A Selectively Deprotectable 2,6-Diaminogalactose Scaffold for the Solid-Phase Synthesis of Potential RNA Ligands

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Abstract: In the context of aminoglycosides as efficient binders to RNA, a 2,6-diaminogalactose scaffold was developed for combinatorial syntheses of potential RNA ligands in the solid phase. A set of selectively removable, orthogonally stable protecting groups in combination with a linker stable throughout the synthesis, but selectively cleavable in the detachment process, allows for selective deprotection and introduction of a side chain in each position of this scaffold. A few of the synthesized compounds exhibit inhibition of HIV-1 infection in HeLa cells that contain a TAR-controlled reporter gene.

Key words: solid-phase synthesis, RNA ligands, protecting groups, combinatorial chemistry, inhibition of HIV RNA

Small molecules selectively binding to RNA are of particular interest, e.g. as potential antiviral drugs.[1] Aminoglycosides, e.g. kanamycin, neomycin B, or tobramycin, were shown to efficiently bind to RNA.[2] These molecules are potent inhibitors of the interaction of the HIV-1 TAR RNA with the Tat protein.[3] A variety of compounds derived from aminoglycosides as the lead structures have been investigated as ligands of RNA, including spacer-linked dimers,[4] heterocyclic derivatives,[5] macrocyclic oligo-amino sugars,[6] oligomers obtained from diamino sugar carboxylic acids,[7] and peptides rich in arginine and lysine.[8] To take advantage of a combinatorial search for biologically active molecules, we recently developed selectively deprotectable carbohydrate scaffolds for combinatorial syntheses in solid phase.[9] As neamine is an important substructure of aminoglycoside antibiotics, it appeared attractive to apply this scaffold concept to diamino sugars.[10] Amino sugar scaffolds should allow not only for a spatial arrangement of amino groups, and therewith positively charged groups as in natural aminoglycosides, but should also offer variable opportunities to install other side chains, e.g. intercalating groups, at the scaffold, provided a sufficiently orthogonal protecting group concept can be developed.

We here report on the elaboration of such a concept for 2,6-diamino-D-galactose as the carbohydrate framework.

For selective deprotection of a carbohydrate scaffold in each position, a set of orthogonally stable protecting groups is required.[11] In addition, a linker stable throughout all deprotection and substitution reactions is needed if the combinatorial syntheses are performed in solid phase. This linker must be cleavable without the functional side chains introduced into the scaffold during the solid-phase synthesis being affected. To meet these requirements, D-galactose was converted into the O-acetylated 2-azido-galactosyl nitrate **1** (Scheme 1).[12] After cleavage of the *O*-nitrate with hydrazine acetate,[13] and subsequent formation of the trichloroacetimidate **2**,[14] glycosylation of methyl 4-sulfanylbutyrate[9b] furnished sulfanylglycoside **3** as a mixture of anomers (α/β, 3:1) (Scheme 1).

Removal of the *O*-acetyl groups with catalytic sodium methoxide in methanol and subsequent formation of the 4,6-(4-methoxybenzylidene) acetal **4** was followed by 3-O-silylation to give **5a** (Scheme 1). Reduction of the azido group with benzenethiol and tin(II) chloride[15] and subsequent N-acetylation with allyloxycarbonyl chloride (AlocCl) furnished **5b**, which was subjected to regioselective reductive acetal opening with triethylsilane and phenylboronic dichloride[16] to give **6** (Scheme 1). The free 6-hydroxy group was substituted for the azido group by a Mitsunobu reaction using an acyl azide as the source of the nucleophile.[17] The ester group of the thus-obtained sulfanylglycoside **7**, fully protected with distinguishable protecting groups, was saponified to furnish the carboxylic acid **8** (Scheme 1), which can be used for immobilization. Carboxylic acid **8** was coupled to Rink amide polystyrene (100–200 mesh, 0.70 mmol/g) or Rink amide Tentagel resin (0.23 mmol/g) by use of *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU)[18] and *N*-hydroxybenzotriazole (HOBt)[19] in the presence of *N*,*N*-diisopropylethylamine (Scheme 2).

The successful attachment of the scaffold was confirmed by the appearance of a strong IR absorption band of the azido group at 2100 cm^{-1} and high-resolution magic-angle spinning (HRMAS) NMR spectroscopy.[20] In addition, the coupling reactions were monitored by the Kaiser test and by elemental analysis regarding sulfur. Finally, unchanged benzhydryl amino groups were acetylated (capped) with acetic anhydride/pyridine. The selective deprotection reactions on the scaffolds **9** (Scheme 3) were accomplished in analogy to the procedures described for the 2,6-diaminoglucose template.[10] The *N*-Aloc group was removed by palladium(0)-catalyzed allyl transfer to *p*-toluenesulfinic acid as the trapping nucleophile to af-

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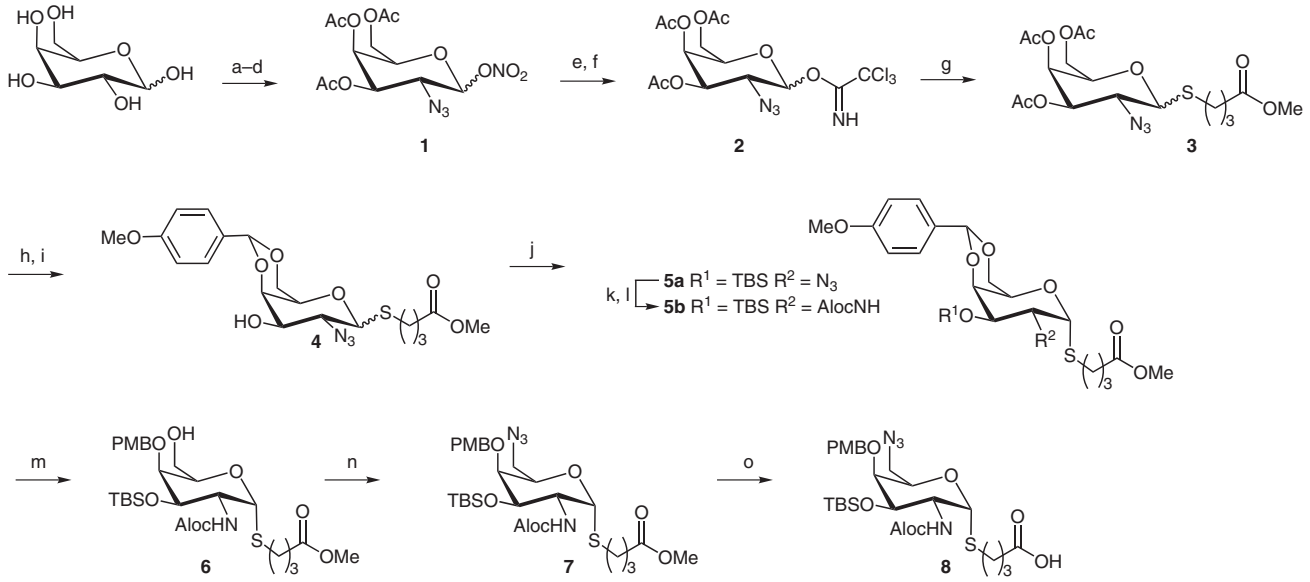
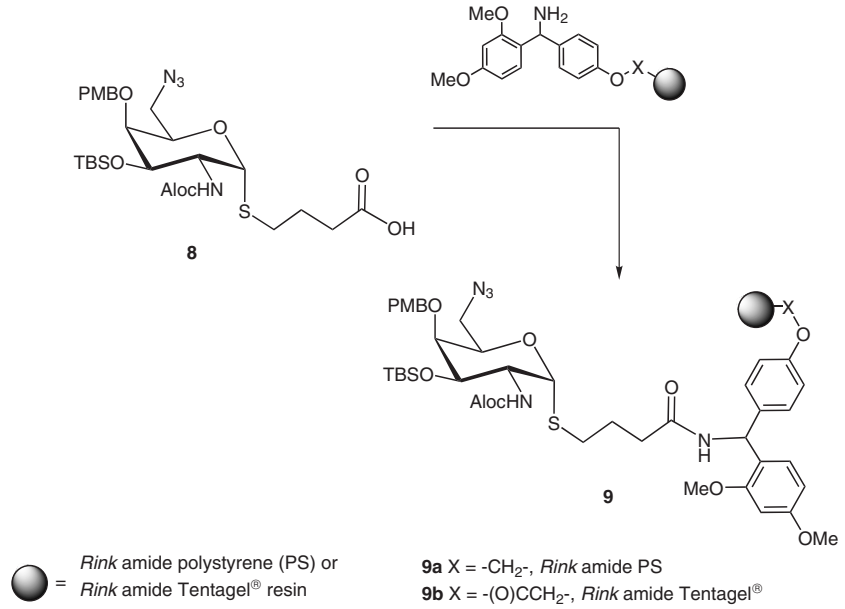


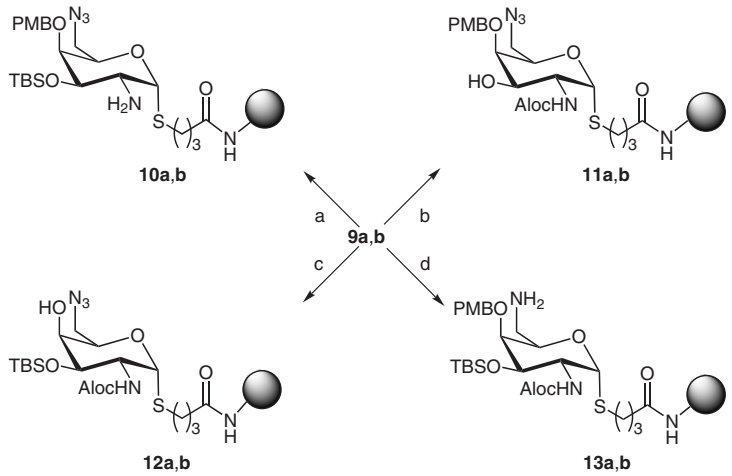
Scheme 1 *Reagents and conditions*: (a) Ac_2O, $HClO_4$ (cat.), 100%; (b) Ac_2O, AcOH, HBr, 100%; (c) *N*-methylimidazole, Zn, EtOAc, 74%; (d) CAN, NaN_3, MeCN, 38%; (e) H_2NNH_2·AcOH, DMF, 79%; (f) Cl_3CCN, K_2CO_3, CH_2Cl_2, 99%; (g) $HS(CH_2)_3CO_2Me$, BF_3·OEt_2, Et_2O, 58%; (h) NaOMe (cat.), MeOH, 100%; (i) $PMPCH(OMe)_2$, DMF, 50 °C, 20 mbar, 55%; (j) TBSOTf, py, DMF, **5a**, 99%; (k) $SnCl_2$, PhSH, Et_3N, MeCN, 100%; (l) AlocCl, py, CH_2Cl_2, **5b**, 90%; (m) TES, $PhBCl_2$, 4 Å MS, –78 °C, CH_2Cl_2, 81%; (n) nicotinoyl azide, Ph_3P, DIAD, toluene, 71%; (o) LiOH·H_2O, THF–H_2O (10:1), 100%.



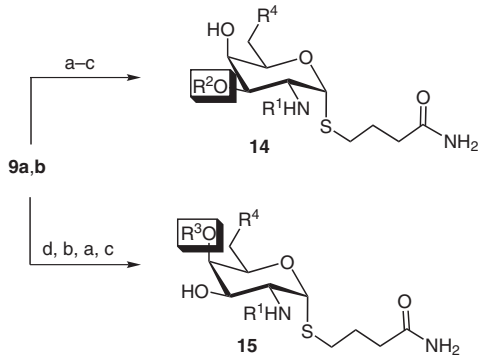
Scheme 2 Coupling of the scaffold **8** to polymer supports

ford **10** (Scheme 3).[21] Deprotection of the 3-position to give **11** was achieved with tetrabutylammonium hydrogen difluoride solution (TBAHDF) in acetonitrile (Scheme 3). The *p*-methoxybenzyl group was removed by selective oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[22] in dichloromethane and water (10 vol%) to furnish **12** (Scheme 3). In the case of Rink amide polystyrene resin, these cleavage conditions resulted in degradation of the polymer and prevented the isolation of the desired products from **12a**. For the reduction of the azido function, a Staudinger protocol[23] was applied, for which tri-*n*-butylphosphane in a tetrahydrofuran–water–triethylamine mixture was used (Scheme 3). This reaction, resulting in **13**, as well as the removal of the *N*-Aloc group were monitored by the Kaiser test. In addition, all cleavage reactions were controlled once again by FTIR and ^{1}H HRMAS NMR spectroscopy.

