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Synthesis of five-membered homothiosugars derived from L-erythrose and D-mannose

Jens Riedner,† Inmaculada Robina,* José G. Fernández-Bolaños, Silvia Gómez-Bujedo and José Fuentes

Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apdo. 553, E-41071 Seville, Spain

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Abstract

The synthesis of homothiosugars by conjugate addition of the hydrogen sulfide anion to the double bond of α,β-unsaturated esters followed by nucleophilic internal displacement of a sulfonyloxy group is described. The new thiolanes were evaluated as enzyme inhibitors. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Thiosugars, in which the ring oxygen atom has been substituted by S, present important biological activities.[1] The presence of sulfur provokes important changes in the chemical properties of these pseudosugars.[2] These features create interest in the synthesis of 5-thiosugars and in their evaluation as therapeutic agents. Many of them are enzyme inhibitors, thus 5-thio-L-galactose[3] and 5-thio-L-fucose,[4] several 5-thio-α-L-fucopyranosyl derivatives[5] and 5-thio-L-arabinose[4b] are competitive inhibitors of α-L-fucosidases. 5-Thio-α-D-glucose and its derivatives[6] as well as 1-deoxy-5-thio-mannojirimycin[7] weakly inhibit α-D-glucosidases. *Salacinol* and *kotalanol*, natural thiosugars with a sulfate moiety, have recently been shown to be potent α-D-glucosidase inhibitors.[8] Other thiosugars, such as 5-thio-D-gluconhydroximo-1,5-lactone, are weak competitive inhibitors of β-D-glucosidases.[9] A thio analog of a pyrrolizidine alkaloid[10] is a specific inhibitor of α-D-mannosidases. 5-Thioglucal[11] has also been shown to be a competitive inhibitor of α-D-glucosidase and α-D-mannosidase, and some thiazoline sugar compounds are inhibitors of *N*-acetyl-β-hesoxaminidases.[12] At the same time, some 1,5-dithiopentopyranoside derivatives and 1,4-dithiotetrafuranose derivatives have shown oral antithrombotic activity.[13] It has also been reported that thioisosteres of Neu5Ac2en derivatives are active against virus sialidase.[14] These wide and important biological activities have prompted the syntheses of thiosugars as promising targets for studying enzymatic activities and as potential therapeutic agents.

* Corresponding author. Fax: 34 95 462 49 60; e-mail: robina@cica.es

† Present address: Department of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland.

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Most syntheses of thiosugars such as 4-thiofuranoses and 5-thiopyranoses are based on the introduction of a thiol group at the 4- or 5-position, respectively, and different approaches have been used. The most common procedure is a nucleophilic replacement of a sulfonyloxy group by an RS^- group. In this way, many thiosugars have been synthesized.[15] Episulfide ring opening by a nucleophile has also been extensively used for the synthesis of this type of compound.[16] 1-Deoxy-5-thio-mannojirimycin[7] has been prepared by nucleophilic internal cyclization. 5-Thiopyranoses and 4-thiofuranoses have also been synthesized[17] by intramolecular cyclization of dithio or monothioacetals. In addition, sulfur participation in displacement reactions of sulfonate esters of 5-thiopyranoses with several nucleophiles gave ring contracted 4-thiofuranose derivatives.[2c] Recently, general syntheses of 5-thio- and 4-thiosugars have been carried out by nucleophilic ring openings with KSCN on cyclic sulfates of *vic*-diols, followed by reduction with $LiAlH_4$.[18] Another recent procedure for the synthesis of these compounds involves thiocyclization of C_2-symmetric bis-epoxides promoted by the sulfide ion, followed in some cases by ring isomerization.[19] Other syntheses of thiosugars starting from achiral compounds and using enzymes as catalyst have been reported.[20] In this paper, we report the synthesis of polyhydroxylated chiral thiolanes having a side chain that constitutes a new type of homothiosugars.

2. Results and discussion

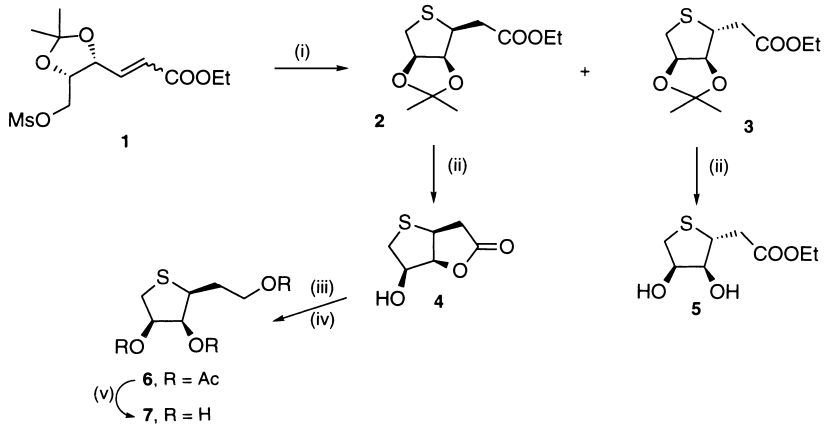
The preparation of polyhydroxylated chiral thiolanes can be performed by a new procedure that involves the introduction of a thiol group in a sugar moiety by conjugate addition, followed by nucleophilic internal displacement of a sulfonyloxy group, in a 5-*exo*-*tet* cyclization mode according to Baldwin's rules.[21] These tandem reactions have already been applied for the synthesis of homochiral hydroxylated pyrrolidines starting from D- and L-erythrose, D-mannose and D-allose.[22]

