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Synthesis of the first example of a nucleoside analogue bearing a 5′-deoxy-β-D-*allo*-septanose as a seven-membered ring sugar moiety ☆

Gwenaëlle Sizun [a], David Dukhan [a], Jean-François Griffon [a], Ludovic Griffe [a], Jean-Christophe Meillon [a], Frédéric Leroy [a], Richard Storer [a,†], Jean-Pierre Sommadossi [b], Gilles Gosselin [a,*]

[a] *Idenix Pharmaceuticals, Medicinal Chemistry Laboratory, Cap Gamma, 1682 Rue de la Valsière, B.P. 50001, F-34189 Montpellier, France*
[b] *Idenix Pharmaceuticals, One Kendall Square, Building 1400, Cambridge, MA 02139, USA*

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ABSTRACT

The first example of a nucleoside analogue bearing a 5′-deoxy-β-D-*allo*-septanose as a seven-membered ring sugar moiety, namely 9-(5-deoxy-β-D-*allo*-septanosyl)-adenine, is reported. This compound was synthesized in 14 steps from the commercially available D-*glycero*-D-*gulo*-1,4-lactone. When evaluated in cell culture experiments against a broad range of viruses, it did not exhibit any significant antiviral effect or cytotoxicity.

1. Introduction

To date, septanoses (seven-membered ring sugars)[2–7] have not been extensively studied compared to the pyranose and furanose systems. However, a few papers showing growing interest in the biological studies of septanose derivatives have been published these last years. The first observations were published by Kuszmann and co-workers,[8,9] who studied the antithrombotic activity of a series of 4-substituted phenyl 1,6-dithio-hexoseptanosides, all the compounds tested possessing good activity. More recently, Peczuh and co-workers[10] investigated the ability of the jack bean lectin concanavalin A (ConA) to bind septanose monosaccharides. A series of methyl α- and β-septanosides–ConA complexes were measured, showing that the lectin ConA selectively binds β-septanosides. This was the first direct evidence of unnatural septanose sugars being bound to a natural protein. Nucleoside analogues bearing a five-membered sugar ring or acyclic derivatives[11] have been approved as antiviral drugs. Only few reports have appeared on derivatives with four- and six-membered sugar rings.[12]

On the other hand, and to the best of our knowledge, only six examples of nucleosides with a seven-membered carbohydrate moiety (called oxepane nucleosides according to Sabatino and Damha)[13] have been described in the literature (Chart 1). The first one is a nucleoside containing a dihydro-oxepine ring as the sugar moiety, which was unexpectedly obtained following an unusual ring-expansion reaction in an attempt to synthesize 4′-α-ethenyl ribonucleoside analogues via Wittig reaction of 4′-α-formyl ribonucleoside derivatives.[14]

The second example comprises septanosyl-1,2,3-triazoles, which were synthesized as potential glycosidase inhibitors.[15] The last four oxepane nucleoside examples were synthesized with the goal either to be used as monomeric units of modified oligonucleotides,[13,16] or to impart some degree of conformational restriction to the natural nucleosides.[16,17]

As part of an ongoing project aiming at designing new nucleoside analogues with potential antiviral activity, we embarked upon the synthesis and study of novel series of oxepane nucleosides.[18] Here, we report on the first example of a 5′-deoxy-β-D-*allo*-septanose nucleoside analogue.[1] The title compound, namely 9-(5-deoxy-β-D-*allo*-septanosyl)-adenine (**14**), was synthesized in 14 steps from the commercially available D-*glycero*-D-*gulo*-1,4-lactone. It was evaluated as a potential inhibitor of the replication of several classes of viruses.

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* Corresponding author. Tel.: +33 4 99 64 27 31; fax: +33 4 67 63 73 26.
E-mail address: gosselin.gilles@idenix.com (G. Gosselin).
† Present address: SUMMIT plc, 91 Milton Park, Abingdon, Oxfordshire OX14 4RY, UK.

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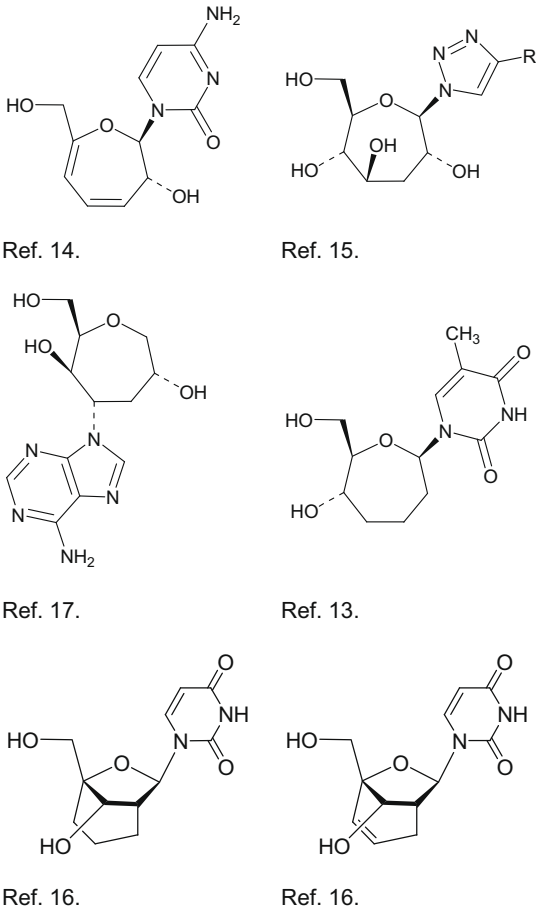


Chart 1. Previously described nucleoside analogues containing a seven-membered ring sugar.

