield, besides 49% of recovered epoxide 14.

To improve the yield of the etherification, we prepared the cyclic sulfate 8 (Scheme 3). It was obtained in 69% from diol 13 by treatment with thionyl chloride and subsequent oxidation with NaIO₄ in the presence of catalytic Ru(II)Cl₂·xH₂O [24]. The cyclic sulfate 8 was a colorless solid that darkened upon storage, even in the refrigerator (0–5 °C) and so was used immediately. The reaction between the cyclic sulfate 8 and the oxyanion derived from alcohol 7 in HMPA/THF took place smoothly to furnish the ether-linked pseudo-disaccharide 15 in a yield of 86% upon acidic aqueous work-up. The polar solvent proved crucial for the high yield. Alcohol 15 was acetylated and converted to the carboxylic acid 18 in a yield of 88% by dihydroxylation of 16 by OsO₄/NMO, cleavage of the resulting diol by NaIO₄, and oxidation of the resulting aldehyde by NaH₂PO₄/NaClO₂. Treatment of acid 18 with oxalyl chloride in the presence of catalytic DMF furnished the acid chloride. Though the
reaction was carried out for 1 h, the conversion was completed within 5 min, as observed by monitoring the reaction mixture by IR spectroscopy. The acid chloride was stable enough to allow routine characterization (IR, \(^1\)H-NMR and \(^13\)C-NMR). It reacted with 6-(benzoxo)-5-nitrosopyrimidine-2,4-diamine (9) to afford amide 19, accompanied by a color change from purple to blue-green. As purification of amide 19 by chromatography led to yields below 50%, presumably caused by a strong absorption of amide 19 on silica gel, the crude amide 19 was treated directly with triphenylphosphine in xylene under reflux to furnish guanine 6 in an overall yield of 50% from 18 (Scheme 3). The reductive cyclisation was accompanied by a color change from blue-green to brown.

**Scheme 3.** Synthesis of pseudodisaccharide-guanine hybrid 6 from cyclic sulfate 8.

Reagents and conditions: (a) SOCl\(_2\), Pyr., CH\(_2\)Cl\(_2\); (b) RuCl\(_2\).xH\(_2\)O, NaIO\(_4\), 69% for 2 steps; (c) 7, NaH, HMPA/THF, 86%; (d) Ac\(_2\)O, DMAP, Et\(_3\)N; (e) OsO\(_4\), NMO; (f) NaIO\(_4\); (g) NaH\(_2\)PO\(_4\), NaClO\(_2\), 88% for 4 steps; (h) (COCl)\(_2\), DMF(cat.), CH\(_2\)Cl\(_2\); (i) 9, Pyr., THF; (j) Ph\(_3\)P, xylene, reflux; 50% for 3 steps.

With guanine 6 in hand, we performed a few scouting reactions to test its macrocyclization reactions via direct intra-molecular N-glycosylation. The first results showed that acetonide in 6 was not a good glycosyl donor for N-glycosylation. We then hydrolysed 6 to its corresponding vicinal diol. The macrocyclization is under investigation and the results will be reported in due course.

3. Experimental

**General**

Commercially available reagents were used without further purification. Water-free solvents were dried: THF was distilled from Na/benzophenone; toluene from Na; CH\(_2\)Cl\(_2\), MeCN, MeOH, pyridine, and triethylamine from CaH\(_2\); acetone, and chloroform were dried over 4 Å molecular sieves. Technical solvents were distilled: AcOEt, CH\(_2\)Cl\(_2\) from K\(_2\)CO\(_3\); Et\(_2\)O from FeSO\(_4\).7 H\(_2\)O; cyclohexane, hexane, MeOH, and toluene without any other additive. The reactions were carried out in oven-dried glassware, under an N\(_2\) or Ar atmosphere, unless stated otherwise. Qualitative TLC: precoated silica-gel
plates (Merck silica gel 60 F254); detection by heating with ‘mostain’ (400 mL of 10% H2SO4 soln., 20 g of (NH4)6Mo7O24·4H2O, 0.4 g of Ce(SO4)2·4 H2O), or by UV. FCC (flash column chromatography): silica gel Fluka 60 (0.04–0.063 mm) or Merck silica gel 60 (0.063–0.200 mm) under slightly elevated pressure (0.1–0.4 bar). Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries and are uncorrected. Optical rotations were measured with a PerkinElmer digital polarimeter: 1-dm cell at 25 °C, 589 nm, concentration (c) in g/100 mL. Infrared spectroscopy (IR) were recorded on a Perkin Elmer Spectrum RX-I FT-IR: ca. 2% soln. in CHCl3; absorptions in cm⁻¹.

