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N-Glycoside neoglycotrimers from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide

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Abstract—2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide is available on large scale from D-glucose by means of a three-step sequence involving acetylation, activation as the glycosyl bromide, and stereospecific displacement with azide anion. The azide functionality then serves as a convenient anchor upon which to introduce new functionality, usually with retention of the β-stereochemistry. Here we report the synthesis of an amide-linked *N*-glycosyl trimer, by employing a Staudinger–aza-Wittig process on the azide, as well as a hybrid *N*-glycosyl triazole–amide-linked trimer in which the sugars are separated by 1,2,3-triazole heterocycles. Both of these neoglycotrimers are isolated in good yield with high β-selectivity in each case.

Keywords: Neoglycotrimer; N-Glycoside; Staudinger reaction; Dipolar cycloaddition

1. Introduction

Since the original suggestion by Fuchs and Lehmann,[1] and later Nicolaou,[2] that amide-linked carbohydrate oligomers would be of interest as new materials with potentially valuable properties, there have been numerous reports on the synthesis and subsequent study of such molecules. Most of the previous work has centered on *C*-glycosidic linkages where, for example, an exocyclic carboxylic acid group is pre-installed at the anomeric carbon, which is then conjugated to an aminodeoxy sugar 'amino acid' through an amide linkage.[3] Extensive work by Fleet and co-workers has led to an understanding of the intramolecular folding properties of oligomeric structures constructed from furanose building blocks.[4–7] Sugar-derived acyclic amino acids containing furan rings have been used to produce novel oligomers,[8] and more recent work by the Fleet group has led to novel 'carbohydrate–cyclodextrins' through coupling acyclic carbohydrate-based amino acid analogs.[9,10] The interest in the synthesis of carbopeptoids has been complemented by studies into their structure, particularly their folding properties, for example, by NMR spectroscopy,[5,7,11–13] circular dichroism,[10,14] and most recently by molecular dynamics simulations.[15,16]

Although these oligomers have great potential,[17] both as practical molecules in medicinal chemistry and from a theoretical perspective in terms of their folding properties, the synthesis of diverse collections of related compounds is undoubtedly hindered by the availability of sugar-derived amino acid precursors, as well as by the tedious workups and isolation procedures required. A long term goal of our research is to develop chemistry that alleviates such problems in workup such that the synthesis of collections of related oligomeric structures becomes routine. In this paper, we describe methods for the synthesis of two related N-glycoside neoglycotrimers, **1** and **2**, in Figure 1 that are produced from readily available precursors by classical Staudinger–aza-Wittig chemistry using bis(diphenylphosphino)ethane (dppe) as a convenient replacement for triphenylphosphine (to give **1**), and by Cu(I)-catalyzed dipolar cycloaddition with a sugar-derived alkyne (to give **2**). Both methods produce very clean products and avoid some of the issues related to oligomer purification.

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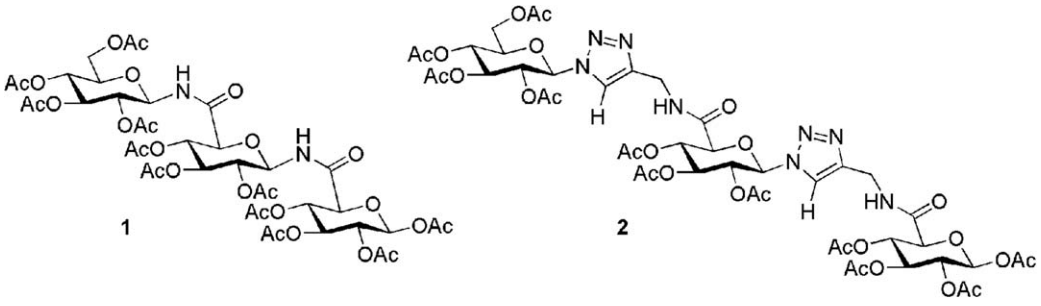


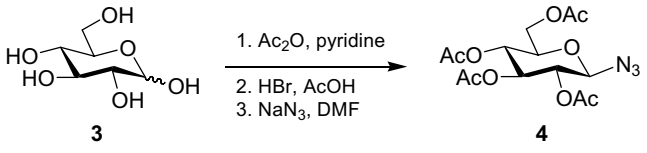
Figure 1.

2. Results and discussion

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (**4**) is available in three steps from D-glucose (**3**) as a highly crystalline solid on multigram scale by the sequence shown in Scheme 1.[18] The precursor bromide is exclusively the α-anomer, which leads to isolation of only the β-azide after stereospecific displacement by azide; the X-ray crystal structure of **4** has recently been reported.[19]

