Stereoselective Preparation of Protected Thymine Polyoxin C and Approaches Towards Synthesis of Its C2′-Modified Analogues

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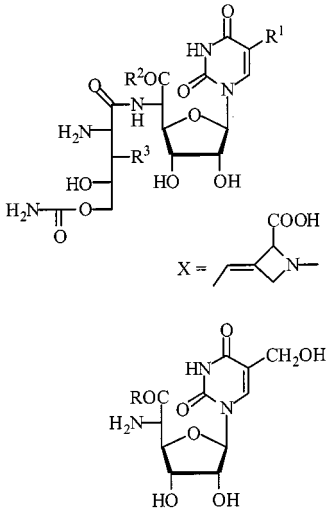
Polyoxins form an important class of pyrimidine peptide antifungal agents. The preparation of thymine polyoxin C, which is the nucleosidic component of some polyoxins, is reported, together with attempts to synthesize C2′-fluoro analogues. Epimeric 3-hydroxyazidolactones **2a** and **2b**, obtained from diastereoisomeric epoxy hydroxy esters, were dehydrated to afford butenolide **3**. Dihydroxylation and further functional manipulation yielded thymine polyoxin C. Attempts to form the 2,2′-anhydronucleoside and to direct nucleophilic fluorination with DAST on a monoprotected nucleoside were unsuccessful. Electrophilic fluorination of azidolactone with NFSI permitted the formation of an α-fluorolactone, which is an interesting intermediate for the preparation of a C2′-fluoro analogue.

Introduction

Polyoxins form an important class of peptidyl nucleosidic antibiotics, isolated from culture broths of *Streptomyces cacoi var. asoensis* by Isono and co-workers (Figure 1).[1,2] They are known antifungal agents[3] that selectively and competitively inhibit membrane-bound enzyme chitin synthase from yeasts and other fungi.[4] However, polyoxins are only weakly active against whole cells of pathogenic fungi such as *Candida albicans*, presumably due to their hydrolytic instability and/or their inefficient transport into the cell.[5]



Polyoxins	R^1	R^2	R^3
A	CH_2OH	X	OH
B	CH_2OH	HO	OH
D	COOH	HO	OH
E	COOH	HO	H
F	COOH	X	OH
G	CH_2OH	HO	H
H	CH_3	X	OH
J	CH_3	HO	OH
K	H	X	OH
L	H	HO	OH

	R
C	HO
I	X

Figure 1. Structures of polyoxins

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Since the discovery of polyoxins, two major associated synthetic research areas have evolved: One focused mainly on synthetic methodology development to provide polyoxins in an efficient and enantioselective fashion, the other focused on the search for more potent and safer analogues of polyoxins.[6] The majority of polyoxin syntheses have employed existing natural products, particularly carbohydrates,[7] nucleosides,[8] and cyclitols.[9] Only Vogel et al. have reported a total asymmetric synthesis of the thymine polyoxin C starting from an achiral material.[10] Moreover, the structural features of polyoxins permit several interesting modifications. Among these, the more frequently encountered are: modification of the *N*-terminal amino acid,[11] replacement of the pyrimidine base,[12] and substitution of the furanose ring oxygen atom[13] with other atoms.

Over the last decade, our laboratory has developed a highly flexible methodology based on (1) stereocontrolled addition to an α,β-epoxy aldehyde (with a lithium enolate or with trimethylsilylthiazole) and (2) the regio- and stereoselective opening of epoxides with sodium azide. This strategy has already been applied to the synthesis of the C2′-deoxy analogue of thymine polyoxin C[14] and to the preparation of the amino acid moiety of polyoxin J, known as 5-*O*-carbamoylpolyoxamic acid.[15] Here we would like to report the synthesis of thymine polyoxin C using the same methodology. We have also attempted an approach towards the first C2′-fluoro analogue of thymine polyoxin C. The controlled introduction of fluorine into organic molecules, especially biomolecules, has received much attention in recent years.[16] In the case of C2′-fluoro nucleosides, the strong electronegativity of fluorine causes dramatic changes in the sugar moiety conformation and so affects the biological activity. The powerfully electron-withdrawing nature of fluorine also increases the chemical and metabolic stability of nucleosides.[16] The C2′-fluoro analogue of thymine polyoxin C might be a more resistant and efficient antifungal agent than the natural product.

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Results and Discussion

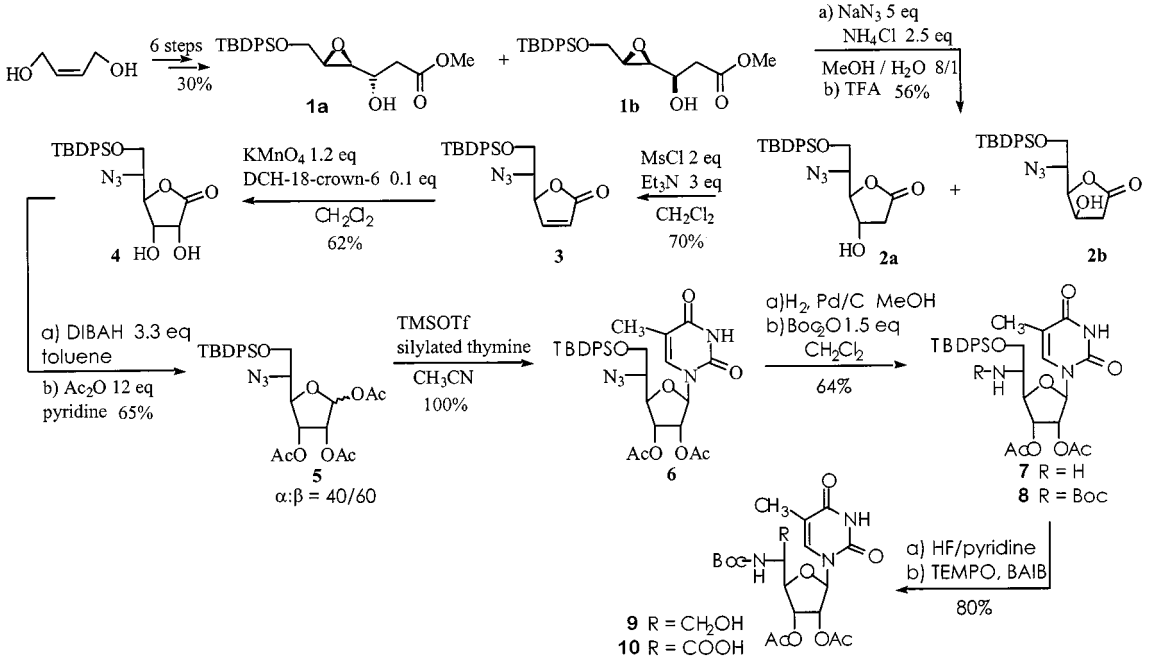
Preparation of Thymine Polyoxin C in Protected Form

The synthesis of thymine polyoxin C (Scheme 1) employed a diastereoisomeric mixture of α,β-epoxy hydroxy esters **1a** and **1b** (**1a/1b** = 70:30). Compounds **1a** and **1b** were obtained as previously described by us in 6 steps, starting from *cis*-2-butene-1,4-diol (total yield 30%).[14] Compounds **1a** and **1b** were refluxed for 48 h with sodium azide (5 equiv.) and ammonium chloride (2.5 equiv.) in an $MeOH/H_2O$ mixture (8:1). This reaction permitted the regio- and stereoselective opening of the oxirane functionality, resulting in the epimeric azidolactones **2a** and **2b**, the corresponding methyl esters, and starting material. When the mixture was refluxed for longer than 48 h, dehydration products appeared. Treatment with trifluoroacetic acid yielded only azidolactones **2a** and **2b**, obtained after purification in 56% total yield. The mixture of the two diastereoisomeric lactones was then treated with mesyl chloride in the presence of triethylamine, affording butenolide **3** in 70% yield after dehydration.[17] Dihydroxylation of compound **3** under the conditions described by Mukayiama,[18] in the presence of potassium permanganate and dicyclohexano-18-crown-6, afforded only the dihydroxylated lactone **4**, in 68% yield. Half-reduction of the lactone by careful addition of DIBAH at −78 °C followed by acetylation afforded triacetate **5** (α/β = 40:60). Nucleoside formation was effected according to Vorbrüggen's procedure,[19] by treatment of compound **5** with silylated thymine in the presence of trimethylsilyl trifluoromethanesulfonate to furnish **6** in a stereoselective and quantitative manner. Reduction of the azide functionality by catalytic hydrogenation followed by *tert*-butoxycarbonyl protection afforded compound **8** (64% for the two steps). Removal of the *tert*-butyldiphenylsilyl group was effected by treatment with HF/pyridine, in 80% yield. The resulting primary alcohol was oxidized to the corresponding acid by one-step oxidation, using BAIB (iodobenzene diacetate) with a catalytic amount of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) free radical, to give thymine polyoxine C in protected form.[20]

