Propane-1,3-diyl Dithioacetals of Carbohydrates; Part 7: Preparation of Aminocyclitols and Iminosugars by Intramolecular Cyclizations of D-Glucosamine Propane-1,3-diyl Dithioacetal Derivatives

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Dedicated to Professor Dieter Hoppe on the occasion of his 65th birthday

Abstract: Versatile 3,4,5-tri-*O*-protected 2-acylamino-2-deoxy-6-*O*-tosyl-D-glucose propane-1,3-diyl dithioacetal intermediates were efficiently synthesized from D-glucosamine propane-1,3-diyl dithioacetal or its derivatives. Intramolecular cyclizations from these intermediates produced biologically important aminocyclitols as well as iminosugars. The 3,4-*O*-methylene protection on the intermediates did not hinder the cyclizations. The resultant aminocyclitols and iminosugars bearing orthogonal protecting groups are ideal for regioselective modification. Hence, deprotection methodology is also discussed.

Key words: chiral pool, intramolecular cyclizations, aminocyclitol, iminosugar, protecting-group cleavage

As important bioactive compounds, nitrogen-containing carbohydrate mimics, such as aminocyclitols (i.e., 2-deoxystreptamine derivatives) and iminosugars (i.e., nojirimycin analogues) have been the subject of intense interest over the last decade.[1] In the preceding paper we described the protecting group manipulation and lithiated dianion chemistry of derivatives of D-glucosamine propane-1,3-diyl dithioacetal (**1**) (Figure 1), herein we report a very short synthetic route to aminocyclitols and iminosugars from D-glucosamine propane-1,3-diyl dithioacetal derivatives.[2] Highlights of the synthetic design are efficient intramolecular cyclization[3] and a single common intermediate, derived from D-glucosamine propane-1,3-diyl dithioacetal, to both aminocyclitols and iminosugars. As D-glucosamine propane-1,3-diyl dithioacetal is an inexpensive chiral pool substrate and building block that is readily available from renewable mass (e.g. chitin), this makes the synthesis more attractive.

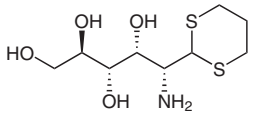

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Figure 1

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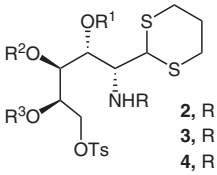
As it will be shown in this paper, certain D-glucosamine propane-1,3-diyl dithioacetal derivatives **2**, **3**, and **4** bearing a 6-*O*-tosyl group will serve as suitable common precursors for both aminocyclitols and iminosugars (Figure 2).



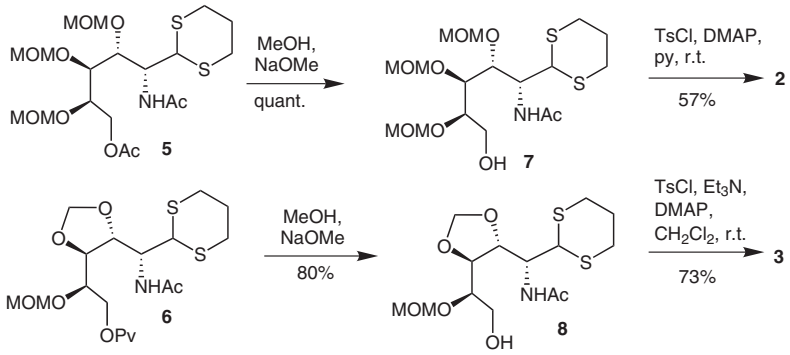
2, R = Ac, $R^1 = R^2 = R^3$ = MOM
3, R = Ac, R^1,R^2 = -CH_2-, R^3 = MOM
4, R = Tfa, R^1,R^2 = -CH_2-, R^3 = MOM

Figure 2

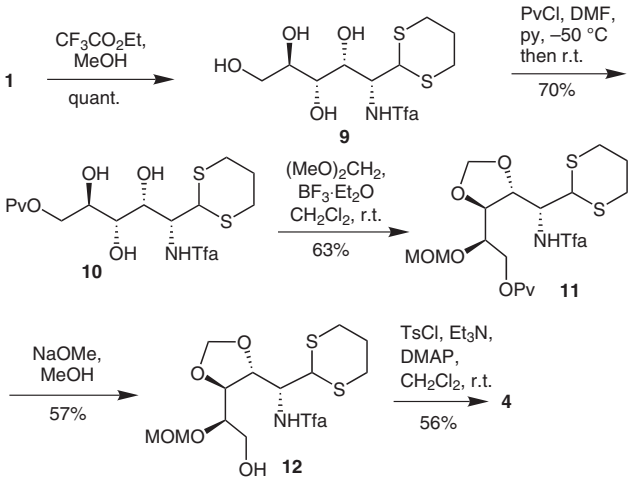
Starting from the previously reported compounds **5** and **6**,[2] two-step synthesis of the versatile intermediates **2** and **3** will be briefly described (Scheme 1). The 6-*O*-ester protection on compounds **5** and **6** was removed by sodium methoxide, and the resulting alcohols **7** and **8** were converted into *O*-tosyl derivatives **2** and **3**, respectively; the 3,4,5-*O*-methoxymethyl or 5-*O*-methoxymethyl-3,4-*O*-methylene protection tolerates very basic conditions which will be presented in the cyclization procedures.

Compound **4** bearing *N*-trifluoroacetyl (Tfa) protection, which has been used for lithiated dianion chemistry,[4] was also readily synthesized from compound **1** using the same protecting group manipulation methodology (Scheme 2).

Compound **2** was subjected to similar lithiating condition reported previously[2] [*n*-BuLi (2.2 equiv), THF, –78 °C]. Without disturbing the *O*-tosyl group, the imidate–dithiane dianion **13** was formed and, in principle, both have a chance to attack C6 to yield the cyclized products. But the resultant compound was identified as an aminocyclitol **14**, which is formed by coupling of C1 and C6 . No C–N coupling compound was found under such reaction conditions. Interestingly, when compound **2** was refluxed in tetrahydrofuran with sodium hydride, the iminosugar **16** was the main product (Scheme 3). This is easily understood as the sodium hydride deprotonated amide readily forms the imidate anion **15** and this is not sufficiently basic to deprotonate the dithiane. Synthesis of the iminosugar by monolithiation of the amide was also unsuccessful.

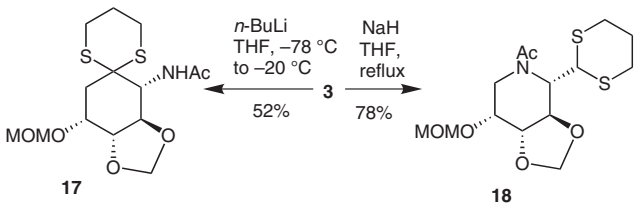


Scheme 1



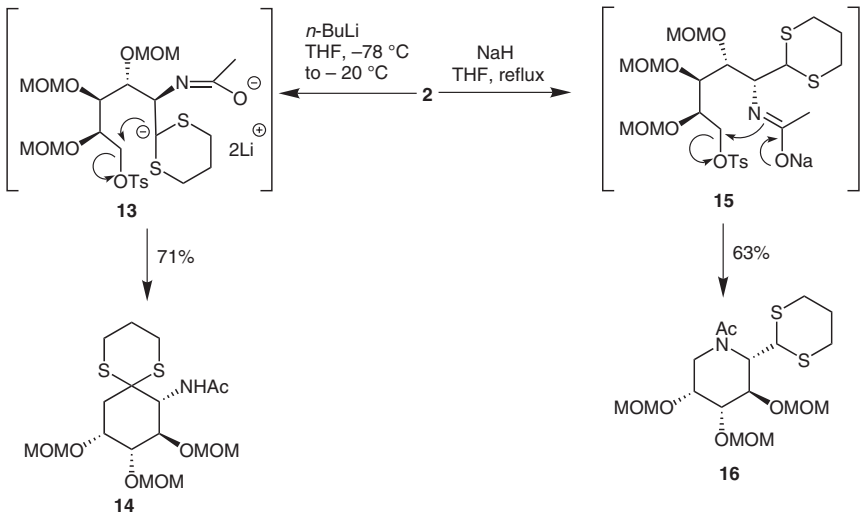
Scheme 2

Compound **3** was subjected to both cyclization conditions used for **2**. Aminocyclitol **17** was produced in 52% yield, which is lower than the yield for the cyclization of **2** to give **14**, but the iminosugar **18** was formed in 78% yield, which is better than the yield for the cyclization of **2** to give **16** (Scheme 4). It is worth mentioning that the *trans*-acetal arrangement, in general, does not support intramolecular cyclization reactions, and may even be used to prevent such cyclizations.[3,5] However, in this case, the cyclizations to both aminocyclitol and iminosugar work well even with the 3,4-*O*-*trans*-formaldehyde protection in place.



