Supplementary information

^{77}Se and ^{125}Te NMR Spectroscopy on Selectivity Study of Organochalcogenanes Compounds with *L*-amino acids

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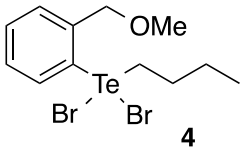
Experimental Considerations

The organochalcogenanes **1-4** were synthesized and characterized as recently described.[1] The thermal stability and reactivity studies were performed by nuclear magnetic resonance (300 MHz and 500 MHz), model Avance III Bruker equipped with a direct BBO probe (broad-band-observed) and LC-MS, when necessary. The natural abundance of ^{77}Se and ^{125}Te are 7.58 % and 6.99 %, respectively. The ^{1}H NMR chemical shifts are reported in ppm relative to TMS peak. The data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, qd = quadruplet, qt = quintet, st = sextuplet, m = multiplet), and coupling constant (*J*) in Hertz and integrated intensity. The ^{13}C NMR chemical shifts are reported in ppm relative to TMS peak. The ^{77}Se and ^{125}Te NMR chemical shifts are reported in ppm relative to internal standard $C_6H_5SeSeC_6H_5$ (463 ppm) or $C_6H_5TeTeC_6H_5$ (422 ppm), respectively.

[1] a) L. Piovan, L. Wu, Z. Zhang and L. H. Andrade *Org. Biomol. Chem.* 2011, **9**, 1347-1351. (b) L. Piovan, M. F. M. Alves, L. Juliano, D. Bromme, R. L. O. R. Cunha and L. H. Andrade *J. Braz. Chem. Soc.* 2010, **21**, 2108-2118.

Thermal stability study of organochalcogenanes 1-4

The compounds **1-4** compounds were, individually, submitted to different temperatures.



4

In a 5 mm NMR tube, 5 mg of organotellurane **4** were diluted in a mixture of 400 μL of DMSO-d_6 and 200 μL of 20 mM Tris/DCl in D_2O. A capillary tube of $(C_6H_5Te)_2$ was used as a chemical shift standard (422 ppm). An initial ^{125}Te NMR spectrum of organotellurane **4** was recorded at 25 °C (Figure S1). As we can see, in 885 ppm there is a signal with chemical shift assigned for the organotellurane **4**.

The same sample was heated up to 70 °C for 15 minutes and the ^{125}Te NMR spectrum was recorded.[2] In this case, a change was observed regarding chemical shift, 885 ppm at 25 °C (Figure S1) to 1266.6 ppm at 70 °C (Figure S2).

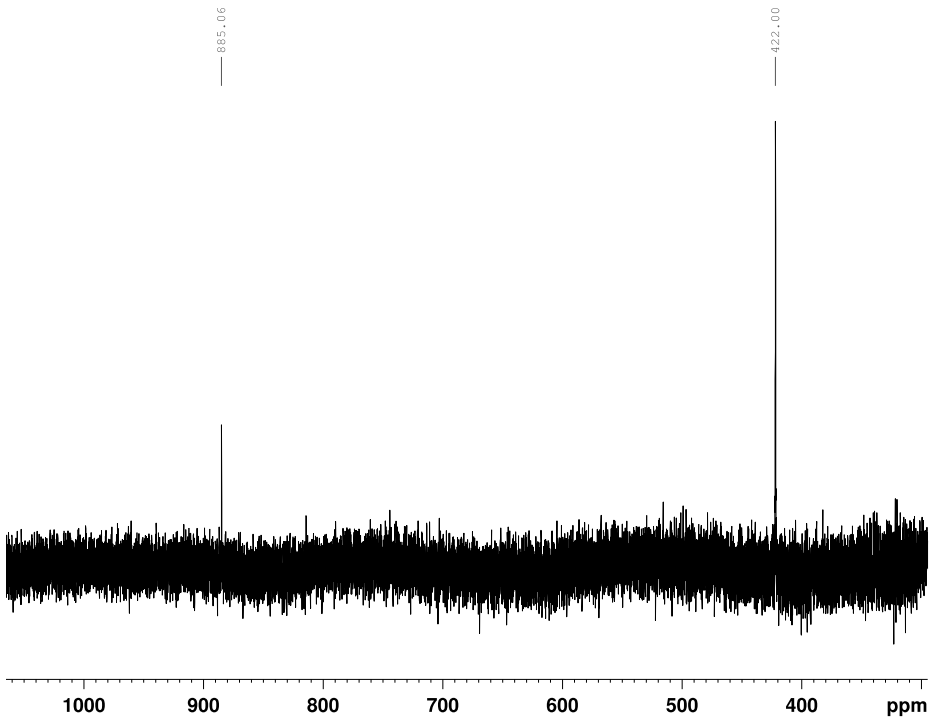


Figure S1: ^{125}Te NMR spectrum of organotellurane **4** in DMSO-d_6 at 25 °C

[2] All experiments were tested by 15 minutes, because it was the time employed in all enzyme inhibitory profile.

