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Synthesis of new 2-*C*-(2,3:5,6-di-*O*-isopropylidene)-β-D-mannofuranosyldithioacetate derivatives

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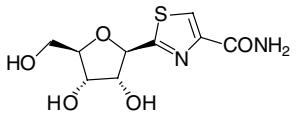
Abstract—Various new *C*-glycosides have been synthesized through the thioacylation reaction of different amines by a 2-*C*-mannofuranosyldithioacetate. Amino acids, di- and polyamines (putresceine, spermine, spermidine) and one amino alcohol were in particular used to generate glycothiopeptidic or precursors of 'bola' structures.

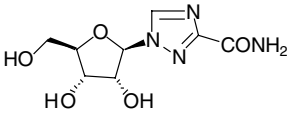
Keywords: Dithioesters; *C*-Glycosides; Thioacylation; Polyamines; Amino acids

1. Introduction

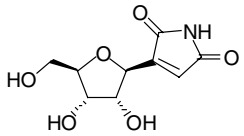
C-glycosides[1] are subject to growing interest owing to their potential biological activities often associated with their non-hydrolytic C–C junction. At the same time they provide versatile synthons for linking peptides, lipids, and nucleobases to prepare analogues of biomolecules or synthetic *C*-nucleosides such as tiazofurin, ribavirin, and showdomycin, displaying potent therapeutic effects. Therefore a large number of synthetic approaches to *C*-glycosides and *C*-nucleosides have been reported, and new methodologies for the linkage of a carbohydrate to a functionalized chain via C–C bond formation at the anomeric center are gaining increasing attention.



Tiazofurin (anticancer)



Ribavirin (antiviral)



Showdomycin (antitumor)

In our ongoing work concerning dithioesters as sulfur sources and versatile functionalities,[2] we examined the synthetic potential of the first *C*-glycoside with thioacylating properties. As we previously mentioned, dithioester **2** (Scheme 1) was easily obtained on a scale of a few grams and isolated as a single β anomer after purification, by sulfhydrolysis of the methylated iminium salt derived from **1**.[3] The intermediate thioamide **1** was synthesized by a Horner–Wadsworth–Emmons reaction, followed by an intramolecular Michael-type addition (Moffatt procedure).[4]

Since dithioesters react cleanly, and usually selectively, with a broad variety of amines[5] (including functionalized amino derivatives), we turned toward the thioacylation reaction for an efficient synthesis of new

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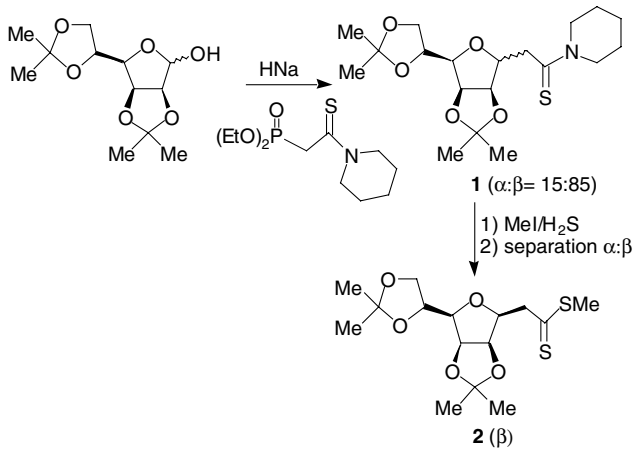
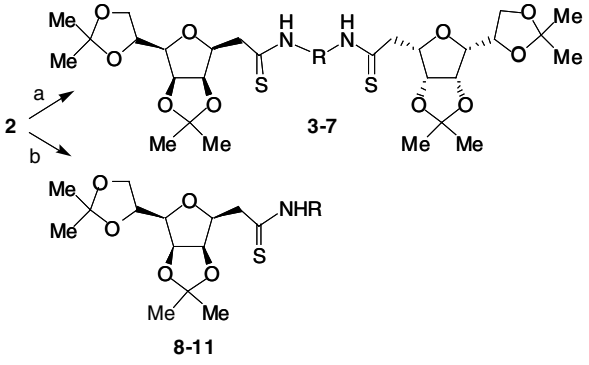


Scheme 1.



Scheme 2.

sugar-based structures by reacting dithioester **2** with mono- and diamines (Scheme 2).

2. Results and discussion

In a first approach, we planned the use of α,ω-diamines to prepare new *C*-glycosides. Indeed, such divalent mannofuranosyl derivatives are interesting as precursors of bolaamphiphiles,[6] as well as for their potential biological activities as recently emphasized for some other multivalent mono- or disaccharides.[7]

Moreover, these activities might be enhanced by the use of known biologically active polyamines such as spermine or spermidine.[8] Thus, using a slight excess of **2** and various polyamines, the bis[2-*C*-D-mannofuranosylethanethioamides] **3**–**7** were synthesized in fairly good yields (Table 1). It is worth noting that for spermine and spermidine (entry 3 and 4), selective α,ω-thioacylation was observed, and no reaction of the secondary amine

Table 1. Reaction of **2** with di-, poly- and functionalized amines

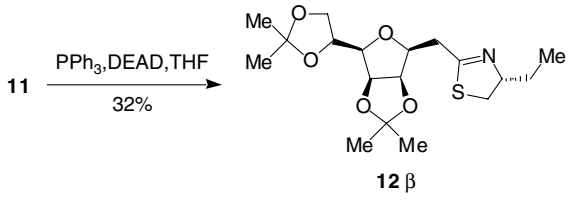
Entry	Amine	Product	Yield (%)
1	1,12-Dodecyldiamine	**3**	71
2	Putresceine	**4**	90
3	Spermidine	**5**	90
4	Spermine	**6**	46[a]
5	L-Ornitine	**7**	46[a]
6	L-Phenylalanine	**8**	80
7	L-Alanine	**9**	90
8	L-Methionine	**10**	86
9	(*R*)-2-Aminobutanol	**11**	84

[a] Non-optimized yields.

functions occurred. The bis derivative **7** (Table 1, entry 5) was obtained in moderate yield due to a more difficult purification step. However, this product was highly valuable as it represents the possibility to also graft diamines bearing an amino acid moiety on a *C*-glycoside.