Wittig reaction of 2,3-*O*-isopropylidene-L-erythrose and (carbethoxymethylene)triphenylphosphorane as described[22] gave a *Z*:*E* mixture of alkenes that were transformed into the corresponding mesylates **1** (Scheme 1), which were purified by column chromatography. The reaction of the *Z*-alkene with NaHS in dry ethanol gave after 4 h at room temperature a mixture of the thiolanes **2** and **3** in 83% yield and a ratio **2**:**3**=3:1, measured by integration of signals in the ^1H NMR spectrum. Under identical conditions, the *E*-alkene gave a mixture of **2** and **3** in 80% yield and a ratio **2**:**3**=2.3:1. The course of this reaction is the conjugate addition of the hydrogen sulfide anion to the double bond of the α,β-unsaturated ester, followed by nucleophilic internal displacement. The conjugate addition of HS^- to α,β-unsaturated systems has literature precedents[23] and has been applied to the synthesis of sulfur containing rings.[24]

The *threo*-selectivity in the conjugate addition can be rationalized to occur through a Conforth type TS model in a similar way to that described for the synthesis of homochiral pyrrolidines.[22] Nevertheless, the conjugate addition is less stereoselective due to the higher nucleophilicity of hydrogen sulfide anion compared with ammonia, since it has been demonstrated[22] that the corresponding pyrrolidines were not interconverted under similar reaction conditions. Attempts to improve the selectivity, by temperature and changing solvents or using TBAF as catalyst, did not meet with success.

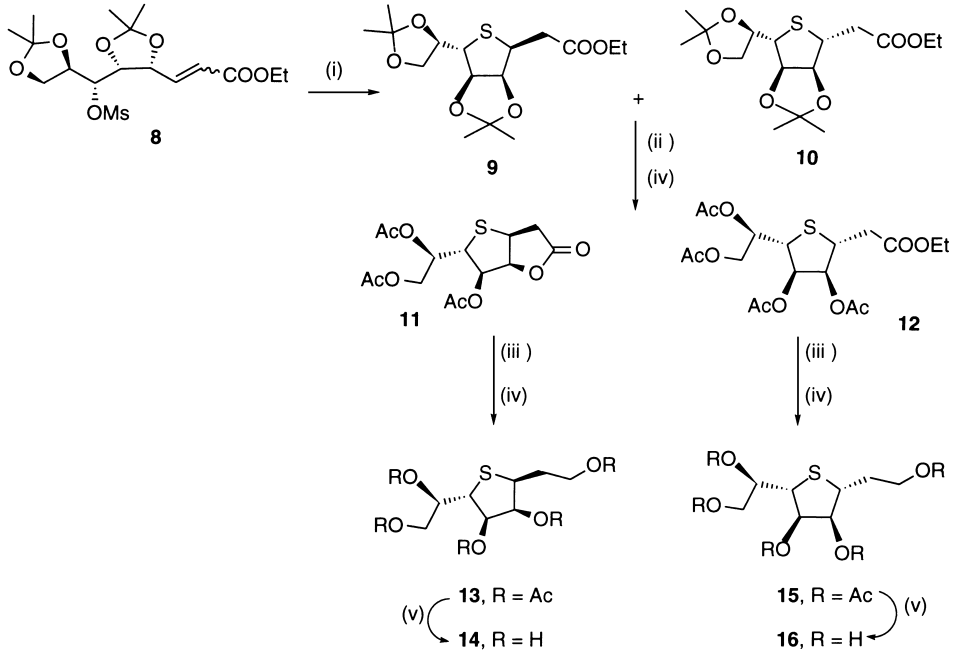
Treatment of the (2.3:1) mixture of **2** and **3** with TFA/H_2O for 24 h at room temperature gave the lactone **4** and the unprotected thiolane **5** in 44 and 33% yield, respectively. Reprotection of diol **5** as acetonide gave **3**, confirming the assigned configurations. Reduction of **4** with $LiAlH_4$ followed by conventional acetylation gave the triacetate **6** in 52% overall yield based on **4**. Zemplén deacetylation of **6** gave **7** in 66% yield.

The above sequence of reactions was also carried out starting from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose. Wittig reaction in benzene at reflux followed by mesylation afforded a 12:1 mixture of



Scheme 1. Reactions and conditions: (i) NaHS/EtOH; (ii) TFA–H_2O–EtOH; (iii) $LiAlH_4$/THF; (iv) Ac_2O/Py; (v) NaOMe/MeOH

Z and *E* mesylates **8** (Scheme 2). Treatment with NaHS/EtOH at room temperature for 10–12 h gave a mixture of thiolanes **9** and **10** (90%, ratio **9**:**10**=1.5:1) that could not be separated by column chromatography. When the above mixture was treated with TFA/H_2O, followed by conventional acetylation, the tri-*O*-acetyl lactone **11** and the tetraacetate **12** were obtained in 77 (from **9**) and 34% (from **10**) yield, respectively. Reduction of **11** and **12** with $LiAlH_4$ followed by conventional acetylation gave the pentaacetate of 3,6-anhydro-6-thio-D-*glycero*-L-*altro*-octitol **13** and its 3,6-anhydro-6-thio-D-*glycero*-L-*allo* epimer **15** isolated in 43 and 50% overall yield, respectively, from **11** and **12**. Deacetylation of **13** and **15** with MeONa/MeOH gave the corresponding polyhydroxy derivatives (**14** and **16**) in 97 and 88% yield, respectively.



