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Systematic study on free radical hydrothiolation of unsaturated monosaccharide derivatives with exo- and endocyclic double bonds†

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Exo- and endocyclic double bonds of glycals and terminal double bonds of enoses were reacted with various thiols by irradiation with UV light in the presence of a cleavable photoinitiator. The photoinduced radical-mediated hydrothiolation reactions showed highly varying overall conversions depending not only on the substitution pattern and electron-density of the double bond but also on the nature and substitution pattern of the thiol partner. Out of the applied thiols thiophenol, producing the highly stabilized thiyl radical, exhibited the lowest reactivity toward each type of alkene. In most cases, the hydrothiolations took place with full regio- and stereoselectivities. Successful addition of 1,2 : 3,4-di-*O*-isopropylidene-6-thio-α-D-galactopyranose to a 2,3-unsaturated *N*-acetylneuraminic acid derivative, providing a (3 → 6)-*S*-linked pseudodisaccharide, demonstrated that the endocyclic double bond of Neu5Ac-2-ene, bearing an electron-withdrawing substituent, shows sufficient reactivity in the photoinduced thiol–ene coupling reaction.

Introduction

Over the last decade, the photoinduced thiol–ene coupling, free-radical addition of a thiol to a nonactivated carbon–carbon double bond, has been recognised as a robust ligation tool possessing many of the attributes of click chemistry.[1,2] The great synthetic potential of the reaction has been amply demonstrated in the areas of polymer chemistry and material sciences for network formation,[3] dendrimer synthesis,[4] and polymer functionalization.[5]

The photoinduced thiol–ene coupling was also applied as a metal-free click process for *S*-glycoconjugation producing glycodendrimers,[6] calix[4]arene-based glycoclusters,[7] *S*-linked protein glycoconjugates[8] as well as thioglucoside-containing micellar structures appropriate for controlled drug delivery.[9] In these approaches thioglycosylation occurred by the addition of 1-thioglycoses across the terminal double bonds of alkenyl tags of dendritic or polymeric scaffolds. Carbohydrates equipped with alkenyl auxiliaries have been used also as the ene reactants in the thio-click strategy to afford alkyl-tethered glycosyl-cysteines[10] or glycopeptides,[11] β-cyclodextrin-based saccharide clusters[12] and sucrose-containing polymers.[13] Thio-linked mimics of α(2 → 3) and α(2 → 6)-linked sialosides were also prepared by photoinduced hydrothiolation of 6-*O*-allyl or 3-*O*-allyl substituted galactose derivatives with the 2-thiosialic acid.[14]

The carbohydrate skeleton itself with an exo- or endocyclic double bond has scarcely been applied as the ene partner, with only three articles published until now.[15–17] Dondoni and co-workers were the first to exploit the thiol–ene reaction for the synthesis of *S*-disaccharides by reacting sugar thiols with exo- and endoglycals.[15,16] They found that hydrothiolation of the exocyclic double bond of hex-5-enopyranoside and pent-4-enofuranoside derivatives with 1-thioglycoses afforded *S*-disaccharides with high yields and diastereoselectivites of up to 99%.[15] Addition of 1-thioglycoses across the endocyclic double bond of glycals showed regioselectivity but a lack of stereoselectivity, furnishing the stereoisomeric 1-deoxy-*S*-disaccharides in about 1 : 1 ratios.[16]

The incorporation of 2-acetoxy-glycals and 2,3-unsaturated glycosides within the thiol–ene coupling strategy was reported for the first time by our group.[17] We have shown that reactions between 2-acetoxy-D-glucal and a range of thiols including

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amino acid, peptide, and sugar thiols gave 1,2-*cis*-α-*S*-glucoconjugates and *S*-disaccharides with full regio- and stereoselectivities in good to excellent yields. Addition of 1-thioglycoses to a 2,3-unsaturated glycoside (Ferrier glycal) was found to proceed also with high selectivity offering easy access to 3-deoxy-*S*-disaccharides.[17]

Regarding the great potential of hydrothiolation of the easily available glycals in the synthesis of thioglycosides, which are especially valuable glycoside mimics, further exploration and exploitation of the reaction can be foreseen. Here we present a systematic study of the reactivity of the acetylated and benzylated derivatives of 2-hydroxy-D-glucal towards a range of thiols in the photoinduced thiol–ene coupling reaction, in comparison to the reactivity of saccharides bearing an exomethylene moiety. Free radical hydrothiolation of the endocyclic double bond of sialic acid glycal is also shown.

Results and discussion

To study the scope of the hydrothiolation reaction of unsaturated monosaccharides, 2-acetoxy-3,4,6-tri-*O*-acetyl-D-glucal **1**[18] was reacted with thiols **2b–h** applying the optimized conditions established in our recent work for the synthesis of **3a**.[17] Thus, the reactions were carried out in toluene at room temperature with a 2 : 1 thiol : ene ratio by irradiation at λ_{max} 365 nm for 3 × 15 min in the presence of 2,2-dimethoxy-2-phenylacetophenone (DPAP) (3 × 0.1 equiv.) as the cleavable photoinitiator[1a] (Table 1). In the case of ethanethiol and 2-methylpropane-2-thiol, a higher thiol–ene ratio was applied because of the volatility of the reagents. When the reaction showed low conversion after 45 min, further portions of thiol and initiator were added and the irradiation was continued (Scheme 1).[19]

Unexpectedly, thiophenol did not react with compound **1**. Our attempts to elicit a reaction between **1** and **2b** by applying high excess of thiol, increasing the amount of DPAP, and prolongation of the irradiation time were unsuccessful.

Aromatic thiols are better chain transfer reagents in free-radical additions than aliphatic thiols, since in the former case the energy required to break the S–H bond is lowered by the resonance stabilization of the thiyl radical formed.[20] This fact seems to be in contradiction to the observed reactivities of ethanethiol and thiophenol towards compound **1**. We assume that the resolution of this contradiction lies in the reversibility of the reaction. The reactivity of the olefin partner in a thiol–ene free-radical chain reaction is dependent on the extent of substitution. Terminal alkenes are found to be the most reactive, while internal 1,2-disubstituted alkenes exhibit much lower overall reaction rates. The reduced rates and conversions observed for 1,2-disubstituted enes are a result of the reversibility of the addition of the thiyl radical across the internal double bond.[1,20] In this case the reversible equilibrium in the addition step depicted in Scheme 2 is shifted backward by the high stability of the aromatic thiyl radical causing a complete lack of reaction between **1** and thiophenol.

Hydrothiolation of 2-acetoxy glycal **1** with thiols **2c–2h** took place with full regio- and stereoselectivities affording the corresponding α-D-1-thioglycosides, but with various conversions. Phenylmethanethiol **2c** showed low reactivity toward **1** affording the hydrothiolation product **3c** with 22% yield. Similarly, addition of (4-methoxyphenyl)methanethiol **2d** across the double bond of compound **1** proceeded with low conversion furnishing **3d** only with 10%. The possible explanation for the low conversions observed could be the stability of the thiyl radicals generated from **2c** and **2d**, which favours rather the backward than the forward reaction in the reversible thiyl addition step.[21]

Reaction of 2-methylpropane-2-thiol with glycal **1** gave the α-thioglucoside **3e** with 25% isolated yield. The low conversion might be the result of either the stability of the thiyl radical or a steric congestion between the 2-acetoxy moiety and the bulky *tert*-butyl group, both anchored to the α-side of the sugar ring in the intermediate C-2 radical.

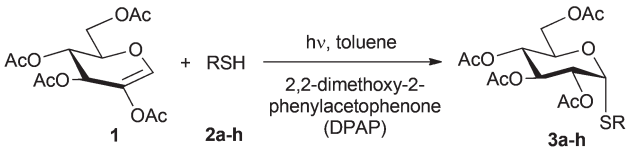
The significantly different conversion in the reaction of **1** with 2,3-di-*O*-acetyl-1-thioglycerol **2f**[22] compared to that with acetonide-protected 1-thioglycerol **2g**[23] highlights that the conversion of the reactants in the radical-mediated hydrothiolation reaction can be tuned by the substitution pattern of the thiol. While thiol **2f** possessing electron withdrawing substituents afforded **3f** in 67% yield, the acetal-protecting group of **2g** proved to be disadvantageous during addition across the endocyclic double bond of **1** furnishing product **3g** with a yield of only 31%.