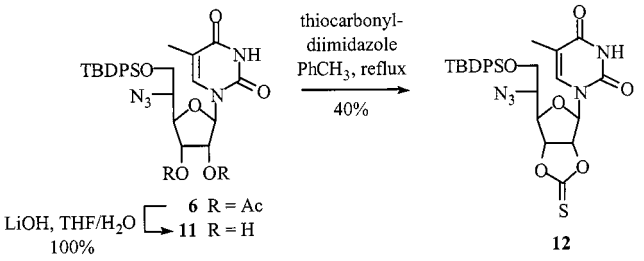
Approach Towards the Synthesis of C2′-Fluoro Analogue of Thymine Polyoxine C

Our first approach towards the preparation of a C2′-fluoro analogue consisted of forming a 2,2′-anhydronucleoside potentially susceptible to opening by nucleophilic attack by a fluorine anion. Methods described in the literature[21] for the preparation of 2,2′-anhydropyrimidine nucleosides are based on the presence of a *cis*-oriented diol system in which the two secondary alcohols display different reactivities. In our case, we chose Patchett's procedure.[21c] Complete deacetylation of nucleoside **6** was achieved in the presence of lithium hydroxide in a tetrahydrofuran/water mixture, quantitatively furnishing the deprotected compound **11** (Scheme 2). Patchett's procedure, which consists of treatment with thiocarbonyldiimidazole in toluene under reflux for 30 min, afforded the cyclic derivative **12** in 40% yield. A longer reflux time resulted in degradation products. In our hands, unfortunately, any attempts to transform **12** into the C2′-anhydro nucleoside were unsuccessful.

Another strategy, based on differential protection of the two hydroxy groups on the carbon atoms C2′ and C3′, was developed (Scheme 3). Treatment of the azidolactone **4** with benzaldehyde and catalytic amounts of *para*-toluenesulfonic acid in anhydrous toluene under Dean−Stark conditions yielded benzylidene acetal **13** as a 35:65 mixture of two diastereoisomers, in 67% yield after purification. Chemo- and regioselective reductive cleavage by means of $TiCl_4$ com-



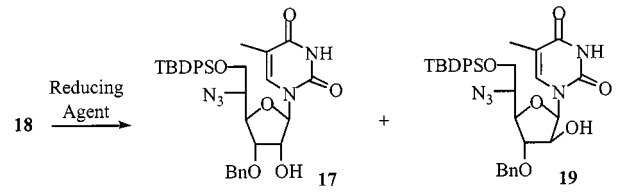
Scheme 1. Synthesis of protected thymine polyoxin C



Scheme 2

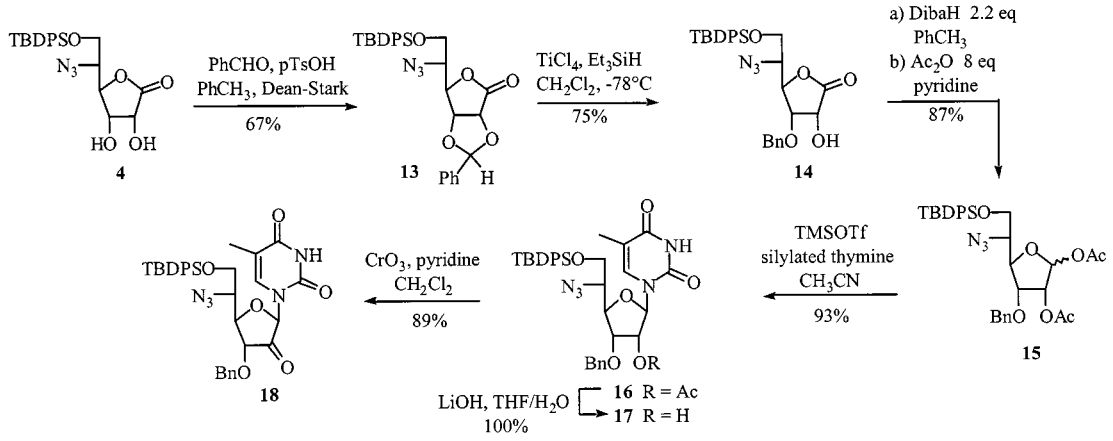
plexation/Et_3SiH reduction resulted exclusively in the monoprotected lactone **14**, in 75% yield.[22] The diastereoselectivity of the reaction was governed by the complexation of titanium with the oxygen atoms of the carbonyl and that of the adjacent benzylidene acetal moiety, rendering one of the C−O bonds more easily cleavable by reduction. The diastereoselectivity was also established by the acetylation reaction performed in the next step.

Table 1. Reduction of oxo nucleoside **18**



Reducing agent	Procedure	**17/19**	Yield (%)
$NaBH_4$	MeOH, 0 °C	50:50	100
K-Selectride	THF, −78 °C	40:60	60
K-Selectride	THF, −90 °C	10:90	66

To circumvent these difficulties, a new approach was explored. The lactone **2a** was benzylated with benzyl bromide

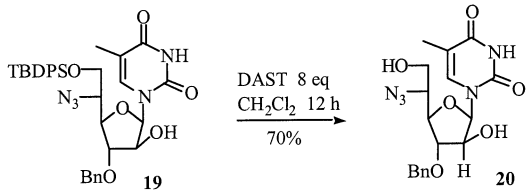


Scheme 3. Synthesis of 2′-oxo nucleoside **18**

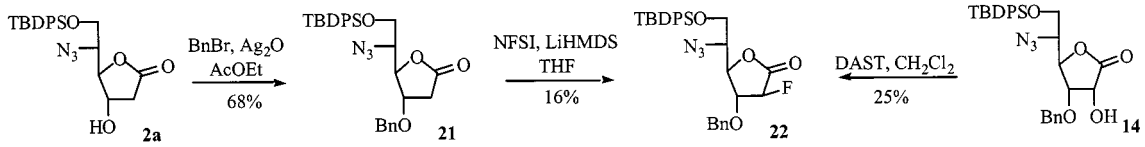
The thymine base was then introduced in three steps. Reduction of the lactone and diacetylation, followed by Vorbrüggen's reaction,[19] afforded nucleoside **16** in 81% yield after purification (3 steps). Removal of the acetate functionality was effected by lithium hydroxide in 96% yield. Direct fluorination of compound **17** with DAST [(diethylamino)sulfur trifluoride] was not attempted because of the well-known dehydrating properties of DAST with "ribo" nucleosides.[23] The inversion of the C2′ configuration to obtain the "arabino" compound was accomplished by means of an oxidation/reduction procedure (Table 1).[24] Oxidation of compound **17** in the presence of CrO_3·$(pyridine)_2$ complex was successful, producing compound **18** in 79% yield. Attempts at oxidation with other reagents (PDC and DMSO/Ac_2O) gave starting material or degradation products. Reduction of the carbonyl functionality was achieved by using $NaBH_4$ or K-Selectride®, the best result being obtained with K-Selectride at −90 °C (**17/19** = 10:90). After separation of epimers **17** and **19** on a reversed phase, we attempted to fluorinate **19** with DAST (Scheme 4). Although this kind of fluorination is well documented,[25] this reaction was unsuccessful in our hands, and exclusively provided the deprotected nucleoside **20**.

and Ag_2O in ethyl acetate, in 68% yield (Scheme 5).[26] It was noteworthy that the reaction was unsuccessful when performed in DMF. Electrophilic monofluorination of lactone **21** was accomplished in the presence of NFSI (*N*-fluorobenzenesulfonimide) and LiHMDS [lithium bis(trimethylsilyl)amide][27] in tetrahydrofuran at −78 °C. Purification on silica gel allowed lactone **22** to be isolated in 16% yield. The configuration of the carbon atom bearing the fluorine atom was confirmed by the S_N2 reaction of compound **14** with DAST.[28] This reaction was accomplished in dichloromethane at −78 °C to give the product **22** in 25% yield.

From the results presented here, it seems likely that introduction of a heteroatom, and especially fluorine, at the C2′ position of thymine polyoxine C should occur at the begin-



Scheme 4



Scheme 5. Synthesis of fluorinated azido butyrolactone **22**

ning of the synthetic pathway developed here, and in any case before the introduction of the base. A question had arisen of why compound **19** did not react with DAST in the desired way and why the cyclic derivative **12** did not afford the 2,2′-anhydro nucleoside. We attempted to explain these results with modeling studies and by inspection of the ^{1}H NMR coupling constants of the sugar moiety of compound **19** and **12** (Figure 2, Table 2).