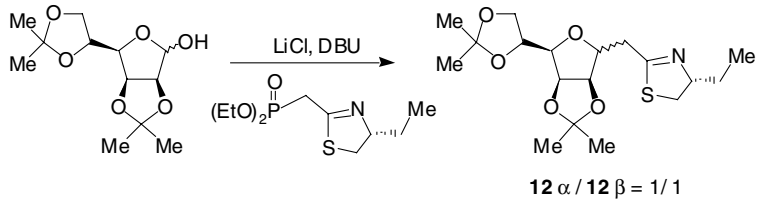
This satisfactory result incited us to prepare other amino acid derivatives. Such compounds bearing both an amino acid and a sugar moiety can be related to proteoglycans, glycoproteins, or glycopeptides that appear in all cells in some form or another and have been implicated in various biological processes.[9]

As summarized in Table 1 (entries 6–8), the method was exemplified using various amino acids, and good yields were obtained in all cases (compounds **8**–**10**). The thioamide **11**, obtained by thioacylation of the (*R*)-2-aminobutanol with **2** (entry 10), led by intramolecular cyclization using the Mitsunobu protocol[10] to the mannofuranosyl thiazoline derivative **12**β (Scheme 3). The presence of the thiazoline heterocycle could be interesting for its enzymes-inhibition properties, as was previously demonstrated for other thiazoline-containing sugars.[11]



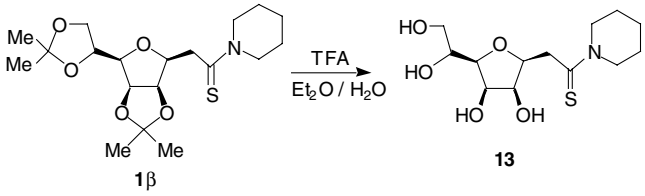
Scheme 3.

Compared to the previous method, which gave only one anomer **12**, the more straightforward route to **12**, involving a direct Horner–Emmons reaction with the D-mannofuranose and the corresponding thiazolinyl phosphonate,[12] gave the product **12** as an inseparable mixture of the **12**α/**12**β anomers in a 1:1 ratio (Scheme 4), and in low yield (15% after purification).



Scheme 4.

Finally, one example of hydrolysis of the acetonido protecting groups was carried out on compound **1** under classical conditions,[13] and the corresponding *C*-glycoside **13** with free hydroxyl groups was isolated in nearly quantitative yield (Scheme 5).



Scheme 5.

In conclusion, the *C*-glycosyl dithioester **2** was an efficient thioacylating reagent toward a variety of amines; its use enabled the synthesis of several new *C*-glycosides. Among all the compounds described herein, some of them (**3**, **8**, **9**, and **11**) were tested by the NCI, and *C*-glycoside **3** exhibited interesting antitumor activity toward various cell lines.[†]

3. Experimental

3.1. General remarks

Most of the reactions were carried out under nitrogen with magnetic stirring, unless otherwise specified. Reactions were monitored by TLC using silica gel plates. Synthesized products were purified by column chromatography on silica gel or crystallized if necessary. Solvents were dried by distillation, prior to use. The NMR spectra were recorded in $CDCl_3$, with a Bruker DPX 250 or a Bruker DRX 400 spectrometer. Chemical shifts (δ) are expressed in ppm relative to Me_4Si for ^1H and ^{13}C nuclei, and the coupling constants (J) are given in Hz; conventional abbreviations are used. Optical rotation values were measured on a Perkin–Elmer 241 polarimeter for the sodium D line at 20 °C. The infrared spectra were recorded with a Perkin–Elmer 16 PC spectrometer as liquid films, and absorbances are given in ν (cm^{-1}). Elemental microanalyses were performed at Caen with an automatic apparatus CHNS-O Thermo-Quest. High-resolution mass spectra were recorded with a QTOF Micro Waters spectrometer in the positive-ion electrospray-ionization mode.

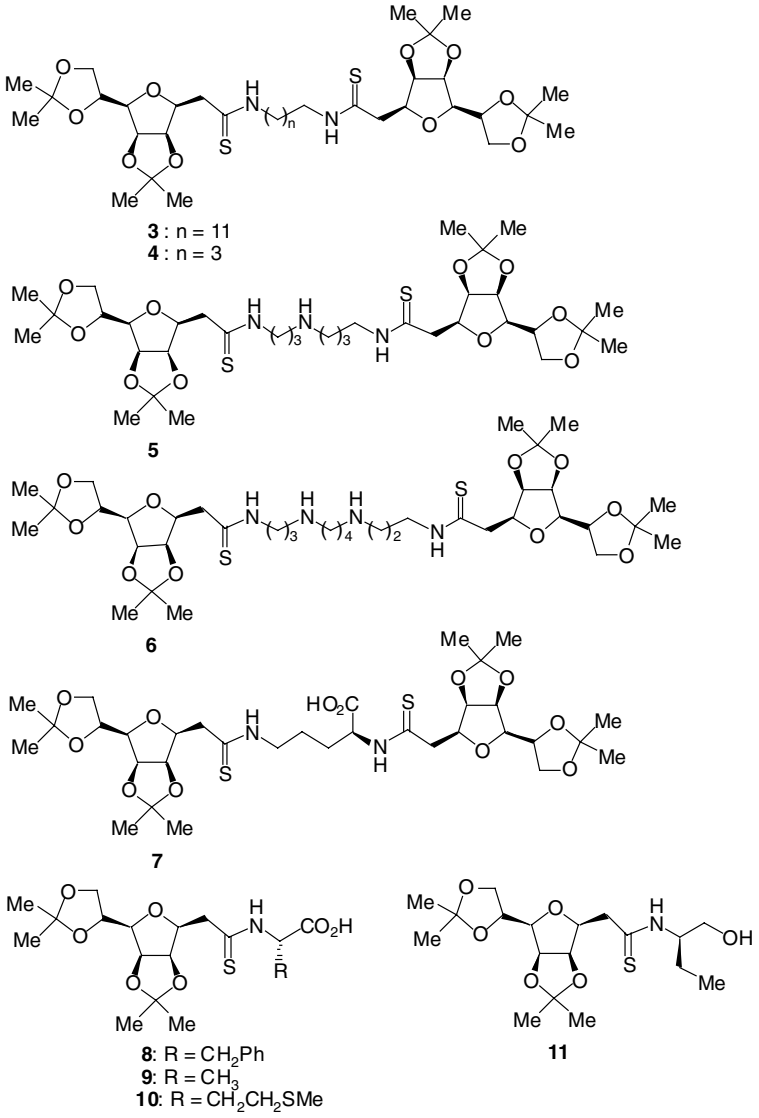
3.2. General procedure for thioacylation of functionalized amines with the dithioester 2

