Synthesis of Modified Polyoxins by Reaction of Uridine-5′-aldehyde with Trimethylsilyl Cyanide and Amino Acids

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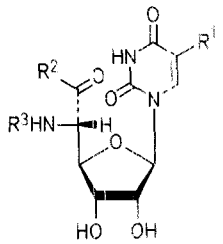
The synthesis of six modified polyoxin derivatives containing an alkylamino group replacing the peptide bond has been accomplished, in a one pot reaction, by condensation of 2′,3′-*O*-isopropylideneuridine-5′-aldehyde with trimethylsilyl cyanide, boron trifluoride etherate and an amino acid, in methanol. The reaction affords stereoselectively the diastereoisomer having at C-5′ the same absolute configuration as the natural polyoxins.

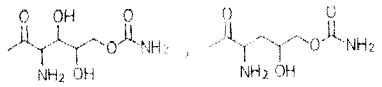
Polyoxins, **1**, neopolyoxins and nikkomycins are a group of peptidyl nucleoside antibiotics produced by species of *Streptomyces*.[1,2] These compounds inhibit chitin synthetase of a variety of phytophathogenic fungi.[3] Polyoxins also inhibit chitin synthetase of *Candida Albicans*, a medically important human pathogen, in cell free systems,[4,5] but they are poorly active against the whole cell.[5] These differences in activity are attributed to transport problems, which make difficult the polyoxin molecule to get into the cell, and to intracellular metabolic cleavage[7] of the peptide bond, which inactivate the molecule. The need to increase the stability of the compounds to cellular peptidases[7,8,9] and the fact that the peptidyl portion of the polyoxin molecule can be significantly altered without losing activity against chitin synthetase,[8] prompted us to substitute the metabolically labile peptide bond between nucleoside and amino acid by a secondary amino group.



1 R^1 = CO_2H, CH_2CH, CH_3, H

R^2 = OH,

R^3 =



2 R^1 = H, R^2 = OH, R^3 = H

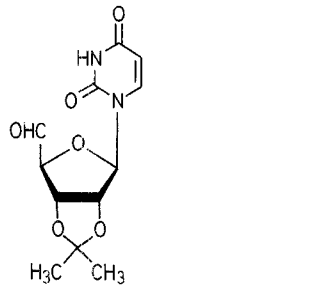
The usual procedure for the synthesis of polyoxin derivatives is the condensation of the nucleoside amino acid **2** with polyoxamic or other amino acids.[1,2,10] Nucleoside **2** has been obtained by isolation and degradation of natural polyoxins,[3,11,12] by reaction of suitably protected hexose derivatives with pyrimidine bases[13,14] and by elaboration from a uridine-5′-carboxaldehyde derivative.[15] The generation of the asymmetric center at C-5′ of **1** by this latter procedure, gives a mixture of **2** (a β-D-allofuranuronic acid derivative) and its diastereoisomer at C-5′, **3** (an α-L-talofuranuronic acid derivative), in similar yields. Other approaches to synthesize polyoxin derivatives from uridine-5′-carboxaldehyde were not stereoselective either.[9] Recently, the synthesis of α-aminonitriles by reaction of aldehydes or ketones with trimethylsilyl cyanide, and an amine or ammonia in methanol has been reported.[16] When a chiral amine was used, the generation of the α-aminonitrile new asymmetric carbon atom was achieved with stereoselectivity.[17]

In light of these reports, it occurred to us that the amino group of suitably protected amino acids could react with trimethylsilyl cyanide and uridine-5′-carboxaldehyde, according to this modified Strecker synthesis, to afford modified polyoxin derivatives bearing a secondary amino group between nucleoside and amino acid. Here we report these attempts and discuss the stereochemistry of the reaction.

In a model experiment 2′,3′-*O*-isopropylideneuridine-5′-aldehyde[18] **(4)**, was treated with trimethylsilyl cyanide, boron trifluoride etherate and benzylamine **(5)** in refluxing methanol to afford a mixture of the two possible 5′-diastereoisomers (*R*)-**11** and (*S*)-**11** in 52 and 26% yield respectively. The ^{1}H-NMR spectrum of the mixture of diastereoisomers **11** showed two doublets at δ = 3.87 and 4.15, the integrals of which were in the ratio (2:1), which were assigned to H-5′ of (*R*)-**11** and (*S*)-**11**, respectively.

