Enantioselective Preparation of β^2-Amino Acids with Aspartate, Glutamate, Asparagine, and Glutamine Side Chains¹)

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(*S*)-β^2-Homoamino acids with the side chains of Asp, Glu, Asn, and Gln have been prepared and suitably protected (*N*-Fmoc, $CO_2{}^tBu$, CONHTrt) for solid-phase peptide syntheses. The key steps of the syntheses are: *N*-acylation of 5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one (DIOZ) with succinic and glutaric anhydrides (*Scheme 2*), alkylation of the corresponding Li-enolates with benzyl iodoacetate and *Curtius* degradation (*Scheme 4*), and removal of the chiral auxiliary (*Scheme 5*). In addition, numerous functional-group manipulations ($CO_2H \rightleftharpoons CO_2{}^tBu$, $CO_2Bn \rightleftharpoons CO_2H$, CbzNH → FmocNH, $CO_2H \rightarrow CO_2NH_2 \rightarrow$ CONHTrt; *Schemes 2*, *4*, *5*, and *6*) were necessary, in order to arrive at the four target structures. The configurational assignments were confirmed by X-ray crystal-structure determinations (*Scheme 2* and *Fig. 3*). The enantiomeric purities of a β^2hAsn and of a β^2hGln derivative were determined by HPLC on a *Chiralcel* column to be 99.7 : 0.3 and > 99 : 1, respectively (*Fig. 4*). Notably, it took up to twelve steps to prepare a suitably protected trifunctional product with a single stereogenic center (overall yield of 10% from DIOZ and succinic anhydride)!

1. Introduction. – Although β^3-amino acids can be conveniently synthesized from the corresponding α-analogues by simply introducing a CH_2 group between the C=O and the α-C-atom (*i.e.*, *Arndt–Eistert* homologation)⁵), no such general method is known for the preparation of β^2-amino acids. As outlined in *Fig. 1*, a wide variety of routes have been explored for the synthesis of β^2-amino acids depending upon the bond formed in the key step.

Formation of bond ① by diastereoselective *Mannich*-type reaction [1–11], *i.e.*, aminomethylation of chiral acyl derivatives with synthetic equivalents of the $[H_2NCH_2]^+$ cation, has been applied for the preparation of a large range of β^2-amino acids, most of them having alkyl or aryl side chains. The *Mitsunobu* reaction, instead, was used for the conversion of 2-(hydroxymethyl)carboxylic acid esters to the corresponding amino or azido derivatives, thus forming bond ② [1][12][13]. Another route is the *Curtius* rearrangement of enantiomerically pure monosubstituted succinic acid derivatives [1][14][15], which were themselves synthesized by alkylation of chiral

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⁴) Part of the Master Thesis (Diplomarbeit) of *S. K.*, ETH-Zürich, 2003.

⁵) With the exceptions of Fmoc-β^3hHis(Trt)-OH and Fmoc-β^3hCys(Trt)-OH, all 'proteinogenic' β^3-amino acids, which can be prepared by *Arndt–Eistert* homologation of the corresponding α-amino acids, are commercially available.

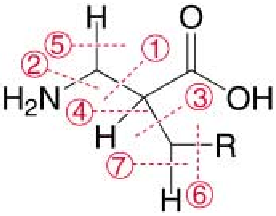

Fig. 1. *Analysis of the key C–C-, C–N-, or C–H-bond-forming reactions for β^2-amino acid synthesis*

N-acyloxazolidinones with bromo- or iodoacetates (bonds ① and ②) [9][16–18] or by alkylation of succinic [19] or malic acid enolates [20] with electrophiles (bonds ③ and ②). Another approach is the coupling of an electrophile with cyclic [21–28] or acyclic [1][8][29–33] chiral enolates derived from 3-aminopropanoic acid (bond ③). Similarly, by the enantioselective nucleophilic addition of Et_2Zn to a 3-nitroacrylate derivative, the feasibility of the process with *umpolung* has been demonstrated [34]. The conjugate 1,4-addition (*Michael*-type reaction) of chiral N-nucleophiles to 2-substituted acrylates, followed by diastereoselective protonation, is yet another method for their preparation, in which bonds ② and ④ are formed [35–38]. Finally, chiral metal complexes have permitted the isolation of enantiomerically enriched β^2-amino acids by construction of the ① + ④ [39], ④ + ⑤ [40], or ④ + ⑦ bonds [41], albeit often with low enantioselectivities and, in any case, applied only for derivatives with alkyl or aryl side chains.

