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Stereospecific Synthesis of β^3-Amino Acid Derivatives from Propargylic Alcohols: Efficient Solution-Phase Synthesis of Oligopeptides without Coupling Agents

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Abstract: A stereospecific synthesis of β^3-amino acids has been accomplished starting from readily available and enantioenriched propargylic alcohols. This conversion can be effected in only three steps by selenium-mediated organic transformations of the carbon–carbon triple bond. This method is especially attractive because the reactive *Se*-phenyl selenocarboxylate intermediates can be trapped with the amine functionality of an amino acid derivative. Through this strategy a chain elongation at the N-terminus has been effected. The N-deprotection and repetition of the homologation with other *Se*-phenyl selenocarboxylate intermediates produced β- and mixed α/β-oligopeptides without the use of coupling agents.

Keywords: oligopeptides · propargylic alcohols · selenium · amino acids

Introduction

The synthesis of optically active β^3-amino acids and of their derivatives has received considerable interest over the past decades because these one-carbon homologues of α-amino acids are fundamental building blocks for the preparation of pharmaceutically important compounds,[1] natural products,[2] and β-peptides.[3] Pioneering work by Seebach et al. and Gellman et al. revealed that incorporating β^3-amino acids into peptide chains induces new secondary and tertiary structures and, in selected cases, leads to biological activity.[4] Related studies showed that the physical properties of the molecules are also remarkably similar to those of natural proteins. In other words, the β-peptide assembly looks and acts a lot like a real protein. Furthermore, the enzymes in the body do not act on β-peptide bonds. All these features confer to β-peptides valuable characteristics as promising candidates in pharmaceutical applications as peptidomimetics[5] as well as powerful new tools for basic research. Due to their importance, different approaches have been developed for the synthesis of β^3-amino acids in optically active form. Homologation of α-amino acids[6] and enzymatic resolution[7] are widely applied routes in the cases of specific β^3-amino acids. The development of general and reliable methodologies for the asymmetric synthesis of β^3-amino acids is of widespread synthetic interest and many stereoselective routes have therefore been proposed.[8] These include the stereoselective addition of enolates (or their equivalents) to imines,[9] the diastereoselective conjugate addition of a nitrogen nucleophile to α,β-unsaturated carboxylic acid derivatives,[10] the asymmetric reduction of α,β-unsaturated acid derivatives,[11] and the 1,3-dipolar cycloaddition of chiral nitrones to substituted alkenes.[12] Naturally occurring aspartic acid[13] and functionalized succinates[14] have also been employed for the synthesis of specific β^3-amino acids.

We describe here a new and mild process for the stereospecific conversion of optically active propargylic alcohols **1** (see Scheme 1) into N-protected β^3-amino acids. We also report on the further use of the *Se*-phenyl selenocarboxylate intermediates **4** for a clean phase-solution synthesis of oligopeptides.

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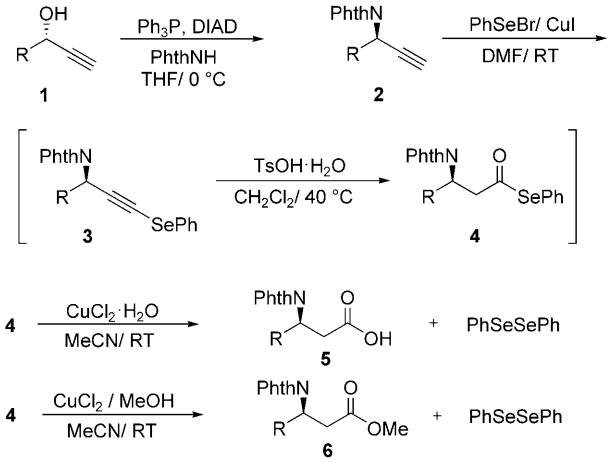
Results and Discussion

In a previous paper[15] we described a facile synthesis of *Se*-phenyl selenocarboxylates from readily accessible terminal alkynes through the corresponding alkynyl phenyl selenide intermediates. This procedure proved to be highly flexible and compatible with different functional groups present in the molecules. Thus, by reaction with phthalimide under Mitsunobu conditions,[16] optically active propargylic alcohols **1** were easily converted into *N*-phthalimido propargylic amines **2** (Scheme 1) with complete inversion of the configuration at the stereogenic carbon atom. According to the general procedure reported in the literature,[17] the amines **2** were then converted into the corresponding alkynyl phenyl selenides **3**. Reaction of these optically active alkynyl phenyl selenides **3** with an excess of *p*-toluenesulfonic acid monohydrate afforded the *Se*-phenyl selenocarboxylates **4**. These compounds were the result of two consecutive regiospecific addition reactions of *p*-toluenesulfonic acid and of water. The whole process represents a formal oxidative hydration of a terminal alkyne. A similar procedure which employs the rearrangement of an *N*-sulfonyltriazole intermediate has recently appeared in the literature.[2,18]



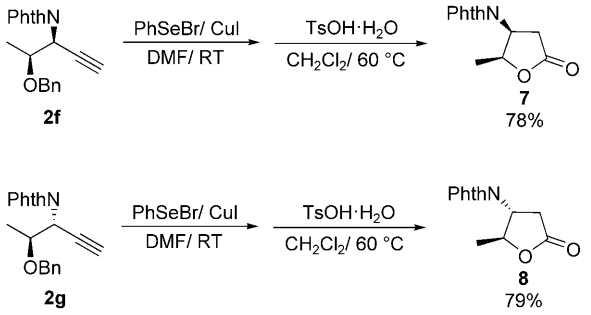
Scheme 1. Multistep synthesis of *N*-phthaloyl-β^3-amino acids **5** and *N*-phthaloyl-β^3-aminoesters **6** from propargylic alcohols **1**.

In view of the weakness of the carbon–selenium bond these *Se*-phenyl selenocarboxylate intermediates **4** are more reactive than the corresponding thio or oxo esters in reactions with oxygen or nitrogen nucleophiles.[19] The *Se*-phenyl selenocarboxylates **4** are reactive intermediates, which, after activation, can react with water or with alcohols to give carboxylic acids **5** or esters **6**, respectively. This positive result prompted us to use this protocol as a general stereospecific synthesis of the β^3-amino acids. We focused our attention on the use of substrates that were either commercially available or easy to prepare. Propargylic alcohols **1** can be easily obtained by the stereoselective addition of alkynes to aldehydes[20] or by the asymmetric reduction of α,β-acetylenic ketones.[21] In our hands, the oxazaborolidine-borane reduction of prochiral 1-trialkylsylyl-1-alkyn-3-ones[22] in particular gave a high level of enantioselectivity in almost every case. The enantioenriched propargylic alcohols **1a–l** were transformed into the corresponding *N*-phthaloyl propargylic amines **2a–l** (Table 1). The complete inversion of configuration at the stereogenic carbon atom was confirmed in the cases of compounds **2d** and **2h** whose enantiomeric ratios were identical to those of the corresponding starting alkynols (HPLC analysis on chiral stationery phase). The results of these reactions are collected in Table 1.

Reaction of **2** with phenylselenenyl bromide in *N,N*-dimethylformamide at room temperature and in the presence of copper(I) iodide[17] produced the corresponding alkynyl phenyl selenides **3** which were sufficiently pure to be directly employed in the following step (Scheme 1). The treatment of **3** with an excess of *p*-toluenesulfonic acid monohydrate in refluxing dichloromethane[15] gave the *Se*-phenyl selenocarboxylates **4**. Compounds **4** were then treated with copper(II) chloride hydrate in acetonitrile[15] to give the corresponding *N*-protected β^3-amino acids **5** in excellent global yields from **3**. Moreover the reaction of the crude Se-phenyl selenocarboxylate intermediates **4** with dry copper(II) chloride in acetonitrile and in the presence of methanol[15] gave the corresponding *N*-protected β^3-amino acid methyl esters **6** in good overall yield from **3**. The results of these experiments are collected in Table 2. A comparison of the enantiomeric ratios reported in Table 2 with those in Table 1 indicates that no racemization occurred during the conversion of **3** into **4** or into **6**. Interestingly, the leaving phenylselenol group was oxidized by copper(II) to diphenyl diselenide, which was almost quantitatively recovered at the end of the reactions.

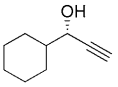
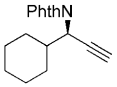
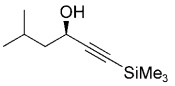
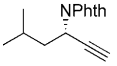
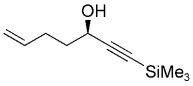
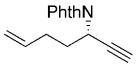
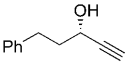
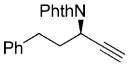
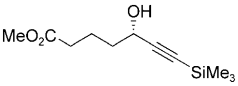
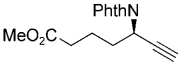
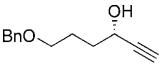
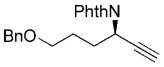
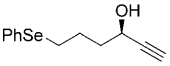
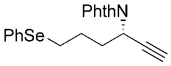
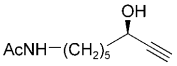
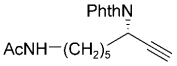
The present method seems to be of general application since different functionalities present in the substrates such as alkenyl, phenyl, ether, ester, and amide groups are tolerated under the mild reaction conditions employed. The *N*-phthaloyl β^3-amino acids **5** (Table 2) can be easily deprotected by reaction with hydrazine hydrated to give the corresponding β^3-amino acids hydrochloride. We have recently described this procedure in the case of the synthesis of and D-BAOA ($R = nC_5H_{11}$ in Scheme 1)[23] and iturinic acid ($R = nC_{11}H_{23}$ in Scheme 1).[24]

As indicated in Scheme 2 the acid and ester derivatives of propargylic amines **2f** and **2g** could not be obtained because



Scheme 2. Formation of lactone **7** from **2f** and lactone **8** from **2g**.

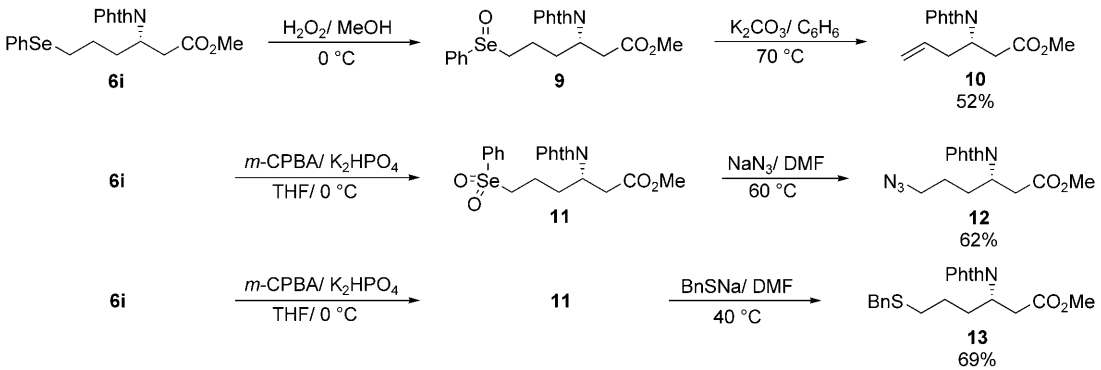
Table 1. Stereospecific conversion of propargylic alcohols **1** into the corresponding *N*-phthaloyl propargylic amines **2**.[a]

Propargylic alcohols **1**		*N*-Phthaloyl propargylic amines **2**		e.r.[b]	Yield [%]
	**1a**		**2a**	94:6	70
	ent-**1a**		*ent*-**2a**	98:2	56
	**1b**[c]		**2b**	99:1	85
	**1c**[c]		**2c**	96:4	67
	**1d**		**2d**	95:5	53
	ent-**1d**		*ent*-**2d**	96:4	60
	**1e**[c]		**2e**	93:7	67
	ent-**1e**		*ent*-**2e**	94:6	88
	**1f**[d]		**2f**	–[e]	90
	**1g**[d]		**2g**	–[e]	81
	**1h**		**2h**	92:8	67
	**1i**		**2i**	97:3	83
	ent-**1i**		*ent*-**2i**	93:7	91
	**1l**		**2l**	96:4	65

[a] The reaction was effected as reported by Mitsunobu. [b] Determined by chiral HPLC. [c] The reaction was performed on the trimethylsilyl derivative. [d] The enantiomeric ratio was 85:15 (chiral HPLC). [e] Enantiomeric ratio was not determined.

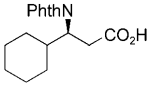
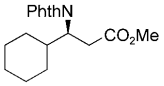
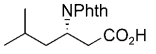
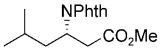
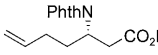
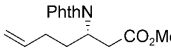
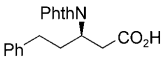
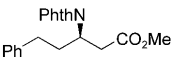
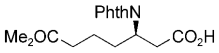
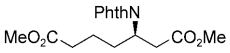
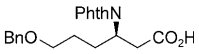
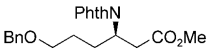
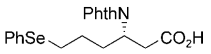
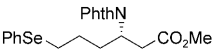
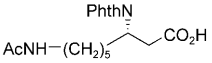
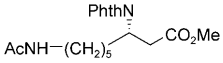
the treatment of their alkynyl phenyl selenide intermediates with *p*-toluenesulfonic acid monohydrate afforded the lactones **7** and **8** in high yields. The formation of these lactones is in agreement with previous observations[25] which indicated that when an alkynyl phenyl selenide holds an oxygen atom in a suitable position the reaction with *p*-toluenesulfonic acid gives rise to a proton-induced ring-closure reaction affording γ-lactones. The structure of lactones **7** and **8** was assigned on the basis of the stereochemistry of **1f**[26] and was also supported by NOE measurements.

