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Tetrahedron
Tetrahedron 62 (2006) 8309–8317

Cobalt-mediated solid phase synthesis of 3-*O*-alkynylbenzyl galactosides and their evaluation as galectin inhibitors

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Received 16 March 2006; revised 2 June 2006; accepted 15 June 2006
Available online 7 July 2006

Abstract—Methyl β-D-galactoside was converted to the corresponding 3,4-*O*-stannylene acetal, which was selectively benzylated with 3-iodobenzyl bromide and coupled to a polymer-bound propargylic ether via a Sonogashira reaction. The polymer-bound carbohydrate substrate was cleaved from the resin with different carbon nucleophiles in a cobalt-mediated Nicholas reaction. The product 3-*O*-alkynylbenzyl galactosides were screened towards galectin-1, -3, -7, -8N and -9N in a competitive fluorescence polarisation assay. Particularly potent inhibitors were identified against galectin-7 with affinity enhancements up to one order of magnitude due to the 3-*O*-alkynylbenzyl moiety.

1. Introduction

Cells can communicate with the outer world by exchanging information via their surfaces. Cell surface glycoconjugates, e.g., glycoproteins and glycolipids, code for information such as cell identity and are involved in cell signalling pathways, which are the reasons why carbohydrate-recognising proteins, lectins, are potential targets for pharmaceutical research. The galectins are a sub-class of lectins defined by having an affinity for β-galactosides, a carbohydrate recognition domain (CRD) of approximately 130 amino acids and with a conserved amino acid sequence motif of about seven residues.[1] There are today 14 known galectins that can be found in mammals,[2] and they have a wide variety of biological functions, such as inducing apoptosis of T-cells, antiapoptotic and pro-inflammatory functions as well as modulation of cell adhesion and migration. The galectins can be found in almost all types of tissues and organs.[3] The biological importance of galectins discovered over the past few years makes the discovery of novel and potent galectin inhibitors more interesting than ever.[4] Among natural saccharide ligands, galectins bind lactose, Lac*N*Ac (Fig. 1) and related disaccharides. Most galectins also bind to longer saccharides more efficiently. These longer saccharides are typically characterised by having an additional sugar residue added to C-3 of Gal in lactose or Lac*N*Ac. X-ray studies of galectins[5] show highly conserved CRDs as well as extended binding sites that could accommodate the additional sugar residues at the galactose C-3. We recently showed that an affinity-enhancing effect can be achieved by derivatising Lac*N*Ac with 3- or 4-substitued benzamides or a 4-methoxybenzyl ether.[6] Hence, synthesis of galactosides carrying 3- or 4-substituted benzyl ethers at O-3 of galactose emerged as a route towards galectin inhibitors (Fig. 2). Within this context, the use of alkyne-substituted benzyl ethers appeared attractive, as alkyne derivatives can be exploited in various diversifying reactions, among others the Nicholas reaction.

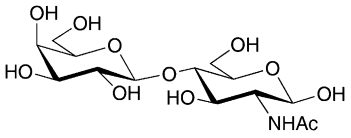

Figure 1. Lac*N*Ac (*N*-acetyllactosamine).

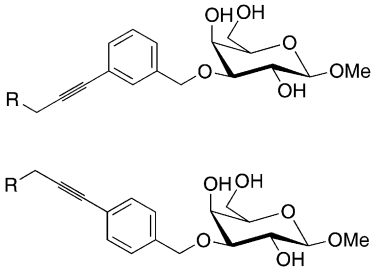

Figure 2. Targeted potential galectin inhibitors.

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doi:10.1016/j.tet.2006.06.057

An important tool for investigating biologically active compounds is parallel synthesis on solid phase.[7] By using solid phase techniques, many tedious purification steps can be avoided thus, accelerating access to new compounds. One disadvantage, however, is that extra steps are needed for initial attachment of the substrate to the resin as well cleavage from the solid support at the end of the sequence. If additional diversity could be introduced during cleavage, this reaction step could be seen as an advantage rather than an impediment, especially if new carbon–carbon bonds could be formed. Our group has recently developed a method to this effect using a solid phase variant of the Nicholas reaction[8] and we herein describe its use in the preparation of potential galectin inhibitors, using different carbon and oxygen nucleophiles to introduce diversity.

2. Results and discussion

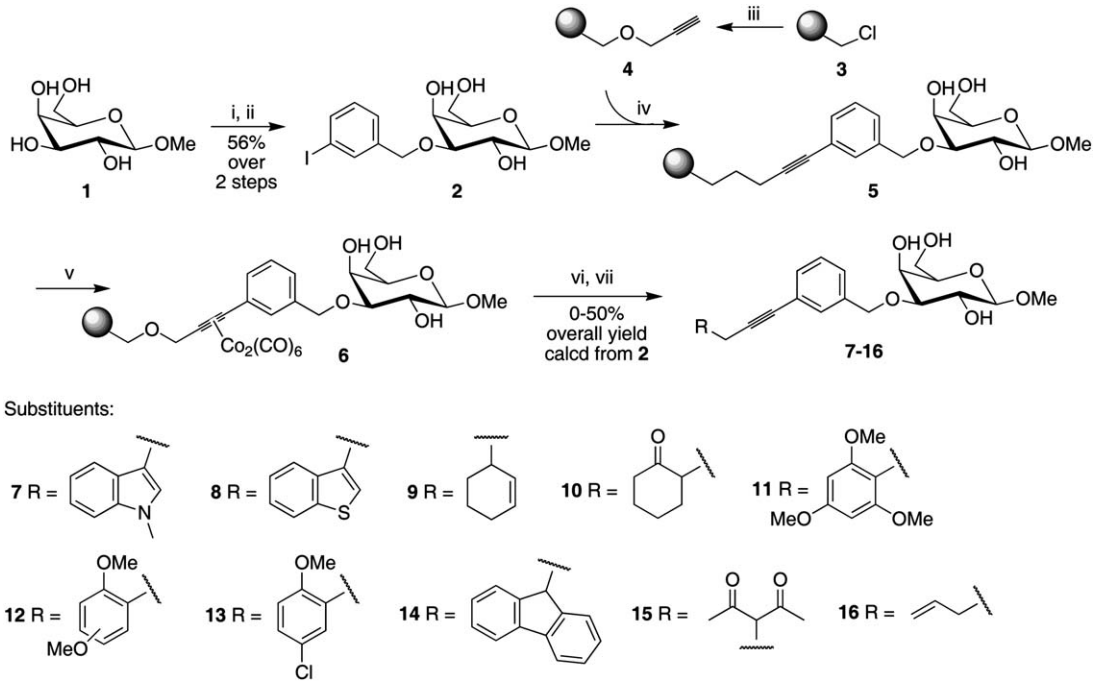
The enticing prospect of performing the synthesis without protecting the carbohydrate hydroxyl groups could be achieved by regioselective benzylation at O-3 of methyl β-D-galactoside **1**.[9] Functionalisation with *meta*- or *para*-iodobenzyl ether allows the use of the Sonogashira reaction to introduce an alkyne functionality on the aromatic ring. This approach would also allow us to connect the carbohydrate onto a solid phase under mild conditions, by using a polymer-bound propargylic ether in the Sonogashira reaction.[10] Furthermore, attaching the galactoside to a solid phase should minimise the risk of galactose hydroxyl groups acting as nucleophiles in the Nicholas reaction.

Methyl β-D-galactoside **1** was converted to the 3,4-*O*-stannylene acetal, which was selectively benzylated with 3-iodobenzyl bromide as the electrophile to afford **2** in 56% yield (Scheme 1). Propargylic alcohol was attached to Merrifield resin in a Williamson reaction,[11] affording **4**, verified by IR analysis. The iodobenzyl derivative **2** was then attached to resin **4** under Sonogashira conditions. IR analysis revealed the disappearance of the terminal alkyne C–H vibration, while a new broad peak in the region of 3500 cm^{-1} showed that the carbohydrate had been successfully attached, affording **5**. Resin **5** could be stored under dry conditions for several months without any sign of deterioration.

