Preparation of Protected β^2- and β^3-Homocysteine, β^2- and β^3-Homohistidine, and β^2-Homoserine for Solid-Phase Syntheses[1]

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The Ser, Cys, and His side chains play decisive roles in the syntheses, structures, and functions of proteins and enzymes. For our structural and biomedical investigations of β-peptides consisting of amino acids with proteinogenic side chains, we needed to have reliable preparative access to the title compounds. The two β^3-homoamino acid derivatives were obtained by *Arndt–Eistert* methodology from Boc-His(Ts)-OH and Fmoc-Cys(PMB)-OH (*Schemes 2–4*), with the side-chain functional groups' reactivities requiring special precautions. The β^2-homoamino acids were prepared with the help of the chiral oxazolidinone auxiliary DIOZ by diastereoselective aldol additions of suitable Ti-enolates to formaldehyde (generated *in situ* from trioxane) and subsequent functional-group manipulations. These include OH → O^{t}Bu etherification (for β^2hSer; *Schemes 5* and *6*), OH → STrt replacement (for β^2hCys; *Scheme 7*), and $CH_2OH \rightarrow CH_2N_3 \rightarrow CH_2NH_2$ transformations (for β^2hHis; *Schemes 9–11*). Including protection/deprotection/re-protection reactions, it takes up to ten steps to obtain the enantiomerically pure target compounds from commercial precursors. Unsuccessful approaches, pitfalls, and optimization procedures are also discussed. The final products and the intermediate compounds are fully characterized by retention times (t_R), melting points, optical rotations, HPLC on chiral columns, IR, ^{1}H- and ^{13}C-NMR spectroscopy, mass spectrometry, elemental analyses, and (in some cases) by X-ray crystal-structure analysis.

1. Introduction. – β-Amino acids, compared to their α-counterparts, possess one more 'freely rotating' C–C σ-bond. Intuitively, greater backbone flexibility of oligomers built exclusively of such residues (β-peptides) might be expected to lead to increased conformational complexity. However, this has been found to be only partially true: depending upon the substitution pattern of the β-amino acids, several different secondary structures have been found, *e.g.*, five types of helices [3–9], sheet [10][11], and turn structures [10][12–14]; the big surprise, however, is that these secondary structures are present in solution with peptide chains as short as four residues[5]. In addition, β-peptides turn out to be stable to rat metabolism [22], to exhibit slow microbial degradation [23], and to be inherently stable to a range of proteases and peptidases [3][24–28], rendering them promising candidates as peptidomimetics in drug design. β-Peptides with biological activity have been tested,

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[5] For reviews on β-peptides, see [15–21].

so far, as somatostatin mimics [29–32], for cholesterol transport inhibition [33], and as antiproliferative [34] and antimicrobial [27][35–42] compounds.

To profit as much as possible from the knowledge about α-protein chemistry and to study the rapidly evolving field of the chemistry and biology of β-peptides, especially towards the synthesis of what can be referred to as 'β-proteins', all-β-amino acids[6]) with proteinogenic side chains had to become available. It is evident that only β-amino acids with side chains in the 2- or/and 3-position, *i.e.*, β^2- and β^3-amino acids, have a high degree of similaritiy to α-amino acids (*Figure*), while the cyclic β-amino acid derivatives [4][6] are fundamentally different.

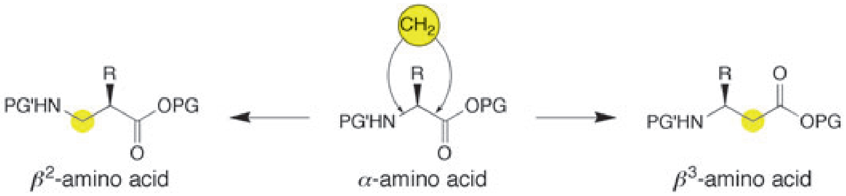

Figure. *Representation of the molecular formulae of α-, β^2-, and β^3-amino acids*

Among all 'proteinogenic' β^3-amino acids, suitably protected for solid-phase synthesis by the Fmoc strategy[7]), only Fmoc-β^3hHis(Tr)-OH and Fmoc-β^3hCys(Tr)-OH have not hitherto been reported in the literature and will be discussed herein. All others are commercially available and are prepared by *Arndt–Eistert* homologation of the corresponding α-amino acids [53]. On the other hand, there is no general method for the preparation of enantiomerically pure β^2-amino acids; they are certainly not available by any stereoselective transformation of α-amino acids. They can be prepared *via* coupling of an appropriate electrophile with cyclic [54–61] or acyclic [2][62–70] enolates derived from 3-aminopropanoic acid. In some of these routes, harsh conditions[8]) are required to cleave auxiliary groups, and this is, of course, unsuitable for the preparation of β^2-amino acids with functionalized side chains[7]). In addition, partial racemization may occur during hydrolysis steps. With Li-enolates, reactive electrophiles are required [65], and, when two *N*-acyl groups (Boc_2, phthalyl) are used on the 3-aminopropanoic acid derivative, β-elimination can take place [65][67]. Thus, most methods are applicable only to the preparation of β^2-amino acids with alkyl, benzyl, or the – unnatural – aryl side chains. In another approach, the amino acid side chain is first attached to an auxiliary as part of an acyl group, followed by aminomethylation with synthetic equivalents of the $[H_2NCH_2]^+$ cation (*Mannich* reaction; *Scheme 1*) [2][7][31][64][71–76]. Also, alkylation of an enolate with the appropriate side chain by a haloacetate electrophile, followed by *Curtius* degradation, leads to the net attachment of an aminomethyl group (a *Mannich* transformation [77]; *Scheme 1*) [76][78–80].

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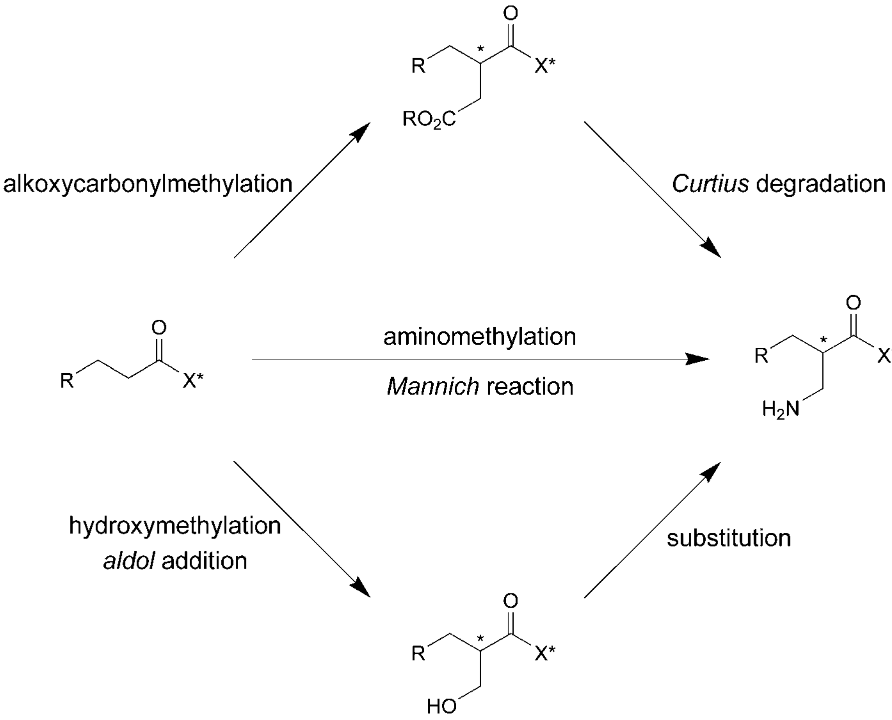
[6]) For extensive reviews on syntheses of β-amino acids, see [43–52].

[7]) For solid-phase synthesis by the Fmoc strategy, functionalized side chains must be protected with acid-labile protecting groups.

[8]) For example, prolonged stirring or heating with acids.

Scheme 1. *Three Synthetic Approaches towards the Preparation of the β^2-Amino Acid Skeleton*



β^2-Amino acids can also be prepared by regioselective coupling of an electrophile containing the amino acid side chain with an unsymmetric succinic acid derivative, which is then subjected to a regioselective *Curtius* rearrangement [80][81]. Asymmetric hydrogenation has also been used in the preparation of β^2-amino acids [82][83], but high enantioselectivities were observed with only particular substrates.

We have employed hydroxymethylation for the preparation of various β^2-amino acids. This does not only lead to a β^2hSer derivative [64], but, *via* replacement of the OH by an STr group, provides access to a β^2hCys derivative, as well. On the other hand, substitution of the OH group with amino or azido nucleophiles gives products of an overall attachment of an aminomethyl group (*Scheme 1*), thus opening another simple route for the preparation of β^2-amino acids. This strategy was successfully employed for the preparation of a β^2hHis derivative, as reported herein.

The syntheses of the title compounds by routes generally outlined in the previous sections, in the *Figure*, and in *Scheme 1* are described in this paper, including full experimental details.

2. Preparation of Fmoc-β^3hHis(Tr)-OH and Fmoc-β^3hCys(Tr)-OH.– Histidine is a remarkable amino acid, in which the basic 1*H*-imidazolyl side chain is crucial to the biological activity of many proteins and peptides. The nucleophilic character of the unprotected 1*H*-imidazole ring can be expected to be a source of difficulty in the usual approach to α-amino-acid homologation, since the first step of the transformation involves the activation of the carboxy group to become a strong electrophile. A similar assertion can be drawn if the 1*H*-imidazolyl group is not protected 'in the right way', using, for example, protecting-groups with donor properties (*i.e.*, with σ-donor effect). In fact, first attempts at synthesizing the homohistidine derivatives by *Arndt–Eistert* homologation from Fmoc-His(τ-BOM)-OH, Fmoc-His(τ-Tr)-OH, Boc-His(τ-Bn)-OH, Boc-His(π-Bn)-OH, and Boc-His(τ-BOM)-OH were unsuccessful⁹). Only Ts-protected histidines reacted with CH_2N_2 to form the corresponding diazo ketones, probably due to the strong electron-withdrawing effect of the tosylate, which renders the 1*H*-imidazolyl N-atom less nucleophilic¹⁰). Thus, commercially available Fmoc-His(Ts)-OH and Boc-His(Ts)-OH were converted *via* their mixed anhydrides (NMM/$ClCO_2Et$ or $NEt_3/ClCO_2{}^iBu$) to the diazo ketones **1** and **2** in 56 and 86% yields, respectively (*Scheme 2*). Attempts at converting diazo ketone **1** to a β^3-homohistidine derivative were shown to be ineffective, due to the insolubility of **1** in most solvents suitable for the *Wolff* rearrangement (*e.g.*, BnOH, H_2O, THF, dioxane, *etc.*). On the other hand, decomposition of diazo ketone **2** in the presence of the corresponding alcohol (MeOH, BnOH), by reaction with catalytic amounts of Ag^+ (CF_3CO_2Ag dissolved in Et_3N) gave the Boc-protected methyl or benzyl ester as a mixture of three products in a 1:1:1 ratio. It was found that the Ag^+ ion interacts with the 1*H*-imidazole ring inducing the partial displacement of the Ts protecting group from the τ-N to the π-N, as well as the complete removal of this protecting group. With this result at hand, it was decided to use Boc-His(Ts)-OH as starting material for conversion to the β^3-amino acid derivative Fmoc-β^3hHis(Tr)-OH. To this end, a *Wolff*-rearrangement procedure with *in-situ* deprotection of the histidine side chain had to be worked out. Four mild cleavage conditions for the deprotection of *N'*-Ts-histidine derivatives are known in the literature; they involve the treatment of the Ts-histidines with HOBt in methanolic solutions [86], the reaction with pyridinium hydrochloride [87], the employment of Mg in dry MeOH [88], or the use of pyridine in Ac_2O [89]; the latter procedure gave the best results, allowing isolation of the esters **3** and **4** in good yields from the diazo ketone **2** (*Scheme 2*)¹¹).

Since the use of histidine derivatives with unprotected 1*H*-imidazolyl side chains for peptide couplings in solution or on solid support are known to cause side reactions, we protected the 1*H*-imidazolyl group of the ester **3** with a Tr group: treatment with TrCl) and Et_3N afforded compound **5** in quantitative yield. Hydrolysis of the methyl ester with LiOH in MeOH/H_2O gave the acid **6** as a single product (*Scheme 2*). The Boc-β^3hHis(Tr)-OH (**6**) was thus prepared from α-Boc-His(Ts)-OH in *ca.* 75% yield over four steps.

It is known that the α-amino-acid analogue of carboxylic acid **6**, as well as peptides containing histidine, can be selectively N^α-Boc- or N^{Im}-Tr-deprotected by means of

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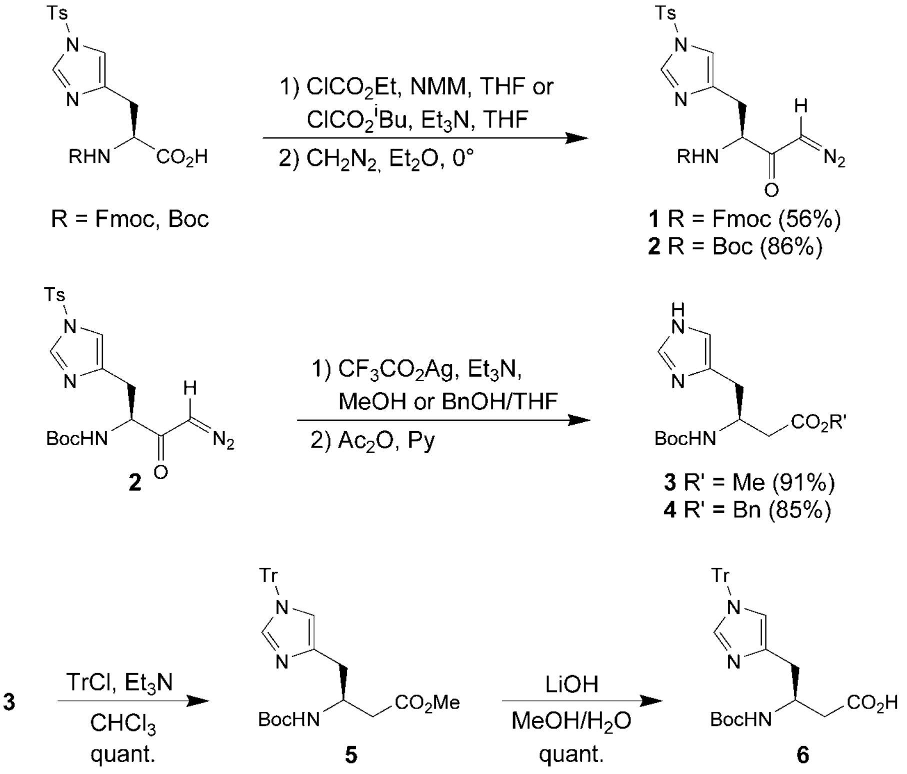
⁹) Throughout this paper, we use the common abbreviations of peptide chemistry; see [84]. The symbols τ and π are used to define whether the protecting group is positioned at N(1) (*i.e.*, the less-hindered position) or N(3) of the 1*H*-imidazolyl ring. When no symbol is specified, the protecting group is attached to the less-hindered N(1)-atom.

¹⁰) Even though the Boc group is electron-withdrawing, the attempted conversion of Fmoc-His(Boc)-OH to the diazo ketone resulted in a complex mixture of inseparable products. This is probably due to the high instability of urethane protecting groups when bound to the 1*H*-imidazolyl N-atom [85].

¹¹) It should be noted that the same reaction conditions employed towards the preparation of the acid derivative (H_2O instead of MeOH or BnOH) did not prove successful.

Scheme 2. *Preparation of the β^3-Homohistidine Derivative* **6** *by* Arndt–Eistert *Homologation of Boc-His(Ts)-OH, Followed by Tr-Protection and Saponification of the Methyl Ester Group in* **5**



different reaction conditions. For example, treatment with 1N HCl in 90% AcOH for 20 min at room temperature leads to cleavage of the Boc group, leaving the Tr protection intact [90–92]. When these conditions for the Boc deprotection of the β-amino acid derivatives **5** and **6** were applied, only partial cleavage occurred even after one day. On prolonged exposure, partial degradation was detected. More-acidic conditions, however, caused the cleavage of both protecting groups. Therefore, synthetic applications of carboxylic acid **6** are limited to the synthesis of peptides with an N-terminal β-homohistidine.

Recently, *Wyatt* and co-workers [93] accomplished the synthesis of Boc-β^3hHis-(Boc)-OH *via* the *Kolbe* reaction, *i.e.*, by reducing α-Mts-His(Mts)-OMe to the corresponding amino alcohol, the OH group of which was then activated and replaced by CN; the CN group was, in turn, hydrolyzed to the MeNH group, which was Boc-protected to give the final product in 7% yield over five steps. The authors state that this derivative is suitable for direct use in the synthesis of peptides, but so far no applications are known[12]).

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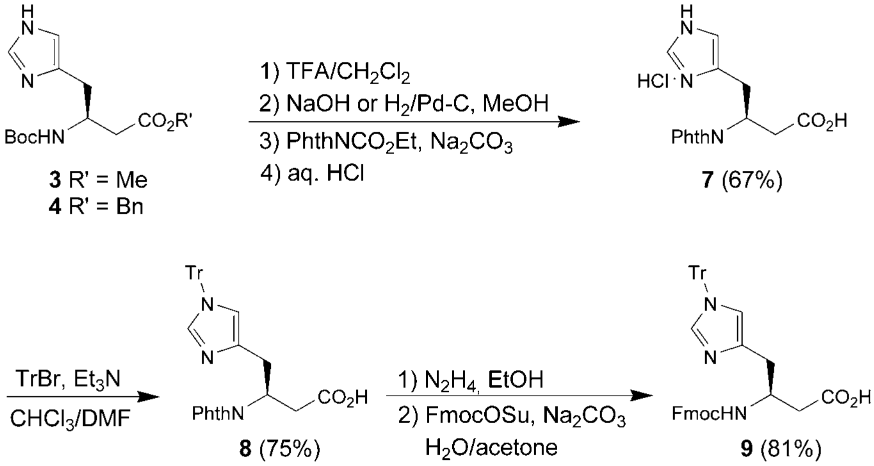
[12]) The difference in reactivity between the two Boc groups should be less pronounced than that between the Boc and the Tr group in our case (see **6**).

The successful preparation of Fmoc-β^3hHis(Tr)-OH was accomplished by using the Boc-protected homohistidine esters **3** and **4** as starting materials. As such, Boc deprotection, followed by saponification or hydrogenolysis of the ester groups, gave the completely unprotected β^3-homohistidine, which was then phthaloyl(Phth)-protected and acidified to yield the HCl salt **7** in 67% yield. Subsequent tritylation and *N*-Phth/*N*-Fmoc protecting-group exchange afforded the acid **9** in 61% yield over the three steps (*Scheme 3*)[13]).

