Carbohydrate Research 343 (2008) 2535–2544

Contents lists available at ScienceDirect

Carbohydrate Research

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

Synthesis of novel glycophanes derived from glucuronic acid by ring closing alkene and alkyne metathesis

Dearbhla Doyle, Paul V. Murphy *

Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland

ARTICLE INFO

Article history:
Received 27 April 2008
Received in revised form 30 May 2008
Accepted 7 June 2008
Available online 14 June 2008

Keywords:
Ring closing alkene metathesis
Ring closing alkyne metathesis
Macrocycles
Cyclophanes
Glycophanes
Amide

ABSTRACT

Cyclophanes and their analogues are of interest in bioactive molecule development and in biomimetic, supramolecular and materials chemistry. Novel hybrids of sugars and cyclophanes (glycophanes) have been prepared via the coupling of alkenyl and alkynyl glucopyranosiduronic acids with phenylene-1,4-diamine and xylene-1,4-diamine and subsequent intramolecular metathesis. Structural studies showed that the geometric arrangements of the sugar groups in the macrocycles containing secondary amides differ from those in macrocycles that contain tertiary amides. This is due to the amides adopting different configurational preferences. The compounds had low solubility in water, precluding an investigation of their recognition phenomena in this medium.

1. Introduction

The presence of reactive functional groups on a molecular scaffold provides a basis for modification of its properties. Polyfunctional compounds, such as saccharides and their derivatives, have thus found wide application as scaffolds for novel bioactive molecule design and synthesis.[1] Macrocyclic compounds, such as cyclophanes and their analogues, have also displayed properties as scaffolds in bioactive molecule development.[2] Previously, macrocycles **1** and **2** (Chart 1), which can be considered hybrids of saccharides and cyclophanes (glycophanes), have been synthesized using ring closing alkene metathesis[3] of preorganized substrates derived from glucuronic acid.[4] Of those investigated, only the tertiary amide containing dienes proceeded to give macrocycles. For example, the diamide **3** is folded in a manner that makes intramolecular metathesis possible due to both tertiary amide groups adopting *E*-configured amides (or *cis*-amides according to peptide nomenclature). Thus, reaction of **3** (R = Ac) gives **1** by RCM and subsequent de-O-acetylation. Glycophane **2** was obtained from a similar dimethylated substrate. Metathesis of **4** did not give the product of intramolecular metathesis; oligomeric derivatives were formed as a result of intermolecular metatheses. The latter outcome is accounted for by the amides of **4** adopting *Z*-configurations (*trans*-amides according to peptide nomenclature) that preclude the folding required to facilitate RCM. The glycophanes obtained from these studies have potential as scaffolds due to the presence of numerous functional groups,[5] and they are being exploited as such within our group.[6] In addition to roles as scaffolds, glycophanes have been prepared for application in biomimetic and supramolecular chemistry.[7] For example, the pentenyl derivative **2**[8,9] displayed behaviour similar to β-cyclodextrin in being able to bind 8-anilino-1-naphthalenesulfonate, a hydrophobic probe.[9] The development of highly rigid glycophanes such as **1** could provide a basis for generating chiral polyhydroxylated shape persistent macrocycles with potential in material science.[10] The preparation and structural analysis of glycophanes incorporating secondary amides by RCM and ring closing alkyne metathesis[11,12] is thus reported herein.

2. Results and discussion

2.1. Synthesis of dienes and a diyne for metathesis

The substrate **5** was prepared as described previously[9] (Scheme 1), and conditions for its selective alkylation were investigated to obtain a compound **6**, which contained both a tertiary amide and a secondary amide. The conditions that worked best involved careful addition of sodium hydride and iodomethane to **5** in DMF giving **6** in 23% yield. The N,N-dimethylated analogue was also produced from this reaction, and **5** was recovered unreacted.

* Corresponding author. Fax: +353 1 7162501.
E-mail address: Paul.V.Murphy@ucd.ie (P. V. Murphy).

0008-6215/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2008.06.007

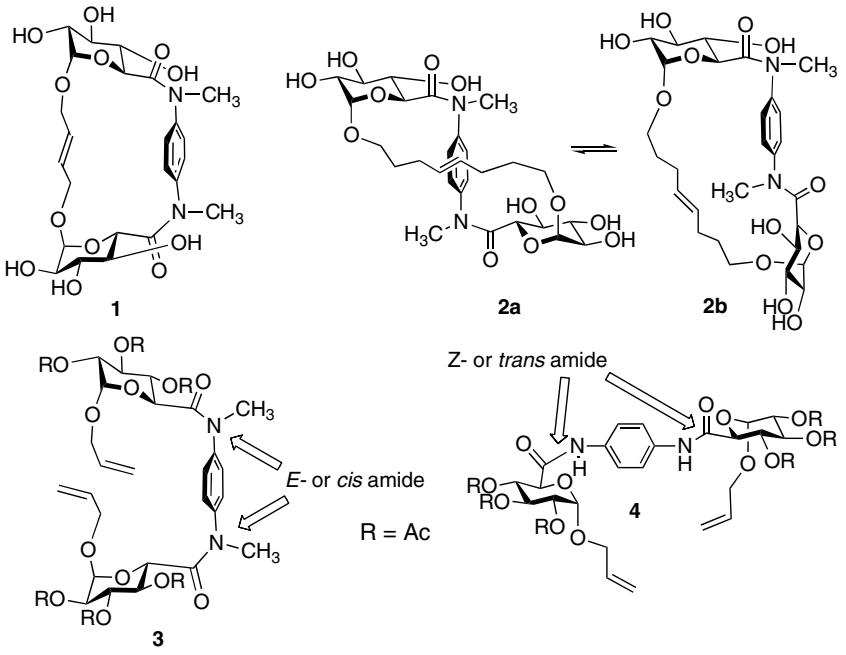
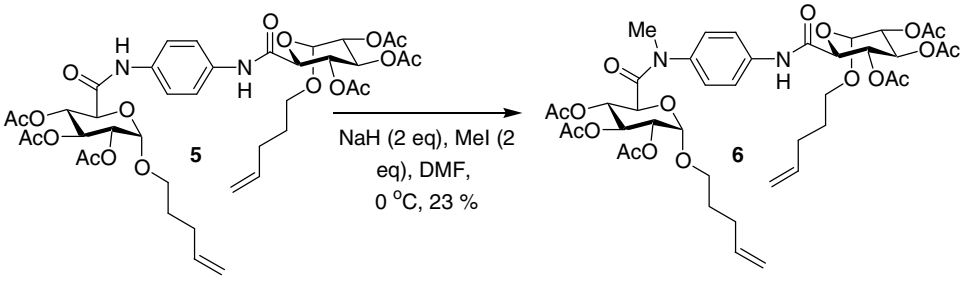


Chart 1.

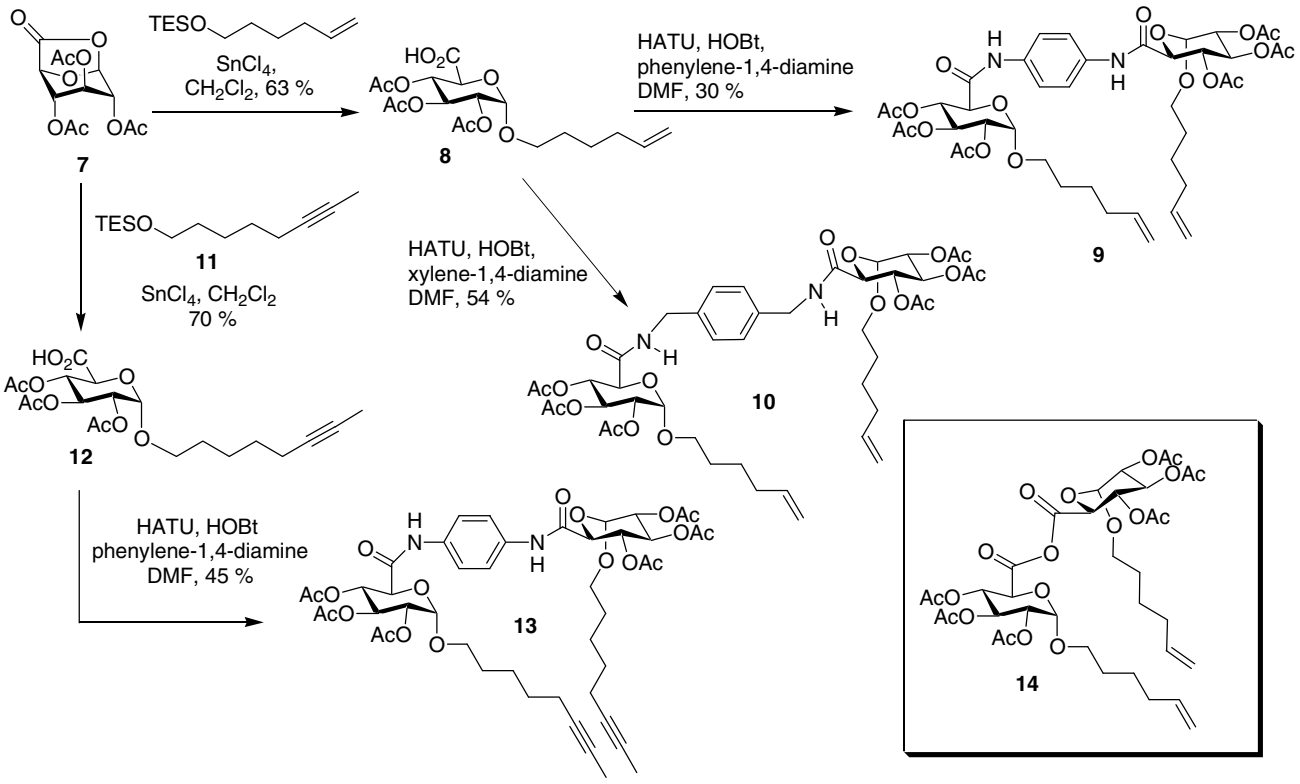


Scheme 1.