Scheme 2. Reactions and conditions: (i) NaHS/EtOH; (ii) TFA–H_2O–EtOH; (iii) $LiAlH_4$, THF; (iv) Ac_2O/Py; (v) NaOMe/MeOH

The structures of these compounds were based on analytical and spectroscopic data (see Experimental). In the case of compounds **4** and **11**, a conformational analysis was performed using a Monte Carlo approach (MC)[25]. The initial structure was minimized previously using the Amber* force field. The lactone ring is rigid in both compounds. The theoretical coupling constants for the bicyclic system (Table 1) are in good agreement with the experimental ones, showing planar conformation for the lactone ring and a conformation near to $^4T_5$ for the thiolane ring. By rotation of the C5–O bond of **4**, 200 different conformers were considered, the energy global minimum being of −75.7 kJ mol^{-1}, which corresponds to the conformation depicted in Fig. 1, with a hydrogen bond between the O–H and the endocyclic oxygen atom. The distance of this bond is 2.27 Å. The torsion angles around O5–C5 between H–O5–C5–C4 and H–O5–C5–C6 were 57.7 and 176.3°, respectively. In the case of compound **11** the rotations around the C–OAc bonds showed a complex conformational equilibrium, the global minimum being of −89.9 kJ mol^{-1}. At least 95 conformations were found in a range of 3 kJ mol^{-1} over the global minimum.

Table 1
Calculated and experimental coupling constant (Hz) for the bicyclic system of **4** and **11**

Comp	$J_{2,3}$		$J_{2',3}$		$J_{3,4}$		$J_{4,5}$		$J_{5,6}$		$J_{5,6'}$	
	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.
4	1.1	1.2	8.0	7.3	5.7	5.2	3.1	3.4	6.0	7.3	10.6	8.6
11	1.1	0.9	7.8	7.2	6.7	5.1	3.6	3.6	-	-	11.1	10.1

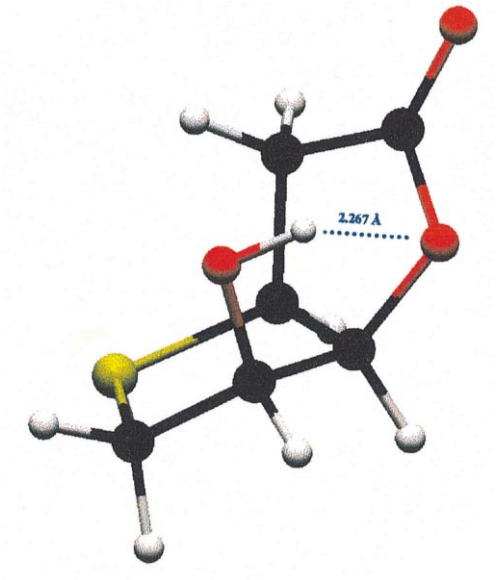


Figure 1. Main conformation of compound **4**

2.1. Glycosidase inhibition studies

The thiosugars **4**, **5**, **7**, **14** and **16** were evaluated as inhibitors towards 23 commercially available glycosidases: α-L-fucosidase (from bovine epididymis), α-galactosidases (from coffee beans, *Asper-*

gillus niger and *Escherichia coli*), β-galactosidases (from *Escherichia coli*, bovine liver, *Aspergillus niger*, *Aspergillus orizae* and jack beans), α-glucosidases (maltase) (from yeast and rice), α-glucosidase (isomaltase) (from baker's yeast), amyloglucosidases (from *Aspergillus niger* and *Rhizopus* mold), β-glucosidases (from almonds and *Caldocellum saccharolyticum*), α-mannosidases (jack beans, almonds), β-mannosidase (from *Helix pomatia*), α-*N*-acetylgalactosaminidase (from chicken liver), β-*N*-acetylglucosaminidases (from jack beans and bovine epididymis A and bovine epididymis B). None of the compounds showed activity at 1 mM concentration towards the selected enzymes, except for compound **14** that led to 50% of inhibition towards α-glucosidase (maltase) from yeast.[26]

3. Conclusion

The conjugate addition of sodium hydrogen sulfide on suitably protected *O*-mesyl derivatives of unsaturated aldonic esters and tandem cyclization (S_N2 displacement) is a new and good method for the synthesis of polyhydroxylated chiral thiolanes, which are glycomimetics of potential biological interest.

4. Experimental

4.1. General methods

Melting points are uncorrected. Optical rotations were measured at 22±1°C for solutions in dichloromethane or methanol. ^{1}H NMR spectra (300 and 500 MHz) were obtained for solutions in $CDCl_3$; *J* values are given in hertz. EIMS spectra (70 eV) were measured with a Kratos MS-80RFA instrument, with an ionizing current or 100 mA, an accelerating voltage of 4 kV, and a resolution of 1000 (10% valley definition). The FABMS spectra were measured with the same instrument. Ions were produced by a beam of xenon atoms (6–7 KeV) using a matrix consisting of glycerol or thioglycerol and NaI as salt; $(CsI)_{37}Cs$ was used as reference. TLC was performed on silica gel F_{254} (Merck), with detection by UV light or charring with H_2SO_4. Silica Gel 60 (Merck, 230 mesh) was used for preparative chromatography. The calculations for conformational analysis were performed on a Silicon graphics work station with the Amber* force field as integrated in MacroModel[25] V 5.5. Only one MC search was done with randomly selected torsions. The initial structure of the MC was previously minimized in water using Amber* and then submitted to 1000 steps. An energy window of 50 kJ mol^{-1} was used as energy criterion to accept a given conformation.

