(Phenylthio)nitromethane in the Total Synthesis of Polyoxin C

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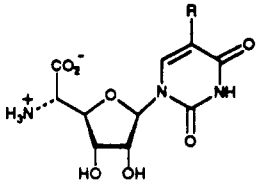
The stereospecific total synthesis of polyoxin C and the nucleoside analogue, uracil polyoxin C, is described. Condensation of (phenylthio)nitromethane with methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside **5** gave the (*Z*)-nitro olefin **6**. Addition of potassium trimethylsilanoate and ozonolysis gave the α-hydroxy thioester **7**, which was formed with excellent diastereoselectivity. The alcohol **7** was converted into polyoxin C (**1**) and uracil polyoxin C (**2**) via the azide **11** and base incorporation using the Vorbrüggen method.

Polyoxin C (**1**) is a pyrimidine nucleoside antibiotic isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis*.[1] Since the sugar component of amino acid **1** is common to all of the members of the polyoxins[1-3] as well as the nikkomycins (neopolyoxins),[4] polyoxin C (**1**) was important in the the structure determination of many nucleoside antifungal agents. Despite their significance, few chemical syntheses of amino acid nucleosides (e.g. **1-3**) have been reported.[5-9] Uracil polyoxin C (**2**) has been



1 R = CH_2OH
2 R = H
3 R = Me

synthesized by Moffatt and co-workers[5] from uridine via cyanohydrin formation at the C-5′ aldehyde. Moffatt et al.[6] have also described a general synthetic approach for the synthesis of a variety of purine and pyrimidine amino acid nucleosides. Both syntheses, however, suffer from the lack of diastereoisomeric control in formation of the α-amino acid center. In addition to the syntheses, a fully protected sugar derivative of **2** has been prepared in several steps from D-glucose.[7] Thymine polyoxin C (**3**) has been prepared[8] from higher order carbohydrates and has been utilized in the total synthesis of polyoxin J.[8b,c] Recently, a new strategy for the synthesis of glycosyl α-amino acids from D-serinal derivatives has been illustrated in the total synthesis of thymine polyoxin C (**3**).[9] We report the stereospecific synthesis of polyoxin C (**1**) based on nitro olefin methodology developed in this laboratory.[10] By utilizing (phenylthio)nitromethane[11] for the stereospecific 1-carbon homologation of the readily available aldehyde **5**,[12] the amino acid nucleoside **1**, as well as base analogues (e.g. **2**), were prepared via the key triacetate intermediate **11**.

D-Ribose was converted into methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[13] (**4**) (50%) (Scheme I). Subsequent Collins oxidation[12] afforded the corresponding aldehyde **5** (70%) which was allowed to react with (phenylthio)nitromethane[11] (1:1 *t*-BuOH/THF, 0.1 equiv of *t*-BuOK, 0-25 °C). Dehydration of the resultant crude β-nitro alcohols (MsCl, *i*-Pr_2EtN, -78 °C to -30 °C, 30 min) gave the crystalline nitro olefin **6** (93%). The addition of potassium trimethylsilanoate[14] (DMF, 0 °C, 30 min) to nitro alkene **6** yielded the corresponding nitronate, which was diluted with MeOH and ozonolyzed in situ (O_3, -78 °C). Hydrolytic workup (5% methanolic citric acid)[15] and purification by flash chromatography *afforded a single diastereoisomeric α-hydroxy thioester* **7** (94%).

This diastereofacial selectivity merits special note. In nucleophilic additions to aldehydes of dialdose derivatives including **5**, modest to good diastereoselectivity has been achieved only in the cases where Lewis acid catalysis[16] or chelation control[16a,c] has been employed. However, in osmylation reactions of alkenyl furanosides[16a] and pyranosides,[16a,17] high diastereofacial selectivity (8:1 → 20:1) has been observed. Modest to excellent selectivity (2:1-11:1) has also been reported in the addition of phosphorus compounds to simple xylofuranose (*Z*)-nitro olefins.[18] For the cis nitro olefin **6**, the eclipsed conformation **12** is strongly favored due to the avoidance of 1,3-allylic strain.[19] However, partial rotation (≈30°) about

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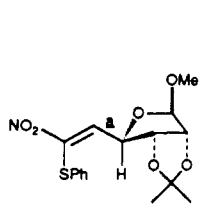
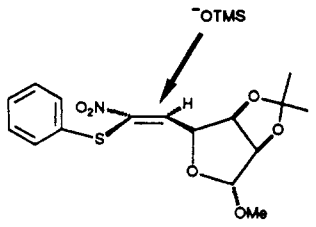


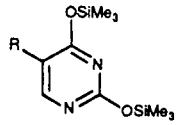
12



12a

bond a in **12** allows the system to adopt the conformation **12a** in which the stereoelectronic demands for antiperiplanar attack of the nucleophile can be met.[19,20] Not surprising, nucleophilic addition of potassium trimethylsilanoate to nitro olefin **6** seems to occur as conformation **12a** predicts, resulting in the observed 5(*S*)-α-hydroxy thioester **7** in high diastereoisomeric excess (≫15:1).[21] The stereochemistry of the alcohol **7** was unequivocally established by conversion to D-allose. Hydrolysis[22] of **7** gave the corresponding methyl ester, which was reduced using sodium borohydride[23] to afford the allofuranoside. Subsequent treatment in aqueous dioxane with Dowex 50W H^+ resin[24] gave the unprotected pyranose, which was identical by ^1H and ^{13}C NMR (400 and 101 MHz, respectively) with authentic D-allose[25a] and distinctively different from authentic D-talose.[25]