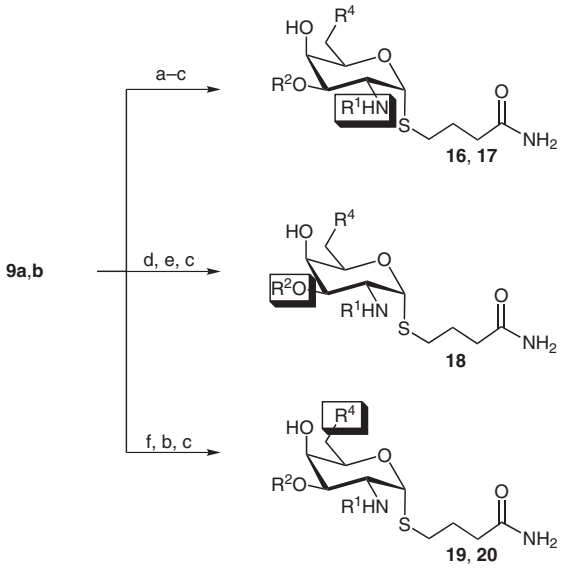
For the selective introduction of side chains at the 3- and 4-positions of the monosaccharide scaffold, carbamoylation (and esterification) reactions of **9a** and **9b** were examined (Scheme 4). Carbamoylation of the resin-linked scaffolds **11** and **12** (obtained from **9a**/**9b**, en route to **14**



Scheme 3 *Reagents and conditions*: (a) $Pd(PPh_3)_4$, $TolSO_2H$, dioxane; (b) 50% (w/v) TBAHDF, MeCN; (c) DDQ, CH_2Cl_2–H_2O (9:1); (d) 1. *n*-Bu_3P, THF; 2. THF–H_2O–Et_3N (2:1:1).



Scheme 4 Formation of carbamates on resin-linked scaffolds **9a**/**b**. *Reagents and conditions*: (a) 50% (w/v) TBAHDF, MeCN; (b) 10% (w/v) RNCO, DMAP (cat.), dioxane; (c) 50% TFA, CH_2Cl_2, MeS–PS; (d) DDQ, CH_2Cl_2–H_2O (9:1).



Scheme 5 Synthesis of O- and N-acylated diaminogalactose derivatives. *Reagents and conditions*: (a) $Pd(PPh_3)_4$, $TolSO_2H$, dioxane; (b) amino acid, TBTU, HOBt·H_2O, DIPEA; (c) 50% TFA, 5% Me_2S, CH_2Cl_2; (d) 50% (w/v) TBAHDF, MeCN; (e) amino acid, DIC, DMAP (cat.), DMF; (f) 1. *n*-Bu_3P, THF; 2. THF–H_2O–Et_3N (2:1:1).

and **15**, respectively, Scheme 4) was performed with aryl isocyanates in the presence of catalytic amounts of 4-(*N*,*N*-dimethylamino)pyridine (Scheme 4). After carbamoylation of the 4-position, it was necessary to remove the silyl ether with tetrabutylammonium hydrogen difluoride prior to the release from the polymer. Otherwise the *tert*-butyldimethylsilyl group is only incompletely cleaved during the subsequent treatment with trifluoroacetic acid, and mixtures of silylated and desilylated derivatives were obtained. The cleavage from the solid support with 50% trifluoroacetic acid in dichloromethane and sulfanylmethyl polystyrene furnished the desired products **14** and **15** in sufficient purity and satisfying yields (Scheme 4, Table 1).

As an alternative to the formation of urethanes, acylation reactions were performed at scaffolds **10**, **11**, and **13** to generate a library of amino acid– or peptide–carbohydrate conjugates. Esterification of scaffolds **11** using *N*,*N*′-diisopropylcarbodiimide in the presence of 4-(*N*,*N*-dimethylamino)pyridine according to Steglich[24] gave esters **18** in good yields (Scheme 5). Only during the reaction of **11b** (Tentagel) with Fmoc-His(Trt)-OH did some racemization occur. For coupling of the acyl components to the free amino groups in the 2-position (**10**) or 6-position (**13**) (to generate **16**/**17** or **19**/**20**, respectively), *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU),[25] *N*-hydroxybenzotriazole (HOBt), and *N*,*N*-diisopropylethylamine were used (Scheme 5).

After three or four steps, the crude amino acid– or peptide–carbohydrate conjugates **16**–**20** were isolated as mixtures of the 3-hydroxy compound and its silyl ether in satisfying yields in most cases (Scheme 5). After separation by semipreparative HPLC, their structures were confirmed by mass spectrometry. The values given for the purity of products **16**–**20** were determined by UV absorption, and are too low owing to the presence of impurities with large extinction coefficients. The change of the cation scavenger in the detachment reaction from sulfanyl-

Table 1 Synthesis of a Library of Carbamoylated Diaminogalactose Derivatives **14** and **15**[a]

Product **14** or **15**	Resin **9**	R^1	R^2	R^3	R^4	Yield[b] (%)	Purity[c] (%)
14a	**9b**	Aloc	4-FC_6H_4NHCO	–	N_3	~100	52
14b	**9b**	Aloc	4-NCC_6H_4NHCO	–	N_3	81	38
14c	**9a**	Aloc	4-ClC_6H_4NHCO	–	N_3	85	46
14d	**9a**	Aloc	3,4-ClC_6H_3NHCO	–	N_3	82	67
14e	**9a**	Aloc	2,4-FC_6H_3NHCO	–	N_3	~100	42
14f	**9a**	Aloc	4-Me-3-$O_2NC_6H_3NHCO$	–	N_3	34	13
14g	**9a**	Aloc	4-ClC_6H_4NHCO	–	N_3	31	-
14h	**9a**	Aloc	3-FC_6H_4NHCO	–	N_3	79	36
14i	**9a**	Aloc	2-ClC_6H_4NHCO	–	N_3	93	86
14j	**9a**	Aloc	4-$EtO_2CC_6H_4NHCO$	–	N_3	60	32
14k	**9a**	Aloc	3-AcC_6H_4NHCO	–	N_3	63	50
14l	**9a**	Aloc	4-$EtOC_6H_4NHCO$	–	N_3	98	33
15a	**9b**	Aloc	–	4-FC_6H_4NHCO	N_3	58	91
15b	**9b**	Aloc	–	4-NCC_6H_4NHCO	N_3	78	85
15c	**9a**	Aloc	–	4-ClC_6H_4NHCO	N_3	37	33

[a] See Scheme 4 for reagents and conditions.
[b] Yield of crude product.
[c] Purities of crude products were determined by RP-HPLC (UV 210–220 nm). Since impurities can have a high extinction coefficient, these values usually are too low.

methyl polystyrene to dimethyl sulfide solution appeared advantageous. The yields as well as the purity of the products were improved (Table 2). For the biological evaluation of the synthesized compounds on cells in vivo, a careful purification of products **14**–**20** was necessary. However, the solubility of compounds **14**–**20** in solvents needed for purification by semipreparative HPLC is low, and caused problems. Therefore, considerable loss of the synthesized products could not be prevented in the course of purification.

In additional experiments, the extension of the amino acid side chain was explored. To this end, the 9-fluorenylmethoxycarbonyl (Fmoc) group of the carbohydrate-linked amino acid was removed by use of piperidine in *N*,*N*-dimethylformamide. Subsequently, a second N-protected amino acid was coupled to give the peptide derivatives **16g** and **17g**, **19f** and **20f**, and **18d**–**f**. It is noteworthy that the replacement of the Fmoc group by a less hydrophobic protecting group such as the *N*-benzoyloxycarbonyl (Z) group afforded products **18e** and **18f** in comparable yields. The sulfanylglycoside linker introduced as an option for a later activation and glycoside formation also has influence on the solubility of compounds **14**–**20**. Components of a library of analogous glucose derivatives containing a 3-sulfanylpropionamide showed increased solubility in acetonitrile and, logically, these compounds were easier to purify. Despite these problems during the purification, almost all synthesized diaminogalactoside derivatives **14**–**20**, except for the arginine derivatives, were isolated in sufficiently pure form (by analytical HPLC). They were obtained in amounts adequate for a biological evaluation in experiments on cell cultures. It should be noted that the crude products exhibited considerable cytotoxicity; this is obviously due to the toxicity of the accompanying impurities.

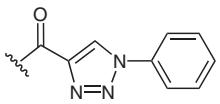
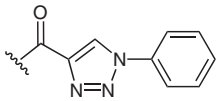
Because of these experiences, prior to probing the antiviral effects of these compounds, their cytotoxicity had to be investigated. The vitality of the cultured HeLa P4 cells was monitored in terms of the concentration of ATP in all metabolically active cells, which was measured in a luminometric assay of the ATP-dependent oxidative decarboxylation of luciferin at 37 °C.[26] It was shown that the purified compounds showed no cytotoxicity at a concentration of 100 μM. Some of them, however, exhibited low cytotoxicity at a concentration of 200 μM. The antiviral effects of the synthesized carbohydrate derivatives **14**–**20** were determined for HeLa P4 cells that had been transfected with the HIV-1 receptors CD4, CCR5, and CXCR4 and a β-galactosidase reporter gene under control of the HIV-LTR promoter. These cells were infected with a solution of the virus strain HIV-1_{Lai} in the absence (control) or presence of synthetic compounds **14**–**20** in varying concentrations (10, 25, 50, 100, and 200 μM). The virus proliferation was determined by measuring the galactosi-

dase reporter enzyme in a chemiluminescence assay.[26] Briefly summarized, the results are the following. The 3-*O*- and 4-*O*-carbamates of the diaminogalactose structures **14** and **15** exhibited no cytotoxicity in concentrations of 200 μM, but also showed no inhibitory activity. Likewise, the 3-*O*-amino acid and peptide conjugates **18** exhibit neither cytotoxicity nor an inhibitory effect, except for **18b**, which caused 30% inhibition of virus production at a concentration of 200 μM. Of the 3-*O*-silyl-2-*N*-amino acyl derivatives **17**, some compounds showed inhibition of virus proliferation even at a concentration of 10 μM: Fmoc-Gly derivative **17a**, 30%; Fmoc-Leu **17b**, 30%; Fmoc-Glu **17c**, 45%; Fmoc-Gln **17f**, 25%. The most potent compound, however, belonged to the 6-*N*-acyl series **19** and **20**. The *N*-(phenylacetyl) derivative **20e** caused 60% inhibition of virus production compared to the control at a concentration of 10 μM. However, only one other compound of this series **19** and **20**, the Fmoc-Gln derivative **20c**, exerted weak inhibition (45% at a concentration of 45 μM) (Figure 1).

