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SYNTHESIS OF SELENOHYDANTOINS FROM ISOSELENOCYANATES AND α-AMINO ACIDS

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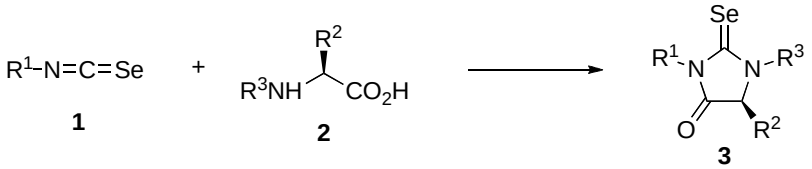
Abstract – Selenohydantoins were synthesized by the reaction of isoselenocyanates with α-amino acids in high yields. Reaction of isoselenocyanates with β-amino acids gave a six-membered ring compound and acyclic selenoureas.

Hydantoin skeletons, in another name, imidazolidine-2,4-diones, are well-known structures which have often been found in anticonvulsant drugs.[1-4] Their sulfur and selenium analogues, namely, thiohydantoins and selenohydantoins, have been attracted much attention in the last few decades due to the effects of exo chalcogen atoms on their biological activities.[5-13] As one of the synthetic method of 2-thioxo version of thiohydantoins, as expected from their structures, reaction of isothiocyanates with α-amino acids is often employed, especially when synthetic demand requires them in optically active form.[14-25] Similarly, selenohydantoins would be expected to be synthesized from isoselenocyanates and α-amino acids (Scheme 1), but such investigation has been very limited in literatures. Iskierko *et al.* reported that phenyl isoselenocyanate reacts with *N*-terminal amino acids of a peptide chain, β-insulin, to construct selenohydantoin skeleton.[26] Koketsu *et al.* reported that phenyl isoselenocyanate reacts with some methyl aminoacetate hydrochlorides in the presence of triethylamine to afford selenohydantoins in



Scheme 1. Synthesis of Selenohydantoins from Isoselenocyanates and α-Amino Acids

† Dedicated to Professor Albert Eschenmoser in celebration of his 85th birthday

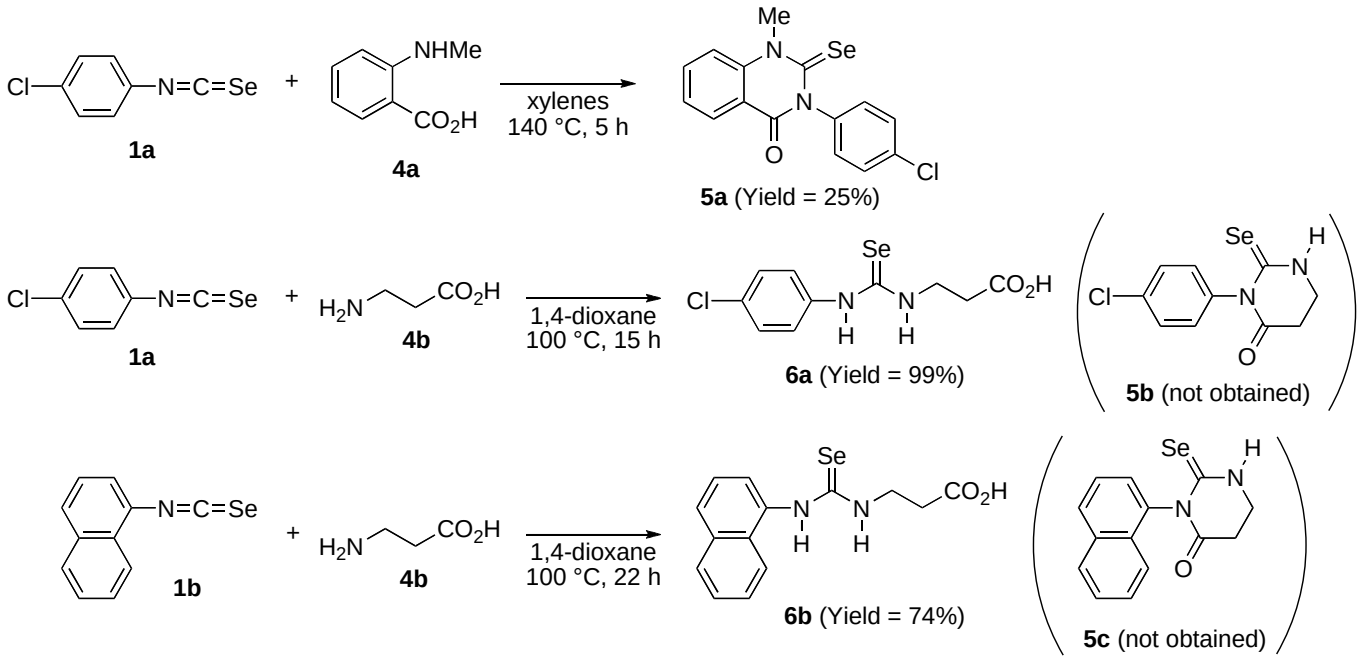
Table 1. Synthesis of Selenohydantoins from Isoselenocyanates and α-Amino Acids[a)]