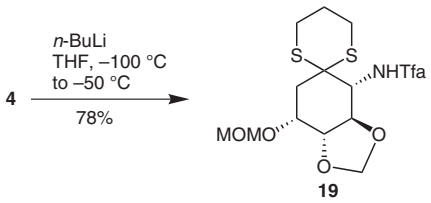
Scheme 4

According to our recent investigations, compound **4**, as a newly developed system, works excellently in the lithiated dianion chemistry. Compared to *N*-acetyl derivatives, i.e., compound **2** and **3**, the lithiated dianion from compound **4** is produced at a lower temperature (ca. –100 °C) and reacts with various electrophiles more rapidly and with higher yield. Furthermore, removing *N*-trifluoroacetyl protection should be much easier compared to removing *N*-acetyl protection. This will be extremely important in the later phase of the synthesis.



Scheme 3

The cyclization of compound **4** to aminocyclitol **19** is shown in Equation 1; compound **19** is formed in high yield as expected. However, when compound **4** was treated with sodium hydride in refluxing tetrahydrofuran, elimination of the *O*-tosyl group and cleavage of the *N*-trifluoroacetyl group was observed and none of the desired product was formed.

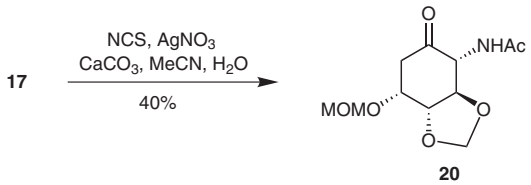


Equation 1

Highly functionalized aminocyclitols and iminosugars bearing different protecting groups can be produced in high yield according to our new methodology. The following part discusses the deprotection manipulation and brings the work closer to natural products or bioactive compounds.

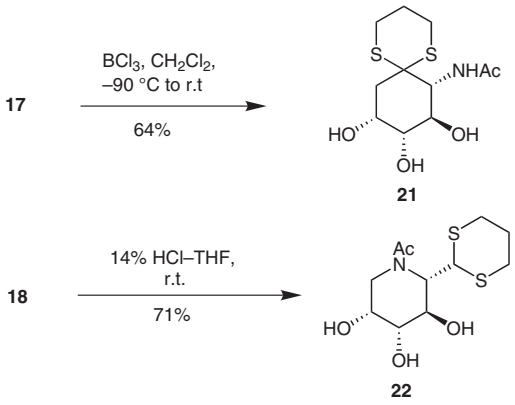
The most interesting feature of the highly functionalized aminocarbocycles **14**, **17**, and **19** as well as iminosugars **16** and **18** produced by our new methodology is the orthogonal protection. Typically, dithiane, *O*-acetal, and *N*-acyl protection can be classified as oxidation/heavy metal, acid-, and base-sensitive protection, respectively. Each can be removed by established methods without interfering with other protecting groups. In principle, even the 3,4-*O*-methylene group can be discriminated from the *O*-methoxymethyl protection if the correct conditions are used. This is a great advantage for synthesis directed at bioactivity investigation because it allows selective modification at a certain site. Three different types of protecting groups are present on compounds **14**, **16**, **17**, **18**, and **19** and a large number of deprotection manipulations can be visualized, but we will only demonstrate several typical cases.

Conversion of the dithiane protection to a carbonyl function can be realized on compounds **17** and **18** by oxidative cleavage (the mercury salt method is only feasible for **17**). Equation 2 shows the formation of ketone **20** with *N*-chlorosuccinimide and silver nitrate from aminocyclitol **17**.



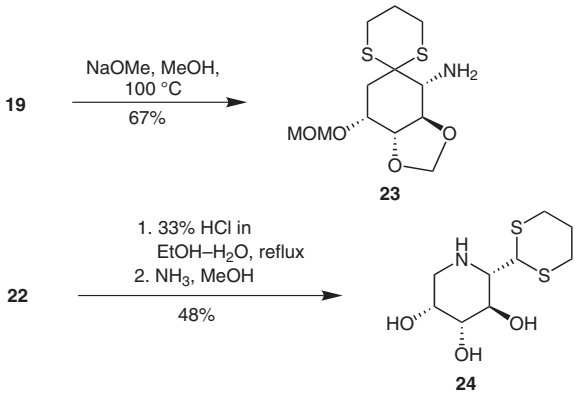
Equation 2

Acid-labile protecting groups on aminocyclitol **17** can be removed by boron trichloride at low temperature to yield compound **21**; attempts to produce compound **21** with hydrochloric acid failed due to decomposition. However, removing acid-labile protecting groups on iminosugar **18** using hydrochloric acid works well to yield compound **22** (Scheme 5).



Scheme 5

N-Acyl deprotection is demonstrated in Scheme 6, where *N*-trifluoroacetyl protection on **19** was readily removed using sodium methoxide to give the free amine **23**. On the other hand, *N*-acetyl protection on **22** can be removed by refluxing 6 M hydrochloric acid–ethanol (in this procedure, cleavage of dithiane was also detected) to give **24** after basification (Scheme 6).



Scheme 6

In conclusion, versatile synthetic intermediates **2**, **3**, and **4** were readily prepared in a few steps from D-glucosamine propane-1,3-diyl dithioacetal (**1**), which is inexpensive and readily available from renewable mass, for example, chitin. From the common intermediates **2**, **3**, and **4**, aminocyclitols **14**, **17**, and **19** and iminosugars **16** and **18**, members of the two main categories of nitrogen-containing carbohydrate mimics and the subject of recent a research hot spot, were efficiently synthesized by intramolecular cyclization reactions. In particular, *N*-trifluoroacetyl derivative **4** proved excellent for preparation of aminocyclitol **19** (78% yield) by lithiated dianion chemistry, while *N*-acetyl derivative **3** was good for producing the iminosugar **18** (78% yield). The 3,4-*O*-methyl-

ene protection on intermediates **3** and **4** did not hinder the cyclization procedures. The resultant orthogonally protected aminocyclitols **14**, **17**, and **19** as well as iminosugars **16** and **18** serve as ideal precursors for regioselective modification. Typical selective deprotection reactions proved viable when the correct conditions were used. The whole work demonstrates that derivatives of D-glucosamine propane-1,3-diyl dithioacetal (**1**) are powerful and versatile building blocks and established a new and efficient methodology to both aminocyclitols and iminosugars.

NMR spectra were recorded on Bruker AMX 400 spectrometer. The chemical shift is specified as δ (ppm) and the signal of the solvent was used as the internal standard ($CDCl_3$ ^1H: δ = 7.24, ^{13}C: δ = 77.23, C_6D_6 ^1H: δ = 7.16, ^{13}C: δ = 128.39, CD_3OD ^1H: δ = 4.85, ^{13}C: δ = 49.15). ESI-MS were recorded on a Quattro LCZ or on a MicroTof. MALDI-TOF MS were recorded on a Reflex IV.

O-Acetylation; General Procedure

The compound with free hydroxy groups was dissolved in anhyd pyridine–Ac_2O (2:1). The mixture was stirred at r.t. until the starting material was completely converted into the *O*-acetyl product, which can take hours to several days (monitored by TLC). The reaction may be accelerated by the addition of a catalytic amount of DMAP. The solvent was then evaporated under reduced pressure and traces of pyridine were removed by coevaporation with toluene. The crude product was purified by extraction from H_2O with CH_2Cl_2 and, if necessary, by column chromatography.

2-Acetamido-2-deoxy-3,4,5-tri-*O*-methoxymethyl-D-glucose Propane-1,3-diyl Dithioacetal (7)

The 3,4,5-tri-*O*-methoxymethyl derivative **5** was de-O-acylated with NaOMe in MeOH. The reaction was followed by TLC and when it showed complete conversion, the mixture was neutralized with ion-exchange resin (Amberlyst 15, Acros) and filtered. The liquid phase was evaporated to dryness to yield the 6-hydroxy compound **7** as an oil in quantitative yield. It was used in the next step without further purification.

$[\alpha]_D^{20}$ –2.9 (*c* 1.00, MeOH).

^1H NMR (400 MHz, C_6D_6): δ = 5.64 (d, *J* = 10.1 Hz, 1 H, NHC=O), 4.82 (ddd, *J* = 10.1 Hz, *J* = 10.1 Hz, *J* = 1.1 Hz, 1 H, H2), 4.79 (d, *J* = 6.1 Hz, 1 H, 3-OCH_2O), 4.76 (d, *J* = 6.4 Hz, 1 H, 4-OCH_2O), 4.73 (d, *J* = 6.6 Hz, 1 H, 5-OCH_2O), 4.71 (d, *J* = 6.4 Hz, 1 H, 4-OCH_2O), 4.68 (dd, *J* = 7.9 Hz, *J* = 1.1 Hz, 1 H, H3), 4.64 (d, *J* = 6.1 Hz, 1 H, 3-OCH_2O), 4.63 (d, *J* = 6.6 Hz, 1 H, 5-OCH_2O), 4.13–4.08 (m, 2 H, H4/5), 4.04 (dd, *J* = 11.9 Hz, *J* = 4.1 Hz, 1 H, H6a), 3.96 (d, *J* = 9.4 Hz, 1 H, H1), 3.93 (dd, *J* = 11.9 Hz, *J* = 5.4 Hz, 1 H, H6b), 3.26 (s, 3 H, 4-OCH_3), 3.18 (s, 3 H, 5-OCH_3), 3.12 (s, 3 H, 3-OCH_3), 3.10–3.02 (m, 1 H, SCH_{ax}-a), 2.86–2.79 (m, 1 H, SCH_{ax}-b), 2.21–2.10 (m, 2 H, SCH_{eq}), 1.66 (s, 3 H, $NCOCH_3$), 1.50–1.43 (m, 2 H, $SCCH_2CS$), 0.88 (br s, 1 H, OH).