Table 2 Synthesis of a Library of O- and N-Acylated Diaminogalactose Derivatives **16–20**[a]

Products **16–20**	Resin **9**	R^1	R^2	R^4	Yield[b] (%)	Purity[c] (%)
16a	**9a**	Fmoc-Gly-	H	N_3	60	–
17a	**9a**	Fmoc-Gly-	TBS	N_3	–	40
16b	**9a**	Fmoc-Leu-	H	N_3	82	–
17b	**9a**	Fmoc-Leu-	TBS	N_3	–	33
16c	**9a**	Fmoc-Glu-	H	N_3	51	–
17c	**9a**	Fmoc-Glu-	TBS	N_3	–	36
16d	**9a**	Fmoc-Arg-	H	N_3	64	–
17d	**9a**	Fmoc-Arg-	TBS	N_3	–	–
16e	**9a**	Fmoc-His-	H	N_3	56	–
17e	**9a**	Fmoc-His-	TBS	N_3	–	36
16f	**9a**	Fmoc-Gln-	H	N_3	74	–
17f	**9a**	Fmoc-Gln-	TBS	N_3	–	10
16d	**9b**	Fmoc-Arg-	H	N_3	~100	–
17d	**9b**	Fmoc-Arg-	TBS	N_3	–	–
16e	**9b**	Fmoc-His-	H	N_3	~100	24
17e	**9b**	Fmoc-His-	TBS	N_3	–	35
16f	**9b**	Fmoc-Gln-	H	N_3	~100	25
17f	**9b**	Fmoc-Gln-	TBS	N_3	–	33
16g	**9b**	Fmoc-His-Gly-	H	N_3	~100	53
17g	**9b**	Fmoc-His-Gly-	TBS	N_3	–	4
18a	**9b**	Aloc	Fmoc-Arg-	N_3	51	–
18b	**9b**	Aloc	Fmoc-Gln-	N_3	46	43
18c	**9b**	Aloc	Fmoc-His-	N_3	50	60 (24)[d]
18d	**9b**	Aloc	Fmoc-His-Gly-	N_3	~100	70
18e	**9b**	Aloc	Z-Gly-Gly-	N_3	~100	67
18f	**9b**	Aloc	Z-Gly-His-	N_3	~100	30
19a	**9b**	Aloc	H	Fmoc-His-	84	37
20a	**9b**	Aloc	TBS	Fmoc-His-	–	54

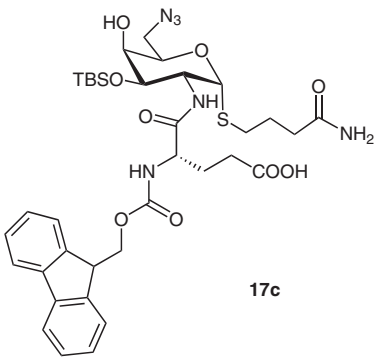
Table 2 Synthesis of a Library of O- and N-Acylated Diaminogalactose Derivatives **16–20**[a] (continued)

Products **16–20**	Resin **9**	R^1	R^2	R^4	Yield[b] (%)	Purity[c] (%)
19b	**9b**	Aloc	H	Fmoc-Arg-	96	–
20b	**9b**	Aloc	TBS	Fmoc-Arg-	–	–
19c	**9b**	Aloc	H	Fmoc-Gln-	~100	21
20c	**9b**	Aloc	TBS	Fmoc-Gln-	–	79
19d	**9b**	Aloc	H		~100	30
20d	**9b**	Aloc	TBS		–	58
19e	**9a**	Aloc	H	$PhCH_2CONH$-	35	–
20e	**9a**	Aloc	TBS	$PhCH_2CONH$-	–	35
19f	**9b**	Aloc	H	Fmoc-His-Gly-	~100	34
20f	**9b**	Aloc	TBS	Fmoc-His-Gly-	–	63

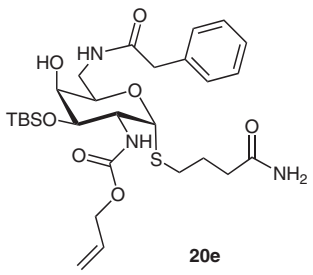
[a] See Scheme 5 for reagents and conditions.
[b] Yield of crude product.
[c] Purities of crude products were determined by RP-HPLC (UV 210–220 nm).
[d] A mixture of epimers was obtained.

The concept of selectively removable, orthogonally stable protecting groups as given in the 2,6-diaminogalactose scaffolds **9** allows for a selective introduction of side chains in the scaffold in solid-phase syntheses. After three (or four) steps in solid phase and cleavage from the resin, the crude compounds **14–20** were obtained in satisfying yields. The crude products contain impurities which have high UV extinction coefficients and cause cytotoxicity on the cells used in in vivo inhibition experiments. Sufficient purification of the scaffold derivatives **14–20** turned out to be the most difficult and time-consuming procedure. Therefore, further syntheses aimed at structure optimization of inhibitors should preferably be performed in solution rather than on solid phase. Among the synthesized compounds, 6-*N*-acyl and 2-*N*-aminoacyl derivatives showed the most potent inhibition of HIV-1 infection in HeLa cells determined via a TAR-controlled reporter gene product.

Solvents were distilled and pre-dried according to standard procedures.[27] Reagents were bought in the highest available commercial quality and used without further purification. Rink amide PS was purchased from Novabiochem and Rink amide Tentagel from Rapp Polymere, Tübingen, Germany. Analytical TLC was carried out on silica gel 60 F_{254} (Merck). Flash chromatography was performed (silica gel, 0.032–1.063 mm, ICN Biomedicals). IR spectra were recorded on a Perkin-Elmer FT-IR 1760X spectrometer. RP-HPLC analyses were carried out on a Knauer Maxi Star HPLC system with a Phenomenex Luna C18(2) column (5 μm, 250 × 4.60 mm), and at a pump rate of 1 mL/min. Semipreparative RP-HPLC separations were performed on a Knauer HPLC system with a Phenomex Luna C18(2) column (10 μm, 250 × 21 mm), and at a pump rate of 10 mL/min. H_2O–MeCN mixtures were used as the solvents. The following gradients were used for analytical HPLC: gradient A: H_2O–MeCN, 70:30, 10 min, then 70:30 to 50:50, 2 min, then 50:50 to 30:70, 2



17c



20e

Figure 1 The most efficient inhibitors **17c** and **20e** of HIV-1 proliferation from the compound library **14–20**

min, then 30:70 to 0:100, 2 min, then 0:100, 23 min; gradient B: H_2O–MeCN, 70:30 to 0:100, 30 min, then 0:100, 10 min; gradient C: H_2O–MeCN, 90:10 to 0:100, 30 min, then 0:100, 10 min; gradient D: H_2O–MeCN, 50:50 to 0:100, 30 min, then 0:100, 10 min. The following gradients were used for semipreparative HPLC: gradient E: H_2O–MeCN, 70:30, 20 min, then 70:30 to 50:50, 4 min, then 50:50 to 30:70, 6 min, then 30:70 to 0:100, 4 min, then 0:100, 20 min; gradient F: H_2O–MeCN, 70:30 to 0:100, 60 min, then 0:100, 15 min; gradient G: H_2O–MeCN, 70:30 to 0:100, 90 min, then 0:100, 25 min. ^1H, ^{13}C, and 2D NMR spectra were recorded on a Bruker AC-300 or a Bruker AM-400 spectrometer. Centered multiplets are abbreviated as m_c. Optical rotations $[\alpha]_D^{20}$ were measured on a Perkin Elmer polarimeter 241. ESI-MS spectra were measured on a ThermoQuest Navigator instrument and FD-MS spectra on a Finnigan-MAT 95 spectrometer.

Methyl 4-[(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α,β-D-galactopyranosyl)sulfanyl]butyrate (3)

Activated 4 Å MS (10 g) were added to a soln of **2** (19.7 g, 0.041 mol) in Et_2O (750 mL). The suspension was stirred at r.t. for 1 h and cooled to 0 °C. Methyl 4-sulfanylbutyrate (10.9 g, 0.081 mol) was added. $BF_3{\cdot}OEt_2$ (26.4 mL, 29.8 g, 0.21 mol) was dissolved in Et_2O (30 mL) and slowly added to the reaction mixture. Stirring was continued at 0 °C for 1 h and subsequently at r.t. for 6 h. After filtration of the mixture, the filtrate was washed with sat. aq $NaHCO_3$ (700 mL). The organic phase was washed with sat. aq $NaHCO_3$ (3 × 500 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue was performed by flash chromatography (silica gel, cyclohexane–EtOAc, 3:1); this afforded **3**.

Yield: 11.0 g (58%), α/β = 3:1; colorless amorphous solid; R_f = 0.12 (cyclohexane–EtOAc, 3:1).

IR (NaCl): 2113 (N_3) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.44 (d, $^3J_{1,2}$ = 5.5 Hz, 0.75 H, H-1α), 5.39 (d, $^3J_{3,4}$ = 2.5 Hz, 0.75 H, H-4α), 5.34 (d, $^3J_{3,4}$ = 2.6 Hz, 0.25 H, H-4β), 5.07 (dd, $^3J_{2,3}$ = 11.0 Hz, $^3J_{3,4}$ = 3.3 Hz, 0.75 H, H-3α), 4.84 (dd, $^3J_{2,3}$ = 10.3 Hz, $^3J_{3,4}$ = 3.3 Hz, 0.25 H, H-3β), 4.52 (t, $^3J_{5,6}$ = 6.2 Hz, 0.75 H, H-5α), 4.35 (d, $^3J_{1,2}$ = 10.2 Hz, 0.25 H, H-1β), 4.20 (dd, $^3J_{1,2}$ = 5.5 Hz, $^3J_{2,3}$ = 11.0 Hz, 0.75 H, H-2α), 4.11–4.01 (m, 2 H, H-6αβ), 3.85 (t, $^3J_{5,6}$ = 7.0 Hz, 0.25 H, H-5β), 3.64 (s, 3.25 H, 0.25 Hβ, CO_2CH_3), 2.87–2.49 (m, 2 H, SCH_2CH_2), 2.45–2.39 (m, 2 H, $CH_2CO_2CH_3$), 2.11 (s, 3 H, CH_3), 2.01, 2.00 (s, 6 H, CH_3), 2.00–1.88 (m, 2 H, SCH_2CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.3, 170.4, 170.1, 170.0 (C=O), 85.0 (C1β), 83.5 (C1α), 74.4 (C5β), 73.0 (C3β), 70.2 (C3α), 67.5 (C4α), 67.1 (C5α), 66.6 (C4β), 61.6 (C6), 60.5 (C2β), 57.8 (C2α), 51.6 (CO_2CH_3), 32.7 ($CH_2CO_2CH_3$, α), 32.5 ($CH_2CO_2CH_3$, β), 30.4 (SCH_2CH_2, β), 29.7 (SCH_2CH_2, α), 25.1 (SCH_2CH_2, β), 24.6 (SCH_2CH_2, α), 20.7 (3 × CH_3, OAc).

MS (FD): *m*/*z* (%) = 447.7 (100) $[M]^+$.

Methyl 4-{[2-Azido-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-α,β-D-galactopyranosyl]sulfanyl}butyrate (4)

A soln of NaOMe in MeOH was added dropwise to a soln of **3** (9.69 g, 21.6 mmol) in anhyd MeOH (300 mL) to adjust the pH to 9.0. The mixture was stirred for 1 h and neutralized with an acidic ion-exchange resin (Amberlite IR120). After filtration of the mixture, the solvent was removed in vacuo. The residue was dissolved in anhyd DMF (250 mL) and treated with $PMPCH(OMe)_2$ (5.5 mL, 5.90 g, 32.4 mmol) and cat. $PTSA{\cdot}H_2O$. The reaction was carried out at 20–30 mbar and 50 °C for 1 h. After neutralization of the mixture with Et_3N (2 mL), the solvent was removed in vacuo. The crude product was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 4:1); this gave the α-anomer **4α** as the first fraction (55%) and the β-anomer **4β** as the second fraction (27%).

α-Anomer 4α

Yield: 5.24 g (55%); pale yellow amorphous solid; $[\alpha]_D^{20}$ 172.1 (*c* 1.0, $CHCl_3$); R_f = 0.15 (cyclohexane–EtOAc, 4:1); R_f = 0.53 (cyclohexane–EtOAc, 1:1).

