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Carbohydrate Research 338 (2003) 2057–2066
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Synthesis of 3-(α- and β-D-arabinofuranosyl)-6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine

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Received 2 June 2003; accepted 11 July 2003

Abstract

Di-*O*-isopropylidene- and *O*-methanesulfonyl-protected 1-*C*-(6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)pentitols were prepared in three to four steps from D-galactose, D-glucose, D-mannose, and 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose. Acid-catalysed treatment of (1*S*)- and (1*R*)-1-*C*-(6-chloro-1,2,4-triazolo[4,3-*b*]-pyridazin-3-yl)-2,3:4,5-di-*O*-isopropylidene-1-*O*-methanesulfonyl-D-arabinitols in refluxing 1,2-dimethoxyethane furnished 3-(α- and β-D-arabinofuranosyl)-6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine, respectively. Several structures, including the structure of the 3-(β-D-arabinofuranosyl)-6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine, were also determined by single-crystal X-ray diffraction analysis.

Keywords: Pentitols; 1,2,4-Triazolo[4,3-*b*]pyridazines; Cyclisation; Glycosides; Nucleosides

1. Introduction

Due to antibiotic, antitumor, and antiviral activities of various analogues of nucleosides, there has been a considerable interest in the synthesis of this class of compounds, including *C*-nucleosides.[1] Examples of naturally occurring *C*-nucleosides are showdomycin,[2] pyrazomycin,[3] formycin,[4] and pseudouridine.[5] Among a wide diversity of *C*-nucleosides prepared, two syntheses of 3-β-D-ribofuranosyl-(substituted 1,2,4-triazolo[4,3-*b*]pyridazines have been reported previously using 5-*O*-benzoyl-α,β-D-ribofuranosyl)benzylthioformimidate[6] and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid[7] as the key intermediates.

In connection with synthesis of *C*-glycosides and *C*-nucleoside analogues, we have previously reported two synthetic approaches: (a) stereoselective 1,3-dipolar cycloadditions to azomethine imines derived from (un)protected aldoses and *N*,*N*-dihydropyrazolo[3,4-*d*]pyridazines[8–12]; and (b) oxidative cyclisation of hydrazones derived from α-hydrazinoazines and unprotected aldoses[13] or anhydroaldose derivatives.[14] In this manner, acyclo and cyclic analogues of *C*-nucleosides were prepared. In continuation of our research in this field, we now report the synthesis of two novel *C*-nucleoside analogues, 3-(β-D-arabinofuranosyl)-6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine and its α-anomer.

2. Results and discussion

The starting pentitols **5**–**7** were prepared by reaction of D-galactose (**1**), D-glucose (**2**), and D-mannose (**3**), respectively, with 3-chloro-6-hydrazinopyridazine (**4a**), followed by oxidative cyclisation of the intermediate hydrazones according to the one-pot procedure previously described.[13] Four hydroxy groups of the pentitols **5**–**7** were protected with 2,2-dimethoxypropane (DMP) in anhydrous acetone in the presence of sulfuric acid to give bis-acetonides **8**–**11**. Acetonisation of the (1*S*)-1-*C*-D-lyxitol (**5**) led to 1,2:3,4-di-*O*-isopropylidene derivative **8** with the unprotected primary hydroxy group at the position 5. On the other hand, ketalisation of the (1*S*)- (**6**) and (1*R*)-l-*C*-D-arabinitol (**7**) in acetone

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doi:10.1016/S0008-6215(03)00347-1

in the presence of sulfuric acid, has already been described to furnish bis-ketals **9**–**11** with the unprotected secondary hydroxy groups at position 1 or 3.[13] A slightly modified procedure, using a mixture of acetone and DMP in the presence of sulfuric acid, gave almost identical results. Thus, ketalisation of (1*S*)-1-*C*-D-arabinitol (**6**) gave a mixture of the (1*S*)-1-*C*-(2,3:4,5- (**9**) and the (1*S*)-1-*C*-(1,2:4,5-di-*O*-isopropylidene)-D-arabinitol (**10**) in a ratio of 2:3. Isomers **9** and **10** were separated by medium-pressure liquid chromatography (MPLC) to afford isomerically pure compounds **9** and **10** in 20 and 30% yield, respectively. In comparison to the previously reported separation by crystallisation, chromatographic separation turned out to be more convenient method for separation of regioisomers **9** and **10**, since crystallisation has to be performed very carefully and with certain skill. Acetonisation of the (1*R*)-1-*C*-D-arabinitol (**7**) proceeded regioselectively to give the 2,3:4,5-di-*O*-isopropylidene derivative **11** in 82% yield. In order to obtain also the isomeric (1*R*)-1-*C*-(1,2:4,5-di-*O*-isopropylidene)-D-arabinitols **14a**,**b** with a free hydroxy group at the position 3, a modified one-pot synthetic approach was employed. 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose (**12**) was first treated with 6-substituted 3-hydrazinopyridazines **4a**,**b** to give the intermediates **13a**,**b**, which were oxidised, either with *N*-chlorosuccinimide (NCS) in DMF in the presence of catalytic amounts of HCl gas, or with bromine in dichloromethane to furnish the corresponding (1*R*)-1-*C*-(6-substituted 1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-D-arabinitols **14a** and **b** in 25 and 32% yield, respectively (Scheme 1).

In the next step, protected pentitols **9**–**11**, and **14a** were treated with methanesulfonyl chloride in pyridine at 0 °C to give the corresponding *O*-methanesulfonyl derivatives in **15**–**18** in 80–99.7% yields. Finally, mesylates **15** and **16** with a free hydroxy group at the position 1 were transformed into *C*-nucleoside analogues **19** and **20** using a slightly modified protocol, employed previously by Buchanan and co-workers for the synthesis of 3-β-D-arabinofuranosylpyrazole.[15] Thus, heating of 1-*O*-mesylates **15** and **16** in 1,2-dimethoxyethane (DME) in the presence of equimolar amounts of 4% hydrochloric acid for 30 h furnished the *C*-nucleoside analogues **19** and **20** in 81 and 54% yield, respectively. Compound **20** was isolated in the form of its HCl salt (Scheme 2).

The structures of all novel compounds **8** and **14**–**20** were determined by spectroscopic methods (IR, NMR, MS) and by elemental analysis. Compounds **14a**, **16**, and **20** were not prepared in analytically pure form. Their identity was confirmed by ^{13}C NMR spectroscopy and HRMS. Total assignment of ^{1}H and ^{13}C signals of *C*-nucleoside analogues **19** and **20** was performed by 2D NMR spectroscopy using HMQC and HMBC techniques (Fig. 1).

Structures of pentitol **5**, **9**, **14a**, **17**, and *C*-nucleoside analogue **20** were determined by single-crystal X-ray diffraction analysis (Figs. 2–7).