The dienes **9** and **10** and the diyne **13** were prepared as outlined in Scheme 2. Glycosidation using the lactone donor **7** with 5-hexenoxytriethylsilane in the presence of tin(IV) chloride gave the α-glycoside **8**.[13] Reaction of the acetylene derivative **11** under similar conditions gave **12** (70%). The reaction of **8** and **12** with phenylene-1,4-diamine promoted by HATU and HOBt gave **9** (30%) and **13** (45%), respectively. The alternative approach of using the acid chloride derivative of **8** as an intermediate in the diamide synthesis gave the desired product in lower yield. The nucleophilicity of the second amino group of the phenylene-1,4-diamine residue is reduced after acylation of the first amino group, explaining the low efficiency of diamide formation. The reaction of **8** with the more nucleophilic xylene-1,4-diamine gave **10** in a higher yield of 54%. The anhydride **14** (ESI-LRMS: found *m/z* 809.1 $[M+Na]^+$) was isolated as a by-product from these coupling reactions.

2.2. Metathesis reactions

Metathesis of the secondary anilides **5** and **9** gave the corresponding ring closed alkene product **15** (40%) and the alkene precursor of **17** (48%), respectively (Scheme 3). Mass spectrometric analysis of fractions isolated after chromatography of the residues obtained from these metathesis reactions indicated that by-products were formed (<25%), which included acyclic and macrocycle derivatives (Chart 2); the by-products arose from competing intermolecular-metathesis (cross metathesis, CM) and in one case subsequent macrocyclization. The observation of RCM from **5** and **9**, which contained secondary anilides, contrasted with the behaviour of **4**,[9] which gave exclusively products of CM related to those shown in Chart 2. The NMR spectra of the ring closed alkene containing products from **5** and **9** did not facilitate determination of the ratio of *cis* and *trans* alkenes present due to signal overlap; one major isomer generally resulted, which is presumably the *trans* alkene as is generally the major product in metathesis reactions. Unreacted **5** (35%) and **9** (34%) were also recovered. The ring closing metathesis reactions of **6** and **10** proceeded more efficiently than for **5** and **9**, giving alkene products in 73% and 80% yield, respectively. Presumably the access to the *E*-configured amide in **6** due to its tertiary amide and the increased flexibility of **10** facilitated access to isomers where intramolecular metathesis occurs more efficiently. Catalytic hydrogenation of two of the initially formed alkenes gave **17** and **19**. Ring closing alkyne metathesis was investigated using **13**, following the procedure detailed previously by Grela and co-workers.[14,15] The terminally methylated alkyne dimer **13** was thus heated at reflux in the presence of $Mo(CO)_6$ and 2-fluorophenol in chlorobenzene. The alkyne containing macrocycle **21** was obtained in 27% yield. The low yield is due to decomposition of **13** or the products formed. De-O-acetylation of **17**, **19** and **21** gave **18**, **20** and **22**, respectively. In general, the solubility of the novel glycophanes described herein was



Scheme 2.

significantly lower in water than observed previously for **1** and **2**, which precluded investigation of their ability to bind ANS, as had been described for **2** previously.

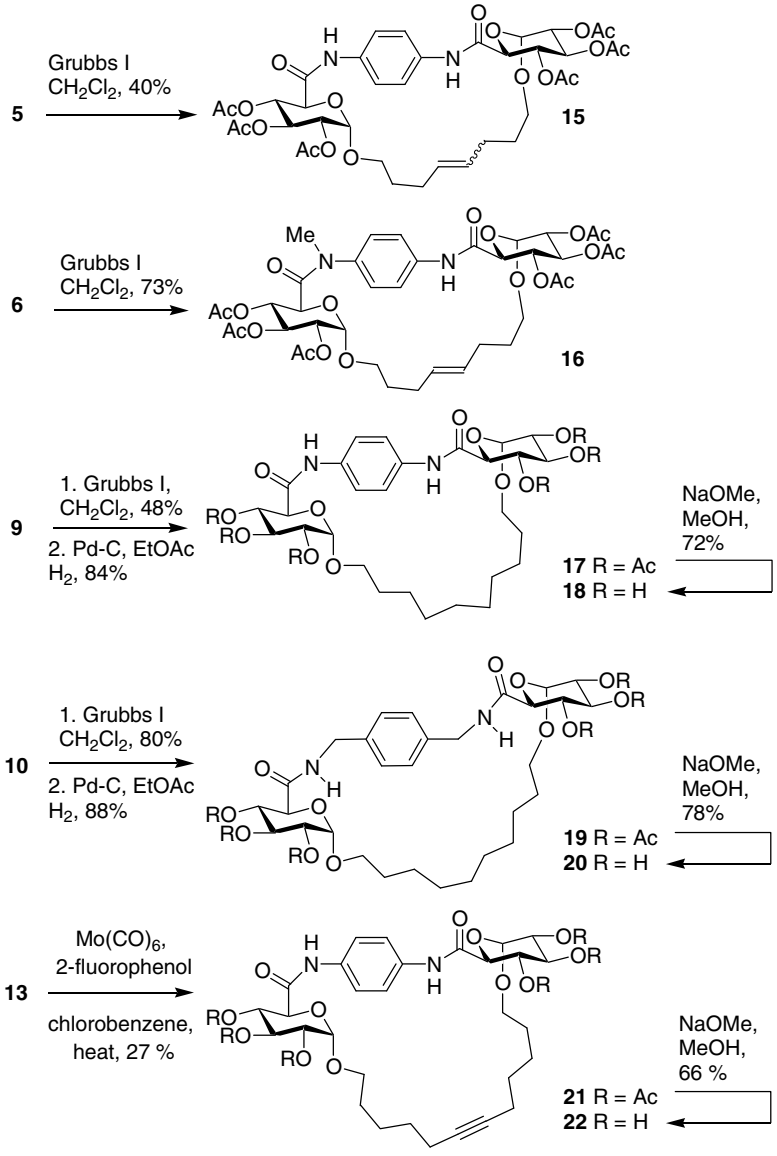
The preparation of **24** was also carried out by catalytic hydrogenation of **23**[9] and subsequent de-O-acetylation (Scheme 4).

2.3. Structure of the glycophanes

The configuration of the amides (*E* or *Z* configuration) in the macrocycles **14–22** needed to be clarified, as macrocyclic structures containing secondary anilides had not been prepared during previous work. The configurational preferences for the amide groups in glucuronic acid anilides, such as **1** and **2** (Chart 1) and **25** and **26** (Chart 3) have been studied previously (computational methods, NOESY, ROESY, X-ray crystallography).[7–16] In tertiary anilides, amide bond rotation is sufficiently slow to allow both *E*- and *Z*-isomers to be detected by ^{1}H NMR. The *E*-amide was exclusively adopted in **1**, due to constraints imposed by the macrocycle, and this *E*-configuration was highly preferred for tertiary anilides such as **2** and **26**. The *Z*-amide was exclusively adopted by secondary anilides such as **4** and **25**. What has been noted in previous studies is that the chemical shift of the glucuronic acid H-5 proton adjacent to a *Z*-configured amide is more up-field than for the H-5 proton adjacent to an *E*-configured amide. For example, the ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) for **25** showed one signal set for the *Z*-isomer and the signal for H-5 was at δ 4.15 (d, J = 9.1 Hz), whereas the ^{1}H NMR spectrum for **26** ($CDCl_3$, 300 MHz) had two signal sets with the signal for H-5 of the *E*-isomer observed at δ 4.52 (J = 10.2 Hz), whereas that for the H-5 proton of the minor *Z*-isomer was observed at δ 3.97 (J = 9.5 Hz). These observations partially guided the structural analysis described herein. Thus, for all macrocycles containing secondary amides (e.g., **14**, **17–22**) one set of signals was observed indicating there is a strong preference for the *Z*-isomer. The NMR spectra are also consistent with the C_2 symmetry of these macrocycles. The coupling constants for the sugar protons (for H-5 see Table 1) of the acetylated glycophanes indicated that the glucuronic acid residues adopted $^4C_1$ conformation. The $^4C_1$ conformation is also preferred for the polyhydroxylated compounds although $J_{4,5}$ is 8.2 Hz for **18** and **22** indicating that there may be population of the $^1C_4$ conformation by a glucuronic acid residue in these cases. For the compounds with tertiary amides two sets of signals were observed (e.g., **24**), which are consistent with structural isomers resulting from exchange between the *E*- and *Z*- configured amides. The NMR assignments of the H-5 protons of the glucuronic acid residues are listed in Table 1. Similar trends in chemical shift to that observed for **1**, **2**, **25** and **26** can generally be observed with the novel glycophanes, with one exception, which occurred for **16**, where the signal assigned to H-5 [δ 4.30 (d, J = 10.2 Hz)] was at higher field than the signal assigned to the glucuronic acid H-5 closest to secondary amide [δ 4.35 (d, J = 10.2 Hz)]. Signals for H-5 protons adjacent to *Z*-amides of compounds **2b**, **6**, **14–22**, **24b**, **25** and **26** all occurred in the range δ 3.97–4.36, whereas signals for H-5 protons adjacent to *E*-amides of compounds **1**, **2**, **6**, **16**, **24** and **26** occurred in the range δ 4.30–5.08. These data support the proposal that the *Z*-amide is adopted in all macrocycles based on secondary anilides.

The macrocycles that contain the tertiary amide showed a higher preference for the *E*-configuration compared to the *Z*-configuration, consistent with observations for **1** and **2**. For example, the ^{1}H NMR spectrum of **24** showed two signal sets, indicating that there are two isomers **24a** and **24b**, similar to what was observed for **2a** and **2b**.[9] The chemical shift for H-5 (600 MHz, D_2O) of the major isomer **24a** was at δ 4.49 (d, J = 9.8 Hz), whereas the chemical shifts for the H-5 protons of **24b** were located at δ 5.08 (d, J = 9.7 Hz) and δ 4.17 (d, J = 9.9 Hz). The ratio of **24a:24b** was determined by integration of signals in the ^{1}H NMR spectra and was found to be 55:45 at 30 °C, a preference lower than that observed for alkenyl derivative **2a:2b** (85:15).

Examination of the ^{1}H NMR data for **16** also supported the proposal that the tertiary amide component of this molecule adopts the *E*-configuration. The configurational assignments and conformation were also investigated by 2D-NOESY and ROESY studies, which further supported the suggestion that all secondary anilides adopted the *Z*-configuration whereas the tertiary anilides



Scheme 3.