IR (NaCl): 2100 (N_3) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}-PMB), 6.90 (d, ^3J = 8.8 Hz, 2 H, H_{Ar}-PMB), 5.54 (s, 1 H, C*H*, acetal), 5.45 (d, $^3J_{1,2}$ = 5.28 Hz, 1 H, H-1), 4.22 (m_c, 1 H, H-6a), 4.25 (br s, 1 H, H-4) 4.10 (t, $^3J_{1,2}$ = 5.28 Hz 1 H, H-2), 4.10 (m_c, 1 H, H-6b), 4.08 (br s, 1 H, H-5), 3.96–3.89 (m, 1 H, H-3), 3.81 (s, 3 H, OCH_3-PMB), 3.67 (s, 3 H, CO_2CH_3), 2.64 (m_c, 2 H, SCH_2CH_2), 2.55 (br s, 1 H, 3-OH), 2.43 (t, ^3J = 7.2 Hz, 2 H, $CH_2CO_2CH_3$), 2.00–1.92 (m, 2 H, SCH_2CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.4 (C=O), 160.5 (C_p-PMB), 129.8 (C_i-PMB) 127.7 (C_m-PMB), 113.8 (C_o-PMB), 101.4 (CH-PMB), 84.3 (C1), 75.2 (C4), 69.6 (C3), 69.3 (C6), 63.3 (C5), 61.3 (C2), 55.4 (OCH_3-PMB), 51.8 (CO_2CH_3), 32.9 ($CH_2CO_2CH_3$), 30.3 (SCH_2CH_2), 24.8 (SCH_2CH_2).

MS (FD): *m*/*z* (%) = 439.6 (100) $[M]^+$.

β-Anomer 4β

Yield: 2.58 g (27%); pale yellow amorphous solid; $[\alpha]_D^{20}$ –23.6 (*c* 1.0, $CHCl_3$); R_f = 0.05 (cyclohexane–EtOAc, 4:1); R_f = 0.20 (cyclohexane–EtOAc, 1:1).

IR (NaCl): 2113 (N_3) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}-PMB), 6.91 (d, ^3J = 8.8 Hz, 2 H, H_{Ar}-PMB), 5.50 (s, 1 H, C*H*, acetal), 4.31 (dd, ^2J = 12.5 Hz, ^3J = 1.4 Hz, 1 H, H-6a), 4.28 (d, $^3J_{1,2}$ = 9.8 Hz, 1 H, H-1), 4.21–4.19 (m, 1 H, H-4), 4.00 (dd, ^2J = 12.7 Hz, ^3J = 1.8 Hz, 1 H, H-6b), 3.81 (s, 3 H, OCH_3-PMB), 3.67 (s, 3 H, CO_2CH_3), 3.66–3.61 (m, 2 H, H-2, H-3), 3.47–3.45 (m, 1 H, H-5), 2.82 (m_c, 3 H, SCH_2CH_2, 3-OH), 2.50 (t, ^3J = 7.1 Hz, 2 H, $CH_2CO_2CH_3$), 2.08–1.95 (m, 2 H, SCH_2CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.6 (C=O), 160.5 (C_p-PMB), 130.0 (C_i-PMB) 127.8 (C_m-PMB), 113.8 (C_o-PMB), 101.5 (CH-PMB), 83.7 (C1), 74.7 (C4), 73.4 (C3), 70.0 (C5), 69.3 (C6), 63.5 (C2), 55.4 (OCH_3-PMB), 51.8 (CO_2CH_3), 32.7 ($CH_2CO_2CH_3$), 29.3 (SCH_2CH_2), 25.2 (SCH_2CH_2).

MS (FD): *m*/*z* (%) = 439.6 (100) $[M]^+$.

Methyl 4-{[2-Azido-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-α-D-galactopyranosyl]sulfanyl}butyrate (5a)

TBSOTf (3.96 mL, 4.56 g, 17.2 mmol) was added to a soln of **4α** (5.06 g, 11.5 mmol) and py (9.36 mL, 9.08 g, 115.0 mmol) in anhyd DMF (100 mL) at 0 °C. After 20 min, the reaction mixture was added to sat. aq $NaHCO_3$ (60 mL) at 0 °C. After addition of CH_2Cl_2 (100 mL) and H_2O (100 mL), the organic layer was extracted with CH_2Cl_2 (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel) gave **5a**.

Yield: 6.22 g (99%); colorless amorphous solid; $[\alpha]_D^{20}$ 144.5 (*c* 1.0, $CHCl_3$); R_f = 0.68 (CH_2Cl_2–EtOAc, 20:1); R_f = 0.73 (cyclohexane–EtOAc, 1:1).

IR (NaCl): 2100 (N_3) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, ^3J = 9.0 Hz, 2 H, H_{Ar}-PMB), 6.89 (d, ^3J = 9.0 Hz, 2 H, H_{Ar}-PMB), 5.51 (s, 1 H, C*H*, acetal), 5.46 (d, $^3J_{1,2}$ = 5.09 Hz, 1 H, H-1), 4.26–4.20 (m, 2 H, H2, H-6a), 4.08 (m_c, 1 H, H-4), 4.07 (dd, ^2J = 12.5 Hz, ^3J = 1.6 Hz, 1 H, H-6b), 4.00 (br s, 1 H, H-5), 3.94 (dd, $^3J_{2,3}$ = 10.2 Hz, $^3J_{3,4}$ = 3.5 Hz, 1 H, H-3), 3.80 (s, 3 H, OCH_3-PMB), 3.67 (s, 3 H, CO_2CH_3), 2.64 (m_c, 2 H, SCH_2CH_2), 2.43 (t, ^3J = 7.2 Hz, 2 H, $CH_2CO_2CH_3$), 1.96 (m_c, 2 H, SCH_2CH_2), 0.92 (s, 9 H, $CH_3{}^{t\text{-Bu}}$, TBS), 0.17 (s, 3 H, CH_3, TBS), 0.13 (s, 3 H, CH_3, TBS).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.4 (C=O), 160.1 (C_p-PMB), 130.0 (C_i-PMB) 127.4 (C_m-PMB), 113.6 (C_o-PMB), 100.8 (CH-PMB), 84.6 (C1), 76.4 (C4), 70.9 (C3), 69.4 (C6), 63.6 (C5), 61.1 (C2), 55.4 (OCH_3-PMB), 51.8 (CO_2CH_3), 32.9 ($CH_2CO_2CH_3$), 30.3 (SCH_2CH_2), 25.8 ($CH_3^{t\text{-Bu}}$, TBS), 24.9 (SCH_2CH_2), 18.2 ($C^{t\text{-Bu}}$, TBS), –4.4 (CH_3, TBS), –4.6 (CH_3, TBS).

MS (FD): *m/z* (%) = 553.2 (5%) $[M]^+$, 497.0 (100%) [M – *t*-Bu + H]$^+$, 420.9 (6%) [M – $SCH_2CH_2CH_2CO_2CH_3$ + H]$^+$.

Methyl 4-[(2-{[(Allyloxy)carbonyl]amino}-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-α-D-galactopyranosyl)sulfanyl]butyrate (5b)

A soln of **5a** (6.22 g, 11.2 mmol) in MeCN (100 mL) was added dropwise to a soln of anhyd $SnCl_2$ (3.18 g, 16.8 mmol), PhSH (6.86 mL, 7.40 g, 67.2 mmol) and Et_3N (6.52 mL, 5.10 g, 50.4 mmol) in anhyd MeCN (100 mL) at r.t. After the mixture had stirred at r.t. for 8 h, 1 M aq NaOH (150 mL) was added to it. The soln was diluted with CH_2Cl_2 (150 mL) and stirred until it became colorless. The organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was co-evaporated with toluene (3 × 100 mL) and dried under high vacuum. The crude amine was dissolved in anhyd CH_2Cl_2 (100 mL), and py (9.13 mL, 8.86 g, 112 mmol) was added to the soln. Dropwise addition of AlocCl (2.38 mL, 2.70 g, 22.4 mmol) at 0 °C followed. After stirring for 16 h at r.t., the mixture was diluted with CH_2Cl_2 (100 mL) and extracted with sat. aq $NaHCO_3$ (3 × 150 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel) afforded pure product **5b**.

Yield: 5.05 g (73%, two steps); colorless oil; $[\alpha]_D^{20}$ 123.5 (*c* 1.0, $CHCl_3$); R_f = 0.15 (cyclohexane–EtOAc, 4:1); R_f = 0.57 (cyclohexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}-PMB), 6.87 (d, ^3J = 9.0 Hz, 2 H, H_{Ar}-PMB), 5.90 (m_c, 1 H, CH_2=C*H*-, Aloc), 5.56 (d, $^3J_{1,2}$ = 4.70 Hz, 1 H, H-1), 5.50 (s, 1 H, C*H*, acetal), 5.30 (d, ^3J = 16.2, 1 H, CH_2=CH-, Aloc, (*trans*)), 5.19 (d, ^3J = 10.6 Hz, 1 H, CH_2=CH-, Aloc, (*cis*)), 4.73 (d, ^3J = 8.2, 1 H, N*H*-C2), 4.61–4.48 (m, 3 H, H-2, -CH_2-, Aloc), 4.23 (dd, ^2J = 12.5 Hz, ^3J = 1.6 Hz, 1 H, H-6a), 4.11–4.06 (m, 2 H, H-4, H-6b), 4.01 (br s, 1 H, H-5), 3.80 (s, 3 H, OCH_3-PMB), 3.78 (m_c, 1 H, H-3), 3.67 (s, 3 H, CO_2CH_3), 2.67 (m_c, 2 H, SCH_2CH_2), 2.42 (dt, ^3J = 7.0 Hz, ^2J = 2.3 Hz, 2 H, $CH_2CO_2CH_3$), 1.95 (m_c, 2 H, SCH_2CH_2), 0.85 (s, 9 H, $CH_3^{t\text{-Bu}}$, TBS), 0.05 (s, 6 H, 2 × CH_3, TBS).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.4 (C=O, Ester), 160.5 (C_p-PMB), 155.8 (C=O, Aloc), 132.9 (-*C*H=CH_2, Aloc), 130.4 (C_i-PMB), 127.7 (C_m-PMB), 117.8 (-CH=*C*H_2, Aloc), 113.7 (C_o-PMB), 100.9 (CH-PMB), 86.8 (C1), 76.3 (C4), 70.1 (C3), 69.6 (C6), 65.8 (CH_2, Aloc), 63.8 (C5), 55.6 (OCH_3-PMB), 51.8 (CO_2CH_3), 51.6 (C2), 32.9 ($CH_2CO_2CH_3$), 31.2 (SCH_2CH_2), 25.7 ($CH_3^{t\text{-Bu}}$, TBS), 25.1 (SCH_2CH_2), 18.2 ($C^{t\text{-Bu}}$, TBS), –4.1 (CH_3, TBS), –4.5 (CH_3, TBS).

MS (FD): *m/z* (%) = 612.2 (100) $[M + H]^+$, 555.1 (62) [M – *t*-Bu + H]$^+$.

Methyl 4-[(2-{[(Allyloxy)carbonyl]amino}-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4-*O*-(4-methoxybenzyl)-α-D-galactopyranosyl)sulfanyl]butyrate (6)

A suspension of acetal **5** (1.03 g, 1,68 mmol) and activated 4 Å MS (1.0 g) in CH_2Cl_2 (65 mL) was stirred at r.t. for 1 h. The suspension was cooled to –78 °C and TESH (0.81 mL, 0.586 g, 5.04 mmol) was added dropwise. Subsequently, $PhBCl_2$ (0.74 mL, 0.907 g, 5.71 mmol) was added. After 5 min, Et_3N (2 mL) and MeOH were added and the soln was stirred for 5 min. The cold soln was diluted with CH_2Cl_2 (50 mL) and filtered, and the filtrate was washed with sat. aq $NaHCO_3$ (3 × 100 mL) and 1 M HCl (100 mL) and finally stirred with 1 M citric acid (100 mL) for 30 min. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel) afforded pure product **6**.