In conclusion, two novel *C*-nucleoside analogues were prepared in four steps from commercially available D-glucose and D-mannose. The overall procedure consists of: (a) one-pot formation of (1*R*)- and (1*S*)-1-*C*-(6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-D-arabinitols; followed by (b) selective ketalisation of four hydroxy groups leaving the free hydroxy group at the position 1; which is (c) mesylated; and (d) in the last step, the mesylate is deprotected and cyclised into 3-(α- and β-D-arabinofuranosyl)-6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine. This synthetic approach offers access to 1,2,4-triazolo[4,3-*x*]azine-based *C*-nucleosides, since various aldoses and hydrazonoazines can be employed as starting materials for the preparation of 1-*C*-(1,2,4-triazolo[4,3-*x*]azin-3-yl)-substituted polyols as the key intermediates.

3. Experimental

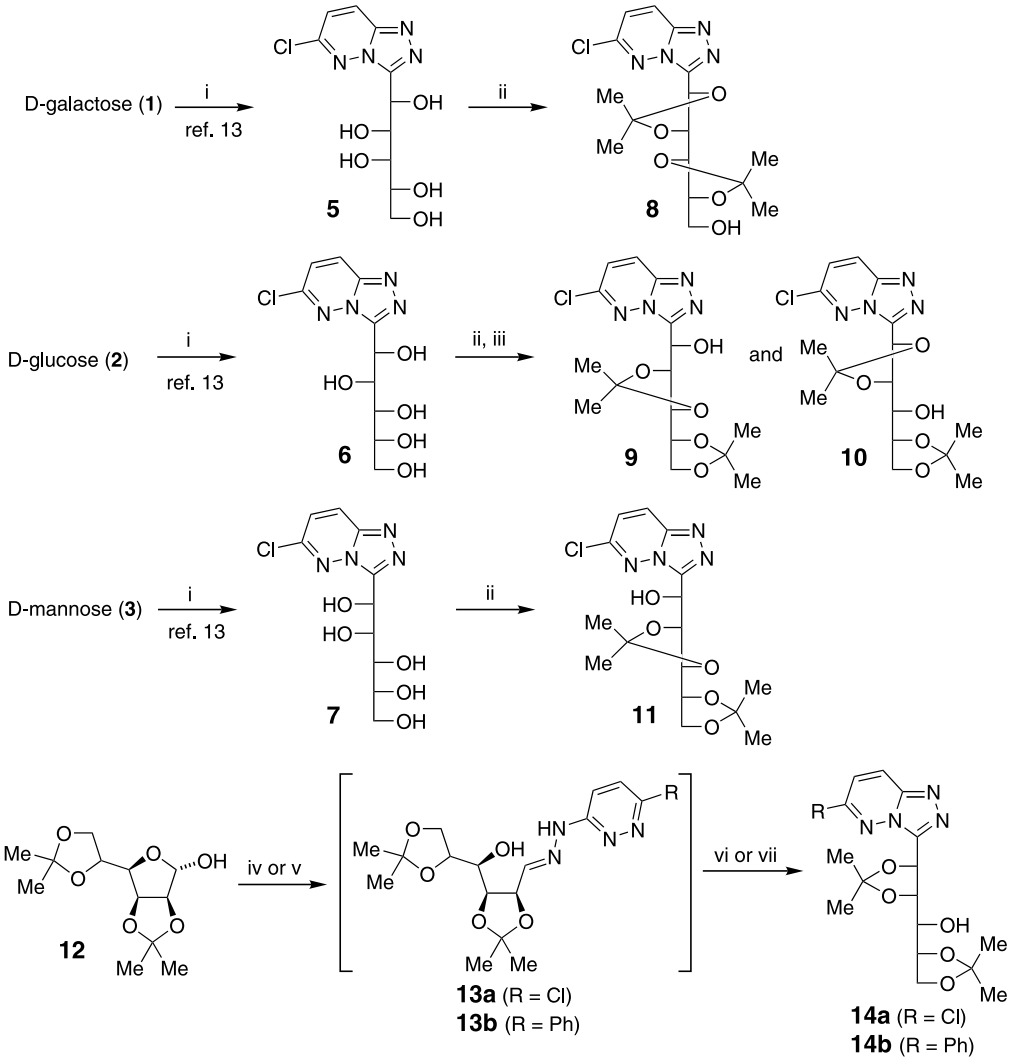
3.1. General methods

Melting points were determined on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ as solvents and Me_4Si as the internal standard. Mass spectra were recorded in the electron-impact (EIMS) mode or in the fast-atom bombardment mode (FABMS) on an AutoSpecQ spectrometer, and IR spectra were determined on a Perkin–Elmer spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser, model 2400. MPLC was performed with a Büchi isocratic system with detection on silica gel (E. Merck, Silica Gel 60, 0.015–0.040 mm). Column dimensions (dry filled): 36 × 460 mm; back pressure: 10–15 bar; detection: UV 254 nm; sample amount: ~1 g of isomeric mixture per each run.

3.2. General procedure for the preparation of 1-*C*-(6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-di-*O*-isopropylidenepentitols 8–11

Compounds **8**–**11** were prepared according to modified procedure described in the literature.[13]

Unprotected 1-*C*-(6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)pentitol **5**–**7** (3.05 g, 10 mmol) was added to a stirred mixture of anhyd acetone (40 mL), DMP (10 mL), and H_2SO_4 (97%, 1.6 mL, 30 mmol), and the mixture was stirred at room temperature (rt) for 2 h. Then the reaction mixture was neutralised by careful addition of satd aq $NaHCO_3$ (50 mL) and evaporated in vacuo to one-half of the initial volume (~50 mL). The