Complex formation was effected by treating the substrate with an excess of cobalt octacarbonyl, forming the desired alkyne–cobalt complex **6**, indicated by the deep red colouring of the resin.

In almost all examples of the Nicholas reaction in solution as well as on solid phase, the solvent of choice has been dichloromethane.[12] However, our initial experiments in dichloromethane always resulted in unidentified by-product formation. Hence, we made a comparison of different solvents and found that the Nicholas reaction failed in tetrahydrofuran and acetonitrile, but gave a clean reaction in toluene. Toluene also allowed us to run the reaction at room temperature.

Polymer-bound scaffold **6** was treated with 10 different nucleophiles (Table 1, entries 1–10) under the modified Nicholas conditions. The solutions typically turned red within 2 min indicating initiation of the reaction. After 17 h, the reactions were quenched via the addition of triethylamine, and the cobalt–alkyne complex was then cleaved with iodine.[13] After workup, the crude products **7–16** were



Scheme 1. Preparation of *meta*-substituted 3-*O*-alkynylbenzyl galactosides **7–16**. Reaction conditions: (i) Bu_2SnO, MeOH, reflux, 2 h; (ii) 3-iodobenzyl bromide, *n*-Bu_4NBr, 1,4-dioxane, reflux, 2 h; (iii) NaH, propargyl alcohol, 15-crown-5, THF, 16 h; (iv) $Pd(PPh_3)_4$, CuI, **4**, THF/Et_3N (1:1), rt, 16 h; (v) $Co_2(CO)_8$, dichloromethane, rt, 4 h; (vi) $BF_3 \cdot OEt_2$, nucleophile (see Table 1, entries 1–10), toluene, rt, 16 h or two cycles of 10 min/30 min; (vii) I_2, THF, 0 °C, 1.5 h (yields, see Table 1).

Table 1. Nicholas reaction with polymer-bound substrate **6**

Entry	Nucleophile	Product	Overall yield (%)[b]
1	*N*-Methylindole	**7**	25
2	Benzo[*b*]thiophene	**8**	<5
3[a]	3-Trimethylsilyl-1-cyclohexene	**9**	18
4	1-Trimethylsilyloxy-cyclohexene	**10**	14
5[a]	1,3,5-Trimethoxybenzene	**11**	48
6[a]	1,3-Dimethoxybenzene	**12**	40
7	4-Chloroanisole	**13**	n.r.
8	Fluorene	**14**	n.r.
9[a]	4-(Trimethylsilyoxy)-3-penten-2-one	**15**	<5
10	Allyltrimethylsilane	**16**	50

[a] Two short consecutive reactions.
[b] Isolated yield after chromatography for the four-step sequence calculated from **2**.

purified either by flash chromatography or by HPLC. 1,3-Dimethoxybenzene and 1,3,5-trimethoxybenzene initially gave products, but these decomposed rapidly under the conditions used (entries 5, 6). Products **11** and **12** were formed within 1 min according to TLC analysis and decomposition products could be detected after about 15 min. Fortunately, a shorter reaction time, i.e., 15 min, in combination with a second reaction cycle of 30 min resulted in good yields for 1,3,5-tri- (**11**) and 1,3-di-methoxybenzene (**12**). Also included in the second run was 4-(trimethylsilyloxy)-3-penten-2-one (**15**) but only traces of nucleophile could be isolated. The reaction with 1,3-dimethoxybenzene not surprisingly yielded **12** as a mixture of two regioisomers, inseparable by HPLC (entry 6). Having completed the synthesis of the *meta*-substituted 3-*O*-benzylated galactosides **7**–**16**, our attention turned towards synthesis of the *para*-substituted analogues. Starting again from **1**, the key alkyne-complex **18** was synthesised following the same protocol as for **6** (Scheme 2). With the earlier problems for the methoxy-substituted benzenes in mind, we opted to run the whole set with the methodology used for **11** and **12**.

Unfortunately, this methodology failed to afford any product for 1,3-di- and 1,3,5-trimethoxybenzene (only unidentified decomposition products were observed). For the other nucleophiles products were formed, but the yields were substantially lower. The poor yield may be caused by the *para*-alkenyl in combination with the unprotected hydroxyls, rendering the benzyl ether less stable.

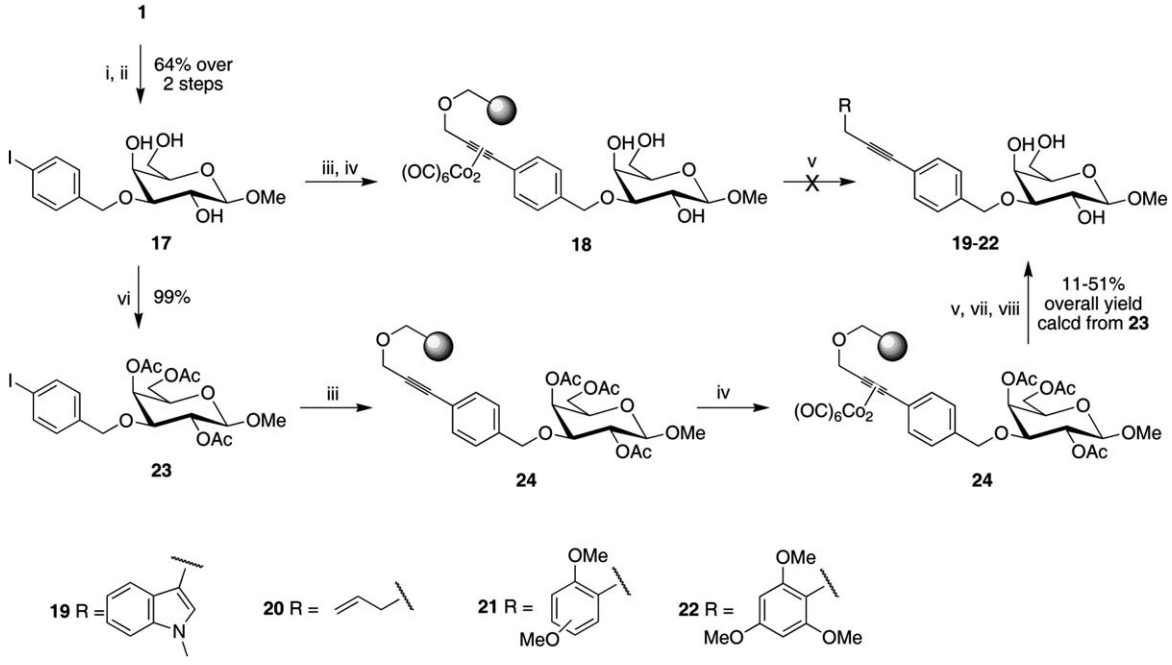
To avoid possible difficulties caused by the unprotected hydroxyls we decided to acetylate **17**, affording **23** in 99% yield, followed by attachment to the solid phase **3** as before, yielding **24** (Scheme 2). After complexation of **24** with dicobalt hexacarbonyl, the nucleophiles that had given the highest yields with substrate **6** earlier were applied in the Nicholas reaction. Oxidative removal of the cobalt complex and deacetylation under Zemplen conditions[14] (catalytic amount of sodium methoxide in methanol) afforded products **19**–**22** without any by-product formation (Table 2, entries 1–4).

Our initial fears that the hydroxyl groups would compete with the *C*-nucleophiles during the Nicholas reaction turned

Table 2. Nicholas reaction with polymer-bound substrate **24**

Entry	Nucleophile	Product	Overall yield (%)[a]
1	*N*-Methylindole	**19**	24
2	Allyltrimethylsilane	**20**	45
3[a]	1,3-Dimethoxybenzene	**21**	51
4	1,3,5-Trimethoxybenzene	**22**	11

[a] Isolated yield after chromatography for the five-step sequence calculated from **23**.



