Sulfur Atom Participation in Thiooligosaccharide Chemistry: Synthesis of 1′-Thiotrehalulose and 1′-*epi*-Thiotrehalulose and Comparative Reactivity with the O-Linked Disaccharide Analogue, Trehalulose†

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Received December 4, 1997

1′-Thiotrehalulose (1-*S*-α-D-glucopyranosyl-1-thio-D-fructose, **6**) and 1′-*epi*-thiotrehalulose (1-*S*-β-D-glucopyranosyl-1-thio-D-fructose, **12**) have been prepared, and their reactivity toward base and acid catalysts has been compared with that of their α-O-linked natural counterpart trehalulose (**14**). Under conventional, pyridine-catalyzed acetylation conditions, **6** and **12** afforded exclusively the C-2 *E* open-chain enol acetates at the D-fructose moiety **7** and **13,** when **14** led to the expected peracetylated disaccharides. Upon protonic activation, **6**, **12**, and **14** underwent intramolecular glycosidation reactions, yielding D-fructosyl D-glucosyl 1,1′:2,2′ mixed thioacetals and acetals, respectively, whose structures are under control of stereoelectronic factors. A much higher intramolecular glycosylation reaction rate was observed for the S-linked thioanalogues as compared to trehalulose, supporting involvement of episulfonium intermediates at the anomeric position activation step. Nevertheless, the close transformation patterns with either S- or O-linked disaccharides favors in both cases oxocarbenium entities as main intermediates in glycosylation reactions involving protonic activation. An unexpected tautomerization reaction at the D-glucose moiety, resulting in a fructofuranosyl glucofuranosyl spiro-oxathiane derivative presumably via a sulfonium intermediate, was also observed for derivatives of **6** and **12** under strong protonating conditions. These results stress on the importance of sulfur atom participation reactions in thiooligosaccharide chemistry.

Introduction

Thiosugars, i.e., sugars in which an oxygen atom has been replaced by sulfur, are close analogues of the natural saccharides that have been widely used for structure−activity relationship studies involving carbohydrate−enzyme interactions.[1] A particular effort has been directed toward the synthesis of S-linked thiooligosaccharides, in view of the reported stability of the thioglycosidic linkage in enzymatic processes involving the corresponding *O*-glycosides.[2] The greater physical size and enhanced polarizability of the sulfur atom may result, however, in important differences in reactivity that are particularly noticeable when ionic species take part as transient intermediates.

Stabilization of both positive and negative charges by sulfur atom participation is already known as a main feature in the chemistry of thioether and thioacetals.[3] Sulfur-stabilized anion intermediates have been proposed in order to account for base-induced structural rearrangements observed in the 2-thioaldose and aldose thioacetal series.[4] However, attempts to trap the postulated open-chain transient enolates were unsuccessful. More recently, the partial anomerization of thioglycosidic bonds in the presence of diethylamine, likely to occur

† Presented, in part, at the Eighth European Carbohydrate Symposium, Sevilla, Spain, July 2−7, 1995; Abstract A-60.

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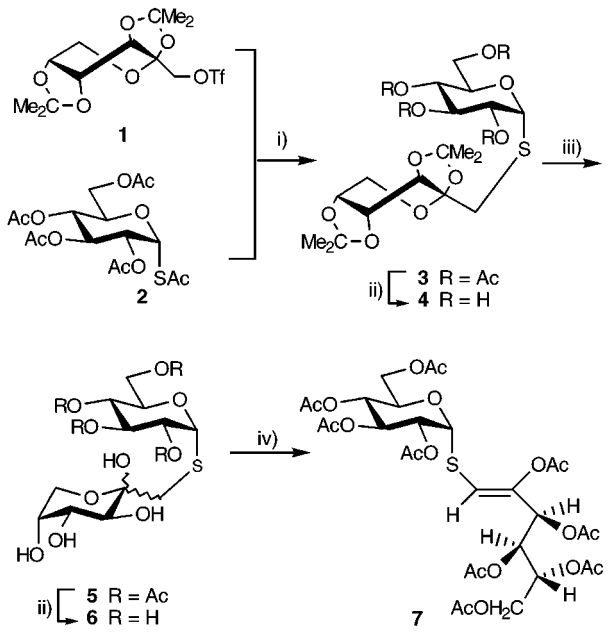
S0022-3263(97)02203-2 CCC: $15.00
Published on Web 05/05/1998

through sulfenyl-stabilized anomeric carbanions, has been reported.[5] On the other hand, transient bicyclic episulfonium cations have been postulated in order to account for the kinetics and stereoselectivity observed during acid-promoted substitution and glycosylation reactions of aldopyranoside[6] and sialic acid derivatives[7] bearing sulfur substituents. Theoretical studies still question, however, whether episulfonium or oxocarbenium entities are the actual stereodeterminants in glycosylation reactions involving glycosyl donors incorporating a vicinal phenylthio functionality.[8]

In continuation of our program in thiooligosaccharide synthesis,[2e,f,9] a comparative study of base- and acid-catalyzed transformations in S-linked thiooligosaccharides and their O-linked counterparts has now been carried out in an attempt to characterize ionic intermediates, their involvement in the stereochemistry of the reactions, and the identification of possible mechanistic pathways. The 1-*O*(*S*)-D-glucopyranosyl-D-fructose disaccharide framework has been chosen as a model because of the possibility of trapping reaction intermediates by intramolecular glycosylation reaction.[10] The synthesis of 1-*S*-α- and *β*-D-glucopyranosyl-1-thio-D-fructose (**6** and **12**, 1′-thiotrehalulose and 1′-*epi*-thiotrehalulose, respectively), their reactivity toward base-catalyzed acylation, and their acid-promoted intramolecular glycosylation and tautomerization reactions are then now reported. Evidence is shown for sulfur atom participation in these processes from the kinetic of the reactions and the structure of the products, in comparison with results obtained for 1-*O*-α-D-glucopyranosyl-D-fructose (**14**, trehalulose). Taking into account that trehalulose is a commercial disaccharide obtained by enzymatic transglucosylation of sucrose,[11] the synthesis of the S-linked thioanalogue may be of additional interest since it could provide a substrate analogue for enzymatic studies.

Scheme 1[a]



[a] Reagents: (i) NaOMe, MeOH; DMF, 40 °C; Ac_2O−Py (70%); (ii) NaOMe, MeOH; (iii) 90% TFA; (iv) Ac_2O−Py (90%).

Results

Synthesis and Base-Catalyzed Acetylation of 1′-Thiotrehalulose (6) and 1′-*epi*-Thiotrehalulose (12). 1-*S*-α-D-Glucopyranosyl-1-thio-D-fructose (**6**) and its *β*-linked anomer (**12**) were prepared[12] by reaction of the sodium salt of either 1-thio-α-D-glucopyranose or the related *O*-acetylated *β*-anomer, obtained extemporaneously from the respective precursors[13,14] **2** or **8**, with 2,3:4,5-di-*O*-isopropylidene-1-*O*-[(trifluoromethyl)sulfonyl]-*β*-D-fructopyranose[15] (**1**). Reacetylation and chromatographic purification of both reaction mixtures yielded **3** and **9** in respective overall yields of 70 and 75%, despite the known low reactivity of the neopentylic C-1 position in D-fructose derivatives (Schemes 1 and 2, respectively).[16] Retention of the anomeric configuration at the 1-thioglucopyranose moiety was confirmed from the $J_{1',2'}$ values (5.8 and 10.0 Hz for the α- and *β*-linked disaccharides **3** and **9**, respectively). The high-field chemical shift for the proton and carbon atoms at C-1 Fru ($\delta_{H\text{-}1a,1b}$ 3.25−2.80; $\delta_{C\text{-}1}$ 35−38 ppm), and C-1 Glc ($\delta_{H\text{-}1'}$ 5.66−4.71; $\delta_{C\text{-}1'}$ 83−87 ppm) was in further agreement with the presence of the C-1−S−C-1′ linkage. Sequential removal of the isopropylidene (→**5** and →**11**) and *O*-acetyl protecting groups yielded the expected thiodisaccharides **6** and **12** (Schemes 1 and 2, respectively). The order of deprotection steps in the above reaction sequence is of importance. Thus, when saponification of the acetates (→**4** and →**10**) was carried out before acid hydrolysis of the acetal groups, the overall yield drastically decreased as a consequence of intramolecular glycosylation reactions as will be further discussed.

