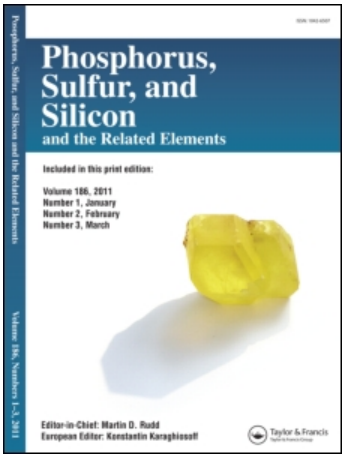

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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Kerstin Polchow[a]; Jürgen Voss[a]
[a] Institut für Organische Chemie der Universität, D-20146 Hamburg, Germany

Online publication date: 21 December 2010

To cite this Article Polchow, Kerstin and Voss, Jürgen(2005) 'Preparation of Anhydro-Thiohexofuranosides from Methyl Fructofuranosides Via the Thio-Mitsunobu Reaction[1]', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 2, 353 — 363
To link to this Article: DOI: 10.1080/104265090508424a
URL: http://dx.doi.org/10.1080/104265090508424a

Phosphorus, Sulfur, and Silicon, 180:353–363, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090508424

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Preparation of Anhydro-Thiohexofuranosides from Methyl Fructofuranosides Via the Thio-Mitsunobu Reaction[1]

Kerstin Polchow
Jürgen Voss
Institut für Organische Chemie der Universität Hamburg,
Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany

Methyl α-D-fructofuranoside was transformed regioselectively into the corresponding 6-S-thioacetate in one step by use of the thio-Mitsunobu reaction. Reaction of the trimesylate derived from this thioacetate with sodium hydrogen carbonate led to the thietanosugar methyl 4,6-anhydro-1,3-di-O-mesyl-4-thio-α-D-tagatofuranoside. Methyl β-D-fructofuranoside gave the corresponding 6-S-thioacetate and, with excess thioacetic acid, the 1-S, 6-S-bis-thioacetate. Whereas this mono-thioacetate did not yield a thietano derivative, the bis-thioacetate gave the bis-thietane methyl 1,3:4,6-dianhydro-1,4-dithio-β-D-sorbofuranoside with sodium hydrogen carbonate.

Keywords Cyclisation; intramolecular S_N2; methyl fructofuranosides; reaction; thietanosugars; thio-Mitsunobu reaction

We have very successfully applied the thio-Mitsunobu reaction for the chemoselective preparation of 5-*S*-acetyl-5-thiopentofuranosides[3–6] from the corresponding methyl pentofuranosides, the secondary hydroxy groups of which were mostly unprotected. Also, methyl D-glucohexopyranoside has proved to be a suitable starting material for the direct introduction of the acetylthio group into an aldohexose.[7] The thio-Mitsunobu reaction of methyl ketosides has, however, not yet been investigated. We have studied the reaction of methyl α-D- (**2**) and methyl β-D-fructofuranoside (**3**) with thioacetic acid in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine. As in the above mentioned cases, we were interested in the base-promoted

Received June 22, 2004; in final form July 8, 2004.
We thank the *University of Hamburg* and the *Fondsder Chemischen Industrie* for financial support K. P. thanks the *University of Hamburg* for a Graduate Fellowship.
Address correspondence to Jürgen Voss, Institut für Organische Chemie der Univsität Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany. E-mail: voss@chemie.uni-hamburg.de

cleavage of the sugar thioacetates and concomitant intramolecular cyclization of the thiolates to thietano- or thiolanosugars.

RESULTS AND DISCUSSION

Methyl fructofuranosides are not as easily available as other methyl glycosides, e.g. methyl glucopyranoside. Due to the fact that in solution fructose exists as a mixture of the two furanoid and the two pyranoid isomers, "simple derivatizations of D-fructose, such as glycosidations ... usually yeld product mixtures of, at worst, all five tautomeric forms, from which separation of the major component is cumbersome and highly detrimental to the yields obtainable."[8] As recently as 1999 a novel synthesis of methyl fructofuranosides has been published.[9] We decided to prepare the desired starting compounds **2** and **3** by a two-step procedure from D-fructose via its 1,2:4,5-di-*O*-isopropylidene derivative **1** (Scheme 1). Compound **1** can be prepared in large amounts,[10] although the percentage yield is only moderate. Acid-catalyzed methanolysis under carefully optimized conditions transformed **1** into a mixture of **2**, **3** and **4**, which can be separated by column chromatography.*

The thio-Mitsunobu reaction of methyl α-D-fructofuranoside (**2**) with each 1.3 equivalents of thioacetic acid, triphenylphosphine and diisopropyl azodicarboxylate (DIAD) for a prolonged reaction time of 72 h led to the 6-thioacetate **5** as the only product. It was obtained with 39% yield after purification by column chromatography (Scheme 2).