The β^3-amino acid methyl esters **6i** and *ent*-**6i** represent important precursors for the synthesis of variously substituted β^3-amino acid derivatives because the phenylseleno group can be easily transformed by elimination or substitution. Some examples are reported in Scheme 3, oxidation of **6i** to the corresponding selenoxide **9** occurred smoothly in methanol at 0 °C with an excess of hydrogen peroxide.[27] The subsequent elimination was effected in benzene at 70 °C and in the presence of anhydrous potassium carbonate. The unsaturated β^3-amino acid derivative **10** was thus obtained in 52% yield. The unsaturated β^3-amino acid derivatives **6c** (Table 2) and **10** have reactive side chains that could be used for a range of synthetic transformations.[28,29] The reaction of **6i** with an excess of *m*-chloroperoxybenzoic acid (*m*-CPBA) in tetrahydrofuran and in the presence of potassium hydrogen phosphate[30] gave the corresponding selenone **11**. This is a valuable synthetic intermediate because of the excellent leaving group ability of the selenonyl group in nucleophilic substitution reactions.[31] Thus, by simply re-



Scheme 3. Synthesis of substituted β^3-amino acid derivatives **10**, **12**, and **13** from selenium-containing β^3-amino ester **6i**.

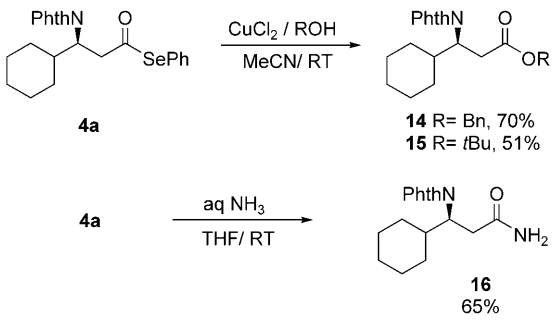
Table 2. Multistep preparation of enantiomerically enriched *N*-phthaloyl β^3-aminoacids **5** and esters **6** from *N*-phthaloyl propargylic amines **2**.

N-phthaloyl propargylic amines	*N*-phthaloyl β^3-amino acids		Yield[a] [%]	*N*-Phthaloyl β^3-aminoesters		Yield[a] [%]	e.r.[b]
2a		**5a**	62		**6a**	50	94:6
ent-**2a**	*ent*-**5a**		65	*ent*-**6a**		59	98:2
2b		**5b**	68		**6b**	20	99:1
2c		**5c**	65[c]		**6c**	30	96:4
2d		**5d**	46		**6d**	35	95:5
ent-**2d**	*ent*-**5d**		80	*ent*-**6d**		80	96:4
2e		**5e**	52		**6e**	56	93:7
ent-**2e**	*ent*-**5e**		62	*ent*-**6e**		51	94:6
2h		**5h**	50		**6h**	47	92:8
2i		**5i**	46		**6i**	43	97:3
ent-**2i**	*ent*-**5i**		35	*ent*-**6i**		45	93:7
2l		**5l**	67[c]		**6l**	45[d]	96:4

[a] Total yield calculated form **2**. [b] Determined by chiral HPLC. [c] The acid was obtained by oxidation with hydrogen peroxide. [d] Obtained by esterification of the corresponding acid with diazomethane.

acting the selenone intermediates **11** with sodium azide or sodium benzylthiolate in *N,N*-dimethylformamide the optically active β^3-amino acid derivatives such as **12** and **13** were obtained in good overall yield. Product **12** represents an important building block in the synthesis of peptidomimetics because of the particular reactivity of the azido group.[32]

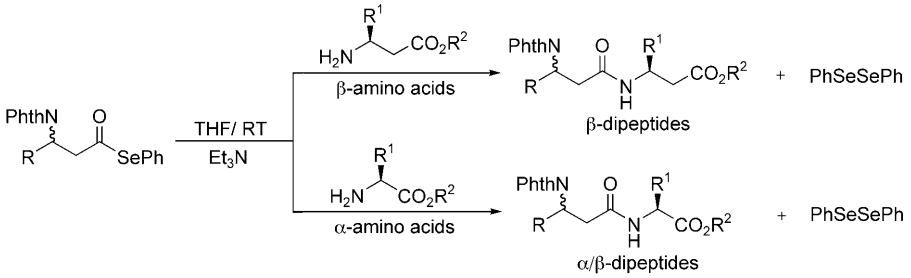
The *Se*-phenyl selenocarboxylate intermediates **4a** were also allowed to react with benzyl and *tert*-butyl alcohols in acetonitrile and in the presence of dry copper chloride. From compound **2a** the benzyl and *tert*-butyl β^3-amino ester



Scheme 4. Preparation of esters **14**, **15** and amide **16** from **4a**. Yields from **2a**.

derivatives **14** and **15** were obtained in reasonable overall yield (Scheme 4).

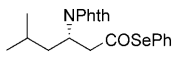
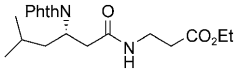
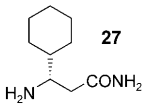
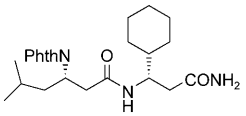
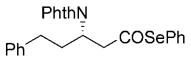
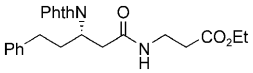
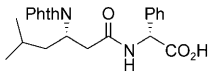
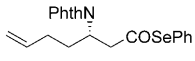
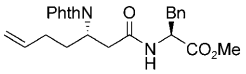
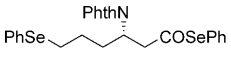
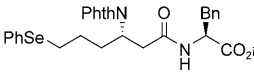
We then examined the reactivity of *Se*-phenyl selenocarboxylate **4** with nitrogen nucleophiles. The simple treatment of the *Se*-phenyl selenocarboxylate intermediate **4a** with an excess of dilute ammonia solution in tetrahydrofuran gave the corresponding carboxamide **16** in 65% yield starting from **2a** (Scheme 4). This great reactivity of the *Se*-phenyl selenocarboxylate intermediates **4** was then employed to develop a clean synthesis of β- and mixed α/β-dipeptides, which were simply obtained by reaction with C-protected β- or α-amino acids, respectively (Scheme 5). Reactions were performed in tetrahydrofuran at room temperature and in the presence of triethylamine. The β- and α/β-dipeptides **17**–**22** were obtained in good to excellent yields from the corresponding *N*-phthaloyl propargylic amines **2**. The results of these experiments are collected in Table 3. The leaving phenylselenol group, after oxidation by air, was almost quantitatively recovered as diphenyl diselenide at the end of the reactions Due to the nature of the transformations involved, no racemization occurred during the formation of the dipeptides **20**–**22**, as confirmed by their diastereoisomeric purity determined through proton nuclear magnetic resonance.



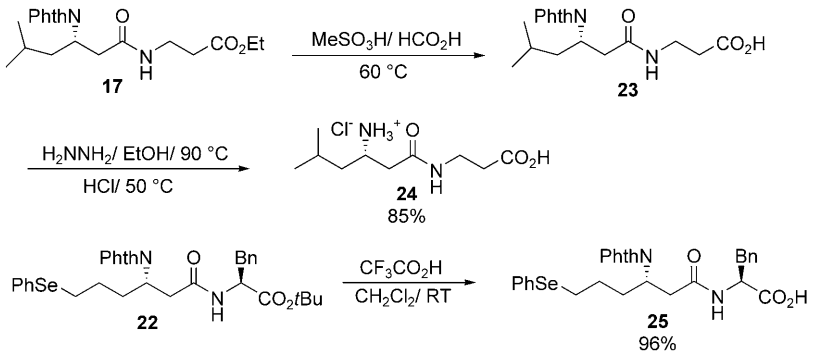
Scheme 5. Synthesis of β- and α/β-dipeptides from *Se*-phenyl selenocarboxylate intermediates **4**.

These N- and C-terminus protected dipeptides are interesting building blocks for the convergent solution-phase synthesis of oligopeptides after the proper selective deprotection of the N- and/or C-terminus. Thus, the reaction of dipeptide **17** with methanesulfonic acid at 60 °C and in formic acid as solvent[33] gave the intermediate acid **23** (Scheme 6). Finally, the treatment of the crude **23** with hydrazine hydrate in refluxing ethanol[34] afforded the β-dipeptide hydro-

Table 3. Coupling of *Se*-phenyl selenocarboxylate intermediates **4** with β- and α-amino acids.[a]

Se-Phenyl selenocarboxylate intermediates		β- or α-Amino acids	β- or α/β-Dipeptides		Yield[b] [%][c]
	**4b**	β-Ala-OEt·HCl		**17**	64
	4b			**18**	70[d]
	*ent*-**4d**	β-Ala-OEt·HCl		**19**	66
	4b	(*R*)-Phe-Gly		**20**	74[d]
	**4c**	PheOMe·HCl		**21**	70[d]
	**4i**	Phe-O*t*Bu·HCl		**22**	45[e]

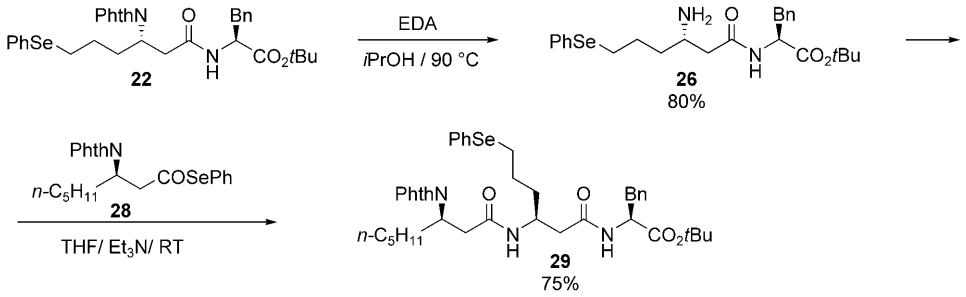
[a] The reaction was effected as described in Scheme 5. [b] Pure products after column chromatography. [c] Total yield calculated starting from **2**. [d] Diastereoisomeric ratio ≥ 97:3 (^{1}H NMR spectroscopy). [e] 94: 6 diastereoisomeric ratio (^{1}H NMR spectroscopy).



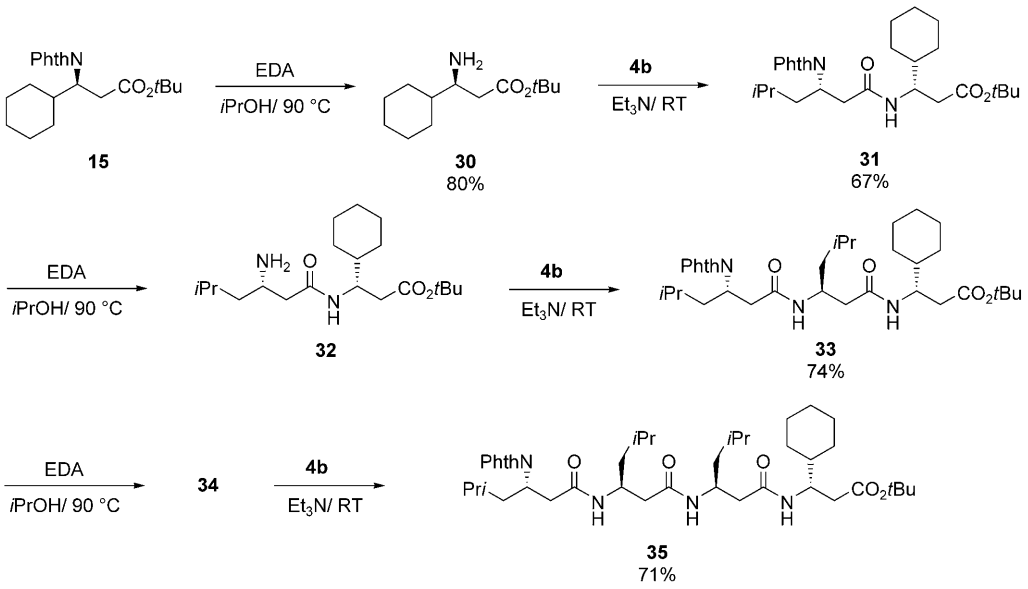
Scheme 6. N- and/or C-deprotection of some dipeptides.

chloride **24** in 85% yield. On the contrary the dipeptide **22** gave the deprotected dipeptide **25** in nearly quantitative yield after standard treatment with trifluoroacetic acid in dichloromethane.

Moreover, the *Se*-phenyl selenocarboxylate intermediates **4** have been successfully employed for the sequential solution-phase synthesis of oligopeptides by iterative couplings after selective deprotection of the N-terminus. The phthaloyl protective group is commonly cleaved by hydrazine hydrate in ethanol at room temperature or at reflux.[34] In our hands, however, the treatment of the β^3-amino ester **6a** and of the β-dipeptide **17** with hydrazine gave the corresponding amino hydrazide as major products. Also the benzyl ester **14** reacted at the carboxyl group with hydrazine as well as with ethylenediamine (EDA) in butanol at 90 °C.[35] We then found that the simple treatment of *tert*-butyl ester derivative **22** and of the amide **16** with ethylenediamine in isopropyl alcohol at 90 °C gave the corresponding *N*-deprotected derivatives **26** (Scheme 7) and **27** (Table 3) in excellent yields. This reaction requires the use of isopropyl alcohol as solvent because in butanol a partial transesterification is observed. Compounds **27** and **26** were employed for the solution-phase synthesis of β-dipeptide **18** (Table 3) and the mixed α/β-tripeptide **29** (Scheme 7), respectively. Racemization during these transformations was considered to be unlikely given the nature of the reactions involved. Similar deprotection of the *N*-phthaloyl amino ester **15** with EDA gave the amino ester **30** in 80% yield (Scheme 8). The reaction of **30** with crude *Se*-phenyl selenocarboxylate **4b** in tetrahydrofuran at room temperature and in the presence of triethylamine gave the dipeptide **31** in 67% yield. By reiterative *N*-deprotection followed by coupling with **4b** the length of the oligopeptide was extended. Reaction of the dipeptide **31** with ethylenediamine gave the amino free dipeptide **32**, which reacted with **4b** to afford the β-tripeptide **33** in 74% com-



Scheme 7. Multistep liquid-phase synthesis of α/β-tripeptide **29**. EDA = ethylenediamine.