Entry	Isoselenocyanate		α-Amino acid			Solvent	Temp. (°C)	Time (h)	Product	Yield[b)] (%)
		R^1		R^2	R^3					
1	**1a**	*p*-ClC_6H_4	**2a**	H	Me	1,4-dioxane	100	5	**3a**	98
2	**1a**	*p*-ClC_6H_4	**2b**	H	Ph	xylene	120	3	**3b**	66
3	**1a**	*p*-ClC_6H_4	**2c**	Me	H	1,4-dioxane	100	24	**3c**	64
4	**1a**	*p*-ClC_6H_4	**2d**	*i*-Pr	H	1,4-dioxane	100	24	**3d**	26
5	**1a**	*p*-ClC_6H_4	**2e**	*i*-Pr	*i*-Bu	1,4-dioxane	100	7	**3e**	99
6	**1a**	*p*-ClC_6H_4	**2f**	$PhCH_2$	H	1,4-dioxane	100	24	**3f**	60
7	**1a**	*p*-ClC_6H_4	**2g**	$MeS(CH_2)_2$	H	1,4-dioxane	100	20.5	**3g**	89
8	**1a**	*p*-ClC_6H_4	**2h**	$–(CH_2)_3–$		1,4-dioxane	100	21	**3h**	99
9	**1b**	1-naphthyl	**2a**	H	Me	1,4-dioxane	100	3.5	**3i**	99
10	**1b**	1-naphthyl	**2e**	*i*-Pr	*i*-Bu	1,4-dioxane	100	4	**3j**	99
11	**1c**	cyclohexyl	**2a**	H	Me	1,4-dioxane	100	5.5	**3k**	64
12	**1c**	cyclohexyl	**2h**	$–(CH_2)_3–$		1,4-dioxane	100	24	**3l**	55
13	**1d**	*n*-$C_{18}H_{37}$	**2a**	H	Me	1,4-dioxane	100	4	**3m**	93

a) Conditions: isoselenocyanate (**1**, 0.2 mmol), α-amino acid (**2**, 0.2 mmol), solvent (10 mL). b) Isolated yield.

high yields.[27] During the study about the development of facile synthetic routes of selenium-containing heterocycles,[28-33] we found that isoselenocyanates react with free α-amino acids without adding bases to give selenohydantoins in high yields, and that the efficiency of the reaction strongly depends on the substituents.