2. Results and discussion

2.1. Synthesis

Our synthetic strategy to obtain the hitherto unknown nucleoside analogue **14** was based on the synthesis of a suitably protected septanose derivative **9**, which was activated as its trichloroacetimidate and reacted with 6-chloropurine.

Septanose derivative **9** (Scheme 1) was obtained from the commercial D-*glycero*-D-*gulo*-1,4-lactone through the known[19] bis(ethylidene)-protected *talo* derivative **1**. Deoxygenation at C-5 was achieved using the Barton–McCombie reaction;[20] the free hydroxyl group of **1** was activated for radical reduction with 1,1′-thiocarbonyldiimidazole. Reduction was performed using azobisisobutyronitrile (AIBN) and tris(trimethylsilyl)silane as the reducing agent, providing the deoxylactone **2**.

Complete reduction of **2** with sodium borohydride in methanol afforded the polyol 5-deoxy-2,3:6,7-di-*O*-diethylidene-D-*allo*-heptan-1-itol (**3**), which was treated as a crude with dimethoxytrityl chloride (DMTrCl) to provide the protected compound **4**. In this case, only the primary alcohol group reacted due to the steric hindrance of the hydroxyl group at C4. Compound **5** was obtained after successively treating **4** with NaH and with 4-chlorobenzyl chloride. The primary alcohol of **5** was then selectively deprotected using formic acid, and the free hydroxyl group was oxidized using the convenient Dess–Martin periodinane reagent to afford the heptose **7**. Deprotection was achieved using formic acid in ether to yield the cyclic sugar **8**. The driving force of this reaction at the terminal acetal position is the easy cyclisation that occurs readily afterwards. The primary hydroxyl function of **8** was selectively protected by treatment with imidazole and *tert*-butyldimethylsilyl chloride (TBDMSCl) to give the suitably protected septanose derivative **9**.

The synthesis of the nucleoside analogue **14** from the septanose derivative **9** is summarized in Scheme 2. To achieve the condensation of a carbohydrate with a base, a good leaving group is needed at the anomeric position. In this context, we prepared the trichloroacetimidate derivative of **9**. Indeed, trichloroacetimidate activation is currently one of the most frequently used alternative strategies for glycoside bond formation.[21–23] Treatment of **9** with trichloroacetonitrile in the presence of catalytic amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[24] afforded the corresponding trichloroacetimidate derivative **10**.

Trichloroacetimidate sugar **10** was then allowed to react with the N-silylated derivative of 6-chloropurine in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in toluene at reflux to give nucleoside **11** in 15% isolated yield after purification by silica gel chromatography. The structure of compound **11** was confirmed by nuclear Overhauser effect (NOE), which showed that only the β anomer was obtained. Upon irradiation of the doublet at δ 6.58 (H-1′), a reversible NOE was observed with the multiplet at 4.40 (H-6′) (Fig. 1).

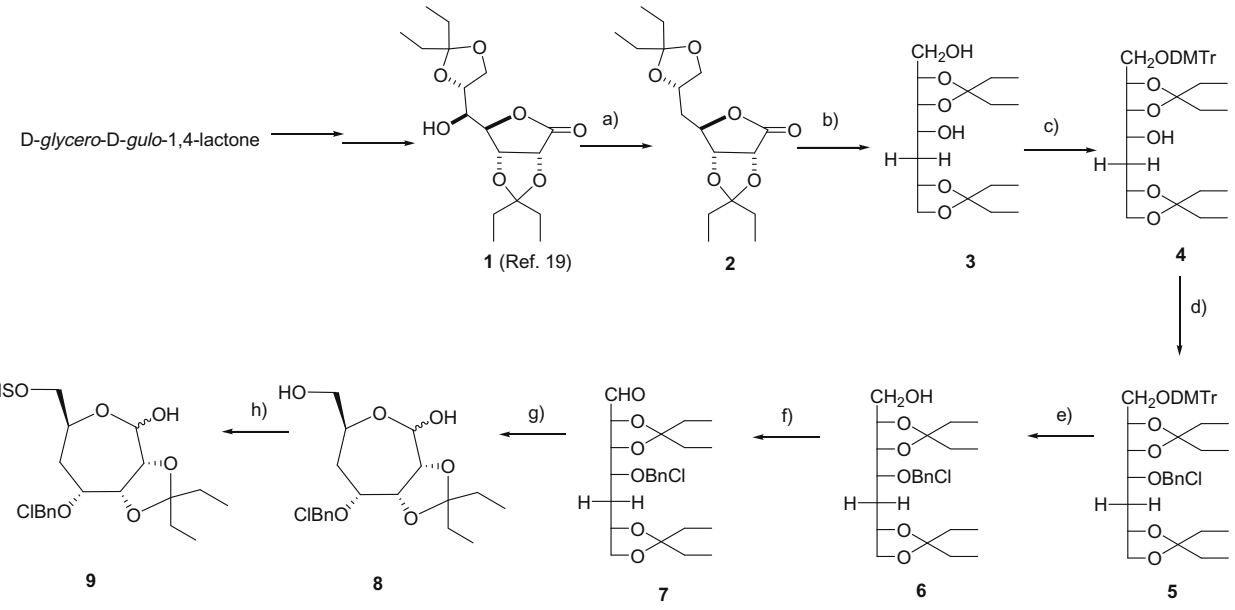
Performing the aminolysis at 100 °C provided **12** from **11**. Nucleoside **12** was then treated with BCl_3 to remove the chlorobenzyl-protecting group. Under the used conditions, cleavage of the silyl-protecting group and partial deacetalization also occurred. Thus, reaction of **12** with BCl_3 concomitantly afforded the partially protected nucleoside derivative **13** and the desired nucleoside **14.**