Scheme 2. Preparation of *para*-substituted 3-*O*-alkynylbenzyl galactosides **19**–**22**. Reaction conditions: (i) Bu_2SnO, MeOH, reflux, 2 h; (ii) 4-iodobenzyl bromide, *n*-Bu_4NBr, 1,4-dioxane, reflux, 2 h; (iii) $Pd(PPh_3)_4$, CuI, **4**, THF/Et_3N (1:1), rt, 16 h; (iv) $Co_2(CO)_8$, dichloromethane, rt, 3 h; (v) $BF_3\cdot OEt_2$, nucleophile (see Table 2, entries 1–4), toluene, rt, 2 h; (vi) Ac_2O, pyridine, rt, 16 h; (vii) I_2, THF, 0 °C, 2 h; (viii) NaOMe, MeOH, rt, 16 h (yields, see Table 2).

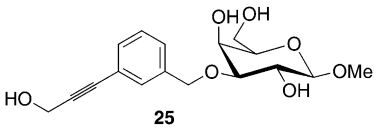


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Figure 3.

out to be unwarranted. We could never detect any other carbohydrate-containing products when using **6** as the substrate. The lower yields for the unprotected carbohydrates are probably caused by boron trifluoride etherate coordinating to the free hydroxyl groups, as well as material loss in the isolation steps.

The final compounds **2**, **7**, **9–12**, **16** and **19–22** as well as compound **25** (Fig. 3) were tested against galectin-1, -3, -7, -8N (N-terminal domain) and -9N (N-terminal domain) using fluorescence polarisation techniques (Table 3).[15,16] While the results for galectin-1, -3 and -8N were less impressive, inhibitors of galectin-7 and -9N with more than an order magnitude improved affinity were discovered (entries **16**, **25**, **21** and **2**, respectively).

Three sub-millimolar inhibitors, compounds **16**, **25** and **21**, were found for galectin-7. The K_d value of 0.39 mM for **16** is more than one order of magnitude improvement over the underivatised reference galactoside **1** and remarkably potent for a monosaccharide derivative. The best inhibitors are the simple straight-chain allyl- and hydroxymethyl-substituted alkynes **16** and **25**, which suggests that the binding pocket of galectin-7 close to galactose O-3 is relatively small and does not allow larger cyclic structures to bind. Several structures of galectin-7 as complexes with ligands have been solved,[17] this allowed computational analysis of galectin-7 in complexation with compounds **16**, **25** and **21**. Although conformational searches of the complexes gave several energy minima for each inhibitor/galectin-7 complex, a coherent picture emerged. The conformations and positions of the galactose ring and the 3-*O*-benzyl group were in all cases similar. The N-terminal of galectin-7, which was close to the alkynyl groups, possessed a high degree of conformational freedom. Hence, conclusive analysis of the conformations of the alkynyl chains proved to be challenging. Nevertheless, some general conclusions could be drawn. The two compounds carrying benzyl ethers substituted in the *meta*-position with straight-chain substituents, **16** and **25**, preferred similar conformations and similar interactions with galectin-7. While the alkynylbenzyl moiety of **16** displayed a better surface complementarity with galectin-7 (Fig. 4a), the hydroxyl group of the alkyne moiety of **25** could form a hydrogen bond with Asn-2 (Fig. 4b).

Table 3. K_d (mM) values against galectin-1, -3, -7, -8N and -9N measured in a competitive fluorescence polarisation assay

		Galectin				
		1	3	7	8N	9N
1	Methyl β-D-galactoside	10	4.4	4.8	5.3	3.4
meta-Substituted benzyl ethers, R=						
2	I	11	2.1	1.3	2.7	*0.26*
7	3-(*N*-Methylindol-3-yl)prop-1-ynyl	n.i.[a]	n.i.	n.i.	n.i.	n.i.
9	(Cyclohexen-3-yl-methyl)prop-1-ynyl	n.i.	n.i.	8.4	1.8	5.7
10	(Cyclohexanon-2-yl-methyl)prop-1-ynyl	11	2.4	4.6	1.5	3.0
11	(1,3,5-Trimethoxyphenyl)prop-1-ynyl	n.i.	4.5	1.5	1.9	4.2
12	(1,3-Dimethoxyphenyl)prop-1-ynyl	n.i.	4.8	1.2	n.i.	1.5
16	Allylprop-1-ynyl	27	2.4	*0.39*	1.0	1.0
25[b]	Hydroxymethylprop-1-ynyl	6.9	2.9	*0.65*	3.8	1.9
para-Substituted benzyl ethers, R=						
19	3-(*N*-Methylindol-3-yl)prop-1-ynyl	n.i.	n.i.	n.i.	n.i.	n.i.
20	Allylprop-1-ynyl	n.i.	4.3	4.9	n.i.	13
21	(1,3-Dimethoxyphenyl)prop-1-ynyl	n.i.	5.4	*0.74*	2.4	2.0
22	(1,3,5-Trimethoxyphenyl)prop-1-ynyl	2.2	1.3	1.5	0.93	1.8

[a] Non-inhibitory.
[b] Prepared via solution phase methods.

The low-energy complexes with **21**, which carries a dimethoxybenzyl-substituted alkyne moiety at the *para*-position, revealed preferred interaction modes significantly different from those of the *meta*-substituted **16** and **25**. The dimethoxybenzyl group of **21** fills a narrow cleft with good surface complementarity (Fig. 4c). The favoured complex calculated between **21** and galectin-7 could also explain why the structurally similar 1,3,5-trimethoxy-substituted **22** has a K_d twice as high as **21**. The third methoxy group of **22** would inevitably sterically interfere with the alkyne moiety if a complex similar to that between **21** and galectin-7 was formed.

The best inhibitor of galectin-9N was **2**, which carries a structurally simple *meta*-iodobenzyl ether at the 3-*O* position. Compound **2** is almost 13 times higher in affinity than methyl β-D-galactoside itself. Disappointingly, additional substitution on the benzyl group lowers the affinity. Although **2** might not be a good structure for further development into galectin-9N inhibitors, it shows significant selectivity over the other galectins investigated. This confirms that the galectin binding sites close to galactose C-3 differ enough to allow for the much desired development of selective inhibitors.

3. Conclusions

We have demonstrated that the Nicholas reaction of alkynyl benzyl ethers can be used to provide a straightforward and flexible route to novel galectin inhibitors. The solid phase approach simplified the purification steps and enabled the use of unprotected carbohydrate in the formation of the *meta*-substituted products. The inhibitors were tested for their affinity towards galectin-1, -3, -7, -8N and -9N using fluorescence polarisation techniques and the majority exhibited affinity for one or more of the tested galectins. In particular, potent monosaccharide inhibitors of galectin-7 were discovered.