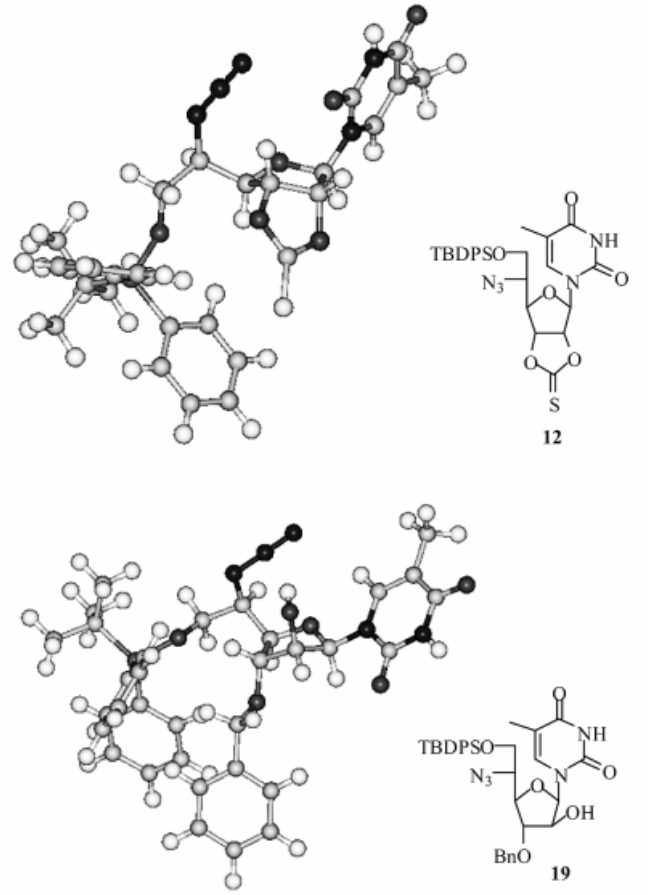


Figure 2. Energetically optimized conformers of compounds **12** and **19**

Compound **19** displays an energy minimum[29] near the *S*-type conformation, while the conformation of compound **12** approaches that of the *N*-type.[30] For compound **19**, coupling constants ($J_{1'2'}$ = 2.4 Hz and $J_{2'3'}$ = 0 Hz) are consistent with the measured torsion angles (47.6° and 91.1°, respectively). Moreover, for compound **12**, values of $J_{2'3'}$ and $J_{3'4'}$ (1.4 and 7.4 Hz, respectively) are fairly well in agreement with the corresponding dihedral angles (111.07° and 34.91°). Large values are observed for $J_{4'5'}$ (6.3 and 7.7 Hz for compounds **19** and **12**, respectively). This is mainly due to diminished free rotation around the C4′−C5′ bond and to the positive interactions developed between the azido group and the oxygen atoms either of the sugar ring or at the C2′ position. In both cases, the azido group is oriented towards the sugar ring, rendering the hydroxy group inactive towards DAST fluorination in the case of **19**. It also isolates the base, so that antiperiplanar attack on the C2′ position of compound **12** does not occur even at elevated temperature.

Table 2. Selected coupling constants (400 MHz NMR, $CDCl_3$) and parameters determined from modeling studies of compounds **12** and **19**

		12	**19**
Coupling constants [Hz]	$J_{1'2'}$	1.4	2.4
	$J_{2'3'}$	7.4	0
	$J_{3'4'}$	3.7	3.3
	$J_{4'5'}$	7.7	6.3
Dihedral angle [°]	H1C1−C2H2	111.07	47.6
	H2C2−C3H3	34.91	91.1
	H3C3−C4H4	−165.91	−118.4
	H4C4−C5H5	−67.92	−68.6
E [kcal/mol]		−51.34	−41.17

In conclusion, our methodology produced protected thymine polyoxin C in 12 steps and 18.5% overall yield, starting from a mixture of diastereoisomeric epoxyhydroxy esters **1a** and **1b**. We attempted to explain the lack of reactivity at the C2′ position in those systems by calculating their optimal conformations, taking coupling constants into account. Further studies are underway in two directions: (a) optimization of the α-fluorination of lactones, and (b) introduction of the heteroatom in the course of the aldol reaction.

Experimental Section

(1′*R*,5*S*)-5-(1′-Azido-2′-*tert*-butyldiphenylsilyloxyethyl)furan-2(5*H*)-one (3): NH_4Cl (366 mg, 2.5 equiv.) and NaN_3 (780 mg, 5 equiv.) were added to a solution (0.11 M) of the epoxy hydroxy esters **1a/1b** (1 g, 2.4 mmol) in MeOH/H_2O (8:1). The mixture was refluxed for 48 h and the methanol was evaporated. The product was diluted with Et_2O and washed with water and brine. After drying ($MgSO_4$) and concentration, the product was treated with trifluoroacetic acid (20 mL) for 5 min at room temperature and then concentrated. Chromatography on silica gel (petroleum ether/CH_2Cl_2/ethyl acetate, 5:4:1) afforded 576 mg of lactones **2a**[14] and **2b** (total yield 56%). − **Compound 2a:** See ref.[14] − **Compound 2b:** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.72−7.67 (m, 4 H, arom.), 7.49−7.37 (m, 6 H, arom.), 4.65 (ddd, *J* = 3.7, 5.0, 5.4 Hz, 1 H, 3-H), 4.35 (dd, *J* = 3.6, 9.2 Hz, 1 H, 4-H), 4.07 (dd, *J* = 2.5, 9.2 Hz, 1 H, 2′-Ha), 3.84 (m, 2 H, 2′-Hb and 1′-H), 2.77 and 2.58 (ABX, *J* = 0, 5.4, 17.8 Hz, 2 H, 2-H), 1.09 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR

(63 MHz, $CDCl_3$): δ = 174.9 (C=O), 135.6, 135.5 (CH arom.), 132.6, 132.3 (Cq arom.), 130.2, 130.0, 128.0, 127.9 (CH arom.), 80.3 (C4), 68.0 (C3), 64.1 (C2′), 60.3 (C1′), 38.6 (C2), 26.8 (CH_3 TBDPS), 19.2 (Cq TBDPS). − Triethylamine (565 μL, 3 equiv.) and mesyl chloride (210 μL, 2 equiv.) were added to a solution of lactones **2a** and **2b** in anhydrous CH_2Cl_2 (15 mL), cooled to −5 °C. The reaction mixture was stirred for 3 h at −5 °C. After dilution with CH_2Cl_2, the organic layer was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 8:2) to give 380 mg (70%) of **3**. − IR ($CHCl_3$): $\tilde{\nu}$ = 2111, 1762 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.70−7.66 (m, 4 H, arom.), 7.50−7.39 (m, 7 H, arom.), 7.47 (dd, *J* = 5.8, 1.6 Hz, 1 H, 4-H), 6.20 (dd, *J* = 2.0, 5.8 Hz, 1 H, 3-H), 5.12 (dt, *J* = 1.6, 2.0, 6.6 Hz, 1 H, 5-H), 3.91 and 3.95 (part AB of ABX system, *J* = 4.5, 5.6, 11.0 Hz, 2 H, 2′-H), 3.66 (ddd, *J* = 4.5, 5.6, 6.6 Hz, 1 H, 1′-H), 1.08 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.9 (C=O), 153.6 (C4), 135.6 (CH arom.), 132.3 (Cq arom.), 130.2, 128.0 (CH arom.), 123.0 (C3), 81.1 (C5), 64.2 (C1′), 63.8 (C2′), 26.8 (CH_3 TBDPS), 19.1 (Cq TBDPS). − MS (DCI, NH_3); *m*/*z* (%): 425 (100) [MNH_4^+]. − $C_{22}H_{25}N_3O_3Si$ (407.5): calcd. C 64.84, H 6.68, N 10.31; found C 64.80, H 6.58, N 10.61.