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(12) Attempts to displace a 1-iodo leaving group in the D-fructose diacetonide were unsuccessful, whereas a reverse strategy using 2,3:4,5-di-*O*-isopropylidene-1-thio-*β*-D-fructopyranose and 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl chloride or the corresponding α-D-glucopyranosyl bromide gave much lower yields (30−35%) of the respective thiodisaccharides **3** and **9**.

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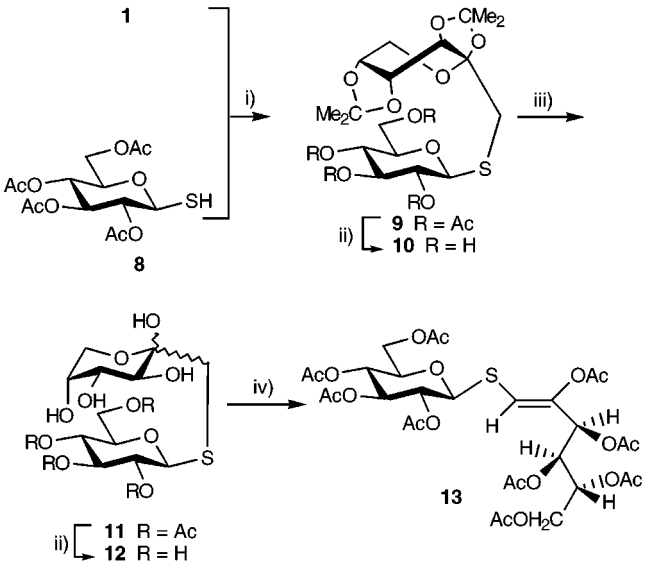
Scheme 2[a]



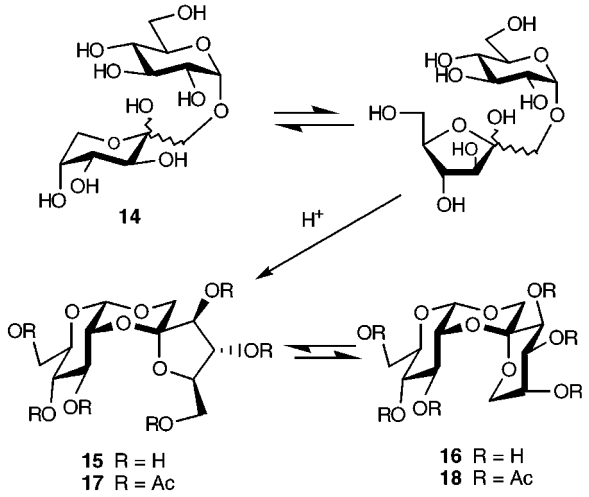
[a] Reagents: (i) NaH, THF/DMF, 40 °C (75%); (ii) NaOMe, MeOH; (iii) 90% TFA; (iv) Ac_2O−Py (89%).

Attempts to prepare the peracetylated derivatives of **6** and **12** upon treatment of the unprotected thiodisaccharides with acetic anhydride−pyridine at room temperature under conventional based-catalyzed peracetylation conditions unexpectedly failed, the enol ester derivatives of the *keto*-D-fructose form (**7** and **13**) being obtained in both cases. A single geometrical isomer at the double bond was exclusively obtained, the *E* configuration with the bulky polyacetoxy chain and thioglucosyl substituents in trans relative disposition being assigned on the basis of NOESY experiments (intense NOE contacts were observed between H-1/H-3 and H-1/H-4). The low-field NMR resonances for the olefinic proton ($\delta_{H\text{-}1}$ 6.08 and 6.30, respectively) and carbons ($\delta_{C\text{-}1}$ 114.4 and 114.2; $\delta_{C\text{-}2}$ 142.2 and 142.1, respectively), as compared with the δ values expected for the respective atoms in cyclic forms of D-fructose,[17] confirmed the proposed structures.

Reactivity of Trehalulose (14), 1′-Thiotrehalulose (6), and 1′-*epi*-Thiotrehalulose (12) in Acidic Media. Trehalulose (**14**) was stable for hours in 9:1 trifluoroacetic acid−water at 20 °C. However, in 15:1 mixtures, at temperatures higher than 40 °C, formation of intramolecular glycosides involving O-2′ of the D-glucose moiety was observed (Scheme 3). The β-D-fructofuranosyl derivative **15** was preferentially obtained using short reaction times (45 min), which further rearranged into the β-D-fructopyranosyl tautomer **16** as the major reaction product after 16 h. The reaction could be directed with high selectivity toward the kinetic **15** (∼60%) or the thermodynamic **16** product (∼85%) in the pyridinium poly(hydrogen fluoride) complex (7:3 hydrogen fluoride−pyridine) as solvent and catalyst at 0 or 20 °C, respectively. The final thermodynamic mixture at equilibrium in pure hydrogen fluoride contained unreacted trehalulose **14**, **15**, and **16** in a 5:10:84 ratio (Table 1).

In contrast, 1-thiotrehalulose (**6**) was already transformed to a great extent into O-2′ intramolecular glycosides in 9:1 trifluoroacetic acid−water at 20 °C within 10 min. Under these relatively weak protonating conditions, the resulting structures were similar to those obtained from the O-linked counterpart **14**, i.e., only the β-D-fructofuranoside **19** and the β-D-fructopyranoside **20** derivatives, with the D-glucosyl moiety retaining the initial α-pyranosyl anomeric configuration, were formed (Scheme 4). Under more strenuous conditions (15:1 trifluoroacetic acid−water or various hydrogen fluoride−pyridine mixtures), further rearrangement occurred, resulting in the α-D-fructofuranosyl α-D-glucopyranoside (**21**) and α-D-fructofuranosyl α-D-glucofuranoside (**22**) mixed intramolecular glycosides. Compound **21** was always a minor component of the acetalation−anomerization mixture (7−11%), and the relative proportion of the difuranosyl derivative **22** rapidly increased with the acidity, mainly at the expense of **19** and **20**, rising to 75% in a 15:1 trifluoroacetic acid−water ratio at 40 °C and 30 min reaction time. In pure hydrogen fluoride, **22** underwent additional tautomerization processes that affected both the D-glucose and D-fructose moieties. After 30 min at room temperature, the β-D-glucopyranosyl derivatives **23** and **24** were the almost exclusive reaction products, in similar relative proportion. No more change in the composition of the mixture was observed for longer reaction times (Table 2).

Scheme 3



The reactivity of 1′-*epi*-thiotrehalulose (**12**) with regard to protonic activation was even higher than that of its α-linked anomer **6**. After treatment with 9:1 trifluoroacetic acid−water at 20 °C for 10 min, 84% of the β-D-fructofuranosyl mixed thioacetal **23** and 8% of the β-D-fructopyranosyl tautomer **24** were obtained (Scheme 4). An increase in the acidity resulted in a gradual increase in the proportion of **24** at the expense of **23**. A small amount of the α-D-glucofuranosyl derivative **22** was also detected in the reaction mixture. Using pure hydrogen fluoride, a thermodynamic equilibrium containing **24** (47%), **23** (39%), and **22** (2%), almost identical with that obtained starting from 1′-thiotrehalulose, was obtained within 30 min (Table 3).

The structures of the intramolecular glycosidation/tautomerization products **15**, **16**, and **19**−**24** were established on the basis of their ^{13}C NMR data as well as the ^{1}H (Table 4) and ^{13}C NMR data for the corresponding peracetates **17**, **18**, and **25**-**30**. Involvement of O-2′ in the dioxane or oxathiane system was confirmed by the downfield shift of the C-2′ resonance in unprotected