4.2. Reaction of (Z)- and (E)-2,3-dideoxy-4,5-O-isopropylidene-6-O-methylsulfonyl-L-erythro-hex-2-enonates **1a** and **1b** with NaHS

To a solution of the sulfonate **1a** (300 mg, 0.97 mmol) in dry ethanol (30 mL) NaHS (720 mg, 9.71 mmol) was added and stirred for 4 h at room temperature. The solvent was evaporated under reduced pressure and the residue was taken up with sat. aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water, dried and evaporated. The crude product was chromatographed on silica gel (ether:petroleum ether, 1:2 → 2:1) yielding a mixture of ethyl 3,6-anhydro-2-deoxy-6-thio-4,5-*O*-isopropylidene-L-*arabino*-hexonate **2** and its L-*ribo* epimer **3** as a pale yellow oil (198 mg, 83%, ratio 3:1).

To a solution of the sulfonate **1b** (50 mg, 0.16 mmol) in dry ethanol (5 mL) NaHS (120 mg, 1.67 mmol) was added and stirred for 4 h at room temperature. Work-up procedure as described above afforded a mixture of thiolanes **2** and **3** as a pale yellow oil (32 mg, 80%, ratio 2.3:1).

Ethyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-6-thio-L-*arabino*-hexonate **2**: ν(C=O) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 4.87 (dt, 1H, $J_{4,5}$=3.4 Hz, 1/2($J_{5,6a}$+$J_{5,6b}$=1.7 Hz, H-5), 4.76 (dd, 1H, $J_{3,4}$=2.7 Hz, H-4), 4.17 (q, 2H, $J_{H,H}$=7.1 Hz, CH_2CH$_3$), 3.50 (ddd, 1H, $J_{2a,3}$=4.5 Hz, $J_{2b,3}$=3.9 Hz, H-3), 2.88 (d, 2H, H-6a, H-6b), 2.86 (dd, 1H, $J_{2a,2b}$=16.6 Hz, H-2a), 2.63 (dd, 1H, H-2b), 1.27 (t, 3H, CH$_2$CH_3), 1.53, 1.47 (s, 3H each, CMe_2), 1.27 (t, 3H, CH$_2$CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 171.5 (CO), 110.9 (*C*Me$_2$), 83.1, 82.7 (C-4, C-5), 60.5 (*C*H$_2$CH$_3$), 48.1 (C-3), 37.7, 37.7 (C-2, C-6), 25.6, 24.5 (C*Me*$_2$), 14.0 (CH$_2$*C*H$_3$).

*4.3. Reaction of a mixture of ethyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-6-thio-*L-arabino-*hexonate **2** and its* L-ribo *epimer **3** with trifluoroacetic acid*

To a mixture of **2** and **3** (ratio 2.3:1, **2**, 325 mg, 1.32 mmol; **3**, 139 mg, 0.565 mmol) in ethanol (55 mL), aqueous TFA (80%, 61 mL) was added. The reaction was allowed to stand for 24 h at room temperature until TLC (dichloromethane:methanol, 20:1) showed total consumption of the starting material. The solvents were evaporated in vacuo and the residue was treated with sat. aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water, dried and evaporated. Column chromatography of the crude product on silica gel (dichloromethane:methanol, 40:1 → 20:1) gave 3,6-anhydro-2-deoxy-6-thio-L-*arabino*-hexono-1,4-lactone **4** (93 mg, 44%, from **2**) as a white solid and ethyl 3,6-anhydro-2-deoxy-6-thio-L-*ribo*-hexonate **5** (39 mg, 33%, from **3**) as an oil.

Compound **4** crystallized from dichloromethane–methanol had mp 150–151°C; $[\alpha]_D$ −170, $[\alpha]_{546}$ −199 (*c* 1, methanol); IR: ν 3428 cm^{-1} (OH), 1750 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$), δ 4.96 (dd, 1H, $J_{3,4}$=5.2 Hz, $J_{4,5}$=3.4 Hz, H-4), 4.38 (ddd, 1H, $J_{5,6a}$=7.3 Hz, $J_{5,6b}$=8.6 Hz, H-5), 3.99 (ddd, 1H, $J_{2a,3}$=7.3 Hz, $J_{2b,3}$=1.2 Hz, H-3), 3.09 (dd, 1H, $J_{2a,2b}$=18 Hz, H-2a), 2.93 (m, 2H, H-6a, H-6b), 2.58 (dd, 1H, H-2b); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 178.1 (CO), 87.3 (C-4), 77.5 (C-5), 42.4 (C-3), 40.4 (C-2), 34.7 (C-6). FABMS *m/z*: 161 $[M+1]^+$. Anal. calcd for $C_6H_8O_3S$; C, 45.00; H, 5.00. Found C, 44.70; H, 4.82.

