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Synthesis of Positional Thiol Analogs of β-D-Galactopyranose

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Approaches toward the synthesis of thio-β-D-galactose derivatives are described. These compounds were prepared from the parent carbohydrates: D-galactose, methyl β-D-galactoside and methyl β-D-glucoside, respectively. It was found that not only the strategies of protecting group introduction and selective deprotection, but also the choices of solvent and nucleophilic reagent concentration were crucial to allow the efficient introduction of sulfur at different positions of the galactose ring. The effects from the solvent, the nucleophilic reagent concentration, and the protecting group patterns have been investigated. The results clearly show that ester protecting groups play highly important roles for the synthesis of thio-containing carbohydrates, requiring nonpolar solvents to suppress the neighboring group participation. For the Lattrell–Dax (nitrite-mediated) inversion reaction, employed in the synthetic route to the 2-thio-β-D-galactoside, intramolecular nucleophilic attack, as well as stronger stereospecific ester activation, are necessary to overcome hindrance from 4,6-O-benzylidene protection.

Introduction

Interactions between carbohydrates and proteins are increasingly being recognized as crucial in many biological processes, and form the main device for a variety of cellular events such as adhesion, communication, proliferation, and cell death. In addition, carbohydrate recognition is involved in important disorders in, for example, infectious diseases and cancer.[1–6] To thoroughly understand and control these interactions, and to be able to develop new therapies and drugs, well-defined carbohydrate ligands need to be synthesized. Thioglycosides, where the glycosidic oxygen atom is replaced with sulfur are often the glycosyl donors of choice for the synthesis of thio-oligosaccharides. Investigations of protein-thio-oligosaccharide binding indicate that thiolinkages offer a higher degree of flexibility between glycols units and possess more conformers than their natural *O*-linked ligands.[7] This effect is also shown for the related glycosyldisulfides, resulting in the coverage of larger conformational space in the binding site due to the increased flexibility and extended length of the disulfide bond compared to natural *O*-glycosides.[8,9] Furthermore, *S*-linked oligosaccharides also have an additional benefit over their *C*-linked counterparts when used as enzyme inhibitors: the interglycosidic sulfur atom may act as a hydrogen-bond acceptor which, as in the natural substrate, could play an important role in binding of the ligand.[10,11]

Thio-β-D-galactopyranosides are in this sense especially important compounds for the study of biological processes, since the galactose motif is ubiquitous in bioactive carbohydrate structures. For example, in an early study, the binding of a series of alkyl or aryl 1-thio-β-D-galactopyranosides to β-D-galactosidase from *E. coli* was investigated.[12] The results indicated that the *S*-linked structures function as efficient competitive inhibitors, not being degraded by the enzyme. Moreover, galectins constitute a family of structurally related β-galactoside-binding proteins of increasing importance in for example cancer processes.[3]

Efficient synthetic protocols to thio-β-D-galactopyranoside derivatives are thus of high interest, since these structures can serve as acceptors in the synthesis of bioactive

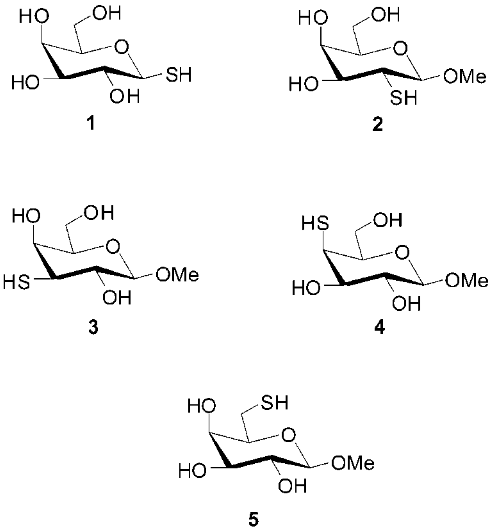

Figure 1. Thio-β-D-galactopyranosides targeted.

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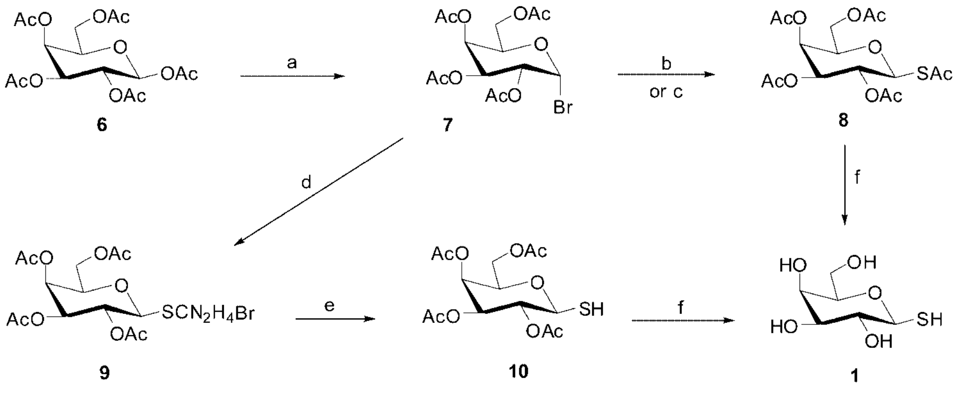
thio-oligosaccharides. Syntheses of different thiosaccharides have also been developed by several research groups for the use as biological probes, potential protein or enzyme inhibitors.[13,14] However, a systematic investigation of the synthesis of the positional thio-β-D-galactose derivatives has not been performed. This issue has been addressed in this study, where a full range of thio-β-D-galactose derivatives has been synthesized (Figure 1). The effects of the nucleophile, the solvent, and the protecting pattern have furthermore been investigated.