1,4-Dioxane solution containing equimolar amounts of *p*-chlorophenyl isoselenocyanate (**1a**) and *N*-methylglycine (**2a**) was stirred and heated to 100 °C. After stirring for 5 h, complete consumption of substrates was monitored by TLC. Extraction with Et_2O/H_2O and purification by a silica gel column chromatography gave 3-(*p*-chlorophenyl)-1-methyl-2-selenoxohydantoin (**3a**) in 98% isolated yield (Table 1, entry 1). Reaction of *N*-phenylglycine (**2b**) hardly proceeded under the same conditions, as expected from low nucleophilicity of N atom of **2b** due to the electronic effect of phenyl group. However, higher reaction temperature (120 °C) in xylene produced 1-phenyl derivative **3b** (entry 2). Reaction of alanine (**2c**) proceeded slowly to give **3c** (entry 3). Although valine (**2d**) was not suitable probably due to the low nucleophilicity based on the steric hindrance (entry 4), *N*-isobutyl derivative (**2e**) reacted with **1a** to give **3e** in excellent yield (entry 5). Phenylalanine (**2f**), methionine (**2g**), and proline (**2h**) could also be used for the reaction, and the corresponding selenohydantoins **3f-h** were obtained in high to excellent yields (entries 6-8). When other isoselenocyanates such as 1-naphthyl (**1b**), cyclohexyl (**1c**), and *n*-octadecyl (**1d**) isoselenocyanates were subjected to the reaction, the corresponding selenohydantoins **3i-m** were produced in moderate to excellent yields (entries 9-13).



Scheme 2. Reaction of Isoselenocyanates with *β*-Amino Acids

Next, we examined the reaction of isoselenocyanates with β-amino acids (Scheme 2). When the reaction of **1a** with *N*-methylanthranilic acid (**4a**) was carried out in refluxing xylene for 5 h, a six-membered ring compound **5a** was obtained in 25% yield. On the other hand, reaction of **1a** with β-analine (**4b**) in 1,4-dioxane at 100 °C for 15 h gave only acyclic selenourea **6a** in quantitative yield, without formation of cyclic compound **5b**. Reaction of 1-naphthyl derivative **1b** with **4b** gave similar results to afford **6b** without any formation of **5c**. These results suggested that the cyclization occurs via nucleophilic attack of nitrogen in **2** on the central carbon of cumulene moiety of **1**, followed by intramolecular dehydrative condensation, probably in both reactions using α- and β-amino acids. Transition states in the intramolecular dehydration process in the reactions with β-amino acids might be thermodynamically disadvantageous than those with α-amino acids due to conformational reason.[34]

In summary, we have developed a novel synthetic reaction of selenohydantoins from isoselenocyanates and α-amino acids. Nucleophilicity arising from bulkiness and electronic effect of substituents on amino acids involved in the efficiency of the reaction. Nucleophilic attack of N atom of amino acids on isoselenocyanates followed by intramolecular dehydration might be the most plausible pathway.

EXPERIMENTAL

General. 1,4-Dioxane was distilled from sodium benzophenone ketyl. Xylene (mixture of isomers) was purchased as reagent grade and was not purified. Isoselenocyanates were prepared by a reported procedure.[35] α- and β-Amino acids were used as purchased.

Melting points were determined on a melting point apparatus, Yamato MP-41. ^{1}H, ^{13}C, and ^{77}Se NMR spectra were recorded on a JEOL JNM-400 (400, 100, and 76 MHz, respectively) spectrometer using Me_4Si (for ^{1}H and ^{13}C) and Me_2Se (for ^{77}Se) as internal standards. IR spectra were determined on a Jasco A-202 spectrometer. Mass spectra (EI) were taken on a Hitachi M-80 operating in the electron impact mode (70 eV). Angles of rotation were measured by HORIBA SEPA-300 polarimeter. Column chromatography was conducted by using Fuji-Davison silica gel BW-127ZH. Analysis by TLC was carried out on MERCK silica gel plates Kiselgel 60F254.

Synthesis of selenohydantoins. To an argon-purged, three-necked flask, isoselenocyanate (**1**, 0.2 mmol), 1,4-dioxane (10 mL) or xylene (10 mL), and α-amino acid (**2**, 0.2 mmol) were placed and stirred. The solution was heated to 100-130 °C, and stirring was continued for 3-24 h (see Table 1). The progress of the reaction was monitored by TLC on silica gel. After the substrates were consumed, the mixture was cooled to 0 °C by an ice bath. Water was added, and the product was extracted with Et_2O for several times. The combined organic layer was dried over anhydrous magnesium sulfate. Filtration, evaporation, and silica gel column chromatography gave pure selenohydantoins (**3**). Structures of by-products were not determined.

