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'One-pot' synthesis and redox evaluations of chiral chalcogenocysteinol and β-bis-chalcogenoamine derivatives from *L*-Serine Methyl Ester

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Abstract: The synthesis of a new class of chiral chalcogenocysteinols and bis-chalcogenoamines is described in this study. Compounds were prepared from commercially available *L*-serine using simple reactions to obtain the desired products. Additionally, compounds were evaluated for potential antioxidant applications by cyclic voltammetry and showed to have appropriate electrochemical oxidation potential. Density functional theory (DFT) calculations were used to better characterize oxidative sites in the bis-chalcogenoamines, giving theoretical support to the experimental findings.

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Introduction

Over the past decades, organochalcogenides have been established as functional elements in biochemistry and medicine.[1] In particular, organochalcogenium compounds have been gaining increasing attention due to their biological properties in antitumoral,[2] antiviral,[3] and antimicrobial[4] activities, for instance. Another important property is that such compounds are considered cholesterol reducing agents[5]. A relevant biological field involving organochalcogenium compounds is related with the antioxidant behavior of these molecules. It is known that their antioxidant activity[6] is related to the prevention of several diseases, including Parkinson's, Alzheimer's, cancer,[7,8] relapse prevention after antipsychotic discontinuation in first-episode schizophrenia,[9] diabetes, and atherosclerosis[10], among others. Reactive oxygen species (ROS) may trigger a variety of biological processes that may induce the development of such diseases due to oxidative/antioxidant unbalance.[11] The use of antioxidant agents for ROS depletion consists of chemo-protective action against these diseases.[12] In this context, organochalcogenium compounds appear to be effective class to achieve this objective.[13] Several organosulfur, organoselenium and organotellurium compounds are described in the literature as antioxidant agents, showing higher levels for ROS depletion[14]. At this point, the development of efficient synthetic methods for the introduction of sulfur, selenium (Se) and tellurium (Te) atoms in organic molecules remains a challenge. In this context and in the course of our ongoing research towards the synthesis and application of organochalcogenium compounds, an efficient methodology for the synthesis of chiral chalcogenocysteinols **2a-f** and β-bis-calcogenoamine **5a-t** derivatives from *L*-Serine Methyl Ester is described here, in addition to the redox behavior of the synthesized compounds via electrochemical studies and DFT calculations, which is depicted in Figure 1.

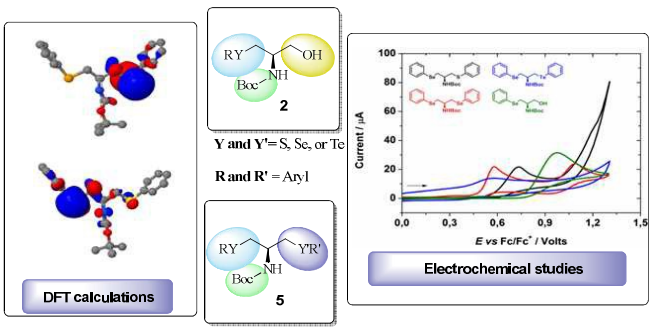


Figure 1. Synthesis and redox evaluation of chiral β-organochalcogen amines.

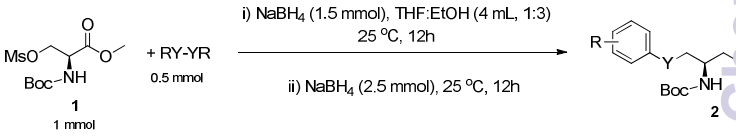
Results and discussion

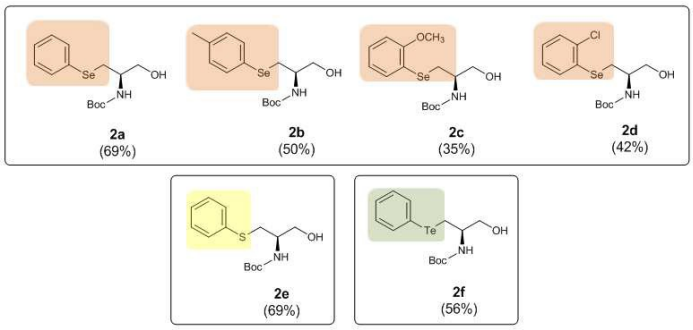
In order to identify the optimal protocol for the synthesis of the desired β-organochalcogeno aminoalcohol **2a**, the reactions were first carried out under argon atmosphere employing Mesyl *N*-Boc protected Methyl Ester **1** (1 mmol), PhSeSePh (0.5 mmol) and a reducing agent for the selenolate formation. The desired β-phenylselenocysteinol **2a** was then obtained in the most effective yield using $NaBH_4$(1.5 mmol) as a reducing agent in a mixture of THF: EtOH (4 mL, 1:3) was left at 25 °C for 12h. Next, $NaBH_4$ (2.5 mmol) was added and the mixture was stirred for an additional 12h involving a *one-pot* process of the nucleophilic selenium introduction followed by aminoester reduction. The use of Zn^0/HCl in [bmim].BF_4 as a promoter for selenolate formation or the use of $NaBH_4$ in reflux afforded the respective compound **2a** in lower yields.

The optimal reaction condition was obtained using $NaBH_4$ as a reducing agent for the cleavage of diphenyldiselenide and ester reduction at 25°C in a *one-pot* process (for a detailed protocol, see the experimental procedure).

In order to demonstrate the generality of this methodology, the scope of this reaction to prepare β-chalcogenocysteinols **2** using a variety of dichalcogenides was investigated, as depicted in Figure 2.

Figure 2. Preparation of β-chalcogenocysteinols **2**





[a]Yields refer to pure isolated products and are characterized by ^{1}H and ^{13}C NMR.

Chalcogenocysteinol **2** compounds were obtained in moderate to good yields as observed in Figure 2. The reaction was tolerant to electron donating or electron withdrawing substituents at *ortho* and *para* position in the aromatic ring of the organoselenium moiety,

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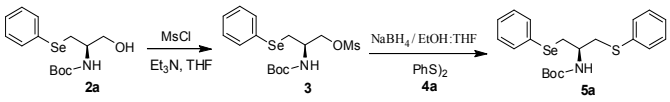
which allowed the preparation of a series of respective products. The influence of the dichalcogenide portion was evaluated and selenium and sulfur afforded the respective compounds in similar yields of 69% (Figure **2**, Entries **2a** and **2e**). When tellurium was used to obtain the corresponding phenyltellurocysteinol **2f,** a decrease in the yield was observed, which was likely due to the instability of the respective tellurolate anion in the reaction medium.