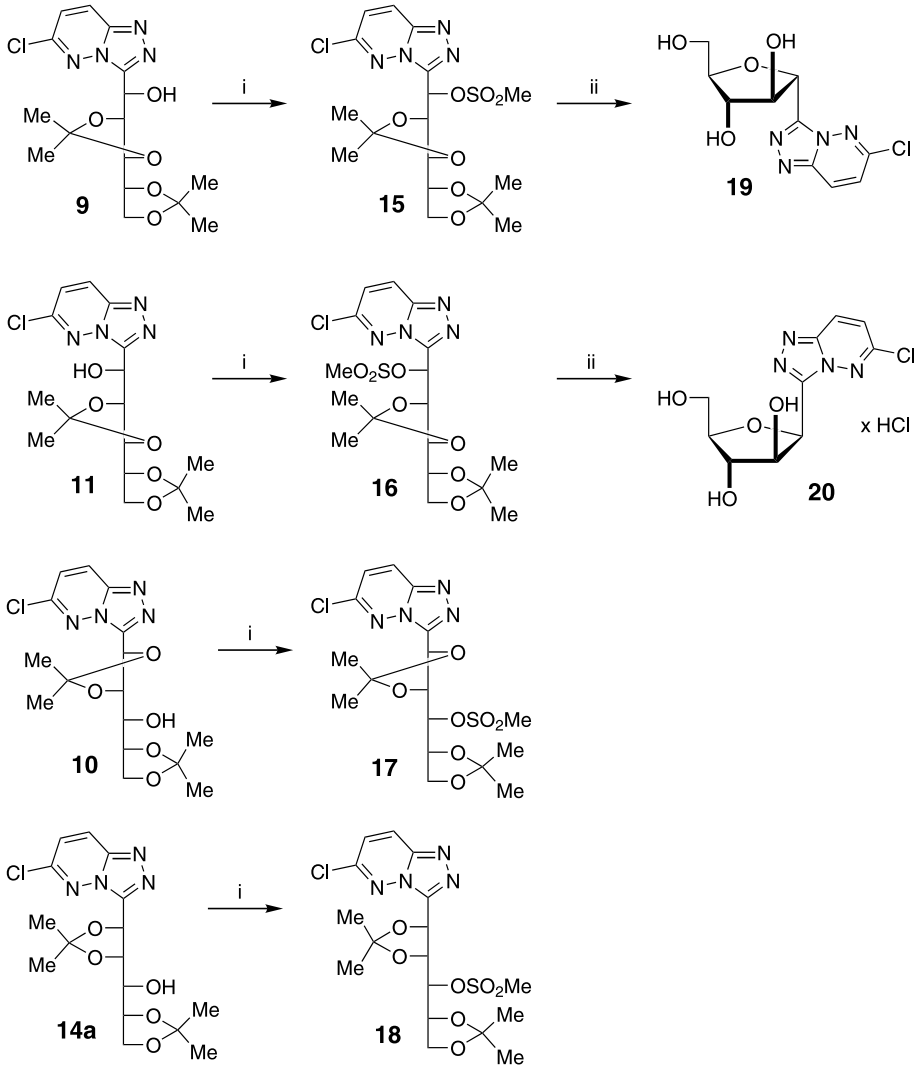


Scheme 1. Reaction conditions: (i) 3-chloro-6-hydrazinopyridazine (**4a**), MeOH, 37% aq HCl (cat.), reflux 2 h, then Br_2, room temperature; (ii) acetone–DMP (4:1), 97% H_2SO_4, room temperature; (iii) MPLC; (iv) 3-chloro-6-hydrazinopyridazine (**4a**) MeOH, 37% aq HCl (cat.), room temperature; (v) 3-hydrazino-6-phenylpyridazine (**4b**), CH_2Cl_2, CF_3COOH (cat.), room temperature; (vi) NCS, DMF, HCl (cat.), room temperature (**13a**→**14a**); (vii) Br_2, CH_2Cl_2, room temperature (**13b**→**14b**).

product was extracted with CH_2Cl_2 (3 × 30 mL), the organic phases were combined, dried over anhyd Na_2SO_4, and filtered, and the filtrate was evaporated in vacuo. The residue was triturated with Et_2O (10 mL) or petroleum ether (10 mL), and the precipitate was collected by filtration to give **8**–**11**.

3.2.1. (1*S*-)-1-*C*-(6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-1,2:3,4-di-*O*-isopropylidene-D-lyxitol (8). Prepared from compound **5**, trituration with petroleum ether; 2.972 g (77%); white solid; mp 175–180 °C; $[\alpha]_D^{23}$ −49.0° (*c* 0.20, CH_2Cl_2). IR (KBr); ν_{max} 3436, 2989, 1530, 1471, 1372, 1212, 1072. ^{1}H NMR (DMSO-d_6): δ 1.17, 1.27, 1.42, 1.47 (12 H, 4s, 1:1:1:1, 2 × Me_2C); 3.46 (1 H, deg dt, $J_{4,5a}$ 5.3, $J_{5a,5b}$ 11.7 Hz, 5-Ha); 3.56 (1 H, ddd, $J_{4,5b}$ 4.1, $J_{5b,OH}$ 5.7 Hz, 5-Hb); 3.81 (1 H, ddd, $J_{3,4}$ 7.5 Hz, 4-H); 4.08 (1 H, dd, $J_{2,3}$ 5.7 Hz, 3-H); 4.83 (1 H, t, 5-OH); 5.08 (1 H, dd, $J_{1,2}$ 7.1 Hz, 2-H); 5.58 (1 H, d, 1-H); 7.59 (1 H, d, $J_{7',8'}$ 9.7 Hz, 7′-H); 8.52 (1 H, d, 8′-H). ^{13}C NMR ($CDCl_3$): δ 26.4, 26.8, 27.1, 27.4, 62.5, 71.1, 78.2, 79.1, 80.7, 110.1, 112.3, 123.0, 126.5, 143.6, 147.7, 149.9. EIMS: *m*/*z* 385 (MH^+). Anal. Calcd for $C_{16}H_{21}ClN_4O$: C, 49.94; H, 5.50; N, 14.56. Found: C, 49.87; H, 5.65; N, 14.35.

3.2.2. (1*S*)-1-*C*-(6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-2,3:4,5- (9) and (1*S*)-1-*C*-(6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-1,2:4,5-di-*O*-isopropylidene-D-arabinitol (10). A mixture of compounds **9** and **10** in a ratio of 2:3 was prepared from compound **6**, with workup by trituration with Et_2O. This mixture was separated by MPLC (95:5 EtOAc–EtOH) and fractions containing the products **9** and **10**



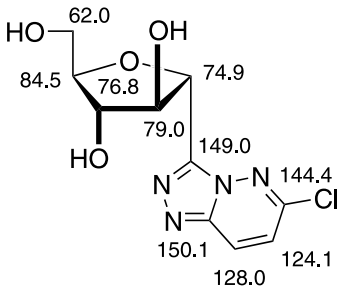
Scheme 2. Reaction conditions: (i) $MeSO_2Cl$, pyridine, 0 °C; (ii) DME, 4% aq HCl (1 equivalent), reflux.

were evaporated in vacuo to give isomerically pure compounds **9** and **10**.

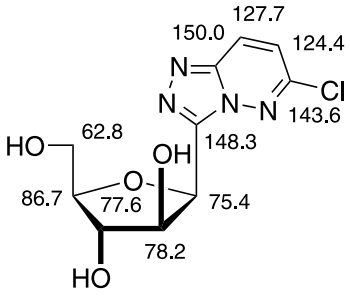
3.2.2.1. Compound 9. Yield: 779 mg (20%), Lit. [13] 26%; white solid; mp 185–187 °C; Lit. [13] 186–187 °C; $[\alpha]_D^{23}$ +13.7° (*c* 1.22, $CHCl_3$); Lit. [13] +14.8°.