2.2. Antiviral evaluations

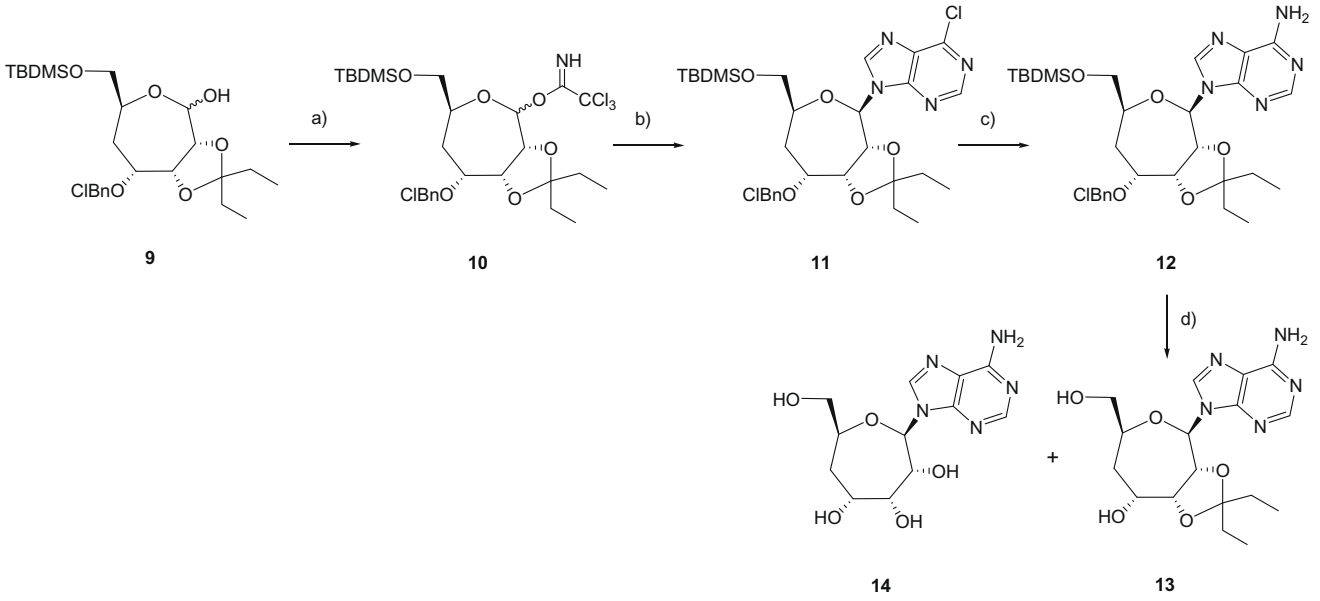
9-(5-Deoxy-β-D-*allo*-septanosyl)-adenine **14** was evaluated in cell-based assays (following methods described in Ref. 25) against viruses representative of three genera of the ssRNA$^+$ *Flaviviridae* family: *Pestivirus* (Bovine Virus Diarrhoea Virus), *Flavivirus* (Yellow Fever, Dengue and West Nile Viruses) and *Hepacivirus* (Hepatitis C Virus, HCV), and against one genus of the ssRNA$^+$ *Picornaviridae* family, *Enterovirus* (Coxsackie Virus B2 and Poliovirus Sabin-1). It was also tested against a virus of the ssRNA family, *Retroviridae* (Human Immunodeficiency Virus, HIV-1), against two representatives of a ssRNA$^-$ family, *Paramyxoviridae*: *Pneumovirus* (Respiratory Syncytial Virus) and *Morbillivirus* (Measles Virus) and against a virus representative of a dsDNA virus family, *Poxviridae* (Vaccinia Virus). Unfortunately, against all these viruses, the new nucleoside analogue **14** showed neither antiviral activity nor cytotoxicity at the highest concentration tested (generally 75 μM).

3. Summary and conclusion

The hitherto unknown 9-(5-deoxy-β-D-*allo*-septanosyl)-adenine **14** was synthesized as the first example of a nucleoside analogue bearing a seven-membered 5′-deoxy-β-D-*allo*-septanose sugar moiety. Unfortunately, when evaluated in cell culture experiments against a broad range of viruses, this compound exhibited no significant antiviral effect or cytotoxicity. Several factors could be responsible for the inactivity of 9-(5-deoxy-β-D-*allo*-septanosyl)-adenine **14**, such as its inability to enter cells or to serve as a substrate for intracellular enzymes catalyzing phosphorylation, or perhaps a lack of inhibition of the viral polymerases by its triphosphate.[12,26] Further research would be needed to support these hypotheses, and other results on new kinds of oxepane nucleoside analogues will be reported in due course.



