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A 2′-deoxycytidine long-linker click adduct forming two conformers in the asymmetric unit

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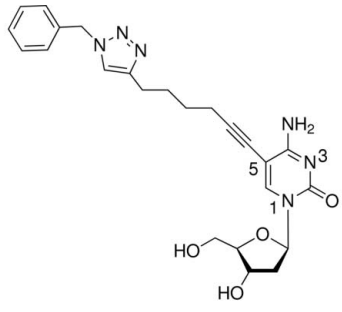
The title compound {systematic name: 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-[6-(1-benzyl-1*H*-1,2,3-triazol-4-yl)hex-1-ynyl]pyrimidin-2(1*H*)-one}, $C_{24}H_{28}N_6O_4$, shows two conformations in the crystalline state, *viz.* (I-1) and (I-2). The pyrimidine groups and side chains of the two conformers are almost superimposable, while the greatest differences between them are observed for the sugar groups. The N-glycosylic bonds of both conformers adopt similar *anti* conformations, with χ = −168.02 (12)° for conformer (I-1) and χ = −159.08 (12)° for conformer (I-2). The sugar residue of (I-1) shows an *N*-type (C3′-*endo*) conformation, with P = 33.1 (2)° and τ_m = 29.5 (1)°, while the conformation of the 2′-deoxyribofuranosyl group of (I-2) is *S*-type (C3′-*exo*), with P = 204.5 (2)° and τ_m = 33.8 (1)°. Both conformers participate in hydrogen-bond formation and exhibit identical patterns resulting in three-dimensional networks. Intermolecular hydrogen bonds are formed with neighbouring molecules of different and identical conformations (N—H···N, N—H···O, O—H···N and O—H···O).

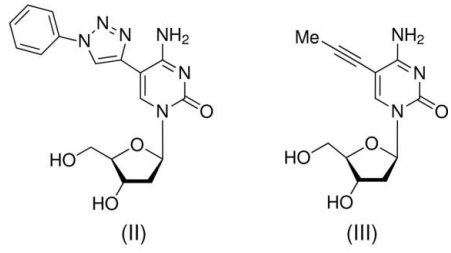
Comment

The Cu^I-catalysed Huisgen–Meldal–Sharpless alkyne–azide 'click' reaction has emerged as a convenient and effective approach to conjugate two molecules irreversibly under simple reaction conditions (Kolb *et al.*, 2001; Meldal & Tornøe, 2008). This strategy has become particularly attractive for applications in synthetic chemistry (Meldal & Tornøe, 2008), bioconjugation (Wang *et al.*, 2003), drug discovery (Kolb & Sharpless, 2003), molecular diagnostics (Kolb & Sharpless, 2003) and materials science (Moses & Moorhouse, 2007). The ease of click chemistry has inspired researchers to construct a variety of chemically modified nucleosides and oligonucleotide conjugates for medicinal, biological and nanotechnological applications (El-Sagheer & Brown, 2010). Our laboratory and others have reported on the click functionalization of alkynylated 7-deazapurine, 8-aza-7-deazapurine and pyrimidine 2′-deoxyribonucleosides with various reporter groups on the nucleoside and oligonucleotide levels (Gramlich *et al.*, 2008; Seela *et al.*, 2008, 2010). The click chemistry approach has also been extended to the crosslinking of nucleosides and oligonucleotides (Kočalka *et al.*, 2008; Pujari *et al.*, 2010; Xiong & Seela, 2011).