Results and Discussion

Regioselectivity is a well-known problem in carbohydrate chemistry due to several hydroxy groups of similar reactivity. Therefore, strategies of protecting group introduction and selective deprotection are essential in carbohydrates synthesis. The most common hydroxy groups protecting groups are esters, ethers, and acetals, where especially, acetyl, benzoyl, benzyl and benzylidene groups are frequently used. However, for sulfur-containing carbohydrates, the benzyl ether group is less attractive because of deprotection difficulties by common reduction protocols.[15] Organic sulfur compounds are very poisonous to metal hydrogenation catalysts, consequently hampering the deprotection. Thus, the ester and benzylidene protecting groups remain the more prevalently used for the synthesis of sulfur-containing carbohydrates. Selective protection protocols can furthermore be used to generate a variety of structures by hydroxy epimerization strategies. For example, epimerization of carbohydrate structures to the corresponding epi/hydroxy stereoisomer by the Lattrell–Dax (nitrite-mediate) inversion reaction is an efficient means to generate compounds with inverse configuration. Enhanced control of this reaction can also be achieved by stereospecific ester activation,[16] where neighboring ester groups are important for the inversion reactivity. Furthermore, the protecting group pattern during the inversion of the equatorial hydroxy group at C-2 proved especially sensitive, and 4,6-*O*-benzylidene protection resulted in low conversions. Consequently, the ester protecting strategy is essential for the synthesis of sulfur-containing carbohydrates when Lattrell–Dax epimerization protocols are employed. However, due to neighboring group participation of ester functionalities in triflate-activated carbohydrates, where 5- or 6-membered acyloxonium intermediates may form during thiolation, the solvent also plays important roles.[17]

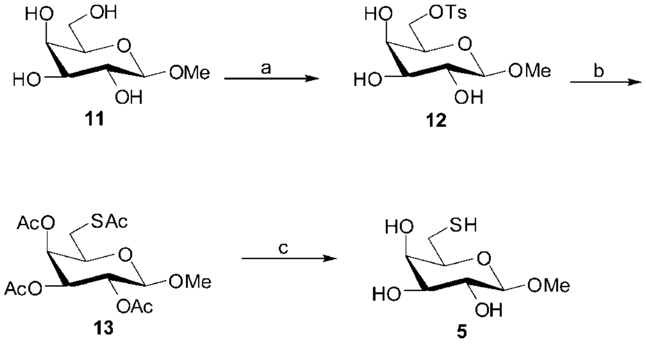
Compound **1** can easily be synthesized following standard coupling methods at the anomeric center. Two main strategies for the synthesis of **1** have been developed from the corresponding glycosyl bromide **7**, both of which in few steps using either thioacetate or thiourea coupling.[18,19] A drawback of the first, two-phase method (pathway **b** in Scheme 1),[13] is that hydrolysis of **7** generated the byproduct in the aqueous phase, thus decreasing the yields. In the alternative thiourea approach (pathways **d-e-f** in Scheme 1),[19] the advantage was to avoid byproduct formation, and obtain compound **10**, which can be used for 1-*S* glycosylation protocols. The overall yield was, however, not improved. A more direct solution to the problem is presented as the new, modified pathway **c-f** in Scheme 1. Treatment of the glycosyl bromide directly with tetrabutylammonium thioacetate in dry toluene or potassium thioacetate in dry acetone, afforded the thioglycoside in high yield (59% over three steps).

Compound **5** can also be easily produced due to the ease of functionalization of the primary 6-OH group compared to the secondary hydroxy groups. Synthesis of compound **5** was reported by Wachter and Branchaud, however devoid of any analytical data.[20] The synthetic route of compound **5** is outlined in Scheme 2. Tosylation of **11** with tosyl chloride, subsequent acetylation, displacement with thioacetate, and final deprotection afforded compound **5** in good yield. It has previously been shown, for other carbohydrate derivatives, that this strategy can be simplified to circumvent the non-acetylated intermediate **13** in the reaction sequence.[21]



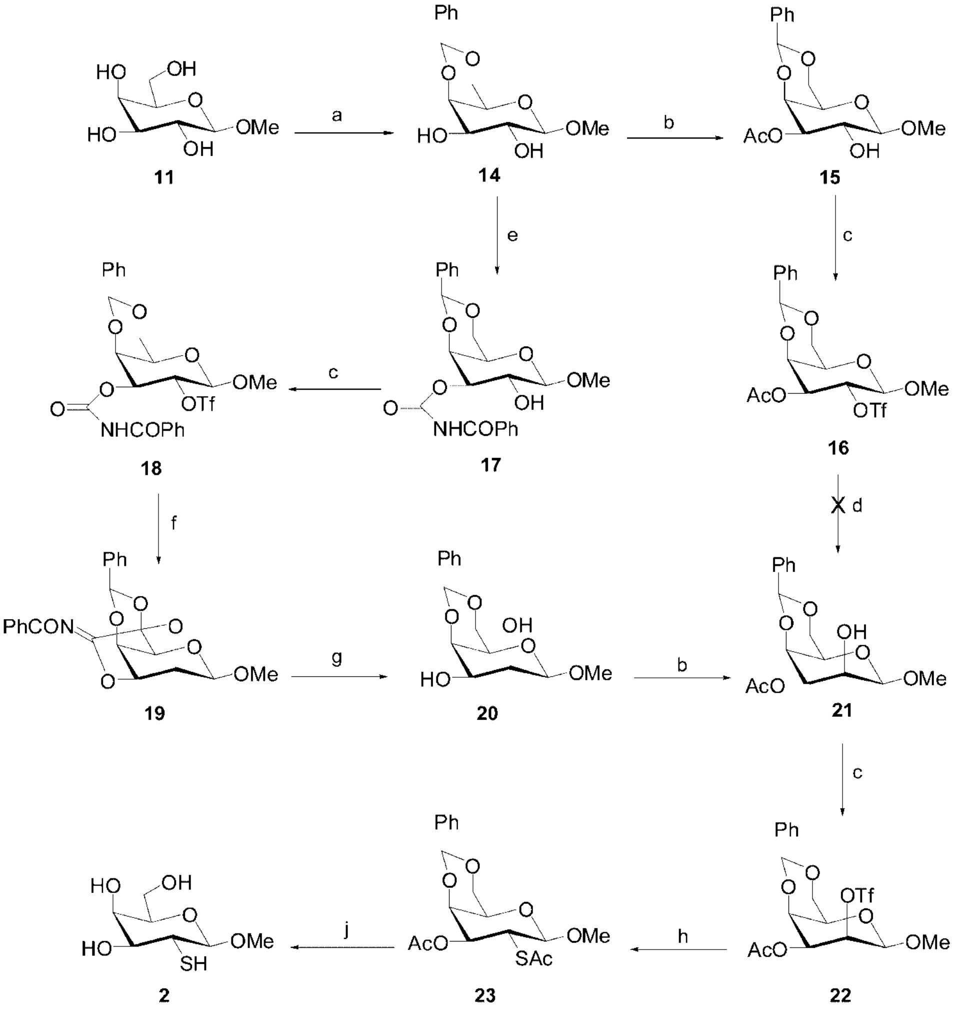
Scheme 1. Synthesis of 1-thio-β-D-galactopyranose (**1**); (a) HOAc-HBr, CH_2Cl_2, room temp., overnight, 70%; (b) HSAc, 1 M Na_2CO_3, CH_2Cl_2, $TBAHSO_4$, room temp., 2 h, 55%; (c) i: TBASAc, toluene, room temp., 2 h; or ii: KSAc, acetone, room temp., 2 h, 88%; (d) thiourea, DMF or acetone, 60 °C, 4 h, 69%; (e) ethanolamine, acetone, 60 °C, 2 h, 81%; (f) NaOMe, MeOH, room temp., 2 h, 95%.