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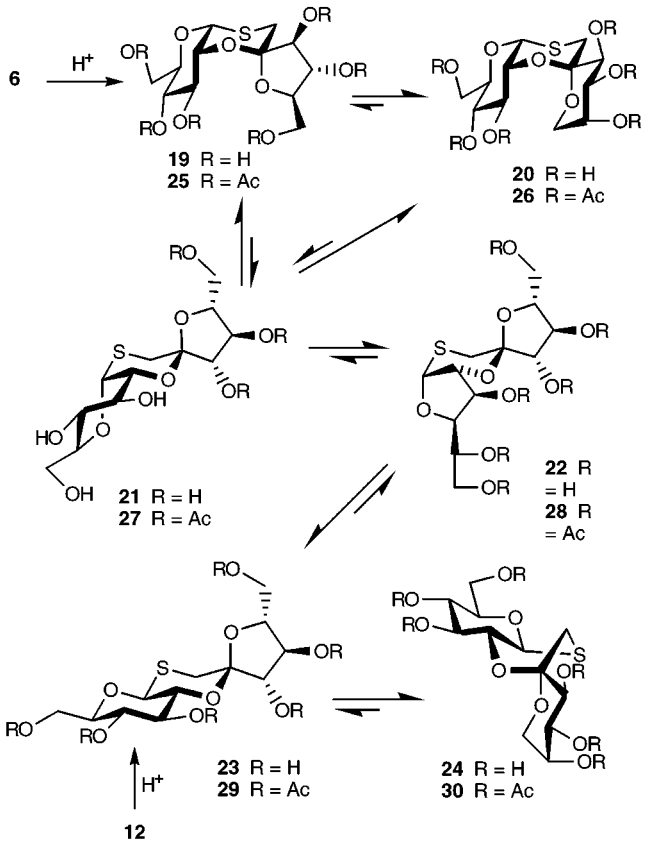
Table 1. Products Formed by the Action of Protonating Agents on Trehalulose (14)

expt no.	starting sugar (g)	protonic reagent (mL)	reaction temp (°C)	reaction time	products formed (%) **15**	products formed (%) **16**	residual trehalulose (%)
1	0.34	TFA−H_2O 15:1 (5)	40	45 min	40	32	27
2	0.34	TFA−H_2O 15:1 (5)	50	16 h	31	44	25
3	0.2	HF−Py 4:3 (1.0)	20	20 min	35	5	60
4	0.4	HF−Py 7:3 (1.2)	0	20 min	60	25	15
5	0.2	HF−Py 7:3 (0.8)	20	20 min	10	85	5
6	0.8	HF (0.4)	20	5 min	16	74	10
7	0.8	HF (0.4)	20	30 min	12	80	8
8	0.8	HF (0.4)	20	1 h	10	84	5

Scheme 4



derivatives and the upfield shift of the H-2′ resonance in the hexaacetates as compared to the starting (thio)-disaccharides **6**, **12**, and **14** and the partially acetylated derivatives **3** and **9**, respectively.

The ^{13}C NMR chemical shifts for carbon atoms of the furanosyl moieties (C-2 to C-5 and C-1 to C-4 for D-fructosyl and D-glucosyl entities, respectively) were strongly downfield shifted as compared with pyranosyl heterocycles. The α- or β-anomeric configuration and the $^4C_1$(D) conformation for the D-glucopyranosyl entities were evident from the vicinal coupling constant values around the pyranosyl ring. A notable exception to this general scheme was found for compound **21**, in which the $^3J_{H,H}$ values were indicative of a skew conformation. The corresponding *J* values for D-fructopyranose subunits were in agreement with a $^1C_4$(D) conformation. Taking into consideration that α-D-fructopyranosides typically adopt the reverse $^4C_1$(D) conformation,[18] the β-anomeric configuration was assigned for the fructosyl moieties in compounds **16**, **20**, and **24**. The C-5 chemical shift values (~70 ppm) further supported this structural assignment, the expected values for related α-D-fructopyranosides being ~65 ppm.[17,18]

The α- (in **21**−**23**) or β-anomeric configuration (in **15** and **19**) for the D-fructofuranosyl entities was deduced from the ^{13}C chemical shift for the corresponding anomeric carbon atoms ($\delta_{C\text{-}2\alpha}$ 102.8−103.9; $\delta_{C\text{-}2\beta}$ 97.0−98.5).[17,18a] Additional evidence was obtained from the $J_{3,4}$ coupling constants in the corresponding peracetates (**27**−**29**, **17**, and **25**, respectively), since it has been reported that this value falls within the ranges 1.4−2.4 Hz or 5.0−9.7 Hz for α- or β-D-fructofuranoside derivatives, respectively.[19] The experimental values (1.0−1.8 and 4.7−5.0 Hz) agreed with the proposed structures. Finally, the α-anomeric configuration for the D-glucofuranose moiety of **22** was assigned on the basis of structural considerations: the opposite configuration would result in a highly strained five-membered−six-membered *trans*-fused bicyclic system. Moreover, an anti relative disposition would be expected in this case for H-1′ and H-2′. The observed $J_{1',2'}$ value in the corresponding peracetate **28** (4.1 Hz), indicative of a gauche relationship, supports the presence of the α-thioglycosidic linkage.

Previous results have shown that the ^{13}C chemical shift for the anomeric carbon atoms involved in spiroacetal frameworks can be considered with confidence as a fingerprint for a given intermolecular spiroacetal structure, since substitution at the glycosyl residues does not significantly affect these values provided that the conformation of the three heterocycles remained unchanged.[18a,20] This observation was already applied in order to assign partial structures for ketohexosyl entities in spirodioxanyl pseudo-oligosaccharides having identical conformations at the central dioxane ring.[21] In agreement with this point, compounds **15**, **16**, and **19**−**23** had $\delta_{C\text{-}2}$ values almost identical with data previously found for di-D-fructose dianhydrides having analogous spirodioxanyl−D-fructose partial structures with the central 1,4-dioxane ring in a chair conformation, and the same analogy was observed for the respective peracetates **17**, **18**, **25**−**29**. In the case of **24** and **30**, the β-D-fructopyranoside C-2 resonance (98.7 and 98.0 ppm) was significantly downfield shifted as compared with **16** and **20** (95.3 and 95.8 ppm) and their peracetates **18** and **26** (94.1 and 95.6 ppm, respectively), suggesting a deviation from the chair conformation for the oxathiane system. Comparison with the values reported for di-β-D-fructopyra-

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Table 2. Products Formed by the Action of Protonating Agents on 4 and 6

expt no.	starting sugar (g)	protonic reagent (mL)	reaction temp (°C)	reaction time	products formed (%)						residual
					19	**20**	**21**	**22**	**23**	**24**	**6** (%)
1	**4** (0.17)	TFA−H_2O 9:1 (5)	20	10 min	23	15					62
2	**4** (0.25)	TFA−H_2O 9:1 (6)	20	5 h		18		48			34
3	**4** (0.4)	TFA−H_2O 15:1 (8)	40	30 min	5	5		75			15
4	**4** (0.1)	HF−Py 4:3 (0.2)	20	20 min	28	38	10	13			11
5	**4** (0.3)	HF−Py 7:3 (0.7)	0	20 min	18	48	11	11			10
6	**6** (0.17)	HF−Py 7:3 (0.5)	20	15 min	11	23	9	45			11
7	**4** (0.1)	HF−Py 7:3 (0.2)	20	15 min	10	24	7	45			13
8	**4** (0.25)	HF (0.3)	20	30 min		2		5	36	42	5

Table 3. Products Formed by the Action of Protonating Agents on 10

expt no.	starting sugar (g)	protonic reagent (mL)	reaction temp (°C)	reaction time (min)	products formed (%)			residual
					22	**23**	**24**	**12** (%)
1	0.15	TFA−H_2O 9:1 (1)	20	10		84	8	8
2	0.25	TFA−H_2O 15:1 (5)	40	45	3	74	16	7
3	0.1	HF−Py 4:3 (0.2)	20	20		59	41	
4	0.3	HF−Py 7:3 (0.5)	20	20	2	52	45	
5	0.25	HF (0.3)	20	30	2	39	47	

nose 1,2′:2,1′-dianhydride derivatives ($\delta_{C\text{-}2}$ 97.8−98.1 ppm),[18a] in which the central ring adopts a boat conformation,[22] were in total agreement, supporting a similar conformational arrangement for these compounds.

The anomeric configuration of D-fructose moieties was further corroborated on the peracetylated derivatives by 1D NOESY experiments. Thus, compounds **17**, **18**, **25**, **26**, and **30** exhibited intense H-3/H-1a (equatorial) NOE contacts, in agreement with the spatial proximity of these protons in β-fructoside derivatives. This effect was absent in the α-fructosides **27**−**29**. In the case of **30**, an additional NOE contact between H-1b Fru (pseudoaxial) and H-2′ Glc supports the proposed boat conformation for the central oxathiane ring.