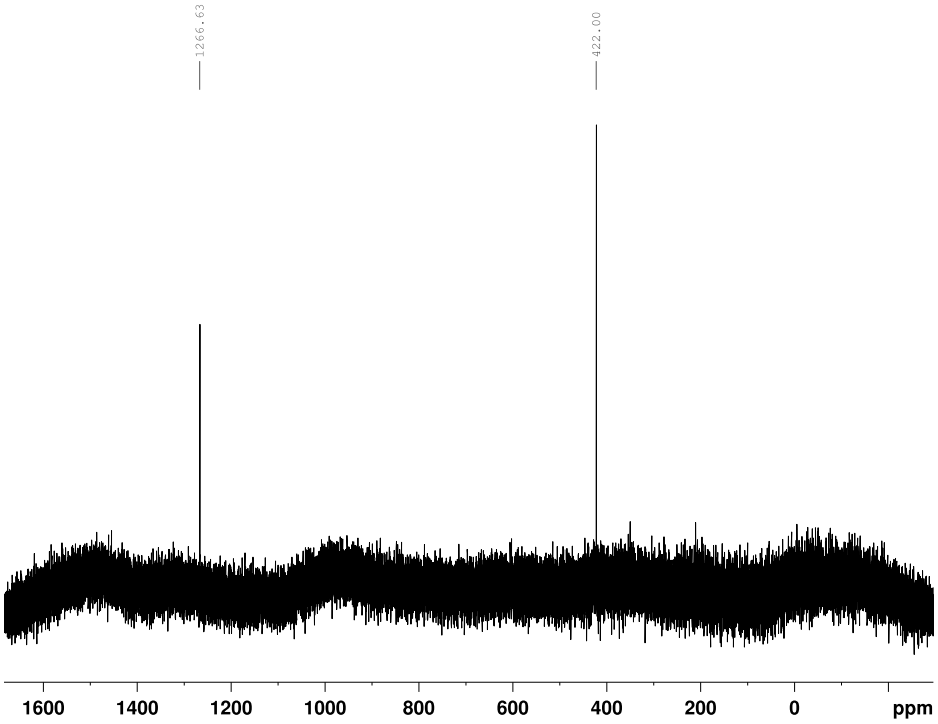


Figure S2: ^{125}Te NMR spectrum of organotellurane **5** in D_2O at 25 ^{o}C

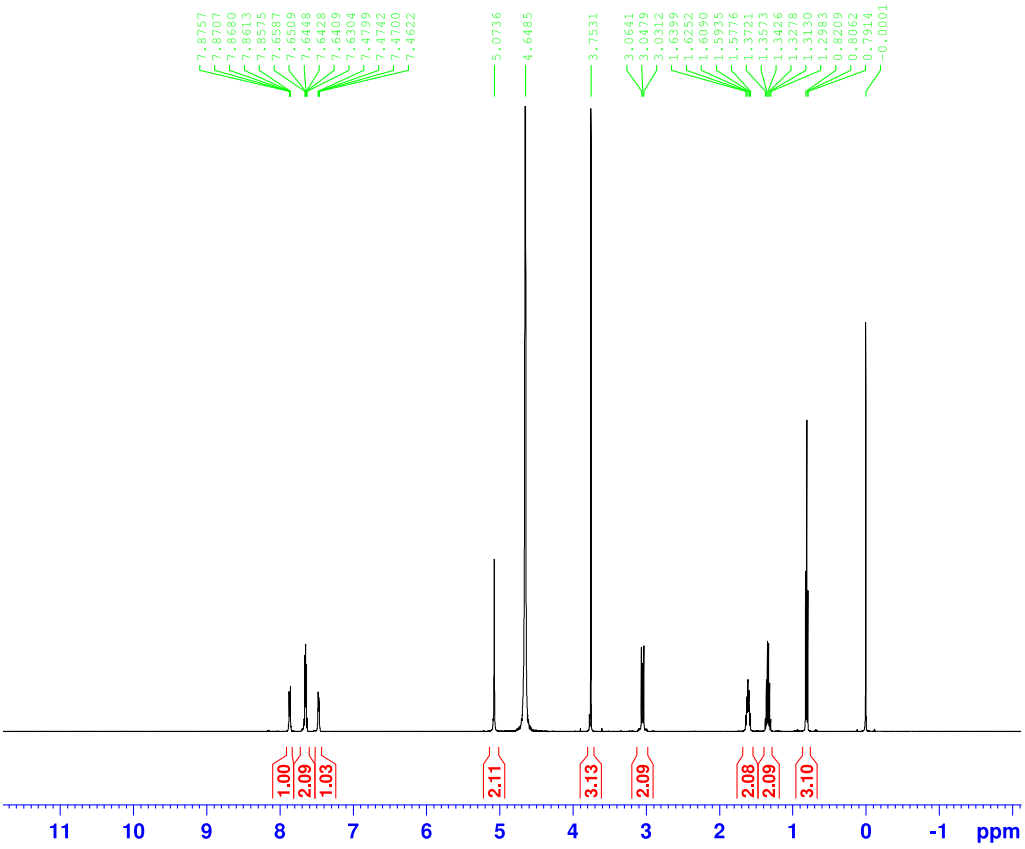


Figure S3: ^{1}H NMR spectrum of organotellurane **5** in D_2O at 25 ^{o}C

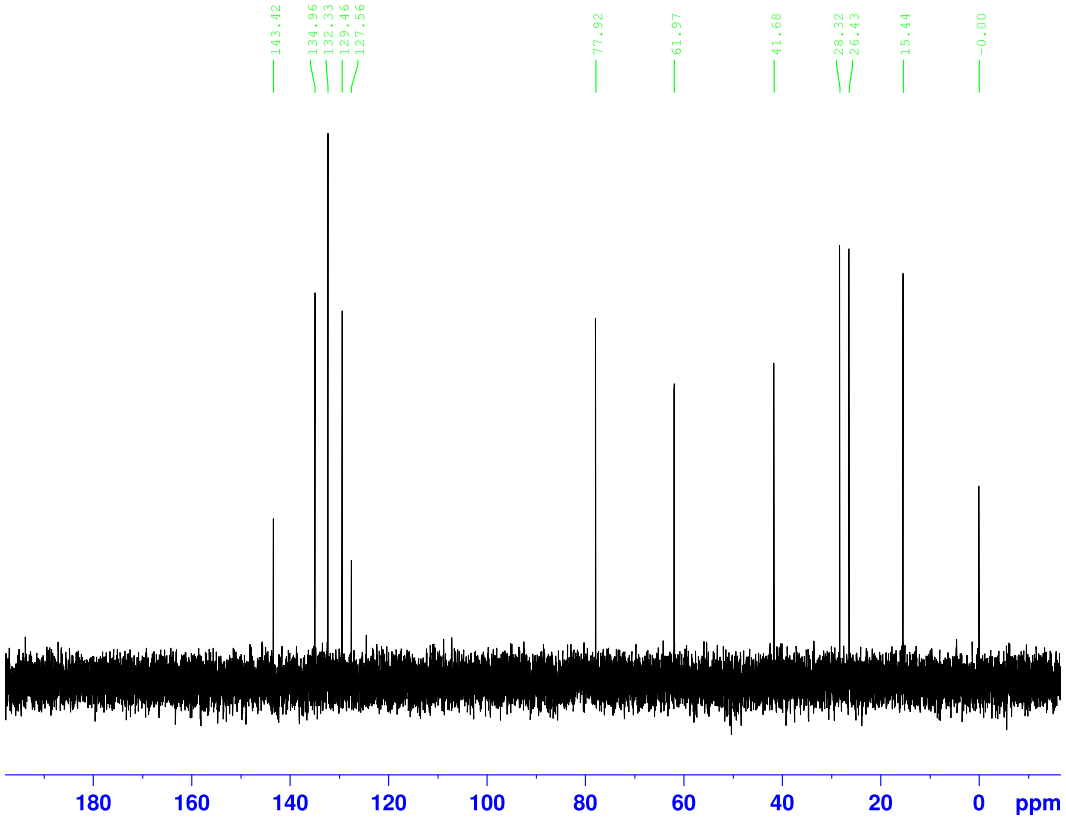
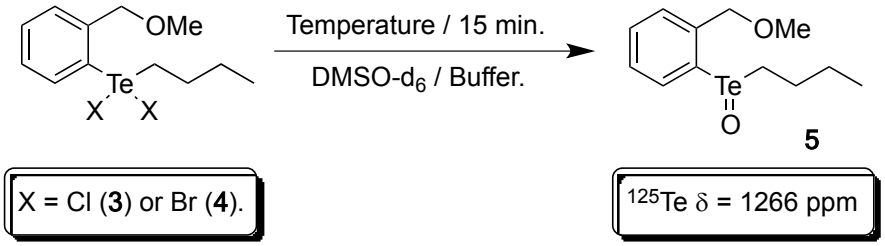


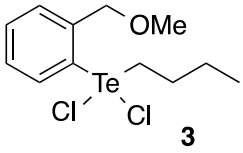
Figure S4: ^{13}C NMR spectrum of organotellurane **5** in D_2O at 25 °C

Spectral dada of compound **5**:



1-(butyltellurinyl)-2-(methoxymethyl)benzene

^{1}H NMR (500MHz, DMSO-d_6, 25 °C, TMS, δ ppm): 7.85-7.87 (m, 1H); 7.63-7.65 (m, 2H); 7.46-7.47 (m, 1H); 5.07 (s, 2H); 3.75 (s, 3H); 3.04 (t, J = 8.1 Hz, 2H); 1.61 (qt, J = 7.4 Hz, 2H); 1.39 (sext, J = 7.4 Hz, 2H); 0.89 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (300MHz, DMSO-d_6, 25 °C, TMS, δ ppm): 143.4; 134.9; 132.3; 132.2; 129.5; 127.6; 77.9; 62.0; 41.7; 28.3; 26.4; 15.4. **^{125}Te NMR** (94.74 MHz, DMSO-d_6, 25 °C, $C_6H_5TeTeH_5C_6$ standard δ ppm 422): 1266.6. **LC-MS** [M+ + 1]: Calculated value: 324.0369; found value: 325.0388.



3

In a 5 mm NMR tube, 5 mg of organotellurane **3** were diluted in a mixture of 400 μL of DMSO-d_6 and 200 μL of 20 mM Tris/DCl in D_2O. A capillary tube of $(C_6H_5Te)_2$ was used as a chemical shift standard (422 ppm). An initial ^{125}Te NMR spectrum of organotellurane **3** was recorded at 25 °C (Figure S5). As we can see, in 930 ppm there is a signal with chemical shift assigned for the organotellurane **3**.

The same sample was heated up at 60 °C for 15 minutes and the ^{125}Te NMR spectrum was recorded. In this case, a change was observed regarding chemical shift, 885 ppm at 25 °C (Figure S5) to 1266.6 ppm at 60 °C.

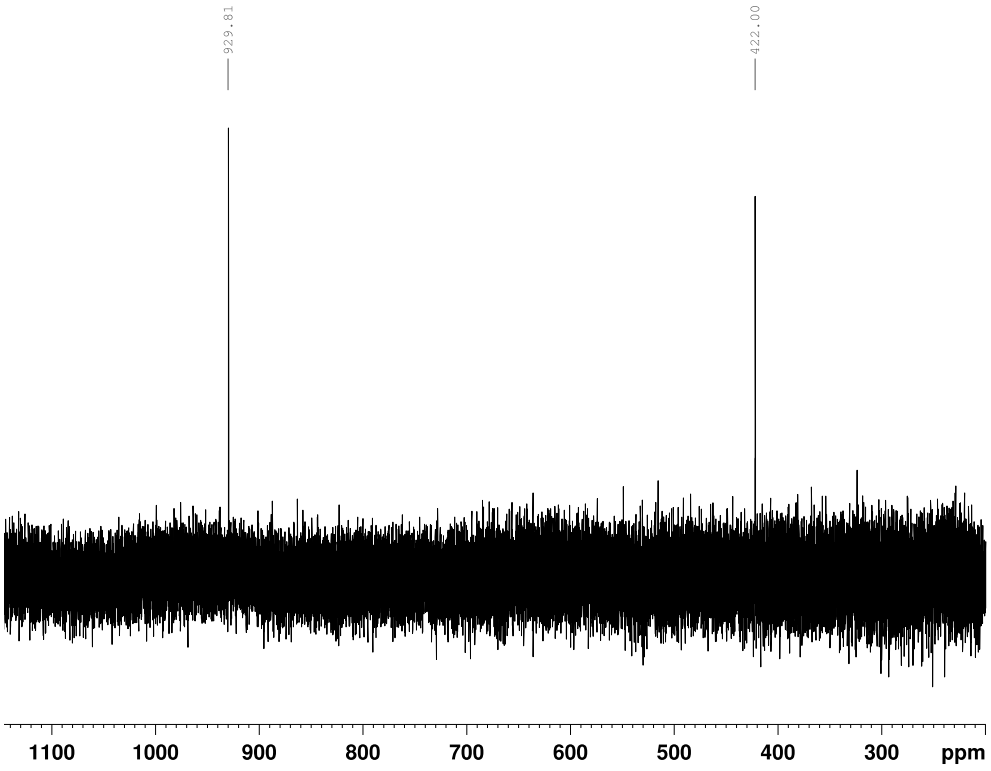
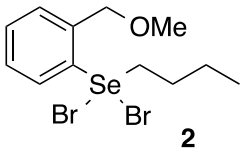


Figure S5: ^{125}Te NMR spectrum of organotellurane **3** in DMSO-d_6 at 25 °C



2

In a 5 mm NMR tube, 5 mg of organoselenane **2** were diluted in a mixture of 400 μL of DMSO-d_6 and 200 μL of 20 mM Tris/DCl in D_2O. A capillary tube of $(C_6H_5Se)_2$ was used as a chemical shift standard (463 ppm). An initial NMR of ^{77}Se NMR spectrum of organoselenane **2** was recorded at 25 °C (Figure S6). As we can see, in 483 ppm there is a signal with chemical shift assigned for the organoselenane **2**.