Scheme 1. Reagents and conditions: (a) (i) 1,1′-thiocarbonyldiimidazole, 1,2-dichloroethane, reflux, (ii) $(Me_3Si)_3SiH$, AIBN, toluene, reflux; (b) $NaBH_4$, MeOH, 0 °C to rt; (c) DMTrCl, pyridine, rt; (d) (i) NaH, DMF, 0 °C, (ii) ClBnCl, 0 °C to rt; (e) HCOOH, Et_2O, rt; (f) Dess–Martin periodinane, CH_2Cl_2, rt; (g) HCOOH, Et_2O, rt; (h) TBDMSCl, imidazole, pyridine, rt.



Scheme 2. Reagents and conditions: (a) DBU, trichloroacetonitrile, CH_2Cl_2 rt; (b) (i) 6-chloropurine, BSA, 1,2-dichloroethane, reflux, (ii) TMSOTf, toluene, 80 °C; (c) MeOH/NH_3, 100 °C; (d) BCl_3, CH_2Cl_2, −78 °C to rt.

4. Experimental

4.1. General methods

All reactions were performed with reagent-grade materials under an atmosphere of nitrogen. All chemicals and solvents were of reagent grade unless otherwise specified. D-*Glycero*-D-*gulo*-1,4-lactone was from Aldrich. Evaporation of the solvent was carried out in a rotary evaporator under reduced pressure. Thin layer chromatography (TLC) was performed on precoated aluminium sheets of Silica Gel 60 F254 (Merck, Art. 5554), visualization of products being accomplished by UV absorbance at 254 nm and by charring with a soln of $(NH_4)_2SO_4$ (150 g) in 30:3:45 EtOH–H_2SO_4–water with heating. Column chromatography was carried out on Silica Gel 60 40–63 μm (Merck, Art. 11567) or LiChoprep RP-18 (40–63 μm, Merck 1.13900.0250). ^1H (400 MHz) and ^{13}C (100 MHz) spectra were recorded on a Bruker DRX 400 or 400 Advance II spectrometer using Me_2SO-d_6 or $CDCl_3$ as solvent. ^1H and ^{13}C NMR chemical shifts (δ) are quoted in parts per million (ppm) referenced to the residual solvent peak [Me_2SO-d_6] set at δ_H 2.49 ppm or [$CDCl_3$] set at δ_H 7.26 ppm. The accepted abbreviations are as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Low-resolution LC mass spectra (LR LCMS) were recorded on Q-TOF Micromass, electrospray ionisation (ESI) mass spectrometer, equipped with a Hypersil BDS C18 column (50 × 2.1 mm), eluting with a gradient of 0–80% MeCN in water at a flow rate of

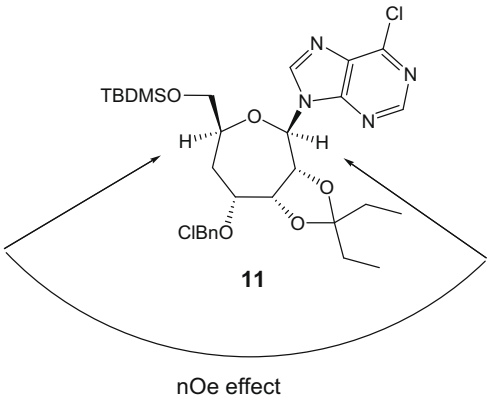


Figure 1. 1D NOE correlations for compound **11**.

0.2 mL min^{-1}. Mass spectra were recorded on a Q-TOF Micromass mass spectrometer (ESIMS) or on a Jeol JMS DX 300 mass spectrometer (HRFABMS).

4.2. 5-Deoxy-2,3:6,7-di-*O*-diethylidene-D-*allo*-heptono-1,4-lactone (2)

2,3:6,7-Di-*O*-diethylidene-D-*glycero*-L-*talo*-heptono-1,4-lactone[19] (**1**) (9.36 g, 27.18 mmol) was dissolved in 1,2-dichloroethane (190 mL) and treated with 1,1′-thiocarbonyldiimidazole (8.72 g, 48.92 mmol). The mixture was stirred at reflux overnight and concentrated under diminished pressure. The residue was dissolved in anhyd toluene (190 mL) and treated with tris(trimethylsilyl)silane (10.1 mL, 32.62 mmol) and AIBN (1.56 g, 9.51 mmol). The mixture was stirred at reflux for 1 h, and then evaporated to dryness. The residue was dissolved in EtOAc, and the soln was successively washed with saturated aq $NaHCO_3$ and saturated brine. The organic layer was dried over Na_2SO_4, and the solvent was removed under diminished pressure. The crude residue was subjected to silica gel chromatography, eluting with a gradient 2–30% diethyl ether in petroleum ether, to give **2** as a yellow oil (9.36 g, 94%). R_f 0.40 (3:2 Et_2O–petroleum ether). ^1H NMR (400 MHz, Me_2SO-d_6: δ 4.89 (d, 1H, *H*-3, J_{3-2} 5.8 Hz), 4.65 (d, 1H, *H*-2, J_{2-3} 5.8 Hz), 4.03–3.90 (m, 2H, *H*-6 and *H*-7a), 3.41 (t, 1H, *H*-7b, J_{7b-7a} 7.5 Hz), 1.90–1.75 (m, 2H, *H*-5), 1.50–1.38 (m, 8H, 4 (CH_2CH_3)), 0.73–0.63 (m, 12 H, 4 (CH_2CH_3)). ESIMS (*m/z*): 329 $[M+H]^+$, 657 $[2M+H]^+$.