(1′*R*,3*R*,4*R*,5*R*)-5-[1′-Azido-2′-(*tert*-butyldiphenylsilyloxy)ethyl]-3,4-dihydroxy-3,4-dihydrofuran-2(5*H*)-one (4): $KMnO_4$ (280 mg, 1.2 equiv.) was added in small portions to a vigorously stirred solution of compound **3** (600 mg, 1.47 mmol) and dicyclohexano-18-crown-6 (55 mg, 0.1 equiv.) in CH_2Cl_2 (10 mL) at −40 °C, and the mixture was stirred for 3 h. The reaction mixture was then allowed to warm to −10 °C and the reaction was stopped by adding 600 mg of Na_2SO_3 followed by careful acidification with HCl (1 N). After filtration through a Celite pad, the product was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (petroleum ether/EtOAc, 6:4) afforded 64 mg of the starting product **3** and 400 mg (62%) of the desired compound **4**. − $[\alpha]_D^{24}$ = −8.82 (*c* = 0.51, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3560, 3391, 2112, 1789 cm^{-1}. − ^1H NMR (250 MHz, C_6D_6): δ = 7.79−7.74 (m, 4 H, arom.), 7.32−7.28 (m, 6 H, arom.), 4.52 (d, *J* = 5.4 Hz, 1 H, 3-H), 4.37 (d, *J* = 5.2 Hz, 1 H, 5-H), 4.20 (d, *J* = 5.4 Hz, 1 H, 4-H), 3.63 (m, 2 H, 2′-H), 3.31 (m, 1 H, 1′-H), 1.08 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, C_6D_6): δ = 176.0 (C=O), 136.0 (CH arom.), 132.8 (Cq arom.), 130.4, 130.0, 128.0 (CH arom.), 83.3 (C5), 68.9 and 68.7 (C4 and C3), 63.7 (C2′), 63.4 (C1′), 27.0 (CH_3 TBDPS), 19.3 (Cq TBDPS). − MS (DCI, NH_3); *m*/*z* (%): 459 (100) [MNH_4^+]. − $C_{22}H_{27}N_3O_5Si$ (441.6): calcd. C 59.84, H 6.16, N 9.52; found C 59.75, H 6.10, N 9.62.

(2*R*,3*R*,4*R*,5*R*)-1,2,3-tri-*O*-Acetyl-5-azido-5-deoxy-6-*O*-*tert*-butyldiphenylsilyl-D-allofuranose (5): DIBAL (1 M in toluene, 1.4 mL, 3.3 equiv.) was added to a solution of **4** (190 mg, 0.431 mmol) in toluene (5 mL), cooled to −78 °C. After stirring for 3.5 h at −78 °C, the solution was hydrolyzed with 1.5 mL of HCl (1 N), and stirring was maintained for 1 h at 0 °C. The product was extracted four times with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give 180 mg of lactol. The residue was dissolved in pyridine (3 mL) and acetic anhydride (483 μL, 12 equiv.) was added. The mixture was stirred for 7 h at room temperature. The pyridine was evaporated at reduced pressure and co-evaporated with CCl_4. Purification on silica gel (petroleum ether/CH_2Cl_2/ethyl acetate, 7:24:6) produced 160 mg (65%; α/β = 40:60) of **5** (starting from **4**). − IR ($CHCl_3$): $\tilde{\nu}$ = 2110, 1751 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.64−7.60 (m, 8 H, arom.), 7.43−7.24 (m, 12 H, arom.), 6.35 (d, *J* = 4.5 Hz, 1 H, 1-H α), 6.08 (s, 1 H, 1-H β), 5.42 (dd, *J* = 4.8, 6.8 Hz, 1 H, 3-H α), 5.28 (dd, *J* = 2.8, 5.2 Hz, 1 H, 3-H β), 5.29 (d, *J* = 2.8 Hz, 1 H, 2-H β), 5.20 (dd, *J* = 4.5, 6.8 Hz, 1 H, 2-H α), 4.32 (dd, *J* = 2.8, 4.8 Hz, 1 H, 3-H α), 4.25 (dd, *J* = 5.2, 6.8 Hz, 1 H, 4-H β), 3.75−3.62 (m, 6 H, 5-H and 6-H α + β), 2.06 (s, 3 H, CH_3 OAc β), 2.03 (s, 3 H, CH_3 OAc α), 2.02 (s, 3 H, CH_3 OAc β), 2.01 (s, 3 H, CH_3 OAc α), 1.91 (3 H, CH_3 OAc β), 1.90 (s, 3 H, CH_3 OAc α), 1.03 (s, 18 H, CH_3 TBDPS α+β). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.6, 169.3, 169.0 (C=O), 135.6, 135.5 (Cq arom.), 132.8, 132.6 (Cq arom.), 130.2, 130.0 (CH arom.), 128.0, 127.9 (CH arom.), 98.1 (C1 β), 93.7 (C1 α), 82.3 (C4 α), 79.7 (C4 β), 74.4 (C3 β), 70.6 (C2 β), 69.9 (C3 or C2 α), 69.1 (C3 or C2 α), 64.8 (C5 β), 64.2 (C5 α), 63.6, 63.4 (C1 α + β), 26.7 (CH_3 TBDPS α + β), 20.9, 20.5, 20.4, 20.3, 20.2, 20.1 (CH_3 OAc α + β), 19.2 (Cq TBDPS α + β). − MS (DCI, NH_3); *m*/*z* (%): 587 (100) [MNH_4^+].

(2′*R*,3′*R*,4′*R*,5′*R*)-1′-(2′,3′-Diacetoxy-5′-azido-6′-*tert*-butyldiphenylsilyl-β-D-allofuranosyl)-5-methyluracil (6): A suspension of thymine (1 g, 7.9 mmol), hexamethyldisilazane (15 mL), and trimethylsilyl chloride (0.3 mL) in anhydrous pyridine (5 mL) was refluxed for 2 h until the solution became clear. Pyridine, hexamethyldisilazane, and trimethylsilyl chloride were removed by distillation under reduced pressure and then the silylated thymine was distilled off (b.p. 55 °C/1.5 × 10^{-3} mbar). This distilled silylated thymine (400 mg) and a solution of trimethylsilyl trifluoromethanesulfonate (1.6 mL, 0.55 M in toluene) were added to a solution of compound **5** (420 mg, 0.740 mmol) in anhydrous acetonitrile (3 mL). The mixture was refluxed for 4 h. The product was diluted at 0 °C with CH_2Cl_2 and hydrolyzed with a saturated, aqueous solution of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 5:5) to give 468 mg of compound **6** in quantitative yield. − $[\alpha]_D^{24}$ = +4.8 (*c* = 1.05, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3390, 2108, 1751, 1698 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 8.88 (s, 1 H, NH), 7.68−7.63 (m, 4 H, arom.), 7.46−7.36 (m, 6 H, arom.), 7.24 (d, *J* = 1.1 Hz, 1 H, 6-H thym.), 6.09 (d, *J* = 4.3 Hz, 1 H, 1′-H), 5.35 (m, 2 H, 2′-H and 3′-H), 4.16 (t, *J* = 3.3 Hz, 1 H, 4′-H), 3.90 (dd, *J* = 3.3, 5.8 Hz, 1 H, 5′-H), 3.80 (m, 2 H, 6′-H), 2.05 (s, 3 H, CH_3 OAc), 2.04 (s, 3 H, CH_3 OAc), 1.81 (d, *J* = 1.1 Hz, 3 H, C5−CH_3), 1.07 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.5, 169.3, 169.0 (C=O OAc), 163.3, 150.5 (C2−C4), 135.6, 134.9 (Cq arom.), 132.5 (Cq arom.), 130.1, 127.9 (CH arom.), 122.2 (C5), 85.7 (C1′), 80.7 (C4′), 71.9 and 69.9 (C2′ and C3′), 64.4 (C5′), 63.7 (C6′), 26.7 (CH_3 TBDPS), 20.5 and 20.4 (CH_3 OAc), 19.1 (Cq TBDPS), 12.8 (C5−CH_3). − MS (DCI, NH_3); *m*/*z* (%): 653 (100) [MNH_4^+], 636 (64.3) [MH^+]. − $C_{31}H_{37}N_5O_8Si$ (635.7): calcd. C 58.66, H 5.72, N 11.03; found C 58.55, H 5.52, N 10.61.