^{13}C NMR (100 MHz, C_6D_6): δ = 170.3 (NC=O), 99.4 (3-OCH_2O), 98.0 (4-OCH_2O), 97.5 (5-OCH_2O), 81.7 (C5), 79.6 (C4), 78.0 (C3), 62.8 (C6), 56.5 (3-OCH_3), 56.2 (4-OCH_3), 55.8 (5-OMe), 51.6 (C2), 46.4 (C1), 27.2 (SCH_2C), 26.4 (SCH_2C), 26.0 ($SCCH_2CS$), 23.0 (CH_3-Ac).

ESI-MS: *m*/*z* = 466.2 $[M + Na]^+$, 909.3 $[2 M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{33}NNaO_8S_2$: 466.1540; found: 466.1540.

2-Acetamido-2-deoxy-3,4,5-tri-*O*-methoxymethyl-6-*O*-tosyl-D-glucose Propane-1,3-diyl Dithioacetal (2)

To a soln of the 3,4,5-tri-*O*-methoxymethyl compound **7** (2.58 g, 5.8 mmol) in anhyd pyridine (50 mL) was added *p*-TsCl (1.66 g, 8.7 mmol); the mixture was stirred overnight at r.t.. Another portion of *p*-TsCl (0.88 g, 4.36 mmol) and catalytic amount of DMAP was added and the mixture was stirred for 2 h. The reaction was quenched with H_2O and the mixture was extracted with CH_2Cl_2. Evaporation of the solvent under reduced pressure and purification by MPLC (cyclohexane–EtOAc, 2:1) yielded the 6-*O*-tosylate **2** as a white solid; yield: 1.96 g (57%); mp 97 °C.

$[\alpha]_D^{20}$ +7.4 (*c* 1.00, MeOH).

^1H NMR (300 MHz, C_6D_6): δ = 7.76 (d, *J* = 8.2 Hz, 2 H, H_{ortho}-Ts), 7.29 (d, *J* = 8.2 Hz, 2 H, H_{meta}-Ts), 5.85 (d, *J* = 10.1 Hz, 1 H, NHC=O), 4.65 (d, *J* = 6.6 Hz, 1 H, OCH_2O), 4.63 (d, *J* = 6.6 Hz, 1 H, OCH_2O), 4.62 (d, *J* = 6.5 Hz, 1 H, OCH_2O), 4.54 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.58 (d, *J* = 6.5 Hz, 1 H, OCH_2O), 4.59 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.43 (dd, *J* = 10.1 Hz, *J* = 9.3 Hz, 1 H, H2), 4.19 (d, *J* = 7.9 Hz, 1 H, H3), 4.18 (dd, *J* = 10.5 Hz, *J* = 3.4 Hz, 1 H, H6a), 4.12 (dd, *J* = 10.5 Hz, *J* = 7.0 Hz, 1 H, H6b), 3.99 (dd, *J* = 6.9 Hz, *J* = 3.3 Hz, *J* = 2.8 Hz, 1 H, H5), 3.73 (dd, *J* = 7.9 Hz, *J* = 2.8 Hz, 1 H, H4), 3.74 (d, *J* = 9.3 Hz, 1 H, H1), 3.32 (s, 3 H, OCH_3), 3.28 (s, 6 H, OCH_3), 3.05–2.98 (m, 1 H, SCH_{ax}-a), 2.94–2.87 (m, 1 H, SCH_{ax}-b), 2.54–2.46 (m, 2 H, SCH_{eq}), 2.39 (s, 3 H, CH_3-Ts), 1.97 (s, 3 H, $NCOCH_3$), 1.95–1.89 (m, 2 H, $SCCH_2CS$).

^{13}C NMR (75 MHz, C_6D_6): δ = 170.3 (NC=O), 144.9 (C_q-Ts), 130.0 (C_q-Ts), 129.9 (2C, C_{meta}-Ts), 128.1 (2C, C_{ortho}-Ts), 98.9 (OCH_2O), 97.6 (OCH_2O), 96.7 (OCH_2O), 78.9 (C4), 77.0 (C3), 75.7 (C5), 69.4 (C6), 56.6 (OCH_3), 56.2 (OCH_3), 55.9 (OCH_3), 50.7 (C2), 46.2 (C1), 27.2 (SCH_2C), 26.4 (SCH_2C), 25.5 ($SCCH_2CS$), 23.2 (CH_3-Ac), 21.7 (CH_3-Ts).

ESI-MS: *m*/*z* = 598.3 $[M + H]^+$, 620.4 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{39}NNaO_{10}S_3$: 620.1631; found: 620.1628.

2-Acetamido-2-deoxy-5-*O*-methoxymethyl-3,4-*O*-methylene-D-glucose Propane-1,3-diyl Dithioacetal (8)

To a soln of **6** (5.00 g, 11.1 mmol) in MeOH (50 mL), NaOMe (4.00 g, 74.1 mmol) was added at r.t. The mixture was stirred overnight and then neutralized by addition of AcOH. The volatile components were removed under reduced pressure. EtOAc and H_2O were added to the residue and the organic phase was separated and concentrated under reduced pressure. The residue was purified by MPLC (EtOAc–cyclohexane, 2:1) to give **8** as a colorless oil that crystallized slowly during storage; yield: 3.25 g (80%). An analytical sample was recrystallized (EtOAc); mp 123.7–124.1 °C.

$[\alpha]_D^{20}$ +0.7 (*c* 1.00, $CHCl_3$).

^1H NMR (400 MHz, C_6D_6): δ = 5.88 (d, *J* = 10.1 Hz, 1 H, NH), 4.99 (s, 1 H, 3,4-OCH_2O), 4.87 (s, 1 H, 3,4-OCH_2O), 4.70 (d, *J* = 6.9 Hz, 1 H, CH_2-MOM), 4.68 (d, *J* = 6.9 Hz, 1 H, CH_2-MOM), 4.60–4.51 (m, 2 H, H4, H2), 3.99 (d, *J* = 8.4 Hz, 1 H, H1), 3.75 (dd, *J* = 3.1 Hz, *J* = 12.4 Hz, 1 H, H6a), 3.71–3.65 (m, 2 H, H3, H5), 3.60 (dd, *J* = 4.4 Hz, *J* = 12.4 Hz, 1 H, H6b), 3.36 (s, 3 H, CH_3-MOM), 3.16 (br s, 1 H, OH), 2.96–2.81 (m, 2 H, dithiane), 2.69–2.62 (m, 2 H, dithiane), 2.00 (s, 3 H, Ac), 1.97–1.76 (m, 2 H, dithiane).

^{13}C NMR (100 MHz, C_6D_6): δ = 170.5 (Ac), 97.0 (3,4-OCH_2O), 95.4 (CH_2-MOM), 80.8 (C5), 77.1 (C3), 76.8 (C4), 62.7 (C6), 56.0 (CH_3-MOM), 51.3 (C2), 48.3 (C1), 28.4 (dithiane), 28.0 (dithiane), 25.5 (dithiane), 23.2 (Ac).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{25}NNaO_6S_2$: 390.1016; found: 390.1058.

Anal. Calcd for $C_{14}H_{25}NO_6S_2$: C, 45.76; H, 6.86; N, 3.81. Found: C, 45.80; H, 6.72; N, 3.66.

2-Acetamido-2-deoxy-5-*O*-methoxymethyl-3,4-*O*-methylene-6-*O*-tosyl-D-glucose Propane-1,3-diyl Dithioacetal (3)

To a soln of **8** (1.00 g, 2.7 mmol), Et_3N (1.0 mL, 7.1 mmol), and DMAP (0.30 g, 2.4 mmol) in CH_2Cl_2 (40 mL) at r.t. was added TsCl (1.20 g, 6.3 mmol) and the mixture was stirred overnight. The reaction was quenched by addition of MeOH and all solvent was removed under reduced pressure. The residue was purified by MPLC (EtOAc–cyclohexane, 2:3) to give **3** as a colorless oil; yield: 1.02 g (73%).