Yield: 840 mg (81%); colorless oil; $[\alpha]_D^{20}$ 82.9 (*c* 1.0, $CHCl_3$): R_f = 0.10 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, ^3J = 8.6 Hz, 2 H, H_{Ar}-PMB), 6.88 (d, ^3J = 8.7 Hz, 2 H, H_{Ar}-PMB), 5.91 (m_c, 1 H, CH_2=C*H*-, Aloc), 5.38 (d, $^3J_{1,2}$ = 4.7 Hz, 1 H, H-1), 5.32 (d, ^3J = 16.7 Hz, 1 H, CH_2=CH-, Aloc, (*trans*)), 5.22 (dd, ^3J = 10.6 Hz, ^2J = 1.3 Hz, 1 H, CH_2=CH-, Aloc, (*cis*)), 4.96 (d, ^2J = 11.1 Hz, 1 H, PMB-CH_2-Ha), (4.70 (d, ^3J = 9.6 Hz, 1 H, N*H*-C2), 4.61–4.54 (m, 3 H, H-2, -CH_2-, Aloc), 4.49 (d, ^2J = 11.1 Hz, 1 H, PMB-CH_2-Hb), 4.11 (t, ^3J = 5.3 Hz, 1 H, H-5), 3.80 (s, 4 H, H-6a, OCH_3-PMB), 3.73 (m_c, 2 H, H-3, H-4), 3.66 (s, 3 H, CO_2CH_3), 3.55 (dd, ^2J = 11.6 Hz, ^3J = 4.5 Hz, 1 H, H-6b), 2.66 (m_c, 2 H, SCH_2CH_2), 2.42 (m_c, 2 H, $CH_2CO_2CH_3$), 1.94 (m_c, 2 H, SCH_2CH_2), 0.92 (s, 9 H, $CH_3^{t\text{-Bu}}$, TBS), 0.15 (s, 3 H, CH_3, TBS), 0.12 (s, 3 H, CH_3, TBS).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.7 (C=O, Ester), 159.5 (C_p-PMB), 155.7 (C=O, Aloc), 132.9 (-*C*H=CH_2, Aloc), 130.5 (C_i-PMB), 127.8 (C_m-PMB), 118.0 (-CH=*C*H_2, Aloc), 114.0 (C_o-PMB), 86.3 (br s, C1), 77.0 (C3), 74.5 (CH_2-PMB), 72.5 (C5), 72.2 (C4), 65.7 (CH_2, Aloc), 62.5 (C6), 55.4 (OCH_3-PMB), 52.1 (C2), 51.8 (CO_2CH_3), 32.9 ($CH_2CO_2CH_3$), 31.1 (SCH_2CH_2), 25.8 ($CH_3^{t\text{-Bu}}$, TBS), 25.1 (SCH_2CH_2), 18.1 ($C^{t\text{-Bu}}$, TBS), –3.9 (CH_3, TBS), –4.8 (CH_3, TBS).

MS (FD): *m/z* (%) = 613.5 (100) $[M]^+$.

Methyl 4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-4-*O*-(4-methoxybenzyl)-α-D-galactopyranosyl)sulfanyl]butyrate (7)

Ph_3P (1.31 g, 5.0 mmol), DIAD (0.99 mL, 1.01g, 5.0 mmol), and nicotinoyl azide[17b] (0.74 g, 5.0 mmol) were added to **6** (770 mg, 1.25 mmol) in anhyd toluene (60 mL) at r.t. The mixture was stirred for 2 h. MeOH (20 mL) was added and the soln was concentrated in vacuo. The residue was triturated with Et_2O at 0 °C, the soln was filtered, and the filtrate was concentrated in vacuo. Purification by flash column chromatography (silica gel) gave pure azide **7**.

Yield: 499 mg (62%); colorless oil; $[\alpha]_D^{20}$ 82.9 (*c* 1.0, $CHCl_3$); R_f = 0.10 (cyclohexane–EtOAc, 3:1).

IR (NaCl): 2102 (N_3) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (d, ^3J = 8.9 Hz, 2 H, PMB), 6.88 (d, ^3J = 8.6 Hz, 2 H, PMB), 5.91 (m_c, 1 H, CH_2=C*H*-, Aloc), 5.31 (m_c, 2 H, H-1, CH_2=CH-, Aloc, (*trans*)), 5.21 (dd, ^3J = 10.4 Hz, ^2J = 1.4 Hz, 1 H, CH_2=CH-, Aloc, (*cis*)), 4.98 (d, ^2J = 11.0 Hz, 1 H, PMB-CH_2-Ha), 4.68 (d, ^3J = 9.6 Hz, 1 H, N*H*-C2), 4.61–4.53 (m, 3 H, H-2, -CH_2-, Aloc), 4.43 (d, ^2J = 11.1 Hz, 1 H, PMB-CH_2-Hb), 4.20–4.16 (m, 1 H, H-5), 3.80 (s, 3 H, OCH_3-PMB), 3.74 (m_c, 1 H, H-3), 3.66 (s, 3 H, CO_2CH_3), 3.62 (m_c, 1 H, H-4), 3.55 (dd, ^3J = 12.7 Hz, ^2J = 8.1 Hz, 1 H, H-6a), 3.05 (dd, ^3J = 12.7 Hz, ^2J = 4.5 Hz, 1 H, H-6b), 2.67 (m_c, 2 H, SCH_2CH_2), 2.43 (t, ^3J = 7.3 Hz, 2 H, $CH_2CO_2CH_3$), 1.95 (m_c, 2 H, SCH_2CH_2), 0.91 (s, 9 H, $CH_3^{t\text{-Bu}}$, TBS), 0.14 (s, 3 H, CH_3, TBS), 0.12 (s, 3 H, CH_3, TBS).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.4 (C=O, Ester), 159.6 (C_p-PMB), 155.6 (C=O, Aloc), 132.9 (-*C*H=CH_2, Aloc), 130.5 (C_i-PMB), 129.9 (C_m-PMB), 118.0 (-CH=*C*H_2, Aloc), 113.9 (C_o-PMB), 86.2 (br s, C1), 77.4 (C4), 74.6 (CH_2-PMB), 72.2 (C3), 71.4 (C5), 65.9 (CH_2, Aloc), 55.4 (OCH_3-PMB), 51.8 (C2, CO_2CH_3), 51.3 (C6), 32.8 ($CH_2CO_2CH_3$), 31.0 (SCH_2CH_2), 25.8 ($CH_3^{t\text{-Bu}}$, TBS), 25.0 (SCH_2CH_2), 18.0 ($C^{t\text{-Bu}}$, TBS), –3.9 (CH_3, TBS), –4.9 (CH_3, TBS).

MS (FD): *m/z* (%) = 638.2 (100) $[M]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-4-*O*-(4-methoxybenzyl)-α-D-galactopyranosyl)sulfanyl]butyric Acid (8)

$LiOH·H_2O$ (0.55 g, 13.2 mmol) was added in one portion to a soln of ester **7** (2.10 g, 3.3 mmol) in THF–H_2O (10:1, 44 mL). The mixture was stirred at r.t. for 16 h and neutralized with an acidic cation exchanger (Amberlite IR120). After filtration of the mixture, the solvent was removed in vacuo and subsequently subjected to lyophilization. The crude carboxylic acid **8** that was obtained was used for coupling to the polymer support.

Yield: 1.96 g (94%); colorless oil; $[\alpha]_D^{20}$ 93.6 (*c* 1.0, $CHCl_3$); R_f = 0.10 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (m, 2 H, PMB), 6.86 (d, ^3J = 8.6 Hz, 2 H, PMB), 5.89 (m_c, 1 H, CH_2=C*H*-, Aloc), 5.30 (m_c, 2 H, H-1, CH_2=CH-, Aloc, (*trans*)), 5.20 (dd, ^3J = 10.4 Hz, ^2J = 1.3 Hz, 1 H, CH_2=CH-, Aloc, (*cis*)), 4.96 (d, ^2J = 10.7 Hz, 1 H, PMB-CH_2-Ha), 4.68 (d, ^3J = 9.6 Hz, 1 H, N*H*-C2), 4.60–4.51 (m, 3 H, H-2, -CH_2-, Aloc), 4.54 (d, ^2J = 10.4 Hz, 1 H, PMB-CH_2-Hb), 4.20–4.16 (m, 1 H, H-5), 3.79 (s, 3 H, OCH_3-PMB), 3.72 (m_c, 1 H, H-3), 3.61 (m_c, 1 H, H-4), 3.53 (dd, ^3J = 12.8 Hz, ^2J = 8.0 Hz, 1 H, H-6a), 3.05 (dd, ^3J = 12.7 Hz, ^2J = 4.6 Hz, 1 H, H-6b), 2.77–2-58 (m, 2 H, SC$H_2$$CH_2$), 2.46 (t, ^3J = 7.1 Hz, 2 H, C$H_2$$CO_2CH_3$), 1.94 ($m_c$, 2 H, SCH_2CH_2), 0.89 (s, 9 H, C$H_3$$^{t\text{-Bu}}$, TBS), 0.13 (s, 3 H, C$H_3$, TBS), 0.10 (s, 3 H, C$H_3$, TBS).

Polymer-Bound Building Blocks 9a and 9b

Resin 9a

In a solid-phase reaction vessel, Fmoc-protected Rink amide polystyrene (2.63 g, 1.84 mmol, loading 0.70 mmol/g, 100–200 mesh, crosslinked with 1% divinylbenzene) was swollen in DMF (30 mL) for 1 h, before a 50% soln of morpholine in DMF (40 mL) was added. The mixture was shaken for 30 min at r.t. The polymer was washed with DMF and the removal of the Fmoc group was repeated. Finally, the resin was washed with DMF and dried thoroughly in vacuo. Carboxylic acid **8** (1.149 g, 1.84 mmol) was dissolved in DMF (40 mL) and activated with HBTU (0.698 g, 1.84 mmol), $HOBt·H_2O$ (0.282 g, 1.84 mmol), and DIPEA (3.4 mL, 2.38 g, 18.4 mmol). The soln was mixed for 3–5 min and finally added to the prepared Rink amide PS. The mixture was shaken for 17 h at r.t. The polymer was washed with DMF (10 mL), DMF–MeOH (10 mL, 1:1), MeOH–CH_2Cl_2 (10 mL, 1:1), MeOH–Et_2O (10 mL, 1:1), and Et_2O (10 mL) and dried thoroughly in vacuo; yield: 0.67 mmol/g (determined by elementary analysis of sulfur), corresponding to a coupling yield of 95%. Finally, unchanged benzhydryl amino groups were acylated with a soln of Ac_2O–py (20 mL, 2:1, v/v) in CH_2Cl_2 (20 mL) for 45 min. The polymer was washed with CH_2Cl_2 (10 mL), CH_2Cl_2–MeOH (10 mL, 1:1), CH_2Cl_2 (10 mL), and Et_2O (10 mL), and dried thoroughly in vacuo; this gave resin **9a**.

IR (KBr): 2100 (N_3) cm^{-1}.

Resin 9b

Resin **9b** was obtained by a reaction between Fmoc-protected Rink amide Tentagel (6.391 g, 1.47 mmol, loading 0.23 mmol/g), carboxylic acid **8** (0.916 g, 1.47 mmol), HBTU (0.472 g, 1.47 mmol), $BtOH·H_2O$ (0.225 g, 1.47 mmol), and DIPEA (2.43 mL, 1.90 g, 14.7 mmol); yield: 0.19 mmol/g (determined by elementary analysis regarding sulfur), corresponding to a coupling yield of 82%. The capping reaction was carried out according to the method described above for polymer **9a**.

IR (KBr): 2100 (N_3) cm^{-1}.

