2-(Selenocyanatomethyl)-2-propenol — A convenient synthon for ligation via the deselenative allylic rearrangement of allyl selenosulfides: preparation, functional group compatibility, and application

David Lachkar, Caroline Boudet, Xavier Guinchard, and David Crich

Abstract: The preparation and reactions of 2-(selenocyanatomethyl)-2-propenol are described and reveal the compatibility of the allylic selenocyanate group with a range of mild oxidizing and Lewis acidic conditions. 2-(Selenocyanatomethyl)-2-propenol and its derivatives are employed in the functionalization of simple and amino acid derived thiols in methanolic solution at room temperature to give 2-(hydroxymethyl)allyl sulfides in good to excellent yield.

Key words: selenocyanates, selenosulfides, selenosulfoxides, ligation.

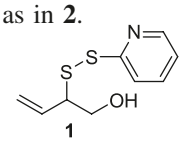
Résumé : Nous décrivons la préparation et les réactions de dérivatisation du 2-(sélénocyanatométhyl)-prop-2-énol, montrant ainsi la compatibilité fonctionnelle du groupement sélénocyanate allylique envers les réactions en conditions oxydantes et en présence d'acides de Lewis. Cet alcool et ses dérivés fonctionnalisés ont été engagés dans des réactions de fonctionnalisation de thiols à température ambiante dans des conditions douces pour conduire à des sulfures de 2-(hydroxyméthyl)allyle avec de bons rendements.

Mots-clés : sélénocyanates, sélénosulfures, sélénosulfoxydes, ligature.

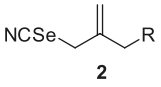
Introduction

Organoselenium chemistry is a major component of the organic chemist's toolbox,[1] and the organoselenocyanates are some of the most readily available and versatile of the chalcogenide-based reagents. For our part, we have developed the use of allylic seleno Bunte salts and allylic selenocyanates as convenient precursors to the allyl selenosulfides, substrates for dechalcogenative rearrangement to allyl alkyl sulfides (Scheme 1),[2] and as our contribution to the burgeoning field[3] of chemical ligation. In continuation of this program we required a minimal hydroxyl-substituted allylic selenocyanate to serve as a handle for introduction of the allylic selenocyanate group into a range substrates. We report here on the synthesis of 2-(selenocyanatomethyl)allyl alcohol for this purpose, on functional group compatibility of the selenocyanate moiety, and on its incorporation into various substrates.

In earlier work on the desulfurative allylic rearrangement of allyl alkyl disulfides, we developed 2-(2-pyridyldithio)-3-propenol (**1**) or its analogs as precursors to the necessary allyl alkyl disulfides,[2b,4] but were foiled in many of our attempts to derivatize the hydroxyl group by the relative sensitivity of the allylic disulfide functionality.[5] For this reason, we turned to the allylic selenocyanates[6] with the expectation of greater stability to a number of derivatization reactions.[2b] To avoid possible problems arising from facile 1,3-sigmatropic rearrangement of disymmetric allylic selenocyanates, we targeted systems in which such rearrangements would have a degenerate nature, namely, those based on methallyl selenocyanate substituted at the 2 postion as in **2**.



1



2

We focused on 2-(selenocyanatomethyl)-3-propenol (**6**), as the smallest possible alcohol derived from methallyl selenocyanate. To this end, *p*-methoxybenzyl alcohol was alkylated with methallyl chloride to give the ether[7] **3**, which was converted with sulfuryl chloride into the known[8] methallyl chloride **4** in 29% yield (Scheme 2). Reaction with potassium

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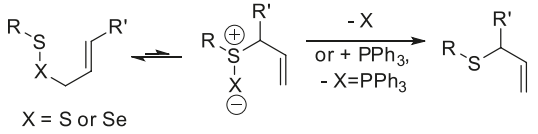
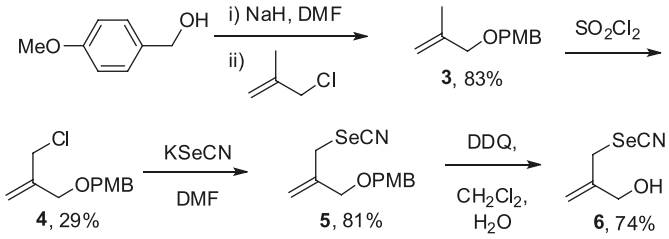
Scheme 1. Dechalcogenative allylic selenosulfide and disulfide rearrangements.



Scheme 2. Preparation of 2-(selenocyanatomethyl)-3-propenol.



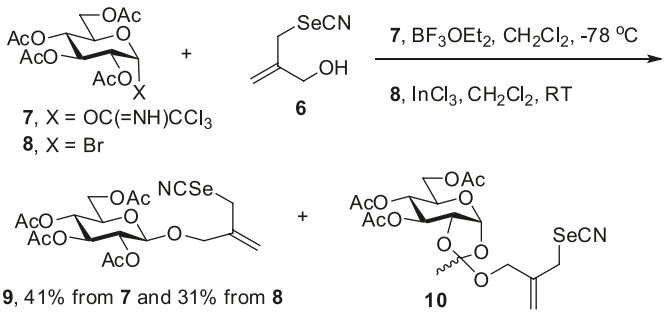
selenocyanate in DMF then afforded the selenocyanate **5** in 81% yield. Exposure to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in wet dichloromethane finally gave the desired alcohol **6** in 74% yield and demonstrated the stability of the allylic selenocyanate functionality to the mild oxidative conditions used for removal of the *p*-methoxybenzyl ether (Scheme 2).

With **6** in hand we turned to its application as a glycosyl acceptor. Activation of tetraacetyl-α-glucopyranosyl trichloroacetimidate[9] (**7**) in the presence of **6** with BF_3 etherate afforded the desired β-glycoside **9** in 41% yield (Scheme 3) typically accompanied by the orthoester products **10**. Orthoesters of this general type are typical byproducts in neighboring group participation directed glycosylation reactions and are particularly problematic when the acceptor is a primary alcohol.[10] When acetobromoglucose **8** was employed as donor and indium trichloride[11] as promotor the glycoside **9** was obtained in 31% yield, but attempts at activation of **8** with more typical silver-based reagents resulted only in the formation of decomposition products. While the yields from these glycosylations are only moderate, they are nevertheless instructive as they demonstrate the stability of the allylic selenocyanate functionality toward selected Lewis acidic conditions.

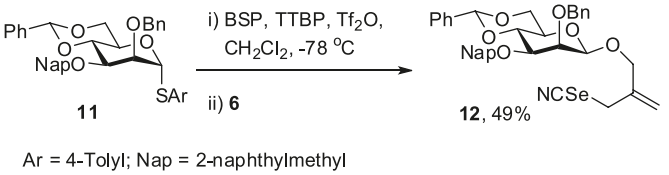
In a second glycosylation reaction, donor **11** was coupled to **6** using the 1-benzenesulfinylpiperidine (BSP) / trifluoromethanesulfonic anhydride conditions[12] in the presence of the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[13] (Scheme 4). Glycoside **12** was obtained as a single isomer in 49% yield.