Scheme 8. Multistep liquid-phase synthesis of the β-tetrapeptide **35** in 28% yield. EDA = ethylenediamine.

bined yield. Deprotection of **33** gave the β-tripeptide **34**, which by coupling with **4b** gave the β-tetrapeptide **35** in a combined yield of 71%

Conclusions

It is noteworthy that these selenium-mediated β- and α/β-oligopeptides syntheses occur without the use of coupling reagents and activating agents. The results presented indicate that the phthaloyl group represents a useful β-amino acids protecting group in oligopeptide synthesis. Although some applications of *Se*-phenyl selenocarboxylate derivatives of α-amino acids have appeared in the literature,[19a] the results described here represent the first application of these intermediates for the synthesis of β- and mixed α/β-oligopeptides under mild experimental conditions. This methodology seems to be of general application since different functionalities such as alkenyl, phenyl, ether, selenoether, ester, and amide groups are tolerated. We think that the present procedure favorably compares with other previously described methods for the synthesis of β^3-amino acids. Further applications of this methodology for the synthesis of γ- and δ-amino acid derivatives are currently ongoing in our laboratory.

Experimental Section

General remarks: ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DR 200 at 200 and 50.3 MHz, respectively, or on a Bruker DRX 400 instrument (at 400 and 100.62 MHz, respectively); unless otherwise specified $CDCl_3$ was used as the solvent. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual protonated solvent peak (^{1}H NMR) or to the appropriate solvent peak (^{13}C NMR). Coupling constants (*J*) are quoted in Hertz (Hz) to the nearest 0.1 Hz. FT-IR spectra were recorded with a Jasco model 410 spectrometer on a Diffuse Reflectance sampling cell. Only significant absorption maxima (ν_{max}) are reported, and all absorptions are reported in wavenumbers (cm^{-1}). GC-MS analysis were obtained with a HP-6890 gas chromatograph (HP-5MS capillary column 30 m, ID 0.25, film 0.25 μm) equipped with a HP-5973 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. HPLC was carried out using a HP 1100 system equipped with a UV/Vis detector with chiral columns and solvents specified. Melting points are uncorrected. Optical rotations were measured in a 50 mm cell with a Jasco DIP-1000 digital polarimeter 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}. Elemental analyses were carried out on a Carlo Erba 1106 elemental analyzer. Et_2O and CH_2Cl_2 commercial grade were used without purification. THF, DMF, MeOH, and EtOH were dried by using standard procedures. Unless otherwise specified all the reactions were carried out under an argon atmosphere. Reactions were monitored by thin-layer chromatography (TLC) carried out on aluminum foil sheets pre-coated with silica (Merck silica gel 60 F_{254}), which were visualized by the quenching of UV fluorescence (λ_{max}254 nm) and/or by staining with 5% w/v phosphomolybdic acid in EtOH followed by heating. Column chromatography was performed on Merck silica gel 60 (70–230 mesh).

The syntheses and spectral data of propargylic alcohols **1a–l** as well as methyl esters **6a–e** and **6h–l** can be found in the Supporting Information.

Synthesis of *N*-phthaloyl propargylic amines 2a–l:

2-[(1*R*)-1-cyclohexylprop-2-yn-1-yl]-1*H*-isoindole-1,3(2*H*)-dione (2a): To a stirred solution of propargylic alcohol **1a** (0.53 g, 3.86 mmol) and phthalimide (0.79 g, 5.40 mmol) in THF (30 mL) was added triphenylphosphine (1.41 g, 5.10 mmol). Diisopropyl azodicarboxylate (DIAD; 1.17 mL, 5.80 mmol) was subsequently added dropwise at 0°C. After 8 h the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel using a 80:20 mixture of petroleum ether and diethyl ether as eluent. Compound **2a** was obtained as a colorless oil in 70% yield. $[\alpha]_D^{24} = -13.26$ ($c = 1.46$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.92$–7.62 (m, 4H; CH), 4.71 (dd, ^3J(H,H) = 10.25 Hz, ^4J(H,H) = 2.5 Hz, 1H; CHN), 2.41 (d, ^4J(H,H) = 2.5 Hz, 1H; CH), 2.31–2.11 (m, 2H; CH_2), 1.89–1.49 (m, 5H; CH_2, CH), 1.34–0.79 ppm (m, 4H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta = 167.0$ (2C), 134.0 (2C), 131.5 (2C), 123.3 (2C), 79.4, 72.4, 46.9, 39.5, 30.3, 29.2, 25.2, 21.8, 21.4 ppm; GC-MS: *m/z* (%): 267(2) [M^+], 199 (5), 185 (100), 157 (20), 130 (14), 104 (10); elemental analysis calcd (%) for

$C_{17}H_{17}NO_2$: C 76.38, H 6.41, N 5.24; found: C 76.59, H 6.18, N 4.99. Analytical HPLC analysis: Chiralpack AD–H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (0.8:99.2), flow rate: 0.5 mL min^{-1}, UV detection at 230 nm; t_r (*R* enantiomer) = 46.63 min: e.r. = 94:6.

The synthetic procedure illustrated above was also employed for the synthesis of *N*-protected propargylic amines *ent*-**2a**, **2b, 2c**, **2d**, *ent*-**2d, 2f**, and **2g** but in the case of **2d** and *ent*-**2d** tributylphosphine was employed, whereas for compounds **2e**, *ent*-**2e, 2h, 2i**, *ent*-**2i** as well as for **2l** di-*tert*-butyl azodicarboxylate (DBAD) was utilized. For products **2b**, **2c**, **2e** and *ent*-**2e** a standard desilylative step was necessary before purification by column chromatography. Yields, physical and spectral data of the new compounds are reported below.

2-[(1*S*)-1-cyclohexylprop-2-yn-1-yl]-1*H*-isoindole-1,3(2*H*)-dione (*ent*-2a): Yield 56%; oil; $[\alpha]_D^{23} = 11.52$ ($c = 1.50$ in $CHCl_3$); Analytical HPLC analysis: Chiralpack AD–H column (250×4 mm, Daicel), eluent: iPrOH/hexane (0.8:99.2), flow rate: 0.5 mL min−1, UV detection at 230 nm; t_r (*S* enantiomer) = 53.06 min: e.r. = 98:2.

2-[(1*S*)-1-Isobutylprop-2-yn-1-yl]-1*H*-isoindole-1,3(2*H*)-dione (2b): Yield 85%; oil; $[\alpha]_D^{22} = -10.52$ ($c = 1.14$ in dioxane); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.92$–7.61 (m, 4H; CH), 5.21–5.05 (m, 1H; CHN), 2.10–1.88 (m, 2H; CH_2), 1.69–1.53 (m, 1H; CH), 0.94 (d, ^3J(H,H) = 4.9 Hz, 3H; CH_3), 0.91 (d, ^3J(H,H) = 4.9 Hz, 3H; CH_3), 0.21 ppm (s, 9H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 166.9 (2C), 133.9 (2C), 131.4 (2C), 123.3 (2C), 101.9, 86.7, 41.9, 40.6, 27.7, 26.0, 25.1 (2C), 0.12 ppm (3C); GC–MS: *m/z* (%): 313(6) [M^+], 298 (28), 270 (21), 256 (100), 204(70), 130 (55), 102 (19), 73 (24); elemental analysis calcd (%) for $C_{18}H_{23}NO_2Si$: C 68.97, H 7.40, N 4.47; found: C 69.49, H 7.65, N 4.19. Analytical HPLC: Chiracel OD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (1:99), flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_r (*R* enantiomer) = 13.57 min, t_R (*S* enantiomer) = 14.21 min: e.r. = 1:99.

2-[(1*S*)-1-Ethynylpent-4-en–1-yl]-1*H*--isoindole-1,3(2*H*)-dione (2c): Yield 67%; m.p. 50–55°C; $[\alpha]_D^{25} = 10.26$ ($c = 2.38$ in $CHCl_3$); 1H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.91$–7.65 (m, 4H; CH), 5.76 (ddt, ^3J(H,H) = 16.8, 10.3 and 6.6 Hz, 1H; CH), 5.09–5.06 (m, 1H; CHN), 5.05–5.01 (m, 1H; CH_2), 4.99–4.97 (m, 1H; CH2), 2.30–2.08 (m, 2H; CH_2), 2.20–2.01 (m, 2H; CH_2), 0.97–0.15 ppm (s, 9H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 166.8 (2C), 136.5, 133.9 (2C), 131.8, 123.3 (2C), 115.8, 101.4, 88.6, 41.7, 32.4, 30.4, 27.6, −0.18 ppm (3C); GC–MS: *m/z* (%): 311(6) [M^+], 296 (27), 256 (44), 220 (26), 204 (100), 149 (39), 130 (77), 102 (25), 73 (49); elemental analysis calcd (%) for $C_{18}H_{21}NO_4Si$: C 69.41, H 6.80, N 4.50; found: C 69.66, H 6.59, N 4.86. Analytical HPLC: Chiracel OD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (1:99), flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_r (*R* enantiomer) = 5.10 min, t_R (*S* enantiomer) = 7.65 min: e.r. = 4:96.

2-[(1*R*)–1-(2-Phenylethyl)prop-2-yn-1-yl]-1*H*-isoindole-1,3(2*H*)-dione (2d): Yield 53%; oil; $[\alpha]_D^{26} = -17.27$ ($c = 1.72$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.91$–7.62 (m, 4H; CH), 7.30–7.01 (m, 5H, CH), 5.15–4.99 (m, 1H; CHN), 3.92–2.55 (m, 2H; CH_2), 2.54–2.31 (m, 2H; CH_2), 2,05 ppm (s, 1H; CH); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 166.8 (2C), 140.0, 134.0 (2C), 131.6 (2C), 128.3 (4C), 126.0, 123.4 (2C), 79.9, 72.2, 41.0, 34.4, 32.4 ppm; GC–MS: *m/z* (%): 288 (12) [M^+], 261 (34), 185 (100), 157 (28), 142 (62), 130 (29), 104 (24), 76 (22); elemental analysis calcd (%) for $C_{19}H_{15}NO_2$: C 78.87, H 5.23, N 4.84; found: C 78.99, H 6.61, N 4.49. Analytical HPLC: Chiralpack AD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (10:90), flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_r (*R* enantiomer) = 13.90 min: e.r. = 95:5.

2-[(1*S*)-1-(2-Phenylethyl)prop-2-yn-1-yl]-1*H*-isoindole-1,3(2*H*)-dione (*ent*-2d): Yield 60%; oil; $[\alpha]_D^{26} = 20.90$ ($c = 2.97$ in $CHCl_3$). Analytical HPLC: Chiralpack AD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (10:90), flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_r (*S* enantiomer) = 15.30 min: e.r. = 96:4.

Methyl (5*R*)-5-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hept-6-ynoate (2e): Yield 67%; m.p. 59–60°C; $[\alpha]_D^{25} = 7.22$ ($c = 1.79$ in Et_2O); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.82$–7.62 (m, 4H; CH), 5.11–4.95 (m, 1H; CHN), 3.69 (s, 3H, CH_3O), 2.45–2.29 (m, 2H; CH_2), 2.20–2.01 (m, 2H; CH_2), 1.82–1.65 (m, 2H; CH_2), 0.97–0.19 ppm (s, 9H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta = 173.3$, 166.8 (2C), 134.0 (2C), 131.7 (2C), 123.3 (2C), 101.1, 88.6, 51.5, 41.8, 33.0, 32.6, 21.6, −0.23 ppm (3C); GC-MS: *m/z* (%): 357(24) [M^+], 310 (36), 270 (22), 256 (100), 204(52), 130 (66), 102 (16), 73 (22); elemental analysis calcd (%) for $C_{19}H_{23}NO_4Si$: C 63.84, H 6.49, N 3.92; found: C 64.01, H 6.14, N 3.77. Analytical HPLC: Chiracel OD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (5:95), flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_r (*R* enantiomer) = 10.58 min, e.r. = 93:7.

Methyl (5*S*)-5-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hept-6-ynoate (*ent*-2e): Yield 56%; m.p. 58–61°C; $[\alpha]_D^{21} = -5.09$ ($c = 1.63$ in Et_2O). Analytical HPLC: Chiracel OD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (5:95), flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_r (*S* enantiomer) = 14.17 min, e.r. = 94:6.

2-{(1*R*)-1-[(1*S*)-1-(Benzyloxy)ethyl]prop-2-ynyl}-1*H*-isoindole-1,3(2*H*)-dione (2f): Yield 81%; oil; $[\alpha]_D^{19} = -5.55$ ($c = 1.33$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 7.92–7.60 (m, 4H; CH), 7.49–7.15 (m, 5H; CH), 5.13 (dd, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 2.5 Hz, 1H; CHN), 4.79 (d, ^2J(H,H) = 11.5 Hz, 1H, CH_2O), 4.69 (d, ^2J(H,H) = 11.5 Hz, 1H, CH_2O), 4.25 (dq, ^3J(H,H) = 7.7 Hz, ^3J(H,H) = 6.3 Hz, 1H; CHO), 2.41 (d, ^4J(H,H) = 2.5 Hz, 1H, CH), 1.20 ppm (d, ^3J(H,H) = 6.3 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 166.8 (2C), 137.2, 134.1 (2C), 131.5 (2C), 128.1 (2C), 127.5 (2C), 123.4 (3C), 78.6, 75.3, 73.4, 72.6, 45.5, 17.0 ppm; GC-MS: *m/z* (%): 274(4) [M^+−45], 213(30), 185 (100), 128 (40), 91 (48), 76 (7); elemental analysis calcd (%) for $C_{20}H_{17}NO_3$: C 75.22, H 5.37, N 4.39; found: C 75.53, H 5.11, N 4.65.