The isomeric 1-thioacetate **6** or the 1,6-bis-thioacetate **7** could not be detected. Although the expected NMR spectra of **5** and **6** should be very similar, we were able to prove the structure of the product to be **5** by its ^{1}H- and ^{13}C-NMR spectra. Each two signals of the two CH_2 groups present in the molecule are detected at 3.02/3.26 ppm and 3.55/3.64 ppm. On account of their chemical shifts, the first two signals are to be assigned to a CH_2-SAc[11] group and the second two signals to a CH_2-OH group.[12] As the signals at 3.02 ppm and 3.26 ppm appear, two dublets of dublets with a geminal coupling of $^2J = 13.7$ Hz and vicinal couplings of $^3J = 7.3$ Hz and $^3J = 4.4$ Hz are due to H-6 and H-6′, whereas the signals at 3.55 ppm and 3.64 ppm, which appear as two dublets with only a geminal coupling of $^2J = 12.1$ Hz,

*The preparation of methyl fructofuranosides from **1** by use of I_2 in methanol has been described by W. A. Szarek, A. Zamojski, K. N. Tiwari, and E. R. Ison, *Tetrahedron Lett.*, **27,** 3827 (1986), but the authors did not report the experimental details (amounts of **1** and of the reagents, separation of the anomers). Therefore, we explored and applied the acid-catalyzed methanolysis of **1**.

must be due to H-1 and H-1′. The reverse assignment of the coupling patterns to the signals would be valid for the isomer **6**. This assignment was corroborated by ^{1}H-^{1}H-COSY and ^{1}H-^{13}C-COSY experiments. It was in agreement with the structures of the follow-up products, in particular with that of **9**, the NMR spectrum of which was more straightforward.

Mesylation of **5** in pyridine as solvent afforded the trimesylate **8** in nearly quantitative yield. Due to the electron-withdrawing and the anisotropy effect of the mesylate groups, the respective ^{1}H NMR signals of **8** are shifted downfield to $\delta = 4.34$ (H-1), 4.66 (H-1′), 5.17 (H-3) and 5.10 (H-4) as compared with $\delta = 3.55$ (H-1), 3.64 (H-1′), 4.04 (H-3) and 3.75 (H-4) in **5**. In the last step of the reaction sequence, **8** was treated with sodium hydrogen carbonate in refluxing 2-methoxyethanol containing 5% water. The best result was achieved with 1.5 equivalents of the base after a reaction time of 11 h. Under these conditions a total yield of 48% of the 4,6-anhydro-4-thiofuranoside **9** together with 5% of the disulfide **10** was obtained. The structure of **9** is obvious from its ^{1}H NMR spectrum. The two dublets at 4.45 and 4.69 ppm with a geminal coupling constant of $^{2}J = 11.1$ Hz are unequivocally due to H-1 and H-1′, whereas the two dublets of dublets at 2.97 and 3.40 ppm with geminal ($^{2}J = 10.3$ Hz) and vicinal ($^{3}J = 3.4/4.3$ Hz) coupling constants must be assigned to H-6 and H-6′. Due to the incorporation of C-4 into a thietane ring, its ^{13}C NMR signal is shifted to $\delta = 46.0$ ppm as compared with $\delta \approx 80$ ppm in related open chained compounds such as **8**. Since the intramolecular nucleophilic attack of the thiolate occurs under inversion on C-4, **9** belongs to the D-tagatose series. If more base and shorter reaction time were applied a mixture of 18% **9** and 22% **10** and the epoxydisulfide **11** (9%) was obtained (Scheme 3), from which pure **10** and **11** could be separated.

The ^{1}H NMR signals of H-3 and H-4 in **10** appear at $\delta > 5$ ppm as in the case of **8**. The epoxide protons H-3 and H-4 in **11** exhibit a typical coupling constant of 2.9 Hz and the ^{13}C NMR signals of C-3 and C-4 are shifted from $\delta \approx 80$ ppm to $\delta = 57.5$ ppm and 58.3 ppm. The disulfides **10** and **11** are only formed during the work-up procedure by oxidation of the intermediate thiolate anions, as we have shown by monitoring with thin layer chromatography. The formation of the epoxydisulfide **11** can be explained by a base-catalyzed splitting of the mesylate at C-4 and intramolecular nucleophilic substitution of the second mesylate on C-3 as leaving group by the alkoxide on C-4 under inversion. The resulting **11** exhibits, therefore, the D-*psico*-configuration.

The reaction of methyl β-D-fructofuranoside (**3**) with each 1.27 equivalents of triphenylphosphine, DIAD, and thioacetic acid also gave 32% of the 6-thioacetate **12** as the only product (Scheme 4). A reaction time

of 72 h at room temperature was necessary. In this case, pyridine had to be used as solvent since the solubility of **3** in tetrahydrofuran is too low. The structural elucidation of **12** was achieved by NMR spectroscopy with the same argumentation as for the α-anomer **5**. The two dublets (^2J = 11.7 Hz) at 3.52 and 3.61 ppm belong to the protons of the 1-CH_2OH group, whereas the two dublets of dublets (^2J = 13.8 Hz, ^3J = 7.5/4.7 Hz) at 3.06 and 3.29 ppm must be assigned to the 6-CH_2SAc group in agreement with the ^{1}H, ^{1}H-COSY and ^{1}H, ^{13}C-COSY results. All three equivalents of the reagents were applied in the thio-Mitsunobu reaction of **3** a 27% yield of the 1,6-bis-thioacetate **13** (Scheme 4).