(I)

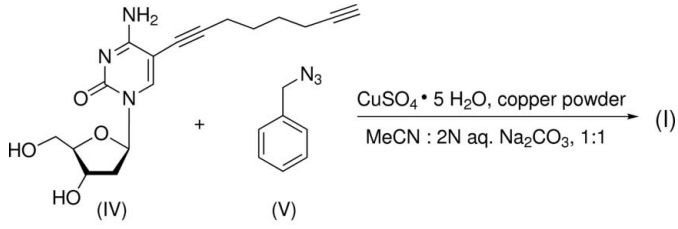
Systematic numbering



(II) (III)

Scheme 1

Recently, 5-ethynyl-2′-deoxycytidine and phenylazide have been employed as substrates in the click reaction, yielding the click conjugate (II) (see Scheme 1) (Dodd *et al.*, 2010; Andersen *et al.*, 2011), and its solid-state structure was elucidated (Dodd *et al.*, 2010). We used 5-octadiynyl-2′-deoxycytidine, (IV) (Seela *et al.*, 2008), and benzyl azide, (V), as starting materials for the copper(I)-mediated click reaction to afford the title click product 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-[6-(1-benzyl-1*H*-1,2,3-triazol-4-yl)hex-1-ynyl]pyrimidin-2(1*H*)-one, (I) (see Scheme 2). The synthetic



(IV) (V)

Scheme 2

procedure for (I) is given in the *Experimental* section. Slow crystallization from hot water gave the click conjugate (I) as colourless crystals. Consequently, we became interested in performing a single-crystal X-ray analysis of (I), which is reported herein. The crystal structure of (I) is compared with

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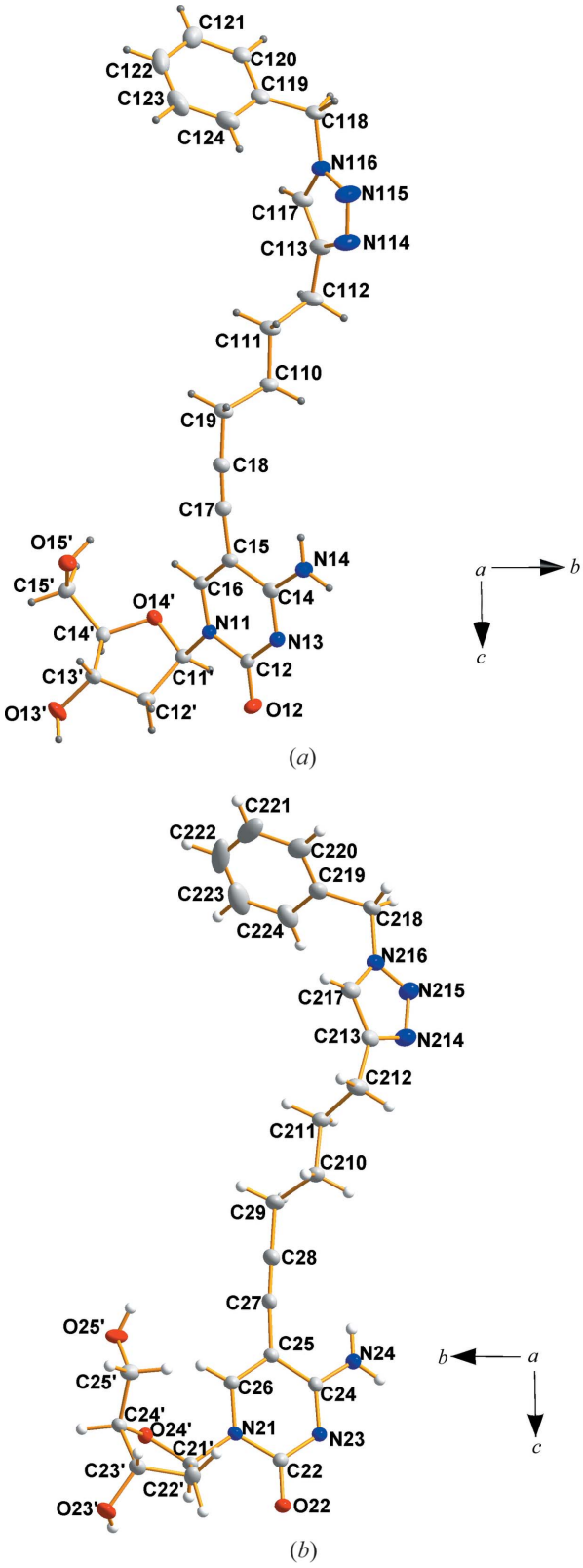

Figure 1
Perspective views of (*a*) conformer (I-1) and (*b*) conformer (I-2), showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 50% probability level.

the two conformers of the click conjugate 5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-2′-deoxycytidine, (II) (Dodd *et al.*, 2010), and the two conformers of 5-propynyl-2′-deoxycytidine, (III) (Seela *et al.*, 2007).