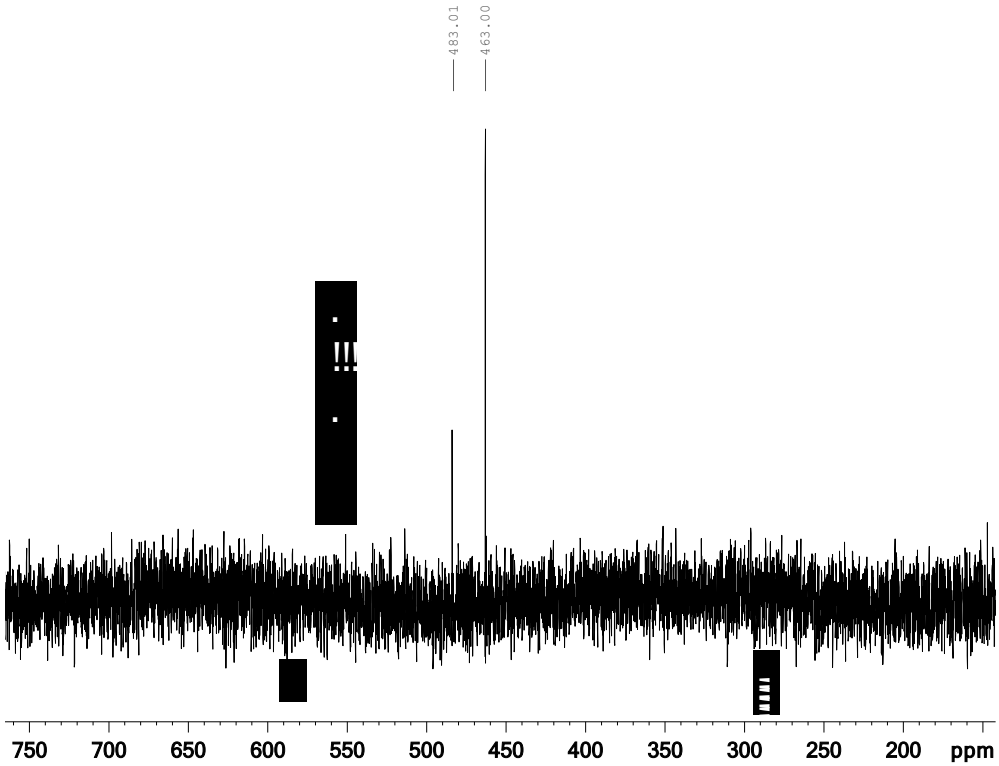


Figure S6: ^{77}Se NMR spectrum of organoselenane **2** in DMSO-d_6 at 25 °C

The same sample was heated up at 37 °C for 15 minutes and the ^{77}Se NMR spectrum was recorded. In this case, a significant change was observed regarding chemical shift, 483 ppm at 25 °C (Figure S6) to 403 ppm at 37 °C (Figure S7). The new compound is the product **7** from loss of bromine atom. It was also observed that the solution color turned slightly

orange by the output of bromine. The selenium chemical shift is now in 403.5 ppm, between the compound **2** (483.6 ppm) and starting material (237.0 ppm).

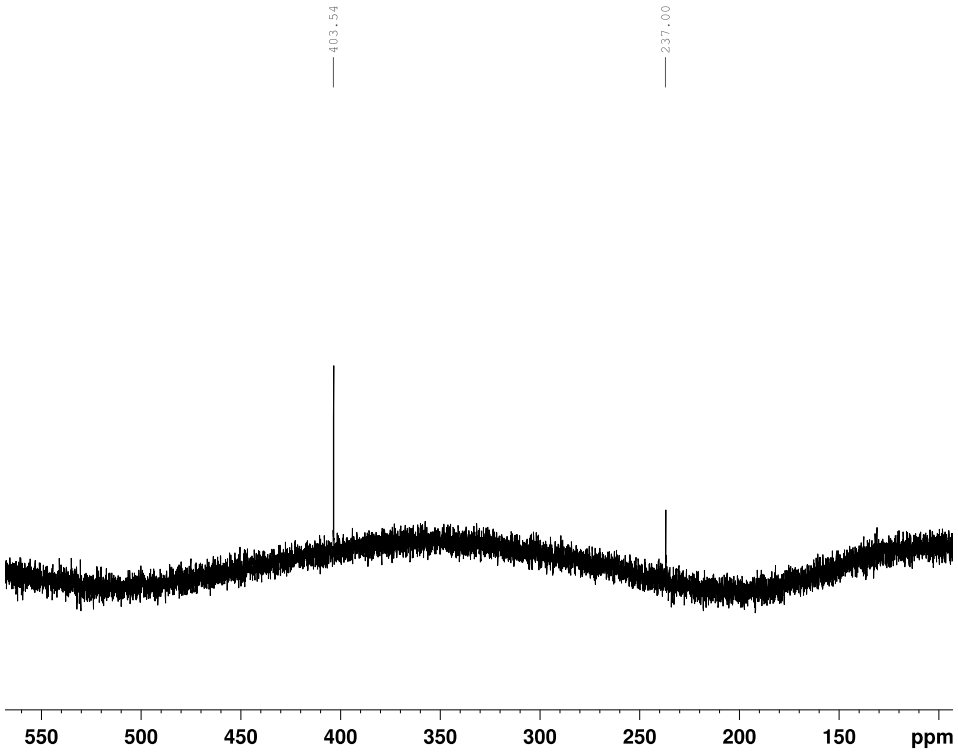
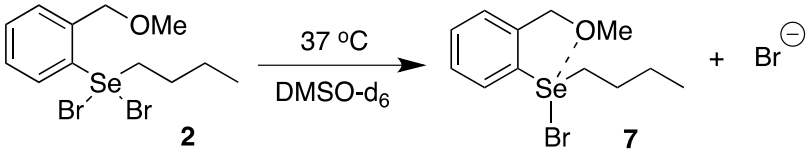


Figure S7: ^{77}Se NMR spectrum of organoselenane **7** in DMSO-d_6 at 37 ^{o}C[3]

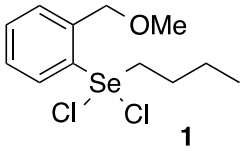
Spectral dada of compound **7**:



^{1}H NMR (300MHz, DMSO-d_6, 37 ^{o}C, TMS, δ ppm): 7.68 (m, 1H); 7.35 (m, 2H); 7,27 (m, 1H); 4.71 (s, 2H); 3.53 (t, *J* = 6.7 Hz, 2H); 3.39 (s, 3H); 1.77 (q, *J* = 8.4 Hz, 2H); 1.40 (sext, *J* = 7.6 Hz, 2H); 0.88 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (300MHz, DMSO-d6, 37 ^{o}C, TMS, δ ppm): 139.4; 135.6; 131.7; 128.2; 127.9; 126.2; 74.5; 58.2; 34.9; 34.2; 20.7; 13.0. **^{77}Se NMR** (57.24

[3] The sign is very low. The experiment was recorded with 40k scans (48 hours). The chemical shift was calibrated electronically.

MHz, DMSO-d6, 37 °C, $C_6H_5SeSeH_5C_6$ standard δ ppm 463 was calibrated electronically): 403.5.



1

In a 5 mm NMR tube, 5 mg of organoselenane **1** were diluted in a mixture of 400 μL of DMSO-d_6 and 200 μL of 20 mM Tris/DCl in D_2O. A capillary tube of $(C_6H_5Se)_2$ was used as a chemical shift standard (463 ppm). An initial NMR of ^{77}Se NMR spectrum of organoselenane **1** was recorded at 25 °C (Figure S8). As we can see, in 550 ppm there is a signal with chemical shift assigned for the organoselenane **1**.