NMR-spectra were recorded on Bruker magnetic resonance spectrometer (1H at 300 MHz, 13C at 75 MHz): chemical shifts δ in ppm relative to a residual undeuterated solvent peak. MS spectra were recorded on an IONSPEC Ultima ESI-FT-ICR spectrometer at 4.7 T.

3-O-Benzyl-1,2-O-isopropylidene-α-D-allofuranose, 5,6-cyclic sulfate (8). A solution of thionyl chloride (0.11 mL, 1.5 mmol) in CH2Cl2 (0.85 mL) was added dropwise to an ice-cooled solution of diol 13 (230 mg, 0.74 mmol) in CH2Cl2 (5 mL) and pyridine (0.24 mL, 3 mmol). The mixture was stirred for 5 min, when TLC revealed the disappearance of starting material. The mixture was diluted with CH2Cl2 and washed with water. The combined aqueous layers were extracted with CH2Cl2. The combined organic layers were dried (Na2SO4) and concentrated. The residue was dissolved in CH2Cl2/MeCN/H2O (2/2/3), to which was added NaIO4 (320 mg, 1.5 mmol) followed by Ru(II)Cl2·xH2O (10 mg). After 10 min, the mixture was diluted with CH2Cl2, the organic layer was separated, the water layer was extracted with CH2Cl2. The combined organic layers were dried (Na2SO4) and concentrated in vacuo.

The residue was purified by Flash Column Chromatography (FCC, EtOAc/cyclohexane, 1/3→1/1) to afford the cyclic sulfate 8 as a white solid (191 mg, 69%). m.p. 120–122 °C (dec.) (EtOAc/hexane). 1H-NMR (CDCl3, 300 MHz): δ (ppm) 7.40–7.37 (m, 5 H), 5.74 (d, 1 H, J = 3.3 Hz), 5.17 (dt, 1 H, J = 2.4, 7.2 Hz), 4.79 (dd, 1 H, J = 7.8, 9.0 Hz), 4.75 (d, 1 H, J = 12.0 Hz), 4.62 (d, 1 H, J = 12.0 Hz), 4.60 (d, 1 H, J = 6.9 Hz), 4.57 (dd, 1 H, J = 1.2, 5.4 Hz), 4.23 (dd, 1 H, J = 2.4, 9.0 Hz), 3.99 (dd, 1 H, J = 4.5, 9.0 Hz), 1.59 (s, 3 H), 1.36 (s, 3 H). 13C-NMR (CDCl3, 75 MHz): δ (ppm) 136.51, 128.53, 128.36, 113.53, 103.95, 79.99, 77.13, 77.05, 76.41, 72.59, 67.86, 26.90, 26.46. HR-MS(ESI), m/z 395.07695 [M+Na]+ (C16H20NaO8S+, required 395.07711).