Attempts to apply this strategy in the present case however proved less successful. Treatment of compound **12** with potassium thioacetate in DMF failed to produce a non-acetylated intermediate.



Scheme 2. Synthesis of methyl 6-thio-β-D-galactopyranoside (**5**); (a) TsCl, pyridine, 0 °C to room temp., 2 h, 72%; (b) i: Ac_2O, pyridine, DMAP, room temp., 3 h; ii: KSAc, DMF, 60 °C, 2 h, 68%; (c) NaOMe, MeOH, room temp., 2 h, 93%.

Efficient synthetic routes to **2** have not been coherently reported in the literature. When designing a viable synthesis to this compound, we opted for an inversion strategy. Methyl β-D-galactoside was preferably chosen as starting material due to the low cost, and for this reason, a suitable methyl taloside derivative, where the hydroxy group in the 2-position was free and all other positions were protected, was necessary for the synthesis of the 2-*S* galactose derivatives. In this case, the inversion of the equatorial OH at C-2 in the galactose derivative initially had to be performed. As mentioned above, an efficient route to OH inversion in carbohydrate chemistry involves the triflation of a given hydroxy group, followed by inversion with nitrite (Lattrell–Dax reaction).[16,22–27] However, an investigation of the literature revealed surprisingly few examples of the inversion of the equatorial OH at C-2, using this or other methods. Interestingly, a literature report for the inversion of an



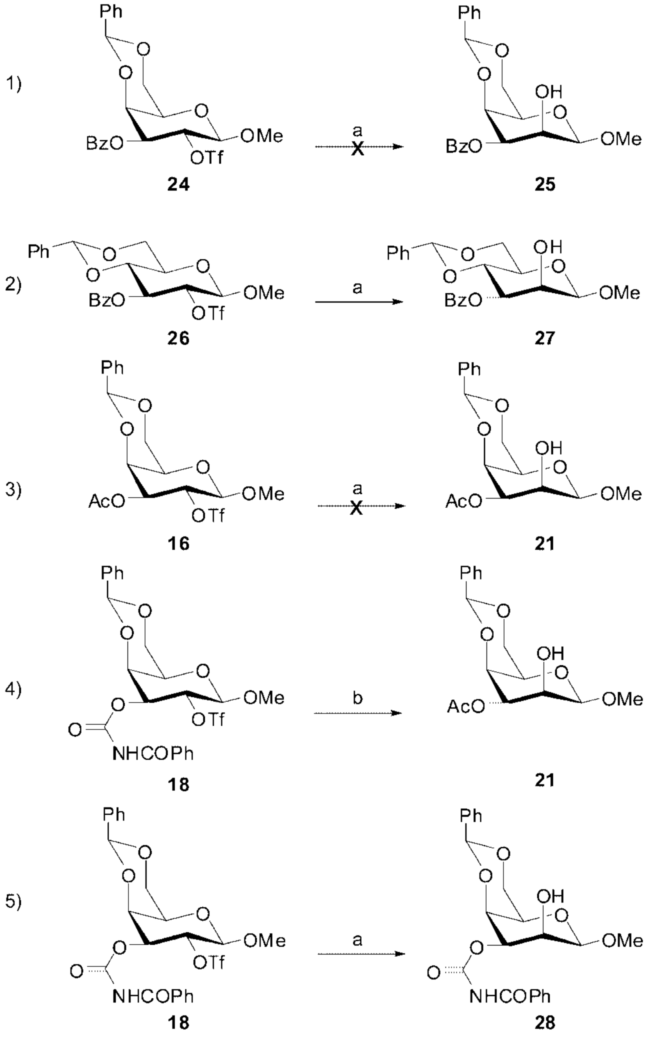
Scheme 3. Synthesis of 2-thio-β-D-galactopyranoside (**2**); (a) $PhCH(OMe)_2$, TsOH, DMF, room temp., 16 h, 70%; (b) i: Bu_2SnO, dry MeOH, reflux, 2 h; ii: Ac_2O, DMF, room temp., 2 h, 72%; (c) Tf_2O, pyridine, CH_2Cl_2, –30 to 0 °C, 2 h; (d) $TBANO_2$, toluene, 50 °C, 2 h; (e) PhCONCO, CH_2Cl_2, –30 to 0 °C, 3 h, 60%; (f) NaH, THF, 0 °C to room temp., 3 h; (g) NaOH, THF, room temp., 12 h, then 80 °C, 3 h, 82% for 2 steps; (h) TBASAc, toluene, room temp., 2 h, 68%; (j) i: NaOMe, MeOH, 2 h; ii: $CHCl_3$, HCl, H_2O, room temp., 87%.

equatorial OH at C-2 in the methyl α-D-glucoside derivative, where the 2-OH was free and the other hydroxy groups protected following a 4,6-*O*-benzylidene/3-OBz protecting strategy, showed that the reaction was performed at 80 °C for 6 hours.[23] In addition, our previous study for inversion of an equatorial OH at C-2 in methyl β-D-glucoside derivatives, where the same protecting group strategy was used, indicated that the reaction could only be performed at 50 °C for 6 h.[16] Clearly, this suggested that the inversion of an equatorial OH at C-2 is considerably more difficult compared to the common inversion reactions. In these studies, the 4,6-*O*-benzylidene functionality was prevalently used because of the selective and simultaneous protection of two hydroxy groups.

