Tetrahedron: *Asymmetry* 22 (2011) 207–214

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A short stereoselective synthesis of the protected uracil 3′-*epi*-polyoxin C

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ARTICLE INFO

Article history:
Received 6 December 2010
Accepted 2 February 2011
Available online 1 March 2011

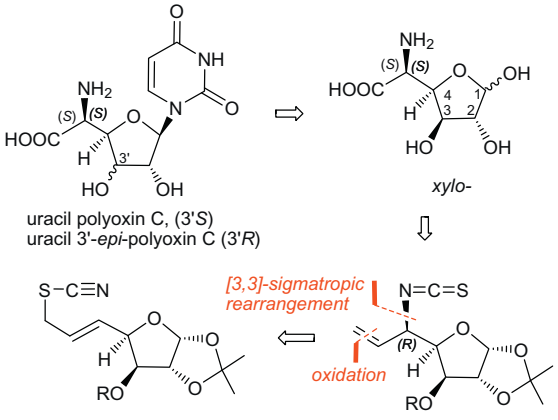
ABSTRACT

A short synthetic approach to the protected uracil 3′-*epi*-polyoxin C **20** has been developed. The stereoselective [3,3]-sigmatropic rearrangement of the corresponding 7-thiocyanato-α-D-*xylo*-hept-5-enfuranose **6** was employed as the key step to construct the C-5 stereocentre in 5-isothiocyanato-α-D-*gluco*-hept-6-enfuranose **8** and the formal synthesis of uracil 3′-*epi*-polyoxin C has been accomplished for the first time. This synthesis provides a facile method for multigram scale preparation and thus is useful for the research into the polyoxins' structure–activity relationship and to search for more potent and effective anticandidal agents.

1. Introduction

Polyoxins are a class of pyrimidine nucleoside peptide antibiotics that were first isolated from *Streptomyces cacao* var *aoensis*.[1] Polyoxins and closely related compounds, such as the nikkomycins display significant activity against phytopathogenic fungi[2] and are ineffective against other microorganisms, plants or animals.[3] Since 1970, with the first published synthesis[4] of the sugar component of the nucleoside portion of the polyoxins, the synthesis of polyoxin C,[5] polyoxin L,[6] polyoxin J,[7] and/or fragments of the polyoxins[8] have been undertaken by various groups. Amongst them, polyoxin C constitutes as a basic amino acid nucleoside common to most members of polyoxin and nikkomycin dipeptides and is a valuable intermediate for the synthesis of these analogues. D-Ribose is frequently used in the preparation of the core structure of polyoxin C due to its characteristic structural feature and the key step involved in the construction of a C-5 stereocentre with an amine functionality. The different biological activities of the polyoxins and nikkomycins compared to the enzyme chitin synthase in *Candida albicans* suggested that analogues of the polyoxins could be more effective as anticandidal agents. In this regard, some attention has been paid to the synthesis of structural analogues of the polyoxins,[9,10] but so far there has been only one report[11] concerning the preparation of the diastereoisomers of polyoxins and nikkomycins.

Over the course of our ongoing research program directed towards the use of the aza-Claisen rearrangement of allylic thiocyanates, we have described the synthesis of natural products and analogues possessing an amino acid pattern.[12] This paper concerns a simple approach to the stereoselective introduction of a nitrogen atom at C-5 of D-glucose via aza-Claisen rearrangements of allylic thiocyanates (Scheme 1) leading to the protected uracil 3′-*epi*-polyoxin C. Analogous methodology was previously used for the stereoselective synthesis of thymine polyoxin C[13] and polyoxamic acid.[14]



Scheme 1. Retrosynthetic route to 3′-*epi*-polyoxin C.

2. Results and discussion

As shown in Scheme 2, our synthesis began with the reduction of esters[16] **2** and **3** using a standard procedure with diisobutylaluminum hydride in CH_2Cl_2, which resulted in the formation of allylic alcohols **4** (90%) and **5** (94%). Thiocyanates **6** and **7** were prepared by the nucleophilic displacement of the *O*-mesyl group in the corresponding mesylates derived from allylic alcohols **2** and **3**, by thiocyanate (KSCN, in acetonitrile).

With allylic thiocyanates **6** and **7** in hand, we then performed the thermal aza-Claisen rearrangement, which was carried out at

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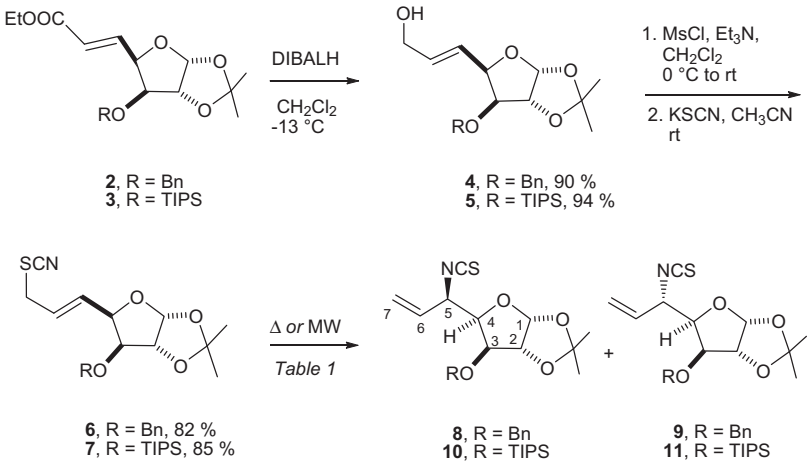
doi:10.1016/j.tetasy.2011.02.004



Scheme 2.

90 °C in heptane under a nitrogen atmosphere to give the isothiocyanates **8** and **9** in 77% yield and **10** and **11** in 71% yield, as an easily separable mixtures of diastereoisomers (**8**:**9** = 70:30 ratio, **10**:**11** = 76:24, determined by ^{1}H NMR spectroscopy, Table 1).

Table 1
[3,3]-Sigmatropic rearrangement of thiocyanates **6** and **7**

Entry	Thiocyanate	Conditions	Time (h)	Ratio[a] **8**:**9** (**10**:**11**)	Yield[b] (%)
1	**6**	Δ, 90 °C, heptane	24	75:25	77
2		MW, 70 °C, *o*-xylene	3	90:10	55
3		MW, 80 °C, *o*-xylene	3	87:13	53
4		MW, 70 °C, hexane	1	92:8	43
5		MW, 90 °C, cyclohexane	0.5	94:6	60
6		MW, 40 °C, CH_2Cl_2	2.5	88:12	45
8	**7**	Δ, 90 °C, heptane	24	76:24	71
9		MW, 70 °C, *o*-xylene	1	90:10	60
10		MW, 70 °C, hexane	1	88:12	62
11		MW, 90 °C, cyclohexane	1	90:10	55
12		MW, 40 °C, CH_2Cl_2	3	75:25	56

[a] Determined by ^{1}H NMR. Ratio in the crude reaction mixtures.
[b] Isolated combined yields.

A remarkable acceleration of the thermal [3,3]-sigmatropic rearrangement of **6** and **7** from 24 h (entries 1 and 8) to 0.5–1 h (Table 1, entries 5 and 11) with good stereoselectivity was observed using microwave irradiation conditions[15] in cyclohexane at 90 °C (Table 1). The reaction was performed in closed vessels in a focused microwave reactor (CEM Discover), with control of the power and temperature by an infrared sensor. It has been reported[16] that an Overman rearrangement of trichloro- and trifluoroacetimidates, derived from the allylic alcohol **4**, proceeds without stereoselectivity and takes place an inseparable mixture of diastereoisomers.

The configuration of the newly introduced stereocentre at C-5 in **10** was established by an X-ray diffraction analysis as (*R*) (Fig. 1).