$[\alpha]_D^{20}$ +14.8 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ = 7.75 (d, *J* = 8.2 Hz, 2 H, H_{aryl}), 7.29 (d, *J* = 8.2 Hz, 2 H, H_{aryl}), 5.81 (d, *J* = 9.8 Hz, 1 H, NH), 4.96 (s, 1 H, 3,4-OCH_2O), 4.79 (s, 1 H, 3,4-OCH_2O), 4.62 (d, *J* = 6.8 Hz, 1 H, CH_2-MOM), 4.57 (d, *J* = 6.8 Hz, 1 H, CH_2-MOM), 4.50 (m, 1 H, H3), 4.46 (m, 1 H, H2), 4.24 (dd, *J* = 2.9 Hz, *J* = 11.0 Hz, 1 H, H6a), 4.05 (dd, *J* = 4.6 Hz, *J* = 11.0 Hz, 1 H, H6b), 3.96 (d, *J* = 8.2 Hz, 1 H, H1), 3.82–3.77 (m, 1 H, H5), 3.67 (dd, *J* = 6.4 Hz, *J* = 6.9 Hz, 1 H, H4), 3.26 (s, 3 H, CH_3-MOM), 2.96–2.84 (m, 2 H, dithiane), 2.67–2.61 (m, 2 H, dithiane), 2.38 (s, 3 H, CH_3-Ts), 1.97 (s, 3 H, Ac), 1.94–1.84 (m, 2 H, dithiane).

^{13}C NMR (100 MHz, C_6D_6): δ = 170.2 (Ac), 144.8 (C_{aryl}), 132.7 (C_{aryl}), 129.7 (2C, C_{aryl}), 127.9 (2C, C_{aryl}), 96.5 (3,4-OCH_2O), 95.4 (CH_2-MOM), 77.5 (C3), 76.4 (C4), 75.1 (C5), 69.1 (C6), 56.1 (CH_3-MOM), 51.6 (C2), 48.2 (C1), 28.4 (dithiane), 28.0 (dithiane), 25.5 (dithiane), 23.2 (Ac), 21.5 (CH_3-Ts).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{31}NNaO_8S_3$: 544.1104; found: 544.1110.

Anal. Calcd for $C_{21}H_{31}NO_8S_3$: C, 48.35; H, 5.99; N, 2.68. Found: C, 48.54; H, 6.08; N, 2.39.

2-Deoxy-2-trifluoroacetamido-D-glucose Propane-1,3-diyl Dithioacetal (9)

Compound **1** (3.0 g, 11.2 mmol) was suspended in a mixture of anhyd MeOH (20 mL) and ethyl trifluoroacetate (5 mL). The mixture was stirred overnight at r.t. All volatile components were removed under vacuum to give **9** as a white solid in quantitative yield; mp 176.0–177.0 °C.

$[\alpha]_D^{20}$ –48.1 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 3.59 (br s, 2 H, H6), 3.59 (m, 2 H, H2, H1), 2.85 (m, 1 H, H3), 2.51 (m, 1 H, H4), 2.36 (m, 1 H, H5), 1.76–1.70 (m, 2 H, dithiane), 1.51–1.39 (m, 2 H, dithiane), 0.77–0.68 (m, 2 H, dithiane).

^{13}C NMR (100 MHz, CD_3OD): δ = 158.2 (q, *J* = 37.0 Hz, 1 C, CO-Tfa), 116.6 (q, *J* = 286.8 Hz, 1 C, CF_3-Tfa), 73.2 (C5), 72.5 (C4), 68.3 (C6), 63.6 (C3), 54.8 (C2), 46.6 (C1), 27.7 (dithiane), 27.3 (dithiane), 25.8 (dithiane).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{18}F_3NNaO_5S_2$: 388.0471; found: 388.0473.

Anal. Calcd for $C_{11}H_{18}F_3NO_5S_2$: C, 36.16; H, 4.97; N, 3.83. Found: C, 36.39; H, 4.80; N, 3.69.

2-Deoxy-6-*O*-pivaloyl-2-trifluoroacetamido-D-glucose Propane-1,3-diyl Dithioacetal (10)

The acetamido compound **9** (1.0 g, 2.74 mmol) was dissolved in pyridine (8 mL) and DMF (3 mL) and cooled to –50 °C, a soln of pivaloyl chloride (0.47 mL, 3.8 mmol, 1.4 equiv) in DMF (3 mL) was added dropwise over a period of 1 h. The mixture was kept stirring at this temperature for a further 1 h and warmed to r.t.. Then it was stirred overnight at r.t. and quenched by addition of MeOH. All volatile components were then removed under reduced pressure. The remaining syrup was separated between CH_2Cl_2 and H_2O. The organic phase was washed sequentially with dil aq HCl, sat. $NaHCO_3$, and brine. Then the organic phase was evaporated to dryness and purified by MPLC (EtOAc–cyclohexane, 1:1); yield: 861 mg (70%).

$[\alpha]_D^{20}$ –7.0 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (d, *J* = 9.4 Hz, 1 H, NH), 4.48 (m, 1 H, H2), 4.61 (dd, 1 H, *J* = 1.3 Hz, *J* = 6.1 Hz, H3), 4.25(br s, 1 H, 4-OH), 4.20 (dd, *J* = 5.2 Hz, *J* = 12.0 Hz, 1 H, H6a), 4.09 (dd, *J* = 3.0 Hz, *J* = 12.0 Hz, 1 H, H6b), 3.39 (br s, 1 H, 3-OH), 3.96 (d, *J* = 8.0 Hz, 1 H, H1), 3.67 (m, 1 H, H5), 3.29 (m, 1 H, H4), 2.96 (br s, 1 H, 5-OH), 2.81–2.73 (m, 2 H, dithiane), 2.58–2.49 (m, 2 H, dithiane), 1.90–1.73 (m, 2 H, dithiane), 1.03 (s, 9 H, CH_3-Pv).

^{13}C NMR (100 MHz, CD_3Cl): δ = 179.9 (CO-Pv), 157.8 (d, *J* = 37.5 Hz, 1 C, CO-Tfa), 115.5 (d, *J* = 287.8 Hz, 1 C, CF_3-Tfa), 71.9 (C5), 71.2 (C4), 69.6 (C3), 65.7 (C6), 53.9 (C2), 46.5 (C1), 38.9 (C_q-Pv), 27.9 (dithiane), 27.7 (dithiane), 27.0 (3C, CH_3-Pv), 25.2 (dithiane).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{26}F_3NNaO_6S_2$: 472.1046; found: 472.1047.

Anal. Calcd for $C_{16}H_{26}F_3NO_6S_2$: C, 42.75; H, 5.83; N, 3.12. Found: C, 43.21; H, 6.10; N, 2.90.

2-Deoxy-5-*O*-methoxymethyl-3,4-*O*-methylene-6-*O*-pivaloyl-2-trifluoroacetamido-D-glucose Propane-1,3-diyl Dithioacetal (11)

6-*O*-Pivaloyl derivative **10** (1.00 g, 2.2 mmol) was added to CH_2Cl_2 (10 mL) and dimethoxymethane (10 mL), then $BF_3{\cdot}OEt_2$ (2.0 mL, 15.8 mmol) was added. The mixture was stirred at r.t. for 1 h. Sat. aq $NaHCO_3$ was then added to quench the reaction. The two phases were separated and the aqueous phase was washed with Et_2O. The combined organic phases were washed with brine and concentrated under reduced pressure. The residue was purified by MPLC (EtOAc–cyclohexane, 1:10) to give **11** as a colorless oil; yield: 0.71 g (63%).

$[\alpha]_D^{20}$ –7.0 (*c* 1.00, MeOH).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.62 (d, *J* = 10.2 Hz, 1 H, NH), 5.08 (s, 1 H, 3,4-OCH_2O), 4.91 (s, 1 H, 3,4-OCH_2O), 4.79 (d, *J* = 6.8 Hz, 1 H, CH_2-MOM), 4.70 (dd, *J* = 0.9 Hz, *J* = 6.3 Hz, 1 H, H3), 4.66 (d, *J* = 6.8 Hz, 1 H, CH_2-MOM), 4.59 (pseudo t, $J_1 = J_2$ = 9.6 Hz, 1 H, H2), 4.45 (dd, *J* = 3.5 Hz, *J* = 12.2 Hz, 1 H, H6), 4.13 (dd, *J* = 4.4 Hz, *J* = 12.1 Hz, 1 H, H6), 3.92 (d, *J* = 9.6 Hz, 1 H, H1), 3.85 (dt, *J* = 3.6 Hz, *J* = 3.6 Hz, *J* = 7.5 Hz, 1 H, H5), 3.77 (dd, *J* = 6.3 Hz, *J* = 7.5 Hz, 1 H, H4), 3.39 (s, 3 H, CH_3-MOM), 3.02–2.94 (m, 2 H, dithiane), 2.70–2.63 (m, 2 H, dithiane), 2.04–2.00 (m, 2 H, dithiane), 1.18 (s, 9 H, Pv).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.1 (CO-Pv), 157.5 (q, *J* = 37.5 Hz, 1 C, CO-Tfa), 115.7 (q, *J* = 287.8 Hz, 1 C, CF_3-Tfa), 95.9 (CH_2-MOM), 96.6 (3,4-OCH_2O), 77.2 (C3), 75.9 (C4), 74.9 (C5), 62.2 (C6), 56.1 (CH_3-MOM), 52.1 (C2), 46.3 (C1), 38.8 (Me_3C-Pv), 27.3 (dithiane), 27.0 (3C, CH_3-Pv), 26.9 (dithiane), 25.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{30}F_3NNaO_7S_2$: 528.1308; found: 528.1315.