The α-hydroxy thioester **7** was converted to the triflate (Tf_2O, pyridine, CH_2Cl_2, 0 °C),[26] and subsequent mild hydrolysis of the thioester ($Hg(OAc)_2$, MeOH, 25 °C, 2 h)[22] gave the methyl ester **8** (83% overall). The amine functionality was introduced by displacement of the triflate **8** with NaI (DMF, 25 °C, 5 min) followed by NaN_3 (60 °C, 20 min) to yield the azide **9** (92%). Deisopropylidination (Dowex 50W H^+, MeOH, 65 °C)[24] afforded the diol, which was acetylated directly (Ac_2O, pyridine, 25 °C)[27] to yield the diacetate **10** (83%). Anomeric acetolysis[28] smoothly gave the triacetate **11** (90%) in which no C-5 epimerization could be detected. Reaction of the triacetate **11** with tris-*O*-(trimethylsilyl)-5-(hydroxymethyl)uracil[29] (**15**, Scheme II) under the conditions reported by Vorbrüggen (TMSOTf, CH_3CN, 25 °C)[30] gave exclusively the β-nucleoside **13** (66%). The azide **13** was reduced using Ph_3P in aqueous THF,[31] and the esters were saponified ($Ba(OH)_2$, aqueous dioxane, 25 °C, 3 h).[6] Ion exchange chromatography (Dowex 50W H^+) of the residue afforded the amino acid nucleoside polyoxin C (**1**) (51%). The product was identical with authentic material (mp, TLC, $[\alpha]_D$, IR, 400-MHz ^1H NMR).[1] Likewise, reaction of the key triacetate **11** with bis-*O*-(trimethylsilyl)uracil[29] (**16**) under similar conditions[30] gave exclusively the β-nucleoside **14** (79%). Hydrogenation in the presence of palladium on $BaSO_4$ in acidic methanol and subsequent hydrolysis[6] afforded uracil polyoxin C (**2**) (74%) which was identical with authentic material (mp, TLC, $[\alpha]_D$, 400-MHz ^1H NMR).[1b,4b,5]



15 R = Me_3SiOCH_2
16 R = H

The synthesis described herein demonstrates the utility of (phenylthio)nitromethane for the stereospecific 1-carbon homologation of the C-5 aldehyde **5** to the corresponding α-amino acids **1** and **2**. The method is superior to Strecker-type strategies which suffer from the lack of stereocontrol. By utilizing this methodology, both natural and synthetic polyoxin analogues can be prepared.

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of dry N_2 at room temperature in oven-dried glassware unless otherwise noted. Reaction temperatures were recorded as bath temperatures. Melting points were determined on a Riechert hot stage or Mel-Temp apparatus and appear uncorrected. Infrared spectra were recorded on a Perkin Elmer 283 grating spectrometer or a Mattson Alpha Centauri (FTIR) spectrometer. Optical rotations were recorded on an Optical Activity AA-100 polarimeter using either a 0.5- or a 0.1-dm cell. ^1H NMR spectra were recorded on either a Varian XL400 (400 MHz) or VXR300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on either a Varian XL400 (101 MHz) or a VXR300 (75 MHz) spectrometer. ^1H NMR spectra recorded in $CDCl_3$ used Me_4Si as an internal reference; ^{13}C NMR spectra recorded in this solvent used the solvent peak at δ 77.0 as an internal reference. ^1H NMR recorded in D_2O used the HOD peak at δ 4.63 or the CD_3OD peak at δ 3.30 as an internal reference. Mass spectra were recorded on a VG70-250SE mass spectrometer by the Analytical Servics Laboratory, Northwestern University. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN, or G. D. Searle and Co., Skokie, IL. Column chromatography was performed on E. Merck silica gel 60, 230–400 mesh ASTM. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel 60 F_{254} plates.

Solvents for chromatography were distilled at atmospheric pressure prior to use. Hexanes refer to the ACS reagent boiling range 35–60 °C. Anhydrous THF was distilled from Na/benzophenone ketyl. Anhydrous CH_2Cl_2 and CH_3CN were distilled from CaH_2. DMF was dried by distillation at reduced pressure from BaO and stored over 4-Å molecular sieves. *i*-Pr_2EtN and pyridine were dried by distillation from CaH_2 and stored over KOH. MeOH was dried by distillation from Mg and stored over 3-Å sieves. *t*-BuOH was dried by distillation from Na ribbon and stored over 4-Å sieves. All other chemicals were used without further purification unless otherwise noted. All solvents used to extract aqueous solutions were dried with either $MgSO_4$ or Na_2SO_4 and evaporated in vacuo on a rotary evaporator at or below 40 °C. Reported yields refer to chromatographically and spectroscopically homogeneous material.

