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Note

Synthesis of O-protected thiohydroximate-linked pseudodisaccharides

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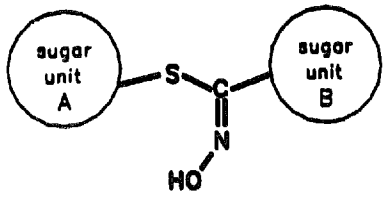
Many biologically important molecules involve two sugar units connected through one atom (e.g., the acetal function in disaccharides) or several atoms (e.g., the phosphoric ester in dinucleotides). Replacing these naturally-occurring bridges by other sequences results in structural analogues, or isosteres of natural compounds, which may behave as enzyme inhibitors [1]. S-, N-, and C-Disaccharides are already known [2–5] whereas pseudodinucleotides [6] and pseudodisaccharides displaying various functional bridges such as disulfide [7], hydrazine [8], carbonate [9] and xanthate [10], carbamate [11] and thiocarbamate [12], thiourea [13], etc., have also been synthesized.

Surprisingly, almost no examples of a carboxylate ester function bridging two sugar units have been reported, with the exception of Ogawa's serendipitous oxidative transformation [14] or the sporadically observed Tischenko-type side reactions [15].

In connection with our recent studies on the synthesis of artificial glucosinolates [16], a new class of pseudodisaccharides has been synthesized, in which the two sugar units are linked by a (Z)-thiohydroximate function (Scheme 1).



Scheme 1.

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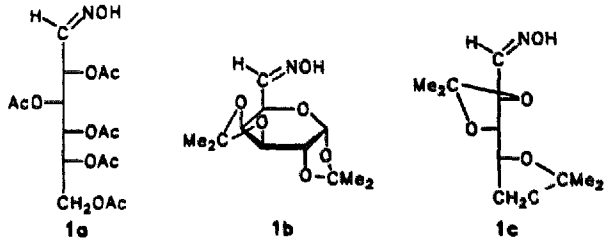
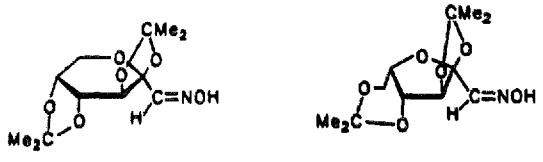
Protected thiohydroximate-linked pseudodisaccharides of this type were obtained through 1,3-nucleophilic addition of a 1-thioglycose to selected sugar-derived nitrile oxides.

Oxime precursors **1a–1d** were obtained in good yields using a standard method reported in the literature [17–20]. In the same manner, the previously unknown oxime **1e** was prepared in 60% yield from the corresponding aldehydo sugar [21].



1a 1b 1c

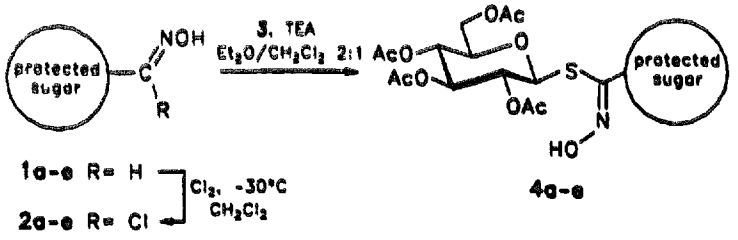


1d 1e

As shown by ^1H NMR analysis, compounds **1a–c** were obtained as $Z+E$ diastereoisomeric mixtures, while neopentylic-type oximes **1d** and **1e** appeared as single isomers.

The reaction of chlorine gas with compounds **1** in dichloromethane solution at low temperature ($-30°C$) produced the corresponding hydroximoyl chlorides **2** which were used directly in the next step.

Nucleophilic addition of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**3**) [22] to the nitrile oxides, generated in situ from the related hydroximoyl chlorides **2**, gave the protected thiohydroximate-linked pseudodisaccharides **4** in 60–91% yields (Scheme 2).



Scheme 2.