Encouraged by these results, we investigated the compatibility of **6** with typical conditions for phosphitylation such as would be necessary for incorporation into nucleotides.[14] Thus, **6** was allowed to react with dibenzyl *N*,*N*-di(isopropyl)phosphoramidite in the presence of tetrazole as promoter, to give a presumed intermediate phosphite **13**, followed by exposure to *m*-CPBA as oxidant (Scheme 5). Unfortunately, complex reaction mixtures were obtained under all reaction conditions investigated from which the anticipated phosphate **14** could only be isolated in modest yield. A cyclic byproduct **16** was obtained in varying quantities from all reaction mixtures and affords a possible explanation for the complexity: Arbuzov-type reaction initiated by intramolecular attack of the first formed phosphite on the electron-deficient selenocyanate.

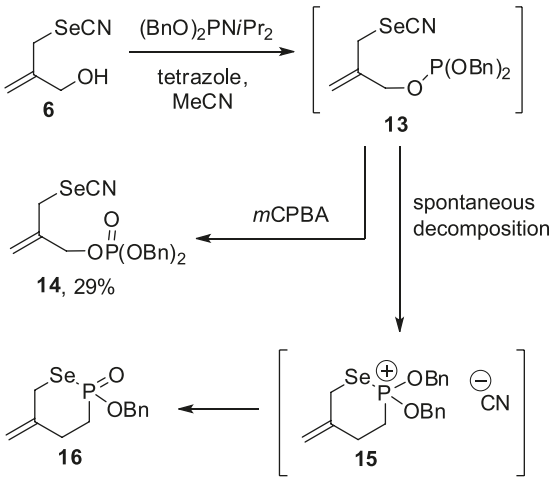
Scheme 3. Formation of 2-(selenocyanatomethyl)allyl tetraacetyl-α-D-glucopyranoside (**9**).



Scheme 4. Formation of 2-(selenocyanatomethyl)allyl β-D-mannopyranoside (**12**).



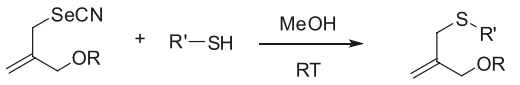
Scheme 5. Reaction of **6** with a phosphoramidite.



Finally, attention was turned to the ligation reaction. Thus, selenocyanates **5**, **6**, **9**, and **12** were allowed to react with a variety of aliphatic thiols in methanol at room temperature under an argon atmosphere. After stirring overnight, and filtration to remove precipitated selenium, chromatography on silica gel afforded the coupled products with the yields set out in Table 1.

In an attempt to probe the mechanism of the ligation reaction, we monitored the reaction of selenocyanate **6** with benzylmercaptan in deuteriomethanol at room temperature by ^1H and ^{77}Se NMR spectroscopy (Figs. 1 and 2). In the ^1H NMR spectrum a slight upfield shift of the signals attributed to **6** is observed on addition of the thiol, followed by the formation of a set of new signals assigned to the intermediate selenosulfide. This substance is then transformed rapidly and cleanly into the final product (**18**). The kinetics of the reaction are such

Table 1. Ligation of **6** and its derivatives with assorted thiols.



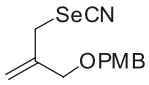
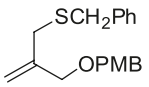
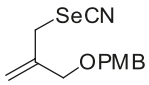
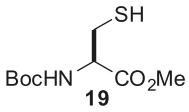
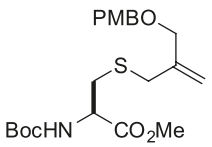
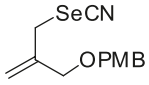
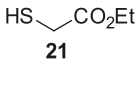
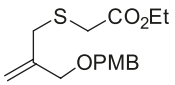
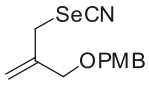
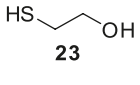
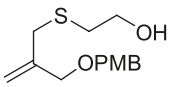
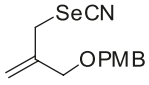
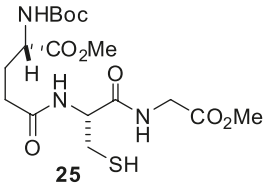
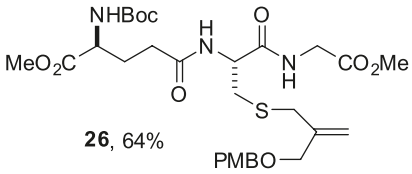
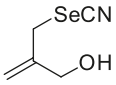
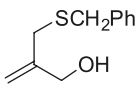
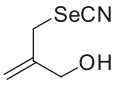
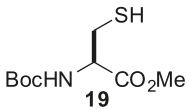
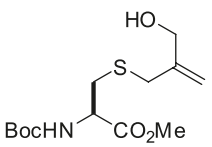
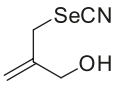
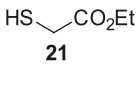
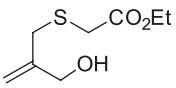
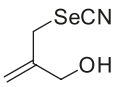
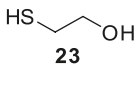
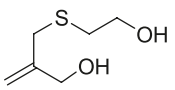
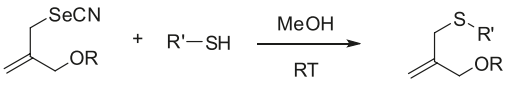
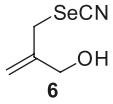
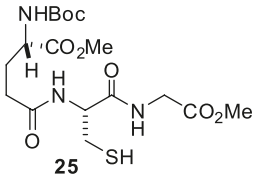
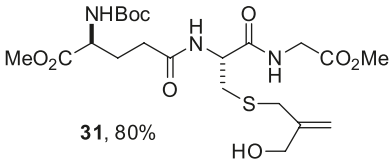
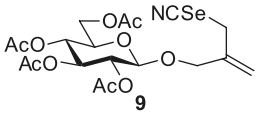
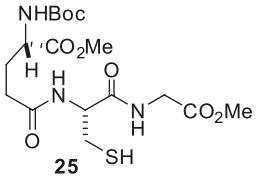
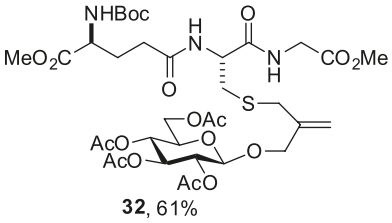
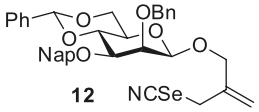
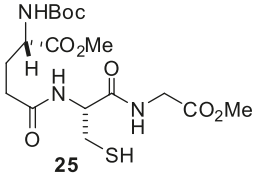
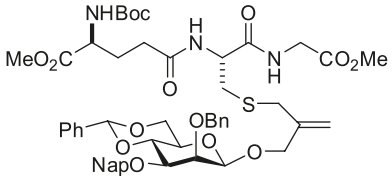
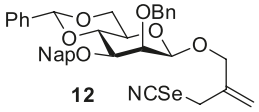
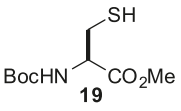
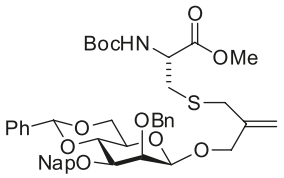
Entry	Substrate	Thiol	Product, yield
1	 **5**	$PhCH_2SH$ **17**	 **18**, 76%
2	 **5**	 **19**	 **20**, 83%
3	 **5**	 **21**	 **22**, 92%
4	 **5**	 **23**	 **24**, 57%
5	 **5**	 **25**	 **26**, 64%
6	 **6**	$PhCH_2SH$ **17**	 **27**, 86%
7	 **6**	 **19**	 **28**, 52%
8	 **6**	 **21**	 **29**, 57%
9	 **6**	 **23**	 **30**, 91%

Table 1 (*concluded*).