Anal. Calcd for $C_{19}H_{30}F_3NO_7S_2$: C, 45.14; H, 5.98; N, 2.77. Found: C, 45.45; H, 6.14; N, 2.76.

2-Deoxy-5-*O*-methoxymethyl-3,4-*O*-methylene-2-trifluoroacetamido-D-glucose Propane-1,3-diyl Dithioacetal (12)

To a soln of **11** (1.0 g, 1.98 mmol) in MeOH (10 mL) was added 30% NaOMe in MeOH (3.0 mL) at r.t. The mixture was stirred overnight and then neutralized by addition of AcOH. The volatile components were removed under reduced pressure. EtOAc and H_2O were added to the residue and the organic phase was separated and concentrated under reduced pressure. The residue was purified by MPLC (EtOAc–cyclohexane, 1:5) and gave **12** as a colorless oil that crystallized slowly during storage; yield: 475 mg (57%); mp 144 °C (dec.).

$[\alpha]_D^{20}$ –13.4 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, *J* = 9.8 Hz, 1 H, NH), 5.1 (s, 1 H, 3,4-OCH_2O), 5.0 (s, 1 H, 3,4-OCH_2O), 4.78 (d, *J* = 7.0 Hz, 1 H, CH_2-MOM), 4.76 (d, *J* = 6.9 Hz, 1 H, CH_2-MOM), 4.72 (dd, *J* = 0.8 Hz, *J* = 6.5 Hz, 1 H, H4), 4.67 (pseudo t, *J* = 9.5 Hz, 1 H, H2), 4.00 (d, *J* = 9.0 Hz, 1 H, H1), 3.88 (dd, *J* = 2.5 Hz, *J* = 12.1 Hz, 1 H, H6a), 3.77–3.74 (m, 1 H, H3), 3.70–3.64 (m, 2 H, H5, H6b), 3.46 (s, 3 H, CH_3-MOM), 3.04–2.95 (m, 2 H, dithiane), 2.75–2.66 (m, 2 H, dithiane), 2.10–1.99 (m, 2 H, dithiane), 1.75 (br s, 1 H, 6-OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6 (d, *J* = 37.5 Hz, 1 C, CO-Tfa), 115.7 (d, *J* = 288.0 Hz, 1 C, CF_3-Tfa), 97.0 (3,4-OCH_2O), 95.5 (CH_2-MOM), 80.9 (C5), 77.1 (C3), 76.8 (C4), 62.8 (C6), 56.0 (CH_3-MOM), 51.9 (C2), 46.7 (C1), 27.6 (dithiane), 27.2 (dithiane), 25.1 (dithiane).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{22}F_3NNaO_6S_2$: 444.0733; found: 444.0736.

Anal. Calcd for $C_{14}H_{22}F_3NO_6S_2$: C, 39.90; H, 5.26; N, 3.32. Found: C, 40.03; H, 5.03; N, 3.17.

2-Deoxy-5-*O*-methoxymethyl-3,4-*O*-methylene-6-*O*-tosyl-2-trifluoroacetamido-D-glucose Propane-1,3-diyl Dithioacetal (4)

To a soln of **12** (1.5 g, 3.6 mmol), Et_3N (1.5 mL, 10.6 mmol), and DMAP (0.45 g, 3.6 mmol) in CH_2Cl_2 (30 mL) was added TsCl (1.50 g, 7.8 mmol) at r.t. and the mixture was stirred overnight. The reaction was quenched by addition of MeOH and the solvent was removed under reduced pressure. The residue was purified by MPLC (EtOAc–cyclohexane, 1:5) to give **4** as a colorless oil; yield: 1.2 g (56%).

$[\alpha]_D^{20}$ +18.7 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.3 Hz, 2 H, H_{aryl}), 7.29 (d, *J* = 8.3 Hz, 2 H, H_{aryl}), 6.56 (d, *J* = 9.8 Hz, 1 H, NH), 4.95 (s, 1 H, 3,4-OCH_2O), 4.80 (s, 1 H, 3,4-OCH_2O), 4.64 (d, *J* = 6.8 Hz, 1 H, CH_2-MOM), 4.58 (d, *J* = 6.8 Hz, 1 H, CH_2-MOM), 4.49 (pseudo t, *J* = 9.2 Hz, 1 H, H2), 4.61 (dd, 1 H, *J* = 1.3 Hz, *J* = 6.1 Hz, H3), 4.27 (dd, *J* = 3.1 Hz, *J* = 10.9 Hz, 1 H, H6a), 4.05 (dd, *J* = 4.5 Hz, *J* = 10.9 Hz, 1 H, H6b), 3.91 (d, *J* = 9.2 Hz, 1 H, H1), 3.81–3.77 (m, 1 H, H5), 3.61 (dd, *J* = 6.1 Hz, *J* = 7.1 Hz, 1 H, H4), 3.28 (s, 3 H, CH_3-MOM), 2.96–2.87 (m, 2 H, dithiane), 2.66–2.59 (m, 2 H, dithiane), 2.38 (s, 3 H, CH_3-Ts), 1.99–1.90 (m, 2 H, dithiane).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5 (d, *J* = 37.5 Hz, 1 C, CO-Tfa), 117.1 (CF_3-Tfa), 129.8 (3 C, C_{aryl}), 129.0 (3 C, C_{aryl}), 96.5 (3,4-OCH_2O), 95.6 (CH_2-MOM), 77.0 (C3), 76.5 (C4), 75.0 (C5), 68.5 (C6), 56.2 (CH_3-MOM), 52.3 (C2), 46.4 (C1), 27.6 (dithiane), 27.2 (dithiane), 25.1 (dithiane), 21.5 (CH_3-Ts).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{28}F_3NNaO_8S_3$: 598.0821; found: 598.0822.

(2*R*,3*R*,4*R*,5*R*)-2-Acetamido-3,4,5-tris(methoxymethoxy)cyclohexanone Propane-1,3-diyl Dithioacetal (14)

To a soln of the 6-*O*-tosyl compound **2** (98 mg, 0.16 mmol) in anhyd THF (5 mL) was added dropwise a 1.6 M *n*-BuLi in hexane (0.31 mL, 0.5 mmol) at –78 °C. The pink soln was warmed to –40 °C over 1 h and and this point the soln became yellowish. At –20 °C after stirring for a total of 2 h, the mixture was quenched with H_2O. The phases were separated, the aqueous phase was extracted with Et_2O (3 ×), and the combined organic phases were dried ($MgSO_4$). The solvent was evaporated and the residue was purified by MPLC (EtOAc–cyclohexane 1:2) to give **14** as a colorless syrup; yield: 48 mg (71%).

$[\alpha]_D^{20}$ –25.1 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, C_6D_6): δ = 6.41 (d, *J* = 10.2 Hz, 1 H, NHC=O), 5.05 (dd, *J* = 10.2 Hz, *J* = 3.3 Hz, 1 H, H2), 4.67 (dd, *J* = 8.4 Hz, *J* = 6.4 Hz, 2 H, OCH_2O), 4.56 (dd, *J* = 6.5 Hz, *J* = 3.9 Hz, 2 H, OCH_2O), 4.53 (dd, *J* = 6.7 Hz, *J* = 4.7 Hz, 2 H, OCH_2O), 4.46 (ddd, *J* = 8.4 Hz, *J* = 5.8 Hz, *J* = 2.5 Hz, 1 H, H5), 4.13 (dd, *J* = 4.3 Hz, *J* = 3.3 Hz, 1 H, H3), 4.11 (dd, *J* = 4.3 Hz, *J* = 2.5 Hz, 1 H, H4), 3.20 (s, 3 H, OCH_3), 3.16 (s, 3 H, OCH_3), 3.15 (s, 3 H, OCH_3), 3.15–3.06 (m, 1 H, SCH_{ax}-a), 2.64–2.56 (m, 1 H, SCH_{ax}-b), 2.50–2.31 (m, 2 H, SCH_{eq}), 2.41 (d, *J* = 8.4 Hz, 2 H, H6), 1.78 (s, 3 H, $NCOCH_3$), 1.55–1.52 (m, 2 H, $SCCH_2CS$).