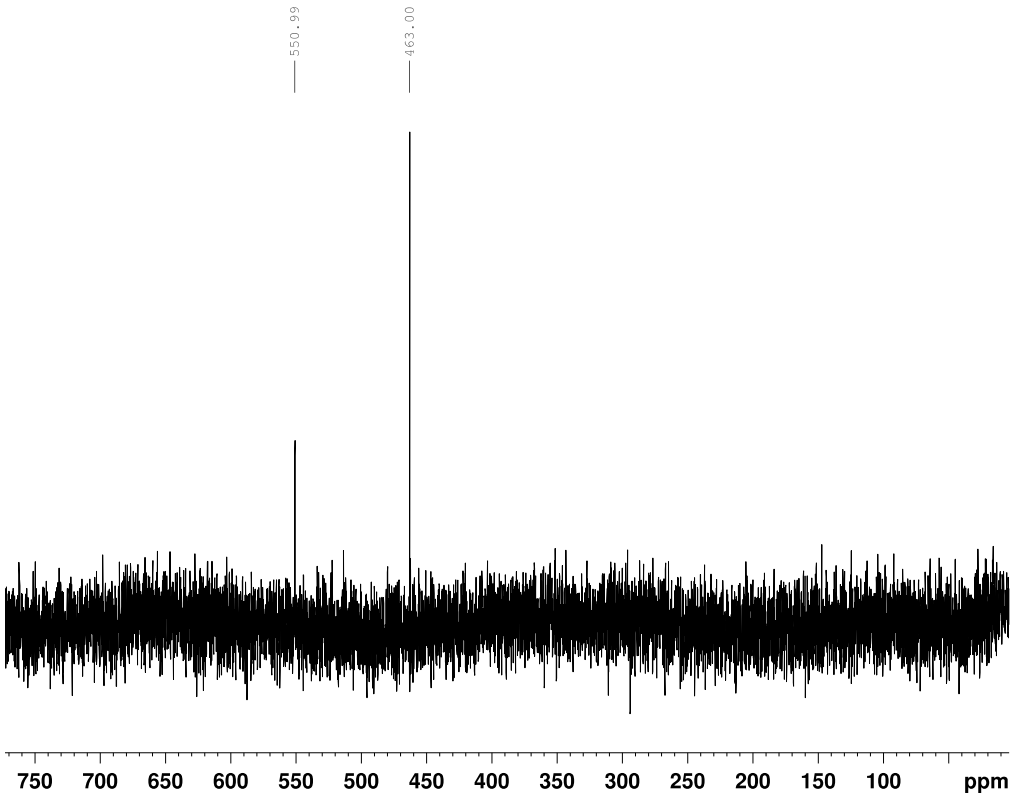


Figure S8: ^{77}Se NMR spectrum of organoselenane **1** in DMSO-d_6 at 25 °C

The same sample was heated up at 37 °C for 15 minutes and the ^{77}Se NMR spectrum was recorded. Once again, a significant change was observed regarding chemical shift, 550 ppm at 25 °C (Figure S8) to 461 ppm at 37 °C (Figure S9). The new compound is the product **6** from loss of chlorine atom. It was also observed that the solution color turned strong yellow by the output of chlorine atom. The selenium chemical shift is now in 460 ppm, between the compound **1** (551 ppm) and starting material (237 ppm).

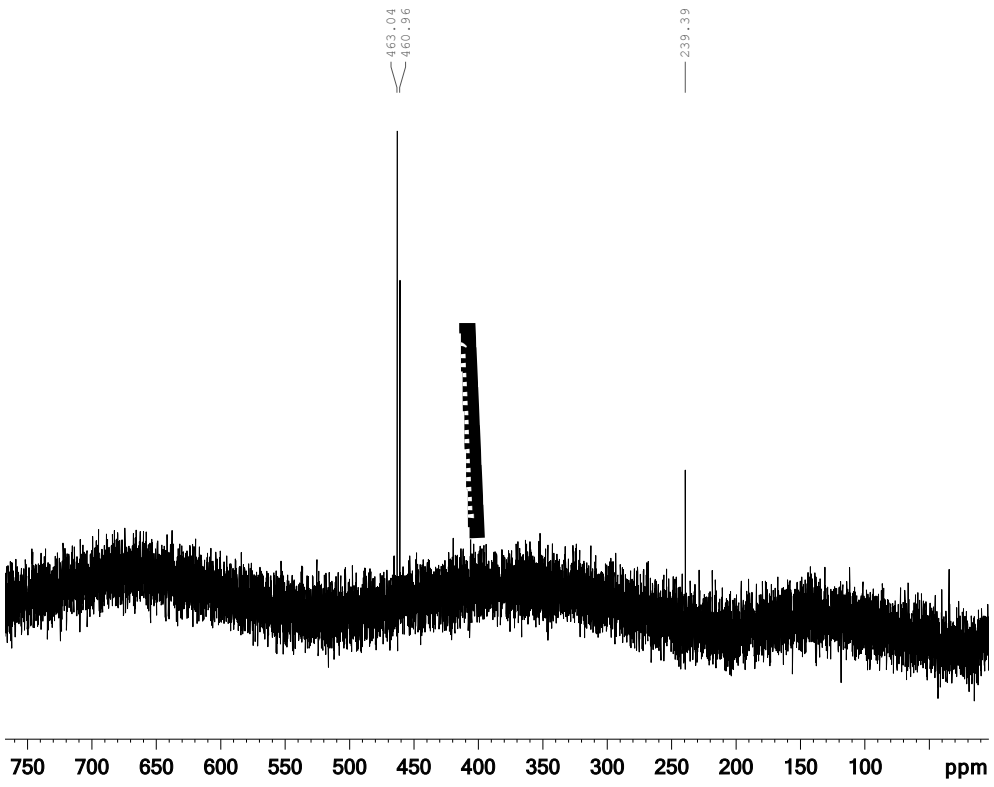
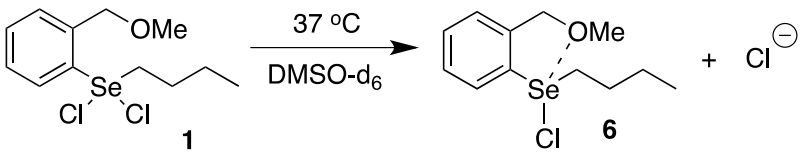


Figure S9: ^{77}Se NMR spectrum of organoselenane **6** in DMSO-d_6 at 37 °C

Spectral dada of compound **6**:

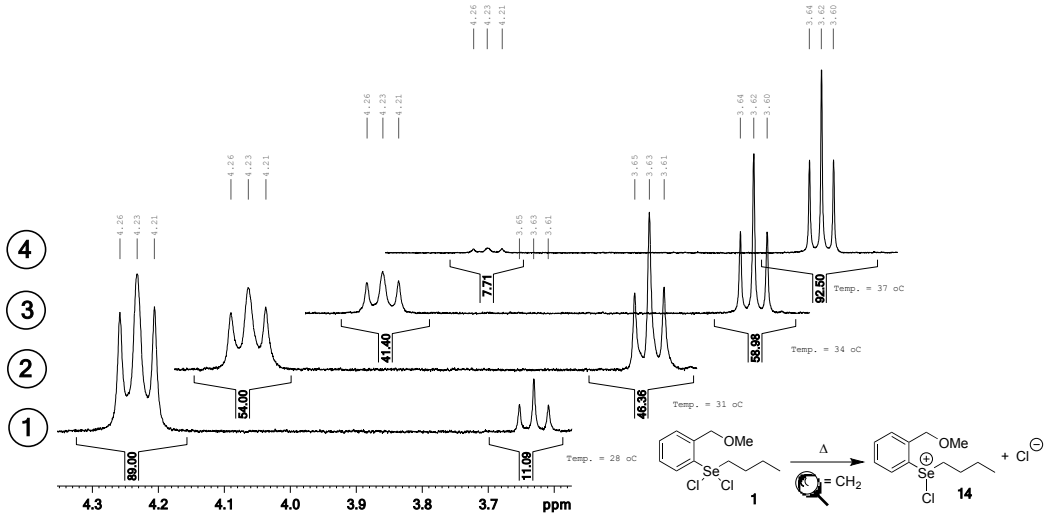


^{1}H NMR (300MHz, DMSO-d6, 37 °C, TMS, δ ppm): 7.70 (m, 1H); 7.28 (m, 1H); 7.30 (m, 2H); 4.75 (s, 2H); 3.63 (t, *J* = 6.5 Hz, 2H); 3.41 (s, 3H); 1.69 (q, *J* = 6.9 Hz, 2H); 1.39 (sext, *J* = 7.4 Hz, 2H); 0.89 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (300MHz, DMSO-d6, 37 °C, TMS, δ ppm):

137.9; 135.6; 132.1; 128.1; 127.7; 126.2; 74.6; 58.4; 45.1; 34.0; 19.4; 13.1. **^{77}Se NMR** (57.24 MHz, DMSO-d6, 37 ^{o}C, $C_6H_5SeSeH_5C_6$ standard δ ppm 463): 461.0.