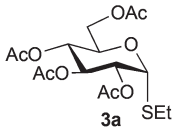
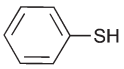
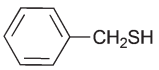
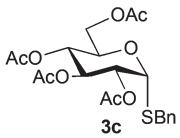
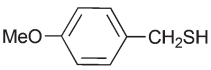
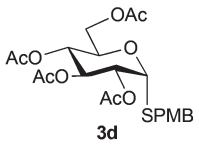
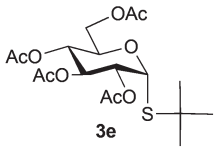
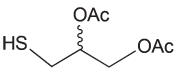
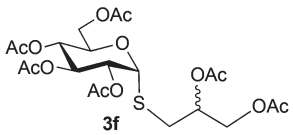
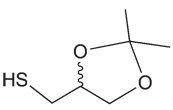
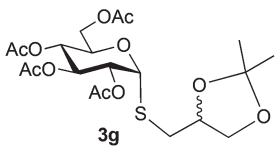
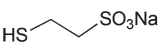
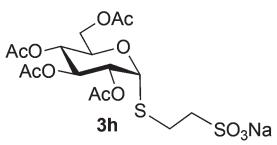
Recently, Dondoni and co-workers have reported that photoinduced hydrothiolation of the terminal double bond of a galactose derived alkene with peracetylated 1-thioglucose afforded the corresponding *S*-disaccharide in 81% isolated yield; however, an attempted reaction of 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranose with the same alkene failed, and only decomposition occurred.[15] These results support our finding that in the thiol–ene coupling the reactivity of a given thiol is strongly influenced by the substituents.

Finally, the sodium sulfonatoethyl mercaptan **2h** (Mesna), used as a detoxifying adjuvant in cancer chemotherapy, was reacted with **1**. We were pleased to find that compound **2h** added readily across the endocyclic double bond of **1** in MeOH and gave **3h** in good yield. To the best of our knowledge, this is the first example of using a salt as the thiol partner in the photoinduced hydrothiolation reaction.

In our earlier experiments, depending on the solubility of the reactants, toluene, toluene–MeOH or MeOH have been used as the solvents for the thiol–ene couplings. Toluene has proven to be a good solvent for the apolar thiols; however, low efficiency of the reaction has been observed in toluene–MeOH or MeOH with some polar thiols. In those cases, significantly enhanced yields could be reached by changing the toluene–MeOH systems to DMF–water.[17] Here, we decided to study how the solvent affects the reaction when low conversion was observed in toluene. Thus, the reaction of 2-acetoxy glycal **1** and thiol **2c** was carried out in different solvents with a thiol–ene ratio of 2 : 1, irradiating at λ_{max} 365 nm for 3 × 15 min

Table 1 Free radical addition of thiols to 2-acetoxy glycal **1**

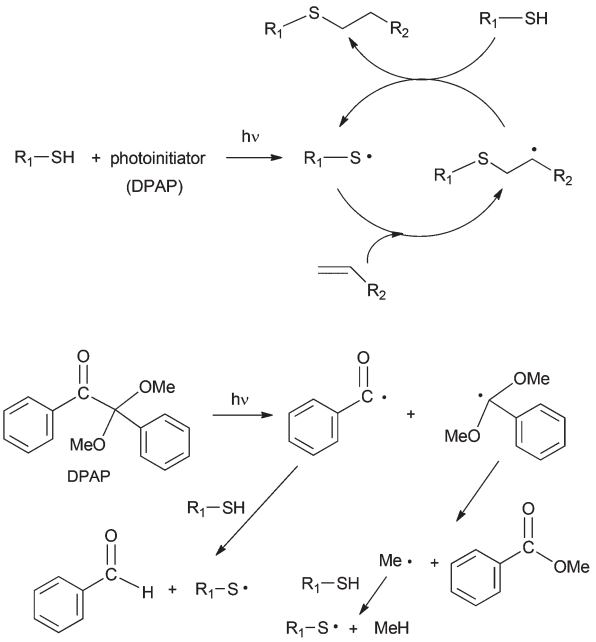


Thiol	Thiol : ene ratio	Product	Yield[a] (%)
HSEt **2a**	15 : 1	 **3a**	81
 **2b**	50 : 1	no reaction[b]	
 **2c**	4 : 1	 **3c**	22[c]
 **2d**	4 : 1	 **3d**	10[c]
 **2e**	15 : 1	 **3e**	25[c]
 **2f**	2 : 1	 **3f**	67
 **2g**	2 : 1	 **3g**	31[c]
 **2h**	2 : 1	 **3h**	64[d]

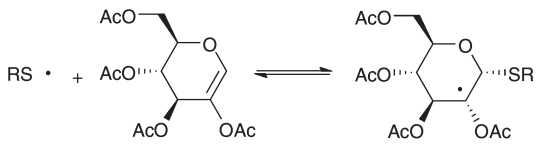
[a] Yield of isolated compounds after 3 × 15 min irradiation under Ar, using 3 × 0.1 equiv. of DPAP. [b] 6 × 15 min irradiation, 6 × 0.1 equiv. of DPAP. [c] 4 × 15 min irradiation, unreacted **1** was recovered with 55–60%. [d] The reaction was carried out in abs. MeOH.

(Table 2). Unfortunately, the conversion of glycal **1** remained below 25% in all runs, as established by ^{1}H NMR analysis. The same yields were obtained for product **3c** in toluene, methanol and dichloromethane, while switching to DMF, some drop in conversion was observed. Interestingly, a 1 : 1 mixture of DMF and water was a better solvent than pure DMF, but was not superior to toluene, methanol or dichloromethane. We also attempted to elicit a reaction between glycal **1** and thiophenol by changing the solvent to methanol, dichloromethane or DMF–water, but without any success.

Next, we decided to study the photoinduced hydrothiolation reactions of the benzylated 2-hydroxyglycal **4**.[24] It is known that the overall reaction rate of the thiol–ene reaction is directly related to the electron density on the ene: for a given



Scheme 1 Sequential thiyl-addition and hydrogen abstraction steps during a thiol–ene coupling, and the mechanism for the initiation with the cleavable photoinitiator 2,2-dimethoxy-2-phenylacetophenone (DPAP).



Scheme 2 Reversible addition of the thiyl radical to the endocyclic double bond of **1**.

Table 2 Reaction of 2-acetoxy glycal **1** with thiol **2c** in different solvents

Entry	**1** : **2c**[a] ratio	DPAP (%)	Solvent	Conv.[b] (%)	**3c**[c] (%)
1	1 : 2	3 × 10	Toluene	22	19
2	1 : 2	3 × 10	MeOH	24	19
3	1 : 2	3 × 10	CH_2Cl_2	23	19
4	1 : 2	3 × 10	DMF	16	14
5	1 : 2	3 × 10	DMF–H_2O (1 : 1)	23	18

[a] Reactions were performed with 0.1 mmol of **1** in 2 mL of solvent. [b] Reacted glycal determined using ^{1}H NMR analysis of the crude mixture. [c] Isolated yield.

thiol, electron-rich enes react much more rapidly than electron-poor ones.[1,20] Compound **4**, possessing a more electron-rich double bond than that of **1**, was expected to show higher conversions with the thiols which exhibited low reactivity towards compound **1**. Hydrothiolation of **4** with ethanethiol went to completion rapidly and with full selectivity to give the expected α-thioglucoside **5a** in 71% yield (Table 3). The slight decrease of the yield compared to that of **3a** was a result of the lability of the benzyl-type protecting groups under radical mediated hydrothiolation reaction.[25–27]

To our delight, when glycal **4** was reacted with thiophenol, a fair conversion of **4** was observed after 45 min irradiation affording the α-glucoside **5b** in a yield of 21%. Applying higher excess of thiol or longer exposure to UV light did not give rise to a noticeable increase of the conversion. Despite the moderate yield, this reaction clearly demonstrates that the highly stable thiophenyl radical can be trapped by an internal double bond of sufficient electron-density and the equilibrium of the thiyl addition can be forced toward the irreversible hydrogen abstraction step to give the final addition product.

Reaction of 2-methylpropane-2-thiol with **4** gave α-thioglucoside **5e** with 40% isolated yield. The good conversion of **4** with **2e** revealed that rather the stability of the thiyl radical than steric hindrance had caused the low reactivity of **2e** towards the acetoxy-glycal **1**. Previously, we have found that reaction between **1** and 1-thioglycerol **2i** showed very low conversion of the glycal when either toluene–MeOH or MeOH was used as the solvent, furnishing the corresponding α-thioglucoside in only 15–17% yield.[17] As we expected, thiol **2i** reacted more readily with the more electron-rich double bond of **4** providing product **5i** in 46% yield.