^{13}C NMR (100 MHz, C_6D_6): δ = 169.9 (NC=O), 97.4 (OC=O), 97.1 (OC=O), 95.9 (OC=O), 78.4 (C4), 77.2 (C3), 71.4 (C5), 56.0 (OCH_3), 55.9 (OCH_3), 55.6 (OCH_3), 54.2 (C1), 52.7 (C2), 37.0 (C6), 27.7 (SCH_2C), 26.9 (SCH_2C), 25.2 ($SCCH_2CS$), 23.5 (CH_3-Ac).

ESI-MS: *m*/*z* = 426.2 [M + H]$^+$, 448.2 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{31}NNaO_7S_2$: 448.1434; found: 448.1434.

2-Acetamido-2,6-anhydro-2-deoxy-3,4,5-tri-*O*-methoxymethyl-D-glucose Propane-1,3-diyl Dithioacetal (16)

To a soln of 6-*O*-tosyl compound **2** (302 mg, 0.51 mmol) in anhyd THF (10 mL) was added 60% NaH in oil (50 mg, 1.25 mmol) at 0 °C. The mixture was heated to reflux temperature and stirred for 2 h and then quenched by addition of EtOH and H_2O. The mixture was extracted with Et_2O (3 ×) and the combined organic phases were dried ($MgSO_4$) and filtered. The solvent was evaporated under reduced pressure and resulting residue purified by MPLC (EtOAc–cyclohexane, 2:1) to give **16** as a colorless syrup; yield: 135 mg (63%).

$[\alpha]_D^{20}$ –71.0 (*c* 1.00, $CHCl_3$).

Isomers from the rotating restriction of amide were observed and resolved by NMR. For the sake of clarity they are listed here as separate compounds.

Isomer 1:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.38 (dd, *J* = 6.4 Hz, *J* = 6.1 Hz, 1 H, H2), 4.80 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.77 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.72 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.68 (d, *J* = 6.6 Hz, 1 H, OCH_2O), 4.66 (d, *J* = 6.6 Hz, 1 H, OCH_2O), 4.65 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.44 (d, *J* = 6.8 Hz, 1 H, H1), 4.10 (dd, *J* = 10.3 Hz, *J* = 6.3 Hz, 1 H, H3), 4.04 (dd, *J* = 10.2 Hz, *J* = 3.2 Hz, 1 H, H4), 3.96 (br s, 1 H, H5), 3.77 (br d, *J* = 14.9 Hz, 1 H, H6a), 3.54 (br d, *J* = 14.9 Hz, 1 H, H6b), 3.38 (s, 6 H, OCH_3), 3.34 (s, 3 H, OCH_3), 2.86–2.78 (m, 2 H, SCH_{ax}), 2.76–2.69 (m, 2 H, SCH_{eq}), 2.12 (s, 3 H, $NCOCH_3$), 2.00–1.94 (m, 1 H, $SCCH_2CS$), 1.89–1.84 (m, 1 H, $SCCH_2CS$).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1 (NC=O), 96.9 (OCH_2O), 96.8 (OCH_2O), 96.6 (OCH_2O), 75.2 (C4), 72.9 (2C, C3/5), 56.2 (OCH_3), 55.9 (OCH_3), 55.9 (OCH_3), 53.9 (C2), 47.6 (C6), 46.2 (C1), 30.2 (SCH_2C), 29.8 (SCH_2C), 25.5 ($SCCH_2CS$), 21.8 (CH_3-Ac).

Isomer 2:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.80 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.80 (br d, *J* = 15.1 Hz, 1 H, H6a), 4.73 (d, *J* = 6.9 Hz, 1 H, OCH_2O), 4.70 (d, *J* = 7.1 Hz, 1 H, OCH_2O), 4.68 (d, *J* = 6.9 Hz, 1 H, OCH_2O), 4.67 (d, *J* = 6.9 Hz, 1 H, OCH_2O), 4.61 (d, *J* = 7.2 Hz, 1 H, H1), 4.58 (d, *J* = 6.9 Hz, 1 H, OCH_2O), 4.26 (dd, *J* = 6.5 Hz, *J* = 6.1 Hz, 1 H, H2), 4.16 (dd, *J* = 10.5 Hz, *J* = 6.1 Hz, 1 H, H3), 4.05 (dd, *J* = 6.4 Hz, *J* = 3.3 Hz, 1 H, H4), 3.98 (br s, 1 H, H5), 3.43 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 2.99–2.94 (m, 1 H, SCH_{ax}-a), 2.91 (br d, *J* = 14.8 Hz, 1 H, H6b), 2.90–2.85 (m, 1 H, SCH_{ax}-b), 2.81–2.73 (m, 2 H, SCH_{eq}), 2.21 (s, 3 H, $NCOCH_3$), 2.05–2.02 (m, 1 H, $SCCH_2CS$), 1.84–1.78 (m, 1 H, $SCCH_2CS$).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.0 (NC=O), 97.4 (OCH_2O), 96.4 (OCH_2O), 95.2 (OCH_2O), 74.6 (C4), 74.1 (C3), 71.2 (C5), 60.8

(C2), 56.4 (OCH_3), 55.8 (OCH_3), 55.7 (OCH_3), 47.8 (C1), 41.0 (C6), 31.4 (2C, SCH_2C), 25.5 ($SCCH_2CS$), 22.2 (CH_3-Ac).

ESI-MS: *m*/*z* = 448.1 $[M + Na]^+$, 873.3 $[2 M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{31}NNaO_7S_2$: 448.1434; found: 448.1426.

(2*R*,3*R*,4*R*,5*R*)-2-Acetamido-5-(methoxymethoxy)-3,4-(methylenedioxy)cyclohexanone Propane-1,3-diyl Dithioacetal (17)

To a soln of **3** (1.38 g, 2.6 mmol) in anhyd THF (70 mL) at –78 °C under argon was added 1.6 M *n*-BuLi in hexane (7 mL, 11.2 mmol). The mixture was slowly warmed to –20 °C over 5 h and then it was quenched by addition of sat. aq NH_4Cl. The organic phase was separated and the aqueous phase was washed with EtOAc. The combined organic phases were washed with brine and evaporated under reduced pressure. The residue was purified by MPLC (EtOAc–cyclohexane, 1:1) to give **17** as a colorless oil that occasionally crystallized during storage; yield: 0.48 g (52%). An analytical sample was recrystallized (EtOAc); mp 179.4–180.0 °C.

$[\alpha]_D^{20}$ –8.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (d, *J* = 9.6 Hz, 1 H, NH), 5.09 (s, 1 H, 3,4-OCH_2O), 5.03 (s, 1 H, 3,4-OCH_2O), 4.69 (d, *J* = 6.7 Hz, 1 H, MOM), 4.65 (d, *J* = 6.7 Hz, 1 H, MOM), 4.43 (pseudo t, *J* = 10.4 Hz, 1 H, H2), 4.33–4.28 (m, 1 H, H5), 3.98 (dd, *J* = 9.5 Hz, *J* = 10.9 Hz, 1 H, H3), 3.40 (dd, *J* = 2.7 Hz, *J* = 9.5 Hz, 1 H, H4), 3.36 (s, 3 H, MOM), 2.99 (dd, *J* = 2.8 Hz, *J* = 15.5 Hz, 1 H, H6a), 2.96–2.87 (m, 2 H, dithiane), 2.78–2.64 (m, 2 H, dithiane), 2.06 (dd, *J* = 3.2 Hz, *J* = 15.5 Hz, 1 H, H6b), 2.05 (s, 3 H, CH_3-Ac), 1.98–1.85 (m, 2 H, dithiane).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0 (CO-Ac), 96.5 (3,4-OCH_2O), 95.7 (MOM), 80.3 (C4), 73.6 (C3), 69.6 (C5), 58.5 (C2), 55.5 (MOM), 55.4 (C1), 42.4 (C6), 27.0 (dithiane), 25.9 (dithiane), 24.0 (dithiane), 23.2 (CH_3-Ac).

HRMS-ESI(+): *m*/*z* $[M + Na]^+$ 372.0907. $C_{14}H_{23}NNaO_5S_2$ requires 372.0910.

Anal. Calcd for $C_{14}H_{23}NO_5S_2$: C, 48.12; H, 6.63; N, 4.01. Found: C, 47.81; H, 6.99; N, 3.96.

2-Acetamido-2,6-anhydro-2-deoxy-5-*O*-methoxymethyl-3,4-*O*-methylene-D-glucose Propane-1,3-diyl Dithioacetal (18)

To a soln of **3** (300 mg, 0.58 mmol) in anhyd THF (10 mL) at r.t. under argon was added 60% NaH in oil (30 mg, 0.75 mmol). Then the mixture was refluxed for 2 h and then it was cooled to r.t. and quenched by addition of sat. aq NH_4Cl. The organic phase was separated and the aqueous phase was washed with EtOAc. The combined organic phases were washed with brine and evaporated under reduced pressure. The residue was purified by MPLC (EtOAc–cyclohexane, 2:3) to give **18** as a colorless oil; yield: 157 mg (78%).