In our subsequent strategy, the conversion of isothiocyanate **8** into the protected amine was necessary. The reaction of **8** with CH_3ONa in methanol at 0 °C gave thiourethane **12** in 94% yield. The treatment of **12** with mesitylnitrile oxide in acetonitrile afforded urethane[20] **14** in 92% yield (Scheme 3).

In order to correlate the stereochemistry of isothiocyanate **8** with **10** at C-5, a sample of compound **10** was converted into carbamate **13** and subsequent reaction with benzyl bromide/NaH furnished **14**. A comparison of the ^{1}H and ^{13}C NMR data of **14** with the compound prepared from **8** demonstrated that the stereochemistry at C-5 in **14** was as expected as the (*R*)-configuration, which

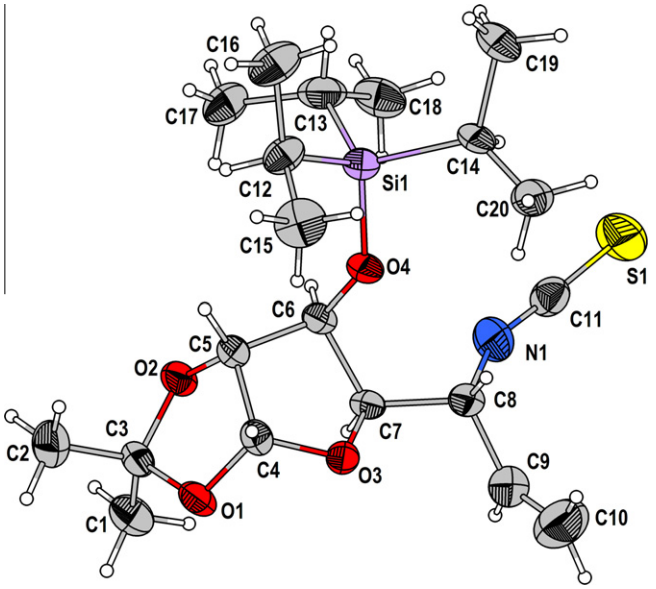
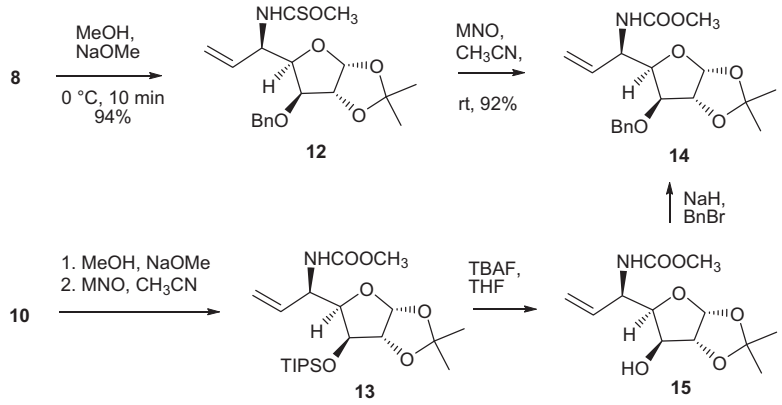


Figure 1. ORTEP structure of **10** showing crystallographic numbering.

was required for continuation of the synthesis of 3′-*epi*-polyoxin C (Scheme 3).

In order to rationalise the observed stereoselectivity of the rearrangement, high-level density functional theory (DFT) calculations, which include electron correlation effects, were carried out. The solvent effects were also taken into account, in order to obtain a more realistic model of the reaction.

Two transition structures were located using the JAGUAR 7.7. program.[21] The B3LYP/6-31G(d,p) (vacuum) geometry of the transition states TS1 and TS2 is given in Figure 2 along with the bond distances. Single-point energy calculations of the solution phase transition states at the B3LYP/cc-pVTZ(cyclohexane)//B3LYP/6-31G(d,p) (vacuum) were performed. From the calculations, for the pathway **6**→TS1→**8**, the activation energy was found to be 1.95 kcal/mol lower than for the pathway **6**→TS2→**9** using a standard Poisson-Boltzmann continuum solvation model as implemented in JAGUAR 7.7.[21] The nature of vacuum B3LYP transition states was verified with frequency calculations, yielding only one large imaginary frequency. Harmonic zero-point energy corrections at B3LYP/6-31G(d,p) obtained from the frequency



Scheme 3.

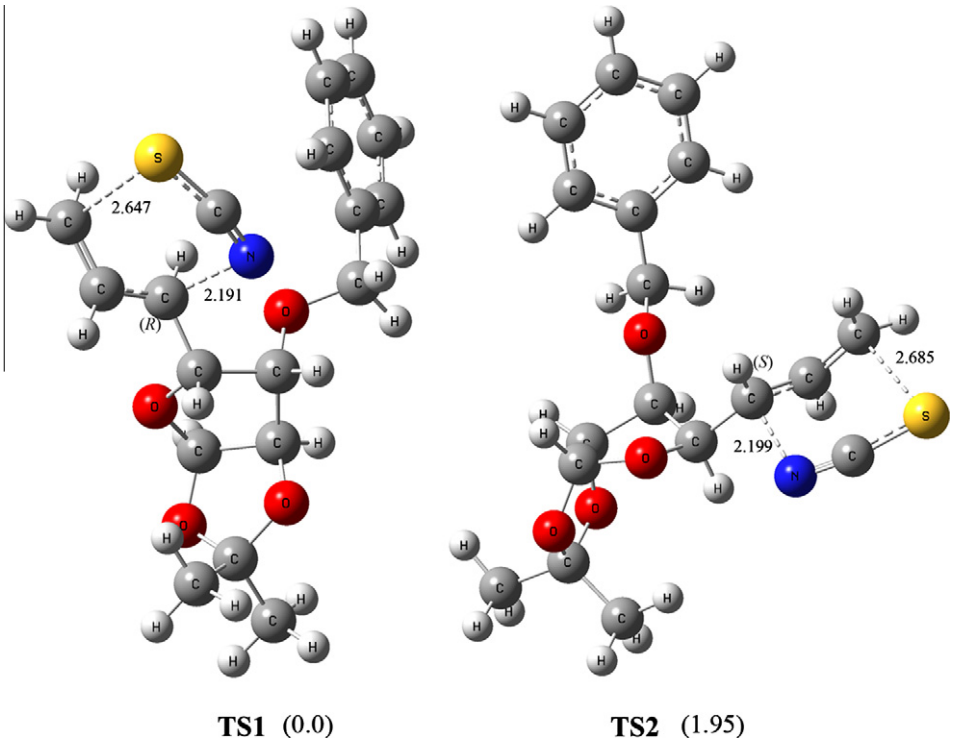


Figure 2. Transition structures for the rearrangement **6**→**8** + **9**. Relative energies of transition states (in kcal/mol) are shown in parentheses and bond distances (in Å).

calculations of the vacuum transition states were applied to the transition state energies.

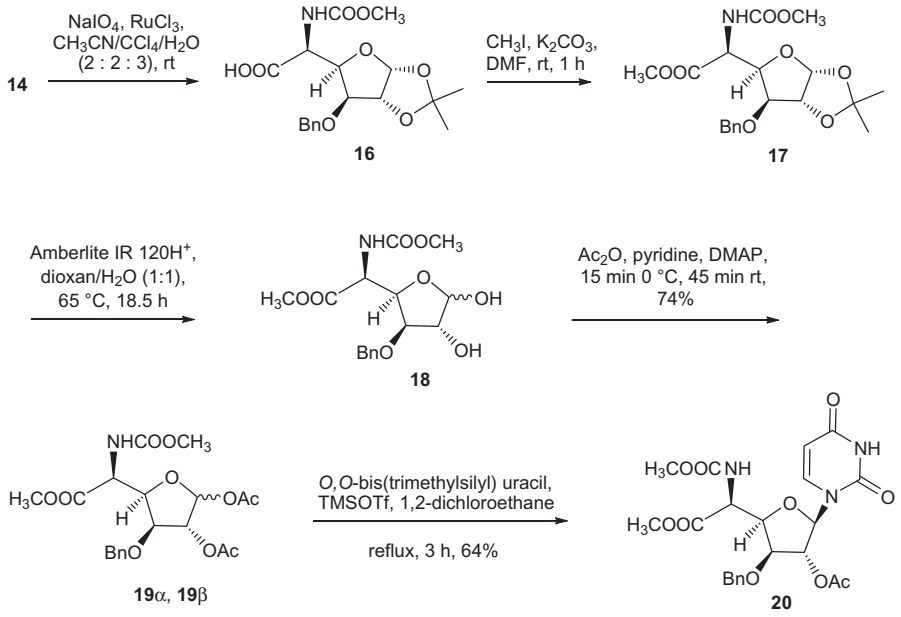
Thus, the predicted diastereomeric ratio of **8**:**9** at 90 °C was 93.7:6.3. This result is in very good agreement with the experimental data (**8**:**9** = 94:6; Table 1, entry 5).