3-(*p*-Chlorophenyl)-1-methyl-2-selenoxohydantoin (3a). Yellow solid; mp 171.8-172.0 °C; ^{1}H NMR ($CDCl_3$) δ = 3.48 (s, 3 H), 4.06 (s, 2 H), 7.26 (d, J = 8.9 Hz, 2 H), 7.48 (d, J = 8.9 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 36.75 (Me), 55.01 (CH_2), 129.45 (ArH), 129.95 (ArH), 132.54 (ArH), 135.39 (ArH), 169.60 (C=O), 185.37 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 304.22 ppm; IR (KBr) ν (relative intensity) = 830 (m), 1180 (m), 1200 (s), 1250 (m), 1300 (m), 1320 (s), 1500 (s), 1760 (s) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 42 (27), 111 (23), 125 (27), 217 (86), 288 (M^+, 100); HRMS (EI) Calcd for $C_{10}H_9ClN_2OSe$: 287.95687. Found: 287.95667.

3-(*p*-Chlorophenyl)-1-phenyl-2-selenoxohydantoin (3b). Yellow solid; mp 223.8-224.0 °C; ^{1}H NMR ($CDCl_3$) δ = 4.42 (s, 2 H), 7.25-7.60 (m, 9 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 56.36 (CH_2), 126.15 (ArH), 128.80 (ArH), 129.54 (ArH), 129.66 (ArH), 130.14 (ArH), 132.45 (ArH), 135.59 (ArH), 138.78 (ArH), 169.15 (C=O), 185.20 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 364.22 ppm; IR (KBr) ν (relative intensity) = 650 (m), 700 (m), 730 (w), 770 (m), 800 (s), 1090 (m), 1160 (s), 1280-1300 (m), 1500 (s), 1750 (s) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 77 (60), 105 (83), 217 (20), 286 (13), 350 (100); HRMS (EI) Calcd for $C_{15}H_{11}ClN_2OSe$: 349.97252. Found: 349.97190.

3-(*p*-Chlorophenyl)-5-methyl-2-selenoxohydantoin (3c). Colorless solid; mp 194.8-196.0 °C; ^{1}H NMR ($CDCl_3$) δ = 1.61 (d, J = 7.1 Hz, 3 H), 4.18 (q, J = 7.1 Hz, 1 H), 7.28 (d, J = 8.9 Hz, 2 H), 7.49 (d, J = 8.9 Hz, 2 H), 8.50 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 16.39 (Me), 56.61 (CH), 129.49 (ArH), 129.77 (ArH), 131.66 (ArH), 135.55 (ArH), 173.29 (C=O), 184.39 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 291.65 ppm; IR (KBr) ν (relative intensity) = 740 (m), 820 (m), 1095 (m), 1180 (s), 1265 (s), 1760 (s), 3150 (m) cm^{-1};

MS (EI), *m*/*z* (relative intensity, %) = 111 (19), 139 (21), 217 (100), 288 (M^+, 84); HRMS (EI) Calcd for $C_{10}H_9ClN_2OSe$: 287.95687. Found: 287.95713.

3-(*p*-Chlorophenyl)-5-isopropyl-2-selenoxohydantoin (3d). Colorless solid; mp 155.7-157.0 °C; ^{1}H NMR ($CDCl_3$) δ = 1.06 (d, *J* = 10.0 Hz, 3 H), 1.13 (d, *J* = 10.5 Hz, 3 H), 1.71 (m, 1 H), 2.29-2.48 (m, 1 H), 7.24 (d, *J* = 8.9 Hz, 2 H), 7.48 (d, *J* = 8.9 Hz, 2 H), 8.85 (brs, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 16.33 (Me), 18.82 (Me), 30.98 (Me_2CH), 66.22 (NCH), 129.51 (ArH), 129.80 (ArH), 131.63 (ArH), 135.57 (ArH), 172.28 (C=O), 184.59 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 278.80 ppm; IR (KBr) ν (relative intensity) = 760 (m), 830 (w), 1280 (s), 1520 (s), 1760 (s), 3150 (m) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 111 (35), 138 (39), 217 (97), 316 (100); HRMS (EI) Calcd for $C_{12}H_{13}ClN_2Ose$: 315.98817. Found: 315.98794; $[\alpha]_D^{25}$ –29.5° (*c* 1.0, $CHCl_3$).