The mesylation of **12** afforded a quantitative yield of the trimesylate **14**. Typical chemical shifts of $\delta > 5$ ppm are observed for H-3 and H-4 in the mesylates **14** and **15**. The nucleophile promoted thioacetate cleavage of **14** and cyclization of the thiolate to form **16** was not successful. After a reaction time of 11 h with 1.5 equivalents of sodium hydrogen carbonate, only a trace (1.4%) of the disulfide **15** could be isolated by column chromatography from the dark brown reaction mixture (Scheme 5). The reason for different behavior of α-anomer **8** and the β-anomer **14** might be electronic or steric repulsion between the attacking thiolate group and the glycosidic methoxy group of **14**.

Although it was not possible to remove the triphenylphosphine oxide from **13** completely by chromatography, **13** was mesylated and the resulting dimesylate **17** [91% yield; δ (H-3/H-4) = 5.15/5.18] was reacted for 18 h with an excess of 20 equivalents of sodium hydrogen carbonate. Column chromatography of the mixture afforded two products: 60% of the desired 1,3:4,6-dianhydro-1,4-dithio-β-D-sorbofuranoside (**18**) and 11% of a byproduct which, according to its NMR spectra, exhibits the structure of the 1,3-anhydro-6-*S*-methyl-1,6-dithio-D-psico derivative **19** (Scheme 5). The ^{13}C NMR signals of the thietane carbon atoms C-3 (56.1 ppm) and C-4 (49.1 ppm) in **18** and C-3 (50.8 ppm) in **19** exhibit the typical shift to lower values (cf. **9**). The formation of **19**, in particular, the origin of the *S*-methyl group, can be explained only by a participation of the solvent 2-methoxyethanol.

CONCLUSIONS

Our study has shown that the methyl fructofuranosides **2** and **3**, as expected, react chemoselectively with thioacetic acid under the Mitsunobu conditions. A primary hydroxy group is transformed into a thioacetate whereas the less reactive secondary hydroxy groups are not attacked. The reaction is, moreover, also regioselective. Only the 6-*S*-thioacetates **5** and **12** but not the 1-*S*-thioacetates are formed (if not a substantial excess of reagents is applied, which leads to the 1-*S*,6-*S*-bis-thioacetate **13**

in case of the β anomer **3**). The low reactivity of a hydroxy group in the 1-position in S_N2 reactions as compared with the 6-position is a result of the pronounced steric hindrance. It carries three substituents in the β-position (neopentyl effect) and, in the first step of the Mitsunobu reaction, triphenylphosphane has to be transferred from an exceptionally bulky phosphonium cation to the hydroxy group.[13]

Base-promoted cleavage and concomitant intramolecular cyclization of the mesylated thioacetates **8** and **17** leads to the thietanoketofuranosides **9**, **18**, and **19**. In striking contrast with these successful reactions and the positive results in the aldohexopyranoside series,[2,7] our strong efforts to prepare suitable thioacetates and cyclic thioanhydrides in the fructopyranoside series were in vain,[2] although we were successful in the L-sorbofuranoside as well as the L-sorbopyranoside series.[2,14]

EXPERIMENTAL

General Procedure

Corrected melting points were determined on an Electrothermal apparatus. Optical rotations were measured on a Perkin Elmer 341 polarimeter. Thin layer chromatography (TLC) was performed on Al foils coated with SiO_2 F_{254} (Merck, Darmstadt). The spots were detected by the extinction of the fluorescence, or, after spraying with 20% H_2SO_4 in EtOH, by heating. Column chromatography (CC) was performed on Kieselgel 60 F, 0.063–0.200 mm (Merck, Darmstadt). Eluents were distilled prior to use. IR (KBr pellets or films) spectra were measured on an ATI Mattson Instruments Genesis Series FT-IR spectrometer. The spectra were evaluated by use of the WinFirst 1.5 software (Analytical Technology Inc.). NMR spectra were measured on a Bruker AMX 400 spectrometer at 400 MHz for ^1H and at 101 MHz for ^{13}C. Chemical shifts δ (ppm) are related to $SiMe_4$ which was used as internal standard in $CDCl_3$. Spectra measured in acetone-d_6 were calibrated to $\delta(^1H) = 2.09$ ppm of the CD_2H signal and $\delta(^{13}C) = 30.56$ ppm of the CD_3 signal and subsequently related to $SiMe_4$. Spectra measured in D_2O were calibrated to $\delta(^1H) = 4.75$ ppm of the HOD signal and δ (^{13}C) was calculated from the resonance frequency of the deuterium lock signal. In order to enhance the resolution, the ^1H NMR spectra were recalculated from the FID by use of the program WinNMR 5.1 (Bruker). In most cases, unequivocal assignments of the signals were achieved by performing ^1H-^1H-COSY-, ^1H-^{13}C-COSY-, DEPT-135- or PENDANT experiments. Solvents were purified and dried by standard laboratory procedures,[15] THF was kept over KOH for several days and subsequently refluxed

and distilled over metallic potassium. Thioacetic acid (Merck, Darmstadt) was purified by four times distillation at low temperature in a vacuum.

