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One-step synthesis of *N*-acetylcysteine and glutathione derivatives using the Ugi reaction

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ABSTRACT

Fully protected natural and unnatural *N*-acetylcysteine, dipeptide Cys–Gly, glutathione, and homoglutathione derivatives were synthesized by the Ugi four-component reaction using various benzylthio aldehydes and ketones as carbonyl building blocks. The scope and limitations of the method were investigated. Formation of imidazoline by-products in the Ugi reaction was discussed. 2,2,2-Trifluoroethanol was shown to be a superior reaction media than methanol in some reactions. Also, the 4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl derivative (OBO-ester) of isocyanoacetic acid was shown to be superior to use than ethyl isocyanoacetate as a peptide synthesis precursor in cases when higher reactivity of an isocyanide is required.

1. Introduction

Glutathione (GSH) is present in all living organisms and plays an important role in life processes.[1] This simple tripeptide (γ-Glu-Cys-Gly) is a powerful antioxidant preventing oxidation of SH groups of peptides. The ratio of GSSG/GSH is an important marker of oxidative stress. The principle of action as an antioxidant is based on the fact that it reduces other toxic substances before they can attack other molecules. Also, it binds free radicals, heavy metals, and toxic substances. Due to these properties it slows aging processes and protects cells from damage.[2] GSH is one of the strongest anti-cancer agents manufactured by the body.[3] However, most tumor cells contain GSH in high concentration and this may be an important factor in resistance to chemotherapy.[4] A specific function of GSH in maintenance of the ascorbate pool in plant cells has been demonstrated.[5] Apparently, GSH is a very important biomolecule and its depletion in an organism causes diseases and aging. On the other hand, many diseases (such as cancer, AIDS, and neurodegenerative diseases) lead to decrease of GSH level, making an organism more vulnerable.[6] Therefore, maintenance of the proper level of GSH is important for health. Homologs of GSH can be found in different plant species, where some of the constitutive amino acids differ from those found in GSH. For instance, homoglutathione (hGSH, L-α-glutamyl-L-cysteine-β-alanine) can be found in several tissues and organs of legumes.[7]

Although GSH is a commonly available substance, its unnatural analogs have been available very scarcely by classic methods of peptide synthesis.[8] It is well known that the replacement of natural amino acids in biologically relevant peptides may influence their properties dramatically.[9] Therefore, the development of new methodology for the synthesis of unnatural analogs of GSH is a modern synthetic problem.

N-Acetylcysteine (NAC) is a precursor of glutathione in an organism but it also possesses antioxidant properties. It is a pharmacological agent used mainly as a mucolytic agent and in the management of paracetamol overdose. We report herein our investigations toward the direct synthesis of unnatural cysteine and glutathione analogs by the Ugi reaction. The synthesis of several NAC derivatives by the Ugi reaction is also described in this article.

2. Results and discussion

To our knowledge, there is only one example of a GSH derivative synthesized by an Ugi three-component reaction (U-3CR) using a cyclic aldimine as a precursor.[10] We supposed that GSH derivatives could be prepared in one step by U-4CR between a protected glutamic acid, an amine component, a carbonyl compound bearing a protected thiol group and ethyl isocyanoacetate as the glycine building block (Scheme 1).[11] In this strategy, the cysteine moiety is constructed directly by the Ugi reaction. This method would open access to fully protected α-substituted cysteine and

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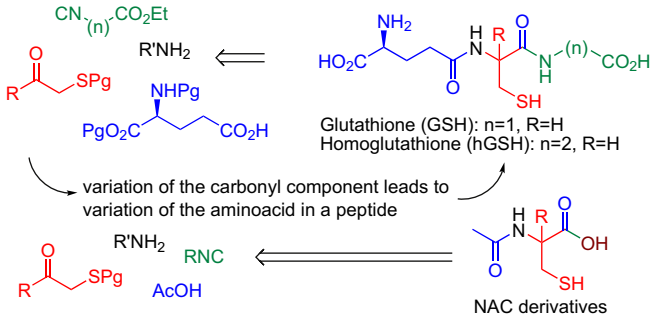
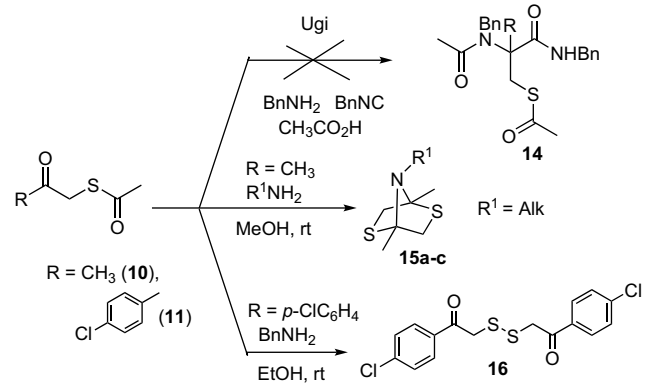
glutathione derivatives. Also, subsequent modification of the peptide would be possible after partial deprotection.[12]



Scheme 1. Multicomponent approach to GSH and NAC.

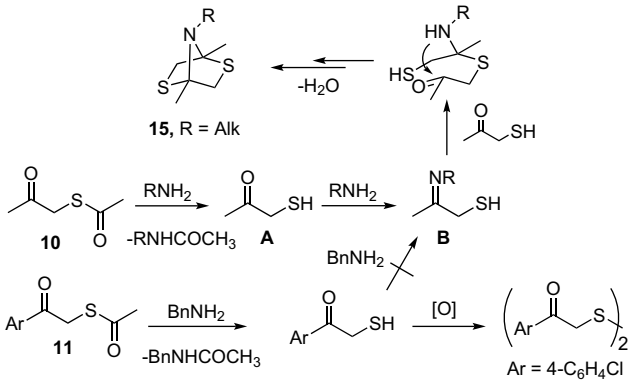
We have found that *S*-protected mercapto carbonyls should be used in the reaction[13] and our first attempts were made to employ an acetyl protecting group because it is removable under mild conditions in high yield (0.2 M NaOH aq).[14] The corresponding carbonyl compounds bearing an acetylthio group were prepared by known methods (Scheme 4) and subjected to the Ugi reaction, but this led to unexpected results. No Ugi products **14** were obtained in reaction of **10**–**11** with benzylisocyanide, acetic acid, and benzylamine under classic conditions (Scheme 2). However, it was found that carbonyl compounds **10**–**11** react smoothly with aliphatic amines in MeOH or EtOH, to form unreactive species, and this process appears to be much more favorable than the Ugi reaction. Aliphatic ketone **10** forms bicyclic products **15a–c**, but aromatic ketone **11** forms the disulfide **16**. These results can be explained by the high susceptibility of the acetylthio group to nucleophilic attack. A possible mechanism of these reactions is outlined in Scheme 3. We suppose that both reactions proceed via α-mercapto ketones **A** since formation of bicyclic products of type **15** in reaction of **A** with amines is a known process.[15] Formation of bicyclic products is very sensitive to steric effects, for example, *i*-PrNH$_2$ reacts with **10** slowly but does not give any **15**. Formation of disulfide **16** is explained by the lower reactivity of an aromatic carbonyl group, which caused oxidation of the thiol group by air to be more favorable than formation of the Schiff base **B**.

Finally we used the benzyl group as a more inert protecting group.[12] The corresponding carbonyl compounds were prepared



R_1	Compound	Yield,%
Bn	**15a**	90
$CH_2CH_2CH_2OMe$	**15b**	83
C_2H_5	**15c**	93

Scheme 2. Use of thioacetic protecting group in the Ugi reaction.

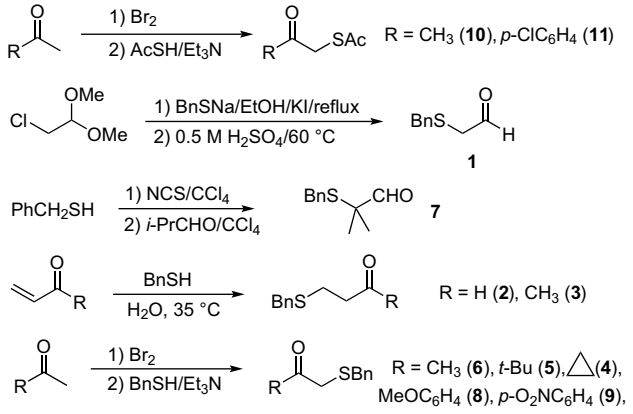


Scheme 3. Possible mechanisms of the reaction of **10** and **11** with amines.

based on literature procedures (Scheme 4) and first tested in a model Ugi reaction with benzylisocyanide, benzylamine, and acetic acid to investigate the scope of the method.

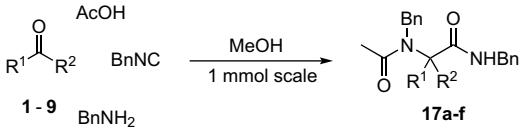
The results are summarized in Table 1. The reaction was found to be sensitive to steric effects and the nature of the carbonyl group. Aromatic ketones **8** and **9** were completely unreactive even on heating because of reduced carbonyl activity (entry 10). Cyclopropyl ketone **4** was also unreactive; ~11% of the desired peptide was isolated together with the minor byproduct with an opened cyclopropyl ring (entry 6). Bulky *tert*-butyl ketone **5** did not give any Ugi product (entry 7). Other ketones **3** and **6** formed the corresponding *N*-acetylcysteine analogs in more than 60% yield, representing good results in the Ugi reaction with ketones (entries 5 and 8).

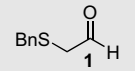
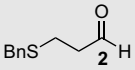
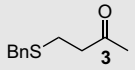
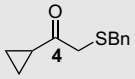
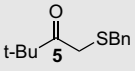
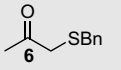
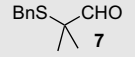
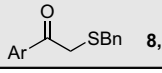
These results were achieved by simple mixing of all four components together in a solvent. But surprisingly, application of such conditions to aldehydes **1** and **2**, which were expected to be more reactive than ketones initially gave poor results (entries 1 and 3). Both reactions were accompanied by precipitation of a viscous oil. These results can be explained by side condensation processes, which become dominant in the case of **1**. After a brief examination of reaction conditions we have found that the influence of the side processes can be greatly diminished by using specific conditions. The best results were achieved when trifluoroethanol was used as a solvent and an aldehyde was slowly added to the mixture of an amine, an acid, and an isocyanide. Such a technique maintains a low concentration of the aldehyde to minimize the influence of the competitive processes. As a result, no oil was formed and the Ugi products were obtained in good yields (entries 2 and 4). Further, we have found that precipitation of the oil occurs only with primary amines. Secondary amines do not give any oil under these



Scheme 4. Synthesis of the carbonyl compounds.

Table 1
Model Ugi reaction with carbonyl compounds **1–9**[a]



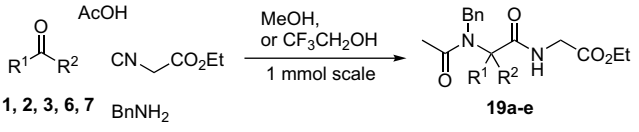
N	Carbonyl	Product	Yield, %	Note
1		**17a**	15	-20 °C
2			52	rt[b]
3		**17b**	47	rt
4			76	rt[b]
5		**17c**	64	rt
6		**17d**	11	Reflux
7		—	0	rt
8		**17e**	78	rt
9		**17f**	80	rt
10	 **8, 9**	—	0	Reflux

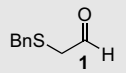
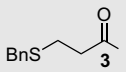
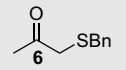
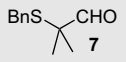
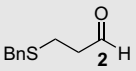
[a] All reactions were run on a 1 mmol scale in 1 mL of methanol, except if otherwise noted.
[b] In CF_3CH_2OH.

conditions.[16] In contrast to enolisable aldehydes, the non-enolisable or sterically hindered aldehydes, e.g., **7,** represent the best substrates for the Ugi reaction. The corresponding product was obtained in high yield (entry 9) simply by mixing all four components together in methanol. As a result, the scope of carbonyl compounds suitable for use in further studies was limited to aliphatic aldehydes and ketones such as **1**, **2**, **3**, **6**, and **7**.

Having investigated the reactions with benzylisocyanide we proceeded to synthesize derivatives of the dipeptide Cys–Gly. Ethyl isocyanoacetate (**18**) was used as the isocyanide component for the Ugi reaction, and the other components (benzylamine and acetic acid) were the same as in previous model reactions. The results are summarized in Table 2. It is noteworthy that ethyl isocyanoacetate behaved differently to benzylisocyanide. Due to the presence of an electron withdrawing group this isocyanide was less reactive; this especially became apparent in reactions with ketones **3**, **6**, and aldehyde **1**. The latter gave a poor yield (Entry 1) even in optimal conditions apparently because the lesser reaction ability of **18** led to increased relative rate of side processes. As a result, we could not avoid formation of the oil observed in the previous experiments. Also formation of significant amounts of side products (but not the oil) was observed in reactions of ketones **3** and **6**. Accordingly, the yields of the desired dipeptides **19c**,**d** were unsatisfactory (entries 2 and 4). Formation of these side products (which appeared to be imidazolines, vide infra) was monitored by TLC and was completely avoided using trifluoroethanol instead of methanol, but the yields were still less than 50% (entries 3 and 5).[17,18] In contrast to ketones, aldehydes **2** and **7** react smoothly and give the desired dipeptides in good yields (entries 6 and 8). We may conclude that the side processes for aldehyde **2** are less favorable than that for **1** therefore they do not influence so dramatically.