The oxidative cleavage of the vinyl group in **14** was achieved using catalytic amounts of $RuCl_3$ in the presence of an excess of $NaIO_4$ ($CH_3CN/CCl_4/H_2O$ = 2:2:3) to afford amino acid **16** in 74% yield. Compound **16** was converted into the corresponding methyl ester **17** by treatment with CH_3I/K_2CO_3 in DMF in 90% yield (Scheme 4).

Exposure of compound **17** to Amberlite IR 120 H^+ resulted in the cleavage of the 1,2-*O*-isopropylidene group and the corresponding lactol **18** was isolated as an inseparable mixture of anomers. The resulting furanose **18** was subsequently treated with acetic anhydride in dry pyridine and DMAP as a catalyst to produce diacetates **19**α and **19**β as a mixture of anomers in 74% yield. Although these anomers were separated by column chromatography and fully characterized, the synthesis was continued with the mixture of these compounds. Finally, nucleoside formation was carried out according to Vorbruggen's procedure[17] by treatment of compounds **19** with silylated uracil in the presence of trimethylsilyl trifluoromethanesulfonate to furnish **20** in 64% yield (Scheme 4).

3. Conclusion

A stereoselective synthetic approach to the protected form of uracil 3′-*epi*-polyoxin C **20** has been accomplished from the known α-D-glucofuranose **2**. The stereoselective [3,3]-sigmatropic rearrangement of the corresponding thiocyanate **6** was employed as the key step to construct the C-5 stereocentre and the uracil 3′-*epi*-polyoxin C **20** has been synthesized for the first time. Significantly, the synthesis provides a facile method for multigram scale preparation and will be convenient for research of the polyoxins'



Scheme 4.

structure–activity relationship and to search for more potent and effective anticandidal agents.

4. Experimental

4.1. General

All commercial reagents were used in the highest available purity from Aldrich, Fluka, Merck or Acros Organics without further purification. Solvents were dried and purified before use according to standard procedures. For flash column chromatography on silica gel, Kieselgel 60 (0.040–0.063 mm, 230–400 mesh, Merck) was used. Solvents for flash chromatography (hexane, ethyl acetate, methanol, dichloromethane) were distilled before using. Thin layer chromatography was run on Merck silica gel 60 F_{254} analytical plates; detection was carried out with either ultraviolet light (254 nm), or spraying with a solution of phosphomolybdic acid, potassium permanganate basic solution, a solution of concentrated H_2SO_4, with subsequent heating. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on a Varian Mercury Plus 400 FT NMR spectrometer (400.13 MHz for ^1H and 100.6 MHz for ^{13}C) using TMS as internal reference. For ^1H δ are given in parts per million (ppm) relative to TMS (δ = 0.0) and for ^{13}C relative to $CDCl_3$ (δ = 77.0). The multiplicity of the ^{13}C NMR signals concerning the ^{13}C–^1H coupling was determined by the DEPT method. Chemical shifts (in ppm) and coupling constants (in Hertz) were obtained by first-order analysis; assignments were derived from COSY and H/C correlation spectra. Infrared (IR) spectra were measured with a Nicolet Avatar 330 FT-IR spectrometer as KBr pellets and expressed in ν values (cm^{-1}). Optical rotations were measured on a P3002 Krüss polarimeter and reported as follows: $[\alpha]_D$ (c in grams per 100 mL, solvent). Melting points were recorded on a Kofler hot block and are uncorrected. Microwave reactions were carried out on the focused microwave system (CEM Discover). The temperature content of the vessel was monitored using a calibrated infrared sensor mounted under the vessel. At the end of all reactions the contents of vessel were cooled rapidly using a stream of compressed air. Small quantities of reagents (μL) were measured with appropriate syringes (Hamilton). All reactions were performed under an atmosphere of nitrogen unless otherwise noted.

4.1.1. (*E*)-3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enfuranose 4

Diisobutylaluminum hydride (29.5 mL of a 1.2 M toluene solution) was added dropwise to a solution of ester **2** (3.40 g, 9.76 mmol) in dry CH_2Cl_2 (44 mL) which was pre-cooled to −13 °C. The resulting mixture was stirred at the same temperature for 50 min and then quenched with methanol (2 mL). The mixture was warmed to room temperature and poured into 30% aq K/Na tartrate (145 mL). After being stirred for 30 min, the mixture was then extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were dried over Na_2SO_4, after which the solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (2:1 hexane/ethyl acetate) to afford 2.70 g (90%) of allylic alcohol **4** as a colourless oil: $[\alpha]_D^{25} = -59.3$ (c 0.54, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 7.36–7.27 (m, 5H, Ph), 6.01 (dtd, $J_{6,5}$ = 15.7 Hz, $J_{7,6}$ = 5.1 Hz, $J_{7,6}$ = 5.0 Hz, $J_{7,CH3}$ = 0.6 Hz, 1H, H_6), 5.95 (d, $J_{2,1}$ = 3.8 Hz, 1H, H_1), 5.88 (tdd, $J_{6,5}$ = 15.7 Hz, $J_{5,4}$ = 7.1 Hz, $J_{7,5}$ = 1.4 Hz, $J_{7,5}$ = 1.4 Hz, 1H, H_5), 4.67–4.63 (m, 3H, H_2, H_4, CH_2Ph), 4.53 (d, $J_{H,H}$ = 12.2 Hz, 1H, CH_2Ph), 4.17 (m, 2H, H_7), 3.87 (d, $J_{4,3}$ = 3.1 Hz, 1H, H_3), 1.50 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). δ_C ($CDCl_3$, 100 MHz): 137.5 (C_i), 134.1 (CH), 128.4 (2 × CH_{Ph}), 127.9 (CH_{Ph}), 127.6 (2 × CH_{Ph}), 125.0 (CH), 111.5 (C), 104.8 (CH), 83.4 (CH), 82.9 (CH), 80.6 (CH), 72.2 (CH_2), 62.9 (CH_2), 26.7 (CH_3), 26.2 (CH_3). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.78; H, 7.06.