1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranose (1) was prepared according to Brady.[10] M.p. 119°C (lit.: 119°C). IR: ν 3460 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 3.66 (d, 1 H, H-3), 3.98 (d, 1 H, H-1), 4.01 (d, 1 H, H-6), 4.12 (dd, 1 H, H-6′), 4.15 (d, 1 H, H-4), 4.18 (d, 1 H, H-1′), 4.21 (ddd, 1 H, H-5); $^2J_{H\text{-}1,H1'}$ 8.8 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 6.9 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 5.9 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 0.7 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 2.6 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 13.4 Hz. ^{13}C NMR ($CDCl_3$): δ 26.0 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 28.0 (CH_3), 60.7 (C-6), 70.4 (C-3), 72.3 (C-1), 73.4 (C-5), 77.3 (C-4), 104.6 (C-2), 109.4 (*C*Me_2), 111.9 (*C*Me_2). The ^1H NMR and ^{13}C NMR spectra were in agreement with literature data.[16]

Methyl α-D-fructofuranoside (2), methyl β-D-fructofuranoside (3), and 1,2-O-isopropylidene-β-D-fructopyranose (4)

A 0.02% methanolic HCl solution was prepared from acetyl chloride (0.08 mL) and methanol (260 mL). After 30 min, **1** (5.00 g, 19.2 mmol) was added and the mixture was stirred at 20°C for 16 h. The solution was neutralized with triethyl amine and evaporated to dryness. Repeated CC (EtOAc/EtOH 3:1) of the residue gave the 4 fractions F1–F4.

F1: recovered **1** (0.48 g, 1.84 mmol, 10%).

F2: **4** (1.76 g, 7.99 mmol, 42%). IR: ν 3402 (OH) $cm^{-}1$. ^1H NMR (D_2O): δ 1.28 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 3.56 (dd, 1H, H-6), 3.61 (d, 1 H, H-3), 3.67 (dd, 1 H, H-4), 3.83 (dd, 1 H, H-6′), 3.85-3.87 (m, 2 H, H-1, H-5), 4.03 (d, 1 H, H-1′); $^2J_{H\text{-}1,H1'}$ 9.3 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 10.1 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 3.1 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 1.8 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 1.2 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 12.6 Hz. ^{13}C NMR (D_2O): δ 25.3 (CH_3), 26.5 (CH_3), 64.5 (C-6), 67.4 (C-3), 69.3 (C-5), 70.7 (C-4), 71.0 (C-1), 106.2 (C-2), 113.1 (*C*Me_2). The ^1H NMR and ^{13}C NMR spectra were in agreement with literature data.[17]

F3: **2** (0.56 g, 2.88 mmol, 15%). ^1H NMR (D_2O): δ 3.30 (s, 3 H, OCH_3), 3.65 (d, 1 H, H-1), 3.67 (dd, 1 H, H-6), 3.77 (d, 1 H, H-1′), 3.80 (dd, 1 H, H-6′), 3.92–3.95 (m, 2 H, H-4, H-5), 4.08 (d, 1 H, H-3); $^2J_{H\text{-}1,H1'}$ 10.9 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 3.0 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 5.6 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 1.4 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 12.2 Hz. ^{13}C NMR (D_2O): δ 48.6 (OCH_3), 58.1 (C-1), 61.6 (C-6), 77.8 (C-4), 80.4 (C-3), 83.7 (C-5), 108.7 (C-2). The ^1H NMR and ^{13}C NMR spectra were in agreement with literature data.[16]

F4: **3** (0.98 g, 5.05 mmol, 26%). ^1H NMR (D_2O): δ 3.37 (s, 3 H, OCH_3), 3.69 (d, 1 H, H-1), 3.69 (dd, 1 H, H-6), 3.77 (d, 1 H, H-1′), 3.84 (dd, 1 H, H-6′), 3.90 (dvt, 1 H, H-5), 4.10 (vt, 1 H, H-4), 4.21 (d, 1 H,

H-3); $^{2}J_{H\text{-}1,H1'}$ 12.2 Hz, $^{3}J_{H\text{-}3,H\text{-}4}$ 8.0 Hz, $^{3}J_{H\text{-}4,H\text{-}5}$ 7.5 Hz, $^{3}J_{H\text{-}5,H\text{-}6}$ 7.2 Hz, $^{3}J_{H\text{-}5,H\text{-}6'}$ 3.2 Hz, $^{2}J_{H\text{-}6,H\text{-}6'}$ 12.2 Hz. ^{13}C NMR (D_2O): δ 49.3 (OCH_3), 60.1 (C-1), 63.0 (C-6), 75.4 (C-4), 77.2 (C-3), 81.6 (C-5), 104.2 (C-2). The ^{1}H NMR and ^{13}C NMR spectra were in agreement with literature data.[18]

Methyl 6-S-acetyl-6-thio-α-D-fructofuranoside (5)