2-{(1*S*)-1-[(1*S*)-1-(Benzyloxy)ethyl]prop–2-ynyl}-1*H*-isoindole-1,3(2*H*)-dione (2g): Yield 90%; m.p. 74–76°C; $[\alpha]_D^{18} = 43.94$ ($c = 1.30$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.91$–7.62 (m, 4H; CH), 7.48–7.19 (m, 5H; CH), 5.12 (dd, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 2.5 Hz, 1H; CHN), 4.69 (d, ^2J(H,H) = 11.5 Hz, 1H, CH_2O), 4.67 (d, ^2J(H,H) = 11.5 Hz, 1H, CH_2O), 4.23 (dq, ^3J(H,H) = 7.7 Hz, ^3J(H,H) = 6.3 Hz, 1H; CHO), 2.42 (d, ^4J(H,H) = 2.5 Hz, 1H, CH), 1.24 ppm (d, ^3J(H,H) = 6.3 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 166.9 (2C), 137.8, 133.8 (2C), 131.7 (2C), 128.05 (2C), 127.4 (2C), 123.3 (3C), 86.3, 73.8, 73.4, 72.6, 46.8, 17.4 ppm;

2-{(1*R*)-1-[3-(Benzyloxy)propyl]prop-2-ynyl}-1*H*-isoindole-1,3(2*H*)-dione (2h): Yield 67%; oil; $[\alpha]_D^{25} = 5.76$ ($c = 1.66$ in dioxane); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.91$–7.62 (m, 4H; CH), 7.40–7.19 (m, 5H, CH), 5,15–4,99 (m, 1H; CHN), 4,51 (s, 2H; CH_2O), 3.43 (t, ^3J(H,H) = 6.2 Hz, 2H; CH_2O), 2.39 (s, 1H, CH), 2.35–2.05 (m, 2H; CH_2), 1.92–1.61 ppm (m, 2H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 166.9 (2C), 138.2, 134.1 (2C), 131.6 (2C), 128.3 (2C), 127.5 (3C), 123.3 (2C), 80.0, 72.9, 72.0, 69.1, 41.2, 30.2, 26.5 ppm; GC-MS: *m/z* (%): 242 (12) [M^+−91], 226 (10), 212 (13), 184 (76), 148 (50), 130 (57), 91 (100), 77 (21); elemental analysis calcd (%) for $C_{21}H_{19}NO_3$: C 75.66, H 5.74, N 4.20; found: C 75.40, H 5.85, N 4.49. Analytical HPLC: Chiracel OD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (4:96), flow rate: 1 mL min−1, UV detection at 254 nm; t_r (*S* enantiomer) = 28.80 min, t_r (*R* enantiomer) = 31.35 min: e.r. = 8:92.

2-{(1*S*)-1-[3-(Phenylseleno)propyl]prop-2-yn-1-yl}-1*H*-isoindole-1,3(2*H*)-dione (2i): Yield 83%; oil; $[\alpha]_D^{24} = -12.50$ ($c = 1.50$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.91$–7.62 (m, 4H; CH), 7.51–7.35 (m, 2H, CH), 7.25–7.05 (m, 3H, CH), 5.11–4.95 (m, 1H; CHN), 3.05–2.76 (m, 2H; CH_2), 2.35 (s, 1H, CH), 2.31–2.09 (m, 2H; CH_2), 2,99–2.69 ppm (m, 2H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 166.6 (2C), 133.9 (2C), 132.5 (2C), 131.3(2C), 129.5, 128.7(2C), 126.6, 123.2 (2C), 79.6, 72.6, 40.6, 32.9, 26.4 ppm (2C); GC-MS: *m/z* (%): 383 (16) [M^+], 226 (43), 198(55), 184 (100), 160 (27), 130 (71), 77 (22); elemental analysis calcd (%) for $C_{20}H_{17}NO_2Se$: C 62.83, H 4.48, O 8.37, N 3.66; found: C 63.87, H 5.01, O 8.55, N 3.99. Analytical HPLC: Chiralpack AD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (5:95), flow rate: 1 mL min−1, UV detection at 254 nm; t_r (*S* enantiomer) = 34.30 min: e.r. = 97:3.

2-{(1*R*)-1-[3-(Phenylseleno)propyl]prop-2-yn-1-yl}-1*H*-isoindole-1,3(2*H*)-dione (*ent*-2i): Yield 91%; oil; $[\alpha]_D^{27} = 13.31$ ($c = 1.87$ in $CHCl_3$). Analytical HPLC: Chiralpack AD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (5:95), flow rate: 1 mL min−1, UV detection at 254 nm; t_r (*R* enantiomer) = 28.20 min: e.r. = 93:7.

***N*-[(6*S*)-6-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oct-7-ynyl]acetamide (2l)**: Yield 65%; oil; $[\alpha]_D^{23} = -8.88$ ($c = 0.615$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.91$–7.62 (m, 4H; CH), 5.72–5.45 (br s, 1H; NH), 5.11–4,93 (m, 1H; CHN), 3.31–3.11 (m, 2H; CH_2N), 2.41 (d, ^4J(H,H) = 2.5 Hz, 1H; CH), 1.91 (s, 3H, CH_3), 1.52–1.19 ppm (m, 8H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta = 170.2$, 167.0 (2C), 134.2 (2C), 131.9 (2C), 123.4 (2C), 80.0, 72.0, 41.2, 39.3, 33.1, 29.2, 26.0, 25.8, 23.2 ppm; GC-MS: *m/z* (%): 269(8) [$M^+ - 43$], 199 (25), 184 (100), 128 (44), 106 (35), 76 (22); elemental analysis calcd (%) for $C_{18}H_{20}N_2O_3$: C 69.21, H 6.45, N 8.97; found: C 69.55, H 6.73, N 8.76. Analytical HPLC: Chiracel OD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (4:96), flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_r (*R* enantiomer) = 22.28 min, t_r (*S* enantiomer) = 24.88 min: e.r. = 4:96.

Synthesis of *N*-phthaloyl β^3-amino acids:

(3*R*)-3-cyclohexyl-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanoic acid (*ent*-5a): To a solution of *ent*-**2a** (0.54 g, 2.02 mmol) in dry DMF (10 mL), copper (I) iodide (0.75 g, 4.00 mmol) and phenylselenenyl bromide (0.52 g, 2.20 mmol) were added. The resulting mixture was stirred, under argon, for 48 h. The reaction was then quenched by careful addition of 7% aq ammonia solution (15 mL). The reaction mixture was then extracted with diethyl ether (3×10 mL) and the combined organic layers were dried over anhydrous sodium sulfate and then evaporated. The crude *ent*-**3a** was dissolved in CH_2Cl_2 (50 mL), and *p*-toluenesulfonic acid monohydrate (0.76 g, 4.00 mmol) was added. The resulting suspension was heated at 40°C. The progress of the reaction was monitored by TLC. After 7 h solid K_2CO_3 (0.55 g, 4.0 mmol) was added and then the mixture was filtered. The filtrate was dried and evaporated to obtain the crude *ent*-**4a** (0.91 g). To a solution of the crude Se-phenyl selenocarboxylate in acetonitrile (20 mL), copper (II) chloride hydrate (0.37 g, 2.17 mmol) was added. The mixture was stirred at room temperature and monitored by TLC. After 13 h the substrate was completely consumed and the reaction mixture was diluted with dichloromethane. Tartaric acid (0.33 g, 2.2 mmol) was then added. The reaction mixture was stirred for few minutes, then filtered through a celite pad and the filtrate concentrated. The crude product was purified by column chromatography on silica gel using a 95:5 mixture of dichloromethane and methanol as eluent. Compound *ent*-**5a** was obtained in 65% yield: m.p. 45–47°C; $[\alpha]_D^{24} = 13.30$ (c = 1.49 in $CHCl_3$); 1H NMR (200 MHz, [D$_6$]DMSO, 25°C): $\delta =$ 11.05 (br s, 1H, OH), 7.81–7.69 (m, 4H; CH), 4.22–4.07 (m, 1H; CHN), 2.95 (dd, ^2J-(H,H) = 15.9 Hz, ^3J(H,H) = 9.8 Hz, 1H; CH_2) 2.75 (dd, ^2J(H,H) = 15.9 Hz, ^3J(H,H) = 4.9 Hz, 1H; CH_2), 1.91–1.41 (m, 5H; CH2, CH), 1.31–0.69 ppm (m, 6H; CH_2); ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25°C): $\delta = 170.0$, 167.9 (2C), 134.5 (2C), 130.9 (2C), 123.0 (2C), 52.6, 39.3, 29.7, 29.2, 25.9, 25.6, 25.5, 23.3 ppm (3C); GC-MS: *m/z* (%): 301(29) [M^+], 242 (14), 218 (100), 200 (100), 173 (97), 148 (45),130 (44), 104 (22); elemental analysis calcd (%) for $C_{17}H_{19}NO_4$: C 67.76, H 6.36, N 4.65; found: C 67.51, H 6.43, N 4.47.

The synthetic procedure illustrated above for the preparation of the *N*-phthaloyl β^3-amino acid *ent*-**5a** from *N*-protected propargylic amines *ent*-**2a** was also utilized for the syntheses of **5a**, **5b**, and **5d–i** . Yields, physical and spectral data of all the new compounds are reported below.

(3*S*)-3-Cyclohexyl-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanoic acid (5a): Yield 62%; m.p. 45°C; $[\alpha]_D^{23} = -12.44$ ($c = 1.32$ in $CHCl_3$).

(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-methylhexanoic acid (5b): Yield 68%; oil, $[\alpha]_D^{26} = 11.13$ ($c = 1.57$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 12.73$ (br s, 1H, OH), 7.89–7.62 (m, 4H; CH), 4.87–4.65 (m, 1H; CHN), 3.30–3.11 (m, 1H; CH_2), 2.89–2.71 (m, 1H; CH_2), 2.21–2.08 (m, 1H; CH), 1.57–1.36 (m, 2H; CH_2), 0.94 (d, ^3J(H,H) = 6.0 Hz, 3H; CH_3), 0.91 ppm (d, ^3J(H,H) = 6.0 Hz, 3H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta = 176.8$, 168.2 (2C), 133.9 (2C), 131.6 (2C), 123.2 (2C), 45.8, 41.1, 36.9, 24.9, 23.0, 21.5 ppm; GC-MS: *m/z* (%): 275(31) [M^+], 216 (25), 200 (100), 174 (95), 160 (56), 148 (80), 130 (87), 104 (41), 76 (37); elemental analysis calcd (%) for $C_{15}H_{17}NO_4$: C 65.44, H 6.22, N 5.09; found: C 65.69, H 6.47, N 4.83.

(3*R*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-phenylpentanoic acid (5d): Yield 46%; m.p. 136°C; $[\alpha]_D^{24} = -11.54$ ($c = 1.21$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 11.23$ (br s, 1H; OH), 7.62–7.83 (m, 4H; CH), 6.99–7.21 (m, 5H, CH), 4.62–4.71 (m, 1H; CHN), 3.05–3.31 (m, 1H; CH_2), 2.77–2.97 (m, 1H, CH_2), 2.39–2.71 (m, 2H; CH_2), 1.89–2.16 ppm (m, 2H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta = 175.3$, 168.1 (2C), 140.3, 133.8 (2C), 131.4 (2C), 128.1 (4C), 125.7, 123.0 (2C), 47.5, 33.3, 32.6 ppm (2C); elemental analysis calcd (%) for C19H17NO4: C 70.58, H 5.30, N 4.33; found: C 70.70, H 5.52, N 4.14.

(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-phenylpentanoic acid (*ent*-5d): Yield 80%; m.p. 138°C; $[\alpha]_D^{24} = 22.17$ ($c = 1.18$ in $CHCl_3$).

(3*R*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-7-methoxy-7-oxoheptanoic acid (5e): Yield 52%; oil; $[\alpha]_D^{23} = 7.86$ ($c = 1.50$ in dioxane); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 12.12 (br s, 1H, OH), 7.85–7.62 (m, 4H; CH), 4.71–4.55 (m, 1H; CHN), 3.60 (s, 3H; CH_3O), 3.18 (dd, ^2J-(H,H) = 16.7 Hz, ^3J(H,H) = 9.0 Hz, 1H; CH_2), 2.83 (dd, ^2J(H,H) = 16.7 Hz, ^3J(H,H) = 5.4 Hz, 1H; CH_2), 2.39–2.21 (m, 2H; CH_2), 2.18–2.03 (m, 1H; CH_2), 1.81–1.66 (m, 1H; CH_2), 1.61–1.45 ppm (m, 2H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 176.3, 173.5, 168.2 (2C), 134.0 (2C), 131.6 (2C), 123.2 (2C), 51.5, 47.1, 36.5, 33.2, 31.6, 21.5 ppm; elemental analysis calcd (%) for $C_{16}H_{17}NO_6$: C 60.18, H 5.37, N 4.39; found: C 60.01, H 5.60, N 5.19.

(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-7-methoxy-7-oxoheptanoic acid (*ent*-5e): Yield 62%; oil; $[\alpha]_D^{23} = -1.77$ ($c = 1.20$ in dioxane).

(3*R*)-6-(Benzyloxy)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hexanoic acid (5h): Yield 50%; oil; $[\alpha]_D^{23} = 1.11$ ($c = 1.95$ in dioxane); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 11.12$ (br s, 1H; OH), 7. 91–7.62 (m, 4H; CH), 7.40–7.19 (m, 5H, CH), 4.78–4.51 (m, 1H; CHN); 4,45 (s, 2H; CH_2O), 3.52–3.40 (m, 2H; CH_2O), 3.33–3.12 (m, 1H; CH_2), 2.33–2.03 ppm (m, 1H; CH_2), 1.98–1.79 ppm (m, 2H; CH_2), 1.70–1.49 ppm (m, 2H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta = 175.5$, 168.2 (2C), 138.1, 133.9 (2C), 131.6 (2C), 128.2 (2C), 127.6 (3C), 123.2 (2C), 72.8, 69.2, 47.4, 39.2, 28.9, 26.4 ppm; elemental analysis calcd (%) for $C_{21}H_{21}NO_5$: C 68.65, H 5.76, N 3.81; found: C 68.78, H 5.98, N 3.65.