Results concerning the preparation of the chalcogencysteinol derivatives **2** were satisfactory from the synthetic point of view, especially because the protocol involved two different transformations in a *one-pot* synthesis, which led to the formation of a variety of the respective compounds in moderate to good yields and in a modular synthetic route. Additionally, the methodology has a 'green' character, since the *one-pot* process avoids additional steps of extraction and purification. With the respective chalcogenocysteinols in hand, this study was extended to the preparation of compounds containing two different organochalcogen moieties in the same molecule, *i.e.*, the bis-chalcogen-β-aminoderivatives **5**. Initially, chalcogenocysteinol **2a** was employed as starting material and directly mesylated using MsCl and Et_3N. After obtaining compound **3**, a variation in the reaction time and temperature was evaluated using diphenyl disulfide **4a** as organochalcogenide moiety and $NaBH_4$ as a reducing agent. This way, phenylthiolate and subsequently product **5a** was obtained (Scheme 1).



Scheme 1. Mesylation and preparation of chiral bis-chalcogen-β-aminoderivatives

Based on the results, the most effective protocol for the preparation of the desired bis-chalcogen-β-amine **5a** was obtained using $NaBH_4$ as a reducing agent for diphenyl disulfide cleavage, in a mixture solvent of EtOH:THF(4mL, 1:3) at 80 °C for 2 h. Increasing the reaction time or the $NaBH_4$ amount to 2 eq. did not significantly increase yield. Additionally, running the reaction at room temperature also enabled the preparation of the desired compound **5a**; although in lower yields than when heated at 80 °C.

In order to demonstrate the generality of this method and search for the preparation of a small library of chiral bis-organochalcogen compounds, the aim of this protocol was to investigate and prepare a variety of bis-chalcogen-β-amine **5** using different dichalcogenides, as depicted in Figure 3.

The influence on the nature of the dichalcogenide in the substitution reaction follows previous behavior thus affording the sulfides and selenides with slightly better yields comparing with tellurium in most cases.

Furthermore, evaluations of electrochemical properties of these derivatives were also analyzed. The electrochemical behavior of compounds in the cyclic voltammetry experiments was performed in order to verify the oxidation potential values for some representative derivatives (Table 1). In general, the cyclic voltammogram (CV) of dichalcogenides displayed irreversible oxidation peaks (E_{pa}) between +0.50V to +1.40V *versus* Fc/Fc^+ redox couple (see ESI, Figures 28-29). All derivatives exhibited one irreversible reduction wave behavior in the cathodic range, and at E_{pc} values between -1.10V to -1.50V, respectively (Table 1).

Figure 3. Synthesis of bis-chalcogen-β-amine.

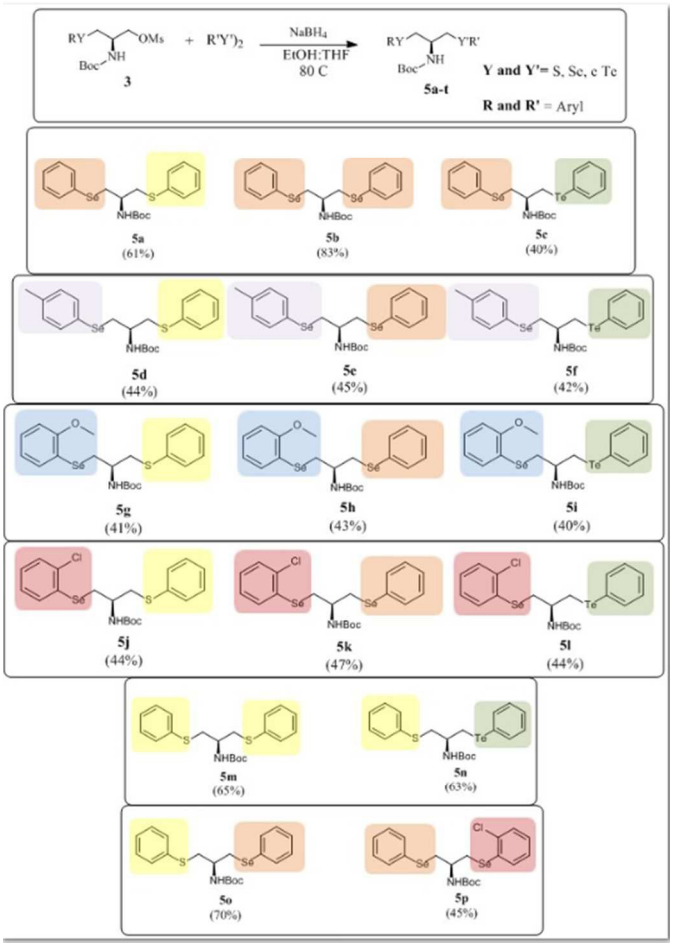


Table 1. Redox potentials of compounds in dry acetronitrile (*E versus* Fc/Fc^+).

	Oxidation		Reduction
Compound	E_{ox1}	E_{ox2}	E_{red1}
2a	+1.000 V[a]	-----	-1.428 V[b]
2e	+1.175 V[a]	-----	-1.452 V[b]
5a	+0.770 V[a]	+1.196 V[a]	-1.373 V[b]
5b	+0.592V[a]	+1.096V[a]	-1.254 V[c]
5c	+0.582 V[a]	-----	-1.429V[b]
5h	+0.554 V[a]	+0.989 V[a]	-1.251 V[c]

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5k	+0.772V[a]	+1.351V[a]	-1.188V[c]

[a]E_{pa} = Anodic peak; [b]E_{pc} = cathodic peak;[c]$E_{1/2} = E_{pa} + E_{pc} / 2$

