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Convenient Preparation of Benzylseleno- and Phenylselenoalkanoic Acids: Reagents for Synthesis of Organoselenium Compounds

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Abstract: An efficient and operationally simple route to benzylseleno- and phenylselenoalkanoic acids from ethyl benzyl/phenylselenoalkanoates is described. This involves preparation of ethyl benzyl/phenylselenoalkanoates as substrates by reaction of dibenzyl/diphenyl diselenide and sodium borohydride with ethyl chloroalkanoates in ethanol followed by basic hydrolysis and subsequent acidification.

Keywords: benzylselenoalkanoic acid, ethyl benzylselenoalkanoates, ethyl phenylselenoalkanoates, phenylselenoalkanoic acid

INTRODUCTION

Selenium, which is an essential trace element, has been recognized to function as an active center of redox enzymes, such as glutathione peroxidase, and as a modifying factor in the toxicities of heavy metals.[1,2] Apart from this, selenium is an integral part of factor 3, a dietary agent that prevents liver necrosis in the rat and exudative diathesis in the chick.[3] Many organoselenium compounds are useful reagents or synthons in organic synthesis.[4,5] Over the past few years, a few synthetic strategies for the selenium-containing higher heterocycles, such as 5-deoxy-5-selenopyranose sugars,[6] and novel selenium analogs[7] of an important antioxidant, α-tocopherol, have been reported.

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Recently, β-lactams have been found to exhibit a wide spectrum of biological activity such as cholesterol absorption inhibiting activity,[8] antiviral activity,[9] and antitumor activity.[10] A lot of studies involving C-3 functionalization of azetidin-2-ones have been carried out in our laboratory,[11–16] and further interest in the development of synthetic methodologies for the synthesis of novel seleno-β-lactams was initiated by the discovery of novel selenium azetidin-2-ones, such as selenopenams and selenocephams, exhibiting potential β-lactamase inhibitory properties.[17] We envisaged synthesizing 3-seleno-β-lactams from selenoethanoic acids. These studies required a convenient method of preparating benzylseleno- and phenylselenoalkanoic acids.

A literature survey revealed the availability of a few methods for the synthesis of higher benzylselenoalkanoic acids. One of the methods involves the reaction of diseleno-dicarboxylic acid, ammonia, rongalite, and benzyl chloride.[18] However, it suffered from some disadvantages such as (i) the requirement for pungent-smelling ammonia, (ii) the need for rongalite, (iii) the multistep procedure, (iv) the use of excess of benzyl chloride, (v) a longer reaction time, and (vi) low to moderate yields of products. The second method involves the reaction of 5-bromopentanoic acid with dibenzyl diselenide and sodium borohydride.[19] However, this also involves much longer reaction time (i.e., 15 h of stirring), coupled with unpredictable performance of the reaction in large-scale preparations.

We have successfully employed ethyl benzyl/phenylselenoalkanoates as the most appropriate substrates for the synthesis of ethyl benzyl/phenylselenoalkanoic acids. The most convenient method for the preparation of ethyl 2-benzylselenoethanoate so far appears to be the $BiCl_3$-Sm-catalyzed reaction of dibenzyl diselenide with ethyl α-bromoacetate in water and THF.[20] However, use of this synthetic approach is also restricted because of the requirement of $BiCl_3$-Sm catalyst and low yield of product. We report here a facile method for the preparation of ethyl benzyl/phenylselenoalkanoates from ethyl chloroalkanoates involving a reaction with sodium borohydride in ethanol under varied reaction conditions.

RESULTS AND DISCUSSION

Starting substrates, such as ethyl 2-chloroethanoate **3a** and ethyl 3-chloropropanoate **3b**, were prepared by esterification of 2-chloroethanoic acid with ethanol in the presence of benzene using *p*-toluene sulfonic acid and 3-chloroproanoyl chloride with ethanol in the presence of pyridine in dry benzene at 0°C, respectively. Whereas, commercially available ethyl 4-chlorobutanoate **3c** was used without further purification.

