Synthesis Y. W. Lim et al. Paper

Improved Synthesis of Glucosinolates

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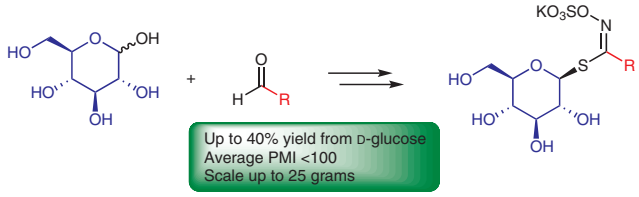

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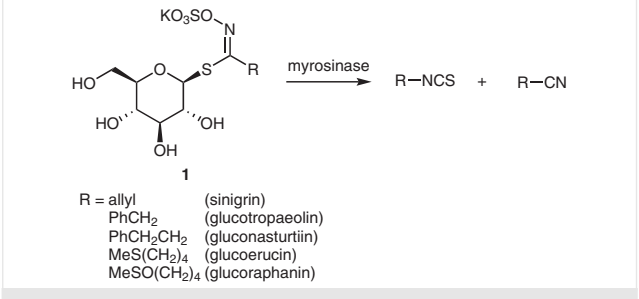
Abstract Herein we describe an improved synthesis of glucosinolates, in which the quantity and cost of materials have been reduced by approximately an order of magnitude compared to typical literature procedures. This allowed us to produce multiple glucosinolates in 10–25 gram batches using vessel sizes no larger than 0.5 litres.

Key words carbohydrates, glucosinolates, green chemistry, isothiocyanates, scale-up

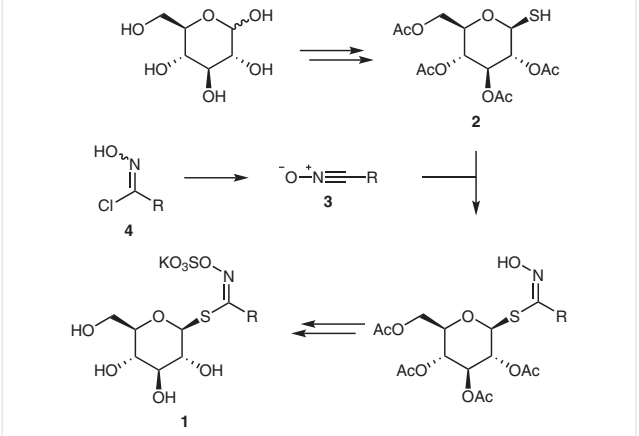
Glucosinolates[1–5] are found extensively in plants of the family Brassicaceae (formerly Cruciferae), among selected others. Within this family, *Brassica oleracea* is undoubtedly one of the most important plants in human nutrition, with its cultivars now comprising a large number of green vegetables. Glucosinolates **1** share the common structure as detailed in Scheme 1, with variation only in the side chain. The number of glucosinolates known is now approximately 200, with several of the most common side chains exemplified in Scheme 1.



Scheme 1 Glucosinolates as isothiocyanate and nitrile precursors

Derived from amino acids,[6] glucosinolates undergo degradation to produce a variety of compounds including isothiocyanates and nitriles. This conversion occurs in the presence of the myrosinase enzyme, contained in a separate compartment within plants. In addition, degradation can be promoted by gut microflora and various other stimuli such as acid/alkali, or high temperatures when cooking such vegetables.[5,7] Isothiocyanates in particular are known for their wide-ranging bioactivities which may be exploited in a multitude of medicinal and antimicrobial applications, including protection against carcinogenesis.[7,8]

However, the poor availability of pure glucosinolates remains a barrier for further studies, with most chemical suppliers providing pack sizes of 100 mg or less. Sinigrin (**1**, R = allyl), the most common glucosinolate, is the least expensive and most readily available, with pack sizes of up to 1 g. The typical route for the synthesis of glucosinolates



Scheme 2 Typical synthesis of glucosinolates

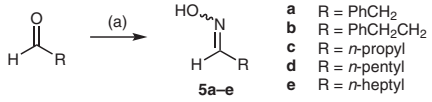
(Scheme 2) was first established by Benn[9] in 1963, and subsequently many others have followed this synthesis to obtain a variety of glucosinolates.[10–16]

This route involves coupling of thiosugar **2** with nitrile oxides **3**, usually generated in situ via base treatment of *N*-hydroxyimidoyl chlorides **4**, which in turn are typically accessed by chlorination of either an aldoxime, or a nitronate (azinate) salt.[10,11] The aldoxime pathway is the most straightforward; however, in the case of sinigrin and others, the nitronate pathway may be necessary to achieve chlorination.[10–12] While most synthetic procedures report the preparation of glucosinolates in milligram to gram quantities, a notable exception is that of Abramski and Chmielewski's preparation of sinigrin in a quantity in the tens of grams.[11] We sought to further improve the synthesis of glucosinolates, with a focus on the more common aldoxime-based pathway. In addition to preparing multigram quantities of synthetic glucosinolates on the laboratory scale, we incorporated green chemistry principles to ensure the cost and quantity of materials were minimised, and the majority of hazardous materials were either removed or replaced. We therefore approached this synthesis with a complete analysis of the entire process, to ensure it could be made as safe and efficient as possible. To ensure our synthesis was robust, reliable and applicable to a wide range of glucosinolates, we elected to continue to use the typical synthesis outlined in Scheme 2, despite the number of steps involved. Whilst elimination of protecting groups offers greater simplicity, we chose not to, as this would likely complicate isolation and purification of intermediates, for comparatively little overall benefit in cost or materials use. Fortunately, we realised certain intermediates did not require isolation or purification, which led to a dramatic reduction in materials use and process steps.

We elected to commence our synthesis from D-glucose, due to its low cost compared to more advanced, commercially available intermediates such as thiosugar **2**. This also ensured we kept to the recommendation of avoiding expensive or rare starting materials, as suggested by Sheldon and co-workers.[17] The common core structure of glucosinolates allows access to a large number of analogues, simply by changing the *N*-hydroxyimidoyl chloride **4** in the synthesis depicted in Scheme 2. In our case, we chose to employ readily available aldehydes to demonstrate the utility of our improved synthesis. Of the common natural glucosinolates, glucotropaeolin (**1**, R = CH_2Ph) and gluconasturtiin (**1**, R = CH_2CH_2Ph) may be prepared from 2-phenylacetaldehyde and 3-phenylpropionaldehyde, respectively, both of which are naturally occurring and commercially available fragrance compounds. In addition to these, we sought access to three glucosinolates with *n*-alkyl side chains, derived from butyraldehyde, hexanal and octanal. It is noteworthy that such alkylglucosinolates are also observed in nature, albeit in low concentrations compared to the more well-known glucosinolates (Scheme 1),[2] yet it is expected that they too would undergo degradation to provide the antimicrobial isothiocyanates in a similar manner to the natural glucosinolates.

We initially prepared two exemplary glucosinolates, gluconasturtiin (2-phenylethylglucosinolate) and *n*-heptylglucosinolate, with procedures closely following those typical in literature syntheses.[13,15] This also allowed us to gain insight into where costs and materials use could be reduced. The experimental for this synthesis is given in the Supporting Information, and all modifications to this methodology are discussed below.

Embarking on our improved synthesis, we formed oximes **5** via reaction of the corresponding aldehydes with hydroxylamine hydrochloride (Scheme 3). Sodium hydroxide was used to incompletely neutralise the hydroxylamine salt, as complete neutralisation leads to side reactions in the case of aliphatic aldehydes, presumably via aldol condensations under the alkaline conditions.

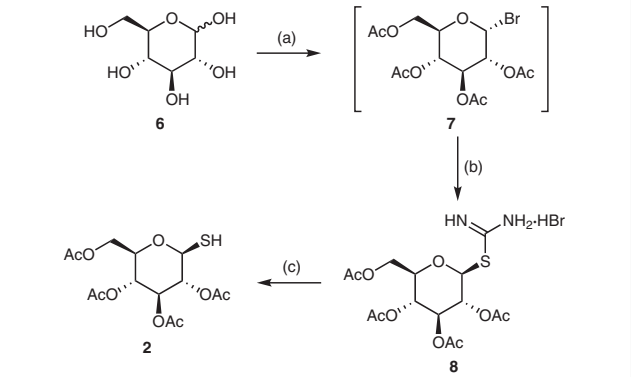


Scheme 3 Preparation of oximes **5**. *Reagents and conditions*: (a) $NH_2OH{\cdot}HCl$, NaOH, MeOH, H_2O (**5a**,**b**), r.t. to 40 °C, 2 h, 83–98%.

