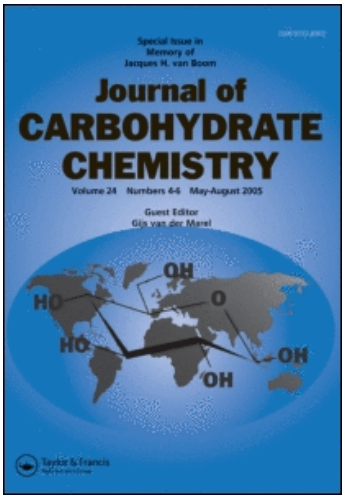

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SYNTHESIS OF 1,5-DITHIO-D-GLUCOPYRANOSE AND SOME OF ITS BIOLOGICALLY RELEVANT DERIVATIVES.

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ABSTRACT

5-Thio-D-glucose was transformed into the 1,5-dithio analog **5** through a sequence involving anomeric bromination followed by a Cerny hydrosulfurization reaction. The nucleophilic reactivity of this first representative of a new class of sugar mercaptans was investigated through the synthetic elaboration of some biologically relevant dithiosaccharides and particularly the first thia-analogs of glucosinolates **18** and **19**.

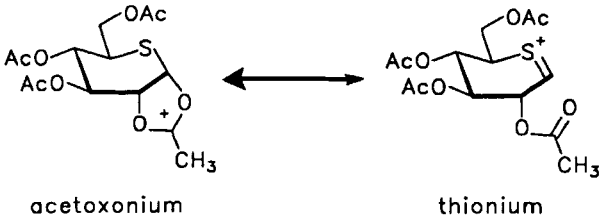
INTRODUCTION

The usefulness of sulfur-containing carbohydrates both as modified biological substrates and synthetic intermediates has been well documented[1] and the search for new sulfur sugars is currently in progress. Sugars having sulfur *in the ring* are relatively recent compounds,[2,3] while 1,5-dithioglycopyranosides and 1,4-dithioglycofuranosides have been far much less studied.[4] We describe herein the first synthesis of the parent compound of a new class of sugar mercaptans, namely tetra-*O*-acetyl-1,5-dithio-D-glucopyranose **5**, and some of its transformations into biologically relevant derivatives.

RESULTS AND DISCUSSION

Treatment of 5-thio-D-glucose[5] with acetic anhydride in pyridine afforded 1,2,3,4,6-penta-*O*-acetyl-5-thio-α,β-D-glucopyranose (**1**) in 95% yield.[6] Bromination of **1** in dichloromethane using 30% hydrogen bromide in acetic acid gave both anomers **2** and **3** in 80% combined yield.[7]

Following a slightly modified Cerny procedure,[8] nucleophilic substitution with thiourea of either **2** or **3** in refluxing 2-butanone gave from both compounds 2-*S*-(2,3,4,6-tetra-*O*-acetyl-5-thio-α,β-D-glucopyranosyl)isothiouronium bromide (**4**) as *ca.* 1:4 mixture of α,β-anomers. The formation of an anomeric mixture, as also observed by Korytnyk et al.,[7] could be an indication of a low degree of participation via the acetoxonium intermediate (Scheme I).