4. Experimental

4.1. General methods

All reactions involving moisture or air sensitive compounds were performed under a nitrogen or argon atmosphere using oven-dried glass equipment. Solvents were either used as purchased from commercial sources or purified using standard procedures[18] as appropriate. All reagents were used as purchased. Column chromatography was carried out using Matrix Si 60 Å, 35–70 μm. Thin layer chromatography (TLC) was performed using precoated alumina-backed plates (Merck 25 DC Alufolien Kieselgel 60 F_{254}). Visualisation was effected either by UV fluorescence (υ=254 nm) or by heating the plates after treatment with

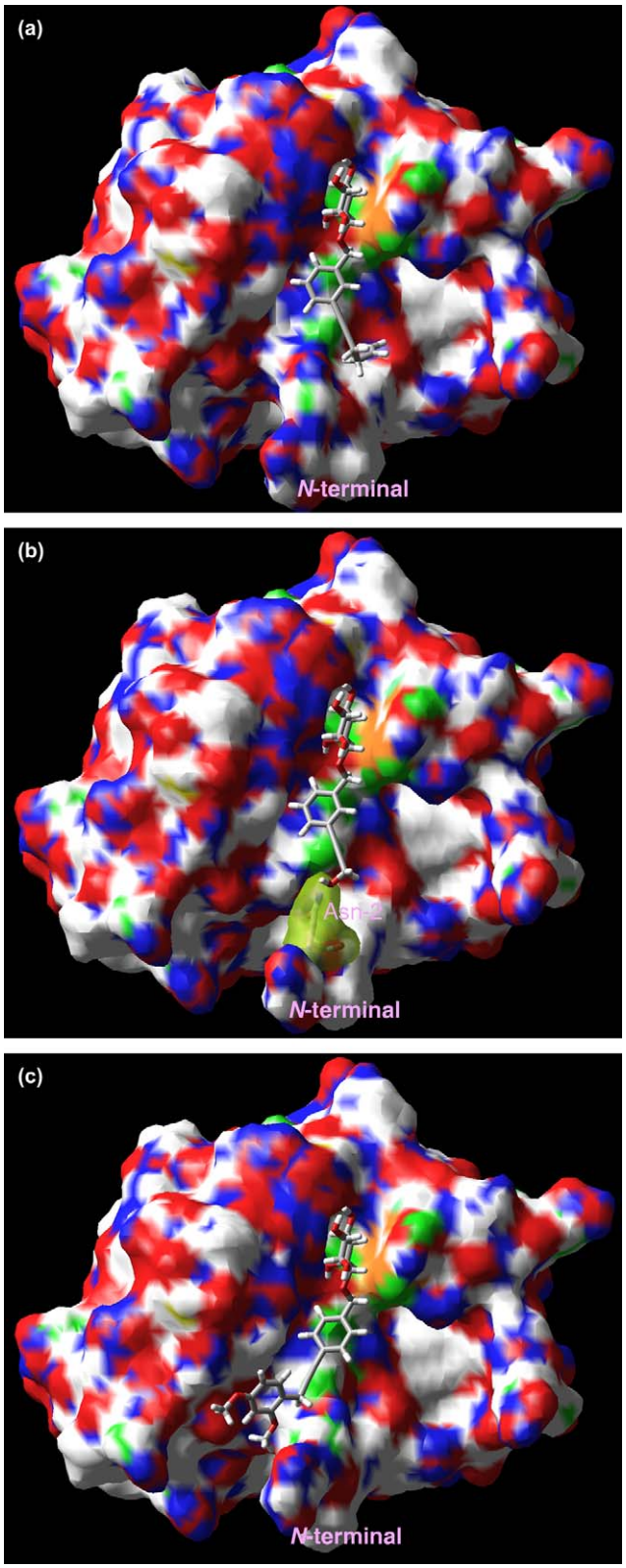

Figure 4. Energy minimised structure of galectin-7 in complex with (a) **16**, (b) **25** and (c) **21**. Molecular modelling was performed with MMFFs force field in water implemented in Macromodel 9.0. Starting conformations were built from the galactose/galectin-7 crystal structure.[12]

10% H_2SO_4. Preparative HPLC was conducted on a Waters 600E system using an XTerra Ms C_{18} 5 μm column and equipped with a Waters 490 Multiwavelength detector, using a stepwise gradient of 0.1 M NH_4OAc (5% acetonitrile) to pure acetonitrile as the mobile phase. Analytical HPLC was conducted on a Waters 600E system using a Chromasil 100 C_8 3.5 mm column with the same mobile phase as the preparative system. NMR spectra were recorded using either a Varian Unity 500 or a JEOL eclipse+ (^{1}H 400 MHz and ^{13}C 100 MHz). All spectra were recorded either in chloroform-d_1 or in methanol-d_4. All chemical shifts (δ_H and δ_C) are quoted in parts per million relative to tetramethylsilane (δ_H 0.00). Optical rotations were measured using a Perkin–Elmer polarimeter 341 C, which has a thermally jacketed 10^{-1} cm cell (path length of 1 dm) and were given in units of 10^{-1} deg cm^2 g^{-1} at 589 nm (sodium D-line). All infrared spectra were obtained using a Perkin–Elmer 1600 FTIR as KBr tablet samples. Only selected absorbancies are reported. Galectin production and fluorescence polarisation experiments with rat galectin-1 and human galectin-3, -7, -8N and -9N were performed as described earlier.[15,16]

4.1.1. Methyl 3-*O*-(3-iodobenzyl)-β-D-galactopyranoside (2). Methyl β-D-galactoside (3.00 g, 15.5 mmol) was dissolved in MeOH (50 mL) and *n*-Bu_2SnO (4.23 g, 17.0 mmol) was added. The mixture was refluxed for 2 h whereafter the solvent was evaporated under reduced pressure. To the crude residue were added 1,4-dioxane (50 mL), 3-iodobenzyl bromide (9.17 g, 31.0 mmol) and *n*-Bu_4NBr (4.98 g, 15.5 mmol). The mixture was sonicated for 10 min and then refluxed overnight. The solvent was evaporated under reduced pressure and the sticky residue was dissolved in MeOH (70 mL) and cooled to 0 °C for 2 h. A white solid was filtered off and the clear solution was concentrated under reduced pressure. The crude residue was diluted with CH_2Cl_2 (100 mL) and cooled to 0 °C, affording methyl [3-*O*-[3-(3-propargyl)-benzyl]]-β-D-galactopyranoside **2** in the form of white crystals (3.56 g, 56%). $[\alpha]_D^{25}$ +22.2 (*c* 0.021, CD_3OD). ^{1}H NMR (400 MHz; CD_3OD) δ 7.83 (s, 1H), 7.58 (s, *J*=9.0 Hz, 1H), 7.40 (d, *J*=7.1 Hz, 1H), 7.06 (t, *J*=7.8 Hz, 1H), 4.69 (d, *J*=12.1 Hz, 1H), 4.56 (d, *J*=12.1 Hz, 1H), 4.11 (d, *J*=7.8 Hz, 1H), 4.02 (d, *J*=3.2 Hz, 1H), 3.71 (m, 2H), 3.62 (dd, *J*=9.6, 7.8 Hz, 1H), 3.49 (s, 3H), 3.43 (t, *J*=6.1 Hz, 1H), 3.32 (dd, *J*=9.7, 3.3 Hz, 1H); ^{13}C NMR (100 MHz; CD_3OD) δ 142.61, 137.93, 137.71, 131.15, 128.18, 105.10, 94.80, 82.74, 76.55, 71.74, 71.48, 67.03, 62.50, 57.28. Anal. Calcd for $C_{14}H_{19}IO_6$: C, 40.99; H, 4.67; I, 30.94. Found: C, 40.86; H, 4.82; I, 30.78.

4.1.2. Polymer-bound propargyl ether (4). Merrifield resin HL 200–400 mesh (2 g, 2.20 mmol) was mixed with THF (50 mL), 15-crown-5 (874 μL, 4.40 mmol), KI (73 mg, 0.44 mmol) and NaH (60% in mineral oil, 440 mg, 11 mmol) under N_2 for 10 min. Propargyl alcohol (640 μL, 11 mmol) was then added dropwise. The mixture was shaken overnight whereupon the resin was washed with water, DMF, MeOH and CH_2Cl_2 (2×200 mL each) and then dried under N_2. The resin was analysed using IR and exhibited the characteristic alkyne C–H stretch at 3294 cm^{-1}.