4.1.2. (*E*)-5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-triizopropylsilyl-α-D-*xylo*-hept-5-enfuranose 5

According to the same procedure described for the preparation of **4**, ester **3** (1.65 g, 3.98 mmol) and diisobutylaluminum hydride (12 mL of a 1.2 M toluene solution) afforded after flash chromatography on silica gel (5:1 hexane/ethyl acetate) 1.40 g (94%) of allylic alcohol **5** as a colourless oil: $[\alpha]_D^{25} = -22.2$ (c 0.45, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 6.01 (ddd, $J_{6,5}$ = 15.7 Hz, $J_{7,6}$ = 5.2 Hz, $J_{7,6}$ = 5.2 Hz, 1H, H_6), 5.93 (d, $J_{2,1}$ = 3.7 Hz, 1H, H_1), 5.88 (tdd, $J_{6,5}$ = 15.7 Hz, $J_{5,4}$ = 7.6 Hz, $J_{7,5}$ = 1.4 Hz, $J_{7,5}$ = 1.4 Hz, 1H, H_5), 4.62 (dd, $J_{5,4}$ = 7.6 Hz, $J_{4,3}$ = 2.7 Hz, 1H, H_4), 4.47 (d, $J_{2,1}$ = 3.7 Hz, 1H, H_2), 4.25 (d, $J_{4,3}$ = 2.7 Hz, 1H, H_3), 4.18–4.15 (m, 2H, H_7), 1.51 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.11–1.09 (m, 21H, 3 × CH, 6 × CH_3). δ_C ($CDCl_3$, 100 MHz): 134.2 (CH), 126.1 (CH), 111.5 (C), 104.7

(CH), 86.0 (CH), 81.7 (CH), 78.1 (CH), 63.1 (CH_2), 26.9 (CH_3), 26.3 (CH_3), 17.9 (6 × CH_3), 12.2 (3 × CH). Anal. Calcd for $C_{19}H_{36}O_5Si$: C, 61.25; H, 9.74. Found: C, 61.31; H, 9.69.

4.1.3. (*E*)-3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-7-thiocyanato-α-D-*xylo*-hept-5-enfuranose 6

At first, Et_3N (1.82 mL, 13.07 mmol) was added to a solution of alcohol **4** (2.67 g, 8.716 mmol) in dry CH_2Cl_2 (30 mL) pre-cooled to 0 °C, followed by the dropwise addition of methanesulfonyl chloride (0.809 mL, 10.46 mmol). After stirring at 0 °C for 15 min and then at room temperature for 1.5 h, the solvent was removed under reduced pressure. The residue was diluted with Et_2O (50 mL), after which the salts were removed by filtration and washed with diethyl ether. Evaporation of the solvent at reduced pressure afforded a crude mesylate that was used in the subsequent reaction directly without further purification. To a solution of crude mesylate in dry acetonitrile (30 mL) was added KSCN (1.27 g, 13.07 mmol). After being stirred for 2.5 h at room temperature, the solvent was evaporated under reduced pressure. The residue was diluted with diethyl ether (50 mL), after which the salts were filtered off, the solvent was removed, and the residue was chromatographed on silica gel (5:1 hexane/ethyl acetate) to afford 2.49 g (82%) of thiocyanate **6** as a colourless oil: $[\alpha]_D^{25} = -45.6$ (*c* 0.24, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 7.37–7.28 (m, 5H, Ph), 5.99–5.96 (m, 3H, H_1, H_5, H_6), 4.68 (dd, $J_{5,4}$ = 5.1 Hz, $J_{4,3}$ = 3.1 Hz, 1H, H_4), 4.66 (d, $J_{H,H}$ = 12.1 Hz, 1H, CH_2Ph), 4.63 (d, $J_{2,1}$ = 3.8 Hz, 1H, H_2), 4.57 (d, $J_{H,H}$ = 12.1 Hz, 1H, CH_2Ph), 3.92 (d, $J_{4,3}$ = 3.1 Hz, 1H, H_3), 3.66 (m, 1H, H_7), 3.58 (m, 1H, H_7), 1.50 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). δ_C ($CDCl_3$, 100 MHz): 137.3 (C_i), 131.3 (CH), 128.5 (2 × CH_{Ph}), 127.9 (CH_{Ph}), 127.7 (2 × CH_{Ph}), 126.6 (CH), 111.7 (SCN), 111.6 (C), 104.9 (CH), 83.1 (CH), 82.8 (CH), 79.8 (CH), 72.2 (CH_2), 35.7 (CH_2), 26.6 (CH_3), 26.2 (CH_3). Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.04; H, 6.18; N, 3.90.

4.1.4. (*E*)-5,6,7-Trideoxy-1,2-*O*-isopropylidene-3-*O*-triisopropylsilyl-7-thiocyanato-α-D-*xylo*-hept-5-enfuranose 7

Using the same procedure as described for the preparation of compound **6**, alcohol **5** (1.30 g, 3.49 mmol) was converted into crystalline thiocyanate **7** (1.05 g, 73%, 11:1 hexane/ethyl acetate); mp 59–60 °C. $[\alpha]_D^{25} = -61.3$ (*c* 0.44, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 5.96 (m, 2H, H_5, H_6), 5.93 (d, $J_{2,1}$ = 3.6 Hz, 1H, H_1), 4.64 (m, 1H, H_4), 4.46 (d, $J_{2,1}$ = 3.6 Hz, 1H, H_2), 4.29 (d, $J_{4,3}$ = 2.5 Hz, 1H, H_3), 3.64–3.63 (m, 2H, H_7), 1.51 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.09–1.06 (m, 21H, 3 × CH, 6 × CH_3). δ_C ($CDCl_3$, 100 MHz): 132.1 (CH), 126.5 (CH), 111.8 (C), 111.7 (SCN), 104.7 (CH), 85.9 (CH), 81.0 (CH), 78.0 (CH), 35.8 (CH_2), 26.9 (CH_3), 26.3 (CH_3), 18.0 (6 × CH_3), 12.3 (3 × CH). Anal. Calcd for $C_{20}H_{35}NO_4SSi$: C, 58.07; H, 8.53; N, 3.39. Found: C, 58.15; H, 8.45; N, 3.46.

4.1.5. 3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-isothiocyanato-α-D-*gluco*-hept-6-enfuranose 8 and 3-*O*-benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-isothiocyanato-βL-*ido*-hept-6-enfuranose 9

Microwave-assisted synthesis: Thiocyanate **6** (0.25 g, 72 mmol) was weighed in a 10-mL glass pressure microwave tube equipped with a magnetic stirrer bar. The corresponding solvent (4 mL, see Table 1) was added and the tube was closed with a silicon septum after which the reaction mixture was subjected to microwave irradiation (for temperatures and reaction times see Table 1). Removal of the solvent and chromatography on silica gel (7:1 hexane/ethyl acetate) afforded isothiocyanates **8** and **9** (for the yields see Table 1).

Conventional method: A solution of thiocyanate **6** (2.45 g, 7.05 mmol) in dry heptane (15.9 mL) was heated at 90 °C. Evaporation of the solvent and chromatography on silica gel (7:1 hexane/ethyl acetate) gave 1.30 g (53%) of isothiocyanate **8** and 0.44 g (18%) of **9**.

Diastereoisomer **8**: colourless oil; $[\alpha]_D^{25} = -39.4$ (*c* 0.66, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 7.41–7.31 (m, 5H, Ph), 5.97 (ddd, $J_{7trans,6}$ = 17.0 Hz, $J_{7cis,6}$ = 10.3 Hz, $J_{6,5}$ = 5.1 Hz, 1H, H_6), 5.92 (d, $J_{2,1}$ = 3.7 Hz, 1H, H_1), 5.46 (ddd, $J_{7trans,6}$ = 17.0 Hz, $J_{7trans,5}$ = 1.5 Hz, $J_{7trans,7cis}$ = 0.6 Hz, 1H, H_{7trans}), 5.31 (ddd, $J_{7cis,6}$ = 10.3 Hz, $J_{7cis,5}$ = 1.5 Hz, $J_{7trans,7cis}$ = 0.6 Hz, 1H, H_{7cis}), 4.71 (d, $J_{H,H}$ = 11.2 Hz, 1H, CH_2Ph), 4.66 (d, $J_{H,H}$ = 11.2 Hz, 1H, CH_2Ph), 4.63 (d, $J_{2,1}$ = 3.7 Hz, 1H, H_2), 4.62–4.59 (m, 1H, H_5), 4.15–4.12 (m, 2H, H_3, H_4), 1.49 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). δ_C ($CDCl_3$, 100 MHz): 136.9 (C_i), 134.8 (NCS), 132.9 (CH), 128.6 (2 × CH_{Ph}), 128.2 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 117.6 (CH_2), 112.2 (C), 105.5 (CH), 82.1 (CH), 81.6 (CH), 81.3 (CH), 72.6 (CH_2), 57.2 (CH), 26.9 (CH_3), 26.3 (CH_3). Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.08; H, 6.22; N, 4.21.