There are two molecules in the asymmetric unit of (I), denoted (I-1) and (I-2). The three-dimensional structures of conformers (I-1) and (I-2) are shown in Fig. 1, and selected geometric parameters are summarized in Table 1. For the related crystal structures of (II) (Dodd *et al.*, 2010) and (III) (Seela *et al.*, 2007), two conformers were also found in the unit cells. Both nucleoside click conjugates (I) and (II) crystallize in the same space group (monoclinic, $P2_1$) (Dodd *et al.*, 2010), while the space group of (III) is triclinic ($P1$) (Seela *et al.*, 2007).

Fig. 2 shows an overlay of conformers (I-1) and (I-2), indicating that the pyrimidine groups and side chains of the two conformers are almost superimposable, while the greatest differences between them are observed for the sugar groups. Some interesting structural features of the side chains are: (i) the angle between the triazole group and the benzyl ring; (ii) the angle formed by the triple-bonded C7 and C8 atoms with adjacent atom C9; (iii) the angle of inclination of the side chain with respect to the pyrimidine ring plane; (iv) the planarity of the nucleobase. These will be discussed in turn.

The N—C—C angle connecting the methylene group (C118 or C218), the triazole group (N116 or N216) and the phenyl C atom (C119 or C219) is almost identical in both conformers [112.59 (13)° for (I-1) and 112.87 (13)° for (I-2)].

In conformer (I-2), the triple-bonded C27 and C28 atoms, together with adjacent atom C29, form an almost linear entity [C27—C28—C29 = 179.29 (18)°]. For the propynyl groups of conformers (III-1) and (III-2), comparable angles were observed [179.3 (3) and 178.7 (3)°; Seela *et al.*, 2007]. However, for conformer (I-1), this unit is slightly bent [C17—C18—C19 = 173.49 (16)°]. The lengths of the C7—C8 triple bond in the two conformers [1.194 (2) Å for (I-1) and 1.190 (2) Å for (I-2)] are comparable.

The heterocyclic skeletons of (I-1) and (I-2) are nearly planar; the r.m.s. deviations of the ring atoms (N1/C2/N3/C4/C5/C6) from their calculated least-squares planes are 0.0205 and 0.0272 Å, respectively.

The triple-bonded C17 atom of conformer (I-1) almost lies within the pyrimidine ring plane (0.4° inclination), while the triple-bonded C27 atom of conformer (I-2) is slightly displaced from the pyrimidine ring plane (2.7° inclination).

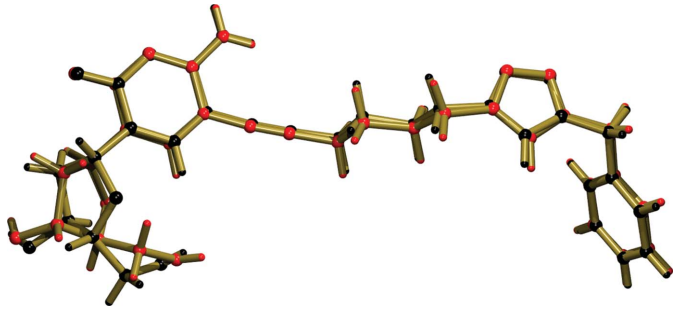

Figure 2
Overlay of conformers (I-1) (darker atoms) and (I-2) (lighter atoms) (black and red, respectively, in the electronic version of the paper).