Consequently, our preliminary efforts toward the synthesis of **2** were to try to obtain the key intermediate talose derivative **21** (pathway **a-b-c-d** in Scheme 3). The 4,6-*O*-benzylidenegalactoside derivative treated with tin dioxide, followed by benzoyl chloride or acetic anhydride, selectively rendered the key galactoside derivative, where the 2-OH was free and all other hydroxy groups protected using a 4,6-*O*-benzylidene/3-OBz or 3-OAc protecting strategy. The key talose derivative could then be obtained from the key compound through the Lattrell–Dax inversion reaction.

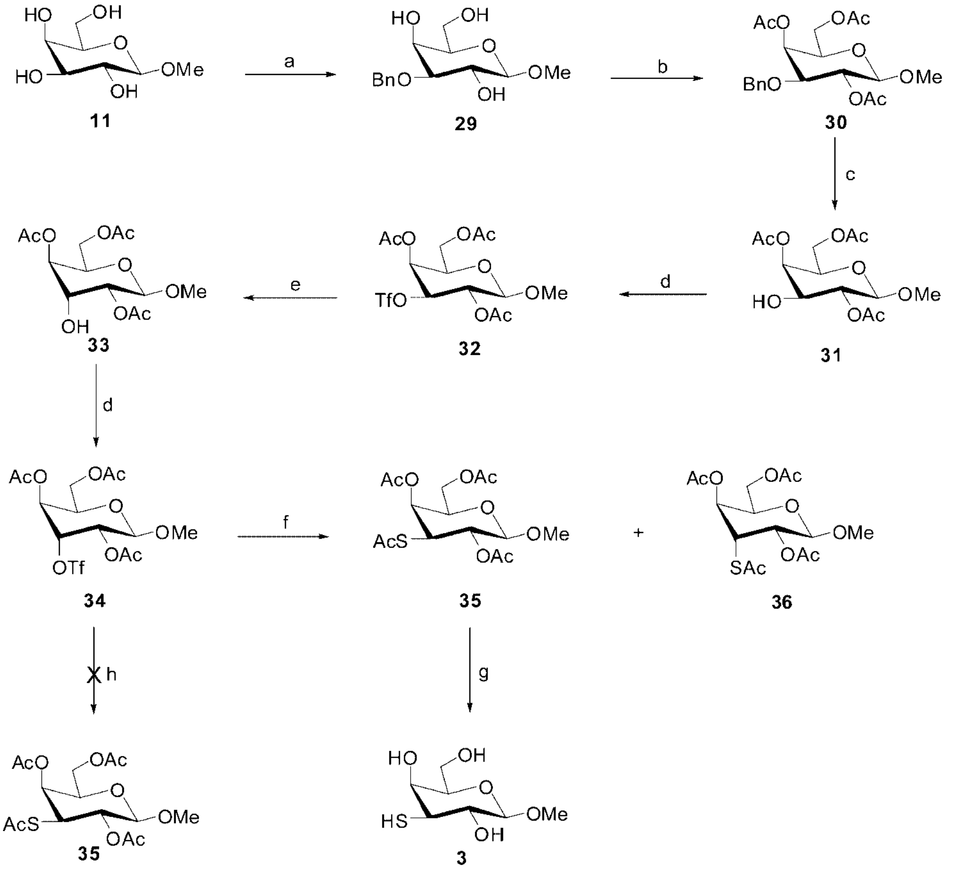
Introduction of a triflate at C-2 in **21** followed by the S_N2 reaction with KSAc provided the desired **23**, which should be easily deprotected to afford **2** (pathway **c-h-j** in Scheme 3). Unfortunately, treatment of galactose derivative **16** with KNO_2 failed to afford the inversion talose derivative **21**. This is likely to be due to steric hindrance from the 4,6-*O*-benzylidene group in the key intermediate of this synthetic route. In an attempt to overcome this problem, the strategy shown at pathway **e-c-f-g** in Scheme 3 was instead tested. The intramolecular benzoylcarbamate *O*-cyclization has been investigated to illustrate that it was an efficient means to overcome the steric hindrance problem for the inversion reaction.[26] Treatment of **14** with benzoyl isocyanate gave **17**, where the selective carbamoylation was performed at C-3 in **14**. Treatment of **17** with triflic anhydride then afforded the cyclization substrate **18**. Treatment of **18** with sodium hydride, and subsequent hydrolysis under more vigorous basic conditions gave inversion product **20**. Finally, product **2** was successfully synthesized according to the synthetic route **a-e-c-f-g-b-c-h-j** in Scheme 3.

To further study the effects of the protecting group pattern as well as the configuration pattern in the inversion of the equatorial 2-OH in β-D-galactose derivatives, several different inversion routes were probed (Scheme 4). As can be seen, galactose derivative **24**, where the 2-OH was free and the other hydroxy groups protected using a 4,6-*O*-benzylidene/3-OBz protection strategy, failed to undergo the inversion reaction (entry **1** in Scheme 4), whereas the inversion reaction for the analog glucose derivative **26** was successful (entry **2** in Scheme 4). As a comparison, the inversion reaction of an alternative galactose derivative **16**, using 3-OAc instead of 3-OBz, was tested (entry **3** in Scheme 4), however also failing to furnish the inversion product. The results suggest that the steric hindrance from the 4,6-*O*-benzylidene group for the inversion reaction in the galactose derivative compared to glucose derivative. In an attempt to overcome the effects from the 4,6-*O*-benzylidene group, the 4-OH and 6-OH groups in compound **24** were instead protected with benzoyl groups. However, subsequent thiolation with thioacetate in DMF or toluene afforded the 2,3-elimination product as a major component, and only traces of inversion product. Nonetheless, an intramolecular relatively strong nucleophilic reagent can overcome the hindrance from the 4,6-*O*-benzylidene group to afford the inversion product (entry **4** in Scheme 4). Furthermore, the results could also imply a potentially stronger activation effect from the benzoylcarbamate moiety compared to an ester group (entry **5** in Scheme 4).



