Regioselective Glycosylation of Glucosamine and Galactosamine Derivates Using O-Pivaloyl Galactosyl Donors

Mathias Oßwald, Uwe Lang, Siglinde Friedrich-Bochnitschek, Waldemar Pfrengle, and Horst Kunz

Institut für Organische Chemie der Universität Mainz, Duesbergweg 10 – 14, D-55128 Mainz, Germany

Reprint requests to Prof. Dr. H. Kunz. Fax: +49 6131 39-24786. E-mail: hokunz@uni-mainz.de

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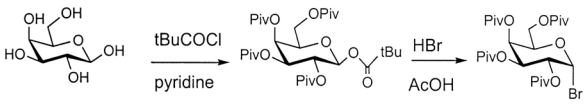
Penta-O-pivaloyl-galactopyranose and tetra-O-pivaloyl-galactopyranosyl bromide after electrophilic activation reacted with 6-O-protected 2-azido-galactosides to give the precursor structures of the Thomsen-Friedenreich antigen disaccharide with high regioselectivity, but low yield. With 4,6-O-benzylidene protected 2-azidogalactosides and 2-O-pivaloyl phenylthio galactosides, T-antigen disaccharides of this type were obtained in good yields. Glycosylation reactions of 4,6-O-benzylidene protected glucosamine derivatives with O-pivaloyl protected galactosyl bromide efficiently gave lactolactosamine disaccharides. Even a thioglycoside was efficiently galactosylated by this method resulting in the formation of a disaccharide thioglycoside useful itself as a potential glycosyl donor.

Key words: O-Pivaloyl Galactosyl Donors, Glycosylation Reactions, T Antigen

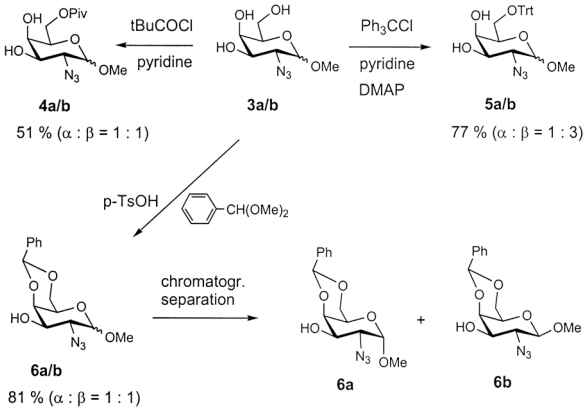
Regioselective galactosylation of glucosamine derivatives is a key step in the synthesis of Lewis^x, Lewis^a [1] or Globo H antigen structures [2]. Similar regioselective galactosylation reactions are required in syntheses of Gal(1-3)Gal [3], Thomsen-Friedenreich (T) antigen [4] and sialyl T antigen [5] structures. In many cases, trichloroacetimidates have been used as the glycosyl donors in these conversions [1 – 4]. Enzymatic galactosylations [5 – 6] have also been applied successfully.

We report on results obtained with O-pivaloyl protected galactosyl donors in the synthesis of β(1-3)-linked galactosyl galactosamine and glucosamine derivatives. In analogy to the corresponding glucose derivatives [7], penta-O-pivaloyl-β-D-galactopyranose **1** and 2,3,4,6-tetra-O-pivaloyl-α-D-galactopyranosyl bromide **2** [8] were obtained from galactose (Scheme 1).



Scheme 1.

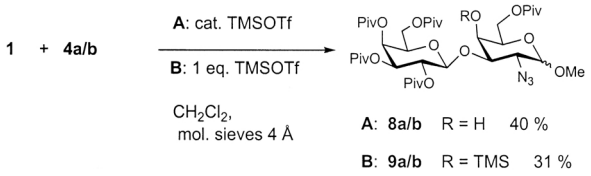
The galactosamine derived glycosyl acceptors were prepared via azidonitration of the O-acetyl-protected galactal [9] and subsequent conversion of the obtained azidonitrate into an anomeric mixture of the methyl 2-azido-galactosides **3a/b** [10]. Selective O-6 protection of **3a/b** was achieved by pivaloylation to give **4a/b** or tritylation to furnish **5a/b** (Scheme 2).



Scheme 2.

In order to obtain a monofunctional acceptor, **3a/b** were converted into the corresponding 4,6-O-benzylidene acetals **6a/b**.

Regioselective galactosylation of 6-O-pivaloyl-2-azido-galactosides **4a/b** was carried out using penta-O-pivaloylgalactose **1** activated by either catalytic (A)

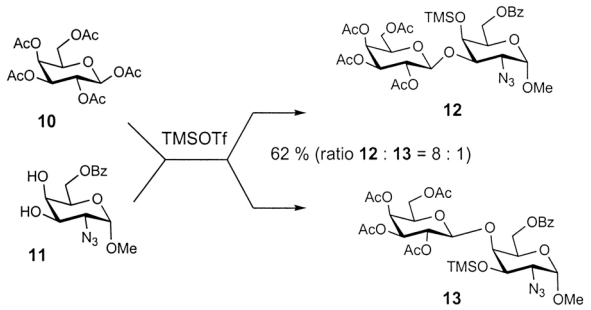


Scheme 3.

or equimolar amounts (B) of trimethylsilyl trifluoromethanesulfonate (TMS triflate, Scheme 3).

Both reactions proceeded slowly in dichloromethane in the presence of molecular sieves. After 2 days at room temperature the reaction was stopped by addition of triethylamine. With catalytic trimethylsilyl trifluoromethanesulfonate (TMSOTf), regioselective formation of β(1- 3)galactosyl-2-azido-galactoside **8a/b** (40% α : β = 4:5) was observed. The pure β-anomer **8b** (23%) was obtained by recrystallisation from ethyl acetate. In the presence of equimolar TMSOTf the 4-O-trimethylsilyl derivatives of the β(1-3)galactosyl-2-azido galactosides **9a/b** were isolated after working-up under exclusion of water. In this latter reaction the corresponding β(1-4) linked disaccharide was formed as a minor product in a ratio of 1:15.

It is noteworthy that an analogous reaction of the O-acetylated galactose **10** with the 6-O-benzoyl derivative **11** of **3a** gave a mixture of the β(1-3)- (**12**) and β(1-4)-galactosyl-azido-galactosides (**13**) in a ratio of 8:1 (Scheme 4).

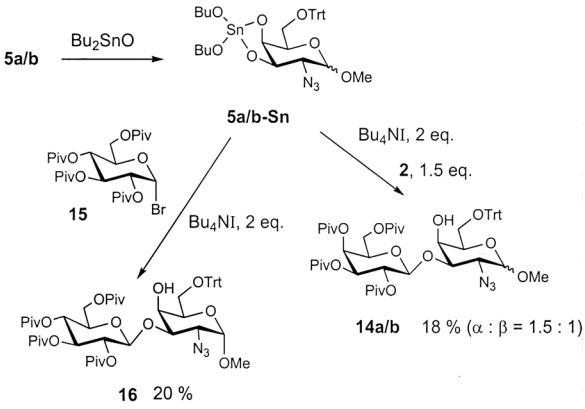


Scheme 4.

Separation of the regioisomeric disaccharides proved to be difficult. Comparison of reactions displayed in Schemes 3 and 4 illustrate the regiodifferentiating effects of the O-pivaloyl protection in both glycosyl donor and acceptor.

As an alternative concept of regiodifferentiation O-pivaloylated galactosyl bromide **2** was used in reaction with 3,4-O-stannylene derivatives of azido-galactosides. Augé and Veyrières [11] investigated the reaction of 3,4-O-stannylene derivatives of galactosides with O-acetyl-protected galactosyl bromide and observed the formation of mixtures containing the trisaccharides as the major components (galactosylation at O-3 and O-4). With O-benzyl-galactosyl bromide regioselective monogalactosylation at O-3 of 1,2,6-tri-O-benzyl protected galactose was achieved. However, the undesired α-linked disaccharide always was the prevailing stereoisomer.

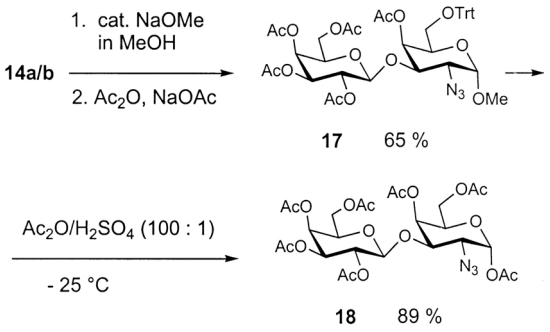
Since the 3,4-O-stannylene derivative of **3a/b** reacted with galactosyl bromide **2** to give a mixture of products, a 6-O-protected acceptor was used. The 6-O-pivaloyl group is supposed to interfere with stannylene-directed glycosylations because of its coordinating abilities. Therefore, 6-O-trityl-2-azido-galactosides **5a/b** were investigated in this study. After treatment with equimolar amounts of dibutyltin oxide in methanol, the 3,4-O-stannylene derivatives **5a/b-Sn** were dried in high vacuum and then reacted with 2 equiv. of tetrabutylammonium iodide and 1.5 equiv. of galactosyl bromide **2** in boiling dioxane (Scheme 5).