Discussion

1′-Thiotrehalulose (**6**) and 1′-*epi*-thiotrehalulose (**12**) are stable in water solution under neutral or even slightly basic conditions. At pH 7, in deuterium oxide solution, both were found as a tautomeric equilibrium of cyclic forms, with the β-fructopyranose and β-fructofuranose tautomers in a relative proportion similar to that reported[23] for trehalulose **14** (∼75:20 β-pyranose−β-furanose). No trace of open chain keto or enol forms could be detected by ^{13}C NMR spectroscopy. The fact that base-catalyzed acetylation of the thiodisaccharides afforded the enol acetates **7** and **13** (Scheme 1), respectively, contrasts with the behavior observed for the related O-disaccharide, which exclusively leads to the conventional disaccharide peracetate. This has evidently to be ascribed to a substantial acidity increase of protons vicinal to the sulfur atom in the keto form of 1-thioketoses, as compared to unsubstituted or O-substituted analogues, resulting in sulfur-stabilized enolate anions trapped by base-catalyzed acetylation (Figure 1). Such a mechanism has already been postulated in order to explain the base-induced epimerization in thiosugars and thiooligosaccharides bearing the sulfur atom adjacent to the anomeric position in an aldose framework.[4,9a] The presence of two active methylene protons in the ketose series increases

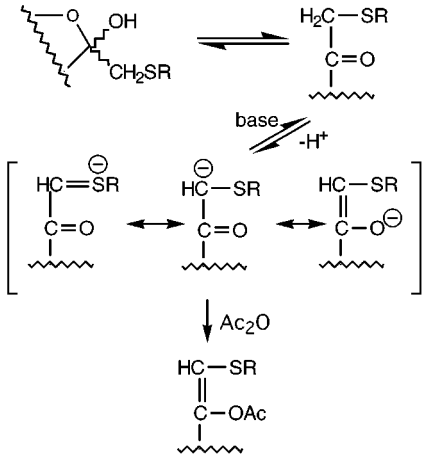

Figure 1. Trapping of the enolic form by acetylation in 1-thiofructose derivatives.

the opportunity of enolate formation, providing further evidence for this mechanistic pathway.

Under acidic conditions, **6**, **12**, and **14** were expected to generate selectively a tertiary fructosyl cation, in agreement with our previous results in the glycosylfructose series.[18a,24] The hydroxyl group located at C-2′ in the D-glucose moiety is then suitably oriented to act as a glycosyl acceptor, trapping the transient cationic entity by formation of intramolecular glycosides (Schemes 3 and 4). In fact, effective activation at the anomeric position of the D-fructose moiety of trehalulose, the glycosyl donor part of the molecule, was only achieved with strong protonating catalysts, e.g., pyridinium poly(hydrogen fluoride) or pure HF, to give D-fructose−D-glucose intermonosaccharide dianhydrides.[25,26] The five-membered furanoid oxocarbenium cation was preferentially formed under kinetic conditions, resulting in the mixed β-D-fructofuranose−α-D-glucopyranose dianhydride **15**. Further tautomerization affected exclusively the D-fructosyl moiety to give the β-D-fructopyranose tautomer **16** as the

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(26) The nomenclature of intermolecular dianhydrides has been the subject of frequent confusion over the years. For the actual IUPAC−IUBMB recommendations see: McNaught, A. D. *Pure Appl. Chem.* **1996**, *68*, 1919, rule 2-Carb-27.

major thermodynamic compound in agreement with the known enhanced thermodynamic stability of β-D-fructopyranosides as compared to D-fructofuranosides.[16] The absence of any detectable α-D-fructoside derivatives in the final equilibrium mixture is in further support of the critical role of stereoelectronic factors in the formation of the spiroketal system in dihexose dianhydrides,[25,27] since such structures would not accommodate the anomeric effect while keeping the D-glucopyranose and the central dioxane system in chair conformations.

Closure of the 1,4-dioxane ring brings O-5 and C-3′ into a 1,3-parallel disposition, an unfavorable arrangement, which makes trehalulose the less reactive of all the isomeric α-glucosylfructoses.[18a,24] Indeed, compounds **15** and **16** are the first examples of spirodioxanyl pseudodisaccharides bearing an axial carbon substituent. This feature makes the system particularly suitable to study the effect of isosteric substitution of oxygen by sulfur in the glycosylation and tautomerization processes. On one hand, changes in reaction rates become more observable. On the other hand, the steric release on going from a *cis*-Decalin-type partial structure (**19** and **20**) to a *trans*-Decalin-like arrangement (**23** and **24**) provides a driving force for alternative mechanisms involving sulfur participation.

Examination of the reactivity of 1′-thiotrehaluloses (**6** and **12**) under acidic conditions point to three important differences as compared to trehalulose (**14**): (i) weak acidic media are effective in promoting the glycosylation reaction; (ii) glycosylation is always faster; and (iii) tautomerization affects not only the D-fructose part of the molecule but also the D-glucose moiety. The two first observations support the existence of anchimeric assistance by the neighboring sulfur atom in the activation step at the D-fructose anomeric position. If generation of the episulfonium entity was the key stereochemical step, the relative proportion of intramolecular glycosides formed after OH-2′-assisted ring opening under kinetic conditions should reflect the initial tautomeric ratio in the reducing thiodisaccharide, since formation of the spiro three-membered ring is not expected to depend on the initial ring size of the sugar. Nevertheless, the outcome of the reaction at the early stages is analogous for 1′-thiotrehalulose **6** and trehalulose **14**, favoring the β-D-fructofuranoside species **19** and **15**, respectively, which suggests a common intermediate. Most probably, the transient episulfonium ion species undergo rapid opening to form the tertiary oxocarbenium ions, which are finally trapped by intramolecular glycosylation (Figure 2). A mechanism involving oxocarbenium entities in glycosylation reactions of 2-thioalkyl aldopyranosides has been previously shown by theoretical methods to be a plausible alternative to the postulated episulfonium intermediates[8] and would also explain the deviation from the expected stereochemistry recently observed in glycosidation reactions using 2-thiophenyl pyranoside glycosyl donors.[28]

Further acid-promoted isomerization of the kinetic products **19** and **20** into **22** implies opening of the

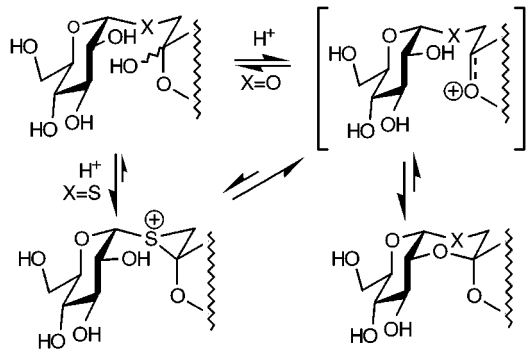

Figure 2. Possible mechanism of intramolecular glycosylation for trehalulose and 1′-thiotrehalulose.

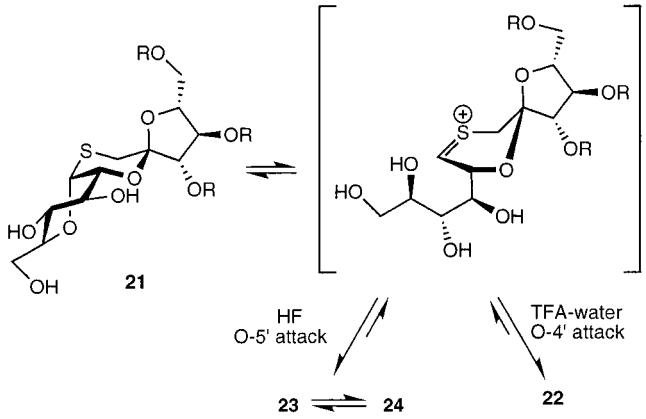

Figure 3. Possible mechanism of tautomerization at the D-glucose moiety in 1′-thiotrehalulose intramolecular glycosides.

D-glucopyranose ring. In view of the known stability of the thioglycosidic linkage under the acidic conditions used in this study,[2a,29] a transacetalation mechanism via a sulfonium intermediate likely accounts for this transformation (Figure 3). Five-membered ring closure involving O-4′ is then kinetically favored, the resulting difuranoid structure accommodating the anomeric effect at the oxathiane ring, in a chair conformation, for both oxygen substituents with all carbon substituents in equatorial disposition. This favorable arrangement allows the selective transformation of **6** into **22** in high yield.