Compound **5**: $[\alpha]_D$ +96 (*c* 0.8, methanol); ^1H NMR (300 MHz, $CDCl_3$), δ 4.41–4.37 (m, 1H, H-5), 4.16 (q, 2H, $J_{H,H}$=7.1 Hz, CH_2CH$_3$), 3.91 (dd, 1H, $J_{3,4}$=7.3 Hz, $J_{4,5}$=3.7 Hz, H-4), 3.58 (ddd, 1H, $J_{2a,3}$=7.6 Hz, $J_{2b,3}$=6.5 Hz, $J_{3,4}$=7.3 Hz, H-3), 3.09 (dd, 1H, $J_{5,6a}$=4.6 Hz, $J_{6a,6b}$=11.8 Hz, H-6a), 2.97 (m, 2H, OH), 2.85 (dd, 1H, $J_{5,6b}$=2.7 Hz, H-6b), 2.80 (dd, 1H, $J_{2a,2b}$=17.0 Hz, H-2a), 2.69 (dd, 1H, H-2b), 1.27 (t, 3H, CH$_2$CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 172.9 (CO), 80.8 (C-4), 74.8 (C-5), 61.2 (*C*H$_2$CH$_3$), 43.7 (C-3), 39.2 (C-2), 33.4 (C-6), 14.0 (CH$_2$*C*H$_3$). HRFABMS: found $(M+1)^+$ 207.0694. $C_8H_{15}O_4S$ requires 207.0691.

*4.4. Reacetonation of the crude product **4**+**5**. Preparation of 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-6-thio-*L-ribo-*hexonate **3***

In an alternative procedure, the crude product mixture described above was washed with dichloromethane affording **4** as white crystals (78 mg, 37%). The remaining mother liquor was then concentrated and 2,2-dimethoxypropane and a catalytic amount of *p*-toluensulfonic acid were added. The reaction was stirred at room temperature overnight. The mixture was neutralized with sat. aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water, dried and evaporated. Column chromatography of the crude product on silica gel (ether:petroleum ether, 1:2 → 2:1) afforded **3** (57 mg,

41%, overall **3**→ **5**→ **3**) as an oil. $[\alpha]_D$ +35.7, $[\alpha]_{546}$ +45.2 (*c* 0.4, dichloromethane); IR: ν 1736 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$), δ 4.93 (ddd, 1H, $J_{4,5}$=5.7 Hz, $J_{5,6a}$=4.9 Hz, $J_{5,6b}$=1.8 Hz, H-5), 4.58 (dd, 1H, $J_{3,4}$=1.9 Hz, H-4), 4.17 (q, 2H, C*H*$_2$CH$_3$), 3.65 (ddd, 1H, $J_{2a,3}$=6.9 Hz, $J_{2b,3}$=8.4 Hz, H-3), 3.08 (dd, 1H, $J_{6a,6b}$=13.0 Hz, H-6a), 2.93 (dd, 1H, H-6b), 1.27 (t, 3H, CH$_2$C*H*$_3$), 1.53, 1.31 (s, 3H each, C*Me*$_2$); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 170.7 (CO), 111.4 (*C*Me$_2$), 87.8 (C-4), 83.3 (C-5), 60.8 (*C*H$_2$CH$_3$), 49.7 (C-3), 38.4 (C-2), 36.8 (C-6), 26.5, 24.7 (C*Me*$_2$), 14.1 (CH$_2$*C*H$_3$). HRFABMS: found M^+ 246.0932. $C_{11}H_{18}O_4S$ requires 246.0926.

4.5. 1,4,5-Tri-O-*acetyl-3,6-anhydro-2-deoxy-6-thio*-L-arabino-*hexitol* ***6***

A solution of **4** (70 mg, 0.44 mmol) in dry THF (3 mL) was added to a suspension of $LiAlH_4$ (90 mg, 2.37 mmol) in dry THF (3 mL) at 0°C. After warming to room temperature, the mixture was stirred for 4 h. The sequential addition at 0°C of water (0.2 mL), 15% NaOH (0.2 mL) and water (0.6 mL) gave a granular solid. After drying the residue after evaporation, the crude product was conventionally acetylated with acetic anhydride (1.5 mL) and pyridine (1.5 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water–ice and extracted with dichloromethane. The organic layer was washed successively with HCl (1 M), sat. aqueous $NaHCO_3$ and water, dried and evaporated. Column chromatography of the residue on silica gel (ether:petroleum ether, 1:3→ 3:1) gave **7** (65 mg, 51% overall from **4**) as an oil. $[\alpha]_D$ −63, $[\alpha]_{546}$ −72 (*c* 1, dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$), δ 5.57 (dd, 1H, $J_{3,4}$=4.4 Hz, $J_{4,5}$=3.4 Hz, H-4), 5.30 (ddd, 1H, $J_{5,6a}$=7.0 Hz, $J_{5,6b}$=9.2 Hz, H-5), 4.12 (dt, 1H, $J_{1a,2a}$=$J_{1a,2b}$=5.7 Hz, $J_{1a,1b}$=11.3 Hz, H-1a), 4.03 (ddd, 1H, $J_{1b,2a}$=8.2 Hz, $J_{1b,2b}$=5.2 Hz, H-1b), 3.64 (ddd, 1H, $J_{2a,3}$=5.7 Hz, $J_{2b,3}$=8.7 Hz, H-3), 3.06 (dd, 1H, $J_{6a,6b}$=10.1 Hz, H-6a), 3.02 (dd, 1H, H-6b), 2.14, 2.04, 2.03 (s, 3H each, COC*H*$_3$), 2.10 (m, 1H, H-2a), 1.85 (ddt, 1H, $J_{2a,2b}$=14.2 Hz, H-2b); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 170.7, 169.9, 169.8 (3 CO), 74.8 (C-5), 73.9 (C-4), 62.5 (C-1), 42.8 (C-3), 30.3, 30.2 (C-6, C-2), 20.7, 20.6, 20.5 (CO*C*H$_3$). HRCIMS: found $(M+1)^+$ 291.0893. $C_{12}H_{19}O_6S$ requires 291.0902.