Finally, *S*-disaccharide **5j** was prepared by the reaction between **4** and the sterically hindered di-*O*-isopropylidenated sugar thiol **2j**.[28] Despite complete conversion of the glycal observed, the isolated yield of **5j** was only 59% because decomposition also occurred due to lability of the benzyl-protecting groups under the conditions of the radical addition.[29]

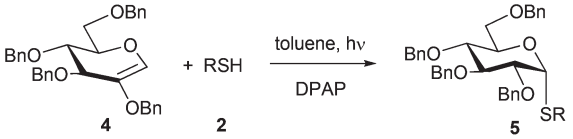
Thereafter, we studied the photoinduced hydrothiolation reactions of glycal **6** with ethanethiol and thiophenol under the optimized conditions (Scheme 3). In this case, addition of thiophenol across the endocyclic double bond of **6** failed, revealing again the lack of reactivity of the resonance stabilized aromatic thiyl radical towards a relatively electron-poor internal double bond. Reaction between glycal **6** and ethanethiol showed almost complete conversion after 45 min affording a mixture of the axially and equatorially linked 2-ethylthio derivatives **7** and **8** and thioglycoside **9** in a ratio of ~5 : 3 : 1.[30,31]

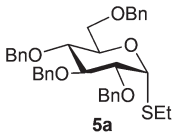
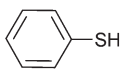
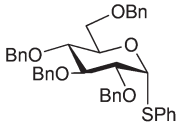
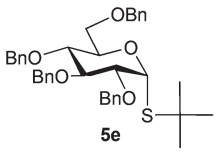
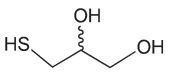
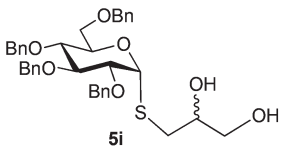
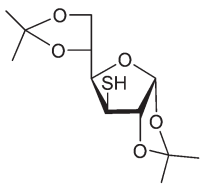
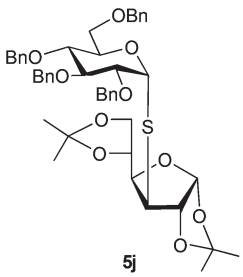
Because of the poor selectivity, which was also reported by Dondoni and co-workers,[16,32] and the difficulty of separation of the diastereoisomers formed, hydrothiolation of glycal **6** was not examined further.

Reactivity of thiophenol towards terminal double bonds of monosaccharides was studied next by applying compounds **10**,[33] **12**[34] and **14**[35] as the ene partners (Table 4). The reactions were carried out in toluene with a 2 : 1 thiol : ene ratio. Hydrothiolation of the galactose derived alkene **10** afforded the addition product **11** in 46% yield. Reaction of 3-exomethylene-glucofuranose derivative **12** with thiophenol showed a slightly lower efficiency but full selectivity furnishing compound **13** as a single diastereoisomer in 32% yield.

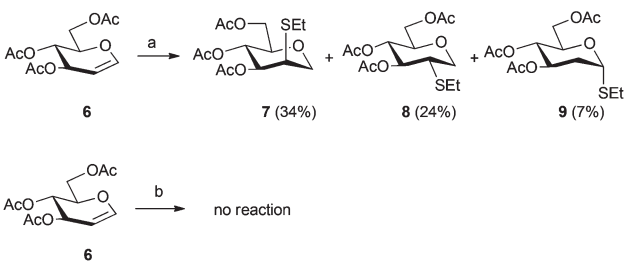
We were pleased to find that in the reaction of exoglycal **14** with thiophenol almost complete conversion of the glycal occurred after 45 min providing the *C*-glycosyl derivative **15** stereoselectively, in high yield. The exclusive formation of the β-glycoside **15** can be explained by the preferred axial attack on

Table 3 Free radical addition of thiols to 2-benzyloxy glycal **4**



Thiol	Thiol : ene ratio	Product	Yield[a] (%)
HSEt **2a**	15 : 1	 **5a**	71
 **2b**	2 : 1	 **5b**	21
 **2e**	15 : 1	 **5e**	40
 **2i**	2 : 1	 **5i**	46[b]
 **2j**	2 : 1	 **5j**	59

[a] Yield of isolated compounds after 3 × 15 min irradiation under Ar, using 3 × 0.1 equiv. of DPAP. [b] The reaction was carried out in abs. MeOH.

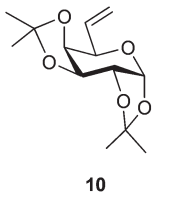
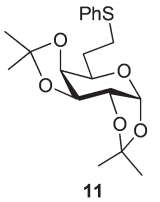
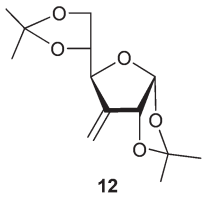
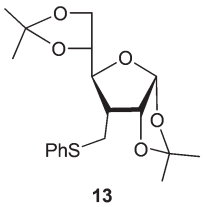
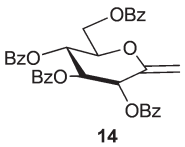
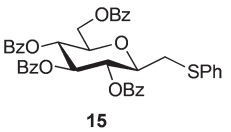
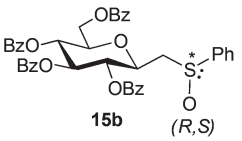
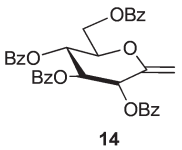
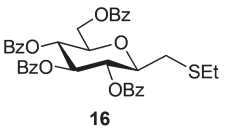


Scheme 3 Reagents and conditions: (a) 15 equiv. of EtSH, toluene, 3 × 15 min irradiation, 3 × 0.1 equiv. of DPAP; (b) 50 equiv. of PhSH toluene, 6 × 15 min irradiation, 6 × 0.1 equiv. of DPAP.

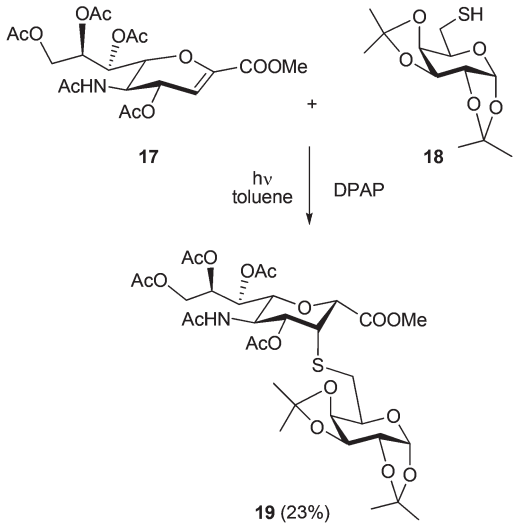
the D-glucopyranosyl radical.[36] Then, the reactivity of **14** toward ethanethiol was also tested. A fast and complete reaction was observed to afford the β-configured **16** in 93% yield. It is important to note that sulfides **15** and **16** had a great propensity for suffering oxidation upon standing in air, especially in the presence of ethyl acetate. When the crude **15** was chromatographed with an ethyl acetate-containing eluent, besides the hydrothiolation product **15**, a significant amount of the sulfoxide derivative **15b** (8%) was also isolated. Therefore, ethyl acetate was avoided during work-up and purification of **15** and **16**.

Finally, we tested the applicability of the 2,3-unsaturated *N*-acetylneuraminic acid (Neu5Ac-2-ene) derivative **17**,[37] an intermediate in the synthesis of the influenza neuraminidase inhibitor Relenza, to the thiol–ene coupling reaction. We envisioned the synthesis of an *S*-linked mimetic of the natural α(2 → 6)-linked sialyl-galactoside structure by hydrothiolation of **17** with 1,2: 3,4-di-*O*-isopropylidene-6-thio-α-D-galactopyranose **18**.[38] Previously, thiol **18** was applied successfully to hydrothiolation of the 2-acetoxy-glycal **1** to afford the corresponding *S*-disaccharide in 69% yield.[17] In the present case,

Table 4 Hydrothiolations of terminal double bonds in monosaccharide derivatives

Alkene	Thiol	Product	Yield[a] (%)
 **10**	PhSH	 **11**	46
 **12**	PhSH	 **13**	32
 **14**	PhSH	 **15**	74[b] 61[c]
		 **15b** (R,S)	8[c]
 **14**	EtSH	 **16**	93[d]

[a] Yield of isolated compounds after 3 × 15 min irradiation under Ar, using 3 × 0.1 equiv. of DPAP and 2 equiv. of thiol. [b] Purified using column chromatography in 98 : 2 CH_2Cl_2–acetone. [c] Column chromatography of the reaction mixture of **15** in 75 : 25 *n*-hexane–EtOAc. [d] 15 min irradiation, 0.1 equiv. of DPAP, 5 equiv. of EtSH.



Scheme 4 Reagents and conditions: 2 equiv. of **18**, 5 × 15 min irradiation, 5 × 0.1 equiv. of DPAP, 23% for **19**; unreacted **17** was recovered in 35% yield.

reaction of **17** and the galactose-6-thiol derivative **18** led to ~50–60% consumption of the glycal, estimated by tlc,[39] and resulted in a mixture of stereoisomers from which only the main product **19** could be isolated in 23% yield (Scheme 4). The low conversion could be a result of the lower electron-density of the double bond in Neu5Ac-2-ene possessing the electron-withdrawing carboxyl moiety. The equatorial orientation of the C-1 group and the axial orientation of the *S*-linkage were evidenced by crosspeaks between H-3 and both H-2 and H-4 hydrogens of the sialyl residue appeared in the ROESY spectrum of **19**.

The formation of the pseudodisaccharide **19** as the main product can be explained by the preferred attack on the less substituted carbon at the less hindered side in the thiyl radical addition step and the preferred axial attack on the C-2 radical in the hydrogen abstraction step. Despite the moderate yield, the approach allowing a simple one-step transformation of the easily available **17** into 2-*S*-linked sialomimetics, stable analogues of the biorelevant *N*-acetylneuraminic acid glycosides,[40] is worthy of further investigation.