Compound **2** (540 mg, 2.78 mmol) was dissolved in THF (10 mL) at 0 °C under N_2. Purified thioacetic acid (0.25 mL, 3.51 mmol) was added. This solution was added to a suspension of triphenylphosphine (TPP, 0.91g 3.47 mmol) and diisopropyl azodicarboxylate (DIAD, 0.68 mL, 3.45 mmol) in THF (10 mL) at 0°C. The reaction mixture was left at room temp. for 72 h. The solvent was removed in a vacuum and the residue was purified by CC (EtOAc/petroleum ether/EtOH 3:5:1) to yield **5** (266 mg, 1.11 mmol, 40%) as a pale yellow syrup. $[\alpha]_{20}^{D}$: +87.7 (*c* 1.0, acetone). IR: ν 3450 (OH), 1687 (C=O) cm^{-1}. ^{1}H NMR (acetone-d_6): δ 2.30 (s, 3 H, $COCH_3$), 3.02 (dd, 1 H, H-6), 3.24 (s, 3 H, OCH_3), 3.26 (dd, 1 H, H-6′), 3.55 (d, 1 H, H-1), 3.64 (d, 1 H, H-1′), 3.75 (dd, 1 H, H-4), 3.83 (ddd, 1 H, H-5), 4.04 (vt, 1 H, H-3), 4.32 (d, 1 H, OH-4), 4.55 (d, 1 H, OH-3); $^{2}J_{H\text{-}1,H\text{-}1'}$ 12.1 Hz, $^{3}J_{H\text{-}3,H\text{-}4}$ 4.0 Hz, $^{3}J_{H\text{-}4,H\text{-}5}$ 6.4 Hz, $^{3}J_{H\text{-}5,H\text{-}6}$ 7.4 Hz, $^{3}J_{H\text{-}5,H\text{-}6'}$ 4.4 Hz, $^{2}J_{H\text{-}6,H\text{-}6'}$ 13.7 Hz, $^{3}J_{H\text{-}3,OH\text{-}3}$ 4.8 Hz, $^{3}J_{H\text{-}4,OH\text{-}4}$ 6.6 Hz. ^{13}C NMR (acetone-d_6): δ 30.4 (CO*C*H_3), 32.2 (C-6), 48.7 (OCH_3), 60.4 (C-1), 81.95, 81.98 (C-4, C-5), 83.5 (C-3), 108.6 (C-2), 195.2 (*C*OCH_3).

Methyl 6-S-acetyl-1,3,4-tri-O-mesyl-6-thio-α-D-fructofuranoside (8)

Compound **5** (156 mg, 0.62 mmol) was dissolved in dry pyridine (20 mL). Methanesulfonyl chloride (0.20 mL, 2.57 mmol) was added at 0°C. The mixture was stirred overnight at 20°C. After evaporation to dryness the crude product was purified by CC (EtOH) to yield **8** (0.294 mg, quant.) as a light yellow syrup. IR: ν 1689 (C=O), 1356 (SO_2), 1179 (SO_2) cm^{-1}. ^{1}H NMR (acetone-d_6): δ 2.40 (s, 3 H, $COCH_3$), 3.31 (s, 3 H, SO_2CH_3), 3.37 (s, 3 H, SO_2CH_3), 3.40 (dd, 1 H, H-6), 3.44 (s, 3 H, SO_2CH_3), 3.45 (s, 3 H, OCH_3), 3.52 (dd, 1 H, H-6′), 4.34 (d, 1 H, H-1), 4.44 (ddd, 1 H, H-5), 4.66 (d, 1 H, H-1′), 5.10 (dd, 1 H, H-4), 5.17 (d, 1 H, H-3); $^{2}J_{H\text{-}1,H\text{-}1'}$ 11.1 Hz, $^{3}J_{H\text{-}3,H\text{-}4}$ 1.5 Hz, $^{3}J_{H\text{-}4,H\text{-}5}$ 4.4 Hz, $^{3}J_{H\text{-}5,H\text{-}6}$ 6.0 Hz, $^{3}J_{H\text{-}5,H\text{-}6'}$ 5.3 Hz, $^{2}J_{H\text{-}6,H\text{-}6'}$ 14.2 Hz. ^{13}C NMR (acetone-d_6): δ 30.5 (CO*C*H_3), 30.9 (C-6), 37.5 (SO_2CH_3), 38.4 (SO_2CH_3), 38.6 (SO_2CH_3), 49.2 (OCH_3), 63.8 (C-1), 83.0 (C-5), 84.8 (C-4), 85.2 (C-3), 106.7 (C-2), 195.1 (*C*OCH_3).

Methyl 4,6-Anhydro-1,3-di-O-mesyl-4-thio-α-D-tagatofuranoside (9)

A solution of **8** (437 mg, 0.91 mmol) in a 19:1 mixture (v/v) of 2-methoxyethanol and H_2O (60 mL, satd. with N_2 for 30 min) was refluxed with $NaHCO_3$ (110 mg, 1.31 mmol) for 11 h. The solvent was evaporated to dryness and the residue was fractionated by CC (EtOAc/petroleum ether 1:1).