1. Experimental

General methods.—Melting points were determined on a Kofler hot stage. Optical rotations were measured at 22°C with a Jobin–Yvon Digital type 71 polarimeter. Unless stated otherwise, NMR spectra were recorded at 300 K for solutions in $CDCl_3$ on a Bruker AM 300 spectrometer (300.13 MHz for ^1H). Chemical shifts are expressed in ppm downfield from Me_4Si and coupling constants are expressed in Hz. Mass spectra were obtained on a Nermag R-10-10C spectrometer by the chemical ionization technique (CIMS) using NH_3 as the ionizing gas. TLC was run on aluminium plates precoated with silica gel $60F_{254}$ (E.

Merck, Darmstadt, Germany); detection was effected by observation with UV light (254 nm), then dipping the chromatograms into a solution of ceric ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$] in 20% H_2SO_4 and charring them with a heat gun. Preparative chromatography was performed by elution from columns of Silica Gel 60 (particle size 0.063–0.200 mm, E. Merck).

*1-Deoxy-1-(*N*-hydroxyimino)-2,3,4,5,6-penta-*O*-acetyl-*D*-glucopyranose* (**1a**).—Prepared according to the literature [17]. Yield 70%; *E*/*Z* 7:3; mp 96°C (MeOH–water), $[\alpha]_D$ +57° (*c* 1.0, $CHCl_3$); lit. [17] mp 97–98°C, $[\alpha]_D$ +57° (*c* 1.0, $CHCl_3$). ^1H NMR: δ 2.05, 2.06, 2.07, 2.09, 2.10, 2.13, 2.14 (7 s, 15 H, OAc), 4.07 (dd, 0.7 H, $J_{5E,6bE}$ 5.4, H-6b*E*), 4.11 (dd, 0.3 H, $J_{5Z,6bZ}$ 6.3, H-6b*Z*), 4.25 (dd, 0.7 H, $J_{5E,6aE}$ 3.6, $J_{6bE,6aE}$ 12.5, H-6a*E*), 4.29 (dd, 0.3 H, $J_{5Z,6aZ}$ 3.2, $J_{6bZ,6aZ}$ 12.5, H-6a*Z*), 5.09 (m, 0.3 H, H-5*Z*), 5.11 (m, 0.7 H, H-5*E*), 5.40 (dd, 0.7 H, $J_{4E,5E}$ 7.8, H-4*E*), 5.41 (ft, 0.3 H, $J_{4Z,5Z}$ 7.8, H-4*Z*), 4.97–5.54 (m, 1.4 H, H-2*E*, H-3*E*), 5.62 (ft, 0.3 H, $J_{3Z,4Z}$ 5.5, H-3*Z*), 6.12 (ft, 0.3 H, $J_{2Z,3Z}$ 5.5, H-2*Z*), 6.60 (d, 0.3 H, $J_{1Z,2Z}$ 5.5, H-1*Z*), 7.36 (br d, 0.7 H, $J_{1E,2E}$ 5.5, H-1*E*).

*6-Deoxy-6-(*N*-hydroxyimino-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**1b**). —Prepared according to the literature [18]. Yield 75%; *E*/*Z* 65:35; mp 110°C (hexane), $[\alpha]_D$ −132° (*c* 1.0, $CHCl_3$); lit. [18] mp 114–115°C, $[\alpha]_D$ −132° (*c* 2,3, $CHCl_3$). ^1H NMR: δ 1.34, 1.47, 1.54, 1.56 [4 s, 12 H, $(CH_3)_2C$], 4.31 (dd, 0.65 H, $J_{4E,5E}$ 2.1, H-4*E*), 4.33–4.38 (m, 1 H, H-2*E*, H-2*Z*), 4.44 (dd, 0.65 H, H-5*E*), 4.62–4.66 (m, 1.35 H, H-3*E*, H-3*Z*, H-4*Z*), 5.02 (d, 0.35 H, H-5*Z*), 5.56 (d, 1 H, $J_{1,2}$ 4.4, H-1*E*, H-1*Z*), 6.80 (d, 0.35 H, $J_{5Z,6Z}$ 3.2, H-6*Z*), 7.46 (d, 0.65 H, $J_{5E,6E}$ 6.3, H-6E).