Scheme 3. *Preparation of Fmoc-β^3hHis(Tr)-OH* (**9**) *Starting from* **3** *or* **4**



In this way, the synthesis of Fmoc-β^3hHis(Tr)-OH was achieved in eight steps with an overall yield of 32%, starting from commercial Boc-His(Ts)-OH.

The non-essential amino acid cysteine is particularly abundant in the proteins of hair, hooves, and the keratin of skin, and its importance is related to the presence of a SH group in the side chain. This group participates in the catalytic reactions of certain enzymes, but is also capable of combining the SH group of one cysteine residue with the SH group of another to form a disulfide bridge, either linking two peptide chains (*e.g.*, insulin) or causing a single peptide chain to fold back on itself, making a loop (*e.g.*, zinc fingers). This latter effect on the secondary structure of proteins is evidently of great importance in maintaining the proper conformation of both structural proteins and enzymes.

For the preparation of Fmoc-β^3hCys(Tr)-OH, two α-cysteine derivatives with differently protected side chains were tested as starting materials and homologated *via* the *Arndt–Eistert* procedure. Commercial Fmoc-Cys(PMB)-OH and Fmoc-Cys-(Acm)-OH were first converted to the corresponding diazo ketones **10** and **11** in moderate-to-good yields (*Scheme 4*). Upon ultrasonication [95] in the presence of

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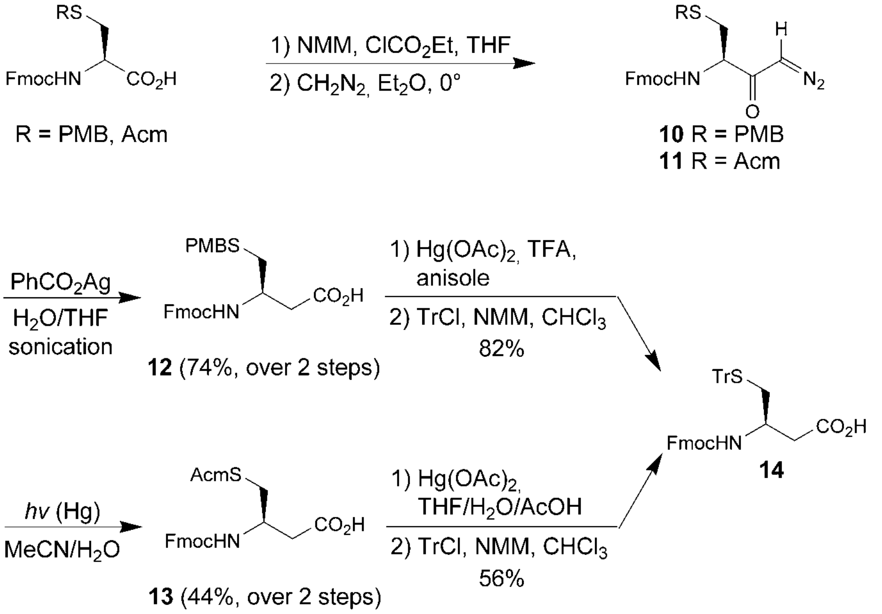
[13]) Direct tritylation of the completely unprotected β-homohistidine by means of TrCl, Et_3N, and Me_2SiCl_2 [94] gave no reproduceable results; the reasons could be the less favored formation of the cyclic silyl intermediate for β-amino acids compared to the α-analogues (six-membered ring *vs.* five-membered ring), or the hampered isolation of the N^{Im}-tritylated homohistidine by precipitation due to the discrete solubility of the zwitterionic starting material.

catalytic amounts of $PhCO_2Ag$ and H_2O, the PMB derivative **10** smoothly underwent *Wolff* rearrangement to provide the acid **12** in good yield. Interestingly, similar conditions for the conversion of the Acm derivative **11** led to the deprotection of the starting material [96–98]; therefore, the diazo ketone **11** was transformed to the β^3-amino acid **13** in moderate overall yield by irradiation with Hg light in a $MeCN/H_2O$ mixture. However, prolonged reaction times of up to 3 days are necessary for complete conversion (*Scheme 4*).

Scheme 4. *Preparation of Fmoc-β^3hCys(Tr)-OH* (**14**) *Starting from Either Fmoc-Cys(PMB)-OH or Fmoc-Cys(Acm)-OH*



Since the cleavage of both the PMB and Acm S-protecting groups involves reaction with Hg salts, the use of amino acids **12** and **13** for solid-phase peptide synthesis by Fmoc strategy are inappropriate; this additional step for the full deprotection of a peptide containing functionalized side chains could possibly lead to problems. Therefore, compounds **12** and **13** were treated under Ar[14]) with $Hg(OAc)_2$ in acidic media to give Fmoc-β^3hCys-OH, which was then protected *in situ* to afford the Tr-protected derivative **14** in moderate-to-good yields.

Thus, Fmoc-β^3hCys(Tr)-OH (**14**) was prepared with an overall yield of 60% and 23% over three steps, starting from Fmoc-Cys(PMB)-OH and Fmoc-Cys(Acm)-OH, respectively. The Acm protecting group was shown to be less stable under *Arndt–Eistert* homologation conditions, and the presence of small amounts of by-products at each step resulted in tedious purifications. The preferable route is clearly that starting from the PMB derivative.

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[14]) Both reactions have to be carried out under complete exclusion of air, due to the ease of disulfide formation!

3. Preparation of β^2-Amino Acid Derivatives with the Side Chains of Serine, Cysteine, and Histidine. – As outlined in a previous work on diastereoselective aldol additions by *Hintermann* and *Seebach* [64], direct hydroxymethylation of a chiral homoglycine derivative with 1,3,5-trioxane appeared to be the method of choice for the construction of the β^2-homoserine skeleton. Thus, phthalyl protection of β-alanine (*i.e.*, β-homoglycine), followed by treatment with oxalyl chloride and *N*-acylation of the lithiated chiral auxiliary (*S*)-DIOZ (**17**), afforded the acyloxazolidinone (*S*)-**18** in good yield (*Scheme 5*). Reaction of the Ti-enolate of (*S*)-**18** with trioxane[15]) gave the hydroxymethyl derivative (*S*,*R*)-**19**[16]) in 89% yield as a single diastereoisomer[17]). For the preparation of the β^2-homoserine derivative, suitably protected for solid-phase synthesis, the OH group of **19** had to be converted to the corresponding *t*-BuO group (see **20**). Thus, treatment of **19** with isobutylene and a catalytic amount of H_2SO_4 led to (*S*,*R*)-**20** in 95% yield[18]). The crystal structures[19]) of both (*S*,*R*)-**19** and (*S*,*R*)-**20** confirmed our configurational assignments (*Scheme 5*).

The next step was the removal of the chiral auxiliary. Unfortunately, this step could not be accomplished with LiOOH or NaOH, due the to opening of the phthaloyl group, which precluded the separation of *N*-deprotected β-homoserine from the chiral oxazolidinone (*S*)-**17**. To obviate this problem, compound **20** was converted to the benzyl ester derivative (*R*)-**21** by treatment with BnOH and BuLi in THF at 0° (*Scheme 6*). Interestingly, it was found that partial epimerization or racemization occurred during this reaction. The epimerization was found to be dependent on both the amount of BuLi used and the reaction temperature employed. By running the reaction at 0° with 1.2 equiv. BuLi (*Entry 1*, *Scheme 6*), *ca.* 25% of the (*S*)-product was formed. If the reaction was carried out at 0°, but with 2.5 equiv. of BuLi, compound **21** was formed as a *ca.* 84:16 mixture of enantiomers (*Entry 2*). Finally, racemization-free conditions were obtained when the reaction was performed at $-30°$ with 2.5 equiv. of BuLi (*Entry 3*). Even though a prolonged reaction time was required for complete conversion, the enantiomerically pure Phth-protected β^2-homoserine (*R*)-**21** was isolated (80%), together with the recovered oxazolidinone (*S*)-**17** (89%). For the synthesis of the (*R*)-Fmoc-β^2hSer(^{t}Bu)-OH **23**, the phthaloyl group was first cleaved by treatment of (*R*)-**21** with ethylenediamine in BuOH [99] to give the amino ester (*R*)-**22** in 78% yield. Hydrogenation and Fmoc protection afforded the acid **23** in 80% yield (*Scheme 6*). The enantiomer purity of the β^2-homoserine derivatives was determined after derivatization to the dinitrophenyl derivative (*R*)-**24**, since the ester **21** did not show enantiomer separation on our *Chiralcel OD-H* column [100]. Thus, the homoserine derivative **22** was allowed to react with *Sanger*'s reagent (1-fluoro-2,4-

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[15]) Trioxane is 'degraded' by $TiCl_4$ to give formaldehyde *in situ*.

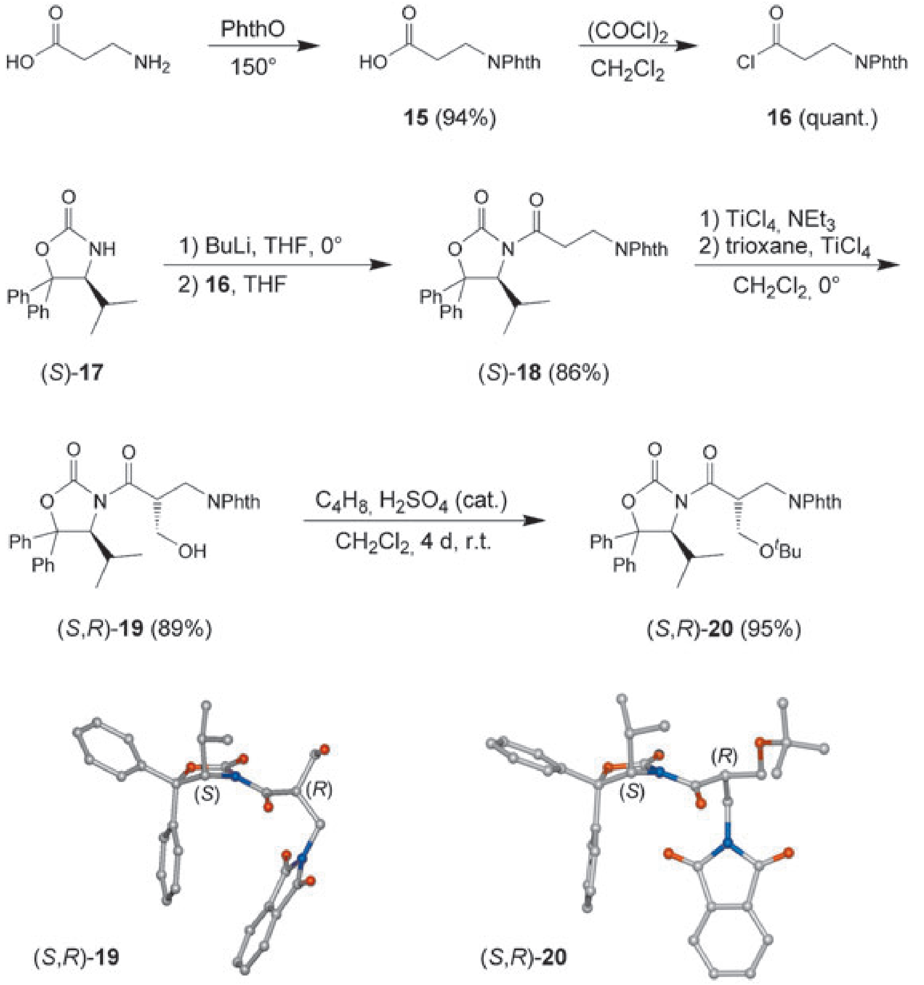
[16]) The first configuration descriptor (*S*) refers to the configuration of the stereogenic center of the oxazolidinone auxiliary group, whereas the second descriptor (*R*) refers to the configuration of the newly formed stereogenic center, the α-C-atom of the β^2-homoamino acid moiety.

[17]) Degradation products are formed if the reaction is not carried out under absolute exclusion of H_2O, which renders purification troublesome.

[18]) Hydroxy protection was initially carried out by treatment of **19** with *tert*-butyl 2,2,2-trichloroacetimidate (TBTA) in the presence of catalytic amounts of trifluoromethanesulfonic acid, but tedious separation of the product from the formed trichloroacetamide excluded its further use.

[19]) We are grateful to Dr. *B. Schweizer* of the Laboratorium für Organische Chemie, ETH-Zürich, for determination of the X-ray crystal structures of **19**, **20**, and **25** (see *Scheme 7*).

Scheme 5. *Acylation of the Chiral Auxiliary (*S*)-***17** *with the Acid Chloride* **16** *to Afford the Chiral Homoglycine Derivative (*S*)-***18**. Hydroxymethylation of (*S*)-**18** and subsequent *t*-Bu protection. Crystal structures of (*S*,*R*)-**19** and (*S*,*R*)-**20**.



dinitrobenzene; DNPF [101][102]) in alkaline solution to give the compound **24** in moderate yield, ready for analysis on the chiral column (*Scheme 6*).

According to this protocol, the β^2-homoserine derivative (*R*)-**23** was obtained with an overall yield of 34% over nine steps.

For the preparation of the β^2-homocysteine[20]), the hydroxymethyl derivative (*S*,*R*)-**19** was chosen as suitable starting material (*Scheme 7*). Thus, treatment of (*S*,*R*)-**19**

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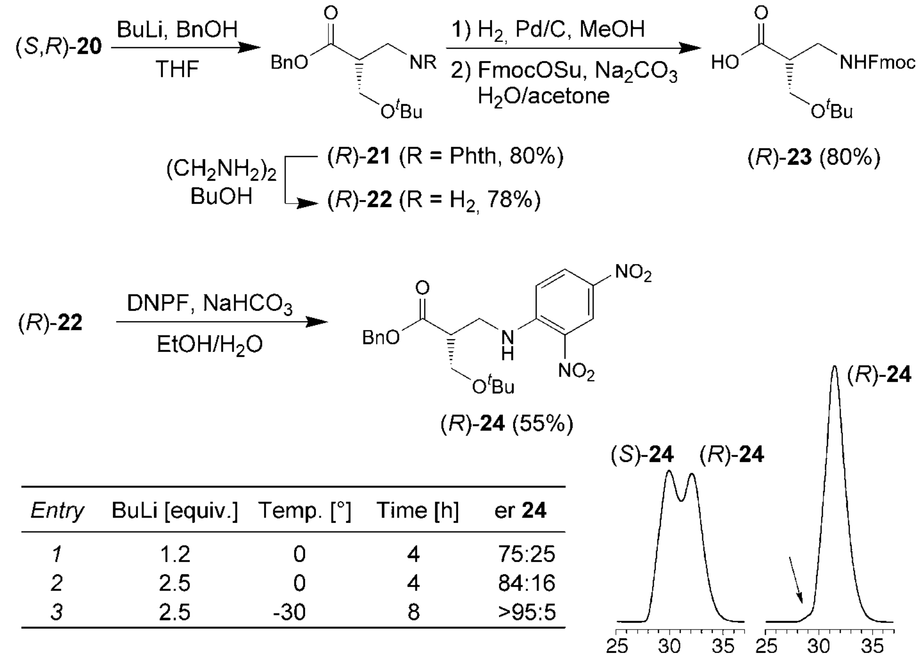
[20]) For our ongoing projects on the synthesis of long-chain β-peptides by the thioligation methodology, we were interested in the synthesis of the Boc-β^2hCys(Tr)-OH, which is the building block for peptides with N-terminal β^2hCys residue.

Scheme 6. *Removal of the Auxiliary from (*S,R*)-***20*** *and Subsequent Conversion to Afford Fmoc-(*R*)-β^2hSer(^{t}Bu)-OH* (**23**). The enantiomeric purity of the β^2-homoserine derivative was established (after derivatization of compound **22** to the 2,4-dinitrophenyl derivative **24**) by HPLC on a *Chiralcel OD-H* column (λ = 390 nm, elution system: i-PrOH/hexane 5 : 95).



Entry	BuLi [equiv.]	Temp. [°]	Time [h]	er **24**
1	1.2	0	4	75:25
2	2.5	0	4	84:16
3	2.5	-30	8	>95:5

under modified *Mitsunobu* conditions with TrSH, Bu_3P, and azodicarboxylic dipiperidide (ADDP) [103], afforded the thiol ether derivative **25** in good yield, but with substantial epimerization (dr 82 : 18). The diastereoisomeric mixture was readily separated by flash chromatography to give (*S,S*)- and (*S,R*)-**25** in 71 and 16% yield, respectively. The configurational assignment was unambiguously confirmed by crystal-structure analysis of the major diastereomer (*Scheme 7*). The next step involved the removal of the chiral auxiliary from **25**, which proved, again, problematic: cleavage with LiOOH or NaOH was unsuccessful due to the opening of the phthaloyl group. On the other hand, cleavage with BnOLi afforded the corresponding benzyl ester, but the following hydrogenolysis to give the free acid proved to be ineffective, most likely because of catalyst poisoning by the sulfide group. Better results were obtained by treating (*S,S*)-**25** with lithium 2-(trimethylsilyl)ethanolate to afford the ester (*S*)-**26** in acceptable yield, which was then Phth-deprotected and Boc-protected to give the β^2-homocysteine derivative (*S*)-**28** in good yield. Final hydrolysis with Bu_4NF [104] gave the acid (*S*)-**29** in 84% yield (*Scheme 7*)[21]. By this approach, Boc-β^2-hCys(Tr)-OH was prepared with an overall yield of 17% over nine steps from 'β-alanine'.