Table 2
Synthesis of Cys–Gly derivatives[a]

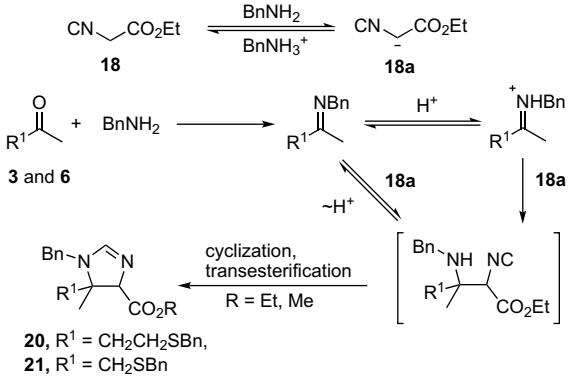


N	Carbonyl	Product	Yield, %	Solvent
1		**19a**	21	CF_3CH_2OH
2		**19b**	13[b]	Methanol
3			43	CF_3CH_2OH
4		**19c**	16[b]	Methanol
5			40	CF_3CH_2OH
6		**19d**	90	Methanol
7			49	Methanol
8		**19e**	72	CF_3CH_2OH

[a] All reactions were run on a 1 mmol scale at rt in 1 mL of the solvent.
[b] Imidazolines were formed as by-products (see text).

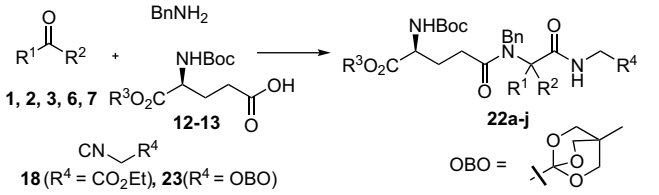
Isocyanoacetate **18** is widely used in the Ugi reaction, but to our knowledge, formation of side products in the four-component variant with ketones has never been discussed before. Therefore we focused on identification of these products and explanation of possible reasons why trifluoroethanol in this case does cause the Ugi reaction to run cleanly, albeit still in moderate yield due to the low reactivity of inputs. After careful chromatography we isolated mixtures of imidazoline derivatives **20** and **21** as the main by-products (Scheme 5). Apparently they were formed in a three-component reaction (3CR) taking place under our conditions competitively. This reaction itself was recently published as a separate synthetic method; however, it was not studied on asymmetric ketones.[19] In our conditions (MeOH) imidazoline formation was accompanied by the transesterification (interestingly, it was not observed in the corresponding Ugi products **19b**–**e**). Quantitative composition of the imidazoline mixtures was established by careful analysis of the NMR spectra after control experiments with benzylamine **18** and ketones **3** and **6** in ethanol in a transesterification-free 3CR.

Further, our observations suggest that in the case of aldehydes the Ugi reaction is faster, therefore imidazolines are not formed. But the Ugi reaction with ketones is slow, therefore both processes



Scheme 5. Side processes occurring in the Ugi reaction with **18** and ketones **3** and **6** in methanol.

Table 3
Synthesis of glutathione derivatives



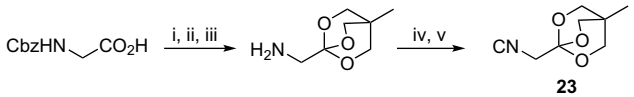
N	R^1 (carbonyl)	R^2	R^3	R^4	Product	Yield, %
1[c]	$-CH_2SBn$ **1**	H	Bn	CO_2Et	**22a**	22
2[a]	$-C(CH_3)_2SBn$ **7**	H	Me	CO_2Et	**22b**	57
3[b]	$-CH_2CH_2SBn$ **2**	H	Me	CO_2Et	**22c**	37
4[c]	$-CH_2CH_2SBn$ **3**	Me	Me	CO_2Et	**22d**	33
5[c]	$-CH_2SBn$ **6**	Me	Me	CO_2Et	**22e**	23
6[c]	$-CH_2CH_2SBn$ **2**	H	Bn	CO_2Et	**22f**	67
7[c]	$-CH_2SBn$ **6**	Me	Bn	CO_2Et	**22g**	37
8[a]	$-C(CH_3)_2SBn$ **7**	H	Bn	CO_2Et	**22h**	71
9[a]	$-C(CH_3)_2SBn$ **7**	H	Bn	OBO	**22i**	76
10[a]	$-CH_2SBn$ **6**	Me	Bn	OBO	**22j**	46
11[a]	$-CH_2CH_2SBn$ **3**	Me	Bn	OBO	**22k**	52

[a] C=0.5 M in methanol.
[b] C=0.5 M in methanol–THF 10:1.
[c] C=0.5 M in CF_3CH_2OH.

occur. We believe that imidazoline formation may take place in four-component Ugi reactions with any other CH-acidic isocyanides in MeOH or EtOH media. However it does not proceed in three-component Ugi reactions with imines as starting materials.[20]

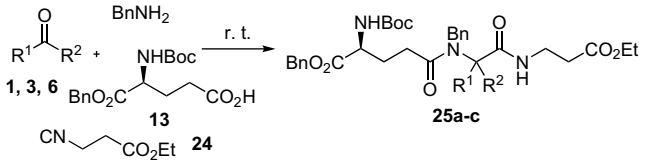
As we stated above, formation of imidazolines could be significantly diminished by changing the solvent to trifluoroethanol. The most reasonable explanation would be the high acidity of this solvent ($pK_a \sim 12.4$ in water), which is at least 1000 times higher in comparison to other alcohols. In this media the equilibrium concentration of the isocyanoacetate *C*-anion **18a**, the key intermediate in the imidazoline formation, should be low enough to prevent this process. We believe that it is due to the acidity factor, because this reaction was shown to proceed in wide range of polar protic and aprotic solvents with different dipole moments and dielectric constants.[19]

Bearing in mind the peculiarities of the reactions with ethyl isocyanoacetate **18**, we proceeded to synthesize glutathione derivatives. Boc-protected glutamic monoesters **12** and **13** used in this study were synthesized by a known method.[21] The results are summarized in Table 3. In comparison to previous experiments, we diluted the reaction mixtures, because of high molecular weight of the acid and hence, higher viscosity of the reaction media. But nevertheless, the increase of molecular complexity influenced negatively on the reaction rate. Ketones react with difficulty under these conditions if **18** is used as an isocyanide component (entries 4, 5, and 7). Also the reaction with aldehyde **1** suffers from competitive side processes, therefore natural glutathione derivative was obtained in low yield (entry 1). Reaction with other aldehydes gives better yields (entries 2, 3, and 6). Obviously the use of **18** has serious limitations. A more reactive isocyanide is required to expand the scope of the method. Such isocyanide can be 4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl (OBO) ester of isocyanoacetic acid **23**, just developed in our laboratory. It was synthesized from commercially available Cbz-glycine (Scheme 6).[22] We expected that



Scheme 6. Synthesis of isocyanide **23**: (i) 3-methyl-3-oxetanemethanol, DCC, DMAP, CH_2Cl_2, rt, 95%; (ii) $BF_3 \cdot Et_2O$, CH_2Cl_2, rt, 98%; (iii) H_2–Pd–C, MeOH, rt, 99%; (iv) HCOOEt, reflux, 80%; (v) $POCl_3$, Et_3N, CH_2Cl_2, −20 °C, 90%.

Table 4
Synthesis of homoglutathione derivatives



N	R^1 (carbonyl)	R^2	Product	Yield, %	Solvent
1	$-CH_2SBn$ **1**	H	**25a**	44	CF_3CH_2OH
2	$-CH_2SBn$ **6**	Me	**25b**	45	CF_3CH_2OH
3	$-CH_2CH_2SBn$ **3**	Me	**25c**	67	MeOH

the negative influence of the COOEt group can be diminished after replacement by an OBO group. Indeed, reaction with **23** gave a better yield (Table 3, entries 9–11), indicating the higher reactivity of the isocyanide in comparison with **18**. Moreover, in contrast to **18**, reaction of ketones **3** and **6** with **23** in methanol proceeds indeed cleanly so that the use of trifluoroethanol is not necessary.

In all cases, no diastereoselectivity was observed and glutathione derivatives **22a–j** were obtained as ~1:1 mixtures of inseparable diastereomers. It should be also noted that the suggested methodology can be used in the synthesis of selenium-containing peptide derivatives, which are compounds of biochemical interest.[23]

The OBO-protecting group was shown to be removable in high yield under mild conditions using a two-step one-pot procedure [(1) TFA–H_2O–CH_2Cl_2, (2) 0.4 M NaOH–H_2O–THF, then acidification with HCl].[22]

To further confirm our view about the influence of COOEt group in isocyanide **18**, we conducted a few reactions with isocyanide **24** and synthesized homoglutathione derivatives (Table 4). Since **24** has an electron withdrawing group at a greater distance from isocyanide functionality it has normal reactivity. As expected, homoglutathione derivatives were obtained in a better yield demonstrating the higher reactivity of the isocyanide in comparison with **18**.

3. Conclusion

We have elaborated a new synthesis of various natural and unnatural substituted totally protected cysteine, glutathione, and homoglutathione derivatives using the Ugi four-component reaction. The scope and limitations of the method were discussed. We have described the formation of imidazoline by-products in the Ugi four-component reaction with ethyl isocyanoacetate **18** concerned with its specific CH-acidic properties. 2,2,2-Trifluoroethanol was shown to be the solvent of choice in the Ugi reaction of **18** with ketones. Also we have demonstrated that the OBO-ester of isocyanoacetic acid **23** is more convenient in the corresponding reactions.

4. Experimental

4.1. General information

^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 (on 400 and 100 MHz correspondingly). Chemical shifts are given in δ (ppm) scale. IR spectra were recorded on UR-20 spectrometer. Elemental analysis was performed in the analytical laboratory of A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences. TLC was performed using 25 DC-Alufolien Kieselgel 60 F_{254} (Merck). Fluka Silica gel 60 (0.063–0.200 mm) was used for column chromatography. Commercial reagents and

solvents were generally used as received. Methylene chloride was distilled over P_2O_5, ethyl acetate, and triethylamine were stood over CaH_2 and then distilled. Benzylamine was stood over CaH_2 and then distilled in vacuo.

4.2. Starting materials

4.2.1. Benzyl thiol

To a warm solution of 78 g (1.02 mol) thiourea in 500 mL of ethanol was added 115 mL (126 g, 1.0 mol) benzyl chloride. The reaction mixture was heated to reflux for 10 min (TLC control, CH_2Cl_2–MeOH 10:1). The resulting colorless transparent solution was concentrated in vacuo almost to dryness and then a solution of 70 g (1.8 mol) NaOH in 600 mL water was added (a white precipitate was formed). The reaction mixture was heated to reflux for an hour and cooled (a precipitate shouldn't appear; if it does, the mixture should be heated longer). The reaction mixture was extracted with methylene chloride (400 mL). The organic phase was dried over Na_2SO_4 and concentrated to give benzyl thiol (118 g, 95%) as a colorless liquid. R_f (EA–hexanes 1:5) 0.60. R_f (EA–hexanes 1:2) 0.81. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.37 (5H, m, Ph), 3.78 (2H, d, CH_2, J=7.6 Hz), 1.79 (1H, t, SH, J=7.6 Hz).[24]

4.2.2. 2-(Benzylthio)acetaldehyde (**1**)[25]

Sodium (1.13 g, 0.0492 mol) was dissolved in dry ethanol (25 mL), and benzyl thiol (6.11 g, 5.78 mL, 0.0493 mol), KI (0.25 g), and dimethyl chloroacetal (6.11 g, 0.0493 mol) were added. The reaction mixture was heated to reflux for 5–7 h (TLC control: EtOAc–hexanes 1:5). The precipitate was filtered off, washed with ethanol, the filtrate was concentrated in vacuo, diluted with water (30 mL), and extracted with methylene chloride (50 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EA–hexanes 1:5, R_f 0.37) to afford 2-(benzylthio)-dimethyl acetal (7.13 g, 68%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.25 (5H, m, Ph), 4.43 (1H, t, J=5.6 Hz, CH), 3.80 (2H, s, $PhCH_2$), 3.36 (6H, s, OCH_3), 2.61 (2H, d, J=5.6 Hz, SCH_2).

2-(Benzylthio)-dimethyl acetal (7.13 g) was heated at ~60 °C with 0.5 M H_2SO_4 (30 mL) for 2–3 h (TLC control, toluene–methanol 20:1). Then the reaction mixture was neutralized with $NaHCO_3$ and extracted three times with 20 mL portions of methylene chloride. The organic phase was dried over Na_2SO_4 and concentrated to afford **1** (5.58 g, 100%) as a slightly yellow liquid, n_d 1.5692 (lit.[25] 1.5699). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (1H, t, J=3.4 Hz, CHO), 7.25–7.38 (5H, m, Ph), 3.65 (2H, s, $PhCH_2$), 3.11 (2H, d, CH_2).