The reaction is normally buffered at a lower pH, in which sodium acetate is often used as a base; however, the change to sodium hydroxide eliminated the need for laborious quenching of the acetic acid formed after neutralisation of the hydroxylamine hydrochloride. Running the reaction in aqueous methanol allowed for concentration of the solution and subsequent precipitation of the product, for the 2-phenylacetaldehyde and 3-phenylpropionaldehyde oximes. In contrast, the aliphatic oximes failed to crystallise, as their melting points are low. Thus, for these substrates, the reaction was performed in methanol only, which was then thoroughly evaporated to provide a slurry of primarily oxime and inorganic materials. This slurry was diluted with ethyl acetate and filtered to remove the inorganic salts, which was followed by concentration of the filtrate to provide the neat oxime. All oximes were obtained in high yield (83–98%) and in good purity, provided the aldehydes were distilled before use.

Typically, thiosugar **2** is obtained from D-glucose (**6**) via acetobromoglucose (**7**, Scheme 4), which in turn is formed in a one-pot procedure via acid-catalysed acetylation and subsequent addition of excess hydrogen bromide (typically as a solution in acetic acid). Literature precedence[18,19] shows that hydrogen bromide can function as the acid catalyst, circumventing the need for typical catalysts such as perchloric acid (explosive) and sulfuric acid (acetylation difficult to control). While hydrogen bromide is not as effective a catalyst for acetylation, this ensures the exothermic reaction may be easily controlled with occasional

submersion in an ice bath. We found we could reduce the typical amount of both acetic anhydride and hydrogen bromide, which also allowed us to add the entire portion of hydrogen bromide at the beginning of the reaction, to act as both acylation catalyst and the brominating agent. Upon complete dissolution of the sugar (<30 min), the reaction was held for several hours to ensure high conversion into the bromosugar **7**.



Scheme 4 Synthesis of thiosugar **2**. *Reagents and conditions*: (a) Ac_2O, 33% (w/w) HBr in AcOH, r.t. to 55 °C, 3 h; (b) thiourea, 80 °C, 1 h, 68% from **6**; (c) Na_2SO_3, H_2O, EtOAc, 40 °C, 1 h, 99%.

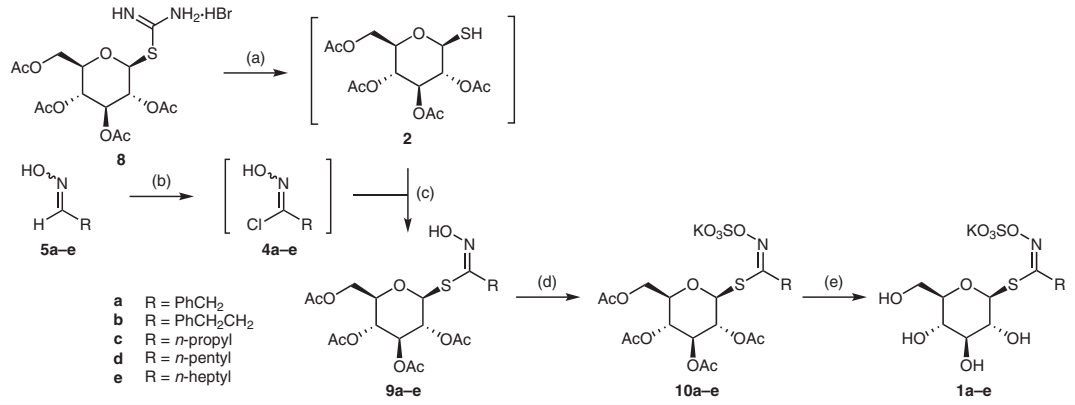
Acetobromoglucose (**7**) is usually isolated by dissolution with dichloromethane, followed by washing with copious amounts of water and sodium bicarbonate solution to remove the large quantity of hydrobromic and acetic acids, then recrystallisation from diethyl ether. To create a suitably safe and scalable synthesis, we sought to eliminate both of these hazardous organic solvents, and the laborious workup. We reasoned that isolation of acetobromoglucose was not strictly necessary, as the reaction of alkyl halides with thiourea can be performed in a variety of solvents. For acetobromoglucose, it is important to avoid the use of alcohols as solvent, which can lead to deacetylation of the sugar.

Therefore, the solution of acetobromoglucose (**7**) was treated with sodium acetate to neutralise the excess hydrogen bromide,[19] then the precipitated sodium bromide was removed by filtration, followed by washing the precipitate with a small quantity of ethyl acetate. This crude filtrate solution, comprised primarily of acetobromoglucose in acetic acid, was directly reacted with thiourea. This simplified protocol provided the glucosylisothiouronium salt **8**, which precipitated from the reaction mixture, and was simply filtered and washed with ethyl acetate. The product was isolated in 68% yield from D-glucose in three chemical steps, and was deemed to be adequately pure. This protocol was routinely performed using 50-gram batches of D-glucose.

Hydrolysis of glucosyl salt **8** to liberate the thiol functionality (thiosugar **2**) was conducted in aqueous sodium sulfite (less odorous than sodium metabisulfite) and ethyl acetate, which serves to extract the thiosugar from the aqueous phase as it forms. To prevent the conversion of thiosugar **2** into the disulfide (i.e., dimerisation),[20] we used degassed solutions and maintained a stream of argon throughout the reaction. The thiol was isolated in very good purity and near quantitative yield from **8**; thus, it was determined the isolation of **2** was not necessary in the scale-up synthesis of glucosinolates. Upon full optimisation of all steps, the thiol was liberated and immediately used as a solution in ethyl acetate to form the thiohydroximates **9** without purification (Scheme 5).

As *N*-hydroxyimidoyl chlorides are known to be unstable,[12,21] we telescoped the formation of the *N*-hydroxyimidoyl chloride and the subsequent coupling with the thiosugar (see Scheme 5). We were inspired by an earlier synthesis of isoxazoles,[22] which also utilises nitrile oxide precursors, adapting this protocol for thiohydroximates. The use of ethyl acetate as solvent allowed us to eliminate *N*,*N*-dimethylformamide from our synthesis, which is typically the solvent of choice for this step.[13,15] We observed that this chlorination step gave an intense blue colour, presumably due to elemental chlorine, generated upon reaction of the hydrochloric acid catalyst with the *N*-chlorosuccinimide.[22] We were able to add the oximes neat, in a single portion to the reaction mixture, which in our hands led to a moderate exotherm at scale (0.1 mol); the internal temperature within the round-bottomed flask typically rose to ca. 50 °C. Upon addition of thiosugar **2**, we observed unreacted *N*-chlorosuccinimide could oxidise thiosugar **2** to its disulfide. We thus employed a ca. 5 mol% excess of oxime for the chlorination step, to ensure full consumption of the *N*-chlorosuccinimide. This also allowed us to monitor the chlorination, which was complete upon loss of the blue colour, indicating the *N*-chlorosuccinimide was fully consumed. Once the chlorination step was fully optimised, we moved on to telescoping this step with the subsequent base-mediated generation of the nitrile oxide, and subsequent coupling with thiosugar **2**. Indeed, precursors **5** and **8** could be simultaneously converted into the thiosugar and the *N*-hydroxyimidoyl chloride, respectively, then the two mixtures combined as solutions of ethyl acetate. Subsequent treatment with a solution of aqueous potassium carbonate allowed conversion of the *N*-hydroxyimidoyl chloride into the required nitrile oxide (not shown in Scheme 5).

Thiosugar **2** was added to the *N*-hydroxyimidoyl chloride before the base, to minimise the dimerisation of nitrile oxide to furoxans.[21,23] This efficient click-like reaction gave us the thiohydroximate products **9** in yields of 70–86% from glucosyl salt **8**, without any isolation of the thiosugar or *N*-hydroxyimidoyl chloride intermediates. Upon completion of the reaction and brief workup, the organic phase was concentrated, then the product recrystallised from aqueous methanol to remove the majority of the impurities, primarily furoxans and succinimide. For 2-phenethyl thiohydroximate **9b**, the product precipitated from solution during the



Scheme 5 Synthesis of glucosinolates. *Reagents and conditions*: (a) Na_2SO_3, H_2O, EtOAc, r.t., 1–1.5 h; (b) *N*-chlorosuccinimide, cat. py (**5a**), cat. concd HCl (**5b–d**), EtOAc, r.t. to 50 °C, 1–4 h; (c) K_2CO_3, H_2O, r.t., 1 h, 70–86% from **8**; (d) i) py·SO_3, cat. py, MeCN, reflux, 1–2.5 h, ii) K_2CO_3, H_2O, EtOAc, 60 °C, 10 min, 51–75% from **9**; (e) cat. KOH, MeOH, r.t., 2–2.5 h, 95% to quantitative.

coupling reaction; after the workup, the precipitate was isolated, and a second crop was obtained after partial concentration of the filtrate. This provided **9b** in comparable purity to the other thiohydroximates, obviating the need for recrystallisation.

The initial attempt at forming benzyl thiohydroximate **9a** was unsuccessful at scale, providing a complex mixture of which ca. 50% of the material was the desired product. Investigation revealed the chlorination of benzyl oxime was generating a number of products, as determined by TLC and NMR analysis, presumably due to the lability of the benzylic position. This was solved by conducting the chlorination with catalytic pyridine, which required a higher temperature and extended reaction time. Subsequent coupling proceeded well, with the yield comparable to the other analogues, despite the smaller scale used (1 g).