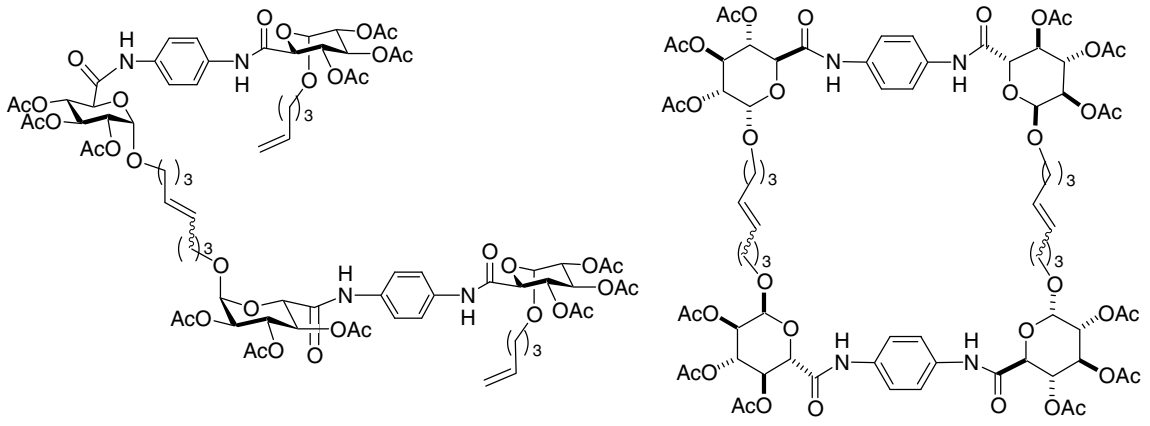
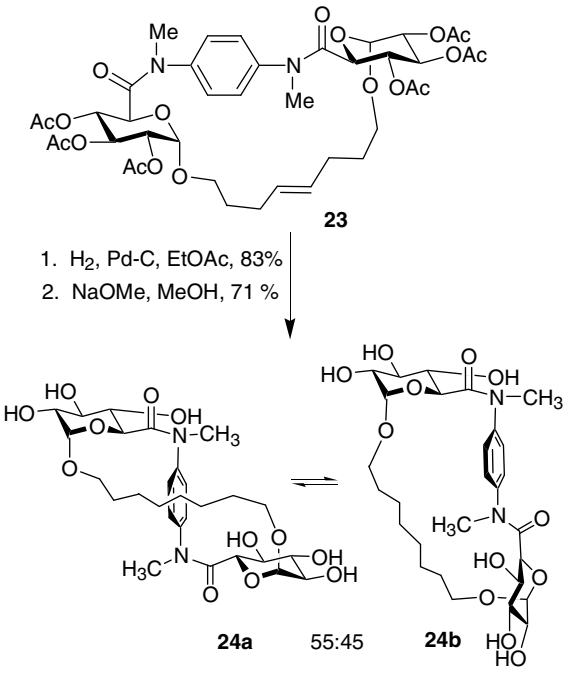


Chart 2. By-products from the metathesis reactions of **5**.



Scheme 4.

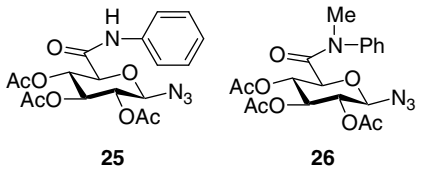


Chart 3.

displayed a preference for the *E*-configuration. Spectra obtained for the per-O-acetylated secondary anilides displayed strong NOE crosspeaks between the NH and the glucuronic acid H-4 and H-5 protons indicative of a *Z*-configured amide; NOE crosspeaks were

Table 1
Selected ^{1}H NMR data[a] for H-5 protons of glucuronic acid residues

Compound	δ H-5 (*E*)	δ H-5 (*Z*)
1 (300 MHz, D_2O)	4.43 (d, *J* = 9.3 Hz)	—
2a (500 MHz, D_2O)	4.40 (d, *J* = 9.9 Hz)	—
2b (500 MHz, D_2O)	5.08 (d, *J* = 10.0 Hz)	4.17 (d, *J* = 9.3 Hz)
6 (500 MHz, $CDCl_3$)	4.43 (d, *J* = 10.2 Hz)	4.35 (d, *J* = 10.2 Hz)
14 (600 MHz, $CDCl_3$)	—	4.30 (d, *J* = 10.2 Hz)
16 (600 MHz, $CDCl_3$)	4.30 (d, *J* = 10.0 Hz)	4.36 (d, *J* = 9.7 Hz)
17 (600 MHz, $CDCl_3$)	—	4.31 (d, *J* = 10.2 Hz)
18 (500 MHz, DMSO)	—	3.98 (d, *J* = 8.2 Hz)
19 (500 MHz, $CDCl_3$)	—	4.31 (d, *J* = 10.1 Hz)
20 (600 MHz, CD_3OD)	—	4.03 (d, *J* = 10.0 Hz)
21 (600 MHz, $CDCl_3$)	—	4.31 (d, *J* = 10.1 Hz)
22 (600 MHz, DMSO)	—	3.98 (d, *J* = 8.2 Hz)
24a (600 MHz, D_2O)	4.49 (d, *J* = 9.7 Hz)	—
24b (600 MHz, D_2O)	5.08 (d, *J* = 9.7 Hz)	4.17 (d, *J* = 9.9 Hz)
25 (300 MHz, $CDCl_3$)	—	4.15 (d, *J* = 9.1 Hz)
26 (300 MHz, $CDCl_3$)	4.52 (*J* = 10.2 Hz)	3.97 (*J* = 9.5 Hz)

[a] All NMR data were obtained at 20 °C, except for **24**, which was obtained at 30 °C.

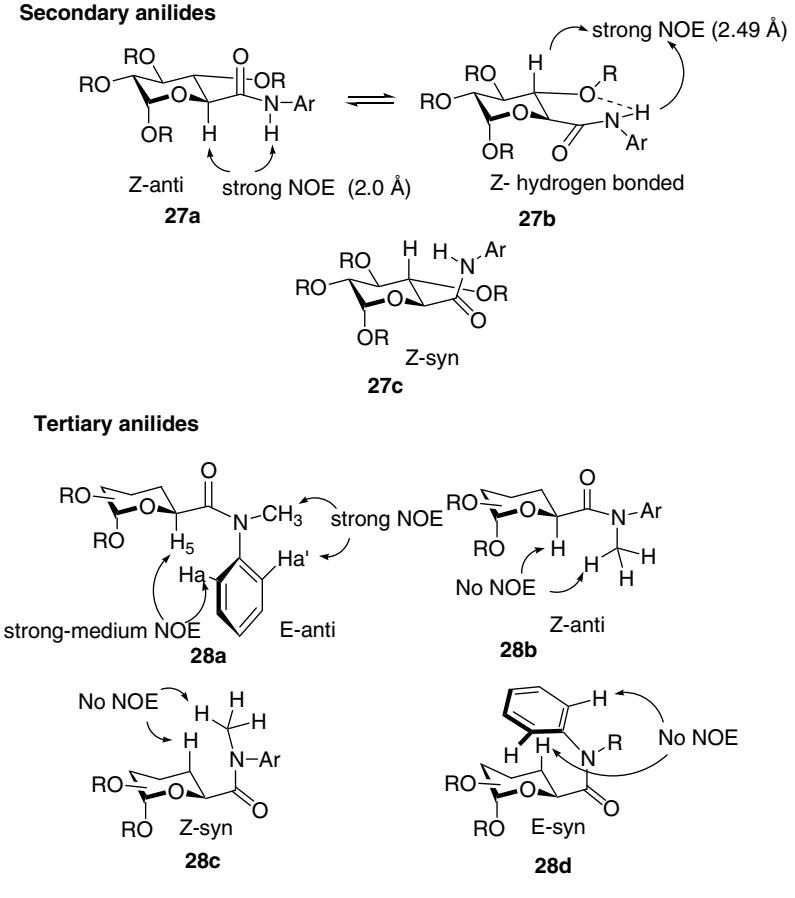


Figure 1. Conformations of glucuronic acid anilides and NOEs observed/not observed.

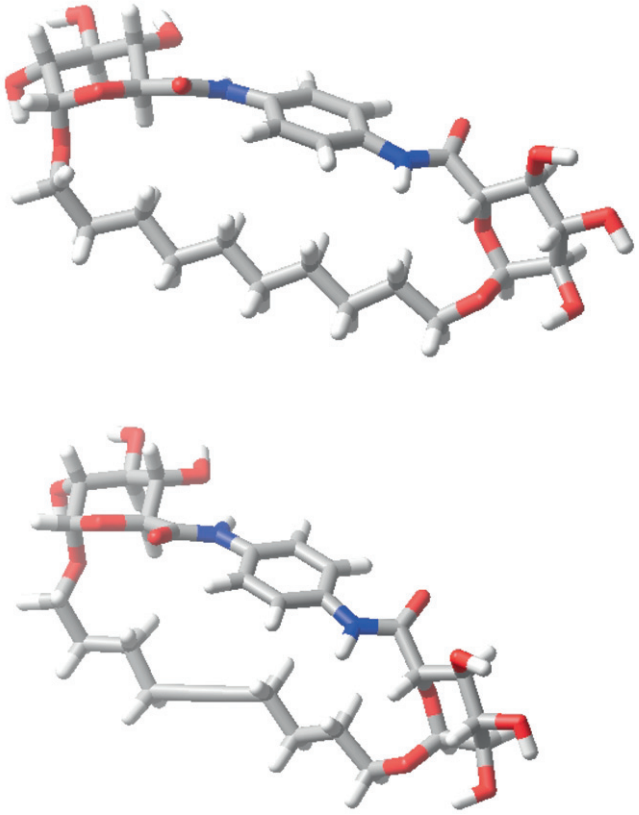


Figure 2. Lowest energy conformers of **18** (top) and **22** (bottom).

not observed between the aromatic protons and H-5 as would be expected if the secondary amide adopted an *E*-configuration. In contrast, the per-O-acetylated tertiary anilides did show medium strength NOE crosspeaks between H-5 and the aromatic protons but not between the *N*-methyl protons and H-5, consistent with a high preference for the *E*-amide rather than the *Z*-amide. The NOEs observed for the novel macrocyclic compounds are summarized in Figure 1. The observation of NOE crosspeaks between H-4 and NH as well as H-5 and NH indicates that the amide could possibly adopt the *Z*-hydrogen bonded conformation **27b** in a dynamic equilibrium with the *Z-anti* conformer **27a**. The distance between H-4 and the NH in a model of **27b** was predicted to be 2.49 Å, and the distance between H-5 and NH in a model of **27a** was 2.01 Å. The NOE crosspeaks which should support *E*-anti structures for tertiary anilides **28a**–**d** are also shown in Figure 1.