4.1.3. Polymer-bound methyl 3-*O*-[3-(3-propargyl)-benzyl]-β-D-galactopyranoside (5). To a solid phase reaction vessel were added polymer-bound propargyl ether **4** (2.20 mmol) and THF/Et_3N (50 mL, 1:1), whereupon the mixture was degassed with N_2 for 10 min. $Pd(PPh_3)_4$

(250 mg, 10 mol %) was then added and the mixture was again degassed for 5 min and then shaken overnight. The resin was washed with water, DMF, MeOH, CH_2Cl_2 and Et_2O (2×100 mL) and dried under N_2. The resin was analysed using IR and the alkyne C–H vibration had been replaced by a broad peak around 3500 cm^{-1}, indicating that reaction had taken place.

4.1.4. Representative procedures for *meta*-substituted products 7–16. *Method A*: To a solid phase vessel containing polymer-bound methyl [3-*O*-[3-(3-propargyl)]-benzyl]-β-D-galactopyranoside (**5**) (2.20 mmol) was added CH_2Cl_2 (50 mL) and the mixture was degassed with N_2 for 10 min. $Co_2(CO)_8$ (2.57 g, 6.6 mmol) was added and the vessel was shaken at ambient temperature for 4 h whereupon the resin was washed with CH_2Cl_2 (6×50 mL) followed by toluene (6×50 mL), affording **6**, which was used directly in the Nicholas reaction. The resin was split into eight parts. To each part were added toluene (5 mL) and one nucleophile (3 equiv). The mixture was shaken for 5 min and then $BF_3 \cdot OEt_2$ (171 μL, 1.35 mmol) was added in one portion. The reactions were shaken overnight whereupon Et_3N was added. The resins were washed with THF and MeOH in alteration until no colourisation of the wash fluid was seen. The solvent was then evaporated under reduced pressure and the crude residues treated with I_2 (10 equiv) in a THF/MeOH mixture (10 mL, 8:2) at ambient temperature until TLC showed complete conversion (normally around 1.5 h). To the reaction mixtures was then added 20 mL of a 1:1 solution of satd $NaHCO_3$ and satd Na_2SO_3. The mixture was extracted with 2×30 mL EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. Reversed phase HPLC afforded products **7**, **10** and **16**. Remaining nucleophiles gave only traces of product.

Method B: To a solid phase vessel containing polymer-bound methyl [3-*O*-[3-(3-propargyl)]-benzyl]-β-D-galactopyranoside (**5**) (1.65 mmol) was added CH_2Cl_2 (50 mL) and the mixture was degassed with N_2 for 10 min. $Co_2(CO)_8$ (1.96 g, 4.95 mmol) was added and the vessel was shaken at ambient temperature for 4 h whereupon the resin was washed with CH_2Cl_2 (6×50 mL) followed by toluene (6×50 mL). The resin was then split into four parts. To each part were added toluene (4 mL) and one nucleophile (1.5 equiv). The mixture was shaken for 5 min and then $BF_3 \cdot OEt_2$ (131 μL, 1.03 mmol) was added. The mixtures were shaken for 10 min and then the resins were washed with toluene (3×2 mL). The combined wash fluids from each mixture were quenched with an excess of triethylamine. The resins were then again treated with nucleophile (1.5 equiv) and $BF_3 \cdot OEt_2$ (131 μL, 1.03 mmol) in toluene (2 mL) for 30 min and then washed with toluene and THF. The solvent was evaporated and the crude residues treated with I_2 (10 equiv) in THF/MeOH (10 mL, 8:2) at ambient temperature until TLC showed complete conversion. To the reaction mixtures was then added 20 mL of a 1:1 solution of satd $NaHCO_3$ and satd Na_2SO_3, and the aqueous phase was extracted with 2×30 mL EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to chromatography on silica with EtOAc as eluent to afford **9**, **11** and **12**. Only traces of **15** were formed.

4.1.5. Methyl [3-*O*-[3-(3-(1-methyl-indol-3-yl)-prop-1-ynyl)]-benzyl]-β-D-galactopyranoside (7). White solid. Yield: 31 mg (25% over four steps, calculated from **2**). $[\alpha]_D^{25}$ +11.9 (*c* 0.007, CD_3OD). ^1H NMR (400 MHz; CD_3OD) δ 7.58 (d, *J*=7.9 Hz, 1H), 7.50 (s, 1H), 7.36 (d, *J*=7.4 Hz, 1H), 7.31 (m, 2H), 7.26 (t, *J*=7.6 Hz, 1H), 7.17 (dd, *J*=7.0, 1.1 Hz, 1H), 7.09 (s, 1H), 7.03 (dd, *J*=7.0, 0.9 Hz, 1H), 4.70 (d, *J*=12.0 Hz, 1H), 4.58 (d, *J*=12.0 Hz, 1H), 4.12 (d, *J*=7.4 Hz, 1H), 4.01 (dd, *J*=2.5, 0.7 Hz, 1H), 3.85 (s, 2H), 3.75–3.72 (m, 4H), 3.61 (dd, *J*=7.8, 1.9 Hz, 1H), 4.51–3.49 (m, 4H), 3.42 (dt, *J*=5.6, 0.8 Hz, 1H), 3.32 (dd, *J*=9.6, 3.3 Hz, 1H); ^{13}C NMR (100 MHz; CD_3OD) δ 140.19, 138.82, 132.04, 131.72, 129.32, 128.60, 128.40, 127.92, 125.35, 122.66, 119.81, 119.65, 110.92, 110.28, 105.94, 89.30, 82.52, 81.87, 76.49, 72.01, 71.73, 67.05, 62.50, 57.26, 32.73, 16.55. HRMS (ES) *m/z* (M+Na) calcd for $C_{26}H_{29}O_6NNa$ *m/e*: 474.1893. Found: 474.1907.

4.1.6. Methyl [3-*O*-[3-(3-(cyclohex-1-enyl)-prop-1-ynyl)]-benzyl]-β-D-galactopyranoside (9). White solid. Yield: 15 mg (18% over four steps, calculated from **2**). $[\alpha]_D^{25}$ +32.8 (*c* 0.005, CD_3OD). ^1H NMR (400 MHz; CD_3OD) δ 7.43 (s, 1H), 7.33 (dt, *J*=4.0, 1.3 Hz, 1H), 7.23–7.22 (m, 2H), 5.73–5.74 (m, 2H), 4.69 (d, *J*=11.9 Hz, 1H), 4.57 (d, *J*=12.0 Hz, 1H), 4.11 (d, *J*=7.7 Hz, 1H), 4.00 (d, *J*=2.8 Hz, 1H), 3.75 (m, 2H), 3.62 (dd, *J*=7.8, 1.9 Hz, 1H), 3.48 (s, 3H), 3.42 (t, *J*=6.55 Hz, 1H), 3.32 (dd, *J*=9.7, 3.3 Hz, 1H), 2.34–2.29 (m, 3H), 1.98–1.94 (m, 2H), 1.92–1.85 (m, 1H), 1.78–1.69 (m, 1H), 1.59–1.49 (m, 1H), 1.42–1.34 (m, 1H); ^{13}C NMR (100 MHz; CD_3OD) δ 140.15, 132.01, 131.70, 131.48, 129.30, 129.05, 128.35, 125.40, 105.95, 89.63, 82.53, 82.46, 76.522, 72.05, 71.74, 67.05, 62.49, 57.28, 36.57, 30.00, 26.91, 26.23, 22.38. HRMS (FAB) *m/z* (M+Na) calcd for $C_{23}H_{30}O_6$ *m/e*: 425.1940. Found: 425.1937. Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.84; H, 7.18.

