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Article

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General, Mild, and Metal-Free Synthesis of Phenyl Selenoesters from Anhydrides, and their Use in Peptide Synthesis

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Dedicated to the memory of Prof. Alessandro Degl'Innocenti

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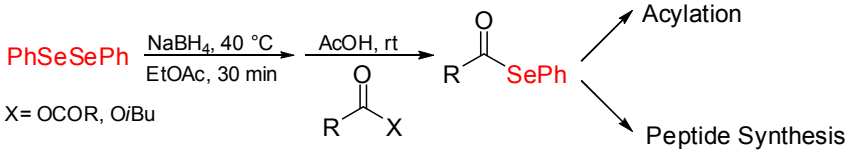


ABSTRACT: A mild, practical and simple procedure for phenyl selenoesters synthesis from several anhydrides and diphenyl diselenide was developed. This transition metal-free method provides a straightforward entry to storable Fmoc-amino acid selenoesters which are effective chemoselective acylating reagents. An application to oligopeptide synthesis was illustrated.

INTRODUCTION

Selenoesters[1] have shown to be useful intermediates in synthetic organic chemistry as precursors of acyl radicals,[2] mild acyl transfer reagents[3] and intermediate to access ketones.[4] In addition, selenoesters have attracted attention in material science[5] and pharmaceutical science.[6] Furthermore, in recent years, some peptide segment assembly strategies, based on native chemical

ligation (NCL) with peptidyl-selenoesters as acyl donors,[7] have been investigated. Various synthetic methods for the synthesis of selenoesters have been developed and they are usually based on the reaction of acyl chloride with selenols,[8] alkali metal selenolates,[9] phenyltributyl stannyl selenides[10] or phenylseleno trimethylsilane,[11] as well as with selenolate anions generated in situ by reduction of diselenides with transition metals.[12] Additional methods, including reaction of carboxylic acids with selenocyanates[13] or phenylselenenyl chloride,[14] alkylation of selenocarboxylates,[15] oxidative coupling of aldehydes with diphenyl diselenide[16] and oxidative hydration of (phenylseleno)acetylenes,[17] have also been reported. However, many of the above cited methods suffer from synthetic drawbacks due to the limited availability and air instability of selenium containing precursors, unsatisfactory yields and limited to narrow substrate scope. Furthermore, the methods reported are sometimes not attractive, as they can be environmentally unsafe due to harsh reaction conditions and toxic catalysts and solvents. Thus, the development of a mild, efficient, versatile and non-metal-mediated method for the synthesis of selenoester is desiderable.

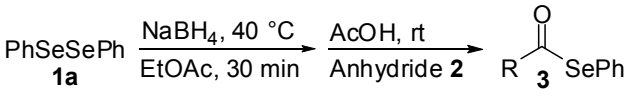
Considering our ongoing research into organoselenium chemistry[18] we wish to report an account on phenyl selenoesters synthesis from anhydrides. Despite some scattered reports on phenyl selenoesters synthesis by reaction of alkali metal benzeneselenolates with symmetric anhydrides,[19] the relevance of this method has not been fully explored. Thus, herein we propose a simple experimental procedure to prepare phenyl selenoesters by reaction of diphenyl diselenide and sodium borohydride in EtOAc, followed by anhydride addition. To date, there have been no reports on reduction of diphenyl diselenide with sodium borohydride in EtOAc as solvent.

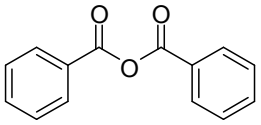
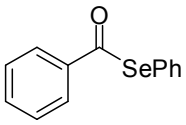
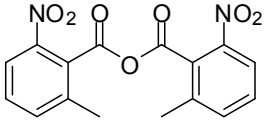
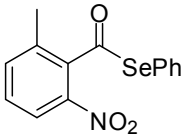
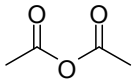
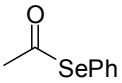
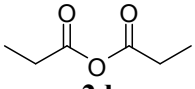
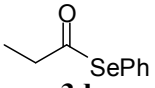
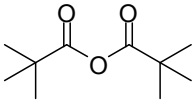
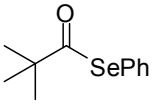
RESULTS AND DISCUSSION

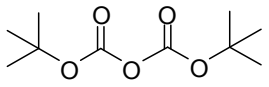
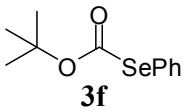
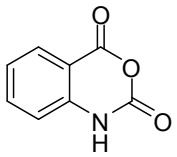
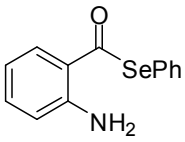
Synthesis of Selenoesters from Anhydrides. We performed a set of experiments using benzoic anhydride **2a** as model substrate to determine the best reaction conditions (see Table S1 and S2, Supporting Information). As a result, the model reaction was carried out with diphenyl

diselenide **1a** (1 equiv) and $NaBH_4$ (2 equiv) at 40 °C in EtOAc for 30 minutes followed by glacial acetic acid addition at room temperature (10 equiv). The treatment of the resulting mixture with benzoic anhydride (2.1 equiv) at room temperature gave (5 h) selenoesters **3a** in 94% isolated yield. Using the optimized conditions, the scope of the reaction was extended to a wide range of aromatic and aliphatic anhydrides (Table 1). All reactions were clean and efficient and the phenyl selenoesters **3a-g** were obtained in good to excellent yields. Notably, the reaction with di-*tert*-butyl dicarbonate generated the new selenocarbonate **3f** in high yield. In this example, glacial acetic acid was not added (Table 1, entry 6) Moreover, this method let us prepare for the first time the free-amino selenoesters **3g** (Table 1, entry 7) starting from isatoic anhydride.

Table 1. Preparation[a] of phenyl selenoesters 3a-g from anhydrides 2



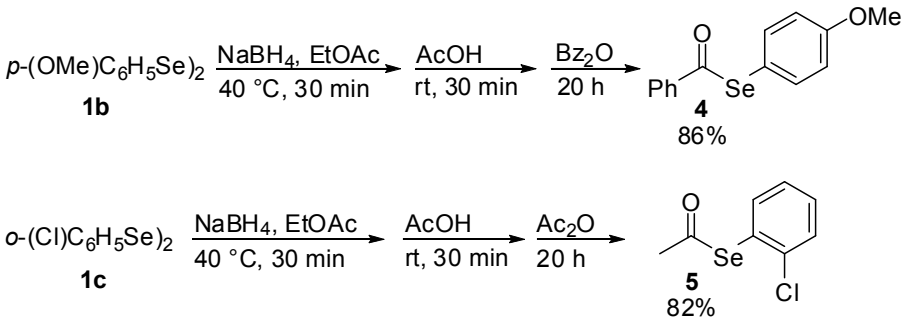
Entry	Anhydride	t (h)	Product	Yield (%)[b]
1	 **2a**	5	 **3a**	94
2	 **2b**	24	 **3b**	86
3	 **2c**	8	 **3c**	90
4	 **2d**	14	 **3d**	88
5	 **2e**	18	 **3e**	89

6	 **2f**	18	 **3f**	92[c]
7	 **2g**	23	 **3g**	74

[a] Conditions: substrate **1a** (1 mmol), $NaBH_4$ (2 equiv), AcOH (10 equiv), anhydride **3** (2.1 equiv), EtOAc (10 mL). [b] Yield of isolated product after chromatographic purification. [c] Glacial acetic acid was not added.

As far as the diselenide is concerned, the influence of an electron-donating or electron-withdrawing group, such as chloro and methoxy groups, on the aromatic ring of the diselenide was also investigated (Scheme 1).

Scheme 1. Synthesis of two selenoesters using different diselenide moieties

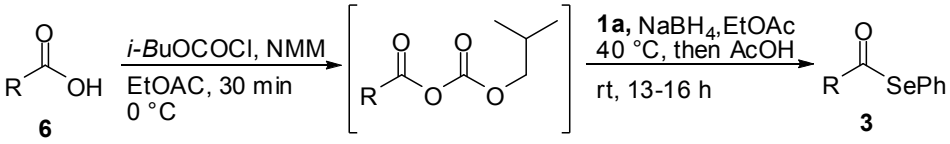


Both groups didn't show a significant influence on the diselenide reduction and the nucleophilic selenium reactivity. Very good yields of the expected selenoesters **4** and **5** were achieved.

Synthesis of Selenoesters from Carboxylic Acids. In order to access more easily a wide library of selenoesters, we envisioned the use of carboxylic acids **6** instead of anhydrides **2** as substrates. Accordingly, the starting acid was converted into the reactive anhydride intermediate with *i*BuOCOCl and *N*-methylmorpholine (NMM), then the selenoesters were obtained by addition of nucleophilic selenium species (Scheme 2). To the best of our knowledge, only three examples for preparing selenoesters from mixed anhidrides have primarly focused on the use of readily oxidable

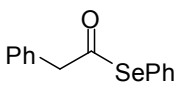
benzenselenol[3b] or ethanolic sodium benzeneseleno(triethoxy)borate[20a] or by employing sodium phenylselenide obtained from benzenselenol.[20b]

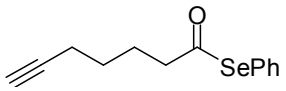
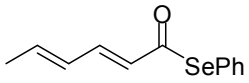
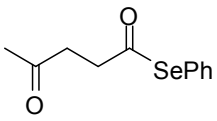
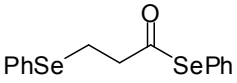
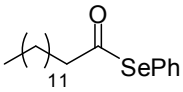
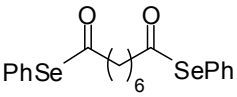
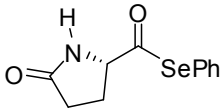
Scheme 2. Synthesis of selenoesters from carboxylic acids



In preliminary experiments it was found that the mixed anhydride intermediate, prepared from phenylacetic acid **6a** and 1.1 equiv. of *N*-methyl morpholine and 1.1 equiv. of isobutyl chloroformate, was stable at 0 °C in EtOAc solution. The anhydride-forming reaction appeared to be complete in 30 minutes at 0°C. After addition of 1.2 equiv. of nucleophilic selenium species (prepared as above) and overnight stirring at room temperature, the corresponding phenyl selenoester **3h** was obtained in a 70% yield. Higher amount of nucleophilic selenium species or shorter reaction time diminished the product yield. A better yield (82%) of product **3h** was obtained when the reaction was carried out with a 10% in excess of mixed anhydride with respect to the nucleophilic selenium species (Table 2). The use of the more powerful nucleophile sodium benzeneselenolate, generated from reduction of diphenyl diselenide with sodium[18a] in a mixture of DMF and THF, resulted in a 50% yield. With the optimized reaction conditions in hand, we demonstrated the scope of our procedure for a variety of carboxylic acids. As shown in Table 2, several functionalized aliphatic acids were smoothly converted into the corresponding phenyl selenoesters in good to excellent yields.

Table 2. Substrate scope of phenyl selenoesters synthesis[a] from aliphatic carboxylic acids 6a-h

Entry	Acid[a]	t (h)	Product	Yield (%)[b]
1	**6a**	16	 **3h**	82

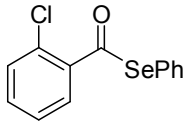
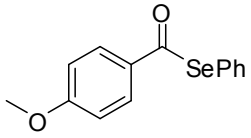
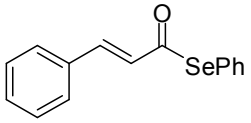
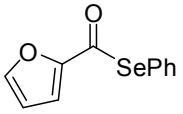
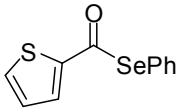
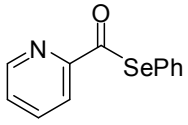
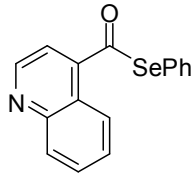
2	**6b**	13	 **3i**	77
3	**6c**	13	 **3j**	74
4	**6d**	14	 **3k**	62
5	**6e**	15	 **3l**	82
6	**6f**	15	 **3m**	91
7	**6g**	13	 **3n**	79
8	**6h**	15	 **3o**	61

[a] Conditions: Acid **6** (2.2 equiv), *i*-BuOCOCl (2.2 equiv) and NMM (2.2 equiv) in EtOAC (10 mL) 30 min at 0 °C. Then a solution prepared from diphenyl diselenide (1 mmol), $NaBH_4$ (2 equiv), AcOH (10 equiv) in EtOAc (10 mL) was added. [b] Yield of isolated products after chromatographic purification.

The procedure showed good functional group compatibility as amide, alkene, alkyne and carbonyl groups were all tolerated under the reaction conditions employed. Notable are the good yields of selenoesters **3j** and **3k**, which show diene and carbonyl reactive sites respectively. Interestingly, the reaction occurred efficiently even with suberic acid (**6g**) giving the corresponding diselenoester **3n** in excellent yield. Interestingly, the preparation of selenoester **3l** possessing a second phenylseleno group on the alkyl chain was achieved. This group could quickly be displaced by elimination or substitution[3d] to give variously substituted derivatives (see preparation of *N*-acryloyl-proline methyl ester in Supporting Information). To further extend the substrate scope of

this method, reactions with aromatic and heteroaromatic carboxylic acids were examined (Table 3). All the substrates produced the corresponding derivatives in very good yields.

Table 3. Substrate scope of phenyl selenoesters synthesis[a] from aromatic and heteroaromatic carboxylic acids 6i-o

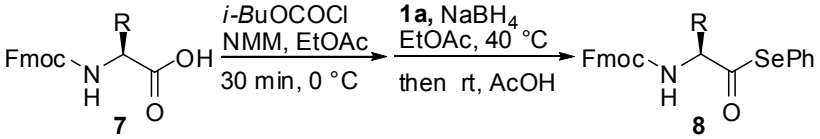
Entry	Acid[a]	t (h)	Product	Yield (%)[b]
1	**6i**	16	 **3p**	75
2	**6j**	15	 **3q**	70
3	**6k**	16	 **3r**	80
4	**6l**	16	 **3s**	79
5	**6m**	13	 **3t**	77
6	**6n**	14	 **3u**	80
7	**6o**	13	 **3v**	76

[a] Conditions: Acid **6** (2.2 equiv), *i*-BuOCOCl (2.2 equiv) and NMM (2.2 equiv) in EtOAC (10 mL) 30 min at 0 °C. Then a solution prepared from diphenyl diselenide (1 mmol), $NaBH_4$ (2 equiv), AcOH (10 equiv) in EtOAc (10 mL) was added. [b] Yield of isolated product after chromatographic purification

The selenoester **3r** was obtained in high yield despite the presence of a Michael acceptor group as the conjugate double bond. Worthy of note is also the first synthesis of two nitrogen-containing heterocyclic selenoesters **3u** and **3v**.