To a stirred solution of amine in the appropriate solvent (10 mL/mmol of **2**), Et_3N and dithioester **2** were successively added. The solution was stirred at room temperature (or warmed at 50 °C for compound **3**) until completion (12 h to 6 days, the reaction being monitored by TLC). Then the solvent was removed, and the crude product was purified by silica gel chromatography.

3.2.1. *N,N′*-Bis-[2-*C*-(2,3:5,6-di-*O*-isopropylidene)-β-D-mannofuranosyl-ethanethioyl]-1,12-dodecyldiamine (3). Compound **3** was prepared according to the general procedure starting from dithioester **2** (860 mg, 2.5 mmol), Et_3N (0.3 mL, 2.16 mmol), and 1,12-dodecyldiamine (210 mg, 1.05 mmol) in THF (reaction time: 6 days). Purification by silica gel chromatography (3:7 AcOEt–petroleum ether) yielded 590 mg (71%) of **3** as a yellow oil: $[\alpha]_D$ −20.8 (*c* 6.4, $CHCl_3$).

IR (KBr): 2936, 1441, 1364, 1211, 1070 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.27 (s, 16H, $(CH_2)_8$), 1.33, 1.37, 1.43, 1.48 (4s, 24H, 8 × CH_3), 1.63 (qt, 4H, 2 × CH_2CH_2NH, J = 6.8 Hz), 3.08 (d, 4H, 2 × CH_2CS, J 5.6 Hz), 3.58 (dd, 2H, 2 × **H-4**, J 6.9, 3.6 Hz), 4.00–4.20 (m, 10H, 4 × **H-6**, 2 × **H-1**, 2 × CH_2NH), 4.35–4.45 (m, 2H, 2 × **H-5**), 4.67 (dd, 2H, 2 × **H-2**, J 6.0, 3.6 Hz), 4.76 (dd, 2H, 2 × **H-3**, J 6.0, 3.6 Hz), 7.90 (br s, 2H, 2 × N**H**). ^{13}C NMR (62 MHz, $CDCl_3$): δ 24.8, 25.6, 26.1, 27.3 (8 × CH_3), 28.2 (10 × CH_2), 46.5 (2 × CH_2CS), 46.6 (2 × CH_2NH), 67.1 (2 × **C-6**), 73.3 (2 × **C-5**), 80.7 (2 × **C-1**), 80.8 (2 × **C-3**), 81.5 (2 × **C-2**), 82.3 (2 × **C-4**), 109.4, 112.9 (4 × $C(CH_3)_2$), 200.9 (2 × **C**S). Anal. Calcd for $C_{40}H_{68}N_2O_{10}S_2$: C, 59.97; H, 8.56; N, 3.50; O, 19.97;

[†] Anticancer evaluations were performed by the US National Cancer Institute (N.I.H.). Results are available on the website of the N.C.I. http://dtp.nci.nih.gov/dtpstandard/dwindex/index.jsp using the NCS number 713554 for **9**, 713555 for **8**, 713556 for **11**, and 713557 for compound **3**.



S, 8.00. Found: C, 59.75; H, 8.47; N, 3.34; O, 20.24; S, 8.40.

3.2.2. *N*,*N*′-Bis-[2-*C*-(2,3:5,6-di-*O*-isopropylidene)-β-D-mannofuranosyl-ethanethioyl]putresceine (4). Compound **4** was prepared according to the general procedure starting from dithioester **2** (300 mg, 0.86 mmol), Et_3N (0.11 mL, 0.79 mmol), and putresceine (340 mg, 0.38 mmol) in THF (reaction time: 3 days). Purification by silica gel chromatography (3:7 AcOEt–pentane) yielded 239 mg (90%) of **4** as a yellow paste: $[\alpha]_D$ −19.5 (*c* 2.4, $CHCl_3$).