The sulfation of thiohydroximates **9** was also improved, although it remains a challenging step, as previously noted.[13] While typical procedures exploit a large excess (ca. 2.5–5 equiv) of pyridine–sulfur trioxide complex,[13–16] we realised this was likely to provide full conversion and/or to allow for partially hydrolysed batches of the complex to be used. Reduction of the amount of complex used was a key focus for this step, primarily due to the high cost of this reagent. Dichloromethane is the solvent of choice when this reagent is used in glucosinolate synthesis; however, we found any aprotic solvent promoted sulfation of the thiohydroximates **9**. Slow conversion was observed in acetone and ethyl acetate, which was attributed to poor solubility of pyridine–sulfur trioxide complex in these solvents. Acetonitrile, however, offered an excellent alternative due to its adequate solubilisation of the complex, plus the higher reflux temperature ensured complete reaction occurred within a few hours. Careful monitoring of the reaction was required, as under extended reaction times the material underwent degradation, as evidenced by the presence of the previously observed thiosugar disulfide in the reaction mixture. With anhydrous acetonitrile, we found just 1.5 equivalents of the complex was sufficient, even when using a batch that was several years old.

Subsequent treatment with potassium carbonate and isolation converted the intermediate pyridinium salts into the potassium salts **10**. This base was chosen in place of the more expensive and less common potassium bicarbonate; a slight excess of base and rapid stirring were used to avoid hydrolysis of the acetate groups. The high polarity of the sulfated products **10** led us to attempt recrystallisation from methanol; unfortunately, this also led to partial desulfation of the material, as observed previously.[13] We noted the products were sparingly soluble in both water and ethyl acetate; thus, recrystallisation from a mixture of these solvents was sufficient to remove all impurities, such as water-soluble reagent byproducts and any residual starting material. This atypical crystallisation using a mixture of immiscible solvents became a single phase with full dissolution of the product only when approaching the boiling point of ethyl acetate.

Deprotection of acetylated glucosinolates is usually performed using either ammonia or potassium methoxide in methanol, to provide the glucosinolates as the natural potassium salts. We elected to use potassium hydroxide in methanol, which would introduce a small quantity of water in the reaction. Nevertheless, this was not deemed to be a problem due to the small amount of base required (0.05 equiv, or 0.0125 equiv per acetate group). The deprotection proceeded swiftly, with full conversion achieved within 2 hours for all substrates. In the preliminary synthesis, the reaction mixtures were neutralised with sulfonic acid functionalised Amberlite®, yet this appeared to cause colouring of the material. For the scale-up batches, neutralisation was achieved with carboxylic acid functionalised Amberlite®, followed by treatment with charcoal for further decolouri-

sation. Concentration and drying under reduced pressure provided the glucosinolates in quantities of up to 25 grams per batch.

The completed synthesis gave us overall yields of 25–40% from D-glucose (seven chemical steps). The improved protocol involves only five isolation steps, of which only advanced intermediates **9** and **10** required purification.

A summary of the synthetic route is given in Table 1, with PMI (process mass intensity) given. Calculations used procedures given in the experimental section and the Supporting Information. While the yields were comparable with the preliminary routes, the clear advantage in this synthesis is shown by the dramatic reduction in PMI. For the syntheses of **1b** and **1e**, the improvement is by approximately an order of magnitude (reduction in PMI 94% (**1b**) and 96% (**1e**)).

Table 1 Comparison between Preliminary and Scale-Up Routes of **1**

Glucosinolate	Route	PMI (g/g)	Overall yield from **6**
1a	scale-up	160	34%
1b	scale-up	62	40%
1b	preliminary	1000	43%
1c	scale-up	91	25%
1d	scale-up	72	32%
1e	scale-up	56	40%
1e	preliminary	1500	29%

The reduction in PMI was principally achieved by eliminating all chromatographic purification, and running all operations at high solvent concentration, in addition to the process improvements mentioned earlier. This also allows such scale-up procedures to be done in standard research lab glassware, in which vessel sizes of up to 0.5 litre were employed, even on a 50 gram reaction scale. This significant reduction in PMI also allows an approximately 10-fold reduction in the cost of materials, as determined based on the current (2017) costing for the procedures described.

Furthermore, the solvent contributions have changed dramatically, both in identity and quantity (ca. 20-fold reduction). As an example, the charts in Figure 1 compare the preliminary and improved synthesis of **1b**. The solvent use was critically evaluated throughout the synthesis, and we successfully eliminated hazardous solvents such as dichloromethane, diethyl ether, *N*,*N*-dimethylformamide and hexanes. The solvent inventory used for scale-up is both simple and safe, eliminating all solvents which are regarded as in need of replacement in pharmaceutical manufacturing.[24,25]

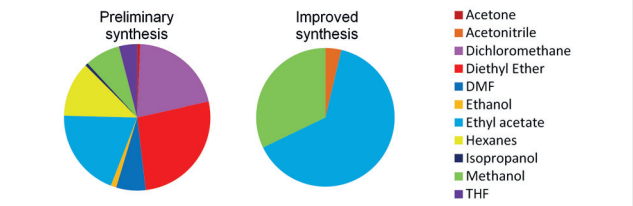


Figure 1 Solvent distribution in the synthesis of gluconasturtiin (**1b**)

In summary, we have demonstrated a complete transformation of the standard aldoxime pathway for the synthesis of glucosinolates. The synthetic procedures have been dramatically simplified and demonstrated to be successful on a multigram scale. This allows for the synthesis of significant quantities of glucosinolates using a fraction of the materials of a typical synthesis. We anticipate this work will enable further progress in glucosinolate research.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker NMR spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C acquisitions. Chemical shifts (δ) are reported in parts per million (ppm) from TMS (0.00 ppm). NMR spectra were referenced to the residual solvent peaks ($CDCl_3$: 7.26 ppm for ^{1}H, 77.16 ppm for ^{13}C; DMSO-d_6: 2.50 ppm for ^{1}H, 39.52 ppm for ^{13}C; D_2O: not referenced). IR spectra were recorded neat on a PerkinElmer Spectrum 100 FT-IR spectrophotometer. High-resolution mass spectra were obtained on an Agilent LC-TOF instrument using an electrospray ionisation (ESI) source in either positive mode or negative mode, as indicated by the reported ion. Elemental analyses were performed on a Eurovector EuroEA3000 CHNS Elemental Analyzer. Unless otherwise stated, products were synthesised using the general procedures outlined below and were used without further purification in all cases. Anhydrous MeCN was obtained by passing commercially available, pre-dried, oxygen-free solvent through activated columns. Aldehydes were distilled immediately before reactions. All other reagents and solvents were of analytical quality and used as received.

All scale-up procedures are given below; preliminary experimental procedures, all of which closely follow prior literature, are given in the Supporting Information, with characterisation data for compounds that are not listed in the experimental section. Copies of NMR spectra for all isolated materials from scale-up procedures (i.e., compounds **1**, **5**, **8**–**10**) are given in the Supporting Information.

Aromatic Oximes 5a and 5b; General Procedure

A solution of NaOH (ca. 0.275 mol) in H_2O (100 mL) was diluted with MeOH (250 mL), then treated successively with hydroxylamine hydrochloride (ca. 0.300 mol) and aldehyde (ca. 0.250 mol). Upon addition of the aldehyde, a minor exotherm was observed, with the internal temperature rising to ca. 40 °C. The reaction mixture was stirred at r.t. for 2 h. The mixture was concentrated to remove the MeOH, then filtered. The precipitate was washed with H_2O (2 × 25 mL) and dried under vacuum to provide the oxime as a white crystalline solid.

2-Phenylacetaldehyde Oxime (5a)

NaOH (10.96 g, 0.274 mol) was treated with hydroxylamine hydrochloride (20.85 g, 0.300 mol) and 2-phenylacetaldehyde (30.06 g, 0.250 mol). Oxime **5a** was obtained as a white crystalline solid (33.19 g, 98%). The NMR data were in excellent agreement with those previously obtained.[26,27]

Mp 82–84 °C (Lit.[28] 83–86 °C).

IR: 3209, 3087, 3029, 2870, 1662, 1497, 1454, 1438, 1328, 1056, 927, 749, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (br s, 1 H (*E* or *Z*)), 7.54 (t, *J* = 6.3 Hz, 1 H (*E*)), 7.41 (br s, 1 H (*E* or *Z*)), 7.35–7.31 (m, 2 H), 7.28–7.21 (m, 3 H), 6.90 (t, *J* = 5.3 Hz, 1 H (*Z*)), 3.74 (d, *J* = 5.2 Hz, 2 H (*Z*)), 3.54 (d, *J* = 6.3 Hz, 2 H (*E*)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1 (*Z*), 150.9 (*E*), 136.6, 136.2, 129.0, 128.94, 128.90, 127.1, 126.9, 36.0 (*E*), 31.8 (*Z*).

HRMS-TOF: *m*/*z* $[M + H]^+$ calcd for $C_8H_{10}NO^+$: 136.0757; found: 136.0758.