(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-6-(phenylseleno)hexanoic acid (5i): Yield 46%; oil; $[\alpha]_D^{23} = -23.63$ ($c = 2.25$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 12.05$ (br s, 1H; OH), 7.85–7.65 (m, 4H; CH), 7.42–7.32 (m, 2H, CH), 7.19–7.06 (m, 3H, CH) 4.71–4.55 (m, 1H; CHN), 2.97–2.69 (m, 4H, CH_2), 2.29–2.13 (m, 1H; CH_2), 1.97–1.69 (m, 1H; CH_2), 1.71–1.51 ppm (m, 2H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 175.5$, 168.1 (2C), 133.9 (2C), 132.7 (2C), 131.5 (2C), 130.4, 128.9 (2C), 126.8, 123.2 (2C), 46.9, 32.1, 31.8, 26.8, 26.5 ppm; elemental analysis calcd (%) for $C_{20}H_{19}NO_4Se$: C 57.70, H 4.60, N 3.36; found: C 57.43, H 4.92, N 3.24.

(3*R*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-6-(phenylseleno)hexanoic acid (*ent*-5i): Yield 46%; oil; $[\alpha]_D^{29} = 8.17$ ($c = 1.51$ in $CHCl_3$).

Synthesis of *N*-phthaloyl β^3-amino acids 5c and 5l: To a solution of **2c** (0.75 g, 3.15 mmol) in dry DMSO (15 mL), copper (I) iodide (6 mg, 31 μmol) and diphenyl diselenide (0.49 g, 1.57 mmol) were added.[36] The resulting mixture was stirred, under argon, for 48 h. The reaction was quenched with water (10 mL) and the mixture was then extracted with diethyl ether (3×10 mL). The combined organic layers were dried over sodium sulfate anhydrous and then evaporated. The crude **3c** was dissolved in CH_2Cl_2 (50 mL) and *p*-toluenesulfonic acid monohydrate (1.19 g, 6.30 mmol) was added. The resulting suspension was heated at 40°C. The progress of the reaction was monitored by TLC. After 4 h solid K_2CO_3 (0.87 g, 6.30 mmol) was added and then the mixture was filtered. The filtrate was dried and evaporated to obtain crude **4c** which was dissolved in tetrahydrofuran (40 mL) at room temperature. Hydrogen peroxide 30% solution (1.50 mL) was then added. When TLC analysis indicated the absence of selenol ester, anhydrous sodium sulfate was added and the resulting suspension filtered off. The filtrate was evaporated and the pure acid **5c** was obtained after column chromatography using a mixture of dichloromethane/methanol 98:2 as eluent.

(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hept-6-enoic acid (5c): Yield 65%; oil; $[\alpha]_D^{24} = 6.56$ ($c = 1.49$ in $CHCl_3$); 1H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 8.04–7.71 (m, 4H; CH), 12.05 (br s, 1H; OH), 5.87 (ddt, ^3J(H,H) = 16.9, 10.3, 6.7 Hz, 1H; CH), 5.20–4.89 (m, 2H; CH_2), 4.79–4.61 (m, 1H; CHN), 3.35 (dd, ^2J(H,H) = 16.4 Hz, ^3J(H,H) = 9.2 Hz, 1H; CH_2), 2.99 (dd, ^2J(H,H) = 16.4 Hz, ^3J(H,H) = 5.5 Hz, 1H; CH_2), 2.51–1.83 ppm (m, 4H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta =$

176.0, 168.2 (2C), 136.7, 133.9 (2C), 131.6 (2C), 123.2 (2C), 115.4, 47.2, 36.5, 31.4, 30.4 ppm; elemental analysis calcd (%) for $C_{15}H_{15}NO_4$: C 65.92, H 5.53, N 5.13; found: C 65.73, H 5.88, N 5.01.

The *N*-phthaloyl amino acid **5l** was obtained as **5c** by hydrogen peroxide treatment of the corresponding *Se*-phenyl selenocarboxylate **4l** which was prepared as described for *ent*-**4a**.

(3*S*)-8-(Acetylamino)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)octanoic acid (5l): Yield 67%; oil; $[\alpha]_D^{18} = -3.39$ ($c = 1.30$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 10.91$ (br s, 1H; OH), 7.91–7.62 (m, 4H; CH), 4.59 (br s, 1H; NH), 4.35–4.29 (m, 1H; CHN), 3.29–3.11 (m, 2H; CH_2N), 3.04–2.92 (m, 1H; CH_2), 2.80–2.65 (m, 1H; CH_2), 1.91 (s, 3H, CH_3), 1.95–1.78 (m, 2H; CH_2), 1.52–1.19 ppm (m, 6H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta = 178.5$, 168.3 (2C), 134.1 (2C), 132.7 (2C), 123.8 (2C), 49.6, 42.5, 39.3, 28.7, 25.8, 25.3, 24.8, 23.2, 20.8 ppm; elemental analysis calcd (%) for $C_{18}H_{22}N_2O_5$: C 62.42, H 6.40, N 8.09; found: C 62.54, H 6.72, N 7.96.

Synthesis of lactones 7 and 8: To a solution of **2f** (0.32 g, 1.00 mmol) in dry DMF (5 mL), copper (I) iodide (0.38 g, 2.00 mmol) and phenylselenenyl bromide (0.26 g, 1.10 mmol) were added. The resulting mixture was stirred, under argon, for 48 h. The reaction was then quenched by careful addition of 7% aqueous ammonia solution (15 mL). The crude **3f** was dissolved in CH_2Cl_2 (15 mL) and *p*-toluenesulfonic acid monohydrate (0.38 g, 2.0 mmol) was added. The resulting suspension was heated at 60°C. The progress of the reaction was monitored by TLC. After 4 h solid K_2CO_3 (0.27 g, 2.03 mmol) was added and then the mixture was filtered. The filtrate was dried and evaporated. The pure lactone **7** was obtained after column chromatography using a mixture of dichloromethane/methanol 90:10 as eluent.

2-[(2*S*,3*S*)-2-Methyl-5-oxotetrahydrofuran-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (7): Yield 78%; m.p. 194–195°C; $[\alpha]_D^{20} = -69.94$ ($c = 1.20$ in $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3, 25°C, TMS): $\delta = 7.71$–7.91 (m, 4H; CH), 5.12–5.01 (ddd, ^3J(H,H) = 8.9, 6.3, 2.0 Hz, 1H; CHN), 4.99–4.81 (dq, ^3J(H,H) = 6.4, 6.3, Hz, 1H, CHO)· 3.05 (dd, ^2J(H,H) = 18.0 Hz, ^3J(H,H) = 8.9 Hz, 1H; CH_2), 2.96 (dd, ^2J(H,H) = 18.0 Hz, ^3J(H,H) = 2.0 Hz, 1H; CH), 1.25 ppm (d, ^3J(H,H) = 6.4 Hz, 3H; CH3); ^{13}C NMR (100 MHz, CDCl3, 25°C, TMS): $\delta =$ 174.3, 167.8 (2C), 134.5 (2C), 131.1 (2C), 123.3 (2C), 78.0, 49.7, 31.7, 14.9 ppm; GC-MS: *m/z* (%): 201(13) [$M^+ - 44$], 173 (100), 146 (8), 104 (16), 76 (19); elemental analysis calcd (%) for $C_{13}H_{11}NO_4$: C 63.67, H 4.52, N 5.71; found: C 63.52, H 4.80, N 5.55.

The synthetic procedure illustrated above was also employed for the synthesis of lactone **8** which has fortunately been separated by chiral HPLC.

2-[(2*S*,3*R*)-2-Methyl-5-oxotetrahydrofuran-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (8): Yield 79%; m.p. 143–144°C; $[\alpha]_D^{20} = 8.79$ ($c = 1.14$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 7.57–7.80 (m, 4H; CH), 4.78–4.69 (dd, 3J(H,H) = 6.2, 5.9 Hz, 1H; CHO), 4.61–4.51 (ddd, ^3J-(H,H) = 9.5, 8.2, 5.9 Hz, 1H, CHN), 3.18 (dd, ^2J(H,H) = 17.6 Hz, ^3J-(H,H) = 8.2 Hz, 1H; CH_2), 2.72 (dd, ^2J(H,H) = 17.6 Hz, ^3J(H,H) = 9.5 Hz, 1H; CH), 1.31 ppm (d, ^3J(H,H) = 6.2 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 173.3, 167.5 (2C), 134.6 (2C), 131.4 (2C), 123.3 (2C), 78.0, 51.9, 31.9, 19.5 ppm; Analytical HPLC: Chiralpack AD-H column (250×4 mm, Daicel), eluent: *i*PrOH/hexane (5:95), flow rate: 1 mL min^{-1}, UV detection at 254 nm; t_r (2*S*,3*R* enantiomer) = 27.94 min, t_r (2*R*,3*S* enantiomer) = 40.17 min: e.r. = 85:15.

Preparation of *N*-phthaloyl β^3-amino esters 10: To a solution of **6i** (100 mg, 230 μmol) in MeOH (2 mL), hydrogen peroxide 30% was added (0.30 mL) at 0°C. The resulting mixture was stirred for 2 h and sodium sulfate anhydrous was added. The mixture was filtered and the organic phase concentrated under vacuum. The crude selenoxide **11** was dissolved in benzene (4 mL) and potassium carbonate anhydrous was added (63 mg, 46 μmol). The resulting suspension was heated at 80°C. The progress of the reaction was monitored by TLC. After 30 min the mixture was cooled, filtrated and evaporated. The pure ester **10** was obtained after column chromatography using a mixture of petroleum ether and diethyl ether 60:40 as eluent.

Methyl (3*S*)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hex-5-enoate (10): Yield 52%; oil; $[\alpha]_D^{22} = 11.04$ ($c = 1.65$ in $CHCl_3$); 1H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 7.92–7.63 (m, 4H; CH), 5.91–5.61 (m, 1H; CH), 5.20–4.92 (m, 2H; CH_2), 4.87–4.65 (m, 1H; CHN), 3.65 (s, 3H; CH_3O), 3.18 (dd, ^2J(H,H) = 16.1 Hz, ^3J(H,H) = 9.4 Hz, 1H; CH_2), 2.81 (dd, ^2J-(H,H) = 16.1 Hz, ^3J(H,H) = 5.5 Hz, 1H; CH2), 2.76–2.65 (m, 1H; CH_2), 2.62–2.48 (m, 1H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 171.3, 168.2 (2C), 134.0 (2C), 133.7, 131.7 (2C), 123.3 (2C), 118.6, 51.9, 47.5, 36.9, 36.2 ppm; GC-MS: *m/z* (%): 258(5)[$M^+ - 15$], 232 (60), 200 (100), 190 (23), 130 (23), 104 (9), 76 (12); elemental analysis calcd (%) for $C_{15}H_{15}NO_4$: C 65.92, H 5.53, N 5.13; found: C 65.76, H 5.73, N 4.97.

Synthesis of azido substituted *N*-phthaloyl β^3-amino esters 12: Commercial *m*-chloroperoxybenzoic acid (0.27 g, 1.55 mmol) was added to a mixture of **6i** (100 mg, 230 μmol) and powdered potassium hydrogenphosphate (0.34 g, 1.94 mmol) in tetrahydrofuran (15 mL) at room temperature. The resulting mixture was stirred and the progress of the reaction was monitored by TLC. When the selenide was completely consumed (3 h) the mixture was diluted with aqueous sodium hydrogen carbonate solution (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were dried over sodium sulfate and evaporated. The crude selenone **11** was dissolved in DMF dry (3 mL) and sodium azide (75 mg, 1.15 mmol) was added. This solution was then stirred at 60°C for 2 h and then water (10 mL) was added. The cooled reaction mixture was then extracted with diethyl ether (3×10 mL) and the combined organic layers were dried over sodium sulfate anhydrous and then evaporated. The residue was purified by column chromatography on silica gel using a mixture of petroleum ether and diethyl ether (50:50) as eluent to give **12** in 62% global yield.

Methyl (3*S*)-6-azido-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hexanoate (12): Oil; $[\alpha]_D^{22} = -6.74$ ($c = 2.24$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.91$–7.68 (m, 4H; CH), 4.79–4.53 (m, 1H; CHN), 3.61 (s, 3H, CH_3O), 3.31 (t, ^3J(H,H) = 6.6 Hz, 2H; CH_2N_3), 3.21 (dd, ^2J-(H,H) = 16.2, ^3J(H,H) = 9.1 Hz, 1H; CH_2), 2.81 (dd, ^2J(H,H) = 16.2, ^3J-(H,H) = 5.5 Hz, 1H; CH_2), 2.32–2.05 (m, 1H; CH_2), 1.91–1.72 (m, 1H; CH_2), 1.67–1.44 ppm (m, 2H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta = 171.2$, 168.3 (2C), 134.1 (2C), 131.7 (2C), 123.4 (2C), 51.9, 50.7, 47.4, 36.7, 29.4, 25.8 ppm; GC–MS *m/z* (%): 261(9) [$M^+ - 55$], 246 (63), 214 (28), 200 (100), 173 (40), 130 (62), 76 (26); FT-IR (diffuse reflectance): 2954.9, 2098, 1773, 1709.5, 1373.1 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{16}N_4O_4$: C 56.96, H 5.10, N 17.71; found: C 57.17, H 5.38, N 17.63.

Synthesis of *N*-phthaloyl β^3-amino esters 13: The selenone **11** was prepared as reported above for the synthesis of **12** starting from **6i** (100 mg, 230 μmol). The crude selenone **11** was dissolved in DMF dry (4 mL) and sodium benzyl thiolate (70 mg, 470 μmol) was added. This solution was then stirred at 40°C for 3 h and then water (10 mL) was added. The cooled reaction mixture was then extracted with diethyl ether (3×10 mL) and the combined organic layers were dried over sodium sulfate anhydrous and then evaporated. The residue was purified by column chromatography on silica gel using a mixture of petroleum ether and diethyl ether (50:50) as eluent to give **13** in 69% global yield.