4.2.3. 3-(Benzylthio)-propanal (**2**)[26]

A mixture of benzyl thiol (3.73 g, 3.52 mL, 0.030 mol), water (30 mL), and acrolein (2.1 mL, ~0.033 mol) was stirred at 30–35 °C for 15 min (TLC control: EtOAc–hexanes 1:5), and was extracted with methylene chloride (2×20 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo to afford **2** (5.15 g, 95%) as a colorless liquid. R_f (EA–hexanes 1:5) 0.29. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (1H, s, CHO), 7.25–7.37 (5H, m, Ph), 3.76 (2H, s, $PhCH_2$), 2.65–2.75 (4H, m, CH_2CH_2).

4.2.4. 4-(Benzylthio)-butanone-2 (**3**)[26]

Obtained by the same procedure as **2** in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.35 (5H, m, Ph), 3.74 (2H, s, $PhCH_2$), 2.66 (4H, s, CH_2CH_2), 2.13 (3H, s, CH_3).

4.2.5. 2-(Benzylthio)-1-cyclopropylethanone (**4**)

Methyl cyclopropyl ketone (8.41 g, 0.10 mol) was dissolved in methanol (60 mL) and a few drops of bromine solution (16.0 g (5.15 mL, 0.1 mol) in 10 mL of methanol) were added. When the solution became colorless, the reaction flask was placed into a cold bath and the remaining amount of bromine was added dropwise at <10 °C. Then water (130 mL) was added to the colorless reaction solution and stirred for 15 min. After this, reaction mixture was carefully hydrolyzed by the addition of 8.4 g $NaHCO_3$ and extracted with methylene chloride (2×50 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by vacuum distillation to afford bromomethyl cyclopropyl ketone (11.9 g, 73%) as a colorless liquid that can be stored in freezer.[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (2H, s, CH_2CO), 2.26–2.20 (1H, m, CHCO), 1.17–1.13 (2H, m), 1.06–1.01 (2H, m).

Bromomethyl cyclopropyl ketone (11.7 g, 0.0718 mol) was dissolved in ether (120 mL). The solution was cooled in an ice–NaCl bath and triethylamine (11.0 mL, 0.0789 mol) was added. Then, benzyl thiol (8.53 mL, 9.02 g, 0.0726 mol) was added dropwise at <10 °C (white precipitate is formed immediately). The reaction mixture was stirred for additional 30 min and was filtered through short SiO_2-column. The filtrate was concentrated in vacuo to afford **4** (14.1 g, 95%) as a colorless liquid. R_f (EA–hexanes 1:2) 0.6. [Found: C, 69.71; H, 6.83. $C_{12}H_{14}OS$ requires C, 69.86; H, 6.84%.] ν_{max} (neat, cm^{-1}): 1690 (C=O), 1600, 1390, 713. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.37 (5H, m, Ph), 3.70 (2H, s, $PhCH_2$), 3.28 (2H, s, SCH_2CO), 2.12–2.80 (1H, m, COCH), 0.91–1.09 (4H, m, CH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 137.4, 129.2, 128.5, 127.2, 40.9, 36.0, 19.3, 11.6.

4.2.6. 1-(Benzylthio)-3,3-dimethylbutanone-2 (**5**)

Methyl *tert*-butyl ketone (13 mL, 0.10 mol) was brominated in 50 mL of ether as described for **4**. The reaction mixture was carefully neutralized by $NaHCO_3$ aq, washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by vacuum distillation to yield 1-brom-3,3-dimethylbutanone-2 (12.13 g, 68%) as a colorless liquid, can be stored in freezer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (2H, s, CH_2CO), 1.25 (9H, s, CH_3).

A solution of 1-bromo-3,3-dimethylbutanone-2 (12.13 g, 0.0677 mol) in acetone (120 mL) was treated as described for **4** to yield **5** (15.25 g, 96%) as a colorless liquid. R_f (EA–hexanes 1:5) 0.5. [Found: C, 70.29; H, 8.10. $C_{13}H_{18}OS$ requires C, 70.22; H, 8.16%.] ν_{max} (neat, cm^{-1}): 1700 (C=O), 1600, 710. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.36 (5H, m, Ph), 3.78 (2H, s, $PhCH_2$), 3.28 (2H, s, $COCH_2$), 1.18 (9H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.4, 137.5, 129.2, 128.5, 127.2, 43.3, 35.8, 34.6, 26.8.

4.2.7. α-(Benzylthio)acetone (**6**)[28]

It was prepared as described for **5**, yield 44%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.37 (5H, m, Ph), 3.70 (2H, s, $PhCH_2$), 3.13 (2H, s, $COCH_2$), 2.25 (3H, s, CH_3).

4.2.8. 2-(Benzylthio)-2-methylpropanal (**7**)[29]

NCS (6.69 g, 0.050 mol) was dissolved in CCl_4 (20 mL) and benzyl thiol (6.2 g, 5.8 mL, 0.050 mol) was added. The reaction is slightly exothermic. The reaction mixture was stirred for 2 h. The precipitate was filtered off, isobutyric aldehyde (3.6 g, 0.050 mol) was added to the yellow solution, and the reaction mixture was left to stand overnight. The resulting colorless solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EA–hexanes 1:6) to yield **7** (4.07 g, 42%) as a colorless liquid (~2 g of crystalline benzyl disulfide was obtained as byproduct because of incomplete chlorination). n_d 1.546 (lit. 1.545). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (1H, s, CHO), 7.23–7.34 (5H, m, Ph), 3.54 (2H, s, CH_2), 1.41 (6H, s, CH_3).

4.2.9. 4-Methoxy-α-(benzylthio)acetophenone (**8**)

4-Methoxyacetophenone (15.1 g, 0.101 mol) was brominated in a mixture of ether (30 mL) and methylene chloride (60 mL) as described for **5**. The reaction mixture was evaporated to dryness and

the residue was recrystallized from ethanol to yield 4-methoxy-α-bromoacetophenone (18.8 g, 82%) as a colorless solid.

A solution of 4-methoxy-α-bromoacetophenone (18.8 g) in acetone (200 mL) was treated as described for **4**. The reaction mixture was filtered, the filtrate was evaporated to dryness, and the residue was recrystallized from a little amount of ethanol to yield **8** (20.7 g, 92%) as a colorless solid. R_f (EA–hexanes 1:1) 0.6. [Found: C, 70.69; H, 9.04; S, 11.70. $C_{16}H_{16}O_2S$ requires C, 70.56; H, 5.92; S, 11.77%.] ν_{max} (KBr, cm^{-1}): 1660 (C=O), 1595, 1240, 1040, 700. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, Ph, *J*=8.9 Hz), 7.25–7.38 (5H, m, Ph), 6.94 (2H, d, Ph, *J*=8.9 Hz), 3.88 (3H, s, CH_3), 3.78 (2H, s, CH_2), 3.65 (2H, s, $PhCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 163.7, 137.5, 131.1 (2C), 129.3 (2C), 128.5 (2C), 128.4 (C_{quat}), 127.2, 113.9 (2C), 55.5, 36.2, 35.8.

*4.2.10. 4-Nitro-α-(benzylthio)acetophenone (**9**)*

It was prepared as described for **8**, yield 68%. R_f (EA–hexanes 1:2) 0.5. [Found: C, 62.75; H, 4.52; S, 11.26. $C_{15}H_{13}NO_3S$ requires C, 62.70; H, 4.56; S, 11.16%.] ν_{max} (Nujol, cm^{-1}): 1680 (C=O), 1600, 1525, 1355, 720. ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (2H, d, Ph, *J*=8.9 Hz), 8.08 (2H, d, Ph, *J*=8.9 Hz), 7.25–7.38 (5H, m, Ph), 3.75 (2H, s, CH_2), 3.70 (2H, s, $PhCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 150.3, 139.9, 136.8, 129.8, 129.3, 128.6, 127.5, 123.8, 36.13, 36.06.

*4.2.11. α-Acetylthioacetone (**10**)[30]*

Acetone (100 mL) was brominated by 3 mL (9.3 g, 58.2 mmol) of bromine. A mixture of triethylamine (8.1 g, 80 mmol), acetone (20 mL), and thioacetic acid (4.53 g, 59.5 mmol) (prepared separately on cooling) was dropwise added (at <10 °C) to the cooled reaction mixture. The reaction mixture was left to stand overnight and filtered, filtrate was evaporated to dryness, the residue chromatographed on silica gel (gradient elution EA–hexanes 1:3→EA) to yield α-acetylthioacetone (5.07 g, 66%) as a liquid. R_f (EA–hexanes 1:2) 0.42. ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (2H, s, CH_2), 2.39 (3H, s), 2.27 (3H, s).

4.2.12. N-(Boc)-L-glutamic acid

L-Glutamic acid (29.4 g, 0.20 mol) was dissolved in 350 mL of aqueous solution of NaOH (25 g, 0.63 mol). The solution (pH∼11) was cooled and a solution of Boc_2O (52.4 g, 0.24 mol) in THF (160 ml) was added at <10 °C (slightly exothermic reaction). Then the reaction mixture was stirred at rt for 20 h. TLC control: MeOH–CH_2Cl_2–AcOH 10:10:1. The organic phase was separated off, the water phase was extracted with hexanes (2×40 mL), acidified by dilute HCl to pH∼2, and extracted with ethyl acetate (2×200). Combined organic phases was dried over Na_2SO_4, evaporated in vacuo, diluted with methylene chloride, and evaporated again. The product is obtained as a sticky oil, which could be crystallized by triturating with hexanes after prior standing for 2–3 days to yield *N*-(Boc)-L-glutamic acid (43.5 g, 89%) as a colorless solid. Mp 113–114 °C (lit.[21] 110–112 °C). ^1H NMR (400 MHz, $CDCl_3$): δ mixture of rotamers 2:1 (signals of the minor rotamer are given in parentheses) 10.1 (2H, br s, COOH), 5.39 (6.63) (1H, d, NH), 4.40 m (4.23 br s) (1H, NCH), 2.52 (2H, t, CH_2CO), 2.19–2.27 (1H, m), 2.05–2.11 (1H, m), 1.46 (9H, s, CH_3).

4.2.13. N-(Boc)-L-glutamic anhydride

It was prepared in 33.7 g (98%) yield using the literature procedure.[21] R_f (EA–hexanes 1:2) 0.32. Mp 118–119 °C (lit.[15] 115–116 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (1H, br s, NH), 4.43 (1H, br s, CH), 3.02–3.08 (1H, m), 2.86–2.92 (1H, m), 2.45 (1H, br s), 1.96 (1H, m), 1.48 (9H, s, CH_3).

*4.2.14. N-(Boc)-L-glutamic acid α-methyl ester (**12**)*

It was prepared using literature procedure.[21] $NaHSO_4$ was used instead of citric acid at the end. R_f (EtOAc) 0.6. Yield 0.241 g (36%) as an amorphous solid. R_f (EA) 0.6. ^1H NMR (400 MHz, $CDCl_3$): δ 5.18 (1H, br s, NH), 4.38 (1H, br s, CH), 3.77 (3H, s, OCH_3), 2.39–2.55 (2H, m, CH_2CO), 2.14–2.27 (1H, m), 1.89–2.03 (1H, m), 1.46 (9H, s, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0 (minor), 174.1, 173.2, 171.7 (m), 155.9, 78.7, 72.9 (m), 54.4 (m), 53.1, 52.1, 43.2 (m), 30.4 (m), 28.6, 28.3 (m), 26.4.

*4.2.15. N-(Boc)-L-glutamic acid α-benzyl ester (**13**)*

It was prepared using literature procedure.[21] $NaHSO_4$ was used instead of citric acid at the end. R_f (EtOAc) 0.6. Yield 10.41 g (38%) as a white solid. $[\alpha]_D^{25}$ −27.3 (*c* 0.1, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (5H, m, Ph), 5.19 (2H, s), 5.19 (1H, br s), 4.41 (1H, m), 2.37–2.52 (2H, m), 2.16–2.27 (1H, m), 1.91–2.05 (1H, m), 1.45 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 172.1, 155.5, 135.2, 128.7, 128.5, 128.3, 80.3, 67.3, 52.9, 30.0, 28.3, 27.6.