Then, **4** reacted under the same experimental conditions with trimethylsilyl cyanide and suitably protected neutral or basic amino acids namely sodium glycinate **(6)**, methyl L-leucinate **(7)**, methyl *N*-ε-benzyloxycarbonyl-L-lysinate **(8)**, methyl *N*-α-benzyloxycarbonyl-L-lysinate **(9)**, and methyl *N*-δ-benzyloxycarbonyl-L-ornithinate **(10)**, to afford diastereoisomeric mixtures of the corresponding 1-[5′-alkylamino-5′-deoxy-β-D-allo

and α-L-talo-furanurononitrile]uracil derivatives of glycine [(*R*)-**12** and (*S*)-**12**)], leucine [(*R*)-**13** and (*S*)-**13**)], α-lysine [(*R*)-**14** and (*S*)-**14**)], ε-lysine [(*R*)-**15** and (*S*)-**15**)] and α-ornithine [(*R*)-**16** and (*S*)-**16**)]. In all cases, the β-D-allo diastereoisomer, having an *R* absolute configuration at C-5′, was the major compound. Compounds **14, 15** and **16** have a carbamate group at a distance of 7, 7, and 6 bonds respectively from C-5′, as compared to the carbamate group of polyoxins which is at 7 bonds. These carbamate groups, which are important for the antifungal activity of polyoxin derivatives, are thought to interact with the same area of chitin synthetase that the glucosamine 2-acetamido group of UDP-glucosamine.[16]



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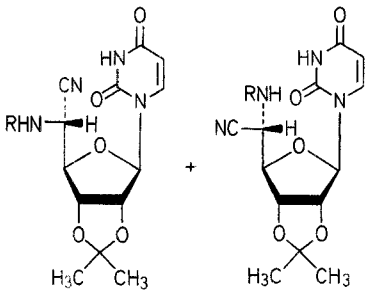
40 - 77 % $Me_3SiCN/Et_2O \cdot BF_3$, amino acid / MeOH, reflux, 2h

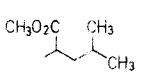
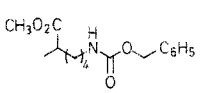
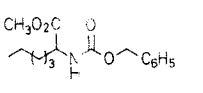
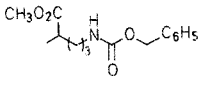


(*R*)-**11**–(*R*)-**16** (*S*)-**11**–(*S*)-**16**

The ^{1}H-NMR spectra of compounds **11**–**16** showed two sets of signals of different intensity which indicated the preferential formation of one of the two possible diastereoisomers and, thus the stereoselectivity in the formation of the new asymmetric center at C-5′. The two compounds of each pair of diastereoisomers showed in all cases identical chromatographic mobility in different solvent systems and could not be separated. However, their absolute configurations were assigned by ^{1}H-NMR spectroscopy as indicated in the following discussion referred to leucine derivatives (*R*)-**13** and (*S*)-**13**.