Scheme 4. Inversions at C-2; (a) $TBANO_2$, CH_3CN, or KNO_2, DMF, 50 °C; (b) i: NaH, THF, 0 °C to room temp., 3 h; ii: NaOH, THF, room temp. to 80 °C; iii: Bu_2SnO, MeOH, reflux; iv: Ac_2O, DMF, room temp.

Previous report also suggest that a 4,6-*O*-benzylidene protection pattern plays a very important role in the synthesis of the 3-thio-β-D-galactose derivatives, with the key step involving the conversion of the 3-OTf gulose derivative to the corresponding galactose derivatives.[27,28] In addition,

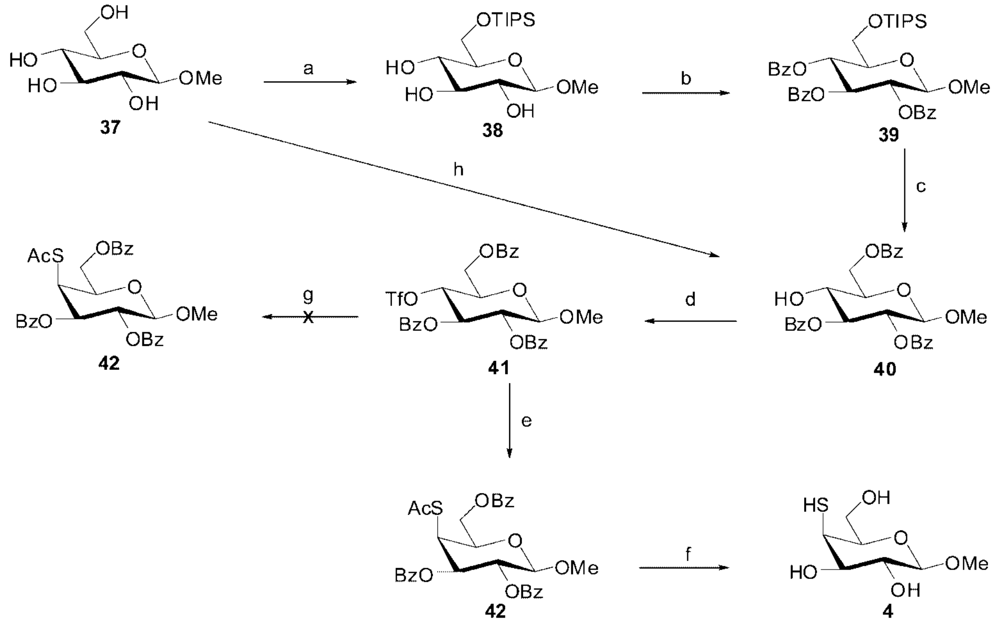


Scheme 5. Synthesis of methyl 3-thio-β-D-galactopyranoside (**3**); (a) i: Bu_2SnO, MeOH, reflux, 2 h; ii: BnBr, TBAI, benzene, reflux, 2 h, 70%; (b) Ac_2O, pyridine, DMAP, room temp., 3 h, 92%; (c) $Pd(OH)_2$, H_2, MeOH, room temp., overnight, 95%; (d) Tf_2O, pyridine, CH_2Cl_2, –30 to 0 °C, 2 h; (e) $TBANO_2$, CH_2Cl_2, 50 °C, 2 h, 62%; (f) TBASAc, toluene, room temp., 4 h, 78%; (g) NaOMe, MeOH, room temp., 2 h, 86%; (h) KSAc, DMF, room temp.

recent reports demonstrated that tetrabutylammonium thioacetate is a useful nucleophile in the successful synthesis of 3-thiogalactose derivatives when esters were used as protecting groups.[29,30] Our initial strategy for the synthesis of the 3-thiogalactose derivative **3** is shown in Scheme 5.

The methyl guloside derivative **33**, where the hydroxy group in the 3-position was free and the other positions were protected with acetyl groups, was essential for the synthesis of the 3-thiogalactose derivative. Compound **33** was also easily obtained in five steps according to the designed synthetic strategy. However, treatment of **33** with triflic anhydride, and subsequent thiolation with KSAc in DMF instead afforded side product **31**, which was generated via the neighboring ester group participation followed by hydrolysis. Our previous study indicated that the efficient stereoselective synthesis of 3-thiogalactose derivative from the corresponding 3-OTf gulose derivatives, where ester protecting groups were used, were highly dependent on the solvent and the nucleophile concentration.[17] In this study, it could be proposed that the choice of the solvent and the nucleophile concentration controlled the product formation. Neighboring group participation could be attenuated by performing the reactions at high nucleophile concentration in toluene. The overall synthetic route for **3** is displayed in Scheme 5. Key intermediate 3-OH gulose derivative **33** was prepared from the corresponding 3-OTf galactose derivative **32**, obtained in 4 steps from methyl β-D-galactoside (route via **a-b-c-d-e** in Scheme 5). Introduction of a triflate group at C-3 in **33** followed by the S_N2 reaction with 40 equiv. of TBASAc in toluene at room temperature provided the desired compound **35**. With this strategy, the byproduct 3-thiogulose derivative **36** was competitively formed in only 4% yield (pathway **f** in Scheme 5). Final deprotection of compound **35** under Zemplén conditions afforded compound **3**.