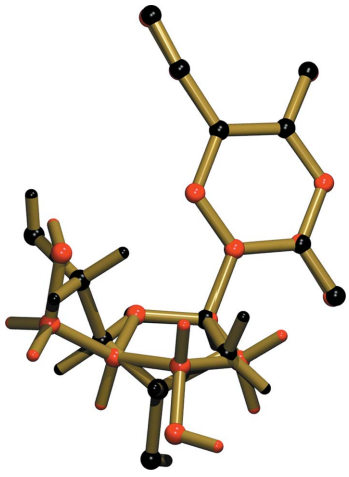

Figure 3
A comparison of the sugar groups of conformers (I-1) and (I-2). The shading is as for Fig. 2.

The orientation of the pyrimidine group relative to the sugar residue (*syn*/*anti*) is defined by the torsion angle χ (O4′—C1′—N1—C2) (IUPAC–IUB Joint Commission on Biochemical Nomenclature, 1983), and usually adopts a conformation in the *anti* range. Indeed, the two conformers of (I) show glycosylic bond torsion angles of χ = −168.02 (12)° for (I-1) and −159.08 (12)° for (I-2), corresponding to *anti* conformations. The conformers of the closely related click compound (II) adopt *anti* conformations within the same range [χ = −165.6 (3)° for (II-1) and −165.2 (4)° for (II-2); Dodd *et al.*, 2010]. A similar torsion angle was also found for conformer (III-2) of 5-propynyl-2′-deoxycytidine, with χ = −156.4 (2)°, while conformer (III-1) shows a torsion angle of χ = −135.0 (2)° around the glycosylic bond (Seela *et al.*, 2007).

The length of the glycosylic N1—C1′ bond is 1.4939 (19) Å for (I-1) and 1.4948 (19) Å for (I-2), which are in the same range as the bond lengths observed for the two conformers of (II) [1.495 (5) Å for (II-1) and 1.484 (5) Å for (II-2); Dodd *et al.*, 2010] and for conformer (III-2) [1.490 (2) Å; Seela *et al.*, 2007], while a shorter glycosylic bond was found for conformer (III-1) [1.475 (2) Å; Seela *et al.*, 2007].

The most pronounced difference between conformers (I-1) and (I-2) is the conformation of the sugar group (Fig. 3). The 2′-deoxyribofuranosyl group of conformer (I-1) shows an *N*-type conformation, with a pseudorotational phase angle P = 33.1 (2)° and a maximum amplitude τ_m = 29.5 (1)°, referring to a major C3′-*endo* sugar pucker (C3′-*endo*-C4′-*exo*, $^3T_4$). Surprisingly, conformer (I-2) exhibits an *S*-type sugar pucker instead of the *N*-type conformation found for (I-1). The pseudorotational phase angle for (I-2) is P = 204.5 (2)° and the maximum amplitude is τ_m = 33.8 (1)°, which corresponds to a major C3′-*exo* sugar pucker (C3′-*exo*-C4′-*endo*, $_3T^4$). It is interesting to note that this phenomenon was also observed for the two conformers of the closely related click compound (II). Conformer (II-1) adopts an *S*-type sugar pucker with a major C3′-*exo* conformation [P = 205.6 (4)°, τ_m = 37.6 (3)°, C3′-*exo*-C4′-*endo*, $_3T^4$], while conformer (II-2) shows an *N*-type sugar pucker with a major C3′-*endo* envelope conformation [P = 18.6 (4)°, τ_m = 34.7 (3)°, ^3E; Dodd *et al.*, 2010]. In contrast, this kind of observation was not made in the case of the two conformers of 5-propynyl-2′-deoxycytidine, (III): for (III-1) and (III-2), similar *S*-type sugar puckers were found (Seela *et al.*, 2007).