The proposal that both **27a** and **27b** can be populated but not the *Z*-syn conformer **27c** is supported by the outcome of Monte Carlo conformational searching techniques carried out on the macrocyclic compounds **18** and **22** using Macromodel 8. The lowest energy structures for **18** and **22** obtained after these simulations are shown in Figure 2, and each conformation obtained has one amide group with a *Z*-anti conformation **27a** whereas the other amide group has the *Z*-hydrogen bonded conformation **27b**. Although the models shown in Figure 2 are not C_2 symmetrical and should give more complex NMR spectra than what is observed, it can be assumed the molecules are dynamic where the *Z*-anti and *Z*-hydrogen bonded conformers rapidly interchange leading to NMR spectra that reflect that the C_2 symmetric nature of the molecule.

3. Summary

A series of novel glycophanes that contain secondary amides have been prepared from glucuronic acid. The key reactions in the preparation of these compounds involve ring closing alkene or alkyne metathesis. Structural studies show that geometric arrangements of the sugar groups in glycophanes based on secondary amides differ from those that are based on tertiary amides. The compounds had lower water solubility than previously prepared **1** and **2**, which precluded investigation of their recognition phenomena in water. The application of glycophanes as scaffolds is underway in our group and the results will be published in due course.

4. Experimental

4.1. General

Optical rotations were determined with a Perkin–Elmer 343 model polarimeter at the sodium D line at 20 °C. NMR spectra were recorded with JEOL JNM-GX270, Varian Inova 300, 400 and 500, and Varian NMRS-500 and Varian NMRS-600 spectrometers. Chemical shifts are reported relative to internal Me_4Si in $CDCl_3$ (δ 0.0) or HOD for D_2O (δ 4.79) or CD_2HOD (δ 3.31) for ^1H and $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.05) for ^{13}C. ^1H NMR signals were assigned with the aid of COSY. ^{13}C NMR signals were assigned with the aid of DEPT, HSQC and/or HMBC. The NOESY ($\tau_{mix} \sim 600$–1500 ms) and ROESY ($\tau_{mix} \sim 200$ ms) studies were recorded as 2D-crossrelaxation experiments. Presaturation for solvent suppression was carried out for macrocycles by transmitter presaturation when required. All NOESY/ROESY experiments were recorded in phase sensitive mode, by using States-TPPI for F1-quadrature detection in the indirect dimension. Coupling constants are reported in Hertz. The IR spectra were recorded with Mattson Galaxy Series FTIR 3000 using thin film between NaCl plates. Melting points were measured on a Gallenkamp melting point apparatus. Elemental analysis was performed on an Exeter Analytical CE440 elemental analyzer. Low and high resolution mass spectra were measured on either a micromass VG 70/70H or VG ZAB-E or autospec spectrometers and were measured in positive and/or negative mode as indicated in each case. Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel and spots visualized by UV and charring with H_2SO_4–EtOH (1:20). Flash column chromatography was carried out with Silica Gel 60 (0.040–0.630 mm, E. Merck) using a stepwise solvent polarity gradient correlated with TLC mobility. Acetonitrile and CH_2Cl_2 were freshly distilled from calcium hydride, THF from Na/Benzophenone and MeOH from Mg. Anhydrous DMF, pyridine and toluene were used as obtained from Sigma–Aldrich.

4.2. Diene 6

A solution of **5**[9] (23 mg, 0.027 mmol) in anhyd DMF (2 mL) was cooled to 0 °C under N_2. A solution of iodomethane in anhyd DMF (8 μL/mL) and a solution of NaH in anhyd DMF were prepared (5.4 mg/mL). Iodomethane (0.1 mL of the prepared solution in DMF, 0.0135 mmol) and NaH (0.1 mL of the prepared solution, 0.0135 mmol) were added to the solution containing **5**, and the mixture was stirred for 30 min over ice. Three further additions of iodomethane and NaH were made at 30 min intervals as described above. The reaction mixture was then diluted with EtOAc (20 mL), and stirred with aq NH_4OH (15 mL). The aq layer was extracted using EtOAc (4 × 15 mL), and the combined organic layers were washed with water (15 mL), dried ($MgSO_4$), filtered, and the solvent was removed under diminished pressure. Chromatography of the residual oil gave **6** (5 mg, 23%); $R_f = 0.3$ (EtOAc–toluene, 1:1); $[\alpha]_D$ +31.7 (*c* 0.8, $CHCl_3$); IR (NaCl plate, film from CH_2Cl_2): 2920, 2850, 1758, 1670, 1515, 1367, 1222, 1045 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.17 (s, 1H, NH), 7.60 (d, 2H, $J = 8.8$ Hz, aromatic H), 7.19 (d, 2H, $J = 8.8$ Hz, aromatic H),

5.84–5.76 (m, 1H, alkene CH), 5.75–5.69 (m, 1H, alkene CH), 5.64 (t, 1H, J = 10.0 Hz, H-3), 5.54 (t, 1H, J = 9.6 Hz, H-4′), 5.31 (t, 1H, J = 10.0 Hz, H-3′), 5.26 (d, 1H, J = 3.5 Hz, H-1), 5.18 (t, 1H, J = 10.0 Hz, H-4), 5.06 (dd, 2H, J = 1.35, 17.3 Hz, alkene CH), 5.02 (d, 2H, J = 10.35 Hz, alkene CH), 4.92 (d, 1H, J = 3.5 Hz, H-1′), 4.88 (dd, 1H, J = 3.6, 10.4 Hz, H-2), 4.82 (dd, 1H, J = 3.5, 10.2 Hz, H-2′), 4.43 (d, 1H, J = 9.8 Hz, H-5′), 4.35 (d, 1H, J = 10.2 Hz, H-5), 3.80–3.75 and 3.51–3.48 (2m, each 1H, OCH_2), 3.25 (s, 3H, $NHCH_3'$), 3.04–2.99 (m, 2H, OCH_2'), 2.18–2.15 (m, 2H, CH_2), 2.11, 2.09, 2.04, 2.02, 1.99, 1.98 (each s, each 3H, each $COCH_3$), 1.94–1.88 (m, 2H, CH_2), 1.78–1.70 (m, 2H, CH_2), 1.30 (m, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.6, 170.4, 170.0, 169.8, 169.7, 168.8 (each ester C=O), 166.5, 165.4 (each amide C=O) 139.0 (aromatic C), 138.0, 137.4 (each alkene CH), 136.8 (aromatic C), 128.4, 121.24 (each aromatic CH), 115.5, 114.8 (each CH_2), 96.2 (C-1′), 96.0 (C-1), 70.9 (C-2), 70.6 (C-2′), 70.5 (C-4′), 70.1 (C-3′), 69.7 (C-4), 69.1 (C-3), 68.6 (C-5), 68.6, 68.0 (each OCH_2), 65.6 (C-5′), 38.4 (NCH_3), 29.9, 29.7, 29.69, 29.6, 29.3, 28.3 (each CH_2), 20.8, 20.7 (2s), 20.6 (2s) (each $COCH_3$); ESI-LRMS: found m/z 885.6 $[M+Na]^+$, 861.4 $[M-H]^-$; ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{41}H_{55}N_2O_{18}$, 863.3450; found, 863.3420.

4.3. 5-Hexenoxytriethylsilane

Chlorotriethylsilane (6.49 mL, 37.9 mmol) was added slowly to a cooled solution of 5-hexen-1-ol (4.0 g, 33.3 mmol) and Et_3N (6.87 mL, 49.35 mmol) in anhyd CH_2Cl_2 (20 mL) under N_2, and the mixture was stirred for 20 min whilst cooling over ice. The mixture was then diluted with CH_2Cl_2 (20 mL), and stirred overnight at room temperature. CH_2Cl_2 (20 mL) was then added and the salts were filtered, through Celite, rinsing with CH_2Cl_2. The filtrate was washed with a satd aq $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed under diminished pressure. The residue was distilled at atmospheric pressure using a Kugelrohr to give the title compound (5.8 g, 81%); bp range 140–145 °C; IR (NaCl plate, film from CH_2Cl_2): 2954, 2360, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.87–5.73 (m, 1H, $CH{=}CH_2$), 5.03–4.92 (m, 2H, $CH{=}CH_2$), 3.63–3.59 (t, 2H, J = 6.5 Hz, OCH_2), 2.10–2.03 (m, 2H, OCH_2CH_2), 1.60–1.51 (m, 2H, $=CHCH_2$), 1.49–1.41 (m, 2H, $OCH_2CH_2CH_2$), 0.99–0.94 (t, 9H, $(CH_2CH_3)_3$), 0.60–0.56 (q, 6H, $(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8 ($CH{=}CH_2$), 114.3 ($CH{=}CH_2$), 62.7 (OCH_2), 33.6 (CH_2), 32.3 (CH_2), 25.2 (CH_2), 6.7 ($(CH_3CH_2)_3Si$), 4.4 (t, $(CH_3CH_2)_3Si$); Anal. Calcd for $C_{12}H_{26}OSi$: C, 67.2; H, 12.2. Found: C, 66.9; H, 12.1.