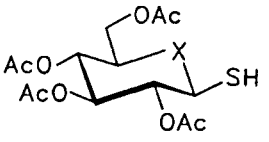


acetoxonium thionium

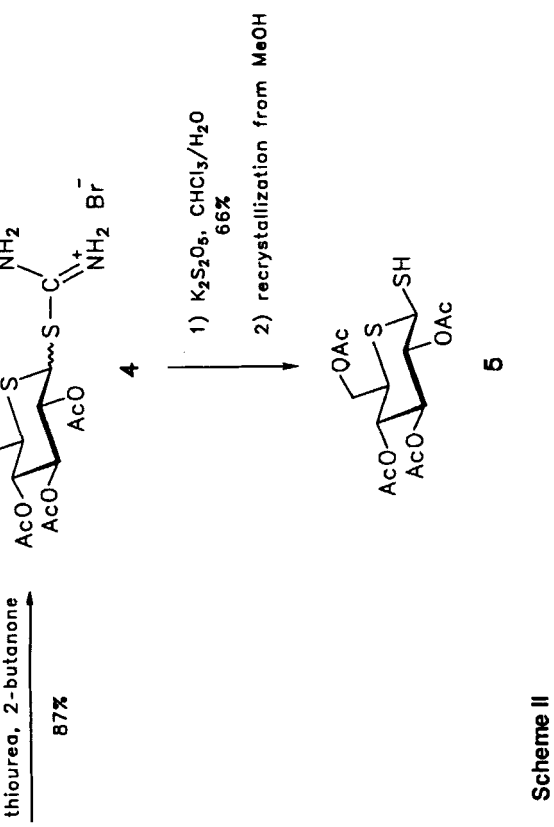
Scheme I

The crude product was then directly submitted to reductive cleavage by potassium metabisulfite. A mixture of anomeric mercaptans was thus obtained (66% combined yield), from which the pure β-anomer **5** could be isolated after one recrystallization from MeOH[9] (Scheme II).

The ^{1}H NMR spectra of **5** and 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**6**) were compared (Table I): the resonances for H-1 were observed at δ 3.82 and 4.55 ppm, respectively, clearly indicating the shielding effect of the endocyclic sulfur atom on the anomeric center. Resonances for H-5 in **5** and **6** were observed at 3.31 and 3.73 ppm, thus emphasizing the same spectroscopic feature. All the other protons resonated within a similar range in both compounds but the compared shift orders for protons H-2, H-3 and H-4 in the spectra of **5** and **6** were reversed, H-3 resonating, respectively, upfield or downfield from the two other protons. The vicinal coupling constant values $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ (*ca.* 10 Hz) are indicative of typical trans-diaxial relationships and therefore consistent with a $^4C_1$(D) conformation.[10]



5 X= S
6 X= O



Scheme II

TABLE I. Compared ^1H NMR shifts[a] for compounds **5** and **6**

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	SH
5	3.82	5.09	5.02	5.28	3.31	4.23	4.12	1.91
6	4.55	4.97	5.19	5.10	3.73	4.25	4.12	2.31

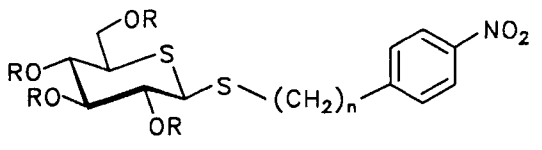
TABLE II. Compared ^{13}C NMR shifts[a] for compounds **5** and **6**

Compound	C-1	C-2	C-3	C-4	C-5	C-6
5	41.0	74.1	71.7	76.5	45.2	60.9
6	78.4	73.3	67.9	73.3	76.0	61.8

a. Recorded in $CDCl_3$ with TMS as an external standard.

In the ^{13}C NMR spectra of compound **5** (Table II), the resonance of C-1 and C-5 at δ 41.0 and 45.2, respectively, was in agreement with a normal upfield effect caused by the sulfur atom; moreover, an expected *beta*-shift was observed for C-4.

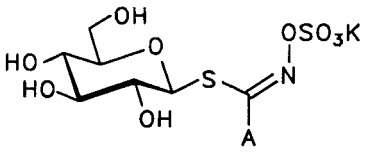
The protected β-thiol **5** smoothly reacted with 1-fluoro-4-nitrobenzene in the presence of cesium carbonate[11] in acetone to furnish 4-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-1,5-dithio-β-D-glucopyranoside (**7**) in 93% yield. A similar condensation of **5** with 4-nitrobenzyl bromide readily gave a 90% yield of 4-nitrobenzyl 2,3,4,6-tetra-*O*-acetyl-1,5-dithio-β-D-glucopyranoside (**8**).



n= 0 **7** R= Ac
9 R= H
n= 1 **8** R= Ac
10 R= H

Compounds **7** and **8** were submitted to standard de-O-acetylation conditions to give the potential[12] glucosidase and thioglucosidase inhibitors **9** and **10** respectively, in nearly quantitative yield.