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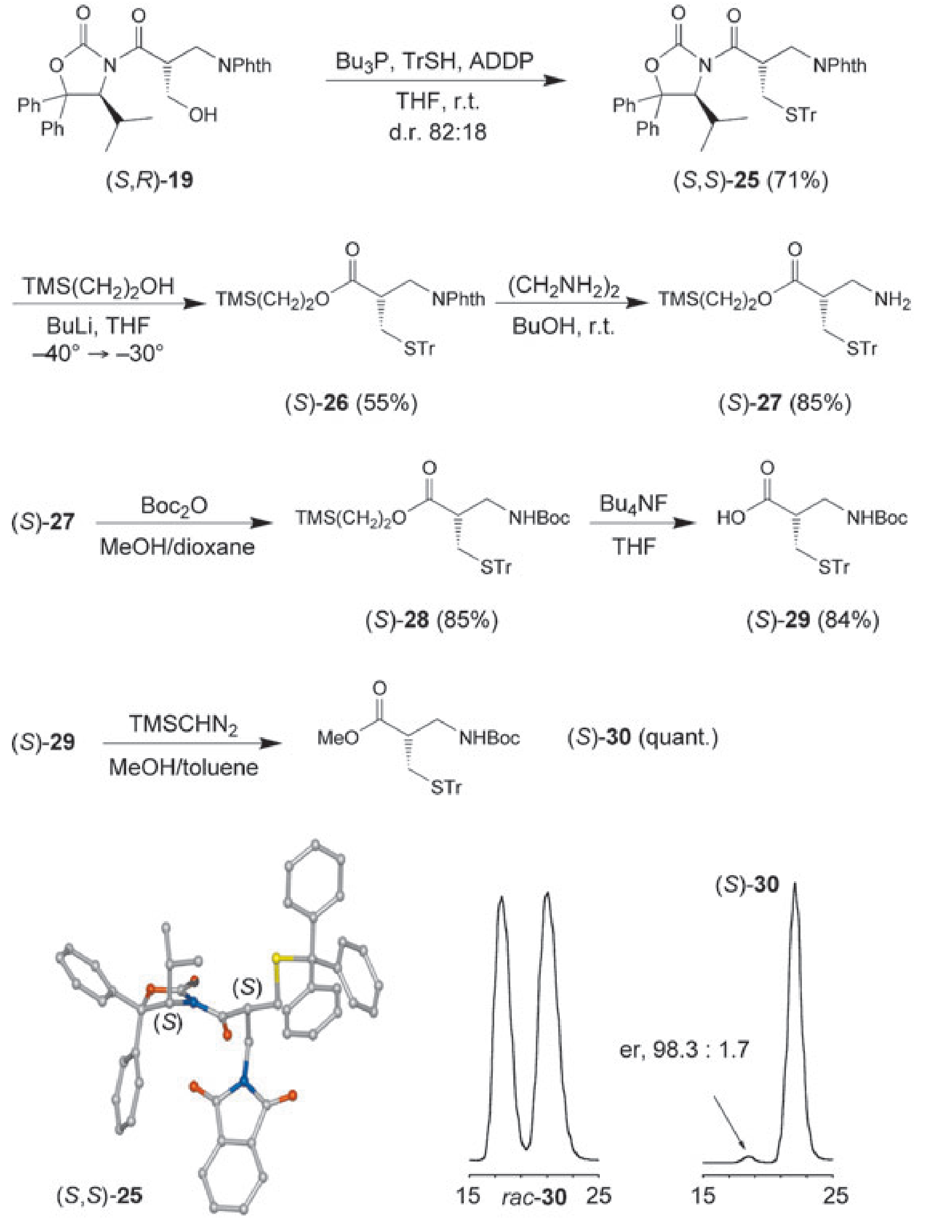
[21] Removal of the chiral auxiliary by treatment of (*S,S*)-**25** with MeOLi turned out to be more efficient, but the following saponification of the methyl ester led to a completely racemized product.

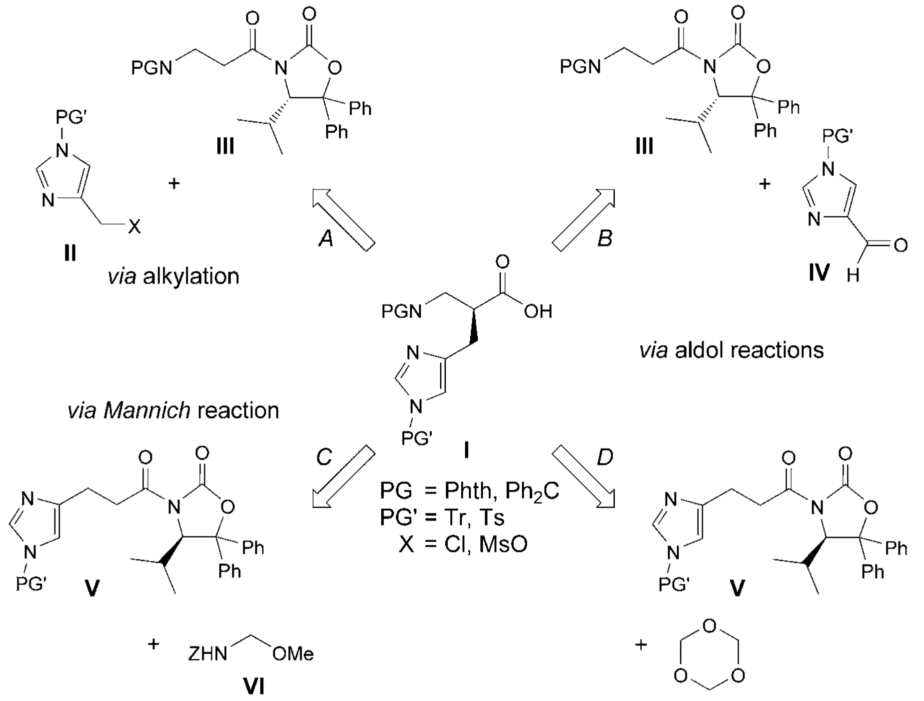
Scheme 7. *Preparation of Boc-(*S*)-β²hCys(Tr)-OH* (**29**) *Starting from the Hydroxymethyl Derivative (*S,R*)*-**19**. Esterification of the acid **29** was necessary for enantioselectivity quantification by HPLC on a chiral column (*Chiralcel OD-H*; $\lambda = 220$ nm, elution system: i-PrOH/hexane 2 : 98). X-Ray crystal structure of the major diastereoisomer (*S,S*)-**25** confirmed the configurational assignment.



To determine the enantiomeric purity of the β^2-homocysteine derivatives, the acid (*S*)-**29** was treated with $TMSCHN_2$ to afford the methyl ester (*S*)-**30** in quantitative yield, which was analyzed with a chiral HPLC column (*Chiralcel OD-H*) to have an enantiomer purity of 98.3% (*Scheme 7*).

As pointed out above, in the syntheses of the β^3-homohistidine derivatives, the presence of the nucleophilic N-atom on the (1*H*-imidazolyl)methyl side chain was found to generate undesired by-products and was expected to cause trouble in the steps towards the preparation of the β^2-analogues as well. Indeed, many routes (*Scheme 8*) have been tested, and most were not successful.

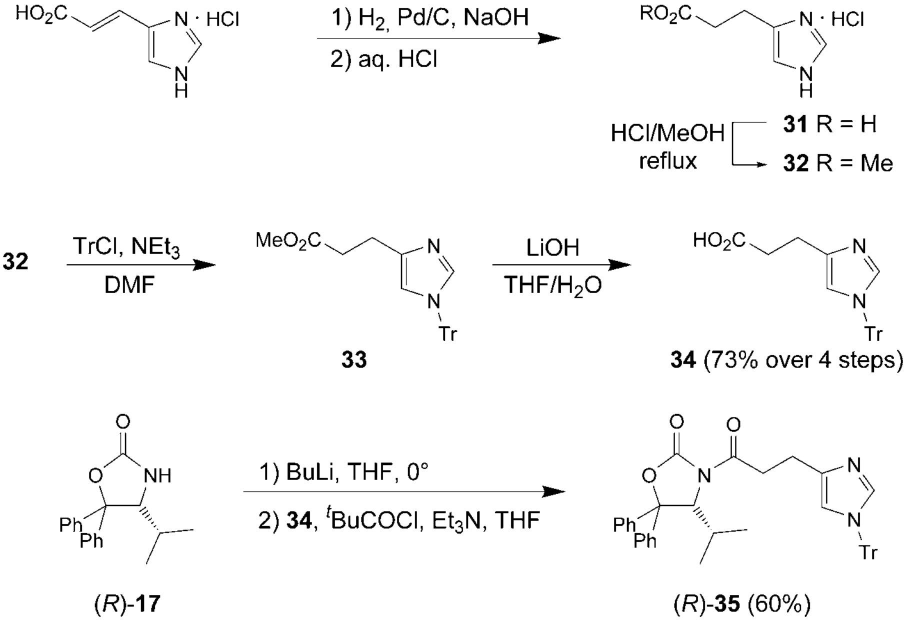
Scheme 8. *Retrosynthetic Analysis for the Preparation of Fmoc-β^2hHis(Tr)-OH* via *Alkylation (*route *A), Mannich-Type Reaction (*route *C), and Aldol Addition (*routes *B* and *D) of Chiral Acyloxazolidinones*



Initial attempts of diastereoselective alkylation (*cf. A* in *Scheme 8*) of homoglycine-derived acyloxazolidinones **III** (PG = Phth [64]; PG = Ph_2C) with (1*H*-imidazol-4-yl)methyl derivatives **II** (PG′ = Trt, X = Cl [105]; PG′ = Ts, X = MsO [106]) were ineffective due to the low reactivity of both electrophiles, and modifications of **II** by use of better leaving groups (X = I, Br) failed, these derivatives being too unstable. In a second approach (*cf. B* in *Scheme 8*), the aldol addition of the oxazolidinone derivatives **III** with aldehydes **IV** (PG′ = Tr [107]; PG′ = Ts [106]), followed by deoxygenation under *Barton–McCombie* conditions [67][108][109], resulted in the isolation of degradation products caused by *retro*-aldol reactions, occurring during the deoxygenation step. Thus, the amidomethylation reaction *via* Ti-enolates was attempted (*cf. C* in *Scheme 8*): treatment of the acyloxazolidinone **V** (PG′ = Tr) with the electrophile **VI** [64][75] resulted in a complex mixture of inseparable products; although the desired compound had been formed, long reaction times were required for good conversion, causing the partial cleavage of the Tr protecting group. Thus, we envisaged the use of a more reactive electrophile, for instance, 1,3,5-trioxane (*cf. D* in *Scheme 8*), with subsequent OH/NH_2 replacement. This route led, eventually, to the synthesis of the desired β^2-homohistidine derivative for solid-phase syntheses, and is presented in detail in the following sections.

For the preparation of the acyloxazolidinone **35**, 1*H*-imidazole-4-acrylic acid (uraconic acid) was selected as the starting material. Hydrogenation of uraconic acid, followed by esterification under acidic conditions, gave the methyl ester **32**, which was Tr-protected to give compound **33**, the crude product of which was saponified to afford the acid **34** in 73% yield over four steps (*Scheme 9*).

Scheme 9. *Preparation of the Acyloxazolidinone (*R*)-***35** *Starting from Uraconic Acid*



N-Acylation of the (*R*)-DIOZ (**17**) was accomplished by nucleophilic addition of the lithiated auxiliary (using BuLi in THF at 0°) to the pivaloyl mixed anhydride of **34** [110] to give the acyloxazolidinone (*R*)-**35** in 60% yield (*Scheme 9*)[22]. The following aldol reaction was effected by reaction of the Ti-enolate of **35** with 1,3,5-trioxane to afford the hydroxymethyl derivative **36** in 70% yield (*Scheme 10*). The diastereoselectivity was *ca.* 9:1 in favor of the diastereoisomer (*R*,*S*)-**36** as deduced from the ^{1}H-NMR spectra of the crude product. The absolute configuration of the newly formed

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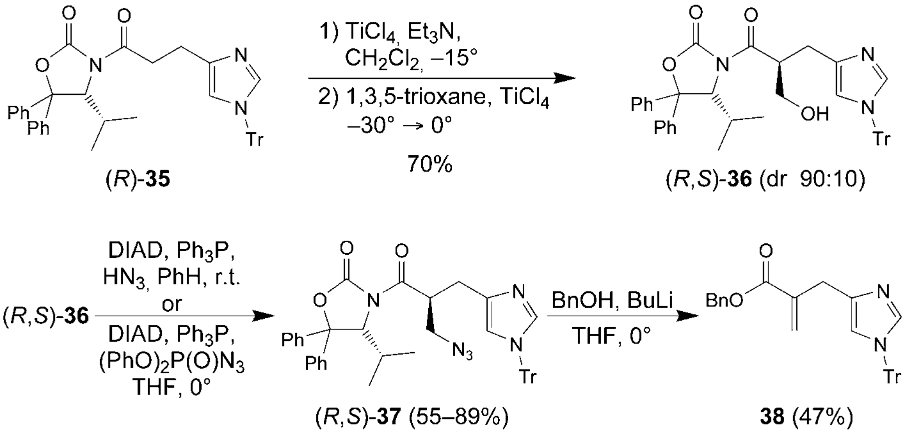
[22] In contrast, the acylation of (*R*)-**17** with the LiCl-activated [111] pivaloyl mixed anhydride of **34**, with Et_3N as base [112] gave **35** in lower yields. A third method involving the addition of the lithiated auxiliary to the corresponding acid chloride of **34** was not considered, since treatment of **34** with oxalyl chloride had caused partial cleavage of the Tr protecting group!

stereogenic center was assigned by analogy with the results from previous aldol reactions of this type [64][72].

The next step required the replacement of the OH group of **36** by a *N*-substituent by means of a *Mitsunobu* reaction. Thus, treatment of (*R*,*S*)-**36** with Ph_3P, DIAD, and either DPPA or hydrazoic acid afforded the azide derivative (*R*,*S*)-**37** in moderate-to-good yields (55 and 89%, resp.). However, attempts to cleave the auxiliary were not successful. Indeed, removal of the oxazolidinone group by BnOH/BuLi afforded the elimination product **38** (*Scheme 10*).

Scheme 10. *Diastereoselective Aldol Reaction of (*R*)-***35** *with 1,3,5-Trioxane.* The following transformation towards the formation of β^2-homohistidine derivatives led, instead, to the formation of compound **38**.



To circumvent this problem, the hydroxymethyl derivative **36** was first treated with BnOH/BuLi to form[23]) the corresponding benzyl ester (*S*)-**39**, which was subsequently transformed to the azide (*S*)-**40** under *Mitsunobu* conditions in good yield (*Scheme 11*). To verify whether both the cleavage of the auxiliary and the conversion to the azide derivative **40** had proceeded with retention of configuration in the α-position to the C=O group, both compounds were injected into an analytical, chiral, normal-phase HPLC column (*Chiralcel OD-H*). Fortunately, both compounds showed good resolution, so that the performance of these two reactions could be validated (*Scheme 11*).

Simultaneous benzyl ester cleavage and azide reduction in derivative **40** by catalytic hydrogenation, followed by Fmoc-protection, afforded the histidine derivative (*S*)-**41** in moderate yield (*Scheme 11*). It should be noted that the Tr protecting group is stable under the hydrogenation conditions only to a certain extent; prolonged reaction times cause complete cleavage of that group[24]).

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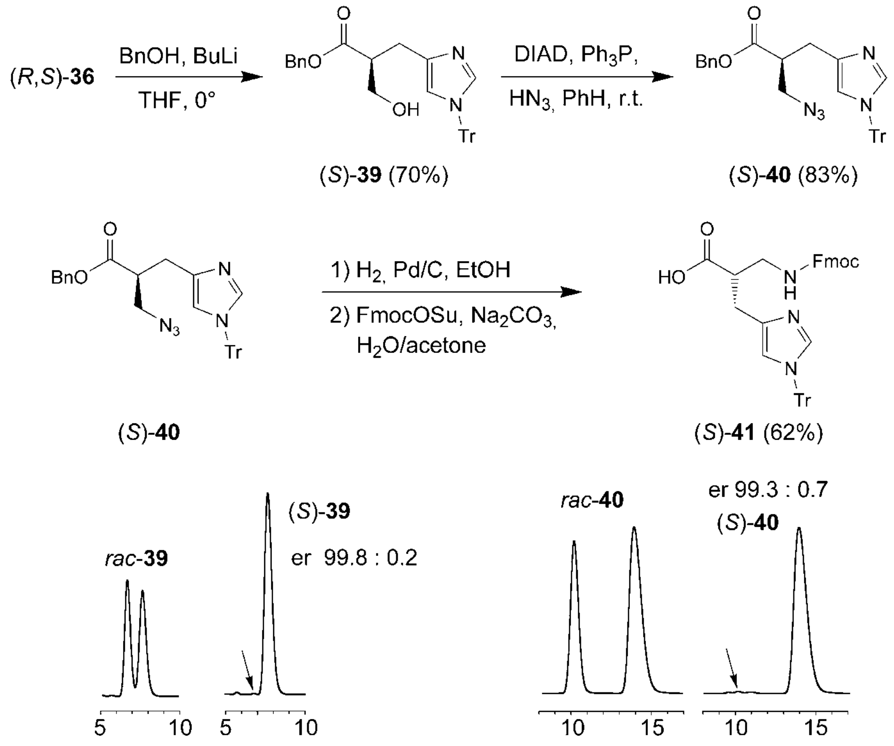
[23]) (*R*)-DIOZ was recovered in 84% yield.

[24]) To prevent significant Tr cleavage, the hydrogenation was carried out for a period of 2 h. The solution was then filtered over *Celite*, and the solvent was evaporated. The reaction progress was followed by IR spectroscopy, using the intensive stretching vibration of the N_3 group in the range 2250–2080 cm^{-1}. If the reaction was not complete, the mixture was treated for a further 2 h under the hydrogenation conditions.

Scheme 11. *Removal of the Auxiliary with BnOLi, Followed by* Mitsunobu *Reaction and Functional-Group Modifications for the Preparation of Fmoc-(*S*)-β^2hHis(Tr)-OH* (**41**). The HPLC traces of the hydroxymethyl derivative **39** and of the azide **40** demonstrate the efficiency of this approach for the preparation of enantiomerically pure β^2-homohistidine (*Chiralcel OD-H*, λ = 220 nm, elution system: i-PrOH/hexane 10 : 90 for **39** and i-PrOH/hexane 5 : 95 for **40**).



In this way, the syntheses of (*S*)-Fmoc-β^2hHis(Tr)-OH was achieved with an overall yield of 11% over ten steps from 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one (DIOZ).

4. Conclusions and Outlook. – The preparation of Fmoc-β^3hHis(Tr)-OH and Fmoc-β^3hCys(Tr)-OH were achieved *via Arndt–Eistert* homologation. Thus, all 20 β^3-amino acids with proteinogenic side chains appropriately protected for solid-phase syntheses by the Fmoc strategy have now been prepared by this method. We were also able to develop a useful route for the preparation of three β^2-amino acids making use of 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one (DIOZ) as a chiral auxiliary for a diastereoselective aldol reaction (with trioxane). The enantiomer purity of these amino acids was determined by HPLC on a *Chiralcel OD-H* column of the (*R*)- and (*S*)-derivatives **24**, **30**, **39**, and **40**. Our protocol can easily be scaled-up to produce multigram amounts of these amino acids in enantiomerically pure form. Ongoing work in our laboratory is focussed in the use of the above mentioned amino acids for the constructions of large β-peptides for structural [1][113] and biological investigations, towards the synthesis of what can be referred to as 'β-proteins'.