Carbamates 14

Ten portions of resin **9a** (100 mg each, loading 0.67 mmol/g) and two portions of resin **9b** (100 mg each, loading 0.19 mmol/g) were filled into 5-mL syringes. To each of the syringes, DMF (2.5 mL) was added, and the polymer was swollen for 1 h. A 50% soln of TBAHDF in MeCN (2.5 mL) was added, and the syringes were shaken for 4 h. Then the resins were washed with DMF (10 mL), DMF–MeOH (10 mL, 1:1), MeOH–CH_2Cl_2 (10 mL, 1:1), MeOH–Et_2O (10 mL, 1:1), and Et_2O (10 mL) and dried thoroughly in vacuo. The loaded polymers were swollen in dioxane (2.5 mL) for 30 min and then treated with a 1% DMAP in dioxane (2 mL). After removal of the liquid phase, twelve separate 10% solns of the appropriate isocyanates R^2NCO in dioxane (1.5 mL) were each added to one of the resin portions and the mixtures were shaken for 16 h at r.t. The resins were washed with dioxane (10 mL), DMF (10 mL), DMF–MeOH (10 mL, 1:1), MeOH–CH_2Cl_2 (10 mL, 1:1), MeOH–Et_2O (10 mL, 1:1), and Et_2O (10 mL) and dried thoroughly in vacuo. Prior to cleavage of the products from the polymer supports, sulfanylmethyl polystyrene was added to the resins, and each polymer was washed with anhyd CH_2Cl_2 (20 mL). Cleavage of products **14a–l** from the polymer supports was achieved by addition of 50% TFA in anhyd CH_2Cl_2 (2.5 mL) to each of the mixtures. After 30 min of shaking, the solns were filtered through the syringes (this step was repeated once again). The filtrates and the corresponding washing solns were combined separately and concentrated in vacuo. Each of the twelve residues was dissolved in CH_2Cl_2 (2 mL) and filtered over solid $NaHCO_3$ (2 mL layer in a 5-mL solid-phase-extraction cartridge). After filtration, the solvents were removed in vacuo and the thus obtained products **14a–l** were weighed and analyzed by RP-HPLC and ESI-MS and purified by semipreparative RP-HPLC.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[(4-fluorophenyl)carbamoyl]-α-D-galactopyranosyl)sulfanyl]butyramide (14a)

Yield: 9.5 mg (ca. 100%, crude product); yellow amorphous solid.

Analytical HPLC: gradient A, t_R = 16.92 min (52%).

Semipreparative HPLC: gradient E, t_R = 31.02 min; yield: 3.5 mg (45%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 565.3 (7) $[M + K]^+$, 549.3 (100) $[M + Na]^+$, 527.3 (18) $[M + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-3-*O*-[(4-cyanophenyl)carbamoyl]-2,6-dideoxy-α-D-galactopyranosyl)sulfanyl]butyramide (14b)

Yield: 6.5 mg (81%, crude product); yellow oil.

Analytical HPLC: gradient A, t_R = 17.60 min (38%).

Semipreparative HPLC: gradient E, t_R = 30.00 min; yield: 1.5 mg (19%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 572.3 (7) $[M + K]^+$, 556.3 (100) $[M + Na]^+$, 534.3 (25) $[M + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-3-*O*-[(4-chlorophenyl)carbamoyl]-2,6-dideoxy-α-D-galactopyranosyl)sulfanyl]butyramide (14c)

Yield: 31.0 mg (85%, crude product); colorless amorphous solid.

Analytical HPLC: gradient A, t_R = 18.28 min (46%).

Semipreparative HPLC: gradient E, t_R = 32.57 min; yield: 9.2 mg (25%, based on polymer-bound carbohydrate); colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, ^3J = 8.9 Hz, 2 H, H_{Aryl}, carbamate), 7.11 (d, ^3J = 8.9 Hz, 2 H, H_{Aryl}, carbamate), 5.67 (m_c, 1 H, CH_2=C*H*-, Aloc), 5.60 (d, ^3J = 9.3 Hz, 1 H, N*H*-C2), 5.31 (d, ^3J = 5.4 Hz, 1 H, H-1), 5.08 (dd, ^3J = 17.3 Hz, ^3J = 1.3 Hz, 1 H, CH_2=CH-, Aloc, (*trans*)), 4.96 (dd, ^3J = 10.6 Hz, ^3J = 1.0 Hz, 1 H, CH_2=CH-, Aloc, (*cis*)), 4.69 (dd, ^3J = 11.6 Hz, ^3J = 2.9 Hz, 1 H, H-3), 4.43 (m_c, 1 H, H-2), 4.37 (m_c, 2 H, -CH_2-, Aloc), 4.22 (m_c, 1 H, H-5), 3.89 (m_c, 1 H, H-4), 3.53 (dd, ^2J = 12.8 Hz, ^3J = 8.2 Hz, 1 H,

H-6a), 3.22 (m_c, 1 H, H-6b), 2.58 (m_c, 2 H, SCH_2CH_2), 2.21 (t, ^3J = 7.4 Hz, 2 H, $CH_2CO_2CH_3$), 1.84 (m_c, 2 H, SCH_2CH_2).

ESI-MS: *m/z* (%) = 1651.5 (2) [3M + Na]$^+$, 1107.4 (100) [2M + Na]$^+$, 581.1 (24) [M + K]$^+$, 565.2 (98) [M + Na]$^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-3-*O*-[(3,4-dichlorophenyl)carbamoyl]-2,6-dideoxy-α-D-galactopyranosyl)sulfanyl]butyramide (14d)

Yield: 31.8 mg (82%, crude product); colorless amorphous solid.

Analytical HPLC: gradient A, t_R = 18.68 min (67%), the isolation failed.

ESI-MS (crude product): *m/z* (%) = 1177.2 (45) [2M + Na]$^+$, 599.1 (100) [M + Na]$^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[(2,4-difluorophenyl)carbamoyl]-α-D-galactopyranosyl)sulfanyl]butyramide (14e)

Yield: 47.0 mg (ca. 100%, crude product); brown oil.

Analytical HPLC: gradient A, t_R = 17.70 min (42%).

Semipreparative HPLC: gradient E, t_R = 30.77 min; yield: 11.6 mg (32%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m/z* (%) = 1111.3 (100) [2M + Na]$^+$, 567.1 (40) [M + Na]$^+$, 545.2 (5) [M + H]$^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[(4-methyl-3-nitrophenyl)carbamoyl]-α-D-galactopyranosyl)sulfanyl]butyramide (14f)

Yield: 13.0 mg (34%, crude product); brown oil.

Analytical HPLC: gradient A, t_R = 19.18 min (13%).

Semipreparative HPLC: gradient E, t_R = 31.87 min; yield: 0.8 mg (2%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m/z* (%) = 606.2 (19) [M + K]$^+$, 590.2 (100) [M + Na]$^+$, 568.2 (5) [M + H]$^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[(4-nitrophenyl)carbamoyl]-α-D-galactopyranosyl)sulfanyl]butyramide (14g)

Yield: 11.6 mg (31%, crude product); pale yellow amorphous solid. The desired product could not be detected.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[(3-fluorophenyl)carbamoyl]-α-D-galactopyranosyl)sulfanyl]butyramide (14h)

Yield: 28.0 mg (79%, crude product); pale yellow amorphous solid.

Analytical HPLC: gradient A, t_R = 18.58 min (36%).

Semipreparative HPLC: gradient E, t_R = 31.87 min; yield: 8.8 mg (25%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m/z* (%) = 1075.4 (89) [2M + Na]$^+$, 1053.4 (100) [2M + H]$^+$, 549.2 (64) [M + Na]$^+$, 527.2 (8) [M + H]$^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[(2-nitrophenyl)carbamoyl]-α-D-galactopyranosyl)sulfanyl]butyramide (14i)

Yield: 34.6 mg (93%, crude product); pale yellow amorphous solid.

Analytical HPLC: gradient A, t_R = 18.67 min (86%).

Semipreparative HPLC: gradient E, t_R = 31.68 min; yield: 15.3 mg (41%, based on polymer-bound carbohydrate); colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, ^3J = 8.6 Hz, 1 H, H_{Aryl}), 8.08 (d, ^3J = 8.6 Hz, 1 H, H_{Aryl}), 7.76 (m_c, 1 H, H_{Aryl}), 7.09 (m_c, 1 H, H_{Aryl}), 5.72 (m_c, 1 H, CH_2=C*H*-, Aloc), 5.49 (d, ^3J = 9.5 Hz, 1 H, N*H*-C2), 5.38 (d, ^3J = 5.3 Hz, 1 H, H-1), 5.13 (d, ^3J = 17.3 Hz, 1 H, CH_2=CH-, Aloc, (*trans*)), 5.00 (d, ^3J = 10.4 Hz, 1 H, CH_2=CH-, Aloc, (*cis*)), 4.79 (dd, ^3J = 11.5 Hz, ^3J = 2.9 Hz, 1 H, H-3), 4.52 (m_c, 1 H, H-2), 4.43 (m_c, 2 H, -CH_2-, Aloc), 4.27 (m_c, 1 H, H-5), 3.98 (m_c, 1 H, H-4), 3.59 (dd, ^2J = 12.5 Hz, ^3J = 1.6 Hz, 1 H, H-6a), 3.27 (dd, ^2J = 12.9 Hz, ^3J = 4.4 Hz, 1 H, H-6b), 2.62 (m_c, 2 H, SCH_2CH_2), 2.26 (t, ^3J = 7.4 Hz, 2 H, $CH_2CO_2CH_3$), 1.89 (m_c, 2 H, SCH_2CH_2).

ESI-MS: *m/z* (%) = 1129.4 (44) [2M + Na]$^+$, 1107.4 (11) [2M + H]$^+$, 576.2 (100) [M + Na]$^+$, 554.2 (19) [M + H]$^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-{[4-(ethoxycarbonyl)phenyl]carbamoyl}-α-D-galactopyranosyl)sulfanyl]butyramide (14j)

Yield: 23.4 mg (60%, crude product); pale yellow amorphous solid.

Analytical HPLC: gradient A, t_R = 17.70 min (32%).

Semipreparative HPLC: gradient E, t_R = 31.42 min; yield: 7.5 mg (32%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m/z* (%) = 1183.4 (100) [2M + Na]$^+$, 1161.4 (30) [2M + H]$^+$, 603.2 (92) [M + Na]$^+$, 581.2 (2) [M + H]$^+$.

4-[(3-*O*-[(3-Acetylphenyl)carbamoyl]-2-{[(allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-α-D-galactopyranosyl)sulfanyl]butyramide (14k)

Yield: 23.3 mg (63%, crude product); pale yellow amorphous solid.

Analytical HPLC: gradient A, t_R = 16.63 min (50%).

Semipreparative HPLC: gradient E, t_R = 28.67 min; yield: 5.4 mg (14%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m/z* (%) = 1673.6 (4) [3M + Na]$^+$, 1123.4 (100) [2M + Na]$^+$, 1101.4 (16) [2M + H]$^+$, 589.2 (28) [M + K]$^+$, 573.2 (73) [M + Na]$^+$, 551.2 (2) [M + H]$^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[(4-ethoxyphenyl)carbamoyl]-α-D-galactopyranosyl)sulfanyl]butyramide (14l)

Yield: 36.1 mg (98%, crude product); pale yellow amorphous solid.

Analytical HPLC: gradient A, t_R = 17.55 min (33%).

Semipreparative HPLC: gradient E, t_R = 31.45 min; yield: 9.8 mg (27%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m/z* (%) = 1144.4 (7) [2M + K]$^+$, 1127.4 (78) [2M + Na]$^+$, 1105.4 (100) [2M + H]$^+$, 575.2 (62) [M + Na]$^+$, 553.2 (2) [M + H]$^+$.