Entry	Substrate	Thiol	Product, yield
10	 **6**	 **25**	 **31**, 80%
11	 **9**	 **25**	 **32**, 61%
12	 **12**	 **25**	 **33**, 63%
13	 **12**	 **19**	 **34**, 57%

that the onset of the formation of **18** is seen before the complete conversion of **6** to the selenosulfide intermediate. A set of minor signals attributable neither to the selenosulfide nor to the final product, and which are lost by the end of the reaction, may represent the selenosulfoxide intermediate, a functional group that to date has not been described in the literature. To probe this possibility further, we turned to ^{77}Se NMR spectroscopy. The rapid transformation of **6** to the selenosulfide is clearly seen, with its disappearance later as the reaction proceeds to completion. A minor unidentified signal is formed over the course of the reaction at δ 500 but, as this signal persists at the end of the reaction, it cannot be the selenosulfoxide intermediate and must represent a minor selenium-containing byproduct. Unfortunately, selenosulfoxides, like their thiosulfoxide cousins,[2] must retain their status as hypothetical reaction intermediates for the present.

In conclusion, 2-(selenocyanatomethyl)-3-propenol (**6**) is a readily prepared functionalized allylic selenocyanate whose alcohol moiety may be derivatized by glycosylation under standard conditions without detriment to the selenium functionality. Attempted derivation of **6** as a phosphite ester was, however, mostly unsatisfactory because of the apparent incompatibility of the selenocyanate group with a strong intramolecular nucleophile. Alcohol **6** itself and its derivatives react with a variety of thiols in methanolic solution at room temperature to give the corresponding mixed dialkyl sulfides with the corresponding loss of selenium. Finally, compatibility of the selenocyanate functionality with oxidative removal of a *p*-methoxybenzyl ether and Lewis and (or) Brønsted acidic conditions of glycosylation reactions has been demonstrated.

Experimental

^{1}H NMR (300 or 500 MHz), ^{13}C NMR (75 MHz), and ^{77}Se NMR (95 MHz) spectra were recorded on Bruker spectrometers. ^{1}H and ^{13}C NMR chemical shifts are given in ppm with respect to tetramethylsilane, following referencing to the in-

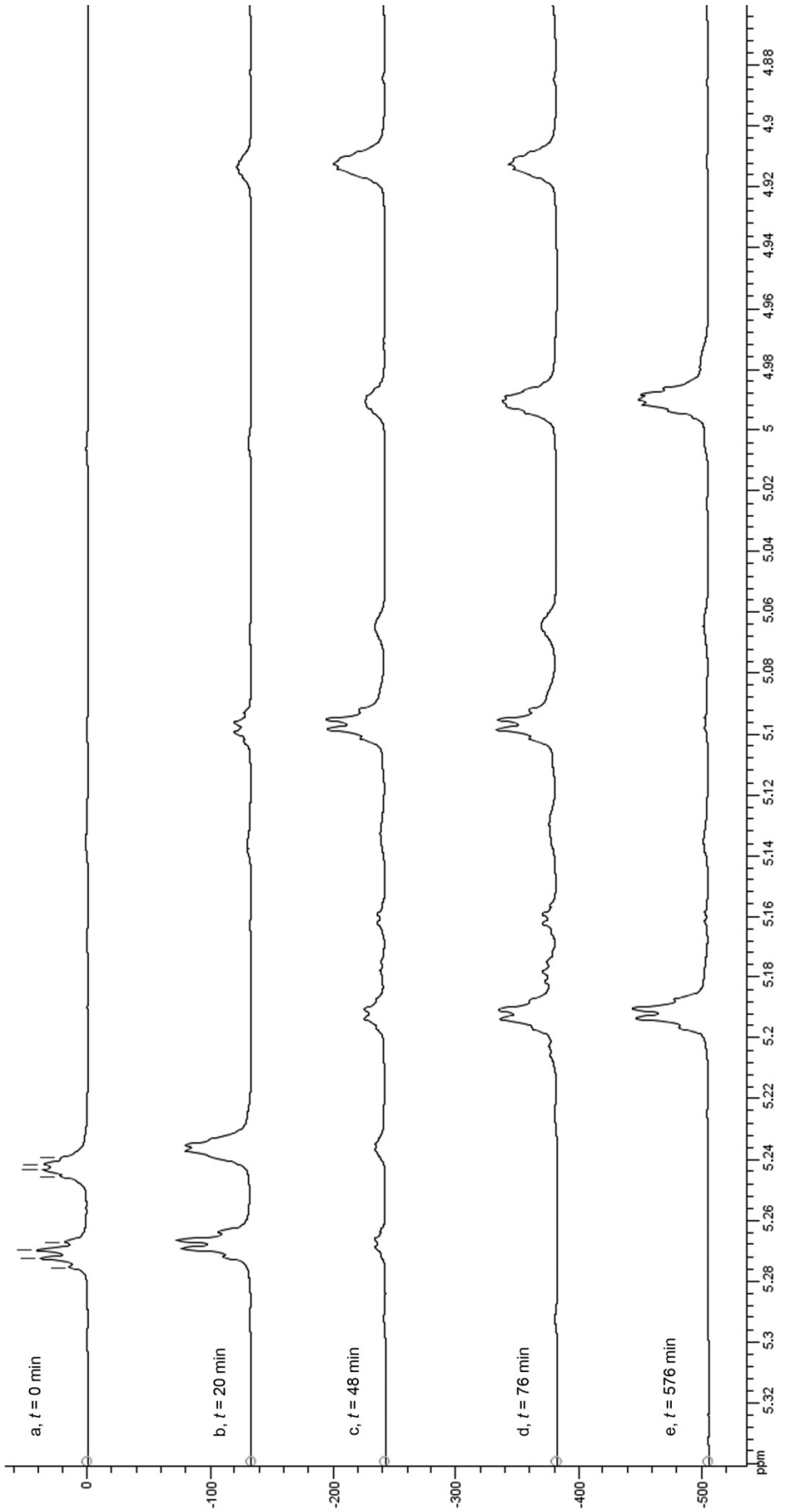
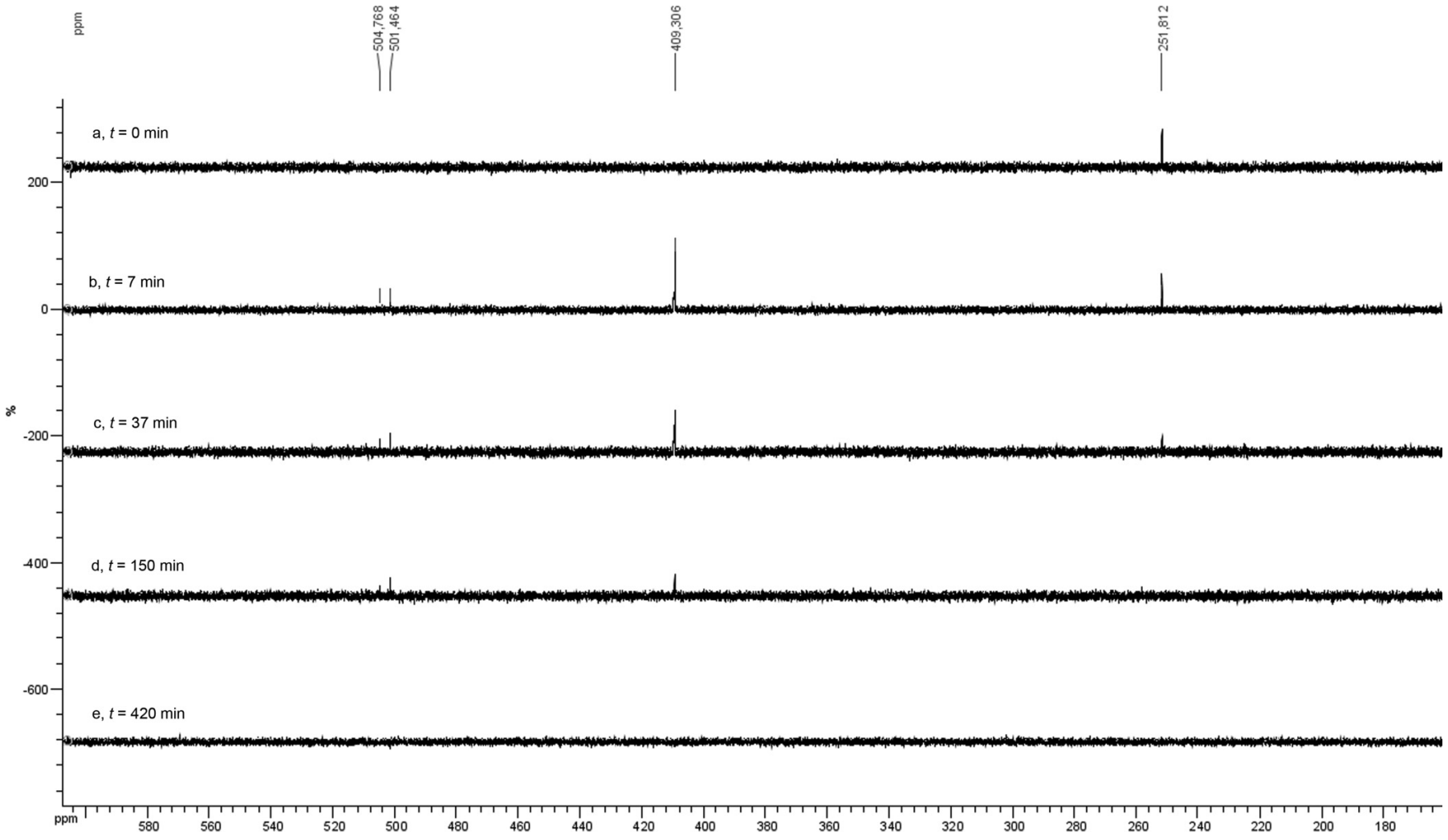