Application to *N*-Fmoc-L-amino acids. The preparation of selenoester **3o** from L-pyroglutamic acid has inspired us to apply the above methodology to *N*-Fmoc-L-amino acids **7** (Table 4). Despite the many methods reported for the synthesis of selenoesters, examples of these compounds from Cbz-, Phth- and Boc-protected L-amino acids are scarcely represented in literature. In these reports, mixed anhydride derivatives of a restricted number of protected proteinogenic L-amino acids were reacted with benzeneselenol[3b,21] or benzeneseleno(trietoxy)borate.[20,22] Recently, Arora and co-workers[7c] have reported the preparation of some phenyl selenoesters of *N*-Fmoc-L-amino acids by *in situ C*-activation with DCC, and their use in molecular biology studies. In view of our previous observation, slight excesses (10% mol) of isobutyl chloroformate and NMM were employed and the mixed anhydride-forming reaction appeared to be complete in 30-40 minutes at 0 °C in EtOAc. Then 1.2 equiv. of nucleophilic selenium species (prepared as above) were added and the reaction mixture was allowed to warm to room temperature. This procedure was applied to the chemoselective and efficient preparation of various *N*-Fmoc-L-amino acid selenoesters **8** (Table 4).

Table 4. Results of the reaction of synthesis of *N*-Fmoc-L-amino acid selenoesters 8a-n



Entry	*N*-Fmoc-L-amino acid	t (h)	Product	Yield (%)[a]

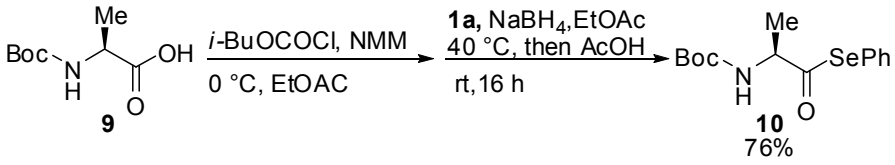
	7			8		
1	Fmoc-Gly-OH	**7a**	14	Fmoc-Gly-SePh	**8a**	72[b]
2	Fmoc-Ala-OH	**7b**	15	Fmoc-Ala-SePh	**8b**	84
3	Fmoc-Val-OH	**7c**	16	Fmoc-Val-SePh	**8c**	95
4	Fmoc-Leu-OH	**7d**	15	Fmoc-Leu-SePh	**8d**	94
5	Fmoc-Phe-OH	**7e**	14	Fmoc-Phe-SePh	**8e**	75[b]
6	Fmoc-Pro-OH	**7f**	15	Fmoc-Pro-SePh	**8f**	91
7	Fmoc-Met-OH	**7g**	16	Fmoc-Met-SePh	**8g**	86[b]
8	Fmoc-Trp-OH	**7h**	17	Fmoc-Trp-SePh	**8h**	85
9	Fmoc-Gln-OH	**7i**	16	Fmoc-Gln-SePh	**8i**	95[c]
10	Fmoc-Cys(Trt)-OH	**7j**	15	Fmoc-Cys(Trt)-SePh	**8j**	83[d]
11	Fmoc-Asp(O*t*Bu)-OH	**7k**	14	Fmoc-Asp(O*t*Bu)-SePh	**8k**	82[b]
12	Fmoc-Ser(O*t*Bu)-OH	**7l**	15	Fmoc-Ser(O*t*Bu)-SePh	**8l**	86
13	Fmoc-Lys(Boc)-OH	**7m**	15	Fmoc-Lys(Boc)-SePh	**8m**	86[b]
14	Fmoc-Tyr(O*t*Bu)-OH	**7n**	16	Fmoc-Tyr(O*t*Bu)-SePh	**8n**	79[b]

[a] Isolated yield. [b] A mixture of EtOAc/THF was employed to dissolve the *N*-Fmoc-L-amino acid. [c] A mixture of EtOAc/DMF was employed to dissolve the *N*-Fmoc-L-amino acid. [d] THF was employed to dissolve the *N*-Fmoc-L-amino acid.

Fourteen representative proteinogenic *N*-Fmoc-protected L-amino acids **7a-n**, also containing acid-labile protecting groups in the side-chain, were conveniently transformed into the corresponding crystalline phenyl selenoesters **8a-n** in 72%-95% ranging yield. The structures of known **8a-c** and **8f** were confirmed by spectroscopic data in agreement with those already reported.[7c] The ^{13}C NMR spectra of compounds **8a-n** showed the characteristic peak for the carbonyl carbon of the selenoester moiety around 195 ppm. Selenoesters from *N*-Fmoc(Pbf)-L-arginine and *N*-Fmoc(Trt)-hystidine were not obtained under our reaction conditions. Interesting is the successful preparation of selenoesters **8h** and **8i** from the unprotected *N*-Fmoc-L-tryptophan and *N*-Fmoc-L-glutamine, respectively. The experimental conditions of the new procedure were found to be highly compatible

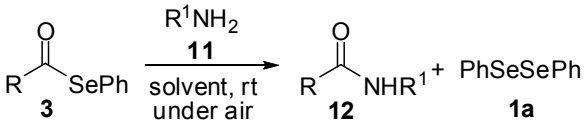
with acid-labile protections, as also proved by the transformation of *N*-Boc-L-alanine **9** into the known[21] selenoester **10** in a 76% yield (Scheme 3).

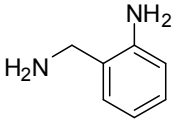
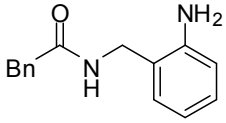
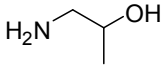
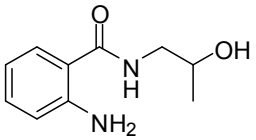
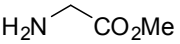
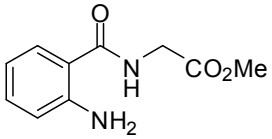
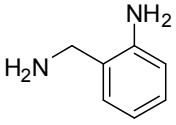
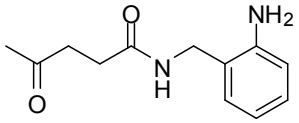
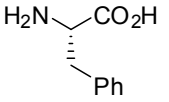
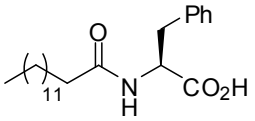
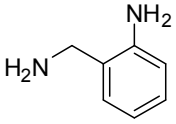
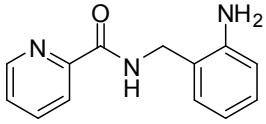
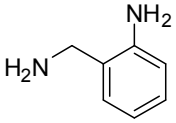
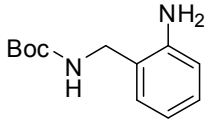
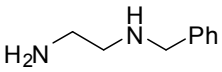
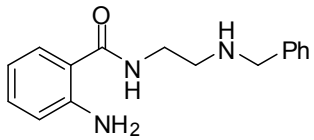
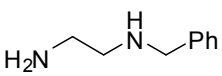
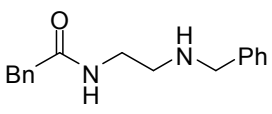
Scheme 3. Synthesis of acid-labile *N*-Boc-L-alanine selenoester 10

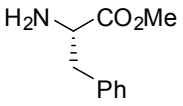
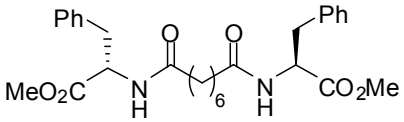


Acylation Reactions. In view of the weakness of the carbon-selenium bond, selenoesters are reactive intermediates which, after activation, can react with water or alcohols[3c] to give the corresponding carboxylic acids or esters, respectively. Furthermore, selenoesters undergo aminolysis much more rapidly[3d] than the thioacyl analogues as reported by Connors and Bender.[23] Despite the recent exploitations in selenoesters-based ligation approaches,[7] there are no reports on the regular use of selenoesters as acyl donors. Chemoselective acylation of amines is one of the most basic reactions for the protection or activation of amino groups in organic and pharmaceutical synthesis. A variety of reagents have been developed by devising a leaving group for the above purpose and continuing efforts have been made in order to create an ideally chemoselective reagent.[24] It is reasonably assumed that our protocol allows the synthesis of a variety of selenoesters which could successfully be employed as selective acylating agents under mild conditions. Thus, the acylation of various amines **11** with 10% excess of some selenoesters of the type **3** (Table 5) was carried out at room temperature and in different solvents to test the influence of the solvent too. The results obtained are summarized in Table 5. All examined selenoesters served as excellent *N*-acylating reagents of primary amines, amino alcohols, amino acids and amino esters.

Table 5. Acylation of amines and diamines with phenyl selenoesters 3



Entry	Selenoester[a]	Amine	t (h)	Solvent	Product	Yield (%)[b]
1	**3h**	 **11a**	2	MeCN	 **12a**	97[c]
2	**3g**	 **11b**	24	THF	 **12b**	84
3	**3g**	 **11c**	14	MeCN[d]	 **12c**	81
4	**3k**	 **11a**	3	MeCN	 **12d**	81
5	**3m**	 **11d**	24	EtOH[d]	 **12e**	85
6	**3u**	 **11a**	2	MeCN	 **12f**	96
7	**3f**	 **11a**	6	DMF	 **12g**	89[e]
8	**3g**	 **11e**	24	EtOH	 **12h**	94
9	**3h**	 **11e**	3	MeCN		92

					12i	
10	**3n**	 **11f**	5	DMF[d]	 **12j**	86[f]

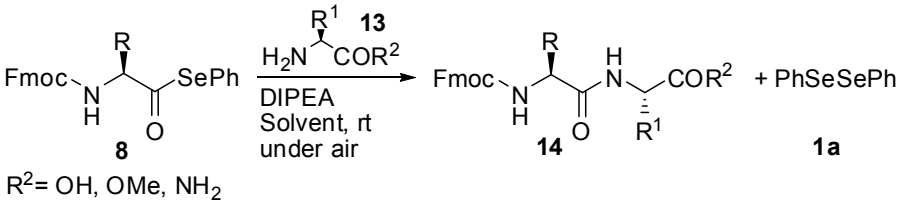
[a] A 10% mol excess of selenoesters was employed. [b] Yield of isolated product after chromatographic purification. [c] 92% yield in THF or EtOAc after 4 h. [d] DIPEA was added. [e] The same yield was obtained in MeCN. [f] An excess of aminoester was employed.

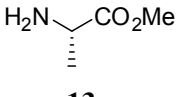
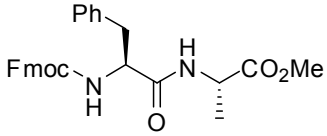
Reaction of selenoester **3h** with 2-aminobenzylamine **11a** in THF or EtOAC gave, after 4 h, the amide **12a** in 92% yield. Solvent replacement with MeCN or DMF decrease reaction time to 2h increasing the yield up to 97% with MeCN (Table 5, entry 1). Moreover, selenoesters can selectively acylate an aliphatic amine in the presence of an aromatic one (Table 5, entries 1, 4, 6 and 7). In a competitive acylation experiment of a 1:1 mixture of benzylamine and aniline with **3c** in THF, only the acylated product of benzylamine was detected by GC-MS. Noteworthy, aromatic amine such as aniline was not acylated even in DMF for two days. As depicted in Table 5, entry 2, when both hydroxy and amino groups are present in the substrate as in **11b**, acyltransfer only occurred at the amino group. This result was largely supported by the use of EtOH as a compatible solvent in acylation reactions (Table 5, entries 5 and 8). In a molecule with both primary- and secondary amino groups such as *N*-benzylethane-1,2-diamine **11e**, acyltransfer only occurred at the primary amino group (Table 5, entries 8 and 9). We observed that this peculiar difference in reactivity could be annulled by changing the solvent. Secondary amine such as piperidine was slowly acylated (16 h) with **3a** in 72% yield using DMF (see Figure S1, Supporting Information). We checked that the solvent properties manage the acylation control of selenocarbonate **3f** too. The *N*-Boc derivative **12g** was obtained when MeCN or DMF were used as reaction solvent (Table 6, entry 7). Notably, compounds **12b**, **12c** and **12h**, are anthranilamide derivatives which are found in numerous drugs and drug candidates,[25] whereas compounds **12f** and **12h** possessing three nitrogen atoms with different acid-base properties could be applied in chelation chemistry.[26] In order to evaluate their acyl-transfer potentiality, acylation of some amines with selenoesters **4** and **5** was

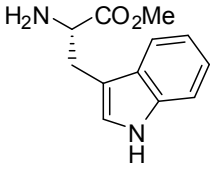
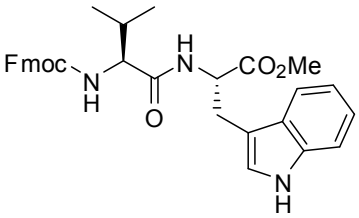
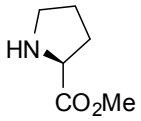
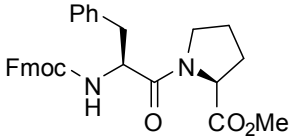
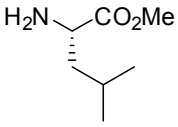
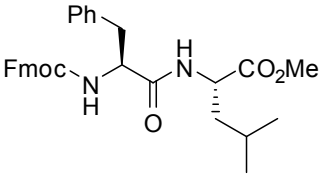
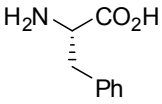
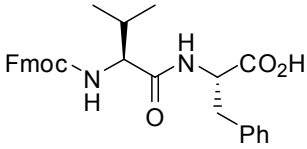
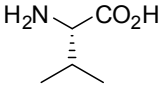
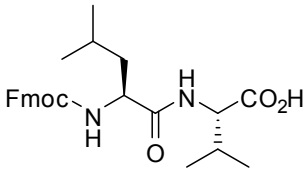
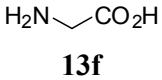
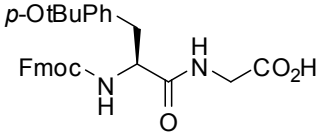
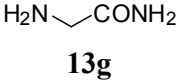
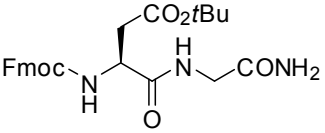
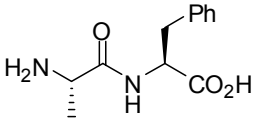
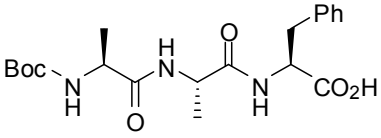
also examined. We did not observe any influence of chloro and methoxy substituents on the leaving group ability of the phenylseleno portion (see Figure S2, Supporting Information).

Based on these results, it seemed likely that selenoesters **8a-n** and **10** might also serve as convenient acylating species for the solution phase synthesis of oligopeptides. Despite its synthetic interest, the formation of amide bonds between amino acid-derived selenoester intermediates and protected or free *C*-terminal L-amino acids and peptides has been scarcely reported.[3b,3d,7c,21] Moreover, racemization of activated amino acids is a critical concern in peptide synthesis.[27] Previously, mixed anhydride as intermediate in peptide synthesis, was proposed by Vaughan.[28a] However, this approach suffer the drawback of lack of regioselectivity in the nucleophilic addition for one position over the second one, then, a lot of coupling agents were developed.[28b,c] Thus, we decided to study the preparation of some model dipeptides in order to evaluate the potential of selenoesters **8a-n** as stable reagents in peptide synthesis. Accordingly, when selenoesters **8c-e**, **8k** and **8n** were reacted with L-amino acid, ester or amide **13** in the proper solvent at room temperature various dipeptides **14** were produced (Table 6).

