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Note

Thiol addition to protected allyl glycosides: an improved method for the preparation of spacer-arm glycosides

Paul B. van Seeventer, Johannes A.L.M. van Dorst, John F. Siemerink, Johannis P. Kamerling, Johannes F.G. Vliegenthart *

Bijvoet Center, Department of Bio-Organic Chemistry, Utrecht University, P.O. Box 80.075, NL-3508 TB Utrecht, The Netherlands

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Abstract

A useful method for the preparation of differently functionalized sulfide spacer-arm glycosides is presented. Several protected allyl glycosides were variously elongated via a radical addition reaction with pentanethiol, methyl 3-mercaptopropionate, or 2-mercaptoethanol. The hydroxyl function of protected 3-(2-hydroxyethylthio)propyl glycosides was subsequently transformed into an azide function. © 1997 Elsevier Science Ltd.

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Glycoconjugates exposing their carbohydrate structures on the surface of cells or occurring in soluble form in body fluids are important in many biological recognition processes. The need for synthetic analogues of these glycoconjugates has led to the development of an array of methodologies for the preparation of neoglycoproteins and neoglycolipids, and for the attachment of oligosaccharides to other carriers [1].

Allyl glycosides have been used frequently for the preparation of neoglycoconjugates. Allyl glycosides can be transformed to formylmethyl glycosides by reductive ozonolysis [2], and then be conjugated to amine functions via reductive amination [3]. They can also be copolymerized with acrylamide [4]. A more effective approach is the coupling of cysteamine to allyl glycosides [5], followed by *N*-acryloylation, and copolymerization of the product with acrylamide [6]. Comparison of the formed copolymers showed the latter to be superior in recognition of the oligosaccharides by antibodies [7], presumably by the fact that the presence of a longer spacer-arm resulted in more exposed carbohydrates.

The fact that allyl glycosides are being widely used and the increasing demand for longer spacer-arms for use in neoglycoconjugate synthesis, prompted us to extend and adapt the method as described in ref. [5] to obtain a more flexible and efficient variant thereof. Here, we report on the elongation of protected allyl α- or β-glycosides with pentanethiol, methyl 3-mercaptopropionate, or 2-mercaptoethanol in the presence of azobisisobutyronitrile (AIBN) as a radical initiator. An alternative approach

* Corresponding author.

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Table 1
Data for the protected sulfide spacer-arm glycosides **5–15**

Starting compound	Reacted with thiol	Product	Yield (%)	$[\alpha]_D$ (*c* 1)	Molecular formula	Elemental Analysis (%)			
						Calcd		Found	
						C	H	C	H
1	$HS(CH_2)_4CH_3$	**5**	71	−9°	$C_{22}H_{36}O_{10}S$	53.64	7.37	53.65	7.50
1	$HS(CH_2)_2COOMe$	**8**	95	−8°	$C_{21}H_{32}O_{12}S$	49.60	6.34	49.60	6.41
1	$HS(CH_2)_2OH$	**12**	75	−10°	$C_{19}H_{30}O_{11}S$	48.92	6.48	48.74	6.35
2	$HS(CH_2)_4CH_3$	**6**	98	−105°	$C_{20}H_{34}O_8S$	55.28	7.89	55.23	7.65
2	$HS(CH_2)_2COOMe$	**9**	92	−119°	$C_{19}H_{30}O_{10}S$	50.66	6.71	50.48	6.70
2	$HS(CH_2)_2OH$	**13**	89	−131°	$C_{17}H_{28}O_9S$	49.99	6.91	49.79	6.89
3	$HS(CH_2)_4CH_3$	**7**	88	−19°	$C_{34}H_{52}O_{18}S$	52.30	6.71	52.42	6.68
3	$HS(CH_2)_2COOMe$	**10**	86	−15°	$C_{33}H_{48}O_{20}S$	49.74	6.07	49.81	6.17
3	$HS(CH_2)_2OH$	**14**	76	−18°	$C_{31}H_{39}O_{19}S$	49.80	5.26	49.78	5.25
4	$HS(CH_2)_2COOMe$	**11**	94	+63°	$C_{27}H_{33}NO_{12}S$	54.45	5.58	54.28	5.66
4	$HS(CH_2)_2OH$	**15**	78	+26°	$C_{25}H_{31}NO_{11}S$	54.24	5.64	54.09	5.65

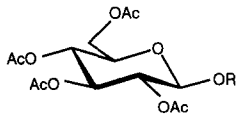
using *O*-acetylated 2-bromoethyl glycosides and thiols yielding sulfide spacer-arm glycosides has been reported earlier [8].

Allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**1**), allyl 2,3,4-tri-*O*-acetyl-α-L-fucopyranoside (**2**), allyl (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (**3**), and allyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**4**) were prepared according to [5]. Compounds **1–4** were reacted with pentanethiol, methyl 3-mercaptopropionate, or 2-mercaptoethanol in the presence of AIBN in 1,4-dioxane at 75 °C, leading to the sulfide spacer-arm glycosides **5–15**. All elongations led in general to high yields (Table 1). The addition of pentanethiol (**5–7**) results in the formation of a highly lipophilic aglycon, of interest in the development of biochemical assays. Furthermore, methyloxycarbonyl- (**8–11**) and hydroxyl-functionalized (**12–15**) aglycons are potential spacers, useful for the preparation of neoglycoconjugates applying known conjugation methodologies [9,10]. The 3-(2-hydroxyethylthio)propyl glycosides (**12–15**) can be of use for the preparation of amino-functionalized spacer-arm glycosides as well. When pyruvate acetal moieties, acetyl groups, or sialic acid and uronic acid residues are present, the widely used conjugation strategy using acyl azides [9] is not applicable. In these cases, amino-functionalized spacer-arm glycosides [11] are desired for the preparation of neoglycoconjugates. The primary hydroxyl function of protected 3-(2-hydroxyethylthio)propyl glycosides can be transformed easily into an azide function. In this way compounds **12–15** were converted via the Mitsunobu reaction [12] using triphenylphosphine, diethylazodicarboxylate, and hydrazoic acid into the 3-(2-azidoethylthio)propyl glycosides **16–19** (Table 2), which in turn can be transformed into the desired amino-functionalized spacer-arm glycosides. Conversion of **12–15** to the corresponding tosylate [13] or chloride [14], followed by substitution with sodium azide, was also investigated, but proved to be less efficient.

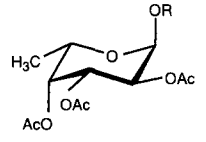
Table 2
Data for the protected 3-(2-azidoethylthio)propyl glycosides **16–19**

Starting compound	Product	Yield (%)	$[\alpha]_D$ (*c* 1)	Molecular formula	Elemental Analysis (%)					
					Calcd			Found		
					C	H	N	C	H	N
12	**16**	71	−9°	$C_{19}H_{29}N_3O_{10}S$	46.43	5.95	8.55	46.35	6.05	8.54
13	**17**	90	−112°	$C_{17}H_{27}N_3O_8S$	47.10	6.28	9.69	47.14	6.32	9.55
14	**18**	74	−20°	$C_{31}H_{45}N_3O_{18}S$		n.d. [a]			n.d. [a]	
15	**19**	64	+21°	$C_{25}H_{30}N_4O_{10}S$	51.90	5.23	9.68	51.94	5.21	9.59

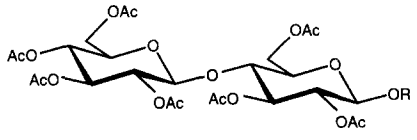
[a] n.d., Not determined.