The new molecules **6** and **7** were characterized by ^{1}H, ^{13}C and ^{77}Se NMR. In both cases, the formation of the starting material, organoselenides, in small amounts (237.0 ppm) was observed. The sample temperature containing the organoselenane **1** was gradually increased to show the effect of instability (Figure S10).[4]

[4] Piovan, L.; Milani, P.; Silva, M. S.; Moraes, P. G.; Demasi, M.; Andrade, L. H. *Eur. J. Med. Chem.* **2014**, *73*, 280-285.

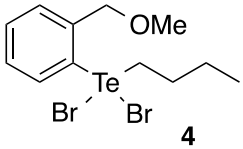


Spectrum[a]	Temperature (°C)	Ratio (1 : 14)
1	28	88 : 12
2	31	54 : 46
3	34	42 : 58
4	37	08 : 92

[a] The ^{1}H signal in 4.23 ppm refers to CH_2 group attached to selenium atom of organoselenurane **1** and the ^{1}H signal in 3.63 ppm refers to CH_2 group attached to selenium atom of organoselenurane **14**.

Figure S10: Conversion of organoselenurane **1** to the cationic specie **6** in DMSO-d_6.

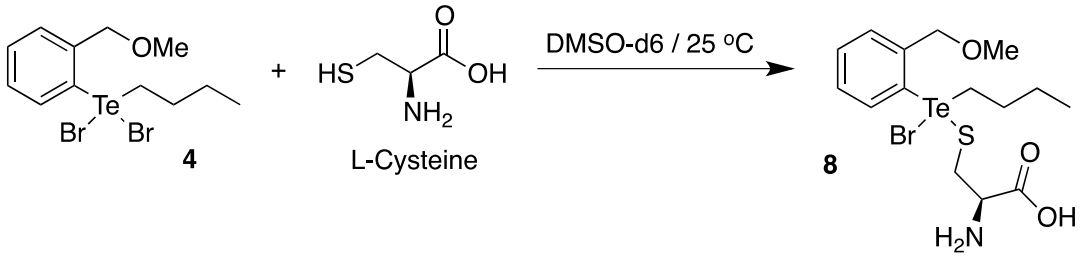
Reactivity study of organochalcogenanes 1-4



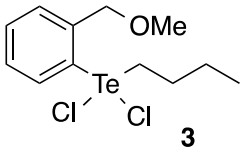
4

Initially, in a 5 mm NMR tube, 5 mg of organotellurane **4** were diluted in 400 μL of DMSO-d_6. A capillary tube of $(C_6H_5Te)_2$ was used as a chemical shift standard (422 ppm). An initial ^{125}Te NMR spectrum of organotellurane **4** was recorded at 25 ^{o}C. Then, *L*-cysteine (1.5 mg; 1.2 equiv.) was added in the same sample, and after 15 minutes at 25 ^{o}C, ^{125}Te NMR spectrum was recorded. In this case, a significant change was observed regarding chemical shift, 885 ppm at 25 ^{o}C (Figure S1) to 358 ppm at 25 ^{o}C (Figure S11), due to formation of product **8**. The comparison between the spectra of compounds **4** and **8** was performed (Figure S12: ^{1}H NMR spectrum and Figure S13: ^{13}C NMR spectrum).

Spectral dada of compound **8**:



^{1}H NMR (300MHz, DMSO-d6, 25 ^{o}C, TMS, δ ppm): 7.64 (dd, *J* = 7.4 Hz and 1.3 Hz, 1H); 7.32 (dd, *J* = 7.4 Hz and 1.5 Hz, 1H); 7,23 (ddd, *J* = 7.4 Hz, 7.3 Hz and 1.5 Hz, 1H); 7,15 (ddd, *J* = 7.4 Hz, 7.3 Hz and 1.3 Hz, 1H); 4.36 (s, 2H); 4.18 (dd, *J* = 7.1 Hz and 4.1 Hz, 1H); 3.40 (dd, *J* = 14.6 Hz and 4.1 Hz, 1H); 3.24 (s, 3H); 3.12 (dd, *J* = 14.6 Hz and 7.1 Hz, 1H); 2.84 (t, *J* = 7.4 Hz, 2H); 1.69 (q, *J* = 7.6 Hz, 2H); 1.35 (sext, *J* = 7.6 Hz, 2H); 0.86 (t, *J* = 7.6 Hz, 3H). **13C NMR** (300MHz, DMSO-d6, 25 ^{o}C, TMS, δ ppm): 169.7; 141.2; 135.5; 128.7; 128.5; 126.7; 116.9; 76.9; 57.0; 51.3; 38.17; 33.1; 24.6; 13.3; 7.0. **^{125}Te NMR** (94.73 MHz, DMSO-d6, 25 ^{o}C, $C_6H_5TeTeH_5C_6$ standard δ ppm 422): 358.4 **LC-MS** [M^+ + 1]: Calculated value: 506.97227; found value: 507.9748.



3

Initially, in a 5 mm NMR tube, 5 mg of organotellurane **3** were diluted in 400 μL of DMSO-d_6. A capillary tube of $(C_6H_5Te)_2$ was used as a chemical shift standard (422 ppm). An initial ^{125}Te NMR spectrum of organotellurane **3** was recorded at 25 ^{o}C. Then, *L*-cysteine (1.5 mg; 1.2 equiv.) was added in the same sample, and after 15 minutes at 25 ^{o}C, ^{125}Te NMR spectrum was recorded. In this case, a significant change was observed regarding chemical shift, 885 ppm at 25 ^{o}C (Figure S5) to 350 ppm at 25 ^{o}C (Figure S14), due to formation of product **9**. The comparison between the spectra of compounds **3** and **9** was performed (Figure S15: ^{1}H NMR spectrum and Figure S16: ^{13}C NMR spectrum).

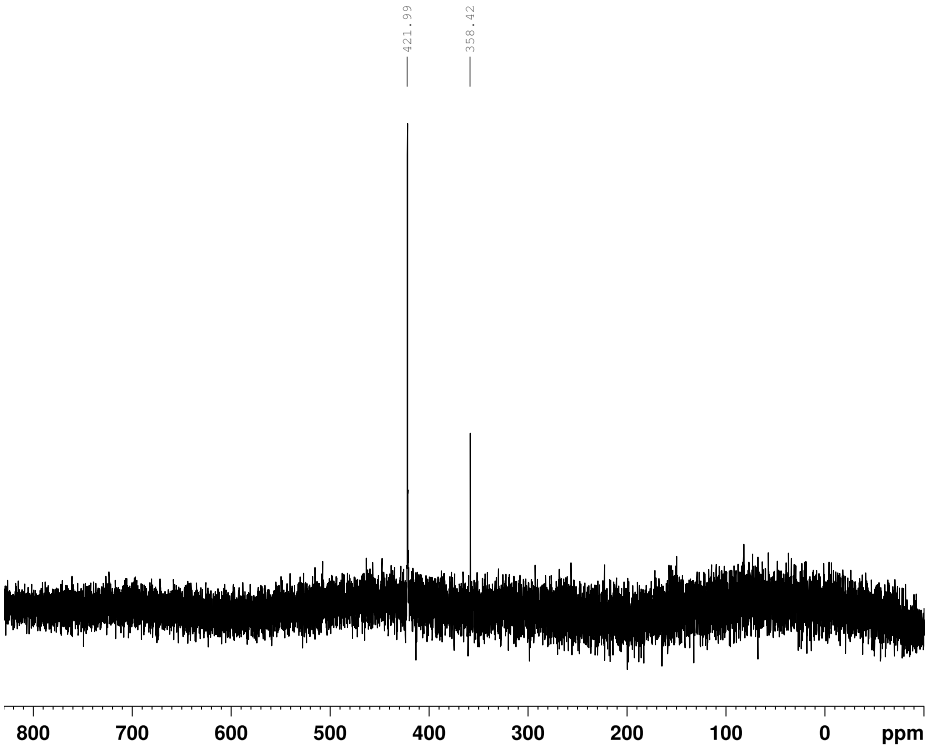
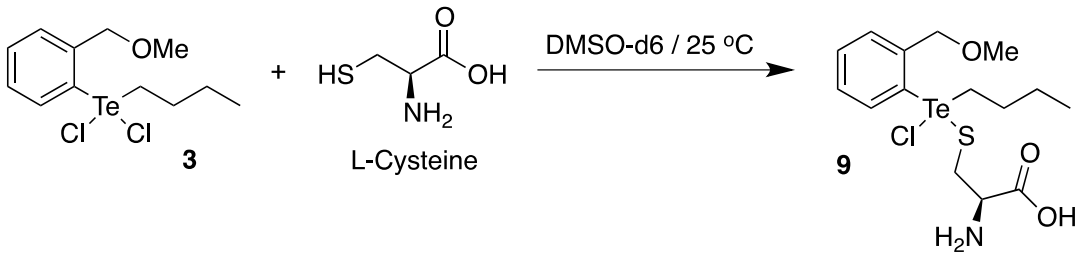