5,6-Anhydro-3-O-benzyl1,2-O-isopropylidene-α-D-allofuranose (14). To a solution of diol 13 (305 mg, 0.98 mmol) and triphenylphosphine (310 mg, 1.18 mmol) in dry toluene (6 mL) was added disopropyl azodicarboxylate (0.25 mL, 94% pure, 1.18 mmol) dropwise at room temperature. The mixture was stirred under reflux overnight. The solvent was removed in vacuo, the residue was purified by FCC (EtOAc/cyclohexane, 1/3) to give epoxide 14 as a colorless oil (189 mg, 66%). IR (Film, cm⁻¹): 3021 (s), 2934 (w), 2870 (w), 1751 (w), 1455 (w), 1384 (w), 1375 (w), 1315 (w), 1254 (w), 1163 (w), 1131 (m), 1102 (s), 1022 (s). 1H-NMR (CDCl3, 300 MHz): δ (ppm) 7.40–7.29 (m, 5 H), 5.75 (d, 1 H, J = 3.9 Hz), 4.75 (d, 1 H, J = 11.4 Hz), 4.59–4.55 (m, 2 H), 4.21 (dd, 1 H, J = 3.0, 9.0 Hz), 3.66 (dd, 1 H, J = 4.2, 8.7 Hz), 3.19 (dd, 1 H, J = 3.0, 7.2 Hz), 2.81–2.73 (m, 2 H), 1.59 (s, 3 H), 1.36 (s, 3 H). 13C-NMR (CDCl3, 75 MHz): δ (ppm) 137.26, 128.57, 128.20, 128.16, 113.12, 104.21, 77.73, 77.57, 77.54, 72.02, 50.70, 44.45, 26.87, 26.60. [α]D25 +85.92° (c 1.05 in CHCl3).
2,6-Anhydro-1,3,5-tri-O-benzyl-4-O-(3-O-benzyl-1,2-O-isopropylidene-6-deoxy-α-D-allofuranos-6-yl)-7,8,9-trideoxy-D-glycero-D-mannonon-8-enitol (15). To a mixture of NaH (60% in oil, 93 mg, 2.32 mmol) in HMPA (3 mL) and THF (1 mL) was added alcohol 7 (1.10 g, 2.32 mmol) in THF (15 mL). The resulting slightly yellow solution was stirred at room temperature for 20 min, and then treated with cyclic sulfate 8 (720 mg, 1.93 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature overnight when TLC revealed the disappearance of the cyclic sulfate. The reaction mixture was treated with H2SO4/THF/H2O (1/100/0.3, 3 mL), stirred for 1 h, treated with saturated aqueous NaHCO3 solution, and extracted with EtOAc. The combined organic layers were dried (MgSO4), concentrated, and the residue purified by FCC (EtOAc/cyclohexane, 1/2→1/1) to afford 15 as a colorless oil (1.28 g, 86%). IR (Film, cm−1): 3475 (w), 3067 (w), 3032 (w), 3009 (m), 2928 (m), 2872 (w), 1732 (w), 1672 (w), 1496 (w), 1454 (w), 1374 (w), 1313 (w), 1224 (m), 1094 (s), 1027 (s). 

1H-NMR (CDCl3, 300 MHz): δ (ppm) 7.34–7.23 (m, 20 H), 5.84–5.70 (m, 1 H), 5.72 (d, 1 H, J = 3.3 Hz), 5.08–5.01 (m, 2 H), 5.72–4.48 (m, 9 H), 4.05–3.91 (m, 4 H), 3.86–3.48 (m, 8 H), 2.88 (d, 1 H, J = 2.4 Hz), 2.38–2.25 (m, 2 H), 1.57 (s, 3 H), 1.35 (s, 3 H). 13C-NMR (CDCl3, 75 MHz): δ (ppm) 138.22, 137.94, 137.90, 137.40, 134.16, 128.29, 128.19, 127.94, 127.87, 127.64, 127.39, 117.17, 112.86, 104.03, 78.66, 78.13, 77.71, 77.60, 75.14, 74.94, 73.86, 73.55, 73.29, 72.28, 72.13, 71.81, 71.10, 70.29, 68.96, 34.61, 26.93, 26.67. [α]25D +45.45° (c 1.00 in CHCl3). HR-MS (ESI), m/z 789.36095 [M+Na]+ (C46H54NaO10+). 