4.1.7. Methyl [3-*O*-[3-(3-(2-cyclohexanonyl)-prop-1-ynyl)-benzyl]]-β-D-galactopyranoside (10). White solid. Yield: 16 mg (14% over four steps, calculated from **2**). $[\alpha]_D^{25}$ +14.5 (*c* 0.010, CD_3OD). ^1H NMR (400 MHz; CD_3OD) δ 7.45 (s, 1H), 7.37 (dt, *J*=4.3, 1.7 Hz, 1H), 7.26–7.24 (m, 2H), 4.72 (d, *J*=12.0 Hz, 1H), 4.60 (d, *J*=12.0 Hz, 1H), 4.14 (d, *J*=7.7 Hz, 1H), 4.04 (dd, *J*=2.4, 0.9 Hz, 1H), 3.78–3.70 (m, 2H), 3.65 (dd, *J*=7.8, 1.9 Hz, 1H), 3.52 (s, 3H), 3.46 (dd, *J*=5.6, 1.1 Hz, 1H), 3.35 (dd, *J*=5.5, 3.3 Hz, 1H), 2.74 (dd, *J*=11.9, 4.9 Hz, 1H), 2.69–2.61 (m, 1H), 2.48–2.40 (m, 1H), 2.40 (d, *J*=6.2 Hz, 1H), 2.36 (d, *J*=7.8 Hz, 1H), 2.15–2.08 (m, 1H), 1.96–1.90 (m, 1H), 1.84–1.73 (m, 1H), 1.71–1.60 (m, 1H), 1.54–1.40 (m, 1H); ^{13}C NMR (100 MHz; CD_3OD) δ 212.05, 138.83, 130.64, 130.31, 127.92, 127.05, 123.87, 104.62, 87.60, 81.29, 81.20, 75.18, 70.67, 70.40, 65.70, 61.13, 55.91, 49.50, 41.38, 33.31, 27.70, 24.72, 19.12. Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.15; H, 7.18.

4.1.8. Methyl [3-*O*-[3-(3-(2,4,6-trimethoxy-phenyl)-prop-1-ynyl)]-benzyl]-β-D-galactopyranoside (11). White solid. Yield: 48 mg (48% over four steps, calculated from **2**). $[\alpha]_D^{25}$ +22.8 (*c* 0.015, CD_3OD). ^1H NMR (400 MHz; CD_3OD) δ 7.40 (s, 1H), 7.31 (t, *J*=3.6 Hz, 1H), 7.23–7.16 (m, 2H), 6.20 (s, 2H), 4.67 (d, *J*=11.9 Hz, 1H), 4.56 (d, *J*=11.9 Hz, 1H), 4.12 (d, *J*=7.8 Hz, 1H), 4.00 (d, *J*=2.7 Hz,

1H), 3.82 (s, 6H), 3.77 (s, 3H), 3.73 (t, J=6.6 Hz, 2H), 3.59 (t, J=9.5 Hz, 1H), 3.56 (s, 2H), 3.48 (s, 3H), 3.35 (s, 2H); ^{13}C NMR (100 MHz; CD_3OD) δ 161.84, 159.92, 139.97, 132.05, 131.70, 129.20, 128.02, 125.75, 107.03, 105.90, 91.84, 90.57, 82.44, 78.91, 76.47, 72.06, 71.70, 67.04, 62.48, 57.26, 56.37, 55.81, 13.63. HRMS (FAB) *m/z* (M+Na) calcd for $C_{26}H_{32}O_9$ *m/e*: 511.1944. Found: 511.1942.

4.1.9. Methyl [3-*O*-[3-(3-(2,4-dimethoxy-phenyl)-prop-1-ynyl)]-benzyl]-β-D-galactopyranoside and methyl [3-*O*-[3-(3-(2,6-dimethoxy-phenyl)-prop-1-ynyl)]-benzyl]-β-D-galactopyranoside (12). White solid. Isomeric mixture. Yield: 39 mg (40% over four steps, calculated from **2**). $[\alpha]_D^{25}$ +17.2 (*c* 0.023, CD_3OD). ^{1}H NMR (400 MHz; CD_3OD) δ 7.51 (br s, 2H), 7.40–7.36 (m, 3H), 7.32–7.16 (m, 3H), 6.62 (d, J=8.37 Hz) and 6.48 (d, J=2.4 Hz, 1H), 6.51 (br s, 2H, 0.5H), 4.73 (d, major isomer, J=11.9 Hz, 2H), 4.61 (d, major isomer, J=11.9 Hz, 2H), 4.14 (d, major isomer, J=7.8 Hz, 1H), 4.03 (d, major isomer, J=2.8 Hz, 1H), 3.85 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.75–3.71 (m, 4H), 3.70–3.66 (m, 2H), 3.65–3.58 (m, 4H), 3.51 (s, major isomer, 3H), 3.48–3.41 (m, 2H), 3.37–3.32 (m, 1H); ^{13}C NMR (100 MHz; CD_3OD) δ 161.50, 159.10, 140.22, 132.09, 131.74, 130.23, 129.34, 129.24, 129.20, 128.45, 128.142, 125.33, 118.44, 105.97, 105.39, 105.10, 99.21, 88.85, 86.00, 82.55, 76.54, 72.04, 71.76, 67.07, 62.50, 61.58, 57.28, 56.45, 55.96, 55.83, 162.68, 20.04. HRMS (FAB) *m/z* (M+Na) calcd for $C_{25}H_{30}O_8$ *m/e*: 481.1838. Found: 481.1837.

4.1.10. Methyl [3-*O*-(3-hex-5-en-1-ynyl)-benzyl]-β-D-galactopyranoside (16). White solid. Yield: 50 mg (50% over four steps, calculated from **2**). $[\alpha]_D^{25}$ +19.5 (*c* 0.030, CD_3OD). ^{1}H NMR (400 MHz; CD_3OD) δ 7.46 (s, 1H), 7.36 (t, J=4.4 Hz, 1H), 7.26 (d, J=4.0 Hz, 2H), 5.95 (m, 1H), 5.12 (d, J=17.6 Hz, 1H), 5.05 (d, J=10.4 Hz, 1H), 4.73 (d, J=12.0 Hz, 1H), 4.61 (d, J=12.0 Hz, 1H), 4.14 (d, J=8.0 Hz, 1H), 3.74 (d, J=3.2 Hz, 1H), 3.67 (m, 2H), 3.66 (dd, J=8.0, 1.8 Hz, 1H), 3.52 (s, 3H), 3.45 (t, J=4.8 Hz, 1H), 3.45 (dd, J=8.0, 3.2 Hz, 1H), 2.48 (t, J=6.4 Hz, 2H), 2.34 (m, 2H); ^{13}C NMR (100 MHz; CD_3OD) δ 138.94, 137.076, 130.82, 130.42, 128.08, 127.173, 124.12, 114.93, 104.75, 88.99, 81.30, 80.74, 75.33, 70.80, 70.53, 65.80, 61.27, 56.10, 33.00, 18.79. HRMS (ES) *m/z* (M+Na) calcd for $C_{20}H_{26}O_6Na$ *m/e*: 385.1627. Found: 385.1611.