Methyl 2,3-*O*-Isopropylidene-β-D-ribofuranoside (4). To D-ribose (50.0 g) in acetone (190 mL) and MeOH (190 mL) was added concentrated HCl (5 mL), and the solution was allowed to reflux for 18 h. The reaction was cooled, neutralized with pyridine, poured into H_2O (500 mL), and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (100 mL), dried ($MgSO_4$), and evaporated. The residue was distilled to afford the known[32] methyl ribofuranoside **4** (34 g, 50%) as a colorless oil: bp 110 °C (10 mm Hg); ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (s, 1 H), 4.74 (d, 1 H, *J*

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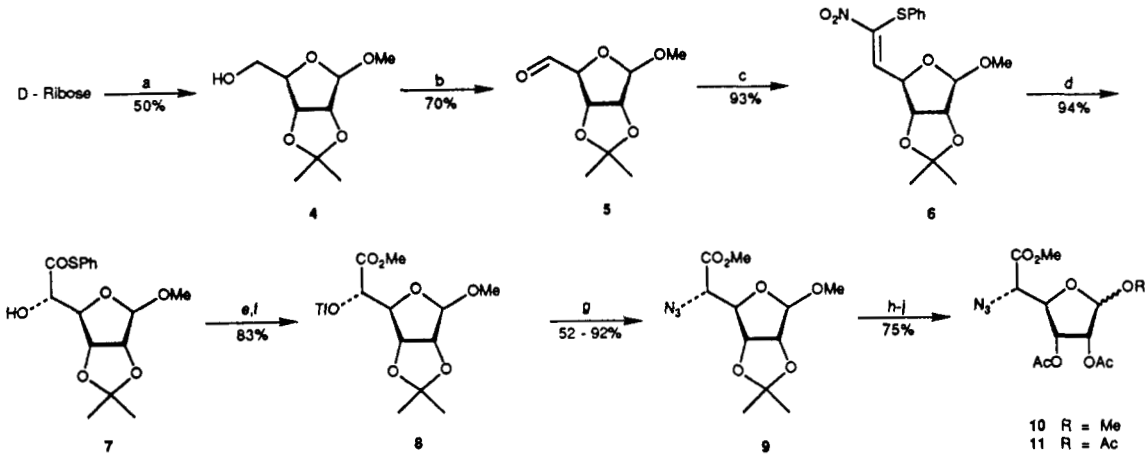
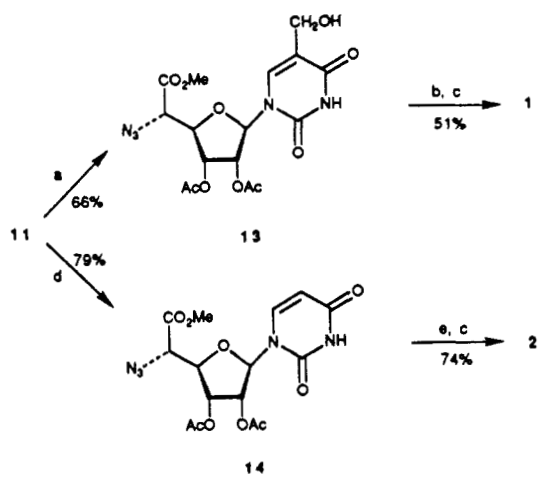
Scheme I[a]



[a] Reagents: (a) MeOH, acetone, HCl, reflux; (b) CrO_3, pyridine, CH_2Cl_2, 25 °C; (c) $PhSCH_2NO_2$, 1:1 *t*-BuOH–THF, 0.1 equiv of *t*-BuOK, 0 °C to 25 °C; MsCl, *i*-Pr_2EtN, −78 °C to −30 °C, 30 min; (d) KOTMS, DMF, 0 °C, 30 min; MeOH, O_3, −78 °C; 5% methanolic citric acid; (e) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (f) $Hg(OAc)_2$, MeOH, 25 °C; (g) NaI, DMF, 25 °C, 5 min; NaN_3, 60 °C, 20 min; (h) Dowex 50W H^+, MeOH, 65 °C; (i) Ac_2O, pyridine; (i) AcOH, CH_2Cl_2, Ac_2O, cat. H_2SO_4.

Scheme II[a]



[a] Reagents: (a) TMSOTf, CH_3CN, **15**, 25 °C; (b) Ph_3P, THF, 1.5 equiv of H_2O, 25 °C, 12 h; (c) $Ba(OH)_2$, dioxane, 25 °C, 3 h; (d) TMSOTf, CH_3CN, **16**, 25 °C; (e) 10% Pd on $BaSO_4$ (prehydrogenated for 30 min), MeOH, H^+, H_2, 25 °C, 30 min.

= 6 Hz), 4.50 (d, 1 H, *J* = 6 Hz), 4.33 (m, 1 H), 3.58 (m, 2 H), 3.35 (s, 3 H), 3.24 (m, 1 H), 1.40 (s, 3 H), 1.24 (s, 3 H).

Methyl 2,3-*O*-Isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (5). To a solution of anhydrous CH_2Cl_2 (750 mL) and pyridine (48.5 mL) was added CrO_3 (30.0 g) over 15 min. To the resultant red solution was added dropwise the alcohol **4** (5.0 g) in anhydrous CH_2Cl_2 (50 mL), and the reaction mixture was allowed to stir for 20 min. The mixture was poured into cold saturated aqueous $NaHCO_3$ (750 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was azeotroped with toluene (3 × 25 mL), dissolved in CH_2Cl_2 (50 mL), and treated with activated charcoal (1 g) and silica (5 g). The solution was filtered through a pad of Celite (2 cm) and flushed with CH_2Cl_2 (150 mL), and the eluant was evaporated to yield the known[33] aldehyde **5** (3.47 g, 71%) as a white deliquescent solid: ^1H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1 H), 5.08 (s, 1 H), 5.04 (d, 1 H, *J* = 6 Hz), 4.49 (d, 1 H, *J* = 6.4 Hz), 4.47 (s, 1 H), 3.45 (s, 3 H), 1.49 (s, 3 H), 1.32 (s, 3 H).

Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-6-nitro-6-(phenylthio)-β-D-*ribo*-hex-5(*Z*)-enofuranoside (6). To a solution of (phenylthio)nitromethane[11] (1.82 g, 10.73 mmol) in a mixed solvent system of 1:1 THF/*t*-BuOH (90 mL) at 0 °C was added *t*-BuOK (1 M in *t*-BuOH; 0.1 equiv, 1.1 mL). To the resulting creamy suspension was added a solution of the aldehyde **5** (10.73 mmol, 2.17 g) in anhydrous THF (25 mL). The reaction mixture was allowed to warm to 25 °C and maintained for 12 h, poured into H_2O (100 mL), and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was filtered through a pad of silica (2 cm), flushing with CH_2Cl_2 (200 mL). The eluant was evaporated, and to the residue, in anhydrous CH_2Cl_2 (90 mL) and at −78 °C, was added MsCl (32.19 mmol, 2.5 mL) followed by (*i*-Pr)$_2$EtN (32.19 mmol, 3.0 mL). The mixture was allowed to warm to −30 °C, maintained for 30 min, and then poured into cold saturated aqueous $NaHCO_3$ (100 mL), and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (3:7 Et_2O–hexanes) to give the nitro olefin **6** (3.53 g, 93%) as yellow crystalline solid: mp 103 °C (Et_2O/hexanes); $[\alpha]_D$ −55.7° (*c* 1.235 in $CHCl_3$); IR (KBr) 3010, 2954, 1544, 1482, 1448, 1382, 1337, 1268, 1219, 1162, 1113, 1097, 1059, 1038, 960, 914, 870, 800, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 1 H, *J* = 8.4 Hz), 7.38–7.31 (m, 5 H), 5.34 (d, 1 H, *J* = 8.7 Hz), 5.10 (s, 1 H), 4.70 (m, 2 H), 3.41 (s, 3 H), 1.52 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 143.8, 130.9, 130.4, 129.6, 128.4, 113.1, 109.9, 85.20, 84.62, 84.21, 55.05, 26.37, 24.94; MS (EI) *m/e* 353 ($M^{+\cdot}$), 338, 307, 217, 189, 163, 85; exact mass (EI) calcd for $C_{15}H_{16}NO_6S$ (M^+ − Me) 338.0698, found (M^+ − Me) 338.0694. Anal. Calcd for $C_{16}H_{19}NO_6S$: C, 54.38; H, 5.42; N, 3.96. Found: C, 53.92; H, 5.36; N, 3.89.

Phenyl (Methyl 2,3-*O*-isopropylidene-β-D-allofuranosid)thiouronate (7). To the nitro olefin **6** (1.12 g, 3.17 mmol) in DMF (5 mL) was added potassium trimethylsilanolate (3.81 mmol, 0.49 g) at 0 °C. After 30 min, the reaction mixture was cooled to −78 °C and diluted with methanol (30 mL). Ozone was introduced via pipette until a colorless endpoint was reached, then the reaction mixture was purged of excess ozone with a stream of N_2, poured into H_2O (50 mL), and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, and the residue was dissolved in 5% methanolic citric acid (5 mL). After 10 min, the solution was poured into pH 7 phosphate buffer (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), and evaporated to yield the α-hydroxy thioester **7** (1.0 g, 94%) as a white crystalline solid: mp 95.5–96.5 °C (Et_2O); $[\alpha]_D$ −180° (*c* 1.28 in $CHCl_3$); IR (KBr) 3428, 3000, 2951, 1728, 1452, 1398, 1385, 1220, 1163, 1100, 1066, 1029, 960, 878, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 5 H), 5.03 (s, 1 H), 4.96 (d, 1 H, *J* = 6 Hz), 4.78 (d, 1 H, *J* = 1.6 Hz), 4.75 (d, 1 H, *J* = 2 Hz), 4.66 (d, 1 H, *J* = 6 Hz), 4.48 (t, 1 H, *J* = 2 Hz), 3.51 (s, 3 H), 1.47 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 134.7, 129.5, 129.2, 126.9, 112.6, 110.4,

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89.49, 85.60, 79.85, 78.74, 55.96, 26.31, 24.82; MS (EI) m/e 340 ($M^{\bullet+}$), 325, 309, 293, 265, 247, 231, 203, 171, 110; exact mass (EI) calcd for $C_{16}H_{20}O_6S$ ($M^{\bullet+}$) 340.0981, found ($M^{\bullet+}$) 340.0978. Anal. Calcd for $C_{16}H_{20}O_6S$: C, 56.46; H, 5.92. Found: C, 56.17; H, 5.89.