In acetonitrile solution, the oxidation steps of these compounds are associated with oxidation by a reaction with molecular oxygen to form chalcogenoxide species (X=O, when X = S, Se or Te). The ability of the compound to act as an antioxidant in this case is directly related to the chalcogen atom[15]. Compounds **2a** and **2e** present a single chalcogen atom (Se and S, respectively) and show only one oxidation peak as observed in Table 1. The CV of bis-chalcogen-β-aminoderivatives **5a** (Se, S), **5b** (Se, Se), **5h** (Se, Se), and **5k** (Se, Se) shows a second oxidation peak at a higher potential, as shown in Figures 4 and 5, and Table 1. This second oxidation peak is most probably due to the oxidation of the other chalcogen atom of the cationic intermediate generated at the first oxidation peak. Sulfur is more electronegative than selenium and, indeed, E_{ox2} of **5a** (+1.196 V) is more positive than E_{ox2} of **5b** (+1.096 V), showing an E_{ox2} of **5a** quite similar to compound **2e** (+1.175 V, only one S atom). The CV of **5c** shows a single but broader oxidation peak (Figure 4). This can be attributed to a simultaneous oxidation of the two chalcogen atoms present in the same molecule (the Te atom oxidizes first, followed by the Se oxidation), since its redox potentials are very close (see Table 1). In the negative range, a reduction process between -1.10V to -1.50V was observed. This irreversible cathodic peak (E_{red1}) for all compounds likely involves the formation of anion radical species in solution.[16]

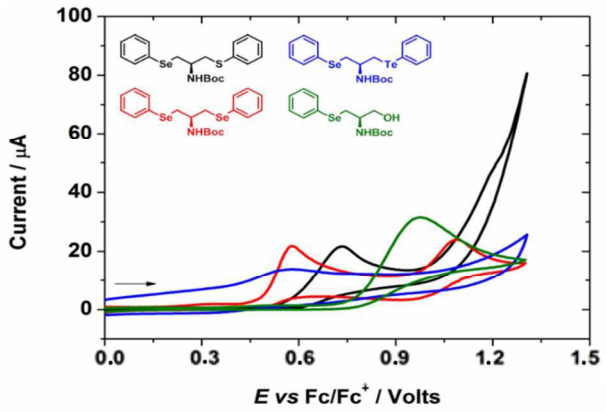

Figure 4. Comparative cyclic voltammograms at oxidation range of compounds **2a** (green line), **5a** (black line), **5b** (red line) and **5c** (blue line) in dry CH_3CN solutions, using 0.1 M $TBAPF_6$ as support electrolyte and glassy carbon working electrode, at a scan rate of 100 mV/s.

When comparing the oxidation process of derivatives containing different electronic donors or acceptor groups in bis-chalcogen-β-aminoderivatives compounds at the *ortho*-position, a less positive redox shift of compound **5h** in relation to compounds **5b** and **5k**, respectively, could be observed (Figure 5). This can be attributed to easier selenium atom oxidation with electron donating groups attached in the aromatic ring than the acceptor *ortho*-substituents.

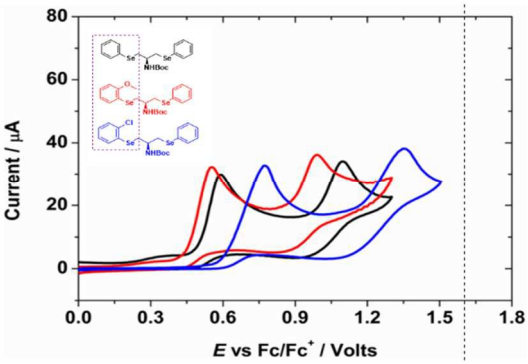

Figure 5. Comparative cyclic voltammograms of compounds **5b** (black line), **5h** (red line) and **5k** (blue line) in dry CH_3CN solutions using 0.1 M $TBAPF_6$ as support electrolyte and glassy carbon working electrode, at a scan rate of 100 mV s^{-1}.

A second oxidation potential regarding another chalcogen atom presented in the molecule is also observed. This second potential consists of the oxidation processes for the less active chalcogenium atom. It is important to highlight that in some cases, the same organoyl-chalcogenium portion has different second oxidation potential values (Figure 5). Since molecular effects could influence oxidation, this observation may be rationalized reflecting the mono-oxidated molecular behavior of the bis-chalcogen-β-aminoderivatives **5.**

Density Functional Theory (DFT) results

The oxidation properties of **5a**, **5b**, **5c**, **5h** and **5k** were theoretically analyzed both qualitatively and quantitatively through the density functional theory (DFT), as shown in Figure **6**. The reactive sites for the oxidation of these compounds can be identified as their nucleophilic centers. The characterization of these nucleophilic sites can be obtained by local Fukui functions associated with these compounds when participating in redox reactions. The nucleophilic centers, $f(r)^-$, are determined as:

$$f(\mathbf{r})^- = \rho^0(\mathbf{r}) - \rho^+(\mathbf{r}) \approx \rho(HOMO) \quad (1)$$

where, $\rho^0(\mathbf{r})$ and $\rho^+(\mathbf{r})$ are the electronic densities of the neutral and positively charged compound, respectively, while $\rho(HOMO)$ is the charge density of the highest occupied molecular orbital.

The optimized structures and HOMO orbitals for compounds (from top to bottom) **5c**, **5a**, **5b**, **5k**, and **5h** are shown in Figure 6. The information given by the HOMO orbitals is the same as the information from ρ *(HOMO)*. As expected, the Te site is the

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most reactive site in compound **5c,** while in compound **5a** it is the Se site. Compound **5b** shows no apparent preference between the two Se sites. By comparing the HOMO orbitals of compounds **5b**, **5k**, and **5h,** it is possible to observe that the presence of donating (OCH_3) and withdrawing (Cl) groups can significantly alter the electronic configuration and the spatial distribution of the nucleophilic centers. When OCH_3 is in the *ortho* position at compound **5h**, the HOMO orbital is concentrated (although delocalized) on one side of the molecule, showing that the electron-donation is much stronger than its inductive electron-withdrawing effect. On the other hand, for the Cl atom at the *ortho* position of **5k**, the contribution to the HOMO orbital at the Se atom close to the Cl is diminished. However, the remaining contributions to the HOMO orbital reveal that the electron-withdrawing effect of Cl is partially compensated by its electron-donating resonance effect. This shows the strong influence of the substituent in the electronic and chemical characteristics of these compounds, which is reflected in their oxidation potentials. The first oxidation potentials of compounds **5c**, **5a**, **5b**, **5k**, and **5h** were also calculated and are shown in Table 2.