Methyl (3*S*)-6-(benzylthio)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-hexanoate (13): Yield 69%; oil; $[\alpha]_D^{22} = -18.75$ ($c = 1.05$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.89$–7.62 (m, 4H; CH), 7.32–7.11 (m, 5H; CH), 4.78–4.53 (m, 1H; CHN), 3.65 (s, 2H, CH_2), 3.61 (s, 3H, CH_3O), 3.19 (dd, ^2J(H,H) = 16.1, ^3J(H,H) = 9.4 Hz, 1H; CH_2), 2.78 (dd, ^2J(H,H) = 16.1, ^3J(H,H) = 5.4 Hz, 1H; CH_2), 2.43 (t, ^3J(H,H) = 7.1 Hz, 2H; CH_2), 2.35–2.03 (m, 1H; CH_2), 1.92–1.67 (m, 1H; CH_2), 1.62–1.41 ppm (m, 2H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta = 171.2$, 168.2 (2C), 138.3, 134.0 (2C), 132.8 (2C), 129.2 (2C), 128.9 (2C), 127.7, 123.3 (2C), 51.7, 47.5, 36.7, 36.2, 31.3, 30.6, 25.9 ppm; GC–MS: *m/z* (%): 397(7) [M^+], 306 (63), 200 (30), 148 (23), 127(100), 91 (97), 65 (11); elemental analysis calcd (%) for $C_{22}H_{23}NO_4S$: C 66.48, H 5.83, N 3.52; found: C 66.27, H 5.99, N 3.66.

Synthesis of *N*-phthaloyl β^3-amino esters 14 and 15: To a solution of **2a** (0.27 g, 1.01 mmol) in dry DMF (4 mL), copper (I) iodide (0.38 g, 2.00 mmol) and phenylselenenyl bromide (0.26 g, 1.10 mmol) were added. The resulting mixture was stirred, under argon, for 48 h. The reaction was then quenched by careful addition of 7% aqueous ammonia solution (20 mL). The reaction mixture was then extracted with diethyl ether (3×5 mL) and the combined organic layers were dried over anhy-

drous sodium sulfate and then evaporated. The crude **3a** was dissolved in CH_2Cl_2 (20 mL), and *p*-toluenesulfonic acid monohydrate (0.38 g, 2.00 mmol) was added. The resulting suspension was heated at 40 °C. The progress of the reaction was monitored by TLC. After 6 h solid K_2CO_3 (0.27 g, 2.03 mmol) was added and then the mixture was filtered. The filtrate was dried and evaporated to obtain the crude **4a**. To a mixture of the crude *Se*-phenyl selenocarboxylate and anhydrous copper (II) chloride (0.15 g, 1.12 mmol) in dry acetonitrile (10 mL), benzyl alcohol (0.54 g, 5.00 mmol) was added. The mixture was stirred at room temperature and monitored by TLC. After 11 h the substrate was completely consumed and the reaction mixture was diluted with dichloromethane. A 10% NaOH solution (200 μL) was added and stirring was continued for few minutes. After addition of sodium sulfate anyhydrous, the reaction mixture was filtered through a celite pad and the filtrate concentrated. The crude product was purified by column chromatography on silica gel using an 8:2 mixture of light petroleum and diethyl ether as eluant.

Benzyl (3*S*)-3-cyclohexyl-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanoate (14): Yield 70%; oil; $[\alpha]_D^{25} = -11.59$ ($c = 2.31$ in $CHCl_3$); 1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 7.93–7.61 (m, 4H; CH), 7.30–7.11 (m, 5H; CH), 4.99 (s, 2H; CH_2O), 4.38 (ddd, ^3J(H,H) = 11.1, 4.2, and 4.1 Hz, 1H; CHN), 3.11 (dd, ^2J(H,H) = 15.7 Hz, ^3J(H,H) = 11.1 Hz, 1H; CH_2), 2.75 (dd, ^2J(H,H) = 15.7 Hz, ^3J(H,H) = 4.1 Hz, 1H; CH_2), 2.12–1.42 (m, 5H; CH_2, CH), 1.22–0.81 ppm (m, 6H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.1, 168.3 (2C), 135.4, 133.7 (2C), 131.5 (2C), 128.2 (5C), 123.1 (2C), 66.3, 53.1, 39.2, 34.3, 30.3, 29.5, 25.8, 25.6 ppm (2C); GC-MS: *m/z* (%): 391 (2) [M^+], 285 (66), 242 (11), 200 (16), 174 (26), 148 (16), 91(100), 76 (6), 55 (10); elemental analysis calcd (%) for $C_{24}H_{25}NO_4$: C 73.64, H 6.44, N 3.58; found: C 73.87, H 6.25, N 3.65.

The ester **17** was prepared by the same procedure employed for the synthesis of **16** but with the use of *tert*-butyl alcohol instead of benzyl alcohol.

***tert*-Butyl (3*S*)-3-cyclohexyl-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-propanoate (15)**: Yield 51%; oil; $[\alpha]_D^{25} = -11.47$ ($c = 1.65$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 7.92–7.62 (m, 4H; CH), 4.32 (ddd, ^3J(H,H) = 10.7 , 4.3 e 4.2 Hz, 1H; CHN), 3.11 (dd, ^2J(H,H) = 15.1 Hz, ^3J(H,H) = 10.7 Hz, 1H; CH_2), 2.75 (dd, ^2J(H,H) = 15.1 Hz, ^3J(H,H) = 4.3 Hz, 1H; CH_2), 2.20–1.42 (m, 5H; CH_2, CH), 1.23 (s, 9H; CH_3), 1.22–0.81 ppm (m, 6H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 170.5, 168.3 (2C), 133.8 (2C), 131.6 (2C), 123.0 (2C), 80.5, 53.4, 39.3, 35.9, 30.3, 29.6, 27.6 (3C), 25.9, 25.6, 25.5 ppm; GC-MS: *m/z* (%): 357 (1) [M^+], 301(100), 284 (35), 242 (41), 218 (76), 200 (69), 174 (78), 160 (35), 148 (47), 139 (37), 104 (23), 76 (16), 57 (58); elemental analysis calcd (%) for $C_{21}H_{27}NO_4$: C 70.56, H 7.61, N 3.92; found: C 70.10, H 7.98, N 3.77.

Synthesis of (3*S*)-3-cyclohexyl-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanamide (16): The *Se*-phenyl selenocarboxylate intermediate **4a** prepared from **2a** as described above in the synthesis of ester **14** was dissolved in tetrahydrofuran (20 mL) at room temperature and under a non inert atmosphere. To this mixture a 7% aqueous ammonia solution (2 mL) was carefully added with vigourous stirring. The mixture was stirred at room temperature and monitored by TLC. After 14 h the reaction mixture was dried over sodium sulfate anhydrous, concentrated, and the residue washed with light petroleum (3×10 mL). The solid residue was dried over P_2O_5 to obtain **16** in 90% yield. m.p. 60 °C; $[\alpha]_D^{25} = -44.69$ ($c = 1.26$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 7.89–7.62 (m, 4H; CH), 5.61- 5.20 (br s, 2H; NH_2), 4.41 (ddd, ^3J(H,H) = 11.2 Hz, ^3J(H,H) = 4.7 Hz, ^3J(H,H) = 4.4 Hz, 1H; CHN), 3.14 (dd, ^2J(H,H) = 14.7 Hz, ^3J(H,H) = 11.2 Hz, 1H; CH_2), 2.78 (dd, ^2J(H,H) = 14.7 Hz, ^3J(H,H) = 4.7 Hz, 1H; CH_2), 2.11–1.52 (m, 5H; CH_2, CH), 1.31–0.80 ppm (m, 6H; CH_2,); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 173.2, 168.6 (2C), 133.9 (2C), 131.5 (2C), 123.2 (2C), 53.6, 35.8, 30.2, 29.7, 25.9, 25.6, 25.5 (2C) ppm; elemental analysis calcd (%) for $C_{17}H_{20}N_2O_3$: C 67.98, H 6.71, N 9.33; found: C 68.12, H 6.34, N 9.43.

Synthesys of dipeptides: general procedure: To a tetrahydrofuran solution (15 mL) of *Se*-phenyl selenocarboxylate **4b** obtained from propargylic amine **2b** (0.24 g, 1.00 mmol) as described above for *ent*-**2a**, triethylamine was added (277 μL, 2.00 mmol). Under a non inert atmosphere the β-alanine ethyl ester hydrochloride (0.16 g, 1.00 mmol) was added and the resulting mixture was stirred at room temperature. After complete consumption of **4b** (8 h) the reaction mixture was evaporated. The residue was chromatographed using a silica gel column and a mixture of dichloromethane/methanol 98:2 as eluent. The amides **19** were obtained in a pure form and diphenyl diselenide was recovered.

Ethyl 3-{[(3*S*)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-methylhexanoyl]amino}propanoate (17): Yield 64%; oil; $[\alpha]_D^{21} = 14.71$ ($c = 2.42$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.83–7.57$ (m, 4H; CH), 6.21–6.04 (br s, 1H; NH), 4.85–4.62 (m, 1H; CHN), 4.09 (q, ^3J(H,H) = 7.1 Hz, 2H; CH_2O), 3.42–3.35 (m, 2H; CH_2N), 2.99 (dd, ^2J(H,H) = 14.7, ^3J(H,H) = 9.6 Hz, 1H; CH_2), 2.58 (dd, ^2J(H,H) = 14.7, ^3J(H,H) = 5.7 Hz, 1H; CH_2), 2.49–2.29 (m, 2H; CH_2), 2.18–2.04 (m, 1H; CH), 2.19–2.09 (m, 2H; CH_2), 1.21 (t, ^3J(H,H) = 7.1 Hz, 3H; CH_3), 0.94 (d, ^3J(H,H) = 5.9 Hz, 3H; CH_3), 0.91 ppm (d, ^3J(H,H) = 6.1 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.2, 169.7, 168.2 (2C), 133.7 (2C), 131.6 (2C), 123.0 (2C), 60.4, 46.7, 41.0, 39.2, 34.6, 33.7, 24.9, 23.0, 21.4, 13.9 ppm; GC-MS: *m/z* (%): 374 (7) [M^+], 329 (35), 318 (100), 258 (14), 216 (36), 200 (35) 174 (100), 159 (86), 130 (37), 116 (72), 98 (15); elemental analysis calcd (%) for $C_{20}H_{26}N_2O_5$: C 64.15, H 7.00, N 7.48; found: C 63.88, H 7.32, N 7.25.

The synthetic procedure illustrated above for the preparation of the β-dipeptide **17** from *N*-protected propargylic amine **2b** was also applied for the syntheses of **18–22** but in the preparation of compound **22** the reaction was conducted in dioxane and only one equivalent of Et_3N was added, then the reaction was treated with 2N hydrochloric acid and extracted with ethyl acetate. Yields, physical and spectral data of the other dipeptides are reported below.

(3*S*)-*N*-[(1*S*)-3-Amino-1-cyclohexyl-3-oxopropyl]-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-methylhexanamide (18): Yield 70%; m.p. 205–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.89–7.63$ (m, 4H; CH), 6.19–6.11 (m, 2H; NH_2), 5.37–5.25 (br s, 1H; NH), 4.85–4.78 (m, 1H; CHN), 3.99–3.87 (m, 1H; CHN), 3.09 (dd, ^2J(H,H) = 14.3 Hz, ^3J(H,H) = 10.8 Hz, 1H; CH_2), 2.58 (dd, ^2J(H,H) = 14.3 Hz, ^3J(H,H) = 4.9 Hz, 1H; CH_2), 2.47 (dd, ^2J(H,H) = 15.7 Hz, ^3J(H,H) = 4.2 Hz, 1H; CH_2), 2.38 (dd, ^2J(H,H) = 15.7 Hz, ^3J(H,H) = 7.1 Hz, 1H; CH_2), 2.15–1.95 (m, 1H; CH), 1.59–1.41 (m, 6H; CH_2), 1.39–1.30 (m, 2H; CH_2), 1.07–0.98 (m, 1H; CH); 0.97 (d, ^3J(H,H) = 5.8 Hz, 3H; CH_3), 0.95–0.82 (m, 2H; CH_2), 0.88 (d, ^3J(H,H) = 5.8 Hz, 3H; CH_3), 0.81– 0.56 ppm (m, 2H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.9, 170.2, 168.5 (2C), 134.0 (2C), 131.8 (2C), 123.3 (2C), 51.0, 47.3, 41.4, 40.8, 39.8, 38.0, 29.8, 28.8, 26.0, 25.8, 25.6, 25.2, 23.2, 21.8 ppm; elemental analysis calcd (%) for $C_{24}H_{33}N_3O_4$: C 67.42, H 7.78, N 9.83; found: C 67.21, H 7.97, N 9.76.

Ethyl 3-{[(3*S*)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-phenylpentanoyl]amino}propanoate (19): Yield 66%; oil; $[\alpha]_D^{22} = 21.36$ ($c = 1.70$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.83–7.62$ (m, 4H; CH), 7.21–6.95 (m, 5H, CH), 6.21–6.03 (br s, 1H, NH), 4.79–4.62 (m, 1H; CHN), 4.07 (q, ^3J(H,H) = 7.2 Hz, 2H; CH_2O), 3.39–4.15 (m, 2H; CH_2N), 3.01 (dd, ^2J(H,H) = 16.8, ^3J(H,H) = 9.3 Hz, 1H; CH_2), 2.68 (dd, ^2J(H,H) = 16.8, ^3J(H,H) = 6.0 Hz, 1H; CH_2), 2.62–2.32 (m, 6H, CH_2), 1.19 ppm (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.2, 169.5, 168.2 (2C), 140.5, 133.6 (2C), 131.5 (2C), 128.0 (4C), 125.6, 122.0 (2C), 60.4, 48.5, 39.0, 34.6, 33.6, 33.4, 32.6, 13.1 ppm; GC-MS: *m/z* (%): 422 (21) [M^+], 377(26), 318 (100), 272 (25), 200 (37) 173 (69), 158 (56), 116 (80), 91 (96); elemental analysis calcd (%) for $C_{24}H_{26}N_2O_5$: C 68.23, H 6.20, N 6.63; found: C 68.01, H 6.52, N 6.46.