*1-Deoxy-1-(*N*-hydroxyimino)-2,3:4,5-di-*O*-isopropylidene-*D*-xylose* (**1c**).—Prepared according to the literature [19]. Yield 80%; *E*/*Z* 4:1, mp 84–86°C (hexane), $[\alpha]_D$ +2° (*c* 1.0, $CHCl_3$); lit. [19] mp 88–89°C, $[\alpha]_D$ +2° (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.39, 1.44, 1.45, 1.47 [4 s, 12 H, $(CH_3)_2C$], 3.79 (ft, 0.8 H, $J_{4E,5bE}$ 7.1, $J_{5aE,5bE}$ 7.9, H-5b*E*), 3.82 (ft, 0.2 H, $J_{4Z,5bZ}$ 6.8, H-5b*Z*), 3.93 (dd, 0.2 H, $J_{4Z,5aZ}$ 5.1, $J_{5aZ,5bZ}$ 7.1, H-5a*Z*), 4.00–4.07 (m, 1.6 H, H-3*E*, H-5a*E*), 4.09 (dd, 0.2 H, $J_{3Z,4Z}$ 7.1, H-3*Z*), 4.20 (ddd, 0.8 H, $J_{4E,5aE}$ 6.7, H-4*E*), 4.33 (ddd, 0.2 H, H-4*Z*), 4.43 (ft, 0.8 H, $J_{2E,3E}$ 7.9, H-2*E*), 5.13 (ft, 0.2 H, $J_{2Z,3Z}$ 7.6, H-2*Z*), 6.88 (br s, 0.2 H, H-1*Z*), 7.44 (d, 0.8 H, $J_{1E,2E}$ 7.3, H-1*E*).

*1-Deoxy-1-(*N*-hydroxyimino)-2,3:4,5-di-*O*-isopropylidene-β-*D*-fructopyranose* (**1d**). —Prepared according to the literature [20]. Yield 90%; mp 136°C (hexane–EtOAc), $[\alpha]_D$ −38° (*c* 1.0, $CHCl_3$); lit. [20] mp 138.5–139.5°C, $[\alpha]_D$ −38° (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.35, 1.38, 1.46, 1.55 [4 s, 12 H, $(CH_3)_2C$], 3.78 (d, 1 H, H-6b), 3.93 (dd, 1 H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 13.0, H-6a), 4,26 (dd, 1 H, H-5), 4.62 (dd, 1 H, $J_{4,5}$ 8.0, H-4), 4.67 (d, 1 H, $J_{3,4}$ 2.6, H-3), 7.53 (s, 1 H, H-1), 7.60 (br s, 1 H, NOH).

*1-Deoxy-1-(*N*-hydroxyimino)-2,3:4,5-di-*O*-isopropylidene-α-*L*-sorbofuranose* (**1e**).—Prepared from the corresponding aldehyde [21] similarly to compound **1d**. Yield 60%; mp 119°C (hexane–EtOAc); $[\alpha]_D$ −3° (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.37, 1.43, 1.52 [3 s, 12 H, $(CH_3)_2C$], 4.06–4.08 (m, 2 H, H-6a, H-6b), 4.12–4.15 (m, 1 H, H-5), 4.33 (d, 1 H, $J_{4,5}$ 2.2, H-4), 4.69 (s, 1 H, H-3), 7.65 (s, 1 H, H-1). CIMS: *m*/*z* 274 $(M+H)^+$. Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.65; H, 6.97; N, 5.05.

General procedure for the preparation of thiohydroximate-linked pseudodisaccharides (**4a–e**).—Following the procedure described by Tronchet et al. [23], the oxime **1** (1.4 mmol) was converted into the corresponding hydroximoyl chloride **2**, which was used without further purification. To a 2:1 ether–CH_2Cl_2 solution of raw **2** under Ar was succes-

sively added 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**3**) [22] (1 mmol) dissolved in dry CH_2Cl_2 (2 mL) and freshly distilled Et_3N (3 mmol). After stirring for 1 h, the mixture was acidified with 1 N H_2SO_4, extracted with CH_2Cl_2, and the organic layer dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by column chromatography using 1:1 EtOAc–petroleum ether as eluent to afford protected pseudodisaccharides **4**.