Conversion of the β-D-fructoside α-D-glucopyranoside derivatives **19** and **20** into **22** implies tautomeric rearrangement at both monosaccharide subunits. The presence of the α-D-fructofuranoside α-D-glucopyranoside isomer **21** in the reaction mixtures indicates that inversion of the anomeric configuration at the D-fructose moiety precedes D-glucose isomerization. Although compound **21** satisfies the same stereoelectronic requirements as for **22** respective to the central oxathiane system, the D-glucopyranose structure must adopt a sterically strained skew conformation that acts as the driving force for ring opening and further D-glucose isomerization. Participation of sulfur is essential in this process, since a 1,4-dioxane isosteric structure would be also possible in the trehalulose dianhydride series and no D-glucose tautomerization is observed at all in this

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case. Actually, the oxygen analogue of **21** has been recently isolated from the product of thermal treatment of sucrose and its peracetate showed identical conformational features as the peracetate of **21** (i.e., **27**).[30]

Under more strenuous conditions, ring closure at the open-chain sulfonium ion species leads to the thermodynamically more stable β-D-glucopyranose derivatives **23** and **24**. Although O-5′ adopts an equatorial disposition in these compounds, it must be considered that the anomeric effect is weaker in thioglycosides as compared with glycosides[31] and is overcome by the stabilization energy on going from an α-D-glucofuranose to a β-D-glucopyranose structure. In the final thermodynamic equilibrium mixture, the α-D-fructofuranose derivative **23** and its β-D-fructopyranose isomer **24** are present in almost equivalent relative proportions, pointing out that the gain in stabilization associated with D-fructose tautomerization is virtually balanced by the conformational destabilization at the 1,4-oxathiane ring, which changes from chair to boat conformation to fit the anomeric effect at the O-5−C-2−O-2′ segment.

Under thermodynamic reaction conditions, the composition of the equilibrium mixture was identical starting from thiotrehalulose (**6**), 1′-*epi*-thiotrehalulose (**12**), or any of the isolated intramolecular glycosides, proving the reversible character of both glycosylation and tautomerization processes and reflecting the relative stability of the substituted 1,4-oxathiane systems as governed by stereoelectronic factors.[32]

Conclusions

Enolization, glycosylation, and tautomerization reactions are strongly accelerated in thiooligosaccharides bearing a sulfur substituent adjacent to the anomeric position, as compared to related oligosaccharides, as a result of sulfur participation in the stabilization of ionic intermediates. Base-catalyzed enolization may lead to epimerization in the case of aldoses and open-chain derivatives in the case of ketoses. The increase in glycosylation and tautomerization rates is ascribable to efficient activation of the anomeric position involving episulfonium ion species that, at least in the ketose series, further undergo fast opening to oxocarbenium cations, the latter being common reaction intermediates for O- and S-linked oligosaccharides. Acid-promoted tautomerization also occurs at the thioglucosyl moiety in related thiodisaccharides provided that an effective driving force exists, transient open-chain sulfonium cations being the key reaction intermediates in this case.

Experimental Section

General Methods. ^{1}H (^{13}C) NMR spectra were recorded at 200 (50.3), 400, and 500 (125.7) MHz. Spectra of unacetylated products were recorded for solutions in D_2O (^{1}H, external Me_4Si; ^{13}C, internal acetone 31.1 ppm). For acetylated compounds, solutions in $CDCl_3$ or C_6D_6 were used (internal Me_4Si). 1D selective NOESY experiments were carried out using the double pulse field gradient selective excitation (DPFGSE) technique,[33] with a mixing time of 400 ms. FAB mass spectra (Xe, acceleration potential 9 kV) were measured in the positive mode. Glycerol (unacetylated products) and *m*-nitrobenzyl alcohol (peracetylated derivatives) were used as the liquid matrixes. Melting points are uncorrected. Acetylations were effected conventionally with 1:1 pyridine−Ac_2O (10 mL for 1 g of sample). Deacetylations were carried out using the Zemplén technique (catalytic NaOMe in MeOH). LC of unprotected dianhydrides was carried out with a Perkin-Elmer chromatograph, fitted with a LC 30 refractometric detector and a 10205 integrator. A Lichrosorb NH_2 (7 mm) column (250 × 4.6 mm, eluent 78:22 MeCN−water) was used under the following conditions: flow rate 3 mL/min; injection amount 50 mL of 1−5% (w/v) solutions of sample. Elemental analyses were performed under Ar by the Service Central de Microanalyse du CNRS (Solaize).

Materials. Trehalulose (Südzucker AG, Mannheim) was obtained as an aqueous solution (60.4%) with 98.3% purity. Prior to use, it was freeze-dried and kept over P_2O_5. Anhydrous hydrogen fluoride (HF) was a commercial product obtained in steel cylinders. Prior to use, it was distilled and kept in polyethylene bottles at −25 °C. The stable complex of pyridinium poly(hydrogen fluoride) [7:3 (w/w) hydrogen fluoride−pyridine][34] was prepared by careful addition of dried (KOH) pyridine into anhyd HF in a dry ice−acetone bath. The complex was stored at −25 °C in a polyethylene bottle inside a polyethylene bag and was used within 2 weeks. Different ratios of HF−pyridine were obtained by addition of anhyd pyridine or HF to the 7:3 complex.

2,3:4,5-Di-*O*-isopropylidene-1-*S*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1-thio-β-D-fructopyranose (3). To a suspension of 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-α-D-glucopyranose[13] (**2**) (1.02 g, 2.51 mmol) in MeOH (50 mL) was added methanolic NaMeO (M, 2.6 mL). The suspension was stirred at room temperature for 18 h and then concentrated, and the resulting amorphous powder was dried (P_2O_5) and dissolved in DMF (15 mL). To this solution, 2,3:4,5-di-*O*-isopropylidene-1-*O*-[(trifluoromethyl)sulfonyl]-β-D-fructopyranose[15] (**1**) (0.98 g, 2.50 mmol) in DMF (4 mL) was added under N_2. After being stirred overnight at 40 °C, the solution was cooled at 0 °C and acetylated with Ac_2O−Py (1:1, 30 mL). Conventional workup and purification by column chromatography (1:2 → 1:1 EtOAc−petroleum ether) gave **3** (1.06 g, 70% yield) as a syrup: $[\alpha]^{22}_D = +120.4$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.66 (d, 1 H, $J = 5.8$ Hz), 5.38 (t, 1 H, 9.9 Hz), 5.02 (dd, 1 H, $J = 5.8$, 9.9 Hz), 5.01 (t, 1 H, $J = 9.9$ Hz), 4.54 (dd, 1 H, $J = 2.5$, 7.9 Hz), 4.47 (ddd, 1 H, $J = 2.6$, 4.2, 9.9 Hz), 4.27 (dd, 4.2, 12.4 Hz), 4.17 (dd, 1 H, $J = 1.7$, 12.9 Hz), 4.10 (d, 1 H, $J = 2.5$ Hz), 4.08 (dd, 1 H, $J = 2.6$, 12.4 Hz), 3.84 (dd, 1 H, $J = 1.7$, 12.9 Hz), 3.70 (d, 1 H, $J = 12.9$ Hz), 2.94 (d, 1 H, $J = 13.8$ Hz), 2.86 (d, 1 H, $J = 13.8$ Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.0, 169.6, 169.5, 109.0, 108.4, 102.5, 82.3, 72.7, 70.6, 70.5, 70.4, 70.1, 68.4, 67.6, 61.7, 61.4, 37.9, 26.3, 25.6, 25.1, 23.9, 20.6 (2C), 20.5. Anal. Calcd for $C_{26}H_{38}O_{14}S$: C, 51.48; H, 6.31; S, 5.28. Found: C, 51.38; H, 6.55; S, 5.25.

2,3:4,5-Di-*O*-isopropylidene-1-*S*-(α-D-glucopyranosyl)-1-thio-β-D-fructopyranose (4). To a solution of **3** (0.5 g, 0.82 mmol) in MeOH (40 mL) was added methanolic NaOMe (M, 0.3 mL). The mixture was stirred for 2 h at room temperature and then demineralized with Amberlite IRN-77 (H^+) cation-exchange resin, filtered, and concentrated to yield **4** (0.34 g, 96% yield): $[\alpha]^{22}_D = +55.6$ (*c* 0.9, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 5.51 (d, 1 H, $J = 5.3$ Hz), 4.72 (dd, 1 H, $J = 2.5$, 7.9 Hz), 4.48 (d, 1 H, $J = 2.5$ Hz), 4.35 (dd, 1 H, $J = 1.3$, 7.9 Hz), 4.05 (ddd, 1 H, $J = 2.6$, 5.2, 9.4 Hz), 3.98 (dd, 1 H, $J = 1.3$, 12.9 Hz), 3.92 (ddd, 1 H, $J = 2.6$, 5.5, 13.2 Hz), 3.83 (m, 2 H),

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3.72 (d, 1 H, 12.9 Hz), 3.70 (td, 1 H, J = 5.2, 13.2 Hz), 3.50 (td, 1 H, J = 3.9, 9.4 Hz), 3.08 (d, 2 H); ^{13}C NMR (50.3 MHz, D_2O) δ 109.8, 109.6, 102.6, 85.5, 73.7, 72.8, 72.4, 71.3, 70.3, 69.7(2C), 60.9, 60.6, 37.2, 25.3, 24.8, 24.4, 23.0. Anal. Calcd for $C_{18}H_{30}O_{10}S$: C, 49.30; H, 6.89; S, 7.31. Found: C, 49.15; H, 6.94; S, 7.40.