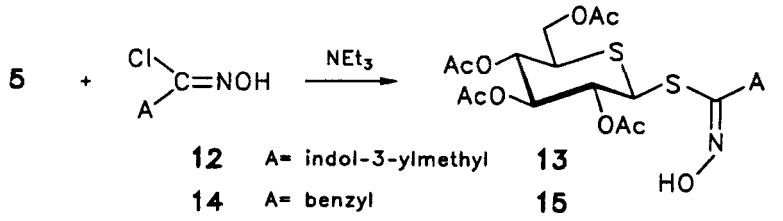
The nucleophilic reactivity of **5** was further explored by studying the addition to nitrile-oxides, a reaction which has formerly been developed[13] for the elaboration from **6** of glucosylthiohydroximates - key-synthons for the synthesis of naturally-occurring glucosinolates **11**. The latter are important secondary plant metabolites generally encountered in *Cruciferae*[14] and prone to enzymic degradation under the action of myrosinases (EC 3.2.3.1).



A= alkyl,alkenyl,aryl, hydroxyalkenyl, indol-3-ylmethyl

11

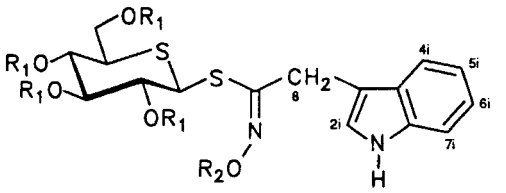
As an extension of previously described work,[15] indol-3-ylacethydroximoyl chloride (**12**) indeed reacted with **5** in the presence of triethylamine to give the 5-thioglucobrassicin thiohydroximate (**13**) in 75% yield. In the same way, **5** reacted with 2-phenylacethydroximoyl chloride (**14**) to produce 5-thioglucotropaeolin thiohydroximate (**15**) in a similar yield.

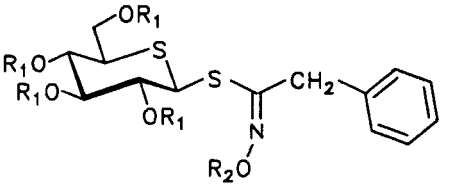


12 A= indol-3-ylmethyl **13**

14 A= benzyl **15**

O-sulfation of the hydroximino group of **13** or **15** using *in situ* prepared SO_3-pyridine complex, followed by neutralization with potassium hydrogen carbonate furnished compound **16** in 60% yield or **17** in 75% yield. Final deprotection of the sugar moiety using a methanolic solution of potassium methoxide afforded 5-thioglucobrassicin (**18**) or 5-thioglucotropaeolin (**19**).





16 R_1= Ac R_2= SO_3K **17** R_1= Ac R_2= SO_3K

18 R_1= H R_2= SO_3K **19** R_1= H R_2= SO_3K

CONCLUSION

In this paper, we have shown by means of the synthesis of a first representative compound **5** that a new class of sugar mercaptans is formally available through a short sequence of quasi-standard steps.

The nucleophilic reactivity of **5** has been exemplified by the synthetic elaboration of potential enzyme inhibitors. The respective inhibitory effects of **9** and **10** on glucosidases and of **18** and **19** on myrosinases are currently under investigation and will be published elsewhere.

EXPERIMENTAL

General methods. Melting points were determined with a Kofler-block apparatus and are uncorrected. Optical rotations were measured with a Jobin-Yvon Digital type 71 polarimeter at 22 °C. NMR spectra were recorded at 300 K in $CDCl_3$ (unless otherwise specified) on a Bruker AM 300 (300.13 MHz for ^1H and 75.47 MHz for ^{13}C). Chemical shifts are expressed in parts per million downfield from TMS. Mass spectra were recorded on Nermag-R-10-10C (LRMS) and VG Analytical 70SV (HRMS) spectrometers. Thin layer chromatography was run on aluminium plates precoated with silica gel $60F_{254}$ (E. Merck, Darmstadt, Germany); detection was effected by observation under short wavelength UV light (254 nm), then dipping the chromatograms into a solution of ceric ammonium nitrate $[Ce(NH_4)_2(NO_3)_6]$ in 20% sulfuric acid and charring them with a heat gun. Column chromatography was performed using silica gel 60 (0.063-0.200 mm, E. Merck) and flash chromatography was conducted with silica gel (0.040-0.063 mm, E. Merck).