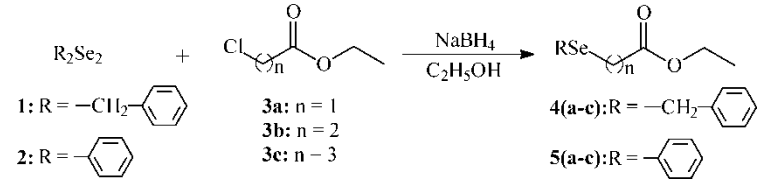
Initial studies were carried out by treating dibenzyl diselenide **1** and sodium borohydride with ethyl 2-chloroethanoate **3a** in ethanol. Cleavage of dibenzyl diselenide **1** by sodium borohydride in ethanol leads to the formation of nucleophilic selenium reagent $PhCH_2Se^-Na^+$, which on

treatment with ethyl 2-chloroethanoate **3a** affords ethyl 2-benzylselenoethanoate **4a** in quantitative yield (Scheme 1). The selenide anion ($PhCH_2Se^-$) generated in situ was observed to be very unstable at room temperature or higher temperature because it led to the regeneration of dibenzyl diselenide **1** and a semisolid product that could not be isolated in pure form. The stability of this anionic species was enhanced by carrying out the reaction at 0°C temperature. Dropwise addition of ethyl 2-chloroethanoate **3a** was completed in 5 min after the generation of selenide anion, which was indicated by the disappearance of yellow color of the solution. At this stage, the addition of ethyl 2-chloroethanoate **3a** resulted in the formation of ethyl 2-benzylselenoethanoate **4a**.

In an effort to demonstrate the synthetic potential of this reaction, the reaction was carried out with ethyl 3-chloropropanoate **3b** and ethyl 4-chlorobutanoate **3c**, and the results are summarized in Table 1. Ethyl 3-benzylselenopropanoate **4b** and ethyl 4-benzylselenobutanoate **4c** were efficiently formed at higher temperature (Table 1, entries 2 and 3). Similarly, ethyl phenylselenoalkanoates **5a–c** were synthesized by the reaction of the appropriate substrates, ethyl chloroalkanoates **3a–c** with $PhSe^-Na^+$ in ethanol,[21] prepared in situ from diphenyl diselenide **2** and sodium borohydride (Scheme 1, Table 1). However, in this case, after the addition of ethyl chloroalkanoates **3a–c** at 0°C, the reaction temperature was slowly increased to 55–60°C and stirring continued. Progress of the reaction was monitored by thin-layer chromatography (TLC), and disappearance of the spot for starting diphenyl diselenide on TLC confirmed the completion of reaction.

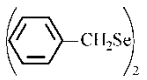
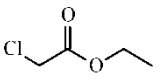
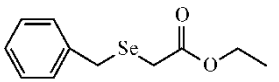
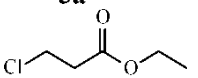
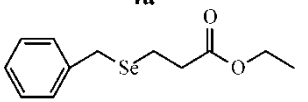
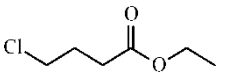
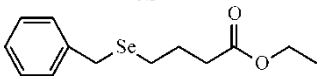
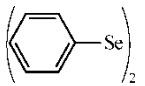
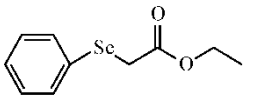
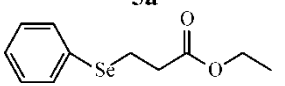
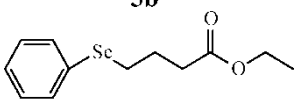
The ethyl benzyl/phenylselenoalkanoates **4, 5(a–c)** on hydrolysis using KOH in methanol afforded precipitates of potassium benzyl/phenylselenoalkanoates **6, 7(a–c)**. These were further acidified with conc. hydrochloric acid to obtain benzyl/phenylselenoalkanoic acids **8, 9(a–c)** as crystalline solids in excellent yields (Scheme 2, Table 2). The structures of these ethyl benzyl/phenylselenoalkanoates **4, 5(a–c)** and corresponding benzyl/phenylselenoalkanoic acids **8, 9(a–c)** were established on the basis of their spectral data such as IR, ^{1}H NMR, ^{13}C NMR, and ^{77}Se NMR.