Table 6. Solution phase synthesis of peptides employing selenoesters 8 as neutral acylating agents



Entry	Selenoester	Amine	t (h) Solvent	Amide	Yield (%)[a]
1	**8e**	 **13a**	1 DMF[b]	 **14a**	90[c]

2	**8c**	 **13b**	20 DMF[b]	 **14b**	65[c]
3	**8e**	 **13c**	2 MeCN[b]	 **14c**	79[c]
4	**8e**	 **13d**	5 DMF[d]	 **14d**	90
5	**8c**	 **11d**	13 DMF[b]	 **14e**	79
6	**8d**	 **13e**	16 DMF[b]	 **14f**	96
7	**8n**	 **13f**	15 DMF[b]	 **14g**	78
8	**8k**	 **13g**	16 EtOH[e]	 **14h**	94
9	**10**	 **15**	6 MeCN[f]	 **16**	73

[a] Isolated yield. [b] 2 equiv. of amino ester or amino acid were employed. [c] The degree of racemization was determined by HPLC analysis (for details and chromatograms, see Supporting

Information). [d] 1.2 equiv. of amino ester was employed. [e] 1.4 equiv. of glycinamide was employed. [f] 1.4 equiv. of selenoester **10** was employed *vs* dipeptidyl acid **15**.

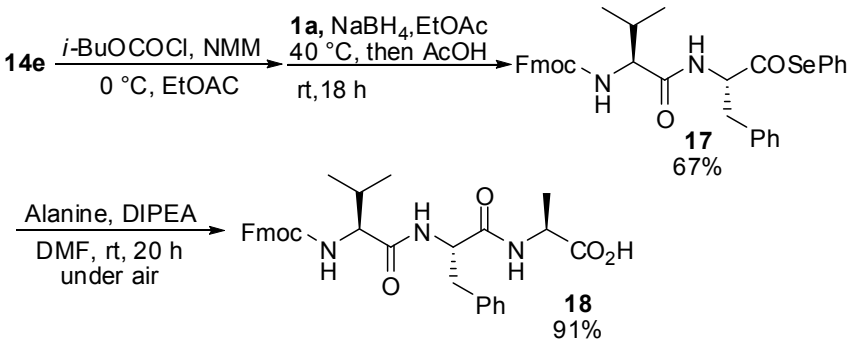
Selenoesters **8e** underwent complete conversion into dipeptide[27f] **14a** in 24 h with L-alanine methyl ester hydrochloride and DIPEA in THF. The same reaction carried out in EtOAc was complete in 16 h. To further accelerate the coupling, we changed the solvent from EtOAc to MeCN providing an additional boost (3 h) to the reaction time which, in DMF, was only 1 h (Table 6, entry 1). The HPLC analysis of the dipeptide ester **14a** synthesized in THF or in DMF showed practically the absence of racemization under the applied reaction conditions (d.r. = 99.5:0.5, Figure S4, Supporting Information). We also tested the coupling of selenoester **8c** with L-tryptophane methyl ester hydrochloride (Table 6, entry 2) in DMF because, as reported elsewhere,[27d] amide bond formation involving valine is relatively slow, thus producing mixtures of epimers. Notably, no epimerization was observed by HPLC and NMR analysis of the isolated dipeptide after 20 h reaction time (d.r. > 99.9:0.1, Figure S7, Supporting Information). The very low level of epimerization observed agreed the one recently reported for similar couplings.[7c] Moreover, the extent of epimerization was also measured for other difficult couplings,[27d] as in case of the reaction of **8e** with L-proline methyl ester hydrochloride in DMF. Although the reaction went to completeness in just 2 h, the expected dipeptide ester **14c** (Table 6, entry 3) was obtained with a minimum extent of racemization (d.r. = 98.3:1.7, Figure S10, Supporting Information). We also evaluated the configurational stability of a selenoesters as (*D*)-**8e** (see Supporting Information). As previously described, selenoesters undergo methanolysis in presence of anhydrous copper(II) chloride in MeCN at room temperature.[3d] HPLC analysis on chiral stationary phase was used to examine the enantiomeric ratio of *N*-Fmoc-D-phenylalanine methyl esters obtained by methanolysis of a sample of (D)-**8e** stored at room temperature for six months and the same compound obtained from a sample of (D)-**8e** stored at 0 °C for an identical period of time. Chromatograms showed the absence of racemization in both cases, and the measured e.r. was

comparable to the one of a *N*-Fmoc-D-phenylalanine methyl ester sample (e.r. > 99.9:0.1) obtained from freshly prepared (D)-**8e** (Figures S14, S17, and S18, Supporting Information).

Further, we successfully synthesized the *N*-Fmoc-dipeptidyl ester as **14d** (Table 6, entry 4) and the series of *N*-Fmoc-dipeptidyl acids **14e-g** (Table 6, entries 5-7,), as well as the *N*-Boc-tripeptidyl acid **16** (Table 6, entry 9), by reacting selenoesters **8c-e** and **8n** with the corresponding amino ester, amino acids or dipeptidyl acid, respectively. As expected, reaction of selenoester **8k** with an excess of glycinamide hydrochloride **13g** and DIPEA in EtOH gave the *N*-Fmoc-dipeptidyl amide **14h** in excellent yield. Under the usual experimental conditions, the homogeneous phase coupling reactions occurred without detectable epimerization as observed by ^{1}H and ^{13}C NMR spectra.

In addition, we next checked whether this protocol could be extended to longer peptides. As a proof of concept, a tripeptide synthesis was performed in the N→C direction. Accordingly, *N*-Fmoc-dipeptidyl acid **14e** (Scheme 4) was transformed into the corresponding selenoester **17** which was easily coupled to L-alanine in DMF at room temperature to prepare the *N*-Fmoc-protected tripeptide **18** in excellent yield.

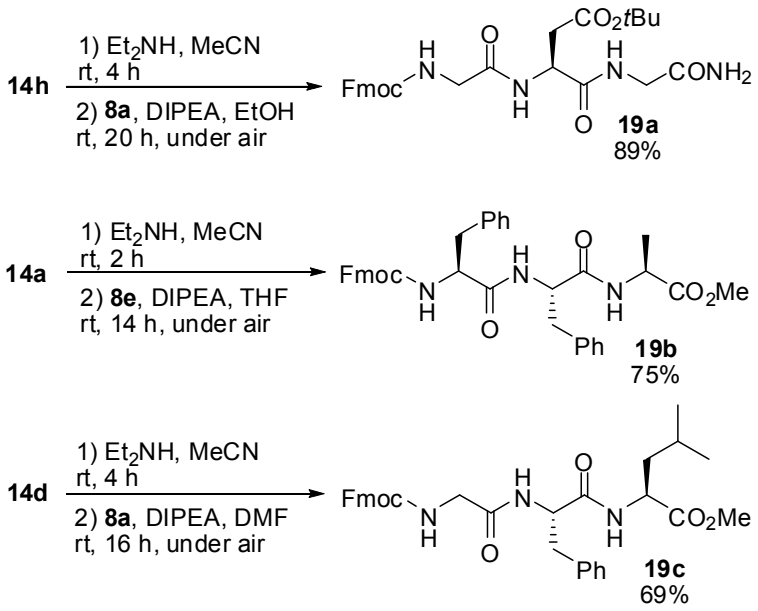
Scheme 4. N→C solution phase synthesis of tripeptide 18 using selenoester as reactive intermediate



The potential application of our protocol for the solution synthesis of *N*-Fmoc-tripeptides via C→N route was investigated. A linear approach was selected for the preparation of Fmoc-tripeptide esters **19b**, **19c** and amide **19a** (Scheme 5). Thus, chain extension from *N*-terminus of Fmoc protected

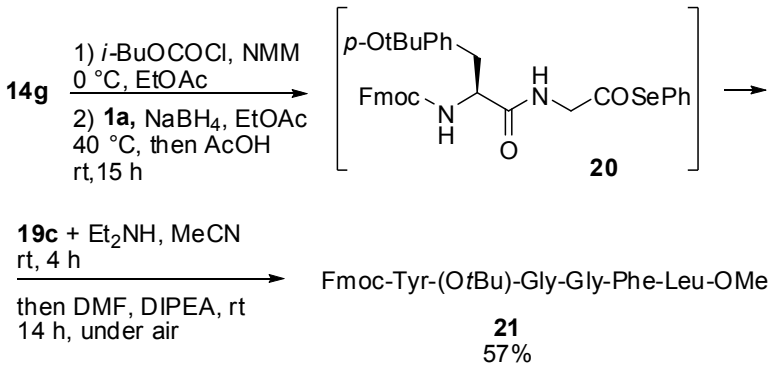
dipeptides **14a**, **14d** and **14h** leading to tripeptides was undertaken. Selective removal of Fmoc-protecting group with diethylamine in MeCN at room temperature gave the free amino dipeptide intermediate which was immediately reacted with an excess of selenoesters **8a** and **8e** to furnish the protected tripeptides **19a-c** in good global yields.

Scheme 5. C→N solution phase synthesis of tripeptides using selenoesters as neutral acylating agents



Finally, in an effort to apply our protocol to the convergent synthesis of fully protected Leu-enkephalin[29] pentapeptide **21**, we studied the coupling of two fragments. The key step was the preparation and the coupling of crude *N*-Fmoc-dipeptidyl selenophenyl ester intermediate **20** with the unprotected tripeptide intermediate obtained from **19c** (Scheme 6). Thus, *N*-Fmoc-dipeptide **14g** (Table 6) was converted, as for **14e** (Scheme 4), into the corresponding selenoester **20** which was directly employed for the successive reaction without purification. Removal of the Fmoc protecting group from **19c** furnished the corresponding free tripeptide intermediate which was reacted with a slight excess of crude selenoester **20**. The fully protected Leu-enkephalin **21** was obtained in 57% global yield after purification and its structure was confirmed by MALDI -MS/MS analysis (Figure S20, Supporting Information).

Scheme 6. Synthesis of pentapeptide 21 by 2+3 fragment condensation strategy using selenoester as active intermediate



CONCLUSIONS

In summary, herein we proposed a mild and easy procedure for the preparation of phenyl selenoesters from anhydrides. The novelty of this protocol is mainly related to the use of EtOAc as solvent and to the simplicity of the procedure that prevents the typical drawbacks of using volatile benzeneselenol or transition metals. Phenyl selenoesters were tested as stable, mild and completely chemoselective reagents in a series of acylation processes conducted under air, in which diphenyl diselenide is the exclusive byproduct. The present protocol was extensively and successfully applied to *N*-Fmoc-L-amino acids as substrates and the phenyl selenoesters obtained were utilized as neutral acylating agents for the synthesis of dipeptide esters and acids. In this study, preliminary investigations on the susceptibility to racemization were carried out; the results obtained allowed us to synthesize tripeptides and the fully protected Leu-enkephalin pentapeptide. Thus, this procedure represents a further valuable tool for the construction of the peptide bond. The extension of this strategy to the synthesis of longer peptide targets and to solid-phase peptide synthesis is currently under investigation.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reactions were carried out using bench solvents. All chemicals were of reagent grade and were used without further purification. All air sensitive reactions were carried out under argon atmosphere. Chromatography was performed on silica gel (Merck 60, 70-230 mesh), and analytical TLC was carried out on pre-coated silica gel plates (Merck 60 F254, 0.25 mm) using UV light and 0.5% w/v potassium permanganate aqueous solution(followed by gentle heating) for visualization. Melting points were measured on a hot plate apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 200 and 400 MHz. Carbon magnetic resonance (^{13}C NMR) spectra were recorded at 50 and 100 MHz. Unless otherwise specified $CDCl_3$ was used as solvent and chemical shifts (δ) are reported in parts per million (ppm). The NMR spectra were calibrated using the proton or carbon signals of residual, non-deuterated solvents peak: δ_H 7.27 and δ_C77.0 for $CDCl_3$, δ_H 2.50 and δ_C 39.5 for $(CD_3)_2SO$. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broadened), coupling constants, number of protons, assignments (where possible). Coupling constant (*J*) are quoted in Hertz (Hz) to the nearest 0.1 Hz. Infrared (IR) spectra were recorded on a diffuse reflectance sampling cell. Only significant absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). GC-MS analysis were obtained with a gas chromatograph (HP-5MS capillary column 29.0 m, ID 0.25, film 0.25 μm) equipped with a mass selective detector at an ionizing voltage of 70 eV; for the ions containing selenium only the peaks arising from selenium-80 isotope are given. Optical rotations were measured in a 50 mm cell using the D-line of sodium at the specified temperature. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (*c*) are quoted in g 100 mL^{-1}. HPLC analysis were performed on a HPLC system equipped with a UV/Vis detector with chiral columns and solvents specified. All chromatograms were run at 25 °C. Combustion analyses were carried out on an elemental analyzer. HRMS analyses were performed using a MALDI-TOF-TOF analyzer equipped with an Nd:YLF Laser with λ = 345-nm wavelength of <500 ps pulse length and p to 1000 Hz repetition rate, in reflectron positive mode with a mass accuracy of 3 ppm.

The diselenides **1b** and **1c** were prepared as described in literature.[30] Acid **6e** was synthesized as previously reported.[31] LL-Alanyl-phenylalanine **15** is previously known and commercially available.[32]

General Procedure for the Synthesis of Selenoesters 3a-g from Anhydrides. Diphenyl diselenide (0.32 g, 1 mmol) and sodium borohydride (76 mg, 2.0 mmol) were placed in an oven-dried round-bottom flask under argon flow. EtOAc (10 mL) was added to the content of the flask and the mixture was heated at 40 °C for 30-40 min yielding a white mixture after cooling to room temperature. Glacial acetic acid (0.58 mL, 10 mmol) was added (caution, gas evolved) at room temperature and after 30 min the resulting mixture was treated with 2.1 mmol of anhydride. The progress of the reaction was monitored by TLC (5-24 h). After addition of water (10 mL) the mixture was extracted with three 30 mL portions of EtOAc. The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtrated and concentrated *in vacuo.* The residue was purified by column chromatography on silica as specified below.

Se-Phenyl benzenecarboselenoate (**3a**)**:** According to general procedure the title compound was obtained (0.50 g, 94% yield) using a diethyl ether-hexane mixture (2:98) as eluent. Spectral data were in accordance with the literature.[2a]

Se-Phenyl 2-methyl-6-nitrobenzenecarboselenoate (**3b**)**:** According to general procedure **t**he crude selenoester was purified by chromatography using an ethyl acetate-hexane mixture (1:9) as eluent to give **3b** (0.54 g, 84% yield): light yellow solid; mp 84–86 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.61-7.52 (m, 3H), 7.46 (d, J = 8.0 Hz, 1H), 7.42-7.33 (m, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 144.7, 136.5, 135.9 (2C), 135.6, 130.2, 129.5 (2C), 129.4, 129.0, 125.9, 121.9, 18.8; FTIR 3073, 1738, 1704, 1424, 1190, 865, 738 cm^{-1}; Anal. Calcd for $C_{14}H_{11}NO_3Se$: C, 52.51; H, 3.46; N, 4.37. Found: C, 52.33; H, 3.84; N, 4.15.