Table 2. Calculated oxidation potentials in acetonitrile solvent (PCM model) and using Fc/Fc^+ as a reference.

Compound	E_{ox1}
5c	+0.67 V[a]
5a	+1.06 V[a]
5b	+0.91 V[a]
5k	+1.09 V[a]
5h	+0.87 V[a]

Experimental and theoretical results are described in Tables 1 and 2, respectively. Although there is a difference in the absolute values (around 0.3 V[a]), the energetic orderings of E_{ox1} follows the experimental findings taking compound **5b** as a reference. For the compounds in which one Se atom is substituted by an S or a Te atom, we have:

$$\mathbf{E_{ox1}(5a) > E_{ox1}(5b) > E_{ox1}(5c),}$$

and for the compounds with donating or withdrawing substituent at *ortho* position, we have:

$$\mathbf{E_{ox1}(5k) > E_{ox1}(5b) > E_{ox1}(5h).}$$

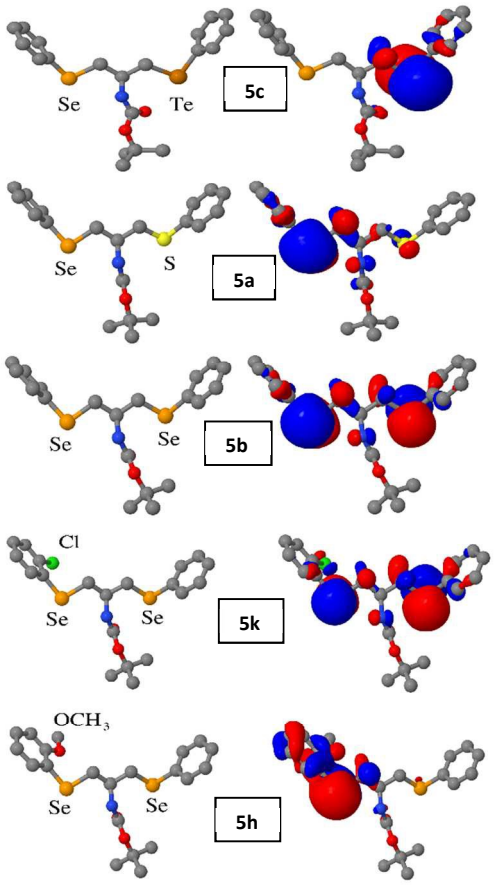

Figure 6 Optimized structures (right column) and the highest occupied molecular orbitals (left column) for compounds **5c**, **5a**, **5b**, **5k**, and **5h** (from top to bottom).

Conclusion

In summary, the preparation of a new class of chiral selenium-, telluro-, and thio-N-Boc-β-chalcogen aminoderivatives from *L*-Serine Methyl Ester was described. These compounds were prepared via a concise and flexible route, in good yields, which permitted the preparation of a wide range of compounds with highly modular character. The compounds were evaluated for redox properties *via* electrochemistry and DFT calculations, which revealed a convergent response for the molecules tested.

Acknowledgments

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The authors gratefully acknowledge CAPES, CNPq (Ed. Universal 478054/2012-2, 443625/2014-0, Produtividade em Pesquisa 305104/2012-8, 312085/2014-1, Pesquisador Visitante- 401397/2014-9, PNPD) for financial support. The calculations have been performed using the computational facilities of CPAD/UFSM.

Experimental section

General

Hydrogen nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Bruker DPX-600 MHz,DPX-400 MHz or DPX-200 MHz spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million and referenced to the peak of TMS. Data are reported as follows: chemical shift (d), multiplicity (br = broad, s = sinplet, d = douplet, dd = double douplet, t = triplet, m = multiplet), and coupling constant (*J*) in hertz and integrated intensity. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained at 50 MHz or 100 MHz. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm and referenced to the solvent peak of $CDCl_3$. Selenium-77 nuclear magnetic resonance (^{77}Se NMR) spectra were obtained at 114 MHz. Spectra were recorded in $CDCl_3$ solutions and used as internal standard diphenyldiselenide. Chemical shifts are reported in parts per million and referenced to the internal standard peak at 463 ppm.[17] High-resolution mass spectra were obtained on a XEVO G2 Q-TOF spectrometer. Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm. For visualization, TLC plates were placed under ultraviolet light or stained with either iodine vapor or acidic vanillin. Anhydrous solvents were obtained as follows: THF was distilled from sodium and benzophenone. Triethylamine was distilled from CaH_2. All other solvents were used as purchased. The corresponding Mesyl N-Boc protected Methyl Ester**1a** was previously prepared and characterized.[18]

Cyclic voltammetric measurements were performed using an AutoLab galvano stat/potentio stat Eco Chemie PGSTAT 302N. In all electrochemical analyses, a three-electrode system was used and consisted of a glassy carbon working electrode, a platinum wire auxiliary electrode and a platinum *pseudo*-reference electrode (ferrocene was used as internal standard; Fc/Fc^+ couple in acetonitrile; $E_{1/2}$ = 0.497 V). All electrochemical experiments were carried out under aerobic conditions[19] at room temperature using dry CH_3CN solution of compounds containing 0.1 mol/L tetrabutylammoniumhexafluorophosphate ($TBAPF_6$) as the supporting electrode.

General procedure for the synthesis β-chalcogenocysteinols 2a-f

Under an argon atmosphere, $NaBH_4$ (0.056 g, 1.5 mmol) was added to a solution of diorganyl dichalcogenide (0.159g, 0.5 mmol) in THF (3.3 mL) at room temperature. Ethanol (1.1 mL) was added dropwise and the mixture was stirred for 10 min. After this time, a solution of Mesyl N-Boc protected Methyl Ester **1**(1 mmol) in THF (3.0 mL) was added, and the resulting mixture was stirred at room temperature for 12 h. After that time, an additional portion of $NaBH_4$ (0.0945g, 2.5 mmol) and more ethanol (1.1 mL) were added to the reaction mixture, which was left under stirring for another 12 h. The reaction was quenched with 10 mL of an NH_4Cl solution, and the aqueous layer was extracted with CH_2Cl_2 (3.0 × 20 mL). The combined organicextracts were dried over $MgSO_4$, filtered, and evaporated todryness. The crude products were purified in a silica gel column for chromatographic purification, using hexane–ethylacetate (30:70) as the eluent, furnishing the pure chiral chalcogenocysteinols **2 a-f**.