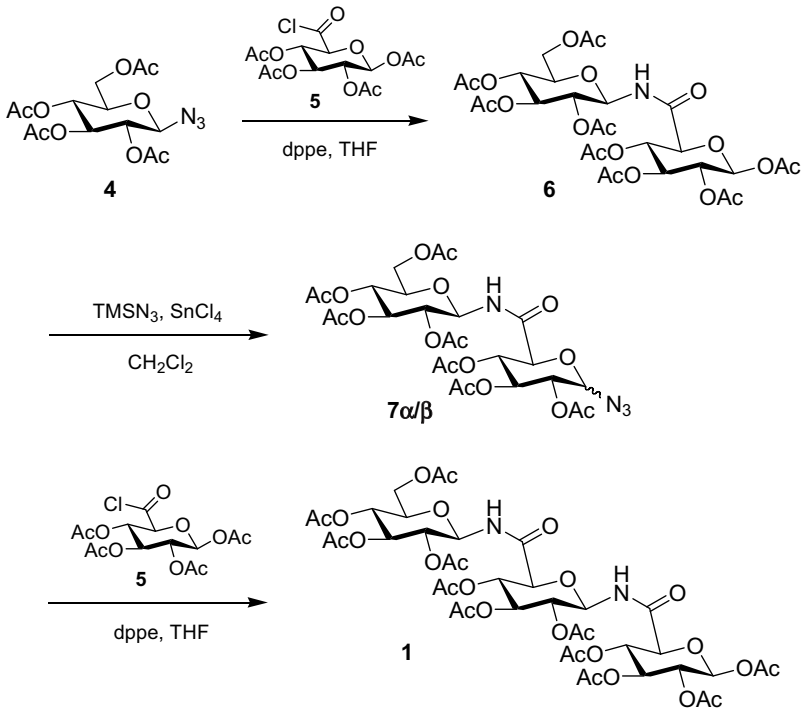
Whereas the use of triphenylphosphine is often problematic when applied to sugars, we have found that bis(diphenylphosphino)ethane (dppe) serves as a useful replacement as the byproduct bis(phosphineoxide) is very polar and does not streak on silica gel as is often the case with $Ph_3P{=}O$.[20] Application of dppe to amide-linked oligomer synthesis could therefore offer advantages over other methods of amide coupling, because in all examples using glycosyl azide precursors the β-configuration of the azide is retained in the amide product.[20] In the present context, reacting azide **4** with glucopyranuronoyl chloride **5**, in the presence of dppe, resulted in a single amide product (**6**, Scheme 2) isolated in 72% yield after an aqueous workup and column chromatography. There is no contamination from the phosphine oxide byproduct. Evidence for the retention of β-stereochemistry in **6** comes from its ^{1}H NMR spectrum in which the 1H triplet at 5.29 ppm (assigned from a COSY experiment) with $J = 9.4$ Hz is consistent with H-1 of the glucopyranosyl ring being aligned *anti* to both the exocyclic N–H and C-2–H bonds. This orientation about C-1 of the glucopyranose ring is in close agreement with other examples of glucosyl amides formed by this method.[20]

To convert **6** into a glycosyl azide suitable for synthesis of the desired trimer (**1**), we first investigated the classical bromination method using HBr in AcOH. Unfortunately, this led to a complex mixture of products from which the expected α-bromide could not be isolated. Turning our attention to alternative methods for the introduction of an azide group at C-1 of the glucopyranuronosyl ring, we employed trimethylsilylazide ($TMSN_3$) and $SnCl_4$, which has been shown to give mainly the α-anomer when an amide group is present at C-6.[21] Participation of the amide group in **6** could be reasonably expected and this was confirmed when an inseparable mixture of anomers of **7** was isolated in ~5:1 α/β ratio. The signal for H-1 of the major isomer appears at 5.70 ppm with a $J_{1,2}$ coupling of 4.4 Hz, which is in close agreement with previously reported analogs.[21]



Scheme 1.

The anomeric azides (**7α/β**) could not be cleanly separated and were used as a mixture for the second round of Staudinger–aza-Wittig chemistry. Thus, reacting **7α/β** with acid chloride **5** in the presence of dppe (Scheme 2) again proceeded smoothly and the major amide product (**1**, 53% yield) was isolated by flash chromatography, again without any trace of phosphine oxide impurity. The mass spectrum of this material confirmed that it was indeed a trimer (HRMS calculated for $C_{40}H_{52}N_2O_{27}$: 1015.2655 [+Na], found: 1015.2618 [+Na]); however, analysis of the ^{1}H NMR spectrum suggested the β-stereochemistry for the newly formed amide linkage at C-1 of the middle glucopyranuronosyl ring, that is, compound **1** in Scheme 2. The H-1 signal for simple β-analogs of **1** typically appears around 5.4 ppm,[20] while the corresponding proton in the α-isomers is usually found in the 5.8–5.9 ppm region.[22,23] The protons at C-1 of the glucopyranose and C-1 of the middle glucopyranuronosyl rings are part of a complex set of signals that overlap in the region 4.9–5.4 ppm, which matches the previously reported β-analogs and not the α-isomers. Additionally, the N–H/H-1 coupling constants of 9.5 and 9.3 Hz, obtained from the N–H signals at 7.14 and 7.32 ppm, respectively, are consistent with the β-stereochemistry at both anomeric positions; the corresponding coupling constants in the α-isomers are typically around 7 Hz. Isolation of **1** as the β-anomer infers that the α-phosphinimine intermediate formed from the major α-isomer of azide **7** must be undergoing



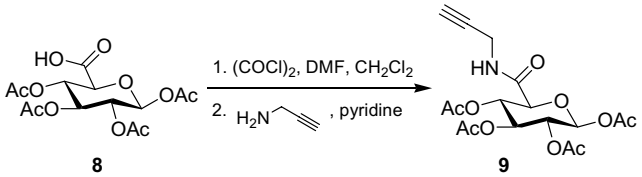
Scheme 2.

ring-opening–ring-closing epimerization to give the corresponding β-ylide, which then reacts with the acid chloride **5** to give the isolated product. Such phosphinimine epimerizations have been reported by others.[22]

While glycosyl phosphinimines may be capable of anomeric interconversion, dipolar cycloaddition reactions between the precursor glycosyl azides and alkynes are known to result in retention of the anomeric stereochemistry in the glycosyl 1,2,3-triazole products. We have used this reaction to advantage in numerous systems to produce collections of triazole-linked carbohybrids.[24,25] Interest in the use of this chemistry for conjugating biologically important molecules together has grown recently and has been included in the 'click chemistry' paradigm described by Sharpless and co-workers.[26] Because the cycloaddition reaction is completely atom economical and generates no waste, this chemistry offers a convenient way to produce novel sugar-based oligomers.[27] Additionally, several catalytic systems have been developed recently that result in the formation of only the 1,4-disubstituted triazole isomer,[28,29] some of which allow for the chemistry to be performed in water or aqueous alcohol mixtures.[30] This method thus offers the possibility of catalytic 'green' chemistry conditions with complete control over the stereo- and regiochemical identity of the products.

For the construction of neoglycooligomers, we required a suitable alkyne partner to react with β-glucosyl azide **4** and produced amide-linked alkyne **9**, from protected glucuronic acid **8**,[21] by the sequence shown in Scheme 3. The X-ray crystal structure of **9** is shown in Figure 2 with the crystallographic data compiled in Table 1 and selected bond lengths and angles being shown in Table 2. As would be expected, the pyranosyl ring in **9** is clearly in the $^4C_1$ conformation and the terminal alkyne is accessible to the azide partner as is required for cycloaddition to occur.