4.3. Reaction of acetylthio ketones 10 and 11 with aliphatic amines (synthesis of 15a–c and 16)

*4.3.1. 7-Benzyl-1,4-dimethyl-2,5-dithia-7-azabicyclo[2.2.1]-heptane (**15a**)*

A solution of **10** (0.132 g, 1 mmol) and benzylamine (0.107 g, 1 mmol) in 0.5 mL of ethanol was kept 2 h at rt. Precipitate was filtered, washed with ethanol, and dried to give 0.104 g of white solid. R_f (EA–hexanes 1:2) 0.73. [Found: C, 61.84; H, 6.93. $C_{13}H_{17}NS_2$ requires C, 62.11; H, 6.82%.] ν_{max} (KBr, cm^{-1}): 1600, 1490, 1450, 1430, 1230, 1135, 780, 720. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (2H, d, Ph), 7.34 (2H, t, Ph), 7.25 (1H, t, Ph), 3.75 (1H, d, *J*=16.0 Hz, CH_2N), 3.61 (1H, d, *J*=16.0 Hz, CH_2N), 3.43 (2H, d, *J*=9.0 Hz, CH_2S), 3.28 (2H, d, *J*=9.0 Hz, CH_2S), 1.63 (6H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 128.3, 127.6, 126.7, 82.5 (2C), 50.2 (2C), 47.2, 21.3 (2C).

*4.3.2. 7-(3-Methoxypropyl)-1,4-dimethyl-2,5-dithia-7-azabicyclo[2.2.1]heptane (**15b**)*

A solution of **10** (0.264 g, 2 mmol) and 3-methoxypropylamine-1 (0.267 g, 3 mmol) in 1 mL of methanol was kept for 40 min at rt. Then it was evaporated, the residue was chromatographed to afford **15b** (83%) as a white oil. R_f (EA–hexanes 1:2) 0.47. [Found: C, 51.63; H, 8.33; S, 27.25. $C_{10}H_{19}NOS_2$ requires C, 51.46; H, 8.21; S, 27.48%.] ν_{max} (KBr, cm^{-1}): 1480, 1410, 1220, 1100. ^1H NMR (400 MHz, $CDCl_3$): δ 3.46 (2H, m, OCH_2), 3.35 (2H, d, *J*=9.0 Hz, CH_2S), 3.17 (2H, d, *J*=9.0 Hz, CH_2S), 3.34 (3H, s, OCH_3), 2.50 (2H, m, CH_2N), 1.77 (2H, m, CH_2), 1.73 (6H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.4 (2C), 70.2, 58.5, 50.0 (2C), 39.8, 30.9, 20.9 (2C).

*4.3.3. 7-Ethyl-1,4-dimethyl-2,5-dithia-7-azabicyclo-[2.2.1]heptane (**15c**)*

Compound **15c** was prepared from **10** as described for **15b**. Yield 93%. White oil. R_f (EA–hexanes 1:2) 0.58. [Found: C, 50.92; H, 7.91; S, 33.70. $C_8H_{15}NS_2$ requires C, 50.75; H, 7.99; S, 33.87%.] ν_{max} (KBr, cm^{-1}): 1480, 1420, 1230. ^1H NMR (400 MHz, $CDCl_3$): δ 3.37 (2H, d, *J*=9.0 Hz, CH_2S), 3.19 (2H, d, *J*=9.0 Hz, CH_2S), 2.47 (2H, m, CH_2N), 1.76 (6H, s, CH_3), 1.19 (3H, t, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.4 (2C), 50.0 (2C), 37.6, 21.0 (2C), 16.5.

*4.3.4. 2,2′-Dithiobis[1-(4-chlorophenyl)ethanone] (**16**)[31]*

Compound **16** was prepared from **11** as described for **15a**. R_f (EA–hexanes 1:1) 0.5. White solid. Mp 123–124 °C (lit. 123–124 °C). [Found: C, 51.93; H, 3.16; S, 17.21. $C_{16}H_{12}Cl_2S_2O_2$ requires C, 51.76; H, 3.26; S, 17.27%.] ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (4H, d, *J*=8.3 Hz, Ph), 7.46 (4H, d, *J*=8.3 Hz, Ph), 4.16 (4H, s, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0 (CO), 140.3, 133.7, 130.2, 129.2, 45.1 (CH_2).

4.4. Synthesis of NAC derivatives 17a–f

Method A. A solution of carbonyl compound **3**, **6** or **7** (1 mmol), benzylamine (1 mmol), acetic acid (1 mmol), and benzylisocyanide

(1 mmol) in 1 mL of methanol was kept at rt for 1 h for aldehyde **7** and 2–3 days for ketones **3** and **6**. Then the mixture was evaporated, the residue was chromatographed (gradient elution EA–hexanes 1:1 → EA). The product appears as an oil that could be crystallized.

Method B. An aldehyde **1** or **2** (1 mmol) was slowly (in 20 min) added dropwise to a mixture of benzylamine (1 mmol), acetic acid (1 mmol), and ethyl isocyanoacetate (1 mmol) in 1 mL of trifluoroethanol. The reaction mixture was stirred at rt for additional 40 min and was evaporated, the residue was chromatographed (gradient elution EA–hexanes 1:1 → EA). The product appears as an oil that could be crystallized.

4.4.1. N^2-Acetyl-N^1,N^2,S-tribenzylcysteinamide (**17a**)

Method B. Yield 0.207 g, 52%. Orange solid. Mp 93–95 °C. R_f (EA–hexanes 1:1) 0.36. [Found: C, 72.34; H, 6.61. $C_{26}H_{28}N_2O_2S$ requires C, 72.19; H, 6.52%.] ν_{max} (Nujol, cm^{-1}): 3310 (NH), 1670 (amide), 1630 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.08 (15H, m, Ph), 6.89 (1H, br t, NH), 5.06 (1H, t, NC*H*CO), 4.58 (2H, s, PhCH_2N), 4.45 (1H, dd, *J*=6.0, 14.9 Hz, PhCH_2NH), 4.28 (1H, dd, *J*=5.3, 14.9 Hz, PhCH_2NH), 3.71 (2H, s, PhCH_2S), 2.97 (1H, dd, *J*=8.6, 13.6 Hz, CH_2SBn), 2.66 (1H, dd, *J*=6.6, 13.6 Hz, CH_2SBn), 2.09 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 169.4, 138.01, 137.96, 137.1, 129.0, 128.8, 128.65, 128.60, 127.7, 127.44, 127.41, 127.2, 126.1, 57.0 (N*C*HCO), 49.5 (Ph*C*H$_2$N), 43.5 (Ph*C*H$_2$NH), 36.4 (PhCH$_2$*S*), 30.0 (BnS*C*H$_2$), 22.2 (*C*H$_3$CO).

4.4.2. N^2-Acetyl-N^1,N^2,S-tribenzylhomocysteinamide (**17b**)

Method B. Yield 0.341 g, 76%. White solid. Mp 67–69 °C. R_f (EA–hexanes 1:1) 0.42. [Found: C, 72.50; H, 6.88. $C_{27}H_{30}N_2O_2S$ requires C, 72.61; H, 6.77%.] ν_{max} (Nujol, cm^{-1}): 3300 (NH), 1680 (amide), 1630 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.11 (15H, m, Ph), 6.82 (1H, t, *J*=5.0 Hz, NH), 5.07 (1H, dd, CH), 4.57 (2H, s, PhCH$_2$N), 4.41 (1H, dd, *J*=5.8, 15.0 Hz, PhCH_2NH), 4.30 (1H, dd, *J*=5.8, 15 Hz, PhCH_2NH), 3.64 (2H, s, PhCH_2*S*), 2.45–2.22 (3H, m), 2.07 (3H, s, CH$_3$CO), 1.82 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 170.1, 138.3, 138.2, 137.3, 128.9, 128.7, 128.5, 127.7, 127.5, 127.4, 127.0, 126.1, 56.8 (N*C*HCO), 49.6 (Ph*C*H$_2$N), 43.4 (Ph*C*H$_2$NH), 36.1 (PhCH$_2$*S*), 28.2, 28.0, 22.3 (*C*H$_3$CO).

4.4.3. N^2-Acetyl-N^1,N^2-dibenzyl-4-(benzylthio)isovalinamide (**17c**)

Method A. Yield 0.295 g, 64%. White solid. Mp 115–116 °C. R_f (EA–hexanes 1:1) 0.3. [Found: C, 72.93; H, 7.02. $C_{28}H_{32}N_2O_2S$ requires C, 73.01; H, 7.00%.] ν_{max} (Nujol, cm^{-1}): 3355 (NH), 1660 (amide), 1640 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.24 (15H, m, Ph), 5.89 (1H, t, NH, *J*=5.0 Hz), 4.55 (1H, d, PhCH_2N, *J*=18.0 Hz), 4.47 (1H, d, PhCH_2N, *J*=18.0 Hz), 4.44 (2H, d, PhCH_2NH, *J*=5.0 Hz), 3.65 (2H, s, PhCH_2*S*), 2.48–2.32 (2H, m), 2.28 (1H, dt, *J*=5.0, 11.0 Hz), 2.09 (3H, s), 1.99 (1H, dt, *J*=5.0, 11.0 Hz), 1.39 (3H, s, CH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 172.1, 138.5, 138.4, 138.2, 129.1, 129.0, 128.7, 128.6, 127.9, 127.5, 127.1, 126.2, 64.9 (NC$_{quat}$CO), 49.1 (PhCH$_2$N), 43.9 (PhCH$_2$NH), 36.0 (PhCH$_2$SCH$_2$*C*H$_2$), 25.8 (S*C*H$_2$CH$_2$), 23.3 (CH$_3$), 21.9 (*C*H$_3$CO).

4.4.4. N^2-Acetyl-N^1,N^2,S-tribenzyl-2-methylcysteinamide (**17e**)

Method A. Yield 0.349 g, 78%. White solid. [Found: C, 72.41; H, 6.83. $C_{27}H_{30}N_2O_2S$ requires C, 72.61; H, 6.77%.] ν_{max} (Nujol, cm^{-1}): 3290 (NH), 1685 (amide), 1640 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.22 (15H, m, Ph), 6.14 (1H, t, NH, *J*=5.0 Hz), 4.74 (1H, d, PhCH_2N, *J*=18.2 Hz), 4.68 (1H, d, PhCH_2N, *J*=18.2 Hz), 4.46 (1H, dd, PhCH_2NH, *J*=5.0, 12.0 Hz), 4.42 (1H, dd, PhCH_2NH, *J*=5.0, 12.0 Hz), 3.72 (1H, d, *J*=13.1 Hz, PhCH_2*S*), 3.67 (1H, d, *J*=13.1 Hz, PhCH_2*S*), 3.55 (1H, d, *J*=12.6 Hz), 3.01 (1H, d, *J*=12.6 Hz), 2.13 (3H, s, CH$_3$CO), 1.44 (3H, s, CCH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.57, 172.3, 138.6, 138.2, 137.9, 129.11, 128.9, 128.7, 128.6, 127.9, 127.4, 127.3, 126.1, 65.1 (NC$_{quat}$CO), 50.0 (PhCH$_2$N), 44.0 (PhCH$_2$NH), 37.9 (PhCH$_2$SCH$_2$C), 23.3, 23.0 (*C*H$_3$CO).

4.4.5. N^2-Acetyl-N^1,N^2-dibenzyl-2-methyl-S-(1-methyl-1-phenylethyl)cysteinamide (**17f**)

Method A. Yield 0.369 g, 80%. White solid. Mp 127–128 °C. R_f (EA–hexanes 1:2) 0.32. [Found: C, 73.13; H, 6.95. $C_{28}H_{32}N_2O_2S$ requires C, 73.01; H, 7.00%.] ν_{max} (Nujol, cm^{-1}): 3270 (NH), 1680 (amide), 1635 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.05 (16H, m, Ph+NH), 5.62 (1H, s, CH), 5.40 (1H, d, *J*=17.4 Hz, PhCH_2N), 4.68 (1H, d, *J*=17.4 Hz, PhCH_2N), 4.36 (1H, dd, *J*=6.1, 14.7 Hz, PhCH_2NH), 4.14 (1H, dd, *J*=5.3, 14.7 Hz, PhCH_2NH), 3.88 (1H, d, *J*=12.0 Hz, PhCH_2*S*), 3.83 (1H, d, *J*=12.0 Hz, PhCH_2*S*), 1.87 (3H, s, CH$_3$CO), 1.60 (3H, s), 1.52 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 168.3, 138.5, 138.1, 137.0, 129.3, 128.6, 128.5, 128.2, 127.4, 127.0, 126.8, 125.6, 60.5 (NCHCO), 50.5 (SC$_{quat}$), 50.2 (PhCH$_2$N), 43.4 (PhCH$_2$NH), 33.7 (PhCH$_2$*S*), 26.6, 26.5, 22.7 (*C*H$_3$CO).

4.5. Synthesis of Cys–Gly dipeptide derivatives 19a–f

Method C. A solution of carbonyl compound (1 mmol), benzylamine (1 mmol), acetic acid (1 mmol), and ethyl isocyanoacetate (1 mmol) in methanol (1 mL) for aldehyde **7** or trifluoroethanol (1 mL) for ketones **3** and **6** was kept at rt for 1 h for aldehyde **7** and 2–3 days for ketones. Then the mixture was evaporated, the residue was chromatographed (gradient elution EA–hexanes 1:1 → EA). The product appears as an oil that could be crystallized in some cases.

Method D. Similar to *method B* (use **18** or **23** instead of benzylisocyanide).