S-*(2,3,4,6-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-2,3,4,5,6-penta*-O-*acetyl*-D-*gluconothiohydroximate* (**4a**).—Yield 0.55 g (72%); amorphous; $[\alpha]_D$ −12° (*c* 1.0, $CHCl_3$). ^1H NMR: δ 2.00, 2.03, 2.05, 2.06, 2.08, 2.11, 2.13 (7 s, 27 H, CH_3CO), 3.88 (m, 1 H, H-5), 4.03 (dd, 1 H, $J_{5',6'b}$ 6.0, H-6'b), 4.20 (dd, 1 H, $J_{5',6'a}$ 3.0, $J_{6'a,6'b}$ 12.7, H-6'a), 4.23 (dd, 1 H, $J_{5,6b}$ 2.0, H-6b), 4.34 (dd, 1 H, $J_{5,6a}$ 4.5, $J_{6a,6b}$ 12.5, H-6a), 5.00 (ft, 1 H, $J_{2,3}$ 9.6, H-2), 5.11 (ft, 1 H, $J_{4,5}$ 9.6, H-4), 5.15 (m, 1 H, H-5'), 5.25 (ft, 1 H, $J_{3,4}$ 9.5, H-3), 5.30 (d, 1 H, $J_{1,2}$ 9.8, H-1), 5.45 (dd, 1 H, $J_{4',5'}$ 8.7, H-4'), 5.74 (dd, 1 H, $J_{3',4'}$ 3.1, H-3'), 5.89 (d, 1 H, $J_{2',3'}$ 8.3, H-2'), 8.80 (s, 1 H, NOH). CIMS: *m/z* 768 $(M+H)^+$. Anal. Calcd for $C_{30}H_{41}NO_{20}S$: C, 46.93; H, 5.38; N, 1.82; S, 4.18. Found: C, 46.81; H, 5.37; N, 1.86; S, 4.06.

S-*(2,3,4,6-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-1,2:3,4-di*-O-*isopropylidene-α*-D-*galactopyranuronothiohydroximate* (**4b**).—Yield 0.58 g (91%); mp 177–179°C (EtOAc); $[\alpha]_D$ −74° (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.35, 1.39, 1.45, 1.65 [4 s, 12 H, $(CH_3)_2C$], 2.00, 2.01, 2.03, 2.07 (4 s, 12 H, CH_3CO), 3.91 (m, 1 H, H-5), 4.10 (dd, 1 H, $J_{5,6b}$ 2.6, H-6b), 4.26 (dd, 1 H, $J_{5,6a}$ 5.1, $J_{6a,6b}$ 12.2, H-6a), 4.36 (dd, 1 H, $J_{2',3'}$ 2.0, H-2'), 4.61 (d, 1 H, H-4'), 4.62 (s, 1 H, H-5'), 4.67 (dd, 1 H, $J_{3',4'}$ 7.5, H-3'), 5.02 (ft, 1 H, $J_{2,3}$ 9.4, H-2), 5.08 (ft, 1 H, $J_{4,5}$ 9.4, H-4), 5.21 (ft, 1 H, $J_{3,4}$ 9.4, H-3), 5.65 (d, 1 H, $J_{1',2'}$ 5.1, H-1'), 5.68 (d, 1 H, $J_{1,2}$ 9.4, H-1), 9.26 (br s, 1 H, NOH). CIMS: *m/z* 636 $(M+H)^+$. Anal. Calcd for $C_{26}H_{37}NO_{15}S$: C, 49.13; H, 5.87; N, 2.20; S, 5.04. Found: C, 49.15; H, 5.93; N, 2.09; S, 4.95.