Carbamates 15

One portion of resin **9a** (100 mg, loading 0.67 mmol/g) and two portions of resin **9b** (100 mg each, loading 0.15 mmol/g) were filled in 5-mL syringes. To each of the syringes CH_2Cl_2 (2.5 mL) was added, and the polymers were swollen for 1 h. A mixture of DDQ (158.9 mg, 0.70 mmol for **9a** or 52.2 mg, 0.23 mmol for **9b**) in CH_2Cl_2 (2.5 mL) and 10 vol% H_2O were added to the polymers. The syringes were shaken for 30 min. The resins were washed thoroughly with CH_2Cl_2 (10 mL) and an additional portion of DDQ was added. After 30 min the polymer support was washed with DMF (10 mL), DMF–MeOH (10 mL, 1:1), MeOH–CH_2Cl_2 (10 mL, 1:1), MeOH–Et_2O (10 mL, 1:1), and Et_2O (10 mL) and directly used for carbamoylation. The preparation of the carbamates was carried out according to the protocol for the preparation of derivatives **14**. The procedures for the removal of the TBS protecting group and the cleavage of the

desired products from polymer support were performed as described for the isolation of carbamates **14**. The products **15** thus obtained were weighed and analyzed by RP-HPLC and ESI-MS and purified by semipreparative RP-HPLC.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-4-*O*-[(4-fluorophenyl)carbamoyl]-α-D-galactopyranosyl)sulfanyl]butyramide (15a)
Yield: 4.6 mg (58%, crude product); colorless amorphous solid.

Analytical HPLC: gradient A, t_R = 18.25 min (91%).

Semipreparative HPLC: gradient E, t_R = 31.07 min; yield: 1.9 mg (24%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 565.3 (5) $[M + K]^+$, 549.3 (100) $[M + Na]^+$, 527.3 (20) $[M + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-4-*O*-[(4-cyanophenyl)carbamoyl]-2,6-dideoxy-α-D-galactopyranosyl)sulfanyl]butyramide (15b)
Yield: 6.2 mg (78%, crude product); colorless amorphous solid.

Analytical HPLC: gradient A, t_R = 17.60 min (85%).

Semipreparative HPLC: gradient E, t_R = 30.00 min; yield: 1.1 mg (14%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 572.3 (5) $[M + K]^+$, 556.3 (100) $[M + Na]^+$, 534.3 (10) $[M + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-4-*O*-[(4-chlorophenyl)carbamoyl]-2,6-dideoxy-α-D-galactopyranosyl)sulfanyl]butyramide (15c)
Yield: 13.3 mg (37%, crude product); pale brown amorphous solid.

Analytical HPLC: gradient A, t_R = 18.07 min (33%).

Semipreparative HPLC: gradient E, t_R = 32.57 min; yield: 3.8 mg (10%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 1629.4 (4) $[3M + H]^+$, 1107.4 (7) $[2M + Na]^+$, 1085.4 (100) $[2M + H]^+$, 565.2 (10) $[M + Na]^+$, 543.2 (16) $[M + H]^+$.

N-Acylated Derivatives 16 and 17
In a solid-phase reaction vessel, resin **9a** (1.3 g, 1.84 mmol, loading 0.70 mmol/g) was swollen for 1 h in anhyd dioxane (20 mL). The mixture was degassed by ultrasonication under an argon atmosphere, before $TolSO_2H$ (0.781 g, 4.58 mmol) was added. $Pd(PPh_3)_4$ (0.213 g, 0.184 mmol) was added and the mixture was shaken in the dark at r.t for 16 h. Polymer support **10a** was washed with dioxane (10 mL), DMF (10 mL), CH_2Cl_2 (10 mL), MeOH–CH_2Cl_2 (10 mL, 1:1), CH_2Cl_2–Et_2O (10 mL, 1:1), and Et_2O (10 mL), and dried thoroughly in vacuo. Amino acids Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Glu(O*t*-Bu)-OH, Fmoc-Arg(Pmc)-OH, Fmoc-His(Trt)-OH, and Fmoc-Gln(Trt)-OH (5 equiv, 0.35 mmol) were each activated with TBTU (112.0 mg, 0.35 mmol), HOBt·H_2O (54.0 mg 0.35 mmol), and DIPEA (0.115 mL, 90.0 mg, 0.70 mmol) in DMF (2.5 mL). One of the solns of activated amino acids was added to each of six 5-mL syringes containing resin **10a** (100 mg each), and the mixtures were shaken at r.t. for 16 h. Finally, the polymer support was washed with DMF (10 mL), DMF–MeOH (10 mL, 1:1), MeOH–CH_2Cl_2 (10 mL, 1:1), MeOH–Et_2O (10 mL, 1:1), and Et_2O (10 mL) and then dried thoroughly in vacuo. Prior to cleavage of the products from the polymer support, the polymers were washed with anhyd CH_2Cl_2 (20 mL). Cleavage of the products from the polymer support was achieved by addition of 50% TFA and 5% Me_2S soln in anhyd CH_2Cl_2 (2.5 mL). After 30 min of shaking, the solns were filtered from the syringes (this step was repeated once again). Each of the solns was combined and concentrated in vacuo. To each of the six residues cold Et_2O (1 mL) was added, and the mixtures were kept cold at 0 °C for 5 min. The solns were carefully removed and the residues were dried in vacuo. Mixtures of the desilylated **16** and/or silylated **17** products were obtained, analyzed by RP-HPLC and ESI-MS, and purified by semipreparative RP-HPLC.

The reactions on Tentagel were carried out according to the above protocol, starting from polymer **9b** (1.5 g, 0.345 mmol), by use of $TolSO_2H$ (270 mg, 1.73 mmol), $Pd(PPh_3)_4$ (79.7 mg, 0.69 mmol), TBTU (73.8 mg, 0.23 mmol), HOBt·H_2O (35.2 mg, 0.23 mmol), DIPEA (78.7 μL, 59.4 mg, 0.46 mmol), and Fmoc-Arg(Pmc)-OH, Fmoc-His(Trt)-OH, and Fmoc-Gln(Trt)-OH (0.23 mmol, respectively). For the synthesis of products **16g** and **17g** the procedure required additional steps. Before the product was cleaved from the resin, the Fmoc protecting group was removed as described for the preparation of building blocks **9**, and the coupling of Fmoc-His(Trt)-OH (0.23 mmol) followed according to the peptide-coupling protocol given above.

4-[(6-Azido-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-glycyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (17a)
Yield: 26.6 mg (60%, crude product); brown amorphous solid.

Analytical HPLC: gradient A, t_R = 25.72 min (40%).

Semipreparative HPLC: gradient F, t_R = 31.45 min; yield: 5.3 mg (12% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 1435.7 (13) $[2M + K]^+$, 1419.7 (87) $[2M + Na]^+$, 721.3 (100) $[M + Na]^+$.

4-[(6-Azido-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-L-leucyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (17b)
Yield: 39.2 mg (82%, crude product); brown amorphous solid.

Analytical HPLC: gradient A, t_R = 27.85 min (33%), not isolated by semipreparative HPLC.

ESI-MS (crude product): *m*/*z* (%) = 793.11 (10) $[M + K]^+$, 777.18 (100) $[M + Na]^+$, 663.21 (25) [3-OH, $M + Na]^+$.

4-[(6-Azido-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-L-glutamyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (17c)
Yield: 24.9 mg (51%, crude product); brown amorphous solid.

Analytical HPLC: gradient A, t_R = 22.72 min (36%).

Semipreparative HPLC: gradient F, t_R = 30.10 min; yield: 4.8 mg (10% based on polymer-bound carbohydrate); pale yellow amorphous solid.

ESI-MS: *m*/*z* (%) = 809.26 (100) $[M + K]^+$, 793.31 (40) $[M + Na]^+$.

4-[(6-Azido-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-L-arginyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (16d) and Its 3-OTBS Derivative 17d
From reaction on aminomethyl-PS: Yield: 31.5 mg (64%, crude product); brown amorphous solid; desired product not detected.

From reaction on Tentagel resin: Yield: 23.9 mg (ca. 100%).

Analytical HPLC: gradient B, t_R = 10.68 min (12%), 12.36 min (17%), 16.33 min (29%), 19.73 min (7%). This gave mixture of **16d** and **17d**; separation of products and isolation failed.

ESI-MS (crude product): *m*/*z* (%) = 798.59 (30) $[M + H]^+$ (**17d**), 684.52 (20) $[M + H]^+$ (**16d**), 576.50 (15) $[M – Fmoc + H]^+$ (**17d**), 420.20 (5) [2-NH_2, M – Fmoc-Arg]$^+$ (**17d**), 195.04 (100%), 179.05 (65) $[DBF + H]^+$.

4-[(6-Azido-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (16e)
From reaction on Tentagel resin: Yield: 19.8 mg (ca. 100%, crude product), yellow oil.

Analytical HPLC: gradient B, t_R = 10.62 min (24%).

Semipreparative HPLC: gradient G, t_R = 20.32 min; yield: 3.9 mg (31% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 687.49 (5) $[M + Na]^+$, 665.49 (100) $[M + H]^+$, 179.05 (5) $[DBF + H]^+$.

4-[(6-Azido-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (17e)
From reaction on Tentagel resin.

Analytical HPLC: gradient B, t_R = 17.08 min (35%).

Semipreparative HPLC: gradient G, t_R = 50.73 min; yield: 1.0 mg (7% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 779.57 (100) $[M + Na]^+$, 557.47 (5) $[M - Fmoc + H]^+$.

4-[(6-Azido-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-L-glutaminyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (16f)
Yield: 21.6 mg (ca. 100%, crude product), yellow amorphous solid.

Analytical HPLC: gradient B, t_R = 11.37 min (25%), 24. 47 min (26%).

Semipreparative HPLC: gradient G t_R = 18.67 min; yield: 1.0 mg (7% based on polymer-bound carbohydrate); pale yellow amorphous solid.

ESI-MS: *m*/*z* (%) = 678.48 (8) $[M + Na]^+$, 472.32 (15) $[M - Fmoc+K]^+$, 456.31 (40) $[M - Fmoc+Na]^+$, 434.26 (100) $[M - Fmoc + H]^+$, 195.05 (35%), 179.05 (60) $[DBF + H]^+$.

4-[(6-Azido-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-L-glutaminyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (17f)
Analytical HPLC: gradient B, 21.12 min (33%), not isolated by semipreparative HPLC.

ESI-MS (crude product): *m*/*z* (%) = 770.55 (5) $[M + Na]^+$, 656.44 (5) $[M + H]^+$ (**16f**), 548.42 (<5) $[M - Fmoc + H]^+$, 434.26 (10) $[M - Fmoc + H]^+$ (**16f**), 179.05 (100) $[DBF + H]^+$.

4-[(6-Azido-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl-l-glycyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (16g)
Yield: 24.9 mg (~100%, crude product); colorless amorphous solid.

Analytical HPLC: gradient B, t_R = 13.52 min (53%).

Semipreparative HPLC: gradient G, t_R = 16.92 min; yield: 1.2 mg (9% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 722.45 (100) $[M + H]^+$, 695.49 (<5%, 6-NH_2, $[M + H]^+$, 434.26 (40%), 263.42 (85%).

4-[(6-Azido-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-{[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl-glycyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (17g)
Analytical HPLC: gradient B, t_R = 20.45 min (4%).

Semipreparative HPLC: gradient G, t_R = 16.92 min; yield: 1.2 mg (8% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 836.52 (100) $[M + H]^+$, 637.38 (15) $[M - Fmoc + Na + 1]^+$, 584.44 (25), 263.42 (50), 179.07 (20) $[DBF + H]^+$.

O-Acylated Derivatives 18
Six portions of resin **9b** (100 mg each, loading 0.19 mmol/g) were placed in six 5-mL syringes, and the above-described procedure for the removal of the TBS protecting group (preparation of carbamates **14**) was applied. The appropriate Fmoc- and Z-terminated amino acids (0.23 mmol each) were activated with DIC (47.4 μL, 37.9 mg, 0.23 mmol) and DMAP (2.6 mg, 0.21 mmol) in DMF (2.5 mL) and then added to the polymers. After shaking of the mixtures for 16 h at r.t., the polymer supports were washed with DMF (10 mL), DMF–MeOH (10 mL, 1:1), MeOH–CH_2Cl_2 (10 mL, 1:1), MeOH–Et_2O (10 mL, 1:1), and Et_2O (10 mL) and dried thoroughly in vacuo. The cleavage of the products from the polymer support was carried out according to the procedure described for preparation of derivatives **16** and **17**. The synthesis of derivatives **18d–f** contained additional steps, which are described in the protocol for the preparation of compounds **16g** and **17g**. Products **18** thus obtained were analyzed by RP-HPLC and ESI-MS and purified by semipreparative RP-HPLC.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[*N*-(9-fluorenylmethoxycarbonyl)-L-arginyl]-α-D-galactopyranosyl)sulfanyl]butyramide (18a)
Yield: 7.4 mg (51%, crude product); colorless amorphous solid; the isolation failed.