D-Allose. From the Hydrolysis of Thioester 7. To the α-hydroxy thioester **7** (0.79 g, 2.32 mmol) in anhydrous MeOH (15 mL) at 25 °C was added $Hg(OAc)_2$ (6.07 mmol, 2.0 g) followed by a catalytic amount of H_2O (1 drop). The reaction mixture was allowed to stir at 25 °C for 2 h, poured into H_2O (25 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (15:85 Et_2O–hexanes) to give the corresponding methyl ester (0.43 g, 71%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.00 (s, 1 H), 4.90 (d, 1 H, J = 6 Hz), 4.60 (d, 1 H, J = 5.7 Hz), 4.54 (d, 1 H, J = 4.5 Hz), 4.30 (t, 1 H, J = 4.2 Hz), 4.02 (d, 1 H, J = 4.2 Hz), 3.82 (s, 3 H), 3.42 (s, 3 H), 1.47 (s, 3 H), 1.31 (s, 3 H); MS (EI) m/e 247 (M^+ – Me), 231, 215, 173, 113, 98, 85; exact mass (EI) calcd for $C_{10}H_{15}O_7$ (M^+ – Me) 247.0818, found (M^+ – Me) 247.0810. To this methyl ester (50 mg, 0.191 mmol) in anhydrous MeOH (1 mL) at 0 °C was added $NaBH_4$ (0.143 mmol, 6 mg). After 2 h, the reaction mixture was quenched with H_2O (1 mL) and evaporated. The residue was chromatographed on silica (4:96 MeOH–$CHCl_3$) to afford the alcohol (28.1 mg, 95%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1 H), 4.92 (d, 1 H, J = 6 Hz), 4.60 (d, 1 H, J = 5.6 Hz), 4.29 (d, 1 H, J = 3.2 Hz), 3.73 (m, 4 H), 3.44 (s, 3 H), 2.38 (br s, 1 H), 1.49 (s, 3 H), 1.33 (s, 3 H); MS (EI) m/e 219 (M^+ – Me), 203, 187, 173, 159, 127, 113, 98, 85; exact mass (EI) calcd for $C_9H_{15}O_6$ (M^+ – Me) 219.0869, found (M^+ – Me) 219.0878. To this alcohol (28 mg, 0.12 mmol) in aqueous dioxane (1 mL) was added Dowex 50W H^+ resin (fine mesh, ≈20 mg). After 4 days at 25 °C the reaction mixture was filtered through a glass wool plug, washed with MeOH (5 mL), and evaporated to give D-allose[25] (21.5 mg, quantitative) as a white powder: ^1H NMR (400 MHz, D_2O) δ 4.67 (d, 1 H, J = 8.4 Hz), 3.95 (s, 1 H), 3.66 (d, 1 H, J = 12.4 Hz), 3.57 (m, 1 H), 3.5–3.4 (m, 2 H), 3.20 (m, 1 H); ^{13}C NMR[25a] (101 MHz, D_2O) δ 93.70, 73.89, 71.54, 71.46, 67.09, 61.45. The sample was identical with authentic material (Sigma).

Methyl [Methyl 2,3-*O*-isopropylidene-5-*O*-[(trifluoromethyl)sulfonyl]-β-D-allofuranosid]uronate (8). To the alcohol **7** (410 mg, 1.2 mmol) and pyridine (12 mmol, 0.97 mL) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added Tf_2O (2.29 mmol, 0.39 μL). After 10 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with H_2O (25 mL) and saturated aqueous $CuSO_4$ (2 × 25 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (1:9 EtOAc–hexanes) to give the corresponding triflate (0.533 g, 94%) as a pale yellow oil: $[\alpha]_D$ –72.5° (*c* 0.75 in $CHCl_3$); IR (neat) 3009, 2960, 1710, 1485, 1450, 1428, 1390, 1380, 1250, 1215, 1146, 1095, 990, 935, 866, 750, 690, 610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 5 H), 5.24 (d, 1 H, J = 6.8 Hz), 5.06 (s, 1 H), 4.93 (dd, 1 H, J = 6, 1.6 Hz), 4.64 (d, 1 H, J = 6 Hz), 4.62 (dd, 1 H, J = 6.8, 1.2 Hz), 3.44 (s, 3 H), 1.50 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 134.6, 130.3, 129.6, 124.7, 113.3, 110.8, 86.83, 85.45, 84.85, 80.36, 56.74, 26.50, 24.96; MS (EI) m/e 472 ($M^{\bullet+}$), 457, 363, 305, 235, 173, 137, 109; exact mass (EI) calcd for $C_{17}H_{19}F_3O_8S_2$ ($M^{\bullet+}$) 472.0474, found ($M^{\bullet+}$) 472.0471. To the thioester (0.446 g, 0.944 mmol) in anhydrous MeOH (10 mL) was added $Hg(OAc)_2$ (2.83 mmol, 0.9 g) followed by a catalytic amount of H_2O (1 drop). After 2 h, the reaction mixture was poured into H_2O (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (20 mL) and saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (2:8 Et_2O–hexanes) to give the methyl ester **8** (0.329 g, 88%) as a colorless oil: $[\alpha]_D$ –43.3° (*c* 0.60 in $CHCl_3$); IR (neat) 2942, 1767, 1470, 1452, 1241, 1172, 1112, 1070, 1022, 952, 866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (d, 1 H, J = 6 Hz), 5.02 (s, 1 H), 4.88 (dd, 1 H, J = 6, 1.2 Hz), 4.61 (d, 1 H, J = 6 Hz), 4.56 (dd, 1 H, J = 6, 1.2 Hz), 3.87 (s, 3 H), 3.78 (s, 3 H), 1.48 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 113.3, 110.8, 85.41, 85.01, 81.99, 80.48, 56.34, 53.37, 26.48, 24.98; MS (EI) m/e 393 (M^+ – H), 379, 363, 305, 245, 169, 126; exact mass (EI) calcd for $C_{11}H_{14}F_3O_9S$ (M^+ – Me) 379.0310, found (M^+ – Me) 379.0303.