1,2,3,4,6-Penta-*O*-acetyl-5-thio-α,β-D-glucopyranose (1). 5-thio-D-glucopyranose (500 mg, 2.5 mmol) was added to a solution of acetic anhydride (3.2 mL) and pyridine (6 mL) at 0 °C. The reaction mixture was kept 1 h at 0 °C, then 18 h at room temperature. After cooling again, the excess of acetic anhydride was destroyed with MeOH. The resulting solution was concentrated and traces of pyridine were removed by repeated evaporation of toluene from the residue. The crude product was purified by flash chromatography (eluent ethyl acetate/petroleum ether 4:6 v/v) to furnish 1 as a colorless syrup (984 mg, 95%, α/β 9:1); $[\alpha]_D$ +170° (*c* 1.0, chloroform) (lit.[6] $[\alpha]_D$ +178° (*c* 4.77, chloroform)); ^1H NMR ($CDCl_3$) **α-anomer** δ 1.99, 2.01, 2.07, 2.18 (4s, 12H, OAc), 3.58 (m, 1H, H-5), 4,06 (dd, 1H, $J_{5,6b}$ = 3.2 Hz, H-6b), 4.37 (dd, 1H, $J_{5,6a}$ = 4.9 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 5.23 (dd, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 5.31 (ft, 1H , $J_{4,5}$ = 10.6 Hz, H-4), 5,43 (ft, 1H, $J_{3,4}$ = 9.9 Hz, H-3), 6,16 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1); **β-anomer** δ 3.31 (m, 1H, H-5), 4.12 (dd, 1H, $J_{5,6b}$ = 3.6 Hz, H-6b), 4.28 (dd, 1H, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 5.10 (ft, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 5.88 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1).

2,3,4,6-Tetra-*O*-acetyl-5-thio-α- and -β-D-glucopyranosyl bromide (2) and (3). To a solution of 1 (744 mg, 18 mmol) in dichloromethane (4 mL) was added a solution of HBr in glacial acetic acid (30% w/v, 2 mL). The resulting solution was stored at 0 °C for 1 h, then 16 h at room temperature. The mixture was diluted with

cold water (30 mL) and extracted with dichloromethane (2 x 15 mL). After successive washings with 5% sodium hydrogen carbonate solution and water, the organic extract was dried over magnesium sulfate and concentrated. The residue was applied to a column of silica gel under medium pressure (eluent ether/petroleum ether 1:1 v/v). Elution of the column afforded, after concentration of the appropriate fractions, compound **2** (α-bromide 469 mg) as a syrup and crystalline **3** (β-anomer 313 mg). Overall yield 80%; **α-anomer** $[\alpha]_D$ +214° (*c* 1.0, chloroform) (lit.[7] $[\alpha]_D$ +227° (*c* 1.0, chloroform)); ^{1}H NMR ($CDCl_3$) δ 2.02, 2.05, 2.07, 2.09 (4s, 12H, OAc), 3.70 (m, 1H, H-5), 4.14 (dd, 1H, $J_{5,6b}$ = 2.8 Hz, H-6b), 4.46 (dd, 1H, $J_{5,6a}$ = 4.7 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.91 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 5.32 (ft, 1H , $J_{4,5}$ = 10.3 Hz, H-4), 5.53 (ft, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 5.55 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); **β-anomer** mp 104 °C; $[\alpha]_D$ -4° (*c* 1.0, chloroform) (lit.[7] $[\alpha]_D$ -6.5° (*c* 1.0, chloroform)); ^{1}H NMR ($CDCl_3$) δ 2.00, 2.03, 2.07, 2.08 (4s, 12H, OAc), 3.30 (m, 1H, H-5), 4.14 (dd, 1H, $J_{5,6b}$ = 3.0 Hz, H-6b), 4.25 (dd, 1H, $J_{5,6a}$ = 5.9 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.73 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 5.02 (ft, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 5.33 (ft, 1H , $J_{4,5}$ = 10.2 Hz, H-4), 5.35 (ft, 1H, $J_{2,3}$ = 10.2 Hz, H-2).