The reaction of azide **4** and alkyne **9** was accomplished using the copper sulfate/ascorbic acid catalyst system,[30] and we were gratified to find that the *t*-butyl alcohol/water solvent system worked well with these compounds; although the materials never completely dissolve, there is obviously enough dissolution to allow the reaction to occur. The triazole product (**10**) was isolated by either directly filtering the precipitate from the cooled reaction mixture or, in an attempt to improve overall yield, by extraction from the aqueous reaction mixture. In either case, pure material was obtained that gave the expected mass spectral data (mass calculated for $C_{31}H_{40}N_4O_{19}$: 795.2184 [+Na], found: 795.2203 [+Na]). The presence of a triazole heterocycle was



Scheme 3.

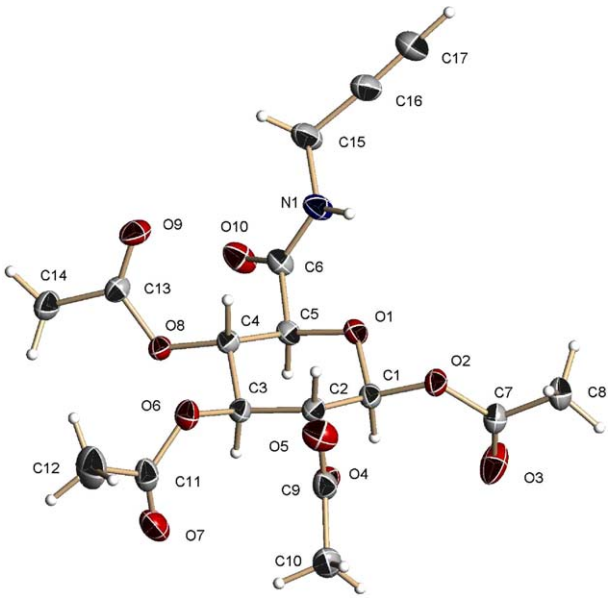


Figure 2. X-ray structure of alkyne **9** showing 50% probability ellipsoids.

Table 1. Crystallographic data for amide-linked alkyne **9**

Empirical formula	$C_{17}H_{21}N_1O_{10}$
Formula weight	399.35
Crystal size (mm)	$0.42 \times 0.24 \times 0.187$
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
V (Å^3)	2379.1(2)
Density (calculated) (Mg/m^3)	1.301
F(000)	840
Absorption coefficient (mm^{-1})	0.109
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal shape, color	Block, colorless
θ Range for data collection	1.56–28.28°
Limiting indices	$-7 \leqslant h \leqslant 7$, $-23 \leqslant k \leqslant 23$, $-26 \leqslant l \leqslant 26$
Reflections collected	21061
Independent reflections	2899 (R(int) = 0.0324)
Completeness to $\theta = 28.28°$	100.0%
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2899/0/257
Goodness-of-fit on F^2	1.065
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0335$, $wR_2 = 0.0894$
R indices (all data)	$R_1 = 0.0347$, $wR_2 = 0.0906$
Largest diff. peak and hole (e × Å^{-3})	0.273 and −0.192

indicated from the ^{1}H NMR spectrum with a singlet appearing at 7.82 ppm, which is typical for a proton at H-5 of a 4-substituted 1,2,3-triazole ring attached at C-1 of a pyranose ring.[25] The question of whether the anomeric identity of the precursor β-azide had been retained in the glycosyl triazole product is answered by considering the 1H doublet at 5.85 ppm. The coupling constant $J_{1,2} = 9.0$ Hz is only reconcilable with the β-stereochemistry shown for **10** in Scheme 4. Additional support for this assignment comes from the X-ray crystal structure of the related azide **12** (Scheme 4, X-ray structure shown in Fig. 3), the synthesis of which is described below.

To introduce an azide at C-1 of the glucopyranuronosyl ring for a second cycloaddition, we treated **10** with HBr in acetic acid, which resulted in smooth formation of the corresponding glycosyl bromide, **11** (Scheme 4). The doublet at 6.44 ppm, with $J_{1,2} = 4$ Hz, clearly indicates that the α-bromide had been formed. Displacement with NaN_3 proved to be straightforward and glycosyl azide **12** was isolated in good yield as a crystalline solid, the structure of which was solved by X-ray diffraction (Fig. 3, Tables 3 and 4). Isolation of only the β-anomer of **12** (^{1}H NMR: H-1 at 4.77 ppm, $J_{1,2} = 8.8$ Hz) after stereospecific S_N2 reaction with azide anion indicates that the precursor was in fact the α-bromide (**11**). Analysis of the crystal structure of **12** (Fig. 3) confirms not only the β-stereochemistry of the newly formed glycosyl azide but also that the earlier cycloaddition, that is, **4** to **10** (Scheme 4), was indeed completely regioselective resulting in the formation of the 1,4-disubstituted 1,2,3-triazole and that the β-stereochemistry of the precursor glycosyl azide (**4**) had been retained during the dipolar cycloaddition step.

The second iteration of the dipolar cycloaddition chemistry, this time involving azide **12** and alkyne **9**, proved problematic in that the conditions applied previously (copper sulfate/ascorbic acid in aqueous alcohol) did not give appreciable amounts of triazole product, which was most likely due to the insolubility of azide **12** (even at reflux) in the solvents used (aqueous *t*-butyl alcohol, aqueous ethanol). We therefore switched our attention to organic solvents and the $Cu(PPh_3)_3Br$ catalyst described by Santoyo-González and co-workers.[29] Gratifyingly, this provided the trimeric compound **2** in 54% yield as a solid that gave mass spectral data in agreement with its structure; mass calculated for $C_{46}H_{58}N_8O_{27}$: 1177.3309 (+Na), found: 1177.3302 (+Na). Again the cycloaddition proved to be regioselective as the 1,4-disubstituted isomer was formed exclusively (singlets at 8.18 and 8.24 ppm in the ^{1}H NMR spectrum of **2** collected in DMSO-d_6). The β-orientation of the new triazole ring about the anomeric carbon is also deduced from the ^{1}H NMR spectrum of **2** with the signal for H-1 of the two pyranuronosyl rings showing at 6.37 and 6.42 ppm with $J_{1,2}$ being 9.0 and 8.8 Hz, respectively.