4.5.1. Ethyl N-acetyl-N,S-dibenzylcysteinylglycinate (**19a**)

Method D. Yield 0.090 g, 21%. Sticky oil. R_f (EA) 0.53. [Found: C, 64.56; H, 6.83. $C_{23}H_{28}N_2O_4S$ requires C, 64.46; H, 6.59%.] ν_{max} (Nujol, cm^{-1}): 3250 (NH), 1750 (COO), 1680 (amide), 1625 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.13 (10H, m, Ph), 7.01 (1H, br t), 5.14 (1H, t), 4.60 (1H, d, *J*=17.8 Hz, PhCH_2N), 4.52 (1H, d, *J*=17.8 Hz, PhCH_2N), 4.21 (2H, q, *J*=7.1 Hz, OCH_2CH$_3$), 4.00 (1H, dd, *J*=6.1, 18.2 Hz, NHCH_2COO), 3.85 (1H, dd, *J*=5.1, 18.2 Hz, NHCH_2COO), 3.70 (2H, s, PhCH_2*S*), 2.94 (1H, dd, *J*=8.6, 13.6 Hz, CH_2SBn), 2.60 (1H, dd, *J*=6.6, 13.6 Hz, CH_2SBn), 2.15 (3H, s), 1.29 (3H, t, *J*=7.1 Hz, OCH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 169.9, 169.5, 137.8, 136.8, 129.0 (2C), 128.8 (2C), 128.6 (2C), 127.5, 127.1, 126.2 (2C), 61.4 (OCH$_2$CH$_3$), 56.8 (NCHCO), 49.7 (Ph*C*H$_2$N), 41.2 (NCH$_2$CO), 36.3 (PhCH$_2$*S*), 29.3 (BnS*C*H$_2$), 22.2 (*C*H$_3$CO), 14.2 (OCH$_2$*C*H$_3$).

4.5.2. Ethyl N-acetyl-N-benzyl-4-(benzylthio)isovalylglycinate (**19b**)

Method C. Yield 0.197 g, 43%. Sticky oil. R_f (EA) 0.42. [Found: C, 65.49; H, 6.84. $C_{25}H_{32}N_2O_4S$ requires C, 65.76; H, 7.06%.] ν_{max} (Nujol, cm^{-1}): 3280 (NH), 1750 (COO), 1680 (amide), 1635 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.20 (10H, m), 6.26 (1H, t, *J*=4.6 Hz), 4.55 (1H, d, *J*=18.2 Hz, PhCH_2N), 4.49 (1H, d, *J*=18.2 Hz, PhCH_2N), 4.23 (2H, q, *J*=7.2 Hz, OCH_2CH$_3$), 4.00 (2H, d, *J*=4.6 Hz, NHCH_2COO), 3.67 (1H, d, *J*=14.1 Hz, PhCH_2*S*), 3.64 (1H, d, *J*=14.1 Hz, PhCH_2*S*), 2.37 (2H, m), 2.30 (1H, dt, *J*=3.0, 9.7 Hz), 2.10 (3H, s, CH$_3$CO), 2.02 (1H, t), 1.38 (3H, s), 1.30 (3H, t, *J*=7.2 Hz, OCH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 172.2, 170.2, 138.3, 138.1, 129.2, 129.0, 128.5, 127.5, 127.0, 126.1, 64.8 (NC$_{quat}$CO), 61.5 (OCH$_2$CH$_3$), 49.14 (PhCH$_2$N), 41.8 (NCH$_2$CO), 35.93, 35.85, 25.5 (S*C*H$_2$CH$_2$), 23.3, 21.6 (*C*H$_3$CO), 14.2 (OCH$_2$*C*H$_3$).

4.5.3. Ethyl N-acetyl-N,S-dibenzyl-2-methylcysteinylglycinate (**19c**)

Method C. Yield 0.177 g, 40%. White solid. Mp 85–87 °C. [Found: C, 65.02; H, 6.96. $C_{24}H_{30}N_2O_4S$ requires C, 65.13; H, 6.83%.] ν_{max} (Nujol, cm^{-1}): 3345 (NH), 1750 (COO), 1675 (amide), 1640 (amide), 745, 705. ^1H NMR (400 MHz, $CDCl_3$): δ 7.5–7.23 (10H, m), 6.47 (1H, t, *J*=5.4 Hz), 4.73 (2H, s, PhCH_2N), 4.23 (2H, q, *J*=7.2 Hz, OCH_2CH$_3$), 4.10 (1H, dd, *J*=4.0, 18.5 Hz, NHCH_2COO), 3.95 (1H, dd, *J*=4.0, 18.5 Hz, NHCH_2COO), 3.75 (1H, d, *J*=13.4 Hz, PhCH_2*S*), 3.70 (1H, d, *J*=13.4 Hz, PhCH_2*S*), 3.60 (1H, d, *J*=12.7 Hz), 3.02 (1H, d, *J*=12.7 Hz), 2.14 (3H, s, CH$_3$CO), 1.41 (3H, s), 1.30 (3H, t, *J*=7.2 Hz, OCH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$):

δ 173.8, 172.4, 170.1, 138.5, 138.02, 129.2, 128.9, 128.6, 127.5, 127.3, 126.1, 64.9 ($NC_{quat}CO$), 61.5 (OCH_2CH_3), 50.2 ($PhCH_2N$), 41.9 (NCH_2CO), 37.9, 37.67, 23.2, 22.9 (CH_3CO), 14.2 (OCH_2CH_3).

4.5.4. Ethyl N-acetyl-N-benzyl-3-(benzylthio)valylglycinate (**19d**)

Method C. Yield 0.411 g, 90%. White solid. Mp 107–109 °C. R_f (EA–hexanes 1:1) 0.5. [Found: C, 65.42; H, 6.96. $C_{25}H_{32}N_2O_4S$ requires C, 65.76; H, 7.06%.] ν_{max} (Nujol, cm^{-1}): 3280 (NH), 1740 (COO), 1685 (amide), 1630 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (1H, t, *J*=5.5 Hz, NH), 7.39–7.04 (10H, m, Ph), 5.71 (1H, s, NCHCO), 5.30 (1H, d, PhC*H*$_2$N, *J*=17.0 Hz), 4.73 (1H, d, PhC*H*$_2$N, *J*=17.0 Hz), 4.17 (2H, q, *J*=7.2 Hz, OC*H*$_2$CH$_3$), 3.95 (1H, d, PhC*H*$_2$S, *J*=11.2 Hz), 3.86 (1H, d, PhC*H*$_2$S, *J*=11.2 Hz), 3.89 (1H, dd, *J*=5.5, 18.0 Hz, NHC*H*$_2$COO), 3.72 (1H, dd, *J*=5.5, 18.0 Hz, NHC*H*$_2$COO), 2.02 (3H, s, CH_3CO), 1.59 (3H, s), 1.55 (3H, s), 1.26 (3H, t, *J*=7.2 Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 169.5, 168.9, 138.4, 138.0, 129.4, 128.6, 127.0, 126.8, 125.7, 61.3 (OCH_2CH_3), 60.5 (NCHCO), 50.7 (SC_{quat}), 50.1 ($PhCH_2N$), 41.0 (NCH_2CO), 33.7 (PhCH$_2$S), 26.8, 26.2, 22.8 (CH_3CO), 14.2 (OCH_2CH_3).

4.5.5. Ethyl N-acetyl-N,S-dibenzylhomocysteylglycinate (**19e**)

Method D. Yield 0.317 g, 72%. White solid. Mp 97–98 °C. R_f (EA–hexanes 1:1) 0.4. [Found: C, 65.42; H, 6.69. $C_{24}H_{30}N_2O_4S$ requires C, 65.13; H, 6.83%.] ν_{max} (Nujol, cm^{-1}): 3235 (NH), 1750 (COO), 1685 (amide), 1625 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.14 (10H, m), 7.03 (1H, t, *J*=5.4 Hz), 5.13 (1H, dd, *J*=6.1, 8.8 Hz), 4.60 (1H, d, *J*=17.8 Hz, PhC*H*$_2$N), 4.50 (1H, d, *J*=17.8 Hz, PhC*H*$_2$N), 4.19 (2H, q, *J*=7.2 Hz, OC*H*$_2$CH$_3$), 3.96 (1H, dd, *J*=5.4, 18.0 Hz, NHC*H*$_2$COO), 3.84 (1H, dd, *J*=5.4, 18.0 Hz, NHC*H*$_2$COO), 3.64 (2H, s, PhC*H*$_2$S), 2.46–2.17 (3H, m), 2.12 (3H, s, CH_3CO), 1.82–1.73 (1H, m), 1.28 (3H, t, *J*=7.2 Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 170.7, 169.5, 138.3, 137.2, 128.9, 128.5, 127.5, 127.0, 126.1, 61.37 (OCH_2CH_3), 56.5 (NCHCO), 49.7 ($PhCH_2N$), 41.2 (NCH_2CO), 36.0 (PhCH$_2$S), 27.9, 27.8, 22.4 (CH_3CO), 14.19 (OCH_2CH_3).

4.5.6. N^2-Acetyl-N^2,S-dibenzyl-N^1-[(4-methyl-2,6,7-trioxabicyclo-[2.2.2]oct-1-yl)methyl]cysteinamide (**19f**)

Method D. Yield 0.181 g, 39%. White solid. Mp 152–154 °C. R_f (EA) 0.49. [Found: C, 64.52; H, 6.60. $C_{26}H_{32}N_2O_5S$ requires C, 64.44; H, 6.66%.] ν_{max} (Nujol, cm^{-1}): 3310 (NH), 1680 (amide), 1630 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.13 (10H, m, Ph), 6.50 (1H, br t), 5.22 (1H, t), 4.58 (1H, d, *J*=18 Hz, PhC*H*$_2$N), 4.52 (1H, d, *J*=18 Hz, PhC*H*$_2$N), 3.92 (6H, s), 3.71 (2H, s, PhC*H*$_2$S), 3.41 (2H, m), 2.91 (1H, dd, *J*=8.0, 13.9 Hz, C*H*$_2$SBn), 2.66 (1H, dd, *J*=7.1, 13.9 Hz, C*H*$_2$SBn), 2.09 (3H, s), 0.83 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 169.4, 138.0, 137.2, 129.0 (2C), 128.8 (2C), 128.5 (2C), 127.3, 127.1, 126.1 (2C), 107.0, 72.7, 56.6 (NCHCO), 49.3 ($PhCH_2N$), 43.8 (NCHOBO), 36.3 (PhCH$_2$S), 30.6 (C_{quat}), 29.8 ($BnSCH_2$), 22.2 (CH_3CO), 14.4.

4.6. Imidazolines 20 and 21

4.6.1. Ethyl 1-benzyl-5-[2-(benzylthio)ethyl]-5-methyl-4,5-dihydro-1H-imidazole-4-carboxylate (**20**)

A mixture of carbonyl compound (1 mmol), benzylamine (1 mmol), and ethyl isocyanoacetate (1 mmol) and Na_2SO_4 (0.1 g) in ethanol (1 mL) was kept at rt for 2 days. Then the mixture was evaporated, the residue was chromatographed (gradient elution CH_2Cl_2–EtOH–NH_{3aq} 100:5:0.5). The product was obtained in 0.201 g (51%) unoptimized yield as an oily 2:1 mixture of two inseparable diastereomers. [Found: C, 69.89; H, 7.03. $C_{23}H_{28}N_2O_2S$ requires C, 69.66; H, 7.12%.] ν_{max} (neat, cm^{-1}): 1750 (COO), 1600 (C=N); *Major*: ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.20 (10H, m, Ph), 6.85 (1H, s, CH), 4.46 (1H, s, CH), 4.29–4.16 (2H, m, OC*H*$_2$CH$_3$), 4.07 (2H, s, PhC*H*$_2$N), 3.69 (2H, s, PhC*H*$_2$S), 2.39 (2H, m), 1.94–1.74 (2H, m), 1.30 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.10 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 156.7 (C=N), 138.1, 137.2, 128.8, 128.6, 127.9, 127.7, 127.1, 75.3 (*C*HCOO), 66.8 (C_{quat}), 60.9 (OCH_2CH_3), 46.0 ($PhCH_2N$), 38.9 (SCH_2CH_2), 36.3 (PhCH$_2$S), 25.2 (SCH_2CH_2), 19.9 (CCH_3), 14.3 (OCH_2CH_3). *Minor*: ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.20 (10H, m, Ph), 6.84 (1H, s, CH), 4.46 (1H, s, CH), 4.29–4.16 (2H, m, OC*H*$_2$CH$_3$), 4.06 (1H, d, *J*=15.2 Hz, PhC*H*$_2$N), 3.98 (1H, d, *J*=15.2 Hz, PhC*H*$_2$N), 3.70 (1H, d, *J*=13.6 Hz, PhC*H*$_2$S), 3.65 (1H, d, *J*=13.6 Hz, PhC*H*$_2$S), 2.49 (1H, m), 2.21 (1H, m), 1.94–1.74 (2H, m), 1.34 (3H, s), 1.30 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 156.6 (C=N), 138.2, 137.5, 128.8, 128.5, 127.8, 127.7, 127.0, 77.8 (*C*HCOO), 67.6 (C_{quat}), 61.1 (OCH_2CH_3), 46.0 ($PhCH_2N$), 36.3 (PhCH$_2$S), 35.2 (SCH_2CH_2), 26.7 (CCH_3), 25.9 (SCH_2CH_2), 14.3 (OCH_2CH_3).