3-Phenylpropionaldehyde Oxime (5b)

NaOH (11.06 g, 0.277 mol) was treated with hydroxylamine hydrochloride (20.83 g, 0.300 mol) and 3-phenylpropionaldehyde (33.58 g, 0.250 mol). Oxime **5b** was obtained as a white crystalline solid (36.2 g, 97%). The NMR data were in excellent agreement with those previously obtained.[29]

Mp 83–84 °C (Lit.[28] 92–94 °C).

IR: 3189, 3062, 3028, 2860, 1662, 1500, 1456, 1431, 1311, 1078, 938, 920, 912, 850, 758, 724, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (br s, 1 H (*E* or *Z*)), 7.91 (br s, 1 H (*E* or *Z*)), 7.47 (t, *J* = 5.9 Hz, 1 H (*E*)), 7.33–7.29 (m, 2 H), 7.23–7.19 (m, 3 H), 6.76 (t, *J* = 5.3 Hz, 1 H (*Z*)), 2.85–2.81 (m, 2 H), 2.75–2.69 (m, 2 H (*Z*)), 2.53 (td, *J* = 7.8, 6.0 Hz, 2 H (*E*)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0 (*Z*), 151.6 (*E*), 140.8, 140.6, 128.7, 128.5, 128.4, 126.4, 32.9 (*E*), 32.1 (*Z*), 31.4 (*E*), 26.5 (*Z*).

HRMS-TOF: *m*/*z* $[M + H]^+$ calcd for $C_9H_{12}NO^+$: 150.0913; found: 150.0915.

Alkyl Oximes 5c–e; General Procedure

A solution of NaOH (ca. 0.275 mol) in MeOH (80 mL) was treated with a solution of hydroxylamine hydrochloride (ca. 0.300 mol) in MeOH (170 mL), then treated with freshly distilled aldehyde (ca. 0.250 mol). Upon addition of the aldehyde, a minor exotherm was observed, with the internal temperature rising to ca. 40 °C. The reaction mixture was stirred at r.t. for 2 h. The mixture was concentrated to remove the MeOH, filtered, then the precipitated salt was washed with EtOAc (100 mL). The filtrate was concentrated to provide the oxime as a clear colourless liquid or a white crystalline solid.

Butyraldehyde Oxime (5c)

NaOH (11.10 g, 0.278 mol) was treated with hydroxylamine hydrochloride (20.88 g, 0.300 mol) and butyraldehyde (18.16 g, 0.252 mol). Oxime **5c** was obtained as a clear colourless liquid with ca. 4.9% (w/w) EtOAc (19.15 g, 83%). The NMR data were in excellent agreement with those previously obtained.[27]

IR: 3259, 3107, 2964, 2936, 2876, 1461, 933, 885 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.09 (br s, 1 H (*E* or *Z*)), 8.70 (br s, 1 H (*E* or *Z*)), 7.42 (t, *J* = 6.2 Hz, 1 H (*E*)), 6.72 (t, *J* = 5.4 Hz, 1 H (*Z*)), 2.36 (td, *J* = 7.5, 5.4 Hz, 2 H (*Z*)), 2.18 (td, *J* = 7.3, 6.2 Hz, 2 H (*E*)), 1.52 (sext, *J* = 7.5 Hz, 2 H), 0.98–0.93 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1 (*Z*), 152.4 (*E*), 31.5 (*E*), 27.0 (*Z*), 20.1 (*E*), 19.6 (*Z*), 14.0 (*Z*), 13.7 (*E*).

HRMS-TOF: *m*/*z* $[M + H]^+$ calcd for $C_4H_{10}NO^+$: 88.0757; found: 88.0760.

Hexanal Oxime (5d)

NaOH (10.99 g, 0.275 mol) was treated with hydroxylamine hydrochloride (20.90 g, 0.301 mol) and hexanal (25.13 g, 0.251 mol). Oxime **5d** was obtained as a white crystalline solid (27.24 g, 94%). The NMR data were in excellent agreement with those previously obtained.[29]

Mp 44–47 °C (Lit.[30] 51 °C).

IR: 3250, 2958, 2929, 2861, 1466, 1324, 1049, 931, 722 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (br s, 1 H (*E* or *Z*)), 7.78 (br s, 1 H (*E* or *Z*)), 7.42 (t, *J* = 6.1 Hz, 1 H (*E*)), 6.72 (t, *J* = 5.5 Hz, 1 H (*Z*)), 2.37 (td, *J* = 7.6, 5.5 Hz, 2 H (*Z*)), 2.19 (td, *J* = 7.5, 6.2 Hz, 2 H (*E*)), 1.48 (quin, *J* = 7.2 Hz, 2 H), 1.37–1.28 (m, 4 H), 0.91–0.87 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3 (*Z*), 152.6 (*E*), 31.7, 31.4, 29.6, 26.4, 25.9, 25.0, 22.50, 22.49, 14.06, 14.05.

HRMS-TOF: *m*/*z* $[M + H]^+$ calcd for $C_6H_{14}NO^+$: 116.1070; found: 116.1073.

Octanal Oxime (5e)

NaOH (11.08 g, 0.277 mol) was treated with hydroxylamine hydrochloride (20.86 g, 0.300 mol) and octanal (32.13 g, 0.251 mol). Oxime **5e** was obtained as a white crystalline solid (35.17 g, 98%). The NMR data were in excellent agreement with those previously obtained.[31]

Mp 49–51 °C (Lit.[30] 60 °C).

IR: 3209, 2957, 2925, 2855, 1466, 1323, 921, 865, 825, 721 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (br s, 1 H (*E* or *Z*)), 7.52 (br s, 1 H (*E* or *Z*)), 7.42 (t, *J* = 6.1 Hz, 1 H (*E*)), 6.71 (t, *J* = 5.5 Hz, 1 H (*Z*)), 2.37 (td, *J* = 7.6, 5.5 Hz, 2 H (*Z*)), 2.19 (td, *J* = 7.5, 6.2 Hz, 2 H (*E*)), 1.48 (quin, *J* = 7.3 Hz, 2 H), 1.36–1.22 (m, 8 H), 0.90–0.86 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4 (*Z*), 152.7 (*E*), 31.86, 31.85, 29.6, 29.5, 29.2, 29.13, 29.11, 26.7, 26.2, 25.1, 22.6, 14.2.

HRMS-TOF: *m*/*z* $[M + H]^+$ calcd for $C_8H_{18}NO^+$: 144.1383; found: 144.1384.

S-(2,3,4,6-Tetra-*O*-acetyl-1-β-D-glucopyranosyl)isothiouronium Bromide (8)

A magnetically stirred solution of D-glucose (**6**; 50.04 g, 0.278 mol) in Ac_2O (140 mL, 1.48 mol) was treated with a solution of 33% (w/w) HBr in AcOH (80 mL, 0.444 mol), and allowed to react, using an ice bath to maintain a temperature of 45–55 °C. After complete consumption of the D-glucose, the mixture was stirred at 35 °C for 3 h. Then, the mixture was neutralised with NaOAc (13.64 g, 0.166 mol), and filtered to remove the precipitated NaBr, which was washed with a small quantity of EtOAc (20 mL). The filtrate was treated with thiourea (21.12 g, 0.277 mol), then placed on a heating mantle preheated to 80 °C. Upon dissolution of the thiourea, the solution was seeded with a small quantity of product **8** (1.02 g, 2.1 mmol), and allowed to react further (1 h total heating time). The mixture was cooled in a fridge overnight, filtered, washed with EtOAc (80 mL), then dried under reduced pressure to provide compound **8** (93.35 g, 68% excluding seed material). The NMR data were in excellent agreement with those previously obtained.[32]

Mp 192–193 °C (Lit.[32] 203–204 °C).

IR: 3268, 3055, 1753, 1655, 1371, 1252, 1221, 1055, 1036 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.12 (br s, 4 H), 5.67 (d, J = 9.9 Hz, 1 H), 5.32 (t, J = 9.4 Hz, 1 H), 5.14–5.09 (m, 2 H), 4.23–4.16 (m, 2 H), 4.11–4.07 (m, 1 H), 2.06 (s, 3 H), 2.03 (s, 3 H), 2.00 (s, 3 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.9, 169.4, 169.23, 169.16, 166.2, 79.8, 75.3, 72.4, 68.7, 67.4, 61.6, 20.5, 20.3, 20.23, 20.16.

HRMS-TOF: m/z [M – Br]$^+$ calcd for $C_{15}H_{23}N_2O_9S^+$: 407.1119; found: 407.1111; m/z [M + Na]$^+$ calcd for $C_{15}H_{23}{}^{79}BrN_2O_9SNa^+$: 509.0200; found: 509.0186.

Anal. Calcd for $C_{15}H_{23}N_2O_9SBr$: C, 36.97; H, 4.76; N, 5.75; S, 6.58. Found: C, 36.70; H, 4.67; N, 5.62; S, 6.71.