$[\alpha]_D^{20}$ –67.9 (*c* 1.00, $CHCl_3$).

Similar to compound **16**, isomers of compound **18** were observed and recorded by NMR.

Isomer 1:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (dd, *J* = 5.7 Hz, *J* = 9.4 Hz, 1 H, H2), 5.10 (s, 1 H, 3,4-OCH_2O), 4.99 (s, 1 H, 3,4-OCH_2O), 4.76 (d, *J* = 6.7 Hz, 1 H, MOM), 4.61 (d, *J* = 6.7 Hz, 1 H, MOM), 4.28 (m, 1 H, H5), 4.05 (d, *J* = 9.4 Hz, 1 H, H1), 3.90–3.81 (m, 2 H, H3, H6), 3.60 (dd, *J* = 2.6 Hz, *J* = 10.0 Hz, 1 H, H4), 3.32 (s, 3 H, MOM), 3.16 (dd, *J* = 1.5 Hz, *J* = 15.1 Hz, 1 H, H6), 3.05–2.84 (m, 2 H, dithiane), 2.77–2.52 (m, 2 H, dithiane), 2.13 (s, 3 H, CH_3-Ac), 1.97–1.88 (m, 2 H, dithiane).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.2 (CO-Ac), 96.2 (MOM), 95.8 (3,4-OCH_2O), 75.5 (C4), 72.1 (C3), 70.4 (C5), 53.4 (C2), 55.8 (MOM), 47.1 (C6), 41.5 (C1), 27.8 (dithiane), 27.7 (dithiane), 25.2 (dithiane), 22.1 (CH_3-Ac).

Isomer 2:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.14 (s, 1 H, 3,4-OCH_2O), 5.07 (s, 1 H, 3,4-OCH_2O), 4.93 (dd, *J* = 2.3 Hz, *J* = 15.2 Hz, 1 H, H6), 4.66 (d, *J* = 6.8 Hz, 1 H, MOM), 4.62 (d, *J* = 6.8 Hz, 1 H, MOM), 4.52–4.44 (m, 2 H, H2, H1), 4.28 (m, 1 H, H5), 3.98 (dd, *J* = 4.8 Hz, *J* = 9.9 Hz, 1 H, H3), 3.72 (dd, *J* = 2.7 Hz, *J* = 9.9 Hz, 1 H, H4), 3.31 (s, 3 H, MOM), 2.92–2.71 (m, 4 H, dithiane), 2.69 (dd, *J* = 1.4 Hz, *J* = 15.2 Hz, 1 H, H6), 2.22 (s, 3 H, CH_3-Ac), 2.09–2.00 (m, 1 H, dithiane), 1.87–1.75 (m, 1 H, dithiane).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3 (CO-Ac), 96.3 (3,4-OCH_2O), 95.2 (MOM), 75.7 (C4), 72.3 (C3), 68.9 (C5), 60.2 (C2), 55.5 (MOM), 45.1 (C1), 41.8 (C6), 30.7 (dithiane), 30.3 (dithiane), 25.2 (dithiane), 22.5 (CH_3-Ac).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{23}NNaO_5S_2$: 372.0910; found: 372.0925.

Anal. Calcd for $C_{14}H_{23}NO_5S_2$: C, 48.12; H, 6.63; N, 4.01. Found: C, 47.74; H, 6.67; N, 3.58.

(2*R*,3*R*,4*R*,5*R*)-5-(Methoxymethoxy)-3,4-(methylenedioxy)-2-(trifluoroacetamido)cyclohexanone Propane-1,3-diyl Dithioacetal (19)

To a soln of **4** (150 mg, 0.26 mmol) in anhyd THF (2 mL) at –100 °C under argon was added 1.6 M *n*-BuLi in hexane (0.48 mL, 0.78 mmol). The mixture was slowly warmed to –50 °C over 3 h and then it was quenched by the addition of sat. aq NH_4Cl. The organic phase was separated and the aqueous phase was washed with EtOAc. The combined organic phases were washed with brine and evaporated under reduced pressure. The residue was purified by MPLC (EtOAc–cyclohexane, 1:5) to give **19** as a white solid; yield: 82 mg (78%); mp 160.0 °C (dec.).

$[\alpha]_D^{20}$ +8.0 (*c* 1.00, MeOH).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 9.6 Hz, 1 H, NH), 5.17 (d, *J* = 0.75 Hz, 1 H, 3,4-OCH_2O), 5.13 (d, *J* = 0.75 Hz, 1 H, 3,4-OCH_2O), 4.76 (d, *J* = 6.7 Hz, 1 H, CH_2-MOM), 4.73 (d, *J* = 6.7 Hz, 1 H, CH_2-MOM), 4.44–4.39 (m, 2 H, H2, H5), 4.11 (dd, *J* = 9.4 Hz, *J* = 10.8 Hz, 1 H, H3), 3.47 (dd, *J* = 2.7 Hz, *J* = 9.4 Hz, 1 H, H4), 3.44 (s, 3 H, MOM), 3.09 (dd, *J* = 2.9 Hz, *J* = 15.6 Hz, 1 H, H6a), 3.03–2.96 (m, 2 H, dithiane), 2.80–2.73 (m, 2 H, dithiane), 2.16 (dd, *J* = 2.9 Hz, *J* = 15.6 Hz, 1 H, H6b), 2.03–1.97 (m, 2 H, dithiane).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.0 (very weak d, *J* = 35.3 Hz, 1 C, CO-Tfa), 116.0 (very weak q, *J* = 223.5 Hz, 1 C, CF_3-Tfa), 96.8 (3,4-OCH_2O), 95.7 (MOM), 80.2 (C4), 73.1 (C3), 69.3 (C5), 59.4 (C2), 55.7 (MOM), 55.0 (C1), 43.0 (C6), 27.0 (dithiane), 25.8 (dithiane), 23.5 (dithiane).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{20}F_3NNaO_5S_2$: 426.0627; found: 426.0623.

(2*R*,3*R*,4*R*,5*R*)-2-Acetamido-5-(methoxymethoxy)-3,4-(methylenedioxy)cyclohexanone (20)

A soln of the dithiane **17** (150 mg, 0.43 mmol) in MeCN (0.5 mL) was added quickly to a well-stirred mixture of NCS (225 mg, 1.7 mmol), $AgNO_3$ (327 mg, 1.9 mmol), and $CaCO_3$ (300 mg, 3 mmol) in aq 80% MeCN (4 mL). After 30 min, the mixture was filtered and the solvent was concentrated. The residue was purified by column (EtOAc–cyclohexane, 1:1) to give **20** as a white solid; yield: 45 mg (40%); mp 156–158 °C (dec.).

$[\alpha]_D^{20}$ –21.5 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.5 Hz, 1 H, NH), 5.26 (s, 1 H, 3,4-OCH_2O), 5.18 (s, 1 H, 3,4-OCH_2O), 4.90 (dd, *J* = 8.5 Hz, *J* = 12.0 Hz, 1 H, H2), 4.78 (d, *J* = 6.7 Hz, 1 H, CH_2-MOM), 4.71 (d, *J* = 6.7 Hz, 1 H, CH_2-MOM), 4.57 (m, 1 H, H5), 4.17 (dd, *J* = 9.4 Hz, *J* = 2.2 Hz, 1 H, H4), 3.99 (dd, *J* = 9.4 Hz, *J* = 12.0 Hz, 1 H, H3), 3.35 (s, 3 H, CH_3-MOM), 2.99 (dd, *J* = 3.7 Hz, *J* = 15.9

Hz, 1 H, H6a), 2.06 (dd, *J* = 3.7 Hz, *J* = 15.9 Hz, 1 H, H6b), 2.1 (s, 3 H, CH_3-Ac).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.1 (C1), 170.7 (CO-Ac), 98.4 (3,4-OCH_2O), 97.1 (CH_2-MOM), 80.7 (C4), 76.5 (C3), 69.9 (C5), 61.8 (C2), 56.1 (CH_3-MOM), 45.5 (C6), 23.4 (CH_3-Ac).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{17}NNaO_6$: 282.0953; found: 282.0931.

(2*R*,3*R*,4*R*,5*R*)-2-Acetamido-3,4,5-trihydroxycyclohexanone Propane-1,3-diyl Dithioacetal (21)

To a soln of **17** (50 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) at –90 °C under argon was added 10% BCl_3 in 2-chloroethanol (1.6 mL, 1.4 mmol).The mixture was then warmed to r.t. over a period of 20 min and stirred for a further 3 h. Sat. $NaHCO_3$ was added to neutralize the mixture and then all the volatile components were removed under reduced pressure. The residue was extracted with MeOH and filtered. The filtrate was concentrated under reduced pressure again and the residue was purified by MPLC (acetone–cyclohexane, 1:1) to give **21** as a white powder; yield: 27 mg (64%). An analytical sample was recrystallized (MeOH–EtOAc); mp 200.9–201.5 °C.