4.6. 3,6-Anhydro-2-deoxy-6-thio-L-arabino-*hexitol* ***7***

Compound **6** (35 mg, 0.12 mmol) was dissolved in dry methanol (5 mL) and a catalytic amount of NaOMe was added. After 2.5 h deacetylation was complete. The reaction mixture was neutralized with Amberlite (IR-120 H^+) and filtered. Evaporation of the solvents afforded **7** (13 mg, 66%). ^{13}C NMR (75.4 MHz, CD_3OD), δ 77.8, 76.0, 61.4, 45.7, 35.3, 33.1.

4.7. Ethyl 3,6-anhydro-2-deoxy-4,5:7,8-di-O-*isopropylidene-6-thio*-D-glycero-L-altro-*octonate* ***9*** *and its* D-glycero-L-*allo epimer* ***10***

To a solution of the mesylates **8** (*E*:*Z*=12:1) (941 mg, 2.31 mmol) in dry ethanol (60 mL), NaHS (1.694 g, 23.1 mmol) was added and the mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and the resulting dry residue was taken up with sat. aqueous $NaHCO_3$ and extracted with dichloromethane. The organic phase was washed with water, dried and concentrated. Column chromathography on silica (ether:petroleum ether, 1:3 → 1:1) afforded the thiolanes **9** and **10** (716 mg, 90%, **9**:**10**=1.5:1).

Compound **9**: ^{1}H NMR (500 MHz, $CDCl_3$), δ 4.86 (t, 1H, $J_{3,4}$=$J_{4,5}$=5.5 Hz, H-4), 4.77 (dd, 1H, $J_{5,6}$=1.5 Hz, H-5), 4.30 (ddd, 1H, $J_{6,7}$=3.9 Hz, $J_{7,8a}$=6.2 Hz, $J_{7,8b}$=7.7 Hz, H-7), 4.15 (q, 2H, C*H*$_2$CH$_3$), 4.04 (dd, 1H, $J_{8a,8b}$=8.1 Hz, H-8a), 4.00 (ddd, 1H, $J_{2a,3}$=7.8 Hz, $J_{2b,3}$=7.1 Hz, H-3), 3.79 (t, 1H, H-

8b), 3.29 (dd, 1H, H-6), 2.84 (ddd, 1H, $J_{2a,2b}$=16.7 Hz, H-2a), 2.57 (ddd, 1H, H-2b), 1.50, 1.47 (s, 3H each, C*M*e$_2$), 1.35, 1.31 (s, 3H each, C*M*e$_2$), 1.26 (t, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (125.7 MHz, CDCl$_3$), δ 171.4 (C-1), 111.3 (*C*Me$_2$), 109.7 (*C*Me$_2$ side chain), 87.5 (C-5), 83.9 (C-4), 77.7 (C-7), 68.0 (C-8), 60.5 (*C*H$_2$CH$_3$), 55.1 (C-6), 47.4 (C-3), 34.6 (C-2), 26.1, 26.0, 25.6, 24.6 (CO*C*H$_3$), 14.05 (CH$_2$*C*H$_3$).

Compound **10**: ^{1}H NMR (500 MHz, CDCl$_3$), δ 4.62 (dd, 1H, $J_{5,6}$=4.2 Hz, $J_{4,5}$=6.4 Hz, H-5), 4.49 (dd, 1H, $J_{4,3}$=4.4 Hz, H-4), 4.24 (ddd, 1H, $J_{6,7}$=5.4 Hz, $J_{7,8a}$=6.2 Hz, $J_{7,8b}$=7.0 Hz, H-7), 4.15 (q, 2H, C*H*$_2$CH$_3$), 4.05 (dd, 1H, $J_{8a,8b}$=8.1 Hz, H-8a), 3.73 (dd, 1H, H-8b), 3.72 (m, 1H, H-3), 3.52 (dd, 1H, H-6), 2.81 (dd, 1H, $J_{2a,3}$=6.1 Hz, $J_{2a,2b}$=16.0 Hz, H-2a), 2.65 (dd, 1H, $J_{2b,3}$=8.7 Hz, H-2b), 1.53, 1.45 (s, 3H each, C*M*e$_2$), 1.36, 1.31 (s, 3H each, C*M*e$_2$), 1.26 (t, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (125.7 MHz, CDCl$_3$), δ 170.8 (C-1), 112.7, 109.7 (*C*Me$_2$), 87.7 (C-4), 85.4 (C-5), 76.7 (C-7), 67.9 (C-8), 60.6 (*C*H$_2$CH$_3$), 54.7 (C-6), 47.7 (C-3), 39.2 (C-2), 27.6, 26.4, 25.5, 25.4 (CO*C*H$_3$), 14.05 (CH$_2$*C*H$_3$). HRFABMS: found (M+23)$^+$ 369.1348. $C_{16}H_{26}O_6SNa$ requires 369.1349.