IR (NaCl): 3284, 1456, 1412, 1374, 1210, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.33, 1.37, 1.43, 1.48 (4s, 24H, 8 × C**H**$_3$), 1.72 (m, 4H, 2 × C**H**$_2$CH$_2$NH), 3.03–3.12 (ddd, 4H, 2 × C**H**$_2$CS, *J* 14.2, 7.5, 5.6 Hz), 3.59 (dd, 2H, 2 × **H-4**, *J* 7.0, 3.6 Hz), 3.68–3.74 (m, 4H, 2 × C**H**$_2$NH), 4.04 (m, 6H, 4 × **H-6**, 2 × **H-1**), 4.39 (dt, 2H, 2 × **H-5**, *J* 7.0, 4.8 Hz), 4.67 (dd, 2H, 2 × **H-2**, *J* 6.1, 3.7 Hz), 4.75 (dd, 2H, 2 × **H-3**, *J* 6.1, 3.6 Hz), 8.16 (br s, 2H, 2 × N**H**). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.8, 25.5, 26.1, 27.2 (8 × **C**H$_3$), 25.4 (2 × **C**H$_2$CH$_2$N), 45.6 (2 × **C**H$_2$N), 46.3 (2 × **C**H$_2$CS), 66.9 (2 × **C-6**), 73.4 (2 × **C-5**), 80.7 (2 × **C-1**), 80.8 (2 × **C-3**), 81.5 (2 × **C-2**), 82.2 (2 × **C-4**), 109.4, 112.9 (4 × **C**(CH$_3$)$_2$), 201.5 (2 × **C**S). HRMS: (MH^+) Calcd for $C_{32}H_{53}N_2O_{10}S_2$: 689.3063. Found: 689.3121.

3.2.3. 1-*N*,8-*N*-Bis-[2-*C*-(2,3:5,6-di-*O*-isopropylidene)-β-D-mannofuranosyl-ethanethioyl]spermidine (5). Compound **5** was prepared according to the general procedure starting from dithioester **2** (300 mg, 0.86 mmol), Et_3N (0.12 mL, 0.86 mmol), and spermidine (60 mg, 0.41 mmol) in THF (reaction time: 24 h). Purification by silica gel chromatography (2:3 AcOEt–pentane, then MeOH) yielded 276 mg (90%) of **5** as a yellow oil: $[\alpha]_D$ −14.6 (c 2.0, $CHCl_3$).

IR (NaCl): 3284, 1456, 1412, 1374, 1210, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.33, 1.37, 1.43, 1.48 (4s, 24H, 8 × C**H**$_3$), 1.59 (qt, 2H, HNCH$_2$C**H**$_2$CH$_2$-CH$_2$NH, *J* 7.0 Hz), 1.72 (qt, 2H, HNCH$_2$CH$_2$C**H**$_2$-CH$_2$NH, *J* 7.1 Hz), 1.82 (qt, 2H, HNCH$_2$C**H**$_2$CH$_2$NH, *J* 6.2 Hz), 1.85–1.98 (br s, 1H, CH$_2$N**H**CH$_2$), 2.66 (t, 2H, HNC**H**$_2$CH$_2$CH$_2$CH$_2$NH, *J* 6.9 Hz), 2.75 (t, 2H, HNCH$_2$CH$_2$C**H**$_2$NH, *J* 6.2 Hz), 3.03 (m, 4H, 2 × C**H**$_2$CS), 3.58 (dd, 2H, 2 × **H-4**, *J* 7.0, 3.5 Hz), 3.65 (qd, 2H, HNCH$_2$CH$_2$CH$_2$C**H**$_2$NH, *J* 6.8 Hz), 3.74 (m, 2H, SCNHC**H**$_2$CH$_2$CH$_2$NH), 4.04 (m, 6H, 4 × **H-6**, 2 × **H-1**), 4.38 (m, 2H, 2 × **H-5**), 4.67–4.71 (dd, 2H, 2 × **H-2**, *J* 6.2, 3.5 Hz), 4.75 (dd, 2H, 2 × **H-3**, *J* 6.2, 3.6 Hz), 8.56 (br s, 1H, N**H**CS), 9.12 (s, 1H, N**H**CS). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.3, 24.4, 25.0, 25.1, 25.6, 25.7, 26.7, 26.8 (8 × **C**H$_3$), 25.4 (HNCH$_2$**C**H$_2$CH$_2$CH$_2$NH), 26.9 (HNCH$_2$CH$_2$**C**H$_2$-CH$_2$NH), 27.2 (HNCH$_2$**C**H$_2$CH$_2$NH), 45.4 (SCNH-**C**H$_2$CH$_2$CH$_2$NH), 46.0 (2 × **C**H$_2$CS), 46.1 (HNCH$_2$-CH$_2$CH$_2$**C**H$_2$NH), 47.9 (SCNHCH$_2$CH$_2$**C**H$_2$NH), 49.2 (HN**C**H$_2$CH$_2$CH$_2$CH$_2$NH), 66.9, 67.0 (2 × **C-6**), 73.3, 73.4 (2 × **C-5**), 80.7 (2 × **C-1**), 80.8, 80.9 (2 × **C-3**), 81.4 (2 × **C-2**), 82.0, 82.1 (2 × **C-4**), 109.2, 109.3, 112.6, 112.7 (4 × **C**(CH$_3$)$_2$), 200.9, 201.6 (2 × **C**S). HRMS: (MH^+) Calcd for $C_{35}H_{60}N_3O_{10}S_2$: 746.3642. Found: 746.3712.

3.2.4. 1-*N*,12-*N*′-Bis-[2-*C*-(2,3:5,6-di-*O*-isopropylidene)-β-D-mannofuranosyl-ethanethioyl]spermine (6). Compound **6** was prepared according to the general procedure starting from dithioester **2** (300 mg, 0.86 mmol), Et_3N (0.12 mL, 0.86 mmol), and spermine (83 mg, 0.41 mmol) in THF (reaction time: 3 days). Purification by silica gel chromatography (2:3 AcOEt–pentane, then MeOH) yielded 152 mg (46%) of **6** as a pale-brown very viscous oil: $[\alpha]_D$ −12.4 (*c* 2.1, $CHCl_3$).