(R)-2-*tert*-Butyl carbamoyl-1-hydroxy-3-(phenylselanyl)propane (2a). Physical state: white solid. Melting point: 46-47^{0}C. Yield: 69%. NMR ^{1}H (600 MHz, $CDCl_3$): δ= 7.54 (d, J^1 = 6.0 Hz, 2H), 7.26 – 7.25 (m, 3H), 5.06 (s, 1H), 3.87-3.78 (m, 1H), 3.75 (dd, J^1 = 6.0 Hz, J^2 = 12.0 Hz, 1H), 3.66(dd, J^1 = 6.0 Hz, J^2 = 12 Hz, 1H), 3.16-3.04 (m, 2H), 1.42 (s, 9H) ppm. NMR ^{13}C (151 MHz, $CDCl_3$): δ=155.8, 132.9, 129.6, 129.2, 127.2, 79.8, 64.2, 52.2, 29.4, 28.3 ppm. NMR ^{77}Se (114 MHz, $CDCl_3$): δ= 251.845 ppm. HRMS-ESI: m/z calcd for $C_{14}H_{21}NO_3Se$ [M + Na^+] 354.0579, found: 354.0593.

(R)- 2-*tert*-Butyl carbamoyl-1-hydroxy-3-(4-tolylselanyl)propane (2b). Physical state: red oil. Yield: 50%. NMR^{1}H (400 MHz, $CDCl_3$): δ =7.43 (d, *J* = 12.0 Hz, 2H), 7.07 (d, *J* = 12.0 Hz, 2H), 5.14 (s, 1H),3.85-3.76 (m, 1H), 3.71 (dd, J^1 = 4.0 Hz, J^2= 8.0 Hz, 1H), 3.63 (dd, J^1 = 4.0, J^2= 8 Hz, 1H), 3.12-2.98 (m, 2H), 2.3 (s, 3H),1.41 (s, 9H) ppm. NMR^{13}C (100 MHz, $CDCl_3$): δ = 155.6, 137.2, 133.2, 130.0, 125.9, 79.6, 64.0, 52.3, 29.8, 28.3, 21.1 ppm. NMR^{77}Se (114 MHz, $CDCl_3$): δ= 244.449 ppm. HRMS-ESI: m/z calcd for $C_{15}H_{23}NO_3Se$ [M + Na^+] 368.0735, found: 368.0716.

(R)- 2-*tert*-Butyl carbamoyl-1-hydroxy-3-(2-methoxyphenylselanyl)propane(2c). Physical state: red oil. Yield: 35 %. NMR^{1}H (400 MHz, $CDCl_3$): δ= 7.47 (d, *J* = 4 Hz, 1H), 7.22 – 7.19 (m, 1H), 6.90 – 6.81 (m, 2H), 5.41 (s, 1H), 3.85 (s, 3H),3.75 (dd, J^1 = 4 Hz, J^2 = 8.0 Hz, 1H), 3.70-3.60 (m, 2H), 3.18 – 3.03 (m, 2H), 1.41 (s, 9H). NMR^{13}C (100 MHz, $CDCl_3$): δ =157.7, 155.7, 132.2, 128.1, 121.4, 118.6, 110.4, 79.4,63.7, 55.9, 51.8, 28.2, 27.0 ppm. NMR^{77}Se (114 MHz, $CDCl_3$): δ=183.32 ppm. HRMS-ESI: m/z calcd for $C_{15}H_{23}NO_4Se$ [M + Na^+] 384.0685; found: 384.0723.

(R)- 2-*tert*-Butyl carbamoyl-1-(2-chlorophenylselanyl)-3-hydroxypropane (2d). Physical state: yellow oil. Yield: 42%. NMR^{1}H (400 MHz, $CDCl_3$): δ = 7.55-7.34 (m, 2H), 7.30-7.24 (m, 2H), 5.38 (s, 1H), 3.88-3.77 (m, 1H), 3.76 (dd, J^1 = 8.0 Hz, J^2 =12.0 Hz, 1H), 3.64 (dd, J^1 =8.0 Hz, J^2= 12.0 Hz, 1H). 3.19-3.08 (m, 2H), 1.41 (s, 9H). NMR^{13}C (100 MHz, $CDCl_3$): δ = 155.6, 134.7, 131.0, 129.2, 127.1, 79.5, 66.2, 48.1, 31.3, 28.4 ppm. NMR ^{77}Se(114 MHz, $CDCl_3$): δ= 194.89 ppm. HRMS-ESI: m/z calcd for $C_{14}H_{20}ClNO_3Se$ [M + Na^+] 388.0189, found: 388.0199.

(R)-2-*tert*-Butyl carbamoyl-1-hydroxy-3-(phenylthio)propane (2e). Physical state: white solid. Melting point: 49-50 ^{0}C. Yield: 69%. NMR^{1}H (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.21 – 7.17 (m, 1H), 5.16 (s, 1H),3.85-3.73 (m, 2H), 3.67 (dd, J^1 =4.0 Hz, J^2=8.0Hz, 1H), 3.21 – 3.04 (m, 2H), 1.44 (s, 9H). NMR^{13}C (100 MHz, $CDCl_3$): δ = 155.9, 135.6, 129.5, 128.9, 126.3, 79.8, 63.3, 51.8, 35.0, 28.3 ppm. HRMS-ESI: m/z calcd for $C_{14}H_{21}NO_3S$ [M + Na^+] 306.1134, found: 306.1130.

(R)- 2-*tert*-Butyl carbamoyl-1-hydroxy-3-(phenyltellanyl)propane (2f). Physical state: red oil. Yield: 56%. NMR^{1}H (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.0 Hz, 2H), 7.31-7.26 (m, 1H), 7.22-7.16 (m, 2H), 5.09 (s, 1H), 3.86 - 3.73 (m, 1H), 3.72-3.60 (m, 2H), 3.19-3.05 (m, 2H), 1.43 (s, 9H). NMR^{13}C (100 MHz, $CDCl_3$): δ = 155.7, 138.4, 129.3, 127.8, 111.7, 79.7, 65.3, 52.9, 28.3, 11.5 ppm. HRMS-ESI: m/z calcd for $C_{14}H_{21}NO_3Te$ [M + Na^+] 404.0746, found: 404.0501

General procedure for the synthesis bis-chalcogen-β-amine 5 a-p.