4.1.11. Methyl 3-*O*-(4-iodobenzyl)-β-D-galactopyranoside (17). Methyl *O*-β-D-galactoside (3.00 g, 15.5 mmol) was dissolved in MeOH (50 mL) and *n*-Bu_2SnO (4.23 g, 17.0 mmol) was added. The mixture was refluxed for 2 h whereafter the solvent was evaporated. To the crude residue were added 1,4-dioxane (50 mL), 4-iodobenzyl bromide (9.17 g, 31.9 mmol) and *n*-Bu_4NBr (4.98 g, 15.5 mmol). The mixture was sonicated for 10 min and then refluxed overnight. The solvent was evaporated under reduced pressure and the sticky residue was dissolved in MeOH (50 mL) and cooled to 0 °C for 2 h. A white solid was formed and filtered off, and the clear solution was then concentrated under reduced pressure. The crude residue was diluted with CH_2Cl_2 (100 mL) and cooled to 4 °C overnight, affording, after filtration, methyl 3-*O*-(4-iodo)-benzyl-β-D-galactopyranoside **17** as white crystals (4.06 g, 64%). $[\alpha]_D^{25}$ +18.2 (*c* 0.012, CD_3OD). ^{1}H NMR (400 MHz; CD_3OD) δ 7.63 (d, J=8.3 Hz, 2H), 7.20 (d, J=8.3 Hz, 2H), 4.68 (d, J=12.2 Hz, 1H), 4.56 (d, J=12.2 Hz, 1H), 4.10 (d, J=7.8 Hz, 1H), 4.00 (d, J=3.1 Hz, 1H), 3.75–3.66 (m, 2H), 3.62 (dd, J=7.8, 1.8 Hz, 1H), 3.48 (s, 3H), 3.42 (dt, J=6.6, 1.0 Hz, 1H), 3.31 (dd, J=9.6, 3.3 Hz, 1H); ^{13}C NMR (100 MHz; CD_3OD) δ 139.88, 138.50, 131.01, 105.98, 93.53, 82.63, 76.53, 71.75, 67.05, 62.47, 57.28. Anal. Calcd for $C_{14}H_{19}IO_6$: C, 40.99; H, 4.67. Found: C, 41.12; H, 4.65.

4.1.12. Methyl 2,4,5-*O*-triacetyl-3-*O*-(4-iodobenzyl)-β-D-galactopyranoside (23). Methyl 3-*O*-(4-iodobenzyl)-β-D-galactopyranoside (0.85 g, 2.1 mmol) was dissolved in pyridine (25 mL) and Ac_2O (25 mL) was added. The mixture was refluxed for 2 h whereupon the solvent was evaporated under reduced pressure and the crude residue was subjected to chromatography on silica gel using toluene/EtOAc (5:2) as eluent to afford methyl 2,4,5-*O*-triacetyl-3-*O*-(4-iodobenzyl)-β-D-galactopyranoside **23** as a white solid (1.10 g, 99%). $[\alpha]_D^{25}$ +49.1 (*c* 0.0085, $CDCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.64 (d, J=7.4 Hz, 2H), 7.00 (d, J=7.4 Hz, 2H), 5.49 (s, 1H), 5.10 (t, J=9.0 Hz, 1H), 4.64 (d, J=12.4 Hz, 1H), 4.33 (d, J=12.4 Hz, 1H), 4.30 (d, J=8.0 Hz, 1H), 4.20–4.13 (m, 2H), 3.80 (t, J=6.4 Hz, 1H), 3.53–3.45 (m, 4H), 2.13 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.70, 170.58, 169.58, 137.61, 137.30, 129.65, 102.15, 93.50, 77.23, 70.93, 70.83, 70.45, 65.92, 62.03, 56.98, 21.15, 21.04, 20.96. Anal. Calcd for $C_{20}H_{25}IO_9$: C, 44.79; H, 4.70. Found: C, 44.89; H, 4.88.

4.1.13. Polymer-bound methyl [2,4,5-*O*-triacetyl-3-*O*-(4-iodobenzyl)]-β-D-galactopyranoside (24). To a solid phase reaction vessel were added polymer-bound propargylic ether **4** (1.10 mmol), THF/Et_3N (20 mL, 1:1 mixture), CuI (21 mg, 10 mol %) and methyl *O*-[2,4,5-triacetyl-3-(4-iodobenzyl)]-β-D-galactopyranoside **23** (649 mg, 1.21 mmol). The mixture was thoroughly degassed by bubbling N_2 for 5 min. $Pd(PPh_3)_4$ (127 mg, 10 mol %) was added and the mixture was again degassed for 5 min and then shaken overnight. The resin was washed with THF, CH_2Cl_2 and MeOH repeatedly and thereafter dried under N_2. The resin **24** was analysed using IR and did not exhibit the alkyne C–H stretch at 3294 cm^{-1} seen in **23**, indicating that Sonogashira coupling had taken place.

4.1.14. Representative procedure for *para*-substituted products 19–22. To a solid phase vessel containing polymer-bound methyl *O*-[2,4,5-triacetyl-3-(4-iodobenzyl)]-β-D-galactopyranoside **24** (0.22 mmol) was added CH_2Cl_2 (10 mL) and the mixture was degassed with N_2 for 5 min. $Co_2(CO)_8$ (291 mg, 0.66 mmol) was added and the vessel was shaken at ambient temperature for 3 h whereafter the resin was washed with CH_2Cl_2 (4×10 mL) followed by toluene (4×10 mL), forming polymer-bound complex **25**. To the resin were then added toluene (10 mL) and the nucleophile (0.66 mmol). The mixture was degassed for 5 min and then $BF_3\cdot OEt_2$ (42 μL, 0.66 mmol) was added. The mixture was shaken for 2 h and then quenched with Et_3N. The resin was washed with CH_2Cl_2 and THF. The solvent was then evaporated under reduced pressure and the crude residue treated with I_2 (558 mg) in THF (20 mL) at ambient temperature until TLC showed complete conversion (normally around 2 h). To the reaction mixtures was then added

20 mL of a 1:1 solution of satd $NaHCO_3$ and satd Na_2SO_3. Extraction with 2×30 mL EtOAc, drying over Na_2SO_4 and evaporation of the solvent under reduced pressure was followed by flash chromatography (SiO_2, CH_2Cl_2/MeOH 20:1). Removal of the acetyl moieties was effected by dissolving the product in MeOH (1 mL) and adding 1 mL of a solution of NaOMe in MeOH (20 mg NaOMe/10 mL MeOH). The mixture was stirred overnight at room temperature and neutralised with Amberlyst 120 H+ when TLC indicated complete conversion. The solvent was removed in vacuo and the residue was subjected to flash chromatography to afford products **19**–**22**.

4.1.15. Methyl 3-*O*-[4[(1-methyl-indol-3-yl)-prop-1-ynyl]-benzyl]-β-D-galactopyranoside (19). White solid. Yield: 23.4 mg (24% over five steps, calculated from **23**). $[\alpha]_D^{25}$ +20.0 (*c* 0.01, CD_3OD). ^1H NMR (400 MHz; CD_3OD) δ 7.58 (d, *J*=8.0 Hz, 1H), 7.36–7.31 (m, 4H), 7.28 (d, *J*=8.3 Hz, 1H), 7.13 (dt, *J*=7.1, 1.0 Hz, 1H), 7.06 (s, 1H), 7.01 (dt, *J*=7.9, 0.9 Hz, 1H), 4.69 (d, *J*=12.1 Hz, 1H), 4.58 (d, *J*=12.1 Hz, 1H), 4.09 (d, *J*=7.8 Hz, 1H), 3.98 (d, *J*=3.1 Hz, 1H), 3.82 (s, 2H), 3.74–3.66 (m, 5H), 3.61 (dd, *J*=7.8, 1.8 Hz, 1H), 3.48 (s, 3H), 3.40 (t, *J*=5.7 Hz, 1H), 3.31 (dd, *J*=9.7, 3.3 Hz, 1H); ^{13}C NMR (100 MHz; CD_3OD) δ 139.59, 138.85, 132.45, 128.95, 128.62, 127.88, 124.61, 122.66, 119.79, 119.66, 110.96, 110.28, 105.97, 89.27, 82.52, 81.78, 76.52, 72.11, 71.76, 67.08, 62.49, 57.28, 32.73, 16.56. HRMS (ES) *m/z* (M+Na) calcd for $C_{26}H_{29}O_6NNa$ *m/e*: 474.1893. Found: 474.1891.