Synthesis of compound **4** was reported by Maradufu and Perlin, using displacement of the corresponding brosylated glucose derivative and devoid of analytical data for the target compound.[31] In our preliminary study, the key intermediate methyl β-D-glucoside derivative **40**, where the hydroxy group in the 4-position was free and the other positions were protected with benzoyl groups, was obtained in three steps from methyl β-D-glucoside (pathway **a-b-c** in Scheme 6).[32] Initially, methyl β-D-glucoside (**37**) was selectively converted into the corresponding 6-TIPS (triisopropylsilyl) derivative **38** by standard imidazole-activated treatment with TIPSCl in DMF in the presence of imidazole. Subsequent benzoylation of all other positions afforded **39**,



Scheme 6. Synthesis of methyl 4-thio-β-D-galactopyranoside (**4**); (a) TIPSCl, DMF, imidazole, room temp., 1 h; (b) BzBr, DMF, room temp., 2 h, 80% for 2 steps; (c) TBAF, THF, 0 °C, 1 h, 85%; (d) Tf_2O, pyridine, CH_2Cl_2, –30 to 0 °C, 2 h; (e) TBASAc, toluene, room temp., 4 h, 76%; (f) NaOMe, MeOH, room temp., 2 h, 86%; (g) KSAc, DMF, room temp.; (h) i: Bu_2SnO, MeOH, reflux, 2 h; ii: BzCl, toluene, 0 °C to room temp., 6 h, 75%.

which yielded the key intermediate 4-OH glucoside derivative **40** through benzoyl group migration during the fluoride-induced deprotection. More recently, a very convenient route to obtain the key intermediate methyl 4-OH glucoside derivative **40** was however developed, based on a one-pot organotin-mediated multiprotection procedure (pathway **h** in Scheme 6).[33,34] Our initial strategy included the introduction of a triflate at C-4 in compound **40** to afford glucoside **41**, followed by inversion with potassium thioacetate in DMF to yield the desired C-4 inverted compound **42**. Unfortunately, attempted thiolation of compound **41** with potassium thioacetate in DMF afforded a reaction mixture (pathway **g** in Scheme 6). It was assumed that the problem was caused by formation of the six-membered acyloxonium ring arising from the 6-OBz group in the polar solvents. To suppress this neighboring group participation, thiolation of compound **41** with tetrabutylammonium thioacetate in toluene was instead used, in this case, affording the C-4 inverted compound **42** (pathway **e** in Scheme 5). Subsequent deprotection of galactoside **42** yielded compound **4** in good yield.

Conclusions

A range of thio-β-D-galactose derivatives have been successfully synthesized by using the strategies of different protecting group patterns and selective deprotection, as well as the choices of solvent and nucleophilic reagent concentration. The results indicate that ester protecting groups play a highly important role for the synthesis of sulfur-containing carbohydrates, where the inversion of triflated hydroxy groups has to be performed with nitrite anion. Non-polar solvents are efficient to suppress the neighboring group participation when esters are used as protecting groups in thiolation of carbohydrates. The influences on the nitrite-mediate inversion reaction of 2-OTf galactose derivatives as well as glucose derivatives with different protecting patterns have been investigated. It was found that although the inversion of 2-OTf-galactose derivatives was more difficult to perform compared to 2-OTf-glucose derivatives due to the steric hindrance from the 4,6-*O*-benzylidene, the stronger nucleophilic attack, as well as stronger stereospecific ester activation can conquer the hindrance to afford the desired inversion product. In addition, 2-OTf galactose derivatives, using ester protecting groups instead of the 4,6-*O*-benzylidene, was found to be an efficient means for the inversion due to the less hindrance from the ester groups.

Experimental Section

General: All commercially available starting materials and solvents were reagent grade and used without further purification. Chemical reactions were monitored with thin-layer chromatography using precoated silica gel 60 (0.25 mm thickness) plates (Macherey–Nagel). Flash column chromatography was performed on silica gel 60 (SDS 0.040–0.063 mm). Optical rotations were measured with a Perkin–Elmer 343 polarimeter at the sodium D line at ambient temperature. ^1H and ^{13}C-NMR spectra were recorded with a Bruker Avance 400 instrument or a Bruker DMX 500 instrument at 298 K in $CDCl_3$ or D_2O, using the residual signals from $CHCl_3$ (^1H: δ = 7.25 ppm; ^{13}C: δ = 77.0 ppm), and from H_2O (^1H: δ = 4.70 ppm) as internal standard. ^1H peak assignments were made by first order analysis of the spectra, supported by standard ^1H-^1H correlation spectroscopy (COSY). ^{13}C peak assignments were made by first order analysis of the spectra, supported by standard ^1H-

^{13}C correlation spectroscopy (HMQC). Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany. HRMS was carried out by Instrumentstationen, Kemicentrum, Lund University, Sweden.

General Synthesis of Triflate Derivatives: To a solution of the suitably *O*-protected methyl β-D-glycoside derivative, carrying an unprotected OH at C-2, C-3 or C-4 (0.94 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.65 mL) at –20 °C. Trifluoromethanesulfonic anhydride (1.88 mol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred while allowing to warm from –20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification.

General Inversion of Triflate Derivatives: $TBANO_2$ or KNO_2 (5 equiv.) was added to a solution of the above triflate residue in dry toluene (CH_3CN, CH_2Cl_2 or DMF). After stirring at 0 to 50 °C for 1–6 h, the mixture was diluted with CH_2Cl_2 and washed with water, then brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash column chromatography afforded the inversion compounds.

General Procedure for the Synthesis of Thiolacetate Derivatives: TBASAc or KSAc (1–40 equiv.) was added to a solution of the protected triflate residue in dry toluene or dry DMF, respectively. After stirring at room temperature for 2–4 h, the mixture was diluted with ethyl acetate and washed with brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash column chromatography afforded the thiolacetate derivative.

General Method for Single or Multiple Regioselective Acylation via the Respective Stannylene Intermediates: Methyl β-D-galactoside derivatives and dibutyltin oxide (2–4 equiv.) were dissolved in methanol, and refluxed for two hours. After evaporation of the solvent, the residue was dried under vacuum, and then dissolved in toluene. A solution of benzoyl chloride or acetic anhydride (1–3 equiv.) in anhydrous toluene was added dropwise, and then allowed to react at 90 °C for 2 h. The resulting mixture was directly purified by flash column chromatography, affording the selectively protected derivative.

General Deprotection of Carbohydrates Derivatives Protected with Ester: The protected methyl β-D-glycoside derivative was dissolved in methanol at room temp., and sodium methoxide (1.1 equiv.) in methanol was added dropwise. The reaction mixture was stirred at room temp. for 2 h under nitrogen protection and monitored with TLC. After consumption of the starting material, the solvent was removed under vacuum. Purification of the residue by flash column chromatography afforded the deprotection product.