New Journal of Chemistry Accepted Manuscript

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Journal Name

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DOI: 10.1039/C7NJ00194K ARTICLE

Published on 19 June 2017. Downloaded by University of New Mexico on 19/06/2017 17:36:34.

Under an argon atmosphere, $NaBH_4$ (0.045 g, 1.2 mmol) was added to a solution of diorganyldichalcogenide (0.054g, 0.25 mmol) in THF (3.3 mL) at room temperature. Ethanol (1.1 mL) was added dropwise and the mixture was stirred for 10 min. After this time, a solution of Mesyl β-organochalcogenamine **3** in THF (3.0 mL) was added, and the resulting mixture was stirred at 80 ^oC for 2 h. The reaction was quenched with 10 mL of an NH_4Cl solution, and the aqueous layer was extracted with CH_2Cl_2 (3.0 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The crude products were purified in a silica gel column for chromatographic purification, using hexane–ethyl acetate (5 : 95) as the eluent.

(R) 2-*tert*-Butylcarbamoyl-1-(phenylselanyl)-3-(phenylthio) propane (5a).Physical state: white solid. Melting point: 46-47^{0}C. Yield: 61%. NMR ^{1}H (600 MHz, $CDCl_3$): 7.50 (d, *J* =6 Hz, 2H), 7.34 (d, *J* =6 Hz, 2H), 7.27-7.23 (m, 5H), 7.19-7.16 (m, 1H), 4.90 (s, 1H), 4.04-3.94 (m, 1H), 3.29-3.18 (m, 2H), 3.13 (dd, J^1 =6.0 Hz , J^2= 12.0 Hz, 1H), 3.09 (dd, J^1 =6.0 Hz, J^2= 12.0 Hz, 1H), 1.39 (s, 9H) ppm. NMR ^{13}C (151 MHz, $CDCl_3$): 154.8, 135.5, 132.8, 129.6, 129.2, 128.9, 127.1, 126.4, 79.5, 50.0, 38.0, 31.9, 28.2ppm. NMR ^{77}Se (114 MHz, $CDCl_3$): δ=248.55 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{25}NO_2SSe$ [M + Na^+]: 446.0663, found: 446.0645

2-*tert*-Butyl carbamoyl-1,3-bis(phenylselanyl) propane (5b). Physical state: white solid. Melting point: 46-47^{0}C. Yield: 83%. NMR ^{1}H (400 MHz, $CDCl_3$): 7.53-7.44 (m, 5H), 7.25-7.19 (m, 5H), 4.83 (s, 1H), 4.04-3.96 (m, 1H), 3.25-3.15 (m, 2H), 3.09 (dd, J^1 =4.0 Hz , J^2= 8.0 Hz, 2H),1.38 (s, 9H). NMR ^{13}C (100 MHz, $CDCl_3$): 154.8, 132.8, 129.6, 129.1, 127.1,126.9, 79.6, 50.5, 32.7, 28.2 ppm. NMR^{77}Se (114 MHz, $CDCl_3$): δ=257.30 ppm, 250.06 ppm, 242,66 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{25}NO_2Se_2$ [M + Na^+]: 494.0108, found:.494.0098

(S)-2-*tert*-Butyl carbamoyl- 1-(phenylselanyl)-3-(phenyltellanyl) propane (5c). Physical state: colorless oil. Yield: 40%. NMR ^{1}H (400 MHz, $CDCl_3$): 7.74 (d, *J* =4 Hz, 2H), 7.60 –7.48 (m, 5H), 7.22 – 7.19 (m, 3H), 4.83 (s, 1H), 3.99-3.89 (m, 1H), 3.30 – 3.19 (m, 2H), 3.13 (dd, J^1 =8.0 Hz, J^2= 16.0 Hz, 2H), 1.44 (s, 9H) ppm. NMR ^{13}C (100 MHz, $CDCl_3$): 155.0, 138.6, 133.0, 132.6, 130.85, 129.3, 129.2, 129.1, 127.8, 127.2, 126.9, 79.3, 51.1, 35.5, 28.3, 19.1 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{25}NO_2SeTe$ [M + Na^+]: 544.0005, found: 544.0023.

(R)-2-*tert*-Butyl carbamoyl-1-(phenylthio)-3-(4-tolylselanyl)propane (5d).Physical state: red oil. Yield: 47%. NMR ^{1}H (400 MHz, $CDCl_3$):7.43-7.37 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.19-7.15 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.79 (s, 1H), 4.01 – 3.83 (m, 1H), 3.26-3.13 (m, 2H). 3.12- 3.07 (m, 2H), 2.31 (s, 3H), 1.42 (s, 9H) ppm. NMR ^{13}C (100 MHz, $CDCl_3$): 154.7, 138.6, 132.9, 132.6, 130.9, 129.3, 129.2, 129.1, 127.8, 127.20, 126.9, 79.3, 51.1, 35.6, 34.5, 28.3, 19.1 ppm. HRMS-ESI: m/z calcd for $C_{21}H_{27}NO_2SSe$ [M + Na^+]: 460.0820 found: 460.0848.

(R)-2-*tert*-Butyl carbamoyl-1-(phenylselanyl)-3-(4-tolylselanyl)propane (5e). Physical state: yellow oil. Yield: 45%. NMR ^{1}H (400 MHz, $CDCl_3$): 7.40 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.20 (m, 5H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.79 (s, 1H), 4.04-3.89 (m, 1H), 3.25-3.05 (m, 4H), 2.31 (s, 3H), 1.38 (s, 9H) ppm. NMR ^{13}C (100 MHz, $CDCl_3$): 154.8, 137.3, 133.4, 132.9, 130.0, 129.1, 127.1, 79.7, 51.1, 35.5, 33.1, 28.3, 21.0 ppm. NMR^{77}Se (114 MHz, $CDCl_3$): δ=248.63 ppm, 241.13 ppm. HRMS-ESI: m/z calcd for $C_{21}H_{27}NO_2Se_2$ [M + Na^+]: 508.0264, found: 508.0280.