The incorporation of β^2-amino acids into β-peptides has uncovered intriguing effects, leading to turn structures [42][43] or a novel type of helix, which consists of alternating ten- and twelve-membered H-bonded rings [7][44]. For our ongoing work on the synthesis of more complex β^2/β^3- and all-β^2-peptides, we needed ample access to all 19, appropriately protected[6]), β^2-amino acids with proteinogenic side chains. At the time this project was initiated, the above mentioned methods were only applied to the construction of the 'easy' β^2-amino acids, but not much was known about the derivatives with functionalized side chains. For this reason, the application of a method developed in our group, relying on the use of 5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one (DIOZ) as a chiral auxiliary, was envisaged for the preparation of the β^2-amino acids shown in *Fig. 2*. Indeed, our modified *Evans* oxazolidinone has been shown to be a versatile auxiliary for diastereoselective alkylations, aldol additions, 1,4-additions, cycloadditions, and numerous other reactions [8][45–53]. Derivatives of this auxiliary have turned out to possess several desirable properties, such as high crystallinity, ease of removal and recovery, and good selectivity.

Results and Discussion. – Since the aspartic and the glutamic acid side chains are interchangeable with the corresponding amides (asparagine and glutamine, resp.), and since they differ from each other only by a CH_2 unit, it was decided to prepare all four β^2-amino acids by the same approach. As mentioned above, a prerequisite of the final

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[6]) For solid-phase synthesis by the Fmoc strategy, all functionalized side chains have to be protected orthogonally to the Fmoc group itself. They should be stable under basic conditions but labile in acidic media, thus trityl (Trt) and ^{t}Bu groups are the protecting groups of choice.

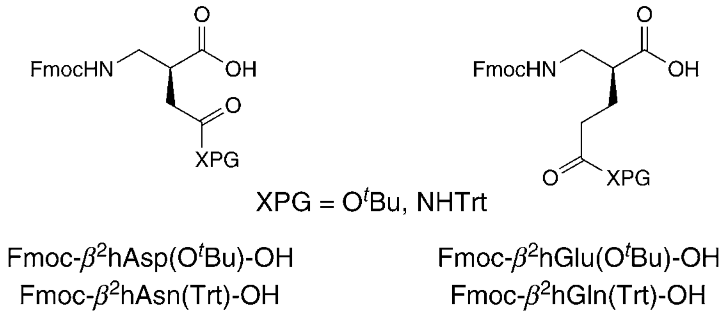
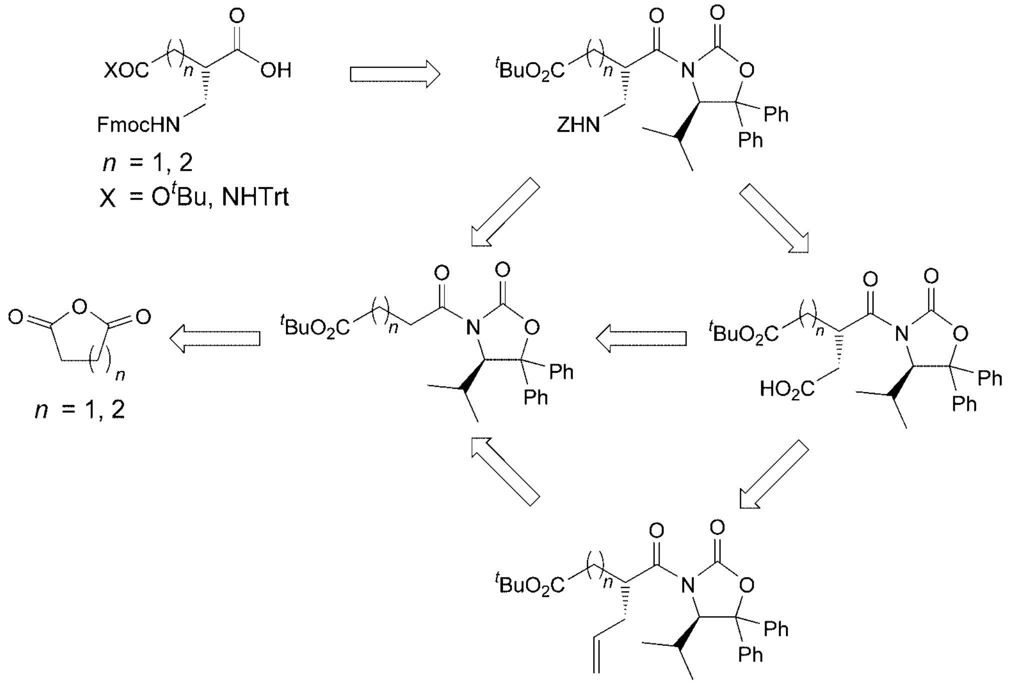