3-(*p*-Chlorophenyl)-1-isobutyl-5-isopropyl-2-selenoxohydantoin (3e). Pink solid; mp 139-142 °C; ^{1}H NMR ($CDCl_3$) δ = 0.96 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 1.26 (d, *J* = 6.8 Hz, 3 H), 2.18-2.25 (m, 1 H), 2.45-2.49 (m, 1 H), 3.14 (dd, *J* = 13.9, 5.6 Hz, 1 H), 3.92 (d, *J* = 3.4 Hz, 1 H), 4.60 (dd, *J* = 13.9, 9.5 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 15.54 (Me), 17.09 (Me), 19.69 (Me), 20.32 (Me), 26.81 (Me_2CH), 28.81 (Me_2CH), 53.55 (NCH_2), 66.81 (NCH), 129.24 (ArH), 130.06 (ArH), 132.56 (ArH), 135.12 (ArH), 171.70 (C=O), 184.64 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 296.72 ppm; IR(KBr) ν (relative intensity) = 3475 (w), 3097 (w), 2927 (s), 1890 (w), 1755 (s), 1458 (m), 1380 (m), 1218 (w), 1126 (m), 968 (w), 829 (m), 767 (w), 725 (w) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 153 (92), 225 (94), 283 (100), 357 (2).

5-Benzyl-3-(*p*-chlorophenyl)-2-selenoxohydantoin (3f). Colorless solid; mp 190.1-190.3 °C; ^{1}H NMR ($CDCl_3$) δ = 2.98-3.77 (m, 1 H), 4.41 (dd, *J* = 6.6, 4.5 Hz, 2 H), 6.94-7.47 (m, 9 H), 8.23 (brs, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 36.99 (CH_2), 62.05 (CH), 128.01 (ArH), 129.04 (ArH), 129.45 (ArH), 129.50 (ArH), 129.67 (ArH), 131.49 (ArH), 133.60 (ArH), 135.54 (ArH), 171.92 (C=O), 184.54 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 294.89 ppm; IR (KBr) ν (relative intensity) = 700 (w), 740 (w), 1180 (m), 1250 (m), 1500 (s), 1520 (s), 1750 (s), 3120 (w) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 91(93), 111 (54), 138 (47), 217 (60), 284 (77), 364 (100); HRMS (EI) Calcd for $C_{16}H_{13}ClN_2OSe$: 363.98817. Found: 363.98867.

3-(*p*-Chlorophenyl)-5-[2-(methylthio)ethyl]-2-selenoxohydantoin (3g). Colorless solid; mp 139.4 - 140.0 °C; ^{1}H NMR ($CDCl_3$) δ = 2.13 (s, 3 H), 2.26-2.47 (m, 2 H), 2.74 (t, *J* = 6.5 Hz, 2 H), 4.27 (dd, *J* = 7.7, 4.5 Hz, 1 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.49 (d, *J* = 8.7 Hz, 2 H), 8.65 (brs, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 15.15 (Me), 29.29 (SCH_2), 29.98 (CH_2), 59.80 (CH), 129.49 (ArH), 129.78 (ArH), 131.69 (ArH), 135.54 (ArH), 172.81 (C=O), 184.43 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 283.20 ppm; IR (KBr)

ν (relative intensity) = 1520 (s), 1720 (s), 2950 (m) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 75 (29), 111 (38), 138 (33), 157 (35), 194 (38), 207 (55), 219 (34), 287 (89), 348 (100); HRMS (EI) Calcd for $C_{12}H_{13}ClN_2OSSe$: 347.96024. Found: 347.96070.