$[\alpha]_D^{20}$ –36.4 (*c* 1.00, MeOH).

The NMR data were recorded from the peracetylated derivative of the product by general acetylation procedure.

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 5.94 (d, *J* = 10.1 Hz, 1 H, NH), 5.41 (t, *J* = 10.1 Hz, 1 H, H3), 5.24–5.21 (m, 1 H, H5), 4.99 (dd, *J* = 3.6 Hz, *J* = 10.1 Hz, 1 H, H4), 4.36 (t, *J* = 10.1 Hz, 1 H, H2), 3.03 (dd, *J* = 3.6 Hz, *J* = 15.8 Hz, 1 H, H6), 2.95–2.86 (m, 2 H, dithiane), 2.72–2.61 (m, 2 H, dithiane), 2.14 (dd, *J* = 2.8 Hz, *J* = 15.8 Hz, 1 H, H6), 2.04 (s, 3 H, CH_3-Ac), 1.97 (s, 3 H, CH_3-Ac), 1.96 (s, 3 H, CH_3-Ac), 1.94 (s, 3 H, CH_3-Ac), 1.90–1.82 (m, 2 H, dithiane).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (CO-Ac), 170.2 (CO-Ac), 169.8 (CO-Ac), 169.4 (CO-Ac), 71.4 (C4), 69.0 (C3), 68.1 (C5), 58.2 (C2), 53.9 (C1), 38.9 (C6), 26.7 (dithiane), 25.7 (dithiane), 22.6 (dithiane), 23.1 (CH_3-Ac), 21.1 (CH_3-Ac), 20.6 (CH_3-Ac), 20.5 (CH_3-Ac).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{19}NNaO_4S_2$: 316.0648; found: 316.0649.

Anal. Calcd for $C_{11}H_{19}NO_4S_2$: C, 45.03; H, 6.53; N, 4.47. Found: C, 44.91; H, 6.50; N, 4.61.

(2*S*,3*R*,4*R*,5*R*)-2-Acetamido-2,6-anhydro-2-deoxy-D-glucose Propane-1,3-diyl Dithioacetal (22)

To a soln of **18** (207 mg, 0.59 mmol) in THF (25 mL) at 0 °C was added concd HCl (4 mL). The mixture was then stirred overnight at r.t.. Solid Na_2CO_3 was added to quench the reaction and the slurry was stirred for 10 min before it was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by MPLC (acetone–cyclohexane, 5:4) to give **22** as a white powder; yield: 123 mg (71%). An analytical sample was recrystallized (CH_2Cl_2–EtOAc); mp 179.0–180.5 °C (dec.).

$[\alpha]_D^{20}$ –36.5 (*c* 1.00, $CHCl_3$).

The NMR data were recorded from the peracetylated derivative of the product by general acetylation procedure. Isomers were observed and recorded.

Isomer 1:

^{1}H NMR (400 MHz; $CDCl_3$): δ = 5.65 (dd, *J* = 4.6 Hz, *J* = 8.6 Hz, 1 H, H2), 5.30–5.26 (m, 1 H, H5), 5.25–5.21 (m, 2 H, H4, H3), 4.07 (d, *J* = 8.6 Hz, 1 H, H1), 3.78 (d, *J* = 15.5 Hz, 1 H, H6), 3.48 (d, *J* = 15.5 Hz, 1 H, H6), 2.99–2.83 (m, 2 H, dithiane), 2.73–2.52 (m, 2 H, dithiane), 2.06 (s, 3 H, CH_3-Ac), 2.02 (s, 3 H, CH_3-Ac), 1.99 (s, 3 H, CH_3-Ac), 1.97 (s, 3 H, CH_3-Ac), 1.93–1.86 (m, 2 H, dithiane).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (CO-Ac), 170.0 (CO-Ac), 169.9 (CO-Ac), 169.8 (CO-Ac), 68.2 (C4), 67.9 (C5), 67.1 (C3), 51.2 (C2), 45.3 (C6), 42.5 (C1), 27.8 (dithiane), 27.5 (dithiane), 25.0 (dithiane), 21.4 (CH_3-Ac), 21.1 (CH_3-Ac), 20.7 (CH_3-Ac), 20.6 (CH_3-Ac).

Isomer 2:

^{1}H NMR (400 MHz, $CDCl_3$); δ = 5.32 (dd, *J* = 3.4 Hz, *J* = 11.1 Hz, 1 H, H4), 5.30–5.26 (m, 1 H, H5), 5.15 (dd, *J* = 4.8 Hz, *J* = 11.1 Hz, 1 H, H3), 4.73 (dd, *J* = 1.8 Hz, *J* = 15.4 Hz, 1 H, H6a), 4.50–4.41 (m, 2 H, H2, H1), 3.02–2.93 (m, 1 H, H6b), 2.98–2.71 (m, 4 H, dithiane), 2.21 (s, 3 H, CH_3-Ac), 2.15–1.71 (m, 1 H, dithiane), 2.06 (s, 3 H, CH_3-Ac), 1.99 (s, 3 H, CH_3-Ac), 1.94 (s, 3 H, CH_3-Ac).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (CO-Ac), 170.1 (CO-Ac), 170.0 (CO-Ac), 169.9 (CO-Ac), 68.3 (C3), 67.9 (C4), 67.2 (C5), 57.5 (C2), 46.2 (C1), 40.6 (C6), 30.7 (dithiane), 30.6 (dithiane), 25.0 (dithiane), 21.8 (CH_3-Ac), 21.1 (CH_3-Ac), 20.7 (CH_3-Ac), 20.5 (CH_3-Ac).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{19}NNaO_4S_2$: 316.0648; found: 316.0665.

Anal. Calcd for $C_{11}H_{19}NO_4S_2$: C, 45.03; H, 6.53; N, 4.47. Found: C, 44.80; H, 6.59; N, 4.46

(2*R*,3*R*,4*R*,5*R*)-2-Amino-5-(methoxymethoxy)-3,4-(methylenedioxy)cyclohexanone Propane-1,3-diyl Dithioacetal (23)

Compound **19** (60 mg, 0.15 mmol) was dissolved in MeOH (1 mL) and 30% NaOMe in MeOH (1 mL) was added. The clear soln was heated in a sealed tube at 100 °C for 10 h. Then the solvent was evaporated and the residue was partitioned between H_2O and EtOAc. The organic phase was collected, washed with brine, and evaporated. The resulted syrup was purified by MPLC (EtOAc–cyclohexane, 1:1) to give **23** as colorless oil; yield: 31 mg (67%).

$[\alpha]_D^{20}$ –39.0 (*c* 1.00, MeOH).

^{1}H NMR (500 MHz, C_6D_6): δ = 4.96 (d, *J* = 2.0 Hz, 2 H, 3,4-OCH_2O), 4.68 (dd, *J* = 6.6 Hz, *J* = 28.6 Hz, 2 H, CH_2-MOM), 4.21 (pseudo t, *J* = 9.9 Hz, 1 H, H3), 4.07 (m, 1 H, H5), 3.10 (d, *J* = 10.2 Hz, 1 H, H2), 2.88 (dd, *J* = 2.7 Hz, *J* = 9.5 Hz, 1 H, H4), 3.27 (s, 3 H, CH_3-MOM), 2.65 (dd, *J* = 2.9 Hz, *J* = 15.4 Hz, 1 H, H6a), 3.02–2.92 (m, 2 H, dithiane), 2.45–2.40 (m, 1 H, dithiane), 2.20–2.16 (m, 1 H, dithiane), 1.58–1.50 (m, 3 H, dithiane, H6b).

^{13}C NMR (125 MHz, C_6D_6): δ = 96.6 (3,4-OCH_2O), 95.6 (CH_2-MOM), 80.3 (C4), 77.1 (C3), 70.1 (C5), 66.8 (C2), 55.3 (CH_3-MOM), 54.6 (C1), 43.4 (C6), 27.81 (dithiane), 25.76 (dithiane), 24.8 (dithiane).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{21}NNaO_4S_2$: 330.0804; found: 330.0807.

2-Amino-2,6-anhydro-2-deoxy-D-glucose Propane-1,3-diyl Dithioacetal (24)

Compound **22** (293 mg, 1 mmol) was dissolved in a mixture of H_2O (3 mL) and EtOH (2 mL). 6 M HCl (1 mL) was added and the mixture was refluxed for 3 h. All the volatile components were removed from the mixture under vacuum. Methanolic NH_3 was added to the residue and the mixture was evaporated to dryness again. The residue was purified by MPLC (cyclohexane–acetone, 1:3) to give **24** as a light yellow solid; yield: 120 mg (48%); mp 112 °C.

$[\alpha]_D^{20}$ +3.7 (*c* 1.00, MeOH).

The compound was then peracetylated according to the standard procedure. NMR analysis was performed on the peracetylated derivative, and was found identical to the NMR spectrum of the peracetylated derivative of compound **22**.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{18}NO_3S_2$: 252.0728; found: 252.0713.

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