2-*S*-(2,3,4,6-Tetra-*O*-acetyl-5-thio-α,β-D-glucopyranosyl)isothiouronium bromide (4). A solution of **2** or **3** (1.57 g, 3.7 mmol) and thiourea (420 mg, 5.5 mmol) in anhydrous 2-butanone (20 mL) was boiled under reflux for 10 h, cooled and concentrated under reduced pressure. The crude mixture of anomers (87% overall, α/β 1:4) was used in the next step without further characterization. An analytical sample was obtained by recrystallization from 2-propanol; ^{1}H NMR (DMSO-d_6) **β-anomer** δ 1.95, 2.00, 2.03 (3s, 12H, OAc), 3,83 (m, 1H, H-5), 4.08 (dd, 1H, $J_{5,6b}$ = 3.2 Hz, H-6b), 4.20 (dd, 1H, $J_{5,6a}$ = 5.3 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 5.04-5.19 (m, 3H, H-2, H-3, H-4), 5.54 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 9.36 (bs, NH_2); **α-anomer** δ 3.70 (m, 1H, H-5), 4.08 (dd, 1H, H-6b), 4.27 (dd, 1H, $J_{5,6a}$ = 5.3 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 5.04-5.19 (m, 1H, H-4), 5.26 (ft, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.33 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 5.66 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 9.36 (bs, NH_2).

Anal. Calcd for $C_{15}H_{23}BrN_2O_8S_2$ (503.38): C, 35.79; H, 4.61; N, 5.56. Found: C, 35.60; H, 4.56; N, 5.12.

2,3,4,6-Tetra-*O*-acetyl-1,5-dithio-β-D-glucopyranose (5). A solution of potassium pyrosulfite (0.55 g, 2.5 mmol) in water was heated at 85 °C under a reflux condenser. The chloroform (8 mL) was then introduced, followed by compound **4** (1.4 g, 2.8 mmol). The mixture was boiled for 15 min with constant stirring, then cooled. The organic layer was separated, washed with water, dried over magnesium sulfate and concentrated. Flash chromatography (eluent ethyl acetate/petroleum ether 4:6 v/v) afforded a crystalline mixture of α,β-1,5-dithio-D-glucopyranose (698 mg, overall 66%, mp 124-125 °C, α/β 1:9). Recrystallization from MeOH gives **5** (419 mg, 60% yield from the mixture); mp 128 °C; $[\alpha]_D$ +11° (*c* 1.0, chloroform); IR (KBr) 2570 (SH) 1740 (COO) cm^{-1}; ^{1}H NMR and ^{13}C NMR see Table I and Table II. LRMS

(CI, NH_3): m/z 398 $(M+NH_4)^+$. HRMS Calcd for $C_{14}H_{20}O_8S_2$: 380.0599. Found: 380.0590.

4-Nitrophenyl 2,3,4,6-Tetra-*O*-acetyl-1,5-dithio-β-D-glucopyranoside (7). 1-Fluoro-4-nitrobenzene (238 mg, 1.7 mmol) was added to a solution of **5** (427 mg, 1.1 mmol) in dry acetone (30 mL). A solution of cesium carbonate (365 mg, 1.1 mmol) in water (5 mL) was added, the mixture was shaken overnight, poured into ice-cold water (50 mL) and stirred vigorously. The aqueous phase was extracted with dichloromethane (2 x 50 mL) and the extract was dried over magnesium sulfate and concentrated. The residue **7** was purified by chromatography under medium pressure on a column of silica gel with ethyl acetate/petroleum ether (4:6 v/v) to give crystalline **7** (526 mg, 93%); mp 123-125 °C; $[\alpha]_D$ +53° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 2.01, 2.03, 2.05, 2.06 (4s, 12H, OAc), 3.34 (m, 1H, H-5), 4.12 (dd, 1H, $J_{5,6b}$ = 3.4 Hz, H-6b), 4.26 (dd, 1H, $J_{5,6a}$ = 5.5 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.32 (d, 1H, $J_{1,2}$ = 10.7 Hz, H-1), 5.12 (ft, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 5.26 (ft, 1H, $J_{2,3}$ = 10.1 Hz, H-2), 5.29 (ft, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 7.62 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.19 (d, 2H, J = 8.8 Hz, H_{Ar}). HRMS Calcd for $C_{20}H_{23}NO_{10}S_2$: 501.0763. Found: 501.0750.