Tetrahydro-2-(*p*-chlorophenyl)-1*H*-pyrrolo[1,2-*c*]imidazole-1-one-3-selone (3h). Yellow solid; mp 147.3-148.5 °C; ^{1}H NMR ($CDCl_3$) δ = 1.59-2.60 (m, 4 H), 3.64-3.82 (m, 1 H), 3.98-4.31 (m, 2 H), 7.28 (d, *J* = 8.9 Hz, 2 H), 7.47 (d, *J* = 8.9 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 26.44 (CH_2), 26.47 (CH-CH_2), 49.77 (NCH_2), 66.20 (CH), 129.39 (ArH), 129.65 (ArH), 132.38 (ArH), 135.17 (ArH), 172.27 (C=O), 187.83 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 356.13 ppm; IR (KBr) ν (relative intensity) = 1095 (m), 1180 (m), 1240 (m), 1260 (m), 1415 (s), 1760 (s) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 41 (11), 68 (17), 153 (19), 217 (100), 250 (6), 314 (M^+, 48); HRMS (EI) Calcd for $C_{12}H_{11}ClN_2OSe$: 313.97252. Found: 313.97210; $[\alpha]_D^{25}$ +4.0° (*c* 1.0, $CHCl_3$).

1-Methyl-3-(1-naphthyl)-2-selenoxohydantoin (3i). Brown solid; mp 182.0-182.3 °C; ^{1}H NMR ($CDCl_3$) δ = 3.52 (brs, 3 H), 4.17 (brs, 2 H), 7.24-8.02 (m, 7 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 36.77 (Me), 55.14 (CH_2), 120.83 (ArH), 121.47 (ArH), 122.12 (ArH), 125.37 (ArH), 125.70 (ArH), 126.02 (ArH), 126.26 (ArH), 126.63 (ArH), 127.28 (ArH), 127.82 (ArH), 128.74 (ArH), 129.93 (ArH), 130.42 (ArH), 130.88 (ArH), 134.36 (ArH), 170.18 (C=O), 186.26 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 304.54 ppm; IR (KBr) ν (relative intensity) = 760-800 (m), 1190 (m), 1240 (m), 1300 (s), 1400 (m), 1520 (m), 1780 (s) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 101 (10), 115 (20), 127 (74), 141 (83), 153 (98), 233 (88), 304 (100); HRMS (EI) Calcd for $C_{14}H_{12}N_2OSe$: 304.01149. Found: 304.01099.

1-Isobutyl-5-isopropyl-3-(1-naphthyl)-2-selenoxohydantoin (3j). Colorless solid; mp 60-63 °C; ^{1}H NMR ($CDCl_3$) δ = 1.03-1.07 (m, 7 H), 1.17 (d, *J* = 7.1 Hz 1 H), 1.30 (dd, *J* = 14.8, 7.0 Hz, 3 H), 2.22-2.32 (m, 1 H), 2.53 (tt, *J* = 10.5, 3.5 Hz, 1 H), 3.22 (dt, *J* = 19.3, 6.5 Hz, 1 H), 4.06 (dd, *J* = 23.4, 3.4 Hz, 1 H), 4.67 (dd, *J* = 13.8, 9.9 Hz, 1 H), 7.33-7.98 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ = 15.75 (Me), 16.54 (Me), 17.18 (Me), 17.47 (Me), 19.72 (Me_2CH), 19.79 (Me_2CH), 20.35 (Me), 20.40 (Me), 26.93 (Me), 27.00 (Me), 28.48 (Me_2CH), 29.03 (Me_2CH), 53.44 (NCH_2), 53.48 (NCH_2), 66.83 (NCH), 67.12 (NCH), 122.11 (ArH), 122.50 (ArH), 125.32 (ArH), 125.37 (ArH), 126.47 (ArH), 126.52 (ArH), 127.08 (ArH), 127.24 (ArH), 127.66 (ArH), 127.78 (ArH), 128.66 (ArH), 128.69 (ArH), 130.14 (ArH), 130.19 (ArH), 130.24 (ArH), 130.28 (ArH), 131.04 (ArH), 131.18 (ArH), 134.34 (ArH), 172.33 (C=O), 172.37 (C=O), 185.64 (C=Se), 185.74 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 297.29, 301.29 ppm; IR (KBr) ν (relative intensity) = 3529 (w), 3058 (w), 2962 (m), 1751 (s), 1477 (s), 1249 (s), 1172 (m), 794 (w), 771 (s) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 127 (49), 154 (47), 223 (100), 252 (32), 267 (28), 293 (23), 308 (40), 332 (22), 304 (98); HRMS (EI) Calcd for $C_{20}H_{24}N_2OSe$: 388.10539. Found: 388.10527.