Methyl (Methyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosid)uronate (9). To the triflate **8** (0.35 g, 0.89 mmol) in DMF (2 mL) was added NaI (0.93 mmol, 0.14 g). After 20 min, NaN_3 (2.92 mmol, 0.19 g) was added, and the reaction mixture was allowed to warm to 60 °C. After 30 min, the solution was poured into H_2O (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica (2:8 Et_2O–hexanes) to afford the azide **9** (0.13 g, 52%) as a pale yellow oil: $[\alpha]_D$ –55.3° (*c* 0.89 in $CHCl_3$); IR (neat) 2958, 2365, 2110, 1749, 1377, 1261, 1205, 1095, 867, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.01 (s, 1 H), 4.89 (dd, 1 H, J = 6, 0.8 Hz), 4.62 (d, 1 H, J = 6 Hz), 4.48 (dd, 1 H, J = 8.8, 1.2 Hz), 3.86 (s, 3 H), 3.84 (d, 1 H, J = 9.2 Hz), 3.35 (s, 3 H), 1.51 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 112.9, 110.3, 86.25, 85.04, 81.66, 63.35, 55.81, 52.78, 26.46, 25.00; MS (EI) m/e 272 (M^+ – Me), 205, 173, 142, 113, 98; exact mass (EI) calcd for $C_{10}H_{14}N_3O_6$ (M^+ – Me) 272.0883, found (M^+ – Me) 272.0876. On a smaller scale, reaction of triflate **8** (16 mg, 0.041 mmol) in DMF (0.5 mL) with NaI (0.041 mmol, 6 mg) at room temperature for 20 min, followed by NaN_3 (0.122 mmol, 8 mg) at 60 °C for 30 min, afforded the azide **9** (11 mg, 92%).

Methyl (Methyl 5-azido-5-deoxy-2,3-di-*O*-acetyl-D-allofuranosid)uronate (10). To the azide **9** (126 mg, 0.439 mmol) in MeOH (5 mL) was added Dowex 50W H^+ resin (0.25 g), and the reaction mixture allowed to warm to 65 °C. After 12 h, the solution was filtered, washed with MeOH (10 mL) and CH_2Cl_2 (10 mL), and evaporated. The residue was dissolved in pyridine (4 mL), and Ac_2O (redistilled, 1 mL) was added. After 1 h, the reaction mixture was poured onto ice (5 g), allowed to stir for 30 min, and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with H_2O (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and saturated aqueous $CuSO_4$ (20 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (3:7 EtOAc–hexanes) to afford the diacetate **10** (120 mg, 83%) as a mixture of anomers: IR (neat) 2976, 2956, 2846, 2114, 1752, 1439, 1371, 1241, 1081, 1052, 1016, 947, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) β anomer δ 5.56 (dd, 1 H, J = 6.8, 4.8 Hz), 5.25 (d, 1 H, J = 4.8 Hz), 4.93 (s, 1 H), 4.51 (t, 1 H, J = 6.8 Hz), 4.03 (d, 1 H, J = 5.6 Hz), 3.85 (s, 3 H), 3.41 (s, 3 H), 2.13 (s, 3 H), 2.07 (s, 3 H); α anomer δ 5.34 (dd, 1 H, J = 7.6, 3.2 Hz, 5.18 (d, 1 H, J = 4.4 Hz), 4.99 (dd, 1 H, J = 7.6, 4.8 Hz), 4.47 (t, 1 H, J = 2.8 Hz) 4.44 (d, 1 H, J = 2.8 Hz), 3.86 (s, 3 H), 3.47 (s, 3 H), 2.16 (s, 3 H), 2.14 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) β anomer δ 169.5, 169.3, 168.1, 106.7, 80.13, 74.38, 71.69, 63.56, 55.85, 52.81, 20.54, 20.34; α anomer δ 170.2, 169.7, 167.5, 101.6, 82.25, 70.68, 69.31, 63.13, 55.60, 52.93, 20.63, 20.44; MS (EI) m/e 300 (M^+ – OMe), 217, 157, 115; exact mass (EI) calcd for $C_{11}H_{14}N_3O_7$ (M^+ – OMe) 300.0832, found (M^+ – OMe) 300.0831.

Methyl (Methyl 5-azido-5-deoxy-1,2,3-tri-*O*-acetyl-D-allofuranosid)uranoate (11). To the diacetate **10** (0.12 g, 0.362 mmol) in CH_2Cl_2 (1 mL) and AcOH (1 mL) at 0 °C was added Ac_2O (redistilled, 300 μL) followed by a catalytic amount of H_2SO_4 (1 drop). The reaction mixture was allowed to stir at 0 °C for 1 h then warmed to 25 °C and allowed to stir for a further 1 h. The reaction mixture was poured onto ice (5 g) and allowed to stir for 30 min, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layers were washed with H_2O (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (3:7 EtOAc–hexanes) to give the triacetate **11** (0.117 g, 90%) as a pale yellow oil: IR (neat) 3016, 2955, 2116, 1754, 1437, 1371, 1217, 1068, 1066, 1010, 967, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) β anomer δ 6.16 (s, 1 H), 5.54 (dd, 1 H, J = 7.2, 4.8 Hz), 5.36 (d, 1 H, J = 4.8 Hz), 4.61 (dd, 1 H, J = 7.2, 4.4 Hz), 4.34 (d, 1 H, J = 4.4 Hz), 3.80 (s, 3 H), 2.13 (s, 6 H), 2.04 (s, 3 H); α anomer δ 6.44 (d, 1 H, J = 4.6 Hz), 5.33 (dd, 1 H, J = 6.8, 2.4 Hz), 5.23 (dd, 1 H, J = 6.8, 4.6 Hz), 4.62 (t, 1 H, J = 2.8 Hz), 4.41 (d, 1 H, J = 3 Hz), 3.84 (s, 3 H), 2.13 (s, 3 H), 2.11 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) β anomer δ 169.3, 169.1, 169.0, 167.1, 97.91, 80.90, 74.06, 69.68, 62.81, 52.88, 20.93, 20.46, 20.27; α anomer δ 169.8, 169.6, 169.2, 167.2, 93.83, 83.33, 69.96, 68.97, 63.08, 53.10, 21.45, 20.95, 20.50; MS (EI) m/e 328 (M^+ – OMe), 300 (M^+ – OAc), 245, 203, 143, 101; exact mass (EI) calcd for $C_{11}H_{14}N_3O_7$ (M^+ – OAc) 300.0832, found (M^+ – OAc) 300.0844. Anal. Calcd for $C_{13}H_{17}N_3O_9$: C,