In conclusion, we have developed routes to two types of amide-linked neoglycotrimers. The first route produces a carbopeptoid-like trimer that relies on efficient Staudinger–aza-Wittig chemistry using bis(diphenylphosphino)ethane (dppe) as the phosphine to avoid the workup problems associated with other phosphines. The second pathway uses the regioselective Cu(I)-catalyzed dipolar cycloaddition between glycosyl azides and a glucopyran-

Table 2. Selected bond lengths (Å) and bond angles (°) for amide-linked alkyne **9**

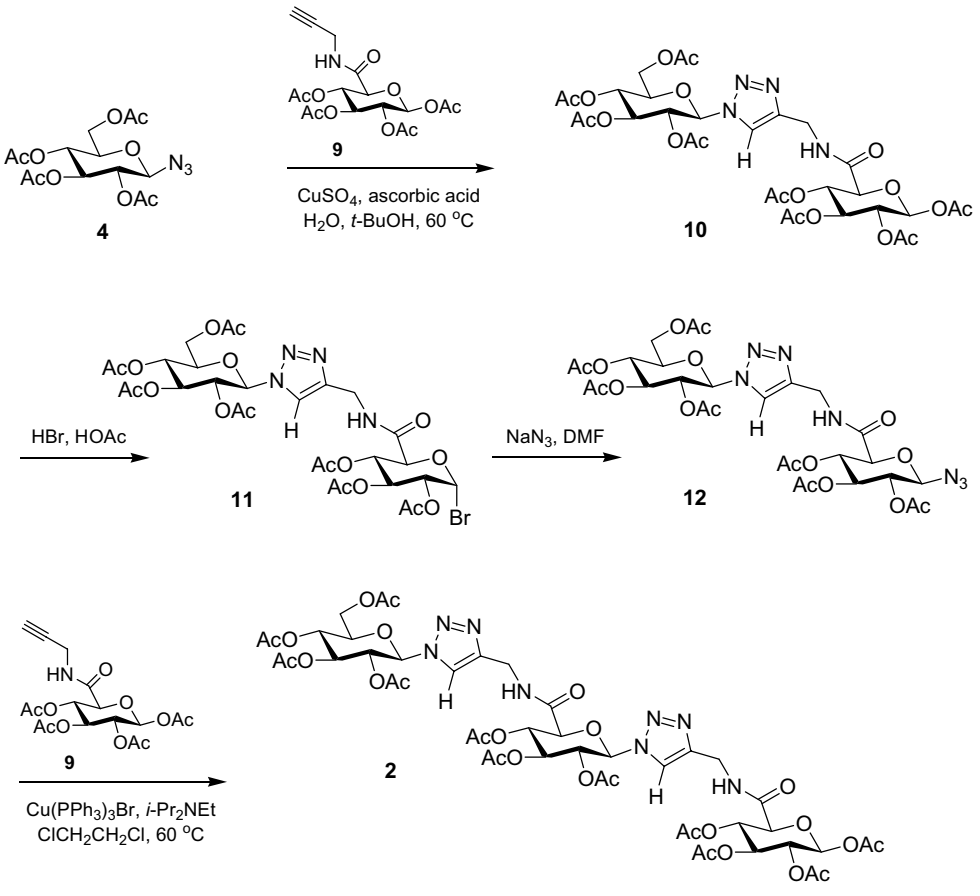
Bond lengths			
C-1–C-2	1.518(19)	C-5–C-6	1.524(2)
C-2–C-3	1.521(19)	C-6–N-1	1.3363(19)
C-3–C-4	1.512(19)	C-6–O-10	1.2251(18)
C-4–C-5	1.541(19)	N-1–C-15	1.455(2)
Bond angles			
O-1–C-1–O-2	104.33(11)	C-5–C-6–O-10	120.42(13)
C-2–C-1–O-2	110.58(11)	C-5–C-6–N-1	115.65(13)
C-1–O-1–C-5	113.39(10)	N-1–C-15–C-16	112.58(14)
O-1–C-5–C-6	108.36(11)	C-6–N-1–C-15	177.0(2)

uronosyl-derived alkyne to produce a triazole-linked trimer with retention of stereochemistry at each anomeric center. We are currently studying the intramolecular folding interactions of the deprotected, that is, polyhydroxylated, derivatives of these compounds.

3. Experimental

3.1. General methods

Reactions were monitored by TLC using pre-coated aluminum-backed plates and compounds were visualized using a 5% H_2SO_4 in EtOH solution with subsequent burning. NMR spectra were recorded on a Varian Gemini 2000 system at 400 MHz for ^1H and 100 MHz for ^{13}C. In the reported spectra, '*glc*' refers to signals for protons in the glucopyranose ring(s) and '*glcU*' refers to protons in the glucuronosyl ring(s). Low resolution mass spectra (LRMS) were collected using a Bruker Esquire-HP 1100 instrument at YSU and high resolution spectra (HRMS) were collected on a Micromass LCT instrument at The Ohio State University Campus Chemical Instrumentation Center. Optical rotations were determined on a Perkin–Elmer 343 automatic polarimeter as solutions in CH_2Cl_2 or DMF. Diffraction data for compounds **9** and **12** were collected on a Bruker AXS SMART APEX CCD diffractometer at 100(2) K using monochromatic Mo Kα radiation with omega scan technique using the SMART software.[31] The unit cell was refined and the data were integrated using SAINT+.[32] The structures were solved by direct methods and refined by full matrix least squares against F^2 with all reflections using SHELXTL.[33] Refinement of an extinction coefficient was found to be insignificant. All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and refined with an isotropic displacement parameter 1.5 (CH_3) or 1.2 times (all



Scheme 4.