3.2.2.2. Compound 10. Yield: 1.157 g (30%), Lit. [13] 39%; white solid; mp 205–208 °C, Lit. [13] 208–209 °C; $[\alpha]_D^{23}$ −37.4° (*c* 1.05, $CHCl_3$), Lit. [13] −38.1°.

3.2.3. (1*R*)-1-*C*-(6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-2,3:4,5-di-*O*-isopropylidene-D-



Compound **19**



Compound **20**

Fig. 1. Total assignment of ^{13}C signals of compounds **19** and **20**.

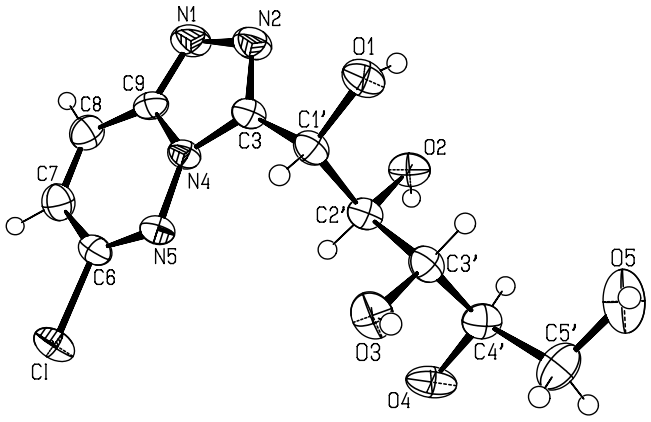


Fig. 2. ORTEP view of the asymmetric unit of compound **5** with labelling of non-hydrogen atoms. (Ellipsoids are at 50% probability level. H atoms are drawn as circles of arbitrary radii.)

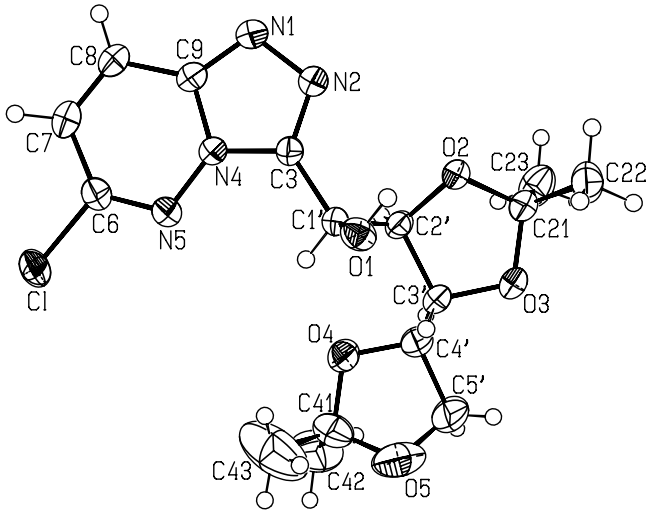


Fig. 3. ORTEP view of the asymmetric unit of compound **9** with labelling of non-hydrogen atoms. (Ellipsoids are at 50% probability level. H atoms are drawn as circles of arbitrary radii.)

arabinitol (11). Prepared from compound **7**; workup by trituration with Et_2O; 3.143 g (82%); Lit. [13] 78%; white solid; mp 154–156 °C; Lit. [13] 155–156 °C; $[\alpha]_D^{23}$ −11.1° (*c* 0.92, $CHCl_3$); Lit. [13] −11.4°.

3.3. (1*R*)-1-*C*-(6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-1,2:4,5-di-*O*-isopropylidene-D-arabinitol (14a)

Hydrochloric acid (37%, 0.1 mL, ~1 mmol) was added to a solution of 3-chloro-6-hydrazinopyridazine (**4a**) (1.445 g, 10 mmol) and 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**12**) (2.6 g, 10 mmol) in MeOH (40 mL), and the mixture was stirred at rt for 2 days. Volatile components were evaporated in vacuo to give the crude hydrazone **13a** as a solid residue, which was redissolved

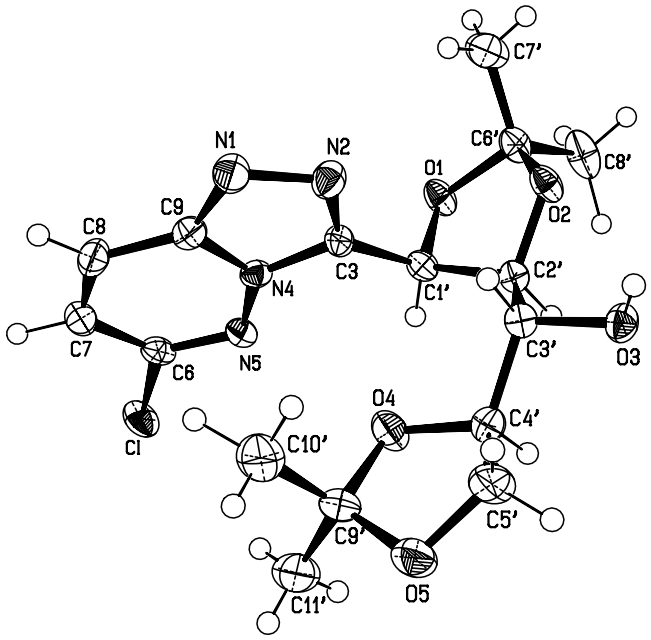


Fig. 4. ORTEP view of the asymmetric unit of compound **14a** with labelling of non-hydrogen atoms. (Ellipsoids are at 50% probability level. H atoms are drawn as circles of arbitrary radii.)

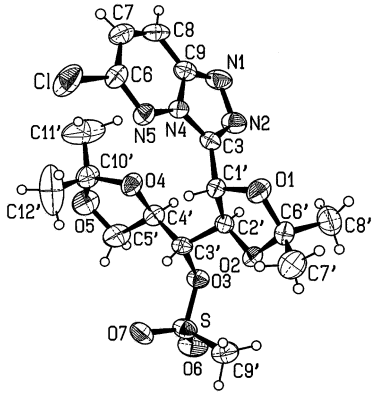


Fig. 5. ORTEP view of the asymmetric unit of compound **17** with labelling of non-hydrogen atoms. (Ellipsoids are at 50% probability level. H atoms are drawn as circles of arbitrary radii.)