In conclusion, we report here new procedure for the synthesis of 2-benzylseleno- and 2-phenylselenoalkanoic acids, which is operationally simple and superior to the methodologies reported earlier.

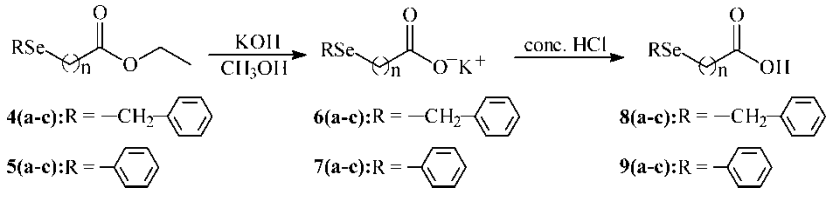


Scheme 1.

Table 1. Synthesis of ethyl benzyl/phenylselenoalkanoates **4, 5(a–c)**

Entry	Reactants		Product	Temp. (°C)	Time (min)	Yield[a] (%)
1	 **1**	 **3a**	 **4a**	0	5	90
2	**1**	 **3b**	 **4b**	0–15	15	87
3	**1**	 **3c**	 **4c**	0–40	25	84
4	 **2**	**3a**	 **5a**	50–55	45	94
5	**2**	**3b**	 **5b**	55–60	75	90
6	**2**	**3c**	 **5c**	55–60	90	89

[a]Yields quoted are for the isolated products characterized by IR, ^{1}H NMR, ^{13}C NMR, and ^{77}Se NMR.

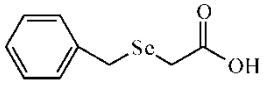
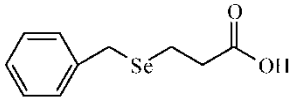
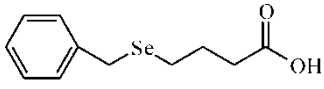
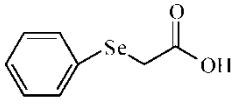
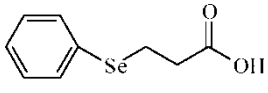
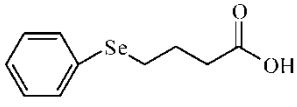


Scheme 2.

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a FTIR spectrophotometer (υ_{max} in cm^{-1}). ^1H NMR

Table 2. Benzyl/phenylselenoalkanoic acids **8, 9(a–c)**

Entry	Product	Yield[a](%)	Mp(°C)
1	 **8a**	96	63–64
2	 **8b**	92	67–68
3	 **8c**	89	70–71
4	 **9a**	95	42–43
5	 **9b**	91	45–46
6	 **9c**	90	49–50

[a]Yields quoted are for the isolated products characterized by IR, ^1H NMR, ^{13}C NMR, and ^{77}Se NMR.

(300 MHz), ^{13}C NMR (75 MHz), and ^{77}Se NMR (57 MHz) spectra were recorded on Jeol 300-MHz NMR spectrometer. Chemical shifts are given in parts per million (ppm) relative to TMS as an internal standard ($\delta = 0$ ppm) for ^{1}H NMR, $CDCl_3$ ($\delta = 77.0$ ppm) for ^{13}C NMR spectra, and $SeMe_2$ ($\delta = 0$ ppm) for ^{77}Se NMR spectra. Elemental analysis (C, H, Se) were recorded on Perkin-Elmer 2400 elemental analyzer. Column chromatography was performed using Merck silica gel (60–120 mesh). TLC was performed using Merck silica gel G. For visualization, TLC plates were stained with iodine vapors. All commercially available compounds/reagents were used without further purification.