Fig. 1. Vinylic proton region of the ^{1}H NMR spectra for the reaction of **6** with benzyl mercaptan. (*a*) **6**; (*b*) **6** + benzylmercaptan; (*c*) after 48 min with formation of selenosulfide; (*d*) after 76 min; and (*e*) after 576 min.

Fig. 2. ^{77}Se NMR spectra of the reaction of **6** with benzyl mercaptan. (*a*) **6**; (*b*) **6** + benzylmercaptan; (*c*) after 37 min with formation of selenosulfide; (*d*) after 150 min; and (*e*) after 420 min.



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ternal solvent signal. ^{77}Se NMR chemical shifts are given in ppm with respect to dimethylselenide with the aid of referencing to the internal solvent signal. Multiplicities are given as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublet), dt (doublet of triplet), and m (multiplet). Coupling constants (*J*) are given in Hz. Infrared spectra were recorded on a PerkinElmer FT-IR instrument and the data are reported in reciprocal centimetres (cm^{-1}). Mass spectra were recorded on a Micromass LCT (ESI). Reactions were performed using oven-dried $MgSO_4$ glassware under an atmosphere of dry argon. TLC plates (Merck 60 F_{254} aluminum sheets) were visualized by UV and (or) spraying with vanillin (1%) + sulfuric acid (5%) in EtOH followed by heating. THF and CH_2Cl_2 were dried by standing over molecular sieves under argon. Unless otherwise noted, all reagent-grade chemicals and solvents were obtained from commercial suppliers and were used as received. Specific rotations are expressed in deg cm^3 g^{-1} dm^{-1} and *c* is expressed in g/100 cm^3.

2-(Chloromethyl)allyl *p*-methoxybenzyl ether (4)

p-Methoxybenzyl methallyl ether (**3**)[7] (9.2 mmol, 1.77 g) in CH_2Cl_2 (100 mL) was treated with $LiClO_4$ (1.8 mmol, 0.2 g) and pyridine (11. mmol, 0.89 mL) and cooled to –78 °C before SO_2Cl_2 (11.0 mmol, 0.89 mL) was added. After 1 h at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and washed with brine. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by chromatography over silica gel (eluent, MTBE/Hept 5:95) to give **4** (0.60 g, 29%) whose spectral data correspond to those reported in the literature.[8]

2-(Selenocyanatomethyl)allyl *p*-methoxybenzyl ether (5)

KSeCN (11.8 mmol, 1.7 g) was added to a solution of **4** (5.9 mmol, 1.34 g) in DMF (24 mL) and the solution was stirred at 40 °C for 3 h. Water was added and the solution was extracted twice with MTBE. The combined organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was purified by chromatography on silica gel (eluent, AcOEt/Hept 1:3) to give **5** (1.41 g, 81%) as a yellow oil. IR (neat, cm^{-1}): 817, 921, 1031, 1077, 1174, 1246, 1302, 1514, 1610, 2148, 2836. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.78 (s, 2H), 3.83 (s, 3H), 4.12 (s, 2H), 4.46 (s, 2H), 5.27 (s, 1H), 5.33 (s, 1H), 6.91 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 31.9 (CH_2), 55.4 (CH_3), 70.8 (CH_2), 72.3 (CH_2), 102.4 (CN), 114.1 (2 CH), 118.6 (CH_2),[3] 129.7 (2 CH), 129.8 (Cq), 140.5 (Cq), 159.6 (Cq). HRMS (ESI) calcd for $C_{13}H_{19}N_2O_2Se$: 315.0606; found: 315.0634 $[M + NH_4]^+$.