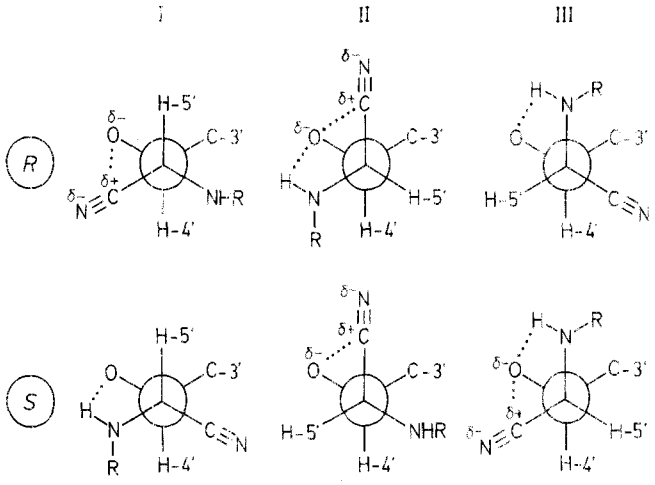
The $J_{4',5'}$ coupling constants observed for the major diastereoisomer (*R*)-**13** are 5.1 Hz ($CDCl_3$) and 7.7 Hz (DMSO-d_6). For the minor compound (*S*)-**13** the $J_{4',5'}$ values are 7.7 Hz ($CDCl_3$) and 11.1 Hz (DMSO-d_6). Since H-4′ is in a relatively rigid cycle of furan, the observed differences between the $J_{4',5'}$ values indicate a preference of the minor diastereoisomer for the rotamer around the C-4′–C-5′ in which both protons are in an *anti* disposition. In DMSO-d_6, the $J_{4',5'}$ of both diastereoisomers increases and, thus, the preference for the rotamer in which H-4′ and H-5′ are in an *anti* relationship. This preference is almost exclusive in the minor compounds (*S*)-**13** ($J_{4',5'}$ = 11.1 Hz). The increase of $J_{4',5'}$ observed in dimethyl sulfoxide indicates that in chloroform solution there are polar and/or hydrogen bond effects, which stabilize those rotamers in which H-4′ and H-5′ are *gauche*. These effects, shown in Fig. 1, disappear in DMSO-d_6. Fig 2 shows the three main rotamers around C-4′–C-5′ for (*R*)-**13** and (*S*)-**13**. Rotamers *R*-III and *S*-III are most strained from the steric point of view since RHN-, the bulkiest of groups attached to C-5′, is *gauche* to C-3′ and O-5′, the bulkiest groups attached to C-4′. Thus, their contribution to the rotational equilibrium should be low. Taking into acoount the "A" values for conformational equilibria[19] for CN(0.17) and $NHCH_3$ (1.0 Kcal/mol), the fact that C-3′ is more crowded than the ribofuranose ring oxygen, and the observed $J_{4',5'}$ values, it can be deduced that the I rotamers are preferred over the II, and that the approximate order of energy content of these four rotamers should be *S*-I < *R*-I < *R*-II < *S*-II. According to this, the minor diastereoisomer, which shows the highest $J_{4',5'}$ coupling constant and, thus, the highest preference for the rotamer in which H-4′ and H-5′ are *anti*, should have an *S* absolute configuration. Similarly, the major compound having a smaller value of $J_{4',5'}$, which indicates that none of the rotamers is clearly preferred, should have an *R* configuration at C-5′. The lower values of $J_{4',5'}$ observed in deuterochloroform are explained by the electrostatic

Table. Polyoxin Derivatives **11**–**16** Prepared

Product	R	Yield (%)	*R* : *S* Ratio	Molecular Formula[a]	MS (70 eV) *m/e* (%)
11	$CH_2C_6H_5$	77	2 : 1	$C_{20}H_{22}N_4O_5$ (398.4)	–
12	CH_2CO_2Na	48	6 : 5	$C_{15}H_{17}N_4NaO_7$ (388.3)	323 (2); 294 (2); 256 (5); 253 (2)
13		70	4 : 1	$C_{20}H_{28}N_4O_7$ (436.5)	436 (M^+, 3); 421 (10); 409 (2); 377 (78); 319 (90)
14		60	2 : 1	$C_{28}H_{35}N_5O_9$ (585.6)	499 (4); 364 (2); 319 (4); 253 (5)
15		50	5 : 2	$C_{28}H_{35}N_5O_9$ (585.6)	450 (2); 423 (2); 319 (7); 253 (3)
16		40	2 : 1	$C_{27}H_{33}N_5O_9$ (571.6)	485 (10); 377 (4); 319 (5); 253 (3)

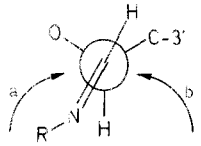
[a] Satisfactory microanalysis obtained: C ±0.27, H ±0.29, N ±0.36 (Exception: **14**; C −0.43).

and hydrogen bond stabilization of rotamers II and III, which in this solvent have a greater contribution to the rotational equilibrium than in dimethyl sulfoxide.