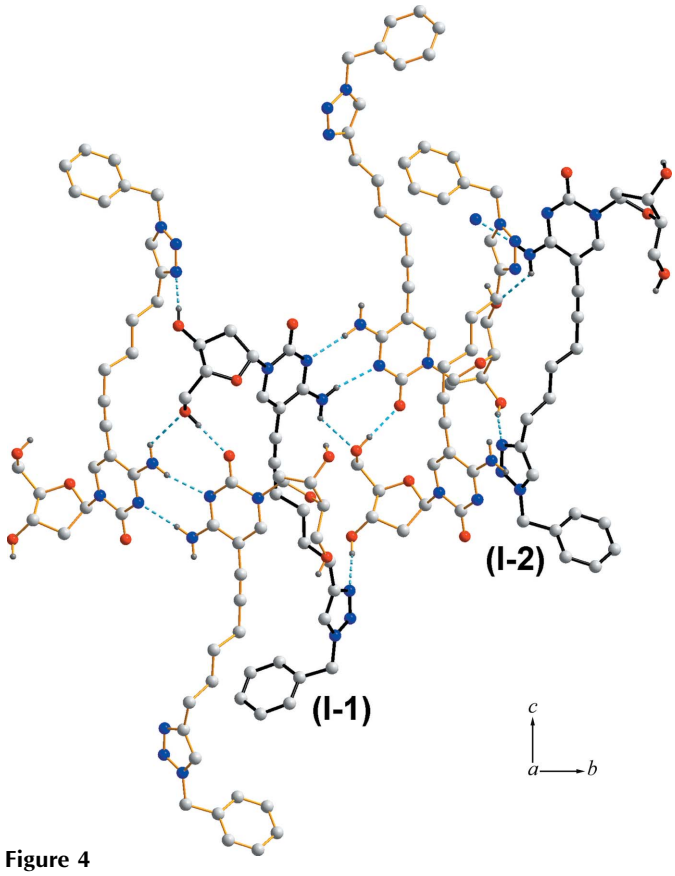

Figure 4
The crystal packing of (I), showing the intermolecular hydrogen-bonding network (parallel to the *bc* plane).

The γ torsion angle (O5′—C5′—C4′—C3′) characterizes the orientation of the exocyclic 5′-hydroxy group relative to the 2′-deoxyribose ring. Conformers (I-1) and (I-2) display different conformations about the C4′—C5′ bond. For (I-1), the torsion angle γ is 60.40 (17)°, corresponding to a synclinal (+*sc*; *gauche*, *gauche*) conformation, while in (I-2) the C4′—C5′ bond adopts an antiperiplanar (+*ap*; *gauche*, *trans*) orientation with γ = 174.40 (12)°. In the case of click compound (II), conformer (II-2) shows a similar torsion angle with γ = 169.9 (3)° (+*ap*; *gauche*, *trans*), while in conformer (II-1) the C5′-hydroxy group was disordered (Dodd *et al.*, 2010).

In the crystal structure of nucleoside click conjugate (I), conformers (I-1) and (I-2) are linked into an infinite three-dimensional network by several intermolecular hydrogen bonds (Table 2 and Fig. 4). The two conformers exhibit identical hydrogen-bond patterns, and hydrogen bonds are formed with neighbouring molecules of different and identical conformations. The amino group of each conformer acts as a hydrogen-bond donor. Amino group N4—H4*A* of one conformer acts as donor to atom N3 of the pyrimidine group of the other conformer (N14—H14*A*···N23^{i} and N24—H24*A*···N13^{v}; see Table 2 for symmetry codes and geometry). The other amino group, N4—H4*B*, functions as a hydrogen-

bond donor to atom O5′ of the exocyclic sugar hydroxy group of a neighbouring molecule of identical conformation (N14—H14*B*···O15′^{ii} and N24—H24*B*···O25′^{i}). The 5′-hydroxy group is also an H-atom donor, and atom O2 attached to the nucleobase of the other conformer acts as the acceptor site (O15′—H15*C*···O22^{iv} and O25′—H25*C*···O12^{vi}). Apart from the nucleobase and the sugar group, the side chains of the two conformers participitate in hydrogen bonding as well. Atom N14 of the triazole ring functions as a hydrogen-bond acceptor and hydroxy group O3′—H3*C* of the same conformer acts as donor (O13′—H13*C*···N114^{iii} and O23′—H23*C*···N214^{v}).