2-(Selenocyanatomethyl)prop-2-en-1-ol (6)

Water (330 μL) and DDQ (1.1 mmol, 230 mg) were added to a solution of **10** (0.68 mmol, 200 mg) in CH_2Cl_2 (6.6 mL) and the resulting solution was stirred for 3 h. It was quenched with an aqueous saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, and washed with brine. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by chromatography on silica gel (eluent, AcOEt/Hept 1:1) to give **6** (87.6 mg, 74%) as a yellow oil. IR (neat, cm^{-1}): 727, 915, 1022, 1054, 1197, 1366, 1426, 1646, 1738, 2150, 2923, 3394. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.6–2.8 (br s, OH), 3.79 (s, 2H), 4.25 (s, 2H), 5.26 (s, 1H), 5.27 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 31.5 (CH_2), 63.9 (CH_2), 102.6 (CN), 117.1 (CH_2), 142.8 (Cq). ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ: 251.8. HRMS (ESI) calcd for C_5H_6NOSe: 176.9693; found: 175.9606 $[M - H]^-$.

2-(Selenocyanatomethyl)allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (9)

***From trichloroacetimidate* 7**

A solution of **6** (0.28 mmol, 50 mg) in CH_2Cl_2 (1 mL) and 4 Å molecular sieves was stirred 30 min at room temperature and then cooled at –78 °C. $BF_3.OEt_2$ (0.16 mmol, 20 μL) and **7** (0.71 mmol, 350 mg) were added and the solution was stirred at 0 °C for 2 h 30 min. The reaction mixture was then quenched with NEt_3, filtered, and evaporated in vacuo. The crude product was purified by chromatography on silica gel (eluent, AcOEt/Hept 1:1) to give **9** (58.3 mg, 41%) as a colorless oil.

***From bromide* 8**

Compound **6** (0.28 mmol, 50 mg) was added to CH_2Cl_2 (2 mL) and 4 Å molecular sieves. The solution was stirred for 30 min at room temperature and the donor **8** was added (0.381 mmol, 140 mg). $InCl_3$ (0.14 mmol, 31.4 mg) was then added and the solution was stirred for 3 days at room temperature. The reaction mixture was diluted in CH_2Cl_2 and filtered through a Celite pad. The filtrate was evaporated in vacuo and the crude product was purified by chromatography on silica gel (eluent, AcOEt/Hept 1:1) to give **14** (45.1 mg, 31%) as a colorless oil. $[\alpha]_D^{25}$ –15.4 (*c* 0.54, $CHCl_3$). IR (neat, cm^{-1}): 697, 907, 1367, 1431, 1744, 2153, 2940. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.98 (s, 3H), 2.00 (s, 3H), 2.03 (s, 3H), 2.07 (s, 3H), 3.64–3.77 (m, 3H), 4.13–4.23 (m, 3H), 4.41 (d, J = 12.3 Hz, 1H), 4.53 (d, J = 7.9 Hz), 4.98 (dd, J = 7.9, 9.7 Hz, 1H), 5.06 (t, J = 9.7 Hz, 1H), 5.18 (t, J = 9.5 Hz, 1H), 5.23 (s, 1H), 5.29 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 20.6 (2 CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.3 (CH_2), 61.8 (CH_2), 68.3 (CH), 71.2 (CH), 72.0 (CH), 72.7 (CH), 69.9 (CH_2), 100.0 (CH), 101.6 (CN), 119.1 (CH_2), 139.3 (Cq), 169.3 (CO), 169.4 (CO), 170.2 (CO), 170.6 (CO). ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ: 248.0. HRMS (ESI) calcd for $C_{19}H_{29}N_2O_{10}Se$: 525.0982; found: 525.1033 $[M + NH_4]^+$.

4-Methylphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-naphthalenylmethyl)-α-D-thiomannopyranoside (11)

A mixture of (4-methylphenyl) 4,6-*O*-benzylidene-β-D-thiomannopyranoside (2.4 mmol, 900 mg) and *n*-Bu_2SnO (2.9 mmol, 722 mg), in dry toluene (25 mL), was refluxed overnight. The resulting solution was cooled at room temperature and then concentrated under reduced pressure. The residue was dissolved in dry DMF (10 mL) and then CsF (4.8 mmol, 730 mg) and NAPBr (3.6 mmol, 780 mg) were added. The resulting mixture was stirred 6 h at room temperature, diluted with CH_2Cl_2, and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in dry DMF (10 mL), cooled at 0 °C, and NaH (4.8 mmol, 231 mg) was added. After 10 min of stirring, BnBr (4.8 mmol, 570 μL) was added. The resulting mixture was stirred overnight at room temperature, quenched with an aqueous saturated $NaHCO_3$ solution, and extracted twice with CH_2Cl_2. The combined organic layer was brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (eluent, 10% *t*-BuOMe

in heptane) to give 4-methylphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-naphthalenylmethyl)-α-D-thiomannopyranoside (**11**, 1.32 g, 91%) as a clear viscous oil. $[\alpha]^{22}_D$ +102.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.89 (t, *J* = 10.0 Hz, 1H), 4.02–4.07 (m, 2H), 4.23 (dd, *J* = 10.0 Hz, *J* = 4.5 Hz, 1H), 4.26–4.37 (m, 2H), 4.72 (d, *J* = 13.5 Hz, 1H), 4.75 (d, *J* = 13.5 Hz, 1H), 4.81 (d, *J* = 12.5 Hz, 1H), 4.94 (d, *J* = 12.5 Hz, 1H), 5.44 (s, 1H), 5.64 (s, 1H), 7.08 (d, *J* = 7.5 Hz, 2H), 7.29–7.48 (m, 10H), 7.52–7.55 (m, 2H), 7.70–7.73 (m, 1H), 7.78–7.83 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 65.4, 68.5, 72.9, 73.0, 76.2, 77.8, 79.0, 87.3, 101.5, 125.6, 125.8, 126.0, 126.1, 126.1, 126.2, 127.6, 127.8, 127.9, 128.0, 128.1, 128.4, 128.8, 129.8, 129.9, 132.2, 132.9, 133.6, 135.8, 137.6, 137.7, 137.9. HRMS (ESI) calcd for $C_{38}H_{36}O_5S$: 622.2627; found: 622.2641 $[M + NH_4]^+$.

2-(Selenocyanatomethyl)allyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2-naphthylmethyl)-β-D-mannopyranoside (12)

A stirred solution of thioglycoside **11** (0.54 mmol, 330 mg), TTBP (1.0 mmol, 248 mg), BSP (0.6 mmol, 119 mg) in CH_2Cl_2 (10 mL) was cooled to –78 °C and treated with Tf_2O (0.6 mmol, 96 μL). The resulting solution was stirred for 1 h before addition of a solution of **6** (0.63 mmol, 110 mg) in CH_2Cl_2 (2 mL). After stirring for 1 h at –78 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, warmed to room temperature and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo and the residue was purified by chromatography on silica gel (eluent, XXXX 1:4) to give **12** (172 mg, 49%) as a colorless oil. $[\alpha]_D^{23}$ –31.2 (*c* 0.92, $CHCl_3$). IR (neat, cm^{-1}): 1086, 1377, 1454, 2149, 2874, 3047. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.34–3.42 (m, 1H), 3.60–3.75 (m, 3H), 3.94–4.02 (m, 2H), 4.2 (d, *J* = 12.5 Hz, 1H), 4.29 (t, *J* = 9.6 Hz, 1H), 4.34–4.38 (m, 1H), 4.51 (s, 2H), 4.81–4.86 (m, 1H), 4.90–5.02 (m, 3H), 5.28 (s, 1H), 5.33 (s, 1H), 5.69 (s, 1H), 7.31–7.90 (m, 17H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 31.7, 67.9, 68.7, 70.3, 72.8, 75.1, 76.2, 78.1, 78.8, 101.4, 101.8, 119.2, 125.8, 126.1, 126.3, 126.6, 127.9, 128.1, 128.3, 128.4, 128.8, 129.1, 133.2, 133.4, 135.9, 137.7, 138.5, 139.8. ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ: 247.4. HRMS (ESI) calcd for $C_{36}H_{39}N_2O_6Se$: 675.1968; found: 675.1996 $[M + NH_4]^+$.