(2′*R*,3′*R*,4′*R*,5′*R*)-1-(2′,3′-Di-*O*-acetyl-5′-*tert*-butoxycarbonylamino-6′-*O*-*tert*-butyldiphenylsilyl-5′-deoxy-D-allofuranosyl)-5-methyluracil (8): A suspension of compound **6** (156 mg, 0.246 mmol) and 10% Pd/C (16 mg) in methanol (3 mL) was degassed and then pressurized with H_2. After stirring for 8 h, the suspension was filtered through a Celite pad and then concentrated in vacuo to give the amine **7**. The residue was dissolved in CH_2Cl_2 (3.3 mL) and Boc_2O (80 mg, 1.5 equiv.) was added. The reaction mixture was stirred for 12 h at room temperature. The mixture was dissolved with CH_2Cl_2 and washed with water. The organic layer was dried ($MgSO_4$) and concentrated. Purification on silica gel (CH_2Cl_2/ethyl acetate, 7:3) gave 112 mg (64%) of compound **8** (starting from **6**). − IR ($CHCl_3$): $\tilde{\nu}$ = 3445, 3391, 1751, 1698 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 9.14 (br. s, 1 H, NH), 7.64−7.61 (m, 4 H, arom.), 7.43−7.33 (m, 6 H, arom.), 7.04 (s, 1

H, 6-H), 6.08 (d, J = 5.0 Hz, 1 H, 1′-H), 5.51 (dd, J = 3.7, 4.0 Hz, 1 H, 3′-H), 5.32 (dd, J = 5.0, 4.0 Hz, 1 H, 2′-H), 5.06 (d, J = 9.0 Hz, 1 H, NH), 4.18 (dd, J = 3.7, 8.1 Hz, 1 H, 4′-H), 3.87−3.74 (m, 3 H, 5′-H and 6′-H), 2.14 (s, 3 H, CH_3 OAc), 2.04 (s, 3 H, CH_3 OAc), 1.88 (s, 3 H, C5−CH_3), 1.45 (s, 9 H, CH_3 Boc), 1.07 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.6, 169.5 (C=O OAc), 163.5 (C2), 155.7 (C=O Boc), 150.6 (C4), 135.5 (C6), 132.8, 132.6 (Cq arom.), 130.0, 127.9, 127.8 (CH arom.), 112.1 (C5), 85.9 (C1′), 80.6 (C4′), 80.4 (Cq Boc), 71.8 (C2′), 71.2 (C3′), 62.8 (C6′), 53.5 (C5′), 28.3 (CH_3 Boc), 26.9 (CH_3 TBDPS), 20.7, 20.5 (CH_3 OAc), 19.3 (Cq TBDPS), 12.6 (C5−CH_3). − MS (DCI, NH_3); *m/z* (%): 727 (100) [MNH_4^+], 710 (74) [MH^+].

(2′*R*,3′*R*,4′*R*,5′*R*)-1-(2′,3′-Di-*O*-acetyl-5′-*tert*-butoxycarbonylamino-5′-deoxy-D-allofuranosyl)-5-methyluracil (9): HF/pyridine (70%, 140 μL, 8 equiv.) was slowly added to a solution of compound **8** (100 mg, 0.21 mmol) in THF/pyridine (1.3 mL/676 μL). After stirring for 3 h, HF/pyridine (70 μL, 4 equiv.) was again added and the reaction was allowed to continue for additional 3 h. The reaction mixture was diluted with Et_2O and then hydrolyzed with a saturated, aqueous solution of $NaHCO_3$. The aqueous phase was extracted with Et_2O, dried ($MgSO_4$), and concentrated. Purification on silica gel (Et_2O/AcOEt 6:4) gave 52 mg (80%) of compound **9**. − IR ($CHCl_3$): ṽ = 3625, 3440, 3391, 1749, 1689 cm^{-1}. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.34 (br. s, 1 H, NH), 7.16 (d, J = 1.02 Hz, 1 H, 6-H), 5.84 (d, J = 5.0 Hz, 1 H, 1′-H), 5.53−5.40 (m, 2 H, 2′-H and 3′-H), 5.48 (d, J = 9.0 Hz, 1 H, NH), 4.20 (dd, J = 4.5, 5.5 Hz, 1 H, 4′-H), 3.93−3.77 (m, 3 H, 5′-H and 6′-H), 3.04 (br. s, 1 H, OH), 2.11 (s, 3 H, CH_3 OAc), 2.06 (s, 3 H, CH_3 OAc), 1.92 (d, J = 1.02 Hz, 3 H, C5−CH_3), 1.44 (s, 9 H, CH_3 Boc). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.9, 169.8 (C=O OAc), 163.8 (C2), 156.0 (C=O Boc), 150.8 (C4), 135.5 (C6), 111.9 (C5), 88.1 (C1′), 81.7 (C4′), 80.2 (Cq Boc), 72.2 (C2′), 71.0 (C3′), 61.6 (C6′), 53.1 (C5′), 26.7 (CH_3 Boc), 20.6 and 20.4 (CH_3 OAc), 12.4 (C5−CH_3). − MS (DCI, NH_3); *m/z* (%): 489 (100) [MNH_4^+], 472 (87) [MH^+].

(2′*R*,3′*R*,4′*R*,5′*S*)-(2′,3′-Di-*O*-acetyl-5′-*tert*-butoxycarbonylamino-5′-deoxy-D-allofuranosyl)uronic Acid Derivative 10: TEMPO (1.5 mg, 0.2 equiv.) and BAIB (33 mg, 2.2 equiv.) were added to a solution of compound **9** (22 mg, 0.047 mmol) in CH_3CN/H_2O (100 μL/100 μL). The solution was stirred for 5 h and concentrated to give **10** quantitatively. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.2 (br. s, 1 H, COOH), 9.40 (br. s, 1 H, NH), 7.12 (s, 1 H, 6-H), 5.82 (d large, 1 H, 1′-H), 5.63 (m, 1 H, 2′′-H), 5.54 (m, 2 H, 3′-H and NH), 4.62 (dd, 1 H, 4′-H), 4.42 (m, 1 H, 5′-H), 2.12 (s, 3 H, CH_3 OAc), 2.08 (s, 3 H, CH_3 OAc), 1.81 (s, 3 H, C5−CH_3), 1.45 (s, 9 H, CH_3 Boc). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.9, 169.7 (C=O OAc), 164.2 (C2), 155.3 (C=O Boc), 151.0 (C4), 135.5 (C6), 111.8 (C5), 91.6 (C1′), 82.2 (C4′), 80.0. (Cq Boc), 72.6 (C2′), 70.0 (C3′), 54.0 (C5′), 28.3 (CH_3 Boc), 20.6 and 20.5 (CH_3 OAc), 12.3 (C5−CH_3).

(2′*R*,3′*R*,4′*R*,5′*R*)-1-(5′-*tert*-Butoxycarbonylamino-5′-deoxy-2′,3′-*O*-thiocarbonyl-D-allofuranosyl)-5-methyluracil (12): $LiOH·H_2O$ (11 mg, 4 equiv.) was added at 0 °C to **7** (40 mg, 0.062 mmol) in THF/H_2O (600 μL/100 μL). After stirring for 4 h at 0 °C, the mixture was hydrolyzed with 1 N HCl and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give the deprotected compound **11**. A mixture of **11** (20 mg, 0.036 mmol) and thiocarbonyldiimidazole (8 mg, 1.1 equiv.) in toluene (500 μL) was refluxed for 30 min. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/ethyl acetate, 8:2). Compound **12** (8 mg, 40%) was obtained. − IR ($CHCl_3$): ṽ = 1695, 1384 cm^{-1}. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (br. s, 1 H, NH), 7.64−7.61 (m, 4 H, arom.), 7.42−7.23 (m, 11 H, arom.), 6.92 (d, J = 1.2 Hz, 1 H, 5-H), 5.70 (dd, J = 1.4, 7.4 Hz, 1 H, 2′-H), 5.63 (d, J = 3.7, 7.4 Hz, 1 H, 3′-H), 5.45 (d, J = 1.4 Hz, 1 H, 1′-H), 4.22 (dd, J = 3.7, 7.7 Hz, 1 H, 4′-H), 3.83 (ddd, J = 1.4, 2.2, 7.7 Hz, 1 H, 5′-H), 3.76−3.70 (AB part of ABX system, J = 1.4, 2.2, 6.0 Hz, 2 H, 6′-H), 1.91 (d, J = 1.2 Hz, 3 H, C5−CH_3), 1.04 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214 (C=S), 160.0, 149.7 (C2, C4), 135.6 (CH arom.), 132.6 (Cq arom.), 130.0, 127.9 (CH arom.), 112.5 (C5), 95.6 (C1), 87.7 (C4), 85.9, 85.7 (C2′ and C3′), 63.9 (CH_2OSi), 62.7 (CHN_3), 26.7 (CH_3 TBDPS), 19.0 (Cq TBDPS), 12.4 (C5−CH_3). − MS (DCI, NH_3); *m/z* (%): 594 (41.7) [MH^+], 611 (33.4) [MNH_4^+].