in anhyd DMF (50 mL). Then NCS (2.3 g, 20 mmol) and HCl gas (20 mL, ~1 mmol) were added, and the mixture was stirred at rt for 5 days. Then water (100 mL) was added, and the precipitate was collected by filtration to give **14a**. Yield: 970 mg (25%); white solid; mp 175–182 °C; $[\alpha]_D^{23}$ −40.0° (*c* 0.18, CH_2Cl_2). IR (KBr); ν_{max} 3281, 2991, 1473, 1368, 1236, 1066, 866. ^{1}H NMR (DMSO-d_6): δ 0.45, 1.04, 1.43, 1.50 (12 H, 4s, 1:1:1:1, 2 × Me_2C); 3.56 (1 H, dd, $J_{4,5a}$ 5.8, $J_{5a,5b}$ 7.8 Hz, 5-Ha); 3.72–3.95 (3 H, m, 3-H, 4-H, 5-Hb); 4.54 (1 H, deg t, $J_{1,2}$ 6.0 Hz, 2-H); 5.28 (1 H, d, $J_{3,OH}$ 6.0 Hz, OH); 5.76 (1 H, d, 1-H); 7.54 (1 H, d, $J_{7',8'}$ 9.8 Hz, 7′-H); 8.49

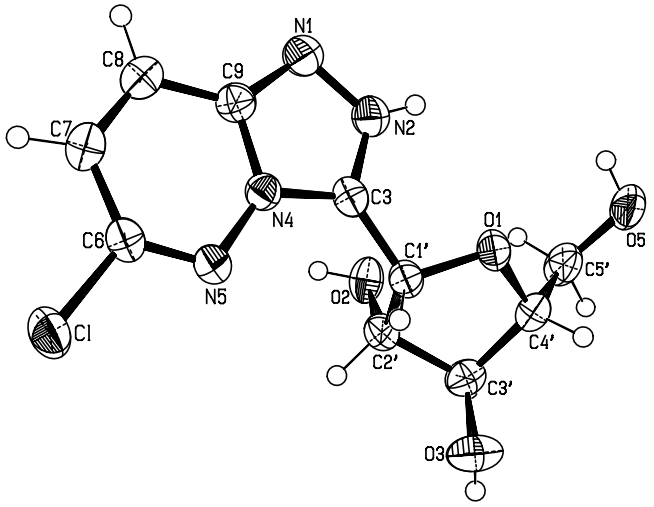


Fig. 6. ORTEP view of the protonated 1-(6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-β-D-*arabino*-furanoside unit (cation of compound **20**) at the 50% probability level. (H atoms are drawn as circles of arbitrary radii.)

(1 H, d, 8′-H). ^{13}C NMR ($CDCl_3$): δ 25.3, 25.8, 26.3, 26.6, 67.8, 69.00, 71.2, 75.7, 78.0, 109.4, 110.9, 122.9, 126.7, 143.0, 147.6, 150.0. HREIMS: Calcd for $C_{16}H_{22}ClN_4O_5$, 385.1290; Found *m/z* 385.1279 (MH^+). Anal. Calcd for $C_{16}H_{21}ClN_4O_5$: C, 49.94; H, 5.50; N, 14.56. Found: C, 49.79; H, 5.08; N, 14.36.

3.4. (1*R*)-1,2:4,5-Di-*O*-isopropylidene-1-*C*-(6-phenyl-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-D-arabinitol (14b)

CF_3COOH (100%, 0.08 mL, ~1 mmol) was added to a solution of 3-hydrazino-6-phenylpyridazine (**4b**) (930 mg, 5 mmol) and 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**12**) (1.30 g, 5.0 mmol) in anhyd CH_2Cl_2 (40 mL), and the mixture was stirred at rt for 4 days. Then a solution of Br_2 (0.026 mL, 5.0 mmol) in anhyd CH_2Cl_2 (10 mL) was added slowly, and the mixture was stirred at rt for 1 h. Volatile components were evaporated in vacuo, and the solid residue was crystallised from 95% EtOH to give **14b**. Yield: 685 mg (32%); white solid; mp 172–178 °C; $[\alpha]_D^{23}$ −87.9° (*c* 0.18, $CHCl_3$). IR (KBr); ν_{max} 3402, 3234, 2985, 1348, 1218, 1069. ^{1}H NMR (DMSO-d_6): δ 1:11, 1.28, 1.58, 1.71 (12 H, 4s, 1:1:1:1, 2 × Me_2C); 3.58 (1 H, dd, $J_{2,3}$ 2.2, $J_{3,4}$ 8.5 Hz, 3-H); 3.92 (1 H, dd, $J_{4,5a}$ 5.1, $J_{5a,5b}$ 8.4 Hz, 5-Ha); 4.12 (1 H, dd, $J_{4,5b}$ 6.3 Hz, 5-Hb); 4.19 (1 H, ddd, 4-H); 4.46 (1 H, br s, 3-OH); 4.81 (1 H, dd, $J_{1,2}$ 6.8 Hz, 2-H); 6.16 (1 H, d, 1-H); 7.55–7.60 (3 H, m, 3 H of Ph); 7.66 (1 H, d, $J_{7',8'}$ 9.8 Hz, 7′-H); 7.98–8.01 (2 H, m, 2 H of Ph); 8.23 (1 H, d, 8′-H). ^{13}C NMR ($CDCl_3$): δ 25.3, 25.9, 26.5, 26.6, 67.9, 68.8, 71.6, 75.6, 78.1, 109.4, 110.7, 120.2, 125.4, 127.5, 128.9, 129.4, 131.4, 132.7, 134.1, 147.4, 147.5, 154.3. Anal. Calcd for $C_{22}H_{26}N_4O_5$: C, 61.96; H, 6.15; N, 13.14. Found: C, 62.21; H, 6.09; N, 13.28.

3.5. General procedures for the preparation of *O*-methanesulfonyl derivatives of 1-*C*-(6-chloro1-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-di-*O*-isopropylidenepentitols 15–18

Procedure A. $MeSO_2Cl$ (0.6 mL, 7.7 mmol) was added to a stirred mixture of each of the 1-*C*-(6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-di-*O*-isopropylidene pentitols **9**, **10**, **14a** (1.93 g, 5.0 mmol) and anhyd Py (2.5 mL) at 0 °C (ice-bath), and the mixture was stirred at 0–5 °C for 2 h. Then cold water (0–5 °C, 50 mL) was added, and the precipitate was collected by filtration and dried at rt in vacuo over P_4O_{10} for 12 h to give **15**, **17** and **18**.

Procedure B. $MeSO_2Cl$ (0.6 mL, 7.7 mmol) was added to a stirred mixture of **11** (1.93 g, 5.0 mmol) and anhyd Py (2.5 mL) at 0 °C (ice-bath), and the mixture was stirred at 0–5 °C for 2 h. Then cold water (0–5 °C, 50 mL) was added, and the product was extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were combined, dried over anhyd Na_2SO_4, and filtered, and the filtrate was evaporated in vacuo. The amorphous foamy residue was dried at rt in vacuo over P_4O_{10} for 12 h to give **16**.

3.5.1. (1*S*)-1-*C*-(6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-2,3:4,5-di-*O*-isopropylidene-1-*O*-methanesulfonyl-D-arabinitol (15).