ESI-MS (crude product): *m*/*z* (%) = 768.38 (100) $[M + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[*N*-(9-fluorenylmethoxycarbonyl)-L-glutaminyl]-α-D-galactopyranosyl)sulfanyl]butyramide (18b)
Yield: 6.5 mg (46%, crude product); colorless amorphous solid.

Analytical HPLC: gradient B, t_R = 15.92 min (43%).

Semipreparative HPLC: gradient E, t_R = 25.77 min; yield: 0.8 mg (6%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 1501.58 (64) $[2M + Na]^+$, 778.27 (3) $[M + K]^+$, 762.28 (100) $[M + Na]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl]-α-D-galactopyranosyl)sulfanyl]butyramide (18c)
Yield: 7.1 mg (50%, crude product); colorless amorphous solid.

Analytical HPLC: gradient B, t_R = 17.27 min (60%, major epimer **18c**), t_R = 18.30 min (24%, minor epimer **18c***).

Semipreparative HPLC: gradient A, t_R = 29.00 min (**18c**); yield: 1.8 mg (13%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 1519.59 (39) $[2M + Na]^+$, 1497.61 (6) $[2M + Na]^+$, 787.27 (3) $[M + K]^+$, 771.29 (100) $[M + Na]^+$, 749.31 (16) $[M + H]^+$.

Semipreparative HPLC: gradient A, t_R = 31.13 min (**18c***); yield: 0.4 mg (3%, based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 1519.60 (10) $[2M + Na]^+$, 787.28 (6) $[M + K]^+$, 771.29 (61) $[M + Na]^+$, 749.31 (100) $[M + H]^+$, 412.15 (3) $[M - Fmoc - His - 3\text{-}TBSO + Na]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-2,6-dideoxy-3-*O*-[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl-glycyl]-α-D-galactopyranosyl)sulfanyl]butyramide (18d)
Yield: 26.6 mg (ca. 100%, crude product); colorless amorphous solid.

Analytical HPLC: gradient B, t_R = 12.10 min (5%), 14.97 min (70%, **18d**), 17.10 min (17%), 20.23 min (5%).

Semipreparative HPLC: gradient G, t_R = 19.15 min; yield: 6.1 mg (40% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 828.33 (100) $[M + Na]^+$, 806.36 (24) $[M + H]^+$, 412.16 (14) [3-OH, $M + Na]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-3-*O*-[*N*-(benzyloxycarbonyl)-glycyl-glycyl]-2,6-dideoxy-α-D-galactopyranosyl)sulfanyl]butyramide (18e)
Yield: 13.7 mg (ca. 100%, crude product); colorless amorphous solid; cleavage of product from polymer support with a TFA–H_2O–TIPS–CH_2Cl_2 mixture (50:5:5:40).

Analytical HPLC: gradient B, t_R = 10.67 min (7%), 11.08 min (67%, **18e**), 12.80 min (4%), 13.40 min (21%); the isolation failed.

ESI-MS: *m*/*z* (%) = 660.30 (20) $[M + Na]^+$, 91.08 (100) $[PhCH_2]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-6-azido-3-*O*-[*N*-(benzyloxycarbonyl)-glycyl-L-histydyl]-2,6-dideoxy-α-D-galactopyranosyl)sulfanyl]butyramide (18f)
Yield: 14.1 mg (ca. 100%, crude product); colorless amorphous solid; cleavage of product from polymer support with a TFA–H_2O–TIPS–CH_2Cl_2 mixture (50:5:5:40).

Analytical HPLC: gradient C, t_R = 11.32 min (30%).

Semipreparative HPLC: gradient G, t_R = 20.63 min; yield: 1.8 mg (13% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 756.17 (20) $[M + K]^+$, 740.20 (100) $[M + Na]^+$, 412.14 (5) [3-OH, $M + Na]^+$.

N-Acylated Derivatives 19 and 20
One portion of resin **9a** (100 mg, loading 0.67 mmol/g) and five portions of resin **9b** (100 mg each, loading 0.19 mmol/g) were each placed separately in one of six 5-mL syringes. To each of the syringes, THF (2.5 mL) was added, and the polymer was swollen for 1 h. A soln of *n*-Bu_3P (0.115 mL, 0.46 mmol, for **9a** or 0.349 mL for **9b**) in a THF–H_2O–Et_3N mixture (2:1:1, 2.5 mL) was added to each of the syringes, which were then shaken for 2 h. This step was repeated once again, and the resin was washed with DMF (10 mL), DMF–MeOH (10 mL, 1:1), MeOH–CH_2Cl_2 (10 mL, 1:1), MeOH–Et_2O (10 mL, 1:1), and Et_2O (10 mL) and dried thoroughly in vacuo. The N-acylation was carried out according to the protocol for the synthesis of compounds **16** and **17**; the following carboxylic acids were used: phenylacetic acid (0.23 mmol), Fmoc-His(Trt)-OH (0.70 mmol), Fmoc-Arg(Pmc)-OH (0.70 mmol), Fmoc-Gln(Trt)-OH (0.70 mmol), 1-phenyl-1*H*-[1,2,3]triazole-4-carboxylic acid (0.70 mmol), and Fmoc-Gly-OH (0.70 mmol). The cleavage of the products from the polymer support was carried out according to the procedure described for preparation of derivatives **16** and **17**. The synthesis of **19f** and **20f** required additional steps, as described in the protocol for the preparation of compounds **16g** and **17g**. Products **19** and **20** thus obtained were analyzed by RP-HPLC and ESI-MS and purified by semipreparative RP-HPLC.

4-[(2-{[(Allyloxy)carbonyl]amino}-2,6-dideoxy-6-{[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (19a)
Yield: 13.4 mg (84%, crude product); pale yellow amorphous solid.

Analytical HPLC: gradient B, t_R = 13.22 min (37%).

Semipreparative HPLC: gradient G, t_R = 13.28 min; yield: 1.6 mg (12% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 745.32 (15) $[M + Na]^+$, 723.36 (20) $[M - H]^+$, 604.35 (50), 179.05 (100) $[DBF + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-6-{[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (20a)
Analytical HPLC: gradient B, t_R = 22.67 min (54%).

Semipreparative HPLC: gradient G, t_R = 28.65 min; yield: 2.5 mg (16% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 856.46 (5) $[M + Ca]^{2+}$, 742.36 (65) [3-OH, $M + Ca]^{2+}$, 604.35 (40), 179.04 (100) $[DBF + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-2,6-dideoxy-6-{[*N*-(9-fluorenylmethoxycarbonyl)-L-arginyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (19b)
Yield: 15.6 mg (96%); yellow amorphous solid.

Analytical HPLC: gradient B, t_R = 7.53 min (44%), 15.00 min (14%), 17.17 min (42%); the isolation failed.

ESI-MS (crude product): *m*/*z* (%) = 764.32 (5) $[M + Na]^+$, 742.34 (10) $[M + H]^+$, 500.12 (5) [6-NH_2, M – Fmoc-Arg + $Na]^+$, 179.03 (100) $[DBF + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-6-{[*N*-(9-fluorenylmethoxycarbonyl)-L-arginyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (20b)
The desired product could not be detected.

4-[(2-{[(Allyloxy)carbonyl]amino}-2,6-dideoxy-6-{[*N*-(9-fluorenylmethoxycarbonyl)-L-glutaminyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (19c)
Yield: 16.2 mg (ca. 100%, crude product); colorless amorphous solid.

Analytical HPLC: gradient B, t_R = 12.90 min (21%).

Semipreparative HPLC: gradient G, t_R = 19.08 min; yield: 0.9 mg (7% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 736.43 (10) $[M + Na]^+$, 697.86 (20) $[M - NH_2]^+$, 641.74 (50), 401.38 (85), 360.41 (100).

4-[(2-{[(Allyloxy)carbonyl]amino}-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-6-{[*N*-(9-fluorenylmethoxycarbonyl)-L-glutaminyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (20c)
Analytical HPLC: gradient B, t_R = 21.72 min (79%).

Semipreparative HPLC: gradient G, t_R = 46.70 min; yield: 1.7 mg (11% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 850.49 (45) $[M + Na]^+$, 828.58 (5) $[M + H]^+$, 628.41 (80) [M – Fmoc + $Na]^+$, 606.48 (90) [M – Fmoc + $H]^+$, 469.41 (95), 179.07 (100) $[DBF + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-2,6-dideoxy-6-{[(1-phenyl-1*H*-1,2,3-triazol-4-yl)carbonyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (19d)
Yield: 14.4 mg (ca. 100%, crude product); colorless oil.

Analytical HPLC: gradient B, t_R = 10.78 min (30%).

Semipreparative HPLC: gradient G, t_R = 11.65 min; yield: 1.9 mg (19% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 557.37 (100) $[M + Na]^+$, 406.25 (45).

4-[(2-{[(Allyloxy)carbonyl]amino}-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-6-{[(1-phenyl-1*H*-1,2,3-triazol-4-yl)carbonyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (20d)
Analytical HPLC: gradient B, t_R = 20.62 min (58%).

Semipreparative HPLC: gradient G, t_R = 44.4 min; yield: 1.0 mg (8% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 671.51 (100) $[M + Na]^+$, 406.25 (40).

4-[(2-{[(Allyloxy)carbonyl]amino}-2,6-dideoxy-6-[(phenylacetyl)amino]-α-D-galactopyranosyl)sulfanyl]butyramide (19e)
Yield: 13.0 mg (35%, crude product); brown amorphous solid. The desired product could not be detected.

4-[(2-{[(Allyloxy)carbonyl]amino}-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-6-[(phenylacetyl)amino]-α-D-galactopyranosyl)sulfanyl]butyramide (20e)
Analytical HPLC: gradient A, t_R = 25.98 min (35%).

Semipreparative HPLC: gradient E, t_R = 24.93 min; yield: 1.9 mg (5% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 618.17 (100) $[M + Na]^+$, 596.13(<5) [3-TBSO, $M + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-2,6-dideoxy-6-{[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl-glycyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (19f)
Yield: 18.8 mg (~100%, crude product); colorless amorphous solid.

Analytical HPLC: gradient B, t_R = 12.42 min (34%).

Semipreparative HPLC: gradient G, t_R = 19.15 min; yield: 2.9 mg (20% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 802.4 (15) $[M + Na]^+$, 780.42 (100) $[M + H]^+$, 558.47 (10) $[M – Fmoc + H]^+$, 179.07 (50) $[DBF + H]^+$.

4-[(2-{[(Allyloxy)carbonyl]amino}-3-*O*-(*tert*-butyldimethylsilyl)-2,6-dideoxy-6-{[*N*-(9-fluorenylmethoxycarbonyl)-L-histydyl-glycyl]amino}-α-D-galactopyranosyl)sulfanyl]butyramide (20f)
Analytical HPLC: gradient B, t_R = 20.47 min (63%).

Semipreparative HPLC: gradient G, t_R = 46.62 min; yield: 2.2 mg (13% based on polymer-bound carbohydrate); colorless amorphous solid.

ESI-MS: *m*/*z* (%) = 916.59 (5) $[M + H]^+$, 894.67 (100) $[M + H]^+$, 672.59 (<5) [3-TBSO, $M – Fmoc + H]^+$, 543.36 (60), 466.94 (40), 179.07 (10) $[DBF + H]^+$.

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