4.6.2. Ethyl 1-benzyl-5-[(benzylthio)methyl]-5-methyl-4,5-dihydro-1H-imidazole-4-carboxylate (**21**)

The product was prepared as described for **20** in 0.12 g (31%) unoptimized yield as an oily 2:1 mixture of two separable diastereomers. [Found: C, 69.23; H, 6.94. $C_{22}H_{26}N_2O_2S$ requires C, 69.08; H, 6.85%.] ν_{max} (neat, cm^{-1}): 1750 (COO), 1600 (C=N); *Major*: ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.20 (10H, m, Ph), 6.83 (1H, s, CH), 4.81 (1H, s, CH), 4.27–4.16 (2H, m, OC*H*$_2$CH$_3$), 4.07 (1H, d, *J*=15.2 Hz, PhC*H*$_2$N), 4.05 (1H, d, *J*=15.2 Hz, PhC*H*$_2$N), 3.74 (2H, s, PhC*H*$_2$S), 2.83 (1H, d, *J*=12.8 Hz, C*H*$_2$SBn), 2.70 (1H, d, *J*=12.8 Hz, C*H*$_2$SBn), 1.29 (3H, t, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 1.14 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 156.4 (C=N), 138.1, 137.2, 128.9, 128.8, 128.6, 128.1, 127.9, 127.2, 75.4 (*C*HCOO), 67.2 (C_{quat}), 60.9 (OCH_2CH_3), 46.3 ($PhCH_2N$), 40.6 ($BnSCH_2$), 37.4 (PhCH$_2$S), 19.2 (CCH_3), 14.3 (OCH_2CH_3). *Minor*: ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.20 (10H, m, Ph), 6.87 (1H, s, CH), 4.45 (1H, s, CH), 4.28–4.17 (2H, m, OC*H*$_2$CH$_3$), 4.08 (1H, d, *J*=15.2 Hz, PhC*H*$_2$N), 4.08 (1H, d, *J*=15.2 Hz, PhC*H*$_2$N), 3.65 (1H, d, *J*=13.6 Hz, PhC*H*$_2$S), 3.59 (1H, d, *J*=13.6 Hz, PhC*H*$_2$S), 2.78 (1H, d, *J*=12.6 Hz, C*H*$_2$SBn), 2.66 (1H, d, *J*=12.6 Hz, C*H*$_2$SBn), 1.38 (3H, s), 1.30 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 156.4 (C=N), 138.0, 137.2, 128.7, 128.5, 127.8, 127.7, 127.2, 78.2 (*C*HCOO), 61.5 (C_{quat}), 61.1 (OCH_2CH_3), 46.6 ($PhCH_2N$), 37.8 (PhCH$_2$S), 36.3 ($BnSCH_2$), 26.0 (CCH_3), 14.1 (OCH_2CH_3).

4.7. General procedure for synthesis of glutathione derivatives 22a–k

Method E. A solution of carbonyl compound (1 mmol), benzylamine (1 mmol), acid **12** or **13** (1 mmol), and ethyl isocyanoacetate (1 mmol) in methanol (2 mL) for aldehyde **7** or trifluoroethanol (2 mL) for ketones **3** and **6** was kept at rt for 2 h for aldehyde **7** and 2–3 days for ketones. Then the mixture was evaporated and the residue was chromatographed (gradient elution EA–hexanes 1:2 or 1:1→3:2 or 1:0). In the case of **23** all reactions were run in methanol. In all cases the products were obtained as 1:1 mixtures of diastereomers.

Method F. Similar to *method B* (use **18** or **23** instead of benzylisocyanide and **12** or **13** instead of acetic acid). Use gradient elution EA–hexanes 1:2 or 1:1→3:2 or 1:0.

4.7.1. Ethyl N,S-dibenzyl-N-{(4S)-4-(benzyloxycarbonyl)-4-[(tert-butoxycarbonyl)amino]butanoyl}-cysteinylglycinate (**22a**)

Method F. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.153 g, 22%. Sticky oil. [Found: C, 65.41; H, 7.02. $C_{39}H_{49}N_3O_8S$ requires C, 65.07; H, 6.86%.] ν_{max} (Nujol, cm^{-1}): 3320 (NH), 1750 (COO), 1720 (carbamate), 1670 (amide), 1630 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.11 (16H, m, Ph+NH), 5.43–5.30 (2H, m, N*H*+NC*H*CO), 5.18–5.12 (2H, m, PhC*H*$_2$O), 4.65–4.38 (3H, m, PhC*H*$_2$N+C*H*NBoc), 4.20 (2H, m, OC*H*$_2$CH$_3$), 4.13–3.81 (2H, m, C*H*$_2$NH), 3.72 (3.68) (2H, s, PhC*H*$_2$S), 3.14–2.98 (1H, m, BnSCH*H*), 2.67 (2.51) (1H, m, BnSCH*H*), 2.41–2.2 (3H, m), 2.03–1.8 (1H, m), 1.42 (9H, s, $C(CH_3)_3$), 1.28 (3H, t, OCH$_2$C*H*$_3$, *J*=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ [174.2, 172.5 (172.4), 170.0 (169.9), 169.7 (169.6)

(C=O)], 155.8 (155.6), 137.9 (137.8), 136.9 (136.7), 135.4 (135.3), 129.00 (128.99), 128.9 (128.8), 128.60, 128.55, 128.4, 128.3, 127.6, 127.5, 127.1, 127.0, 126.4, 126.2, 79.9 (O*C*(CH_3)$_3$), 67.20 (67.16) (Ph*C*H_2O), 61.4 (61.3) (O*C*H_2CH$_3$), 57.6 (57.1) (N*C*HCO), 53.0 (52.89) (*C*HNBoc), 49.6 (49.3) (PhCH_2N), 41.4 (41.2) (NCH_2CO), 36.4 (36.3) (Ph*C*H_2S), 29.7 (29.6) (CH$_2$*C*H$_2$CON), 29.5 (29.4) (BnSCH_2), 28.3 (C(*C*H$_3$)$_3$), 27.7 (*C*H$_2$CH$_2$CON), 14.19 (14.18) (OCH$_2$*C*H$_3$).

4.7.2. Ethyl N-{(4S)-4-(methyloxycarbonyl)-4-[(tert-butoxycarbonyl)amino]butanoyl}-N-benzyl-3-(benzylthio)valylglycinate (**22b**)

Method E. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.375 g, 57%. White solid. Mp 55–60 °C. [Found: C, 61.90; H, 7.04. $C_{34}H_{47}N_3O_8S$ requires C, 62.08; H, 7.20%.] ν_{max} (Nujol, cm^{-1}): 3300 (NH), 1750 (COO), 1715 (carbamate), 1680 (amide), 1640 (amide). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4–7.12 (10H, m, Ph), 6.74 (6.67) (1H, br d, NH), 5.62 (5.58) (1H, s, NC*H*CO), 5.20–4.70 (3H, m, PhC*H*$_2$N+NH), 4.25–4.17 (3H, q, OC*H*$_2$CH$_3$+C*H*NHBoc), 3.95–3.83 (4H, m, C*H*$_2$NH+PhC*H*$_2$S), 3.66 (3H, s, OCH$_3$), 2.40–2.04 (3H, m), 1.95–1.78 (1H, m), 1.58 (3H, s, CH$_3$), 1.53 (1.52) (3H, s, CH$_3$), 1.43 (9H, s, C(CH$_3$)$_3$), 1.29 (3H, t, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ [175.5, 173.0 (172.9), 169.6 (169.5), 168.8 (C=O)], 155.6 (155.4), 138.3 (138.1), 138.1 (138.0), 129.3, 128.7, 128.5, 126.9, 125.8, 125.7, 79.7 (O*C*(CH$_3$)$_3$), 61.41 (61.37) (OCH$_2$CH$_3$), 60.77 (N*C*HCO), [53.2 (52.9), 52.3 (OCH$_3$+*C*HNBoc)], 50.3 (SC$_{quat}$), 50.1 (PhCH$_2$N), 41.1 (40.9) (NCH$_2$CO), 33.7 (Ph*C*H$_2$S), 30.5 (30.2) (CH$_2$*C*H$_2$CON), 28.3 (C(*C*H$_3$)$_3$), 28.0 (27.9) (*C*H$_2$CH$_2$CON), 26.8 (26.6) (*C*CH$_3$), 26.3 (26.2) (*C*CH$_3$), 14.2 (OCH$_2$*C*H$_3$).

4.7.3. Ethyl N-{(4S)-4-(methyloxycarbonyl)-4-[(tert-butoxycarbonyl)amino]butanoyl}-N,S-dibenzylhomocysteylglycinate (**22c**)

Method F. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.235 g, 37%. Sticky oil. [Found: C, 61.22; H, 7.14. $C_{33}H_{45}N_3O_8S$ requires C, 61.57; H, 7.05%.] ν_{max} (Nujol, cm^{-1}): 3310 (NH), 1750 (COO), 1720 (carbamate), 1680 (amide), 1630 (amide). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.14 (10H, m, Ph), 6.98, 5.37, 5.27, 4.98, 4.67–4.91 (2H, PhCH$_2$N), 4.34 (1H, m, C*H*NHBoc), 4.20 (2H, q, OC*H*$_2$CH$_3$, *J*=7.1 Hz), 4.11–3.81 (2H, m, C*H*$_2$NH), 3.73–3.50 d, d, s (5H, COOCH$_3$, PhCH$_2$S), 2.55–1.75 (8H, m, 4CH$_2$), 1.43 (9H, s, C(CH$_3$)$_3$), 1.29 (3H, t, OCH$_2$C*H*$_3$, *J*=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ [174.2, 173.2 (172.9), 170.8 (170.7), 169.8 (169.7) (C=O)], 155.8 (155.6), 138.3, 138.1 (138.0), 129.2, 128.97 (128.92) (2C), 128.4 (2C), 127.5, 127.0, 126.0 (2C), 79.9 (O*C*(CH$_3$)$_3$), 61.3 (OCH$_2$CH$_3$), 57.3 (56.9) (N*C*HCO), 52.8 (52.6), 52.44 (52.37), 49.6 (49.3) (PhCH$_2$N), 41.3 (41.1) (NCH$_2$CO), 35.9 (Ph*C*H$_2$S), 29.7 (29.5) (CH$_2$CH$_2$CON), [28.5, 28.1, 28.3, 28.0, 27.0 (C(*C*H$_3$)$_3$+*C*H$_2$CH$_2$CON+SCH$_2$*C*H$_2$)], 14.2 (OCH$_2$*C*H$_3$).

4.7.4. Ethyl N-{(4S)-4-(methyloxycarbonyl)-4-[(tert-butoxycarbonyl)amino]butanoyl}-N-benzyl-4-(benzylthio)isovalylglycinate (**22d**)

Method E. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.111 g (on 0.5 mmol scale), 33%. Sticky oil. [Found: C, 62.43; H, 7.52. $C_{34}H_{47}N_3O_8S$ requires C, 62.08; H, 7.20%.] ν_{max} (Nujol, cm^{-1}): 3240 (NH), 1750 (COO), 1715 (carbamate), 1670 (amide), 1630 (amide). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.21 (10H, m, Ph), 6.53 (6.43) (1H, t, NH), 5.29 (5.25) (1H, d, NH), 4.60 and 4.49 (2d) (4.52, s) (2H, PhCH$_2$N), 4.23 (1H, m, C*H*NHBoc), 4.22 (4.21) (2H, q, OC*H*$_2$CH$_3$, *J*=7.1 Hz), 4.10 (1H, m, C*H*$_2$NH), 3.90 (1H, m, C*H*$_2$NH), 3.75–3.59 m (5H, COOCH$_3$, PhCH$_2$S), 2.53–2.18 (6H, m, 3CH$_2$), 2.05 (1H, m), 1.82 (1H, m), 1.43 (9H, s, C(CH$_3$)$_3$), 1.39 (3H, s, CH$_3$), 1.29 (3H, t, OCH$_2$C*H*$_3$, *J*=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ [173.8, 173.5, 173.4, 173.2 (2C) (C=O)], 172.9 (C=O), 170.3 (C=O), 155.5, 138.2, 138.1 (138.0), 129.2 (129.1) (2C), 128.97 (128.92) (2C), 128.4 (2C), 127.5, 127.0, 126.0 (2C), 79.9 (O*C*(CH$_3$)$_3$), 65.3 (65.2) (NC$_{quat}$CO), 61.31 (61.27) (OCH$_2$CH$_3$), 52.8, 52.34 (52.29), 48.3 (48.1) (PhCH$_2$N), 41.6 (NCH$_2$CO), [36.9, 36.0, 35.93, 35.89 (2C) (PhCH$_2$SCH$_2$CH$_2$)], 30.5 (30.4) (CH$_2$CH$_2$CON), 28.3 (C(CH$_3$)$_3$), 28.0 (27.7) (*C*H$_2$CH$_2$CON), 25.9 (25.8) (SCH$_2$CH$_2$), 22.0 (21.1) (*C*CH$_3$), 14.2 (OCH$_2$*C*H$_3$).