Experimental Part

1. *General. Abbreviations:* Acm: (Acetamido)methyl, ADDP: azidodicarboxylic dipiperidide, Boc: (*tert*-butoxy)carbonyl, DIAD: diisopropyl azodicarboxylate, DNPF: 1-fluoro-2,4-dinitrobenzene, FC: flash chromatography, Fmoc-OSu: *N*-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}oxy)succinimide, HOBt: 1-hydroxy-1*H*-benzotriazole, h.v.: high vacuum, 0.01 – 0.1 Torr, NMM: *N*-methylmorpholine, PMB: *para*-methoxybenzyl, TIS: tetraisopropylsilane, Ts: 4-toluenesulfonyl, Tr: trityl. Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*) and from KOH (Et_2O), resp. Et_3N was distilled from CaH_2 and stored over 4-Å molecular sieves. Amino acids were purchased from *Fluka* or *Senn*. All other reagents were used as received from *Fluka*. TLC: *Merck* silica gel *60 F₂₅₄* plates; detection with UV, anisaldehyde soln. (9.2 ml anisaldehyde, 12.5 ml conc. H_2SO_4, 3.75 ml AcOH, 340 ml EtOH), or 'Mostain' soln. (25 g of phosphormolybdic acid, 10 g of $Ce(SO_4)_2 \cdot H_2O$, 60 ml of conc. H_2SO_4, 940 ml of H_2O), FC: *Fluka* silica gel *60* (40 – 63 μm); at *ca.* 0.2 bar. Anal. HPLC: *Waters* HPLC System (pump type *515*, data module type *746*, tunable absorbance detector type *484*), *Chiralcel OD-H* column. M.p.: *Büchi-510* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 1600 FT-IR* spectrophotometer. NMR Spectra: *Bruker AMX-II-500* (^{1}H: 500 MHz, ^{13}C: 125 *MHz*), *Bruker AMX-400* (^{1}H: 400 MHz, ^{13}C: 100 *MHz*), *Bruker AMX-300* (^{1}H: 300 MHz, ^{13}C: 75 MHz), *Varian Mercury XL 300* (^{1}H: 300 MHz, ^{13}C: 75 *MHz*); chemical shifts δ in ppm downfield from internal Me_4Si (= 0 ppm); *J* values in Hz. MS: *IonSpec Ultima 4.7 T FT* ion-cyclotron resonance (ICR, HR-MALDI, in 2,5-dihydroxybenzoic acid matrix) spectrometer; in *m/z* (% of basis peak). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

2. *Synthesis of* N-*Fmoc- or* N-*Boc-Protected Diazo Ketones: General Procedure 1* (*GP 1*). *GP 1a:* Similar to the procedure reported in [114], the *N*-Fmoc- or *N*-Boc-protected amino acid was dissolved in THF (0.2M) under Ar and cooled to – 25°. After addition of NMM (1.05 equiv.) and $ClCO_2Et$ (1.05 equiv.), the mixture was stirred at – 25° for 30 min. The resulting white suspension was allowed to warm to 0°, and a soln. of CH_2N_2 in Et_2O was added until the rich yellow color persisted. Stirring was continued for 2 – 12 h as the mixture was allowed to warm to r.t. Excess CH_2N_2 was destroyed by the addition of a few drops of AcOH and vigorous stirring. The mixture was then diluted with Et_2O, and washed with sat. aq. $NaHCO_3$ soln. (1 ×), sat. aq. NH_4Cl soln. (1 ×) and sat. aq. NaCl soln. (1 ×). The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure. FC afforded the pure diazo ketone.

GP 1b: As in *GP 1a*, except that Et_3N (1.05 equiv.) and $ClCO_2{}^iBu$ (1.05 equiv.) were used instead of NMM and $ClCO_2Et$.

3. *Preparation of Homologated Histidine: General Procedure 2* (*GP 2*). Similar to the procedure reported in [114], the diazo ketone **2** (1 equiv.) was dissolved in MeOH or THF/BnOH 9 : 1 (0.25M) and cooled to – 25° under Ar with the exclusion of light. A soln. of CF_3CO_2Ag (0.11 equiv.) in Et_3N (2.3 equiv.) was added, and the resulting mixture was slowly allowed to warm to r.t. in the dark. After completion of the reaction (TLC control, 4 – 6 h) the solvent was removed under reduced pressure, and Ts deprotection was performed according to a known procedure [89]: Ac_2O (70 equiv.) and pyridine (1 equiv.) were added to the residue, and the mixture was stirred until disappearance of the Ts-protecting group of the 1*H*-imidazole (TLC control). If necessary, Ac_2O and pyridine were added again. To the mixture was then added, at 0°, MeOH (6.6 ml/mmol of **2**), and stirring was continued for another h. The solvent was concentrated under reduced pressure, the residue taken up in H_2O, and the pH was adjusted to *ca.* 8 by addition of solid Na_2CO_3. After extraction with CH_2Cl_2 (5 ×) the combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure. FC afforded the pure β^3-homohistidine derivative.

4. *Tr Protection: General Procedure 3* (*GP 3*). *GP 3a:* Similar to the procedure reported in [115], the amino acid was dissolved in $CHCl_3$ (1M) and cooled to 0°. Et_3N (3 equiv.), and a soln. of TrCl or TrBr (2 – 4 equiv.) in $CHCl_3$ (2M) was added dropwise. Stirring was continued for 2 – 3 d as the mixture was allowed to warm to r.t. Thereafter, 2M AcOH (1 equiv.) was added; the $CHCl_3$ was evaporated, and the residue was extracted with AcOEt (3 ×). The combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure. FC afforded the pure Tr-protected amino acid.

GP 3b: As in *GP 3a*, except that the amino acid dissolved in $CHCl_3$ (0.1M) was treated with solid TrCl or TrBr (2 – 4 equiv.).

5. *Fmoc Protection: General Procedure 4* (*GP 4*). *GP 4a:* The *N*-deprotected amino acid was dissolved in 0.6M Na_2CO_3 (3.7 equiv.) and treated with a soln. of Fmoc-OSu (1.6 equiv.) in acetone (0.2M). If necessary, the pH was re-adjusted to 9 – 10 with additional aq. Na_2CO_3 soln., and the mixture was stirred for 2.5 h. H_2O was then added, and the mixture was extracted with Et_2O (2 ×). The org. phase was re-extracted with 0.3M Na_2CO_3 (1 ×); the combined aq. phases were carefully adjusted to pH 1 – 2 at 0° with 1M HCl and extracted with AcOEt

(3 ×). The combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure. FC yielded the pure product.

GP 4b: The *N*-deprotected amino acid was dissolved in 0.15м Na_2CO_3 (2–3 equiv.) and treated with a soln. of FmocOSu (1–1.2 equiv.) in acetone (0.1м). If necessary, the pH was re-adjusted to 9–10 with additional aq. Na_2CO_3 soln., and the mixture was stirred at r.t. for 4 h. The acetone was carefully removed under reduced pressure at 30°, and the resulting mixture was diluted with H_2O. At this point, the pH of the soln. was adjusted to 9–10 using 0.6м aq. Na_2CO_3. The aq. mixture was then extracted with Et_2O (2 ×). The aq. phase was separated, cooled to 0°, and AcOEt was added to the mixture. With continuous stirring of the biphasic system at 0°, the pH of the aq. phase was adjusted to 4–5 by slow addition of 10% aq. citric acid. The org. layer was separated, and the aq. layer was extracted with AcOEt (2 ×). The combined org. layers were washed with sat. aq. NaCl soln., dried (Na_2SO_4), and concentrated under reduced pressure. FC yielded the pure product.

6. *Hydroxymethylation of Acyloxazolidinones: General Procedure 5* (*GP 5*). *GP 5a:* Similar to the procedure reported in [64], the corresponding acyloxazolidinone was dissolved in CH_2Cl_2 (0.2м) and cooled to *ca.* –20°, and $TiCl_4$ (1.05 equiv.), quickly followed by Et_3N (1.1 equiv.), was added to the soln. ($T < -10°$). The formed dark red soln. was stirred for 30 min at –10°, then solid 1,3,5-trioxane (1.2 equiv.) and $TiCl_4$ (1.1 equiv.) were added, and the soln. was stirred for an additional 3–6 h at *ca.* 0° (TLC control). A white suspension formed, and the red color disappeared. The reaction was quenched with sat. aq. NH_4Cl soln., diluted with Et_2O, and washed with 1м HCl (2 ×), 1м NaOH (1 ×), and sat. aq. NaCl soln (1 ×). The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure. FC afforded the pure product.

GP 5b: As in *GP 5a*, except that the reaction was quenched with 1м NaOH and diluted with Et_2O. The org. phase was separated, washed with 1м NaOH and sat. aq. NaCl soln., and each aq. phase was re-extracted with Et_2O.

7. *Hydrogenolysis of Bn Esters and N_3 Groups: General Procedure 6* (*GP 6*). *GP 6a:* The corresponding substrate was dissolved in MeOH (0.17–0.02м) and *ca.* 10% (*w*/*w*) Pd/C (10%) was added. The apparatus was evacuated and flushed with H_2 (3 ×), and the soln. was stirred under an atmosphere of H_2 (balloon) for 1–2 h (TLC control). Subsequent filtration through *Celite* and concentration under reduced pressure yielded the crude product, which was used in the next step without further purification.

GP 6b: The corresponding substrate was dissolved in EtOH (0.1м) and *ca.* 10% (*w*/*w*) Pd/C was added. The apparatus was evacuated and flushed with H_2 (3 ×), and the soln. was stirred under an atmosphere of H_2 (balloon) for 2 h. The mixture was then filtered through *Celite* and concentrated under reduced pressure. For the case of compounds containing an N_3 group, the reaction progress was monitored by IR spectroscopy, since the N_3 group shows very strong asymmetric stretching vibrations in the range 2250–2080 cm^{-1}. If the reaction was not complete, the mixture was treated for a further 2 h under the same conditions. The crude product was used in the next step without further purification.

8. *Phth Deprotection: General Procedure 7* (*GP 7*). To a soln. of the Phth-protected compound in BuOH (0.06–0.2м) at r.t., $(CH_2NH_2)_2$ (4 equiv.) was added dropwise under Ar, and the mixture was stirred for 1–2 h. The solvent was then co-evaporated with toluene (3 ×) and with EtOH (2 ×) to give the crude deprotected amine. FC afforded the pure compound.

9. Mitsunobu *Reaction: General Procedure 8* (*GP 8*). *GP 8a:* Similar to the procedure reported in [116], a soln. of HN_3 in benzene was prepared from NaN_3 and H_2SO_4, and its conc. was determined by titration with NaOH on phenolphthalein. To a stirred soln. of the corresponding alcohol in benzene (0.13м) cooled at 0°, solid Ph_3P (1.1 equiv.) was added, followed by dropwise addition of the HN_3 soln. (1.1 equiv.) and DIAD (1.1 equiv.). The soln. was stirred for 50 min at r.t., and the benzene was then evaporated under reduced pressure. FC gave the pure compound.

GP 8b: To a stirred soln. of the corresponding alcohol in THF (0.1м) at 0°, DIAD (1 equiv.), Ph_3P (1 equiv.) and $(PhO)_2P(O)N_3$ (1.2 equiv.) were added. The mixture was strirred at 0° for 4 h as a white precipitate formed. The mixture was stirred for additional 14 h at r.t., and the solvent was evaporated under reduced pressure. FC afforded the pure compound.

*(*S*)-1-Diazo-3-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)-4-{1-[(4-methylphenyl)sulfonyl)]-1*H*-imidazol-4-yl}butan-2-one* (Fmoc-(*S*)-His(Ts)-CHN_2; **1**). Transformation of Fmoc-ʟ-His(Ts)-OH (5.00 g, 9.41 mmol) according to *GP 1a* and FC (CH_2Cl_2/Et_2O 5:1) yielded **1** (2.97 g, 56%). Yellow solid. R_f (CH_2Cl_2/Et_2O 5:1) 0.12. $[\alpha]_D^{r.t.} = -26.0$ ($c = 0.99$, $CHCl_3$). IR ($CHCl_3$): 3423*w*, 3008*w*, 2113*s*, 1720*s*, 1639*m*, 1596*w*, 1507*m*, 1476*w*, 1450*w*, 1385*s*, 1362*s*, 1175*s*, 1078*s*, 1045*w*. ^1H-NMR (400 MHz, $CDCl_3$): 2.37 (*s*, Me); 2.91–3.04 (*m*, CH_2); 4.17 (*t*, $J = 6.7$, CH); 4.33–4.37 (*m*, CH); 4.41–4.45 (*m*, CH_2O); 5.28 (br. *s*, CHN_2); 6.19 (br. *d*, NH); 7.07 (*s*, 1 Im H); 7.28–7.33 (*m*, 4 arom. H); 7.37–7.42 (*m*, 2 arom. H); 7.51–7.59 (*m*, 2 arom. H); 7.77 (*d*, $J = 8.4$, 2 arom. H); 7.92 (*s*, 1 Im H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.65 (Me); 29.75 (CH_2); 47.26, 53.95, 57.56 (CH); 66.88 (CH_2);

114.98, 120.00, 125.04, 125.17, 127.10, 127.32, 127.77, 130.43 (CH); 134.79 (C); 136.37 (CH); 140.10, 141.37, 143.69, 146.39, 155.98, 193.21 (C). MALDI-MS: 578.2 (2.47), 528.2 (61.77), 414.1 (12.22), 392.2 (47.15), 390.1 (42.36), 374.1 (100.00), 350.1 (53.95), 311.0 (15.44), 252.1 (43.65). HR-MALDI-MS: 528.1591 ($[C_{29}H_{26}N_3O_5S]^+$; calc. 528.1593).

(S)-3-{[(tert-Butoxy)carbonyl]amino}-1-diazo-4-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}butan-2-one (Boc-(*S*)-His(Ts)-CHN_2; **2**). Transformation of Boc-L-His(Ts)-OH (25.0 g, 61.0 mmol) according to *GP 1b* and FC (CH_2Cl_2/Et_2O 5:1 → CH_2Cl_2/Et_2O 1:1) yielded **2** (22.8 g, 86%). Yellow foam. R_f (CH_2Cl_2/Et_2O 5:1) 0.12. $[\alpha]_D^{r.t.} = -21.8$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3428*w*, 3128*w*, 2981*w*, 2112*s*, 1708*s*, 1638*m*, 1596*w*, 1496*m*, 1382*s*, 1368*s*, 1174*s*, 1092*w*, 1079*m*, 1050*w*, 1024*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.42 (*s*, ^{t}Bu); 2.43 (*s*, Me); 2.90 (*dd*, $J = 14.8$, 5.3, 1 H, CH_2); 3.01 (*dd*, $J = 14.8$, 5.8, 1 H, CH_2); 5.33–5.48 (br. *m*, CHN); 5.39 (br. *s*, CHN_2); 5.80–5.90 (br. *d*, NH); 7.06 (*s*, 1 Im H); 7.35 (*d*, $J = 8.6$, 2 arom. H); 7.79 (*d*, $J = 8.4$, 2 arom. H); 7.92 (*s*, 1 Im H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.72, 28.32 (Me); 29.90 (CH_2); 53.81, 57.12 (CH); 80.05 (C); 114.93, 127.35, 130.45 (CH); 134.94 (C); 136.35 (CH); 140.31, 146.37, 155.40, 193.81 (C). MALDI-TOF-MS: 456.1 (7.94), 434.1 (15.87), 406.1 (100.00), 356.5 (30.95), 350.1 (67.46), 270.2 (14.29), 252.1 (43.65). Anal. calc. for $C_{19}H_{23}N_5O_5S$ (433.49): C 52.64, H 5.35, N 16.16; found: C 52.72, H 5.36, N 15.96.

Methyl (S)-3-{[(tert-Butoxy)carbonyl]amino}-4-(1H-imidazol-4-yl)butanoate (Boc-(*S*)-β^3hHis-OMe; **3**). A soln. of **2** (22.8 g, 52.6 mmol) in MeOH (0.25 M) was treated according to *GP 2*. FC(CH_2Cl_2/MeOH sat. with NH_3 12:1) of the crude product yielded **3** (13.5 g, 91%). White solid. R_f (CH_2Cl_2/MeOH 15:1) 0.26. $[\alpha]_D^{r.t.} = -5.5$ ($c = 1.03$, $CHCl_3$). IR ($CHCl_3$): 3436*w*, 2981*m*, 1729*s*, 1703*s*, 1503*s*, 1438*m*, 1368*m*, 1165*s*, 1050*w*, 824*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.42 (*s*, ^{t}Bu); 2.47 (*dd*, $J = 15.4$, 6.5, 1 H, CH_2CO_2Me); 2.56 (*dd*, $J = 15.4$, 5.8, 1 H, CH_2CO_2Me); 2.88 (*d*, $J = 6.1$, CH_2CH); 3.68 (*s*, MeO); 4.17–4.24 (br. *m*, CHN); 5.53 (br. *s*, NH); 6.84 (*s*, 1 Im H); 7.58 (*s*, 1 Im H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.38 (Me); 31.31, 38.25 (CH_2); 47.60 (CH); 51.77 (Me); 79.57 (C); 135.02 (CH); 155.46, 172.20 (C). MALDI-MS: 306.1 (18.15), 284.1 (100.00), 228.1 (37.07), 184.1 (69.17). Anal. calc. for $C_{13}H_{21}N_3O_4$ (283.33): C 55.11, H 7.47, N 14.83; found: C 55.12, H 7.34, N 14.86.

Benzyl (S)-3-{[(tert-Butoxy)carbonyl]amino}-4-(1H-imidazol-4-yl)butanoate (Boc-(*S*)-β^3hHis-OBn; **4**). A soln. of **2** (390 mg, 0.88 mmol) in THF/BnOH 9:1 (0.25M) was treated according to *GP 2*. FC (CH_2Cl_2/MeOH 12:1) and recrystallization (CH_2Cl_2/hexane) of the crude product yielded **4** (276 mg, 85%). White solid. R_f (CH_2Cl_2/MeOH 14:1) 0.19. M.p. 123–124°. $[\alpha]_D^{r.t.} = -6.9$ ($c = 1.02$, $CHCl_3$). IR ($CHCl_3$): 3432*w*, 2982*m*, 1729*s*, 1704*s*, 1502*s*, 1456*w*, 1392*m*, 1368*m*, 1162*s*, 1048*w*, 824*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (*s*, ^{t}Bu); 2.49 (*dd*, $J = 15.4$, 6.7, 1 H, CH_2CO_2Bn); 2.60 (*dd*, $J = 15.4$, 5.8, 1 H, CH_2CO_2Bn); 2.85 (*d*, $J = 6.0$, CH_2CH); 4.21–4.23 (br. *m*, CHN); 5.12 (*s*, $PhCH_2$); 5.50 (br. *s*, NH); 6.77 (*s*, 1 Im H); 7.30–7.39 (*m*, 5 arom. H); 7.54 (*s*, 1 Im H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.35 (Me); 31.15, 38.35 (CH_2); 47.61 (CH); 66.49 (CH_2); 79.52 (C); 128.30, 128.33, 128.58, 134.94 (CH); 135.69, 155.38, 171.51 (C). MALDI-MS: 398.1 (2.51), 382.2 (37.23), 360.2 (45.61), 304.1 (20.31), 282.1 (21.96), 260.1 (100.00). Anal. calc. for $C_{19}H_{25}N_3O_4$ (359.42): C 63.49, H 7.01, N 11.69; found: C 63.49, H 6.94, N 11.66.