IR (NaCl): 3240, 1456, 1372, 1208, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27, 1.31, 1.37, 1.41 (4s, 24H, 8 × C**H**$_3$), 1.52 (m, 4H, HNCH$_2$C**H**$_2$C**H**$_2$CH$_2$NH), 1.76 (qt, 2H, HNCH$_2$C**H**$_2$CH$_2$NH, *J* 6.1 Hz), 2.58 (m, 4H, HNC**H**$_2$CH$_2$CH$_2$C**H**$_2$NH), 2.72 (t, 2H, HNCH$_2$-CH$_2$C**H**$_2$NH, *J* 6.1 Hz), 2.90–3.00 (ddd, 4H, 2 × C**H**$_2$CS, *J* 14.0, 7.5, 5.6 Hz), 3.52 (dd, 2H, 2 × **H-4**, *J* 6.8, 3.5 Hz), 3.67 (t, 2H, NHC**H**$_2$CH$_2$CH$_2$NH, *J* 6.3 Hz), 3.95–4.02 (m, 4H, 4 × **H-6**, *J* 13.4, 5.2, 5.0 Hz), 4.10 (m, 2H, 2 × **H-1**), 4.32 (m, 2H, 2 × **H-5**), 4.66 (dd, 2H, 2 × **H-2**, *J* 6.0, 3.5 Hz), 4.70 (dd, 2H, 2 × **H-3**, *J* 6.0, 3.5 Hz), 9.4 (br s, 2H, 2 × N**H**CS). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.9, 25.5, 26.1, 27.2 (8 × **C**H$_3$), 27.3 (HNCH$_2$**C**H$_2$CH$_2$CH$_2$NH), 28.1 (HNCH$_2$**C**H$_2$CH$_2$-NH), 45.9 (SCNH**C**H$_2$CH$_2$CH$_2$NH), 46.1 (2 × **C**H$_2$CS), 48.1 (SCHNCH$_2$CH$_2$**C**H$_2$NH), 49.7 (NH**C**H$_2$CH$_2$-CH$_2$**C**H$_2$NH), 66.9 (2 × **C-6**), 73.4 (2 × **C-5**), 80.8 (2 × **C-1**), 81.0 (2 × **C-3**), 81.4 (2 × **C-2**), 82.0 (2 × **C-4**), 109.3, 112.7 (4 × **C**(CH$_3$)$_2$), 200.5 (2 × **C**S).

HRMS: (MH^+) Calcd for $C_{38}H_{67}N_4O_{10}S_2$: 803.4220. Found: 803.4315.

3.2.5. *N*,*N*′-Bis-[2-*C*-(2,3:5,6-di-*O*-isopropylidene)-β-D-mannofuranosyl-ethanethioyl]-L-ornitine (7). Compound **7** was prepared according to the general procedure starting from dithioester **2** (1 equiv, 120 mg, 0.34 mmol), Et_3N (0.07 mL, 0.51 mmol), and L-ornitine hydrochloride (29 mg, 0.17 mmol) in THF (reaction time: 3 days). Purification by silica gel chromatography (2:3 AcOEt–pentane, then MeOH) yielded 57 mg (46%) of **7** as a white paste: $[\alpha]_D$ −10.4 (*c* 0.55, $CHCl_3$).

IR (KBr): 3588–3284, 1684, 1456, 1410, 1378, 1210, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.33, 1.36, 1.37, 1.43, 1.48 (5s, 24H, 8 × C**H**$_3$), 1.69 (m, 2H, HNCH$_2$C**H**$_2$CH$_2$CH), 1.84 (m, 1H, HNCH$_2$CH$_2$-C**H**HCH), 2.08 (m, 1H, HNCH$_2$CH$_2$CH**H**CH), 3.03 (m, 4H, 2 × C**H**$_2$CS), 3.56 (m, 2H, 2 × **H-4**), 3.65–3.71 (m, 2H, HNC**H**$_2$CH$_2$CH$_2$CH), 4.05 (m, 6H, 2 × C**H**$_2$-**6**, 2 × **H-1**), 4.38 (m, 2H, 2 × **H-5**), 4.76 (m, 5H, 2 × **H-2**, 2 × **H-3**, C**H**NH), 8.70 (s, 1H, CH$_2$N**H**CS), 9.12 (d, 1H, CHN**H**CS, *J* 5.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.1 (CH$_2$**C**H$_2$CH$_2$), 24.9, 25.0, 25.5, 26.2, 27.3 (8 × **C**H$_3$), 29.1 (CH$_2$CH$_2$**C**H$_2$), 45.6, 45.8 (2 × **C**H$_2$CS), 46.2 (**C**H$_2$CH$_2$CH$_2$), 60.3 (CH$_2$CH$_2$CH$_2$**C**H), 67.1, 67.2 (2 × **C-6**), 73.3, 73.4 (2 × **C-5**), 80.8, 81.0 (2 × **C-1**, 2 × **C-3**), 81.5, 81.8 (2 × **C-2**), 82.1 (2 × **C-4**), 109.5, 109.6, 112.9, 113.0 (4 × **C**(CH$_3$)$_2$), 177.7 (**C**OOH), 200.2, 200.7 (2 × **C**S). HRMS: (MNa^+) Calcd for $C_{33}H_{52}N_2O_{12}S_2Na$: 755.2859. Found: 755.2897.

3.2.6. *N*-[2-*C*-(2,3:5,6-Di-*O*-isopropylidene)-β-D-mannofuranosyl-ethanethioyl]-L-phenylalanine (8). Compound **8** was prepared according to the general procedure starting from dithioester **2** (184 mg, 0.53 mmol), Et_3N (0.11 mL, 0.81 mmol), and L-phenylalanine (134 mg, 0.81 mmol) in 75:25 THF–water (reaction time: 24 h). The solvent was evaporated, and the residual water was removed by azeotropic distillation. Purification by silica gel chromatography (15:85 AcOH–toluene) yielded 197 mg (80%) of **8** as a white paste: $[\alpha]_D$ +24.5 (*c* 1.6, $CHCl_3$).