Dibenzyl 2-(selenocyanatomethyl)allyl phosphate (14)

A stirred solution of **6** (0.28 mmol, 50 mg) in CH_3CN (2.64 mL) was cooled to 0 °C and treated with 1*H*-tetrazole (0.77 mmol, 53.6 mg). Dibenzyl-*N*,*N*-diisopropyl phosphoramidite (0.57 mmol, 187 μL) was then added and the resulting solution was stirred for 1 h. *m*-CPBA (0.99 mmol, 171 mg) was then added and, after 10 min, the reaction mixture was quenched with water. The solution was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by chromatography on silica gel (eluent, AcOEt/Hept 1:1) to give **14** (35.5 mg, 29%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.56 (s, 2H), 4.52 (s, 1H), 4.53 (s, 1H), 4.99–5.09 (m, 4H), 5.20 (s, 1H), 5.27 (s, 1H), 7.32–7.35 (m, 8H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 31.1, 67.7, 67.8, 69.8, 69.9, 120.5, 128.3, 128.9, 129.0, 129.7. ^{31}P NMR (75.5 MHz, $CDCl_3$) δ: –0.43. HRMS (ESI) calcd for $C_{19}H_{24}N_2O_4P^{77}Se$: 455.0633; Found: 455.0643 $[M + NH_4]^+$.

2-(Benzyloxy)-5-methylene-1,3,2-oxaselenaphosphinane 2-oxide (16)

This compound, a colorless oil, was obtained in varying amounts from different preparations of **14**. IR (neat, cm^{-1}): 672, 697, 741, 789, 976, 1008, 1261, 1456. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.30–3.38 (m, 1H), 3.54–3.60 (m, 1H), 4.68–4.78 (m, 2H), 5.11–5.22 (m, 4H), 7.32–7.44 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 24.9, 68.9, 74.6, 74.7, 117.8, 128.4, 128.9, 135.5, 136.9. ^{31}P NMR (75.5 MHz, $CDCl_3$) δ: 8.07. ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ: 208.8; 213.7. HRMS (ESI) calcd for $C_{11}H_{14}O_3PSe$: 304.9846; found: 304.9933 $[M + H]^+$.

General procedure for ligation

To freshly prepared selenocyanate **5** or **6** (1 mmol) in degassed MeOH (10 mL) under an argon atmosphere was added a solution of thiol (1.2 mmol) in MeOH (5 mL). The reaction mixture was stirred at room temperature overnight and filtered through a Celite pad, which was further rinsed with MeOH. The solvent was evaporated to dryness and the residue was purified by column chromatography.

2-(Benzylthiomethyl)allyl *p*-methoxybenzyl ether (18)

Prepared according to the general procedure, by reaction of **5** (1.01 mmol, 300 mg) with benzylmercaptan **17** (1.21 mmol, 143 μL), affording **18** (241 mg, 76%) as a colorless oil. IR (neat, cm^{-1}): 702, 819, 910, 1034, 1087, 1302, 1453, 1512, 1612, 2835. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.11 (s, 2H), 3.63 (s, 2H), 3.80 (s, 3H), 4.07 (s, 2H), 4.43 (s, 2H), 5.05 (s, 1H), 5.19 (s, 1H), 6.86–6.90 (m, 2H), 7.24–7.30 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 34.3 (CH_2), 35.6 (CH_2), 55.5 (CH_3), 71.1 (CH_2), 72.1 (CH_2), 114.0 (2 CH), 115.1 (CH_2), 127.1, 128.7, 129.3 (5 CH), 129.5, 129.6 (2 CH), 130.5 (Cq), 138.4 (Cq), 141.9 (Cq), 159.4 (Cq). HRMS (ESI) calcd for $C_{19}H_{26}NO_2S$: 332.1679; found: 332.1670 $[M + NH_4]^+$.

N-(*tert*-Butoxycarbonyl) *S*-(*p*-methoxybenzyloxymethyl)allyl L-cysteine methyl ester (20)

Prepared according to the general procedure, by reaction of **5** (1.01 mmol, 300 mg) with the L-cysteine derivative **19** (1.26 mmol, 209 μL), affording **20** (356 mg, 83%) as a colorless oil. $[\alpha]_D^{25}$ +8.5 (*c* 0.66, $CHCl_3$). IR (neat, cm^{-1}): 819, 915, 1034, 1246, 1366, 1513, 1613, 1713, 1746, 2976, 3359. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 2.78–2.93 (m, 2H), 3.16–3.26 (m, 2H), 3.75 (3H, CH_3), 3.80 (3H, CH_3), 4.05 (s, 2H), 4.44 (s, 2H, CH_2), 4.51–4.54 (br s, 1H), 5.08 (s, 1H), 5.18 (s, 1H), 5.29–5.34 (br s, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.2 (CH_3), 28.5 (3 CH_3), 33.6 (CH_2), 35.4 (CH_2), 52.7 (CH), 55.5 (CH_3), 70.6 (CH_2), 72.1 (CH_2), 114.0 (2 CH), 115.9 (CH_2), 129.6 (2 CH), 130.4 (Cq), 141.6 (Cq), 159.4 (Cq), 171.8 (CO). HRMS (ESI) calcd for $C_{21}H_{34}N_2O_6S$: 425.1872; found: 426.1928 $[M + NH_4]^+$.

Ethyl 2-(*p*-methoxybenzyloxymethyl)allylthioacetate (22)

Prepared according to the general procedure, by reaction of **5** (0.17 mmol, 50 mg) with ethyl thioglycolate (**21**, 0.20 mmol, 24.4 mg), affording **22** (48.3 mg, 92%) as a colorless oil. IR (neat, cm^{-1}): 818, 911, 1034, 1090, 1171, 1246, 1512, 1609, 1724, 2936. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.30 (t, *J* = 7.0 Hz, 3H), 3.15 (s, 2H), 3.35 (s, 2H), 3.83 (s, 3H), 4.09 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.46 (s, 2H), 5.13 (s, 1H), 5.23 (s, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ: = 32.2, 34.9, 41.5, 55.3, 61.3, 61.7, 71.9, 113.8, 115.9, 129.1, 129.4, 130.3, 140.8, 159.2, 170.4. HRMS (ESI) calcd for $C_{16}H_{26}NO_4S$: 328.1577; found: 328.1557 $[M + NH_4]^+$.