2,6-Anhydro-1,3,5-tri-O-benzyl-4-O-(5-O-acetyl-3-O-benzyl-1,2-O-isopropylidene-6-deoxy-α-D-allofuranos-6-yl)-7,8,9-trideoxy-D-glycero-D-mannonon-8-enitol (16). Triethylamine (0.32 mL, 2.29 mmol) and DMAP (61 mg, 0.50 mmol) in dry CH2Cl2 (2 mL), were added dropwise at 0 °C to a solution of alcohol 15 (0.88 g, 1.15 mmol) and acetic anhydride (0.21 mL, 2.29 mmol) in dry CH2Cl2 (3 mL). The resulting mixture was stirred at room temperature overnight. The reaction was quenched by adding water (1 mL), and the solvent was removed in vacuo. A solution of the residue in EtOAc (20 mL) was washed with water and 0.1 N HCl. The aqueous layer was extracted with EtOAc, the combined organic layers were dried (MgSO4) and concentrated to give the acetate 16 as a slightly yellow oil (0.94 g, 100%). IR (Film, cm−1, CHCl3): 3067 (w), 3032 (w), 3010 (m), 2928 (w), 1732 (w), 1672 (w), 1496 (w), 1454 (w), 1374 (w), 1313 (w), 1224 (m), 1094 (s), 1027 (s). 1H-NMR (CDCl3, 300 MHz): δ (ppm) 7.34–7.26 (m, 20 H), 5.85–5.73 (m, 1 H), 5.64 (d, 1 H, J = 3.7 Hz), 5.31 (ddd, 1 H, J = 4.8, 3.0, 6.6 Hz), 5.11–5.04 (m, 2 H), 4.73 (d, 1 H, J = 11.3 Hz), 4.67 (d, 1 H, J = 11.2 Hz), 4.61–4.40 (m, 7 H), 4.12 (dd, 1 H, J = 5.3, 8.6 Hz), 4.05–3.98 (m, 1 H), 3.90 (dd, 1 H, J = 4.3, 8.9 Hz), 3.83–3.62 (m, 8 H), 2.41–2.05 (m, 2 H), 1.85 (s, 3 H), 1.53 (s, 3 H), 1.31 (s, 3 H). 13C-NMR (CDCl3, 75 MHz): δ (ppm) 170.27 (CO), 138.57, 138.45, 138.37, 137.50, 128.40, 128.38, 128.36, 128.29, 128.14, 127.99, 127.83, 127.74, 127.63, 127.58, 127.43, 117.27, 113.08, 104.17, 79.81, 78.99, 77.20, 76.46, 75.53, 75.22, 73.93, 73.57, 73.97, 73.57, 73.28, 72.84, 72.21, 71.92, 71.75, 69.28, 68.92, 34.43, 26.80, 26.60, 21.00. [α]25D +43.73° (c 1.65 in CHCl3). HR-MS (ESI), m/z 831.37633 [M+Na]+ (C48H56NaO11+). 