Se-Phenyl ethaneselenoate (**3c**)**:** According to general procedure the title compound was obtained (0.36 g, 90% yield) using a diethyl ether-hexane mixture (4:96) as eluent. Spectral data were in accordance with the literature.[33]

Se-Phenyl propaneselenoate (**3d**)**:** According to general procedure the title compound was obtained (0.30 g, 88% yield) using a diethyl ether-hexane mixture (2:98) as eluent. Spectral data were in accordance with the literature.[12c]

Se-Phenyl 2,2-dimethylpropaneselenoate (**3e**)**:** According to general procedure the title compound was obtained (0.43 g, 89% yield) using a diethyl ether-hexane mixture(2:98) as eluent. Spectral data were in accordance with the literature.[34]

O-(tert-Butyl) Se-phenyl selenocarbonate (**3f**)**:** No acetic acid was added after reduction of diphenyl diselenide with sodium borohydride. The product was purified by chromatography using a diethyl ether-hexane mixture(1:99) as eluent to give **3f** (0.48 g, 92%) as a light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72-7.62 (m, 2H), 7.48-7.35 (m, 3H), 1.59 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.7, 135.6 (2C), 129.0, (2C), 128.7, 126.7, 86.2, 28.1 (3C); FTIR 2980, 1728, 1370, 1105, 830, 740 cm^{-1}; EIMS (70 eV) *m/z* $[M - 44]^+$ 214 (2), 157 (42), 77 (30), 57 (100), 51 (16). Anal**.** Calcd for $C_{11}H_{14}O_2Se$: C, 51.37; H, 5.49. Found: C, 51.19; H, 5.79.

Se-Phenyl 2-aminobenzenecarboselenoate (**3g**)**:** According to general procedure **t**he organic phase was concentrated to give a solid residue which was triturated with hexane (2x30 ml) to afford **3f** (0.41 g, 74%): white solid; mp = 123-125 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.3, 1.4 Hz, 1H), 7.68-7.56 (m, 2H), 7.53-7.38 (m, 3H), 7.32 (ddd, J = 8.4, 8.3, 1.4 Hz, 1H), 6.75 (ddd, J = 8.4, 8.3, 1.1 Hz, 1H), 6.66 (dd, J = 8.3, 1.1Hz, 1H), 5.60 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 147.4, 136.8 (2C), 134.8, 131.2, 129.2 (2C), 129.0, 126.3, 119.4, 117.1, 116.7; FTIR 3463, 3360, 1764, 1617, 1481, 1202, 889, 748 cm^{-1}; EIMS (70 eV) *m/z* M^+ 277 (5), 120 (100), 157 (8), 92 (75), 77 (12), 65 (62). Anal**.** Calcd for $C_{13}H_{11}NOSe$: C, 56.53; H, 4.01; N, 5.07. Found: C, 56.44; H, 4.35; N, 5.13.

Preparation of Selenoesters 4 and 5. 1,2-bis(4-Methoxyphenyl)diselenide **1b** (0.15 g, 0.40 mmol) and sodium borohydride (31 mg, 0.8 mmol) were placed in an oven-dried round-bottom flask under argon flow. EtOAc (6 mL) was added to the contents of the flask and the mixture was heated at 40 °C for 30-40 min yielding a white mixture after cooling to room temperature. Glacial acetic acid (0.23 mL, 4 mmol) was added (caution, gas evolved) at room temperature and after 30 min the resulting mixture was treated with benzoic anhydride (0.18 g, 0.82 mmol). After the reaction was complete (15 h) water (10 mL) was added and the mixture extracted with three 20 mL portions of EtOAc. The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtrated and concentrated *in vacuo.* Purification of the residue by column chromatography on silica gel using a diethyl ether-hexane mixture (8:92) as eluent gave *Se-(4-methoxyphenyl) benzenecarboselenoate* (**4**) (0.20 g, 86% yield). Spectral data were in accordance with the literature.[35]

In an oven-dried round-bottom flask, 1,2-bis (2-Chlorophenyl)diselenide **1c** (0.30 g, 0.79 mmol) and sodium borohydride (60 mg, 1.6 mmol) were placed under argon flow. EtOAc (8 mL) was added to the contents of the flask and the mixture was heated at 40 °C for 30-40 min yielding a white mixture after cooling to room temperature. Glacial acetic acid (0.46 mL, 8 mmol) was added (caution, gas evolved) at room temperature and after 30 min the resulting mixture was treated with acetic anhydride (0.15 mL, 1.66 mmol). After the reaction was complete (20 h) water(10 mL) was

added and the mixture extracted with three 20 mL portions of EtOAc. The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtrated and concentrated *in vacuo.* After purification by column chromatography on silica gel using a diethyl ether-hexane mixture (2:98) as eluent *Se-(2-chlorophenyl) ethaneselenoate* (**5**) was obtained as a colorless oil (0.31 g, 82% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.4, 2.0 Hz, 1H), 7.53 (dd, J = 7.6, 1.6 Hz, 1H), 7.36 (dt, J = 7.6, 2.0 Hz, 1H), 7.27 (ddd, J = 7.6, 7.4, 1.6Hz, 1H), 2.5 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.6, 138.2, 138.0, 130.6 (2C), 129.8, 127.2, 33.8; FTIR 3060, 1731, 1450, 1096, 752 cm^{-1}; EIMS (70 eV) *m/z* M^+ 234 (67), 192 (96), 156 (100), 129 (13), 112 (50), 75 (40), 50 (23). Anal. Calcd for C_8H_7ClOSe: C, 41.14; H, 3.02; Found: C, 40.83; H, 3.35.

General Procedure for the Synthesis of Selenoesters 3h-v from Acids. To a solution of acid **6** (2.2 mmol) in EtOAc (10 mL) at 0 °C *N*-methylmorpholine (NMM 0.24 mL, 2.2 mmol) and isobutyl chloroformate (0.28 ml, 2.2 mmol) were added. The reaction mixture was stirred at 0 °C for 40 min under argon atmosphere. Then, a fresh solution of nucleophilic selenium species, prepared as described above by means of reaction of diphenyl diselenide (0.32 g, 1 mmol) and sodium borohydride (76 mg, 2.0 mmol) in EtOAc (10 mL) at 40 °C an successive addition of glacial acetic acid (0.58 mL, 10 mmol) at room temperature, was added directly in one portion through a syringe allowing to reach room temperature gradually. The stirring was continued till the completion of the reaction (13-16 h). The mixture was then poured into water (20 mL) and extracted with EtOAc (3 x 30 mL). The organic layer was washed with brine (10 mL), dried over sodium sulfate and evaporated. The reaction product was purified by column chromatography on silica gel.

Se-Phenyl phenylethaneselenoate (**3h**)**:** According to general procedure the title compound was obtained (0.45 g, 82% yield) using a diethyl ether-hexane mixture (2:98) as eluent. Spectral data were in accordance with the literature.[17a]

Se-Phenyl hept-6-yneselenoate (**3i**)**:** According to general procedure **t**he crude selenoester was purified by chromatography using a diethyl ether-hexane mixture (4:96) as eluent to give **3i** (0.40 g, 75%) as a light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60-7.46 (m, 2H), 7.45-7.30 (m, 3H), 2.75 (t, J = 7.0 Hz, 1H), 2.25 (dt, J = 7.0, 2.6 Hz, 2H), 1.80 (t, J = 2.6 Hz, 2H), 1.90-1.75 (m, 2H), 1.67-1.50 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.1, 135.8 (2C), 129.3 (2C), 128.9, 126.3, 83.6, 68.8, 46.8, 27.4, 24.3, 18.1; FTIR 3290, 2927, 1718, 1438, 956, 739 cm^{-1}; EIMS (70 eV) *m/z* M^+ 266 (3), 157 (25), 109 (69), 81 (100), 79 (72), 53 (37). Anal. Calcd for $C_{13}H_{14}OSe$: C, 58.87; H, 5.32. Found: C, 58.65; H, 5.66.

Se-Phenyl (2E,4E)-hexa-2,4-dieneselenoate (**3j**)**:** According to general procedure the residue was purified by chromatography using a diethyl ether-hexane mixture (4:96) as eluent to give **3j**

(0.37 g, 74% yield) as a light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65-7.50 (m, 2H), 7.48-7.26 (m, 3H), 7.20 (dd, J = 14.3, 9.4 Hz, 1H), 6.36-6.08 (m, 3H), 1.88 (d, J = 5.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.7, 142.3, 141.7, 135.8 (2C), 129.6, 129.2 (2C), 128.8, 127.2, 125.3, 19.0; FTIR 3025, 1689, 1635, 1590, 1438, 1322, 1114, 1008, 776, 738 cm^{-1}; EIMS (70 eV) *m/z* $[M-95]^+$ 157 (10), 95 (100), 77 (10), 67 (38). Anal. Calcd for $C_{12}H_{12}OSe$: C, 57.38; H, 4.82. Found: C, 57.19; H, 5.09.

Se-Phenyl 4-oxopentaneselenoate (**3k**)**:** According to general procedure crude selenoester was purified by chromatography using an ethyl acetate-hexane mixture (1:9) as eluent to give **3k** (0.32 g, 62% yield) as an oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58-7.48 (m, 2H), 7.44-7.30 (m, 3H), 2.99 (t, J = 6.2 Hz, 2H), 2.76 (t, J = 6.2 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.7, 199.3, 135.8 (2C), 129.3 (2C), 128.9, 126.0, 41.0, 37.7, 29.7; FTIR 3419, 3059, 1716, 1367, 1065, 848, 741 cm^{-1};EIMS (70 eV) *m/z* M^+ 256 (1), 157 (15), 99 (100), 77 (16), 71 (16). Anal. Calcd for $C_{11}H_{12}O_2Se$: C, 51.78; H, 4.74. Found: C, 51.57; H, 4.99.

Se-Phenyl 3-(phenylseleno)propaneselenoate **(3l):** Reaction was carried out with 0.6 equiv of diphenyl diselenide, 1.0 equiv of 3-(phenylseleno)propanoic acid **6e** and 1.1 equiv of isobutyl chloroformate. The product was purified by chromatography using a diethyl ether-hexane mixture (2:98) as eluent to give **3l** (0.31 g, 82% yield) as a light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62-7.48 (m, 4H), 7.42-7.28 (m, 6H), 3.21-3.02 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.1, 135.7 (2C), 133.3 (2C), 129.4 (2C), 129.2 (2C), 129.0, 128.8, 127.5, 126.0, 47.9, 21.3; FTIR 3419, 3059, 1716, 1367, 1065, 848, 741 cm^{-1}. Anal. Calcd for $C_{15}H_{14}OSe_2$: C, 48.93; H, 3.83. Found: C, 48.65; H, 4.17.

Se-Phenyl tetradecaneselenoate (**3m**)**:** Reaction was carried out with 0.6 equiv of diphenyl diselenide, 1.0 equiv of myristic acid **6f** and 1.1 equiv of isobutyl chloroformate and NMM. The product was purified by chromatography using a diethyl ether-hexane mixture (2:98) as eluent to give **3m** (0.34 g, 91% yield) as a light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60-7.45 (m, 2H), 7.43-7.30 (m, 3H), 2.71 (t, J = 7.3 Hz, 2H), 1.79-1.60 (m, 2H), 1.43-1.20 (m, 20H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.4, 135.7 (2C), 129.3 (2C), 128.8, 126.5, 47.5, 31.9, 26.6 (2C), 29.3 (3C), 29.2 (2C), 28.8, 25.4, 22.7, 14.1; FTIR 2924, 2854, 1725, 735 cm^{-1}; EIMS (70 eV) *m/z* M^+ 368 (1), 211 (100), 157 (30), 109 (20), 85 (35), 57 (53). Anal. Calcd for $C_{20}H_{32}OSe$: C, 65.38; H, 8.78. Found: C, 65.30; H, 9.09.

Se^1,Se^8-Diphenyl octanebis(selenoate*)* (**3n**)**:** Reaction was carried out with 1.2 equiv of diphenyl diselenide, 1.0 equiv of suberic acid **6g** and 2.2 equiv of isobutyl chloroformate and NMM. The product was purified by chromatography using a diethyl ether-hexane mixture (5:95) as eluent to give **3n** (0.36 g, 79% yield): light yellow solid; mp = 47-48 ºC. ^{1}H NMR (200 MHz,

$CDCl_3$) δ 7.60-7.47 (m, 4H), 7.45-7.32 (m, 6H), 2.72 (t, J = 7.2 Hz, 4H), 1.80-1.62 (m, 4H), 1.48-1.32 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.2 (2C), 153.7 (4C),.129.3 (4C), 128.8 (2C), 126.3 (2C), 47.2 (2C), 28.3 (2C), 25.0 (2C); FTIR 3419, 3055, 2937, 1718, 1438, 953, 742 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_2Se_2$: C, 53.11; H, 4.90. Found: C, 52.86; H, 5.15.

Se-Phenyl 5-oxopyrrolidine-2-carboselenoate (**3o**)**:** According to general procedure the product was purified by chromatography using an ethyl acetate-hexane mixture (4:6) as eluent to give **3o** (0.33 g, 61% yield): white solid; mp = 93–95 ºC; $[\alpha]^{20}_D$ -121.72 (*c* 0.66, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.54-7.28 (m, 5H), 4.42-4.25 (m, 1H), 2.72-2.20 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.5, 179.8, 135.8 (2C), 129,3 (2C), 129.0, 125.2, 65.1, 28.7, 25.5; FTIR 3244, 1725, 1670, 1273, 992, 880, 741 cm^{-1}; EIMS (70 eV) *m/z* $[M - 14]^+$ 245 (10) 241 (68), 204 (40), 157 (100), 126 (81), 84 (21), 51 (40). Anal. Calcd for $C_{11}H_{11}NO_2Se$: C, 49.27; H, 4.13; N, 5.22. Found: C, 49.01; H, 4.39; N, 5.15.

Se-Phenyl 2-chlorobenzenecarboselenoate (**3p**)**:** According to general procedure the title compound was obtained (0.44 g, 75% yield) using a diethyl ether-hexane mixture (2:98) as eluent. Spectral data were in accordance with the literature.[12f]

Se-Phenyl 4-methoxybenzenecarboselenoate (**3q**)**:** According to general procedure the title compound was obtained (0.41 g, 70% yield) using a diethyl ether-hexane mixture (5:95) as eluent. Spectral data were in accordance with the literature.[2a]

Se-Phenyl (2E)-3-phenylprop-2-eneselenoate (**3r**)**:** According to general procedure the title compound was obtained (0.51 g, 80% yield) using a diethyl ether-hexane mixture (4:96) as eluent. Spectral data were in accordance with the literature.[14]

Se-Phenyl furan-2-carboselenoate (**3s**)**:** According to general procedure the title compound was obtained (0.40 g, 79% yield) using a diethyl ether-hexane mixture (1:9) as eluent. Spectral data were in accordance with the literature.[16a]

Se-Phenyl thiophene-2-carboselenoate (**3t**)**:** According to general procedure the title compound was obtained (0.42 g, 77% yield) using a diethyl ether-hexane mixture (4:96) as eluent. Spectral data were in accordance with the literature.[19]

Se-Phenyl pyridine-2-carboselenoate (**3u**)**:** According to general procedure the crude selenoester was purified by chromatography using an ethyl acetate-hexane mixture (2:8) as eluent to give **3u** (0.43 g, 80% yield): white solid; mp = 103–105 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (dt, J = 4.7, 1.4 Hz, 1H), 7.89-7.83 (m, 2H), 7.69-7.50 (m, 3H), 7.49-7.34 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 152.6, 149.3, 137.5, 136.2 (2C), 129.2 (2C), 128.8, 128.3, 126.7, 119.3; FTIR 3055, 1778, 1690, 1434, 1213, 995, 892, 790 cm^{-1}; EIMS (70 eV) *m/z* M^+ 263 (15), 234 (12), 155 (63),

106 (66), 78 (100), 51 (23). Anal. Calcd for $C_{12}H_9NOSe$: C, 54.98; H, 3.46; N, 5.34. Found: C, 54.84; H, 3.81; N, 5.25.