Conclusions

Photoinduced radical-mediated hydrothiolation of acetyl or benzyl-protected endoglycals and monosaccharides bearing an exocyclic double bond at C1-, C3- or C6-position with a range of thiols was studied. In most cases, the thiol–ene coupling reactions took place with full regio- and stereoselectivities; however, the conversions highly varied. We assume that the overall conversion of a given ene substantially depends on the stability of the thiyl radical, most probably due to the reversible nature of the radical addition step. The highly resonance stabilized thiophenyl radical proved to be especially useful for testing the reactivity of the different enes in the thiol–ene coupling reactions. An attempted reaction between thiophenol and either 2-acetoxy-3,4,6-tri-*O*-acetyl-D-glucal **1** or 3,4,6-tri-*O*-acetyl-D-glucal **6** failed even by applying 50 equivalents of the thiol. This hydrothiolation agent displayed moderate reactivity towards both the electron-rich internal double bond of the benzylated 2-hydroxy-glycal **4**, and the electron-poor terminal double bonds of exoglycals **10** and **12** furnishing the final products in 21–46% yields. The reaction of thiophenol and exoglycal **14** afforded the corresponding β-*C*-glycoside in 74% yield. In this case the highly reactive electron-rich terminal double bond of **14** captured the thiyl radical and, therefore, forced the equilibrium of the thiyl radical addition step towards the hydrogen abstraction step affording the product in high yield.

Successful hydrothiolation of a 2,3-unsaturated *N*-acetylneuraminic acid derivative revealed that the endocyclic double bond of Neu5Ac-2-ene, bearing an electron-withdrawing substituent, exhibits sufficient reactivity in thiol–ene coupling reaction.

Experimental section

General information

Ethanethiol, 2-methylpropane-2-thiol, thiophenol, phenylmethanethiol, (4-methoxyphenyl)methanethiol, sodium 2-mercaptoethanesulfonate and 1-thioglycerol were purchased from Sigma Aldrich Chemical Co. Optical rotations were measured at room temperature with a Perkin-Elmer 241 automatic polarimeter. TLC was performed on Kieselgel 60 F254 (Merck) with detection by immersing into 5% ethanolic sulfuric acid solution followed by heating. Column chromatography was performed on Silica Gel 60 (Merck 0.063–0.200 mm). Organic solutions were dried over $MgSO_4$, and concentrated under vacuum. The ^1H (360, 400 and 500 MHz) and ^{13}C NMR (90.54, 100.28 and 125.76 MHz) spectra were recorded with Bruker DRX-360, Bruker DRX-400 and Bruker Avance II 500 spectrometers. Chemical shifts are referenced to Me_4Si or DSS (0.00 ppm for ^1H) and to the residual solvent signals ($CDCl_3$: 77.00 ppm, CD_3OD: 49.15 ppm, DMSO-d_6: 39.52 ppm for ^{13}C). The coupling constant values (J) are given in Hz. Elemental analyses (C, H, S, N) were performed using an Elementar Vario MicroCube instrument. The photocatalytic reactions were carried out at room temperature by irradiation with a Hg-lamp with a borosilicate vessel giving maximum emission at 365 nm.

General method A for the photoinduced addition of ethanethiol and 2-methylpropane-2-thiol to glycals (1, 4, 6 and 14)

To a solution of the starting glycal (1.00 mmol) in dry toluene (7 mL), ethanethiol or 2-methylpropane-2-thiol (5.00 mmol) and 2,2-dimethoxy-2-phenylacetophenone (DPAP, 25 mg, 0.10 mmol) were added. The solution was deoxygenated by argon bubbling and irradiated at room temperature for 15 min. Addition of DPAP and the thiol, deoxygenation and irradiation were repeated twice more (except for the reaction of **14** and ethanethiol which showed complete conversion of the glycal after 15 min). Then the solution was concentrated and the residue was purified using column chromatography.

General method B for the photoinduced addition of thiols to endo- and exocyclic double bonds of monosaccharide derivatives

To a solution of the starting unsaturated monosaccharide (1.00 mmol) in dry toluene[a] (7 mL), thiol (2.0–4.0 equiv.) and 2,2-dimethoxy-2-phenylacetophenone (DPAP, 25 mg, 0.10 mmol) were added. The solution was deoxygenated and irradiated at room temperature for 15 min. Addition of DPAP and irradiation were repeated twice more. Then the solution was concentrated[b] and the residue was purified using column chromatography.

[a]It is indicated when some other solvent was used.

[b]When thiophenol was used as the reagent, the solution was diluted with CH_2Cl_2, washed with 1 M aq. NaOH, dried over $MgSO_4$, concentrated and purified.

Photoinduced addition of thiol 2c to 2-acetoxy glycal 1 in different solvents

To a solution of compound **1** (33.0 mg, 0.10 mmol) in the given solvent[c] (2 mL), thiol **2c** (24 μL, 0.20 mmol) and 2,2-dimethoxy-2-phenylacetophenone (DPAP, 2.5 mg, 0.01 mmol) were added. The solution was deoxygenated and irradiated at room temperature for 15 min. Addition of DPAP and irradiation were repeated twice more. Then the solution was concentrated,[d] and the residue was purified using column chromatography.[e]

[c]Toluene, MeOH, CH_2Cl_2, DMF and DMF–H_2O, 1 : 1, were applied as the solvents.

[d]When DMF–H_2O, 1 : 1, was used as the solvent, the residue coevaporated twice with toluene.

[e]Before purification, the ^1H NMR spectrum of the crude product was recorded.

Phenylmethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (3c)

Compound **1** (330 mg, 1.00 mmol) and phenylmethanethiol (**2c** 2 × 235 μL, 4.00 mmol) were reacted according to general method **B** using 4 irradiation cycles. The crude product was purified using column chromatography (97 : 3 CH_2Cl_2–acetone) to give **3c** (106 mg, 22%) as a syrup. $[\alpha]_D^{22}$ +211.5 (c 0.68 in MeOH), (lit.[41] $[\alpha]_D$ +190); R_f 0.30 (97 : 3 CH_2Cl_2–acetone). Elemental analysis: found: C, 54.6; H, 5.7; S, 7.0. Calc. for $C_2H_{26}O_9S$: C, 54.5; H, 5.8; S, 7.1%; ^1H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 2.01, 2.02, 2.03, 2.10 (12 H, 4 × s, 4 × COCH_3), 3.72 (2 H, ABq, J 13.5, SCH_2), 3.87 (1 H, dd, $J_{5,6A}$ 1.8, $J_{6A,B}$ 12.3, 6-H_A), 4.24 (1 H, dd, $J_{5,6B}$ 4.6, $J_{6A,B}$ 12.3, 6-H_B), 4.36–4.38 (1 H, m, 5-H), 5.00–5.07 (2 H, m, 2-H, 4-H), 5.37 (1 H, t, J 9.7, 3-H), 5.53 (1 H, d, $J_{1,2}$ 5.8, 1-H), 7.19–7.35 (5 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 20.5, 20.5, 20.5, 20.6 (4 × COCH_3), 33.9 (SCH_2), 61.6 (C-6), 67.6, 68.4, 70.3, 70.5 (C-2, C-3, C-4, C-5), 81.0 (C-1), 127.2, 128.5, 128.7, 137.1 (6 C, arom.), 169.5, 169.5, 169.8, 170.4 (4 × CO).

Unreacted **1** was recovered from the reaction mixture (182 mg, 55%).

(4-Methoxyphenyl)methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (3d)

Compound **1** (330 mg, 1.00 mmol) and (4-methoxyphenyl)-methanethiol (2 × 280 μL, 4.0 mmol) were reacted according to general method **B** using 4 irradiation cycles. The crude product was purified using column chromatography (99 : 1 CH_2Cl_2–acetone) to give **3d** (49 mg, 10%) as a syrup. $[\alpha]_D^{22}$ +197.1 (c 0.51 in $CHCl_3$); R_f 0.33 (99 : 1 CH_2Cl_2–acetone). Elemental analysis: found: C, 53.9; H, 5.8; S, 6.65. Calc. for $C_{22}H_{28}O_{10}S$: C, 54.5; H, 5.8; S, 6.6%; ^1H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 2.00, 2.01, 2.03, 2.10 (12 H, 4 × s, 4 × COCH_3), 3.67 (2 H, ABq, J 13.4, SCH_2), 3.80 (3 H, s, OCH_3), 3.96 (1 H, dd, $J_{5,6A}$ 2.0, $J_{6A,B}$ 12.3, 6-H_A), 4.24 (1 H, dd, $J_{5,6B}$ 4.6, $J_{6A,B}$ 12.3, 6-H_B), 4.38–4.41 (1 H, m, 5-H), 4.99–5.06 (2 H, m, 2-H, 4-H), 5.37 (1 H, t, J 9.8, 3-H), 5.51 (1 H, d, $J_{1,2}$ 5.8, 1-H), 6.83 (2 H, d, J 8.6, arom.), 7.21(2 H, d, J 8.6, arom.); ^{13}C NMR

(90 MHz, $CDCl_3$): δ (ppm) 20.6, 20.6, 20.6, 20.7 (4 × CO*C*H_3), 33.3 (S*C*H_2), 55.3 (O*C*H_3), 61.9 (C-6), 67.7, 68.6, 70.4, 70.7 (C-2, C-3, C-4, C-5), 81.0 (C-1), 114.0, 129.0, 130.0, 158.9 (6 C, arom.), 169.6, 169.6, 169.9, 170.6 (4 × *C*O).