Experimental

For the synthesis of (I), copper(II) sulfate pentahydrate (7.5% in water; 12.5 mg, 0.05 mmol) and copper powder (32.0 mg, 0.5 mmol) were added to a solution of (IV) (166.5 mg, 0.5 mmol) and benzyl azide, (V) (133 mg, 1.0 mmol), in a mixture of acetonitrile and a 2 *N* solution of aqueous Na_2CO_3 (1:1 *v*/*v*, 10 ml). The reaction mixture was stirred vigorously in the dark at room temperature for 16 h. After completion of the reaction [monitored by thin-layer chromatography (TLC)], the solvent was evaporated under reduced pressure and the residue was applied to a flash chromatography (FC) column (silica gel, column 8 × 3 cm, eluted with CH_2Cl_2/MeOH, 90:10 *v*/*v*). The solvent was evaporated under reduced pressure and the residue was washed with MeOH/H_2O (10:90 *v*/*v*) to afford (I) as a colourless foam (yield 130 mg, 56%). TLC (silica gel, CH_2Cl_2/MeOH, 90:10 *v*/*v*): R_F 0.4; UV (MeOH, λ_{max}, nm): 260 (ε, dm^{-3} mol^{-1} cm^{-1} 160 200), 297.5 (7 400). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.53–1.60 (*m*, 2H, CH_2), 1.64–1.71 (*m*, 2H, CH_2), 1.95–2.01 (*m*, 1H, H_α—C2′), 2.10–2.14 (*m*, 1H, H_β—C2′), 2.42 (*t*, *J* = 7.2 Hz, 2H, CH_2), 2.63 (*t*, *J* = 7.2 Hz, 2H, CH_2), 3.55–3.60 (*m*, 2H, 2 × H—C5′), 3.76–3.78 (*m*, 1H, H—C4′), 4.17–4.21 (*m*, 1H, H—C3′), 5.10 (*t*, *J* = 5.1 Hz, 1H, HO—C5′), 5.22 (*d*, *J* = 4.2 Hz, 1H, HO—C3′), 5.53 (*s*, 2H, NCH_2), 6.11 (*t*, *J* = 6.6 Hz, 1H, H—C1′), 6.73 (*br s*, 1H, NH), 7.26–7.37 (*m*, 5H, arom. H), 7.67 (*br s*, 1H, NH), 7.90 (*s*, 1H, H5-triazole), 8.08 (*s*, 1H, H—C6). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ 18.8 (CH_2), 24.5 (CH_2), 27.6 (CH_2), 28.3 (CH_2), 40.7 (C2′), 52.7 (CH_2), 61.0 (C5′), 70.1 (C3′), 72.1 (CC), 85.2 (C1′), 87.4 (C4′), 90.4 (CC), 95.4 (C5), 122.0 (triazole CH), 127.8 (arom. C), 128.0 (arom. C), 128.7 (arom. C), 136.3 (triazole C), 143.6 (C6), 147.0 (arom. C), 153.5 (C2), 164.4 (C4). Analysis calculated for $C_{24}H_{28}N_6O_4$: C 62.06, H 6.08, N 18.09%; found: C 61.45, H 5.89, N 17.89%.

Slow crystallization from hot water afforded (I) as colourless crystals (m.p. 446 K). For the diffraction experiment, a single crystal was mounted on a MiTeGen Micro-Mountsfibre in a thin smear of oil.

Crystal data

$C_{24}H_{28}N_6O_4$
M_r = 464.52
Monoclinic, $P2_1$
a = 12.525 (6) Å
b = 15.051 (7) Å
c = 12.719 (6) Å
β = 106.241 (10)°
V = 2302 (2) Å^3
Z = 4
Mo *K*α radiation
μ = 0.09 mm^{-1}
T = 130 K
0.17 × 0.15 × 0.14 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2008)
T_{min} = 0.701, T_{max} = 0.746
131640 measured reflections
11402 independent reflections
10254 reflections with $I > 2\sigma(I)$
R_{int} = 0.037

Table 1
Selected geometric parameters (Å, °) for conformers (I-1) and (I-2).