Based on the above discussion and the similarities of magnetic parameters among all the major [δ = 4.23–4.27 (H-4'); 3.87–3.97 (H-5'); $J_{4',5'}$ = 4.4–5.3 Hz] and among all the minor diastereoisomers [δ = 4.16–4.21 (H-4'); 3.94–4.15 (H-5'); $J_{4',5'}$ = 7.3–7.9 Hz] of compounds **11, 13, 14, 15** and **16**, they were assigned the *R* and *S* absolute configurations at C-5', respectively.

The proposed mechanism[16,17] for this reaction, i.e., addition of CNH to the corresponding Schiff base, also predicts the same distribution of diastereoisomers. Thus, addition of CNH to the more stable rotamer of the imine **17**,[20] from the less hindered "a" face, also affords the diastereoisomer with *R* absolute configuration at C-5'.



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In conclusion, the present method provides a stereoselective, one step synthesis of modified polyoxin derivatives with the same absolute stereochemistry than the natural polyoxins.[21]

All reagents were of commercial quality from freshly opened containers. Me_3SiCN and uridine were purchased from Fluka AG. Amino acids were purchased from Bachem. Reagent quality solvents were used without further purification. Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. Microanalyses were obtained using a Perkin-Elmer 240-C element analyser.

^{1}H-NMR spectra were recorded on a Varian XL-300 spectrometer using TMS as internal standard. Mass spectra were recorded on a Hewlett Packard 5985 spectrometer. Analytical TLC plates were purchased from Merck. Preparative TLC was performed on glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck). Compounds were detected by UV light (254 nm) or by spraying the plates with 30% H_2SO_4 in ethanol and heating.

1-[5'-Alkylamino-5'-deoxy-β-D-allo(α-L-talo)furanurononitrile]uracil Derivatives; General Procedure:

A mixture of 2',3'-*O*-isopropylideneuridine-5'-aldehyde (**4**; 1 g, 3.55 mmol), Me_3SiCN (0.44 mL, 3.55 mmol) and boron trifluoride etherate (2 drops), are stirred for 5 min at room temperature. Then, a solution of benzylamine or the corresponding amino acid (3.55 mmol) in methanol (30 mL) is added and the resulting mixture is heated to reflux for 2 h. The solvent is evaporated under reduced pressure and the residue is purified by preparative TLC as indicated below for each case.

1-[5'-Benzylamino-5'-deoxy-2',3'-*O*-isopropylidene-β-D-allo(α-L-talo)-furanurononitrile]uracil [(*R*)- and (*S*)-11]:

Compound **4** is reacted with Me_3SiCN, boron trifluoride and benzylamine (0.38 g, 3.55 mmol) and worked up as indicated in the general procedure. The resulting oily residue is chromatographed with chloroform/acetone (2:1) as the eluent and the main UV absorbing band is extracted with ethyl acetate/methanol (1:1). The organic extracts are evaporated to dryness to give a foam, chromatographically homogeneous in several solvent systems; yield 1.09 g (77%).

^{1}H-NMR ($CDCl_3$, 300 MHz): (*R*)-**11** + (*S*)-**11**: δ = 1.35, 1.56 [2s, 6H, $(CH_3)_2C$].

(*R*)-**11**: δ = 3.90 (AB system, 2H, J_{gem} = 13.0 Hz, $CH_2C_6H_5$); 3.87 (d, 1H, $J_{4',5'}$ = 5.3 Hz, H-5'); 4.27 (dd, 1H, $J_{3',4'}$ = 3.1 Hz, H-4'); 5.59 (d, 1H, $J_{1',2'}$ = 1.6 Hz, H-1'); 5.74 (d, 1H, $J_{5,6}$ = 8.0 Hz, H-5); 7.22 (d, 1H, H-6).