4.3. 5-Deoxy-2,3:6,7-di-*O*-diethylidene-D-*allo*-heptan-1-itol (3)

The lactone **2** (7.86 g, 23.93 mmol) was dissolved in anhyd MeOH (168 mL) and cooled to 0 °C. Sodium borohydride (2.72 g, 71.80 mmol) was then added portion wise to the stirring mixture. Once the addition was completed, the resulting mixture was stirred at room temperature for 4 h, quenched with an aq soln of 10% AcOH and evaporated to dryness. The residue was dissolved in EtOAc, and the soln washed with saturated brine. The organic layer was dried over Na_2SO_4, and the solvent was removed under diminished pressure to give the title compound **3** as a pale yellow oil (6.45 g, 80%). R_f 0.23 (3:2 Et_2O–petroleum ether). ESIMS (*m/z*): 333 $[M+H]^+$, 665 $[2M+H]^+$.

4.4. 5-Deoxy-2,3:6,7-di-*O*-diethylidene-1-*O*-(4,4′-dimethoxytriphenylmethyl)-D-*allo*-heptan-1-itol (4)

Compound **3** (400 mg, 1.20 mmol) was dissolved in anhyd pyridine (6 mL) and treated with 4,4′-dimethoxytriphenylmethyl chloride (427.8 mg, 1.26 mmol). The resulting soln was stirred at room temperature for two days, diluted with EtOAc and washed thrice with water. The organic layer was dried over Na_2SO_4, and the solvent was removed under diminished pressure. The crude residue was subjected to silica gel chromatography, eluting with 30% diethyl ether in petroleum ether + 1% triethylamine, to give **4** as a yellow oil (0.53 g, 69%). R_f 0.58 (3:2 Et_2O–petroleum ether). ^1H NMR (400 MHz, $CDCl_3$): δ *7.47–6.84* (m, 13H, DMTr), 4.50 (m, 1H, *H*-2), 4.28 (m, 1H, *H*-6), 4.06–3.99 (m, 2H, *H*-3 and *H*-7a), 3.82 (6H under H_2O signal, 2OCH_3), 3.50–3.43 (m, 2H, *H*-4 and *H*-7b), 3.38 (dd, 1H, *H*-1a, $^2J_{1a-1b}$ 9.8 Hz, J_{1a-2} 4.0 Hz), 3.19 (dd, 1H, *H*-1b, $^2J_{1b-1a}$ 9.8 Hz, J_{1b-2} 8.3 Hz), 2.81 (s, 1H, O*H*), 1.84–1.89 (m, 2H, *H*-5a and *H*-5b), 1.67–1.60 (m, 8H, 4(CH_2CH_3)), 0.93–0.86 (m, 12H, 4(CH_2CH_3)). ESIMS (*m/z*): 657 $[M+Na]^+$; 633 $[M-H]^-$, 669 $[M+Cl]^-$.

4.5. 4-*O*-(4-Chlorobenzyl)-5-deoxy-2,3:6,7-di-*O*-diethylidene-1-*O*-dimethoxytriphenylmethyl-D-*allo*-heptan-1-itol (5)

Compound **4** (0.54 g, 0.85 mmol) was dissolved in anhyd dimethylformamide (4.7 mL) and cooled to 0 °C. Sodium hydride (54.4 mg, 1.36 mmol) was then added in separate portions to the stirred mixture. Once the addition was completed, the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was then treated with 4-chlorobenzyl chloride (219 mg, 1.36 mmol) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 2 h, and then diluted with EtOAc. The resulting soln was washed thrice with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give **5** as a yellow oil (0.75 g, quantitative yield). R_f 0.62 (3:2 Et_2O–petroleum ether). ESIMS (*m/z*): 793 $[M+Cl]^-$, 1552 $[2M+Cl]^-$.

4.6. 4-*O*-(4-Chlorobenzyl)-5-deoxy-2,3:6,7-di-*O*-diethylidene-D-*allo*-heptan-1-itol (6)