(2*R*)-{[(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-methylhexanoyl]amino}(phenyl)ethanoic acid (20): Yield 74%; m.p. 185–190 °C; $[\alpha]_D^{24} = -54.37$ ($c = 2.00$ in dioxane); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 11.01(br s, 1H; OH), 8. 71 (d, ^3J(H,H) = 7.2 Hz, 1H; NH), 7.91–7.69 (m, 4H; CH), 7.31–7.12 (m, 5H, CH), 5.25 (s, 1H; CHN), 4.71–4.55 (m, 1H; CHN), 2.89–2.72 (m, 2H; CH_2), 2.11–1.92 (m, 1H; CH), 1.42–1.29 (m, 2H; CH_2), 0.94 (d, ^3J(H,H) = 6.0 Hz, 3H; CH_3), 0.91 ppm (d, ^3J(H,H) = 6.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 172.0, 169.8, 168.2 (2C), 137.4, 134.7 (2C), 131.6, 128.7 (2C), 128.1, 127.8 (2C), 123.3 (2C), 56.6, 46.8, 40.9, 38.5, 33.6, 25.0, 23.5, 21.7 ppm; el-

emental analysis calcd (%) for $C_{23}H_{24}N_2O_5$: C 67.63, H 5.92, N 6.86; found: C 67.95, H 6.33, N 6.53.

Methyl (2*S*)-2-{[(3*S*)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hept-6-enoyl]amino}-3-phenylpropanoate (21): Yield 70%; oil; $[\alpha]_D^{20}=54.97$ ($c=2.04$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.85$–7.62 (m, 4H; CH), 7.40–7.25 (m, 3H; CH), 7.11–7.05 (m, 2H; CH), 5.98 (d, ^3J-(H,H)=7.6 Hz, 1H; NH), 5.73 (ddt, ^3J(H,H)=17.0, 10.3 e 6.6 Hz, 1H; CH), 4.96–4.92 (m, 1H; CH_2), 4.89–4.85 (m, 1H; CH_2), 4.83–4.76 (m, 1H; CHN), 4.76–4.67 (m, 1H; CHN), 3.52 (s, 3H; CH_3O), 3.05- 3.12 (m, 1H; CH_2), 3.04–2.96 (m, 2H; CH_2), 2.79–2.61 (m, 1H; CH_2), 2.20–2.15 (m, 1H; CH_2), 2.07–1.95 (m, 2H; CH_2), 1.82–1.74 ppm (m, 1H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta=171.6$, 169.3, 168.4 (2C), 136.9, 135.7, 133.8 (2C), 131.8 (2C), 129.1 (2C), 128.5 (2C), 127.0, 123.1 (2C), 115.3, 52.9, 52.0, 48.1, 39.3, 37.6, 31.5, 30.4 ppm; GC-MS: *m/z* (%): 434 (2) [M^+], 272 (8), 256 (36), 214 (20), 174 (17), 162 (100), 148 (70), 130 (25), 109 (20), 91 (23); elemental analysis calcd (%) for $C_{25}H_{26}N_2O_5$: C 69.11, H 6.03, N 6.45; found: C 68.98, H 6.41, N 6.15.

***tert*-Butyl (2S)-2-{[(3S)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-6-(phenylseleno)hexanoyl]amino}-3-phenylpropanoate (22)**: Yield 45%; oil; $[\alpha]_D^{20}=19.66$ ($c=1.14$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.85$–7.62 (m, 4H; CH), 7.57–7.45 (m, 2H; CH), 7.30–7.05 (m, 8H; CH), 5.99 (d, ^3J(H,H)=7.9 Hz, 1H; NH), 4.69–4.81 (m, 2H; CHN), 3.10–2.75 (m, 5H; CH_2), 2.69–2.52 (m, 1H; CH_2), 2.27–1.98 (m, 2H; CH_2), 2.89–2.51 (m, 2H; CH_2), 1.22 ppm (s, 9H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta=170.2$, 169.2, 168.3 (2C), 136.0, 133.7 (2C), 132.7 (2C), 131.7, 129.7 (2C), 129.3 (2C), 128.8 (2C), 128.3 (2C), 126.8 (2C), 123.1 (2C), 82.0, 53.2, 47.7, 38.9, 37.8, 32.1, 27.7(3C), 26.9, 26.5 ppm; elemental analysis calcd (%) for $C_{33}H_{36}N_2O_5Se$: C 63.97, H 5.86, N 4.52; found: C 64.12, H 5.63, N 4.65.

N- and/or C-Deprotection of some dipeptides: The dipeptide **17** (109 mg, 291 μmol) was dissolved in formic acid (1 mL) at room temperature and methanesulfonic acid (0.50 mL) was added. The mixture was stirred at 60°C for 14 h. The reaction was then quenched by careful addition of water (10 mL). The reaction mixture was then extracted with dichloromethane (3×5 mL) and the combined organic layers were dried over anhydrous sodium sulfate and then evaporated. The residue was dried over P_2O_5 to obtain pure **23.**

3-{[(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-ethylhexanoyl]amino}propanoic acid **(23)**: Yield 89%; oil; $[\alpha]_D^{29}=8.17$ ($c=0.49$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta=12.01$ (br s, 1H; OH), 7.81–7.58 (m, 4H; CH), 6.71–6.51 (br s, 1H; NH), 4.87–4.56 (m, 1H; CHN), 3.49–3.37 (m, 2H; CH_2), 2.92 (dd, ^2J(H,H)=14.5, ^3J(H,H)=9.2 Hz, 1H; CH_2), 2.58 (dd, ^2J(H,H)=14.5, ^3J(H,H)=5.5 Hz, 1H; CH_2), 2.41–2.29 (m, 2H; CH_2), 2.12–1.93 (m, 1H; CH), 1.42–1.27 (m, 2H; CH_2), 0.86 (d, ^3J-(H,H)=5.9 Hz, 3H; CH_3), 0.79 ppm (d, ^3J(H,H)=5.9 Hz, 3H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta=175.8$, 171.3, 168.5(2C), 134.0 (2C), 131.5 (2C), 123.2 (2C), 47.0, 41.0, 39.2, 35.0, 33.5, 25.0, 23.0, 21.5, ppm; elemental analysis calcd (%) for $C_{18}H_{22}N_2O_5$: C 62.42, H 6.40, N 8.09; found: C 62.16, H 6.72, N 7.88.

Hydrazine hydrate (50 μL, 1.03 mmol) was added to a stirred solution of **23** (0.17 g, 0.49 mmol) in EtOH (4 mL). After stirring for 5 h at 100°C, the reaction mixture was allowed to slowly reach room temperature and concentrated. The residue was treated with 2N hydrochloric acid (3 mL). the solid was allowed to settle down and then filtered. Evaporation of the filtrate gave a residue which was dried under reduced pressure to afford **24** as a white solid in 85% yield.

3-{[(3*S*)-3-Amino-5-methylhexanoyl]amino}propanoic acid hydrochloride (24): M.p. 82–87°C; $[\alpha]_D^{27}=5.63$ ($c=1.66$ in H_2O); ^{1}H NMR (200 MHz, D_2O, 25°C): $\delta=3.47$–3.32 (m, 1H; CHN), 3.27–3.17 (m, 2H; CH_2), 2.34–2.24 (m, 4H; CH_2), 1.51–1.48 (m, 1H; CH), 1.47–1.27 (m, 2H; CH_2), 0.65 ppm (s, 6H; CH_3); ^{13}C NMR (50 MHz, D_2O, 25°C, dioxane): $\delta=$ 176.6, 172.5, 47.9, 40.9, 38.1, 35.3, 33.7, 24.3, 22.1 ppm (2C); elemental analysis calcd (%) for $C_{10}H_{21}ClN_2O_3$: C 47.52, H 8.37, N 11.08; found: C 47.17, H 8.55, N 11.23.

To a solution of dipeptide **22** (50 mg, 80 μmol) in dichloromethane (0.4 mL) at 0°C, trifluoroactic acid (0.40 mL) was added. The mixture was then stirred at room temperature for 20 h. The reaction was evaporated and the residue was dried over P_2O_5. Pure acid **25** was obtained in 96% yield.

***N*-[(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-6-(phenylseleno)hexanoyl]-L-phenylalanine (25)**: Oil; $[\alpha]_D^{24}=12.06$ ($c=2.31$ in MeOH); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta=9.60$ (br s, 1H; OH), 7.88–7.55 (m, 4H; CH), 7.49–7.33 (m, 2H; CH), 7.30–7.05 (m, 8H; CH), 6.35 (d, ^3J(H,H)=7.1 Hz, 1H; NH), 4.85–4.62 (m, 2H; CHN), 3.21–2.55 (m, 6H; CH_2), 2.24–1.98 (m, 1H; CH_2), 1.82–1.52 (m, 3H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta=175.0$, 171.3, 168.6(2C), 135.2, 134.1 (2C), 132.7 (2C), 131.4 (2C), 129.6, 129.1 (2C), 128.9 (2C), 128.7 (2C), 127.3, 126.8, 123.3 (2C), 53.2, 47.9, 38.8, 37.0, 32.2, 26.8, 26.4 ppm;elemental analysis calcd (%) for $C_{29}H_{28}N_2O_5Se$: C 61.81, H 5.01, N 4.97; found: C 61.47, H 5.39, N 4.85.

Preparation of the amide 27 from 16: Ethylenediamine (EDA) (60 μL, 0.92 mmol) was added to a stirred solution of **16** (80 mg, 266 μmol) in *i*PrOH (2 mL). After stirring for 16 h at 90°C, the reaction mixture was allowed to slowly reach room temperature and concentrated. The residue was chromatographed using a silica gel column and a mixture of dichloromethane/methanol 90:10 as eluent. The amide **27** was obtained in a pure form after dried over P_2O_5.

(3*S*)-3-Amino-3-cyclohexylpropanamide (27): Yield 81%; oil; $[\alpha]_D^{30}=-1.89$ ($c=0.65$ in MeOH); 1H NMR (200 MHz,[D_6]DMSO, 25°C,): $\delta=$ 7.61– 7.21 (br s, 2H; NH_2), 3.37–3.20 (br s, 2H; NH_2), 2.99–2.81 (m, 1H; CHN), 2.49–2.23 (m, 1H; CH_2), 2.21–2.01 (m, 1H; CH_2) 1.87–1.52 (m, 5H; CH2, CH), 1.31–0.83 ppm (m, 6H; CH_2,); ^{13}C NMR (50 MHz,[D_6]DMSO, 25°C,): $\delta=177.3$, 54.4, 44.0, 40.6, 30.0, 29.5, 27.4 (3C) ppm; elemental analysis calcd (%) for $C_9H_{18}N_2O$: C 63.49, H 10.66, N 16.47; found: C 63.26, H 10.91, N 16.33.

Multistep liquid-phase synthesis of α/β-tripeptide 29: To a solution of the phthaloyl-protected dipeptide **22** (80 mg, 129 μmol) in *i*PrOH (3 mL), EDA (35 μL, 0.52 mmol) was added and the mixture stirred at 90°C for 7 h. The solvent was then evaporated to give the crude N-terminus deprotected dipeptide which was purified by column chromatography on silica gel using a 98:2 mixture of dichloromethane and methanol as eluent.

***tert*-Butyl (2*S*)-2-{[(3*S*)-3-amino-6-(phenylseleno)hexanoyl]amino}-3-phenylpropanoate (26)**: Yield 80%; oil; $[\alpha]_D^{27}=29.61$ ($c=2.04$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.61$–7.39 (m, 2H; CH), 7.57 (d, ^3J(H,H)=9.6 Hz, 1H; NH) 7.31–7.09 (m, 8H; CH), 4.87–4.62 (m, 1H; CHN), 3.22–2.98 (m, 3H; CH_2, CHN), 2.92–2.82 (m, 2H; CH_2), 2.39–2.22 (m, 1H; CH_2), 2.18–2.09 (m, 1H; CH_2), 2.20–1.92 (br s, 2H; NH_2), 1.82–1.45 (m, 4H; CH_2), 1.41 ppm (s, 9H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta=171.3$, 171.0, 136.4, 132.6 (2C), 130.0, 129.3 (2C), 129.0 (2C), 128.2 (2C), 126.8 (2C), 82.0, 53.6, 48.4, 43.0, 37.8, 31.8, 27.8 (3C), 27.4, 24.8 ppm; elemental analysis calcd (%) for $C_{25}H_{34}N_2O_3Se$: C 63.97, H 5.86, N 4.52; found: C 63.72, H 6.13, N 4.75.

The amine **26** (40 mg, 81 μmol) was dissolved in tetrahydrofuran (5 mL) and Et_3N (11 μL, 80 μmol) was added at room temperature. To this solution *Se*-phenyl selenocarboxylate **28**[23] (40 mg, 93 μmol) was added and the mixture stirred, under non inert atmosphere, until TLC indicated complete reaction (2 h). This was also evidenced by a typical yellow colour of the mixture due to diphenyl diselenide. The reaction was then evaporated and the residue was purified by column chromatography on silica gel using a 98:2 mixture of dichloromethane and methanol as eluent.