4-Nitrobenzyl 2,3,4,6-Tetra-*O*-acetyl-1,5-dithio-β-D-glucopyranoside (8). Compound **8** was prepared and purified as described above for compound **7**. The fluoro reagent was replaced by 4-nitrobenzyl bromide and the reaction needed only 1.5 h stirring. Yield 90%; mp 129-131 °C; $[\alpha]_D$ -55° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 2.00, 2.02, 2.05, 2.08 (4s, 12H, OAc); 3.26 (m, 1H, H-5), 3.75 (d, 1H, $J_{1,2}$ = 10.8 Hz, H-1), 3.94 and 4.03 (2d, 2H, J_{gem} = 12.6 Hz, benzylic CH_2), 4.13 (dd, 1H, $J_{5,6b}$ = 3.4 Hz, H-6b), 4.26 (dd, 1H, $J_{5,6a}$ = 5.7 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 5.02 (ft, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.24 (ft, 1H, $J_{2,3}$ = 10.1 Hz, H-2), 5.26 (ft, 1H, $J_{4,5}$ = 10.1 Hz, H-4), 7.49 (d, 2H, J = 8.7 Hz, H_{Ar}), 8.19 (d, 2H, J = 8.7 Hz, H_{Ar}). HRMS Calcd for $C_{21}H_{25}NO_{10}S_2$: 515.0919. Found: 515.0910.

4-Nitrophenyl 1,5-Dithio-β-D-glucopyranoside (9). A suspension of compound **7** (478 mg, 0.9 mmol) in absolute methanol was treated with a small amount of sodium methoxide 1M solution. The mixture was stirred at room temperature, the reaction being monitored by TLC. After neutralization with DOWEX 50 W ion-exchange resin (acid form), filtration and concentration under reduced pressure, the obtained residue was purified by column chromatography (methanol/dichloromethane 1:9 v/v) to give **9** (300 mg, 95%); mp 154-156 °C; $[\alpha]_D$ +33° (*c* 1.0, acetone); ^1H NMR (DMSO-d_6 + D_2O) δ 2.94 (m, 1H, H-5), 3.11 (ft, 1H, $J_{3,4}$ = 8.7 Hz, H-3), 3.30 (2ft, 2H, H-2, H-4), 3.49 (dd, 1H, $J_{5,6b}$ = 6.3 Hz, H-6b), 3.73 (dd, 1H, $J_{5,6a}$ = 3.3 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6a), 4.50 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 7.66 (d, 2H, J = 8.7 Hz, H_{Ar}), 8.14 (d, 2H, J = 8.7 Hz, H_{Ar}).

Anal. Calcd for $C_{12}H_{15}NO_6S_2$ (333.37): C, 43.23; H, 4.54; N, 4.20. Found: C, 42.85; H, 4.87; N, 4.05.

4-Nitrobenzyl 1,5-Dithio-β-D-glucopyranoside (10). Compound **10** was prepared and purified as described above for compound **9**. Yield 93%; mp 153 °C; $[\alpha]_D$ -37° (*c*

1.0, acetone); ^{1}H NMR (DMSO-d_6 + D_2O) δ 2.74 (m, 1H, H-5), 2.94 (ft, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 3.22 (ft, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.25 (ft, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 3.45-3.51 (m, 1H, H-6b), 3.63 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 3.75 (dd, 1H, $J_{5,6a}$ = 3.2 Hz, $J_{6a,6b}$ = 11.5 Hz, H-6a), 4.02 (s, 2H, benzylic CH_2), 7.61 (d, 2H, J = 8.7 Hz, H_{Ar}), 8.17 (d, 2H, J = 8.7 Hz, H_{Ar}).

Anal. Calcd for $C_{13}H_{17}NO_6S_2$ (347.40): C, 44.94; H, 4.93; N, 4.03. Found: C, 44.50; H, 5.10; N, 4.54.