*4.8. Reaction of a mixture of ethyl 3,6-anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-6-thio-*D-glycero-L-altro-*octonate **9** and its* D-glycero-L-allo *epimer **10** with trifluoroacetic acid*

To a mixture of **9** and **10** (ratio 1.5:1, **9**, 429 mg, 1.24 mmol; **10**, 287 mg, 0.83 mmol) in ethanol (100 mL), TFA (80%, 42 mL) was added. The reaction was left for 6 days at room temperature until TLC (dichloromethane:methanol, 10:1) showed total consumption of the starting material. The solvents were evaporated in vacuo and the residue conventionally acetylated with acetic anhydride (7 mL) and pyridine (7 mL). After 16 h, the reaction mixture was poured into water–ice and extracted with dichloromethane. After washing successively with HCl (1 M), sat. aqueous NaHCO$_3$ and water, the organic layer was dried and evaporated. Column chromatography on silica gel (ether:petroleum ether, 1:3 → 3:1) yielded 5,7,8-tri-*O*-acetyl-3,6-anhydro-2-deoxy-6-thio-D-*glycero*-L-*altro*-octono-1,4-lactone **11** (330 mg, 77%, from **9**) and ethyl 4,5,7,8-tetra-*O*-acetyl-3,6-anhydro-2-deoxy-6-thio-D-*glycero*-L-*allo*-octonate **12** (121 mg, 34%, from **10**).

Compound **11**: $[\alpha]_D$ −141, $[\alpha]_{546}$ −166 (*c* 0.7, dichloromethane); IR: ν 1792, 1752 cm^{-1} (C=O); ^{1}H NMR (500 MHz, CDCl$_3$), δ 5.33 (ddd, 1H, $J_{6,7}$=4.0 Hz, $J_{7,8a}$=4.2 Hz, $J_{7,8b}$=6.0 Hz, H-7), 5.16 (dd, 1H, $J_{3,4}$=5.1 Hz, $J_{4,5}$=3.6 Hz, H-4), 5.03 (dd, 1H, $J_{5,6}$=10.1 Hz, H-5), 4.25 (dd, 1H, $J_{8a,8b}$=12.0 Hz, H-8a), 4.06 (dd, 1H, H-8b), 4.02 (ddd, 1H, $J_{2a,3}$=7.2 Hz, $J_{2b,3}$=0.9 Hz, H-3), 3.93 (dd, 1H, H-6), 3.01 (dd, 1H, $J_{2a,2b}$=18.1 Hz, H-2a), 2.75 (dd, 1H, H-2b), 2.14, 2.11, 2.08 (s, 3H each, COC*H*$_3$); ^{13}C NMR (125.7 MHz, CDCl$_3$), δ 174.0 (C-1), 170.2, 170.0, 169.9 (CO), 81.6 (C-4), 75.8 (C-5), 68.2 (C-7), 63.9 (C-8), 48.1 (C-6), 40.3 (C-3), 38.8 (C-2), 20.6, 20.6, 20.4 (CO*C*H$_3$). HRFABMS: found (M+1)$^+$ 347.0798. $C_{14}H_{19}O_8S$ requires 347.0800. Anal. calcd for $C_{14}H_{18}O_8S$; C, 48.55; H, 5.20; S, 9.25. Found C, 48.70; H, 4.94; S, 9.01.

Compound **12**: $[\alpha]_D$ +26, $[\alpha]_{546}$ +32 (*c* 2, dichloromethane); IR: ν 1751 cm^{-1} (C=O); ^{1}H NMR (500 MHz, CDCl$_3$), δ 5.26 (ddd, 1H, $J_{6,7}$=5.0 Hz, $J_{7,8a}$=4.5 Hz, $J_{7,8b}$=6.2 Hz, H-7), 5.24 (dd, 1H, $J_{4,5}$=3.8 Hz, $J_{5,6}$=5.0 Hz, H-5), 5.16 (dd, 1H, $J_{3,4}$=6.0 Hz, H-4), 4.24 (dd, 1H, $J_{8a,8b}$=11.8 Hz, H-8a), 4.16 (q, 2H, $J_{H,H}$=7.2 Hz, C*H*$_2$CH$_3$), 4.10 (dd, 1H, H-8b), 3.74 (ddd, 1H, $J_{2a,3}$=4.8 Hz, $J_{2b,3}$=9.8 Hz, H-3), 3.69 (t, 1H, H-6), 2.83 (dd, 1H, $J_{2a,2b}$=16.1 Hz, H-2a), 2.56 (dd, 1H, H-2b), 2.12, 2.06, 2.06, 2.05 (s, 3H each, COC*H*$_3$), 1.26 (t, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (125.7 MHz, CDCl$_3$), δ 170.3, 170.2, 169.9, 169.7, 169.6 (CO), 76.3 (C-4), 73.7 (C-5), 69.5 (C-7), 63.4 (C-8), 60.9 (*C*H$_2$CH$_3$), 48.2 (C-6), 42.6 (C-3), 39.4 (C-2), 20.6, 20.5, 20.5, 20.5 (CO*C*H$_3$), 14.0 (CH$_2$*C*H$_3$). HRFABMS: found (M+1)$^+$ 435.1314. $C_{18}H_{27}O_{10}S$ requires 435.1325.

4.9. 1,4,5,7,8-Penta-O-acetyl-3,6-anhydro-2-deoxy-6-thio-D-glycero-L-altro-octitol **13**