Methyl 2,3,5-Tri-*O*-acetyl-6-*S*-acetyl-6-thio-β-D-galactopyranoside (13): Methyl β-D-galactopyranoside (0.97 g, 5 mmol) was dissolved in dry pyridine (4 mL) at 0 °C, and tosyl chloride (1.05 g, 5.5 mmol, 1.1 equiv.) in dry pyridine (2 mL) was added slowly. The reaction mixture was warmed to room temperature and stirred overnight under nitrogen atmosphere. After consumption of the starting material, pyridine (10 mL) and acetic anhydride (5 mL) were added in the reaction mixture. The reaction mixture was stirred at room temperature overnight. When TLC indicated that the starting material had disappeared, the reaction mixture was diluted with water, then extracted with ethyl acetate, and the combined organic phase was washed with 2 M HCl, water and then brine, dried with Na_2SO_4, and concentrated. The crude product was dissolved in dry DMF (15 mL), and the solution was heated to 70 °C. Then potassium thioacetate (2.70 g, 23.7 mmol) was added in portions. The reaction mixture was stirred at 70 °C for 18 h. When TLC indicated that the starting material had disappeared, the reaction mixture was diluted with water, then extracted with ethyl acetate and the combined organic phase was washed with water and then brine, dried with Na_2SO_4, and concentrated. Purification of the residue by flash column chromatography (hexane/ethyl acetate, 2:1) afforded 1.1 g of product (58%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.34 (dd, $J_{3,4}$ = 3.40, $J_{4,5}$ = 0.88 Hz, 1 H, 4-H), 5.11 (dd, $J_{2,3}$ = 10.45, $J_{1,2}$ = 7.93 Hz, 1 H, 2-H), 4.92 (dd, $J_{2,3}$ = 10.45, $J_{3,4}$ = 3.40 Hz, 1 H, 3-H), 4.29 (d, $J_{1,2}$ = 7.93 Hz, 1 H, 1-H), 3.62 (m, $J_{5,6a}$ = 6.99, $J_{5,6e}$ = 6.99 Hz, 1 H, 5-H), 3.45 (s, 3 H, OCH_3), 3.05 (m, $J_{6a,6e}$ = 13.85 Hz, 1 H, 6_a-H), 3.00 (m, 1 H, 6_e-H), 2.33 (s, 3 H, $SCOCH_3$), 2.15 (s, 3 H, $OCOCH_3$), 2.04 (s, 3 H, $OCOCH_3$), 1.96 (s, 3 H, $OCOCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.1 (CO), 170.8 (CO), 170.5 (CO), 169.9 (CO), 102.4 (C-1), 72.5 (C-5), 71.5 (C-3), 69.2 (C-2), 68.4 (C-4), 57.4 (OCH_3), 30.9 (CH_3 SAc), 29.0 (C-6), 21.2 (CH_3 OAc), 21.1 (CH_3 OAc), 21.0 (CH_3 OAc) ppm. $[\alpha]_D^{22}$ = +40.0 (c = 0.9, $CHCl_3$).

Methyl 6-Thio-β-D-galactopyranoside (5): Prepared from compound **13** according to the general ester deprotection procedure (0.87 g, 93%). Overall yield from compound **11**: 46% over 4 steps. ^{1}H NMR (D_2O, 500 MHz): δ = 4.28 (d, $J_{1,2}$ = 7.98 Hz, 1 H, 1-H), 3.92 (d, $J_{3,4}$ = 3.25 Hz, 1 H, 4-H), 3.89 (t, $J_{5,6}$ = 6.95 Hz, 1 H, 5-H), 3.63 (dd, $J_{2,3}$ = 10.05 Hz, 1 H, 3-H), 3.50 (s, 3 H, OCH_3), 3.45 (dd, 1 H, 2-H), 2.96 (d, 2 H, 6-H) ppm. ^{13}C NMR (D_2O, 125 MHz): δ = 104.2 (C-1), 73.3, 73.2 (C-5, C-3), 70.9 (C-2), 69.8 (C-4), 57.7 (OCH_3), 38.5 (C-6) ppm. $[\alpha]_D^{22}$ = –50.2 (c = 0.5, H_2O).

Methyl 3-*O*-Acetyl-4,6-*O*-(phenylmethanediyl)-β-D-talopyranoside (21): Compound **20** (56.5 mg, 0.2 mmol) and dibutyltin oxide (55 mg, 0.22 mmol) were dissolved in methanol (3 mL), and refluxed for two hours. After evaporation of the solvent, the residue was dried under vacuum, and then dissolved in toluene (3 mL). A solution of acetic anhydride (20 mg, 0.2 mmol) in anhydrous toluene (1 mL) was added dropwise, and then allowed to react at room temp. for 2 h. The resulting mixture was directly purified by flash column chromatography (hexane/ethyl acetate, 6:4), affording 47 mg of compound **21** (72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43–7.49 (m, 2 H, CH_{Ph}), 7.31–7.36 (m, 3 H, CH_{Ph}), 5.46 (s, 1 H, Ph-CH-), 4.84 (t, $J_{3,2}$ = 3.3, $J_{3,4}$ = 3.3 Hz, 1 H, 3-H), 4.40 (dd, $J_{6a,5}$ = 1.5, $J_{6a,6b}$ = 12.6 Hz, 1 H, 6_a-H), 4.36 (d, $J_{1,2}$ = 0.8 Hz, 1 H, 1-H), 4.05–4.11 (m, 1 H, 6_b-H), 3.90–3.96 (m, 1 H, 2-H), 3.59 (s, 3 H, OCH_3), 3.42–3.46 (m, 1 H, 5-H), 3.34 (d, $J_{OH,2}$ = 11.3 Hz, 1 H, OH), 2.15 (s, 3 H, $OCOCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.6 (CO), 137.0, 129.2, 128.2, 126.1 (C_{ph}), 101.5 (C-1), 73.7 (C-4), 70.6 (C-3), 69.1 (C-6), 68.7 (C-2), 66.6 (C-5), 57.2 (CH_3 OMe), 21.0 (CH_3 OAc) ppm. $[\alpha]_D^{22}$ = +24.5 (c = 1.0, $CHCl_3$). HRMS: calcd. for $C_{16}H_{20}O_7$ [M + Na$^+$]: 347.1107; found 347.1113.