***tert*-Butyl (2S)-2-{[(3S)-3-{[(3R)-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)octanoyl]amino}-6-(phenylseleno)hexanoyl]amino}-3-phenylpropanoate (29)**: Yield 75%; m.p. 75–78°C; $[\alpha]_D^{23}=2.03$ ($c=2.50$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.82$–7.70 (m, 4H; CH), 7.41–7.32 (m, 2H; CH), 7.31–7.11 (m, 8H; CH), 6.29 (d, ^3J(H,H)=9.0 Hz, 1H; NH), 6.27 (d, ^3J(H,H)=7.8 Hz, 1H; NH), 4.79–4.69 (m, 1H; CHN), 4.68–4.55 (m, 1H; CHN), 4.08–3.97 (m, 1H; CHN), 3.11 (dd, ^2J-(H,H)=14.0 Hz, ^3J(H,H)=6.3 Hz, 1H; CH_2), 3.04 (dd, ^2J(H,H)=14.0 Hz, ^3J=6.4 Hz, 1H; CH_2), 2.94 (dd, ^2J(H,H)=14.4 Hz, ^3J(H,H)=10.3 Hz, 1H; CH_2), 2.55 (m, 2H; CH_2), 2.47 (dd, ^2J(H,H)=14.4 Hz, ^3J-(H,H)=5.3 Hz, 1H; CH_2), 2.36 (dd, ^2J(H,H)=14.9 Hz, ^3J(H,H)=4.9 Hz, 1H; CH_2), 2.23 (dd, ^2J(H,H)=14.9 Hz, ^3J(H,H)=4.8 Hz, 1H; CH_2), 2.11–1.97 (m, 2H; CH_2), 1.72–1.61 (m, 1H; CH), 1.41 (s, 12H; CH_3, CH_2),

1.32–1.18 (m, 6H; CH_2), 0.91–0.72 ppm (t, ^3J(H,H) = 6.7 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 170.5, 170.2, 169.5, 168.4 (2C), 136.5, 133.8 (2C), 133.4 (2C), 131.7 (2C), 130.2, 129.3 (2C), 128.9 (2C), 128.4 (2C), 126.9, 126.6, 123.1 (2C), 82.3, 53.5, 48.9, 45.7, 39.7, 39.3, 37.7, 33.5, 32.6, 31.7, 27.9 (3C), 27.1, 26.4, 26.0, 22.6, 13.9 ppm; elemental analysis calcd (%) for $C_{41}H_{51}N_3O_6Se$: C 64.72, H 6.76, N 5.52; found: C 64.95, H 6.34, N 5.29.

Multistep liquid-phase synthesis of β-tetrapeptide 35: *N*-phthaloyl amino ester **15** (0.28 g, 0.86 mmol) was deprotected as reported above for compound **22** to obtain the amine **30** in 80% yield.

***tert*-Butyl (3*S*)-3-amino-3-cyclohexylpropanoate (30)**: Oil; $[\alpha]_D^{25}$ = 21.41 (c = 0.40 in EtOH); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.01–2.98 (m, 1H; CHN), 2.41 (dd, ^2J(H,H) = 15.2 Hz, ^3J(H,H) = 3.9 Hz, 1H; CH_2), 2.13 (dd, ^2J(H,H) = 15.2 Hz, ^3J(H,H) = 9.5 Hz, 1H; CH_2), 1.75–1.65 (br s, 2H; NH_2) 1.64–1.51 (m, 5H; CH_2, CH), 1.49 (s, 9H; CH_3), 1.42–0.97 (m, 6H; CH_2); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.6, 80.4, 53.1, 43.6, 41.1 (2C), 30.0, 29.3, 28.4 (3C), 26.4 (2C) ppm; elemental analysis calcd (%) for $C_{13}H_{25}NO_2$: C 68.68, H 11.08, N 6.16; found: C 68.42, H 11.29, N 6.23.

To a mixture of the amine **30** (0.65 g, 0.85 mmol) and Et_3N (120 μL, 0.85 mmol) in tetrahydrofuran (5 mL) at room temperature, crude *Se*-phenyl selenocarboxylate **4b** (prepared from 1.0 mmol of **2b** as described above) was added and the mixture stirred until TLC indicated complete reaction (15 h). The reaction was then evaporated and the residue was purified by column chromatography on silica gel using a 97:3 mixture of dichloromethane and methanol as eluent. β-Dipeptide **33** was obtained as a white solid in 67% yield.

***tert*-Butyl (3*S*)-3-cyclohexyl-3-{[(3*S*)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-methylhexanoyl]amino}propanoate (31)**: M.p. 156 °C; $[\alpha]_D^{29}$ = 23.19 (c = 0.50 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.87–7.61 (m, 4H; CH), 6.05 (d, 3J(H,H) = 9.5 Hz, 1H; NH), 4.90–4.79 (m, 1H; CHN), 4.00–3.87 (m, 1H; CHN), 3.04 (dd, ^2J(H,H) = 14.3 Hz, ^3J(H,H) = 10.5 Hz, 1H; CH_2), 2.75 (dd, ^2J(H,H) = 14.3 Hz, ^3J(H,H) = 5.2 Hz, 1H; CH_2), 2.37 (dd, ^2J(H,H) = 15.4 Hz, ^3J(H,H) = 4.6 Hz, 1H; CH_2), 2.32 (dd, ^2J(H,H) = 15.4 Hz, ^3J(H,H) = 6.2 Hz, 1H; CH_2), 2.14–2.04 (m, 1H; CH), 1.41(s, 9H; CH_3), 1.51–1.11 (m, 7H; CH_2, CH), 0.95 (d, ^3J(H,H) = 5.8 Hz, 3H; CH_3), 0.88 (d, ^3J(H,H) = 5.8 Hz, 3H; CH_3), 0.97–0.50 ppm (m, 6H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.3, 169.1, 168.4 (2C), 133.8 (2C), 131.8 (2C), 123.0 (2C), 80.9, 50.4, 47.2, 41.3, 40.8, 39.9, 37.4, 29.6, 29.3, 27.6 (3C), 25.8 (2C), 25.5, 25.1, 23.1, 21.7 ppm; elemental analysis calcd (%) for $C_{28}H_{40}N_2O_5$: C 70.56, H 7.61, N 3.92; found: C 70.19, H 7.88, N 3.79.

To a solution of the phthaloyl-protected dipeptide **31** (120 mg, 257 μmol) in *i*PrOH (3 mL), EDA (71 μL, 1.04 mmol) was added and the mixture stirred at 90 °C for 12 h. The solvent was then evaporated to give the crude N-terminus deprotected dipeptide **32** which was purified by column chromatography on silica (eluent dichloromethane/methanol 90:10 mixture) and directly employed for the successive coupling step.

***tert*-Butyl (3*S*)-3-{[(3*S*)-3-amino-5-methylhexanoyl]amino}-3-cyclohexylpropanoate (32)**: Oil; $[\alpha]_D^{32}$ = 28.93 (c = 0.73 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.18 (s, 1H; NH), 4.12–4.01 (m, 1H; CHN), 3.31–3.11 (m, 1H; CHN), 2.48–2.39 (m, 2H; CH_2), 2.32 (dd, ^2J(H,H) = 15.0 Hz, ^3J(H,H) = 3.2 Hz, 1H; CH_2), 2.05 (dd, ^2J(H,H) = 15.0 Hz, ^3J(H,H) = 9.0 Hz, 1H; CH_2), 2.01–1.92 (br s, 2H; NH_2,), 1.81–1.58 (m, 6H; CH_2,CH), 1.43 (s, 9H; CH_3), 1.30–1.15 (m, 6H; CH_2, CH), 1.10–0.83 (m, 2H; CH2), 0.88 (d, ^3J(H,H) = 4.0 Hz, 3H; CH_3), 0.88 ppm (d, ^3J(H,H) = 3.9 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.5, 171.2, 80.8, 50.6, 47.2, 46.6, 43.9, 41.1, 37.8, 29.7, 29.1, 28.0 (3C), 26.2, 26.1, 26.0, 24.6, 23.1, 22.0 ppm; elemental analysis calcd (%) for $C_{20}H_{38}N_2O$: C 67.76, H 10.80, N 7.90; found: C 67.42, H 11.05, N 7.71.

To a mixture of the amine **32** (84 mg, 250 μmol) and Et_3N (35 μL, 250 μmol) in tetrahydrofuran (5 mL) at room temperature, crude *Se*-phenyl selenocarboxylate **4b** (prepared from 300 μmol of **2b** as described above) was added and the mixture stirred until TLC indicated complete reaction (13 h). The reaction was then evaporated and the residue was purified by column chromatography on silica gel using a 99:1 mixture of dichloromethane and methanol as eluent. β-Tripeptide **33** was obtained as a white solid in 74% yield from **31**.

***tert*-Butyl (3*S*)-3-cyclohexyl-3-[((3*S*)-3-{[(3*S*)-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-5-methylhexanoyl]amino}-5-methylhexanoyl)amino]-propanoate (33)**: M.p. 140–145 °C; $[\alpha]_D^{29}$ = −25.25 (c = 0.50 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.83–7.62 (m, 4H; CH), 6.89 (d, ^3J(H,H) = 9.1 Hz, 1H; NH), 6.18 (d, ^3J(H,H) = 9.6 Hz, 1H; NH), 4.85–4.76 (m, 1H; CHN), 4.21–4.11 (m, 1H; CHN), 4.04–3.96 (m, 1H; CHN), 3.06 (dd, ^2J(H,H) = 14.8 Hz, ^3J(H,H) = 9.9 Hz, 1H; CH_2), 2.75 (dd, ^2J(H,H) = 14.8 Hz, ^3J(H,H) = 5.9 Hz, 1H; CH2), 2.44 (dd, ^2J(H,H) = 14.8 Hz, ^3J(H,H) = 4.7 Hz, 1H; CH_2), 2.38 (dd, ^2J(H,H) = 14.8 Hz, ^3J(H,H) = 5.5 Hz, 1H; CH_2), 2.18 (dd, ^2J(H,H) = 14.2 Hz, ^3J(H,H) = 4.7 Hz, 1H; CH_2), 2.09 (dd, ^2J(H,H) = 14.2 Hz, ^3J(H,H) = 4.6 Hz, 1H; CH_2), 2.08–2.01 (m, 1H; CH), 1.72–1.69 (m, 4H, CH_2), 1.45 (s, 9H; CH_3), 1.35–1.11 (m, 6H; CH_2, CH), 1.30–0.90 (m, 6H; CH_2), 0.95 (d, ^3J(H,H) = 6.1 Hz, 3H; CH_3), 0.88 (d, ^3J(H,H) = 6.3 Hz, 3H; CH_3), 0.82 ppm (d, ^3J(H,H) = 6.6 Hz, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.0, 170.0, 169.3, 168.6 (2C), 133.8 (2C), 131.8 (2C), 123.0 (2C), 81.5, 50.9, 46.7, 44.5, 42.1, 41.6, 41.3, 41.0, 39.3, 37.7, 29.6, 29.2, 28.0 (3C), 26.1, 25.9(2C), 25.0, 24.9 23.0, 22.6, 22.0, 21.8 ppm; elemental analysis calcd (%) for $C_{35}H_{53}N_3O_6$: C 68.71, H 8.73, N 6.87; found: C 68.48, H 8.97, N 6.61.

To a solution of the *N*-phthaloyl tripeptide **33** (50 mg, 84 μmol) in *i*PrOH (2 mL), EDA (22 μL, 330 μmol) was added and the mixture stirred at 90 °C for 12 h. The solvent was then evaporated to give the crude N-terminus deprotected tripeptide **34** which was purified by column chromatography on silica (eluent dichloromethane/methanol 90:10 mixture) and directly employed for the successive coupling step. To a mixture of the amine **34** (40 mg, 70 μmol) and Et_3N (97 μL, 70 μmol) in tetrahydrofuran (3 mL) at room temperature and under a non inert atmosphere, crude *Se*-phenyl selenocarboxylate **4b** (prepared from 100 μmol of **2b** as described above) was added and the mixture stirred until TLC indicated complete reaction (14 h). The reaction was then evaporated and the residue was purified by column chromatography on silica gel using a 90:10 mixture of dichloromethane and methanol as eluent. β-Tetrapeptide **35** was obtained as a solid in 71% yield from **35**.

***tert*-Butyl (3*S*)-3-cyclohexyl-3-({(3*S*)-3-[((3*S*)-3-{[(3*S*)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-methylhexanoyl]amino}-5-methylhexanoyl)-amino]-5-methylhexanoyl}amino)propanoate (35)**: M.p. 180–185 °C; $[\alpha]_D^{29}$ = −6.48 (c = 0.47 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.81–7.62 (m, 4H; CH), 6.95 (d, ^3J(H,H) = 8.8 Hz, 1H; NH), 6.85 (d, ^3J(H,H) = 8.6 Hz, 1H; NH), 6.48 (d, ^3J(H,H) = 9.4 Hz, 1H; NH), 4.81–4.71 (m, 1H; CHN), 4.23–4.14 (m, 1H; CHN), 4.11–3.96 (m, 2H; CHN), 2.93 (dd, ^2J(H,H) = 14.5 Hz, ^3J(H,H) = 9.5 Hz, 1H; CH_2), 2.58 (dd, ^2J(H,H) = 14.5 Hz, ^3J(H,H) = 5.7 Hz, 1H; CH_2), 2.45–2.38 (m, 2H; CH_2), 2.37–2.30 (m, 2H; CH_2), 2.27 (dd, ^2J(H,H) = 14.8 Hz, ^3J(H,H) = 5.4 Hz, 1H; CH_2), 2.18 (dd, ^2J(H,H) = 14.8 Hz, ^3J(H,H) = 4.3 Hz, 1H; CH_2), 2.15–2.05 (m, 2H; CH_2,), 1.79–1.67 (m, 4H, CH_2), 1.45 (s, 9H; CH_3), 1.35–1.05 (m, 8H; CH_2, CH), 0.92 (d, ^3J(H,H) = 5.8 Hz, 3H; CH_3), 0.87 (d, ^3J(H,H) = 6.6 Hz, 6H; CH_3) 0.85 (d, ^3J(H,H) = 5.8 Hz, 6H; CH_3), 0.83 (d, ^3J(H,H) = 6.5 Hz, 3H; CH_3), 0.81 (d, ^3J(H,H) = 6.4 Hz, 3H; CH_3) 0.78 ppm (d, ^3J(H,H) = 6.7 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.0, 170.8, 170.4, 169.4, 168.5 (2C), 133.8 (2C), 131.9 (2C), 123.2 (2C), 81.3, 50.9, 47.0, 45.3, 44.7, 42.9, 42.8, 41.4, 41.3, 40.9, 40.2, 39.8, 37.8, 29.8, 29.3, 28.1 (3C), 26.2, 26.1, 26.0, 25.2(2C), 25.1, 23.3, 22.8, 22.6, 22.3, 22.2, 21.7 ppm; elemental analysis calcd (%) for $C_{42}H_{66}N_4O_7$: C 68.26, H 9.00, N 7.58; found: C 68.00, H 9.36, N 7.37.

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