4.4. 5-Hexenyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronic acid (8)

5-Hexenoxytriethylsilane (1.70 g, 7.92 mmol) was added dropwise to a solution of 6,1-lactone **7**[13] (0.737 g, 2.43 mmol) in anhyd CH_2Cl_2 (30 mL), under N_2. The reaction mixture was stirred for 10 min at room temperature, followed by the dropwise addition of $SnCl_4$ (0.270 mL, 2.30 mmol) and stirring was continued overnight at room temperature. The mixture was stirred with satd aq $NaHCO_3$ (1.5 mL) for 5 min and then filtered through Celite, washing with CH_2Cl_2. The filtrate was concentrated to volume of ~10 mL stirred again with satd aq $NaHCO_3$ (50 mL) for 1 h and the mixture filtered through Celite again washing with both CH_2Cl_2 and H_2O. The layers were separated and the aq layer was extracted with CH_2Cl_2 (3 × 50 mL). The aq layer was acidified to pH 1, using 6.0 M HCl and then extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under diminished pressure to give **8** as a clear oil (0.61 g, 63%); IR (NaCl plate, film from CH_2Cl_2): 3515, 2927, 2857, 1755, 1607, 1429, 1369, 1226, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (br s, 1H, COOH), 5.81–5.77 (m, 1H, $CH{=}CH_2$), 5.56 (t, 1H, J = 10.0 Hz, H-3), 5.23 (t, 1H, J = 10.2 Hz, H-4), 5.17 (d, 1H, J = 3.7 Hz, H-1), 5.04–4.95 (m, 2H, $=CH_2$), 4.89 (dd, 1H, J = 3.7, 10.2 Hz, H-2), 4.38 (d, 1H, J = 10.2 Hz, H-5), 3.77–3.71 and 3.48–3.42 (2m, each 1H, OCH_2), 2.09–2.03 (m, 2H, CH_2), 2.06, 2.05, 2.03 (3s, each 3H, 3 × $COCH_3$), 1.64–1.58 (m, 2H, CH_2), 1.48–1.41 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 170.2, 170.1, 170.0 (ester C=O and CO_2H), 138.3 (alkene CH), 114.8 (alkene CH_2), 95.8 (C-1), 70.5, 69.5, 69.4 (each CH), 69.1 (OCH_2), 67.6 (CH), 33.3, 28.6, 25.1 (each CH_2), 20.6 (2s), 20.5 (each $COCH_3$); ESI-LRMS: found m/z 425.1 $[M+Na]^+$, 401.2 $[M-H]^-$; ESI-HRMS m/z: $[M+Na]^+$ calcd for $C_{18}H_{26}O_{10}Na$, 425.1424; found, 425.1404.

4.5. *N,N′*-1,4-Di-(hex-5-enyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranuronamide)benzene (9)

Hydroxybenzotriazole (38.6 mg, 0.286 mmol) and phenylene-1,4-diamine (11 mg, 0.1 mmol) were added to a solution of **8** (80 mg, 0.2 mmol) in anhyd DMF (2 mL). The mixture was cooled to 0 °C, and anhyd DIPEA (0.03 mL, 0.175 mmol) was added. The reaction mixture was stirred for 20 min under N_2 at 0 °C, before adding HATU (108 mg, 0.286 mmol). The solution was cooled for a further 20 min and was then stirred for 15 h at room temperature under N_2. The reaction mixture was diluted with EtOAc (20 mL), and extracted with water (20 mL). The aq layer was extracted with EtOAc (5 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under diminished pressure, co-evaporating with xylene in order to remove residual DMF. Chromatography of the residue gave the title compound as a clear oil (29 mg, 30%); R_f = 0.8 (EtOAc–cyclohexane, 2:1); IR (film from CH_2Cl_2 on NaCl plate): 2935, 2360, 1754, 1677, 1519, 1369, 1222, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 2H, 2 × NH), 7.43 (s, 4H, aromatic H), 5.81 (m, 2H, alkene CH), 5.80 (t, 2H, J = 9.9 Hz, H-3), 5.20 (d, 2H, J = 3.7 Hz, H-1), 5.15 (t, 2H, J = 9.9 Hz, H-4), 5.01–4.96 and 4.95–4.92 (2m, each 2H, alkene CH), 4.82 (dd, 2H, J = 3.6, 10.1 Hz, H-2), 4.28 (d, 2H, J = 10.2 Hz, H-5), 3.76–3.70 and 3.47–3.41 (each m, each 2H, each OCH_2), 2.16–1.99 (br m, 4H, 2 × CH_2), 2.06, 2.05, 2.00 (each s, each 6H, each $COCH_3$), 1.65–1.60 (m, 4H, CH_2), 1.47–1.40 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.8, 169.7 (each ester C=O), 165.2 (amide C=O), 138.2 (alkene CH), 133.4 (aromatic C), 120.9 (aromatic CH), 114.8 (alkene CH_2), 95.7 (C-1), 70.8 (C-2), 69.8 (C-4), 69.1 (2s) (OCH_2 and C-3), 68.4 (C-5), 33.2, 28.5, 25.1 (each CH_2), 20.7, 20.6, 20.5 (each $COCH_3$); ESI-LRMS: found m/z 877.3 $[M+H]^+$, 899.3 $[M+Na]^+$, 915.3 $[M+K]^+$, 875.3 $[M-H]^-$; ESI-HRMS m/z: $[M+Na]^+$ calcd for $C_{42}H_{56}N_2O_{18}Na$, 899.3426; found, 899.3383.

4.6. *N,N′*-1,4-Di-(hex-5-enyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronamide)xylene (10)

The reaction of **8** (175 mg, 0.43 mmol) with HOBt (135 mg, 1.00 mmol) and xylene-1,4-diamine (26 mg, 0.19 mmol) as described for the preparation of **9** gave **10** as a clear oil (105 mg, 54%); R_f = 0.22 (EtOAc–toluene, 1:1); $[\alpha]_D$ +102.7 (c 3.60, $CHCl_3$); IR (NaCl plate, film from CH_2Cl_2): 3295, 2927, 1754 (ester C=O), 1666 (amide C=O), 1535, 1432, 1368, 1222, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (s, 4H, aromatic H), 6.68 (t, 2H, J = 5.8 Hz, NH), 5.80–6.73 (m, 2H, alkene CH), 5.56 (t, 2H, J = 9.9 Hz, H-3), 5.11 (dd, 2H, J = 9.5, 10.2 Hz, H-4), 5.09 (d, 2H, J = 3.6 Hz, H-1), 5.01–4.93 (m, 4H, $HC{=}CH_2$), 4.77 (dd, 2H, J = 3.6, 10.2 Hz, H-2), 4.48 (dd, 2H, J = 6.1, 14.7 Hz, $NHCH_2$), 4.35 (dd, 2H, J = 5.5, 14.8 Hz, $NHCH_2$), 4.25 (d, 2H, J = 10.3 Hz, H-5), 3.70–3.64 and 3.41–3.35 (2m, each 2H, OCH_2), 2.07–1.99 (m, 4H, 2 × CH_2), 2.06, 2.03, 2.00 (3s, each 6H, 6 × $COCH_3$), 1.63–1.55 (m, 4H, CH_2), 1.46–1.40 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.9, 169.7 (each ester C=O), 167.3 (CONH), 138.2 (alkene CH),

137.0 (aromatic C), 128.2 (aromatic CH), 114.8 (alkene CH), 95.6 (C-1), 70.9, 69.9, 69.3 (each CH), 69.0 (OCH_2), 68.1 (CH), 42.6, 38.5, 33.2, 28.5, 25.1 (each CH_2), 20.7, 20.6, 20.6 (each $COCH_3$); ESI-LRMS: found *m/z* 877.5 $[M+H]^+$, 899.5 $[M+Na]^+$, 875.3 $[M-H]^-$; ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{44}H_{60}N_2O_{18}Na$, 927.3739; found, 927.3766.

4.7. 6-Octynoxytriethylsilane (11)

Triethylsilyl triflate (1.35 mL, 6.0 mmol) was added slowly to an ice-cooled solution of oct-6-yn-1-ol[17] (664 mg, 5.26 mmol), Et_3N (1.08 mL, 7.78 mmol), in anhyd CH_2Cl_2 (40 mL). The reaction mixture was stirred for 4 h at room temperature, and was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (70 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated under diminished pressure. Chromatography of the residue gave **11** (1.05 g, 83%); IR (film from CH_2Cl_2 on NaCl): 2935, 2861, 1752, 1432, 1371, 1224, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (t, 2H, J = 6.7 Hz, OCH_2), 2.09–2.05 (m, 2H, CH_2), 1.72 (t, 3H, J = 2.3 Hz, CH_3), 1.51–1.34 (m, 6H, 3 × CH_2), 0.94 (t, 9H, J = 8.0 Hz, 3 × CH_3), 0.59 (q, 6H, J = 8.0 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 79.0, 75.3 (each alkyne C), 62.7 (OCH_2), 32.4 (CH_2), 28.9, 25.1, 18.7 (each CH_2), 6.60 (TES CH_3), 4.4 (TES CH_2 and CH_3).

4.8. Oct-6-ynyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronic acid (12)

The reaction of lactone **7** (500 mg, 1.65 mmol), tin(IV) chloride (0.35 mL, 3.9 mmol) and 6-octynoxytriethylsilane **11** (788 mg, 3.27 mmol) in anhyd CH_2Cl_2 (20 mL) as described for the preparation of **8** gave **12** as a yellow oil (493 mg, 70%); $[\alpha]_D$ +97.3 (*c* 1.2, $CHCl_3$); IR (NaCl plate, film from CH_2Cl_2): 2935, 2861, 1752, 1432, 1371, 1224, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.54 (t, 1H, J = 9.8 Hz, H-3), 5.20 (t, 1H, J = 9.9 Hz, H-4), 5.16 (d, 1H, J = 3.6 Hz, H-1), 4.86 (dd, 1H, J = 3.6, 10.1 Hz, H-2), 4.34 (d, 1H, J = 10.2 Hz, H-5), 3.82–3.69 and 3.40–3.51 (2m, each 1H, OCH_2), 2.16–2.08 (m, 2H, CH_2), 2.10, 2.07, 2.04 (each s, each 3H, 3 × $COCH_3$), 1.76 (t, 3H, J = 1.0 Hz, CH_3), 1.62 (m, 2H, CH_2), 1.49 (m, 4H, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (COOH), 170.1, 170.0, 169.8 (each $COCH_3$), 95.6 (C-1), 78.6, 75.5 (each alkyne C), 70.3, 69.3, 69.2 (each CH), 68.9 (OCH_2), 67.4 (CH), 28.5, 28.4, 24.9 (each CH_2), 20.4, 20.3 (2s) (each $COCH_3$), 18.4 (CH_2), 3.1 ($CCCH_3$); ESI-LRMS: found *m/z* 429.0 $[M+H]^+$, 451.2 [M + Na]$^+$, 427.3 $[M-H]^-$; ESI-HRMS *m/z*: $[M-H]^-$ calcd for $C_{20}H_{27}O_{10}$, 427.1604; found, 427.1606.