(*S*)-**11**: δ = 4.11 (AB system, 2H, J_{gem} = 13.2 Hz, $CH_2C_6H_5$); 4.15 (d, 1H, $J_{4',5'}$ = 7.3 Hz, H-5'); 4.21 (dd, 1H, $J_{3',4'}$ = 3.9 Hz, H-4'); 4.92 (dd, 1H, $J_{2',3'}$ = 6.6 Hz, H-3'); 5.00 (dd, 1H, $J_{1',2'}$ = 2.3 Hz, H-2'); 5.70 (d, 1H, H-1'); 5.78 (d, 1H, $J_{5,6}$ = 8.2 Hz, H-5); 7.18 (d, 1H, H-6).

1-[5'-(Carboxymethylamino)-5'-deoxy-2',3'-*O*-isopropylidene-β-D-allo(α-L-talo)furanurononitrile]uracil Sodium Salt [(*R*)- and (*S*)-12]:

Aldehyde **4** is reacted with Me_3SiCN, $Et_2O \cdot BF_3$, and sodium glycinate (0.34 g, 3.55 mmol) as indicated in the general procedure. The residue is chromatographed with $CHCl_3$/MeOH (5:1) as the eluent and the main UV absorbing band is extracted with MeOH. The organic extracts are evaporated under reduced pressure; yield 0.66 g (48%); m.p. 160°C (dec.) (EtOAc/MeOH).

^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.30, 1.49 [2s, 6H, $(CH_3)_2C$]; 3.06 (m, 2H, CH_2); 4.11 (m, 1H, H-5'); 4.20 (m, 1H, H-4'); 4.94–5.07 (m, 2H, H-2', H-3'); 5.80, 5.88 (2d, 1H, $J_{1',2'}$ = 1.8 Hz, H-1'); 5.67, 5.69 (2d, 1H, $J_{5,6}$ = 8.0 Hz, H-5); 7.72, 7.79 (2d, 1H, H-6).

1-{5'-Deoxy-5'-[1''-(*S*)-methoxycarbonyl-3''-methyl-*n*-butylamino]-2',3'-*O*-isopropylidene-β-D-allo(α-L-talo)-furanurononitrile}uracil [(*R*)- and (*S*)-13]:

Uridine derivative **4** is reacted with Me_3SiCN, $Et_2O \cdot BF_3$, and methyl L-leucinate (0.51 g, 3.55 mmol) and worked up as before. The resulting syrup is purified by preparative TLC using $CHCl_3$/acetone (2:1) as the eluent and the main UV absorbing band is extracted with EtOAc/MeOH (1:1). The organic extracts are concentrated to dryness under reduced pressure to give a foam, chromatographically homogeneous in several solvent systems; yield: 1.08 g (70%).

^{1}H-NMR ($CDCl_3$, 300 MHz): (*R*)-**13** + (*S*)-**13**: δ = 0.92 [m, 6H, $CH(CH_3)_2$], 1.37, 1.58 [2s, 6H, $(CH_3)_2C$]; 1.73 [m, 1H, $CH(CH_3)_2$]; 7.28 (d, 1H, $J_{5,6}$ = 8.0 Hz, H-6).

(*R*)-**13**: δ = 3.39 (t, 1H, J = 7.0 Hz, H-1''); 3.77 (s, 3H, CO_2CH_3); 3.96 (d, 1H, $J_{4',5'}$ = 5.1 Hz, H-5'); 4.24 (dd, 1H, $J_{3',4'}$ = 3.6 Hz, H-4'); 5.69 (d, 1H, $J_{1',2'}$ = 1.6 Hz, H-1'); 5.78 (d, 1H, H-5).

(*S*)-**13**: δ = 3.57 (dd, 1H, J = 5.5, 8.3 Hz, H-1''); 3.76 (s, 3H, CO_2CH_3); 4.11 (d, 1H, $J_{4',5'}$ = 7.7 Hz, H-5'); 4.20 (dd, 1H, $J_{3',4'}$ = 2.9 Hz, H-4'); 5.59 (d, 1H, $J_{1',2'}$ = 1.4 Hz, H-1'); 5.77 (d, 1H, H-5).

^{1}H-NMR (DMSO-d_6, 300 MHz): (*R*)-**13** + (*S*)-**13**: δ = 0.86 [m, 6H, $CH(CH_3)_2$]; 1.30, 1.50 (2s, 6H, $(CH_3)_2C$); 1.68 [m, 1H, $CH(CH_3)_2$].