4.7.5. Ethyl N-{(4S)-4-(methyloxycarbonyl)-4-[(tert-butoxycarbonyl)amino]butanoyl}-N,S-dibenzyl-2-methylcysteinylglycinate (**22e**)

Method E. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.074 g (on 0.5 mmol scale), 23%. Sticky oil. [Found: C, 61.22; H, 7.11. $C_{33}H_{45}N_3O_8S$ requires C, 61.57; H, 7.05%.] ν_{max} (Nujol, cm^{-1}): 3290 (NH), 1750 (COO), 1715 (carbamate), 1670 (amide), 1640 (amide). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.21 (10H, m, Ph), 6.62 (6.51) (1H, t, NH), 5.37 (5.16) (1H, d, *J*=7.3 Hz NH), 4.74 and 4.66 (2d) (4.70, s) (2H, PhCH$_2$N), 4.23 (1H, m, C*H*NHBoc), 4.22 (4.21) (2H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 4.08 (1H, m, C*H*$_2$NH), 3.95 (1H, m, C*H*$_2$NH), 3.71 (3.68) (3H, s, OCH$_3$), 3.65 (2H, s, PhCH$_2$S), 3.64–3.01 (2H, 4d, SCH$_2$C, *J*=13.0 Hz), 2.41 (2H, m, CH$_2$), 2.20 (1H, m, C*H*H), 1.91 (1H, m, CH*H*), 1.42 (9H, s, C(CH$_3$)$_3$), 1.40 (3H, s, CH$_3$), 1.29 (1.28) (3H, t, OCH$_2$C*H*$_3$, *J*=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ [173.8, 173.71, 173.67, 173.5 (2C) (C=O)], 173.0 (172.9), 170.2, 155.8 (155.5), 138.4, 138.2 (138.1), 129.2 (2C), 128.9 (2C), 128.6 (2C), 127.5, 127.22 (127.19), 126.1 (126.0) (2C), 79.9 (O*C*(CH$_3$)$_3$), 65.4 (65.2) (NC$_{quat}$CO), 61.4 (61.3) (OCH$_2$CH$_3$), [52.96 (52.87), 52.30 (52.26), (OCH$_3$+*C*HNBoc)], 49.5 (49.2) (PhCH$_2$N), 41.8 (41.7) (NCH$_2$CO), [37.98, 37.86, 37.7 (2C) (PhCH$_2$SCH$_2$C)], 30.6 (30.5) (CH$_2$*C*H$_2$CON), 28.33 (28.26) (C(*C*H$_3$)$_3$), 27.7 (27.5) (*C*H$_2$CH$_2$CON), 23.0 (22.8) (*C*CH$_3$), 14.2 (OCH$_2$*C*H$_3$).

4.7.6. Ethyl N,S-dibenzyl-N-{(4S)-4-(benzyloxycarbonyl)-4-[(tert-butoxycarbonyl)amino]butanoyl}-homocysteylglycinate (**22f**)

Method F. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.48 g, 67%. Sticky oil. [Found: C, 65.33; H, 6.98. $C_{39}H_{49}N_3O_8S$ requires C, 65.07; H, 6.86%.] ν_{max} (Nujol, cm^{-1}): 3300 (NH), 1750 (COO), 1715 (carbamate), 1680 (amide), 1640 (amide). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.12 (16H, m, Ph+NH), 5.35–5.29 (2H, m, N*H*+NC*H*CO), 5.14 (2H, m, PhC*H*$_2$O), 4.62–4.35 (3H, m, PhC*H*$_2$N+C*H*NBoc), 4.19 (2H, q, OC*H*$_2$CH$_3$), 4.08–3.80 (2H, m, C*H*$_2$NH), 3.64 (3.63) (2H, s, PhC*H*$_2$S), 2.52–2.2 (6H, m), 1.83–1.69 (2H, m), 1.41 (9H, s, C(CH$_3$)$_3$), 1.27 (3H, t, OCH$_2$C*H*$_3$, *J*=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ [174.1, 172.5 (172.4), 170.8 (170.6), 169.9 (169.7) (C=O)], 155.8 (155.7), 138.3, 137.3 (137.1), 135.5 (135.4), 128.9, 128.6, 128, 128.3, 128.2, 127.50 (127.46), 126.9, 126.4, 126.1, 79.9 (O*C*(CH$_3$)$_3$), 67.0 (PhCH$_2$O), 61.23 (61.18) (OCH$_2$CH$_3$), 57.2 (56.8) (NCHCO), 53.0 (52.9) (*C*HNBoc), 49.5 (49.2) (PhCH$_2$N), 41.3 (41.1) (NCH$_2$CO), 35.9 (PhCH$_2$S), 29.7 (29.6) (CH$_2$*C*H$_2$CON), 28.3 (C(*C*H$_3$)$_3$), 28.1, 27.6 (*C*H$_2$CH$_2$CON+SCH$_2$*C*H$_2$), 14.2 (OCH$_2$*C*H$_3$).

4.7.7. Ethyl N-{(4S)-4-(benzyloxycarbonyl)-4-[(tert-butoxycarbonyl)amino]butanoyl}-N,S-dibenzyl-2-methylcysteinylglycinate (**22g**)

Method E. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 37%. Sticky oil. R_f (EA–hexanes 1:1) 0.46. [Found: C, 64.83; H, 6.95. $C_{39}H_{49}N_3O_8S$ C, 65.07; H, 6.86%.] ν_{max} (Nujol, cm^{-1}): 3320 (NH), 1750 (COO), 1720 (carbamate), 1680 (amide), 1645 (amide). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.23 (15H, m, Ph), 6.60 (6.50) (1H, br t, NH), 5.42 (5.25) (1H, br d, NH), 5.11 (5.09) (2H, s, PhC*H*$_2$O), 4.7, 4.63 (2d) (4.66, s) (2H, PhC*H*$_2$N), 4.28 br s (1H, C*H*NBoc), 4.28 (4.19) (2H, q, OC*H*$_2$CH$_3$), 4.11 (dd, *J*=5.1, 18.4 Hz) and 3.92 (dd, *J*=3.79, 18.4 Hz) (4.02, br s) (2H, NC*H*$_2$COO), 3.72 (1H, d, *J*=13.9 Hz, PhCH$_2$S), 3.68 (1H, d, *J*=13.9 Hz, PhCH$_2$S), 3.61–3.49 (1H, 2d, *J*=12.6 Hz), 3.09–3.00 (1H, 2d, *J*=12.6 Hz) (2H, SCH$_2$C), 2.41 (2H, m), 2.20 (1H, m), 1.94 (1H, m), 1.42 (9H, s, C(CH$_3$)$_3$), 1.39 (3H, s, CH$_3$), 1.28 (1.26) (3H, t, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ [173.8, 173.7, 173.5, 172.4, 172.3, 170.2, (C=O)], 155.8 (155.6) (NCOO), [138.4, 138.2 (138.1), 135.4, 129.2, 128.9, 128.6, 128.3, 128.2, 127.5,

127.2, 126.1, 126.0 (Ph)], 79.8 (OC(CH_3)$_3$), 67.04 (66.96) (PhCH_2O), 65.4 (65.2) ($C_{quat.}$), 61.4 (61.3) (OCH_2CH$_3$), 53.2 (53.1) (*C*HNBoc), 49.5 (49.2) (PhCH_2N), 41.8 (41.7) (NCH_2COO), 37.9 (37.8), 37.8 (37.7), 30.6 (30.5) (CH_2CH_2CON), 28.32 (28.27) (C(CH_3)$_3$), 27.5 (27.2) (*C*H$_2$CH$_2$CON), 23.0 (22.8) (*C*CH$_3$), 14.1 (OCH$_2$*C*H$_3$).

*4.7.8. Ethyl N-{(4S)-4-(benzyloxycarbonyl)-4-[(tert-butoxycarbonyl)amino]butanoyl}-N-benzyl-3-(benzylthio)valylglycinate (**22h**)*

Method E. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.52 g (71%). White solid. R_f (EA–hexanes 1:1) 0.5. [Found: C, 65.73; H, 6.91. $C_{40}H_{51}N_3O_8S$ require C, 65.46; H, 7.00%.] ν_{max} (Nujol, cm^{-1}): 3290 (NH), 1750 (COO), 1715 (carbamate), 1680 (amide), 1640 (amide). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.4–7.12 (10H, m, Ph), 6.67 (6.62) (1H, br d, NH), 5.60 (5.57) (1H, s, NCHCO), 5.28–5.06 (4H, m, PhCH_2O+NH PhCH_2N), 4.65 (4.61) (1H, d, PhCH_2N), 4.22 (3H, m, OCH_2CH$_3$+C*H*NHBoc), 3.95–3.84 (4H, m, CH_2NH+PhCH_2S), 2.37–2.07 (3H, m), 1.94 (1H, m), 1.57 (3H, s, CH$_3$), 1.52 (1.51) (3H, s, CH$_3$), 1.42 (9H, s, C(CH_3)$_3$), 1.29 (3H, t, OCH$_2$CH_3). ^{13}C NMR (100 MHz, CDCl$_3$): δ [175.55 (175.51), 172.5 (172.3), 169.8 (169.7), 168.9 (C=O)], 155.7 (155.5), 138.5 (138.4), 138.01 (137.97), 135.5, 129.3, 128.7, 128.61, 128.58, 128.48, 128.39, 128.3, 128.2, 126.9, 126.8, 125.8, 125.6, 79.63 (79.55) (O*C*(CH$_3$)$_3$), 66.92 (66.87) (PhCH_2O), 61.3 (OCH_2CH$_3$), 60.0 (NCHCO), 53.5 (53.2) (*C*HNBoc), 50.4 (50.3) (SC$_{quat}$), 49.9 (PhCH_2N), 41.0 (40.9) (NCH_2CO), 33.6 (PhCH_2S), 30.7 (30.5) (CH$_2$CH_2CON), 28.4 (C(CH_3)$_3$), 27.9 (27.6) (*C*H$_2$CH$_2$CON), 26.9 (CCH_3), 26.1 (CCH_3), 14.2 (OCH$_2$CH_3).

*4.7.9. Benzyl (2S)-5-{benzyl[2-(benzylthio)-2-methyl-1-{[(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)methyl]carbamoyl}propyl]amino}-2-[(tert-butoxycarbonyl)amino]-5-oxopentanoate (**22i**)*

Method E. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.596 g, 76%. White solid. R_f (EA–hexanes 1:1) 0.38, (EA) 0.58. [Found: C, 65.14; S, 4.34; H, 7.05. $C_{43}H_{55}N_3O_9S$ require C, 65.38; S, 4.06; H, 7.02%.] ν_{max} (Nujol, cm^{-1}): 3340 (NH), 1750 (COO), 1715 (carbamate), 1680 (amide), 1640 (amide). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.39–7.11 (15H, m, Ph), 6.32 (1H, br s, NH), 5.51 (1H, s, NCH), 5.30–5.06 and 4.62–4.54 (5H, m, PhCH_2N+N*H*+PhCH_2O), 4.20 (1H, br s, CHNBoc), 3.93 (3.92) (6H, s, 3CH$_2$), 3.47–3.28 (2H, m, NCH$_2$OBO), 2.33 (m), 2.14, 2.00, 1.80, 1.57 (1.55) (3H, s, CH$_3$), 1.50 (1.49) (3H, s, CH$_3$), 1.42 (9H, s, C(CH$_3$)$_3$), 0.84 (0.83) (3H, s, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 175.4 (175.2), 172.3, 168.30 (168.27), 155.5 (155.4) (NCOO), 138.5 (138.3), 137.9 (137.8), 135.5, [129.3, 128.7, 128.6, 128.5, 128.4, 128.3, 126.9, 125.9, 125.8], 107.0 (C_{quat}), 79.7 (O**C**(CH$_3$)$_3$), 72.7 (3CH$_2$), 67.0 (66.9) (PhCH_2O), ~61 (N*C*HCO), 53.5 (53.1) (*C*HNBoc), 50.1–49.9 (PhCH$_2$N+SC$_{quat}$), 43.8 (43.7) (NCH$_2$OBO), 33.7 (PhCH_2S), 30.6, 30.4 (CH$_2$CH_2CON+C$_{quat}$), 28.3 (C(*C*H$_3$)$_3$), 27.8 (27.4) (*C*H$_2$CH$_2$CON), 26.5 (C(*C*H$_3$)$_2$), 14.4 (*C*CH$_3$).