Diastereoisomer **9**: colourless crystals; mp 29–31 °C; $[\alpha]_D^{25} = -87.8$ (*c* 0.30, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 7.39–7.28 (m, 5H, Ph), 5.98 (d, $J_{2,1}$ = 3.8 Hz, 1H, H_1), 5.64 (ddd, $J_{7trans,6}$ = 16.9 Hz, $J_{7cis,6}$ = 10.2 Hz, $J_{6,5}$ = 5.5 Hz, 1H, H_6), 5.46 (ddd, $J_{7trans,6}$ = 16.9 Hz, $J_{7trans,5}$ = 1.3 Hz, $J_{7trans,7cis}$ = 1.0 Hz, 1H, H_{7trans}), 5.27 (ddd, $J_{7cis,6}$ = 10.2 Hz, $J_{7cis,5}$ = 1.3 Hz, $J_{7trans,7cis}$ = 1.0 Hz, 1H, H_{7cis}), 4.67 (d, $J_{H,H}$ = 11.6, 1H, CH_2Ph), 4.64 (d, $J_{2,1}$ = 3.8 Hz, 1H, H_2), 4.63 (m, 1H, H_5), 4.43 (d, $J_{H,H}$ = 11.6 Hz, 1H, CH_2Ph), 4.11 (dd, $J_{5,4}$ = 8.9 Hz, $J_{4,3}$ = 3.3 Hz, 1H, H_4), 3.87 (d, $J_{4,3}$ = 3.3 Hz, 1H, H_3), 1.50 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). δ_C (100 MHz, $CDCl_3$): 136.7 (C_i), 134.9 (NCS), 130.9 (CH), 128.6 (2 × CH_{Ph}), 128.2 (CH_{Ph}), 127.8 (2 × CH_{Ph}), 119.1 (CH_2), 112.1 (C), 105.1 (CH), 81.9 (CH), 81.6 (CH), 81.3 (CH), 71.9 (CH_2), 59.0 (CH), 26.8 (CH_3), 26.3 (CH_3). Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.38; H, 6.20; N, 4.15.

4.1.6. 5,6,7-Trideoxy-1,2-*O*-isopropylidene-3-*O*-triisopropylsilyl-5-isothiocyanato-α-D-*gluco*-hepto-6-enfuranose 10 and 5,6,7-trideoxy-1,2-*O*-isopropylidene-3-*O*-triisopropylsilyl-5-isothiocyanato-β-L-*ido*-hepto-6-enfuranose 11

Microwave-assisted synthesis: Using the same procedure as described for the preparation of isothiocyanates **8** and **9**, compound **7** (0.25 g, 0.604 mmol) was converted into the corresponding isothiocyanates **10** and **11** (see Table 1).

Conventional method: According to the same procedure described for the preparation of isothiocyanates **8** and **9**, thiocyanate **7** (0.60 g, 1.45 mmol) was converted into the corresponding isothiocyanates **10** (0.38 g, 63%) and **11** (79 mg, 13%), (35:0.5 hexane/ethyl acetate, see Table 1).

Diastereoisomer **10**: white crystals; mp 69–70 °C; $[\alpha]_D^{25} = +47.0$ (*c* 0.55, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 2960, 2940, 2866, 2036, 1084, 1024. δ_H ($CDCl_3$, 400 MHz): 6.04 (ddd, $J_{7trans,6}$ = 16.9 Hz, $J_{7cis,6}$ = 10.3 Hz, $J_{6,5}$ = 5.0 Hz, 1H, H_6), 5.88 (d, $J_{2,1}$ = 3.5 Hz, H_1), 1H, 5.48 (dd, $J_{7trans,6}$ = 16.9 Hz, $J_{7trans,5}$ = 1.5 Hz, 1H, H_{7trans}), 5.34 (dd, $J_{7cis,6}$ = 10.3 Hz, $J_{7cis,5}$ = 1.3 Hz, 1H, H_{7cis}), 4.52–4.47 (m, 2H, H_5, H_3), 4.45 (d, $J_{2,1}$ = 3.5 Hz, 1H, H_2), 4.05 (dd, $J_{5,4}$ = 9.6 Hz, $J_{4,3}$ = 2.6 Hz, 1H, H_4), 1.49 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.20–1.12 (m, 21H, 3 × CH, 6 × CH_3). δ_C ($CDCl_3$, 100 MHz): 134.3 (NCS), 133.4 (CH), 117.3 (CH_2), 112.3 (C), 105.2 (CH), 84.8 (CH), 82.9 (CH), 75.8 (CH), 56.8 (CH), 26.9 (CH_3), 26.3 (CH_3), 18.1 (6 × CH_3), 12.7 (3 × CH). Anal. Calcd for $C_{20}H_{35}NO_4SSi$: C, 58.07; H, 8.53; N, 3.39. Found: C, 58.13; H, 8.61; N, 3.46.

Diastereoisomer **11**: colourless oil; $[\alpha]_D^{25} = -49.7$ (*c* 0.68, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 5.97 (d, $J_{2,1}$ = 3.7 Hz, 1H, H_1), 5.85 (ddd, $J_{7trans,6}$ = 16.9 Hz, $J_{7cis,6}$ = 10.3 Hz, $J_{6,5}$ = 4.9 Hz, 1H, H_6), 5.56 (dd, $J_{7trans,6}$ = 16.9 Hz, $J_{7trans,5}$ = 1.5 Hz, 1H, H_{7trans}), 5.38 (dd, $J_{7cis,6}$ = 10.3 Hz, $J_{7trans,5}$ = 1.2 Hz, 1H, H_{7cis}), 4.61 (dddd, $J_{5,4}$ = 8.3 Hz, $J_{6,5}$ = 4.9 Hz, $J_{7trans,5}$ = 1.5 Hz, $J_{7trans,5}$ = 1.2 Hz, 1H, H_5), 4.48 (d, $J_{2,1}$ = 3.7 Hz, 1H, H_2), 4.32 (d, $J_{4,3}$ = 3.0 Hz, 1H, H_3), 4.07 (dd, $J_{5,4}$ = 8.3 Hz, $J_{4,3}$ = 3.0 Hz, 1H, H_4), 1.49 (s, 3H, CH_3), 1.32 (s, 3H,

CH_3), 1.11–1.09 (m, 21H, 3 × CH, 6 × CH_3). δ_C ($CDCl_3$, 100 MHz): 134.6 (NCS), 131.1 (CH), 118.8 (CH_2), 112.2 (C), 104.8 (CH), 85.3 (CH), 83.0 (CH), 76.3 (CH), 58.8 (CH), 26.9 (CH_3), 26.4 (CH_3), 18.0 (6 × CH_3), 12.8 (3 × CH). Anal. Calcd for $C_{20}H_{35}NO_4SSi$: C, 58.07; H, 8.53; N, 3.39. Found: C, 57.97; H, 8.61; N, 3.29.