S-*(2,3,4,6-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-2,3:4,5-di*-O-*isopropylidene*-D-*xylonothiohydroximate* (**4c**).—Yield 0.51 g (84%); amorphous; $[\alpha]_D$ −60° (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.36, 1.42, 1.47, 1.49 [4 s, 12 H, $(CH_3)_2C$], 2.02, 2.03, 2.07, 2.10 (4 s, 12 H, CH_3CO), 3.72 (m, 1 H, H-5), 3.86 (ft, 1 H, $J_{4',5'b}$ 7.8, H-5'), 4.01 (ft, 1 H, $J_{5'a,5'b}$ 7.8, H-5'), 4.17 (m, 1 H, $J_{4',5'a}$ 7.8, H-4'), 4.17 (dd, 1 H, $J_{5,6b}$ 2.5, H-6b), 4.23 (dd, 1 H, $J_{5,6a}$ 4.3, $J_{6a,6b}$ 12.4, H-6a), 4.60 (dd, 1 H, $J_{3',4'}$ 4.7, H-3'), 4.78 (dd, 1 H, $J_{2',3'}$ 7.9, H-2'), 5.06 (ft, 1 H, $J_{2,3}$ 9.4, H-2), 5.13 (ft, 1 H, $J_{4,5}$ 9.7, H-4), 5.28 (ft, 1 H, $J_{3,4}$ 9.4, H-3), 5.67 (d, 1 H, $J_{1,2}$ 10.4, H-1), 9.29 (br s, 1 H, NOH). CIMS: *m/z* 608 $(M+H)^+$. Anal. Calcd for $C_{25}H_{37}NO_{14}S$: C, 49.41; H, 6.14; N, 2.31; S, 5.28. Found: C, 49,44; H, 6.14; N, 2.24; S, 5.20.

S-*(2,3,4,6-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-2,3:4,5-di*-O-*isopropylidene-β*-D-arabino-*hex-2-ulopyranosothiohydroximate* (**4d**).—Yield 0.42 g (66%); amorphous; $[\alpha]_D$ −16° (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.33, 1.36, 1.40, 1.55 [4 s, 12 H, $(CH_3)_2C$], 2.00, 2.02, 2.04, 2.08 (4 s, 12 H, CH_3CO), 3.66 (m, 1 H, H-5), 3.76 (d, 1 H, H-6'b), 3.94 (dd, 1 H, $J_{6'a,6'b}$ 13.0, H-6'a), 4.11 (dd, 1 H, $J_{5,6b}$ 2.8, H-6b), 4.20 (dd, 1 H, $J_{5,6a}$ 5.0, $J_{6a,6b}$ 12.2, H-6a), 4.26 (d, 1 H, $J_{5',6'a}$ 2.1, H-5'), 4.62 (dd, 1 H, $J_{4',5'a}$ 7.9, H-4'), 5.04 (ft, 1 H, $J_{2,3}$ 9.9, H-2), 5.07 (ft, 1 H, $J_{3',4'}$ 2.4, H-3'), 5.08 (ft, 1 H, $J_{4,5}$ 9.9, H-4), 5.25 (ft, 1 H, $J_{3,4}$ 9.3, H-3), 5.64 (d, 1 H, $J_{1,2}$ 10.3, H-1). CIMS: *m/z* 636 $(M+H)^+$. Anal. Calcd for $C_{26}H_{37}NO_{15}S$: C, 49.13; H, 5.87; N, 2.20; S, 5.04. Found: C, 49.09; H, 5.90; N, 2.13; S, 4.88.

S-*(2,3,4,6-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-2,3:4,6-di*-O-*isopropylidene-α*-L-xylo-*hex-2-ulofuranosothiohydroximate* (**4e**).—Yield 0.38 g(60%); amorphous; $[\alpha]_D$ −16° (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.30, 1.38, 1.43, 1.51 [4 s, 12 H, $(CH_3)_2C$], 2.00, 2.06, 2.08 (3 s, 12 H, CH_3CO), 3.68 (m, 1 H, H-5), 4.01–4.14 (m, 3 H, H-6′a, H-6′b, H-6b), 4.18 (m, 1 H, H-5′), 4.26 (dd, 1 H, $J_{5,6a}$ 4.5, $J_{6a,6b}$ 12.2, H-6a), 4.30 (d, 1 H, $J_{4',5'a}$ 2.8, H-4′), 5.06 (ft, 1 H, $J_{2,3}$ 9.8, H-2), 5.11 (s, 1 H, H-3′), 5.11 (ft, 1 H, $J_{4,5}$ 9.8, H-4), 5.27 (ft, 1 H, $J_{3,4}$ 9.3, H-3), 5.64 (d, 1 H, $J_{1,2}$ 10.3, H-1). CIMS: *m/z* 636 $(M+H)^+$. Anal. Calcd for $C_{26}H_{37}NO_{15}S$: C, 49.13; H, 5.87; N, 2.20; S, 5.04. Found: C, 49.05; H, 5.83; N, 2.09; S, 4.95.

Acknowledgements

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