Figure S11: ^{125}Te NMR spectrum of organotellurane **8** in DMSO-d_6 at 25 °C

Spectral dada of compound **9**:



^{1}H NMR (300MHz, DMSO-d6, 25 °C, TMS, δ ppm): 7.64 (dd, *J* = 7.6 Hz and 1.5 Hz, 1H); 7.32 (dd, *J* = 7.4 Hz and 1.3 Hz, 1H); 7.24 (ddd, *J* = 7.6 Hz, 7.4 Hz and 1.3 Hz, 1H); 7.15 (ddd, *J* = 7.6 Hz, 7.4 Hz and 1.5 Hz, 1H); 4.37 (s, 2H); 3.85 (t, *J* = 5.95 Hz, 1H); 3.24 (s, 3H); 2.95 (dd, *J* = 9.4 Hz and 4.9 Hz, 1H); 2.89 (dd, *J* = 9.4 Hz and 6.4 Hz, 1H); 2.84 (t, *J* = 7.45 Hz, 2H); 1.70 (q, *J* = 7.4 Hz, 2H); 1.36 (sext, *J* = 7.4 Hz, 2H); 0.86 (t, *J* = 7.4 Hz, 3H). **DEPT 135 NMR** (300MHz, DMSO-d6, 25 °C, TMS, δ ppm): 169.1; 141.2; 135.5; 128.7; 128.5; 126.7; 117.0; 79.2; 77.0; 57.0; 54.0; 33.1; 24.6; 13.3; 7.0. **^{125}Te NMR** (94.73 MHz,

DMSO-d6, 25 °C, $C_6H_5TeTeH_5C_6$ standard δ ppm 422): 350.7 **LC-MS** [M^+ + 1]: Calculated value: 463.02278; found value: 464.0256.