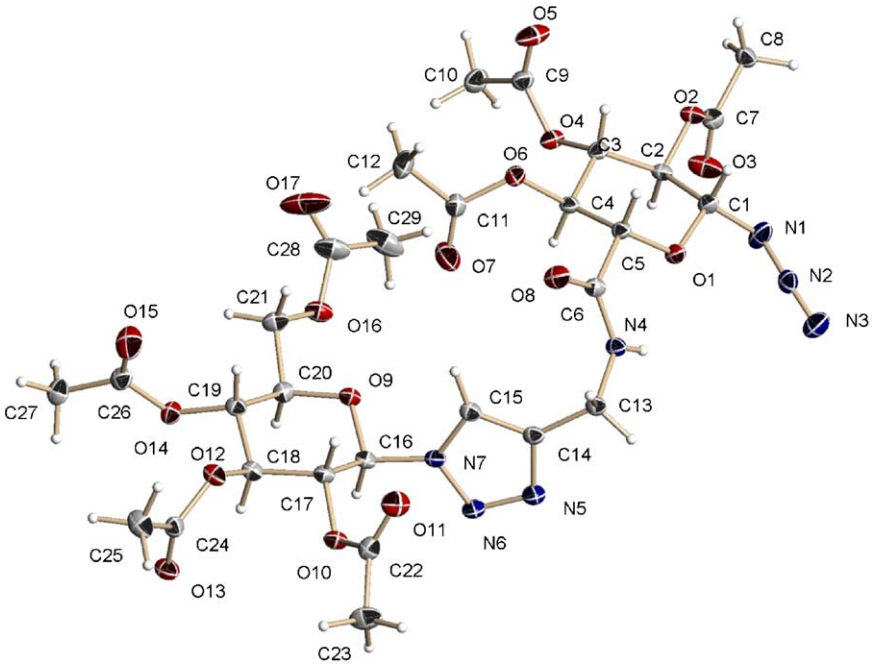


Figure 3. X-ray structure of azide **12** showing 50% probability ellipsoids.

Table 3. Crystallographic data for azide **12**

Empirical formula	$C_{29}H_{37}N_7O_{17}$
Formula weight	755.66
Crystal size (mm)	$0.52 \times 0.27 \times 0.05$
Crystal system	Monoclinic
Space group	$P2_1$
b (Å)	15.837(4) Å, $\beta = 94.613(5)°$
V (Å^3)	1759.6(8)
Density (calculated) (Mg/m^3)	1.426
$F(000)$	792
Absorption coefficient (mm^{-1})	0.119
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal shape, color	Plate, colorless
θ Range for data collection	1.90–30.50°
Limiting indices	$-14 \leqslant h \leqslant 14$, $-22 \leqslant k \leqslant 22$, $-14 \leqslant l \leqslant 15$
Reflections collected	21023
Independent reflections	5518 (R(int) = 0.0332)
Completeness to $\theta = 30.50°$	99.3%
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5518/1/485
Goodness-of-fit on F^2	1.082
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0430$, $wR_2 = 0.1053$
R indices (all data)	$R_1 = 0.0455$, $wR_2 = 0.1070$
Largest diff. peak and hole (e × Å^{-3})	0.415 and −0.222

Table 4. Selected bond lengths (Å) and bond angles (°) for azide **12**

Bond lengths			
C-1–N-1	1.465(2)	C-13–C-14	1.496(3)
C-1–O-1	1.417(2)	N-7–C-16	1.444(2)
C-1–C-2	1.518(3)	C-16–C-17	1.527(3)
N-4–C-13	1.451(2)	C-16–O-9	1.410(2)
Bond angles			
C-1–N-1–N-2	114.66(18)	C-14–N-5–N-6	109.09(17)
C-2–C-1–N-1	106.21(16)	N-5–N-6–N-7	106.67(16)
N-4–C-13–C-14	113.71(16)	N-6–N-7–C-16	119.49(15)
C-13–C-14–C-15	130.52(17)	N-7–C-16–C-17	112.12(15)

others) that of the adjacent carbon or nitrogen atom. CCDC-299743 (**9**) and CCDC-299744 (**12**) contain the Supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0)1223 336033.

3.2. 1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranuronoyl chloride (5)

This is a modification of the method reported by Tosin and Murphy for a related compound.[21] A solution of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronic acid (**8**)[21] (2.0 g, 5.52 mmol) in CH_2Cl_2 (0.02 g/mL) was cooled to 0 °C and oxalyl chloride (0.96 mL, 11.04 mmol) was added. DMF (2.5 mL) was slowly added to the stirring solution and evolution of gas was observed. The pale yellow solution was allowed to stir for 30 min at 0 °C and then for 2 h at rt. The solution was evaporated to leave a purple chalky solid (2.04 g, 97%), which was

stored in a desiccator under vacuum: mp 120–123 °C; $[\alpha]_D$ +6.4 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.05 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 4.46 (d, 1H, $J = 8.6$ Hz, H-5), 5.12 (dd, 1H, $J = 6.3$, 8.1 Hz, H-2), 5.28 (dd, 1H, $J = 8.2$, 8.8 Hz, H-3), 5.41 (t, 1H, $J = 8.7$ Hz, H-4), 5.89 (d, 1H, $J = 6.4$ Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 20.5, 20.6 (2 × C), 20.8, 67.6, 69.7, 70.7, 78.7, 90.9, 168.2, 168.8 (2 × C), 169.4, 169.5.

3.3. *N*-(2,3,4.6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronamide (6)