Se-Phenyl quinoline-4-carboselenoate (**3v**)**:** According to general procedure the crude product was purified by chromatography using an ethyl acetate-hexane mixture (2:8) as eluent to give **3v** (0.48 g, 76% yield): light yellow solid; mp = 73–75 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.08 (d, J = 4.5 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 4.5 Hz, 1H), 7.81 (t, J = 8.4 Hz, 1H), 7.71-7.60 (m, 3H), 7.54-7.43 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 195.2, 149.6, 148.7, 143.6, 135.9 (2C), 130.4, 129.7 (2C), 129.6, 129.5, 128.7, 126.1, 124.9, 121.9, 119.2; FTIR 3069, 1699, 1502, 1222, 1049, 892, 739 cm^{-1}; EIMS *m/z* M^+ 313 (4), 156 (100), 128 (87), 101 (47), 75 (23). Anal. Calcd for $C_{16}H_{11}NOSe$: C, 61.55; H, 3.55; N, 4.49. Found: C, 61.40; H, 3.75; N, 4.35.

Typical Procedure for the Synthesis of Selenoesters from *N*-Fmoc-L-amino Acids 8a-n. To a solution of *N*-Fmoc-L-amino acid **7** (2.0 mmol) in EtOAc (16 mL) at 0 °C *N*-methylmorpholine (NMM 0.24 mL, 2.2 mmol) and isobutyl chloroformate (0.28 ml, 2.2 mmol) were added. A mixture of EtOAc/THF (1:1) was employed to dissolve *N*-Fmoc-L-Gly-OH, *N*-Fmoc-L-Phe-OH, *N*-Fmoc-L-Asp(O*t*Bu)-OH, *N*-Fmoc-L-Met-OH, *N*-Fmoc-L-Lys(Boc)-OH, and *N*-Fmoc-L-Tyr(O*t*Bu)-OH whereas *N*-Fmoc-L-Gln-OH was dissolved in a mixture of EtOAc/DMF (2:1) and *N*-Fmoc-L-Cys(Trt)-OH in THF. The reaction mixture was stirred at 0 ºC for 40 min under argon atmosphere. Then, a fresh solution of nucleophilic selenium species, prepared as described above by means of reaction of diphenyl diselenide (0.38 g, 1.2 mmol) and sodium borohydride (92 mg, 2.4 mmol) in EtOAc (10 mL) at 40 °C an successive addition of glacial acetic acid (0.68 mL, 12 mmol) at room temperature, was added directly in one portion through a syringe. After the addition, the cloudy mixture was allowed to reach room temperature gradually. The stirring continued till reaction completion (14-17 h). The mixture was then poured into water (20 mL) and extracted with EtOAc (3 x 30 mL). The organic layer was washed with brine (10 mL), dried over sodium sulfate and evaporated. The reaction product was purified by column chromatography on silica gel or the solid residue was triturated with hexane or diethyl ether and filtrated to afford the pure crystalline product (^{1}H and ^{13}C NMR).

Se-Phenyl {[(9H-fluoren-9-ylmethoxy)carbonyl]amino}ethaneselenoate (**8a**)**:** According to general procedure the title compound was obtained as a white solid (0.63 g, 72% yield) after column chromatography with dichloromethane as eluent: mp = 133–135 ºC. Spectra matches previously reported data.[7c]

Se-Phenyl (2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}propaneselenoate (**8b**)**:** According to general procedure the residue was purified by chromatography using dichloromethane

as eluent the give **8b** (0.76 g, 84%) yield as a white solid: mp = 163–165 ºC; $[\alpha]^{24}_{D}$ -11.37 (*c* 0.52, $CHCl_3$). Spectra matches previously reported data.[7c]

Se-Phenyl (2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-3-methylbutaneselenoate (**8c**)**:** According to general procedure the title compound was obtained as a white solid (0.90 g, 92% yield) using a hexane-dichloromethane mixture (1:1) as eluent: mp = 140–142 ºC; $[\alpha]^{24}_{D}$ -41.33 (*c* 0.58, $CHCl_3$). Spectra matches previously reported data.[7c]

Se-Phenyl (2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-methylpentaneselenoate (**8d**)**:** According to general procedure the organic solvent was removed to dryness and the residue was triturated with hexane (2x20 ml). The solid was filtered to afford **8d** (0.93 g, 94% yield): white solid; mp = 133–135 ºC; $[\alpha]^{20}_{D}$ -35.20 (*c* 0.70, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (d, J = 7.0 Hz, 2H), 7.70-7.56 (m, 2H), 7.52-7.28 (m, 9H), 5.12 (d, J = 9.1 Hz, 1H), 4.67 (dd, J = 10.6, 4.3 Hz, 1H), 4.57-4.41 (m, 2H), 4.28 (t, J = 6.8 Hz, 1H), 1.82-1.43 (m, 3H), 0.97 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.1, 155.9, 143.7, 143.5, 141.3 (2C), 136.0 (2C), 129.3 (2C), 128.9, 127.7 (2C), 127.1 (2C), 125.8, 124.9 (2C), 120.2 (2C), 67.0, 62.3, 47.2, 40.8, 24.6, 23.0, 21.3; FTIR 3332, 2947, 1730, 1681, 1530, 1235, 1028, 737 cm^{-1}. Anal. Calcd for $C_{27}H_{27}NO_3Se$: C, 65.85; H, 5.53; N, 2.84. Found: C, 65.68; H, 5.89; N, 2.75.

Se-Phenyl (2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-3-phenylpropaneselenoate (**8e**)**:** According to general procedure the organic solvent was removed to dryness and the residue was triturated with hexane (2x30 ml). The solid was filtered to afford **8e** (0.98 g, 93% Yield): light yellow solid; mp = 170–172 ºC; $[\alpha]^{22}_{D}$ -86.74 (*c* 0.56, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 7.79 (d, J = 7.2 Hz, 2H), 7.69-7.25 (m, 14H), 7.24-7.11 (m, 2H), 5.18 (d, J = 9.4 Hz, 1H), 4.84-4.70 (m, 1H), 4.57-4.36 (m, 2H), 4.24 (t, J = 6.6 Hz, 1H), 3.29-3.00 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.4, 155.7, 143.5 (2C), 141.2 (2C), 135.9 (2C), 135.1, 129.4 (2C), 129.3 (2C), 129.0, 128.8 (2C), 127.7 (2C), 127.3, 127.0 (2C), 125.7, 125.0 (2C), 120.0 (2C), 67.2, 64.0, 47.0, 37.5; FTIR 3342, 3065, 1720, 1695, 1528, 1248, 1045, 735 cm^{-1}. Anal. Calcd for $C_{30}H_{25}NO_3Se$: C, 68.44; H, 4.79; N, 2.66. Found: C, 68.19; H, 5.05; N, 2.56.

9H-Fluoren-9-ylmethyl (2S)-2-[(phenylseleno)carbonyl]pyrrolidine-1-carboxylate (**8f**)**:** According to general procedure the residue was purified by chromatography using dichloromethane as eluent to give **8f** (0.87 g, 91% yield); waxy solid, mp = 37–40 ºC; $[\alpha]^{22}_{D}$ -87.41 (*c* 0.83, $CHCl_3$); Spectral data were in accordance with the literature.[7c]

Se-phenyl (2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-(methylthio)butaneselenoate (**8g**)**:** According to general procedure the title compound was obtained as pale yellow solid (0.88 g, 86% yield) after column chromatography with dichloromethane as eluent: mp = 115–117 ºC; $[\alpha]^{24}_{D}$ -35.78 (*c* 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 2H), 7.73-7.61 (m, 2H),

7.55-7.48 (m, 1H), 7.47-7.37 (m, 6H), 7.36 (t, J = 7.6 Hz, 2H), 5.63 (d, J = 8.8 Hz, 1H), 4.71-4.41 (m, 3H), 4.32 (t, J = 6.6 Hz, 1H), 2.68-2.49 (m, 2H), 2.31-2.19 (m, 1H), 2.12 (s, 3H), 2.03-1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203. 3, 155.9, 143.7, 143.5, 141.3 (2C), 135.9 (2C), 129.3 (2C), 129.0 (2C), 127.7 (2C), 127.1, 125.6, 124.9 (2C), 120.0 (2C), 67.1, 62.9, 47.2, 31.0, 29.9, 15.3; FTIR 3286, 2915, 1708, 1690, 1532, 1255, 1053, 740 cm^{-1}. Anal. Calcd for $C_{26}H_{25}NO_3SSe$: C, 61.17; H, 4.94; N, 2.74. Found: C, 60.98; H, 5.19; N, 2.66.

Se-Phenyl (2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-3-(1H-indol-3-yl)propaneselenoate (**8h**)**:** According to general procedure the title compound was obtained (0.96 g, 85% yield) after chromatography using dichloromethane as eluent: white solid; mp = 180–183 ºC; $[\alpha]^{24}{}_D$ -97.92 (*c* 0.39, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.78 (d, J = 7.3 Hz, 2H), 7.58 (t, J = 7.4 Hz, 2H), 7.49-7.12 (m, 13H), 7.01 (s, 1H), 5.41 (d, J = 8.9 Hz, 1H), 4.93-4.75 (m, 1H), 4.55 (dd, J = 10.6, 6.8 Hz, 1H), 4.41 (dd, J = 10.6, 6.8 Hz, 1H), 4.23 (t, J = 6.8 Hz, 1H), 3.42 (dd, J = 14.6, 5.1 Hz, 1H), 3.30 (dd, J = 14.6, 5.1 Hz, 1H); ^{13}C NMR δ (50 MHz, $CDCl_3$) 204.4, 155.9, 143.7, 143.5, 141.2 (2C), 136.1, 136.0 (2C), 129.3 (2C), 129.0 (2C), 127.7 (2C), 127.4, 127.1 (2C), 125.9, 125.1 (2C), 123.3, 122.5, 120.0 (2C), 118.6, 11.4, 109.1, 67.3, 63.6, 47.1, 27.5; FTIR 3473, 3425, 3332, 3054, 1722, 1695, 1532, 1249, 1047, 737 cm^{-1}. Anal. Calcd for $C_{32}H_{26}N_2O_3Se$: C, 67.96; H, 4.63; N, 4.95. Found: C, 67.77; H, 4.95; N, 4.84.

Se-Phenyl (2S)-5-amino-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxopentaneselenoate (**8i**)**:** According to general procedure the organic solvent was removed to dryness and the residue was triturated with diethyl ether (2x30 ml). The solid was filtered to afford **8i** (0.96 g, 95% yield): mp = 193–195 ºC; $[\alpha]^{20}{}_D$ -33.51 (*c* 0.77, DMF); ^{1}H NMR (200 MHz, $DMSOd_6$) δ 8.42 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 7.4, 2H), 7.77 (d, J = 6.8 Hz, 2H), 7.50-7.21 (m, 10H), 6.82 (br s, 1H), 4.57-4.51 (m, 1H), 4.49-4.08 (m, 3H), 2.18 (t, J = 7.1 Hz, 2H), 2.10-1.70 (m, 2H); ^{13}C NMR (50 MHz, $DMSOd_6$) δ 204.5, 172.2, 156.3, 143.7 (2C), 140.8 (2C), 135.8 (2C), 129.4 (2C), 128.8, 127.7 (2C), 127.2 (2C), 125.9, 125.3 (2C), 120.2, (2C), 66.0, 63.5, 46.7, 30.7, 26.2; FTIR 3446, 3300, 1720, 1699, 1654, 1544, 1201, 739 cm^{-1}. Anal. Calcd for $C_{26}H_{24}N_2O_4Se$: C, 61.54; H, 4.77; N, 5.52. Found: C, 61.27; H, 5.13; N, 5.45.

Se-Phenyl (2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-3-(tritylthio)propaneselenoate (**8j**)**:** According to general procedure the organic solvent was removed to dryness and the residue was triturated with hexane (2x30 ml). The solid was filtered to afford **8j** (1.20 g, 83% yield): pale yellow solid; mp = 176–178 ºC; $[\alpha]^{24}{}_D$ -17.74 (*c* 0.44, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74-7.67 (m, 2H), 7.63-7.57 (m, 2H), 7.38-7.12 (m, 24H), 4.91 (d, J = 8.3 Hz, 1H), 4.57 (dd, J = 10.6, 6.5 Hz, 1H), 4.38 (dd, J = 10.6, 6.5 Hz, 1H), 4.21 (t, J = 6.5 Hz, 1H), 4.14 (dt, J = 8.3, 5.5 Hz, 1H), 2.70-2.55 (m, 2H); ^{13}C NMR δ (50 MHz, $CDCl_3$) 202.7, 155.8, 144.0 (3C), 143.7, 143.6, 141.4 (2C),

135.9 (2C), 129.5 (6C), 129.3 (2C), 129.0, 128.2 (6C), 127.9, 127.8, 127.2 (2C), 127.1 (3C), 125.8, 125.1, 125.0, 120.1 (2C), 67.7, 67.1, 62.4, 47.2, 33.4; FTIR 3281, 3057, 1720, 1693, 1537, 1261, 1055, 1038, 741 cm^{-1}. Anal. Calcd for $C_{43}H_{35}NO_3SSe$: C, 71.26; H, 4.87; N, 1.93.Found: C, 71.05; H, 5.25; N, 1.75.

tert-Butyl (3S)-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-oxo-4-(phenylseleno)butanoate (**8k**)**:** According to general procedure the title compound was obtained as solid (0.66 g, 82% yield) using dichloromethane as eluent: mp = 93–95 ºC; $[\alpha]^{22}{}_D$ -8.29 (*c* 0.66, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.88-7.60 (m, 4H), 7.58-7.29 (m, 9H), 6.26 (d, J = 10.0 Hz, 1H, 4.82-4.60 (m, 2H), 4.41 (dd, J = 17.0, 6.6 Hz, 1H), 4.35 (t, J = 6.6 Hz, 1H), 3.08 (dd, J = 17.2, 4.8 Hz, 1H), 2.72 (dd, J = 17.2, 4.3 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.8, 170.0, 155.9, 143.6, 143.5, 141.3 (2C), 135.9 (2C), 129.2 (2C), 128.9, 127.7 (2C), 127.1 (2C), 125.9, 125.1, 125.0, 120.0, (2C), 82.3, 67.4, 59.9, 47.1, 37.1, 28.0 (3C); FTIR 3337, 2982, 1740, 1685, 1526, 1230, 1034, 741 cm^{-1}. Anal. Calcd for $C_{29}H_{29}NO_5Se$: C, 63.27; H, 5.31; N, 2.54. Found: C, 63.12; H, 5.58; N, 2.35.