Thiohydroximates 9; General Procedure

Unless otherwise stated, a mixture of sodium sulfite (ca. 0.100 mol) in H_2O (50 mL) and EtOAc (50 mL) was degassed under argon for ca. 10 min, then added to *S*-(2,3,4,6-tetra-*O*-acetyl-1-β-D-glucopyranosyl)isothiouronium bromide (**8**; ca. 0.100 mol). The biphasic solution was stirred rapidly at r.t., with a stream of argon passing through it, until the precipitate had fully dissolved, then stirred for at least an additional 15 min (total 1–1.5 h). The organic phase was removed to provide 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**2**) as a solution in EtOAc, which was used immediately.

Separately, a solution of oxime (ca. 0.105 mol) in EtOAc (100 mL) was treated successively with concd HCl (0.40 mL, 4.7 mmol) and *N*-chlorosuccinimide (NCS, ca. 0.100 mol) and stirred for 1 h at r.t., upon which the blue colour disappeared (an exotherm was observed, with the internal temperature rising to ca. 50 °C), to provide a solution of *N*-hydroxyimidoyl chloride.

The *N*-hydroxyimidoyl chloride mixture was treated successively with the 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose solution, and a solution of K_2CO_3 (ca. 0.12 mol) in H_2O (40 mL), then the mixture was stirred for 1 h at r.t. The mixture was separated, the organic phase was washed with a small quantity of 2.4 M HCl to fully acidify the product, then the organic phase was concentrated. The crude product was recrystallised from MeOH and H_2O (2:1 (v/v)). The precipitate was collected by filtration, washed with H_2O, then dried under vacuum to provide the thiohydroximate **9** as a white or off-white solid. The solid was contaminated with succinimide, with the amount quoted as determined by ^{1}H NMR analysis; the values are in good agreement with those determined by elemental analysis (actual sulfur content vs calculated). A small quantity of product was recrystallised from MeOH and H_2O to provide an analytical sample.

S-(2,3,4,6-Tetra-*O*-acetyl-1-β-D-glucopyranosyl)-2-phenylethanethiohydroximate (9a)

A mixture of sodium sulfite (408 mg, 3.24 mmol) in H_2O (5 mL) and EtOAc (5 mL) was degassed under argon for ca. 10 min, then added to glucosylisothiouronium salt **8** (1.46 g, 3.00 mmol). The biphasic solution was stirred rapidly at r.t., with a stream of argon passing through it, until the precipitate had fully dissolved, then stirred for an additional 15 min (total 1.5 h). The organic phase was removed to provide thiosugar **2** as a solution in EtOAc, which was used immediately.

Separately, a solution of oxime **5a** (420 mg, 3.11 mmol) in EtOAc (3 mL) was treated successively with pyridine (10 µL, 0.1 mmol) and NCS (398 mg, 2.98 mmol), and stirred for 4 h at 50 °C, to provide a solution of *N*-hydroxy-2-phenylacetimidoyl chloride (**4a**). The imidoyl chloride **4a** mixture was treated successively with the thiosugar **2** solution, and a solution of K_2CO_3 (496 mg, 3.59 mmol) in H_2O (2 mL), then the mixture was stirred for 1 h. The mixture was separated, the organic phase was washed with a small quantity of 2.4 M HCl (1 mL, 2.4 mmol), then the organic phase was concentrated. The crude product was recrystallised from MeOH (2 mL) and H_2O (1 mL), with the precipitate washed with additional H_2O (1 mL), and dried under vacuum to provide compound **9a** as a white solid with ca. 2.1% (w/w) succinimide (1.07 g, 70%). A second recrystallisation from MeOH and H_2O provided the product with no observable succinimide impurity.

Mp 163–164 °C (Lit.[15] 163–164 °C); R_f = 0.50 (hexanes–EtOAc, 1:1).

IR: 3366, 1750, 1741, 1729, 1381, 1229, 1054, 976, 916, 707 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.45 (s, 1 H), 7.35–7.28 (m, 4 H), 7.23 (t, J = 6.9 Hz, 1 H), 5.37 (d, J = 10.1 Hz, 1 H), 5.31 (t, J = 9.4 Hz, 1 H), 4.92 (t, J = 9.7 Hz, 1 H), 4.85 (t, J = 9.7 Hz, 1 H), 4.07 (dd, J = 12.1, 5.6 Hz, 1 H), 3.99 (ddd, J = 9.8, 5.7, 1.8 Hz, 1 H), 3.90 (s, 2 H), 3.85 (dd, J = 12.0, 1.7 Hz, 1 H), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.94 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 169.4, 169.2, 168.9, 148.6, 136.6, 128.7, 128.3, 126.5, 78.2, 74.3, 72.8, 69.7, 67.8, 61.8, 37.2, 20.4, 20.29, 20.25, 20.2.

HRMS-TOF: m/z [M + H]$^+$ calcd for $C_{22}H_{28}NO_{10}S^+$: 498.1428; found: 498.1443.

S-(2,3,4,6-Tetra-*O*-acetyl-1-β-D-glucopyranosyl)-3-phenylpropanethiohydroximate (9b)

Glucosylisothiouronium salt **8** (48.86 g, 0.100 mol) was treated with sodium sulfite (12.61 g, 0.100 mol) to provide thiosugar **2**.

Oxime **5b** (15.66 g, 0.105 mol) was treated with NCS (13.38 g, 0.100 mol) to form *N*-hydroxy-3-phenylpropanimidoyl chloride and subsequently treated with thiosugar **2** and K_2CO_3 (16.63 g, 0.120 mol), with additional EtOAc (50 mL) to promote stirring. After the reaction, the organic phase was acidified with 2.4 M HCl (3.0 mL, 7.2 mmol). The precipitate was washed with EtOAc (50 mL) and H_2O (50 mL), then dried under vacuum to provide compound **9b** as a white solid with ca. 2.3% (w/w) succinimide (37.94 g, 72%). The filtrate was concentrated to ca. 50 g to precipitate additional product; this was filtered and washed successively with MeOH (5 mL) and H_2O (5 mL), and dried under vacuum to provide a second crop as an off-white solid with ca. 4.8% (w/w) succinimide (3.73 g, 7%). A portion of the first crop was recrystallised from MeOH and H_2O to provide an analytical sample.

Mp 200–201 °C (Lit.[15] 198–199 °C); R_f = 0.55 (hexanes–EtOAc, 1:1).

IR: 3311, 1746, 1713, 1379, 1248, 1225, 1041, 952, 695, 617 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.27 (s, 1 H), 7.31–7.26 (m, 4 H), 7.20 (sext, J = 4.2 Hz, 1 H), 5.60 (d, J = 10.1 Hz, 1 H), 5.47 (t, J = 9.4 Hz, 1 H), 4.93 (d, J = 10.0 Hz, 1 H), 4.88 (d, J = 10.1 Hz, 1 H), 4.16–4.12 (m, 1 H), 4.07–3.98 (m, 2 H), 2.95–2.77 (m, 4 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.96 (s, 3 H), 1.78 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 169.5, 169.3, 169.0, 149.0, 140.9, 128.3, 128.2, 125.9, 77.9, 74.3, 72.7, 69.7, 68.2, 62.2, 32.6, 32.3, 20.33, 20.31, 20.2, 20.1.

HRMS-TOF: m/z [M + H]$^+$ calcd for $C_{23}H_{30}NO_{10}S^+$: 512.1585; found: 512.1583.

S-(2,3,4,6-Tetra-*O*-acetyl-1-β-D-glucopyranosyl)butanethiohydroximate (9c)

Glucosylisothiouronium salt **8** (48.75 g, 0.100 mol) was treated with sodium sulfite (12.62 g, 0.100 mol) to provide thiosugar **2**.

Oxime **5c** (9.74 g, 0.105 mol, with ca. 6% (w/w) EtOAc) was treated with NCS (13.33 g, 99.8 mmol) to form *N*-hydroxybutanimidoyl chloride and subsequently treated with thiosugar **2** and K_2CO_3 (16.58 g, 0.120 mol). After the reaction, the organic phase was acidified with 2.4 M HCl (2.5 mL, 6.0 mmol). The crude product was subsequently

recrystallised from MeOH (30 mL) and H_2O (15 mL), with the precipitate washed with additional H_2O (15 mL). This provided product **9c** as an off-white solid with ca. 6.8% (w/w) succinimide (35.39 g, 73%). A portion was recrystallised from MeOH and H_2O to provide an analytical sample.

Mp 150–152 °C; R_f = 0.45 (hexanes–EtOAc, 1:1).

IR: 3322, 2959, 2938, 2876, 1749, 1709, 1378, 1246, 1228, 1040 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.18 (s, 1 H), 5.47–5.42 (m, 2 H), 4.92 (t, *J* = 9.6 Hz, 1 H), 4.86 (t, *J* = 9.7 Hz, 1 H), 4.16–4.01 (m, 3 H), 2.52–2.46 (m, 2 H), 2.01 (s, 3 H), 2.004 (s, 3 H), 1.997 (s, 3 H), 1.95 (s, 3 H), 1.67–1.54 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.9, 169.5, 169.2, 169.0, 149.4, 78.0, 74.3, 72.8, 69.8, 68.2, 62.1, 33.1, 20.4, 20.3, 20.2, 20.1, 13.5.