_p_-Methoxybenzyl 2-(2-hydroxyethyl)thiomethyl ether (24)

Prepared according to the general procedure, by reaction of **5** (0.14 mmol, 40 mg) with 2-mercaptoethanol (**23**, 0.16 mmol, 13.0 mg), affording **24** (23.1 mg, 57%) as a colorless oil. IR (neat, cm^{-1}): 712, 760, 818, 915, 1033, 1066, 1173, 1301, 1511, 1612, 1647, 2835, 2912, 3399. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.68 (t, J = 5.8 Hz, 2H), 3.25 (s, 2H), 3.72 (t, J = 5.8 Hz, 2H), 3.83 (s, 3H), 4.10 (s, 2H), 4.47 (s, 2H), 5.01 (s, 1H), 5.13 (s, 1H), 6.91 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 34.2, 34.3, 35.3, 60.1, 70.6, 71.9, 113.8, 115.4, 129.4, 144.8, 156.3. HRMS (ESI) calcd for $C_{14}H_{20}O_3S$: 268.1133; found: 269.1215 $[M + H]^+$.

_N_-(*tert*-Butoxycarbonyl) _S_-(_p_-methoxybenzyloxymethyl)allyl glutathione dimethyl ester (26)

Prepared according to the general procedure, by reaction of **5** (0.10 mmol, 30 mg) with the glutathione derivative **25** (0.12 mmol, 59.7 mg), affording **26** (40.6 mg, 64%) as a colorless oil. $[\alpha]_D^{25}$ +0.5 (_c_ 0.98, $CHCl_3$). IR (neat, cm^{-1}): 735, 1031, 1169, 1207, 1246, 1512, 1646, 1706, 1742, 2952, 3301. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.98 (m, 1H), 2.15 (m, 1H), 2.87 (m, 2H), 3.29 (s, 2H), 3.75 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 4.07 (s, 2H), 4.14 (s, 2H), 4.45 (s, 1H), 5.21 (m, 1H), 5.37 (m, 1H), 6.89 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 28.3 (3 CH_3), 28.7 (CH_2), 32.9 (CH_2), 34.9 (CH_2), 41.3 (CH_2), 52.4, 55.3, 70.7 (CH_2), 71.9 (CH_2), 113.8, 116.2 (2 CH), 129.5 (2 CH), 141.5 (Cq), 154.2 (Cq), 155.5 (Cq), 170.1 (Cq), 172.2 (Cq), 173.0 (Cq). HRMS (ESI) calcd for $C_{29}H_{44}N_3O_{10}S$: 626.2669; found: 626.2769 $[M + H]^+$.

2-(Benzylthiomethyl)prop-2-en-1-ol (27)

Prepared according to the general procedure, by reaction of **6** (0.57 mmol, 100 mg) with benzyl mercaptan **17** (0.68 mmol, 80 μL), affording **27** (94.5 mg, 86%) as a colorless oil. IR (neat, cm^{-1}): 756, 907, 1028, 1232, 1453, 1494, 2916, 3347. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.06 (s, 2H), 3.58 (s, 2H), 4.15 (s, 2H), 4.92 (s, 1H), 5.12 (s, 1H), 7.17–7.27 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 34.2 (CH_2), 35.4 (CH_2), 64.6 (CH_2), 113.7 (CH_2), 127.1, 128.6, 129.2 (5 CH), 138.1 (Cq), 144.2 (Cq). HRMS (ESI) calcd for $C_{11}H_{18}NOS$: 212.1104; found: 211.0785 $[M + NH_4]^+$.

_N_-(*tert*-Butoxycarbonyl) _S_-(hydroxymethyl)allyl L-cysteine methyl ester (28)

Prepared according to the general procedure, by reaction of **6** (0.57 mmol, 100 mg) with the L-cysteine derivative **19** (0.68 mmol, 160.4 mg), affording **28** (90.3 mg, 52%) as a colorless oil. $[\alpha]_D^{26}$ +8.5 (_c_ 0.55, $CHCl_3$). IR (neat, cm^{-1}): 913, 1055, 1217, 1367, 1437, 1513, 1698, 2978, 3374. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.42 (s, 9H), 2.00 (s, 2H), 3.20 (s, 2H), 3.73 (s, 3H), 4.11–4.22 (m, 2H), 4.49–4.54 (br s, 1H), 5.01 (s, 1H), 5.16 (s, 1H) 5.26–5.31 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.3 (CH_3), 28.5 (3 CH_3), 34.1(CH_2), 35.4 (CH_2), 52.8 (CH), 64.1 (CH_2), 114.2 (CH_2), 144.3 (Cq), 171.8 (CO). HRMS (ESI) calcd for $C_{13}H_{27}N_2O_5S$: 328.1635; found: 328.1184 $[M + NH_4]^+$.

Ethyl 2-(hydroxybenzyloxymethyl)allylthioacetate (29)

Prepared according to the general procedure, by reaction of **6** (0.57 mmol, 100 mg) with ethyl thioglycolate **21** (0.68 mmol, 75 μL), affording **29** (61.8 mg, 57%) as a colorless oil. IR (neat, cm^{-1}): 757, 908, 1125, 1155, 1271, 1367, 1410, 1650, 1725, 2982, 3428. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.1 Hz, 3H), 2.16 (br s, 1H), 3.11(s, 2H), 3.28 (s, 2H), 4.05–4.17 (m, 4H), 5.10 (s, 1H), 5.16 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.3, 21.2, 32.4, 35.1, 60.6, 61.6, 64.2, 114.6, 143.5, 170.7. HRMS (ESI) calcd for $C_8H_{18}NO_3S$: 208.1002; found: 213.0549 $[M + NH_4]^+$.

2-(2-Hydroxyethylthiomethyl)prop-2-en-1-ol (30)

Prepared according to the general procedure, by reaction of **6** (0.13 mmol, 22 mg) with 2-mercaptoethanol **23** (0.14 mmol, 10.7 mg), affording **30** (16.8 mg, 91%) as a colorless oil. IR (neat, cm^{-1}): 695, 820, 1062, 1104, 1254, 1314, 1520, 1605, 3420. ^1H NMR (500 MHz, MeOD) δ: 2.70 (t, J = 6.0 Hz, 2H), 3.27 (s, 2H), 3.75 (t, J = 5.9 Hz, 2H), 4.26 (s, 2H), 5.07 (s, 1H), 5.18 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 34.1, 34.3, 60.3, 64.3, 114.1, 145.6.