Unreacted **1** was recovered from the reaction mixture (197 mg, 60%).

2-Methylpropane-2-yl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (3e)

Compound **1** (165 mg, 0.500 mmol) and thiol (**2e**, 3 × 281 μL, 7.50 mmol) were reacted in toluene (5 mL) according to general method **A** using 4 irradiation cycles. The crude product was purified using silica gel chromatography in 7 : 3 *n*-hexane–EtOAc to give **3e** (52 mg, 25%) as white needles. Mp 73–74 °C (from *n*-hexane–EtOAc) (lit.[42] mp 63–65 °C); $[\alpha]_D^{22}$ +154.4 (*c* 0.30 in $CHCl_3$), (lit.[42] $[\alpha]_D$ +185); R_f 0.60 (6 : 4 *n*-hexane–EtOAc). Elemental analysis: found: C, 51.6; H, 6.6; S, 7.7. Calc. for $C_{18}H_{28}O_9S$: C, 51.4; H, 6.7; S, 7.6%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.35 (9 H, s, 3 × SCC*H*$_3$), 2.02, 2.03, 2.06, 2.07 (12 H, 4 × s, 4 × COC*H*$_3$), 4.05 (1 H, dd, *J* 2.0, *J* 12.3), 4.30 (1 H, dd, *J* 4.7, *J* 12.3), 4.46–4.51 (1 H, m), 4.95 (1 H, dd, *J* 5.9, *J* 10.5), 5.03 (1 H, t, *J* 9.7), 5.28 (1 H, t, *J* 9.9), 5.86 (1 H, d, $J_{1,2}$ 5.9, 1-H); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 20.6, 20.6, 20.6, 20.8 (4 × CO*C*H$_3$), 31.3 (3 × SC*C*H$_3$), 44.4 (Cq), 61.9 (C-6), 67.6, 68.6, 70.5, 70.8 (C-2, C-3, C-4, C-5), 80.1 (C-1), 169.6, 169.8, 169.9, 170.6 (4 × *C*O).

Unreacted **1** was recovered from the reaction mixture (97 mg, 59%).

[(2*R*,*S*)-2,3-Di-*O*-acetoxy]propyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (3f)

Compound **1** (330 mg, 1.00 mmol) and thiol (**2f**, 384 mg, 2.00 mmol) were reacted in toluene (7 mL) according to general method **B**. The crude product was purified using silica gel chromatography in 6 : 4 *n*-hexane–EtOAc to give **3f** (351 mg, 67%) as a colourless syrup; $[\alpha]_D^{22}$ +132.5 (*c* 0.82 in $CHCl_3$); R_f 0.32 (6 : 4 *n*-hexane–EtOAc). Elemental analysis: found: C, 48.3; H, 5.85; S, 6.1. Calc. for $C_{21}H_{30}O_{13}S$: C, 48.3; H, 5.8; S, 6.1%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 2.02, 2.04, 2.07, 2.09 (18 H, 4 × br s, 6 × C*H*$_3$), 2.71–2.77 (1 H, m), 2.85–2.92 (1 H, m), 4.07–4.14 (2 H, m), 4.28–4.40 (3 H, m), 4.99–5.08 (2 H, m), 5.13–5.22 (1 H, m), 5.28–5.35 (1 H, m), 5.70, 5.75 (1 H, 2 × d, *J* 5.6, *J* 5.6); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 20.1, 20.3, 20.3 (6 × *C*H$_3$), 29.6, 29.8 (S*C*H$_2$), 61.3, 61.4 (O*C*H$_2$), 63.1, 63.3 (C-6), 67.4, 67.6, 67.8, 67.9, 69.4, 69.7, 69.9, 70.1, 70.6 (C-2, C-3, C-4, C-5, C-2$_{propyl}$), 81.8, 82.4 (C-1), 169.0, 169.1, 169.3, 169.4, 169.6, 169.9 (6 × *C*O).

[(4*R*,*S*)-2,2-Dimethyl-1,3-dioxolane-4-yl]methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (3g)

Compound **1** (165 mg, 0.500 mmol) and thiol (**2g**, 148 mg, 1.00 mmol) were reacted in toluene (5 mL) according to general method **B**. The crude product was purified using silica gel chromatography in 97 : 3 CH_2Cl_2–acetone to give **3g** (74 mg, 31%) as a colourless syrup; $[\alpha]_D^{22}$ +141.6 (*c* 0.43 in $CHCl_3$); R_f 0.42 (95 : 5 CH_2Cl_2–acetone). Elemental analysis: found: C, 50.1; H, 6.35; S, 6.5. Calc. for $C_{20}H_{30}O_{11}S$: C, 50.2; H, 6.3; S, 6.7%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.35, 1.42, 1.43 (6 H, 3 × s, 2 × CqC*H*$_3$), 2.02, 2.04, 2.04, 2.07, 2.10 (12 H, 5 × br s, 4 × COC*H*$_3$), 2.57–2.85 (2 H, m), 3.65–3.75 (1 H, m), 4.06–4.10 (2 H, m), 4.22–4.33 (2 H, m), 4.38–4.46 (1 H, m), 5.01–5.08 (2 H, m), 5.34–5.40 (1 H, m), 5.70, 5.75 (1 H, 2 × d, *J* 5.7, *J* 5.8); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 20.5, 20.6, 20.6 (4 × CO*C*H$_3$), 25.4, 25.5, 26.7, 26.8 (2 × Cq*C*H$_3$), 32.8, 32.9 (S*C*H$_2$), 61.8, 61.9 (O*C*H$_2$), 67.7, 67.7, 68.4, 68.5, 70.2, 70.5, 74.8, 75.2 (C-2, C-3, C-4, C-5, C-4$_{dioxolane}$), 68.7 (C-6), 81.9, 82.7 (C-1), 109.6, 109.7 (Cq), 169.5, 169.7, 169.8, 170.5 (4 × *C*O).

Unreacted **1** was recovered from the reaction mixture (93 mg, 57%).

Sodium sulfonatoethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (3h)

Compound **1** (165 mg, 0.500 mmol) and thiol (**2h**, 164 mg, 1.00 mmol) were reacted in MeOH (5 mL) according to general method **B**. The crude product was purified using silica gel chromatography in 75 : 25 CH_2Cl_2–MeOH to give **3h** (158 mg, 64%) as a colourless syrup; $[\alpha]_D^{22}$ +126.1 (*c* 0.28 in MeOH); R_f 0.31 (8 : 2 CH_2Cl_2–MeOH). Elemental analysis: found: C, 38.7; H, 5.0; S, 13.4. Calc. for $C_{16}H_{23}NaO_{12}S_2$: C, 38.9; H, 4.7; S, 13.0%; ^{1}H NMR (360 MHz, $CDOD_3$, Me_4Si): δ (ppm) 2.00, 2.03, 2.04, 2.09 (12 H, 4 × s, 4 × C*H*$_3$), 2.90–3.16 (4 H, m, SC*H*$_2$, C*H*$_2$S), 4.12 (1 H, dd, *J* 1.6, *J* 12.2), 4.27 (1 H, dd, *J* 5.9, *J* 12.2), 4.43–4.47 (1 H, m), 4.99–5.07 (2 H, m), 5.30 (1 H, t, *J* 9.8), 5.75 (1 H, d, *J* 5.6, 1-H); ^{13}C NMR (90 MHz, $CDOD_3$): δ (ppm) 20.6, 20.6, 20.6, 20.8 (4 × *C*H$_3$), 26.4 (*C*H$_2$S), 52.9 (NaO$_3$S*C*H$_2$), 63.5 (C-6), 69.2, 70.0, 71.6, 71.9 (C-2, C-3, C-4, C-5), 83.7 (C-1), 171.3, 171.3, 171.5, 172.6 (4 × *C*O).