4.1.7. 3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-(methoxythiocarbonylamino)-α-D-*gluco*-hept-6-enfuranose 12

To a solution of isothiocyanate **8** (1.25 g, 3.60 mmol) in dry methanol (32.4 mL) was added sodium methoxide (0.214 g, 3.96 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then for a further 2.5 h at room temperature. The solvent was removed and the residue was partitioned between CH_2Cl_2 (40 mL) and water (15 mL). The aqueous layer was then extracted with further portions of CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, after which the solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (5:1 hexane/ethyl acetate) to give 1.28 g (94%) of thiocarbamate **12** as a colourless oil: $[\alpha]_D^{25} = +22.4$ (*c* 0.21, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 7.57 (br d, $J_{5,NH}$ = 7.6 Hz, 1H, NH), 7.41–7.31 (m, 5H, Ph), 5.96 (d, $J_{2,1}$ = 3.8 Hz, 1H, H_1), 5.68 (ddd, $J_{7trans,6}$ = 17.2 Hz, $J_{7cis,6}$ = 10.4 Hz, $J_{6,5}$ = 5.5 Hz, 5H, H_6), 5.44–5.40 (m, 1H, H_5), 5.30 (ddd, $J_{7trans,6}$ = 17.2 Hz, $J_{7trans,5}$ = 1.5 Hz, $J_{7trans,7cis}$ = 1.3 Hz, 1H, H_{7trans}), 5.21 (ddd, $J_{7cis,6}$ = 10.4 Hz, $J_{7trans,5}$ = 1.5 Hz, $J_{7trans,7cis}$ = 1.3 Hz, 1H, H_{7cis}), 4.68 (d, $J_{H,H}$ = 11.4 Hz, 1H, CH_2Ph), 4.58 (d, $J_{2,1}$ = 3.8 Hz, 1H, H_2), 4.49 (d, $J_{H,H}$ = 11.4 Hz, 1H, CH_2Ph), 4.28 (dd, $J_{5,4}$ = 4.9 Hz, $J_{4,3}$ = 3.3 Hz, 1H, H_4), 4.04 (d, $J_{4,3}$ = 3.3 Hz, 1H, H_3), 3.94 (s, 3H, OCH_3), 1.49 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). δ_C ($CDCl_3$, 100 MHz): 191.3 (C=S), 136.3 (C_i), 132.7 (CH), 128.7 (2 × CH_{Ph}), 128.4 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 117.5 (CH_2), 111.7 (C), 104.8 (CH), 83.0 (CH), 81.3 (CH), 79.2 (CH), 72.2 (CH_2), 57.0 (OCH_3), 54.6 (CH), 26.7 (CH_3), 26.1 (CH_3). Anal. Calcd for $C_{19}H_{25}NO_5S$: C, 60.14; H, 6.64; N, 3.69. Found: C, 60.35; H, 6.87; N, 3.51.

4.1.8. 5,6,7-Trideoxy-1,2-*O*-isopropylidene-3-*O*-triisopropylsilyl-5-(methoxycarbonylamino)-α-D-*gluco*-hept-6-enfuranose 13

To a solution of isothiocyanate **10** (0.20 g, 0.484 mmol) in dry methanol (4.9 mL) was added sodium methoxide (28.6 mg, 0.53 mmol) at room temperature. After 6.5 h, no starting material was detected (TLC) in the reaction mixture. The solvent was evaporated in vacuo and the residue was partitioned between CH_2Cl_2 (10 mL) and water (2 mL). The water phase was extracted with further portions of CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, after which the solvent was evaporated and the residue was purified through a short column of silica gel (11:1 hexane/ethyl acetate) to give 0.174 g (81%) of thiocarbamate as a colourless oil, which was used immediately in the next step to avoid problems connected with its possible instability. To a solution of thiocarbamate (0.17 g, 0.381 mmol) in dry acetonitrile (3.4 mL) was added mesitylnitrile oxide (68 mg, 0.42 mmol). The reaction mixture was stirred for 3 h at room temperature. Evaporation of the solvent under reduced pressure gave a residue, which was purified by column chromatography on silica gel (9:1 hexane/ethyl acetate) to afford 0.147 g (90%) of crystalline carbamate **13**: mp 77–78 °C; $[\alpha]_D^{25} = +1.5$ (*c* 0.20, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 5.97–5.89 (m, 2H, H_1, H_6), 5.67 (m, 1H, NH), 5.32 (d, $J_{7trans,6}$ = 17.2 Hz, 1H, H_{7trans}), 5.22 (m, 1H, H_{7cis}), 4.68 (m, 1H, H_5), 4.43 (m, 2H, H_2, H_3), 4.14 (m, 1H, H_4), 3.65 (s, 3H, OCH_3), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.16–1.08 (m, 21H, 6 × CH_3, 3 × CH). δ_C ($CDCl_3$, 100 MHz): 156.6 (C=O), 135.3 (CH), 116.6 (CH_2), 111.7 (C), 104.5 (CH), 85.1 (CH), 80.9 (CH), 77.6 (CH), 52.8 (CH), 52.0 (OCH_3), 26.8 (CH_3), 26.3 (CH_3), 18.0 (6 × CH_3), 12.8 (3 × CH). Anal. Calcd for $C_{21}H_{39}NO_6Si$: C, 58.71; H, 9.15; N, 3.26. Found: C, 58.57; H, 9.27; N, 3.37.

4.1.9. 3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-(methoxycarbonylamino)-α-D-*gluco*-hept-6-enfuranose 14

To a solution of thiocarbamate **12** (1.25 g, 3.29 mmol) in dry acetonitrile (29 mL) was added mesitylnitrile oxide (0.58 g, 3.62 mmol) and the resulting mixture was stirred at room temperature. After 3.5 h, the reaction mixture did not contain any starting material **5**, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1) to afford 1.10 g (92%) of carbamate **14** as a colourless oil.

Synthesis of **14** *from* **15**: To a solution of alcohol **15** (50 mg, 0.183 mmol) in dry THF (1 mL), pre-cooled to 0 °C, was added sodium hydride (8.8 mg, 0.22 mmol, 60% dispersion in mineral oil, freed of oil with anhydrous THF). The resulting mixture was stirred for 10 min at 0 °C, after which benzyl bromide (0.026 mL, 0.22 mmol) and tetrabutylammonium iodide (8.1 mg, 0.022 mmol) were added at the same temperature. The mixture was allowed to cool to room temperature and stirring was continued for another 1.5 h. The mixture was then partitioned between Et_2O (5 mL) and ice water (0.4 mL). The aqueous phase was extracted with an additional portion of Et_2O (5 mL), and the combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the residue was subjected to flash chromatography on silica gel (3:1 hexane/ethyl acetate) to afford 51 mg (77%) of compound **14** as a colourless oil: $[\alpha]_D^{25} = +44.2$ (*c* 0.33, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 7.40–7.31 (m, 5H, Ph), 5.96 (d, $J_{2,1}$ = 3.9 Hz, 1H, H_1), 5.77 (ddd, $J_{7trans,6}$ = 17.1 Hz, $J_{7cis,6}$ = 10.4 Hz, $J_{7cis,6}$ = 5.5 Hz, 1H, H_6), 5.71 (m, 1H, NH), 5.29 (ddd, $J_{7trans,6}$ = 17.1 Hz, $J_{7trans,5}$ = 1.2 Hz, $J_{7trans,7cis}$ = 1.2 Hz, 1H, H_{7trans}), 5.16 (ddd, $J_{7cis,6}$ = 10.4 Hz, $J_{7cis,5}$ = 1.2 Hz, $J_{7trans,7cis}$ = 1.2 Hz, 1H, H_{7cis}), 4.75 (m, 1H, H_5), 4.65 (d, $J_{H,H}$ = 11.5 Hz, 1H, CH_2Ph), 4.57 (d, $J_{2,1}$ = 3.9 Hz, 1H, H_2), 4.47 (d, $J_{H,H}$ = 11.5 Hz, 1H, CH_2Ph), 4.19 (m, 1H, H_4), 3.99 (d, $J_{4,3}$ = 3.3 Hz, 1H, H_3), 3.64 (s, 3H, OCH_3), 1.48 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). δ_H ($CDCl_3$, 100 MHz): 156.7 (C=O), 136.6 (C_i), 134.9 (CH), 128.6 (2 × CH_{Ph}), 128.3 (CH_{Ph}), 128.1 (2 × CH_{Ph}), 116.5 (CH_2), 111.6 (C), 104.9 (CH), 82.8 (CH), 81.5 (CH), 79.8 (CH), 72.2 (CH_2), 52.8 (CH), 52.0 (OCH_3), 26.7 (CH_3), 26.2 (CH_3). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.68; H, 6.81; N, 3.70.