(*R*)-**13**: δ = 3.31 (t, 1H, J = 7.6 Hz, H-1''); 3.63 (s, 3H, CO_2CH_3); 4.13 (d, 1H, $J_{4',5'}$ = 7.7 Hz, H-5'); 4.18 (dd, 1H, $J_{3',4'}$ = 3.0 Hz, H-4'); 4.89 (dd, 1H, $J_{2',3'}$ = 6.4 Hz, H-3'); 5.08 (dd, 1H, $J_{1',2'}$ = 2.8 Hz, H-2'); 5.65 (d, 1H, $J_{5,6}$ = 7.9 Hz, H-5); 5.80 (d, 1H, H-1'); 7.73 (d, 1H, H-6).

(*S*)-**13**: δ = 3.42 (t, 1H, J = 8.0 Hz, H-1''); 3.67 (s, 3H, CO_2CH_3); 4.00 (d, 1H, $J_{4',5'}$ = 11.1 Hz, H-5'); 4.13 (m, 1H, H-4'), 4.86 (dd, 1H, $J_{3',4'}$ = 3 Hz, $J_{2',3'}$ = 6.3 Hz, H-3'); 5.14 (dd, 1H, $J_{1',2'}$ = 2.0 Hz, H-2'); 5.66 (d, 1H, $J_{5,6}$ = 8.5 Hz, H-5); 5.76 (d, 1H, H-1'); 7.84 (d, 1H, H-6).

1-{5'-[5''-(Benzyloxycarbonylamino)-1''-(*S*)-(methoxycarbonyl)-pentylamino]5'-deoxy-2',3'-*O*-isopropylidene-β-D-allo(α-L-talo)-furanurononitrile}uracil [(*R*)- and (*S*)-14]:

Compound **4** is reacted with Me_3SiCN, $Et_2O \cdot BF_3$, and methyl *N*-ε-benzyloxycarbonyl-L-lysinate (1.04 g, 3.55 mmol) and worked up as before. The residue is purified by preparative TLC (eluent: $CHCl_3$/acetone, 2:1) and extracted as indicated before for (*R*)- and (*S*)-**13** to give a chromatographically homogeneous foam; yield: 1.25 g (60%).

^{1}H-NMR ($CDCl_3$, 300 MHz): (*R*)-**14** + (*S*)-**14**: δ = 1.36, 1.50 [2s, 6H, $(CH_3)_2C$]; 3.20 (m, 2H, H-5''); 5.75 (d, 1H, $J_{5,6}$ = 8.0 Hz, H-5); 7.19 (d, 1H, H-6).

(*R*)-**14**: δ = 3.41 (t, 1 H, J = 7.0 Hz, H-1″); 3.75 (s, 3 H, CO_2CH_3); 3.97 (d, 1 H, $J_{4',5'}$ = 4.5 Hz, H-5′); 4.23 (t, 1 H, H-4′), 5.50 (d, 1 H, $J_{1',2'}$ = 1.8 Hz, H-1′).
(*S*)-**14**: δ = 3.55 (t, 1 H, J = 7.0 Hz, H-1″); 3.74 (s, 3 H, CO_2CH_3); 4.12 (d, 1 H, $J_{4',5'}$ = 7.5 Hz, H-5′); 4.17 (m, 1 H, H-4′); 5.47 (d, 1 H, $J_{1',2'}$ = 2.0 Hz, H-1′).

1-{5′-[5″-(*S*)-(Benzyloxycarbonylamino)-5″-(methoxycarbonyl)-pentylamino]5′-deoxy-2′,3′-*O*-isopropylidene-β-D-allo(α-L-talo)-furanurononitrile}uracil [(*R*)- and (*S*)-15]:
Aldehyde **4** is reacted with Me_3SiCN, $Et_2O \cdot BF_3$, and methyl *N*-α-benzyloxycarbonyl-L-lysinate (1.04 g, 3.55 mmol) and worked up as indicated in the general procedure. The residue is chromatographed (TLC, eluent: $CHCl_3$/acetone, 2 : 1) and extrated by the same procedure indicated before for (*R*)- and (*S*)-**13** to give a chromatographically homogeneous foam; yield: 1.04 g (50%).