IR (KBr): 3000, 3030, 3060, 2875, 2400-3500, 1750, 1510, 1262, 1062 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.26, 1.36, 1.42 (3s, 12H, 4 × C**H**$_3$), 3.12 (d, 2H, C**H**$_2$CS, *J* 6.4 Hz), 3.22–3.52 (m, 2H, C**H**$_2$Ph, *J* 14.0, 4.9, 5.8 Hz), 3.37 (dd, 1H, **H-4**, *J* 7.7, 3.4 Hz), 3.73–4.02 (m, 2H, 2 × **H-6**, *J* 8.8, 4.6 Hz), 3.79 (dt, 1H, **H-1**, *J* 6.3, 3.4 Hz), 4.35 (dt, 1H, **H-5**, *J* 7.7, 4.6 Hz), 4.67 (dd, 1H, **H-2**, *J* 6.0, 3.4 Hz), 4.73 (dd, 1H, **H-3**, *J* 6.0, 3.4 Hz), 5.45 (ddd, 1H, NHC**H**, *J* 7.4, 5.8, 4.9 Hz), 7.17–7.35 (m, 5H, C$_6$**H**$_5$), 8.55 (d, 1H, N**H**, *J* 7.4 Hz). ^{13}C NMR (62 MHz, $CDCl_3$): δ 24.2, 25.0, 25.4, 26.7 (4 × **C**H$_3$), 35.7 (**C**H$_2$CH), 45.6 (**C**H$_2$CS), 58.1 (NH**C**H), 66.5 (**C-6**), 72.5 (**C-5**), 74.1 (**C-1**), 80.4 (**C-2**), 80.9 (**C-3**),

81.4 (**C-4**), 110.1, 113.5 ($2\times$ **C**$(CH_3)_2$), 127.6 (**C**$_{Ar}$), 128.8 (**C**$_{Ar}$), 129.9 (**C**$_{Ar}$), 136.2 (**C**$_{Ar}$), 180.7 (**C**OOH), 201.3 (**C**S). Anal. Calcd for $C_{23}H_{31}NO_7S$: C, 59.33; H, 6.71; N, 3.01; O, 24.05; S, 6.88. Found: C, 59.61; H, 6.95; N, 2.89; O, 24.09; S, 7.06.

3.2.7. *N*-[2-*C*-(2,3:5,6-Di-*O*-isopropylidene)-β-D-mannofuranosyl-ethanethioyl]-L-alanine (9). Compound **l** was prepared according to the general procedure starting from dithioester **2** (351 mg, 1.01 mmol), Et_3N (0.23 mL, 0.81 mmol), and L-alanine (149 mg, 1.67 mmol) in 75:25 THF–water (reaction time: 20 h). Purification by silica gel chromatography (15:85 AcOH–toluene) yielded 362 mg (90%) of **9** as a white paste: $[\alpha]_D$ −28.2 (*c* 1.1, $CHCl_3$).

IR (KBr): 2400–3600, 3300, 2890, 1730, 1530, 1350, 1211, 1090 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.33, 1.38, 1.44, 1.49 (4s, 12H, $4\times$ C**H**$_3$), 1.56 (d, 3H, CHC**H**$_3$, *J* 7.1 Hz), 3.13 (d, 2H, C**H**$_2$CS, *J* 6.3 Hz), 3.59 (dd, 1H, **H-4**, *J* 7.3, 3.3 Hz), 3.97 (dt, 1H, **H-1**, *J* 6.3, 3.4 Hz), 4.03–4.13 (m, 2H, **H-6**, *J* 8.5, 5.1 Hz), 4.42 (dt, 1H, **H-5**, *J* 3.3, 5.1 Hz), 4.73 (dd, 1H, **H-2**, *J* 6.0, 3.4 Hz), 4.78 (dd, 1H, **H-3**, *J* 7.3, 6.0 Hz), 5.1 (qt, 1H, C**H**CH$_3$, *J* 7.0 Hz), 8.52 (d, 1H, N**H**, *J* 7 Hz). ^{13}C NMR (62 MHz, $CDCl_3$): δ 15.9 (**C**H$_3$CH), 23.4, 24.1, 24.7, 25.9 ($4\times$ **C**H$_3$), 44.9 (**C**H$_2$CS), 52.4 (CH$_3$**C**H), 65.7 (**C-6**), 71.9 (**C-5**), 79.2 (**C-1**), 79.4 (**C-2**), 80.1 (**C-3**), 81.0 (**C-4**), 109.7, 113.1 ($2\times$ **C**$(CH_3)_2$), 176.6 (**C**OOH), 201.7 (**C**S). Anal. Calcd for $C_{17}H_{27}NO_7S$: C, 52.43; H, 6.99; N, 3.60; O, 28.76; S, 8.23. Found: C, 52.71; H, 7.15; N, 3.28; O, 28.51; S, 8.41.

3.2.8. *N*-[2-*C*-(2,3:5,6-Di-*O*-isopropylidene)-β-D-mannofuranosyl-ethanethioyl]-L-methionine (10). Compound **10** was prepared according to the general procedure starting from dithioester **2** (150 mg, 0.43 mmol), Et_3N (0.06 mL, 0.43 mmol), and L-methionine (58 mg, 0.41 mmol) in 75:25 THF–water (reaction time: 20 h). Purification by silica gel chromatography (40:60 AcOEt–pentane, then MeOH) yielded 157 mg (86%) of **10** as a colorless, very viscous oil: $[\alpha]_D$ −14.2 (*c* 2.3, $CHCl_3$).