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (**4**, 0.747 g, 2.0 mmol), acid chloride **5** (1.218 g, 3.2 mmol), and dppe (0.518 g, 1.3 mmol) were mixed in dry THF (0.1 g/mL) at rt. After disappearance of the intermediate ylide was confirmed by TLC, satd $NaHCO_3$ (3 mL) was added and the mixture was allowed to stir vigorously overnight. Following removal of the solvent under vacuum, the crude product was extracted into $CHCl_3$ (3 × 20 mL) and the combined extracts were washed with water (20 mL). After drying over anhydrous $MgSO_4$ and evaporating, the crude product was purified by flash column chromatography (1:2, hexanes/EtOAc) to yield **6** as a colorless crystalline solid (0.99 g, 72%): mp 185–188 °C; $[\alpha]_D$ +4.7 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.026 (s, 6H, 3 × $COCH_3$), 2.029 (s, 3H, $COCH_3$), 2.050 (s, 3H, $COCH_3$), 2.052 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 2.19 (s, 3H, $COCH_3$), 3.79 (ddd, 1H, $J = 2.1$, 4.4, 10.1 Hz, H-5_{glc}), 4.04 (d, 1H, $J = 10.1$ Hz, H-5_{glcU}), 4.05 (dd, 1H, $J = 1.9$, 12.5 Hz, H-6_{glc}), 4.31 (dd, 1H, $J = 4.5$, 12.5 Hz, H-$6'_{glc}$), 4.95 (t, 1H, $J = 9.61$ Hz), 5.00 (dd, 1H, $J = 9.6$, 10.0 Hz, H-4_{glcU}), 5.06 (t, 1H, $J =$ 9.79 Hz), 5.10–5.16 (m, 2H), 5.29 (t, 1H, $J = 9.43$ Hz), 5.31 (t, 1H, $J = 9.52$ Hz, H-2_{glc}), 5.75 (d, 1H, $J =$ 8.24 Hz, H-1_{glcU}), 7.13 (d, 1H, $J = 9.34$ Hz, N–H); ^{13}C NMR ($CDCl_3$): δ 20.56 (2 × C), 20.59 (3 × C), 20.66, 20.73, 20.8, 61.5, 67.8, 68.5, 69.9, 70.1, 71.8, 72.5, 72.5, 73.6, 77.6, 90.9, 166.3, 168.5, 168.9, 169.2 (2 × C), 169.4, 169.5, 170.3, 171.0. LRMS calcd for $[C_{28}H_{37}NO_{19}+Na]^+$: 714.186. Found: 714.2. ESIMS *m*/*z* calcd for $[C_{28}H_{37}NO_{19}+Na]^+$: 714.1857. Found: 714.1808.

3.4. *N*-(2,3,4.6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-azidodeoxy-2,3,4-tri-*O*-acetyl-α/β-D-glucopyranuronamides (7α/β)

Amide **6** (0.368 g, 0.53 mmol) was dissolved in dry CH_2Cl_2 (4 mL) under N_2. $TMSN_3$ (0.174 mL, 1.33 mmol) and $SnCl_4$ (0.03 mL, 0.265 mmol) were added successively and the mixture was allowed to stir at rt for 15 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and satd $NaHCO_3$ (25 mL) and the suspension stirred vigorously for 30 min. After separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined extracts were washed with water (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered, and reduced to an off-white foam. Flash column chromatography (4:5, hexanes/EtOAc) gave the product as a colorless foam (0.23 g, 64%), which was a mixture of α/β isomers (5:1) by ^1H NMR: for the major (α-) isomer ($CDCl_3$): δ 2.02 (s, 3H, $COCH_3$), 2.04 (s, 6H, 2 × $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 3.80 (ddd, 1H, $J = 2.1$, 4.3, 10.2 Hz, H-5_{glc}), 4.08 (dd, 1H, $J = 2.0$, 12.4 Hz, H-6_{glc}), 4.30 (dd, 1H, $J = 4.4$, 12.6 Hz, H-$6'_{glc}$), 4.37 (d, 1H, $J = 10.3$ Hz, H-5_{glcU}), 4.86–4.95 (m, 2H), 5.06 (t, 1H, $J = 9.8$ Hz), 5.17 (t, 1H, $J = 9.4$ Hz), 5.33 (t, 1H, $J = 9.6$ Hz), 5.42 (t, 1H, $J = 9.9$ Hz), 5.70 (d, 1H, $J = 4.4$ Hz, H-1_{glcU}), 7.12 (d, 1H, $J = 9.3$ Hz, N–H).

3.5. Amide-linked trimer 1

The α/β mixture of azides (**7**, 0.690 g, 1.023 mmol), acid chloride **5** (0.623 g, 1.637 mmol), and dppe (0.245 g, 0.614 mmol) were mixed in dry THF (0.1 g/mL) at rt. When disappearance of the intermediate ylide was confirmed by TLC, satd $NaHCO_3$ (3 mL) was added and the mixture was allowed to stir vigorously overnight. Workup as for **4** gave a syrup that was purified by flash column chromatography (1:3, hexanes/EtOAc) to yield the title compound as a colorless solid (0.546 g, 53%): mp 178–180 °C; $[\alpha]_D$ +5.2 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.03 (s, 9H, 3 × $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.06 (s, 6H, 2 × $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.14 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 2.21 (s, 3H, $COCH_3$), 3.76 (m, 1H, H-5_{glc}), 3.97 (d, 1H, $J = 10.1$ Hz, H-5_{glcU}), 4.05 (dd, 1H, $J = 1.7$, 12.5 Hz, H-6_{glc}), 4.09 (d, 1H, $J = 10.1$ Hz, H-5_{glcU}), 4.29 (dd, 1H, $J = 4.6$, 12.4 Hz, H-$6'_{glc}$), 4.88–5.08 (m, 5H), 5.12–5.18 (m, 3H), 5.28–5.37 (m, 3H), 5.79 (d, 1H, $J = 8.1$ Hz, H-1_{glcU}), 7.14 (d, 1H, $J = 9.5$ Hz, N–H), 7.32 (d, 1H, $J = 9.3$ Hz, N–H); ^{13}C NMR ($CDCl_3$): δ 20.48 (3 × C), 20.53 (3 × C), 20.63 (2 × C), 20.69 (2 × C), 20.74, 61.3, 61.8, 68.3, 68.7, 70.2, 70.3, 70.6, 71.9, 72.1, 72.9 (2 × C), 73.9 (2 × C), 77.81, 77.87, 91.3, 166.7, 166.8, 168.8, 169.2, 169.4, 169.5, 169.6 (2 × C), 169.7, 170.6, 171.2 (2 × C), 171.3; ESIMS *m*/*z* calcd for $[C_{40}H_{52}N_2O_{27}+Na]^+$: 1015.2655. Found: 1015.2618.