5-Thioglucobrassicin Thiohydroximate (13). To a stirred solution of indol-3-ylacethydroximoyl chloride[15] (**12**) (97 mg, 0.4 mmol) in an anhydrous ether/dichloromethane (2:1 v/v) mixture under argon were successively added 2,3,4,6-tetra-*O*-acetyl-1,5-dithio-β-D-glucopyranose (**5**) (120 mg, 0.3 mmol) dissolved in dry dichloromethane (2 mL) and freshly distilled triethylamine (0.13 mL, 0.9 mmol). Triethylammonium hydrochloride immediately precipitated from the solution. After stirring for 1 h, the mixture was acidified with H_2SO_4 (0.5 M), extracted with dichloromethane and the organic layer was dried ($MgSO_4$) and concentrated to dryness. The remaining solid was purified by column chromatography using ethyl acetate/petroleum ether (1:1 v/v) as eluent to afford **13** as an amorphous solid (131 mg, 75%); $[\alpha]_D$ +43° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.88, 1.94, 1.97, 2.05 (4s, 12H, OAc), 2.64 (m, 1H, H-5), 3.91 (dd, 1H, $J_{5,6b}$ = 3.4 Hz, H-6b), 4.06 and 4.17 (2d, 2H, J_{gem} = 16.6 Hz, H-8a, H-8b), 4.11 (dd, 1H, $J_{5,6a}$ = 5.1 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 4.45 (d, 1H, $J_{1,2}$ = 11.1 Hz, H-1), 4.75 (ft, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.05 (ft, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 5.15 (ft, 1H, $J_{4,5}$ = 10.3 Hz, H-4), 7.13 (d, 1H, $J_{2i,NH}$ = 2.3 Hz, H-2i), 7.17 (ft, 1H, J = 7.3 Hz, H-5i), 7.23 (ft, 1H, J = 7.3 Hz, H-6i), 7.39 (d, 1H, J = 7.6 Hz, H-7i), 7.65 (d, 1H, J = 7.6 Hz, H-4i), 8.29 (s, 1H, NH); LRMS (IC, NH_3): m/z 553 $(M+1)^+$. HRMS Calcd for $C_{24}H_{28}N_2O_9S_2$: 552.1236. Found: 552.1220.

5-Thioglucotropaeolin Thiohydroximate (15). This compound was prepared as described above for compound **13**, using 2-phenylacethydroximoyl chloride (**14**) as the electrophilic partner. Final purification by column chromatography with ethyl acetate/petroleum ether (4:6 v/v) elution afforded **15** as an amorphous solid. Yield 75%; $[\alpha]_D$ +46° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.93, 1.95, 2.00, 2.07 (4s, 12H, OAc), 3.10 (m, 1H, H-5), 4.06 (dd, 1H, $J_{5,6b}$ = 3.4 Hz, H-6b), 3.98 (s, 2H, benzylic CH_2), 4.22 (dd, 1H, $J_{5,6a}$ = 5.1 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.31 (d, 1H, $J_{1,2}$ = 10.7 Hz, H-1), 4.85 (ft, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.09 (ft, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 5.22 (ft, 1H, $J_{4,5}$ = 10.4 Hz, H-4), 7.26-7.40 (m, 5H, H_{Ar}), 8.50 (s, 1H, NOH); LRMS (IC, NH_3): m/z 514 $(M+1)^+$. HRMS Calcd for $C_{22}H_{27}NO_9S_2$: 513.1127. Found: 513.1120.

Pro-5-thioglucobrassicin (16). To a cooled (0 °C) and stirred solution of pyridine (2 mL) in dry dichloromethane (2 mL) under argon, a solution of chlorosulphonic acid (0.3 mL, 4.5 mmol) in dry dichloromethane (2 mL) was added over a period of 15 min, followed by a solution of **13** (120 mg, 0.2 mmol) in dry dichloromethane (5 mL). After stirring for 24 h at room temperature, the medium was treated with a solution of potassium hydrogen carbonate (120 mg, 1.4 mmol) in