IR (NaCl): 3550–3100, 1614, 1456, 1422, 1398, 1210, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36, 1.38, 1.45, 1.51 (4s, 12H, $4\times$ C**H**$_3$), 2.08 (m, 1H, C**H**HCH$_2$S), 2.11 (s, 3H, SC**H**$_3$), 2.31 (m, 1H, CH**H**CH$_2$S), 2.52 (m, 2H, CH$_2$C**H**$_2$S), 3.00 (m, 2H, C**H**$_2$CS), 3.53 (dd, 1H, **H-4**, *J* 7.7 Hz), 4.08 (m, 3H, $2\times$ **H-6**, **H-1**), 4.39 (qt, 1H, **H-5**, *J* 6.0 Hz), 4.79 (br s, 2H, **H-2**, **H-3**), 4.92 (m, 1H, HNC**H**), 9.10 (d, 1H, N**H**CS, *J* 5.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.6 (S**C**H$_3$), 24.5, 25.1, 25.8, 26.9 ($4\times$ **C**H$_3$), 30.3 (**C**H$_2$SCH$_3$), 45.5 (**C**H$_2$CS), 60.0 (HN**C**H), 66.8 (**C-6**), 72.8 (**C-5**), 80.5 (**C-1**), 80.6 (**C-3**), 81.4 (**C-2**), 81.7 (**C-4**), 109.1, 112.5 ($2\times$ **C**$(CH_3)_2$), 177.0 (**C**OOH), 200.6 (**C**S). HRMS: (MH^+) Calcd for $C_{19}H_{32}NO_7S_2$: 450.1542 Found: 450.1614.

3.2.9. *N*-[2-*C*-(2,3:5,6-Di-*O*-isopropylidene)-β-D-mannofuranosyl-ethanethioyl]-(*R*)-2-amino-1-butanol (11). Compound **11** was prepared according to the general procedure starting from dithioester **2** (235 mg, 0.68 mmol), Et_3N (0.14 mL, 1.05 mmol), and (*R*)-2-aminobutanol (94 mg, 1.05 mmol) in THF (reaction time: 3 days). Purification by silica gel chromatography (3:2 AcOEt–petroleum ether) yielded 94 mg (84%) of **11** as a brown viscous oil: $[\alpha]_D$ +11.7 (*c* 5.5, $CHCl_3$).

IR (KBr): 2400–3600, 2936, 1200, 1110 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 0.98 (t, 3H, C**H**$_3$CH$_2$, *J* 7.3 Hz), 1.32, 1.36, 1.44, 1.48 (4s, 12H, $4\times$ C**H**$_3$), 1.70 (qt, 2H, CH$_3$C**H**$_2$CH, *J* 7.3 Hz), 2.72 (br s, 1H, O**H**), 3.07 (d, 2H, C**H**$_2$CS, *J* 6.6 Hz), 3.59 (dd, 1H, **H-4**, *J* 6.9, 3.5 Hz), 3.65–3.81 (m, 2H, $2\times$ **H-6**, *J* 11.1, 3.9, 3.7 Hz), 4.05 (m, 3H, C**H**$_2$OH, **H-1**), 4.37 (q, 1H, **H-5**, *J* 6.2 Hz), 4.50 (m, 1H, NHC**H**), 4.67 (dd, 1H, **H-2**, *J* 6.0, 3.5 Hz), 4.76 (dd, 1H, **H-3**, *J* 6.0, 3.5 Hz), 8.17 (d, 1H, N**H**, *J* 7.8 Hz). ^{13}C NMR (62 MHz, $CDCl_3$): δ 10.4 (**C**H$_3$CH$_2$), 23.3 (**C**H$_2$CH$_3$), 24.3, 24.8, 25.7, 26.8 ($4\times$ **C**H$_3$), 46.7 (**C**H$_2$CS), 58.2 (**C**HNH), 62.8 (**C-6**), 66.5 (**C**H$_2$OH), 72.9 (**C-5**), 80.4 (**C-1**), 80.6 (**C-2**), 81.0 (**C-3**), 81.9 (**C-4**), 109.1, 112.7 ($2\times$ **C**$(CH_3)_2$), 200.9 (**C**S). HRMS: (MH^+) Calcd for $C_{18}H_{32}NO_6S$: 390.1950. Found: 390.1942.

3.3. Preparation of (*R*)-2-*C*-[(2,3:5,6-di-*O*-isopropylidene)-β-D-mannofuranosyl-methyl]-4-ethyl-2-thiazoline (12β)

To a stirred solution of thioamide **11** (1.074 g, 2.86 mmol, 1 equiv) and triphenylphosphine (1.126 g, 4.29 mmol, 1.5 equiv) in anhyd THF (30 mL) was added dropwise diethyl azodicarboxylate (DEAD) (0.748 g, 4.29 mmol, 1.5 equiv), diluted in anhyd THF (5 mL). The solution was stirred during 3 days at room temperature, and the solvent was removed under reduced pressure. The residual product was purified by silica gel chromatography (2:3 Et_2O–petroleum ether) to give 340 mg (32%) of product as a pale-yellow paste: $[\alpha]_D$ +27.6 (*c* 0.5, $CHCl_3$).

IR (NaCl): 2984–2934, 1732, 1166 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 0.98 (t, 3H, C**H**$_3$CH$_2$, *J* 6.5 Hz), 1.33, 1.38, 1.45, 1.47 (4s, 12H, $4\times$ C**H**$_3$), 1.55–1.75 (m, 2H, C**H**$_2$CH$_3$), 2.75–2.95 (m, 2H, C**H**$_2$), 2.96–3.05 (m, 1H, SC**H**H), 3.30–3.40 (m, 1H, SCH**H**), 3.55 (m, 1H, **H-4**), 3.90 (dt, 1H, **H-1**, *J* 6.6, 2.9 Hz), 4.05–4.15 (m, 2H, $2\times$ **H-6**), 4.37–4.50 (m, 2H, C**H**N, **H-5**), 4.70–4.75 (m, 2H, **H-2**, **H-3**). ^{13}C NMR (62 MHz, $CDCl_3$): δ 10.9 (**C**H$_3$CH$_2$), 25.0, 25.6, 26.3, 27.3 ($4\times$ **C**H$_3$), 28.2 (**C**H$_2$CH$_3$), 33.7 (**C**H$_2$S), 38.1 (**C**H$_2$), 67.2 (**C-6**), 73.4 (**C-5**), 78.8 (**C**H$_2$CH$_3$), 79.7 (**C-1**), 81.0 (**C-3**), 81.5 (**C-2**), 81.9 (**C-4**), 109.4, 112.8 ($2\times$ **C**$(CH_3)_2$), 166.4 (**C**NS). HRMS: [(M+H_2O)H^+] Calcd for $C_{18}H_{32}NO_6S$: 390.1872. Found: 390.1872. Under the analysis conditions (solvent: 1:1 H_2O–MeOH + 0.2% HCO_2H), the thiazoline ring of **12** opened and transformed in reaction with 1 equiv of H_2O to give the corresponding *N*-[2-*C*-(2,3:5,6-di-*O*-isopropylidene)-β-D-mannofuranosyl)eth-