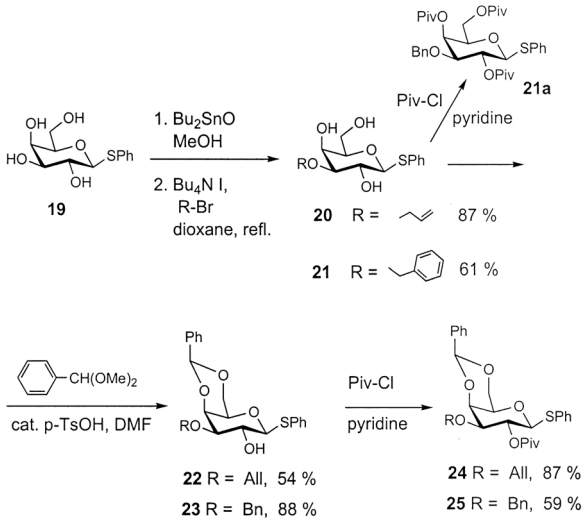
Scheme 5.

According to TLC monitoring, the 1,3-linked disaccharide **14a/b** was formed with high selectivity. However, the removal of tin-containing impurities required repeated chromatography. Therefore, the yield of sufficiently pure galactosyl(β1-3)-2-azido-galactosides **14a/b** was low.

A similar result was obtained with 2,3,4,6-tetra-O-pivaloyl-α-D-glucopyranosyl bromide **15** [7] as the glycosyl donor. Again, only repeated purification resulted in the isolation of the pure glucosyl(β1-3)-2-azido-α-galactoside **16**.



Scheme 6.



Scheme 7.

It had to be concluded that a regioselective galactosylation of 2-azido galactosides using O-pivaloyl-protected galactosyl donors preventing additional protecting group manipulations can be achieved either directly or via a stannylene intermediate. However, the yields of the desired galactosyl(β1-3)-2-azido-galactosides are unsatisfying. It should be briefly outlined that the precursors **8**, **9** and **10** of the Thomsen-Friedenreich antigen can be converted into disaccharide donors suitable for conjugation with serine or threonine derivatives [10,12]. Removal of the O-pivaloyl groups from disaccharide **14a/b** was achieved by Zemplén transesterification with catalytic amounts of sodium methoxide in methanol at 30 °C. The crude product was treated with acetic anhydride/sodium acetate to furnish the O-acetylated galactosyl-2-azido-galactoside isolated after purification as crystals enriched in the α anomer **17** (Scheme 6).

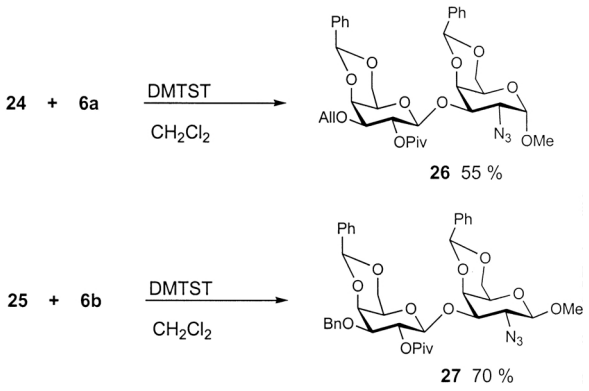
Acetolysis [13] of **17** using acetic anhydride/conc. sulfuric acid (100:1) at −25 °C resulted in the formation of the α-acetate **18**, which can be converted into the corresponding glycosyl bromide according to known procedures [10, 13].

In addition to the regioselective galactosylation, precursors of the T antigen saccharide have also been prepared by galactosylation of 4,6-O-benzylidene-2-azido-galactosides **6** using thioglycosides [14] as the glycosyl donors. To obtain galactosyl thioglycosides, which can be differentiated in all positions [15], phenylthio galactoside **19** was prepared from peracetylated galactose with thiophenol in the presence of boron trifluoride etherate [16] and subsequent treatment with catalytic NaOMe in methanol. It was subjected to regioselective 3-O-benzylation or allylation via its 3,4-O-stannylene derivative [17,18] to give compounds **20** or **21**, respectively (Scheme 7). It is remarkable that the thioglycoside does not affect this alkylation reaction and no accompanying alkylation at O-6 was observed.

After conversion of the 3-O-protected thiogalactosides **20**, **21** into their 4,6-O-benzylidene acetals **22**, **23**, pivaloylation of the 2-OH function furnished the thiogalactosyl donors **24** and **25**.

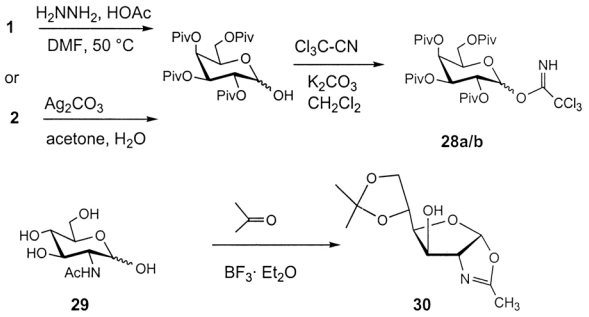
Thiogalactoside **24** was activated with dimethylmethylthiosulfonium triflate (DMTST) [14] and reacted with galactoside **6a** as the acceptor to form the galactosyl(β1-3)-2-azido-galactoside **26**. The analogous reaction of phenylthio galactoside **25** with acceptor **6b** gave the precursor disaccharide **27** of T antigen in good yield. Both disaccharides **26** and **27** offer possibilities of selective deprotection and diversification in a number of positions. They also can be transformed into glycosyl donors of type **18** according to known procedures [10,13]. It is worth mentioning that the bicyclic thiogalactoside donors **24** and **25** show enhanced reactivity compared to O- pivaloylated monocyclic analogues. Thus, reaction of **6b** with **21a** prepared in order to characterise **21** gave only 25% of the corresponding disaccharide under identical reaction conditions.

From the results of the reactions shown in Scheme 8 it is concluded, that reactions of 2-O-pivaloylated glycosyl donors produce the desired disaccharides with high β-selectivity. Orthoester formation was not observed, which facilitates purification of the products. The reactions of monofunctionalized acceptors (Scheme 8) give higher yields than the regioselective glycosylations shown in the Schemes 3 and 5.



Scheme 8.

As a consequence of these experiences, monofunctional glucosamine acceptors were investigated in reactions with O-pivaloylated galactosyl donors to furnish lacto-lactosamine derivatives. Besides galactosyl bromide **2** the O-pivaloylated O-galactosyl trichloroacetimidates **28a/b** [19] were used as the donors in reactions with the glycofurano-oxazoline **30** obtained from N-acetylglucosamine **29** by treatment with an excess of boron trifluoride etherate in acetone (Scheme 9).

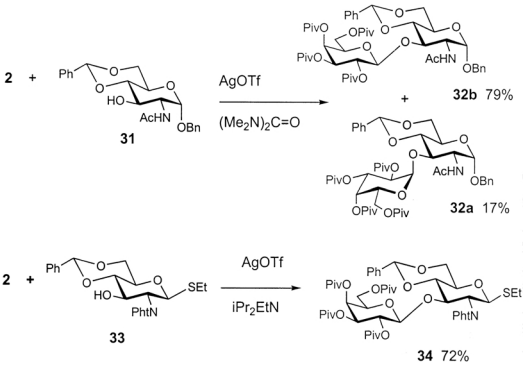


Scheme 9.

Due to its acid-sensitivity, glucofurano-oxazoline **30** was not stable under glycosylation conditions, neither with galactosyl bromide **2** in the presence of silver triflate/collidine nor with trichloroacetimidates activated by boron trifluoride.

However, pivaloyl protected galactosyl bromide **2** reacted with benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-glucopyranoside **31** [20] in the presence of silver triflate/tetramethyl urea [21] to give the lacto-lactosamine disaccharides **32a/b** in high yield (Scheme 10).

The two anomers can readily be separated by chromatography, and the desired β-anomer was isolated in high yield. In a similar reaction galactosyl bromide



Scheme 10.

2 with ethyl thioglycoside **33** of the 4,6-benzylidene-protected N-phthaloyl glucosamine gave the lacto- lactosamine derivative **34**. In order to prevent anomerisation of the product, this galactosylation was promoted by silver triflate in the presence of Huenig's base. In fact, the β-selectivity of the reaction was higher than 20:1. Due to the neutral conditions, some amounts of the corresponding orthoester were formed which could be readily separated by chromatography. The obtained lacto-lactosamine thioglycoside **34** can directly be used for further glycosylations as will be described elsewhere.

The outlined examples of reactions show that O-pivaloyl protected galactosyl donors despite their reduced reactivity are useful in galactosylations of monofunctional glycosyl acceptors of both the glucosamine and the galactosamine series. They can also be applied in regioselective glycosylation reactions of acceptors with 3,4-diol structure. In these cases, the yields of disaccharides are lower obviously due to the sterical demand and reduced reactivity of the pivaloylated galactosyl donors.

Experimental Section

Optical rotation values were recorded on a Perkin Elmer 241 polarimeter and calculated for λ = 589 nm.