Methyl (S)-3-{[(tert-Butoxy)carbonyl]amino}-4-[1-(triphenylmethyl)-1H-imidazol-4-yl]butanoate (Boc-(*S*)-β^3hHis(Tr)-OMe; **5**). A soln. of **3** (207 mg, 0.73 mmol) in $CHCl_3$ (1M) was treated with Et_3N (0.31 ml, 3 equiv.) and TrCl (407 mg, 2 equiv.) according to *GP 3a* for 55 h. FC (AcOEt/hexane 1:3 → AcOEt/hexane 2:1) of the crude product yielded **5** (378 mg, quant.). White foam. R_f (AcOEt/hexane 2:1) 0.41. M.p. 123–124°. $[\alpha]_D^{r.t.} = +0.4$ ($c = 2.00$, $CHCl_3$). IR ($CHCl_3$): 3435*w*, 3008*w*, 2980*w*, 1728*s*, 1703*s*, 1495*s*, 1445*m*, 1367*m*, 1165*s*, 1049*w*, 869*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.40 (*s*, ^{t}Bu); 2.39 (*dd*, $J = 15.4$, 6.9, 1 H, CH_2CO_2Me); 2.55 (*dd*, $J = 15.4$, 5.7, 1 H, CH_2CO_2Me); 2.80 (*d*, $J = 5.6$, CH_2CH); 3.61 (*s*, MeO); 4.18–4.25 (br. *m*, CHN); 5.76 (br. *d*, NH); 6.60 (*s*, 1 Im H); 7.10–7.14 (*m*, 6 arom. H); 7.31–7.34 (*m*, 9 arom. H); 7.36 (*s*, 1 Im H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.42 (Me); 31.91, 38.16 (CH_2); 47.62 (CH); 51.54 (Me); 75.23, 79.04 (C); 119.89, 128.06, 129.75 (CH); 137.35 (C); 138.76 (CH); 142.45, 155.26, 172.09 (C). MALDI-MS: 564.2 (1.36), 548.2 (27.36), 526.3 (2.19), 448.2 (15.60), 243.1 (100.00). Anal. calc. for $C_{32}H_{35}N_3O_4$ (525.65): C 73.12, H 6.68, N 7.99; found: C 73.16, H 6.68, N 7.99.

(S)-3-{[(tert-Butoxy)carbonyl]amino}-4-[1-(triphenylmethyl)-1H-imidazol-4-yl]butanoic Acid (Boc-(*S*)-β^3hHis(Tr)-OH; **6**). Similar to the procedure reported in [117], a soln. of **5** (378 mg, 0.72 mmol) in MeOH (0.03M) was cooled to 0°, treated with 0.1M LiOH (11 ml, 1.5 equiv.), and stirred at this temp. for 7 h. The mixture was then neutralized by the addition of 10% aq. HCl soln., MeOH was removed under reduced pressure, and the aq. layer was extracted with AcOEt (4 ×). The combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield **6** (365 mg, quant.). White foam. The product was used in the next step without further purification. MALDI-MS: 550.2 (1.17), 534.2 (1.62), 518.2 (1.85), 410.0 (1.07), 243.1 (100.00). HR-MALDI-MS: 534.2136 ($C_{31}H_{33}N_3NaO_4^+$; calc. 534.2369).

(S)-4-(1H-Imidazol-4-yl-3-phthalimidobutanoic Acid Hydrochloride (Phth-(*S*)-β^3hHis-OH · HCl; **7**). Compound **3** (13.5 g, 47.6 mmol) was dissolved in CH_2Cl_2 (0.5M) and cooled to 0°. An equal volume of TFA and some drops of TIS (0.01 equiv.) were added, and the mixture was stirred for 4 h at 0° (TLC control). The solvent was evaporated, the residue was taken up in dried toluene or $CHCl_3$ and evaporated twice. The resulting trifluoroacetate salt was dried under h.v., identified by NMR, and used without further purification. A soln. of the trifluoroacetate salt in 1M NaOH (200 ml, 0.24M) was cooled to 0° and stirred overnight. The mixture was then acidified to pH 7 with 1M HCl and concentrated under reduced pressure. The oily residue was dissolved in H_2O (80 ml), and solid Na_2CO_3 (13.6 g, 1 equiv.) was added. Upon dissolution, $PhthNCO_2Et$ (10.4 g, 1 equiv.) was added at once, and the mixture was stirred for 2 h. The mixture was filtered, adjusted to pH 7 with 2M HCl, and concentrated under reduced pressure. The green residue was taken in 300 ml of MeOH, stirred for 20 min, and filtered. The MeOH soln. was evaporated, and the product was dissolved in H_2O, and the pH was adjusted to 1–2. The precipitate formed was collected by suction and washed with 2M HCl to yield **7** (10.7 g, 67%). Slightly brownish solid. The product was used in the next step without further purification. ^{1}H-NMR (300 MHz, CD_3OD): 2.80 (*dd*, *J* = 16.5, 6.0, 1 H, CH_2); 3.20–3.28 (*m*, CH_2); 3.46 (*dd*, *J* = 15.2, 10.4, 1 H, CH_2); 4.90–5.00 (*m*, CHN); 7.29 (*s*, 1 Im H); 7.80 (*s*, 4 Phth H); 8.76 (*s*, 1 Im H).

(S)-3-Phthalimido-4-[1-(triphenylmethyl)-1H-imidazol-4-yl]butanoic Acid (Phth-(*S*)-β^3hHis(Tr)-OH; **8**). To a suspension of **7** (10.1 g, 30 mmol) in $CHCl_3$/DMF 2:1 (0.5M), cooled to 0°, Et_3N (16.9 ml, 4 equiv.) and a soln. of TrBr (10.7 g, 1.1 equiv.) in $CHCl_3$/DMF 2:1 (70 ml) were added dropwise. After TLC control (5 h later), another portion of TrBr (9.77 g, 1 equiv.) was added as solid, and the mixture was stirred overnight. MeOH (100 ml) was then added, and the mixture was heated at 50° for 2 h. The solvent was removed under reduced pressure, the crude product was dissolved in AcOEt, and washed with 10% citric acid (3 ×) and sat. aq. NaCl soln. (1 ×). The org. phase was dried ($MgSO_4$) and concentrated under reduced pressure. FC (CH_2Cl_2 → AcOEt/AcOH 10:0.3) yielded **8** (12.3 g, 75%). White solid. R_f (CH_2Cl_2/ MeOH 9:1) 0.37. $[\alpha]_D^{r.t.} = -58.5$ (c = 1.04, $CHCl_3$). IR (neat): 3058*w*, 2930*w*, 2641*w*, 2323*w*, 2050*w*, 1982*w*, 1771*w*, 1705*s*, 1607*w*, 1491*w*, 1467*w*, 1444*w*, 1390*m*, 1369*m*, 1334*w*, 1284*w*, 1215*w*, 1186*w*, 1156*w*, 1131*w*, 1107*w*, 1087*w*, 1037*w*, 977*w*, 906*w*, 871*m*, 751*m*, 719*s*, 699*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.82 (*dd*, *J* = 15.5, 4.4, 1 H, CH_2CO_2H); 3.19 (*dd*, *J* = 15.5, 10.3, 1 H, CH_2CO_2H); 3.31 (*d*, *J* = 8.1, CH_2CH); 5.16–5.24 (br. *m*, CHN); 6.33 (*d*, *J* = 1.3, 1 Im H); 6.88 (*d*, *J* = 7.4, 6 arom. H); 7.10–7.14 (*m*, 6 arom. H); 7.19–7.23 (*m*, 3 arom. H); 7.53 (*d*, *J* = 1.3, 1 Im H); 7.69–7.75 (*m*, 4 Phth H). ^{13}C-NMR (100 MHz, $CDCl_3$): 29.42, 38.79 (CH_2); 48.92 (CH); 75.51 (C); 119.45, 123.22, 127.95, 128.00, 129.51 (CH); 131.82 (C); 133.71 (CH); 136.19 (C); 138.22 (CH); 141.74, 167.76, 173.43 (C). MALDI-MS: 586.2 (4.64), 564.2 (17.63), 322.1 (7.30), 300.1 (24.29), 243.1 (100.00). HR-MALDI-MS: 564.1896 ($C_{34}H_{27}N_3NaO_4^+$; calc. 564.1824).

(S)-3-({[(9H-Fluoren-9-yl)methoxy]carbonyl}amino)-4-[1-(triphenylmethyl)-1H-imidazol-4-yl]butanoic Acid (Fmoc-(*S*)-β^3hHis(Tr)-OH; **9**). To a suspension of **8** (10.7 g, 19.7 mmol) in EtOH (0.23M) a 1M N_2H_4 soln. in EtOH (19.7 ml, 1 equiv.) was added dropwise, and the mixture was stirred at r.t. for 4 h. The precipitate formed was filtered off and washed with EtOH. The solvent was evaporated, the crude product was dissolved in THF (200 ml) and placed in the fridge overnight. The precipitate formed was filtered, and the solvent was concentrated under reduced pressure to give the expected product. The crude product was Fmoc-protected according to *GP 4a*. FC (AcOEt/AcOH 10:0.3) and precipitation from hexane yielded **9** (10.1 g, 81%). White powder. R_f (CH_2Cl_2/ MeOH 9:1) 0.35. M.p. 125–127°. $[\alpha]_D^{r.t.} = -33.0$ (c = 1.01, $CHCl_3$). IR (neat): 3049*w*, 2930*w*, 2625*w*, 2455*w*, 2323*w*, 2051*w*, 1919*w*, 1716*s*, 1494*w*, 1446*m*, 1323*w*, 1245*m*, 1155*w*, 1129*w*, 1080*w*, 1044*m*, 873*w*, 757*s*, 740*s*, 700*s*, 661*w*, 638*w*. ^{1}H-NMR (400 MHz, CD_3OD): 2.53 (*d*, *J* = 6.2, CH_2); 2.76 (*dd*, *J* = 14.7, 9.4, 1 H, CH_2); 2.86 (*dd*, *J* = 14.7, 4.9, 1 H, CH_2); 4.04–4.08 (br. *t*, CH); 4.12–4.25 (*m*, 3 H, CH_2, CHN); 6.88 (*s*, 1 Im H); 7.06–7.08 (*m*, 6 arom. H); 7.24–7.38 (*m*, 13 arom. H); 7.56 (*d*, *J* = 7.5, 2 arom. H); 7.68 (*s*, 1 Im H); 7.78 (*d*, *J* = 7.5, 2 arom. H). ^{13}C-NMR (100 MHz, CD_3OD): 33.37, 40.33 (CH_2); 48.40, 48.80 (CH); 67.86 (CH_2); 77.70 (C); 120.93, 121.44, 126.25, 126.33, 128.13, 128.18, 128.73, 128.79, 129.35, 129.50, 129.84, 130.83 (CH); 137.05 (C); 138.82 (CH); 142.57, 143.04, 145.19, 145.31, 158.03, 174.73 (C). MALDI-MS: 656.3 (33.64), 414.1 (8.29), 392.2 (41.06), 243.1 (100.00). HR-MALDI-MS: 656.2518 ($C_{41}H_{35}N_3NaO_4^+$; calc. 656.2520).

(R)-1-Diazo-3-({[(9H-fluoren-9-yl)methoxy]carbonyl}amino)-4-{[(4-methoxy)benzyl]thio}butan-2-one (Fmoc-(*R*)-Cys(PMB)-CHN_2; **10**). Transformation of Fmoc-L-Cys(PMB)-OH (9.5 g, 20.5 mmol) according to *GP 1a* for 2 h, and FC (AcOEt/hexane 3:7) yielded **10** (9.6 g, 96%). Yellow solid. R_f (AcOEt/hexane 4:6) 0.20. M.p. 87–91° (dec.). IR ($CHCl_3$): 3429*w*, 3007*w*, 2975*w*, 2850*w*, 2112*s*, 1717*s*, 1609*m*, 1511*s*, 1450*m*, 1302*w*, 1248*s*, 1125*w*, 1036*w*, 823*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.76 (*d*, *J* = 5.6, CH_2); 3.68 (*s*, CH_2); 3.78 (*s*, Me); 4.22 (*t*, *J* = 6.7, $CHCH_2O$); 4.26–4.39 (*m*, CHN); 4.40–4.57 (*m*, CH_2O); 5.31 (*s*, CHN_2); 4.50 (*d*, *J* = 7.5, NH); 6.83 (*dd*, *J* = 6.5, 1.9, 2 arom. H); 7.22 (*d*, *J* = 8.1, 2 arom. H); 7.26–7.43 (*m*, 4 arom. H); 7.59 (*d*, *J* = 7.2, 2 arom. H); 7.77 (*d*,

$J = 7.5$, 2 arom. H). MALDI-MS: 482.1(30), 362 (15), 273 (100). HR-MALDI-MS: 482.1423 ($C_{27}H_{25}NNaO_4S^+$; calc. 482.1397).

*(*R*)-4-{[(Acetamido)methyl]thio}-1-diazo-3-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)butan-2-one* (Fmoc-(*R*)-Cys(Acm)-CHN_2; **11**). Transformation of Fmoc-L-Cys(Acm)-OH (7 g, 16.9 mmol) according to *GP 1a* for 4 h yielded crude **11** (7.4 g). Yellow solid. The crude product was used in the next step without further putification. The anal. data are in agreement with those reported in [98].

*(*R*)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-{[(4-methoxy)benzyl]thio}butanoic Acid* (Fmoc-(*R*)-β^3hCys(PMB)-OH; **12**). Similar to the procedure reported in [95], **10** (7.7 g, 15.8 mmol) was dissolved in THF/H_2O 8 : 2 (0.09M), and $PhCO_2Ag$ (0.9 g, 4.0 mmol) was added with exclusion of light. The mixture was ultrasonicated at r.t. for 6 h. THF was evaporated, the pH was adjusted to 1–2 with 1M HCl, and Et_2O was added. The precipitate formed was filtered off and dissolved in acetone, and the residual AgCl was filtered off over *Celite*. The aq. phase was extracted with Et_2O (5 ×); the combined org. layers were concentrated under reduced pressure to give a solid residue, which was crystallized from AcOEt/hexane affording **12** (5.8 g, 77%). White solid. R_f (AcOEt/hexane 4 : 6) 0.14. M.p. 110–112°. $[\alpha]_D^{r.t.} = -12.5$ ($c = 1.20$, $CHCl_3$). IR ($CHCl_3$): 3429*w*, 3007*w*, 2975*w*, 2850*w*, 1718*s*, 1610*m*, 1512*s*, 1450*m*, 1302*w*, 1248*s*, 1125*w*, 1036*w*, 823*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.65–2.74 (*m*, 2 CH_2); 3.68 (*s*, CH_2S); 3.76 (*s*, Me); 4.11–4.14 (*m*, CHN); 4.22 (*t*, $J = 6.8$, C*H*CH_2O); 4.40 (br. *s*, CH_2O); 5.25–5.31 (br. *d*, NH); 6.82 (*d*, $J = 7.6$, 2 arom. H); 7.20–7.24 (br. *d*, 2 arom. H); 7.30 (*dt*, $J = 7.4, 1.1$, 2 arom. H); 7.39 (*t*, $J = 7.4$, 2 arom. H); 7.58 (*d*, $J = 7.5$, 2 arom H.); 7.75 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 34.92, 35.79, 36.91 (CH_2); 47.21 (CH); 55.25 (Me); 66.88 (CH_2); 77.59, 114.00, 120.00, 125.07, 127.09 (CH); 129.68 (C); 130.04 (CH); 141.33, 143.81, 155.78, 158.74, 174.66 (C). HR-MALDI-MS: 500.1508 ($C_{27}H_{27}NNaO_5S^+$; calc. 500.1502). Anal. calc. for $C_{27}H_{27}NO_5S$ (477.16): C 67.90, H 5.70, N 2.93, O 16.75, S 6.71; found: C 67.87, H 5.86, N 2.94, S 6.65.

*(*R*)-4-{[(Acetamido)methyl]thio}-3-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)butanoic Acid* (Fmoc-(*R*)-β^3hCys(Acm)-OH; **13**). Similar to the procedure reported in [98], a degassed soln. of the crude **11** (7.4 g) in MeCN/H_2O 9 : 1 (33 ml/g) was irradiated with a low pressure Hg vapor lamp at 0° for 24–36 h. The solvent was evaporated, the yellow oily residue was dissolved in sat. aq. $NaHCO_3$ soln. (300 ml), and the mixture was extracted with Et_2O (5 × 100 ml). The aq. phase was carefully acidified to pH 1–2 with 1M HCl at 0°, and extracted with AcOEt (5 × 100 ml). The combined org. layers were concentrated under reduced pressure. Crystallization (AcOEt/MeOH) yielded pure **13** (3.2 g, 44% over 2 steps). White solid. R_f (AcOEt/MeOH/AcOH 90 : 10 : 2) 0.41. $[\alpha]_D^{r.t.} = -12.6$ ($c = 1.20$, $CHCl_3$). The anal. data are in agreement with those reported in [98].