3.6. *N*-(Prop-2-ynyl)-1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronamide (9)

Oxalyl chloride (0.48 mL, 5.52 mmol) was added to a solution of carboxylic acid **8**[21] (1.0 g, 2.76 mmol) in dry CH_2Cl_2 (0.02 g/mL) held at 0 °C. With stirring, DMF (1.2 mL) was added slowly and evolution of gas

was observed. The pale yellow solution was allowed to stir for 30 min at 0 °C and then 2 h at rt. Evaporation afforded a purple solid (**5**), which was immediately dissolved in dry CH_2Cl_2 (20 mL), and to this was added a solution of propargyl amine (0.19 mL, 3.04 mmol) and pyridine (0.67 mL, 8.28 mmol) in CH_2Cl_2 (5 mL). Precipitation of an off-white solid was observed and the mixture was allowed to stir overnight and then poured into ice water (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with 5% H_2SO_4 (3 × 15 mL), then water (15 mL), dried with anhydrous $MgSO_4$, filtered, and reduced to a cream-colored solid, which was recrystallized from CH_3OH to give colorless crystals (0.91 g, 83%): mp 166–167 °C; $[\alpha]_D$ +3.7 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.03 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 2.27 (t, 1H, $J = 2.6$ Hz, C≡C–H), 4.11 (d, 1H, $J = 9.7$ Hz, H-5), 3.99, (ddd, 1H, $J = 2.6$, 5.3, 17.6 Hz, C≡C–CH), 4.06 (ddd, 1H, $J = 2.7$, 5.5, 17.6 Hz, C≡C–CH), 5.12 (dd, 1H, $J = 8.0$, 8.9 Hz, H-2), 5.22 (t, 1H, $J = 9.5$ Hz, H-3), 5.31 (t, 1H, $J = 9.2$ Hz, H-4), 5.77 (d, 1H, 7.9 Hz, H-1), 6.50 (t, 1H, $J = 5.2$ Hz, N–H); ^{13}C NMR ($CDCl_3$): δ 20.6 (2 × C), 20.7, 20.8, 28.9, 68.6, 70.0, 71.7, 72.0, 72.7, 74.0, 91.1, 165.4, 168.5, 168.9, 169.3, 169.5; ESIMS *m*/*z* calcd for $[C_{17}H_{21}NO_{10}+Na]^+$: 422.1063. Found: 422.1063.

3.7. Triazole-linked amide 10

Azide **4** (0.747 g, 2 mmol), alkyne **9** (0.798 g, 2 mmol), ascorbic acid (0.141 g, 0.8 mmol), and $CuSO_4$ (0.100 g, 0.4 mmol) were mixed in water (20 mL) and stirred vigorously while being heated at 60 °C until the reaction was determined complete by TLC. After cooling to rt, cold water was added, and the resulting precipitate was filtered on a glass frit. To obtain the best yield, the reaction mixture was extracted with CH_2Cl_2, the extracts were dried over anhydrous $MgSO_4$, filtered, and reduced to give the product as an off-white solid (1.59 g, 91%): mp 221–224 °C; $[\alpha]_D$ −9.4 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 1.88 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 3.98 (m, 1H, H-5_{glc}), 4.10 (d, 1H, $J = 9.7$ Hz, H-5_{glcU}), 4.16 (m, 1H, H-6_{glc}), 4.30 (dd, 1H, $J = 4.9$, 12.5 Hz, H-$6'_{glc}$), 4.46 (dd, 1H, $J = 5.7$, 15.2 Hz, C≡C–CH), 4.59 (dd, 1H, $J = 6.2$, 15.6 Hz, C≡C–CH), 5.10 (t, 1H, $J = 8.7$ Hz, H-2_{glcU}), 5.19 (t, 1H, $J = 9.6$ Hz, H-4_{glcU}), 5.26 (t, 1H, $J = 9.5$ Hz, H-4_{glc}), 5.31 (t, 1H, $J = 9.3$ Hz, H-3_{glcU}), 5.41 (t, 1H, $J = 9.3$ Hz, H-3_{glc}), 5.47 (t, 1H, $J = 9.3$ Hz, H-2_{glc}), 5.75 (d, 1H, $J = 8.1$ Hz, H-1_{glcU}), 5.85 (d, 1H, $J = 9.0$ Hz, H-1_{glc}), 6.89 (t, 1H, $J = 6.0$ Hz, N–H), 7.82 (s, 1H, triazole-H); ^{13}C NMR ($CDCl_3$): δ 20.3, 20.6 (4 × C), 20.8 (3 × C), 34.6, 61.5, 67.5, 68.7, 70.0, 70.2, 71.8, 72.6, 72.8, 75.0, 85.6, 91.1, 121.1, 144.7, 165.8, 168.5 (2 × C), 169.0, 169.1, 169.5 (2 × C), 169.7, 170.27; ESIMS *m*/*z* calcd for $[C_{31}H_{40}N_4O_{19}+Na]^+$: 795.2184. Found: 795.2203.

3.8. Triazole-linked glycosyl bromide 11

Amide **10** (0.750 g, 0.97 mmol) was dissolved in 33% HBr/AcOH (8 mL) and the brown solution was allowed to stir at rt for 2 h when TLC (5% CH_3OH in toluene) showed consumption of starting material. The reaction mixture was diluted with $CHCl_3$ (50 mL) and neutralized by slow addition of satd $NaHCO_3$. The mixture was extracted with $CHCl_3$ (3 × 30 mL) and the extracts were washed with water (100 mL), dried over $MgSO_4$, filtered, and reduced to a hygroscopic tan foam (0.71 g, 92%): $[\alpha]_D$ +71.2 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 1.88 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 4.02 (ddd, 1H, $J = 2.4$, 4.9, 10.2 Hz, H-5_{glc}), 4.16 (dd, 1H, $J = 2.0$, 12.6 Hz, H-6_{glc}), 4.31 (dd, 1H, $J = 4.9$, 12.6 Hz, H-$6'_{glc}$), 4.47 (dd, 1H, $J = 5.6$, 15.3 Hz, C≡C–CH), 4.51 (d, 1H, $J = 10.3$ Hz, H-5_{glcU}), 4.59 (dd, 1H, $J = 6.0$, 15.4 Hz, C≡C–CH), 4.83 (dd, 1H, $J = 4.1$, 10.0 Hz, H-2_{glcU}), 5.21 (dd, 1H, $J = 9.5$, 10.3 Hz), 5.26 (m, 1H), 5.40 (m, 2H), 5.61 (t, 1H, $J = 9.8$ Hz), 5.89 (m, 1H, H-1_{glc}), 6.64 (d, 1H, $J = 4.0$ Hz, H-1_{glcU}), 7.16 (t, 1H, $J = 5.7$ Hz, N–H), 7.82 (s, 1H, triazole-H); ^{13}C NMR ($CDCl_3$): δ 20.2, 20.5 (2 × C), 20.6 (2 × C), 20.7 (2 × C), 34.4, 61.4, 67.5, 68.3, 69.2, 70.3 (2 × C), 72.4, 72.5, 77.2, 84.9, 85.4, 121.4, 144.4, 165.8, 168.4, 169.0, 169.1 (2 × C), 169.5, 169.6, 170.2.