Analytical TLC was performed on aluminium-backed TLC plates coated with Silica Gel 60 F_{254} (E. Merck, Darmstadt, Germany), detection by UV of λ = 254 nm and by a solution of 2 N H_2SO_4/0.2% 3-methoxyphenol (1:2) in ethanol. Column chromatography was carried out using silica gel (63 – 200 μm), flash-chromatography on silica gel (40 – 63 μm) purchased from E. Merck, Darmstadt, Germany. NMR spectra were recorded on a Bruker WT 200 spectrometer (200 MHz ^{1}H and 50.3 MHz ^{13}C) and a Bruker AM 400 spectrometer (400 MHz ^{1}H and 100.6 MHz ^{13}C). HPLC was performed using a LKB (Pharmacia) 2150 unit

with diode-array detection and a Lichrospher 100 RP 18 column (250 × 4 mm) of Bischoff. Water/methanol served as the eluent.

Melting points have been measured using a Dr. Totolli apparatus (Büchi) and are uncorrected.

*2,3,4,6-Tetra-O-pivaloyl-α-D-galactopyranosyl bromide (**2**)*

To a solution of 1,2,3,4,6-penta-O-pivaloyl-β-D-galactopyranose (**1**) [22] (44 g, 73 mmol) in dry dichloromethane (60 ml) a solution of hydrogen bromide in acetic acid (33%, 72 ml) was added dropwise at 0 °C. After stirring for 12 h at room temp., toluene (400 ml) was added, and the solvents were evaporated *in vacuo*. Codistillation *in vacuo* with toluene (400 ml) and with diethyl ether (400 ml) was repeated. The remaining crude product was dissolved in diethyl ether (500 ml). The solution was carefully washed with sat. sodium bicarbonate solution, dried with $MgSO_4$, and the solvent evaporated *in vacuo*. After recrystallisation the pure crystalline galactosyl bromide (**2**) was isolated.

Yield: 34 g (80%); m. p. 91 – 92°C; $[\alpha]_D^{22}$ = +159.5 (c 1, $CHCl_3$); R_f = 0.57 (light petroleum/diethyl ether 5:1). – ^{1}H NMR ($CDCl_3$): δ = 6.65 (d, 1H, $J_{1,2}$ = 4.0 Hz, 1-H), 5.52 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 2.1 Hz, 4-H), 5.47 (dd, 1H, $J_{2,3}$ = 10.5 Hz, 3-H), 5.00 (dd, 1H, $J_{2,1}$ = 4.0 Hz, 2-H), 4.50 (m, 1H, 5-H), 4.11 (dd, 1H, $J_{6,6'}$ = 11.3 Hz, $J_{6,5}$ = 7.0 Hz, 6-H), 4.04 (dd, 1H, $J_{6',5}$ = 6.7 Hz, 6'-H), 1.25-1.10 (4 × s, 36H, Piv.). – $C_{26}H_{43}BrO_9$ (579.5): calcd. C 53.89, H 7.48; found C 53.96, H 7.35.

*Methyl 2-azido-2-deoxy-6-pivaloyl-α/β-D-galactopyranoside (**4a**/**b**)*

To a solution of methyl 2-azido-2-deoxy-α/β-D-galactopyranoside (**3a/b**) [10] (5.0 g, 23 mmol) in pyridine (100 ml) at −15 °C pivaloyl chloride (1.5 ml, 12 mmol) was added. The solution was stirred at this temperature for 12 h, then additional 3 ml of pivaloyl chloride (24 mmol) were added. After 48 h the solution was brought to room temperature. Pyridine was evaporated *in vacuo*. After codistillation with toluene (50 ml) *in vacuo*, the residue was dissolved in dichloromethane (100 ml) and washed with sat. $NaHCO_3$ solution. After evaporation of the solvent *in vacuo*, drying in high vacuum and recrystallisation from light petroleum/ethyl acetate (10:1), the pure product was obtained as colourless crystals: Yield: 3.5 g (51%); ratio of anomers 1:1; R_f = 0.38 (α anomer), 0.32 (β anomer) in light petroleum/ethyl acetate 2:1. – $C_{12}H_{21}N_3O_6$ (303.3): calcd. C 47.52, H 6.98, N 13.85; found C 47.70, H 6.99, N 13.27. – For an analytical sample the anomers were separated: α anomer: m.p. 48 °C, $[\alpha]_D^{22}$ = +120.0 (c 1.2, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 4.80 (d, 1H, $J_{1,2}$ = 3.5 Hz, 1-H); β-anomer: m.p. 88 – 90 °C, $[\alpha]_D^{22}$ = +43.5 (c 1, $CHCl_3$). – ^{1}H NMR: δ = 4.13 (d, 1H, $J_{1,2}$ =7.7 Hz, 1-H).

*Methyl 2-azido-2-deoxy-6-O-triphenylmethyl-α/β-D-galactopyranoside (**5a**/**b**)*

To a solution of (**3a/b**) [10] (2.0 g, 9 mmol) in pyridine (30 ml), triphenylchloromethane (2.5 g, 9.2 mmol) and 4-dimethylamino-pyridine (DMAP, 0.4 g, 3.2 mmol) were added. The solution was stirred at room temp. for 3 d, finally heated to 40 °C for 2 h and then diluted with toluene (100 ml). After evaporation of the solvents *in vacuo*, the residue was dissolved in diethyl ether (100 ml). The solution was extracted with water (50 ml), 1 N HCl (50 ml) and water, dried with $MgSO_4$, and the solvent was evaporated *in vacuo*. Yield: 3.2 g (77%), mixture of anomers α : β = 1:3. Flash-chromatography in petroleum ether/ethyl acetate (5:1) gave the pure β-anomer: m.p. 144 – 145 °C; $[\alpha]_D^{22}$ = −2.7 (c 1, $CHCl_3$); R_f = 0.48 (light petroleum/ethyl acetate 2:1). – ^{1}H NMR (DMSO- d_6): δ = 7.41 – 7.23 (m, 15 H, Ph), 5.32 (d, 1H, $J_{3,OH}$ = 5.6 Hz, 3-OH), 4.74 (m, 1H, 4-OH), 4.19 (d, 1H, $J_{1,2}$ = 7.9 Hz, 1-H). 3.66, 3.61 (2 × m, 2 × 1H, 4-H, 5-H), 3.41 (dd, 1H, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 3.6 Hz, 3-H), 3.34 (dd, 1H, $J_{2,3}$ = 10.2 Hz, 2-H), 3.19 (dd, 1H, $J_{6,5}$ = 7.1 Hz, $J_{6,6'}$ = 9.2 Hz, 6-H), 3.03 (dd, 1H, $J_{6',5}$ = 4.9 Hz, 6'-H); [α-anomer: δ = 4.77 (d, 1H, $J_{1,2}$ = 3.7 Hz, 1-H)]. – $C_{26}H_{27}N_3O_5$ (461.5): calcd. C 67.67, H 5.91, N 9.11; found C 67.85, H 5.86, N 9.35.

*Methyl 2-azido-4,6-O-benzylidene-2-deoxy-α/β-D-galactopyranoside (**6a**/**b**)*

To a solution of (**3a/b**) [10] (1.5 g, 6.8 mmol) and benzaldehyde dimethylacetal (1.2 ml, 7.9 mmol) in dimethylformamide (10 ml) 0.4 g of p- toluenesulfonic acid was added. The solution was kept at 35 °C for 3 h. Triethylamine (1 ml, 10 mmol) was then added. The solvent was evaporated, the residue dried in high vacuum, and then purified by flash-chromatography in light petroleum/ethyl acetate 1:5. Yield: 1.7 g (81%), colourless crystals, mixture of anomers (1:1); $C_{14}H_{17}N_3O_5$ (307.3): calcd. C 54.72, H 5.57, N 13.67; found C 54.72, H 5.49, N 13.53. For a sample the anomers have been separated by column chromatography (eluent: light petroleum/ethyl acetate, 1:2). α-anomer (**6a**): m. p. 119 – 120 °C; $[\alpha]_D^{22}$ = +183.7 (c 1, $CHCl_3$); R_f = 0.52. – ^{1}H NMR (DMSO-d_6): δ = 7.42 (m, 5H, Ph), 5.59 (s, 1H, CHPh), 5.43 (d, 1H, J_{3OH} = 7.2 Hz, 3-OH), 4.85 (d, 1H, $J_{1,2}$ = 3.4 Hz, 1-H), 4.20 (d, 1H, $J_{3,4}$ = 3.2 Hz, 4-H), 4.05 (m, 2H, 6,6'-H), 3.96 (m, 1H, 3-H), 3.63 (m, 1H, 5-H), 3.53 (dd, 1H, $J_{2,3}$ = 10.8 Hz, 2-H). 3.32 (s, 3H, OCH_3). – ^{13}C NMR (DMSO-d_6): δ = 99.72 (**C**HPh), 98.93 (C-1). β-anomer (**6b**): m. p. 168 – 169 °C; $[\alpha]_D^{22}$ = −3.5 (c 1, $CHCl_3$); R_f = 0.75. – ^{1}H NMR (DMSO-d_6): δ = 7.43 (m, 5H, Ph), 5.59 (s, 1H, CHPh), 5.47 (d, 1H, J_{3OH} = 7.0 Hz, 3-OH), 4.26 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 4.10 (d, 1H, $J_{3,4}$ = 3.4 Hz, 4-H), 4.06 (m, 2H, 6,6'-H), 3.56 (m, 1H, 3-H), 3.53 (m, 1H, 5-H), 3.44 (s, 3H, OCH_3), 3.41 (dd, 1H, $J_{2,3}$ =