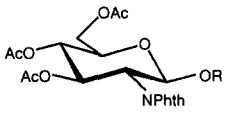
	R
1	$CH_2CH=CH_2$
5	$(CH_2)_3S(CH_2)_4CH_3$
8	$(CH_2)_3S(CH_2)_2COOCH_3$
12	$(CH_2)_3S(CH_2)_2OH$
16	$(CH_2)_3S(CH_2)_2N_3$



	R
2	$CH_2CH=CH_2$
6	$(CH_2)_3S(CH_2)_4CH_3$
9	$(CH_2)_3S(CH_2)_2COOCH_3$
13	$(CH_2)_3S(CH_2)_2OH$
17	$(CH_2)_3S(CH_2)_2N_3$



	R
3	$CH_2CH=CH_2$
7	$(CH_2)_3S(CH_2)_4CH_3$
10	$(CH_2)_3S(CH_2)_2COOCH_3$
14	$(CH_2)_3S(CH_2)_2OH$
18	$(CH_2)_3S(CH_2)_2N_3$



	R
4	$CH_2CH=CH_2$
11	$(CH_2)_3S(CH_2)_2COOCH_3$
15	$(CH_2)_3S(CH_2)_2OH$
19	$(CH_2)_3S(CH_2)_2N_3$

Deprotection, i.e. deacetylation, dephthaloylation, and/or hydrogenolytic reduction of the azide function of compounds **5–19** was carried out efficiently using standard procedures (data not shown), leading to several differently functionalized sulfide spacer-arm glycosides. In conclusion, the results presented here provide a relevant extension of the method of Lee and Lee [5] and have potential for the preparation of neoglycoconjugates.

1. Experimental

General methods.—Reactions were monitored by TLC on Kieselgel 60 F_{254} (E. Merck) by detection with UV light and then charring with aq 50% H_2SO_4. Column chromatography was performed on Kieselgel 60 (E. Merck, 70–230 mesh). Solvents were evaporated under reduced pressure at 40 °C (water bath). Optical rotations were measured for solns in $CHCl_3$ at 20 °C with a Perkin–Elmer 241 polarimeter, using a 10-cm 1-mL cell. The ^1H (300 MHz) NMR spectra were recorded at 27 °C with a Bruker AC 300 spectrometer. Chemical shifts (δ) are given in ppm relative to the signal for internal Me_4Si (δ 0) for solns in $CDCl_3$. Elemental analyses were carried out by H. Kolbe Mikroanalytisches Laboratorium (Mülheim an der Ruhr, Germany).

General procedure for the addition of thiols to allyl glycosides **1–4**; *preparation of* **5–15**.—To a stirred soln of a protected allyl glycoside (0.5 mmol) in 1,4-dioxane (4 mL) was added a thiol (1-mercaptopentane, methyl 3-mercaptopropionate, or 2-mercaptoethanol, 7.5 mmol) and AIBN (15 mg). After stirring for 1–2 h at 75 °C under Ar, TLC (9:1 CH_2Cl_2–acetone) showed a complete conversion of the allyl glycoside into the adduct, and the reaction was quenched with cyclohexene (0.3 mL). After cooling to room temperature the mixture was co-concd with toluene (3 ×). Column chromatography (9:1 CH_2Cl_2–acetone) of the residue yielded the product, isolated as a colorless syrup. For further experimental details, see Tables 1, 3–5.

General procedure for the conversion of the hydroxyl function of the compounds **12–15** *into an azide function via the Mitsunobu reaction; preparation of* **16–19**.—To a stirred soln of a protected 3-(2-hydroxyethylthio)propyl glycoside (0.25 mmol) and triphenylphosphine (0.3 mmol) in dry THF (4 mL) at room temperature under Ar was added dropwise a 1 M hydrazoic acid soln in benzene (0.35 mL) [15], followed by the dropwise addition of diethyl azodicarboxylate (0.3 mmol). After stirring for 2 h at room temperature, TLC (95:5 CH_2Cl_2–acetone) showed the complete conversion of the starting compound into the product, and the mixture was concd. Column chromatography (95:5 CH_2Cl_2–acetone) of the residue afforded the product, isolated as a colorless syrup. For further experimental details, see Tables 2 and 6.