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (5a)

Compound **4** (261 mg, 0.500 mmol) and thiol (**2a**, 3 × 185 μL, 7.50 mmol) were reacted in toluene (5 mL) according to general method **A**. The crude product was purified using silica gel chromatography in 85 : 15 *n*-hexane–EtOAc to give **5a** (207 mg, 71%) as white crystals. Mp 86–87 °C (from EtOH), (lit.[43] mp 88–90 °C); $[\alpha]_D^{22}$ +96.1 (*c* 0.56 in $CHCl_3$); (lit.[43] $[\alpha]_D$ +108); R_f 0.60 (8 : 2 *n*-hexane–EtOAc). Elemental analysis: (found: C, 73.9; H, 6.8; S, 5.6. Calc. for $C_{36}H_{40}O_5S$: C, 73.9; H, 6.9; S, 5.5%); ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.27 (3 H, t, *J* 7.4, C*H*$_3$), 2.45–2.63 (2 H, m, C*H*$_2$), 3.61–3.67 (2 H, m), 3.76 (1 H, dd, *J* 3.5, *J* 10.7), 3.81–3.89 (2 H, m), 4.19 (1 H, br d, *J* 9.7), 4.44, 4.47, 4.60, 4.65, 4.73, 4.76, 4.83, 4.95 (8 × 1 H, 8 × d, *J* 12.1, *J* 10.6, *J* 12.1, *J* 11.8, *J* 12.2, *J* 11.0, *J* 10.8, *J* 10.8, 4 × C*H*$_2$Ph), 5.41 (1 H, d, $J_{1,2}$ 4.4, 1-H), 7.12–7.39 (20 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 14.7 (*C*H$_3$), 23.6 (*C*H$_2$), 68.5 (C-6), 70.4, 77.4, 79.4, 82.5, 83.0 (C-1, C-2, C-3, C-4, C-5), 72.3, 73.4, 74.9, 75.6 (4 × *C*H$_2$Ph), 127.6–138.7 (24 C, arom.).

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (5b)

Compound **4** (261 mg, 0.500 mmol) and thiol (**2b**, 102 μL, 1.00 mmol) were reacted in toluene (5 mL) according to general method **B**. The crude product was purified using silica

gel chromatography in 99 : 1 CH_2Cl_2–EtOAc to give **5b** (67 mg, 21%) as white needles. Mp 77–78 °C (from EtOH) (lit.[44] mp 81–82 °C); $[\alpha]_D^{22}$ +142.7 (*c* 0.33 in $CHCl_3$), (lit.[44] $[\alpha]_D$ +154); R_f 0.58 (8 : 2 *n*-hexane–EtOAc). Elemental analysis: found: C, 76.1; H, 6.5; S, 5.0. Calc. for $C_{40}H_{40}O_5S$: C, 75.9; H, 6.4; S, 5.1%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 3.61 (1 H, br d, *J* 10.2), 3.66–3.72 (1 H, m), 3.77 (1 H, dd, *J* 3.7, *J* 10.7), 3.86–3.93 (2 H, m), 4.33 (1 H, br d, *J* 9.8), 4.41, 4.49, 4.58, 4.68, 4.76, 4.81, 4.85, 5.00 (8 × 1 H, 8 × d, *J* 12.0, *J* 10.8, *J* 12.0, *J* 11.7, *J* 11.8, *J* 10.9, *J* 10.8, *J* 10.8, 4 × CH_2Ph), 5.64 (1 H, d, $J_{1,2}$ 3.7, 1-H), 7.14–7.50 (25 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 68.5 (C-6), 71.1, 77.3, 79.7, 82.5 (C-2, C-3, C-4, C-5), 72.5, 73.3, 75.1, 75.7 (4 × CH_2Ph), 87.0 (C-1), 127.0–138.6 (30C, arom.).

2-Methylpropane-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (5e)

Compound **4** (261 mg, 0.500 mmol) and thiol (**2e**, 3 × 281 μL, 7.50 mmol) were reacted in toluene (5 mL) according to general method **A**. The crude product was purified using silica gel chromatography in 88 : 12 *n*-hexane–EtOAc to give **5e** (122 mg, 40%) as white needles. Mp 91–92 °C (from EtOH) (lit.[45] mp 97–98 °C); $[\alpha]_D^{22}$ +72.9 (*c* 0.40 in $CHCl_3$), (lit.[45] $[\alpha]_D$ +120); R_f 0.55 (85 : 15 *n*-hexane–EtOAc). Elemental analysis: found: C, 74.4; H, 7.1; S, 5.2. Calc. for $C_{38}H_{44}O_5S$: C, 74.5; H, 7.2; S, 5.2%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.38 (9 H, s, 3 × CH_3), 3.57 (1 H, dd, *J* 1.9, *J* 10.6), 3.64–3.69 (1 H, br t, *J* 8.6, *J* 9.7), 3.74–3.83 (3 H, m), 4.25–4.28 (1 H, m), 4.41, 4.45, 4.62 (3 × 1 H, 3 × d, *J* 12.2, *J* 11.0, *J* 12.1, CH_2Ph), 4.70 (2 H, s, CH_2Ph), 4.75, 4.83, 4.96 (3 × 1 H, 3 × d, 3 × *J* 10.8, CH_2Ph), 5.54 (1 H, d, $J_{1,2}$ 4.8, 1-H), 7.12–7.39 (20 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 31.5 (3 × CH_3), 43.7 (Cq), 68.4 (C-6), 70.4, 77.5, 79.4, 81.7, 82.9 (C-1, C-2, C-3, C-4, C-5), 72.4, 73.4, 74.9, 75.7 (4 × CH_2Ph), 127.5–138.7 (24 C, arom.).

[(2*R*,*S*)-2,3-Dihydroxy]propyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (5i)

Compound **4** (261 mg, 0.500 mmol) and thiol (**2i**, 87 μL, 1.00 mmol) were reacted in toluene (5 mL) according to general method **B**. The crude product was purified using silica gel chromatography in 1 : 1 CH_2Cl_2–EtOAc to give **5i** (144 mg, 46%) as white crystals. Mp 60–61 °C (from EtOH); $[\alpha]_D^{22}$ +71.2 (*c* 0.58 in $CHCl_3$); R_f 0.51 (1 : 1 CH_2Cl_2–EtOAc). Elemental analysis: found: C, 70.2; H, 6.6; S, 4.9. Calc. for $C_{37}H_{42}O_7S$: C, 70.45; H, 6.7; S, 5.1%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 2.50–2.79 (3 H, m), 3.38–3.85 (9 H, m), 4.20–4.27 (1 H, m), 4.42–4.57 (3 H, m, CH_2Ph), 4.64–4.77 (3 H, m, CH_2Ph), 4.82, 4.94 (2 × 1 H, 2 × d, *J* 10.9, *J* 10.8, CH_2Ph), 5.33 (1 H, d, $J_{1,2}$ 4.2, 1-H), 7.13–7.37 (20 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 34.3 (SCH_2), 65.2 (OCH_2), 68.6, 68.7 (C-6), 70.7, 70.8, 71.2, 77.4, 79.3, 79.4, 82.2, 84.3, 84.9 (C-1, C-2, C-3, C-4, C-5, C-2′), 72.5, 72.5, 73.3, 73.3, 74.9, 75.6 (4 × CH_2Ph), 127.5–138.4 (24 C, arom.).

1,2:5,6-Di-*O*-isopropylidene-3-*S*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-3-thio-α-D-glucofuranose (5j)

Compound **4** (261 mg, 0.500 mmol) and thiol (**2j**, 276 mg, 1.00 mmol) were reacted in toluene (5 mL) according to general method **B**. The crude product was purified using silica gel chromatography in 85 : 15 *n*-hexane–EtOAc to give **5j** (235 mg, 59%) as white crystals. Mp 89–90 °C (from EtOH). $[\alpha]_D^{22}$ +89.0 (*c* 0.73 in $CHCl_3$); R_f 0.32 (85 : 15 *n*-hexane–EtOAc). Elemental analysis: found: C, 69.0; H, 6.8; S, 3.9. Calc. for $C_{46}H_{54}O_{10}S$: C, 69.15; H, 6.8; S, 4.0%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.24, 1.31, 1.43, 1.50 (12 H, 4 × s, 4 × CH_3), 3.58–3.90 (6 H, m), 4.03–4.23 (4 H, m), 4.44–4.49 (2 H, m), 4.54–4.64 (3 H, m), 4.72–4.85 (4 H, m), 4.94 (1 H, d, *J* 10.8), 5.77 (1 H, d, $J_{1,2}$ 3.2, 1-H), 5.84 (1 H, d, $J_{1',2'}$ 4.7, 1′-H), 7.11–7.38 (20 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 25.3, 26.0, 26.5, 26.9 (4 × CH_3), 50.0 (C-3), 67.7 (C-6), 68.3 (C-6′), 71.0, 74.4, 77.1, 79.1, 80.4, 82.0, 84.4 (C-2, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 71.5, 73.3, 74.9, 75.5 (4 × CH_2Ph), 86.4 (C-1′), 104.7 (C-1), 109.2, 111.7 (2 × Cq), 127.4–138.4 (24 C, arom.).

3,4,6-Tri-*O*-acetyl-1,5-anhydro-2-*S*-ethyl-D-mannitol (7), 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-*S*-ethyl-D-glucitol (8) and ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-*arabino*-hexopyranoside (9)

Compound **6** (544 mg, 2.00 mmol) and ethanethiol (**2a**, 3 × 740 μL, 30.00 mmol) were reacted according to general method **A** to give a mixture of **7**, **8** and **9** which were separated using silica gel chromatography in 1 : 1 *n*-hexane–Et_2O. (After column chromatography, compound **9** was contaminated by the unreacted starting material, from which it could only be separated after catalytic hydrogenation and a subsequent purification using silica gel chromatography in 1 : 1 *n*-hexane–EtOAc.)