Ethyl Benzylselenoalkanoates (4a–c)

General Procedure

Sodium borohydride (2.3 mmol) was added slowly over 10 min, in portions, to a stirred solution of dibenzyl diselenide (**1**, 1.0 mmol) in absolute ethanol (80 mL) at 0°C under nitrogen. After the complete addition of $NaBH_4$, the reaction mixture was stirred for 10 min until the characteristic yellow diselenide color had disappeared. Sodium borohydride was added cautiously because reduction of the diselenide is exothermic and vigorous evolution of hydrogen occurs after each addition. After the evolution of hydrogen had ceased (ca.10 min), ethyl chloroalkanoate (**3**, 2.2 mmol) in ethanol (5 mL) was added dropwise over 5 min with the immediate precipitation of a white solid. The reaction mixture was stirred, and progress of the reaction was monitored by TLC. Disappearance of the spot for starting dibenzyl diselenide **1** and appearance of a spot having an R_f lower than that of diselenide confirmed the completion of the reaction. A small amount of water (3 mL) was added to slow down the reaction. Thereafter, sodium chloride (5 g) was added to saturate it, and the product was extracted with ether (4 × 50 mL). The ether extract was washed with brine (2 × 15 mL) and dried over anhydrous sodium sulfate. After, evaporation of the solvent under reduced pressure, the residue was chromatographed using silica gel (60–120 mesh), eluting with 1% ethyl acetate in hexanes to give pure ethyl benzylselenoalkanoates **4a–c**.

Data

Ethyl 2-benzylselenoethanoate (4a): Yield: 90%; greenish-yellow semisolid; IR (CCl_4): 1734 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 1.20$ (t, 3H, $J = 7.2$ Hz, $-CH_3$), 2.87 (s, 2H, $-SeCH_2$), 3.83 (s, 2H, $PhCH_2-$), 4.04 (q, 2H, $J = 7.2$ Hz, $-OCH_2$), 7.06–7.24 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 12.24, 21.61, 28.10, 60.77, 126.90, 128.40, 129.17,$

138.21, 170.91; ^{77}Se NMR ($CDCl_3$, 57 MHz): $\delta_{Se} = 305.11$; anal. calcd. for $C_{11}H_{14}O_2Se$: C, 51.37; H, 3.64; Se, 30.70; found: C, 51.28; H, 3.53; Se, 30.61.

Ethyl 3-benzylselenopropanoate (4b): Yield: 87%; yellow oil; IR (CCl_4): 1737 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 1.23$ (t, 3H, $J = 7.2$ Hz, $-CH_3$), 2.55 (t, 2H, $J = 6.9$ Hz, $-SeCH_2$), 2.66 (t, 2H, $J = 7.1$ Hz, $-CH_2CO$), 3.77 (s, 2H, $PhCH_2-$), 4.07 (q, 2H, $J = 7.2$ Hz, $-OCH_2$), 7.12–7.26 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 14.47$, 17.61, 27.43, 35.51, 60.41, 126.86, 128.57, 129.00, 139.08, 171.63; anal. calcd. for $C_{12}H_{16}O_2Se$: C, 53.14; H, 5.94; Se, 29.11; found: C, 53.02; H, 5.87; Se, 29.06.

Ethyl 4-benzylselenobutanoate (4c): Yield: 84%; yellow oil; IR (CCl_4): 1735 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H =$ 1.17 (t, 3H, $J = 7.2$ Hz, $-CH_3$), 1.84–1.93 (m, 2H, $-CH_2CH_2CH_2-$), 2.22 (t, 2H, $J = 7.1$ Hz, $-SeCH_2$), 2.47 (t, 2H, $J = 7.1$ Hz, $-CH_2CO$), 3.67 (s, 2H, $PhCH_2-$), 3.67 (q, 2H, $J = 7.2$ Hz, $-OCH_2$), 7.11–7.26 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 14.12$, 16.31, 18.03, 26.53, 34.07, 60.24, 126.72, 128.50, 128.88, 140.02, 172.08; anal. calcd. for $C_{13}H_{18}O_2Se$: C, 54.74; H, 6.35; Se, 27.68; found: C, 54.61; H, 6.24; Se, 27.62.

Ethyl Phenylselenoalkanoates (5a–c)

General Procedure

The ethyl phenylselenoalkanoates **5a–c** were prepared from diphenyl diselenide (**2**, 1.0 mmol) following the general procedure as reported for benzylselenoalkanoates **4a–c**, however, in this case the reaction temperature was slowly increased to 55–60°C.