HRMS-TOF: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{28}NO_{10}S^+$: 450.1428; found: 450.1418.

S-(2,3,4,6-Tetra-*O*-acetyl-1-β-D-glucopyranosyl)-2-hexanethiohydroximate (9d)

Glucosylisothiouronium salt **8** (48.74 g, 0.100 mol) was treated with sodium sulfite (12.63 g, 0.100 mol) to provide thiosugar **2**.

Oxime **5d** (12.10 g, 0.105 mol) was treated with NCS (13.36 g, 0.100 mol) to form *N*-hydroxyhexanimidoyl chloride and subsequently treated with thiosugar **2** and K_2CO_3 (16.56 g, 0.120 mol). After the reaction, the organic phase was acidified with 2.4 M HCl (2.5 mL, 6.0 mmol). The crude product was subsequently recrystallised from MeOH (40 mL) and H_2O (20 mL), with the precipitate washed with additional H_2O (20 mL). This provided product **9d** as a white solid with ca. 0.8% (w/w) succinimide (35.79 g, 74%). A portion was recrystallised from MeOH and H_2O to provide an analytical sample.

Mp 137–138 °C; R_f = 0.55 (hexanes–EtOAc, 1:1).

IR: 3319, 2958, 2938, 2876, 1750, 1709, 1378, 1246, 1228, 1040 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.17 (s, 1 H), 5.47–5.42 (m, 2 H), 4.92 (t, *J* = 9.5 Hz, 1 H), 4.86 (t, *J* = 9.7 Hz, 1 H), 4.15–4.01 (m, 3 H), 2.56–2.43 (m, 2 H), 2.002 (s, 6 H), 1.995 (s, 3 H), 1.95 (s, 3 H), 1.63–1.52 (m, 2 H), 1.35–1.28 (m, 4 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 169.5, 169.2, 169.0, 149.6, 78.0, 74.2, 72.8, 69.8, 68.1, 62.1, 31.1, 30.8, 26.2, 21.8, 20.4, 20.3, 20.2, 13.9.

HRMS-TOF: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{32}NO_{10}S^+$: 478.1741; found: 478.1736.

S-(2,3,4,6-Tetra-*O*-acetyl-1-β-D-glucopyranosyl)-2-octanethiohydroximate (9e)

Glucosylisothiouronium salt **8** (48.75 g, 0.100 mol) was treated with sodium sulfite (12.62 g, 0.100 mol) to provide thiosugar **2**.

Oxime **5e** (15.04 g, 0.105 mol) was treated with NCS (13.34 g, 99.9 mmol) to form *N*-hydroxyoctanimidoyl chloride and subsequently treated with thiosugar **2** and K_2CO_3 (16.52 g, 0.120 mol). After the reaction, the organic phase was acidified with 2.4 M HCl (3.0 mL, 7.2 mmol). The crude product was subsequently recrystallised from MeOH (50 mL) and H_2O (25 mL), with the precipitate washed with additional H_2O (25 mL). This provided product **9e** as an off-white solid with ca. 3.2% (w/w) succinimide (44.70 g, 86%). A portion was recrystallised from MeOH and H_2O to provide an analytical sample.

Mp 129–130 °C (Lit.[33] 127 °C); R_f = 0.60 (hexanes–EtOAc, 1:1).

IR: 3319, 2928, 2857, 1749, 1712, 1377, 1246, 1230, 1042 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.17 (s, 1 H), 5.47–5.42 (m, 2 H), 4.92 (t, *J* = 9.6 Hz, 1 H), 4.86 (t, *J* = 9.7 Hz, 1 H), 4.15–4.01 (m, 3 H), 2.56–2.43 (m, 2 H), 2.003 (s, 6 H), 1.996 (s, 3 H), 1.95 (s, 3 H), 1.63–1.52 (m, 2 H), 1.36–1.19 (m, 8 H), 0.87 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 169.5, 169.2, 169.0, 149.6, 78.0, 74.2, 72.8, 69.8, 68.1, 62.1, 31.2, 31.1, 28.5, 28.4, 26.6, 22.0, 20.4, 20.3, 20.2, 13.9.

HRMS-TOF: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{36}NO_{10}S^+$: 506.2054; found: 506.2033.

2′,3′,4′,6′-Tetra-*O*-acetylglucotropaeolin Monohydrate (10a)

Thiohydroximate **9a** prepared as above (698 mg, 1.40 mmol) was treated successively with MeCN (0.5 mL), pyridine (60 µL, 0.7 mmol) and pyridine–sulfur trioxide complex (332 mg, 2.09 mmol), and the mixture refluxed for 1 h. The solution was cooled to ca. 60 °C, treated with EtOAc (1 mL), then a solution of K_2CO_3 (244 mg, 1.76 mmol) in H_2O (1 mL) was added with rapid stirring. Once effervescence had ceased (ca. 10 min), a thick precipitate was formed. The mixture was slurried in EtOAc (2 mL) and H_2O (2 mL), filtered and dried under vacuum. The residue was suspended in refluxing H_2O (5 mL) and EtOAc (5 mL), cooled, filtered and washed sequentially with H_2O (5 mL) and EtOAc (5 mL); then, this process was repeated again with the same quantities. The precipitate was dried under vacuum to afford compound **10a** as a white solid (667 mg, 75%).

Mp 155–157 °C (Lit.[15] 196–198 °C); R_f = 0.35 (EtOAc–MeOH, 9:1).

IR: 1750, 1729, 1369, 1283, 1248, 1223, 1057, 1032, 905, 817, 793, 729, 642, 601 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.41–7.33 (m, 4 H), 7.30–7.25 (m, 1 H), 5.30–5.25 (m, 2 H), 4.91 (td, *J* = 9.7, 1.6 Hz, 1 H), 4.82 (td, *J* = 9.7, 1.7 Hz, 1 H), 4.05–3.88 (m, 4 H), 3.75 (d, *J* = 12.2 Hz, 1 H), 1.99 (s, 3 H), 1.97 (s, 3 H), 1.94 (s, 3 H), 1.93 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 169.4, 169.1, 168.9, 152.2, 136.0, 128.4, 128.2, 126.7, 78.4, 74.2, 72.7, 69.5, 67.6, 61.5, 37.0, 20.4, 20.3, 20.21, 20.15.

HRMS-TOF: *m*/*z* $[M - K]^-$ calcd for $C_{22}H_{26}NO_{13}S_2^-$: 576.0851; found: 576.0834; *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{27}NO_{13}S_2K^+$: 616.0555; found: 616.0574.

Anal. Calcd for $C_{22}H_{26}NO_{13}S_2K·H_2O$: C, 41.70; H, 4.45; N, 2.21; S, 10.12. Found: C, 41.75; H, 4.25; N, 2.23; S, 10.18.

2′,3′,4′,6′-Tetra-*O*-acetylgluconasturtiin Monohydrate (10b)

Thiohydroximate **9b** prepared as above (36.51 g, 69.7 mmol, contaminated with succinimide) was treated successively with MeCN (35 mL), pyridine (2.8 mL, 35 mmol) and pyridine–sulfur trioxide complex (16.63 g, 104 mmol), and the mixture refluxed for 1 h. The solution was cooled to ca. 60 °C, treated with EtOAc (35 mL), then a solution of K_2CO_3 (11.61 g, 84 mmol) in H_2O (35 mL) was added with rapid stirring. Once effervescence had ceased (ca. 10 min), the solution was diluted with H_2O (35 mL), separated, and the organic phase was concentrated. The residue was suspended in refluxing H_2O (100 mL) and EtOAc (100 mL), cooled, filtered and washed sequentially with H_2O (50 mL) and EtOAc (50 mL); then, this process was repeated again with quantities reduced by 50%. The precipitate was dried under vacuum to afford compound **10b** as an off-white solid (33.46 g, 74%).

Mp 152–154 °C (Lit.[15] 199–201 °C); R_f = 0.40 (EtOAc–MeOH, 9:1).

IR: 1749, 1371, 1275, 1247, 1222, 1056, 1031 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36–7.28 (m, 4 H), 7.21 (t, J = 7.1 Hz, 1 H), 5.65 (d, J = 10.0 Hz, 1 H), 5.49 (t, J = 9.3 Hz, 1 H), 4.92 (t, J = 9.7 Hz, 1 H), 4.90 (t, J = 9.6 Hz, 1 H), 4.16–4.11 (m, 1 H), 4.05–3.98 (m, 2 H), 2.97–2.79 (m, 4 H), 2.03 (s, 3 H), 2.00 (s, 3 H), 1.96 (s, 3 H), 1.74 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 169.5, 169.2, 169.0, 153.0, 140.7, 128.4, 128.2, 126.0, 77.9, 74.4, 72.7, 69.5, 68.1, 62.2, 32.9, 32.4, 20.33, 20.31, 20.2, 20.0.