*4.7.10. Benzyl (2S)-5-[benzyl(1-[(benzylthio)methyl]-1-methyl-2-{[(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)methyl]amino}-2-oxoethyl)-amino]-2-[(tert-butoxycarbonyl)amino]-5-oxopentanoate (**22j**)*

Method E. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.356 g, 46%. White solid. R_f (EA–hexanes 1:1) 0.2, (EA) 0.67. [Found: C, 65.39; H, 7.00. $C_{42}H_{53}N_3O_9S$ requires C, 65.01; H, 6.88%.] ν_{max} (Nujol, cm^{-1}): 3270 (NH), 1750 (COO), 1710 (carbamate), 1670 (amide), 1635 (amide). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.39–7.25 (15H, m, Ph), 6.11 (1H, m, NH), 5.37 (5.22) (1H, d, NH), 5.11 (5.10) (2H, s, PhCH$_2$O), 4.65 (2H, br s, PhCH_2N), 4.24 (1H, br s, CHNBoc), 3.85 (6H, s, 3CH$_2$), 3.70 (2H, m, PhCH_2S), 3.63–2.98 (4H, m, NCH_2OBO, CH_2SBn), 2.38 (2H, m), 2.19 (1H, m), 2.04–1.94 (1H, m), 1.42 (3H, s, CH$_3$), 1.39 (9H, s, C(CH$_3$)$_3$), 0.79 (0.78) (3H, s, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ [173.6, 173.5, 173.4, 172.3 (C=O)], 155.64 (155.56) (NCOO), 138.7, 138.23 (138.21), 135.43 (135.39), [129.20, 129.17, 128.9, 128.6, 128.4, 128.3, 128.2, 127.4, 127.3, 127.1, 126.13, 126.08], 107.2 (C_{quat}), 79.8 (OC(CH$_3$)$_3$), 72.6 (3CH$_2$), 67.03 (66.95) (PhCH$_2$O), 65.38 (65.35) (NC$_{quat}$CO), 53.42 (53.43) (*C*HNBoc), 49.4 (49.3) (PhCH$_2$N), 44.2 (44.1) (NCH$_2$OBO), 37.9, 37.8 (PhCH$_2$S+SCH$_2$C), 30.7, 30.6 (CH$_2$CH_2CON+C$_{quat}$), 28.32 (28.26) (C(CH_3)$_3$), 27.5 (27.2) (CH_2CH$_2$CON), 23.0 (CCH_3), 14.3 (CCH_3).

*4.7.11. Benzyl (2S)-5-{benzyl[3-(benzylthio)-1-methyl-1-{[(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)methyl]carbamoyl}propyl]amino}-2-[(tert-butoxycarbonyl)amino]-5-oxopentanoate (**22k**)*

Method E. Mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. Yield 0.41 g, 52%. White solid. Mp 78–80 °C. R_f (EA–hexanes 1:1) 0.2, (EA) 0.6. [Found: C, 65.85; H, 7.29. $C_{43}H_{55}N_3O_9S$ requires C, 65.38; H, 7.02%.] ν_{max} (Nujol, cm^{-1}): 3280 (NH), 1750 (COO), 1720 (carbamate), 1660 (amide), 1635 (amide). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.39–7.22 (15H, m, Ph), 6.08 (5.96) (1H, br t, NH), 5.27 (1H, d, NH), 5.16–5.09 (2d) (5.11, s) (2H, PhCH$_2$O), 4.56–4.41 (2H, m, PhCH$_2$N), 4.23 (1H, br s, CHNBoc), 3.86 (6H, s, 3CH$_2$), 3.65 (2H, s, PhCH$_2$S), 3.59–3.40 (2H, m, NCH$_2$OBO), 2.51–2.14 (6H, m), 1.98 (2H, m), 1.42 (9H, s, C(CH$_3$)$_3$), 1.37 (s) (1.36, s) (3H, CH$_3$), 0.79 (3H, s, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ [173.3, 173.1, 172.3, 170.9 (C=O)], 155.6 (NCOO), 138.4, 138.30, 138.28, 135.5, [129.07, 129.05, 128.91, 128.88, 128.55, 128.47, 128.3, 127.26, 127.38, 127.0, 126.1], 107.28 (107.25) (C_{quat}), 79.8 (O*C*(CH$_3$)$_3$), 72.6 (3CH$_2$), 66.99 (66.96) (PhCH_2O), 65.3 (NC$_{quat}$CO), 53.3 (*C*HNBoc), 48.1 (PhCH_2N), 44.0 (43.9) (NCH$_2$OBO), 36.11, 36.09 (PhCH$_2$SCH$_2$*C*), 30.63, 30.56 (CH$_2$CH_2CON+C$_{quat}$), 28.3 (C(*C*H$_3$)$_3$), 27.6 (27.5) (*C*H$_2$CH$_2$CON), 26.00 (25.97) (SCH$_2$*C*H$_2$), 21.7 (21.6) (*C*CH$_3$), 14.3 (*C*CH$_3$).

4.8. Homoglutathione derivatives 25a–c

*4.8.1. Ethyl N,S-dibenzyl-N-{(4S)-4-(benzyloxycarbonyl)-4-[(tert-butoxycarbonyl)amino]butanoyl}-cysteinyl-β-alaninate (**25a**)*

Aldehyde **1** (1 mmol) was slowly (in 20 min) added dropwise to a mixture of benzylamine (1 mmol), acid **13** (1 mmol), and **24** (1 mmol) in 1 mL of trifluoroethanol. The reaction mixture was stirred at rt for additional 2 h and was evaporated, the residue was chromatographed (gradient elution EA–hexanes 1:2→2:3) to afford the title compound (0.314 g, 44%) as an 1:1 oily mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. [Found: C, 65.41; H, 6.97. $C_{39}H_{49}N_3O_8S$ requires C, 65.07; H, 6.86%.] ν_{max} (Nujol, cm^{-1}): 3300 (NH), 1750 (COO), 1720 (carbamate), 1670 (amide), 1640 (amide). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.38–7.11 (15H, m, Ph), 6.87 (6.80) (1H, br t, NH), 5.34 (5.30) (1H, d, J=8.1 Hz, NH), 5.19–5.12 (2.5H, m, PhCH_2O+1/2NC*H*CO), 4.80 (0.5H, m, 1/2NC*H*CO), 4.56–4.35 (3H, m, PhCH_2N+C*H*NBoc), 4.15 (2H, m, OCH_2CH$_3$), 3.70 (3.68) (2H, s, PhCH_2S), 3.44 (2H, m, NCH_2CH$_2$), 3.06–2.97 (1H, m, BnSCH*H*), 2.71 (2.58) (1H, m, BnSCH*H*), 2.49 (2.47) (2H, t, J=7.1, NCH$_2$CH_2), 2.41–2.2 (3H, m), 2.03–1.8 (1H, m), 1.43 (9H, s, C(CH$_3$)$_3$), 1.26 (3H, t, OCH$_2$CH_3, J=7.1 Hz). ^{13}C NMR (100 MHz, CDCl$_3$): δ [174.0 (173.76), 172.4, 172.0 (171.9), 169.3 (C=O)], 155.7, 138.0, 136.9 (136.7), 135.4, 129.00 (128.97), 128.85 (128.83), 128.58, 128.55, 128.4, 128.3, 127.6, 127.5, 127.1, 126.5, 126.2, 79.8 (O*C*(CH$_3$)$_3$), 67.1 (PhCH_2O), 60.6 (OCH_2CH$_3$), 57.8 (57.2) (N*C*HCO), 53.1 (53.0) (*C*HNBoc), 49.6 (49.0) (PhCH_2N), 36.4 (PhCH_2S), 35.2 (35.1), 34.0 (33.9), 30.0 (29.9) (CH$_2$CH_2CON), 29.7 (29.6) (BnSCH_2), 28.3 (C(*C*H$_3$)$_3$), 28.0 (27.6) (*C*H$_2$CH$_2$CON), 14.2 (OCH$_2$*C*H$_3$).

*4.8.2. Ethyl N-{(4S)-4-(benzyloxycarbonyl)-4-[(tert-butoxycarbonyl)-amino]butanoyl}-N,S-dibenzyl-2-methylcysteinyl-β-alaninate (**25b**)*

A solution of **6** (1 mmol), benzylamine (1 mmol), acid **13** (1 mmol), and isocyanide **24** (1 mmol) in trifluoroethanol (2 mL) was kept at rt for 3 days. Then the mixture was evaporated, the residue was chromatographed (gradient elution EA–hexanes 1:2 to

2:3). Yield 0.33 g, 45%. Sticky oil. [Found: C, 65.35; H, 6.91. $C_{40}H_{51}N_3O_8S$ requires C, 65.46; H, 7.00%.] ν_{max} (Nujol, cm^{-1}): 3270 (NH), 1750 (COO), 1720 (carbamate), 1680 (amide), 1630 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.23 (15H, m, Ph), 6.54 (1H, br t, NH), 5.37 (5.26) (1H, d, J=7.6 Hz, NH), 5.12 (5.10) (2H, s, PhCH_2O), 4.69–4.59 (2H, m, PhCH_2N), 4.25 (1H, br s, C*H*NBoc), 4.17–4.07 (2H, m, OCH_2CH$_3$), 3.72–3.74 (2H, m, PhCH_2S), 3.59–3.37 (3H, m, BnSC*H*H+NCH_2CH$_2$), 3.00 (2.96) (1H, d, J=12.6 Hz, BnSCH*H*), 2.62–2.31 (6H, m), 2.17 (1H, m), 2.01–1.84 (1H, m), 1.42 (1.39) (9H, s, C(CH$_3$)$_3$), 1.37 (1.36) (3H, s, CH$_3$), 1.24 (1.23) (3H, t, OCH$_2$C*H*$_3$, J=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ [173.8 (173.6), 173.5 (173.3), 173.1 (173.0), 172.30 (172.27) (C=O)], 155.6 (NCOO), [138.4, 138.14 (138.11), 135.4, 129.18 (129.15), 128.91, 128.58, 128.55, 128.4, 128.3, 128.27, 128.21, 127.46, 127.43, 127.16, 126.09, 126.04 (Ph)], 79.8 (OC(CH$_3$)$_3$), 67.05 (66.99) (PhCH$_2$O), 65.37 (65.23) (C$_{quat.}$), 60.54 (60.51) (OCH$_2$CH$_3$), 53.2 (C*H*NBoc), 49.3 (49.2) (PhCH$_2$N), 37.94, 37.84, 37.81 (PhCH$_2$SCH$_2$C), 35.27 (35.21), 33.45, 30.6 (CH$_2$CH$_2$CON), 28.31 (28.26) (C(C*H*$_3$)$_3$), 27.6 (27.3) (C*H*$_2$CH$_2$CON), 22.8 (22.7) (CCH$_3$), 14.2 (OCH$_2$C*H*$_3$).

4.8.3. Ethyl N-{(4S)-4-(methyloxycarbonyl)-4-[(tert-butoxycarbonyl)-amino]butanoyl}-N-benzyl-4-(benzylthio)isovalyl-β-alaninate (**25c**)

A solution of **3** (1 mmol), benzylamine (1 mmol), acid **13** (1 mmol), and isocyanide **24** (1 mmol) in methanol (2 mL) was kept at rt for 3 days. Then the mixture was evaporated, the residue was chromatographed (gradient elution EA–hexanes 1:2 to 2:3) to afford the title compound (0.50 g, 67%) as an 1:1 oily mixture of diastereomers, some NMR signals were assigned to an accompanying diastereomer and are given in parentheses. [Found: C, 66.12; H, 7.07. $C_{41}H_{53}N_3O_8S$ requires C, 65.84; H, 7.14%.] ν_{max} (Nujol, cm^{-1}): 3320 (NH), 1750 (COO), 1720 (carbamate), 1665 (amide), 1640 (amide). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (15H, m, Ph), 6.49 (6.42) (1H, br t, NH), 5.30 (1H, br t, NH), 5.17–5.09 (2H, 2d+s, PhCH_2O), 4.53 (d, J=18.2 Hz) and 4.44 (d, J=18.2 Hz) (4.45, s) (2H, PhCH_2N), 4.23 (1H, br s, C*H*NBoc), 4.13 (2H, q, OCH_2CH$_3$, J=7.1 Hz), 3.63 (2H, s, PhCH_2S), 3.47 (2H, m, NCH_2CH$_2$), 2.53 (2H, t, J=5.8 Hz, NCH$_2$C*H*$_2$), 2.47–2.11 (6H, m), 2.04–1.84 (2H, m), 1.42 (9H, s, C(CH$_3$)$_3$), 1.33 (1.32) (3H, s, CH$_3$), 1.25 (3H, t, OCH$_2$C*H*$_3$, J=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ [173.7 (173.6), 173.2, 173.1, 172.3 (C=O)], 155.6 (NCOO), 138.19 (138.15), 138.1, 135.4, [129.12, 128.93 (128.89), 128.6, 128.5, 128.3, 128.2, 127.5, 127.0, 126.0], 79.8 (OC(CH$_3$)$_3$), 67.02 (66.99) (PhCH$_2$O), 65.20 (65.16) (NC$_{quat}$CO), 53.26 (53.21) (C*H*NBoc), 48.11 (48.05) (PhCH$_2$N), [36.6 (36.1), 35.95, (35.91) (PhC*H*$_2$SCH$_2$C)], 35.24 (35.22), 33.43, 30.6 (CH$_2$CH$_2$CON), 28.3 (C(C*H*$_3$)$_3$), 27.5 (C*H*$_2$CH$_2$CON), 25.78 (SCH$_2$C*H*$_2$), 21.6 (21.2) (CCH$_3$), 14.2 (OCH$_2$C*H*$_3$).

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.04.030.

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