Data

Ethyl 2-phenylselenoethanoate (5a): Yield: 94%; yellow oil; IR (CCl_4): 1734 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 1.19$ (t, 3H, $J = 7.2$ Hz, $-CH_3$), 3.45 (s, 2H, $-SeCH_2$), 4.06 (q, 2H, $J = 7.2$ Hz, $-OCH_2$), 7.22–7.58 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 14.20$, 27.50, 61.09, 127.78, 129.15, 129.40, 133.56, 170.45; ^{77}Se NMR ($CDCl_3$, 57 MHz): $\delta_{Se} =$ 333.78; anal. calcd. for $C_{10}H_{12}O_2Se$: C, 49.39; H, 4.97; Se, 32.47; found: C, 49.32; H, 4.84; Se, 32.40.

Ethyl 3-phenylselenopropanoate (5b): Yield: 90%; yellow oil; IR (CCl_4): 1738 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 1.16$ (t, 3H, $J = 7.2$ Hz, $-CH_3$), 2.58 (t, 2H, $J = 7.1$ Hz, $-SeCH_2$), 2.95 (t, 2H,

$J = 7.1$ Hz, $-CH_2CO$), 4.00 (q, 2H, $J = 7.2$ Hz, $-OCH_2$), 7.13–7.43 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 14.35, 21.85, 35.38, 60.49, 127.27, 129.12, 129.46, 133.40, 171.69$; anal. calcd. for $C_{11}H_{14}O_2Se$: C, 51.37; H, 5.48; Se, 30.70; found: C, 51.29; H, 5.43; Se, 30.64.

Ethyl 4-phenylselenobutanoate (5c): Yield: 89%; colorless oil; IR (CCl_4): 1735 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 1.09$ (t, 3H, $J = 7.2$ Hz, $-CH_3$), 1.84–1.94 (m, 2H, $-CH_2CH_2CH_2-$), 2.31 (t, 2H, $J = 7.2$ Hz, $-SeCH_2$), 2.77 (t, 2H, $J = 7.1$ Hz, $-CH_2CO$), 3.95 (q, 2H, $J = 7.2$ Hz, $-OCH_2$), 7.07–7.38 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 14.13, 25.12, 26.75, 33.59, 59.93, 126.59, 128.73, 129.85, 132.49, 172.08$; anal. calcd. for $C_{12}H_{16}O_2Se$: C, 53.14; H, 5.94; Se, 29.11; found: C, 53.05; H, 5.89; Se, 29.08.

Benzylselenoalkanoic Acids (8a–c)

General Procedure

To a solution of potassium hydroxide (1.4 mmol) in methanol/water (3/1; 4 mL) at 0°C, ethyl benzylselenoalkanoate (**4**, 1 mmol) in methanol (60 mL) was added dropwise. The resultant mixture was stirred for 1 h. Progress of the reaction was monitored by TLC. White fluffy precipitates of potassium benzylselenoalkanoates **6a–c** were obtained, which were further dissolved in a minimum amount of water and acidified with conc. hydrochloric acid. The completion of the reaction was monitored by change of pH, which was checked at regular intervals. The product was extracted with dichloromethane (4×35 mL) and dried over anhydrous sodium sulfate. After evaporation of solvent under reduced pressure, the residue was recrystallized from dichloromethane–hexanes to afford benzylselenoalkanoic acids **8a–c**.

Data

Ethyl 2-benzylselenoethanoic acid (8a): Yield: 96%; white crystalline solid; mp 63–64°C; IR (KBr): 3009 (OH), 1690 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.92$ (s, 2H, $-SeCH_2$), 3.91 (s, 2H, $PhCH_2-$), 7.10–7.27 (m, 5H, Ar*H*), 9.05 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 21.36, 28.52, 127.20, 128.61, 129.33, 137.99, 178.43$; ^{77}Se NMR ($CDCl_3$, 57 MHz): $\delta_{Se} = 305.11$; anal. calcd. for $C_9H_{10}O_2Se$: C, 47.18; H, 4.40; Se, 34.46; found: C, 47.09; H, 4.36; Se, 34.41.