8.1 Hz, 2-H). – ^{13}C NMR (DMSO-d_6): δ = 101.76 (C-1), 99.74 (CHPh).

*Methyl 2-azido-2-deoxy-6-O-pivaloyl-3-O-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)-β-D-galactopyranoside (***8b***)*

To a solution of **4a/b** (1.30 g, 4.28 mmol) and **1** (2.7 g, 4.4 mmol) in dry dichloromethane (50 ml) 2.0 g of molecular sieves (4 Å) were added. After stirring the mixture for 1 h, a catalytic amount (0.05 ml) of trimethylsilyl trifluoromethanesulfonate was added. The mixture was stirred for additional 48 h. After addition of triethylamine (0.15 ml, 0.8 mmol), filtration, washing with water (50 ml) and drying with $MgSO_4$, the solvent was evaporated. The residue was extracted with ethyl acetate, the solution was filtered through silica gel, and the solvent was evaporated to give 1.45 g (42%) of the crude mixture of anomers (**8a/b**). Dissolution of the material in aqueous ethyl acetate resulted in the precipitation of the β- anomer (**8b**) as colourless crystals: Yield: 0.91 g (27%); m. p. 206 – 208 °C; $[\alpha]_D^{22}$ = +15.8 (c 1, $CHCl_3$); R_f = 0.55 (light petroleum/ethyl acetate 5:1). – ^{1}H NMR ($CDCl_3$): δ = 5.38 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 2.0 Hz, 4'-H), 5.23 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{2,1}$ = 7.9 Hz, 2'-H), 5.09 (dd, 1H, 3'-H), 4.78 (d, 1H, 1'-H), 4.29 (m, 2H, 6_a,6_b−H), 4.12 (d, 1H, $J_{1,2}$ = 8.0 Hz, 1-H), 4.01 (m, 3H, 5'-H, $6_{a'}$,$6_{b'}$−H), 3.90 m, 1H, 4-H), 3.58 (m, 2H, H-5, 2-H), 3.37 (dd, 1H, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.2 Hz, 3-H), 2.60 ('s', 1H, 4-OH).

*Methyl 2-azido-deoxy-6-O-pivaloyl-3-O-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)-4-O-trimethylsilyl-α/β-D-galactopyranoside (***9a**/**b***)*

The galactosylation was performed as described for (**8a/b**) or (**8b**), respectively, with (**4a/b**) (0.35 g, 1.15 mmol), **1** (0.70 g, 0.16 mmol) and molecular sieves 4 Å (1 g) in dichloromethane (20 ml). After 1 h under argon atmosphere, 0.2 ml (1.1 mmol) of trimethylsilyl triflate was added via a syringe, and the mixture was stirred for 2 days. Triethylamine (0.16 ml, 1.16 mmol) was added, the mixture filtered and evaporated to dryness. The residue was dissolved in light petroleum/ethyl acetate (20:1) and purified by chromatography in this solvent. Yield: 0.31 g (32%), mixture of anomers (2:1): α-anomer: R_f = 0.68, β-anomer R_f = 0.60 (light petroleum/ethyl acetate 5:1). – ^{1}H NMR ($CDCl_3$): a) common signals of **9a/b**: δ = 5.40 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 1.0 Hz, 4'-H), 5.33 (dd, 1H, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 10.4 Hz, 2'-H), 5.06 (dd, 1H, 3'-H), 4.78 (d, 1H, 1'-H), 4.15 (m, 2H, 6a,6a'-H), 4.04 (dd, 1H, $J_{5,6b}$ = 6.2 Hz, $J_{6a,6b}$ = 11.2 Hz, $6_{b'}$-H), 3.85 (t, 1H, $J_{5,6}$ = 6.3 Hz, 5'-H), 0.16 (s, 9H, $Si(CH_3)_3$). Signals of α-anomer (**9a**): δ = 4.83 (d, 0.6H, $J_{1,2}$ = 3.4 Hz, 1-H), 4.09 (dd, 0.6H, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ 1.0 Hz, 4-H), 3.40 (s, OCH_3). Signals of β-anomer (**9b**): δ = 4.42 (d, 0.3H, $J_{1,2}$ = 7.9 Hz, 1- H), 3.92 (dd, 0.3H, $J_{3,4}$ = 2.8 Hz, $J_{1/2}$ = 1.0 Hz, 4-H), 3.42 (s, OCH_3).

Treatment with aqueous methanol quantitatively converts **9a/b** into **8a/b**.

*Methyl 2-azido-6-O-benzoyl-2-deoxy-3-O-(2,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-4-O-trimethylsilyl-β-D-galactopyranoside (***12***)*

To methyl 2-azido-6-O-benzoyl-2-deoxy-β-D-galactopyranoside [23] (**11**) (0.10 g, 0.31 mmol), penta-O-acetyl-β-D-galactopyranose (**10**) (0.12 g, 0.31 mmol) and molecular sieves 4 Å in dichloromethane (2 ml), trimethylsilyl triflate (0.6 ml, 69 mg, 0.31 mmol) was added. After stirring for 24 h at room temp. triethylamine (40 mg, 0.4 mmol) and additional 0.08 ml (0.4 mmol) of TMS triflate were added, and the stirring was continued for 12 h. After filtration and evaporation, purification was carried out by chromatography in light petroleum/ethyl acetate (2:1) to give **12** which according to the 400 MHz ^{1}H NMR spectrum in $CDCl_3$ contained the regioisomer **13** in a ratio of 8:1 (δ = 0.19, M_3Si). Yield: 145 mg (62%); colourless oil; $[\alpha]_D^{22}$ = +12.3 (c 0.4, $CHCl_3$); R_f = 0.53 (toluene, acetone 9:2). – ^{1}H NMR ($CDCl_3$): Signals of **12**: δ = 8.0 (m, 2H, o-benzoyl), 7.55 (m, 1H, p-benzoyl), 7.43 (m, 2H, m-benzoyl), 5.36 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 0.8 Hz, 4'-H), 5.24 (dd, 1H, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 10.5 Hz, 2'-H), 4.98 (dd, 1H, 3'- H), 4.72 (d, 1H, 1'-H), 4.45 (dd, 1H, $J_{5,6a}$ = 6.2 Hz, $J_{6a,6b}$ = 11.0 Hz, 6a-H), 4.36 (dd, 1H, $J_{5,6b}$ = 6.3 Hz, 6_b-H), 4.13 (d, 1H, $J_{1,2}$ = 8.2 Hz, 1-H), 4.07 (m, 3H, H-6', 4-H), 3.83 (m, 1H, 5'-H), 3.68 (t, 1H, 5-H), 3.55 (dd, 1H, $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 10.2 Hz, 2-H), 3.29 (dd, 1H, $J_{3,4}$ = 3.0 Hz, 3-H), 2.10, 2.06, 1.96 (3 × s, 12H, OAc), 0.17 (s, 9H, Me_3Si).

Stannylene-directed glycosylation

General procedure

The carefully dried acceptor **5a/b** (0.66 – 5.2 mmol) and 1.1 equiv. of di-*n*-butyltin oxide were heated in boiling methanol. After clearance of the solution heating was continued for 2 h. Then, the solvent was evaporated in vacuo, followed by codistillation with toluene twice. Finally, the remaining tin-complex **5a/b-Sn** was dried in high vacuum. The dry complex **5a/b-Sn**, 1.5 equivalents of the glycosyl bromide, 2 equivalents of dry tetrabutylammonium iodide, and freshly activated molecular sieves 4 Å in dry 1,4-dioxane were heated under reflux and argon atmosphere for 15 h (monitoring by TLC). The solvent was evaporated *in vacuo* and the remaining residue was extracted with ethyl acetate. The tin-containing insoluble amounts were filtered off. The solution was evaporated to dryness, and the residue purified by flash-chromatography in light petroleum/ethyl acetate (20:1).