3.9. Triazole-linked azide 12

Bromide **11** (0.68 g, 0.86 mmol) was dissolved in dry DMF (8 mL), sodium azide (0.25 g, 3.85 mmol) was added, and the orange solution was allowed to stir at rt for 6 h. The solvent was removed, the crude mixture was partitioned between water (50 mL) and CH_2Cl_2 (50 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined extracts were washed with water (3 × 150 mL), dried over anhydrous $MgSO_4$, filtered, and reduced to a colorless solid that was recrystallized from EtOH (0.53 g, 82%): mp 193 °C (decomp.); $[\alpha]_D$ −19.7 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 1.87 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.09 (s, 6H, 2 × $COCH_3$), 4.04 (ddd, 1H, $J = 2.4$, 4.9, 10.1 Hz, H-5_{glc}), 4.09 (d, 1H, $J = 9.9$ Hz, H-5_{glcU}), 4.17 (dd, 1H, $J = 2.1$, 12.5 Hz, H-6_{glc}), 4.31 (dd, 1H, $J = 4.9$, 12.6 Hz, H-$6'_{glc}$), 4.50 (dd, 1H, $J = 5.9$, 15.4 Hz, C≡C–CH), 4.61 (dd, 1H, $J = 6.0$, 15.5 Hz, C≡C–CH,), 4.77 (d, 1H, $J = 8.8$ Hz, H-1_{glcU}), 4.94

(t, 1H, $J = 9.2$ Hz), 5.17 (t, 1H, $J = 9.7$ Hz), 5.25 (m, 2H), 5.43 (t, 1H, $J = 9.4$ Hz), 5.48 (t, 1H, $J = 9.3$ Hz), 5.90 (d, 1H, $J = 9.0$ Hz, H-1_{glc}), 7.23 (t, 1H, $J = 6.0$ Hz, N–H), 7.87 (s, triazole-H, 1H); ^{13}C NMR ($CDCl_3$): δ 20.3, 20.6 (4 × C), 20.7, 20.8, 34.7, 61.6, 67.6, 68.9, 70.3, 70.4, 71.7, 72.7, 74.2, 75.0, 85.6, 87.9, 121.1, 144.7, 165.8, 168.5, 168.9, 169.1, 169.4, 169.6, 169.7, 170.2; ESIMS *m/z* calcd for $[C_{29}H_{37}N_7O_{17}+Na]^+$: 778.2144. Found: 778.2158. The X-ray crystal structure of **12** is discussed in the text.

3.10. Triazole-linked trimer 2

Azide **11** (0.200 g, 0.265 mmol), alkyne **3** (0.116 g, 0.292 mmol), $Cu(PPh_3)_3Br$ (0.049 g, 0.53 mmol), and *i*-Pr_2NEt (0.138 mL, 0.795 mmol) were dissolved in dry CH_2Cl_2 (5 mL) and the orange solution was heated to 60 °C and stirred for 1 h after which time TLC analysis showed consumption of the azide starting material. The solution was cooled, the solvent was removed, then CH_3OH (50 mL) was added and the resulting suspension was heated to boiling. After cooling to room temperature, the CH_3OH was decanted and the extraction with CH_3OH was repeated (2 × 50 mL). Evaporation of the CH_3OH gave the product as a colorless solid (0.165 g, 54%): mp 252 °C (decomp.); $[\alpha]_D$ −9.8 (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6): δ 1.83 (s, 3H, $COCH_3$), 1.85 (s, 3H, $COCH_3$), 1.95 (s, 3H, $COCH_3$), 2.00 (s, 6H, $COCH_3$), 2.02 (s, 6H, $COCH_3$), 2.057 (s, 3H, $COCH_3$), 2.062 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 4.10 (m, 1H), 4.18 (m, 1H), 4.26–4.43 (m, 6H), 4.55 (d, 1H, $J = 9.9$ Hz), 5.03 (dd, 1H, $J = 8.5$, 9.6 Hz), 5.16 (t, 1H, $J = 9.7$ Hz), 5.21 (t, 1H, $J = 9.7$ Hz), 5.37 (t, 1H, $J = 9.5$ Hz), 5.50 (t, 1H, $J = 9.6$ Hz), 5.57–5.68 (m, 4H), 6.02 (d, 1H, $J = 8.2$ Hz), 6.37 (d, 1H, $J = 9.0$ Hz), 6.42 (d, 1H, $J = 8.8$ Hz), 8.18 (s, 1H, triazole-H), 8.24 (s, 1H, triazole-H), 8.76–8.81 (m, 2H, 2 × N–H); ^{13}C NMR ($CDCl_3$): δ 19.7 (2 × C), 20.1 (6 × C), 20.2, 20.3 (2 × C), 34.0 (2 × C), 61.6, 67.6, 68.8, 69.0, 69.8 (2 × C), 70.1, 71.5, 72.0, 72.3, 72.9, 73.3, 74.6, 83.7, 83.8, 90.8, 122.1, 122.3, 144.6, 144.7, 165.5, 165.7, 168.4 (2 × C), 168.7, 168.90, 168.94; 169.1, 169.3, 169.4, 169.5, 169.6, 170.0; ESIMS *m/z* calcd for $[C_{46}H_{58}N_8O_{27}+Na]^+$: 1177.3309. Found: 1177.3302.

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Supplementary data

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