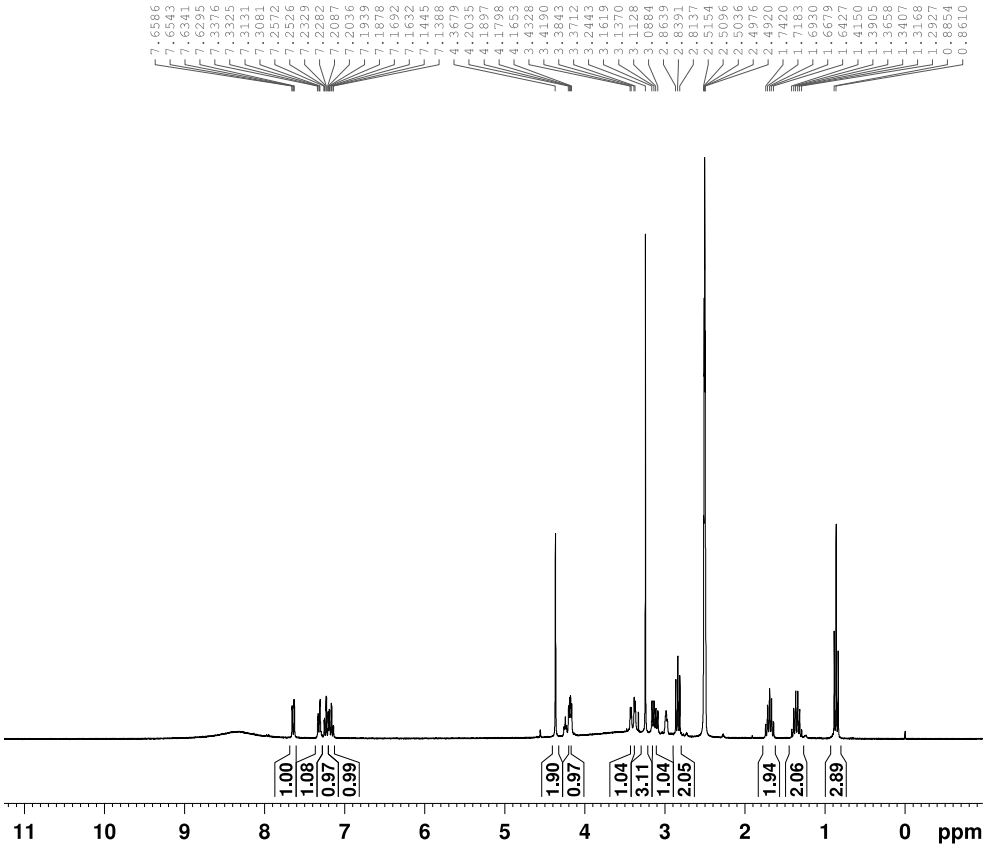


Figure S12: ^{125}Te NMR spectrum of organotellurane **8** in DMSO-d_6 at 25 °C

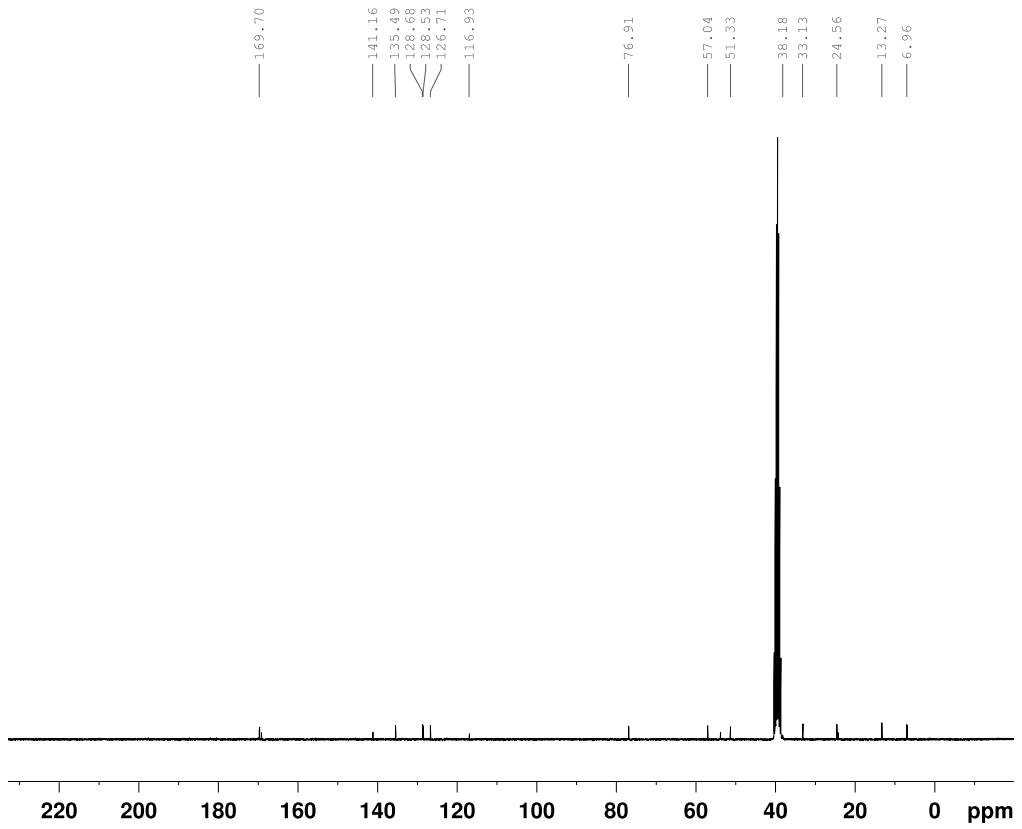


Figure S13: ^{13}C NMR spectrum of organotellurane **8** in DMSO-d_6 at 25 ^{o}C

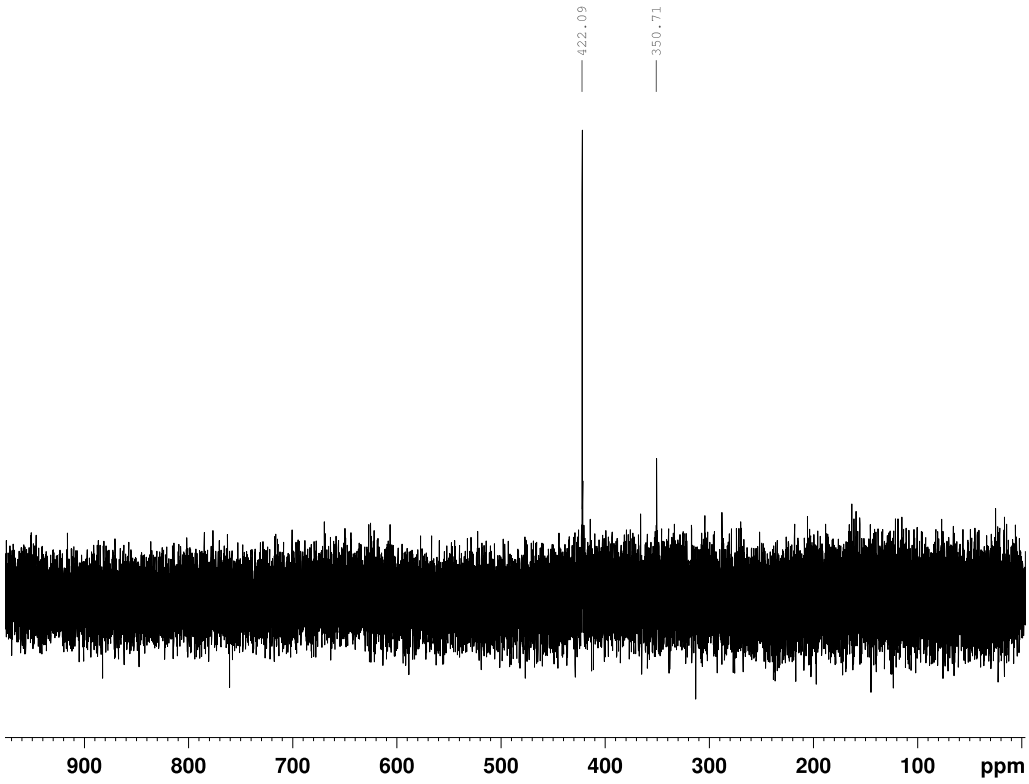


Figure S14: ^{125}Te NMR spectrum of organotellurane **9** in DMSO-d_6 at 25 ^{o}C

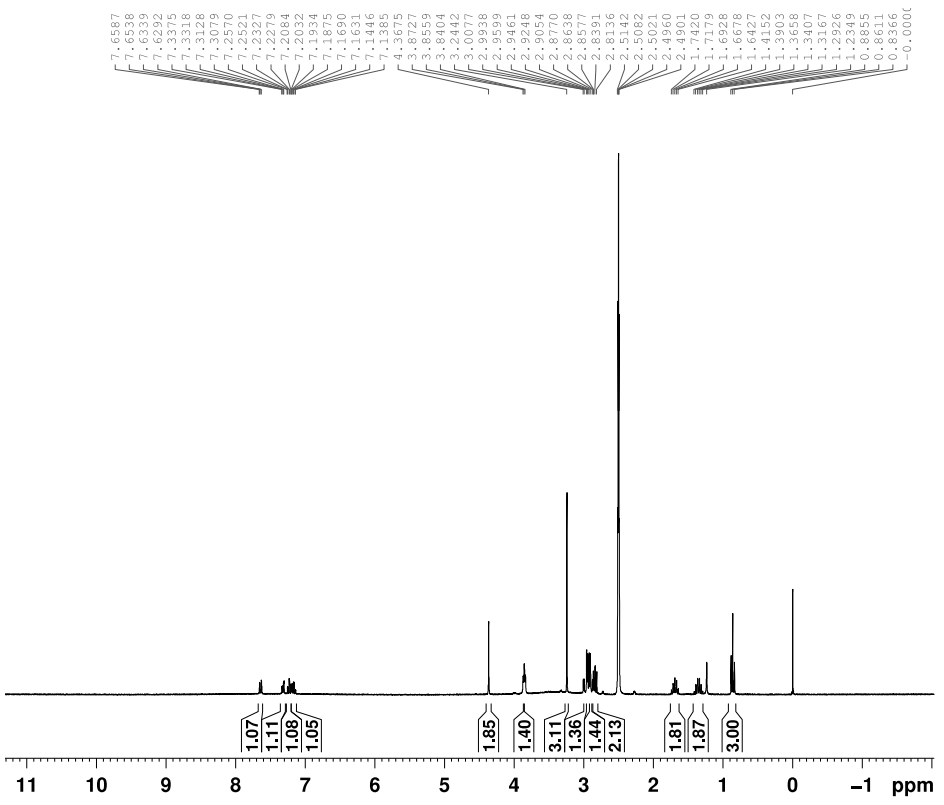


Figure S15: ^{1}H NMR spectrum of organotellurane **9** in DMSO-d_6 at 25 ^{o}C

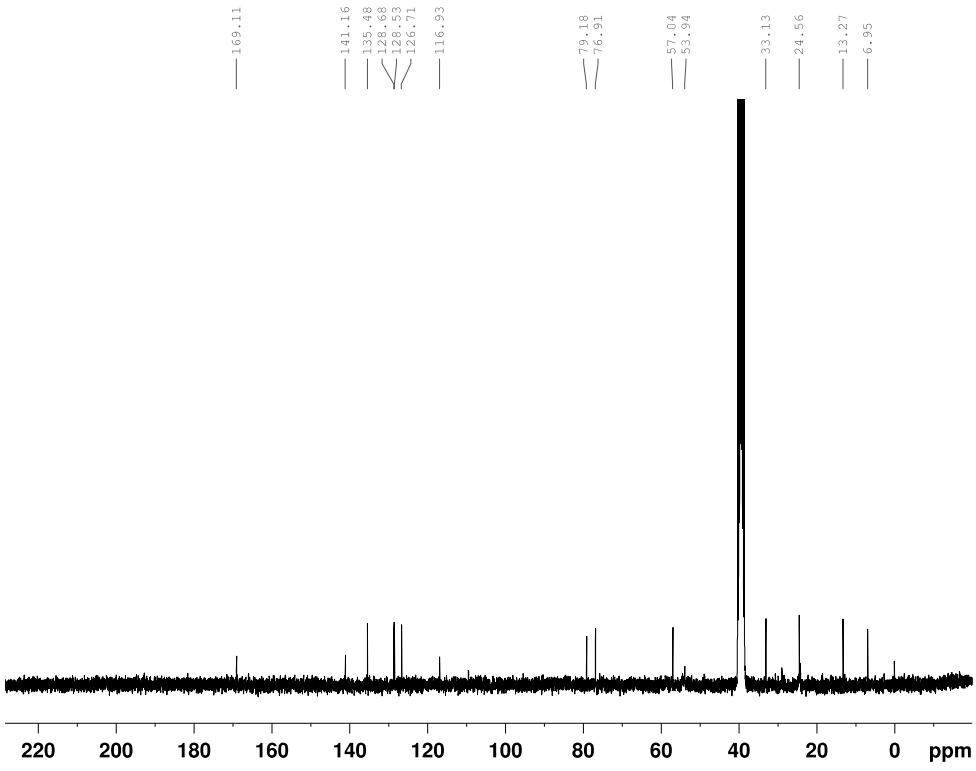
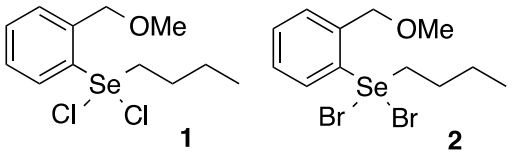
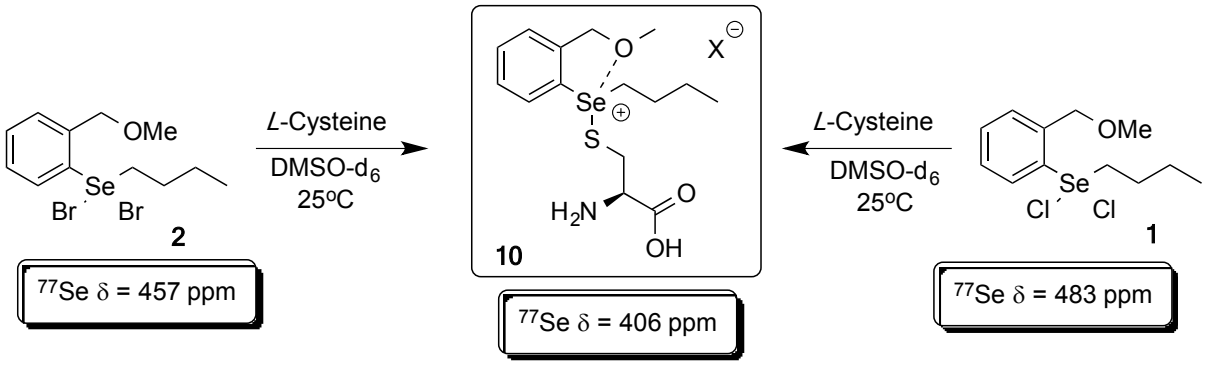


Figure S16: ^{13}C NMR spectrum of organotellurane **9** in DMSO-d_6 at 25 ^{o}C



Initially, in a 5 mm NMR tube, 5 mg of organoselenane **2** or **1** were diluted in 400 μL of DMSO-d_6. A capillary tube of $(C_6H_5Se)_2$ was used as a chemical shift standard (463 ppm). An initial ^{77}Se NMR spectrum of organoselenane **2** or **1** was recorded at 25 °C. Then, *L*-cysteine (1.5 mg; 1.2 equiv.) was added in the same sample, and after 15 minutes at 25 °C, ^{77}Se NMR spectrum was recorded. In this case, a significant change was observed regarding chemical shift, 483 ppm at 25 °C (Figure S4) or 550 ppm at 25 °C (Figure S8) to 406 ppm at 25 °C (Figure S17). In both cases, the proton signals were very broad. ^{77}Se NMR spectra have showed the same chemical shift (Scheme S1).