2-[3-O-(5-O-Acetyl-3-O-benzyl-1,2-O-isopropylidene-6-deoxy-α-D-mannopyranosyl)acetaldehyde (17). To a mixture of alkene 16 (0.850 g, 1.05 mmol) and N-methylmorpholine N-oxide (NMO) (213 mg, 1.58 mmol) in acetone (6 mL) and water (2 mL) was
added osmium tetroxide (0.2 w% in water, 2.6 mL, 0.021 mmol, 0.02 eq.) at 0 °C. The resulting mixture was stirred for 45 h when TLC revealed the disappearance of the alkene 16. Upon addition of sodium sulfite (1.12 g) the yellow suspension turned into a slightly yellow two-layered solution. The upper organic layer was separated, the aqueous layer was extracted with EtOAc, the combined organic layers were dried (MgSO₄) and concentrated to give the crude diol (802 mg, 91%) as a mixture of two epimers in a ratio of ca. 0.75:1 (based on the integrals in the ¹H-NMR spectrum). IR (cm⁻¹, CHCl₃): 3473 (w), 3031 (vw), 2931 (w), 2871 (w), 1737 (m), 1496 (w), 1454 (m), 1372 (m), 1236 (s), 1164 (w), 1090 (s), 1070 (s), 1024 (s). ¹H-NMR (CDCl₃, 300 MHz): δ (ppm) 7.32–7.24 (m, 32.3 H), 5.63 (d, 0.6 H, J = 3.0 Hz), 5.29–5.23 (m, 1.5 H), 5.67–4.39 (m, 13.9 H), 4.17–4.06 (m, 4.0 H), 3.95–3.78 (m, 7.2 H), 3.72–3.42 (m, 13.9 H), 2.04 (d, 1.2 H, J = 0.9 Hz), 1.84–1.83 (m, 5.1 H), 1.78–1.51 (m, 2.9 H), 1.52 (s, 5.3 H), 1.31 (br s, 5.2 H). ¹³C-NMR (CDCl₃, 75 MHz): δ (ppm) 170.29, 138.17, 138.10, 138.07, 138.00, 137.98, 137.49, 137.46, 128.46, 128.42, 128.16, 128.14, 128.02, 127.94, 127.90, 127.83, 127.80, 127.74, 127.70, 127.66, 133.11, 133.09, 104.15, 79.84, 77.20, 76.79, 76.67, 76.40, 76.31, 75.25, 73.61, 73.45, 73.42, 73.18, 71.93, 71.80, 69.47, 69.39, 66.38, 32.81, 32.69, 31.69, 26.82, 26.60, 21.01. HR-MS(ESI), m/z, 865.37635 [M+Na]+ (C₄₈H₅₈NaO₁₃⁺, required 865.37696).

To the diol (630 mg, 0.747 mmol) in MeOH (3 mL) and H₂O (5 mL) was added sodium periodate (190 mg, 0.897 mmol) in H₂O (3 mL) at 0 °C, the mixture was stirred for 60 min, and then extracted with EtOAc. The combined organic layers were dried (MgSO₄) and concentrated to give the aldehyde 17 as a slightly yellow oil which was pure according to the NMR spectrum. IR (cm⁻¹, CHCl₃): 3030 (vw), 2933 (w), 2870 (w), 1739 (m), 1726 (m), 1496 (w), 1454 (w), 1371 (m), 1307 (m), 1234 (s), 1091 (s), 1071 (s), 1025 (s). ¹H-NMR (CDCl₃, 300 MHz): δ (ppm) 9.68 (t, 1 H, J = 2.3 Hz), 7.36–7.21 (m, 20 H), 5.63 (d, 1 H, J = 3.7 Hz), 5.28 (ddd, 1 H, J = 4.6, 3.4, 6.4 Hz), 4.74–4.42 (m, 10 H), 4.13 (dd, 1 H, J = 5.2, 8.9 Hz), 3.96–3.61 (m, 9 H), 2.62 (dd, 1 H, J = 1.1, 2.0 Hz), 2.60 (t, 1 H, J = 2.3 Hz), 1.87 (s, 3 H), 1.55 (s, 3 H), 1.34 (s, 3 H). ¹³C-NMR (CDCl₃, 75 MHz): δ (ppm) 200.50, 170.21, 138.40, 138.07, 138.00, 137.92, 137.79, 137.54, 129.09, 128.50, 128.48, 128.44, 128.38, 128.11, 128.08, 128.03, 127.90, 127.87, 127.82, 127.79, 127.57, 125.36, 113.12, 104.17, 79.80, 77.21, 76.52, 76.43, 76.00, 74.91, 74.43, 73.24, 72.85, 72.18, 71.80, 71.49, 69.65, 68.36, 66.57, 45.32, 26.53, 26.62, 21.52, 21.00. [α]₂⁵D +56.27° (c 2.00 in CHCl₃). HR-MS(ESI), m/z, 833.35133 [M+Na]+ (C₄₇H₅₄NaO₁₂⁺, required 833.35075).