Prepared from **9** by Procedure A: 2.230 g (96%); white solid; mp 121–122 °C (C_6H_6); $[\alpha]_D^{23}$ + 40.6° (*c* 0.21, $CHCl_3$). IR (KBr); ν_{max} 2988, 1464, 1360, 1178, 1067, 946, 840. ^{1}H NMR (DMSO-d_6): δ 0.81, 0.95, 1.38, 1.39 (12 H, 4s, 1:1:1:1, 2 × Me_2C); 3.21 (3 H, s, $MeSO_2$); 3.52–3.63 and 3.82–3.98 (4 H, 2m, 1:3, 3-H, 4-H, 5-Ha,b); 4.89 (1 H, dd, $J_{1,2}$ 7.9, $J_{2,3}$ 5.6 Hz, 2-H); 6.24 (1 H, d, 1-H); 7.65 (1 H, d, $J_{7',8'}$ 9.7 Hz, 7′-H); 8.61 (1 H, d, 8′-H). ^{13}C NMR ($CDCl_3$): δ 24.9, 25.4, 26.7, 27.2, 38.4, 66.6, 67.4, 73.5, 75.7, 78.0, 78.1, 108.6, 110.7, 123.8, 127.3, 143.8, 149.5. Anal. Calcd for $C_{17}H_{23}ClN_4O_7S$: C, 44.11; H, 5.01; N, 12.10. Found: C, 44.36; H, 5.08; N, 12.04.

3.5.2. (1*R*)-1-*C*-(6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-2,3:4,5-di-*O*-isopropylidene-1-*O*-methanesulfonyl-D-arabinitol (16).

Prepared from **11** by Procedure B: 2.08 g (90%); white foam; mp 60–64 °C; $[\alpha]_D^{23}$ −8.6° (*c* 0.11, $CHCl_3$). IR (KBr); ν_{max} 2989, 2938, 1728, 1464, 1368, 1179. ^{1}H NMR (DMSO-d_6) δ 1.20, 1.26, 1.26, 1.30 (12 H, 4s, 1:1:1:1, 2 × Me_2C); 3.19 (3 H, s, $MeSO_2$); 3.73 (1 H, dd, $J_{4,5a}$ 4.9, $J_{5a,5b}$ 8.5 Hz, 5-Ha); 4.05 (1 H, dd, $J_{4,5b}$ 6.1 Hz, 5-Hb); 4.12–4.21 (2 H, m, 3-H, 4-H); 4.81 (1 H, dd, $J_{1,2}$ 6.5, $J_{2,3}$ 4.3 Hz, 2-H); 6.20 (1 H, d, 1-H); 7.64 (1 H, d, 1-H); 7.64 (1 H, d, $J_{7',8'}$ 9.7 Hz, 7′-H); 8.58 (1 H, d, 8′-H). ^{13}C NMR ($CDCl_3$): δ 25.3, 26.3, 27.4, 27.8, 39.3, 67.1, 71.9, 76.9, 78.8, 79.4, 110.0, 111.9, 123.3, 126.5, 143.5, 145.1, 150.0. EIMS: *m/z* 463 (MH^+). HREIMS: Calcd for $C_{17}H_{24}ClN_4O_7S$,

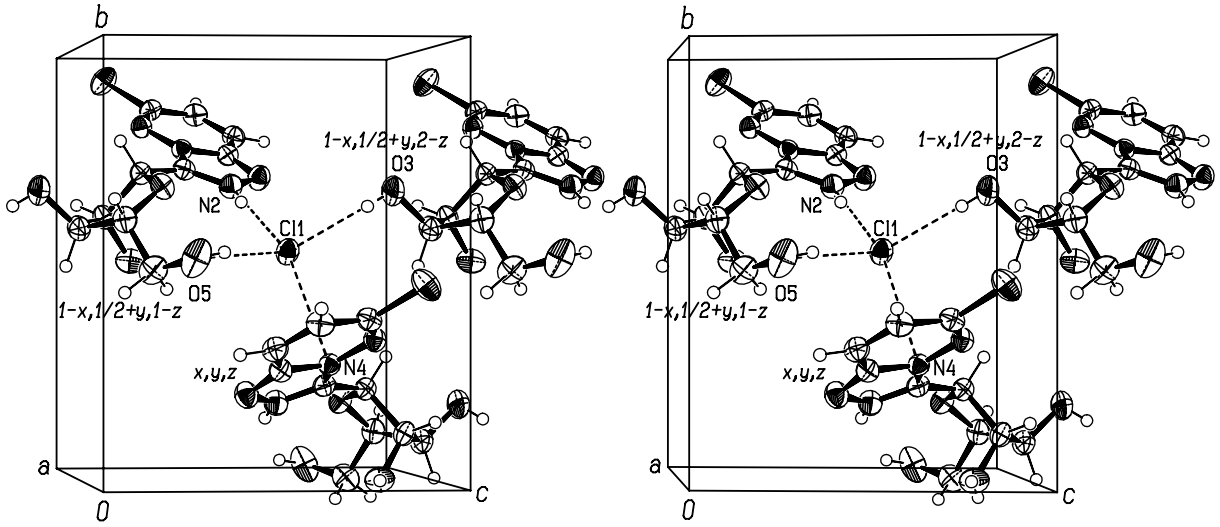


Fig. 7. Stereoscopic view of the packing of compound **20**.

463.1054; Found *m/z* 463.1070 (MH^+). Anal. Calcd for $C_{17}H_{23}ClN_4O_7S$: C, 44.11; H, 5.01; N, 12.10. Found: C, 44.05; H, 5.20; N, 11.22.

3.5.3. (1*S*)-1-*C*-(6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-1,2:4,5-di-*O*-isopropylidene-3-*O*-methanesulfonyl-D-arabinitol (17). Prepared from **10** by Procedure A: 2.18 g (94%); white solid; mp 205–207 °C; $[\alpha]_D^{23}$ −3.6° (*c* 0.22, $CHCl_3$). IR (KBr); ν_{max} 2980, 1466, 1358, 1177, 957, 885. ^{1}H NMR (DMSO-d_6): δ 0.43, 1.04, 1.39, 1.45 (12 H, 4s, 1:1:1:1, 2 × Me_2C); 3.32 (3 H, s, $MeSO_2$); 3.68–3.76 and 4.00–4.12 (3 H, 2m, 1:2, 4-H, 5-Ha,b); 4.86 (1 H, dd, $J_{1,2}$ 5.8, $J_{2,3}$ 9.0 Hz, 2-H); 5.21 (1 H, dd, $J_{3,4}$ 7.3 Hz, 3-H); 5.84 (1 H, d, 1-H); 7.60 (1 H, d, $J_{7',8'}$ 9.7 Hz, 7′-H); 8.56 (1 H, d, 8′-H). ^{13}C NMR ($CDCl_3$): δ 24.9, 25.9, 26.2, 26.3, 38.7, 65.1, 68.2, 73.9, 77.2, 78.8, 108.8, 111.0, 123.6, 127.1, 143.6, 146.2, 149.5. Anal. Calcd for $C_{17}H_{23}ClN_4O_7S$: C, 44.11; H, 5.01; N, 12.10. Found: C, 44.27; H, 5.10; N, 12.21.