water (2mL) and stirred another 30 min; the solvents were evaporated and traces of pyridine removed by coevaporation with toluene. The residue was purified by column chromatography (eluent methanol/dichloromethane 1:9 v/v) to give an amorphous powder **16** (87 mg, 60%); $[\alpha]_D$ +45° (*c* 1.0, methanol); ^{1}H NMR (DMSO-d_6) δ 1.74, 1.90, 1.96, 1.98 (4s, 12H, OAc), 3.69 (m, 1H, H-5), 3.96 (dd, 1H, $J_{5,6b}$ = 3.2 Hz, H-6b), 3.94 and 4.06 (2d, 2H, J_{gem} = 16.5 Hz, H-8a, H-8b), 4.15 (dd, 1H, $J_{5,6a}$ = 5.5 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.86 (ft, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 4.91 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 5.02 (ft, 1H, $J_{4,5}$ = 9.9 Hz, H-4), 5.13 (ft, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 6.95 (ft, 1H, J = 7.1 Hz, H-5i), 7.07 (ft, 1H, J = 7.1 Hz, H-6i), 7.34 (d, 1H, J = 7.9 Hz, H-7i), 7.44 (d, 1H, $J_{2i,NH}$ = 2.4 Hz, H-2i), 7.66 (d, 1H, J = 7.9 Hz, H-4i). HRMS (FAB) Calcd for $C_{24}H_{27}KN_2O_{12}S_3$: 670.0363. Found: 670.0351.

Pro-5-thioglucotropaeolin (17). Compound **17** was obtained as described above for compound **16**. Yield 75%; $[\alpha]_D$ +36° (*c* 1.0, methanol); ^{1}H NMR (DMSO-d_6) δ 1.84, 1.91, 1.97, 1.99 (4s, 12H, OAc), 3.77 (m, 1H, H-5), 3.99 (dd, 1H, $J_{5,6b}$ = 3.2 Hz, H-6b), 3.99 (s, 2H, benzylic CH_2), 4.16 (dd, 1H, $J_{5,6a}$ = 5.5 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.78 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 4.89 (ft, 1H, $J_{2,3}$ = 10.1 Hz, H-2), 5.03 (ft, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.18 (ft, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 7.22-7.42 (m, 5H, H_{Ar}). HRMS (FAB) Calcd for $C_{22}H_{26}KNO_{12}S_3$: 631.0246. Found 631.0251.

5-Thioglucobrassicin (18). To a stirred solution of **16** (80 mg, 0.1 mmol) in anhydrous methanol a few drops of a 1M solution of potassium methoxide were added in order to reach pH 8-9. When the reaction had finished (TLC), the solvent was evaporated. The remaining solid was dissolved in water then submitted to freeze-drying, whereby compound **18** was obtained as an hygroscopic white solid. Yield 80%; $[\alpha]_D$ -3° (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 2.37 (m, 1H, H-5), 2.97 (ft, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 3.42 (ft, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 3.50 (ft, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.69 (dd, 1H, $J_{5,6b}$ = 3.3 Hz, H-6b), 3.75 (dd, 1H, $J_{5,6a}$ = 5.1 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 4.20 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 4.25 and 4.45 (2d, 2H, J_{gem} = 16.1 Hz, H-8a, H-8b), 7.24 (ft, 1H, J = 7.1 Hz, H-5i), 7.31 (ft, 1H, J = 7.1 Hz, H-6i), 7.41 (s, 1H, H-2i), 7.57 (d, 1H, J = 7.9 Hz, H-7i), 7.81 (d, 1H, J = 7.9 Hz, H-4i). HRMS (FAB) Calcd for $C_{16}H_{19}KN_2O_8S_3$: 501.9941. Found: 501.9928.

5-Thioglucotropaeolin (19). Compound **19** was obtained as described above for compound **18**. Yield 85%; $[\alpha]_D$ +3° (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 2.94 (m, 1H, H-5), 3.17 (ft, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 3.50 (ft, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 3.61 (ft, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.83 (dd, 1H, $J_{5,6b}$ = 3.3 Hz, H-6b), 3.96 (dd, 1H, $J_{5,6a}$ = 5.5 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.14 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 4.18 and 4.35 (2d, 2H, J_{gem} = 16.2 Hz, benzylic CH_2), 7.32-7.49 (m, 5H, H_{Ar}). HRMS (FAB) Calcd for $C_{14}H_{18}KNO_8S_3$: 462.9824. Found: 462.9831.

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