1-*S*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-1-thio-D-fructopyranose (5). A solution of **3** (0.32 g, 0.53 mmol) in 90% TFA-water (5 mL) was kept at 30 °C under reduced pressure in a rotary evaporator until evolution of acetone had ceased (10 min). Further concentration, coevaporation with toluene and water, and freeze-drying from an aqueous solution yielded **5** as a syrup (0.27 g, 97% yield): $[\alpha]^{22}_D = +130$ (*c* 1.2, water); ^{13}C NMR (50.3 MHz, D_2O, β-D-fructopyranose form) δ 173.5, 172.7, 172.5, 172.2, 98.8, 70.8−67.8 (8C), 63.6, 62.1, 35.7, 20.3, 20.1 (2C), 19.9. Anal. Calcd for $C_{20}H_{30}O_{14}S$: C, 45.62; H, 5.74; S, 6.09. Found: C, 45.72; H, 5.45; S, 6.09.

1-*S*-α-D-glucopyranosyl-1-thio-D-fructose (1′-Thiotrehalulose, 6). A solution of **5** (0.33 mmol) in MeOH (15 mL) was deacetylated with methanolic NaOMe (M, 0.13 mL) for 2 h at room temperature and then demineralized with Amberlite IRN-77 (H^+) cation-exchange resin and filtered. Evaporation of the solvent gave **6** (112 mg, 95%) as an amorphous powder: $[\alpha]^{22}_D = +70$ (*c* 1.4, water); ^{13}C NMR (50.3 MHz, D_2O, β-D-fructopyranose form) δ 99.1, 85.5, 73.7, 72.8, 71.2, 69.9, 69.8, 69.3, 69.2, 63.7, 60.8, 36.3. Anal. Calcd for $C_{12}H_{22}O_{10}S$: C, 40.22; H, 6.18; S, 8.95. Found: C, 40.04; H, 6.34; S, 8.60.

(*E*)-[1-*S*-(2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enitol-1-yl) 2,3,4,6-Tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (7). Conventional acetylation of **6** (0.1 g, 0.28 mmol) at room temperature overnight and purification by column chromatography (6:1 CCl_4−acetone) afforded **7** (0.18 g, 90% yield): $[\alpha]^{22}_D = +70.6$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1 H), 5.74 (d, 1 H, J = 5.7 Hz), 5.53 (d, 1 H, 4.7 Hz), 5.40 (dd, 1 H, J = 4.7, 7.2 Hz), 5.32 (t, 1 H, J = 9.8 Hz), 5.13 (ddd, 1 H, J = 2.8, 5.8, 7.2 Hz), 5.10 (dd, 1 H, J = 5.7, 9.8 Hz), 5.08 (t, 1 H, J = 9.8 Hz), 4.24 (ddd, 1 H, J = 2.1, 3.3, 9.8 Hz), 4.30 (dd, 1 H, J = 3.3, 12.7 Hz), 4.22 (dd, 1 H, J = 2.8, 12.2 Hz), 4.10 (dd, 1 H, J = 5.8, 12.2 Hz), 4.05 (dd, 1 H, J = 2.1, 12.7 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.4 (3C), 169.8 (2C), 169.3 (2C), 167.0 (2C), 142.2, 114.4, 82.2, 70.3, 70.0, 69.8, 69.3, 68.6, 68.2, 67.4, 61.6, 61.1, 20.5 (9C). Anal. Calcd for $C_{30}H_{40}O_{19}S$: C, 48.91; H, 5.47; S, 4.35. Found: C, 48.77; H, 5.40; S, 4.16.

2,3:4,5-Di-*O*-isopropylidene-1-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-fructopyranose (9). Sodium hydride (87 mg, 2.9 mmol) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose[14] (**8**) (1 g, 2.7 mmol) in dry THF (30 mL). The suspension was stirred under N_2 until hydrogen evolution had ceased. The resulting solution was then concentrated and the amorphous residue dissolved in DMF (10 mL). To this stirred solution, 2,3:4,5-di-*O*-isopropylidene-1-*O*-[(trifluoromethyl)sulfonyl]-β-D-fructopyranose[15] (**1**) (1 g, 2.7 mmol) in DMF (4 mL) was added dropwise. After being stirred overnight at 40 °C, the mixture was concentrated. A solution of the residue in CH_2Cl_2 was washed with water, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:1 petroleum ether−EtOAc), giving **9** (1.2 g, 73% yield): mp 199−200 °C (from EtOH); $[\alpha]^{22}_D = -50$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.15 (t, 1 H, J = 10.0 Hz), 5.04 (t, 1 H, J = 10.0 Hz), 4.93 (t, 1 H, J = 10.0 Hz), 4.71 (d, 1 H, J = 10.0 Hz), 4.55 (dd, 1 H, J = 2.7, 7.9 Hz), 4.30 (d, 1 H, J = 2.7 Hz), 4.20 (dd, 1 H, J = 4.6, 12.4 Hz), 4.15 (dd, 1 H, J = 1.8, 7.9 Hz), 4.06 (dd, 1 H, J = 2.5, 12.4 Hz), 3.89 (dd, 1 H, J = 1.8, 13.8 Hz), 3.69 (d,1 H, J = 13.8 Hz), 3.60 (ddd, 1 H, J = 2.5, 4.6, 10.0 Hz), 3.25 (d, 1 H, J = 14.9 Hz), 2.80 (d, 1 H, J = 14.9 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.4, 169.9, 169.1, 166.9, 108.8, 108.5, 103.0, 83.6, 75.5, 73.8, 71.4, 70.6, 70.4, 70.0, 68.1, 61.7, 61.5, 36.2, 26.5, 25.6 (2C), 23, 8, 20.5, 20.3 (3C). Anal. Calcd for $C_{26}H_{38}O_{14}S$: C, 51.48; H, 6.31; S, 5.28. Found: C, 51.48; H, 6.27; S, 5.03.

2,3:4,5-Di-*O*-isopropylidene-1-*S*-(β-D-glucopyranosyl)-1-thio-β-D-fructopyranose (10). Compound **9** (100 mg, 0.16 mmol) in MeOH (15 mL) was stirred with M methanolic NaOMe (0.1 mL) for 2 h at room temperature. The solution was then demineralized with Amberlite IRN-77 (H^+) cation-exchange resin and filtered. Evaporation of the solvent gave **10** (70 mg, 100% yield): $[\alpha]^{22}_D = -44.5$ (*c* 0.9, water); ^{1}H NMR (200 MHz, D_2O) δ 4.85 (dd, 1 H, J = 2.5, 8.1 Hz), 4.70 (d, 1 H, J = 9.7 Hz), 4.58 (d, 1 H, J = 2.5 Hz), 4.54 (d, 1 H, J = 3.6 Hz), 4.05 (dd, 1 H, J = 3.6, 12.4 Hz), 3.97 (dd, 1 H, J = 1.3, 12.4 Hz), 3.86 (d, 1 H, J = 14.3 Hz), 3.85 (d, 1 H, J = 12.4 Hz), 3.80 (dd, 1 H, J = 1.2, 12.4 Hz), 3.57−3.47 (m, 3 H), 3.39 (dd, 1 H, J = 0.9, 9.7 Hz), 3.16 (d, 1 H, J = 14.3 Hz); ^{13}C NMR (50.3 MHz, D_2O) δ 108.8, 108.5, 103.0, 85.6, 79.9, 77.2, 72.7, 72,4, 70.3, 69.6, 69.5, 60.9 (2C), 37.5, 25.5, 24.9, 24.8, 22.7. Anal. Calcd for $C_{18}H_{30}O_{10}S$: C, 49.30; H, 6.89; S, 7.31. Found: C, 48.97; H, 6.73; S, 6.89.