*Methyl 2-azido-2-deoxy-3-O-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)-6-O-triphenylmethyl-α/β-D-galactopyranoside (***14a**/**b***)*

The disaccharide was synthesised according to the general procedure from **5a/b** (2.4 g, 5.2 mmol) and galactosyl bromide (**2**) (4.5 g, 7.7 mmol) in dry dioxane (150 ml) to give **14a/b**: Yield: 0.9 g (18%), mixture of anomers ($\alpha:\beta$ = 1.5:1) as colourless crystals, m. p. 72 – 74 °C; $[\alpha]_D^{22}$ = + 27.9 (c 1, $CHCl_3$); R_f = 0.52 (light petroleum/ethyl acetate 5:1). – ^{1}H NMR ($CDCl_3$): δ = 7.38 (m, 30H, Ph_3C), 5.28 – 5.22 (m, 4H, $\alpha+\beta$ 4'-H, 3'-H), 5.09 – 5.03 (m, 2H, $\alpha+\beta$ 2'-H), 4.98 – 4.92 (m, 3H, α 1-H, $\alpha+\beta$ 1'-H), 4.66 (d, 1H, $J_{4,OH}$ = 5.8 Hz, α 4-OH), 4.58 (d, 1H, $J_{4,OH}$ = 5.8 Hz, β 4-OH), 4.42 (d, 1H, $J_{1,2}$ = 7.1 Hz, β 1-H), 4.31 – 4.26 (m, 2H, $\alpha+\beta$ 5'-H), 3.99 – 3.79 (m, 10H, $\alpha+\beta$ 3-H, $\alpha+\beta$ 4-H, $\alpha+\beta$ 5-H, $\alpha+\beta$ 6'-H), 3.55 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.9 Hz, α 2-H), 3.53 (s, 3H, β OCH_3), 3.48-3.44 (m, 4H, β H-2, α OCH_3), 3.25 (m, 2H, $\alpha+\beta$ 6a-H), 2.95 (m, 2H, $\alpha+\beta$ 6_b-H), 1.21 – 1.03 (m, 72H, $\alpha+\beta$ $C(CH_3)_3$). $C_{52}H_{69}N_3O_{14}$ (960.1): calcd. C 65.05, H 7.24, N 4.38; found C 65.58, H 7.56, N 4.02.

*Methyl 2-azido-2-deoxy-3-O-(2,3,4,6-tetra-O-pivaloyl-β-D-glucopyranosyl)-6-O-triphenylmethyl-α-D-galactopyranoside (***16***)*

This compound was obtained according to the general procedure from **5a/b** (0.30 g, 0.65 mmol) and 0.60 g (10 mmol) of 2,3,4,6-tetra-O-pivaloyl-α-D-glucopyranosyl bromide [7] (**15**) in dry 1,4-dioxane (20 ml). After chromatography the pure α-anomer (**16**) was isolated: 125 mg (20%), colourless oil; $[\alpha]_D^{22}$ = +96.8 (c 1, $CHCl_3$); R_f = 0.55 (light petroleum/ethyl acetate 5:1). – ^{1}H NMR (DMSO-d_6): δ = 7.30 (m, 15H, CPh_3), 5.33 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, 4'-H), 5.03 (d, 1H, $J_{1,2}$ = 7.9 Hz, 1'-H), 4.92 – 4.87 m, 3H, H-1, 2'-H, 3'-H), 4.60 (d, 1H, $J_{4,OH}$ = 5.1 Hz, 4-OH), 4.13 – 4.02 (m, 2H, 6'-H), 3.94 – 3.77 (m, 4H, 3-H, 4-H, 5-H, 5'-H), 3.51 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 11.0 Hz, 2-H), 3.42 (s, 3H, OCH_3), 3.24 (dd, 1H, $J_{5,6a}$ = 7.8 Hz, $J_{6a,6b}$ = 9.5 Hz, 6a-H), 2.98 (dd, 1H, $J_{5,6b}$ = 3.7 Hz, 6b-H), 1.10 – 0.99 (4 × s, 36H, $CCCH_3)_3$). – $C_{52}H_{69}N_3O_{14}$ (960.1): calcd. C 65.05, H 7.24, N 4.38; found C 65.58, H 7.12, N 4.56.

*Methyl 4-O-acetyl-2-azido-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-6-O-triphenylmethyl-α-D-galactopyranoside (***17***)*

Treatment of **14a/b** (0.75 g 0.78 mmol) with a solution of sodium methanolate (from 25 mg sodium) in methanol (20 ml) at 35 °C for 12 h, neutralisation with acidic ion-exchange resin Lewatit CNP 80, filtration and evaporation of the solvent gave the crude depivaloylated compound [0.45 g, 92%, m.p. 80 – 84 °C; $[\alpha]_D^{22}$ = +20 (c 1, $CHCl_3$)] as a mixture of anomers, $\alpha:\beta$ = 1.2:1. This product was then heated with acetic anhydride (20 ml) and sodium acetate under reflux for 2 h. Acetic anhydride was evaporated *in vacuo*, the residue was dissolved in diethyl ether, and the solution washed with 0.1 N $NaHCO_3$ solution, dried with $MgSO_4$ and evaporated *in vacuo* to give the crude oily product **17**. Yield: 0.43 g (65%). Purification by flash-chromatography in light petroleum/ethyl acetate (4:1) gave (**17**) as crystals enriched in the α-anomer ($\alpha:\beta > 8:1$): yield 0.30 g (45%); m.p. 75 – 78 °C, $[\alpha]_D^{22}$ = +48.2 (c 1, $CHCl_3$); R_f = 0.50 (light petroleum/ethyl acetate 2:1). – ^{1}H NMR (DMSO-d_6): δ = 7.32 – 7.22 (m, 15H, $C(Ph)_3$), 5.23 (d, 1H, $J_{3,4}$ = 3,3 Hz, 4-H), 5.20 (d, 1H, $J_{3,4}$ = 3.5 Hz, 4'-H), 5.11 (dd, 1H, $J_{2,3}$ = 8.4 Hz, 3'-H), 4.96 (d, 1H, $J_{1,2}$ = 3,6 Hz, 1-H), 4.90 – 4.85 (m, 2H, 1'-H, 2'-H), 4.12 (m, 1H, 5'-H), 4.05 (dd, $J_{2,3}$ = 10.8 Hz, 1H, 3-H), 4.02 (m, 1H, 5-H), 3.93 – 3.85 (m, 2H, 6-H), 3.61 (dd, 1H, $J_{2,3}$ = 10.9 Hz, 2-H), 3.45 (s, 3H, OCH_3), 2.93 – 2.91 (m, 2H, 6-H), 2.07 – 1.81 (5 × s, 15H, CH_3). – $C_{42}H_{47}N_3O_{15}$ (833.8): calcd. C 60.50, H 5.68, N 5.04; found C 60.33, H 5.74, N 4.78.

*2-Azido-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-1,4,6-tri-O-acetyl-α/β-D-galactopyranose (***18***)*

To a solution of **17** (200 mg, 0.24 mmol) in acetic anhydride (9 ml) at −20 °C, 8 ml of a cooled (−20 °C) mixture of acetic anhydride/conc. H_2SO_4 (100:1) was added. A yellow colour results from cleavage of the trityl ether. After 24 h, dichloromethane (150 ml) was added. The solution was washed with 0.1 N $NaHCO_3$ solution and with water, dried with $MgSO_4$, and the solvent was evaporated *in vacuo*. The residue was purified by flash- chromatography in light petroleum/ethyl acetate 3:1. Yield: 120 mg (76%), colourless crystals, mixture of anomers, $\alpha:\beta$ = 8:1; m.p. 137 – 138 °C; $[\alpha]_D^{22}$ = +57.5 (c 1, $CHCl_3$); R_f = 0.73 (light petroleum/ethyl acetate 1:1). – ^{1}H NMR ($CDCl_3$) α-anomer: δ = 6.22 (d, 1H, $J_{1,2}$ = 3.7 Hz, 1-H), 5.43 (d, 1H, $J_{3,4}$ = 3.1 Hz, 4-H), 5.24 (d, 1H, $J_{3,4}$ = 3.0 Hz, 4'-H), 5.14 (dd, 1H, $J_{2,3}$ = 10.0 Hz, 3'-H), 4.98 (d, 1H, $J_{1,2}$ = 7.9 Hz, 1'-H), 4.92 (dd, 1H, 2'-H), 4.22 – 4.16 (m, 2H, 5-H, 5'-H), 4.11 (dd, 1H, $J_{2,3}$ = 10.9 Hz, 3-H), 4.06 – 3.97 (m, 3H, 2-H, 6'-H), 3.92 (dd, 1H, $J_{5,6a}$ = 6.7 Hz, $J_{6a,6b}$ = 11.1 Hz, 6a-H), 3.83 (dd, 1H, $J_{5,6b}$ = 7.2 Hz, 6b-H), 2.10 – 1.91 (7 *times* s, 21H, CH_3). Signals of β- anomer: δ = 4.55 (d, 1H, $J_{1,2}$ = 8.0 Hz, 1-H), 3.34 (dd, 1H, $J_{2,3}$ = 10.5 Hz, 2-H). $C_{26}H_{35}N_3O_{17}$ (661.6): calcd. C 47.20, H 5.33, N 6.35; found C 47.03, H 5.26, N 6.36.

*Selective 3-O-alkylation of phenylthio galactoside (***19***)*

General procedure

Phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside [16] (5.0 g, 11.3 mmol) was deacetylated by stirring with methanol (100 ml) and 5 ml of 0.1 M sodium methanolate in methanol at room temp. until completion of the reac-

tion (TLC monitoring, about 4 h). Neutralisation with ion-exchange resin Lewatit CNP, filtration and evaporation of the solvent gave phenyl 1-thio-galactopyranoside (**19**) in a form sufficiently pure for further conversion. Yield: 2.5 g (77%), m.p. 97 – 101 °C, $[\alpha]_D^{22}$ = −52.1 (c 1, MeOH), R_f = 0.37 (CH_2Cl_2/MeOH 1:1).