HRMS-TOF: m/z [M – K]$^-$ calcd for $C_{23}H_{28}NO_{13}S_2^-$: 590.1008; found: 590.1002; m/z [M + H]$^+$ calcd for $C_{23}H_{29}NO_{13}S_2K^+$: 630.0712; found: 630.0703.

Anal. Calcd for $C_{23}H_{28}NO_{13}S_2K{\cdot}H_2O$: C, 42.65; H, 4.67; N, 2.16; S, 9.90. Found: C, 42.50; H, 4.66; N, 2.12; S, 10.01.

2′,3′,4′,6′-Tetra-*O*-acetyl-*n*-propylglucosinolate Hemihydrate (10c)

Thiohydroximate **9c** prepared as above (34.29 g, 71.1 mmol, contaminated with succinimide) was treated successively with MeCN (18 mL), pyridine (2.9 mL, 36 mmol) and pyridine–sulfur trioxide complex (16.97 g, 107 mmol), and the mixture refluxed for 2.5 h. The solution was cooled to ca. 60 °C, treated with EtOAc (36 mL), then a solution of K_2CO_3 (12.30 g, 89.0 mmol) in H_2O (36 mL) was added with rapid stirring. Once effervescence had ceased (ca. 10 min), the mixture was diluted further with H_2O (36 mL), separated, then the organic phase was diluted further with EtOAc (36 mL) and H_2O (36 mL), separated, then finally washed with brine (36 mL). The residue was concentrated to dryness, slurried from hot EtOAc (100 mL), cooled, filtered and washed with EtOAc (50 mL); then, this process was repeated again with the same quantities. The precipitate was dried under vacuum to afford compound **10c** as a white solid (20.87 g, 51%).

Mp 153–156 °C; R_f = 0.30 (EtOAc–MeOH, 9:1).

IR: 3505, 2963, 1743, 1435, 1369, 1224, 1059, 910, 808, 620 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.50 (d, J = 10.1 Hz, 1 H), 5.46 (t, J = 9.4 Hz, 1 H), 4.93 (t, J = 9.9 Hz, 1 H), 4.88 (t, J = 9.8 Hz, 1 H), 4.15 (ddd, J = 9.9, 5.7, 2.7 Hz, 1 H), 4.10–4.02 (m, 2 H), 2.57–2.48 (m, 2 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.96 (s, 3 H), 1.68–1.55 (m, 2 H), 0.96 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.9, 169.5, 169.2, 169.0, 153.5, 78.1, 74.3, 72.7, 69.6, 68.1, 62.1, 33.2, 20.4, 20.31, 20.27, 20.2, 13.5.

HRMS-TOF: m/z [M – K]$^-$ calcd for $C_{18}H_{26}NO_{13}S_2^-$: 528.0851; found: 528.0838; m/z [M + H]$^+$ calcd for $C_{18}H_{27}NO_{13}S_2K^+$: 568.0555; found: 568.0571.

Anal. Calcd for $C_{18}H_{26}NO_{13}S_2K{\cdot}0.5\ H_2O$: C, 37.49; H, 4.72; N, 2.43; S, 11.12. Found: C, 37.58; H, 4.59; N, 2.41; S, 11.12.

2′,3′,4′,6′-Tetra-*O*-acetyl-*n*-pentylglucosinolate Hemihydrate (10d)

Thiohydroximate **9d** prepared as above (34.66 g, 72.0 mmol, contaminated with succinimide) was treated successively with MeCN (18 mL), pyridine (2.9 mL, 36 mmol) and pyridine–sulfur trioxide complex (17.19 g, 108 mmol), and the mixture refluxed for 2.5 h. The solution was cooled to ca. 60 °C, treated with EtOAc (36 mL), then a solution of K_2CO_3 (12.38 g, 89.6 mmol) in H_2O (36 mL) was added with rapid stirring. Once effervescence had ceased (ca. 10 min), a thick precipitate was formed. The mixture was slurried in H_2O (36 mL), filtered and dried under vacuum. The residue was suspended in refluxing H_2O (100 mL) and EtOAc (100 mL), cooled, filtered and washed sequentially with H_2O (50 mL) and EtOAc (50 mL); then, this process was repeated again with quantities reduced by 50%. The precipitate was dried under vacuum to afford compound **10d** as a white solid (27.38 g, 63%).

Mp 156–158 °C; R_f = 0.35 (EtOAc–MeOH, 9:1).

IR: 3506, 2953, 1749, 1728, 1441, 1369, 1276, 1252, 1225, 1052, 899, 795, 644, 622 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.52–5.44 (m, 2 H), 4.93 (t, J = 9.6 Hz, 1 H), 4.88 (t, J = 9.7 Hz, 1 H), 4.17–4.01 (m, 3 H), 2.61–2.47 (m, 2 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.96 (s, 3 H), 1.68–1.51 (m, 2 H), 1.40–1.28 (m, 4 H), 0.89 (t, J = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 169.5, 169.2, 169.0, 153.6, 78.1, 74.3, 72.7, 69.6, 68.1, 62.1, 31.4, 30.8, 26.5, 21.8, 20.4, 20.3, 20.2, 13.9.

HRMS-TOF: m/z [M – K]$^-$ calcd for $C_{20}H_{30}NO_{13}S_2^-$: 556.1164; found: 556.1152; m/z [M + H]$^+$ calcd for $C_{20}H_{31}NO_{13}S_2K^+$: 596.0868; found: 596.0873.

Anal. Calcd for $C_{20}H_{30}NO_{13}S_2K{\cdot}0.5\ H_2O$: C, 39.73; H, 5.17; N, 2.32; S, 10.60. Found: C, 39.63; H, 5.13; N, 2.28; S, 10.49.

2′,3′,4′,6′-Tetra-*O*-acetyl-*n*-heptylglucosinolate Hemihydrate (10e)

Thiohydroximate **9e** prepared as above (42.55 g, 81.5 mmol, contaminated with succinimide) was treated successively with MeCN (21 mL), pyridine (3.3 mL, 41 mmol) and pyridine–sulfur trioxide complex (19.57 g, 123 mmol), and the mixture refluxed for 1.5 h. The solution was cooled to ca. 60 °C, treated with EtOAc (41 mL), then a solution of K_2CO_3 (14.11 g, 102 mmol) in H_2O (41 mL) was added with rapid stirring. Once effervescence had ceased (ca. 10 min), a thick precipitate was formed. The mixture was slurried in H_2O (41 mL), filtered and dried under vacuum. The residue was suspended in refluxing H_2O (100 mL) and EtOAc (100 mL), cooled, filtered and washed sequentially with H_2O (50 mL) and EtOAc (50 mL); then, this process was repeated again with quantities reduced by 50%. The precipitate was dried under vacuum to afford compound **10e** as an off-white solid (35.33 g, 68.5%).

Mp 151–153 °C (Lit.[33] 107–109 °C); R_f = 0.40 (EtOAc–MeOH, 9:1).

IR: 3508, 2934, 1749, 1372, 1276, 1249, 1225, 1088, 1050, 914, 791 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.51–5.44 (m, 2 H), 4.93 (t, J = 9.6 Hz, 1 H), 4.87 (t, J = 9.7 Hz, 1 H), 4.16–4.01 (m, 3 H), 2.61–2.47 (m, 2 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.96 (s, 3 H), 1.65–1.50 (m, 2 H), 1.38–1.22 (m, 8 H), 0.87 (t, J = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 169.5, 169.2, 169.0, 153.6, 78.1, 74.3, 72.7, 69.6, 68.1, 62.1, 31.4, 31.2, 28.6, 28.4, 26.8, 22.0, 20.4, 20.3, 20.2, 13.9.

HRMS-TOF: m/z [M – K]$^-$ calcd for $C_{22}H_{34}NO_{13}S_2^-$: 584.1477; found: 584.1474; m/z [M + H]$^+$ calcd for $C_{22}H_{35}NO_{13}S_2K^+$: 624.1181; found: 624.1172.

Anal. Calcd for $C_{22}H_{34}NO_{13}S_2K{\cdot}0.5\ H_2O$: C, 41.76; H, 5.58; N, 2.21; S, 10.13. Found: C, 41.67; H, 5.57; N, 2.23; S, 9.88.

Glucotropaeolin (1a)

A solution of tetra-*O*-acetylglucotropeolin monohydrate (**10a**; 499 mg, 0.79 mmol) in MeOH (1.6 mL) was treated with a solution of methanolic KOH (2 M; 20 µL, 0.04 mmol). After being stirred for 2 h, the solution was neutralised using Amberlite® IRC76 hydrogen form (40 mg), then decolourised by treatment with charcoal (5 mg). The mixture was filtered, washed with MeOH (2 × 1 mL) and the filtrate concentrated to afford compound **1a** as an off-white hygroscopic solid (336 mg, 95%). The NMR data were in excellent agreement with those previously obtained.[15]

R_f = 0.40 (EtOAc–MeOH, 3:1).