(1′*R*,3*R*,4*R*,5*R*)-5-(1′-Azido-2′-*tert*-butyldiphenylsilyloxyethyl)-3,4-benzylidenedioxy-3,4-dihydrofuran-2(5*H*)-one (13): A mixture of lactone **4** (210 mg, 0.47 mmol), freshly distilled benzaldehyde (144 μL, 3 equiv.), and *para*-toluenesulfonic acid (9 mg, 0.1 equiv.) in anhydrous toluene (2 mL) was refluxed in a Dean−Stark apparatus for 1.5 h. After addition of a saturated solution of $NaHCO_3$, the aqueous phase was extracted with toluene. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (petroleum ether/EtOAc, 9:1) afforded 200 mg of diastereoisomers **13a/13b** (67%, **13a/13b** = 65:35). − IR ($CHCl_3$): ṽ = 2113, 1790 cm^{-1}. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.70−7.66 (m, 8 H, arom.), 7.48−7.26 (m, 22 H, arom.), 5.93 (2s, 2 H, CHPh), 5.02 (d, J = 5.9 Hz, 1 H, 3-H **13a**), 4.92 (d, J = 6.0 Hz, 1 H, 3-H **13b**), 4.79 (d, J = 6.0 Hz, 1 H, 4-H **13b**), 4.74 (2d, J = 5.9 Hz, 2 H, 4-H **13a** and J = 2.4 Hz, 5-H **13a**), 4.71 (d, J = 2.3 Hz, 1 H, 5-H **13b**), 3.87 (m, 6 H, 1′-H and 2′-H), 1.09 (s, 18 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.3 (C=O 13a), 172.1 (C=O 13b), 135.5 (CH arom.), 135.5, 135.3 (Cq arom.), 130.2, 129.9, 128.5, 128.0, 126.7, 126.5 (CH arom.), 106.9 (CHPh **13b**), 104.9 (CHPh **13a**), 82.9 (C5 **13a**), 80.5 (C5 **13b**), 77.9 (C3 or C4 **13b**), 75.7 and 75.6 (C3 and C4 **13a**), 75.1 (C3 or C4 **13b**), 64.4 (C1′ **13a**), 64.2 (C1′ **13b**), 63.1 (C1′ **13a** and **13b**), 26.7 (CH_3 TBDPS), 19.1 (Cq TBDPS). − MS (DCI, NH_3); *m/z* (%): 547 (100) [MNH_4^+]. − $C_{29}H_{31}N_3O_5Si$ (529.7): calcd. C 65.76, H 5.90, N 7.93; found C 65.62, H 5.91, N 7.97.

(1′*R*,3*R*,4*R*,5*R*)-5-(1′-Azido-2′-*tert*-butyldiphenylsilyloxyethyl)-4-benzyloxy-3-hydroxy-3,4-dihydrofuran-2(5*H*)-one (14): $TiCl_4$ (885 μL, 1.2 equiv.) was slowly added to a solution of **13** (400 mg, 0.75 mmol) in anhydrous CH_2Cl_2 (4 mL), cooled to −78 °C. After the resulting solution had been stirred for 10 min, Et_3SiH (142 μL, 1.2 equiv.) was added. The stirring was maintained for 30 min, and then the reaction was quenched with a saturated, aqueous solution of $NaHCO_3$ and filtered through a Celite pad. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Column chromatography with silica gel (petroleum ether/ethyl acetate, 8:2) gave 300 mg (75%) of **14**. − $[\alpha]_D^{24}$ = −30.0 (c = 0.56, $CHCl_3$). − IR ($CHCl_3$): ṽ = 3686, 3556, 2110, 1796 cm^{-1}. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.68−7.64 (m, 4 H, arom.), 7.50−7.39 (m, 6 H, arom.), 7.26−7.19 (m, 5 H, arom.), 4.60 (s, 2 H, CH_2Ph), 4.52 (d, J = 6.0 Hz, 1 H, 4-H), 4.40 (d, J = 4.0 Hz, 1 H, 5-H), 4.06 (d, J = 6.0 Hz, 1 H, 3-H), 3.66 (m, 3 H, 1′-H and 2′-H), 1.08 (s, 9 H, TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.4 (C=O), 136.1 (Cq arom.), 135.6 (CH arom.), 132.3, 132.2 (Cq arom.), 130.2, 128.7, 128.5, 128.0 (CH arom.), 80.3 (C5), 73.9 (C4), 72.6 (CH_2Ph), 68.0 (C3), 63.5 (C2′), 63.4 (C1′), 26.7 (CH_3 TBDPS), 19.1 (Cq TBDPS). − MS (DCI, NH_3); *m/z* (%): 549 (100) [MNH_4^+]. − $C_{29}H_{33}N_3O_5Si$ (531.7): calcd. C 65.64, H 6.08, N 7.92; found C 65.66, H 6.08, N 7.86.

(2*R*,3*R*,4*R*,5*R*)-2,3-Di-*O*-acetyl-5-azido-4-benzyl-6-*O*-*tert*-butyldiphenylsilyl-5-deoxy-D-allofuranose (15): DIBAL (1 M in toluene, 660 μL, 2.5 equiv.) was added to a solution of **14** (140 mg, 0.26 mmol) in toluene (1 mL), cooled to −78 °C. After stirring for 4 h at −78 °C, the solution was hydrolyzed with 1 N HCl. The product was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in pyridine (1 mL), and acetic anhydride (200 μL) was added. The mixture was stirred for 5 h at room temperature. Pyridine was evaporated at reduced pressure and the mixture was co-evaporated with CCl_4. Purification on silica gel (petroleum ether/ethyl acetate, 8:2) produced 140 mg (87%; α/β = 13:87) of **15** (starting from **14**). − IR ($CHCl_3$): $\tilde{\nu}$ = 2109, 1744 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.71−7.64 (m, 8 H, arom.), 7.43−7.24 (m, 12 H, arom.), 7.26−7.23 (m, 10 H, arom.), 6.36 (d, *J* = 4.6 Hz, 1 H, 1-H α), 6.11 (s, 1 H, 1-H β), 5.29 (d, *J* = 4.4 Hz, 1 H, 2-H β), 5.08 (dd, *J* = 4.6, 6.4 Hz, 1 H, 2-H α), 4.47 and 4.29 (AB system, 4 H, CH_2Ph α + β), 4.28 (m, 1 H, 3-H β), 4.25 (m, 1 H, 3-H α), 4.11 (dd, *J* = 4.0, 7.7 Hz, 1 H, 4-H β), 4.09 (m, 1 H, 4-H α), 3.86 (ddd, *J* = 3.7; 7.7, 8.6 Hz, 1 H, 5-H β), 3.73 and 3.65 (AB part of ABX system, *J* = 3.7, 8.6, 10.8 Hz, 2 H, 6-H β), 3.70 (m, 3 H, 6-H α et 5-H α), 2.08 (s, 12 H, CH_3 OAc α + β), 1.07 (s, 18 H, CH_3 TBDPS α + β). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.8 (C=O β), 169.1 (C=O α), 136.6 (Cq arom. α + β), 135.7, 135.6 (CH arom. α + β), 132.9, 132.8 (Cq arom.), 129.9, 128.5, 128.3, 128.1, 127.8, 127.7 (CH arom. α+β), 98.3 (C1 β), 94.0 (C1 α), 82.6 (C4 α), 80.4 (C4 β), 76.7 (C2 β), 75.2 (C2 α), 73.6 (C3 β), 73.4 (CH_2Ph β), 72.8 (CH_2Ph α), 71.3 (C3 α), 65.2 (C5 β), 64.6 (C5 α), 63.6 (C6 α), 63.5 (C6 β), 26.7 (CH_3 TBDPS α + β), 21.0 and 20.7 (CH_3 OAc α + β), 19.1 (Cq TBDPS α + β). − MS (DCI, NH_3); *m*/*z* (%): 635 (100) [MNH_4^+].