3-Cyclohexyl-1-methyl-2-selenoxohydantoin (3k). Yellow solid; mp 151.8-152.4 °C; ^{1}H NMR ($CDCl_3$) δ = 1.24-2.24 (m, 10 H), 3.33 (s, 3 H), 3.73 (s, 2 H), 4.47-4.72 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ =

25.04 (CH_2), 25.87 (CH_2), 28.52 (CH_2), 36.87 (Me), 54.68 (CH), 58.68 (NCH_2), 170.54 (C=O), 186.49 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 236.57 ppm; IR (KBr) ν (relative intensity) = 1140-1355 (m), 1520 (m), 1740 (s), 2900 (m) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 43 (45), 72 (41), 151 (17), 179 (95), 260 (100); HRMS (EI) Calcd for $C_{10}H_{16}N_2OSe$: 260.04279. Found: 260.04236.

Tetrahydro-2-cyclohexyl-1*H*-pyrrolo[1,2-*c*]imidazole-1-one-3-selone (3l). Yellow solid; mp 87.8-88.3 °C; ^{1}H NMR ($CDCl_3$) δ = 0.87-2.40 (m, 13 H), 3.63-3.75 (m, 1 H), 3.83-4.15 (m, 2 H), 4.45-4.70 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 25.04 (CH_2), 25.80 (CH_2), 25.89 (CH_2), 26.29 (CH_2), 26.35 (CH_2), 28.08 (CH-CH_2), 28.89 (CH_2), 50.04 (NCH_2), 57.97 (NCH_2), 65.45 (NCH), 67.08 (COCH), 173.42 (C=O), 189.38 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 295.05 ppm; IR (KBr) ν (relative intensity) = 1130 (m), 1180 (m), 1220-1280 (m), 1440 (s), 1730 (s), 2900 (m) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 70 (74), 98 (67), 149 (11), 177 (48), 205 (100), 286 (M^+, 88); HRMS (EI) Calcd for C12H18N2OSe: 286.05844. Found: 286.05881.

1-Methyl-3-octadecyl-2-selenoxohydantoin (3m). Pale red solid; mp 63.8-64.2 °C; ^{1}H NMR ($CDCl_3$) δ = 0.88 (t, *J* = 5.7 Hz, 3 H), 1.26 (m, 32 H), 1.58 (brs, 2 H), 3.41 (s, 2 H), 3.85 (brs, 3 H) ppm; ^{13}C NMR ($CDCl_3$) δ = 14.13 (CH_3), 22.70 (CH_2), 26.76 (CH_2), 27.80 (CH_2), 29.20 (CH_2), 29.37 (CH_2), 29.52 (CH_2), 29.58 (CH_2), 29.67 (CH_2), 29.71 (CH_2), 31.94 (CH_2), 36.33 (NMe), 44.02 (NCH_2), 54.56 ($COCH_2$), 170.50 (C=O), 185.74 (C=Se) ppm; ^{77}Se NMR ($CDCl_3$) δ = 252.66 ppm; IR (KBr) ν (relative intensity) = 1130-1360 (m), 1540 (m), 1740 (s), 2850 (s), 2950 (s) cm^{-1}; MS (EI), *m*/*z* (relative intensity, %) = 179 (12), 321 (4), 350 (100), 431 (M^+, 57); HRMS (EI) Calcd for $C_{22}H_{42}N_2OSe$: 403.24624. Found: 403.24634.

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34. A possibility that the difference of the efficiency of cyclization between selenoureas generated from α- and β-amino acids comes from *s-trans* and *s-cis* relationships of selenocarbonyl group and carboxyalkyl group on selenoureas can not be ruled out.
35. Isoselenocyanates were prepared by selenation of the corresponding isocyanates with $(Me_2Al)_2Se$. H. Maeda, M. Takashima, K. Sakata, T. Watanabe, M. Honda, and M. Segi, submitted for publication.