2-[3-O-(5-O-Acetyl-3-O-benzyl-1,2-O-isopropylidene-6-deoxy-α-D-allofuranos-6-yl)-2,4,6-tri-O-benzyl-α-D-mannopyranosyl]acetic acid (18). The crude aldehyde 17 in acetonitrile (6 mL) was treated with NaH₂PO₄ (34 mg, 0.25 mmol) in H₂O (2 mL) and H₂O₂ (30%, 0.12 mL, 1.12 mmol), respectively, at 0 °C, followed by addition NaClO₂ (0.17 g, 80%, 1.49 mmol) in H₂O (2 mL) at 0 °C. The resulting mixture was stirred overnight, brought to pH 2.0 with 1N HCl, and extracted with EtOAc. The combined organic layers were dried (MgSO₄) and concentrated to give acid 18 as a colorless gum (0.60 g, 88% from 16). IR(cm⁻¹, CHCl₃): 3062 (w), 3030 (w), 2933 (w), 2872 (w), 1739 (s), 1714 (m), 1496 (w), 1454 (w), 1372 (m), 1306 (w), 1236 (s), 1162 (m), 1095 (s), 1026 (s). ¹H-NMR (CDCl₃, 300 MHz): δ (ppm) 7.33–7.25 (m, 20 H), 5.61 (d, 1 H, J = 3.6 Hz), 5.23 (ddd, 1 H, J = 5.3, 10.2 Hz), 4.58–4.36 (m, 10 H), 4.34–4.30 (m, 1 H), 4.10 (dd, 1 H, J = 5.3, 8.9 Hz), 3.97 (br. s, 1 H), 3.89–3.78 (m, 3 H), 3.73 (d, 1 H, J = 2.2 Hz), 3.64–3.56 (m, 3 H), 2.70 (dd, 1 H, J = 4.3, 15.7 Hz), 2.56 (dd, 1 H, J = 10.2 Hz).
1H, J = 8.6, 15.9 Hz), 1.84 (s, 3 H), 1.52 (s, 3 H), 1.31 (s, 3 H). 13C-NMR (CDCl3, 75 MHz): δ (ppm) 175.43, 170.35, 138.31, 138.06, 137.88, 137.50, 128.43, 128.36, 128.17, 127.97, 127.89, 127.86, 127.56, 133.13, 104.17, 79.80, 77.20, 76.86, 76.45, 75.66, 74.84, 74.47, 73.33, 73.05, 72.24, 71.84, 71.50, 69.45, 68.40, 68.16, 36.25, 26.98, 26.81, 26.61, 20.98. [α]D25 +50.97° (c 4.52 in CHCl3). HR-MS(ESI), m/z, 849.34625 [M+Na]+ (C47H54NaO13+, requires 849.34621), 871.32809 [M−H+Na2]+ (C47H53Na2O13+, requires 871.32816).