1-*S*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-D-fructopyranose (11). Treatment of **9** (0.4 g, 0.66 mmol) with 90% TFA−water (5 mL) at 30 °C under reduced pressure for 15 min, followed by concentration, coevaporation with toluene and water, and freeze-drying from an aqueous solution, afforded **11** (0.31 g, 90% yield): $[\alpha]^{22}_D = -60$ (*c* 1.1, water); ^{13}C NMR (50.3 MHz, D_2O, β-D-fructopyranose form) δ 173.4, 172.7, 172.6, 172.4, 97.6, 83.9, 75.0, 73.8, 70.4, 69.9 (2C), 69.0, 68.1, 63.4, 61.9, 38.2, 20.6, 20.3, 20.2. Anal. Calcd for $C_{20}H_{30}O_{14}S$: C, 45.62; H, 5.74; S, 6.09. Found: C, 45.26; H, 5.40; S, 5.85.

1-*S*-β-D-Glucopyranosyl-1-thio-D-fructopyranose (12). Zemplén deacetylation of the product resulting from treatment of **9** (150 mg, 0.25 mmol) with 90% TFA−water (4 mL) yielded **12** (86 mg, 97% yield): $[\alpha]^{22}_D = -66.7$ (*c* 1.2, water); ^{13}C NMR (50.3 MHz, D_2O, β-D-fructopyranose form) δ 98.4, 86.9, 80.8, 78.0, 73.3, 70.3, 70.9, 70.7, 70.0, 64.6, 61.7, 38.7 Anal. Calcd for $C_{12}H_{22}O_{10}S$: C, 40.22; H, 6.18; S, 8.95. Found: C, 39.84; H, 5.90; S, 8.67.

(*E*)-1-*S*-(2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enitol-1-yl) 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (13). Conventional acetylation of **16** (70 mg, 0.19 mmol) followed by purification by column chromatography (6:1 CCl_4−acetone) gave **13** (115 mg, 89% yield): $[\alpha]^{22}_D = -40.0$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.30 (s, 1 H), 5.58 (dd, 1 H, J = 0.5, 5.9 Hz), 5.47 (t, 1 H, J = 5.9 Hz), 5.15 (m, 2H), 5.00 (t, 1 H, J = 9.8 Hz), 4.57 (d, 1 H, J = 9.8 Hz), 4.27 (dd, 1 H, J = 3.3, 12.3 Hz), 4.25 (dd, 1 H, J = 5.0, 12.4 Hz), 4.11 (dd, 1 H, 6.2, 12.3 Hz), 4.09 (dd, 1 H, J = 2.3, 12.4 Hz), 3.75 (ddd, 1 H, J = 2.3, 5.0 Hz); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 170.4 (2C), 169.9 (2C), 169.4 (2C), 169.2, (3C) 142.1, 114.2, 82.7, 76.0, 73.6, 69.9, 69.6, 68.9, 68.8, 67.8, 61.7, 61.4, 20.5 (6C), 20.4, 20.2. Anal. Calcd for $C_{30}H_{40}O_{19}S$: C, 48.91; H, 5.47; S, 4.35. Found: C, 49.12; H, 5.56; S, 4.34.

Compound **13** was also obtained by acetylation of **11** and purification by column chromatography with the same eluent.

Reactions of 1-*O*- and 1-*S*-Glucosylfructoses (6, 9, and 14) in Pyridinium Poly(hydrogen fluoride) or Anhydrous HF. All reactions were carried out in polyethylene bottles. The glucosylfructose (0.3−2.5 mmol) was dissolved in the appropriate amount (0.2−1.2 mL) of HF−Py in various relative proportions (4:3−7:3) or pure HF at 0 °C and then kept at the final reaction temperature (0−20 °C). The product was precipitated by addition of an excess of ether to give an oil that was decanted, washed several times with ether, dissolved in water, and evaporated. Traces of pyridine were eliminated by coevaporation with toluene. The composition of the product mixture was preliminary assessed by ^{13}C NMR spectroscopy of solutions in D_2O using an antigate pulse sequence. The comparative intensities of the C-1 and C-2 resonances of fructosyl residues were used for this purpose. Results were confirmed by peaks integration in analytical LC chromatograms of the mixtures. Results by these two techniques did not differ by more than 2%.

Reactions of 1-*O*- and 1-*S*-Glucosylfructoses (6, 9, and 14) in Aqueous Trifluoroacetic Acid. The corresponding glycosylfructose (0.5−1.2 mol) was dissolved in the appropriate amount (5−8 mL) of TFA−water in various relative proportions (9:1−15:1), kept at the reaction temperature (20−50 °C),

and then concentrated under reduced pressure, coevaporated several times with water, and freeze-dried from an aqueous solution.

Separation of Intramolecular Glycosides from 6, 12, and 14. Pure samples of the D-fructose D-glucose 1,1′:2,2′-dianhydrides arising from acid treatment of **6**, **12**, and **14** were obtained after semipreparative HPLC of crude product mixtures. The order of elution was as follows. For derivatives of **14** (t_R = 11.99 min): **15** (t_R = 6.44 min) and **16** (t_R = 8.50 min). For derivatives of **6** (t_R = 10.78 min) and **12** (t_R = 9.74 min): **23** (t_R = 5.56 min), **21** (t_R = 5.82 min), **22** (t_R = 5.88 min), **19** (t_R = 6.01 min), **24** (t_R = 7.42 min), and **20** (t_R = 7.94 min). Alternatively, pure samples of the corresponding peracetates were obtained by peracetylation and subsequent column chromatography (12:1 → 6:1 CCl_4−acetone or 1:2 → 1:1 EtOAc−hexanes).

Conventional peracetylation (deacetylation) of unprotected (peracetylated) dianhydrides afforded the corresponding peracetates (unprotected compounds) in almost quantitative yield. Compounds **15** and **16** could be also separated without previous derivatization by column chromatography (1:2 $CHCl_3$−MeOH) or direct crystallization of their mixtures. The yields reported are the best isolated yields obtained from mixtures optimized in the content of the respective compound (see Tables 1−3).

***β*-D-Fructofuranose α-D-glucopyranose 1,1′:2,2′-dianhydride (15):** 48% yield; $[\alpha]^{22}_D$ = +14.5 (*c* 1.1, water); ^{13}C NMR (50.3 MHz, D_2O) δ 98.5, 95.1, 81.7, 77.1, 75.4, 74.7, 72.8 (2C), 71.5, 69.5, 61.3, 60.0; FABMS *m/z* 347 (100, $[M + Na]^+$), 325 (40, $[M + H]^+$). Anal. Calcd for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.20. Found: C, 44.35; H, 6.17.

***β*-D-Fructopyranose α-D-glucopyranose 1,1′:2,2′-dianhydride (16):** 80% yield; mp 263−264 °C (from EtOH); $[\alpha]^{22}_D$ = +24 (*c* 1.1, water); ^{13}C NMR (50.3 MHz, D_2O) δ 95.3, 94.3, 73.8, 72.9, 72.3, 69.5, 69.1, 69.0, 68.9, 68.1, 64.0, 60.1; FABMS *m/z* 347 (100, $[M + Na]^+$), 325 (17, $[M + H]^+$). Anal. Calcd for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.20. Found: C, 44.49; H, 6.44.

3,4,6-Tri-*O*-acetyl-*β*-D-fructofuranose 3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranose 1,1′:2,2′-dianhydride (17): mp 194−195 °C (from EtOH); $[\alpha]^{22}_D$ = +26 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) see Table 4; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.4, 169.8, 98.5, 93.7, 78.5, 76.5, 75.8, 72.5, 71.5, 70.4, 69.3, 68.6, 63.9, 61.6, 20.8, 20.5 (5C); FABMS *m/z* 599 (100, $[M + Na]^+$), 577 (60, $[M + H]^+$). Anal. Calcd for $C_{24}H_{32}O_{16}$: C, 50.0; H, 5.59. Found: C, 49.87; H, 5.43.

3,4,5-Tri-*O*-acetyl-*β*-D-fructopyranose 3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranose 1,1′:2,2′-dianhydride (18): $[\alpha]^{22}_D$ = −15 (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, C_6D_6) see Table 4; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.5 (3C), 170.1, 170.0, 169.8, 94.1, 94.0, 72.5, 71.1, 69.3, 69.1, 68.7, 68.5, 67.8, 66.7, 61.7, 61.5, 21.0, 20.7, 20.5, 20.4; FABMS *m/z* 599 (40, $[M + Na]^+$), 577 (100, $[M + H]^+$). Anal. Calcd for $C_{24}H_{32}O_{16}$: C, 50.0; H, 5.59. Found: C, 50.10; H, 5.58.