43.46; H, 4.77; N, 11.70. Found: C, 43.75; H, 4.91; N, 11.60.

Tris-*O*-(trimethylsilyl)-5-(hydroxymethyl)uracil (15) and Bis-*O*-(trimethylsilyl)uracil (16). To the nucleoside base (1 mmol) in hexamethyldisilazane (3 mL) was added a catalyic amount of TMSCl (1 drop), and the reaction mixture was allowed to reflux for 12 h, cooled, and evaporated. The residue was dissolved in anhydrous CH_3CN (5 mL), resulting in a 0.2 M solution which was used for subsequent reactions.

1-(Methyl 2′,3′-*O*-acetyl-5′-azido-5′deoxy-β-D-allofuranosyluronate)-5-(hydroxymethyl)uracil (13). To the triacetate **11** (49 mg, 0.136 mmol) in anhydrous CH_3CN (1 mL) was added TMSOTf (1.2 equiv, 0.164 mmol, 32 μL). After 5 min, tris-*O*-(trimethylsilyl)-5-(hydroxymethyl)uracil (**15**)[29] (0.2 M in CH_3CN; 1.7 mL) was added. After the reaction was judged complete by TLC (1:9 MeOH–$CHCl_3$, ca. 20 min), the solution was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (2:98 MeOH–$CHCl_3$) to give the β-nucleoside **13** (40 mg, 66%) as a white foam: $[\alpha]_D$ −47.2° (*c* 0.72 in $CHCl_3$); IR (neat) 3485–3203 (br), 2959, 2118, 1748, 1692, 1468, 1376, 1239, 1095, 1060, 1051, 906, 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (br s, 1 H), 7.66 (s, 1 H), 6.21 (d, 1 H, *J* = 7.2 Hz), 5.39 (dd, 1 H, *J* = 6, 2.8 Hz), 5.33 (m, 1 H), 4.54 (d, 1 H, *J* = 3.2 Hz), 4.47 (m, 3 H), 3.88 (s, 3 H), 2.12 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 169.4, 167.2, 162.6, 150.1, 136.2, 115.1, 85.76, 81.95, 72.02, 70.02, 62.96, 58.52, 53.39, 20.49, 20.36; MS (FAB) *m/e* 442 ($M + H^+$), 349, 300, 258, 226, 197; exact mass (EI) calcd for $C_{14}H_{15}N_5O_8$ (M^+ − HOAc) 381.0922, found (M^+ − HOAc) 381.0941.

1-(5′-Amino-5′-deoxy-β-D-allofuranosyluronic acid)-5-(hydroxymethyl)uracil (Polyoxin C, 1). To the azide **13** (44 mg, 0.0997 mmol) in anhydrous THF (1 mL) was added PPh_3 (0.0997 mmol, 26 mg) followed by H_2O (0.15 mmol, 3 μL). The reaction mixture was allowed to stir at 25 °C and after 12 h evaporated. The residue was dissolved in aqueous dioxane (0.5 mL), and saturated aqueous $Ba(OH)_2$ (1 mL) was added. The solution was allowed to stand at 25 °C for 3 h, acidified with concentrated HCl (0.5 mL), and passed through a Dowex 50W H^+ ion-exchange column. The column was flushed with H_2O until there appeared no UV-active material, and the eluant was neutral, then the product was eluted with 10% aqueous NH_4OH. The fractions were concentrated to yield the amino acid **1** (16 mg, 51%) as a tan powder: TLC (4:1:2 BuOH–AcOH–H_2O) R_f = 0.05 (ninhydrin); mp 247–261 °C dec; (lit.[1] 260–267 °C dec); $[\alpha]_D$ +10.5° (*c* 0.38 in H_2O) [lit.[1] $[\alpha]^{24}_D$ +11.2° (*c* 0.5 in H_2O)]; IR (KBr) 3630–3383 (br), 3262, 3213, 3182, 2919, 2887, 2676, 2394, 1690, 1637, 1476, 1401, 1254, 1123, 1056, 773 cm^{-1} [lit.[1b] IR (KBr) 3330, 3060, 1690, 1620, 1480, 1420, 1405, 1060 cm^{-1}]; ^1H NMR (400 MHz, 3% DCl in D_2O) δ 7.10 (s, 1 H), 5.33 (d, 1 H, *J* = 2.8 Hz), 4.26 (t, 1 H, *J* = 6.4 Hz), 4.18 (d, 1 H, *J* = 2.8 Hz), 4.00 (m, 1 H), 3.95 (dd, 1 H, *J* = 6.4, 2 Hz), 3.92 (s, 2 H); MS (FAB) *m/e* 319 ($M + H^+$), 279, 225, 176, 153; exact mass (FAB) calcd for $C_{11}H_{16}N_3O_8$ ($M^{\bullet+}$) 318.0937, found ($M^{\bullet+}$) 318.0912.