(S)- 2-*tert*-Butyl carbamoyl-1-(phenyltellanyl)-3-(4-tolylselanyl)propane (5f).Physical state: yellow oil. Yield: 50%. NMR ^{1}H (400 MHz, $CDCl_3$): 7.72 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.29-7.24 (m, 1H), 7.21-7.15 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 4.77 (s, 1H), 4.03-3.83 (m, 1H), 3.25-3.00 (m, 4H), 2.31 (s, 3H), 1.38 (s, 9H) ppm. NMR ^{13}C (100 MHz, $CDCl_3$): 154.7, 138.5, 138.6, 137.3, 133.5, 130.0 129.2, 129.3, 127.9, 125.8, 111.6, 79.6, 51.4, 35.0, 28.1, 21.2, 15.3 ppm. HRMS-ESI: m/z calcd for $C_{21}H_{27}NO_2SeTe$ [M + Na^+]: 558.0161, found: 558.0206

(R)- 2-*tert*-Butyl carbamoyl 1-(2-methoxyphenylselanyl)-3-(phenylthio)propane (5g).Physical state: yellow oil. Yield:44%. NMR ^{1}H (600 MHz, $CDCl_3$): 7.46 (d, *J* = 6.0 Hz, 1H), 7.35 (d, *J* = 6.0 Hz, 2H), 7.30 – 7.23 (m, 4H), 7.19 – 7.16 (m, 1H), 6.88-6.83 (m, 2H), 5.09 (s, 1H), 4.05-3.96 (m, 1H), 3.88 (s, 3H), 3.34-3.23 (m, 2H), 3.12 (dd, J^1 =6.0Hz, J^2= 12.0 Hz, 1H), 3.11-3.06(m, 1H), 1.40 (s, 9H) ppm. NMR ^{13}C (151 MHz, $CDCl_3$): 158.1, 154.9, 135.7, 133.2, 129.4, 129.5, 129.0, 128.6, 126.4, 126.3, 121.5, 110.6, 79.3, 56.1, 49.80, 38.2, 29.9, 28.1 ppm. HRMS-ESI: m/z calcd for $C_{21}H_{27}NO_3SSe$ [M + Na^+]: 476.0769 found: 476.0774

(R)- 2-*tert*-Butyl carbamoyl 1-(2-methoxyphenylselanyl)-3-(phenylselanyl)propane (5h).Physical state: red oil. Yield: 43%. NMR ^{1}H (400 MHz, $CDCl_3$): 7.57 – 7.50 (m, 2H), 7.47 (d, *J* = 4.0 Hz, 1H), 7.28 – 7.23 (m, 4H), 6.92 – 6.85 (m, 2H), 5.08 (s, 1H), 4.12-4.05 (m, 1H), 3.90 (s, 3H), 3.37-3.19 (m, 2H), 3.12 (dd, J^1 =8.0 Hz, J^2= 16.0 Hz, 1H), 3.08 (dd, J^1 =8.0Hz, J^2= 16.0 Hz, 1H),1.41 (s, 9H) ppm. NMR ^{13}C (100 MHz, $CDCl_3$): 158.0, 154.8, 133.1, 132.6, 129.7, 129.7, 129.1, 128.5, 127.0, 121.5, 118.4, 110.5, 79.5, 55.7, 50.1, 35.6, 32.5, 28.2 ppm. NMR^{77}Se (114 MHz, $CDCl_3$): δ=250.21 ppm, 180.07 ppm. HRMS-ESI: m/z calcd for $C_{21}H_{27}NO_3Se_2$ [M + Na^+]: 524.0214, found: 524.0214.

(S)-2-*tert*-Butyl carbamoyl- 1-(2-methoxyphenylselanyl)-3-(phenyltellanyl)propane (5i).Physical state: red oil. Yield: 50%. NMR ^{1}H (200 MHz, $CDCl_3$): 7.72 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.13 (m, 4H), 6.91 – 6.82 (m, 2H), 5.02 (s, 1H), 4.10-3.96 (m, 1H), 3.88 (s, 3H), 3.33 – 2.96 (m, 4H), 1.38 (s, 9H) ppm. NMR ^{13}C (50 MHz, $CDCl_3$): 158.0, 154.8, 133.1, 132.7. 129.8, 129.1, 127.0, 121.50, 118.4, 111.8, 110.5, 79.2, 55.8, 50.3, 32.5, 28.0, 17.3 ppm. HRMS-ESI: m/z calcd for $C_{21}H_{27}NO_3SeTe$ [M + Na^+]: 574.0111, found: 574.0133.

(R)-2-*tert*-Butyl carbamoyl-1-(2-chlorophenylselanyl)-3-(phenylthio)propane (5j). Physical state: colorless oil. Yield: 44%. NMR ^{1}H (200 MHz, $CDCl_3$): δ =7.32 – 7.18 (m, 9H), 4.90 (s, 1H), 4.10-3.95 (m, 1H), 3.34-3.07 (m, 4H), 1.40 (s, 9H) ppm. NMR ^{13}C (50 MHz, $CDCl_3$):154.9, 135.4, 131.9, 131.3, 130.4, 129.8, 129.6, 129.1, 128.7, 127.8, 127.4, 126.5, 79.7,50.0, 38.2, 30.5, 28.3 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{24}ClNO_2SSe$ [M + Na^+]: 480.0274, found: 480.0249.

(R)- 2-*tert*-Butyl carbamoyl 1-(2-chlorophenylselanyl)-3-(phenylselanyl)propane (5k). Physical state: yellow oil. Yield: 47%. NMR ^{1}H (200 MHz, $CDCl_3$): 7.58 – 7.37 (m, 9H), 4.87 (s, 1H), 4.07-3.86 (m, 1H), 3.18 – 2.98 (m, 4H), 1.39 (s, 9H) ppm. NMR ^{13}C (50 MHz, $CDCl_3$):154.8, 132.9, 132.8, 132.6, 131.9, 129.6, 129.2, 129.1, 127.7, 127.3, 126.9, 126.5, 79.6, 50.3, 35.51. 32.7, 28.3 ppm. NMR^{77}Se (114 MHz, $CDCl_3$): δ=249.16ppm, 243.55 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{24}ClNO_2Se_2$ [M + Na^+]: 527.9718 found: 527.9725

(S)-2-*tert*-Butyl carbamoyl-1-(2-chlorophenylselanyl)-3-(phenyltellanyl)propane (5l). Physical state: red oil. Yield: 54%. NMR ^{1}H (200 MHz, $CDCl_3$):7.63 – 6.94 (m, 9H), 4.77 (s, 1H), 4.15-3.77 (m, 1H), 3.35 – 2.83 (m, 4H), 1.41 (s, 9H) ppm. NMR ^{13}C (50 MHz, $CDCl_3$):154.8, 138.6, 132.9, 132.0, 129.6, 129.3, 129.2, 127.9, 127.8, 127.3, 126.4, 111.3, 79.6, 50.9, 31.3, 28.3, 15.2 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{24}ClNO_2SeTe$ [M + Na^+]: 577.9615 found: 577.9655.