(2′*R*,3′*R*,4′*R*,5′*R*)-1-(2′-*O*-Acetyl-5′-azido-3′-*O*-benzyl-6′-*O*-*tert*-butyldiphenylsilyl-5′-deoxy-β-D-allofuranosyl)-5-methyluracil (16): Silylated thymine (70 mg, see compound **6**) and a solution of trimethylsilyl trifluoromethanesulfonate (240 μL, 0.55 M in toluene) were added to a solution of compound **15** (68 mg, 0.11 mmol) in anhydrous acetonitrile (500 μL). The reaction mixture was refluxed for 2 h, diluted with CH_2Cl_2, and hydrolyzed with a saturated, aqueous solution of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification on silica gel (petroleum ether/ethyl acetate, 5:5) afforded 70 mg (93%) of compound **16**. − $[\alpha]_D^{24}$ = −22.2 (*c* = 0.54, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3390, 3073, 2980, 2107, 1745, 1696 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 9.24 (br. s, 1 H, NH), 7.71−7.64 (m, 4 H, arom.), 7.46−7.34 (m, 6 H, arom.), 7.28−7.10 (m, 5 H, arom. + 6-H), 5.97 (d, *J* = 4.6 Hz, 1 H, 1′-H), 5.30 (dd, *J* = 4.6, 5.5 Hz, 1 H, 2′-H), 4.45 and 4.36 (AB system, *J* = 10.7 Hz, 2 H, CH_2Ph), 4.21 (dd, *J* = 5.5, 5.2 Hz, 1 H, 3′-H), 4.03 (dd, *J* = 3.9, 5.2 Hz, 1 H, 4′-H), 3.97 (ddd, *J* = 3.9, 4.2, 8.0 Hz, 1 H, 5′-H), 3.93−3.71 (AB part of ABX system, *J* = 4.2, 8.0, 11.0 Hz, 6′-H), 2.05 (s, 3 H, CH_3 OAc), 1.96 (d, *J* = 0.85 Hz, 3 H, C5−CH_3), 1.07 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.0 (C=O OAc), 163.7 and 150.2 (C2, C4), 136.7 (Cq arom.), 135.6 (CH arom.), 132.6 (Cq arom.), 130.0, 128.5, 128.1 and 127.9 (CH arom.), 111.6 (C5), 88.1 (C1′), 80.8 (C4′), 75.6 (C2′), 73.7 (C3′), 73.4 (CH_2OBn), 64.6 (C5′), 63.9 (C6′), 26.7 (CH_3 TBDPS), 20.7 (CH_3 OAc), 19.1 (Cq TBDPS), 12.7 (C5−CH_3). − MS (DCI, NH_3): 701 (100) [MNH_4^+], 684 (33) [MH^+].

(2′*R*,3′*R*,4′*R*,5′*R*)-1-(5′-Azido-3′-*O*-benzyl-6′-*O*-*tert*-butyldiphenylsilyl-5′-deoxy-β-D-allofuranosyl)-5-methyluracil (17): $LiOH{\cdot}H_2O$ (5 mg, 1 equiv.) was added at 0 °C to a solution of compound **16** (74 mg, 0.109 mmol) in THF/H_2O (600 μL/100 μL). After stirring for 1 h at 0 °C, fresh $LiOH{\cdot}H_2O$ (10 mg, 2 equiv.) was added. The reaction mixture was stirred for 1 h. After careful neutralization with 1 N HCl, the aqueous phase was extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated. Purification on silica gel (petroleum ether/ethyl acetate, 5:5) gave 67 mg (96%) of compound **16**. − IR ($CHCl_3$): $\tilde{\nu}$ = 3391, 3072, 2105, 1696 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 8.55 (br. s, 1 H, NH), 7.65−7.61 (m, 4 H, arom.), 7.40−7.36 (m, 6 H, arom.), 7.36−7.15 (m, 5 H, arom. + 6-H), 5.71 (d, *J* = 5.4 Hz, 1 H, 1′-H), 4.53 (s, 2 H, CH_2Ph), 4.17 (dd, *J* = 5.4, 5.5 Hz, 1 H, 2′-H), 4.02 (t, *J* = 4.0, 4.1 Hz, 1 H, 4′-H), 3.97 (dd, *J* = 4.1, 5.5 Hz, 1 H, 3′-H), 3.81 (ddd, *J* = 4.0, 4.1, 8.1 Hz, 1 H, 5′-H), 3.70 and 3.64 (AB part of ABX system, *J* = 4.1, 8.1, 10.8 Hz, 6′-H), 1.88 (s, 3 H, C5−CH_3), 1.06 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 163.8 and 150.9 (C2, C4), 136.6 (Cq arom.), 135.6 (CH arom. + C5), 132.6 (Cq arom.), 130.0, 128.6, 128.1, 128.0 and 127.9 (CH arom.), 111.4 (Cq thym.), 89.8 (C1′), 80.7 (C4′), 76.4 (C2′), 73.2 (C3′), 72.7 (CH_2OBn), 64.7 (C5′), 63.9 (C6′), 26.7 (CH_3 TBDPS), 19.1 (Cq TBDPS), 12.7 (C5−CH_3). − MS (DCI, NH_3); *m*/*z* (%): 659 (100) [MNH_4^+], 642 (16.7) [MH^+].

(3′*R*,4′*R*,5′*R*)-1-(5′-Azido-3′-*O*-benzyl-6′-*O*-*tert*-butyldiphenylsilyl-5′-deoxyallofuran-2-ulosyl)-5-methyluracil (18): Chromic anhydride (18 mg, 4 equiv.) was added to pyridine (28 μL, 8 equiv.) in CH_2Cl_2 (200 μL). A brown suspension appeared. After 25 min, compound **17** (28 mg, 0.044 mmol) in CH_2Cl_2 (100 μL) was added in one portion, followed by introduction of acetic anhydride (16 μL, 4 equiv.). After stirring for 1 h, the reaction mixture was filtered through a Celite pad with ethyl acetate. The solvents were evaporated, and the pyridine co-evaporated with CCl_4 to give 23 mg (80%) of compound **18**. − ^1H NMR (250 MHz, $CDCl_3$): δ = 9.40 (br. s, 1 H, NH), 7.70−7.64 (m, 4 H, arom.), 7.44−7.26 (m, 11 H, arom.), 6.94 (m, 1 H, 6-H thym.), 5.05 and 4.70 (AB system, *J* = 11.0 Hz, 2 H, CH_2Ph), 4.96 (s, 1 H, 1′-H), 4.55 (d, *J* = 6.9 Hz, 1 H, 6-H), 4.14 (dd, *J* = 6.9, 6.0 Hz, 1 H, 4′-H), 3.87−3.75 (m, 3 H, 5′-H and 6′-H), 1.93 (s, 3 H, C5−CH_3), 1.07 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 205.6 (C=O), 163.6 and 149.7 (C2, C4), 139.2 (CH arom.), 136.6 (Cq arom.), 135.6 (CH arom.), 132.8 (Cq arom.), 130.0, 128.6, 128.1, 128.0 and 127.9 (CH arom. + C6), 111.9 (C5), 85.4 (C1′), 78.5 (C4′), 75.5 (C3′), 73.4 (CH_2OBn), 64.2 (C5′), 63.5 (C6′), 26.7 (CH_3 TBDPS), 19.1 (Cq TBDPS), 12.3 (C5−CH_3).

Reduction of Compound 18 with $NaBH_4$ at 0 °C: $NaBH_4$ (5 mg, 4 equiv.) was added to a solution of compound **18** (20 mg, 0.031 mmol) in MeOH (300 μL) at 0 °C. After stirring for 2 h, the reaction mixture was hydrolyzed, and the aqueous phase was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give 20 mg of compounds **17**/**19** (100%, **17**/**19** = 50:50).

Reduction of Compound 18 with K-Selectride® at −78 °C or −90 °C : A solution of K-Selectride® (2 equiv., 1 M in THF) was added at −78 °C to compound **18** (25 mg, 0.039 mmol) in anhydrous THF (2 mL). The reaction mixture was stirred for 1 h and 1 mL of H_2O was added. The THF was evaporated, and the residue was dissolved in brine and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. Analytical RP HPLC (Hyperprep C18): H_2O/CH_3CN, 25:7. R_t(**17**) = 23.45 min and R_t(**19**) = 28.96 min. Purification on C18 silica gel (H_2O/CH_3CN, 30:70) afforded 9 mg of compound **19** and 6 mg of compound **17** (global yield 60%). − Identical procedure at −90 °C. Starting from 75 mg of compound **18**, 45 mg of compound **19** and 5 mg of compound **17** were obtained (global yield 66%).

(2′*S*,3′*R*,4′*R*,5′*R*)-1-(5′-Azido-3′-*O*-benzyl-6′-*O*-*tert*-butyldiphenylsilyl-5′-deoxyallofuranosyl)-5-methyluracil (19): IR ($CHCl_3$): $\tilde{\nu}$ = 3393, 2106, 1699, 1668 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 10.9 (br. s, 1 H, NH), 7.66−7.64 (m, 4 H, arom.), 7.40−7.34 (m, 6 H, arom.), 7.25−7.21 (m, 6 H, arom. + 6-H), 6.02 (d, *J* = 2.4 Hz, 1 H, 1′-H), 4.75 (s large, 2 H, 2′-H + OH), 4.63 and 4.44 (AB system, *J* = 7.3 Hz, 2 H, CH_2Ph), 4.00 (d, *J* = 3.3 Hz, 1 H, 3′-H), 3.97 (dd, *J* = 3.3, 6.3 Hz, 1 H, 4′-H), 3.85 (dd, *J* = 3.2, 10.4 Hz, 1 H, 6′-H), 3.77 (ddd, *J* = 3.2, 6.3, 6.9 Hz, 5′-H), 3.70 (dd, *J* = 6.9, 10.3 Hz, 1 H, 6′-H), 1.62 (s, 3 H, C5−CH_3), 1.04 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0 and 150.6 (C2, C4), 137.3 (Cq arom.), 135.8, 135.7 (CH arom. + C6), 132.9, 132.8 (Cq arom.), 130.1; 128.6; 128.2; 128.1 and 127.9 (CH arom.), 108.0 (C5), 87.2 (C1′), 84.2 (C4′), 81.2 (C2′), 73.2 (C3′), 71.7 (CH_2OBn), 64.2 (C6′), 64.0 (C5′), 26.8 (CH_3 TBDPS), 19.3 (Cq TBDPS), 12.6 (C5−CH_3). − MS (DCI, NH_3); *m*/*z* (%): 196 (100), 659 (18) [MNH_4^+], 642 (7.8) [MH^+].