1-(Methyl 2′,3′-di-*O*-acetyl-5′-azido-5′-deoxy-β-D-allofuranosyluronate)uracil (14). To the triacetate **11** (30 mg, 0.084 mmol) in anhydrous CH_3CN (1 mL) was added TMSOTf (1.2 equiv, 0.10 mmol, 20 μL). After 1 min bis(trimethylsilyl)uracil (**16**)[29] (0.2 M in CH_3CN; 1.05 mL) was added. The reaction mixture was allowed to stir at 25 °C for 20 min and then quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 3 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (2:98 MeOH–$CHCl_3$) to afford the β-nucleoside **14** (27.2 mg, 79%) as a white foam: $[\alpha]_D$ −44.2° (*c* 0.86 in $CHCl_3$); IR (KBr) 3524–2960 (br), 2119, 1751, 1699, 1458, 1379, 1260, 1259, 1096, 1093, 1056, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (br s, 1 H), 7.53 (d, 1 H, *J* = 8.2 Hz), 6.20 (d, 1 H, *J* = 7.2 Hz), 5.86 (d, 1 H, *J* = 8.1 Hz), 5.37 (dd, 1 H, *J* = 6.1, 1.6 Hz), 5.31 (m, 1 H), 4.52 (d, 1 H, *J* = 2.1 Hz), 4.46 (m, 1 H), 3.88 (s, 3 H), 2.13 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 169.4, 167.0, 162.1, 105.2, 139.2, 103.9, 85.51, 81.76, 71.74, 69.90, 62.85, 53.40, 20.50, 20.37; MS (FAB) *m/e* 412 ($M + H^+$), 384, 352, 329, 300, 258, 242, 197; exact mass (EI) calcd for $C_{15}H_{18}N_5O_9$ ($M + H^+$) 412.1105, found ($M + H^+$) 412.1117.

1-(5′-Amino-5′-deoxy-β-D-allofuranosyluronic acid)uracil (Uracil Polyoxin C, 2). The azide **14** (27 mg, 0.066 mmol) in MeOH (1 mL) and HCl (1 M; 0.13 mL) was added to 10% Pd on $BaSO_4$ (4 mg, prehydrogenated for 30 min) in MeOH (0.5 mL). After 10 min the solution was filtered through Celite, rinsed with MeOH (3 mL), and evaporated. To the residue in dioxane (0.5 mL) was added saturated aqueous $Ba(OH)_2$ (2 mL), and the reaction mixture was allowed to stand at 25 °C. After 3 h, the reaction was judged complete by TLC (4:1:2 BuOH–AcOH–H_2O) and acidified with concentrated HCl (0.5 mL), and the solution was passed through a Dowex 50W H^+ resin column. The column was eluted with H_2O until there appeared no UV active material and the eluant was neutral, and then the product was eluted with 10% aqueous NH_4OH. The fractions were concentrated to yield the amino acid **2** (14 mg, 74%) as a tan solid: TLC (4:1:2 BuOH–AcOH–H_2O) R_f = 0.12 (ninhydrin); mp 241–245 °C dec (lit.[1b] mp 240–247 °C dec, lit.[5] mp 238–243 °C dec); $[\alpha]_D$ +16.5° (*c* 0.97 in H_2O) [lit.[1b] $[\alpha]^{22}_D$ +15.8° (*c* 0.205 in H_2O), lit.[5] $[\alpha]^{23}_D$ +17.6° (*c* 0.49 in H_2O)]; IR (KBr) 3423–3400 (br), 1637, 1516, 1461, 1365, 1339, 1259, 1075, 1050, 818, 691, 603 cm^{-1}; ^1H NMR (400 MHz, 3% DCl in D_2O) δ 6.68 (d, 1 H, *J* = 8 Hz), 5.04 (d, 1 H, *J* = 8 Hz), 4.91 (d, 1 H, *J* = 3.6 Hz), 3.86 (t, 1 H, *J* = 6.8 Hz), 3.78 (s, 1 H), 3.62 (m, 1 H), 3.55 (m, 1 H) [lit.[4b] ^1H NMR (25.05 MHz, 3% DCl in D_2O) δ 7.48 (d, 1 H, *J* = 8 Hz), 5.85 (d, 1 H, *J* = 8 Hz), 5.72 (d, 1 H, *J* = 3.7 Hz), 4.68 (dd, 1 H, *J* = 6.5, 6.5 Hz), 4.59 (d, 1 H, *J* = 2.8 Hz), 4.43 (dd, 1 H, *J* = 6.5, 3.7 Hz), 4.35 (dd, 1 H, *J* = 6.5, 2.8 Hz)]; MS (FAB) *m/e* 288 ($M + H^+$), 217; exact mass (FAB) calcd for $C_{10}H_{14}N_3O_7$ ($M + H^+$) 288.0832, found ($M + H^+$) 288.0880.

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