2-[3-O-(5-O-Acetyl-3-O-benzyl-1,2-O-isopropylidene-6-deoxy-α-D-allofuranos-6-yl)-2,4,6-tri-O-benzyl-α-D-mannopyranosyl]-N-[2-amino-6-(benzyloxy)-5-nitrosopyrimidin-4-yl]acetamide (19). To a solution of acid 18 (0.470 g, 0.57 mmol) in CH2Cl2 (4 mL) was added oxalyl chloride (0.15 mL, 1.7 mmol) followed by a drop of DMF at 0 °C. The resulting mixture was stirred for 1 h and concentrated in vacuo. The crude acid chloride was pure according to its NMR spectra and used directly for next step. IR (cm−1, CHCl3): 3031 (vw), 2932 (vw), 2868 (vw), 1798 (m), 1740 (s), 1496 (w), 1454 (m), 1371 (s), 1234 (s), 1091 (s), 1069 (s), 1023 (s). 1H-NMR (CDCl3, 300 MHz): δ (ppm) 7.36–7.24 (m, 20 H,), 5.61 (d, 1 H, J = 3.7 Hz), 5.23 (dd, 1 H, J = 6.0, 10.0 Hz), 4.95 (d, 1 H, J = 11.0 Hz), 4.73–4.31 (m, 9 H), 4.10 (dd, 1 H, J = 5.4, 8.9 Hz), 3.97 (t, 1 H, J = 5.8 Hz), 3.86 (dd, 1 H, J = 4.3, 8.8 Hz), 3.81–3.67 (m, 4 H), 3.64–3.57 (m, 3 H), 3.21–3.14 (m, 1 H), 2.99–2.90 (m, 1 H), 1.84 (s, 3 H), 1.52 (s, 3 H), 1.31 (s, 3 H). 13C-NMR (CDCl3, 75 MHz): δ (ppm) 171.27, 170.22, 138.39, 137.93, 137.54, 137.48, 128.55, 128.48, 128.34, 128.16, 128.02, 127.99, 127.84, 127.77, 127.52, 113.12, 109.13, 104.13, 79.89, 77.32, 77.23, 76.30, 75.93, 75.25, 74.78, 74.64, 73.34, 72.56, 72.23, 71.74, 71.21, 69.72, 68.25, 67.23, 49.09, 26.82, 26.61, 20.95, 13.97. [α]D25 +43.68° (c 2.35 in CHCl3).

To a solution of 2,4-diamino-5-nitrosopyrimidine 9 (0.21 g, 0.86 mmol) and pyridine (0.07 mL) in dry THF (12 mL) was added the above acid chloride (0.47 g, 0.57 mmol) in THF (7 mL) at 0 °C dropwise. Once the acid chloride was added, the deep-blue solution turned green. After stirring for 1 h, the purple solid was filtered off, and the filtrate was concentrated in vacuo to afford the amide 19 (600 mg). IR (cm−1, CHCl3): 3328 (w), 3228 (w), 3031 (w), 2933 (w), 2870 (w), 1739 (m), 1631 (m), 1598 (s), 1535 (s), 1497 (m), 1454 (s), 1371 (m), 1347 (s), 1255 (s), 1209 (s), 1091 (s), 1072 (s), 1026 (s). 1H-NMR (CDCl3, 300 MHz): δ (ppm) 12.38 (br. s, 1 H, exchange with D2O), 7.51–7.23 (m, 20 H), 7.17 (br. s, 1 H, exchange with D2O), 6.03 (br. s, 1 H, exchange with D2O), 5.65 (d, 1 H, J = 5.8 Hz), 4.70 (d, 1 H, J = 11.0 Hz), 4.64 (d, 1 H, J = 11.6 Hz), 4.63 (d, 1 H, J = 11.8 Hz), 4.57–4.43 (m, 6 H), 4.14 (dd, 1 H, J = 5.5, 8.9 Hz), 4.06 (br. s, 1 H), 3.88 (dd, 1 H, J = 4.3, 8.9 Hz), 3.83–3.65 (m, 7 H), 2.97 (dd, 1 H, J = 5.3, 14.7 Hz), 2.89 (dd, 1 H, J = 7.6, 14.9 Hz), 1.83 (s, 3 H), 1.51 (s, 3 H), 1.32 (s, 3 H). 13C-NMR (CDCl3, 75 MHz): δ (ppm) 171.45, 170.35, 163.78, 138.91, 138.31, 138.04, 137.86, 137.46, 135.49, 128.64, 128.46, 128.44, 128.32, 128.26, 128.20, 128.06, 127.95, 127.80, 127.72, 127.51, 113.12, 104.15, 79.92, 77.33, 77.24, 76.20, 76.05, 74.74, 74.12, 73.13, 72.25, 71.91, 71.62, 69.40, 68.72, 68.62, 41.33, 26.72, 26.61, 20.97. [α]D25 +43.68° (c 0.053 in CHCl3). HR-MS (ESI), m/z, 1076.4270 [M+Na]+ (C58H63N5NaO14+, required 1076.4264).