3.5.4. (1*R*)-1-*C*-(6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)-1,2:4,5-di-*O*-isopropylidene-3-*O*-methanesulfonyl-D-arabinitol (18). Prepared from **14a** by Procedure A: 1.86 g (80%); white solid; mp 170–171 °C; $[\alpha]_D^{23}$ −0.9° (*c* 0.19, $CHCl_3$). IR (KBr); ν_{max} 2990, 1528, 1473, 1362, 1178, 953. ^{1}H NMR (DMSO-d_6): δ 0.49, 1.16, 1.52, 1.53 (12 H, 4s, 1:1:1:1, 2 × Me_2C); 3.32 (3 H, s, $MeSO_2$); 3.65–3.72 and 3.97–4.16 (3 H, 2m, 1:2, 4-H, 5-Ha,b); 4.86 (1 H, dd, $J_{1,2}$ 5.8, $J_{2,3}$ 9.0 Hz, 2-H); 5.21 (1 H, dd, $J_{3,4}$ 7.2 Hz, 3-H); 5.84 (1 H, d, 1-H); 7.60 (1 H, d, $J_{7',8'}$ 9.8 Hz, 7′-H); 8.56 (1 H, d, 8′-H). ^{13}C NMR ($CDCl_3$): δ 25.1, 25.3, 26.3, 26.8, 38.8, 67.7, 68.6, 74.8, 78.1, 79.6, 110.0, 111.3, 122.6, 126.6, 144.3, 147.9, 149.8. EIMS: *m/z* 462 (M^+); FABMS: *m/z* 463 (MH^+). Anal. Calcd for $C_{17}H_{23}ClN_4O_7S$: C, 44.11; H, 5.01; N, 12.10. Found: C, 44.32; H, 5.31; N, 11.76.

3.6. 3-(α-D-Arabinofuranosyl)-6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine (19)

A mixture of **15** (231 mg, 0.50 mmol), DME (5 mL) and HCl (4%, 0.5 mL, ~0.5 mmol) was stirred under gentle reflux for 30 h. During the reaction, oil separated to the bottom of the initially homogenous reaction mixture. The upper layer was decanted, and the lower oily layer was evaporated in vacuo. DME (5 mL) was added to the residue, and the mixture was left to stand at rt for 7 days. The crystalline precipitate was collected by filtration and washed with anhyd EtOH, CH_2Cl_2, and Et_2O to give **19**. Yield: 116 mg (81%); white solid; mp 190–191 °C; $[\alpha]_D^{21}$ +60.6° (*c* 0.18, EtOH). IR (KBr); ν_{max} 3432, 3120, 1470, 1346, 1129, 1068, 1046, 817. ^{1}H NMR (DMSO-d_6): δ 3.50 (1 H, ddd, $J_{4,5a}$ 2.5 Hz, $J_{5a,5b}$ 12.0, $J_{5a,OH}$ 6.4 Hz, 5-Ha); 3.62 (1 H, ddd, $J_{4,5b}$ 2.9, $J_{5b,OH}$ 5.2 Hz, 5-Hb); 3.87 (1 H, ddd, $J_{3,4}$ 8.1 Hz, 4-H); 4.00 (1 H, ddd, $J_{2,3}$ 6.8, $J_{3,OH}$ 5.4 Hz, 3-H); 4.77 (1 H, dd, 5-OH); 4.79 (1 H, $J_{1,2}$ 7.3, $J_{2,OH}$ 5.8 Hz, 2-H); 5.17 (1 H, d, 1-H); 5.41 (1 H, d, 3-OH); 5.52 (1 H, d, 2-OH); 7.55 (1 H, d, $J_{7'8'}$ 9.8 Hz, 7′-H); 8.56 (1 H, d, 8′-H). ^{13}C NMR (DMSO-d_6): δ 62.0, 74.9, 76.8, 79.0, 84.5, 124.1, 128.0, 144.4, 149.0, 150.1. EIMS and FABMS: *m/z* 287 (MH^+). Anal. Calcd for $C_{14}H_{11}ClN_4O_4$: C, 41.90; H, 3.87; N, 19.54. Found: C, 41.97; H, 4.03; N, 19.30.

3.7. 3-(β-D-Arabinofuranosyl)-6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine hydrochloride (20)

This compound was prepared from **16** using the same procedure described for compound **19** with slight modification of the workup procedure upon evaporation of the lower oily layer. Instead of addition of DME (5 mL), the residue was dissolved in minimum amount of anhyd EtOH (~0.5 mL) and diluted with CH_2Cl_2 (5 mL). Yield: 88 mg (54%); mp 188–190 °C; white solid;

Table 1
Crystal data, data collection, and structure refinement for compounds **5**, **9**, **14a**, **17** and **20**

Compound	**5**	**9**	**14a**	**17**	**20**
Empirical formula	$C_{10}H_{13}ClN_4O_5$	$C_{16}H_{21}ClN_4O_5$	$C_{16}H_{21}ClN_4O_5$	$C_{17}H_{23}ClN_4O_7S$	$C_{10}H_{12}Cl_2N_4O_4$
Rel. formula weight	304.69	384.82	384.82	462.91	323.14
T (K)	293(2)	293(2)	150(2)	293(2)	293(2)
Crystal system	monoclinic	monoclinic	orthorhombic	monoclinic	monoclinic
Space group	$P2_1$, No. 4	$P2_1$, No. 4	$P2_12_12_1$, No. 19	$P2_1$, No. 4	$P2_1$, No. 4
a (Å)	10.5041(5)	9.401(1)	8.3477(1)	6.6919(1)	6.9539(1)
b (Å)	6.4671(4)	9.259(1)	11.0596(2)	11.6361(3)	11.1453(3)
c (Å)	10.6525(5)	11.038(1)	19.6769(4)	14.3550(4)	9.0196(2)
b (°)	119.521(4)	106.95(1)	90.00	96.421(1)	101.415(1)
V (Å^3)	629.69(6)	919.1(2)	1816.62(5)	1110.78(5)	685.22(3)
Z	2	2	4	2	2
P (mg m^{-3})	1.607	1.391	1.407	1.384	1.566
M (mm^{-1})	0.331	0.243	0.246	0.311	0.492
Color, shape	prism, yellow	prism, colorless	prism, pale yellow	prism, colorless	plate, colorless
Dimensions (mm)	$0.64 \times 0.60 \times 0.32$	$0.65 \times 0.57 \times 0.29$	$0.30 \times 0.08 \times 0.03$	$0.30 \times 0.10 \times 0.10$	$0.36 \times 0.36 \times 0.08$
Diffractometer	Enraf Nonius CAD4	Enraf Nonius CAD4	Nonius Kappa CCD	Nonius Kappa CCD	Nonius Kappa CCD
θ_{max} (°)	27.0	29.9	27.5	27.5	27.5
Total reflections	5594	10,709	25,288	15,587	9238
Independent reflections	1507	2818	2371	2655	1628
Observed reflections	1459	2467	2030	1889	1557
Threshold criterion	$I_{net} > 2.5\sigma(I_{net})$	$I_{net} > 2.5\sigma(I_{net})$	$F^2 > 3.0\sigma(F^2)$	$F^2 > 2.0\sigma(F^2)$	$F^2 > 3.0\sigma(F^2)$
Final R and R_w	0.028, 0.016	0.037, 0.045	0.047, 0.046	0.053, 0.057	0.032, 0.034
$(\Delta/\sigma)_{max}$	0.09	0.04	0.005	0.001	0.0007
R_{int}	0.007	0.014	0.045	0.036	0.030
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.207, −0.198	0.402, −0.292	0.440, −0.320	0.443, −0.401	0.443, −0.480