4.9. *N,N′*-1,4-Di-(oct-6-ynyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronamide)benzene (13)

The reaction of **12** (272 mg, 0.635 mmol) with HOBt (197 mg, 1.46 mmol) and phenylene-1,4-diamine (31 mg, 0.285 mmol) as described for the preparation of **9** gave **13** as an oil (130 mg, 45%); R_f = 0.58 (EtOAc–toluene, 1:1); $[\alpha]_D$ +69.4 (*c* 2.9, $CHCl_3$); IR (KBr disc, film from CH_2Cl_2): 3351, 2939, 2862, 1754, 1690, 1549, 1519, 1409, 1369, 1224, 1050, 915, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 2H, NH), 7.43 (s, 4H, aromatic H), 5.57 (t, J = 9.7 Hz, H-3), 5.20 (d, 2H, J = 3.7 Hz, H-1), 5.15 (dd, 2H, J = 9.5, 10.1 Hz, H-4), 4.82 (dd, 2H, J = 3.6, 10.2 Hz, H-2), 4.28 (d, 2H, J = 10.2 Hz, H-5), 3.75–3.70 and 3.46–3.40 (2m, 2H each, OCH_2 each), 2.13–2.07 (m, 4H, 2 × CH_2), 2.06, 2.05, 2.00 (each s, each 6H, 2 × $COCH_3$ each), 1.74 (t, 6H, J = 2.5 Hz, CH_3), 1.62–1.58 (m, 4H, CH_2), 1.49–1.42 (m, 8H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.8, 169.7 (each ester C=O), 165.2 (amide C=O), 133.4 (aromatic C), 120.9 (aromatic CH), 95.7 (C-1), 78.8, 75.7 (each alkyne C), 70.8, 69.8 (each CH), 69.2 (OCH_2), 69.2, 68.4 (each CH), 28.7, 28.5, 25.1 (each CH_2), 20.6 (2s), 20.5 (each $COCH_3$), 18.5 (CH_2), 3.33 ($CCCH_3$); ESI-LRMS: found *m/z* 929.5 $[M+H]^+$, 927.4 $[M-H]^-$; ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{46}H_{60}N_2O_{18}Na$, 951.3739; found, 951.3782.

4.10. 1,1′-*O*-Octane-1,8-diyl-*N,N′*-1,4-phenylene-di-(2,3,4-tri-*O*-acetyl-α-D-glucopyranuronamide) (14)

A degassed (Ar) 3 mM solution of **5**[9] (83 mg, 0.098 mmol) in anhyd CH_2Cl_2 (32 mL) was cannulated into a flask containing the Grubbs first generation catalyst (16.6 mg, ~20%) under Ar. The reaction was stirred for 3.5 days at room temp under Ar during which time the reaction mixture turned from purple to black, and the evolution of gas was observed. The organic solvent was removed under diminished pressure, and chromatography of the residue (a black oil) gave the alkene 15 as an oil (32 mg, 40%); R_f = 0.12 (EtOAc–toluene, 1:1); $[\alpha]_D$ +66.7 (*c* 0.5, $CHCl_3$); IR (NaCl plate, film from CH_2Cl_2): 3357, 2925, 2853, 2360, 1753, 1686, 1520, 1369, 1222, 800 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.16 (s, 2H, NH), 7.36 (s, 4H, aromatic H), 5.59 (t, 2H, J = 9.8 Hz, H-3), 5.41–5.37 (m, 2H, alkene CH), 5.18 (d, 2H, J = 3.7 Hz, H-1), 5.16 (dd, 2H, J = 4.5, 10.0 Hz, H-4), 4.86 (dd, 2H, J = 3.7, 10.0 Hz, H-2), 4.30 (d, 2H, J = 10.2 Hz, H-5), 3.74–3.64 and 3.49–3.41 (each m, each 2H, OCH_2), 2.10–2.02 (m, 4H, 2 × CH_2), 2.09, 2.05, 2.03 (each s, each 6H, each $COCH_3$), 1.74–1.62 (m, 4H, 2 × CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.3, 169.9, 169.8 (each ester C=O), 165.4 (each amide C=O), 133.5 (aromatic C), 130.3 (alkene CH), 121.3 (aromatic CH), 96.0 (C-1), 70.9 (C-2), 70.0 (C-4), 69.4 (C-3), 68.6 (C-5), 68.3 (OCH_2), 28.7, 28.6 (each CH_2), 20.7 (2s) (each $COCH_3$); ESI-LRMS: found *m/z* 821.5 $[M+H]^+$, 843.5 $[M+Na]^+$, 859.4 $[M+K]^+$, 818.3 $[M-H]^-$; ESI-HRMS *m/z*: calcd for $C_{38}H_{49}N_2O_{18}$, 821.2980; found, 821.2996.

4.11. Glycophane 16

A degassed solution of **6** (22 mg, 0.025 mmol) in CH_2Cl_2 (8.5 mL, 3 mM solution) was cannulated directly into a flask containing the Grubbs first generation catalyst (5.4 mg, ~20%), under Ar and the reaction mixture was stirred at room temperature for 3 days under Ar. The organic solvent was removed under diminished pressure and chromatography of the residue gave **16** as a clear oil (15.2 mg, 73%); R_f = 0.46 (EtOAc–cyclohexane, 2:1); IR (NaCl plate, film from CH_2Cl_2): 3477, 2925, 1756, 1668, 1528, 1454, 1370, 1223, 1045 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.36 (s, 1H, NH), 7.31–7.38 (overlapping signals, 2H, J = 8.4 Hz, aromatic H), 7.16 (broad s, 2H, aromatic H), 5.59 (t, 1H, J = 9.7 Hz, H-3), 5.52 (t, 1H, J = 9.7 Hz, H-4′), 5.38–5.30 (m, 1H, alkene CH), 5.29 (d, 1H, J = 2.4 Hz, H-1), 5.28 (t, 1H, J = 10.0 Hz, H-3′), 5.28 (m, 1H, alkene CH), 5.23 (t, 1H, J = 9.7 Hz, H-4), 4.90 (dd, 1H, J = 3.8, 10.3 Hz, H-2), 4.87 (d, 1H, J = 3.8 Hz, H-1′), 4.81 (dd, 1H, J = 3.6, 10.3 Hz, H-2′), 4.60 and 4.68 (each d, J = 11.8 Hz, OCH_2), 4.36 (d, 1H, J = 10.6 Hz, H-5), 4.30 (d, 1H, J = 10.0 Hz, H-5′), 3.76–3.69 and 3.51–3.48 (each m, 1H each, OCH_2), 3.64 and 3.84 (each d, J = 10.0 Hz, OCH_2), 3.29 (s, 3H, NCH_3), 3.00–2.94 and 2.91–2.85 (2m, 1H, each CH_2), 2.22–2.20 and 2.02–2.00 (2m, each 1H, CH_2), 2.13, 2.09, 2.04, 2.03, 1.99, 1.96 (each s, each 3H, 6 × $COCH_3$), 1.83–1.81, 1.77–1.74, 1.71–1.67 and 1.63–1.57 (each m, each 1H, 2 × CH_2), 1.18–1.06 (m, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.8, 170.3, 170.0, 169.9, 169.8, 168.7 (each C=O), 165.5, 165.1 (each amide C=O), 138.6, 137.2 (each aromatic C), 131.8, 128.6 (each alkene CH), 128.5, 119.1 (each aromatic CH), 96.4 (C-1′), 95.9 (C-1), 70.9 (C-2), 70.5 (2s) (C-4 and C-2), 70.2 (C-3′), 69.7 (C-3), 69.4 (C-4), 69.0 (OCH_2), 67.6 (OCH_2), 67.2 (C-5) 64.9, (C-5′), 37.8 (NCH_3), 29.2, 29.1, 28.1, 28.0 (each CH_2) 20.8 (2s), 20.7 (3s), 20.6 (each $COCH_3$); ESI-LRMS: found *m/z* 835.2 $[M+H]^+$, 857.2 $[M+Na]^+$, 833.0 $[M-H]^-$; ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{39}H_{51}N_2O_{18}$, 835.3137; found, 835.3163.

4.12. 1,1′-*O*-Decane-1,10-diyl-*N*,*N*′-1,4-phenylene-di-(2,3,4-tri-*O*-acetyl-α-D-glucopyranuronamide) (17)

A degassed solution of **9** (103 mg, 0.117 mmol) in anhyd CH_2Cl_2 (39 mL, 3.0 mM solution) was cannulated into a flask containing the Grubbs first generation catalyst (22.6 mg, 20 mol %), under Ar. The mixture was stirred at room temp for 3.5 days, under Ar. The solvent was removed under diminished pressure, and chromatography of the residue gave the alkene precursor to **17** (48 mg, 48%); R_f = 0.38 (EtOAc–cyclohexane, 2:1); $[\alpha]_D$ +54.2 (*c* 1.0, $CHCl_3$); IR (film from CH_2Cl_2 on NaCl): 3344, 2923, 1754, 1690, 1519, 1369, 1223, 1049 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.18 (s, 2H, NH), 7.45 (s, 4H, aromatic H), 5.60 (t, 2H, *J* = 9.9 Hz, H-3), 5.40–5.33 (m, 2H, alkene CH), 5.21 (d, 2H, *J* = 3.6 Hz, H-1), 5.19 (t, 2H, *J* = 10.1 Hz, H-4), 4.85 (dd, 2H, *J* = 3.6, 10.1 Hz, H-2), 4.31 (d, 2H, *J* = 10.1 Hz, H-5), 3.77−3.72 and 3.48–3.42 (2m, each 2H, each OCH_2), 2.08, 2.07 (2s, each 6H, 4 × $COCH_3$), 2.05–2.01 (m, 4H, CH_2), 2.03 (s, 6H, 2 × $COCH_3$), 1.63–1.58 (m, 4H, CH_2), 1.43–1.38 (m, 4H, 2 × CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.3, 169.9, 169.8 (each ester C=O), 165.3, (amide C=O), 133.5 (aromatic C), 130.4 (alkene CH), 121.1 (aromatic CH), 96.0 (C-1), 70.9 (C-2), 69.9 (C-4), 69.9 (OCH_2), 69.4 (C-3), 68.5 (C-5), 32.0, 28.6, 25.8 (each CH_2), 20.8, 20.7, 20.6 (each $COCH_3$); ESI-LRMS: found *m/z* 849.5 $[M+H]^+$, 871.5 $[M+Na]^+$, 881.3 $[M+CH_3OH+H]^+$, 887.5 $[M+K]^+$, 847.3 $[M-H]^-$; ESI-HRMS *m/z*: $[M-H]^-$ calcd for $C_{42}H_{51}N_2O_{18}$, 871.3137; found, 871.3154. To a solution of this alkene (42.0 mg, 0.05 mmol) in EtOAc (10 mL) was added 10% Pd–C (8 mg), and the mixture was placed under an atmosphere of H_2 and this was stirred for 15 h at room temperature. The Pd–C was removed by filtration through Celite. The filtrate and washings were removed under diminished pressure and chromatography of the residue gave the title compound as a clear oil (35 mg, 83%); R_f = 0.42 (EtOAc–cyclohexane, 2:1); $[\alpha]_D$ +89.2 (*c* 0.6, $CHCl_3$); IR (NaCl plate, film from CH_2Cl_2): 3351, 2929, 2856, 1754, 1693, 1548, 1519, 1369, 122, 1047 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.14 (s, 2H, NH), 7.46 (s, 4H, aromatic H), 5.59 (t, 2H, *J* = 9.8 Hz, H-3), 5.22 (d, 2H, *J* = 3.5 Hz, H-1), 5.18 (t, 2H, *J* = 9.8 Hz, H-4), 4.85 (dd, 2H, *J* = 3.5, 10.0 Hz, H-2), 4.31 (d, 2H, *J* = 10.2 Hz, H-5), 3.70–3.66 and 3.59–3.47 (each m, each 2H, OCH_2), 2.08 (2s), 2.03 (18H, 6 × $COCH_3$), 1.61–1.59 (m, 4H, CH_2), 1.33–1.26 (m, 12H, 6 × CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.3, 169.9, 165.3 (each ester C=O), 165.3 (amide C=O), 133.6 (aromatic C), 121.0 (aromatic CH), 96.0 (C-1), 70.9 (C-2), 69.9 (C-4), 69.7 (OCH_2), 69.4 (C-3), 68.5 (C-4), 29.2, 29.1, 29.0, 25.6 (each CH_2), 20.8, 20.7, 20.6 (each 2 × $COCH_3$); ESI-LRMS: found *m/z* 851.6 $[M+H]^+$, 873.5 $[M+Na]^+$, 889.7 $[M+K]^+$, 849.6 $[M-H]^-$; ESI-HRMS: *m/z* calcd for $C_{40}H_{55}N_2O_{18}$ $[M+H]^+$: 851.3450, found 851.3478.