Methyl 2-*S*-Acetyl-3-*O*-acetyl-4,6-*O*-(phenylmethanediyl)-2-thio-β-D-galactopyranoside (23): Triflation of compound **21** was performed according to the general triflation procedure yielding compound **22**. Compound **22** was then directly dissolved in dry toluene, then TBASAc (318 mg, 1 mmol) was added to the solution. After stirring at room temperature for 2 h, the mixture was diluted with ethyl acetate and washed with brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/ethyl acetate, 2:1) afforded 38 mg of compound **23** (68%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49–7.56 (m, 2 H, CH_{Ph}), 7.31–7.41 (m, 3 H, CH_{Ph}), 5.54 (s, 1 H, Ph-CH-), 5.17 (dd, $J_{3,2}$ = 11.8, $J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 4.66 (d, $J_{1,2}$ = 8.8 Hz, 1 H, 1-H), 4.34 (dd, $J_{6a,5}$ = 1.5,

$J_{6a,6b}$ = 12.3 Hz, 1 H, 6$_a$-H), 4.29 (br. d, 1 H, 4-H), 4.08 (dd, $J_{6b,5}$ = 1.8 Hz, 1 H, 6$_b$- H), 3.87 (dd, 1 H, 2-H), 3.51 (s, 3 H, OCH$_3$), 3.44–3.55 (m, 1 H, 5-H), 2.33 (s, 3 H, SCOCH$_3$) 2.07 (s, 3 H, OCOCH$_3$) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 193.7 (CO SAc), 170.6 (CO OAc), 137.6, 129.0, 128.2, 126.4 (C$_{Ph}$), 101.5 (C-1), 100.9 (Ph-CH), 72.9 (C-4), 70.3 (C-3), 69.2 (C-6), 66.3 (C-5), 57.8 (CH$_3$ OMe), 45.5 (C-2), 30.8 (CH$_3$ SAc), 20.8 (CH$_3$ OAc) ppm. $[\alpha]_D^{22}$ = +38.2 (*c* = 1.0, CHCl$_3$). HRMS: calcd. for $C_{18}H_{22}O_7S$ [M + Na$^+$]: 405.0984; found 405.0992.

Methyl 2-Thio-β-D-galactopyranoside (2): Prepared from compound **23** according to the general ester deprotection procedure followed by acid treatment (18 mg, 87%). Overall yield from compound **11**: 15% over 9 steps. ^{1}H NMR (D$_2$O, 400 MHz): δ = 4.49 (d, $J_{1,2}$ = 8.8 Hz, 1 H, 1-H), 3.86–3.89 (m, 1 H, 4-H), 3.82 (dd, $J_{3,2}$ = 11.0, $J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 3.73 (dd, $J_{6a,6b}$ = 11.7, $J_{6a,5}$ = 7.9 Hz, 1 H, 6$_a$-H), 3.68 (dd, $J_{6b,5}$ = 4.4 Hz, 1 H, 6$_b$-H), 3.56 (dd, 1 H, 5-H), 3.53 (s, 3 H, OCH$_3$), 2.70 (dd, 1 H, 2-H) ppm. ^{13}C NMR (D$_2$O, 125 MHz): δ = 102.8 (C-1), 74.9 (C-5), 69.6 (C-3), 68.2 (C-4), 61.1 (C-6), 57.0 (CH$_3$ OMe), 55.3 (C-2) ppm. $[\alpha]_D^{22}$ = +58.6 (*c* = 0.5, H$_2$O). HRMS: calcd. for $C_7H_{14}O_5S$ [M + Na$^+$]: 233.0460; found 233.0467.

Methyl 3-Thio-β-D-galactopyranoside (3): Prepared from 76 mg of compound **35** according to the general ester deprotection procedure (36 mg, 86%). Overall yield from compound **11**: 25% over 8 steps. ^{1}H NMR (D$_2$O, 500 MHz): δ = 4.28 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 1-H), 4.09 (d, $J_{4,3}$ = 2.8 Hz, 1 H, 4-H), 3.62–3.71 (m, 3 H, 5-H, 6-H), 3.48 (s, 3 H, OCH$_3$), 3.42 (dd, $J_{2,3}$ = 11.5 Hz, 1 H, 2-H), 3.05 (dd, 1 H, 3-H) ppm. ^{13}C NMR (D$_2$O, 125 MHz): δ = 105.0 (C-1), 77.4 (C-5), 68.6 (C-2), 67.0 (C-4), 61.2 (C-6), 58.6 (C-3), 57.1 (CH$_3$ OMe) ppm. $[\alpha]_D^{22}$ = +72.6 (*c* = 0.5, H$_2$O). $C_7H_{14}O_5S$ + 1/2 H$_2$O: calcd. C 38.35, H 6.90, S 14.62; found C 37.87, H 6.83, S 14.43.

Methyl 4-Thio-β-D-galactopyranoside (4): Prepared from 115 mg of compound **42** according to the general ester deprotection procedure (37 mg, 86%). Overall yield from compound **37**: 49% over 4 steps. ^{1}H NMR (D$_2$O, 500 MHz): δ = 4.19 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1-H), 3.76–3.94 (m, $J_{3,4}$ = 3.25 Hz, 4 H, 3-H, 5-H, 6-H), 3.45 (s, 3 H, OCH$_3$), 3.35–3.42 (m, 1 H, 4-H), 3.18 (dd, $J_{2,1}$ = 8.5, $J_{2,3}$ = 8.9 Hz, 1 H, 2-H) ppm. ^{13}C NMR (D$_2$O, 125 MHz): δ = 104.1 (C-1), 74.9 (C-5), 72.2 (C-3), 71.8 (C-2), 62.7 (C-4), 62.0 (C-6), 57.3 (CH$_3$ OMe) ppm. $[\alpha]_D^{22}$ = –10.2 (*c* = 0.5, H$_2$O). $C_7H_{14}O_5S$ + 1/2 H$_2$O: calcd. C 38.35, H 6.90, S 14.62; found C 38.35, H 7.00, S 14.46.

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