_N_-(*tert*-Butoxycarbonyl) _S_-(hydroxymethyl)allyl glutathione dimethyl ester (31)

Prepared according to the general procedure, by reaction of **6** (0.28 mmol, 50 mg) with the glutathione derivative **25** (0.35 mmol, 154.7 mg), affording **31** (115.1 mg, 80%) as a colorless oil. $[\alpha]_D^{24}$ +2.4 (_c_ 0.92, $CHCl_3$). IR (neat, cm^{-1}): 733, 1028, 1052, 1207, 1365, 1435, 1516, 1645, 1688, 1742, 2980, 3293. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.98 (m, 1H), 2.18 (m, 1H), 2.38 (m, 2H), 2.88 (m, 1H), 2.93 (m, 2H), 3.33 (dd, J = 13.7 Hz, J = 20.2 Hz, 2H), 3.76 (s, 6H), 4.23 (s, 2H), 4.40 (s large, 1H), 4.68 (q, J = 6.9 Hz, 1H), 5.15 (s, 1H), 5.22 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 25.6 (CH_2), 28.5 (3 CH_3), 32.3 (CH_2), 34.4 (CH_2), 41.3 (CH_2), 52.4 (2 CH_3), 53.0 (CH), 64.0 (CH), 68.0 (CH_2), 80.3 (Cq), 114.3 (CH_2), 144.40 (Cq), 155.70 (NH–C=O), 169.95 ((C=O)O–Me), 170.13 ((C=O)NH), 172.47 (C=O), 172.93 (C=O). HRMS (ESI) calcd for $C_{21}H_{36}N_3O_9S$: 506.2094; found: 506.2159 $[M + H]^+$.

_N_-(*tert*-Butoxycarbonyl) _S_-[(2,3,4,6-tetra-_O_-acetyl-β-D-glucopyranosyl)methyl]allyl glutathione dimethyl ester (32)

Prepared according to the general procedure, by reaction of the glucose derivative **9** (0.04 mmol, 21.7 mg) with the glutathione derivative **25** (0.05 mmol, 23.3 mg) in CH_3CN, affording **32** (21.9 mg, 61%) as a colorless oil. $[\alpha]_D^{25}$ –5.6 (_c_ 0.82, $CHCl_3$). IR (neat, cm^{-1}): 910, 1040, 1167, 1367, 1437, 1518, 1660, 1747, 2932, 2953, 3313. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 2.00 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.10 (s, 3H), 2.31–2.41 (m, 2H), 2.75–2.89 (m, 2H), 3.22 (s, 2H), 3.75 (s, 3H), 3.76 (s, 3H), 4.05 (m, 2H), 4.17–4.19 (m, 1H), 4.21–4.26 (m, 1H), 4.33–4.42 (m, 2H), 4.54–4.63 (m, 2H), 4.98–5.14 (m, 2H), 5.14–5.26 (m, 3H), 5.29–5.36 (m, 1H), 6.72–6.82 (br s, 1H), 7.01–7.08 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 20.8, 20.9, 21.0, 28.5, 29.9, 32.3, 32.8, 34.8, 41.5, 52.5, 52.6, 52.7, 52.9, 62.1, 68.7, 70.2, 71.5, 72.0, 73.0, 100.1, 116.8, 140.3, 169.6, 170.1, 170.5, 170.7, 172.3, 173.0. HRMS (ESI) calcd for $C_{35}H_{57}N_4O_{18}S$: 853.3383; found: 853.3362 $[M + NH_4]^+$.

_N_-(*tert*-Butoxycarbonyl) _S_-[(2-_O_-benzyl-4,6-_O_-benzylidene-3-_O_-(2-naphthylmethyl)-β-D-mannopyranosyl)methyl]allyl glutathione dimethyl ester (33)

Prepared according to the general procedure, by reaction of the mannose derivative **12** (0.18 mmol, 120 mg) with the glutathione derivative **25** (0.24 mmol, 105 mg), affording **33** (113 mg, 63%) as a colorless oil. $[\alpha]_D^{26}$ –13.4 (*c* 1.40, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 1.86–2.00 (br s, 1H), 2.04 (s, 2H), 2.10–2.25 (br s, 1H), 2.28–2.38 (m, 1H), 2.76–2.92 (m, 2H), 3.23 (s, 1H), 3.63–3.68 (m, 1H), 3.72 (s, 6H), 3.88–4.03 (m, 4H), 4.06–4.17 (m, 2H), 4.24 (t, J = 9.6 Hz, 1H), 4.28–4.43 (m, 2H), 4.44–4.65 (m, 3H), 4.76–4.82 (m, 2H), 4.89–5.00 (m, 1H), 4.83–5.05 (m, 1H), 5.15–5.21 (m, 2H), 5.27–5.34 (br s, 1H), 5.65 (s, 1H), 6.69–6.81(br s, 1H), 6.97–7.07 (br s, 1H), 7.21–7.93 (m, 17H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.4, 28.5, 32.4, 35.0, 41.5, 52.6, 60.6, 67.9, 68.7, 70.5, 72.5, 75.1, 76.0, 78.0, 78.8, 101.7, 116.4, 125.8, 126.0, 126.2, 126.3, 126.5, 127.9, 128.1, 128.3, 128.4, 128.9, 129.1, 133.1, 133.4, 135.9, 137.9, 138.5, 140.6, 170.1, 170.8, 172.3, 173.0.

_N_-(*tert*-Butoxycarbonyl) _S_-[(2-_O_-benzyl-4,6-_O_-benzylidene-3-_O_-(2-naphthylmethyl)-β-D-mannopyranosyl)methyl]allyl L-cysteine methyl ester (34)

Prepared according to the general procedure, by reaction of the mannose derivative **12** (0.18 mmol, 127 mg) with the L-cysteine derivative **19** (0.23 mmol, 51.3 mg), affording **34** (79.6 mg, 57%) as a colorless oil. $[\alpha]_D^{20}$ –20.1 (*c* 0.45, $CHCl_3$). IR (neat, cm^{-1}): 698, 730, 817, 857, 908, 1049, 1165, 1368, 1453, 1496, 1602, 1709, 2872, 2924. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 2.76–2.92 (m, 2H), 3.17 (s, 1H), 3.26–3.37 (m, 1H), 3.60–3.65 (m, 1H), 3.92–3.95 (m, 2H), 4.03–4.12 (m, 1H), 4.18–4.34 (m, 2H), 4.39–4.51 (m, 2H), 4.68–4.84 (q, J = 10.5 Hz, 2H), 4.87 (d, J = 12.3 Hz, 1H), 4.99 (d, J = 12. 3 Hz, 1H), 5.08 (s, 1H), 5.16 (s, 1H), 5.39 (br s, 1H), 5.63 (s, 1H), 7.24–7.81 (m, 17H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 28.5, 29.9, 33.2, 35.2, 67.8, 68.8, 70.3, 72.5, 75.0, 75.9, 78.0, 78.8, 101.5, 101.7, 116.2, 125.8, 126.0, 126.2, 126.3, 126.4, 127.8, 128.1, 128.2, 128.4, 128.8, 129.1, 133.1, 133.4, 135.9, 137.8, 138.5, 140.5. HRMS (ESI) calcd for $C_{43}H_{53}N_2O_{10}S$: 789.3415; found: 789.3381 $[M + NH_4]^+$.

Monitoring of the reaction of 6 with benzylmercaptan by ^{1}H and ^{77}Se NMR spectroscopy

The reaction of **6** (0.23 mmol, 40 mg) with benzyl mercaptan (0.27 mmol, 34 mg) in CD_3OD (1 mL) was monitored by NMR spectroscopy through an iterative sequence of ^{1}H spectra (64 scans, 500 MHz, 300 K), ^{77}Se NMR spectra (64 scans, 95 MHz, 300 K), and DEPT ^{77}Se spectra (32 scans, 95 MHz, 300 K). Acquisition parameters for F1: size, 32 768 points; spectral width, 47 619 Hz).

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