8-[3-O-(5-O-Acetyl-3-O-benzyl-1,2-O-isopropylidene-6-deoxy-α-D-allofuranos-6-yl)-2,4,6-tri-O-benzyl-α-D-mannopyranosyl)methyl]-O6-benzylguanine (6). A mixture of the amide 19 (600 mg, 0.57 mmol) and triphenyl phosphate (449 mg, 1.71 mmol) in xylene was stirred at 140 °C overnight and then cooled to room temperature. The mixture was passed through silica gel (EtOAc/cyclohexane 1/1→1/0)
to give guanine \textit{6} as a yellowish oil (291 mg, 50% from acid \textit{18}). IR (cm$^{-1}$, CHCl$_3$): 3528 (w), 3420 (w), 3067 (w), 2928 (m), 1738 (m), 1625 (s), 1591 (s), 1455 (m), 1374 (m), 1325 (m), 1227 (s), 1146 (m), 1090 (s). \textit{1}H-NMR (CDCl$_3$, 300 MHz): $\delta$ (ppm) 11.65 (br s, 1 H, NH, exchange with D$_2$O), 7.50–7.20 (m, 25 H), 5.57 (d, 1 H, $J = 3.7$ Hz), 5.53 (s, 2 H), 5.18 (dd, 1 H, $J = 5.0, 10.7$ Hz), 4.80 (br. s, 2 H, exchange with D$_2$O), 4.71–4.35 (m, 10 H), 4.21 (t, 1 H, $J = 8.1$ Hz), 3.86–3.70 (m, 3 H), 3.61 (dd, 1 H, $J = 2.6, 7.7$ Hz), 3.58–3.53 (m, 2 H), 3.47 (dd, 1 H, $J = 4.0, 10.2$ Hz), 3.30 (d, 1 H, $J = 14.0$ Hz), 2.97 (dd, 1 H, $J = 10.8, 16.0$ Hz), 1.84 (s, 3 H), 1.49 (s, 3 H), 1.30 (s, 3 H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ (ppm) 170.14, 160.10, 158.72, 155.66, 148.61, 137.74, 137.65, 137.42, 136.79, 132.20, 132.07, 128.61, 128.56, 128.49, 128.46, 128.40, 128.35, 128.32, 128.22, 128.04, 127.98, 127.92, 127.82, 127.69, 114.66, 13.06, 104.16, 79.68, 77.26, 77.11, 76.47, 75.95, 75.27, 74.37 (CH$_2$), 73.14, 72.70, 72.15, 71.79, 69.86, 67.79, 26.95, 26.78, 26.55, 20.98. [\(\alpha\)]$_{D}^{25}$ +31.76° (c 1.41 in CHCl$_3$). HR-MS (ESI), \(m/z\), 1044.4378 [M+Na]$^+$ (C$_{58}$H$_{63}$N$_5$NaO$_{12}$$^+$, required 1044.4365).

4. Conclusions

In summary, a new linear analogue of guanofosfocin \textit{6} was synthesized in 10 steps from the known sugar diol \textit{13} in 26% overall yield. Key steps were the ring-opening of cyclic sulphate \textit{8} by a sugar sec-alkoxide and the reductive cyclization of 4-N-acyl-2,4-diamino-5-nitrosopyrimidine \textit{19}. The robustness of the above etherification and of the reductive cyclization will find more applications in synthetic organic chemistry. The structure of \textit{6} was characterized as an ether-linked pseudodisaccharide \(\alpha\)-C-glycosidically linked to an 8-alkylated guanine. This compound, together with previously synthesized analogues of guanofosfocins, allows expansion of the relevant research in this field of medicinal chemistry and chemical biology.

Acknowledgments

We thank ETH Zürich and The National Natural Science Foundation of China (No. 21202008) for generous support.

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Sample Availability: Not available.

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