Se-Phenyl (2S)-3-tert-butoxy-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}propaneselenoate (**8l**)**:** According to general procedure the organic solvent was removed to dryness and the residue was triturated with hexane (3x20 ml). The solid was filtered to afford **8l** (0.90 g, 86% yield): white solid; mp = 103–105 ºC; $[\alpha]^{20}{}_D$ -32.11 (*c* 1.01, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.85-7.55 (m, 4H), 7.52-7.30 (m, 9H), 5.89 (d, J = 8.7 Hz, 1H), 4.67 (dd, J = 10.0, 6.1 Hz, 1H), 4.59-4.20 (m, 3H), 3.94 (dd, J = 9.1, 2.3 Hz, 1H), 3.56 (dd, J = 9.1, 3.6 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.3, 156.2, 143.6 (2C), 141.3 (2C), 135.9 (2C), 129.3 (2C), 128.9, 127.8 (2C), 127.1 (2C), 126.2, 125.1, 125.0, 120.0, (2C), 73.8, 67.4, 63.4, 61.4, 47.2, 27.3 (3C); FTIR 3346, 2972, 1724, 1699, 1506, 1216, 1090, 736 cm^{-1}. Anal. Calcd for $C_{28}H_{29}NO_4Se$: C, 64.36; H, 5.59; N, 2.68. Found: C, 64.25; H, 5.95; N, 2.62.

Se-Phenyl (2S)-6-[(tert-butoxycarbonyl)amino]-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}hexaneselenoate (**8m**)**:** According to general procedure the title compound was obtained (1.07 g, 86% yield) using ethyl acetate/dichloromethane (5:95) as eluent: white solid; mp = 115–116 ºC; $[\alpha]^{20}{}_D$ -33.93 (*c* 0.36, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.81-7.52 (m, 4H), 7.50-7.20 (m, 9H), 5.72 (d, J = 8.5 Hz, 1H), 4.67 (dd, J = 10.2, 6.3 Hz, 1H), 4.58 (br s, 1H), 4.51-4.34 (m, 2H), 4.29 (t, J = 6.6 Hz, 1H), 3.28-3.01 (m, 2H), 2.06-1.65 (m, 2H), 1.64-1.30 (m, 4H), 1.50 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.1, 175.4, 156.3, 143.8, 143, 6, 141.3 (2C), 135.9 (2C), 129.2 (2C), 128.9, 127.7 (2C), 127.1 (2C), 125.8, 125.1, 125.0, 120.0, (2C), 79.4, 67.1, 63.7, 47.2, 39.8, 31.0, 29.5, 28.4 (3C), 22.2; FTIR 3337, 2933, 1729, 1688, 1521, 1170, 739 cm^{-1}. Anal. Calcd for $C_{32}H_{36}N_2O_5Se$: C, 63.31; H, 5.97; N, 4.61. Found: C, 63.14; H, 6.29; N, 4.56.

Se-Phenyl (2S)-3-(4-tert-butoxyphenyl)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}propaneselenoate **(8n):** According to general procedure the organic solvent was removed to dryness and the residue was triturated with hexane (3x20 ml). The solid was filtered to afford **8n** (0.95 g, 79% yield): white solid; mp = 104–106 ºC; $[\alpha]^{20}{}_{D}$ -71.94 (*c* 0.38, $CHCl_3$);); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.63-7.53 (m, 2H), 7.48-7.35 (m, 7H), 7.32 (d, J = 7.5 Hz, 2H), 7.05 (d, J = 8.4, 2H), 6.94 (d, J = 8.4 Hz, 2H), 5.18 (d, J = 8.6 Hz, 1H), 4.78-4.66 (m, 1H), 4.57-4.33 (m, 2H), 4.24 (t, J = 6.9 Hz, 1H), 3.20-2.99(m, 2H), 1.30 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.5, 155.8, 154.7, 143.6, 143, 5, 141.3 (2C), 135.9 (2C), 129.8 (2C), 129.3 (2C), 129.0 127.8 (3C), 127.1 (2C), 125.8, 125.0 (2C), 124.4 (2C), 120.0, (2C), 78.5, 67.3, 64.1, 47.1, 37.0, 28.8 (3C); FTIR 3302, 2976, 1718, 1694, 1532, 1260, 1169, 1047, 739 cm^{-1}. Anal. Calcd for $C_{34}H_{33}NO_4Se$: C, 68.22; H, 5.56; N, 2.36. Found: C, 67.97; H, 5.88; N, 2.31.

Synthesis of Selenoester 10. To a solution of *N*-Boc-alanine **9** (0.76 g, 4.0 mmol) in EtOAc (32 mL) at 0 °C *N*-methylmorpholine (NMM 0.49 mL, 4.4 mmol) and isobutyl chloroformate (0.56 ml, 4.4 mmol) were added. The reaction mixture was stirred at 0 °C for 40 min under argon atmosphere. Then, a fresh solution of nucleophilic selenium species, prepared as described above from diphenyl diselenide (0.75 g, 2.4 mmol), sodium borohydride (0.19 g, 4.8 mmol) and glacial acetic acid (1.36 mL, 24 mmol) in EtOAc (20 mL), was added directly in one portion through syringe allowing to reach room temperature gradually. After 16 h the mixture was poured into water (40 mL) and extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (10 mL), dried over sodium sulfate and evaporated and the residue was triturated with hexane (3x20 ml). The suspension was filtered to afford *Se-phenyl (2S)-2-[(tert-butoxycarbonyl)amino]propaneselenoate* (**10**) (0.99 g, 76% yield) as a white solid: mp = 122–124 ºC; (lit.,2[1] 122-123.5 °C); $[\alpha]^{22}{}_{D}$ -50.74 (*c* 0.83, DMF) (lit.,[21] $[\alpha]_D^{20}$ -54.9, *c* 0.83 in DMF); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55-7.32 (m, 5H), 5.04 (d, J = 7.6 Hz, 1H), 4.44 (quint, J = 7.6 Hz, 1H), 1.51(s, 9H), 1.40 (d, J = 7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.7, 154.9, 135.9 (2C), 129.2 (2C), 128.8, 125.9, 80.6, 58.9, 28.3 (3C), 17.8; FTIR 3282, 2980, 1717, 1683, 1526, 1164, 902, 744 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_3Se$: C, 51.22; H, 5.83; N, 4.27. Found: C, 51.08; H, 6.15; N, 4.20.

Chemoselective Acylation of Amines: General Procedure. To a solution of *Se*-phenyl selenocarboxylate **3** (1.1 mmol) in the appropriate solvent (8 mL) amine (1.00 mmol) was added and the resulting mixture was stirred at room temperature open to the air. When amine salts or amino acids were employed (amines **11c**, **11d** and **11f**), 2.0 equiv of DIPEA were added. After complete consumption of amine (2-24 h) the reaction mixture was evaporated. The residue was chromatographed using a silica gel column and the amide **12** was obtained in a pure form. Notably the diphenyl diselenide was also recovered in 70-84% yield.

N-(2-Aminobenzyl)-2-phenylacetamide (**12a**)**:** The general procedure was applied to selenoesters **3h** dissolved in MeCN. The product was purified by chromatography using an ethyl acetate-dichloromethane mixture (2:8) as eluent to give **12a** (0.24 g, 97% yield): white solid; mp = 103–105 ºC; EIMS (70 eV) *m/z* M^+ 240 (53), 149 (48), 1281 (100), 106 (77), 91 (38), 77 (21). Spectral data were in accordance with the literature.[36]

2-Amino-N-(2-hydroxypropyl)benzamid (**12b**)**:** The general procedure was applied to selenoesters **3g** dissolved in THF. The reaction was concentrated to give a solid residue which was triturated with hexane (2x30 ml) to afford, after filtration, **12b** (0.16 g, 84% yield) as a white solid; ^{13}C NMR (50 MHz, $DMSOd_6$) δ 168.4, 149.4, 131.4, 128.2, 116.2, 115.2, 114.4, 64.4, 46.6, 17.1; EIMS (70 eV) *m/z* M^+ 194 (24), 163 (21), 120 (100), 92 (34), 65 (24). Other spectral data were in accordance with the literature.[37]

Methyl N-(2-aminobenzoyl)glycinate (**12c**)**:** The general procedure was applied to selenoesters **3g** dissolved in THF. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine (10 mL), dried over sodium sulfate and evaporated. The solid residue was triturated with hexane (2x20 ml) and filtrated to afford **12c** (0.18 g, 81% yield). Spectral data were in accordance with the literature.[38]

N-(2-aminobenzyl)-4-oxopentanamide (**12d**)**:** The general procedure was applied to selenoesters **3k** dissolved in MeCN. The product was purified by chromatography using a methanol-dichloromethane mixture (4:96) as eluent to give **12d** (0.18 g, 81% yield): white solid; mp = 62–65 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.09 (dt, J = 7.5, 1.6 Hz, 1H), 7.02 (dd, J = 7.5, 1.5 Hz, 1H), 6.72-6.61 (m, 2H), 6.25 (t, J = 6.1 Hz, 1H), 4.33 (d, J = 6.1 Hz, 2H), 3.79 (br s, 2H), 2.77 (t, J = 6.4 Hz, 2H), 2.39 (t, J = 6.4 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.9, 172.2, 145.3, 130.5, 129.1, 121.9, 117.8, 115.8, 40.8, 38.4, 29.8, 29.6; FTIR 3446, 3367, 3250, 3064, 2913, 1711, 1631, 1540, 1560, 1165, 746 cm^{-1}; EIMS (70 eV) *m/z* $[M - 18]^+$ 202 (37) 187 (100), 145 (31), 106 (59), 77 (14). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.18; H, 7.69; N, 12.55.

N-Tetradecanoyl-L-phenylalanine (**12e**)**:** The general procedure was applied to selenoesters **3m** dissolved in EtOH. The solvent was removed to dryness and to the resulting residue 20 ml of 10% hydrochloric acid was added. The solid was filtered, washed with 10% hydrochloric acid and dried under reduced pressure. The solid residue was triturated with hexane (2x20 ml) and filtrated to afford **12e** (0.32 g, 85% yield): white solid; mp = 68–70 ºC. Spectral data were in accordance with the literature.[39]

N-(2-Aminobenzyl)pyridine-2-carboxamide (**12f**)**:** The general procedure was applied to selenoesters **3u** dissolved in MeCN. The product was purified by chromatography using an ethyl

acetate-dichloromethane mixture (2:8) as eluent to give **12f** (0.22 g, 96% yield): pale yellow solid; mp = 105–107 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.52 (ddd, J = 4.8, 1.7, 1.0 Hz, 1H), 8.40 (t, J = 6.6 Hz, 1H), 8.20 (dt, J = 7.8, 1.2 Hz, 1H), 7.85 (dt, J = 7.6, 1.7 Hz, 1H), 7.42 (ddd, J = 7.6, 4.8, 1.0 Hz, 1H), 7.20-7.08 (m, 2H), 6.79-6.59 (m, 2H), 4.61 (d, J = 6.6 Hz, 2H), 4.36 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.6, 149.3, 148.1, 145.0, 137.7, 130.7, 129.2, 126.3, 122.3, 122.1, 118.2, 116.0, 40.6; FTIR 3372, 3242, 1649, 1529, 1151, 816, 747 cm^{-1}; EIMS (70 eV) *m/z* M^+ 227 (17), 209 (18), 121 (100), 94 (15), 79 (24). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.45; H, 6.13; N, 18.38.

tert-Butyl (2-aminobenzyl)carbamate (**12g**)**:** The general procedure was applied to selenoesters **3f** dissolved in DMF. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine (10 mL), dried over sodium sulfate and evaporated. The crude amide was purified by chromatography using an ethyl acetate-dichloromethane mixture (1:9) as eluent to give **12g** (0.20 g, 89 yield). Spectral data were in accordance with the literature.[40]

2-Amino-N-[2-(benzylamino)ethyl]benzamide (**12h**)**:** The general procedure was applied to selenoesters **3g** dissolved in EtOH. The product was purified by chromatography using a methanol-dichloromethane mixture (1:9) as eluent to give **12h** (0.25 g, 94% yield) as colorless oil; ^{1}H NMR (400 MHz, $DMSOd_6$) δ 8.13 (t, J = 5.6 Hz, 1H), 7.43 (dd, J = 8.0, 1.4 Hz, 1H), 7.35-7.26 (m, 4H), 7.23-7.17 (m, 1H), 7.10 (ddd, J = 8.2, 8.0, 1.4 Hz, 1H), 6.65 (dd, J = 8.2, 1.1 Hz, 1H), 6.47 (dt, J = 8.0, 1.1 Hz, 1H), 6.34 (br s, 2H), 3.70 (s, 2H), 3.37-3.26 (m, 3H), 2.64 (t, J = 6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.4, 148.6, 139.4, 132.1, 128.5 (2C), 128.2 (2C), 127.3, 127.2, 117.2, 116.5, 116.1, 53.2, 47.7, 38.9; FTIR 3441, 3337, 3030, 1631, 1584, 1533, 1264, 747 cm^{-1}; EIMS (70 eV) *m/z* M^+ 269 (7), 150 (19), 133 (50), 120 (92), 106 (13), 91 (100), 65 (22). Anal. Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.14; H, 7.39; N, 15.47.

N-[2-(Benzylamino)ethyl]-2-phenylacetamide (**12i**)**:** The general procedure was applied to selenoesters **3h** dissolved in MeCN. The product was purified by chromatography using a methanol-dichloromethane mixture(5:95) as eluent to give **12i** (0.25 g, 92% yield) as colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44-7.10 (m, 10H), 6.18 (t, J = 5.6 Hz, 1H), 3.70 (s, 2H), 3.57 (s, 2H), 3.30 (dt, J = 6.0, 5.6 Hz, 2H), 2.69 (t, J = 6.0 Hz, 2H), 1.61 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.1, 139.9, 135.0, 129.4 (2C), 128.9 (2C), 128.3 (2C), 128.0 (2C), 127.2, 127.0, 53.3, 47.7, 43.8, 39.1; FTIR 3292, 3028, 2929, 2832, 1653, 1551, 1124, 732 cm^{-1}; EIMS (70 eV) *m/z* M^+ 268 (2), 177 (12), 133 (72), 120 (71), 106 (37), 91 (100), 65 (30). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found C, 75.91; H, 7.87; N, 10.50.