Scheme S1: Plausible product of reaction of organoselenuranes **2** or **1** with *L*-cysteine monitored by ^{77}Se NMR in DMSO-d_6 at 25 °C.

The studies of selectivity with selenium (IV) and tellurium (IV) compounds were performed with organochalcogenanes **1** and **3** and with the respective essential amino acids. The studies have showed the same results.

Initially, the organotellurane **3** was chosen to submit the reaction with essential amino acids under DMSO-d6 at 37 °C (Figure S18). In all cases, the results were the same. The organotellurane **3** remained intact with all *L*-amino acids expect with amino acid *L*-cysteine.

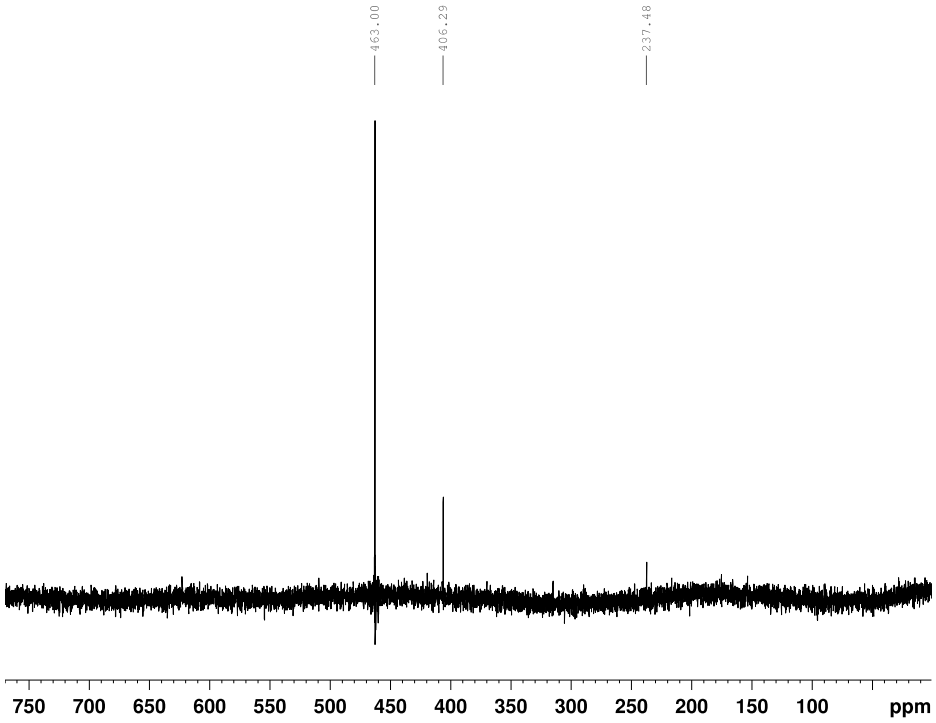


Figure S17: ^{77}Se NMR spectrum of organoselenane **10** in DMSO-d_6 at 25 ^{o}C

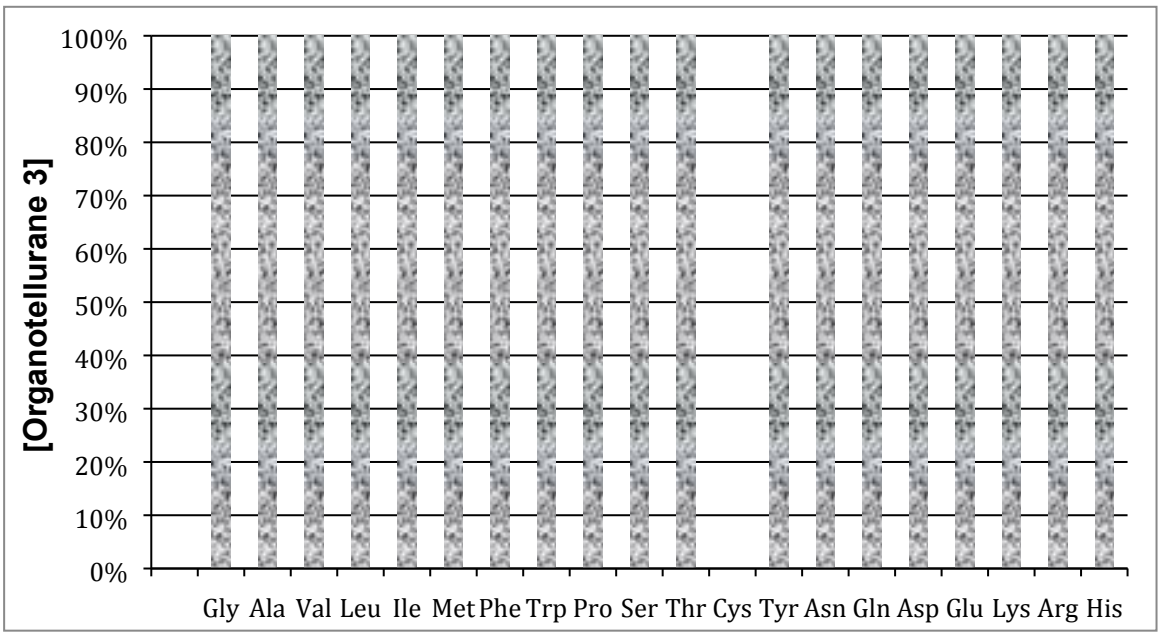


Figure S18: Reactivity study of organotellurane **3** with *L*-Amino Acids monitored by ^{125}Te NMR in DMSO-d6/buffer at 37 ^{o}C.

The next step was the study of selectivity with organoselenane **1**. The organoselenane **1** has reacted only with *L*-cysteine (Figure S19). In all negative results, both compounds did not occurred decomposition. The experiments were repeated after addition of 25 μL of deuterated buffer (20 mM Tris/DCl in D_2O) and the results were the same.

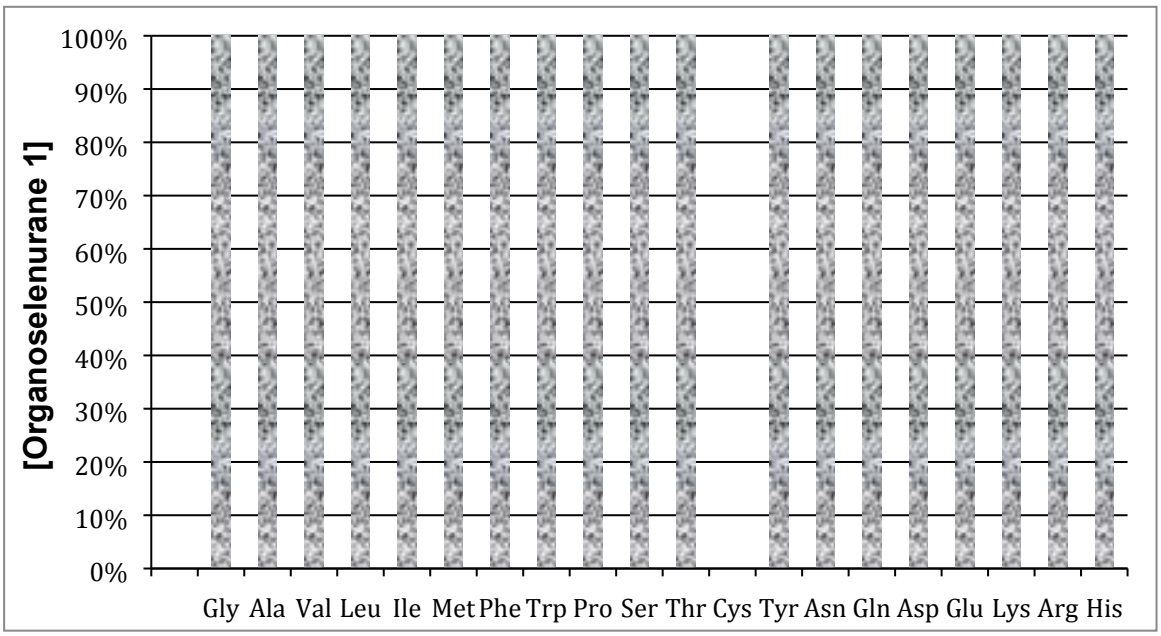


Figure S19: Reactivity study of organoselenurane **1** with *L*-Amino Acids monitored by ^{77}Se NMR in DMSO-d_6/buffer at 37 ^{o}C.