4.1.10. 5,6,7-Trideoxy-1,2-*O*-isopropylidene-5-(methoxycarbonylamino)-α-D-*gluco*-hept-6-enfuranose 15

To a solution of compound **13** (0.10 g, 0.233 mmol) in dry THF (2.30 mL) was added a 1 M solution of Bu_4NF in THF (0.23 mL, 0.233 mmol) at 0 °C. The resulting mixture was stirred for a further 10 min at 0 °C and then for 30 min at room temperature. The solvent was removed and the residue was partitioned between ethyl acetate (5 mL) and water (1 mL). The aqueous phase was extracted with further portions of ethyl acetate (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (2:1 hexane/ethyl acetate) to afford 55 mg (86.5%) of compound **15** as a colourless oil: $[\alpha]_D^{25} = +147.3$ (*c* 0.28, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 6.10 (ddd, $J_{7trans,6}$ = 17.4 Hz, $J_{7cis,6}$ = 10.6 Hz, $J_{6,5}$ = 5.0 Hz, 1H, H_6), 5.95 (d, $J_{2,1}$ = 3.6 Hz, 1H, H_1), 5.34 (ddd, $J_{7trans,6}$ = 17.4 Hz, $J_{7trans,5}$ = 1.8 Hz, $J_{7trans,7cis}$ = 0.6 Hz, 1H, H_{7trans}), 5.30 (ddd, $J_{7cis,6}$ = 10.6 Hz, $J_{7cis,5}$ = 1.7 Hz, $J_{7trans,7cis}$ = 0.6 Hz, 1H, H_{7cis}), 4.90 (d, $J_{5,NH}$ = 8.1 Hz, 1H, NH), 4.63 (br s, 1H, OH), 4.56 (d, $J_{2,1}$ = 3.6 Hz, 1H, H_2), 4.44 (ddddd $J_{5,4}$ = 10.1 Hz, $J_{5,NH}$ = 8.1 Hz, $J_{6,5}$ = 5.0 Hz, $J_{7trans,5}$ = 1.8 Hz, $J_{7cis,5}$ = 1.7 Hz, 1H, H_5), 4.13 (m, 1H, H_3), 3.86 (dd, $J_{5,4}$ = 10.1 Hz, $J_{4,3}$ = 2.0 Hz, 1H, H_4), 3.73 (s, 3H, OCH_3), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). δ_C ($CDCl_3$, 100 MHz): 158.0 (C=O), 135.0 (CH), 116.7 (CH_2), 111.5 (C), 105.1 (CH), 84.3 (CH), 83.0 (CH), 74.1 (CH), 53.0 (OCH_3), 50.8 (CH), 26.8 (CH_3), 26.1 (CH_3). Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.89; H, 7.20; N, 5.27.

4.1.11. Methyl 3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-5-(methoxycarbonylamino)-α-D-*gluco*-hexofuranuronate 17

To a suspension of carbamate **14** (1.05 g, 2.89 mmol) in CCl_4/CH_3CN/H_2O (29 mL, 2:2:3) were successively added $NaIO_4$ (3.09 g, 14.45 mmol) and ruthenium trichloride hydrate (29 mg, 0.14 mmol). After 6 h, no starting compound was detected (TLC) in the reaction mixture, which was then extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, after which the solvent was evaporated in vacuo, and the residue was purified through a short column of silica gel (95:5 CH_2Cl_2/CH_3OH) to afford 0.82 g (74%) of carboxylic acid **16** as a colourless oil, which was used immediately in the subsequent reaction.

To a solution of acid **16** (0.80 g, 2.10 mmol) in dry DMF (28 mL) were successively added K_2CO_3 (0.319 g, 2.307 mmol) and CH_3I (0.196 mL, 3.146 mmol) at room temperature. After the starting material was completely consumed (1 h, judged by TLC), the reaction was stopped, poured into ice water (28 mL) and extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, after which the solvent was removed, and the residue was subjected to flash chromatography on silica gel (3:1 hexane/ethyl acetate) to yield 0.75 g (90%) of ester **17** as a colourless oil; $[\alpha]_D^{25} = -33.4$ (*c* 0.25, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 7.40–7.31 (m, 5H, Ph), 5.96 (d, $J_{2,1}$ = 3.8 Hz, 1H, H_1), 5.70 (br d, $J_{5,NH}$ = 9.4 Hz, 1H, NH), 4.97 (dd, $J_{5,NH}$ = 9.4 Hz, $J_{5,4}$ = 6.4 Hz, 1H, H_5), 4.64 (dd, $J_{5,4}$ = 6.6 Hz, $J_{4,3}$ = 3.7 Hz, 1H, H_4), 4.62 (d, $J_{H,H}$ = 11.4 Hz, 1H, CH_2Ph), 4.58 (d, $J_{2,1}$ = 3.8 Hz, 1H, H_2), 4.46 (d, $J_{H,H}$ = 11.4 Hz, 1H, CH_2Ph), 4.05 (d, $J_{4,3}$ = 3.7 Hz, 1H, H_3), 3.67 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 1.50 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). δ_H ($CDCl_3$, 100 MHz): 170.6 (C=O), 157.0 (C=O), 136.3 (C_i), 128.6 (2 × CH_{Ph}), 128.3 (3 × CH_{Ph}), 112.0 (C), 105.1 (CH), 82.9 (CH), 81.8 (CH), 78.0 (CH), 72.4 (CH_2), 53.5 (CH), 52.4 (2 × OCH_3), 26.9 (CH_3), 26.3 (CH_3). Anal. Calcd for $C_{19}H_{25}NO_8$: C, 57.71; H, 6.37; N, 3.54. Found: C, 57.59; H, 6.19; N, 3.33.

4.1.12. Methyl 1,2-di-*O*-acetyl-3-*O*-benzyl-5-deoxy-5-(methoxycarbonylamino)-α-D-*gluco*-hexofuranuronate 19α and its β-anomer 19β

Ester **17** (0.70 g, 1.77 mmol) was dissolved in 1,4-dioxane (14 mL) and the resulting solution was diluted with water (14 mL). Next, Amberlite IR-120 (H^+) (6.9 g) was added and the mixture was stirred at 65 °C. After 18.5 h, no starting material was detected (TLC), and the reaction was stopped and allowed to cool to room temperature. Insoluble materials were removed by filtration, the solvent was evaporated and the residue was purified through a short column of silica gel (1:2 hexane/ethyl acetate) to afford 0.38 g (60%) of lactol **18** as an inseparable mixture of anomers. To a solution of **18** (0.19 g, 0.535 mmol) in pyridine (4 mL) were added DMAP (13 mg, 0.105 mmol) and acetic anhydride (0.15 mL, 1.587 mmol) at 0 °C. The reaction mixture was stirred for a further 15 min at 0 °C and then for 45 min at room temperature. The stirring solution was poured into ice water (5 mL) and extracted with diethyl ether (2 × 12 mL). The combined organic layers were dried over Na_2SO_4, after which the solvent was evaporated in vacuo, and the residue was subjected to flash chromatography on silica gel (3:1 hexane/ethyl acetate) to afford 90 mg (38%) of **19α** and 85 mg (36%) of **19β** as colourless oils.