F1: **9** (56 mg, 0.16 mmol, 18%), light yellow syrup. IR: ν 1357 ($MeSO_3$), 1174 ($MeSO_3$) cm^{-1}. ^1H NMR (acetone-d_6): δ 2.97 (ddd, 1 H, H-6), 3.23 (s, 3 H, SO_2CH_3), 3.24 (s, 3 H, SO_2CH_3), 3.28 (s, 3 H, OCH_3), 3.40 (dd, 1 H, H-6′), 4.31 (vt, 1 H, H-4), 4.45 (d, 1 H, H-1), 4.69 (d, 1 H, H-1′), 4.97 (d, 1 H, H-3), 5.16 (dvt, 1 H, H-5); $^2J_{H\text{-}1,H\text{-}1'}$ 11.1 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 6.5 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 6.5 Hz, $^4J_{H\text{-}4,H\text{-}6}$ 0.7 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 3.2 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 6.4 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 10.3 Hz. ^{13}C NMR (acetone-d_6): δ 30.6 (C-6), 37.5 (SO_2CH_3), 38.5 (SO_2CH_3), 46.0 (C-4), 49.2 (OCH_3), 64.6 (C-1), 81.7 (C-5), 83.6 (C-3), 108.6 (C-2).

F2: **9** (94 mg, 0.27 mmol, 30%) + **10** (18.5 mg, 0.021 mmol, 5%)

Bis(Methyl 6-deoxy-1,3,4-tri-O-mesyl-α-D-fructofuranosid-6-yl) disulfide (10) and bis(methyl 3,4-anhydro-6-deoxy-1-O-mesyl-α-D-psicofuranosid-6-yl) disulfide (11)

A solution of **8** (294 mg, 0.62 mmol) and $NaHCO_3$ (100 mg, 1.19 mmol) was refluxed (4 h) and worked up as described for **9**.

F1: **11** (31 mg, 0.057 mmol, 9%), light yellow syrup. ^1H NMR (acetone-d_6): δ 2.64 (dd, 1 H, H-6), 2.71 (dd, 1 H, H-6′), 3.19 (s, 3 H, SO_2CH_3), 3.35 (s, 3H, OCH_3), 3.80 (d, 1 H, H-3), 4.02 (d, 1 H, H-4), 4.10 (d, 1 H, H-1), 4.31 (ddd, 1 H, H-5), 4.40 (dd, 1 H, H-1′); $^2J_{H\text{-}1,H\text{-}1'}$ 11.0 Hz, $^4J_{H\text{-}1,H\text{-}4}$ 0.7 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 2.9 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 0.8 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 7.8 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 6.2 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 13.6 Hz. ^{13}C NMR (acetone-d_6): δ 34.2 (C-6), 37.4 (SO_2CH_3), 49.8 (OCH_3), 57.5 (C-3), 58.3 (C-4), 66.2 (C-1), 79.1 (C-5), 104.4 (C-2).

F2: **9** (38 mg, 0.11 mmol, 18%) + **10** (20 mg, 0.023 mmol, 4%).

F3: **10** (97 mg, 0.11 mmol, 18%), light yellow syrup. ^1H NMR (acetone-d_6): δ 2.88 (dd, 1 H, H-6), 3.00 (dd, 1 H, H-6′), 3.09 (s, 3 H, OCH_3), 3.22 (s, 3 H, SO_2CH_3), 3.34 (s, 3 H, SO_2CH_3), 3.39 (s, 3 H, SO_2CH_3), 4.27 (d, 1 H, H-1), 4.40 (dvt, 1 H, H-5), 4.58 (d, 1 H, H-1′), 5.12 (d, 1 H, H-3), 5.19 (ddd, 1 H, H-4); $^2J_{H\text{-}1,H\text{-}1'}$ 11.1 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 1.8 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 4.8 Hz, $^4J_{H\text{-}4,H\text{-}6}$ 0.7 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 6.4 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 4.6 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 14.5 Hz. ^{13}C NMR (acetone-d_6): δ 35.9 (C-6), 37.6 (SO_2CH_3), 38.6 (SO_2CH_3), 38.7 (SO_2CH_3), 49.2 (OCH_3), 64.0 (C-1), 84.1 (C-5), 84.9 (C-4), 85.4 (C-3), 106.5 (C-2).

Methyl 6-S-acetyl-6-thio-β-D-fructofuranoside (12)

Compound **12** was prepared and purified as described for **5** from a solution of **3** (0.85 g, 4.38 mmol) in pyridine (10 mL), thioacetic acid (0.40 ml, 5.60 mmol) and a solution of TPP (1.46 g, 5.57 mmol) and DIAD (1.10 ml, 5.60 mmol) in THF (10 mL). Yield 0.359 g (1.06 mmol, 32%), pale yellow syrup. IR: ν 3408 (OH), 1697 (C=O) cm^{-1}. ^1H NMR (acetone-d_6): δ 2.33 (s, 3 H, $COCH_3$), 3.06 (dd, 1 H, H-6), 3.289 (dd, 1 H, H-6′), 3.290 (s, 3 H, OCH_3), 3.52 (d, 1 H, H-1), 3.61 (d, 1 H, H-1′), 3.78 (ddd, 1 H, H-5), 3.96 (dd, 1 H, H-4), 4.11 (d, 1 H, H-3); $^2J_{H\text{-}1,H\text{-}1'}$ 11.7 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 7.3 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 6.7 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 7.5 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 4.7 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 13.8 Hz. ^{13}C NMR (acetone-d_6): δ 30.5 ($COCH_3$), 33.5 (C-6), 49.4 (OCH_3), 61.6 (C-1), 79.1 (C-3), 80.3 (C-4), 81.3 (C-5), 105.3 (C-2), 195.1 ($COCH_3$).