1-*S*-α-D-Glucopyranosyl-1-thio-*β*-D-fructofuranose 1,1′:2,2′-dianhydride (19): $[\alpha]^{22}_D$ = +14.3 (*c* 0.98, water); ^{13}C NMR (50.3 MHz, D_2O) δ 97.0, 80.2, 79.6, 76.1, 75.0, 74.9, 72.3, 71.6, 69.6, 60.5, 59.5, 33.7. Anal. Calcd for $C_{12}H_{20}O_9S$: C, 42.35; H, 5.92; S, 9.42. Found: C, 41.97; H, 5.67; S, 9.00.

1-*S*-α-D-Glucopyranosyl-1-thio-*β*-D-fructopyranose 1,1′:2,2′-dianhydride (20): 42% yield; $[\alpha]^{22}_D$ = −3.6 (*c* 1.1, water); ^{13}C NMR (50.3 MHz, D_2O) δ 95.8, 76.6, 76.2, 74.9, 73.4, 72.6, 71.7, 70.4, 69.9, 65.5, 61.5, 34.3; FABMS *m/z* 341 (100, $[M + H]^+$. Anal. Calcd for $C_{12}H_{20}O_9S$: C, 42.35; H, 5.92; S, 9.42. Found: C, 42.00; H, 5.75; S, 9.28.

1-*S*-α-D-Glucopyranosyl-1-thio-α-D-fructofuranose 1,1′:2,2′-dianhydride (21): $[\alpha]^{22}_D$ = −4.9 (*c* 0.8, water); ^{13}C NMR (50.3 MHz, D_2O) δ 103.9, 83.0, 82.9, 79.6, 78.2, 72.4, 71.7, 67.4, 66.2, 61.2, 59.7, 24.5. Anal. Calcd for $C_{12}H_{20}O_9S$: C, 42.35; H, 5.92; S, 9.42. Found: C, 42.17; H, 6.01; S, 9.18.

1-*S*-α-D-Glucofuranosyl-1-thio-α-D-fructofuranose 1,1′:2,2′-dianhydride (22): 62% yield; $[\alpha]^{22}_D$ = −57.8 (*c* 0.9, water); ^{13}C NMR (50.3 MHz, D_2O) δ 102.8, 83.3, 83.1, 81.7, 78.3, 76.0, 75.1, 74.6, 69.3, 63.6, 61.2, 23.8; FABMS *m/z* 363 (100, $[M + Na]^+$. Anal. Calcd for $C_{12}H_{20}O_9S$: C, 42.35; H, 5.92; S, 9.42. Found: C, 42.12; H, 5.64; S, 9.19.

1-*S*-*β*-D-Glucopyranosyl-1-thio-α-D-fructofuranose 1,1′:2,2′-dianhydride (23): $[\alpha]^{22}_D$ = +24.3 (*c* 1.15, water); ^{13}C NMR (50.3 MHz, D_2O) δ 103.6, 82.8, 82.5, 81.2, 78.4, 74.8, 74.7, 74.1, 69.8, 61.1, 60.8, 30.5. Anal. Calcd for $C_{12}H_{20}O_9S$: C, 42.35; H, 5.92; S, 9.42. Found: C, 41.88; H, 5.60; S, 9.12.

1-*S*-*β*-D-Glucopyranosyl-1-thio-*β*-D-fructopyranose 1,1′:2,2′-dianhydride (24): $[\alpha]^{22}_D$ = +12.8 (*c* 0.8, water); ^{13}C NMR (50.3 MHz, D_2O) δ 98.7, 80.7, 75.7, 75.5 (2C), 72.4, 69.9, 69.5, 69.1, 63.8, 60.9, 29.3. Anal. Calcd for $C_{12}H_{20}O_9S$: C, 42.35; H, 5.92; S, 9.42. Found: C, 41.99; H, 5.83; S, 9.02.

3,4,6-Tri-*O*-acetyl-1-*S*-(3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosyl)-1-thio-*β*-D-fructofuranose 1,1′:2,2′-dianhydride (25): $[\alpha]^{22}_D$ = +29.8 (*c* 0.94, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) see Table 4; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.2 (4C), 170.1 (2C), 100.9, 79.1, 78.9, 76.5, 72.9, 72.3, 72.2, 70.5, 68.6, 64.4, 61.8, 31.3, 20.8 (3C), 20.7, 20.5, 20.2. Anal. Calcd for $C_{24}H_{32}O_{15}S$: C, 48.64; H, 5.44; S, 5.41. Found: C, 48.50; H, 5.26; S, 5.17.

3,4,5-Tri-*O*-acetyl-1-*S*-(3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosyl)-1-thio-*β*-D-fructopyranose 1,1′:2,2′-dianhydride (26): $[\alpha]^{22}_D$ = −40.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) see Table 4; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.4, 170.3, 170.1, 169.8, 169.7 (2C), 95.6, 74.7, 72.8, 71.7, 71.3, 69.8, 69.2, 68.8, 68.0, 62.0, 61.8, 32.8, 20.8 (3C), 20.7, 20.5 (2C); FABMS *m/z* 615 (50, $[M + Na]^+$) and 593 (15, $[M + H]^+$). Anal. Calcd for $C_{24}H_{32}O_{15}S$: C, 48.64; H, 5.44; S, 5.41. Found: C, 48.48; H, 5.40; S, 5.22.

3,4,6-Tri-*O*-acetyl-1-*S*-(3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosyl)-1-thio-α-D-fructofuranose 1,1′:2,2′-dianhydride (27): $[\alpha]^{22}_D$ = +16.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) see Table 4; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.5, 170.3 (3C), 169.8, 168.9, 103.1, 81.2, 79.7, 77.8, 73.4, 71.8, 68.5, 66.5, 62.7, 61.0, 23.9, 20.4 (6C). Anal. Calcd for $C_{24}H_{32}O_{15}S$: C, 48.64; H, 5.44; S, 5.41. Found: C, 48.36; H, 5.51; S, 5.12.

3,4,6-Tri-*O*-acetyl-1-*S*-(3′,5′,6′-tri-*O*-acetyl-α-D-glucofuranosyl)-1-thio-α-D-fructofuranose 1,1′:2,2′-dianhydride (28): $[\alpha]^{22}_D$ = +14.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) see Table 4; ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 170.4, 170.2, 169.8, 169.5, 169.1, 168.8, 102.3, 81.5, 79.6, 78.4, 78.1, 75.3, 75.0, 74.3, 67.9, 63.3, 62.7, 23.4, 20.5 (6C); FABMS *m/z* 615 (40, $[M + Na]^+$), 593 (20, $[M + H]^+$). Anal. Calcd for $C_{24}H_{32}O_{15}S$: C, 48.64; H, 5.44; S, 5.41. Found: C, 48.32; H, 5.22; S, 5.09.

3,4,6-Tri-*O*-acetyl-1-*S*-(3′,4′,6′-tri-*O*-acetyl-*β*-D-glucopyranosyl)-1-thio-α-D-fructofuranose 1,1′:2,2′-dianhydride (29): mp 106−108 °C; $[\alpha]^{22}_D$ = +55.0 (*c* 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) see Table 4; ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 170.7 (2C), 169.7 (2C), 169.1 (2C), 102.8, 80.9, 79.1, 78.3, 76.9, 75.3, 72.5, 72.3, 68.5, 63.0, 61.9, 30.0, 20.8 (3C), 20.6 (3C); FABMS *m/z* 615 (25, $[M + Na]^+$), 593 (20, $[M + H]^+$). Anal. Calcd for $C_{24}H_{32}O_{15}S$: C, 48.64; H, 5.44; S, 5.41. Found: C, 48.86; H, 5.22; S, 5.75.

3,4,5-Tri-*O*-acetyl-1-*S*-(3′,4′,6′-tri-*O*-acetyl-*β*-D-glucopyranosyl)-1-thio-*β*-D-fructopyranose 1,1′:2,2′-dianhydride (30): $[\alpha]^{22}_D$ = −20.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, C_6D_6) see Table 4; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.0, 169.9 (2C), 169.8, 169.5 (2C), 98.0, 77.3, 76.9, 74.2, 73.8, 71.8, 69.4, 68.4, 68.2, 62.5 (2C), 30.0, 21.0 (2C), 20.9 (4C). Anal. Calcd for $C_{24}H_{32}O_{15}S$: C, 48.64; H, 5.44; S, 5.41. Found: C, 48.31; H, 5.30; S, 5.05.

Acknowledgment. J.M.G.F. and C.O.M. thank the Centre National de la Recherche Scientifique (Paris) for research associate positions.

Supporting Information Available: Tables 4−7 containing ^{1}H and ^{13}C NMR data for all new compounds (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO972203K