$[\alpha]_D^{21}$ +163.7° (c 0.18, EtOH). IR (KBr); ν_{max} 2988, 3353, 1634, 1573, 1329, 1155, 1019. ^{1}H NMR (DMSO-d_6): δ 3.67 (1 H, dd, $J_{4,5a}$ 5.71, $J_{5a,5b}$ 11.4 Hz, 5-Ha); 3.71 (1 H, dd, $J_{4,5b}$ 4.5 Hz, 5-Hb); 3.86 (1 H, dt, $J_{3,4}$ 4.7 Hz, 4-H); 4.11 (1 H, deg t, $J_{2,3}$ 4.4 Hz, 3-H); 4.42 (1 H, dd, $J_{1,2}$ 5.6 Hz, 2-H); 4.64 (broad s, 3 × OH); 5.58 (1 H, d, 1-H); 7.58 (1 H, d, $J_{7'8'}$ 9.4 Hz, 7′-H); 8.47 (1 H, d, 8′-H) ^{13}C NMR (DMSO-d_6): δ 62.8, 75.4, 77.6, 78.2, 86.7, 124.4, 127.7, 143.6, 148.3, 150.0. EIMS: m/z 286 (M^+), 287 (MH^+). EIMS: m/z 286 (M^+); FABMS: m/z 287 (MH^+); HREIMS: Calcd for $C_{10}H_{11}ClN_4O_4$, 286.0480 (M^+); Found m/z 286.0469. Anal. Calcd for $C_{10}H_{12}Cl_2N_4O_4$: C, 37.17; H, 3.74; N, 17.34. Found: C, 37.18; H, 3.92; N, 16.33.

3.8. Single-crystal X-ray structure determinations

Diffraction data for compounds **5** and **9** were collected on an Enraf-Nonius CAD4 diffractometer. A Nonius Kappa CCD diffractometer was used for **14a**, **17** and **20**. Graphite monochromated Mo K_α radiation was used in all cases. For the first two compounds intensities of reflections were corrected for Lorentz-polarization effects and decay using XTAL3.4[16] program package. Data for **14a**, **17** and **20** were processed using DENZO[17] program. Structures were solved by direct methods using SIR92.[18] For all five structures full-matrix least-squares refinement on F magnitudes with anisotropic displacement factors for all non-hydrogen atoms was employed. In all five cases, the following weighting scheme was used: $w = wf^* w_s$, $wf\ (F_o < A) = (F_o/A)^C$, $wf\ (F_o > B) = (B/F_o)^D$, $wf\ \ (A < F_o < B) = 1.0$, $w_s(\sin\theta/\lambda < E) = ((\sin\theta/\lambda)/E)^G$, $w_s(\sin\theta/\lambda > F) = (F/(\sin\theta/\lambda))^H$, $w_s(E < \sin\theta/\lambda < F) = 1.0$, where A was 11, 3.4, 10, 0.0 and 3.1, B 25, 7.0, 22, 20 and 11, C 1.8, 1.1, 1.2, 1.0 and 2.0, D 1.8, 1.0, 0.5, 1.0 and 1.0, E 0.36, 0.50, 0.49, 0.39 and 0.49, F 0.50, 0.61, 0.57, 0.55 and 0.62, G 1.5, 2.0, 2.0, 1.3 and 4.0 and H 1.5, 3.0, 8.0, 9.0 and 5.0 for compounds **5**, **9**, **14a**, **17** and **20**, respectively. The positions of hydrogen atoms of compounds **14a** and **20** were obtained from the difference Fourier map. Most of hydrogen atoms of compounds **5**, **9** and **17** were also located using difference Fourier maps; the remaining were calculated regarding expected geometry. The parameters of hydrogen atoms of compounds **5**, **9** and **17** were not refined. For compounds **14a** and **20** positional and isotropic displacement parameters of hydrogen atoms were refined. For compounds **14a** and **17** the absolute configurations were assigned so as to agree with the known chirality from precursors. For

compounds **5**, **9** and **20** we refined a Flack parameter. Its final value 0.00(4), −0.06(7) and 0.00(7), respectively, is in the agreement with the known chirality from precursors. In the final cycle of the refinement, we used 1478, 2633, 2371, 2336 and 1551 reflections and 181, 236, 320, 217 and 229 parameters for compounds **5**, **9**, **14a**, **17** and **20**, respectively. The resulting crystal data and details concerning data collection and refinement for all five compounds are provided in Table 1.

The asymmetric units of compounds **5**, **9**, **14a** and **17** are shown in Figs. 2–5. The structure of compound **20** consists of $C_{10}H_{12}ClN_4O_4^+$ cations and chloride anions. The view of $C_{10}H_{12}ClN_4O_4^+$ cation is shown in Fig. 6. The packing of compound **20** is presented in Fig. 7. All figures were prepared with the aid of ORTEPII[19] program.

4. Supplementary material

The crystallographic data for compounds **5**, **9**, **14a**, **17** and **20** have also been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition numbers: CCDC 207236–207240, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk/conts/retrieving.html)

Acknowledgements

The financial support from the Ministry of Education, Science and Sport, Slovenia, through grant PS-0502-0103, is gratefully acknowledged. The authors wish to express their gratitude to the Alexander von Humboldt Foundation, Germany, for the donation of a Büchi medium-pressure liquid chromatograph. We thank for the financial contribution of the Ministry of Education, Science and Sport of the Republic of Slovenia through grants X-2000, PS-511-103 and Z1-3246.

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