*(*R*)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-[(triphenylmethyl)sulfanyl]butanoic Acid* (Fmoc-(*R*)-β^3hCys(Tr)-OH; **14**). *a*) Compound **12** (4.3 g, 9.0 mmol) and anisole (1.8 ml, 16.2 mmol) were dissolved in THF (0.1M), and carefully degassed with Ar. The soln. was cooled to 0°, $Hg(OAc)_2$ (2.9 g, 9.0 mmol) was added under Ar, and the mixture was stirred until disappearance of the starting material (TLC control, 30–45 min). THF was evaporated under reduced pressure in an O_2-free atmosphere at $T < 40°$, and the residue was dissolved in degassed THF/H_2O 1 : 1 (200 ml). H_2S Gas was bubbled into the mixture for 5 min, the black precipitate was filtered off on *Celite* under N_2, and washed with degassed THF/H_2O 1 : 1 (4 × 50 ml). THF was evaporated under reduced pressure in an O_2-free atmosphere, and the remaining aq. phase was extracted with degassed CH_2Cl_2. The combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure, in an O_2-free atmosphere. The crude Fmoc-(*R*)-β^3hCys-OH was immediately tritylated under Ar with NMM (2.9 ml, 3 equiv.) and TrCl (8.7 g, 3 equiv.) for 15 h according to *GP 3b*. FC ($CH_2Cl_2 \rightarrow CH_2Cl_2$/AcOH 50 : 1) and precipitation from CH_2Cl_2/hexane yielded **14** (4.4 g, 82%). White solid.

b) Compound **13** (1.4 g, 3.3 mmol) was dissolved in THF/H_2O/AcOH 2 : 1 : 1 (0.04M) and carefully degassed with Ar. A degassed soln. of $Hg(OAc)_2$ (1.05 g, 3.3 mmol) in THF/H_2O/AcOH 2 : 1 : 1 (0.3M) was added dropwise over 2 min at r.t. The white suspension was stirred until complete disappearance of the starting material (TLC control, 30–45 min). H_2S Gas was bubbled into the mixture for 5 min, the black precipitate formed was then filtered off on *Celite* under N_2 and washed with degassed THF/H_2O/AcOH 2 : 1 : 1 (2 × 50 ml). THF was evaporated under reduced pressure in an O_2-free atmosphere, and the remaining aq. phase was extracted with degassed $CHCl_3$ (3 × 50 ml). The combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure, in an O_2-free atmosphere. The crude Fmoc-(*R*)-β^3hCys-OH was immediately tritylated under Ar with NMM (1.07 ml, 3 equiv.) and TrCl (3.3 g, 3 equiv.) for 15 h according to *GP 3b*. FC ($CH_2Cl_2 \rightarrow CH_2Cl_2$/AcOH 50 : 1) and precipitation from CH_2Cl_2/hexane yielded **14** (1.1 g, 56%). White solid.

Data of **14**: R_f (CH_2Cl_2/AcOH 50 : 1) 0.25. M.p. 88–90°. $[\alpha]_D^{r.t.} = +28.9$ ($c = 1.00$, MeOH). IR ($CHCl_3$): 3008*w*, 1719*s*, 1508*m*, 1448*m*, 1248*s*, 1036*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.49–2.52 (*m*, 2 CH_2); 3.75–3.88 (*m*, CHN); 4.18 (*t*, *J* = 6.7, C*H*CH$_2$O); 4.36 (*d*, *J* = 6.7, CH$_2$O); 4.90–4.98 (br. *d*, NH); 7.18–7.21 (*m*, 3 arom. H); 7.24–7.29 (*m*, 8 arom. H); 7.35–7.40 (*m*, 8 arom. H); 7.55 (*d*, *J* = 7.4, 2 arom. H); 7.74 (*dd*, *J* = 7.4, 3.8, 2 arom. H). ^{13}C-NMR (100 MHz, CDCl$_3$): 31.69, 35.82, 37.37 (CH$_2$); 47.22 (CH); 67.19 (C); 77.22, 119.98, 125.04, 126.88, 127.07, 127.71, 128.02, 129.57 (CH); 141.33, 143.81, 144.46, 155.50, 173.95 (C). MALDI-TOF-MS: 622.0 (100.00). Anal. calc. for $C_{38}H_{33}NO_4S$ (599.7): C 76.10, H 5.55, N 2.34, O 10.67, S 5.35; found: C 76.14, H 5.71, N 2.34, S 5.35.

3-Phthalimidopropanoic Acid (Phth-*β*hGly-OH; **15**). A mixture of phthalic anhydride (14.8 g, 0.10 mol) and H-*β*hGly-OH (8.9 g, 1 equiv.) was heated in an open flask to 150° for 2 h. On cooling to r.t., H$_2$O (150 ml) was added, and the solid was filtered and washed with additional H$_2$O. The solid was dried (h.v.) to yield **15** (20.6 g, 94%). White solid. The product was used in the next step without further purification. ^{1}H-NMR (300 MHz, CDCl$_3$): 2.76 (*t*, *J* = 4.0, CH$_2$CO$_2$H); 3.98 (*t*, *J* = 4.1, CH$_2$N); 7.68–7.72 (*m*, 2 Phth H); 7.81–7.85 (*m*, 2 Phth. H).

*(*S*)-4-(1-Methylethyl)-3-(3-phthalimidopropanoyl)-5,5-diphenyloxazolidin-2-one* (**18**). To a soln. of **15** (20.6 g, 94.2 mmol) in CH$_2$Cl$_2$ (300 ml) was added a few drops of dioxane, followed by (COCl)$_2$ (10.5 ml, 1.3 equiv.), and the suspension stirred under Ar at r.t. overnight. The resulting soln. was concentrated under reduced pressure to give the crude acyl chloride **16** (22.4 g, quant.), which was used in the next step without further purification. White solid. ^{1}H-NMR (300 MHz, CDCl$_3$): 3.35 (*t*, *J* = 7.0, CH$_2$COCl); 4.00 (*t*, *J* = 7.0, CH$_2$N); 7.72–7.74 (*m*, 2 Phth H); 7.84–7.87 (*m*, 2 Phth H).

Similar to the procedure reported in [64], to an ice-bath-cooled suspension of the auxiliary (*S*)-**17** (22.1 g, 78.5 mmol, 1 equiv.) in THF (315 ml, 0.25M), BuLi (1.6M in hexane, 49.5 ml, 1 equiv.) was added slowly. To the resulting clear soln., the acyl chloride **16** was added in one portion. Stirring was continued for 2 d as the mixture was slowly allowed to warm to r.t. The mixture was treated with sat. aq. NH$_4$Cl soln., and diluted with Et$_2$O. The org. phase was washed with 1M HCl (2 ×), 1M NaOH (2 ×), and sat. aq. NaCl soln., dried (MgSO$_4$), and concentrated under reduced pressure. FC (Et$_2$O/pentane 1 : 1) afforded **18** (32.6 g, 86%). White solid. The anal. data are in agreement with those reported in [64].

*(4*S*)-3-[(2*R*)-3-Hydroxy-2-(phthalimidomethyl)propanoyl]-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one* (**19**). Compound **18** (7.00 g, 14.5 mmol) was transformed according to *GP 5a* for 2–3 h. Crystallization (AcOEt/hexane) and FC (Et$_2$O/pentane 2 : 1) of the crude product yielded **19** (12.9 g, 89%). White solid. The anal. data are in agreement with those reported in [64].

*(4*S*)-3-[(2*R*)-3-(*tert*-Butoxy)-2-(phthalimidomethyl)propanoyl]-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one* (**20**). A soln. of **19** (5.89 g, 11.5 mmol) in CH$_2$Cl$_2$ (0.23 M) was cooled to – 50° under Ar, and isobutylene (20 ml) and conc. H$_2$SO$_4$ (50 µl) were added. The reaction flask (*Schott* bottle) was hermetically closed, warmed to r.t., and the mixture was stirred for 3 d at r.t. The mixture was cooled again to – 50°, opened to the air, slowly warmed up to r.t., treated with sat. aq. Na$_2$CO$_3$ soln. (200 ml), and diluted with Et$_2$O (400 ml). The org. phase was washed with sat. aq. NaCl soln., dried (MgSO$_4$), and concentrated under reduced pressure. FC (Et$_2$O/pentane 1 : 2 → 2 : 1) of the crude product yielded **20** (6.20 g, 95%). White solid. R_f (Et$_2$O/pentane 1 : 2) 0.22. M.p. 149–150°. $[\alpha]_D^{r.t.} = -116.6$ ($c = 1.01$, CHCl$_3$). IR (CHCl$_3$): 2975*w*, 1776*s*, 1718*s*, 1468*w*, 1450*w*, 1395*m*, 1364*m*, 1177*m*, 1094*w*, 991*w*. ^{1}H-NMR (400 MHz, CDCl$_3$): 0.75 (*d*, *J* = 6.7, Me); 0.93 (*d*, *J* = 7.1, Me); 1.12 (*s*, ^{t}Bu); 1.89–1.97 (*m*, Me$_2$CH); 3.68 (*dd*, *J* = 8.8, 6.0, 1 H, CH$_2$); 3.78 (*dd*, *J* = 8.8, 4.7, 1 H, CH$_2$); 3.87 (*dd*, *J* = 13.9, 6.4, 1 H, CH$_2$); 3.94 (*dd*, *J* = 13.9, 6.5, 1 H, CH$_2$); 4.33–4.39 (*m*, C*H*CH$_2$); 5.48 (*d*, *J* = 2.7, CHN); 7.12–7.42 (*m*, 10 arom. H); 7.66–7.69 (*m*, 2 Phth H); 7.72–7.75 (*m*, 2 Phth H). ^{13}C-NMR (100 MHz, CDCl$_3$): 15.89, 21.78, 27.33 (Me); 30.27 (CH); 36.62 (CH$_2$); 43.61 (CH); 61.51 (CH$_2$); 64.10 (CH); 73.31, 89.11 (C); 123.25, 125.66, 125.89, 127.80, 128.30, 128.37, 128.70 (CH); 132.02 (C); 133.70 (CH); 138.45, 142.20, 152.52, 167.86, 172.09 (C). MALDI-MS: 607.2 (4.52), 591.2 (100.00), 547.3 (25.27), 469.2 (10.61), 451.2 (11.05), 238.2 (8.98). Anal. calc. for $C_{34}H_{36}N_2O_6$ (568.67): C 71.81, H 6.38, N 4.93; found: C 71.65, H 6.31, N 4.95.

*Benzyl (*R*)-3-(*tert*-Butoxy)-2-(phtalimidomethyl)propanoate* (Phth-(*R*)-*β*^{2}hSer(^{t}Bu)-OBn; **21**). To a soln. of BnOH (1.72 µl, 16 mmol) in THF (25 ml), BuLi (1.6M in hexane, 6.88 ml, 11 mmol) was added at – 10°, and the mixture was stirred for 20 min. After cooling to – 30°, a soln. of **20** (2.46 g, 4.32 mmol) in THF (15 ml) was added dropwise, and the mixture was stirred at – 30° for 8 h. Sat. aq. NH$_4$Cl soln. (20 ml) was added, THF was removed under reduced pressure, and the mixture was diluted with Et$_2$O (50 ml). The suspension was stirred for 15 min, and the white solid was filtered off. The residue was washed with Et$_2$O, then dried (h.v.) to yield (*S*)-**17** (1.09 g). White solid. The filtrate was diluted with Et$_2$O, the aq. phase was separated, and the org. phase was washed with sat. aq. NaCl soln., dried (MgSO$_4$), and concentrated under reduced pressure. FC (Et$_2$O/pentane 1 : 2 → 1 : 1) of the crude product yielded **21** (1.36 g, 80%) with e.r. > 95 : 5. Colorless oil. R_f (Et$_2$O/pentane 1 : 2.5) 0.22. $[\alpha]_D^{r.t.} = +4.5$ ($c = 1.00$, CHCl$_3$). IR (CHCl$_3$): 2976*w*, 1774*w*, 1716*s*, 1469*w*, 1438*w*, 1395*m*, 1365*m*, 1177*w*, 1088*w*. ^{1}H-NMR (400 MHz, CDCl$_3$): 1.07 (*s*, ^{t}Bu); 3.16–3.22 (*m*, CH); 3.60 (*ddd*, *J* = 13.1, 8.8, 5.9, CH$_2$); 4.01 (*ddd*, *J* = 17.6, 13.9, 7.1, CH$_2$); 5.08 (*d*, *J* = 12.3, 1 H, PhC*H*$_2$); 5.15 (*d*, *J* = 12.3, 1 H, PhC*H*$_2$); 7.26–7.31 (*m*, 5 arom. H); 7.68 – 7.70 (*m*, 2 Phth H); 7.80 – 7.82 (*m*, 2 Phth H). ^{13}C-NMR (100 MHz, $CDCl_3$): 27.22 (Me); 37.14 (CH_2); 45.10 (CH); 60.66, 66.61 (CH_2); 73.12 (C); 123.27, 128.08, 128.21, 128.41 (CH); 132.09 (C); 133.88 (CH); 135.77, 168.13, 171.82 (C). MALDI-MS: 434.1 (2.68), 418.2 (100.00), 322.1 (8.37). Anal. calc. for $C_{23}H_{25}NO_5$ (395.45): C 69.86, H 6.37, N 3.54; found: C 69.86, H 6.44, N 3.38.

*Benzyl (*R*)-2-(Aminomethyl)-3-(*tert*-butoxy)propanoate* (H-(*R*)-β^{2}hSer(^{t}Bu)-OBn; **22**). Compound **21** (190 mg, 0.48 mmol) was Phth-deprotected according to *GP 7* for 1 h. FC ($CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 95 : 5) of the crude product yielded **22** (100 mg, 78%). Colorless oil. R_f (CH_2Cl_2/MeOH 9 : 1) 0.13. $[\alpha]_D^{r.t.} = +11.2$ ($c = 0.40$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.14 (*s*, ^{t}Bu); 1.41 (*m*, NH_2); 2.71 – 2.68 (*m*, C*H*CH_2); 2.96 (*dd*, J = 13.0, 5.1, 1 H, CH_2); 3.03 (*dd*, J = 13.0, 7.2, 1 H, CH_2) ; 3.55 (*dd*, J = 8.8, 6.5, 1 H, CH_2); 3.61 (*dd*, J = 8.8, 6.1, 1 H, CH_2); 5.17 (*d*, J = 12.4, PhCH_2); 7.37 – 7.29 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 27.35 (Me); 41.52 (CH_2); 49.82 (CH); 60.71, 66.12 (CH_2); 73.04 (C); 128.07, 128.12, 125.51 (CH); 136.09, 173.42 (C). HR-MALDI-MS: 266.1749 ($C_{15}H_{24}NO_3^+$; calc. 266.1757).

*(*R*)-3-(*tert*-Butoxy)-2-[({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)methyl]propanoic Acid* (Fmoc-(*R*)-*β*^{2}hSer(^{t}Bu)-OH; **23**). Transformation of compound **22** (1.10 g, 4.15 mmol) in MeOH (0.17 M) according to *GP 6a* for 2 h gave crude **23** (720 mg, quant.). White solid. Part of the solid (370 mg, 2.11 mmol) was then Fmoc-protected according to *GP 4b* for 4 h. FC (AcOEt/pentane/AcOH 3 : 7 : 0.02) of the crude product yielded **23** (675 mg, 80%). White solid. R_f (AcOEt/hexane/AcOH 1 : 1 : 0.01) 0.27. M.p. 59 – 62°. IR ($CHCl_3$): 3446*w*, 2974*m*, 1753*m*, 1718*s*, 1513*s*, 1446*m*, 1364*m*, 1267*w*, 1092*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.24 (*s*, ^{t}Bu); 2.85 – 2.75 (*m*, C*H*CO_2H); 3.60 – 3.45 (*m*, CH_2); 3.60 – 3.56 (*m*, 1 H, CH_2); 3.70 (*dd*, J = 8.8, 5.4, 1 H, CH_2); 4.21 (*t*, J = 7.1, C*H*CH_2O); 4.38 (*d*, J = 7.1, CHC*H*$_2$O); 5.46 – 5.45 (br. *t*, NH); 7.31 (*t*, J = 7.4, 2 arom. H); 7.40 (*t*, J = 7.4, 2 arom. H); 7.58 (*d*, J = 7.4, 2 arom. H); 7.76 (*d*, J = 7.4, 2 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 27.29 (Me); 39.59 (CH_2); 45.57, 47.20 (CH); 60.45, 66.89 (CH_2); 75.20 (C); 120.00, 125.06, 127.06, 127.71 (CH); 141.32, 143.85, 143.89, 156.58, 174.69 (C). MALDI-MS: 442.2 (10.24), 421.2 (25.30), 420.2 (100.00), 364.1 (21.95). HR-MALDI-MS: 420.1782 ($C_{23}H_{27}NNaO_5^+$; calc. 420.1785). Anal. calc. for $C_{23}H_{27}NO_5$ (397.47): C 69.50, H 6.85, N 3.52; found : C 69.22, H 7.21, N 3.28.

*Benzyl (*R*)-3-(*tert*-Butoxy)-2-[(2,4-dinitrophenyl)amino]propanoate* (**24**). Compound **21** (100 mg, 0.25 mmol) was Phth-deprotected according to *GP 7* for 2 h. FC (CH_2Cl_2) afforded an oily residue that was suspended in H_2O at 0°. Then, $NaHCO_3$ (25 mg, 1.2 equiv.) and a soln. of 1-fluoro-2,4-dinitrobenzene (54 mg, 1.2 equiv.) in EtOH (0.5 ml) were added to the mixture. After 10 min stirring at 0°, sat. aq. NH_4Cl soln. (5 ml) and Et_2O (10 ml) were added to the mixture. The org. phase was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure. FC (Et_2O/pentane 1 : 2 → 2 : 1) of the crude product yielded **24** (63 mg, 55%). Yellow oil. R_f (Et_2O/pentane 1 : 3) 0.28. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.18 (*s*, ^{t}Bu); 3.03 – 2.97 (*m*, C*H*CH_2); 3.76 – 3.63 (*m*, CH_2); 3.85 – 3.78 (*m*, CH_2); 5.20 – 5.15 (*m*, PhCH_2); 7.02 (*d*, J = 9.7, 1 arom. H); 7.35 – 7.30 (*m*, 5 arom. H); 8.20 (*dd*, J = 9.7, 2.8, 1 arom. H); 8.93 – 8.90 (*m*, NH); 9.10 (*d*, J = 2.8, 1 arom. H). HR-MALDI-MS: 454.1580 ($C_{21}H_{25}N_3NaO_7^+$; calc. 454.1591).

*(4*S*)-4-(1-Methylethyl)-5,5-diphenyl-3-{(2*S*)- and (2*R*)-2-(phthalimidomethyl)-3-[(triphenylmethyl)sulfanyl]propanoyl}oxazolidin-2-one* (**25**). Bu_3P (6.91 ml, 2.1 equiv.) was added dropwise at r.t. under Ar to a soln. of the (2′*S*,4*S*)-**19** (6.70 g, 13.1 mmol) and Ph_3CSH (6.30 g, 2.6 equiv.) in anh. THF (300 ml). Then, ADDP (6.91 g, 2.1 equiv.) was added as a solid in one portion. The mixture was stirred at r.t. under Ar for 1 h, as the color of the mixture changed from yellow to colorless, and a white precipitate was formed. Hexane (50 ml) was added, and the white precipitate was filtered off (auxiliary) and washed with hexane. The filtrate was then evaporated under reduced pressure. FC (Et_2O/pentane 1 : 2 → 1 : 1) of the crude product yielded first (2′*R*,4*S*)-**25** (1.60 g, 16%) and then (2′*S*,4*S*)-**25** (7.10 g, 71%). White foams.