(S)-2-[7-((S)-1-Methoxycarbonyl-2-phenyl-ethylcarbamoyl)-heptanoylamino]-3-phenyl-propionic acid methyl ester (**12j**)**:** To a solution of selenoester **3n** (1.0 mmol) in DMF (5 mL) L-Phenylalanine methyl ester hydrochloride (4.00 mmol) and DIPEA (5.0 mmol) were added and the resulting mixture was stirred at room temperature under air atmosphere. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 x 20 mL). The organic layer was washed with 5% sodium hydroxide solution and then with 5% hydrochloric acid solution. The organic phase was washed with brine (10 mL), dried over sodium sulfate and evaporated. The solid residue was triturated with hexane (2x20 ml) and the suspension filtered to give **12j** (0.42 g, 86% yield): white solid; mp = 145–146 ºC; $[\alpha]^{26}{}_{D}$ +89.93 (*c* 0.495, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.20 (m, 6H), 7.19-7.00 (m, 4H), 6.11 (d, J = 7.8 Hz, 2H), 4.90 (dt, J = 7.8, 6.0 Hz, 2H), 3.72 (s, 6H); 3.16 (dd, J = 13.8, 6.0 Hz, 2H), 3.05 (dd, J = 13.8, 6.0 Hz, 2H), 2.17 (t, J = 7.3 Hz, 4H), 1.78-1.45 (m, 4H), 1.40-1.12 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7 (2C), 172.3 (2C), 135.9 (2C), 129.1 (4C), 128.5 (4C), 127.9 (2C), 52.9 (2C), 52.3 (2C), 37.8 (2C), 36.0 (2C), 28.3 (2C), 25.1 (2C); FTIR 3281, 2943, 1739, 1652, 1544, 1250, 1018, 750, 704 cm^{-1}. Anal. Calc. for $C_{28}H_{36}N_2O_6$: C, 67.72; H, 7.31; N, 5.64. Found: C, 67.55; H, 7.70; N, 5.45.

Solution Phase Synthesis of Dipeptides 14a-h. To a solution of selenoester **8e** (105 mg, 0.20 mmol) in 2 mL of DMF, L-alanine methyl ester hydrochloride (56 mg, 0.40 mmol) and DIPEA (0.09 mL, 0.50 mmol) were added and the resulting mixture was stirred at room temperature under air atmosphere. When consumption of the selenoester was complete (16 h, TLC monitoring) the reaction mixture was poured into 5% hydrochloric acid solution (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 10 mL), dried with brine (10 mL) and sodium sulfate. The solid residue, obtained after evaporation of the solvent, was triturated with hexane (2x10 ml) and filtered to afford dipeptide **14a** (0.09 g, 90% yield). Spectral data were in accordance with the literature.[41]

To a solution of selenoester **8c** (96 mg, 0.20 mmol) in 2 mL of DMF L-triptophan methyl ester hydrochloride (102 mg, 0.40 mmol) and DIPEA (0.09 mL, 0.50 mmol) were added and the resulting mixture was stirred at room temperature under air atmosphere. When consumption of the selenoester was complete (20 h, TLC monitoring) the reaction mixture was poured into 5% hydrochloric acid solution (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 10 mL), dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using an ethyl acetate-dichloromethane mixture (2:8) as eluent to give **14b** (70 mg, 65% yield): white solid; mp = 220–222 ºC; $[\alpha]^{22}{}_{D}$ -1.82 (*c* 0.28, DMF); ^{1}H NMR (200 MHz, $DMSOd_6$) δ 10.85 (s, 1H), 8.38 (d, J = 7.2 Hz, 1H), 7.89 (d, J = 7.0 Hz, 2H), 7.74 (d, J = 7.1 Hz, 2H), 7.50-7.20 (m, 7H), 7.15 (s, 1H), 7.10-

6.88 (m, 2H), 4.50 (dd, J = 13.8, 6.8 Hz, 1H), 4.35-4.10 (m, 3H), 3.92 (t, J = 7.2 Hz, 1H), 3.52 (s, 3H), 3.20-2.98 (m, 2H), 2.07-1.80 (m, 1H), 0.83 (d, J = 6.7 Hz, 6H); ^{13}C NMR δ (50 MHz, $DMSOd_6$) 172.2, 171.4, 156.1, 143.9, 143.8, 140.7 (2C), 136.0, 127.6 (2C), 127.1 (2C), 127.0, 125.4 (2C), 123.7, 121.0, 120.1 (2C), 118.4, 118.0, 11.4, 109.2, 65.7, 59.8, 53.1, 51.7, 46.7, 30.5, 27.0, 19.1, 18.2; FTIR 3408, 3305, 2970, 1732, 1693, 1655, 1543, 1252, 1033, 742 cm^{-1}. Anal. Calcd for $C_{32}H_{33}N_3O_5$: C, 71.22; H, 6.16; N, 7.79. Found: C, 70.98; H, 6.51; N, 7.68.

To a solution of selenoester **8e** (105 mg, 0.20 mmol) in 2 mL of DMF L-alanine methyl ester hydrochloride (66 mg, 0.40 mmol) and DIPEA (0.09 mL, 0.50 mmol) were added and the resulting mixture was stirred at room temperature under air atmosphere. When consumption of the selenoester was complete (4 h, TLC monitoring) the reaction mixture was poured into 5% hydrochloric acid solution (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 10 mL), dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using an ethyl acetate-dichloromethane mixture (2:8) as eluent to give **14c** (30 mg, 79% yield) as a colorless oil; $[\alpha]^{24}{}_D$ -35.77 (*c* 0.58, $CHCl_3$). Spectral data were in accordance with the literature.[42]

Methyl N-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-phenylalanyl-L-leucinate (**14d**)**:**[43] The title compound was obtained from reaction of a solution of selenoester **8e** (2.00 g,, 3.79 mmol) in 30 mL of DMF with L-leucine methyl ester hydrochloride (0.83 g, 4.50 mmol) and DIPEA (0.86 mL, 4.90 mmol). The mixture was stirred at room temperature under air atmosphere. When consumption of the selenoester was complete (5 h, TLC monitoring) the reaction mixture was poured into 5% hydrochloric acid solution (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (3 x 20 mL), dried with brine (10 mL) and sodium sulfate. The solid residue obtained after evaporation of the solvent was triturated with hexane (3x20 ml) and filtered to afford dipeptide **14d** (1.75 g, 90% yield); $[\alpha]^{20}{}_D$ -13.32 (*c* 1.03, $CHCl_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7, 170.5, 155.9, 143.7, 143.6, 141.2 (2C), 136.2, 129.4 (2C), 129.1, 128.6 (2C), 127.7 (2C), 127.0 (2C), 125.1, 125.0, 120.0 (2C), 67.1, 55.9, 52.3, 50.8, 47.0, 41.4, 38.4, 24.6, 22.6, 21.8. Spectral data were in accordance with the literature.[43]

N-[(9H-Fluoren-9-ylmethoxy)carbonyl]-L-valyl-L-phenylalanine (**14e**)**:**[44] To a solution of *Se*-phenyl selenocarboxylate **8c** (1.44 g, 3.00 mmol) in DMF (20 mL) phenylalanine (0.99 g, 6.00 mmol) and DIPEA (1.32 mL, 7.5 mmol) were added and the resulting mixture was stirred at room temperature under air atmosphere. After complete consumption of selenoester (13 h), 20 ml of 10% hydrochloric acid were added. The solid was filtered, washed with 10% hydrochloric acid and dried under reduced pressure. The solid residue was triturated with hexane (2x20 ml) and filtrated to afford **14e** (1.15 g, 79% yield); ^{1}H NMR (200 MHz, $DMSOd_6$) δ 12.70 (s, 1H), 8.20 (d, J = 7.9 Hz,

1H), 7.88 (d, J = 6.9 Hz, 2H), 7.77-7.68 (m, 2H), 7.46-7.25 (m, 4H), 7.24-7.09 (m, 6H), 4.50-4.10 (m, 4H), 3.86 (t, J = 7.5 Hz, 1H), 3.04 (dd, J = 14.5, 5.8 Hz, 1H), 2.88 (dd, J = 14.5, 8.7 Hz, 1H), 2.01-1.79 (m, 1H), 0.80 (d, J = 6.7 Hz, 6H); ^{13}C NMR (50 MHz, $DMSOd_6$) δ 172.8, 171.2, 156.0, 143.9, 143.8, 140.7 (2C), 137.5, 129.1 (2C), 128.1 (2C), 127.6 (2C), 127.1 (2C), 126.4, 125.4 (2C), 120.1 (2C), 65.7, 60.0, 53.3, 46.7, 36.8, 30.5, 19.1, 18.2; FTIR 3339, 3301, 2960, 1736, 1694, 1634, 1534, 1251, 1032, 741 cm^{-1}; Anal. Calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76.Found: C, 71.33; H, 6.48; N, 5.67.

N-[(9H-Fluoren-9-ylmethoxy)carbonyl]-L-leucyl-L-valine **(14f):** To a solution of *Se*-phenyl selenocarboxylate **8d** (0.79 g, 1.60 mmol) in DMF (15 mL) valine (0.38 g, 3.20 mmol) and DIPEA (1.40 mL, 4.0 mmol) were added and the resulting mixture was stirred at room temperature under air atmosphere. After complete consumption of selenoester (16 h) the reaction mixture was poured into 5% hydrochloric acid solution (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with 5% hydrochloric acid solution (3 x 10 mL), dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using a methanol-dichloromethane mixture (5:95) as eluent to give **14f** (0.70 g, 96% yield): white solid; mp = 77–80 ºC; $[\alpha]^{20}{}_D$ -19.85 (*c* 0.59, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 7.75 (d, J = 7.3 Hz, 2H), 7.58 (d, J = 6.9 Hz, 2H), 7.46-7.21 (m, 4H), 6.94 (d, J = 7.8 Hz, 1H), 5.89 (d, J = 8.5 Hz, 1H), 4.62-4.12 (m, 5H), 2.32-2.12 (m, 1H), 1.80-1.43 (m, 3H), 0.98-0.70 (m, 12H); ^{13}C NMR δ (50 MHz, $CDCl_3$) 174.5, 172.8, 156.4, 143.6 (2C), 141.2 (2C), 127.7 (2C), 127.0 (2C), 125.0(2C), 119.9 (2C), 67.1, 57.2, 53.5, 47.0, 41.1, 31.0, 24.5, 22.8, 22.0, 18.9, 17.6; FTIR 3284, 2960, 1706, 1654, 1264, 1044, 741 cm^{-1}. Anal. Calcd for $C_{26}H_{32}N_2O_5$: C, 69.01; H, 7.13; N, 6.19. Found: C, 68.85; H, 7.47; N, 6.15.

O-(tert-Butyl)-N-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-tyrosylglycine **(14g):**[45] To a solution of *Se*-phenyl selenocarboxylate **8n** (0.93 g, 1.50 mmol) in DMF (15 mL) glycine (0.23 g, 3.00 mmol) and DIPEA (0.65 mL, 3.75 mmol) were added and the resulting mixture was stirred at room temperature under air atmosphere. When consumption of the selenoester was complete (15 h, TLC monitoring), the reaction mixture was poured into 5% hydrochloric acid solution (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with 5% hydrochloric acid solution (3 x 10 mL), dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using an ethyl acetate-dichloromethane mixture (3:7) as eluent to give **14g** (0.61 g, 78% yield). ^{13}C NMR (100 MHz, CD_3OD) δ 174.5, 172.7, 158.2, 155.2, 145.2 (2C), 142.5 (2C), 133.8, 130.9 (2C), 128.8 (2C), 128.2 (2C), 126.3 (2C), 125.2 (2C), 120.9 (2C), 79.4, 68.0, 57.8, 47.7, 41.8, 38.5, 29.1 (3C).

O-(tert-Butyl)-N-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-α-aspartylglycinamide (**14h**): To a solution of *Se*-phenyl selenocarboxylate **8k** (0.55 g, 1.00 mmol) in EtOH (10 mL) glycinamide hydrochloride (0.16 g, 1.40 mmol) and DIPEA (0.27 mL, 1.5 mmol) were added and the resulting mixture was stirred at room temperature under air atmosphere. When consumption of the selenoester was complete (16 h, TLC monitoring), the reaction mixture was poured into sodium bicarbonate solution (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with 5% hydrochloric acid solution (1 x 10 mL), dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using a methanol-ethyl acetate mixture (2:98) as eluent to give **14h** (0.44 g, 94% yield): white solid; mp = 152–155 ºC; $[\alpha]^{22}{}_{D}$ -15.97 (*c* 1.47, DMF); ^{1}H NMR (400 MHz, $DMSOd_6$) δ 8.07 (t, J = 5.5 Hz, 1H), 7.87 (d, J = 7.5 Hz, 2H), 7.73-7.65 (m, 3H), 7.40 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.15 (s, 1H), 7.08 (s, 1H), 4.39-4.18 (m, 4H), 3.60 (d, J = 5.5 Hz, 2H), 2.69 (dd, J = 16.0, 5.2 Hz, 1H), 2.44 (dd, J = 16.0, 8.9 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (50 MHz, $DMSOd_6$) δ 171.0 (2C), 169.9, 156.3, 144.2, 144.1, 141.1 (2C), 128.0 (2C), 127.4 (2C), 125.6 (2C), 120.5 (2C), 80.5, 66.2, 51.9, 47.0, 42.5, 37.9, 28.1 (3C); FTIR 3309, 2974, 1734, 1696, 1653, 1540, 1274, 1154, 737 cm^{-1}. Anal. Calcd. for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99. Found: C, 63.95; H, 6.55; N, 8.90.

Preparation of Fmoc-D-Phe-OMe for Epimerization Studies. To a solution of freshly synthesized selenoester (*D*)-**8e** (53 mg, 0.10 mmol) (see supporting information) in MeCN dry (2 mL), methanol (0.05 mL, 1.0 mmol) and dry copper (II) chloride (15 mg, 0.11 mmol) were added.[3d] The mixture was stirred under argon atmosphere at room temperature and monitored by TLC. After 2 h the substrate was completely consumed and the reaction mixture was diluted with EtOAc. Citric acid (38 mg, 0.2 mmol) was then added. The reaction mixture was stirred for a few minutes, then filtered through a celite pad and the filtrate was concentrated. The residue was purified by chromatography on silica gel column using dichloromethane as eluent to give *(R) Methyl N-[(9H-fluoren-9-ylmethoxy)carbonyl]-phenylalaninate*[46] (32 mg, 80% yield). Spectral data were in accordance with the literature.[46]

Synthesis of Tripeptides 16. To a solution of *Se*-phenyl selenocarboxylate **10** (0.24 g, 0.70 mmol) in MeCN (6 mL) alanylphenylalanine hydrochloride (0.14 g, 0.50 mmol) and DIPEA (0.27 mL, 1.5 mmol) were added and the resulting mixture was stirred at room temperature under air atmosphere. After 6 h the reaction mixture was poured into 5% hydrochloric acid solution (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 5% hydrochloric acid solution (1 x 10 mL), dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using a methanol-dichloromethane mixture (4:96) as eluent to give *N*-(*tert*-butoxycarbonyl)-L-alanyl-L-alanyl-L-phenylalanine (**16)** (0.15 g,

73% yield): white solid; mp = 52–55 ºC; $[\alpha]^{21}{}_{D}$ -10.83 (*c* 0.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.17 (m, 3H), 7.10 (d, J = 8.1 Hz, 2H), 6.84 (br s, 1H), 6.77 (d, J = 7.7 Hz, 1H), 5.13 (d, J = 7.4 1 Hz, 1H), 4.82 (ddd, J = 7.7, 6.3, 6.1 Hz, 1H), 4.46 (dq, J = 7.4, 7.1 Hz, 1H), 4.21-4.05 (m, 1H), 3.13 (dd, J = 13.9, 6.1 Hz, 1H), 3.06 (dd, J = 13.9, 6.3 Hz, 1H), 1.44 (s, 9H), 1.33 (d, J = 7.0 Hz, 3H), 1.30 (d, J = 7.1 Hz, 3H). Note: carboxylic acid proton was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 171.7, 171.6, 155.5, 135.7, 129.2 (2C), 128.6 (2C), 127.1, 80.2, 53.3, 52.4, 48.8, 37.8, 28.3 (3C), 18.2, 18.0; FTIR 3296, 2979, 1747, 1649, 1366, 1170, 744 cm^{-1}. Anal. Calcd for $C_{20}H_{29}N_3O_6$: C, 58.95; H, 7.17; N, 10.31. Found: C, 58.74; H, 7.55; N, 10.22.