^{1}H-NMR ($CDCl_3$, 300 MHz): (*R*)-**15** + (*S*)-**15**: δ = 1.36, 1.57 [2s, 6 H, $(CH_3)_2C$], 2.77 (m, 2 H, H-1″); 4.39 (m, 1 H, H-5″).
(*R*)-**15**: δ = 3.74 (s, 3 H, CO_2CH_3); 3.90 (d, 1 H, $J_{4',5'}$ = 4.4 Hz, H-5′); 4.27 (t, 1 H, J = 6000 Hz, H-4′), 5.57 (d, 1 H, $J_{1',2'}$ = 1.6 Hz, H-1′); 5.72 (d, 1 H, $J_{5,6}$ = 8.0 Hz, H-5); 7.24 (d, 1 H, H-6).
(*S*)-**15** = 3.75 (s, 3 H, CO_2CH_3); 3.94 (d, 1 H, $J_{4',5'}$ = 7.9 Hz, H-5′); 4.19 (dd, 1 H, $J_{3',4'}$ = 3.5 Hz, H-4′); 5.44 (d, 1 H, $J_{1',2'}$ = 1.4 Hz, H-1′); 5.76 (d, 1 H, $J_{5,6}$ = 8.2 Hz, H-5); 7.16 (d, 1 H, H-6).

1-{5′-[4″-(Benzyloxycarbonylamino)-1″-(*S*)-(methoxycarbonyl)-*n*-butylamino]5′-deoxy-2′,3′-*O*-isopropylidene-β-D-allo(α-L-talo)furanurononitrile}uracil [(*R*)- and (*S*)-16]:
Uridine derivative **4** is reacted with Me_3SiCN, $Et_2O \cdot BF_3$, and methyl *N*-δ-benzyloxycarbonyl-L-ornithinate (0.99 g, 3.55 mmol) and worked up as indicated before. The residue is purified by preparative TLC using $CHCl_3$/acetone (3 : 1) as the eluent, and the main band is extracted with EtOAc/MeOH (1 : 1). The organic extracts are concentrated to dryness under reduced pressure to give a foam, chromatographically homogeneous in several solvent systems; yield: 0.81 g (40%).

^{1}H-NMR ($CDCl_3$, 300 MHz); (*R*)-**16** + (*S*)-**16**: δ = 1.37, 1.56 [2s, 6 H, $(CH_3)_2C$]; 3.25 (m, 2 H, H-4″); 3.76 (s, 3 H, CO_2CH_3).
(*R*)-**16**: δ = 3.43 (m, 1 H, H-1″); 3.92 (d, 1 H, $J_{4',5'}$ = 5 Hz, H-5′); 4.26 (m, 1 H, H-4′); 5.49 (d, 1 H, $J_{1',2'}$ = 1.3 Hz, H-1′); 5.76 (d, 1 H, $J_{5,6}$ = 8.0 Hz, H-5); 7.19 (d, 1 H, H-6);
(*S*)-**16**: δ = 3.50 (m, 1 H, H-1″); 4.14 (d, 1 H, $J_{4',5'}$ = 7.7 Hz, H-5′); 4.16 (m, 1 H, H-4′); 5.45 (d, 1 H, $J_{1',2'}$ = 1.4 Hz, H-1′); 5.78 (d, 1 H, $J_{5,6}$ = 7.9 Hz, H-5); 7.16 (d, 1 H, H-6).

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(21) Although the configuration at C-5′ of natural polyoxins is *S* and that of the modified polyoxins of this paper is *R*, the absolute configurations of both C-5′ carbon atoms is the same. Both carbohydrate moieties are 5′-amino-5′-deoxy-β-D-allofuranuronic acid derivatives. The discrepancy is due to the different order of preference of the CO_2H and CN groups with respect to the C_4-O group in the Cahn-Ingold-Prelog system for determination of absolute configurations.