To a soln of the crude protected alcohol **5** (0.85 mmol) in diethyl ether (2.3 mL) was added formic acid (2.3 mL). The reaction mixture was stirred at room temperature for 30 min and then diluted with EtOAc. The resulting soln was washed with saturated aq $NaHCO_3$. The organic layer was dried over Na_2SO_4 and the solvent was removed under diminished pressure. The crude residue was subjected to silica gel chromatography, eluting with a gradient 30–40% diethyl ether in petroleum ether, to give **6** as a pale yellow oil (120 mg, 31%). R_f 0.43 (3:2 Et_2O–petroleum ether). ^1H NMR (400 MHz, $CDCl_3$): δ *7.26–7.17* (m, 4H, C_6H_4Cl), 4.58 (d, 1H, $CH_2C_6H_4Cl$, *J* 11.1 Hz), 4.36 (d, 1H, $CH_2C_6H_4Cl$, *J* 11.1 Hz), 4.37–4.19 (m, 2H, *H*-2 and *H*-6), 4.12 (m, 1H, *H*-3), 4.01 (dd, 1H, *H*-7a, J_{7a-6} 5.9 Hz, J_{7a-7b} 7.9 Hz), 3.79 (m, 1H, *H*-4), 3.63 (m, 2H, *H*-1), 3.40 (t, 1H, *H*-7b, J_{7b-7a} 8.1 Hz), 2.01 (m, 1H, *H*-5a), 1.90 (m, 1H, *H*-5b), 1.61–1.52 (m, 8 H, 4 (CH_2CH_3)), 0.87–0.79 (m, 12H, 4 (CH_2CH_3)). ESIMS (*m/z*): 457 $[M+H]^+$; 913 $[2M + H]^+$; 455 $[M-H]^-$.

4.7. 4-*O*-(4-Chlorobenzyl)-5-deoxy-2,3:6,7-di-*O*-diethylidene-D-*allo*-heptose (7)

The alcohol **6** (2.46 g, 5.38 mmol) was dissolved in anhyd CH_2Cl_2 (68 mL) and treated with the Dess–Martin reagent (2.51 g, 5.92 mmol). The mixture was stirred at room temperature for 1 h 15, and diethyl ether was added. The precipitate was filtered over successive layers of silica, $MgSO_4$ and sand, and washed with diethyl ether. The filtrate was concentrated under diminished pressure. The crude residue was subjected to silica gel chromatography, eluting with 30% diethyl ether in petroleum ether, to give **7** as a colourless oil (1.80 g, 73%). R_f 0.60 (3:2 Et_2O–petroleum ether). ^1H NMR (400 MHz, $CDCl_3$): δ 9.52 (t, 1H, C*H*O, J_{CHO-H2} 1.4 Hz), 7.27–7.16 (m, 4H, C_6H_4Cl), 4.53–4.45 (m, 2H, $CH_2C_6H_4Cl$ et *H*-2), 4.36–4.26 (m, 2H, $CH_2C_6H_4Cl$ and *H*-6), 4.16 (m, 1H, *H*-3′), 3.95 (dd, 1H, *H*-7a, J_{7a-7b} 7.9 Hz, J_{7a-6} 6.0 Hz), 3.72 (m, 1H, *H*-4), 3.39

(t, 1H, *H*-7b, J_{7b-7a} 7.9 Hz), 1.94 (m, 1H, *H*-5a), 1.75 (m, 1H, *H*-5b), 1.49–1.61(m, 8H, 4(CH_2CH_3)), 0.86–0.81 (m, 12H, 4(CH_2CH_3)). ESIMS (*m/z*): 455 $[M+H]^+$; 489 $[M+Cl]^-$.

4.8. 4-*O*-(4-Chlorobenzyl)-5-deoxy-2,3-*O*-diethylidene-D-*allo*-septanose (8)

To a soln of the heptose **7** (1.77 g, 3.89 mmol) in diethyl ether (17.5 mL) was added formic acid (17.5 mL). The reaction mixture was stirred at room temperature for 1 h 15. The solution was partitioned between EtOAc and saturated aq $NaHCO_3$. The organic phase was washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel, eluting with a gradient 0–4% MeOH in CH_2Cl_2, to give **8** as a colourless oil (0.95 g, 63%). *R*f 0.20 (19:1 CH_2Cl_2-MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.10 (m, 4H, C_6H_4Cl), 5.30 (d, 1H, H-1, J_{1-OH} 7.5 Hz), 4.63 (d, 1H, $CH_2C_6H_4Cl$, *J* 12.0 Hz), 4.49 (d, 1H, $CH_2C_6H_4Cl$, *J* 12.0 Hz), 4.08–4.02 (m, 2H, *H*-2 and *H*-3), 4.04–3.99 (m, 2H, *H*-6 and O*H*-1), 3.92 (d, 1H, *H*-4, J_{4-3} 6.6 Hz), 3.50–3.39 m, 3H, *H*-7 and O*H*-7), 1.50–1.65 (m, 5H, *H*-5a and 2(CH_2CH_3)), 1.19 (m, 1H, *H*-5b), 0.75–0.90 (m, 6H, 2(CH_2CH_3)). ESIMS (*m/z*): 387 $[M+H]^+$; 421 $[M+Cl]^-$.