4.1.16. Methyl [3-*O*-(4-hex-5-en-1-ynyl)-benzyl]-β-D-galactopyranoside (20). White solid. Yield: 21.3 mg (45% over five steps, calculated from **23**). $[\alpha]_D^{25}$ +21.9 (*c* 0.014, CD_3OD). ^1H NMR (400 MHz; CD_3OD) δ 7.34 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=8.2 Hz, 2H), 5.95–5.84 (m, 1H), 5.09 (d ab-quart, *J*=17.1, 1.8 Hz, 1H), 5.00 (d ab-quart, *J*=10.2, 1.8 Hz, 1H), 4.71 (d, *J*=12.1 Hz, 1H), 4.60 (d, *J*=12.1 Hz, 1H), 4.10 (d, *J*=7.8 Hz, 1H), 3.99 (d, *J*=3.2 Hz, 1H), 3.75–3.66 (m, 2H), 3.61 (dd, *J*=7.8, 1.9 Hz, 1H), 3.49 (s, 3H), 3.41 (t, *J*=6.5 Hz, 1H), 3.31 (dd, *J*=9.6, 3.3 Hz, 1H), 2.44 (t, *J*=7.2 Hz, 2H), 2.29 (quart, *J*=6.45 Hz, 2H); ^{13}C NMR (100 MHz; CD_3OD) δ 139.54, 138.29, 132.39, 128.92, 124.61, 116.10, 105.98, 90.19, 82.54, 81.86, 76.53, 72.11, 71.78, 67.08, 62.49, 57.27, 34.21, 19.97. HRMS (FAB) *m/z* (M+Na) calcd for $C_{26}H_{34}O_8$ *m/e*: 385.1627. Found: 385.1636.

4.1.17. Methyl 3-*O*-[4-(2,4-dimethoxyphenyl-prop-1-ynyl)]-benzyl-β-D-galactopyranoside and methyl 3-*O*-[4-(2,6-dimethoxyphenyl-prop-1-ynyl)]-benzyl-β-D-galactopyranoside (21). White solid. Yield: 15.1 mg (51% over five steps, calculated from **23**). Isomeric mixture. $[\alpha]_D^{25}$ +17.3 (*c* 0.01, CD_3OD). ^1H NMR (400 MHz; CD_3OD) δ 7.41–7.32 (m) and 7.19 (t, *J*=8.3 Hz, 5H), 7.26 (d, *J*=8.3 Hz, 1H), 6.63 (d, *J*=8.4 Hz, 1H), 6.51 (br s, 1H), 6.49 (d, *J*=2.4 Hz, 1H), 4.76–4.70 (m, 1H), 4.62–4.59 (m, 1H), 4.13 (dd, *J*=7.8, 5.7 Hz, 1H), 4.03 (dd, *J*=3.1, 0.9 Hz) and 4.01 (dd, *J*=3.1, 0.9 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 2H), 3.78 (s, 2H), 3.75–3.71 (s, 3H), 3.70–3.67 (m, 1H), 3.65–3.60 (m, 3H), 3.52–3.51 (m, 4H), 3.46–3.42 (m, 2H), 3.36 (dd, *J*=39.6, 3.3 Hz, 1H); ^{13}C NMR (100 MHz; CD_3OD) δ 161.51, 159.43, 159.11, 139.66, 139.21, 132.46, 132.46, 132.41, 130.19, 129.23, 128.98, 128.97, 128.88, 125.00, 124.57, 118.48, 106.00, 105.99, 105.98, 105.39, 105.12, 99.22, 90.01, 88.80, 83.04, 82.56, 82.51, 76.54, 76.53, 72.16, 72.13, 71.79, 71.77, 67.10, 62.49, 62.48, 57.28, 57.26, 56.44, 55.95, 55.82, 20.04, 13.91. HRMS (FAB) *m/z* (M+Na) calcd for $C_{26}H_{34}O_8$ *m/e*: 481.1838. Found: 481.1841.

4.1.18. Methyl 3-*O*-[4-(2,4,6-trimethoxyphenyl-prop-1-ynyl)]-benzyl-β-D-galactopyranoside (22). White solid. Yield: 12.0 mg (11% over five steps, calculated from **23**). $[\alpha]_D^{25}$ +19.5 (*c* 0.033, CD_3OD). ^1H NMR (400 MHz; CD_3OD) δ 7.30 (d, *J*=8.2 Hz, 2H), 7.23 (*J*=8.2 Hz, 2H), 6.18 (s, 2H), 4.68 (d, *J*=12.1 Hz, 1H), 4.58 (d, *J*=12.1 Hz, 1H), 4.09 (d, *J*=7.8 Hz, 1H), 3.98 (d, *J*=3.2 Hz, 1H), 3.80 (s, 6H), 3.74–3.65 (m, 2H), 3.60 (dd, *J*=7.8, 1.8 Hz, 1H), 3.56 (s, 2H), 3.42 (dt, *J*=5.6, 0.9 Hz, 1H), 3.29 (dd, *J*=6.4, 3.3 Hz, 1H); ^{13}C NMR (100 MHz; CD_3OD) 159.98, 132.40, 128.88, 125.10, 107.17, 105.99, 91.90, 90.50, 82.50, 76.54, 72.18, 71.77, 67.10, 62.48, 57.27, 56.38, 55.82, 13.62. HRMS (FAB) *m/z* (M+Na) calcd for $C_{26}H_{34}O_8$ *m/e*: 511.1944. Found: 511.1942.

4.1.19. Methyl 3-*O*-[3-(3-hydroxypropargyl)-benzyl]-β-D-galactopyranoside (25). Methyl 3-*O*-(3-iodobenzyl)-β-D-galactopyranoside **2** (200 mg, 0.49 mmol) was dissolved in THF/Et_3N (1:1, 10 mL) together with CuI (9 mg, 10 mol %) and propargylic alcohol (34 μL, 0.59 mmol). The mixture was thoroughly degassed with N_2 for 10 min whereafter $Pd(PPh_3)_4$ (28 mg, 5 mol %) was added. The solution was degassed for an additional 5 min and then stirred at ambient temperature until TLC indicated total conversion. The solvent was evaporated under reduced pressure and the residue subjected to multiple chromatographies (SiO_2, EtOAc/MeOH 10:1) to afford methyl 3-*O*-[3-(3-hydroxypropargyl)-benzyl]-β-D-galactopyranoside **32** (137 mg, 87%) as a white solid. $[\alpha]_D^{25}$ +19.8 (*c* 0.016, CD_3OD). ^1H NMR (400 MHz; CD_3OD) δ 7.51 (br s, 1H), 7.40 (d, *J*=6.8 Hz, 1H), 7.32–7.28 (m, 2H), 4.73 (d, *J*=12.0 Hz, 1H), 4.60 (d, *J*=12.0 Hz, 1H), 4.36 (s, 2H), 4.12 (d, *J*=8.0 Hz, 1H), 4.03 (d, *J*=3.2 Hz, 1H), 3.74–3.70 (m, 2H), 3.65–3.61 (m, 1H), 3.50 (s, 3H), 3.44 (tr, *J*=6.0 Hz, 1H), 3.37 (dd, *J*=9.6, 3.2 Hz, 1H); ^{13}C NMR (100 MHz; CD_3OD) δ 140.08, 131.68, 131.40, 128.09, 128.69, 123.97, 105.64, 88.50, 85.14, 82.29, 76.18, 71.58, 71.42, 66.70, 62.17, 57.08, 56.94, 50.90, 49.37. HRMS (FAB) *m/z* (M+Na) calcd for $C_{17}H_{22}NaO_7$ *m/e*: 361.1263. Found: 361.1259.

Acknowledgements

A 2-azidoethyl glycoside precursor for the probe used for galectins-8N and -9N was provided by the Consortium for Functional Glycomics (grant number NIH GM62116). We thank Barbro Kahl-Knutsson and Susanne Carlsson for help with galectin production and fluorescence polarisation measurements, and Daniel Åberg for performing some test reactions. We gratefully acknowledge financial support from AstraZeneca R&D Mölndal, the Swedish Foundation for Strategic Research and the Swedish Research Council (VR).

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