Bond or angle	(I-1), *X* = 1	(I-2), *X* = 2
N*X*1—C*X*1′	1.4939 (19)	1.4948 (19)
C*X*5—C*X*7	1.431 (2)	1.435 (2)
C*X*7—C*X*8	1.194 (2)	1.190 (2)
C*X*12—C*X*13	1.501 (2)	1.504 (2)
N*X*16—C*X*18	1.467 (2)	1.476 (2)
C*X*8—C*X*7—C*X*5	174.89 (16)	174.68 (16)
C*X*7—C*X*8—C*X*9	173.49 (16)	179.29 (18)
N*X*14—N*X*15—N*X*16	106.71 (14)	106.73 (14)
N*X*16—C*X*18—C*X*19	112.59 (13)	112.87 (13)
C*X*11—C*X*12—C*X*13—N*X*14	76.6 (2)	−79.34 (19)
N*X*15—N*X*16—C*X*18—C*X*19	−119.04 (17)	129.99 (17)
C*X*2—N*X*1—C*X*1′—O*X*4′	−168.02 (12)	−159.08 (12)
C*X*3′—C*X*4′—C*X*5′—O*X*5′	60.40 (17)	174.40 (12)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N14—H14*A*···N23^{i}	0.88	2.14	2.978 (2)	158
N14—H14*B*···O15′^{ii}	0.88	2.45	3.1038 (19)	131
O13′—H13*C*···N114^{iii}	0.84	1.98	2.815 (2)	173
O15′—H15*C*···O22^{iv}	0.84	1.95	2.7813 (18)	173
N24—H24*A*···N13^{v}	0.88	2.07	2.944 (2)	173
N24—H24*B*···O25′^{i}	0.88	2.36	2.9839 (19)	128
O23′—H23*C*···N214^{v}	0.84	2.02	2.833 (2)	164
O25′—H25*C*···O12^{vi}	0.84	1.84	2.6483 (17)	161

Symmetry codes: (i) $-x+2, y-\frac{1}{2}, -z+2$; (ii) $-x+2, y+\frac{1}{2}, -z+1$; (iii) $-x+2, y-\frac{1}{2}, -z+1$; (iv) $x, y-1, z-1$; (v) $-x+2, y+\frac{1}{2}, -z+2$; (vi) $x, y+1, z$.

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.093
S = 1.02
11402 reflections
617 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.57 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Absolute structure: established by known chemical absolute configuration

The known configuration of the parent molecule was used to define the enantiomer employed in the refined model. In the absence of suitable anomalous scattering, Friedel equivalents could not be used to determine the absolute structure. Refinement of the Flack (1983) parameter led to an inconclusive value for this parameter [−0.3 (5)]. Further confirmation of the configuration was sought using the Hooft analysis. The absolute structure parameter *y* (Hooft *et al.*, 2008) was calculated using *PLATON* (Spek, 2009). The resulting Hooft analysis parameters were *P*2(true) = 1.000, *P*3(true) = 0.987, *P*3(false) = 0.000 and *y* = 0.04 (16) calculated for 5342 Bijvoet pairs (95% coverage), indicating that the known absolute configuration used for the analysis is correct.

All H atoms were found in a difference Fourier synthesis. In order to maximize the data/parameter ratio, H atoms were placed in geometrically idealized positions, with C—H = 0.95 (aromatic), 0.99 (methylene) or 1.00 Å (methine) and N—H = 0.88 Å, and constrained to ride on their parent atoms, with U_{iso}(H) = 1.2U_{eq}(C,N). The hydroxy groups were refined as groups allowed to rotate but not tip, with O—H = 0.84 Å and U_{iso}(H) = 1.5U_{eq}(O).

Data collection: *APEX2* (Bruker, 2008); cell refinement: *SAINT* (Bruker, 2008); data reduction: *SAINT*; program(s) used to solve

structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *PLATON* (Spek, 2009) and *DIAMOND* (Brandenburg, 2004); software used to prepare material for publication: *SHELXTL* and *PLATON*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3166). Services for accessing these data are described at the back of the journal.

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