7: (230 mg, 34%) colourless syrup; $[\alpha]_D^{22}$ −34.4 (*c* 0.61, $CHCl_3$); R_f 0.18 (1 : 1 *n*-hexane–Et_2O). Elemental analysis: found: C, 50.15; H, 6.5; S, 9.45. Calcd for $C_{14}H_{22}O_7S$: C, 50.3; H, 6.6; S, 9.6; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.24 (3 H, t, *J* 7.4, CH_3CH$_2$), 2.06, 2.09, 2.10 (9 H, 3 s, 3 × CH_3), 2.58–2.64 (2 H, q, CH_2), 3.37–3.39 (1 H, m, 2-H), 3.58–3.62 (1 H, m, 5-H), 3.83 (1 H, dd, $J_{1\beta,2}$ 2.1, $J_{1\alpha,1\beta}$ 12.2, 1β-H), 4.09 (1 H, dd, $J_{1\alpha,2}$ 2.6, $J_{1\alpha,1\beta}$ 12.2, 1-αH), 4.13 (1 H, dd, $J_{5,6A}$ 2.7, $J_{6A,B}$ 12.2, 6-H_A), 4.19 (1 H, dd, $J_{5,6B}$ 5.5, $J_{6A,B}$ 12.2, 6-H_B), 5.10 (1 H, dd, $J_{2,3}$ 4.4, $J_{3,4}$ 9.3, 3-H), 5.28 (1 H, t, $J_{4,5}$ 9.2, 4-H); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 14.5 (CH_3CH$_2$), 20.5, 20.5, 20.6 (3 × CH_3), 26.4 (CH_2), 45.3 (C-2), 62.3 (C-6), 66.5 (C-4), 69.1 (C-1), 73.7 (C-3), 76.6 (C-5), 169.2, 170.0, 170.4 (3 × CO).

8: (163 mg, 24%) colourless syrup; $[\alpha]_D^{22}$ +71.1 (*c* 0.35, $CHCl_3$); R_f 0.30 (1 : 1 *n*-hexane–Et_2O). Elemental analysis: found: C, 50.05; H, 6.7; S, 9.4. Calcd. for $C_{14}H_{22}O_7S$: C, 50.3; H, 6.6; S, 9.6; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.24 (3 H, t, *J* 7.4, CH_3CH$_2$), 2.03, 2.08, 2.09 (9 H, 3 s, 3 × CH_3), 2.52–2.62 (2 H, m, CH_2), 2.84–2.91 (1 H, m, 2-H), 3.40 (1 H, t, $J_{1\beta,2}$ 11.9, 1β-H), 3.58–3.63 (1 H, m, 5-H), 4.09 (1 H, dd, $J_{5,6A}$ 2.1, $J_{6A,B}$12.3, 6-H_A), 4.14 (1 H, dd, $J_{1\alpha,2}$ 5.1, $J_{1\alpha,1\beta}$ 11.9, 1α-H), 4.25 (1 H, dd, $J_{5,6B}$ 4.8, $J_{6A,B}$ 12.3, 6-H_B), 4.98–5.00 (2 H, m, 3-H,

4-H); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 15.1 (CH_3CH_2), 20.5, 20.6, 20.6 (3 × CH_3), 25.3 (CH_2), 45.1 (C-2), 62.3 (C-6), 69.5 (C-4), 70.2 (C-1), 73.9 (C-3), 76.4 (C-5), 169.6, 170.1, 170.5 (3 × CO).

9: (46 mg, 7%) white crystals, mp 50–52 °C (EtOH), (lit.[46] mp 51–52 °C); $[\alpha]_D^{22}$ +207.7 (*c* 0.25, $CHCl_3$) (lit.[46] $[\alpha]_D$ +183); R_f 0.36 (1 : 1 *n*-hexane–Et_2O). Analysis: found: C, 50.4; H, 6.75; S, 9.6. Calcd for $C_{14}H_{22}O_7S$: C, 50.3; H, 6.6; S, 9.6; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.29 (3 H, t, *J* 7.4, CH_3CH_2), 2.01, 2.05, 2.09 (9 H, 3 s, 3 × CH_3), 2.13–2.30 (2 H, m), 2.50–2.68 (2 H, m), 4.04 (1 H, dd, *J* 1.8, *J* 11.9), 4.33–4.42 (2 H, m), 4.98 (1 H, t, *J* 9.5), 5.21–5.28 (1 H, m), 5.45 (1 H, d, *J* 5.5); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 14.7 (CH_3CH_2), 20.7, 20.7, 20.9 (3 × CH_3), 24.9 (CH_2), 35.2 (C-2), 62.3 (C-6), 68.0, 69.4, 69.6 (C-3, C-4, C-5), 79.6 (C-1), 169.9, 170.0, 170.6 (3 × CO).

6-Deoxy-1,2 : 3,4-di-*O*-isopropylidene-7-*S*-phenyl-α-D-*galacto*-heptopyranose (11)

Compound **10** (256 mg, 1.00 mmol) and thiol (**2b**, 205 μL, 2.00 mmol) were reacted in toluene (7 mL) according to general method **B**. The crude product was purified using silica gel chromatography in 98 : 2 CH_2Cl_2–EtOAc to give **11** (168 mg, 46%) as a colourless syrup. $[\alpha]_D^{22}$ −15.3 (*c* 0.30 in $CHCl_3$); R_f 0.49 (99 : 1 CH_2Cl_2–acetone). Elemental analysis: found: C, 62.4; H, 7.2; S, 8.65. Calc. for $C_{19}H_{26}O_5S$: C, 62.3; H, 7.15; S, 8.75%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.32, 1.33, 1.44, 1.59 (12 H, 4 × s, 4 × CH_3), 1.73–1.82 (1 H, m, 6-H_A), 2.01–2.11 (1 H, m, 6-H_B), 2.95–3.03 (1 H, m, 7-H_A), 3.11–3.18 (1 H, m, 7-H_B), 3.99–4.04 (1 H, m, 5-H), 4.09 (1 H, dd, $J_{4,5}$ 1.6, $J_{3,4}$ 7.9, 4-H), 4.30 (1 H, dd, $J_{2,3}$ 2.3, $J_{1,2}$ 5.0, 2-H), 4.59 (1 H, dd, $J_{2,3}$ 2.3, $J_{3,4}$ 7.9, 3-H), 5.52 (1 H, d, $J_{1,2}$ 5.0, 1-H), 7.12–7.33 (5 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 24.3, 24.9, 25.9, 26.0 (4 × CH_3), 29.3, 29.6 (C-6, C-7), 65.6, 70.4, 70.8, 72.8 (C-2, C-3, C-4, C-5), 96.4 (C-1), 108.5, 109.0 (2 × Cq), 125.7, 128.7, 129.0 (5 C, arom.), 136.2 (Cq, arom.).

3-Deoxy-3-*C*-(phenylthiomethyl)-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (13)

Compound **12** (256 mg, 1.00 mmol) and thiol (**2b**, 205 μL, 2.00 mmol) were reacted in toluene (5 mL) according to general method **B**. The crude product was purified using silica gel chromatography in 98 : 1 : 1 CH_2Cl_2–EtOAc–TEA to give **13** (117 mg, 32%) as white crystals. Mp 41–42 °C; $[\alpha]_D^{22}$ +99.0 (*c* 0.42 in $CHCl_3$); R_f 0.42 (98 : 2 CH_2Cl_2–EtOAc). Elemental analysis: found: C, 62.05; H, 7.3; S, 8.9. Calc. for $C_{19}H_{26}O_5S$: C, 62.30; H, 7.15; S, 8.75%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.32, 1.37, 1.42, 1.53 (12 H, 4 × s, 4 × CH_3), 2.13–2.21 (1 H, m, 3-H), 3.09 (1 H, dd, $J_{3,SCH2A}$ 11.5, J_{SCH2AB} 13.5, SCH_{2A}), 3.52 (1 H, dd, $J_{3,SCH2B}$ 3.2, $J_{SCH2A,B}$ 13.5, SCH_{2B}), 3.77 (1 H, dd, $J_{3,4}$ 9.7, $J_{4,5}$ 7.5, 4-H), 3.89 (1 H, dd, $J_{5,6A}$ 5.6, $J_{6A,B}$ 8.2, 6-H_A), 3.94–3.99 (1 H, m, 5-H), 4.09 (1 H, dd, $J_{5,6B}$ 5.9, $J_{6A,B}$ 8.2, 6-H_B), 4.76 (1 H, t, *J* 3.6, 2-H), 5.71 (1 H, d, $J_{1,2}$ 3.6, 1-H), 7.14–7.40 (5 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 25.3, 26.3, 26.6, 26.8 (4 × CH_3), 27.9 (SCH_2), 48.8 (C-3), 67.9 (C-6), 76.7 (C-5), 80.7 (C-4), 81.0 (C-2), 104.8 (C-1), 109.6, 112.0 (2 × Cq), 125.5, 128.2, 128.8 (5 C, arom.), 136.3 (Cq, arom.).