A suspension of phenyl thio-galactoside (**19**) (9 – 18 mmol) and di-*n*-butyltin oxide (1.5 equivalents) in methanol (100 ml) was heated under reflux for 3 h. The solvent was evaporated *in vacuo* and the amorphous residue was dried in high vacuum. To this crude product dissolved in 1,4-dioxane (100 ml) at 80 °C, tetrabutylammonium iodide (1 g) and an excess (2 to 10-fold) of the alkyl bromide were added. The mixture was then heated under reflux until the TLC monitoring (ethyl acetate) showed complete consumption of **19**. After evaporation of the solvents, the residue was purified by flash-chromatography in ethyl acetate.

*Phenyl 3-O-allyl-1-thio-β-D-galactopyranoside (***20***)*

This compound was obtained from crude **19** (2.5 g, 9.1 mmol) and 3.4 g (13.7 mmol) of Bu_2SnO via reaction of the stannylene intermediate with allyl bromide (10 ml, 115 mmol) in dioxane. Yield: 2.6 g (87%), colourless crystals; m.p. 112 – 114 °C; $[\alpha]_D^{22}$ = −18.0 (c 1, $CHCl_3$); R_f = 0.55 (ethyl acetate). – ^{1}H NMR (DMSO-d_6): δ = 7.45 – 7.17 (m, 5H, SPh), 5.91 (m, 1H, −CH=), 5.32 (dd, 1H, J_{trans} = 17.5 Hz, = CH_{2trans}), 5.30 (d, 1H, $J_{2,OH}$ = 6.2 Hz, 2-OH), 5.09 (dd, 1H, J_{cis} = 10.4 Hz, = CH_{2cis}), 4.67 (t, 1H, $J_{6a,OH}$ = $J_{6b,OH}$ = 5.3 Hz, 6-OH), 4.59 (d, 1H, $J_{1,2}$ = 9.7 Hz, 1-H), 3.22 (dd, 1H, 1H, $J_{2,3}$ = 9.1 Hz, $J_{3,4}$ = 3.1 Hz, 3-H). – $C_{15}H_{20}O_5S$ (312.4): calcd. C 57.68, H 6.45, S 10.26; found C 57.62, H 6.47, S 9.84.

*Phenyl 3-O-benzyl-1-thio-β-D-galactopyranoside (***21***)*

The compound was synthesised according to the general procedure from **19** (4.4 g, 16.1 mmol) and 6.0 g (24.1 mmol) of Bu_2SnO and treatment of the stannylene intermediate with benzyl bromide (5.5 g, 32.2 mmol) to yield **21**, 3.6 g (61%), colourless crystals, m.p. 150 °C; $[\alpha]_D^{22}$ = +26.0 (c 1, $CHCl_3$); R_f = 0.39 ($CHCl_3$/MeOH 3:1). – ^{1}H NMR (DMSO-d_6): δ = 7.50 – 7.28 (m, 10H, SPh, CPh), 5.39 (d, 1H, $J_{2,OH}$ = 6.2 Hz, 2-OH), 4.71 – 4.55 (m, 5H, H-1, 4-OH, OH-6, OCH_2Ph), 3.99 (m, 1H, 4-H), 3.32 (dd, 1H, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 3.0 Hz, 3-H). – $C_{19}H_{22}O_5S$ (362.4): calcd. C 62.97, H 6.12, S 8.85; found C 60.70, H 6.06, S 8.11 (the compound contains Sn-impurities).

*Phenyl 3-O-allyl-4,6-O-benzylidene-1-thio-galactopyranoside (***22***)*

A solution of **20** (3.0 g, 9.6 mmol), α,α-dimethoxy-toluene (1.7 ml, 11.1 mmol) and *p*-toluenesulfonic acid in dimethylformamide (50 ml) was stirred at 35 °C *in vacuo* (50 Torr) for 3 h. After addition of triethylamine (1 ml, 9.9 mmol) the solvents were evaporated, the residue dried in high vacuum and purified by flash-chromatography in ethyl acetate. Yield: 2.1 g (54%), colourless crystals, m. p. 154 – 155 °C; $[\alpha]_D^{22}$ = +15.8 (c 0.5, $CHCl_3$); R_f = 0.83 (ethyl acetate). ^{1}H NMR (DMSO-d_6): δ = 5.57 (s, 1H, CHPh), 5.37 (d, 1H, $J_{2,OH}$ = 6.0 Hz, 2-OH), 4.69 (d, 1H, $J_{1,2}$ = 9.4 Hz, 1-H), 4.33 (d, 1H, $J_{3,4}$ = 3.2 Hz, 4-H), 3.64 (s, 1H, 5-H), 3.57 (m, 1H, 2-H), 3.44 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 3.1 Hz, 3-H). – $C_{22}H_{24}O_5S$ (400.5): calcd. C 65.98, H 6.04, S 8.01; found C 65.74, H 6.14, S 8.70.

*Phenyl 3-O-benzyl-4,6-O-benzylidene-1-thio-β-D-galacto-pyranoside (***23***)*

The compound was prepared from **21** (3.0 g, 8.3 mmol) and α,α-dimethoxy-toluene (3.4 ml, 22.2 mmol) in dimethyl formamide (50 ml) in the presence of *p*-toluenesulfonic acid (0.5 g) as was described for (**22**). Flash-chromatography in ethyl acetate gave (**23**) in a yield of 3.3 g (88%) as colourless crystals; m. p. 159 – 160 °C; $[\alpha]_D^{22}$ = +13.8 (c 1, $CHCl_3$); R_f = 0.86 (light petroleum/ethyl acetate 1:5). – ^{1}H NMR ($DMSO_4$-d_6): δ = 5.58 (s, 1H, CHPh), 5.39 (d, 1H, $J_{\mathbf{2,OH}}$ = 6.0 Hz, 2-OH), 4.72 (d, 1H, $J_{1,2}$ = 9.4 Hz, 1-H), 4.40 (d, 1H, $J_{3,4}$ = 3.1 Hz, 4-H), 3.53 (dd, 1H, $J_{2,3}$ = 9.2 Hz, 3-H). – $C_{26}H_{26}O_5S$ (450.5): calcd. C 69.31, H 5.82, S 7.12; found C 69.26, H 5.84, S 7.24.

*Phenyl 3-O-benzyl-2,4,6-tri-O-pivaloyl-1-thio-β-D-galacto-pyranoside (***21a***)*

To a solution of (**21**) (3.6 g, 9.9 mmol) in pyridine was added pivaloyl chloride (15 ml, 12 mmol). The mixture was stirred at room temp. for 24 h, diluted with toluene (100 ml), and the solvents were evaporated *in vacuo*. The residue was dissolved in diethyl ether (100 ml), washed with 0.1 N HCl (50 ml), sat. $NaHCO_3$ solution (50 ml), and water and was dried with $MgSO_4$. After evaporation of the solvent, the syrupy residue was purified by flash-chromatography in light petroleum/ethyl acetate (7:1) and gave the tri-O-pivaloyl compound **21a** instead of an expected mono pivaloyl derivative. Yield: 1.4 g (23%), colourless crystals, m.p. 82 – 83 °C; $[\alpha]_D^{22}$ = +25.3 (c 1, $CHCl_3$); R_f = 0.63 (light petroleum/ethyl acetate 5:1). – ^{1}H NMR (DMSO-d_6): δ = 5.23 (d, 1H, $J_{3,4}$ = 2.7 Hz, 4-H), 5.07 (d, 1H, $J_{1,2}$ = 10.1 Hz, 1-H), 4.98 (t, 1H, $J_{2,3}$ = 9.8 Hz, 2-H), 3.95 (dd, 1H, 3-H), 1.13 – 1.05 (3 × s, 27H, $C(CH_3)_3$). – $C_{34}H_{46}O_8S$ (614.8): calcd. C 66.43, H 7.54, S 5.21; found C 66.40, H 7.27, S 4.97.

Pivaloylation of 4,6-O-benzylidene-thio-galacto-pyranosides

To the phenyl 4,6-O-benzylidene-thio-galactopyranoside (*ca.* 0.5 mmol) in pyridine (20 ml) pivaloyl chloride (1.5 g, 12 mmol) was added. After stirring for 20 h, pyridine

was evaporated *in vacuo*, two codistillations with toluene (10 ml) were carried out, the residue was dissolved in diethyl ether (50 ml) and the solution was washed with 2 N HCl (30 ml), sat. $NaHCO_3$ solution (30 ml) and water. After drying with $MgSO_4$ and evaporation of the solvent *in vacuo*, the crude product was purified by flash-chromatography in light petroleum/ethyl acetate (4:1).

*Phenyl 3-O-allyl-4,6-O-benzylidene-2-O-pivaloyl-1-thio-β-D-galactopyranoside (***24***)*

The compound was obtained according to the general procedure from **22** (1.5 g, 4.7 mmol). Yield: 2.0 g (87%), colourless crystals, m. p. 132 – 133 °C; $[\alpha]_D^{22} = -9.5$ (c 1, $CHCl_3$); R_f = 0.83 (light petroleum/ethyl acetate 1:2). – ^{1}H NMR (DMSO-d_6): δ = 5.61 (S, 1H, CHPh), 5.06 – 4.97 (m, 2H, 1-H, 2-H), 4.46 (d, 1H, $J_{3,4}$ = 3.2 Hz, 4-H). – ^{13}C NMR (DMSO-d_6): δ = 132.91(C_{ipso} of SPh), 116.29 (=CH_2), 99.79 (CHPh), 84.24 (C-1). – $C_{27}H_{32}O_6S$ (484.6): calcd. C 66.92, H 6.66, S 6.62; found C 66.94, H 6.57, S 6.68.