(2′*S*,3′*R*,4′*R*,5′*R*)-1-(5′-Azido-3′-*O*-benzyl-5′-deoxyallofuranosyl)-5-methyluracil (20): DAST (7 μL, 2 equiv.) was added to compound **19** (16 mg, 0.025 mmol) in CH_2Cl_2 (500 μL). The reaction mixture was stirred for 12 h and additional 6 equiv. of DAST was added. After dilution with CH_2Cl_2, the reaction mixture was neutralized with a saturated, aqueous solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the organic phase was dried ($MgSO_4$) and concentrated. Purification on silica gel (petroleum ether/ethyl acetate, 5:5) afforded 7 mg (70%) of compound **20**. − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.46 (s, 1 H, 6-H), 7.36−7.26 (m, 5 H, phenyl), 6.06 (d, *J* = 3.3 Hz, 1 H, 1′-H), 4.86 (s large, 1 H, 2′-H), 4.73 and 4.53 (AB system, *J* = 11.7 Hz, 2 H, CH_2Ph), 4.53 (s large, 1 H, OH), 4.13 (d, *J* = 3.3 Hz, 1 H, 3′-H), 4.03 (t, *J* = 4.8 Hz, 1 H, 4′-H), 3.93 (m, 1 H, 5′-H), 3.84−3.67 (m, 2 H, 6′-H), 1.60 (s, 3 H, C5−CH_3),^{13}C NMR (63 MHz, $CDCl_3$): δ = 165.2 and 150.6 (C2, C4), 136.7 (Cq arom.), 128.6; 128.3 (CH arom. + C6), 108.8 (Cq thym.), 86.6 (C1′), 83.3 (C4′), 81.6 (C2′), 73.4 (C3′), 71.9 (CH_2OBn), 63.5 (C5′), 62.1 (C6′), 12.4 (C5−CH_3).

(1′*R*,4*S*,5*R*)-5-(1′-Azido-2′-*tert*-butyldiphenylsilyloxyethyl)-4-benzyloxy-3,4-dihydrofuran-2(5*H*)-one (21): Silver(I) oxide (180 mg, 3 equiv.) and benzyl bromide (92 μL, 3 equiv.) were added to lactone **2a** (110 mg, 0.26 mmol) in ethyl acetate (500 μL). The reaction mixture was stirred for 12 h. The mixture was then filtered through a Celite pad and concentrated. Purification on silica gel (petroleum ether/Et_2O, 7:3) gave 10 mg of starting material and 90 mg (68%) of compound **21**. − $[\alpha]_D^{24}$ = −1.3 (*c* = 0.68, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3070, 2108, 1792 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.69−7.66 (m, 4 H, arom.), 7.83−7.48 (m, 6 H, arom.), 7.31−7.19 (m, 5 H, arom.), 4.52 (dd, *J* = 2.2, 4.6 Hz, 1 H, 5-H), 4.44 (s, 2 H, CH_2Ph), 4.16 (ddd, *J* = 2.2, 2.8, 7.1 Hz, 1 H, 4-H), 3.83−3.67 (m, 3 H, 1′-H and 2′-H), 2.80 and 2.56 (AB part of ABX system, *J* = 2.8, 7.1, 18.3 Hz, 2 H, 3-H), 1.09 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.5 (C=O), 136.7 (Cq arom.), 130.1, 128.6, 128.2, 128.0, 127.7 (CH arom.), 82.8 (C5), 74.4 (C4), 71.3 (CH_2Ph), 64.1 (C1′), 63.4 (C2′), 35.3 (C3), 26.7 (CH_3 TBDPS), 19.1 (Cq TBDPS). − MS (DCI, NH_3); *m*/*z* (%): 533 (100) [MNH_4^+]. − $C_{29}H_{33}N_3O_4Si$ (515.7): calcd. C 67.54, H 6.45, N 8.15; found C 67.48, H 6.35, N 8.25.

(1′*R*,3*S*,4*R*,5*R*)-5-(1′-Azido-2′-*tert*-butyldiphenylsilyloxyethyl)-4-benzyloxy-3-fluoro-3,4-dihydrofuran-2(5*H*)-one (22): A solution of compound **21** (75 mg, 0.14 mmol) and NFSI (46 mg, 1 equiv.) in THF (600 μL) was cooled to −78 °C. A solution of LiHMDS (165 μL, 1.06 M in THF) was slowly added. The reaction mixture was stirred for 5 h. After dilution with Et_2O, a saturated aqueous solution of NH_4Cl (500 μL) was added, and the mixture was stirred for 10 min. After extraction with Et_2O, the organic phase was washed with a saturated, aqueous NH_4Cl solution, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (petroleum ether/Et_2O, 7:3), and 14 mg of starting product and 10 mg of compound **22** were obtained (global yield 16%). − IR ($CHCl_3$): $\tilde{\nu}$ = 2109, 1806 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.68−7.63 (m, 4 H, arom.), 7.63−7.26 (m, 11 H, arom.), 5.25 (dd, *J* = 6.9, 51.3 Hz, 1 H, 3-H), 4.69 (dd, *J* = 1.7, 11.3 Hz, 1 H, CH_2Ph), 4.50 (d, *J* = 11.3 Hz, 1 H, CH_2Ph), 4.43 (td, *J* = 6.9, 17.0 Hz, 1 H, 4-H), 4.33 (dd, *J* = 7.0, 3.8 Hz, 1 H, 5-H), 3.83 (ddd, *J* = 1.0, 3.8, 8.5 Hz, 1 H, 1′-H), 3.77−3.70 (AB part of ABX system, *J* = 1.0, 8.5, 10.0 Hz, 2 H, 2′-H), 1.09 (s, 9 H, CH_3 TBDPS). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 168.0 (d, *J* = 22.8 Hz, C=O), 135.9, 135.7 (CH arom.), 132.6 (Cq arom.), 130.2, 128.8, 128.6, 128.3, 128.1 (CH arom.), 91.6 (d, *J* = 199.0 Hz, C3), 78.1 (d, *J* = 20.2 Hz, C4), 76.7 (d, *J* = 7.5 Hz, C5), 73.2 (CH_2Ph), 63.8 (C1′), 63.3 (C2′), 26.8 (CH_3 TBDPS), 19.2 (Cq TBDPS). − ^{19}F NMR (376 MHz, $CDCl_3$): δ = −119.0 (dd, *J* = 18.0, 50.0 Hz). − MS (DCI, NH_3): 551 (100) [MNH_4^+].

Treatment of Compound 14 with DAST: Lactone **14** (40 mg, 0.075 mmol) in CH_2Cl_2 (300 μL) was added slowly at −78 °C to a solution of DAST (11 μL, 1.1 equiv.) in CH_2Cl_2 (300 μL). The reaction mixture was stirred for 30 min at −78 °C, and then for 3 h at room temperature. Further DAST (0.5 equiv.) was added at −78 °C and stirring at room temperature was maintained for 1 h. The reaction mixture was hydrolyzed at 0 °C with a saturated, aqueous solution of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the organic phase was dried ($MgSO_4$) and concentrated. A purification on silica gel (petroleum ether/Et_2O, 7:3) afforded 20 mg of starting material and 10 mg of compound **22** (global yield 25%).

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[29] Molecular mechanics calculations were run with the Insight II (release 98.0) program using the Discover 3 calculation mode (MSI, San Diego, USA). The extensible systematic force field (ESFF) was used. Energetically optimized conformations were obtained by sampling structures during molecular dynamics simulations. They were run for 10 ps at 400 K using the NVT method, with 1 fs time steps. From energy/time curves, six to seven minima were chosen and minimized. The same iterative operations (dynamic simulations and minimizations) were undertaken on these minima until no energy variation was observed. For each minimization, rms < 0.001.

[30] For a comprehensive review of these concepts, see: W. Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag, New York, **1984**.

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