*Data of (2′*R*,4*S*)*-**25**: R_f (Et_2O/pentane 1 : 2) 0.24. M.p. 151 – 154°. $[\alpha]_D^{r.t.} = -170$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3062*w*, 3008*w*, 1781*s*, 1717*s*, 1493*w*, 1469*w*, 1448*w*, 1395*m*, 1366*m*, 1322*w*, 1175*m*, 990*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.66 (*d*, J = 7.0, Me); 0.88 (*d*, J = 7.0, Me); 1.83 (*m*, Me_2C*H*); 2.03 (*dd*, J = 12.8, 4.0, 1 H, CH_2S); 2.83 (*dd*, J = 12.8, 10.6, 1 H, CH_2S); 2.92 (*m*, C*H*CH_2); 3.60 (*dd*, J = 14.1, 6.1, 1 H, CH_2N); 3.77 (*dd*, J = 14.1, 4.3, 1 H, CH_2N); 5.27 (*d*, J = 2.5, CHN); 6.72 – 6.76 (*m*, 1 arom. H); 6.88 – 6.93 (*m*, 2 arom. H); 7.06 – 7.32 (*m*, 20 arom. H); 7.60 – 7.63 (*m*, 2 Phth H); 7.71 – 7.74 (*m*, 2 Phth H). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.60, 21.26 (Me); 30.08 (CH); 31.84, 39.23 (CH_2); 43.51, 65.00 (CH); 66.93, 89.88 (C); 123.24, 125.80, 125.85, 126.55, 127.78, 127.85, 128.07, 128.28, 128.51, 128.66, 129.53 (CH); 132.06 (C); 133.85 (CH); 138.47, 141.86, 144.43, 152.54, 167.71, 172.19 (C). MALDI-MS: 795.3 (18.70), 794.3 (53.81), 793.3 (100.00), 473.2 (27.80). HR-MALDI-MS: 793.2715 ($C_{49}H_{42}N_2NaO_5S^+$; calc. 793.2712). Anal. calc. for $C_{49}H_{42}N_2O_5S$ (770.93): C 76.34, H 5.49, N 3.63, S 4.16; found : C 76.30, H 5.77, N 3.64, S 4.12.

*Data of (2′*S*,4*S*)*-**25**: R_f (Et_2O/pentane 1 : 2) 0.18. M.p. 188 – 189°. $[\alpha]_D^{r.t.} = -54$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3006*w*, 1778*s*, 1719*s*, 1493*w*, 1469*w*, 1449*w*, 1394*m*, 1363*m*, 1319*w*, 1085*w*, 1053*w*, 991*m*. ^{1}H-NMR

(400 MHz, $\mathrm{CDCl_3}$): 0.7 (*d*, *J* = 6.9, Me); 0.9 (*d*, *J* = 6.9, Me); 1.92 (*m*, $\mathrm{Me_2C}$*H*); 2.28 (*dd*, *J* = 11.9, 5.9, 1 H, $\mathrm{CH_2S}$); 2.66 (*dd*, *J* = 11.9, 7.9, 1 H, $\mathrm{CH_2S}$); 3.48 (*dd*, *J* = 13.8, 5.8, 1 H, $\mathrm{CH_2N}$); 3.68 (*dd*, *J* = 13.8, 7.3, 1 H, $\mathrm{CH_2N}$); 4.30 (*m*, C*H*$\mathrm{CH_2}$); 5.36 (*d*, *J* = 2.9, CHN); 6.95 – 7.43 (*m*, 25 arom. H); 7.67 – 7.68 (*m*, 4 Phth H). ^{13}C-NMR (100 MHz, $\mathrm{CDCl_3}$): 16.16, 21.69 (Me); 30.07 (CH); 32.54, 38.62 ($\mathrm{CH_2}$); 41.75, 64.70 (CH); 67.11, 89.16 (C); 123.31, 125.48, 125.84, 126.63, 127.87, 128.25, 128.32, 128.56, 129.60 (CH); 131.83 (C); 133.66 (CH); 138.19, 142.05, 144.41, 152.18, 167.34, 172.05 (C). MALDI-MS: 795.3 (18.90), 794.3 (55.23), 793.2 (100.00), 473.2 (34.14), 243.1 (22.83). HR-MALDI-MS: 793.2715 ($\mathrm{C_{49}H_{42}N_2NaO_5S^+}$; calc. 793.2712). Anal. calc. for $\mathrm{C_{49}H_{42}N_2O_5S}$ (770.93): C 76.34, H 5.49, N 3.63, S 4.16; found: C 76.28, H 5.61, N 3.59, S 4.03.

*2-(Trimethylsilyl)ethyl (*S*)-2-(Phthalimidomethyl)-3-[(triphenylmethyl)sulfanyl]propanoate* (**26**). To a soln. of 2-(trimethylsilyl)ethanol (2.0 ml, 14.02 mmol) in THF (60 ml), BuLi (1.6M in hexane; 6.72 ml, 10.75 mmol) was added dropwise at – 40°, and the mixture was stirred for 15 min at – 30°. After cooling to – 40°, a soln. of (2′*S*,4*S*)-**25** (3 g, 3.89 mmol) in THF (16 ml) was added dropwise, and the mixture was stirred for 30 min at – 40°. At this point, the soln. was slowly warmed to – 30° and stirred for additional 5 h. The reaction was monitored by TLC in order to limit the degradation formed during the reaction. As soon as degradation occurred, the reaction was quenched although not completed. Sat. aq. $\mathrm{NH_4Cl}$ soln. (200 ml) and $\mathrm{Et_2O}$ (400 ml) were added, the formed white precipitate was filtered off (free auxiliary), and the aq. phase was re-extracted with $\mathrm{Et_2O}$ (400 ml). The org. layers were washed with sat. aq. NaCl soln., dried ($\mathrm{MgSO_4}$), and concentrated under reduced pressure. FC ($\mathrm{Et_2O}$/pentane 1 : 3 → 1 : 2) of the crude product yielded, besides the unreacted starting material **25** (809 mg, 27%), (*S*)-**26** (1.3 g, 55%). Colorless oil. R_f ($\mathrm{Et_2O}$/pentane 1 : 2) 0.46. $[\alpha]_D^{r.t.} = +20$ (*c* = 2.85, $\mathrm{CHCl_3}$). IR ($\mathrm{CHCl_3}$): 3007*w*, 2956*w*, 1775*m*, 1719*s*, 1489*w*, 1469*w*, 1443*w*, 1396*m*, 1361*m*. ^{1}H-NMR (400 MHz, $\mathrm{CDCl_3}$): – 0.03 (*s*, 3 Me); 0.81 – 0.87 (*m*, $\mathrm{CH_2Si}$); 2.15 (*dd*, *J* = 12.3, 5.22, 1 H, $\mathrm{CH_2S}$); 2.55 – 2.61 (*m*, C*H*$\mathrm{CH_2}$); 2.66 (*dd*, *J* = 12.3, 8.7, 1 H, $\mathrm{CH_2S}$); 3.60 (*dd*, *J* = 13.8, 6.7, 1 H, $\mathrm{CH_2N}$); 3.73 (*dd*, *J* = 13.8, 7.3, 1 H, $\mathrm{CH_2N}$); 4.04 – 4.12 (*m*, $\mathrm{CH_2O}$); 7.08 – 7.12 (*m*, 3 arom. H); 7.16 – 7.24 (*m*, 6 arom. H); 7.32 – 7.36 (*m*, 6 arom. H); 7.67 – 7.70 (*m*, 2 Phth H); 7.77 – 7.80 (*m*, 2 Phth H). ^{13}C-NMR (100 MHz, $\mathrm{CDCl_3}$): – 1.52 (Me); 17.20, 31.24, 39.08 ($\mathrm{CH_2}$); 44.55 (CH); 63.48 ($\mathrm{CH_2}$); 67.15 (C); 123.32, 126.66, 127.86, 129.60 (CH); 132.00 (C); 133.94 (CH); 144.51, 167.69, 171.99 (C). MALDI-MS: 793.3 (17.80), 632.2 (12.91), 631.2 (44.14), 630.2 (100.00), 602.2 (18.04), 358.1 (20.33), 244.1 (12.73). HR-MALDI-MS: 630.2112 ($\mathrm{C_{36}H_{37}NNaO_4SSi^+}$; calc. 630.2111). Anal. calc. for $\mathrm{C_{36}H_{37}NO_4SSi}$ (607.84): C 71.14, H 6.14, N 2.30, S 5.28; found: C 71.19, H 6.23, N 2.39, S 5.37.

*2-(Trimethylsilyl)ethyl (*S*)-2-Aminomethyl-3-[(triphenylmethyl)sulfanyl]propanoate* (H-(*S*)-β^2hCys(Tr)-$\mathrm{O(CH_2)_2SiMe_3}$; **27**). Compound **26** (1.52 g, 2.5 mmol) was Phth-deprotected according to *GP 7* for 1 h. FC ($\mathrm{CH_2Cl_2}$ → $\mathrm{CH_2Cl_2}$/MeOH 95 : 5) of the crude product yielded **27** (1.02 g, 85%). Colorless oil. R_f ($\mathrm{CH_2Cl_2}$/MeOH 9 : 1) 0.62. $[\alpha]_D^{r.t.} = +17$ (*c* = 3.15, $\mathrm{CHCl_3}$). IR ($\mathrm{CHCl_3}$): 3063*w*, 3007*w*, 2956*s*, 1720*s*, 1595*w*, 1489*m*, 1443*m*, 1385*w*, 1170*m*. ^{1}H-NMR (400 MHz, $\mathrm{CDCl_3}$): 0.03 (*s*, 3 Me); 0.93 – 1.00 (*m*, $\mathrm{CH_2Si}$, $\mathrm{NH_2}$); 2.15 – 2.20 (*m*, C*H*$\mathrm{CH_2}$); 2.27 (*dd*, *J* = 12.18, 6.93, 1 H, $\mathrm{CH_2S}$); 2.57 (*dd*, *J* = 12.18, 7.0, 1 H, $\mathrm{CH_2S}$); 2.70 – 2.82 (*m*, $\mathrm{CH_2N}$); 4.13 – 4.18 (*m*, $\mathrm{CH_2O}$); 7.18 – 7.30 (*m*, 9 arom. H); 7.40 – 7.44 (*m*, 6 arom. H). ^{13}C-NMR (100 MHz, $\mathrm{CDCl_3}$): – 1.48 (Me); 17.42, 30.88, 43.28 ($\mathrm{CH_2}$); 48.50 (CH); 62.98 ($\mathrm{CH_2}$); 66.92 (C); 126.72, 127.84, 127.92, 129.63 (CH); 144.63, 173.59 (C). MALDI-MS: 501.2 (19.28), 500.2 (55.16), 244.1 (15.31), 243.1 (100.00). HR-MALDI-MS: 500.2054 ($\mathrm{C_{28}H_{35}NNaO_2SSi^+}$; calc. 500.2056). Anal. calc. for $\mathrm{C_{28}H_{35}NO_2SSi}$ (477.74): C 70.40, H 7.38, N 2.93, S 6.71; found: C 70.50, H 7.19, N 3.23, S 6.61.

*2-(Trimethylsilyl)ethyl (*S*)-2-({[(*tert*-Butoxy)carbonyl]amino}methyl)-3-[(triphenylmethyl)sulfanyl]propanoate* (Boc-(*S*)-β^2hCys(Tr)-$\mathrm{O(CH_2)_2SiMe_3}$; **28**). A soln. of di(*tert*-butyl) dicarbonate (510 mg, 2.33 mmol) in dioxane (10 ml) was added to a soln. of **27** (1.00 g, 2.09 mmol) in MeOH (50 ml) at r.t. under Ar. The mixture was stirred for 2 h. Then, sat. aq. $\mathrm{NH_4Cl}$ soln. (40 ml) and AcOEt (80 ml) were added, the org. phase was separated, and the aq. phase was re-extracted with AcOEt (80 ml). The combined org. layers were washed with sat. aq. NaCl soln., dried ($\mathrm{MgSO_4}$), and concentrated under reduced pressure. FC ($\mathrm{Et_2O}$/pentane 1 : 5) of the crude product yielded **28** (1.02 g, 85%). Colorless oil. R_f ($\mathrm{Et_2O}$/pentane 1 : 5) 0.28. $[\alpha]_D^{r.t.} = +0.5$ (*c* = 2.90, $\mathrm{CHCl_3}$). IR ($\mathrm{CHCl_3}$): 3454*w*, 3063*w*, 3007*m*, 2956*m*, 1713*s*, 1595*w*, 1505*s*, 1444*w*, 1392*w*, 1368*w*, 1165*s*. ^{1}H-NMR (400 MHz, $\mathrm{CDCl_3}$): 0.03 (*s*, 3 Me); 0.93 – 1.00 (*m*, $\mathrm{CH_2Si}$); 1.39 (*s*, ^{t}Bu); 2.28 – 2.34 (*m*, 2 H); 2.48 – 2.51 (*m*, 1 H); 3.16 – 3.23 (*m*, 2 H); 4.12 – 4.18 (*m*, $\mathrm{CH_2O}$); 4.50 (*m*, NH); 7.18 – 7.24 (*m*, 3 arom. H); 7.25 – 7.30 (*m*, 6 arom. H); 7.36 – 7.43 (*m*, 6 arom. H). ^{13}C-NMR (100 MHz, $\mathrm{CDCl_3}$): – 1.48 (Me); 17.38 ($\mathrm{CH_2}$); 28.35 (Me); 31.00, 41.09 ($\mathrm{CH_2}$); 45.19 (CH); 63.28 ($\mathrm{CH_2}$); 66.91, 79.30 (C); 126.73, 127.94, 129.62 (CH); 144.54, 155.55, 173.02 (C). MALDI-MS: 601.3 (41.90), 600.3 (100.00), 545.2 (20.28), 544.2 (54.52), 500.2 (44.51), 243.1 (56.34). HR-MALDI-MS: 600.2580 ($\mathrm{C_{33}H_{43}NNaO_4SSi^+}$; calc. 600.2580). Anal. calc. for $\mathrm{C_{33}H_{43}NO_4SSi}$ (577.86): C 68.59, H 7.50, N 2.42, S 5.55; found: C 68.57, H 7.28, N 2.62, S 5.38.

*(*S*)-2-({[(*tert*-Butoxy)carbonyl]amino}methyl)-3-[(triphenylmethyl)sulfanyl]propanoic Acid* (Boc-(*S*)-β^2hCys(Tr)-OH; **29**). A soln. of $\mathrm{Bu_4NF \cdot 3\ H_2O}$ (1.0 g, 3.17 mmol) in THF (5 ml) was added dropwise to a

soln. of **28** (950 mg, 1.64 mmol) in THF (20 ml) at 0°. The mixture was then slowly warmed up to r.t. and stirred for 4 h. Sat. aq. NH_4Cl soln. (40 ml) and AcOEt (80 ml) were added, and the aq. phase was extracted. Then, the pH of the aq. phase was adjusted to 5 by addition of a 1M HCl and extracted again with AcOEt (80 ml). Subsequently, the pH of the aq. phase was adjusted to 1 by addition of 1M HCl and extracted again with AcOEt (80 ml). The combined org. layers were washed with sat aq. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure. 2 FC ($CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 95 : 5) and (AcOEt/hexane/AcOH 1 : 2 : 0.01 → 1 : 1 : 0.01) of the crude product yielded **29** (657 mg, 84%). Slightly yellow foam. R_f (AcOEt/hexane/AcOH 1 : 2 : 0.01) 0.28. $[\alpha]_D^{r.t.} = +5$ ($c = 0.55$, $CHCl_3$). IR ($CHCl_3$): 3453*w*, 3060*w*, 2980*w*, 2933*w*, 1711*s*, 1600*m*, 1506*s*, 1444*m*, 1393*w*, 1368*m*, 1166*s*, 1084*s*, 1036*s*. ^{1}H-NMR (400 MHz, CD_3OD): 1.34 (*s*, ^{t}Bu); 2.20 – 2.25 (*m*, 1 H); 2.25 – 2.31 (*m*, 1 H); 2.45 (*dd*, $J = 11.6$, 7.9, 1 H); 3.05 – 3.09 (*m*, 2 H); 7.14 – 7.20 (*m*, 3 arom. H); 7.21 – 7.24 (*m*, 6 arom. H); 7.32 – 7.36 (*m*, 6 arom. H). ^{13}C-NMR (100 MHz, CD_3OD): 28.74 (Me); 32.51, 42.77 (CH_2); 47.16 (CH); 67.92, 80.18 (C); 127.80, 128.92, 130.77 (CH); 146.10, 158.10, 176.75 (C). MALDI-MS: 522.2 (6.10), 500.2 (7.33), 273.0 (17.74), 243.1 (100.00). HR-MALDI-MS: 500.1900 ($C_{28}H_{31}NNaO_4S^+$; calc. 500.1872). Anal. calc. for $C_{28}H_{31}NO_4S$ (477.62): C 70.41, H 6.54, N 2.93, S 6.71; found: C 70.63, H 6.63, N 2.90, S 6.57.

*Methyl (*S*)-2-({[(*tert*-Butoxy)carbonyl]amino}methyl)-3-[(triphenylmethyl)sulfanyl]propanoate* (Boc-(*S*)-β^2hCys(Tr)-OMe; **30**). To a soln. of **29** (48 mg, 0.1 mmol) in MeOH (2 ml) and toluene (0.7 ml) at r.t., $TMSCH_2N_2$ (2M soln. in hexane, 200 µl, 0.4 mmol) was added dropwise to the mixture. The yellow soln. was stirred for 20 min, and AcOH (100 µl) was added. Azeotropic distillation of AcOH with toluene, followed by FC (pentane/Et_2O 1 : 1) of the crude product, yielded **30** (50 mg, quant.). Colorless oil. er > 98 : 2 (HPLC). R_f (Et_2O/pentane 1 : 5) 0.11. $[\alpha]_D^{r.t.} = +5.0$ ($c = 1.63$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.39 (br. *s*, ^{t}Bu); 2.30 – 2.39 (*m*, 2 H); 2.49 – 2.54 (*m*, C*H*CH_2); 3.13 – 3.23 (*m*, 2 H); 3.66 (*s*, MeO); 4.50 (*m*, NH); 7.20 – 7.30 (*m*, 9 arom. H); 7.41 – 7.43 (*m*, 6 arom. H).