4.13. 1,1′-*O*-Decane-1,10-diyl-*N*,*N*′-1,4-phenylene-di-(α-D-glucopyranuronamide) (1)

Sodium methoxide in MeOH (0.1 mL of 1 mM) was added to an ice-cold solution of **17** (27 mg, 0.032 mmol) in MeOH (6 mL). The pH of the solution was adjusted with Amberlite IR-120 (H^+) to pH 5. The Amberlite IR-120 (H^+) was filtered off, and the solvent was removed under diminished pressure to give an oil. This was dissolved in water (2 mL) and then lyophilized to give **18** as a white powder (12 mg, 63%); ^1H NMR (500 MHz, DMSO-d_6): δ 9.93 (s, 2H, NH), 7.59 (s, 4H, aromatic H), 5.24 (d, 2H, *J* = 4.0 Hz, H-1), 4.86 (br s, 2H, OH), 4.69 (br s, 4H, OH), 3.98 (d, 2H, *J* = 8.2 Hz, H-5), 3.62–3.57 (m, 2H, OCH_2), 3.54–3.41 (m, 4H, H-3,4), 3.38–3.33 (m, 2H, OCH_2), 3.30 (H-2, overlapping with solvent), 1.56–1.51 (m, 4H, 2 × CH_2), 1.28 (br s, 12H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 168.3 (amide C=O), 135.1 (aromatic C), 120.3 (aromatic CH), 100.2 (d, C-1), 73.7, 72.4, 72.3 (each CH), 68.7 (OCH_2), 29.9, 29.7, 29.6, 29.1 (each CH_2); ESI-LRMS: found *m/z* 599.3 $[M+H]^+$, 621.3 $[M+Na]^+$, 637.3 $[M+K]^+$, 597.4 $[M-H]^-$; ESI-HRMS *m/z*: $[M-H]^-$ calcd for $C_{28}H_{41}N_2O_{12}$, 597.2660; found, 597.2654.

4.14. 1,1′-*O*-5-Decene-1,10-diyl-*N*,*N*′-1,4-xylene-di-(2,3,4-tri-O-acetyl-α-D-glucopyranuronamide) (19)

Reaction of **10** (105 mg, 0.116 mmol) in CH_2Cl_2 (116 mL) in the presence of the Grubbs first generation catalyst (21 mg, ~20%) over 2 days as described for the preparation of **10** gave the alkene precursor to **19** (81 mg, 80%); R_f = 0.1 (EtOAc–cyclohexane, 1:1); $[\alpha]_D$ +26.4 (*c* 1.5, $CHCl_3$); IR (NaCl plate, film from CH_2Cl_2): 3375, 2925, 2854, 1753, 1678, 1531, 1434, 1369, 1223, 1047 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (s, 4H, 4 × aromatic H), 6.83 (d, 1H, *J* = 3.8 Hz, NH), 6.81 (d, 1H, *J* = 8.6 Hz, NH), 5.55 (t, 2H, *J* = 10.0 Hz, H-3), 5.37 (t, 2H, *J* = 3.8 Hz, CH=CH), 5.16 (t, 2H, *J* = 9.8 Hz, H-4), 5.14 (t, 2H, *J* = 3.8 Hz, H-1), 4.90 (dd, 2H, *J* = 8.6, 15.0, $NHCH_2$), 4.82 (dd, 2H, *J* = 3.8, 10.2 Hz, H-2), 4.27 (d, 2H, *J* = 10.2 Hz, H-5), 3.94 (dd, 2H, *J* = 5.0, 10.0 Hz, $NHCH_2$), 3.62–3.57 and 3.47–3.44 (each m, each 2H, OCH_2), 2.09–1.99 (m, 4H, $CH{=}CHCH_2$), 2.08, 2.06, 2.03 (3s, each 6H, each 2 × $COCH_3$), 1.68–1.50 (m, 4H, CH_2), 1.45–1.36 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.9, 169.8 (each $COCH_3$), 167.4 (amide C=O), 137.1 (aromatic C), 130.4 (alkene CH), 127.8 (aromatic CH), 95.4 (C-1), 70.8 (C-2), 69.7 (C-4), 69.4 (C-3), 69.1 (OCH_2), 67.6 (C-5), 42.4 ($NHCH_2$), 31.7, 28.1, 25.8 (each CH_2), 20.8, 20.6, 20.5 (each $COCH_3$); ESI-LRMS: found *m/z* 877.5 $[M+H]^+$, 894.6 $[M+H_2O]^+$, 899.9 $[M+Na]^+$, 915.5 $[M+K]^+$, 875.3 $[M-H]^-$; ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{42}H_{56}N_2O_{10}Na$, 899.3426; found, 899.3408. Catalytic hydrogenation of this alkene precursor as described in the preparation of **17** gave **19** (42 mg, 88%); R_f = 0.35 (EtOAc–cyclohexane, 2:1); $[\alpha]_D$ +33.5 (*c* 1.07, $CHCl_3$); IR (NaCl plate, film from CH_2Cl_2): 3373, 2924, 2854, 1753 (ester C=O), 1681 (amide C=O), 1530, 1367, 1223, 1047 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (s, 4H, aromatic H), 6.86 (d, 1H, *J* = 3.5 Hz, NH), 6.84 (d, 1H, *J* = 3.5 Hz, NH), 5.56 (t, 2H, *J* = 9.8 Hz, H-3), 5.17 (t, 2H, *J* = 10.1 Hz, H-4), 5.13 (d, 2H, *J* = 3.5 Hz, H-1), 4.91 (dd, 2H, *J* = 8.3, 15.1 Hz, $NHCH_2$), 4.82 (dd, 2H, *J* = 3.7, 10.4 Hz, H-2), 4.31 (d, 2H, *J* = 10.1 Hz, H-5), 3.97 (dd, 2H, *J* = 3.7, 15.1 Hz, $NHCH_2$), 3.61–3.53 (m, 4H, OCH_2), 2.10, 2.08, 2.03 (3s, each 6H, each 2 × $COCH_3$), 1.66–1.57 (m, 4H, CH_2), 1.35–1.23 (m, 12H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.0, 169.8 (each s, each $COCH_3$), 167.5 (amide C=O), 137.1 (aromatic C), 127.8 (aromatic CH), 95.9 (C-1), 70.8 (C-2), 70.0 (OCH_2), 69.7 (C-4), 69.4 (C-3), 67.8 (C-5), 42.5 ($NHCH_2$), 29.0, 28.6, 28.3, 25.6 (each CH_2), 20.8, 20.7, 20.6 (each $COCH_3$); ESI-LRMS: found *m/z* 879.5 $[M+H]^+$, 901.5 $[M+Na]^+$; ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{42}H_{58}N_2O_{18}Na$, 901.3582; found, 901.3555.

4.15. 1,1′-*O*-Decane-1,10-diyl-*N*,*N*′-1,4-xylene-di-(α-D-glucopyranuronamide) (20)

De-O-acetylation of **19** (42 mg, 0.047 mmol) as described for **17** gave **20** as a yellow powder (23.5 mg, 78%); R_f = 0.14 (CH_2Cl_2-MeOH, 9:1); $[\alpha]_D$ +38.6 (*c* 0.4, MeOH); IR (film from MeOH): 3309, 2917, 1630 (amide C=O), 1545, 1464 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ 7.25 (s, 4H, aromatic H), 4.85 (d, 2H, *J* = 3.8 Hz, H-1), 4.24 and 4.59 (each d, 4H, *J* = 14.8 Hz, NCH_2), 4.03 (d, 2H, *J* = 10.0 Hz, H-5), 3.69–3.62 (m, 2H, OCH_2), 3.64 (t, 2H, *J* = 9.5 Hz, H-3), 3.59–3.53 (m, 2H, OCH_2), 3.50 (dd, 2H, *J* = 9.0, 9.8 Hz, H-4), 3.45 (dd, 2H, *J* = 3.8, 9.8 Hz, H-2), 1.72–1.68 (m, 4H, 2 × CH_2), 1.62–1.55 and 1.41–1.28 (2m, 12H, 6 × CH_2); ^{13}C NMR (150 MHz, CD_3OD): δ 172.7 (amide C=O), 138.8 (C), 128.7 (aromatic CH), 100.7 (C-1), 74.7 (C-3), 73.9 (C-4), 73.0 (C-2), 72.2 (C-5), 70.2 (OCH_2), 42.4 ($NHCH_2$), 30.7, 30.5, 30.2, 29.4 (each CH_2); ESI-LRMS: found *m/z* 627.4 $[M+H]^+$, 649.4 $[M+Na]^+$, 665.3 $[M+K]^+$,

625.4 $[M-H]^-$, 671.2 $[M+HCOO]^-$; ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{30}H_{47}N_2O_{12}$, 627.3129; found, 627.3099.