Ethyl 3-benzylselenopropanoic acid (8b): Yield: 92%; white crystalline solid; mp 67–68°C; IR (KBr): 3120 (OH), 1694 (C═O) cm^{-1}; ^1H NMR

($CDCl_3$, 300 MHz): $\delta_H = 2.68$ (t, 2H, $J = 6.9$ Hz, $-SeCH_2$), 2.79 (t, 2H, $J = 7.1$ Hz, $-CH_2CO$), 3.82 (s, 2H, $PhCH_2-$), 7.16–7.41 (m, 5H, Ar*H*), 9.01 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 17.87$, 27.82, 35.76, 127.10, 128.77, 129.20, 140.50, 172.20; anal. calcd. for $C_{10}H_{12}O_2Se$: C, 49.39; H, 4.96; Se, 32.47; found: C, 49.35; H, 4.90; Se, 32.38.

Ethyl 4-benzylselenobutanoic acid (8c): Yield: 89%; white crystalline solid; mp 70–71°C; IR (KBr): 3256 (OH), 1697 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 1.86–1.95$ (m, 2H, $-CH_2CH_2CH_2-$), 2.32 (t, 2H, $J = 7.1$ Hz, $-SeCH_2$), 2.51 (t, 2H, $J = 7.1$ Hz, $-CH_2CO$), 3.71 (s, 2H, $PhCH_2-$), 7.11–7.26 (m, 5H, Ar*H*), 10.94 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 16.49$, 18.27, 26.83, 34.24, 127.00, 128.69, 129.10, 140.70, 172.61; anal. calcd. for $C_{11}H_{14}O_2Se$: C, 51.37; H, 5.48; Se, 30.70; found: C, 51.32; H, 5.50; Se, 30.66.

Phenylselenoalkanoic Acids (9a–c)

General Procedure

The phenylselenoalkanoic acids **9a–c** were prepared from ethyl phenylselenoalkanoates **5a–c** following the general procedure as reported for benzylselenoalkanoic acids **8a–c**.

Data

Ethyl 2-phenylselenoethanoic acid (9a): Yield: 95%; white crystalline solid; mp 42–43°C; IR (KBr): 3289 (OH), 1706 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 3.86$ (s, 2H, $-SeCH_2$), 7.06–7.24 (m, 5H, Ar*H*), 10.94 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 27.33$, 128.09, 129.17, 129.31, 133.61, 177.73; ^{77}Se NMR ($CDCl_3$, 57 MHz): $\delta_{Se} = 340.56$; anal. calcd. for $C_8H_8O_2Se$: C, 44.67; H, 3.75; Se, 36.70; found: C, 44.59; H, 3.71; Se, 36.62.

Ethyl 3-phenylselenopropanoic acid (9b): Yield: 91%; white crystalline solid; mp 45–46°C; IR (KBr): 3324 (OH), 1706 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.65$ (t, 2H, $J = 7.1$ Hz, $-SeCH_2$), 2.97 (t, 2H, $J = 7.0$ Hz, $-CH_2CO$), 7.12–7.26 (m, 5H, Ar*H*), 10.77 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 26.54$, 30.54, 127.36, 129.20, 131.04, 133.60, 178.12; anal. calcd. for $C_9H_{10}O_2Se$: C, 47.17; H, 4.39; Se, 34.46; found: C, 47.12; H, 4.29; Se, 34.38.

Ethyl 4-phenylselenobutanoic acid (9c): Yield: 90%; white crystalline solid; mp 49–50°C; IR (KBr): 3362 (OH), 1708 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 1.85–1.96$ (m, 2H, $-CH_2CH_2CH_2-$), 2.38 (t, 2H,

$J = 7.2$ Hz, $-SeCH_2$), 2.81 (t, 2H, $J = 7.1$ Hz, $-CH_2CO$), 7.12–7.42 (m, 5H, Ar*H*), 10.68 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 24.99$, 26.91, 33.71, 127.00, 129.02, 129.82, 132.99, 179.46; anal. calcd. for $C_{10}H_{12}O_2Se$: C, 49.39; H, 4.96; Se, 32.47; found: C, 49.31; H, 4.92; Se, 32.36.

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