4.9. 4-*O*-(4-Chlorobenzyl)-5-deoxy-2,3-*O*-diethylidene-7-*O*-*tert*-butyldimethylsilyl-D-*allo*-septanose (9)

To a soln of the septanose derivative **8** (0.95 g, 2.46 mmol) in anhyd pyridine (21 mL) were added imidazole (251 mg, 3.68 mmol) and *tert*-butyldimethylsilyl chloride (407 mg, 2.70 mmol). The soln was partitioned between EtOAc and aq HCl 1 M. The organic phase was washed with saturated brine, dried over Na_2SO_4 and evaporated to dryness. The crude residue was subjected to silica gel chromatography, eluting with a gradient 10–40% diethyl ether in petroleum ether, to give **9** as a colourless oil (0.82 g, 67%). R_f 0.65 (3:2 Et_2O–petroleum ether). ^1H NMR (400 MHz, $CDCl_3$): δ 7.21–7.26 (m, 4H, C_6H_4Cl), 5.28 (m, 1H, H-1′), 4.62 (d, 1H, $CH_2C_6H_4Cl$, ^2J 12.1 Hz), 4.53 (d, 1H, $CH_2C_6H_4Cl$, ^2J 12.1 Hz), 4.13–4.19 (m, 2H, H-2′ and H-3′), 3.93–3.95 (m, 2H, H-4′ and H-6′), 3.64 (dd, 1H, H-7′a, $^2J_{7'a-7'b}$ 10.3 Hz, $J_{7'a-6'}$ 5.5 Hz), 3.43 (dd, 1H, H-7′b, $^2J_{7'b-7'a}$ 10.3 Hz, $J_{7'b-6'}$ 6.3 Hz), 2.89 (d, 1H, OH, $J_{OH-1'}$ 4.7 Hz), 2.00 (m, 1H, H-5′a), 1.56–1.72 (m, 4H, 2CH_2CH_3), 1.32 (m, 1H, H-5′b), 0.82–0.90 (m, 15H, 2CH_2CH_3 and $SiC(CH_3)_3$), 0.00 (s, 6H, $Si(CH_3)_2$). ESIMS (*m/z*): 501 $[M+H]^+$; 1001 $[2M+H]^+$; 499 $(M-H)^-$.

4.10. Trichloroacetimidoyl 4-*O*-(4-chlorobenzyl)-5-deoxy-2,3-*O*-diethylidene-7-*O*-*tert*-butyldimethylsilyl-D-*allo*-septanoside (10)

To a soln of septanose **9** (210 mg, 0.42 mmol) in CH_2Cl_2 (9.7 mL) were added successively trichloroacetonitrile (92 μL, 0.92 mmol) and DBU (26 μL, 0.16 mmol). The reaction mixture was stirred at room temperature for 2 h, and more trichloroacetonitrile (46 μL, 0.46 mmol) and DBU (13 μL, 0.08 mmol) were added. The mixture was stirred at room temperature for an additional hour, then concentrated under diminished pressure. The resulting residue was filtered through a silica gel plug, eluting with CH_2Cl_2 and evaporated to dryness to give the septanoside **10** as a dark brown oil (270 mg, quant. yield). R_f 0.83 (3:2 Et_2O–petroleum ether). ESIMS (*m/z*): 647 $[M+H]^+$.

4.11. 9-[4-*O*-(4-Chlorobenzyl)-5-deoxy-2,3-*O*-diethylidene-7-*O*-*tert*-butyldimethylsilyl-β-D-*allo*-septanosyl]-6-chloropurine (11)

N,O-Bis(trimethylsilyl)-acetamide (606 μL, 2.48 mmol) was added to a suspension of 6-chloropurine (191.5 mg, 1.24 mmol) in 1,2-dichloroethane (16.4 mL). The reaction mixture was stirred at reflux for 2 h and evaporated to dryness. The resulting residue was dissolved in anhyd toluene (8.2 mL), and a soln of the trichloroacetimidate **10** (1.2 g, 1.86 mmol) in toluene (8.2 mL) was added. The reaction mixture was treated with TMSOTf (431 μL, 2.23 mmol) and stirred at reflux for 5 h. More TMSOTf (200 μL) was added, and stirring was resumed at reflux for 2 h. The soln was partitioned between EtOAc and satd aq $NaHCO_3$. The organic phase was washed with saturated brine, dried over Na_2SO_4 and evaporated to dryness. The crude residue was subjected to silica gel chromatography, eluting with a gradient 10–100% diethyl ether in petroleum ether, to give **11** as a pale yellow oil (0.18 g, 15%). R_f 0.39 (3:2 Et_2O–petroleum ether). ^1H NMR (400 MHz, Me_2SO-d_6): δ 8.82 (s, 1H, H-8), 8.32 (s, 1H, H-2), 7.38–7.45 (m, 4H, C_6H_4Cl), 6.58 (d, 1H, H-1′, $J_{1'-2'}$ 9.3 Hz), 5.04 (t, H-2′, $J_{2'-1'}$ 8.8 Hz, $J_{2'-3'}$ 8.4 Hz), 4.90 (d, 1H, $CH_2C_6H_4Cl$, ^2J 12.3 Hz), 4.77 (d, 1H, $CH_2C_6H_4Cl$, ^2J 12.3 Hz), 4,52 (dd, 1H, H-3′, $J_{3'-4'}$ 2.9 Hz, $J_{3'-2'}$ 7.8 Hz), 4.40 (m, 1H, H-6′), 4.23 (dd, 1H, H-4′, $J_{4'-5'}$ 7.2 Hz, $J_{4'-3'}$ 2.7 Hz), 3.65 (dd, 1H, H-7′a, $^2J_{7'a-7'b}$ 10.7 Hz, $J_{7'a-6'}$ 5.5 Hz), 3.54 (dd, 1H, H-7′b, $^2J_{7'b-7'a}$ 10.6 Hz, $J_{7'b-6'}$ 5.4 Hz), 2.14 (m, 1H, H-5′a), 1.60–1.74 (m, 5H, H-5′b and 2CH_2CH_3), 0.78–0.95 (m, 15H, 2CH_2CH_3 and $SiC(CH_3)_3$), 0.00 (s, 6H, $Si(CH_3)_2$). LR LC/MS: t_R = 23.92 min. ESIMS (*m/z*): 1275.5 $(2M+H^+)$, 637.2 $(M+H^+)$.