Methyl 1,6-di-S-acetyl-1,6-dithio-β-D-fructofuranoside (13)

Compound **13** was prepared and purified as described for **12** from **3** (402 mg, 2.07 mmol), thioacetic acid (0.40 mL, 5.60 mmol), TPP (1.62 g, 6.17 mmol) and DIAD (1.21 g, 6.15 mmol). Yield 810 mg (0.55 mmol, taking into account a small content of TPP, 27%), pale yellow syrup. IR: ν 3051 (OH), 1689 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.31 (s, 3 H, $COCH_3$), 2.33 (s, 3 H, $COCH_3$), 3.13 (dd, 1 H, H-6), 3.23 (dd, 1 H, H-6′), 3.32 (m, 5 H, H-1, H-1′, OCH_3), 3.92 (dvt, 1 H, H-5), 3.97 (d, 1 H, H-3), 4.00 (dd, 1 H, H-4); $^2J_{H\text{-}1,H\text{-}1'}$ 14.4 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 7.3 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 6.9 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 6.9 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 4.9 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 13.9 Hz. ^{13}C NMR ($CDCl_3$): δ 30.4 ($COCH_3$), 30.5 ($COCH_3$), 31.3 (C-1), 32.8 (C-6), 48.9 (OCH_3), 79.0 (C-5), 79.9 (C-4), 80.2 (C-3), 103.5 (C-2), 195.0 ($COCH_3$), 195.3 ($COCH_3$).

Methyl 6-S-acetyl-1,3,4-tri-O-mesyl-6-thio-β-D-fructofuranoside (14)

Compound **12** (359 mg, 1.42 mmol) was dissolved in dry pyridine (10 mL). Methanesulfonyl chloride (0.70 mL, 8.98 mmol) was added at 0°C and the reaction mixture was stirred overnight at 20°C. After evaporation to dryness the crude product was purified by CC (EtOAc) to yield **14** (700 mg, 1.40 mmol, 99%) as a light yellow syrup. IR: ν 1695 (C=O), 1358 (SO_2), 1176 (SO_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 2.37 (s, 3 H, $COCH_3$), 3.18 (dd, 1 H, H-6), 3.20 (s, 3 H, SO_2CH_3), 3.29 (s, 3 H, SO_2CH_3), 3.32 (s, 3 H, SO_2CH_3), 3.44 (s, 3 H, OCH_3), 3.56 (dd, 1 H, H-6′), 4.28 (ddd, 1 H, H-5), 4.39 (d, 1 H, H-1), 4.44 (d, 1 H, H-1′), 5.19 (dd, 1 H, H-4), 5.33 (d, 1 H, H-3); $^2J_{H\text{-}1,H\text{-}1'}$ 11.0 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 7.0 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 6.6 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 8.0 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 4.3 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 14.3 Hz. ^{13}C NMR (acetone-d_6): δ 30.5 ($COCH_3$), 32.1 (C-6), 37.5 (SO_2CH_3), 38.89

(SO_2CH_3), 38.94 (SO_2CH_3), 50.6 (OCH_3), 67.5 (C-1), 78.6 (C-5), 81.4 (C-3), 83.2 (C-4), 102.3 (C-2), 194.6 (*C*OCH_3).

Bis(methyl 6-deoxy-1,3,4-tri-O-mesyl-β-D-fructofuranosid-6-yl) disulfide (15)

A solution of **14** (670 mg, 1.38 mmol) in a 19:1 (v/v) mixture of 2-methoxyethanol and H_2O (134 mL, saturated with N_2 for 30 min) was refluxed under N_2 with $NaHCO_3$ (170 mg, 2.02 mmol) for 11 h. The solvent was removed with a rotatory evaporator. The residue was extracted with EtOAc. After evaporation to dryness and purification by CC (EtOAc/petroleum ether 1:1), **15** (15 mg, 1.4%) was obtained as a colorless oil. IR: ν 3452 (OH), 1355 (SO_2), 1176 (SO_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 2.81 (dd, 1 H, H-6′), 2.95 (dd, 1 H, H-6), 3.11 (s, 3 H, SO_2CH_3), 3.18 (s, 3 H, SO_2CH_3), 3.19 (s, 3 H, SO_2CH_3), 3.44 (s, 3 H, OCH_3), 4.28 (ddd, 1 H, H-5), 4.34 (s, 2 H, H-1, H-1′), 5.27 (dd, 1 H, H-4), 5.30 (d, 1 H, H-3); $^3J_{H\text{-}3,H\text{-}4}$ 6.2 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 5.6 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 6.9 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 5.6 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 14.2 Hz. ^{13}C NMR (acetone-d_6): δ 37.3 (C-6), 38.1 (SO_2CH_3), 39.4 (2· SO_2CH_3), 50.7 (OCH_3), 66.5 (C-1), 79.1 (C-5), 80.7 (C-3), 82.8 (C-4), 101.9 (C-2).