Table 3
^{1}H NMR data [a] for pentanethiol-elongated allyl glycosides **5–7**

Compound	H-1 ($J_{1,2}$) (d, 1 H)	-O(CH$_2$)$_2$CH$_2$SCH$_2$- (2 t, each 2 H)	-CH$_3$ (t, 3 H)	n [b] Ac (n s, each 3 H)
5	4.753 (8.0)	2.549, 2.484	0.900	2.091, 2.052, 2.026, 2.004
6	5.044 (3.7)	2.596, 2.499	0.900	2.162, 2.068, 1.985
7	4.505 (8.1) [c] 4.451 (8.0) [c]	2.529, 2.474	0.897	2.126, 2.085, 2.035, 2.029, 2.014, 2.007, 1.980

[a] Measured in $CDCl_3$; δ in ppm; J in Hz.
[b] **5**, $n = 4$; **6**, $n = 3$; **7**, $n = 7$.
[c] Resonances of H-1 and H-1′ may have to be interchanged.

Table 4
^{1}H NMR data [a] for methyl 3-mercaptopropionate-elongated allyl glycosides **8–11**

Compound	H-1 ($J_{1,2}$) (d, 1 H)	-CH$_2$SCH$_2$CH$_2$COOMe (m, 6 H)	-COOCH$_3$ (s, 3 H)	n [b] Ac (n s, each 3 H)
8	4.493 (7.9)	2.76–2.54	3.689	2.092, 2.051, 2.027, 2.004
9	5.041 (3.6)	2.80–2.59	3.704	2.163, 2.070, 1.985
10	4.511 (8.2) [c] 4.453 (8.0) [c]	2.78–2.54	3.697	2.127, 2.085, 2.036, 2.030, 2.014, 2.008, 1.980
11	5.366 (8.5)	2.56–2.34	3.671	2.118, 2.032, 1.863

[a] Measured in $CDCl_3$; δ in ppm; J in Hz.
[b] **8**, $n = 4$; **9**, $n = 3$; **10**, $n = 7$; **11**, $n = 3$.
[c] Resonances of H-1 and H-1′ may have to be interchanged.

Table 5
^{1}H NMR data [a] for 2-mercaptoethanol-elongated allyl glycosides **12–15**

Compound	H-1 ($J_{1,2}$) (d, 1 H)	-O(CH$_2$)$_2$CH$_2$SCH$_2$-		-CH$_2$OH (t, 2 H)	n [b] Ac (n s, each 3 H)
		(2 t, each 2 H)	(m, 4 H)		
12	4.513 (7.9)	2.703, 2.589		3.720	2.092, 2.055, 2.026, 2.005
13	5.052 (3.7)	2.729, 2.640		3.743	2.165, 2.074, 1.989
14	4.515 (7.8) [c] 4.460 (7.9) [c]	2.697, 2.573		3.713	2.132, 2.087, 2.042, 2.030, 2.017, 2.010, 1.982
15	5.374 (8.5)		2.51–2.35	3.541	2.121, 2.036, 1.866

[a] Measured in $CDCl_3$; δ in ppm; J in Hz.
[b] **12**, $n = 4$; **13**, $n = 3$; **14**, $n = 7$; **15**, $n = 3$.
[c] Resonances of H-1 and H-1′ may have to be interchanged.

Table 6
^{1}H NMR data [a] for 3-(2-azidoethylthio)propyl glycosides **16–19**

Compound	H-1 ($J_{1,2}$) (d, 1 H)	-O(CH$_2$)$_2$CH$_2$SCH$_2$-		-CH$_2$N$_3$ (t, 2 H)	n [b] Ac (n s, each 3 H)
		(2 t, each 2 H)	(m, 4 H)		
16	4.505 (7.9)	2.698, 2.621		3.455	2.090, 2.050, 2.024, 2.004
17	5.047 (3.7)	2.716, 2.673		3.473	2.164, 2.072, 1.987
18	4.510 (8.0) [c] 4.454 (7.9) [c]	2.690, 2.603		3.448	2.130, 2.086, 2.039, 2.030, 2.016, 2.009, 1.981
19	5.369 (8.5)		2.43–2.32	3.261	2.119, 2.042, 1.864

[a] Measured in $CDCl_3$; δ in ppm; J in Hz.
[b] **16**, $n = 4$; **17**, $n = 3$; **18**, $n = 7$; **19**, $n = 3$.
[c] Resonances of H-1 and H-1′ may have to be interchanged.

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