Synthesis of Selenoester 17 and Tripeptide 18. To a solution of dipeptidil acid **14e** (0.73 g, 1.5 mmol) in 16 mL of ethyl acetate-tetrahydrofuran mixture (5:3) at 0 °C was added *N*-methylmorpholine (NMM 0.18 mL, 1.65 mmol) and isobutyl chloroformate (0.21 ml, 1.65 mmol). The reaction mixture was stirred at 0 °C for 40 min under argon atmosphere. Then, a fresh solution of nucleophilic selenium species, prepared as described above from diphenyl diselenide (0.28 g, 0.9 mmol), sodium borohydride (0.70 g, 1.8 mmol) and glacial acetic acid (0.51 mL, 9.0 mmol) in EtOAc (15 mL), was added directly in one portion through a syringe allowing to reach room temperature gradually. After 18 h the mixture was poured into water (30 mL) and extracted with EtOAc (3 x 30 mL). The organic layer was washed with brine (10 mL), dried over sodium sulfate and evaporated. The residue was purified by chromatography on a silica gel column using an ethyl acetate-dichloromethane mixture (1:9) as eluent to give selenoester **17** (0.63 g, 67% yield): white solid; mp = 240–242 ºC; $[\alpha]^{24}{}_{D}$ -50.43 (*c* 0.96, DMF); ^{1}H NMR (200 MHz, $DMSOd_6$) δ 8.73 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 7.4 Hz, 2H), 7.72 (d, J = 7.2 Hz, 2H), 7.50-7.02 (m, 15H), 4.70-4.60 (m, 1H), 4.42-4.10 (m, 3H), 3.95 (dd, J = 8.9, 7.2 Hz, 1H), 3.15 (dd, J = 13.8, 4.5 Hz, 1H), 2.89 (dd, J = 13.8, 10.1 Hz, 1H), 2.11-1.87 (m, 1H), 0.85 (d, J = 6.7 Hz, 3H), 0.78 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $DMSOd_6$) δ 202.3, 172.1, 156.0, 143.8, 143.7, 140.7 (2C), 136.6, 135.7 (2C), 129.2 (2C), 129.0 (2C), 128.7, 128.1 (2C), 127.5 (2C), 126.9 (2C), 126.4, 125.9, 125.2 (2C), 119.9 (2C), 65.7, 62.9, 60.3, 46.7, 36.3, 30.3, 19.3, 18.0; FTIR 3330, 3050, 1744, 1720, 1690, 1525, 736 cm^{-1}. Anal. Calcd for $C_{35}H_{34}N_2O_4Se$: C, 67.19; H, 5.48; N, 4.48. Found: C, 67.01; H, 5.78; N, 4.55.

A mixture of selenoester **17** (0.50 g, 0.80 mmol), alanine (0.14 g, 1.60 mmol) and DIPEA (0.30 mL, 1.76 mmol) in DMF (10 mL) was stirred at room temperature under air atmosphere. After complete consumption of selenoester (20 h), 10 ml of 10% hydrochloric acid was added. The solid was filtered, washed with 10% hydrochloric acid and dried under reduced pressure. The solid residue was triturated with hexane (3x20 ml) and filtrated to afford *N-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-valyl-L-phenylalanyl-L-alanine* **18** (0.40 g, 91% yield): white solid; mp = 241-243 ºC; $[\alpha]^{20}{}_{D}$ -18.22 (*c* 0.90, in DMF). Spectra matches previously reported data.[47]

Synthesis of Tripeptides 19a-c. Dipeptide **14h** (0.23 g, 0.5 mmol) was dissolved in dry MeCN (1 mL) and 1 mL of diethylamine (DEA) was added. The resulting reaction mixture was stirred at room temperature under argon flow. When consumption of the dipeptide was complete (4 h, TLC monitoring) the reaction mixture was evaporated under reduced pressure and the residue was washed with hexane to remove part of the dibenzofulvene byproduct to give the crude deprotected dipeptide. This was dissolved in 4 mL of EtOH and selenoester **8a** (0.26 g, 0.6 mmol) with DIPEA (0.23 mL, 0.6 mmol) were added at room temperature under air atmosphere. After 14 h the reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 5% hydrochloric acid solution (1 x 10 mL), dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using a methanol-ethyl acetate mixture (4:96) as eluent to give *O-(tert-butyl)-N-[(9H-fluoren-9-ylmethoxy)carbonyl]glycyl-L-α-aspartylglycinamide* **19a** (0.23 g, 89% yield); white solid; mp = 80–83 ºC; $[\alpha]^{22}_{D}$ -10.56 (*c* 0.66, DMF); ^{1}H NMR (400 MHz, DMSOd$_6$) δ 8.23 (d, J = 8.0 Hz, 1H), 8.08 (t, J = 5.7 Hz, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.70 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 5.8 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.10 (br s, 2H), 4.58 (ddd, J = 8.0, 7.7, 5.8 Hz, 1H), 4.32-4.17 (m, 3H), 3.72-3.50 (m, 4H), 2.68 (dd, J = 15.9, 5.8 Hz, 1H), 2.46 (dd, J = 15.9, 7.7 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, DMSOd$_6$) δ 170.7, 170.4, 169.5, 169.2, 156.5, 143.8 (2C), 140.7 (2C), 127.6 (2C), 127.1 (2C), 125.2 (2C), 120.1 (2C), 80.2, 65.8, 49.5, 46.6, 43.5, 42.1, 37.4, 27.6 (3C). FTIR 3312, 2978, 1718, 1670, 1533, 1251, 1156, 1048, 742 cm^{-1}. Anal. Calcd for $C_{27}H_{32}N_4O_7$: C, 61.82; H, 6.15; N, 10.68. Found: C, 61.70; H, 6.51; N, 10.79.

Dipeptide **14a** (0.30 g, 0.63 mmol) was dissolved in dry MeCN (2 mL) and DEA (2 mL) was added. The resulting reaction mixture was stirred at room temperature under argon flow. When consumption of the dipeptide was complete (2 h, TLC monitoring), the reaction mixture was evaporated under reduced pressure and the residue washed with hexane to remove part of the dibenzofulvene byproduct to give the crude deprotected dipeptide. This was dissolved in 8 mL of THF and selenoester **8e** (0.51 g, 0.89 mmol) with DIPEA (0.15 mL, 0.89 mmol) were added at room temperature under air atmosphere. After 14 h the reaction mixture was poured into 5% hydrochloric acid solution (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 5% hydrochloric acid solution (1 x 10 mL), dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using an ethyl acetate-dichloromethane mixture (2:8) as eluent to give methyl *N-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-phenylalanyl-L-phenylalanyl-L-alaninate* **19b** (0.29 g, 75% yield): white solid; mp = 124–126 ºC; $[\alpha]^{26}_{D}$ -18.31 (c 0.39, $CHCl_3$); ^{1}H NMR (400 MHz, DMSOd$_6$) δ 8.53 (d, J = 6.9 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 8.2 Hz, 2H), 7.56 (d,

J = 8.8 Hz, 1H), 7.45-7.35 (m, 2H), 7.34-7.18 (m, 12H), 4.65-4.55 (m, 1H), 4.38-4.03 (m, 5H), 3.61 (s, 3H), 3.06 (dd, J = 13.7, 4.5 Hz, 1H), 2.92 (dd, J = 13.7, 3.3 Hz, 1H), 2.82 (dd, J = 13.7, 9.4 Hz, 1H), 2.70 (dd, J = 13.7, 11.2 Hz, 1H), 1.30 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $DMSOd_6$) δ 172.9, 171.4, 170.9, 155.7, 143.8, 143.7, 140.7 (2C), 138.1, 137.5, 129.3 (2C), 129.2 (2C), 128.0 (2C), 127.9 (2C), 127.6 (2C), 127.1 (2C), 126.3, 126.2, 125.3, 125.2, 120.1 (2C), 65.6, 56.1, 53.5, 51.9, 47.6, 46.5, 37.6, 37.5, 16.9; FTIR 3291, 3064, 1749, 1740, 1694, 1645, 1530, 1260, 1039, 740 cm^{-1}. Anal. Calcd for $C_{37}H_{37}N_3O_6$: C, 71.71; H, 6.02; N, 6.78. Found: C, 71.44; H, 6.35; N, 6.62.

Dipeptide **14d** (0.75 g, 1.46 mmol) was dissolved in dry MeCN (6 mL) and DEA (6 mL) was added. The resulting reaction mixture was stirred at room temperature under argon. When consumption of the dipeptide was complete (4 h, TLC monitoring) the reaction mixture was evaporated under reduced pressure. The residue was dissolved in DMF (8 mL) and selenoester **8a** (0.26 g, 0.6 mmol) with DIPEA (0.23 mL, 0.6 mmol) were added at room temperature under air atmosphere. After 16 h the reaction mixture was poured into 5% hydrochloric acid solution (40 mL) and extracted with EtOAC (3 x 20 mL). The combined organic layers were washed with 5% hydrochloric acid solution (1 x 10 mL), dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using an ethyl acetate-dichloromethane mixture (3:7) as eluent to give methyl *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]glycyl-L-phenylalanyl-L-leucinate[48] **19c** (0.58 g, 69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.4 Hz, 2H), 7.59 (d, J = 7.0 Hz, 2H), 7.40 (t, J = 7.4, 2H), 7.35-7.13 (m, 7H), 6.63 (d, J = 7.9 Hz, 1H), 6.25 (d, J = 6.9 Hz, 1H), 5.43 (br s, 1H), 4.73-4.62 (m, 1H), 4.56-4.32 (m, 3H), 4.20 (t, J = 6.9 Hz, 1H), 3.92-3.78 (m, 2H), 3.68 (s, 3H), 3.18-2.98 (m, 2H), 1.61-1.40 (m, 3H), 0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.8, 169.3, 157.0, 144.1 (2C), 141.7 (2C), 136.6, 129.8 (2C), 129.0 (2C), 128.2 (3C), 127.5 (2C), 125.5 (2C), 120.4 (2C), 67.7, 54.7, 52.7, 51.3, 47.4, 44.8, 41.7, 38.7, 25.1, 23.1, 22.3; FTIR 3295, 3028, 1746, 1700, 1646, 1534, 1258, 1043, 739 cm^{-1}. Anal. Calcd for $C_{33}H_{37}N_3O_6$: C, 69.33; H, 6.52; N, 7.35. Found: C, 69.15; H, 6.84; N, 7.23.

Fragments Synthesis of Pentapeptide 21. To a solution of dipeptidil acid **14g** (0.36 g, 0.7 mmol) in 16 mL of ethyl acetate-tetrahydrofuran mixture (1:1) at 0 °C *N*-methylmorpholine (NMM 0.09 mL, 0.77 mmol) and isobutyl chloroformate (0.10 ml, 0.77 mmol) were added. The reaction mixture was stirred at 0 °C for 40 min under argon atmosphere. Then, a fresh solution of nucleophilic selenium species, prepared as described above from diphenyl diselenide (0.132 g, 0.42 mmol), sodium borohydride (0.32 g, 0.84 mmol) and glacial acetic acid (0.22 mL, 4.2 mmol) in EtOAc (15 mL), was added directly in one portion through syringe allowing to reach room temperature gradually. After 16 h the mixture was poured into water (30 mL) and extracted with EtOAc (3 x 30 mL). The organic layer was washed with brine (10 mL), dried over sodium sulfate,

evaporated to give the crude selenoester **20** that was employed for the successive acylation reaction. Tripeptide **19c** (0.29 g, 0.5 mmol) was dissolved in dry MeCN (2 mL) and 2 mL of diethylamine (DEA) were added. The resulting reaction mixture was stirred at room temperature under argon flow. When consumption of the dipeptide was complete (4 h, TLC monitoring), the reaction mixture was evaporated under reduced pressure and the residue dissolved in 4 mL of DMF and the crude selenoester **20** with DIPEA (0.12 mL, 0.7 mmol) were added at room temperature under air atmosphere. After 14 h the reaction mixture was poured into water and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried with brine (10 mL) and sodium sulfate. The residue was purified by chromatography on a silica gel column using ethyl acetate/dichloromethane (2:80) as eluent to give methyl *O-(tert-butyl)-N-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-tyrosylglycylglycyl-L-phenylalanyl-L-leucinate* **21** (0.24 g, 57% yield): white solid; mp = 130–133 ºC; $[\alpha]^{20}{}_{D}$ -1.38 (c 2.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.93 (br s, 2H), 7.81-7.71 (m, 2H), 7.69 (d, J = 7.1 Hz, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.45-7.20 (m, 5H), 7.17-6.93 (m, 8H), 6.78 (d, J = 8.2 Hz, 2H), 5.40-5.30 (m, 1H), 5.05-4.90 (m, 1H), 4.73-4.60 (m, 1H), 4.52-4.02 (m, 7H), 3.38 (s, 3H), 3.20-2.90 (m, 4H), 1.65-1.39 (m, 3H), 1.20 (s, 9H); 0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 171.9, 170.6, 168.5, 168.1, 156.2, 154.0, 144.1, 143.7 (2C), 141.1 (2C), 136.3, 131.4, 129.9, 129.5 (2C), 128.0 (2C), 127.5 (2C), 126.9 (2C), 126.5, 125.5, 125.2, 123.8 (2C), 119.7 (2C), 78.3, 67.2, 55.5, 53.9, 51.8, 50.5, 46.8, 43.6, 43.2, 41.4, 39.8, 39.5, 28.7, 28.6 (2C), 24.7, 22.5, 22.2; FTIR 3292, 2958, 1743, 1702, 1668, 1639, 1507, 1239, 1160, 898, 741 cm^{-1}. HRMS m/z: $[M+Na]^+$, ($C_{48}H_{57}N_5O_9Na^+$) 870.40750, required 870.40485 (see Supporting Information).

ASSOCIATED CONTENT

Supporting Information

Supporting figures, tables, and epimerization studies, ^{1}H-NMR and ^{13}C-NMR spectra for all new compounds and HPLC charts for the determination of the dr values. This material is available free of charge via the Internet at http://pubs.acs.org.

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