2-*tert*-Butyl carbamoyl -1,3-bis(phenylthio)propane (5m). Physical state: white solid. Melting point: 63-64^{0}C.Yield: 65%. NMR ^{1}H (400 MHz, $CDCl_3$): 7.36 (d, *J* = 8.0 Hz, 5H), 7.29-7.25 (m, 4H), 7.20-7.15 (m, 3H), 4.97 (s, 1H), 4.05-3.86 (m, 1H), 3.35-3.20 (m, 2H), 3.14 (dd, J^1 =4.0 Hz, J^2= 8.0 Hz, 2H), 1.40 (s, 9H) ppm. NMR ^{13}C (100 MHz, $CDCl_3$): 154.9, 129.6, 129.1, 126.3, 78.9, 49.7, 37.5, 28.1 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{25}NO_2S_2$[M + Na^+] 398.1219, found: 398.1265.

(S)- 2-*tert*-Butyl carbamoyl 1-(phenyltellanyl)-3-(phenylthio)propane (5n) Physical state: yellow oil. Yield: 68%. NMR ^{1}H (400 MHz. $CDCl_3$): 7.71 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.22 (m, 3H), 7.18 – 7.13 (m, 3H), 4.85 (s, 1H), 4.03-3.82 (m, 1H), 3.21-3.18 (m, 2H), 3.12 (dd, J^1 =8.0 Hz, J^2= 16.0 Hz, 1H), 3.04 (dd, J^1 =8.0 Hz, J^2= 16.0 Hz, 1H),1.38 (s, 9H) ppm. NMR ^{13}C (100 MHz.$CDCl_3$): 154.7, 138.4, 135.5, 129.6, 129.2, 128.9, 127.7, 126.3, 111.4, 79.4, 50.6, 39.7, 28.2, 14.6 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{25}NO_2STe$ [M + Na^+]: 496.0560 found: 496.0174.

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(S)- 2-*tert*-Butyl carbamoyl-1-(phenylselanyl)-3-(phenylthio)propane(5o). Physical state: colorless oil. Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.51 – 7.48 (m, 2H), 7.36 – 7.32 (m, 2H), 7.28 – 7.20 (m, 5H), 7.20 – 7.12 (m, 1H), 5.11 – 4.66 (m, 1H), 4.07 – 3.85 (m, 1H), 3.27 – 3.16 (m, 2H), 3.16 – 3.05 (m, 2H), 1.39 (s, 9H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): 154.8, 135.5, 134.7, 132.8, 129.7, 129.1, 128.9, 127.1, 126.3, 99.9, 79.6, 50.2, 37.9, 31.8, 28.2 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{25}NO_2SSe$ [M + Na^+]: 446.0663 found:446.0691

(S)-2-*tert*-Butyl carbamoyl-1-(2-chlorophenylselanyl)-3-(phenylselanyl)propane(5p).Physical state: colorless oil. Yield: 45%. ^{1}H NMR (400 MHz, $CDCl_3$) 7.58 – 7.46 (m, 2H), 7.48 – 7.38 (m, 1H), 7.37 – 7.28 (m, 1H), 7.26 – 7.16 (m, 3H), 7.16 – 7.06 (m, 2H), 4.88-4.86 (m, 1H), 4.07 – 3.95 (m, 1H), 3.31 – 3.17 (m, 2H), 3.13 (dd, J^1= 12Hz, J^2=8 Hz, 2H), 1.39 (s, 9H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): 154.8, 132.9, 131.9, 130.4, 129.5, 129.2, 127.7, 127.3, 127.2, 79.5, 50.2, 32.7, 31.42, 28.3 ppm. HRMS-ESI: m/z calcd for $C_{20}H_{24}ClNO_2Se_2$ [M + Na^+]: 527.9718 found: 527.9747.

Computational Details

The Density Functional Theory was used to investigate the oxidation properties of some of the synthesized bis-chalcogen-β-amine compounds, namely, **5a**, **5b**, **5c**, **5h** and **5k**. The exchange and correlation interactions between the electrons in these systems were described by the hybrid B3LYP functional[20]. The atomic orbitals of all atoms were represented by 6-31G(d) basis set, except for Te, for which an effective core potential LANL2DZdp basis set[21] was used. The oxidation potentials were calculated following the steps of the Born-Harber cycle[22], which required the geometry optimization of the non-oxidized compounds as well as the calculation of their thermodynamic properties (Gibbs free energy) both in vacuum and in the appropriate solvent medium. The acetonitrile solvent was simulated through the polarizable continuum model (PCM)[23]. The Fc/Fc^+ oxidation potential was firstly calculated, and its value of 4.98 eV (regarding the Standard Hydrogen Electrode-SHE oxidation potential) was in good agreement with experimental results. It was then used as a reference for the determination of the oxidation potentials of the bis-chacogen-β-amine compounds. All quantum chemistry calculations were carried out using the Gaussian 09 code[24]. Molecular orbital plots were obtained using the open source Jmol code[25].

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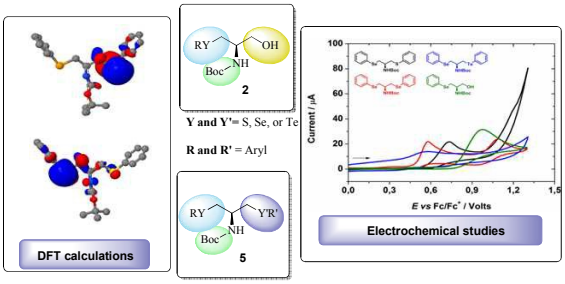

The synthesis of a new class of potential antioxidant chiral chalcogenocysteinols and bis-chalcogenoamines is described in this study.

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