Methyl 1,6-Di-S-acetyl-3,4-di-O-mesyl-1,6-dithio-β-D-fructofuranoside (17)

Compound **17** was prepared and purified as described for **8** from **13** (720 mg, slightly contaminated with TPP, 0.50 mmol) and methanesulfonyl chloride (0.90 mL, 11.6 mmol). After a reaction time of 12 h at 20°C, workup as for **8** and CC **14** (762 mg, 0.31 mmol, 91%) was obtained as a light yellow syrup. IR: ν 1693 (C=O), 1358 (SO_2), 1182 (SO_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 2.36 (s, 3 H, $COCH_3$), 2.38 (s, 3 H, $COCH_3$), 2.83 (s, 3 H, SO_2CH_3), 3.08 (dd, 1 H, H-6), 3.20 (s, 3 H, SO_2CH_3), 3.31 (d, 1 H, H-1), 3.39 (s, 3 H, OCH_3), 3.48 (m, 2 H, H-1′, H-6′), 4.20 (ddd, 1 H, H-5), 5.15 (d, 1 H, H-3), 5.18 (dd, 1 H, H-4); $^2J_{H\text{-}1,H\text{-}1'}$ 14.5 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 6.8 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 5.4 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 8.1 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 4.7 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 14.2 Hz. ^{13}C NMR (acetone-d_6): δ 30.2 (C-1), 30.4 (CO*C*H_3), 30.5 (CO*C*H_3), 32.0 (C-6), 39.1 (SO_2CH_3), 39.5 (SO_2CH_3), 49.7 (OCH_3), 78.2 (C-5), 81.0 (C-3/C-4), 82.9 (C-3/C-4), 103.9 (C-2), 193.8 (*C*OCH_3), 194.5 (*C*OCH_3).

Methyl 1,3:4,6-dianhydro-1,4-dithio-β-D-sorbofuranoside (18) and methyl 1,3-anhydro-4-O-mesyl-6-S-methyl-1,6-dithio-β-D-psicofuranoside (19)

Compound **17** (300 mg, 0.12 mmol) and $NaHCO_3$ (200 mg, 2.38 mmol) were refluxed under N_2 in a 19:1 (v/v) mixture of 2-methoxyethanol and H_2O (200 mL, saturated with N_2 for 30 min) for 18 h. The solvents were removed in a vacuum. The residue was extracted with EtOAc

and the extract was evaporated to dryness. The product mixture was fractionated by CC (EtOAc/petroleum ether 1:1).

F1: **18** (13.6 mg, 0.070 mmol, 60%), light yellowish oil. ^{1}H NMR ($CDCl_3$): δ 3.16 (dd, 1 H, H-6), 3.18 (d, 1 H, H-1), 3.46-3.50 (m, 2 H, H-1′, H-6′), 3.50 (s, 3 H, OCH_3), 4.01 (d, 1 H, H-4), 4.19 (s, 1 H, H-3), 5.48 (dvt, 1 H, H-5); $^2J_{H\text{-}1,H\text{-}1'}$ 9.3 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 6.3 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 2.9 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 6.3 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 10.4 Hz. ^{13}C NMR ($CDCl_3$): δ 32.0 (C-6), 36.4 (C-1), 49.1 (C-4), 50.1 (OCH_3), 56.1 (C-3), 84.0 (C-5), 114.6 (C-2).

F2: **19** (3.8 mg, 0.013 mmol, 11%), light yellow oil. IR: ν 1377 (SO_2), 1117 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3 H, SCH_3), 2.84 (dd, 1 H, H-6), 3.05 (dd, 1 H, H-6'), 3.08 (s, 3 H, SO_2CH_3), 3.28 (d, 1 H, H-1), 3.29 (s, 3 H, OCH_3), 3.54 (d, 1 H, H-1′), 4.35 (d, 1 H, H-3), 4.73 (ddd, 1 H, H-5), 5.08 (dd, 1 H, H-4); $^2J_{H\text{-}1,H\text{-}1'}$ 10.1 Hz, $^3J_{H\text{-}3,H\text{-}4}$ 6.4 Hz, $^3J_{H\text{-}4,H\text{-}5}$ 7.4 Hz, $^3J_{H\text{-}5,H\text{-}6}$ 4.1 Hz, $^3J_{H\text{-}5,H\text{-}6'}$ 5.4 Hz, $^2J_{H\text{-}6,H\text{-}6'}$ 14.5 Hz. ^{13}C NMR ($CDCl_3$): δ 17.2 (SCH_3), 35.3 (C-6), 37.6 (C-1), 38.4 (SO_2CH_3), 49.8 (OCH_3), 50.8 (C-3), 78.3 (C-4), 79.8 (C-5), 107.6 (C-2).

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