*3-(1*H*-Imidazol-4-yl)propanoic Acid Hydrochloride* (**31**). Similar to the procedure reported in [118], uraconic acid (5.01 g, 36.23 mmol) was dissolved in 0.5M NaOH (100 ml), and Pd/C (10%, 0.5 g) was added. The apparatus was evacuated and flushed with H_2 (3 ×), and the mixture was stirred under an atmosphere of H_2 (balloon) for 17 h at r.t. The mixture was filtered through *Celite* and washed with H_2O; the filtrate was adjusted to pH 2 with conc. HCl and concentrated under reduced pressure. Traces of H_2O were co-evaporated with toluene. The white residue was dissolved in EtOH and filtered; the solvent was then evaporated under reduced pressure to yield crude **31** (6.32 g). White solid. ^{1}H-NMR (300 MHz, CD_3OD): 2.72 (*t*, $J = 7.2$, CH_2); 3.00 (*t*, $J = 7.2$, CH_2); 7.33 (*s*, 1 Im H); 8.79 (*s*, 1 Im H). The product was used in the next step without further purification.

*Methyl 3-(1*H*-imidazol-4-yl)propanoate Hydrochloride* (**32**). Similar to the procedure reported in [118], crude **31** was suspended in a soln. of sat. HCl in MeOH (70 ml) and heated at reflux for 2 h. MeOH was evaporated under reduced pressure, followed by azeotropic distillation of MeOH/toluene and toluene/$CHCl_3$ to obtain crude **32** (7.87 g). The product was used in the next step without further purification. Yellow oil. The anal. data are in agreement with those reported in [119][120].

*Methyl 3-[1-(Triphenylmethyl)-1*H*-imidazol-4-yl]propanoate* (**33**). Similar to the procedure reported in [120][121], **32** was dissolved in DMF (35 ml) and cooled to 0°. Et_3N (20 ml, 4 equiv.) and a soln. of TrCl (10.97 g, 1.1 equiv.) in DMF (45 ml) were added dropwise. The mixture was stirred for 3 d at r.t. until a white precipitate was formed. The mixture was poured onto ice (350 g) and extracted with CH_2Cl_2 (5 × 150 ml). The combined org. layers were washed with H_2O (300 ml), dried ($MgSO_4$), and concentrated under reduced pressure to afford crude **33** (15.9 g). Yellow oil. The anal. data are in agreement with those reported in [120]. The product was used in the next step without further purification.

*3-[1-(Triphenylmethyl)-1*H*-imidazol-4-yl]propanoic Acid* (**34**). Similar to the procedure reported in [110], compound **33** was dissolved in THF/H_2O 3 : 1 (130 ml), LiOH · H_2O (3.5 g, 2.3 equiv.) was added, and the mixture was stirred for 15 h at r.t. THF was evaporated under reduced pressure, the residue was diluted with H_2O (200 ml), and the resulting suspension was acidified to pH 2 – 3 with 10% tartaric acid. The mixture was extracted with CH_2Cl_2 (4 × 100 ml); the combined org. layers were washed with 10% tartaric acid (200 ml) and H_2O (100 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oil was dissolved in Et_2O and evaporated several times to obtain a slightly yellow solid. Et_2O (25 ml) was added, the suspension was stirred for 10 min, and the product was filtered off to obtain **34** (10.1 g, 73% over 4 steps). White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.73 – 2.78 (*m*, CH_2); 2.83 – 2.88 (*m*, CH_2); 6.61 (*s*, 1 Im H); 7.10 – 7.15 (*m*, 6 arom. H); 7.26 – 7.37 (*m*, 9 arom. H); 4.49 (*s*, 1 Im H). The anal. data are in agreement with those reported in [110].

*(*R*)-4-(1-Methylethyl)-5,5-diphenyl-3-{3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanoyl}oxazolidin-2-one* (**35**). To a suspension of **34** (13.9 g, 36.4 mmol) in THF (0.25M) at −30°, Et_3N (6.05 ml, 1.2 equiv.) and pivaloyl chloride (4.50 ml, 1 equiv.) were added dropwise, and the mixture was stirred for 70 min at −30°. Meanwhile, a soln. of BuLi (1.52M in hexane; 21.4 ml, 0.94 equiv.) was added to an ice-bath-cooled suspension of

(*R*)*-4-(1-methylethyl)-5,5-diphenyl-1,3-oxazolidin-2-one* ((*R*)-**17**) (9.30 g, 0.91 equiv.) in THF (0.25 M). The soln. formed was added to the mixed anhydride soln. prepared previously. Stirring was continued for 15 h as the mixture was allowed to warm to r.t. The reaction was then quenched with sat. NH_4Cl soln. (100 ml), and diluted with Et_2O (600 ml) and H_2O (400 ml). The org. phase was separated, washed with 10% tartaric acid (400 ml), 1M NaOH (400 ml), and sat. aq. NaCl soln. (400 ml). Each aq. phase was re-extracted with Et_2O (600 ml). The combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was triturated with Et_2O/pentane 2 : 1, and the solid was filtered off, washed with cold Et_2O, and dried to yield unreacted auxiliary **17** (1.77 g, 19%). White solid. The filtrate was concentrated under reduced pressure and FC (CH_2Cl_2/MeOH sat. with NH_3 45 : 1) yielded (*R*)-**35** (14.1 g, 60%). White solid. M.p. 88–90°. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +115.8$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 2969*w*, 1781*s*, 1703*m*, 1494*m*, 1449*m*, 1366*m*, 1320*m*, 1038*w*, 1001*w*, 638*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.72 (*d*, $J = 6.8$, Me); 0.84 (*d*, $J = 7.0$, Me); 1.90–1.98 (*m*, Me_2CH); 2.76–2.90 (*m*, CH_2); 3.06 (*ddd*, $J = 17.1$, 8.8, 6.1, 1 H, CH_2); 3.28 (*ddd*, $J = 17.1$, 9.2, 6.5, 1 H, CH_2); 5.36 (*d*, $J = 3.3$, CHN); 6.50 (*d*, $J = 1.3$, 1 Im H); 7.09–7.12 (*m*, 5 arom. H); 7.23–7.37 (*m*, 20 arom. H); 7.43 (*d*, $J = 1.3$, 1 Im H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.36, 21.81 (Me); 23.39 (CH_2); 29.91 (CH); 35.25 (CH_2); 64.40 (CH); 75.08, 89.26 (C); 117.94, 125.59, 125.94, 127.66, 127.89, 127.93, 127.97, 128.33, 128.53, 128.88, 129.60, 129.82 (CH); 138.29 (C); 138.42 (CH); 139.87, 142.37, 142.57, 152.92, 172.40 (C). HR-MALDI-MS: 668.2888 ($C_{43}H_{39}N_3NaO_3^+$; calc. 668.2884). Anal. calc. for $C_{43}H_{39}N_3O_3$ (645.79): C 79.97, H 6.09, N 6.51; found: C 79.97, H 6.03, N 6.36.

*(4*R*)-3-{(2*S*)-2-(Hydroxymethyl)-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanoyl}-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one* (**36**). Compound (*R*)-**35** (5.90 g, 8.9 mmol) was transformed according to *GP 5b* for 3 h. FC (hexane/AcOEt 1 : 1) of the crude product yielded (2′*S*,4*R*)-**36** (4.3 g, 70%). White solid. M.p. 114–116°. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +82.7$ ($c = 0.95$, $CHCl_3$). IR ($CHCl_3$): 3063*w*, 3008*m*, 2970*m*, 1778*s*, 1700*s*, 1599*w*, 1494*m*, 1450*m*, 1364*m*, 1319*m*, 1280*m*, 1131*m*, 1087*w*, 1051*m*, 1001*m*, 906*m*, 871*m*, 844*m*, 831*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.78 (*d*, $J = 6.7$, Me); 0.91 (*d*, $J = 7.0$, Me); 1.93–2.01 (*m*, Me_2CH); 2.61–2.71 (*m*, CH_2); 3.84 (*dd*, $J = 11.5$, 5.9, 1 H, CH_2); 3.90 (*dd*, $J = 11.5$, 5.5, 1 H, CH_2); 4.01–4.08 (*m*, $CHCH_2$); 5.39 (*d*, $J = 3.2$, CHN); 6.32 (*d*, $J = 1.3$, 1 Im H); 7.03–7.13 (*m*, 5 arom. H); 7.27–7.37 (*m*, 20 arom. H); 7.43 (*d*, $J = 1.3$, 1 Im H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.23, 21.80 (Me); 26.52 (CH_2); 30.00, 45.61 (CH); 63.05 (CH_2); 64.61 (CH); 75.17, 89.18 (C); 119.06, 125.51, 125.85, 127.86, 128.00, 128.33, 128.38, 128.77, 129.56, 129.65, 129.81, 130.08 (CH); 137.61 (C); 138.14 (CH); 138.23, 142.40, 142.50, 152.91, 174.07 (C). HR-MALDI-MS: 698.2982 ($C_{44}H_{41}N_3NaO_4^+$; calc. 698.2989). Anal. calc. for $C_{44}H_{41}N_3O_4 \cdot 1/2\ H_2O$ (684.82): C 77.17, H 6.18, N 6.14; found: C 77.24, H 6.21, N 6.15.

*(4*R*)-3-{2-(Azidomethyl)-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanoyl}-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one* (**37**). *a*) The alcohol (2′*S*,4*R*)-**36** (617 mg, 0,91 mmol) was treated with Ph_3P (276 mg, 1.1 equiv.), HN_3 (1.03M in benzene; 1.0 ml, 1.1 equiv.) and DIAD (0.21 ml, 1.1 equiv.) according to *GP 8a*. FC (Et_2O/pentane 45 : 55 → 1 : 1) yielded (2′*S*,4*R*)-**37** (571 mg, 89%). White solid.

b) The alcohol (2′*S*,4*R*)-**36** (322 mg, 0.48 mmol) was treated with DIAD (98 μl, 1 equiv.), Ph_3P (129 mg, 1 equiv.), and $(PhO)_2P(O)N_3$ (130 μl, 1.2 equiv.) according to *GP 8b*. FC (Et_2O/pentane 45 : 55 → 1 : 1) yielded the (2′*S*,4*R*)-**37** (182 mg, 55%). White solid.

*Data of (2′*S*,4*R*)-***37**: M.p. 79–81°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.78 (*d*, $J = 6.7$, Me); 0.94 (*d*, $J = 7.0$, Me); 1.93–2.02 (*m*, Me_2CH); 2.49 (*dd*, $J = 14.7$, 7.5, 1 H, CH_2); 2.69 (*dd*, $J = 14.7$, 5.1, 1 H, CH_2); 3.60 (*dd*, $J = 12.2$, 4.6, 1 H, CH_2); 3.68 (*dd*, $J = 12.2$, 8.0, 1 H, CH_2); 4.21–4.26 (*m*, $CHCH_2$); 5.39 (*d*, $J = 3.1$, CHN); 6.29 (*d*, $J = 1.2$, 1 Im H); 6.95–7.11 (*m*, 10 arom. H); 7.24–7.39 (*m*, 15 arom. H, 1 Im H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.20, 21.83 (Me); 27.63 (CH_2); 30.02, 43.77 (CH); 52.14 (CH_2); 64.78 (CH); 75.12, 89.18 (C); 119.25, 125.51, 125.86, 127.90, 128.00, 128.02, 128.37, 128.39, 128.79, 129.58, 129.83 (CH); 137.18, 138.25 (C); 138.39 (CH); 142.40, 142.48, 152.65, 173.00 (C). HR-MALDI-MS: 723.3046 ($C_{44}H_{40}N_6NaO_3^+$; calc. 723.3054). Anal. calc. for $C_{44}H_{40}N_6O_3$ (700.83): C 75.41, H 5.75, N 11.91; found: C 75.36, H 5.87, N 11.79.

*(*S*)-Benzyl 2-(Hydroxymethyl)-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanoate* (**39**). To a stirred soln. of BnOH (1.7 ml, 2.2 equiv.) in THF (10 ml) at −5° was added BuLi (1.52M in hexane; 11.1 ml, 2.2 equiv.), and the soln. was stirred at −10° for 10 min. After cooling to −78°, a soln. of (2′*S*,4*R*)-**36** (5.20 g, 7.7 mmol) in THF (0.37 M) was added dropwise. The mixture was stirred at −78° for 30 min, and the temp. was allowed to rise to −20° over 105 min. The soln. was then stirred at −20° for 2 h (TLC control), the reaction was quenched with 10% tartaric acid (175 ml), and the mixture was extracted with CH_2Cl_2 (350 + 175 ml). The combined org. layers were washed with 10% tartaric acid (175 ml), dried ($MgSO_4$), and concentrated under reduced pressure. A soln. of AcOEt/hexane 2 : 1 was added, and the mixture was ultrasonificated for 2 min and filtrated. Drying of white solid (h.v.) yielded (*R*)-**17** (1.83 g). The filtrate was concentrated under reduced pressure and purified by FC (AcOEt/hexane 3 : 1) to yield (*S*)-**39** (2.72 g, 70%) with er > 98 : 2 (HPLC). White solid. M.p. 118–120°. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +1.4$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3065*w*, 3005*m*, 2966*m*, 1727*s*, 1494*s*, 1446*s*, 1386*w*, 1131*s*, 1089*w*, 1050*m*, 1003*m*, 907*m*, 870*m*, 833*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.86–3.04 (*m*, $CHCH_2$, $CHCH_2$); 3.84 (*d*,

J = 5.4, C*H*$_2$OH); 4.1 – 4.3 (br. *s*, OH); 5.06 (*d*, *J* = 12.4, 1 H, PhC*H*$_2$); 5.10 (*d*, *J* = 12.4, 1 H, PhC*H*$_2$); 6.55 (*d*, *J* = 1.4, 1 Im H); 7.08 – 7.15 (*m*, 6 arom. H); 7.27 – 7.35 (*m*, 15 H, 14 arom. H, 1 Im H). ^{13}C-NMR (125 MHz, CDCl$_3$): 27.43 (CH$_2$); 47.40 (CH); 62.52, 66.23 (CH$_2$); 75.26 (C); 119.14, 127.99, 128.05, 128.14, 128.36, 128.52, 129.74 (CH); 135.88, 137.95 (C); 138.32 (CH); 142.33, 173.89 (C). HR-MALDI-MS: 525.2144 ($C_{33}H_{30}N_2NaO_3^+$; calc. 525.2149).

*(*S*)-Benzyl 2-(Azidomethyl)-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanoate* (**40**). The alcohol (*S*)-**39** (2.66 g, 5.30 mmol) was treated with Ph$_3$P (1.58 g, 1.1 equiv.), HN$_3$ (1.11M in benzene; 5.3 ml, 1.1 equiv.), and DIAD (1.19 ml, 1.1 equiv.) according to *GP 8a*. FC (Et$_2$O/pentane 1 : 1) yielded (*S*)-**40** (2.31 g, 83%). Colorless oil. R_f (AcOEt/hexane 1 : 2) 0.22. $[\alpha]_D^{r.t.} = +10.9$ ($c = 1.00$, CHCl$_3$). IR (CHCl$_3$): 3066*w*, 3008*w*, 2966*w*, 2104*s*, 1732*s*, 1600*w*, 1494*m*, 1446*m*, 1131*m*, 1087*m*, 1038*w*, 1002*w*, 908*w*, 870*w*, 830*w*. ^{1}H-NMR (400 MHz, CDCl$_3$): 2.80 (*dd*, *J* = 14.6, 7.7, 1 H, CH$_2$); 2.96 (*ddd*, *J* = 14.6, 6.3, 0.6, 1 H, CH$_2$); 3.02 – 3.09 (*m*, CH); 3.50 – 3.57 (*m*, CH$_2$N$_3$); 5.06, 5.12 (2*d*, *J* = 12.4, PhC*H*$_2$); 6.55 (*t*, *J* = 0.7, 1 Im H); 7.07 – 7.14 (*m*, 6 arom. H); 7.27 – 7.34 (*m*, 14 arom. H); 7.35 (*d*, *J* = 1.4, 1 Im H). ^{13}C-NMR (100 MHz, CDCl$_3$): 28.05 (CH$_2$); 45.47 (CH); 51.68, 66.57 (CH$_2$); 75.22 (C); 119.29, 128.05, 128.07, 128.19, 128.52, 129.40, 129.72, 130.00 (CH); 135.70, 137.51 (C); 138.72 (CH); 142.40, 172.86 (C). HR-MALDI-MS: 550.2209 ($C_{33}H_{29}N_5NaO_2^+$; calc. 550.2214). Anal. calc. for $C_{33}H_{29}N_5O_2$ (527.62): C 75.12, H 5.54, N 13.27; found: C 75.10, H 5.72, N 13.30.

*(*S*)-2-[({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)methyl]-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-propanoic Acid* (Fmoc-(*S*)-β^2hHis(Tr)-OH; **41**). Transformation of (*S*)-**40** (1.44 g, 2.73 mmol) according to *GP 6b* gave the amino acid H-(*S*)-β^2hHis(Tr)-OH (1.26 g) as a white solid. This solid was then Fmoc-protected according to *GP 4b* for 2 h. FC (CH$_2$Cl$_2$/MeOH 16 : 1 → 9 : 1) and crystallization (AcOEt/hexane) yielded (*S*)-**41** (1.07 g, 62%). White solid. R_f (CH$_2$Cl$_2$/MeOH 9 : 1) 0.42. M.p. 130 – 133°. $[\alpha]_D^{r.t.} = -14.5$ ($c = 0.97$, CHCl$_3$). IR (CHCl$_3$): 3444*w*, 3008*w*, 2951*w*, 1716*s*, 1513*m*, 1447*m*, 1152*w*, 1130*w*, 1087*w*, 1011*w*, 871*w*, 831*w*. ^{1}H-NMR (400 MHz, CD$_3$OD): 2.68 – 2.73 (br. *dd*, 1 H, CH$_2$); 2.78 – 2.87 (*m*, CH*H*, C*H*CH$_2$); 3.25 – 3.36 (*m*, CH$_2$); 4.16 (*t*, *J* = 6.8, C*H*CH$_2$O); 4.30 (*d*, *J* = 6.9, CH$_2$O); 6.74 (*s*, 1 Im H); 7.10 – 7.13 (*m*, 6 arom. H); 7.24 – 7.29 (*m*, 2 arom. H); 7.33 – 7.35 (*m*, 11 arom. H); 7.43 (*s*, 1 Im H); 7.60 (*d*, *J* = 7.5, 2 arom. H); 7.76 (*d*, *J* = 7.5, 2 arom. H). ^{13}C-NMR (100 MHz, CD$_3$OD): 28.85, 43.02 (CH$_2$); 47.62, 48.52 (CH); 61.51 (C); 67.76 (CH$_2$); 77.11 (C); 120.94, 121.06, 126.25, 128.17, 128.79, 129.31, 129.39, 130.67, 130.92, 131.20 (CH); 138.86 (C); 139.15 (CH);142.63, 143.56, 158.76, 177.88 (C). HR-MALDI-MS: 656.2518 ($C_{26}H_{25}N_3NaO_2^+$; calc. 656.2520).

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