IR: 3415, 1571, 1454, 1244, 1058, 948, 875, 796, 703, 648, 605 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 7.48–7.37 (m, 5 H), 4.75–4.65 (m, 1 H), 4.15 (s, 2 H), 3.70–3.61 (m, 2 H), 3.43–3.23 (m, 4 H).

^{13}C NMR (100 MHz, D_2O): δ = 162.7, 135.2, 129.2, 128.1, 127.6, 81.4, 79.9, 77.0, 71.8, 68.9, 60.4, 38.3.

HRMS-TOF: *m*/*z* [M – K]$^-$ calcd for $C_{14}H_{18}NO_9S_2^-$: 408.0429; found: 408.0422; *m*/*z* [M + K]$^+$ calcd for $C_{14}H_{18}NO_9S_2K_2^+$: 485.9692; found: 485.9697.

Anal. Calcd for $C_{14}H_{18}NO_9S_2K{\cdot}0.5\ H_2O$: C, 36.83; H, 4.20; N, 3.07; S, 14.05. Found: C, 36.92; H, 4.20; N, 2.94; S, 14.04.

Gluconasturtiin (1b)

A solution of tetra-*O*-acetylgluconasturtiin monohydrate (**10b**; 16.39 g, 25.3 mmol) in MeOH (78 mL) was treated with a solution of methanolic KOH (2 M; 0.65 mL, 1.3 mmol). After being stirred for 2.5 h, the solution was neutralised using Amberlite® IRC76 hydrogen form (1.5 g), then decolourised by treatment with charcoal (50 mg). The mixture was filtered, washed with MeOH (2 × 10 mL) and the filtrate concentrated to afford compound **1b** as an off-white hygroscopic solid (11.76 g, quantitative). The NMR data were in excellent agreement with those previously obtained.[15]

R_f = 0.40 (EtOAc–MeOH, 3:1).

IR: 3421, 2926, 1576, 1497, 1454, 1243, 1058, 879, 792, 701, 631 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 7.31–7.24 (m, 4 H), 7.20 (tt, *J* = 6.9, 2.0 Hz, 1 H), 4.79 (d, *J* = 9.5 Hz, 1 H), 3.74 (dd, *J* = 12.6, 1.7 Hz, 1 H), 3.57 (dd, *J* = 12.6, 5.2 Hz, 1 H), 3.42–3.31 (m, 4 H), 3.02–2.85 (m, 4 H).

^{13}C NMR (100 MHz, D_2O): δ = 163.3, 140.5, 128.72, 128.69, 126.6, 81.6, 80.1, 77.0, 71.8, 69.1, 60.5, 33.9, 32.5.

HRMS-TOF: *m*/*z* [M – K]$^-$ calcd for $C_{15}H_{20}NO_9S_2^-$: 422.0585; found: 422.0587; *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}NO_9S_2K^+$: 462.0289; found: 462.0293.

Anal. Calcd for $C_{15}H_{20}NO_9S_2K{\cdot}0.5\ H_2O$: C, 38.29; H, 4.50; N, 2.98; S, 13.63. Found: C, 38.38; H, 4.45; N, 2.85; S, 13.89.

n-Propylglucosinolate (1c)

A solution of tetra-*O*-acetyl-*n*-propylglucosinolate hemihydrate (**10c**; 20.51 g, 35.6 mmol) in MeOH (72 mL) was treated with a solution of methanolic KOH (2 M; 0.9 mL, 1.8 mmol). After being stirred for 2 h, the solution was neutralised using Amberlite® IRC76 hydrogen form (1.5 g), then decolourised by treatment with charcoal (0.2 g). The mixture was filtered, washed with MeOH (2 × 10 mL) and the filtrate concentrated to afford compound **1c** as an off-white hygroscopic solid (14.18 g, quantitative).

R_f = 0.30 (EtOAc–MeOH, 3:1).

IR: 3399, 2934, 1632, 1574, 1423, 1242, 1058, 908, 883, 801, 630 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 5.02 (d, *J* = 9.8 Hz, 1 H), 3.90 (dd, *J* = 12.6, 1.9 Hz, 1 H), 3.72 (dd, *J* = 12.6, 5.6 Hz, 1 H), 3.59–3.55 (m, 2 H), 3.49–3.43 (m, 2 H), 2.68 (t, *J* = 7.5 Hz, 2 H), 1.73 (sext, *J* = 7.4 Hz, 2 H), 0.98 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, D_2O): δ = 164.7, 81.8, 80.1, 77.1, 72.0, 69.2, 60.7, 34.1, 20.5, 12.7.

HRMS-TOF: *m*/*z* [M – K]$^-$ calcd for $C_{10}H_{18}NO_9S_2^-$: 360.0428; found: 360.0422; *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{19}NO_9S_2K^+$: 400.0133; found: 400.0136.

Anal. Calcd for $C_{10}H_{18}NO_9S_2K{\cdot}H_2O$: C, 28.77; H, 4.83; N, 3.36; S, 15.36. Found: C, 28.69; H, 4.77; N, 3.29; S, 15.08.

n-Pentylglucosinolate (1d)

A solution of tetra-*O*-acetyl-*n*-pentylglucosinolate hemihydrate (**10d**; 16.65 g, 27.5 mmol) in MeOH (56 mL) was treated with a solution of methanolic KOH (2 M; 0.7 mL, 1.4 mmol). After being stirred for 2 h, the solution was neutralised using Amberlite® IRC76 hydrogen form (1.5 g), then decolourised by treatment with charcoal (0.1 g). The mixture was filtered, washed with MeOH (2 × 10 mL) and the filtrate concentrated to afford compound **1d** as an off-white hygroscopic solid (11.73 g, quantitative).

R_f = 0.35 (EtOAc–MeOH, 3:1).

IR: 3419, 2931, 1575, 1423, 1243, 1057, 878, 798, 643, 638 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 5.01 (d, *J* = 9.8 Hz, 1 H), 3.89 (dd, *J* = 12.6, 1.9 Hz, 1 H), 3.72 (dd, *J* = 12.6, 5.6 Hz, 1 H), 3.58–3.53 (m, 2 H), 3.49–3.43 (m, 2 H), 2.70 (t, *J* = 7.6 Hz, 2 H), 1.71 (quin, *J* = 7.2 Hz, 2 H), 1.43–1.29 (m, 4 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, D_2O): δ = 165.0, 81.9, 80.2, 77.1, 72.0, 69.2, 60.7, 32.2, 30.5, 26.7, 21.7, 13.3.

HRMS-TOF: *m*/*z* [M – K]$^-$ calcd for $C_{12}H_{22}NO_9S_2^-$: 388.0741; found: 388.0733; *m*/*z* [M + K]$^+$ calcd for $C_{12}H_{22}NO_9S_2K_2^+$: 466.0005; found: 466.0017.

Anal. Calcd for $C_{12}H_{22}NO_9S_2K$: C, 33.71; H, 5.19; N, 3.28; S, 15.00. Found: C, 33.38; H, 5.31; N, 3.17; S, 14.70.

n-Heptylglucosinolate (1e)

A solution of tetra-*O*-acetyl-*n*-heptylglucosinolate hemihydrate (**10e**; 35.06 g, 55.4 mmol) in MeOH (112 mL) was treated with a solution of methanolic KOH (2 M; 1.4 mL, 2.8 mmol). After being stirred for 2 h, the solution was neutralised using Amberlite® IRC76 hydrogen form (3.0 g), then decolourised by treatment with charcoal (0.1 g). The mixture was filtered, washed with MeOH (2 × 10 mL) and the filtrate concentrated to afford compound **1e** as an off-white hygroscopic solid (25.20 g, quantitative).

R_f = 0.40 (EtOAc–MeOH, 3:1).

IR: 3419, 2927, 2857, 1574, 1457, 1243, 1057, 877, 796, 643, 628 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 5.00 (d, *J* = 9.8 Hz, 1 H), 3.89 (dd, *J* = 12.6, 2.0 Hz, 1 H), 3.72 (dd, *J* = 12.6, 5.5 Hz, 1 H), 3.58–3.52 (m, 2 H), 3.50–3.43 (m, 2 H), 2.70 (t, *J* = 7.6 Hz, 2 H), 1.71 (quin, *J* = 7.3 Hz, 2 H), 1.41–1.24 (m, 8 H), 0.87 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, D_2O): δ = 165.0, 81.9, 80.2, 77.1, 72.0, 69.1, 60.7, 32.2, 31.0, 28.15, 28.06, 27.0, 22.0, 13.4.

HRMS-TOF: *m*/*z* [M – K]$^-$ calcd for $C_{14}H_{26}NO_9S_2^-$: 416.1054; found: 416.1064; *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{27}NO_9S_2K^+$: 456.0759; found: 456.0764.

Anal. Calcd for $C_{14}H_{26}NO_9S_2K$: C, 36.91; H, 5.75; N, 3.07; S, 14.07. Found: C, 36.68; H, 5.78; N, 2.95; S, 14.21.

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Supporting Information

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