1-*S*-Phenyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzoyl-D-*glycero*-D-*gulo*-heptitol (15) and 1-(phenylsulfinyl)-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzoyl-D-*glycero*-D-*gulo*-heptitol (15b)

Compound **14** (225 mg, 0.380 mmol) and thiol (**2b**, 78 μL, 0.760 mmol) were reacted in toluene (4 mL) according to general method **B**. The crude product was purified using silica gel chromatography in 98 : 2 CH_2Cl_2–acetone to give **15** (197 mg, 74%) as a colourless syrup. $[\alpha]_D^{22}$ +4.0 (*c* 0.50 in $CHCl_3$); R_f 0.45 (75 : 25 *n*-hexane–EtOAc). Elemental analysis: found: C, 69.9; H, 4.7; S, 4.4. Calc. for $C_{41}H_{34}O_9S$: C, 70.1; H, 4.9; S, 4.6%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 3.16 (1 H, dd, $J_{1A,2}$ 8.0, $J_{1A,B}$ 14.3, 1-H_A), 3.27 (1 H, dd, $J_{1B,2}$ 2.7, $J_{1A,B}$ 14.3, 1-H_B), 3.97–4.03 (1 H, m, 2-H), 4.09–4.14 (1 H, m, 6-H), 4.43 (1 H, dd, $J_{6,7A}$ 5.3, $J_{7A,B}$ 12.2, 7-H_A), 4.59 (1 H, dd, $J_{6,7B}$ 2.8, $J_{7A,B}$ 12.2, 7-H_B), 5.59 (1 H, t, *J* 9.6), 5.70 (1 H, t, *J* 9.7), 5.91 (1 H, t, *J* 9.5), 7.08–7.54 (17 H, m, arom.), 7.80–8.06 (8 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 35.8 (C-1), 63.1 (C-7), 69.6, 72.0, 74.1, 76.0, 77.8 (C-2, C-3, C-4, C-5, C-6), 126.2–135.9 (30C, arom.), 165.1, 165.3, 165.8, 166.0 (4 × CO).

When the crude **15** was purified using silica gel chromatography using 75 : 25 *n*-hexane–EtOAc as the eluent, the sulfoxide derivative **15b** was isolated in 8% yield and pure **15** was isolated in 61% yield.

Compound **15b**: colourless syrup. $[\alpha]_D^{22}$ +23.5 (*c* 0.47 in $CHCl_3$); R_f 0.56 (1 : 1 *n*-hexane–EtOAc). Elemental analysis: found: 68.2; H, 4.6; S, 4.65%. Calc. for $C_{41}H_{34}O_{10}S$: C, 68.5; H, 4.8; S, 4.5%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 2.91–3.04 (2 H, m), 3.13 (1 H, dd, *J* 4.5, *J* 13.6), 3.34 (1 H, dd, *J* 7.5, *J* 13.6), 3.90–3.95 (1 H, m), 4.00–4.06 (1 H, m), 4.25–4.39 (3 H, m), 4.43–4.56 (2 H, m), 4.68 (1 H, dd, *J* 2.8, *J* 12.3), 5.43–5.54 (2 H, m), 5.62 (1 H, t, *J* 9.8), 5.73 (1 H, t, *J* 9.8), 5.83 (1 H, t, *J* 9.6), 5.96 (1 H, t, *J* 9.6), 7.23–8.11 (50 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 58.4, 60.8 (C-1), 63.1 (C-7), 69.3, 69.4, 71.7, 72.0, 72.1, 72.5, 73.8, 74.1, 76.1, 76.4 (C-2, C-3, C-4, C-5, C-6), 123.8–143.8 (60C, arom.), 165.1, 165.2, 165.5, 165.7, 165.7, 166.2 (8 × CO).

1-*S*-Ethyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzoyl-D-*glycero*-D-*gulo*-heptitol (16)

Compound **14** (140 mg, 0.236 mmol) and thiol **2a** (87 μL, 1.18 mmol) were reacted in toluene (3 mL) according to general method **A**. The crude product was purified using silica gel chromatography in 98 : 2 CH_2Cl_2–acetone to give **16** (143 mg, 93%) as a colourless syrup; $[\alpha]_D^{22}$ +23.5 (*c* 0.47 in $CHCl_3$); R_f 0.45 (75 : 25 *n*-hexane–EtOAc). Elemental analysis: found: C, 67.65; H, 5.05; S, 5.0. Calc. for $C_{37}H_{34}O_9S$: C, 67.9; H, 5.2; S, 4.9%; ^{1}H NMR (360 MHz, $CDCl_3$, Me_4Si): δ (ppm) 1.14 (3 H, t, *J* 7.4, CH_3) 2.57–2.71 (2 H, m, CH_2S), 2.74–2.83 (2 H, m, 1-$H_{A,B}$), 4.00–4.06 (1 H, m, 2-H), 4.14–4.19 (1 H, m, 6-H), 4.46 (1 H, dd, $J_{6,7A}$ 5.4, $J_{7A,B}$ 12.2, 7-H_A), 4.66 (1 H, dd, $J_{6,7B}$ 2.7, $J_{7A,B}$ 12.2, 7-H_B), 5.59 (1 H, t, *J* 9.6), 5.68 (1 H, t, *J* 9.7), 5.93 (1 H, t, *J* 9.6), 7.22–7.56 (12 H, m, arom.), 7.80–8.07 (8 H, m, arom.); ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 14.4 (CH_3), 27.3 (CH_2S), 32.8 (C-1), 63.2 (C-7), 69.6, 71.8, 74.2, 76.0, 80.0 (C-2, C-3, C-4,

C-5, C-6), 128.1–133.3 (24 C, arom.), 165.1, 165.2, 165.8, 166.0 (4 × *C*O).

1,2 : 3,4-Di-*O*-isopropylidene-6-*S*-(5-acetamido-4,7,8,9,-tetra-*O*-acetyl-2,6-anhydro-5-deoxy-3-yl-D-*glycero*-D-*galacto*-uronic acid methyl ester)-6-thio-α-D-galactopyranose (19)

Compound **17** (473 mg, 1.00 mmol) and thiol **18** (553 mg, 2.0 mmol) were reacted according to general method **B**; the addition of DPAP (5 × 25 mg, 5 × 0.100 mmol), deoxygenation and 15 min irradiation were repeated 5 times. The crude product was separated using column chromatography in 7 : 3 *n*-hexane–EtOAc into two fractions. The first fraction with higher mobility (230 mg, R_f 0.78) proved to be a disulfide derivative of **18**.[47] The second fraction (650 mg, R_f 0.05) was a mixture of compounds with a very similar mobility, including two main components. This mixture was purified again using column chromatography in 1 : 9 *n*-hexane–EtOAc to give **19** (173 mg, 23%) as a colourless syrup and unreacted glycal **17** (163 mg, 35%; R_f 0.38). Compound **19**: $[\alpha]_D^{24}$ −20.3 (*c* 0.25, $CHCl_3$); R_f 0.37 (1 : 9 *n*-hexane–EtOAc). Elemental analysis: found: C, 51.4; H, 6.3; N, 1.9; S, 4.3. Calc. for $C_{32}H_{47}NO_{17}S$: C, 51.3; H, 6.3; N, 1.9; S, 4.3%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.32, 1.40, 1.56 (12 H, 3 × s, 4 × CH_3), 1.89, 2.02, 2.05, 2.10, 2.13, 2.16 (15 H, 5 × s, 5 × CH_3), 2.69–2.74 (1 H, m, 6-H_A), 2.84–2.90 (1 H, m, 6-H_B) 3.63–3.65 (1 H, m, 3-H), 3.79 (3 H, s, OCH_3), 3.82–3.84 (2 H, m, 5′-H, 6-H), 4.16–4.22 (2 H, m, 5-H, 9-H_A), 4.27–4.29 (2 H, m, 2′-H, 4′-H), 4.36 (1 H, d, $J_{2,3}$ 1.1, 2-H), 4.57–4.59 (1 H, m, 3′-H), 4.66–4.70 (1 H, m, 9-H_B), 5.26–5.30 (2 H, m, 7-H, 8-H), 5.46 (1 H, d, $J_{1',2'}$ 4.7, 1′-H), 5.66 (1 H, d, *J* 9.3, N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 20.7, 20.8, 20.9 (4 × *C*H_3), 23.2 (*C*H_3), 24.3, 24.8, 25.9 (4 × *C*H_3), 32.4 (C-6′), 47.1 (C-5), 48.7 (C-3), 52.4 (C-1), 62.4 (C-9), 66.9 (C-5′), 68.3 (C-7), 70.4, 70.6, 70.7 (C-2′, C-3′, C-4′), 71.6 (C-8), 73.1 (C-4), 78.0 (C-2), 96.5 (C-1′), 109.1, 108.6 (2 × Cq), 167.4, 170.2, 170.3, 170.5, 170.6 (6 × *C*O).

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