4.16. 1,1′-*O*-6-Dodecyne-1,12-diyl-*N*,*N*′-1,4-phenylene-di-(2,3,4-tri-*O*-acetyl-α-D-glucopyranuronamide) (21)

A solution of **13** (87.4 mg, 0.094 mmol) and $Mo(CO)_6$ (2.5 mg, 0.009 mmol) in chlorobenzene (5 mL) was heated to reflux, under N_2, and 2-fluorophenol (8.3 μL, 0.094 mmol) was then added and the mixture was heated at reflux for 2.5 h. The solvent was removed under diminished pressure, and chromatography of the residue gave **21** as an oil (22 mg, 27%); R_f = 0.6 (EtOAc–cyclohexane, 2:1); $[\alpha]_D$ +73.2 (*c* 1.2, $CHCl_3$); IR (film from CH_2Cl_2 on NaCl): 3351, 2926, 2855, 1759, 1691, 1518, 1369, 1250, 1048 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.18 (s, 2H, NH), 7.43 (s, 4H, aromatic H), 5.58 (t, 2H, *J* = 9.9 Hz, H-3), 5.23 (d, 2H, *J* = 3.7 Hz, H-1), 5.17 (t, 2H, *J* = 9.9 Hz, H-4), 4.84 (dd, 2H, *J* = 3.7, 10.2 Hz, H-2), 4.31 (d, 2H, *J* = 10.1 Hz, H-5), 3.76–3.72 and 3.49–3.45 (each m, 2H, OCH_2), 2.15–2.12 (m, 4H, CH_2), 2.08, 2.07, 2.03 (each s, each 6H, $COCH_3$), 1.67–1.61 (m, 4H, CH_2), 1.50–1.42 (m, 8H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.9, 169.8 (each $COCH_3$), 165.3 (amide C=O), 133.5 (aromatic C), 121.1 (aromatic CH), 95.8 (C-1), 80.2 (alkyne C), 70.9, 69.9 (CH), 69.4 (OCH_2), 69.3, 68.5 (each CH), 28.7, 28.5, 24.9 (each CH_2), 20.7 (2s), 20.6 (each $COCH_3$), 18.5 (CH_2); ESI-LRMS: found *m/z* 875.5 $[M+H]^+$, 873.5 $[M-H]^-$; ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{42}H_{55}N_2O_{18}$, 875.3450; found, 875.3445.

4.17. 1,1′-*O*-6-Dodecyne-1,12-diyl-*N*,*N*′-1,4-phenylene-di-(α-D-glucopyranuronamide) 22

De-O-acetylation of **21** (22 mg, 0.025 mmol) as described for **17** gave **22** as a syrup (10 mg, 66%); ^1H NMR (600 MHz, DMSO-d_6): δ 9.94 (s, 2H, NH), 7.59 (s, 4H, aromatic H), 5.23 (br s, 2H, H-1), 4.86 (br s, 2H, OH), 4.70 (br s, 4H, OH), 3.98 (d, 2H, *J* = 8.2 Hz, H-5), 3.66–3.60 (m, 2H, OCH_2), 3.45 (br s, 4H, H-3,4), 3.38–3.33 (m, 2H, OCH_2), 3.30–3.47 (overlapping signals and solvent, H-2), 2.12 (br s, 4H, CH_2), 1.59–1.55 (m, 4H, CH_2), 1.44–1.39 (m, 8H, CH_2); ^{13}C NMR (150 MHz, DMSO): δ 168.3 (amide C=O), 135.1 (aromatic C), 120.3 (aromatic CH), 100.1 (C-1), 81.0 (alkyne C), 73.6, 72.4, 72.2 (each CH), 68.3 (OCH_2), 29.3, 29.1, 25.4, 18.7 (each CH_2); ESI-LRMS: found *m/z* 623.3 $[M+H]^+$, 645.4 $[M+Na]^+$, 621.4 $[M-H]^-$; ESI-HRMS *m/z*: $[M-H]^-$ calcd for $C_{30}H_{41}N_2O_{12}$, 621.2660; found, 621.2685.

4.18. 1,1′-*O*-Octane-1,8-diyl-*N*,*N*′-1,4-phenylene-di-(α-D-*N*-methyl-glucuronamide) (24)

Catalytic hydrogenation of **23** (55.0 mg, 0.064 mmol) gave the intermediate (46.0 mg, 83%) and subsequent de-O-acetylation of this intermediate (28 mg, 0.033 mmol) gave **24** (14 mg, 71%); ^1H NMR (600 MHz, D_2O): δ 7.43 (br s, 4H, aromatic H), δ 5.08 (d, *J* = 9.7 Hz, H-5, *EZ*-isomer), 4.95 (d, 2H, *J* = 3.85 Hz, H-1, *EE*-isomer), 4.49 (d, 2H, *J* = 9.7 Hz, H-5, *EE*-isomer), 4.17 (d, *J* = 9.9 Hz, H-5, *EZ*-isomer). 3.86–3.75 (m, 2H, OCH_2), 3.71–3.68 (overlapping signals, 2H), 3.65–3.51 (m, overlapping signals), 3.33 (s, 6H, NCH_3), 1.80–1.72 and 1.63–1.52 (each m, each 2H, 2 × OCH_2), 1.43–1.27 (m, 8H, 4 × CH_2); ^{13}C NMR (150 MHz, D_2O): δ 170.6 (amide C=O), 142.2 (aromatic C), 128.3 (aromatic CH), 99.4 (C-1), 72.6, 72.4, 71.1, (C-2 to C-4), 70.3 (OCH_2), 68.1 (C-5), 38.3 (NCH_3), 28.5, 27.7, 24.9 (each CH_2); ESI-LRMS: found *m/z* 599.2 $[M+H]^+$, 621.2 $[M+Na]^+$, 597.4 $[M-H]^-$; ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{28}H_{43}N_2O_{12}$, 599.2816; found, 599.2791.

Acknowledgement

The authors are grateful for financial support from the Programme for Research in Third Level Institutions Cycle 3 administered by the HEA.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.06.007.

References

1. For recent reviews on saccharides as polyfunctional scaffolds see: (a) Velter, I.; La Ferla, B.; Nicotra, F. *J. Carbohydr. Chem.* **2006**, *25*, 97–138; (b) Meutermans, W.; Le, G. T.; Becker, B. *ChemMedChem* **2006**, *1*, 1164; (c) Gentilucci, L.; Tolomelli, A.; Squassabia, F. *Curr. Med. Chem.* **2006**, *13*, 2449–2466; (d) Murphy, P. V.; Dunne, J. L. *Curr. Org. Synth.* **2006**, *3*, 403–437.
2. A triazacyclophane has been investigated in bioactive molecule development see: (a) Opatz, T.; Liskamp, R. M. J. *Org. Lett.* **2001**, *3*, 3499–3502; (b) Monnee, M. C. F.; Brouwer, A. J.; Verbeek, L. M.; van Wageningen, A. M. A.; Liskamp, R. M. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1521–1525.
3. For a review of metathesis relevant to glycobiology see: Leeuwenburgh, M. A.; van der Marel, G. A.; Overkleeft, H. S. *Curr. Opin. Chem. Biol.* **2003**, *7*, 757–765.
4. Velasco-Torrijos, T.; Murphy, P. V. *Org. Lett.* **2004**, *5*, 3961–3964.
5. Murphy, P. V. *Eur. J. Org. Chem.* **2007**, 4177–4187.
6. Murphy, P. V.; Velasco-Torrijos, T., private communication.
7. For selected publications on synthesis and applications of glycophanes see: (a) Bukownik, R. R.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 463–467; (b) Jimenez-Barbero, J.; Junquera, E.; Martin-Pastor, M.; Sharma, S.; Vicent, C.; Penades, S. *J. Am. Chem. Soc.* **1995**, *117*, 11198–11204; (c) Savage, P. B.; William, D.; Dalley, N. K. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1997**, *29*, 335–346; (d) Morales, J. C.; Penades, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 654–657; (e) Belghiti, T.; Joly, J.-P.; Didierjean, C.; Dahaoui, S.; Chapleur, Y. *Tetrahedron Lett.* **2002**, *43*, 1441–1443.
8. Murphy, P. V.; Müller-Bunz, H.; Velasco-Torrijos, T. *Carbohydr. Res.* **2005**, *340*, 1437–1440.
9. Velasco-Torrijos, T.; Murphy, P. V. *Tetrahedron: Asymmetry* **2005**, *16*, 261–272.
10. Shape persistent macrocycles have applications in material science. See: Zhang, W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4416–4439.
11. For a review of ring closing alkyne metathesis see: Zhang, W.; Moore, J. S. *Adv. Synth. Catal.* **2007**, *349*, 93–120.
12. For applications of ring closing alkyne metathesis in carbohydrate chemistry see: (a) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem.* **2000**, *65*, 8758–8762; (b) Fürstner, A. *Eur. J. Org. Chem.* **2004**, *2004*, 943–958; (c) Davies, P. W.; Fürstner, A. *Chem. Commun.* **2005**, 2307–2320.
13. For glycosidation reactions of lactone **8** see: (a) Tosin, M.; Murphy, P. V. *Org. Lett.* **2002**, *4*, 3675–3678; (b) Poláková, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2518–2521; (c) O'Brien, C.; Poláková, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Chem. Eur. J.* **2007**, *13*, 902–909.
14. Grela, K.; Ignatowska, J. *Org. Lett.* **2002**, *4*, 3747–3749.
15. Mortreux, A.; Blanchard, M. *Chem. Commun.* **1974**, 786–787.
16. (a) Tosin, M.; O' Brien, C.; Fitzpatrick, G. M.; Müller-Bunz, H.; Glass, W. K.; Murphy, P. V. *J. Org. Chem.* **2005**, *70*, 4096–4106; (b) Tosin, M.; Murphy, P. V. *J. Org. Chem.* **2005**, *70*, 4107–4117.
17. Gung, B. W.; Gibeau, C.; Jones, A. *Tetrahedron: Asymmetry* **2005**, *16*, 3107–3114.