Anomer **19α**: $[\alpha]_D^{25} = +204.1$ (*c* 0.17, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 7.39–7.31 (m, 3H, Ph), 7.25–7.23 (m, 2H, Ph), 6.42 (d, $J_{2,1}$ = 4.6 Hz, 1H, H_1), 5.51 (br d, $J_{5,NH}$ = 10.0 Hz, 1H, NH), 5.20 (m, 1H, H_2), 5.02 (dd, $J_{4,3}$ = 7.1 Hz, $J_{5,4}$ = 4.1 Hz, 1H, H_4), 4.93 (dd, $J_{5,NH}$ = 10.0 Hz, $J_{5,4}$ = 4.1 Hz, 1H, H_5), 4.57 (d, $J_{H,H}$ = 11.7 Hz, 1H, CH_2Ph), 4.46 (d, $J_{H,H}$ = 11.7 Hz, 1H, CH_2Ph), 4.43 (dd, $J_{4,3}$ = 7.1 Hz, $J_{3,2}$ = 6.0 Hz, 1H, H_3), 3.71 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 2.06 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO). δ_C ($CDCl_3$, 100 MHz): 169.9 (C=O), 169.5 (C=O), 169.2 (C=O), 157.2 (C=O), 136.4 (C_i), 128.5 (2 × CH_{Ph}), 128.3 (CH_{Ph}), 128.0 (2 × CH_{Ph}), 93.5 (CH), 80.0 (CH), 77.7 (CH), 77.4 (CH), 73.1 (CH_2), 54.4 (CH), 52.5 (OCH_3), 52.3 (OCH_3), 20.9 (CH_3), 20.4 (CH_3). Anal. Calcd for $C_{20}H_{25}NO_{10}$: C, 54.67; H, 5.73; N, 3.19. Found: C, 54.51; H, 5.59; N, 3.29.

Anomer **19β**: $[\alpha]_D^{25} = -34.7$ (*c* 0.11, $CHCl_3$). δ_H ($CDCl_3$, 400 MHz): 7.39–7.29 (m, 5H, Ph), 6.18 (s, 1H, H_1), 5.65 (br d, $J_{5,NH}$ = 9.3 Hz, 1H, NH), 5.24 (s, 1H, H_2), 4.99 (m, 2H, H_4, H_5), 4.75 (d, $J_{H,H}$ = 11.6 Hz, 1H, CH_2Ph), 4.49 (d, $J_{H,H}$ = 11.6 Hz, 1H, CH_2Ph), 4.17 (d, $J_{4,3}$ = 5.3 Hz, 1H, H_3), 3.68 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 2.13 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO). δ_C ($CDCl_3$, 100 MHz): 170.3 (C=O), 169.7 (C=O), 169.3 (C=O), 157.1 (C=O), 136.3 (C_i), 128.6 (3 × CH_{Ph}), 128.3 (CH_{Ph}), 128.1 (CH_{Ph}), 99.2 (CH), 82.1 (CH), 81.4 (CH), 78.1 (CH), 72.6 (CH_2), 53.7 (CH), 52.3 (2 × OCH_3), 20.8 (2 × CH_3). Anal. Calcd for $C_{20}H_{25}NO_{10}$: C, 54.67; H, 5.73; N, 3.19. Found: C, 54.79; H, 5.55; N, 3.07.

4.1.13. Methyl 2′-*O*-acetyl-3′-*O*-benzyl-1′,5′-dideoxy-1′-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-5′-(methoxycarbonylamino)-β-D-*gluco*-hexofuranuronate 20

A mixture of uracil (94 mg, 0.839 mmol), 1,1,1,3,3,3-hexamethyldisilazane (2.51 mL, 12.04 mmol) and trimethylsilyl chloride (0.27 mL, 2.11 mmol) was stirred at reflux. After 6 h, the mixture was allowed to cool to room temperature and concentrated. To a solution of the mixture of acetates **19α**, **19β** (80 mg, 0.182 mmol) in dry 1,2-dichloroethane (1.3 mL) was added the above-prepared bis(trimethylsilyl) uracil dissolved in 1,2-dichloroethane (2.6 mL), followed by the dropwise addition of TMSOTf (0.198 mL, 1.094 mmol) at room temperature. The resulting mixture was stirred at reflux for 3 h, then quenched with 7% aq solution of $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (1:2 hexane/ethyl acetate) to give 57 mg (64%) of crystalline compound **20**: mp 60–62 °C; $[\alpha]_D^{25} = +22.2$ (*c* 0.16, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}) 3064, 2956, 1694, 1229, 1050. δ_H ($CDCl_3$, 400 MHz): 8.79 (br s, 1H, NH), 7.58 (d, $J_{6,5}$ = 8.2 Hz, 1H, H_6),

Table 2
Crystal data and structure refinement parameters for compounds **10**

	10
Empirical formula	$C_{20}H_{35}NO_4SSi$
Formula weight	413.65
Temperature, *T* (K)	293(2)
Wavelength, λ (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	9.4548 (3)
b (Å)	12.4226 (4) β = 90 (6)°
c (Å)	20.7169 (6)
V (Å^3)	2433.27 (13)
Z	4
ρ_{calcd} (g/cm^3)	1.129
Absorption coefficient (mm^{-1})	0.204
F(0 0 0)	896
Crystal size (mm)	0.5 × 0.150 × 0.065
Theta (°) range for data collection	2.71–25.00
Index ranges	$11 \leqslant h \leqslant 11$ $-14 \leqslant k \leqslant 14$ $-24 \leqslant l \leqslant 24$
Independent reflections (R_{int})	4292 (0.0637)
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.878
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4292/0/252
Goodness-of-fit on F^2	0.893
Final *R* indices [$I>2\sigma(I)$]	R_1 = 0.0340, wR_2 = 0.0628
R indices (all data)	R_1 = 0.0804, wR_2 = 0.0685
Largest diff. peak and hole (eÅ^{-3})	0.153 and −0.195

7.37–7.28 (m, 5H, Ph), 6.07 (d, $J_{2',1'}$ = 1.9 Hz, 1H, $H_{1'}$), 5.63 (m, 2H, H_5, NH), 5.19 (m, 1H, $H_{2'}$), 5.05 (m, 1H, $H_{5'}$), 4.69 (d, $J_{H,H}$ = 11.4 Hz, 1H, CH_2Ph), 4.55 (d, $J_{H,H}$ = 11.4 Hz, 1H, CH_2Ph), 4.51 (m, 1H, $H_{4'}$), 4.05 (dd, $J_{4',3'}$ = 3.9 Hz, $J_{3',2'}$ = 0.8 Hz, 1H, $H_{3'}$), 3.70 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 2.15 (s, 3H, CH_3CO). δ_C ($CDCl_3$, 100 MHz): 169.9 (C=O), 169.6 (C=O), 162.7 (C=O), 156.6 (C=O), 149.9 (C=O), 139.7 (CH), 135.6 (C_i), 128.7 (5 × CH_{Ph}), 102.5 (CH), 88.3 (C′H), 80.3 (C′H), 80.2 (C′H), 79.1 (C′H), 72.4 (CH_2), 52.9 (C′H), 52.8 (2 × OCH_3), 20.8 (CH_3). Anal. Calcd for $C_{22}H_{25}N_3O_{10}$: C, 53.77; H, 5.13; N, 8.55. Found: C, 53.55; H, 5.26; N, 8.39.

4.2. X-ray crystallography

Single crystals of **10** suitable for an X-ray diffraction were obtained from a mixture of Et_2O and hexane by slow evaporation at room temperature. The intensities were collected at 293(2) K on a Oxford Diffraction XCalibur2 CCD diffractometer using MoKα radiation (λ = 0.71073 Å). Selected crystallographic and other relevant data for the compound **10** are listed in Table 2. The structure was solved by direct methods.[18] All non-hydrogen atoms were refined anisotropically by full-matrix least-squares calculations based on F^2.[18] All hydrogen atoms were included in calculated positions as riding atoms, with SHELXL97[18] defaults. PLATON[19] programme was used for structure analysis and molecular and crystal structure drawings preparation.

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. CCDC 738029. These data can be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Acknowledgements

The present work was supported by the Grant Agency (Nos. 1/0100/09 and 1/0281/08) of the Ministry of Education, Slovak Republic. NMR measurements provided by the Slovak State Programme Project No. 2003SP200280203 are gratefully acknowledged.

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