anoyl]-2-amino-1-butanethiol, giving the exact mass that was found.

3.4. Preparation of (*R*)-2-*C*-[(2,3:5,6-di-*O*-isopropylidene)-β-D-mannofuranosyl-methyl]-4-ethyl-2-thiazoline as a mixture of anomers (12α + 12β)

A solution of thiazolinyl phosphonate (265 mg, 1 mmol) dissolved in acetonitrile (5 mL) was added dropwise to a stirred mixture of diazabicycloundecene (168 mg, 1.1 mmol) and lithium chloride (47 mg, 1.1 mmol). 2,3:5,6-Di-*O*-isopropylidene)-β-D-mannofuranose (312 mg, 1.2 mmol) in acetonitrile (5 mL) was added. The mixture was stirred at 50 °C for 48 h. After filtration of the salts and evaporation of the solvent, the crude mixture was chromatographed on silica gel (2:3 Et_2O–pentane), giving 56 mg (15%) of **12**α/**12**β as a 1:1 inseparable mixture as a yellow paste.

^{1}H NMR (250 MHz, $CDCl_3$): δ 0.97–1.02 (m, 3H, C**H**$_3$CH$_2$), 1.32–1.50 (m, 12H, 4 × C**H**$_3$), 1.55–1.75 (m, 2H, C**H**$_2$CH$_3$), 2.65 (d, 1H, C**H**$_2$-α, *J* 7.6 Hz), 2.75–2.95 (m, 1H, C**H**$_2$-β), 2.96–3.05 (m, 1H, SC**H**H), 3.30–3.40 (m, 1H, SCH**H**), 3.55 (m, 0.5H, **H-4**β), 3.75 (m, 0.5H, **H-4**α), 3.90 (dt, 0.5H, **H-1**β, *J* 6.6, 2.9 Hz), 4.05–4.15 (m, 2.5H, 2 × **H-6**, **H-1**α), 4.37–4.50 (m, 1H, C**H**N, **H-5**), 4.70–4.75 (m, 2H, **H-2**, **H-3**). ^{13}C NMR (62 MHz, $CDCl_3$): δ 10.9 (**C**H$_3$CH$_2$, β), 11.1 (**C**H$_3$CH$_2$, α), 25.0, 25.1, 25.5, 25.6, 26,1 (3 × **C**H$_3$, α + β), 27.3 (**C**H$_3$, α + β), 33.7 (**C**H$_2$S, α), 36.0 (**C**H$_2$S, β), 38.1 (**C**H$_2$-β), 38.3 (**C**H$_2$-α), 67.2 (**C-6**, β), 67.3 (**C-6**, α), 73.4 (**C-5**, β), 73.6 (**C-5**, α), 78.8 (**C**H$_2$CH$_3$, β), 78.9 (**C-1**, α), 79.7 (**C-1**, β), 81.0 (**C-3**, β), 81.1 (**C-3**, α), 81.2 (**C-2**, α), 81.5 (**C-2**, β), 81.9 (**C-4**, β), 82.4 (**C-4**, α), 109.4 (**C**(CH$_3$)$_2$, β), 109.5 (**C**(CH$_3$)$_2$, α), 112.8 (**C**(CH$_3$)$_2$, β), 113.1 (**C**(CH$_3$)$_2$, α), 165.8 (**C**NS, α), 166.4 (**C**NS, β).

3.5. Preparation of *N*-[2-*C*-(2,3:5,6-tetrahydroxy)-β-D-mannofuranosyl-ethanethioyl]piperidine (13)

The thioamide **1**β (192 mg, 0.5 mmol) was dissolved in diethyl ether (3 mL), and 10% trifluoroacetic acid in water (5 mL) was added. The solution was stirred 24 h at room temperature, the solvent was evaporated, and the residual solid was washed 3 times with 5 mL of CH_2Cl_2 and then carefully dried under vacuum for few hours to give 151 mg (98%) of compound **13** as a white powder.

IR (KBr): 3422, 1508 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.50–4.80 (broad signals). The ^{1}H NMR spectrum did not provide important information for the determination of the structure. It demonstrated, however, that all the CH_3 signals of the starting acetonide disappeared.

^{13}C NMR (62 MHz, DMSO-d_6): δ 23.4 (NCH$_2$CH$_2$**C**H$_2$), 25.1 (NCH$_2$**C**H$_2$), 26.4 (NCH$_2$**C**H$_2$), 44.0 (**C**H$_2$CS), 50.8 (N**C**H$_2$), 51.0 (N**C**H$_2$), 63.3 (**C-6**), 69.9 (**C-5**), 70.9 (**C-3**), 71.8 (**C-2**), 79.1 (**C-1**), 80.1 (**C-4**), 199.3 (**C**S). Anal. Calcd for $C_{13}H_{23}NO_5S$: C, 51.13; H, 7.59; N, 4.58; S, 10.5. Found: C, 50.53; H, 7.57; N, 4.59; S, 10.23.

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