4.12. 9-[4-*O*-(4-Chlorobenzyl)-5-deoxy-2,3-*O*-diethylidene-7-*O*-*tert*-butyldimethylsilyl-β-D-*allo*-septanosyl]-adenine (12)

Nucleoside **11** (411 mg, 0.65 mmol) was treated with ammonia-saturated MeOH (80 mL) in a sealed reactor at 100 °C for 3 h, then concentrated under diminished pressure to give **12** as a pale yellow oil used in the next stage without purification. LR LC/MS: t_R = 19.91 min. ESIMS (*m/z*): 618.3 $(M+H^+)$.

4.13. 9-(5-Deoxy-2,3-*O*-diethylidene-β-D-*allo*-septanosyl)-adenine (13) and 9-(5-deoxy-β-D-*allo*-septanosyl)-adenine (14)

To a soln of the crude nucleoside **12** (0.65 mmol) in anhyd CH_2Cl_2 (6.3 mL) at −78 °C was added boron trichloride (1 M in CH_2Cl_2, 1.29 mL, 1.29 mmol). The reaction mixture was stirred at −78 °C for 1 h 30, then allowed to warm to −40 °C and stirred for 1 h 30. The reaction was quenched by addition of 1:1 MeOH–CH_2Cl_2 and stirred at −20 °C for 30 min, then neutralised at 0 °C with aq ammonia and stirred at room temperature for 15 min. The mixture was filtered through a pad of Celite and washed with 1:1 MeOH–CH_2Cl_2. The filtrate was concentrated under diminished pressure, and the resulting residue was purified by reverse phase (C18) silica gel column chromatography eluting with a gradient 0–100% MeCN in water to give the partially protected nucleoside **13** (11 mg, 4.5%, white lyophilised powder) and the desired compound **14** (11 mg, 5.5%, white lyophilised powder).

Compound **13**: ^1H NMR (400 MHz, Me_2SO-d_6): δ 8.47 (s, 1H, H-8), 8.20 (s, 1H, H-2), 7.57–7.65 (m, 2H, NH_2), 6.35 (d, 1H, H-1′, $J_{1'-2'}$ 9.40 Hz), 5.30 (br s, 1H, OH-7′), 5.11 (t, 1H, H-2′, $J_{2'-1'}$ 9.1 Hz, $J_{2'-3'}$ 8.1 Hz), 4.34 (dd, 1H, H-3′, $J_{3'-2'}$ 7.8 Hz, $J_{3'-4'}$ 2.5 Hz), 4.19–4.24 (m, 2H, H-4′ and H-6′), 3.87 (s, 1H, OH-4′), 3.24–3.34 (m, 2H, H-7′), 1.94 (m, 1H, H-5′a), 1.51–1.61 (m, 5H, H-5′b and 2CH_2CH_3), 0.76 (t, 6H, 2CH_2CH_3, $J_{CH3-CH2}$ 7.4 Hz). HRFABMS: calcd for $C_{17}H_{26}O_5N_5$ 380.1934 $[M+H^+]$; found (*m/z*): 380.1937.

Compound **14**: ^1H NMR (400 MHz, Me_2SO-d_6): δ 8.25 (s, 1H, H-8), 8.11 (s, 1H, H-2), 7.21 (s, 2H, NH_2), 5.61 (d, 1H, H-1′, $J_{1'-2'}$ 12.0 Hz), 5.19 (d, 1H, OH-3′, $J_{OH-3'}$ 4.2 Hz), 5.01 (d, 1H, OH-2′, $J_{OH-2'}$ 7.0 Hz), 4.67–4.70 (m, 2H, OH-4′ and OH-7′), 4.23(m, 1H, H-2′), 3.91–4.05 (m, 3H, H-3′, H-4′ and H-6′), 3.23 (m, 2H, H-7′), 1.91 (ddd, 1H, H-5′a, $^2J_{5'a-5'b}$ 13.6 Hz, $J_{5'a-6'}$ 6.9 Hz, $J_{5'a-4'}$ 2.8 Hz), 1.69 (ddd, 1H, H-5′b, $^2J_{H5'b-H5'a}$ 13.4 Hz, $J_{H5'b-H4'}$ 8.0 Hz, $J_{5'b-6'}$ 2.2 Hz). ^{13}C NMR (100 MHz, Me_2SO-d_6): δ 156.4 (C-4), 152.9 (C-2), 150.2 (C-6), 139.9 (C-8), 119.1 (C-5), 85.0 (C-1′), 78.9–77.6 (2C, C-3′ and C-6′), 71.5 (C-2′), 68.3 (C-4′), 65.1 (C-7′), 33.9 (C-5′). HRFABMS: calcd for $C_{12}H_{18}O_5N_5$ 312.1308 $[M+H^+]$; found (*m/z*) 312.1311.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.12.019.

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