*Phenyl 3-benzyl-4,6-O-benzylidene-2-O-pivaloyl-1-thio-β-D-galactopyranoside (***25***)*

The compound was obtained according to the general procedure from **23** (0.30 g, 0.66 mmol). Yield: 0.2 g (59%), colourless crystals, m. p. 153 – 154 °C; $[\alpha]_D^{22} = -4.1$ (c 0.5, $CHCl_3$); R_f = 0.43 (light petroleum/ethyl acetate 1:2). – ^{1}H NMR (DMSO-d_6): δ = 5.64 (s, 1H, CHPh), 5.07 (t, 1H, $J_{1,2} = J_{2,3}$ = 9.8 Hz, 2-H), 5.01 (d, 1H, 1-H), 4.54 (d, 1H, $J_{3,4}$ = 3.2 Hz, 4-H), 3.85 (dd, 1H, $J_{2,3}$ = 9.3 Hz, 3-H), 3.77 (s, 1H, 5-H). – ^{13}C NMR (DMSO-d_6): δ = 132.91 (C_{ipso}, SPh), 99.81 (CHPh), 84.21 (C-1). – $C_{31}H_{34}O_6S$ (534.7): calcd. C 69.64, H 6.41, S 6.00; found C 69.62, H 6.45, S 6.34.

*Methyl 2-azido-(3-O-benzyl-4,6-O-benzylidene-2-O-pivaloyl- βD-galactopyranosyl)-4,6-O-benzylidene-2-deoxy-β-D-galactopyranoside (***27***)*

To a suspension of **25** (1.3 g, 2.4 mmol), **6b** (0.6 g, 1.95 mmol) and molecular sieves 4 Å in dry dichloromethane (30 ml) under argon atmosphere, 2,6-di-*tert*-butyl-pyridine (0.5 ml, 2.5 mmol) and dimethyl methylthiosulfonium trifluoromethanesulfonate (DMTST) [24] (0.52 g, 2 mmol) were added. After stirring for 2 h at room temperature, filtration through Celite® and evaporation of the solvent from the filtrate, the crude product was dissolved in ethyl acetate. After dropwise addition of light petroleum, the crystalline product **27** precipitated. Yield: 1.17 g (82%); m. p. > 250 °C; $[\alpha]_D^{22}$ = +47.9 (c 1, $CHCl_3$); R_f = 0.48 (light petroleum/ethyl acetate 1:2).- ^{1}H NMR (DMSO-d_6): δ = 5.66 (s, 1H, CHPh), 5.62 (s, 1H, CH'Ph), 5.02 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 10.1 Hz, 2'-H), 4.84 (d, 1H, 1'-H), 4.41 (d, 1H, $J_{1,2}$ = 8.0 Hz, 1-H), 4.37 (d, 1H, $J_{3,4}$ = 3.4 Hz, 4-H), 3.81 (dd, 1H, $J_{2,3}$ = 10.1 Hz, $J_{3,4}$ = 3.5 Hz, 3'-H), 3.70 (dd, 1H, $J_{2,3}$ = 10.5 Hz, 3-H), 3.66 (s, 1H, 5'-H), 3.59 (s, 1H, 5-H), 3.47 (s, 3H, OCH_3), 3.44 (dd, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 10.6 Hz, 2-H). – ^{13}C NMR (DMSO-d_6): δ = 101.98 (C-1), 100.63 and 99.62 (2 × CHPh), 99.28 (C-1'). – $C_{39}H_{45}N_3O_{11}$ (731.8): calcd. C 64.01, H 6.22, N 5.74; found C 63.87, H 6.16, N 6.00.

*Methyl 2-azido-3-O-(3-allyl-4,6-O-benzylidene-2-O-pivaloyl-β-D-ga1actopyranosyl)-4,6-O-benzylidene-2-deoxy-α-D-galactopyranoside (***26***)*

In analogy to the preparation of **27**, compound **26** was synthesised from **24** (1.30 g, 1.23 mmol), **6a** (0.38 g, 1.23 mmol) and 2.6 g (1.0 mmol) DMTST. Yield: 0.45 g (66%); colourless solid, m.p. 186 – 188 °C; $[\alpha]_D^{22}$ = +147.7 (c 1, $CHCl_3$); R_f = 0.29 (light petroleum/ethyl acetate 1:2). – ^{1}H NMR ($CDCl_3$): δ = 5.55 (s, 1H, CHPh), 5.53 (s, 1H, CHPh'), 5.35 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 10.1 Hz, 2'-H), 4.92 (d, 1H, $J_{1,2}$ = 3.3 Hz, 1-H), 4.88 (d, 1H, $J_{1,2}$ = 7.9 Hz, 1'-H), 4.44 (d, 1H, $J_{3,4}$ = 3.1 Hz, 4'-H), 3.77 (dd, 1H, $J_{1,2}$ = 3.3 Hz, $J_{2,3}$ = 10.7 Hz, 2-H), 3.59 (dd, 1H, 3'-H), 3.44 (s, 3H, OCH_3). – ^{13}C NMR ($CDCl_3$): δ = 101.05 (C-1'), 100.66, 100.35 (2 × CHPh), 99.97 (C-1). – $C_{35}H_{43}N_3O_{11}$ (681.7): calcd. C 61.66, H 6.36, N 6.16; found C 61.67, H 6.28, N 6.11.

*O-(2,3,4,6-Tetra-O-pivaloyl-α/β-D-galactopyranosyl) trichloroacetimidate (***28a**/**b***)*

2,3,4,6-Tetra-O-pivaloyl-D-galactopyranose: Pivaloylbromogalactose **2** (1.5 g, 2.59 mmol) was dissolved in acetone (10 ml) and water (0.18 ml). At 0 °C silver carbonate was added. After stirring for 30 min. and filtration through silica gel, the solvent was evaporated *in vacuo* to give the crude tetra-pivaloylgalactose quantitatively: 1.3 g, $[\alpha]_D^{22}$ = +51.9 (c 1, $CHCl_3$).

The compound was carefully dried. To this compound (0.8 g, 1.56 mmol) in dichloromethane (5 ml), trichloroacetonitrile (0.46 ml, 4.6 mmol) was added dropwise. Subsequently, dried potassium carbonate (0.36 g) was added. After stirring for 24 h and filtration through Celite®, the solvent was evaporated *in vacuo*, and the product was purified by chromatography in light petroleum/ethyl acetate (7:1) to give **28a/b** ($\alpha : \beta$ = 1:3) as a colourless solid. Yield: 0.89 g (86%), R_f = 0.50, α-anomer (**28a**), 0.38, β-anomer (**28b**) (light petroleum/ethyl acetate 6:1). $C_{18}H_{44}NO_{10}Cl_3$ (661.0): calcd. C 50.88, H 6.71, N 2.12; found C 51.16, H 6.65, N 2.38.

For further identification, the anomers were separated by column chromatography: α-anomer (**28a**): $[\alpha]_D^{22}$ = +80.4 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 8.64 (s, 1H, NH), 6.59 (d, 1H, $J_{1,2}$ = 3.7 Hz, 1-H), 5.56 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 1.1 Hz, 4-H), 5.53 (dd, 1H, $J_{2,3}$ = 10.6 Hz, 3-H), 5.39 (dd, 1H, 2-H). β-anomer (**28b**): $[\alpha]_D^{22}$ = +6.7 (c 1, $CHCl_3$); – ^{1}H NMR ($CDCl_3$): δ = 8.67 (s, 1H, NH), 5.94 (d, 1H, $J_{1,2}$ =

8.2 Hz, 1-H), 5.48 – 5.43 (m, 2H, 4-H, 2-H), 5.19 (dd, 1H, $J_{2,3}$ =10.3 Hz, $J_{3,4}$ = 3.3 Hz, 3-H).

*2-Methyl-4,5-(5,6-isopropylidene-α-D-glucofurano)-Δ²-oxazoline (**30**)*

To a stirred solution of N-acetyl-glucosamine [25] (**29**) (6.6 g, 30 mmol) in dry acetone (300 ml) at 0 °Cboron trifluoride etherate (1.32 ml, 3.5 equivalents) was added dropwise. After stirring for some hours at room temp., **29** was completely dissolved. After stirring for 24 h, the deeply red solution was poured into 2 N sodium hydroxide solution (250 ml). The solution was extracted with chloroform (5 × 100 ml), the combined organic layers were dried with $MgSO_4$, and the solvents were evaporated *in vacuo*. Purification of the brown oil was achieved by chromatography in toluene/ethanol (6:1) on 300 g of silica gel. This chromatography was repeated and gave **30** as a colourless oil. Yield: 4.2 g (60%), $[\alpha]_D^{22} = -3.3$ (c 1, $CHCl_3$); R_f = 0.51 (toluene/ethanol 3:1). ^{1}H NMR ($CDCl_3$): δ = 6.10 (d, 1H, $J_{1,2}$ = 5.1 Hz, 1-H), 4.43 (s, 1H, OH), 4.37 (m, 1H, 2-H), 4.30 – 4.25 (m, 2H, 3-H, 5-H), 4.06 (dd, 1H, $J_{5,6a}$ = 6.2 Hz, $J_{6a,6b}$ = 8.8 Hz, 6a-H), 3.95 (dd, 1H, $J_{5,6b}$ = 4.9 Hz, 6b-H), 3.67 (dd, 1H, $J_{4,5}$ = 7.8 Hz, $J_{3,4}$ = 2.8 Hz, 4-H), 1.96 (d, 3H, $^5J_{CH3,H-2}$ = 1.2 Hz, CH_3-oxazoline), 1.35 and 1.28 (2 × s, 2 × 3H, CH_3-isopropylidene); ^{13}C NMR ($CDCl_3$): δ = 167.0 (C=N), 109.3 (isopropylidene), 107.1 (C-1), 81.8 (C-2), 14.0 (CH_3-CN). – $C_{11}H_{17}NO_5$ (243.26): calcd. C 54.31, H 7.04, N 5.76; found C 54.31, H 7.38, N 5.69.

*Benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)-α-D-glucopyranoside (**32b**) and the corresponding (- - -α-D-galactopyranosyl)-α-D-glucopyranoside (**32a**)*

In a brown glass flask under argon atmosphere, benzyl 2-acetamido-4,6-O- benzylidene-2-deoxy-α-D-glucopyranoside [20] (**31**) (1.5 g, 3.76 mmol) and pivalobromogalactose **2** (2.9 g, 5 mmol) were dissolved in dry dichloromethane (30 ml). Molecular sieves 4 Å were added to the stirred solution. After cooling to 10 °C, silver triflate (1.3 g, 5 mmol) and tetramethyl urea (TMU, 1.35 g, 12 mmol) dissolved in dry dichloromethane (20 ml) were added dropwise. The mixture was stirred at room temp. for 6 h, then additional galactosyl bromide **2** (1.45 g, 2.5 mmol), AgOTf (0.65 g, 2.5 mmol) and TMU (0.7 g, 6 mmol) were added. After 28 h the conversion was complete, the mixture was filtered through Celite®, the filtrate dried with $MgSO_4$ and the solvent evaporated *in vacuo*. Purification and separation was achieved by chromatography on silica gel (300 g) in light petroleum/ethyl acetate (2:1). If necessary, a second chromatography in light petroleum/ethyl acetate (3:1) is carried out.

β-anomer (**32b**): Yield: 2.63 g (79%); colourless oil; $[\alpha]_D^{22}$ = +34.5 (c 1, CH Cl_3); R_f = 0.51 (light petroleum/ethyl acetate 1:1). – ^{1}H NMR ($CDCl_3$) δ = 5.68 (d, 1H, J = 6.7 Hz, NH), 5.54 (s, 1H, CHPh), 5.29 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 2.4 Hz, 4'-H), 5.19 (d, 1H, $J_{1,2}$ = 3.4 Hz, 1-H), 5.10 (dd, 1H, $J_{1,2}$ = 7.5 Hz, $J_{2,3}$ = 10.3 Hz, 2'-H), 5.02 (dd, 1H, 3'-H), 4.84 (d, 1H, $J_{1,2}$ = 7.5 Hz, 1'-H), 4.66 and 4.43 (2 × d, 2x1H, J_{gem} = 11.5 Hz, CH_2-Ph), 4.23 (dd, 1H, $J_{5,6a}$ = 4.2 Hz, $J_{6a,6b}$ = 9.9 Hz, 6a-H), 4.14 (m, 1H, 2-H), 4.03-3.93 (m, 3H, H-3, 6'-H), 3.86 (m, 1H, 5-H), 3.80 – 3.70 (m, 2H, H-4, 6b-H), 3.67 (m, 1H, 5-H). – ^{13}C NMR ($CDCl_3$): δ = 100.4 (C-1'), 97.4 (C-1). – $C_{48}H_{67}NO_{15}$ (898.1): calcd. C 64.20, H 7.52, N 1.56; found C 64.04, H 7.65, N 1.78.

α-anomer (**32a**): Yield: 0.57 g (17%); colourless oil, $[\alpha]_D^{22}$ = +73.9 (c 1, $CHCl_3$; R_f = 0.56 (light petroleum/ethyl acetate 1:1). – ^{1}H NMR ($CDCl_3$): δ = 5.89 (s, 1H, NH), 5.66 (d, 1H, $J_{1,2}$ = 3.5 Hz, 1'-H), 5.44 (m, 2H, 4'-H, CHPh), 5.28 (dd, 1H, $J_{3,4}$, 3.0 Hz, $J_{2,3}$ = 10.5 Hz, 3'-H), 5.22 (dd, 1H, $J_{2,3}$ = 10.9 Hz, 2'-H), 4.86 (d, 1H, $J_{1,2}$ = 3.9 Hz, 1-H), 4.68 (d, 1H, J_{gem} = 12 Hz, CH_{2a}-Ph), 4.49 (m, 2H, CH_{2b}Ph, 5'-H), 4.42 (m, 1H, 2-H), 4.20 (dd, 1H, $J_{3,4}$ = 10.3 Hz, $J_{4,5}$ = 4.8 Hz, 4-H), 4.13 (dd, 1H, $J_{5,6a}$ = 8.2 Hz, $J_{6a,6b}$ = 11.4 Hz, 6a'-H), 4.04 (dd, 1H, $J_{2,3}$ = 9.0 Hz, 2-H), 3.92 (dd, 1H, $J_{5,6b}$ = 6.3 Hz, 6b'-H), 3.86 (m, 1H, 5-H), 3.75 – 3.64 (m, 2H, 6-H). – ^{13}C NMR ($CDCl_{13}$): δ = 97.1 (C-1), 96.0 (C-1'). – $C_{48}H_{67}NO_{15}$ (898.1): calcd. C 64.04, H 7.52, N 1.56; found C 64.93, H 7.60, N 1.77.

*Ethyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-3-O-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside (**34**)*

To a solution of ethyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside [26] (**33**) (5 g, 11.3 mmol) and ethyldiisopropylamine (Huenig's base, 2.6 ml, 15.2 mmol) in dry dichloromethane (250 ml) under argon atmosphere molecular sieves 4 Å were added. After stirring for 30 min silver triflate (3.9 g, 15.2 mmol) was added, and subsequently a solution of **2** (8.5 g, 14.7 mmol) in dry dichloromethane (100 ml). After 6 h additional AgOTf (1.95 g, 7.6 mmol), Huenig's base (1.3 ml, 7.6 mmol) and subsequently (**2**) (4.25 g, 7.3 mmol) dissolved in dichloromethane (50 ml) were added. The stirring was continued for 24 h. The mixture was filtered through Celite®, the solution washed with water (100 ml), 2 N HCl (300 ml), sat. $NaHCO_3$ solution (300 ml) and water and dried with $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified in two portions by chromatography on silica gel (200 g) in light petroleum/ethyl acetate (8:1) to give **34**. Yield: 7.7 g (72%); colourless amorphous solid; $[\alpha]_D^{22}$ = +2.8 (c 1, $CHCl_3$); R_f = 0.59 (light petroleum/ethyl acetate 2.5:1). The separated α-anomer (ratio $\alpha : \beta$ < 1:22, HPLC) has R_f = 0.61. – ^{1}H NMR ($CDCl_3$): δ = 5.53 (s, 1H, CHPh), 5.26 (d, 1H, $J_{1,2}$ = 10.6 Hz, 1-H), 5.20 (dd, 1H, $J_{3,4}$ = 3.1 Hz, $J_{4,5}$ = 0.8 Hz, 4'-H), 4.93 (dd, 1H, $J_{2,3}$ = 10.3 Hz, $J_{1,2}$ = 7.6 Hz, 2'-H), 4.88-4.82 (m, 2H, 3'-H, 3-H), 4.66 (d, 1H,

1'-H), 4.45 (t, 1H, 2- H), 4.36 (dd, 1H, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 10.4 Hz, 6a-H), 3.99 (m, 2H, 6'-H), 3.88 – 3.78 (m, 2H, 4-H, 6b-H), 3.67 (m, 1H, 5-H), 3.55 (m, 1H, 5'-H), 2.69 – 2.58 (m, 2H, CH_2S). – ^{13}C NMR ($CDCl_3$): δ = 101.8 (CHPh), 98.8 (C-1'), 82.0(C-1). – $C_{49}H_{65}NO_{15}S$ (940.0): calcd. C 62.61, H 6.97, N 1.49; found C 62.62, H 7.00, N 1.52.

As a by-product, the corresponding orthoester was isolated: $[\alpha]_D^{22}$ = +7.1 (c 1, $CHCl_3$); R_f = 0.64 (light petroleum/ethyl acetate 2:1). – ^1H NMR ($CDCl_3$): δ = 5.41 (d, 1H, $J_{1,2}$ = 4.0, 1'-H), 5.37 (d, 1H, $J_{1,2}$ = 10.6 Hz, 1-H). – ^{13}C NMR ($CDCl_3$): δ = 129.8 (CO_3-orthoester), 101.1 (CHPh), 95.8 (C-1'), 81.9 (C-1).

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