A solution of **11** (50 mg, 0.14 mmol) in dry THF (2.5 mL) was added to a suspension of $LiAlH_4$ (100 mg, 2.63 mmol) in dry THF (3 mL) at 0°C. After warming to room temperature, the mixture was stirred for 3 h. The sequential addition at 0°C of water (0.2 mL), 15% NaOH (0.2 mL) and water (0.6 mL) gave a granular solid. After drying the residue after evaporation, the crude product was conventionally acetylated with acetic anhydride (4 mL) and pyridine (4 mL), and the mixture was stirred at room temperature overnight. Conventional work-up procedure as described above followed by column chromatography of the residue on silica gel (ether:petroleum ether, 1:2 → 3:1) gave **13** (26 mg, 43%). $[\alpha]_D$ −86, $[\alpha]_{546}$ −100 (*c* 2.5, dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$), δ 5.61 (dd, 1H, $J_{3,4}$=3.9 Hz, $J_{4,5}$=3.3 Hz, H-4), 5.28 (ddd, 1H, $J_{6,7}$=4.3 Hz, $J_{7,8a}$=3.9Hz, $J_{7,8b}$=6.4 Hz, H-7), 5.04 (dd, 1H, $J_{5,6}$=9.8 Hz, H-5), 4.25 (dd, 1H, $J_{8a,8b}$=11.9 Hz, H-8a), 4.09 (dt, 1H, $J_{1a,2a}$=$J_{1a,2b}$=5.6 Hz, $J_{1a,1b}$=11.4 Hz, H-1a), 4.04 (dd, 1H, H-8b), 4.00 (ddd, 1H, $J_{1b,2a}$=5.0 Hz, $J_{1b,2b}$=8.2 Hz, H-1b), 3.84 (dd, 1H, $J_{5,6}$=9.8 Hz, H-6), 3.69 (ddd, 1H, $J_{2a,3}$=10.4 Hz, $J_{2b,3}$=6.1 Hz, H-3), 2.15, 2.11, 2.06, 2.03, 2.01 (s, 3H each, COC*H*$_3$), 1.86 (ddd, 1H, $J_{2a,2b}$=14.4 Hz, H-2a), 1.79 (ddd, 1H, H-2b); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 170.7, 170.3, 170.0, 169.9, 169.8 (CO), 74.7 (C-5), 73.6 (C-4), 68.8 (C-7), 64.1 (C-8), 62.2 (C-1), 47.0 (C-6), 42.4 (C-3), 29.9 (C-2), 20.7, 20.6, 20.5, 20.5, 20.3 (CO*C*H$_3$). HRFABMS: found $(M+1)^+$ 435.1311. $C_{18}H_{27}O_{10}S$ requires 435.1325.

4.10. 3,6-Anhydro-2-deoxy-6-thio-D-glycero-L-altro-octitol **14**

Compound **13** (26 mg, 0.06 mmol) was dissolved in MeOH (5 mL) and catalytic amounts of NaOMe were added. After 2 h at room temperature the mixture was neutralized with Amberlite IR-120 H^+, filtered and the resin was washed with methanol. The combined liquids were evaporated to yield **14** (13 mg, 97%). ^{13}C NMR (125.7 MHz, CD_3OD), δ 78.2, 77.1, 72.4, 67.2, 61.3, 53.2, 45.1, 35.0.

4.11. 1,4,5,7,8-Penta-O-acetyl-3,6-anhydro-2-deoxy-6-thio-D-glycero-L-allo-octitol **15**

A solution of **12** (70 mg, 0.16 mmol) in dry THF (4 mL) was added to a suspension of $LiAlH_4$ (180 mg, 4.73 mmol) in dry THF (3 mL) at 0°C. After warming to room temperature, the mixture was stirred for 3 h. Work-up procedure as described above was followed by conventional acetylation with acetic anhydride (6 mL) and pyridine (6 mL). After 16 h the mixture was elaborated in the conventional way described previously. Column chromatography of the residue on silica gel (ether:petroleum ether, 1:3 → 2:1) gave **15** (35 mg, 50%). $[\alpha]_D$ +5, $[\alpha]_{546}$ +6 (*c* 1.7, dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$), δ 5.29 (ddd, 1H, $J_{6,7}$=5.0 Hz, $J_{7,8a}$=4.5 Hz, $J_{7,8b}$=6.3 Hz, H-7), 5.25 (dd, 1H, $J_{4,5}$=3.8 Hz, $J_{5,6}$=5.0 Hz, H-5), 5.19 (dd, 1H, $J_{3,4}$=6.0 Hz, H-4), 4.27 (dd, 1H, $J_{8a,8b}$=11.8 Hz, H-8a), 4.17 (m, 2H, H-1a, H-1b), 4.11 (dd, 1H, H-8b), 3.68 (t, 1H, H-6), 3.47 (ddd, 1H, $J_{2a,3}$=4.7 Hz, $J_{2b,3}$=9.5 Hz, H-3), 2.16 (m, 1H, H-2a), 1.86 (m, 1H, H-2b), 2.14, 2.08, 2.08, 2.07, 2.06 (s, 3H each, COC*H*$_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 170.8, 170.3, 169.9, 169.8, 169.7 (CO), 76.9 (C-4), 73.8 (C-5), 69.4 (C-7), 63.4 (C-8), 62.1 (C-1), 48.15 (C-6), 44.3 (C-3), 33.4 (C-2), 20.8, 20.6, 20.6, 20.6, 20.6 (CO*C*H$_3$). HRFABMS: found $(M+1)^+$ 435.1311. $C_{18}H_{27}O_{10}S$ requires 435.1325.

4.12. 3,6-Anhydro-2-deoxy-6-thio-D-glycero-L-allo-octitol **16**

Compound **15** (35 mg, 0.08 mmol) was dissolved in MeOH (5 mL) and catalytic amounts of NaOMe were added. After 2 h at room temperature the mixture was neutralized with Amberlite IR-120 H^+,

filtered and the resin was washed with methanol. The combined liquids were evaporated to yield **16** (16 mg, 88%). ^{13}C NMR (75.4 MHz, CD_3OD), δ 80.7, 77.6, 73.0, 66.4, 61.7, 53.9, 47.3, 39.2.

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