Fig. 2. *Target β^2-amino acid derivatives*

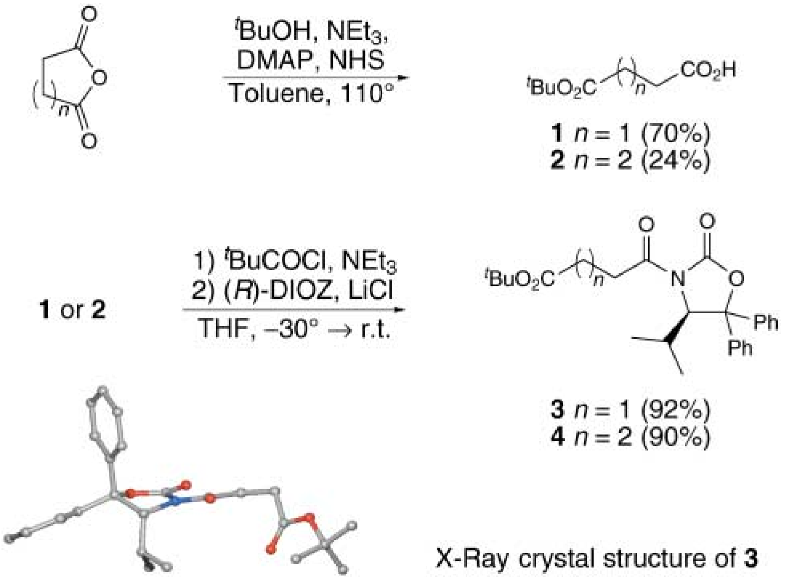
compounds for their use in solid-phase β-peptide synthesis is the Fmoc protection of the β-amino group, and the ^{t}Bu or Trt protecting group on the side chains. Thus, we thought that 3-acyl-DIOZ derivatives of succinic and glutaric acids could serve as precursors for the corresponding β^2-homoaspartic and β^2-homoglutamic acids, respectively. The amino functionality would be introduced either by a diastereoselective *Mannich*-type reaction (*cf.* bond ① in *Fig. 1*) or by a carbalkoxymethylation, followed by *Curtius* degradation (connections ① + ② in *Fig. 1*), to give the desired amino acid skeleton, which could be further elaborated by protecting-group exchange (*Scheme 1*).

Scheme 1. *Retrosynthetic Analysis for the Preparation of the β^2-Amino Acids with Asx and Glx Side Chains*



It should be noted that a similar approach has been previously described by *Wyatt* and co-workers [15] for the synthesis of fully deprotected β^2-homoaspartate; the authors applied a diastereoselective alkylation of a 'classical' *Evans* acyloxazolidinone derived from pent-4-enoic acid with methyl bromoacetate as electrophile, followed by oxidative cleavage of the double-bond, *Curtius* rearrangement, and removal of the auxiliary, to give the Z-β^2hAsp-OH in 97.5% enantioselectivity, but without a protecting group on the side chain. Recently, *Xue et al.* [32] performed the synthesis of an enantiomerically pure (R)-β^2-homoaspartate derivative by a stereoselective alkylation of a Bn- and Z-protected chiral β-homoglycine-oxazolidinone with *tert*-butyl bromoacetate. In our approach, we started from the commercially available succinic and glutaric anhydrides, which were ring-opened by refluxing in toluene with ^{t}BuOH, and catalytic amounts of 4-(dimethylamino)pyridine (DMAP), Et_3N, and *N*-hydroxysuccinimide (NHS) [54] to give the monoesters **1** and **2** in 70 and 24%[7]) yield, respectively (*Scheme 2*). *N*-Acylation of the chiral oxazolidinone (R)-DIOZ with the LiCl-activated [55] pivaloyl mixed anhydrides of **1** and **2** gave the desired acyloxazolidinones **3** and **4**, respectively, in excellent yields.

Scheme 2. *Nucleophilic Ring Opening of the Succinic and Glutaric Anhydrides* (→ **1** and **2**), N-*Acylation of* (R)*-DIOZ to Form the Acyloxazolidinones* **3** *and* **4**, *Respectively, and X-Ray-Crystal Structure of* **3**



Slow evaporation of an Et_2O/pentane mixture from a solution of ester **3** led to the formation of crystals suitable for structure determination by single-crystal X-ray diffraction; as evident from the presentation in *Scheme 2*, the methine H-atom of the ^{i}Pr group points towards the *cis*-Ph group causing a buttressing effect [49] in the face selectivity of reactions of enolates of **3** with electrophiles.

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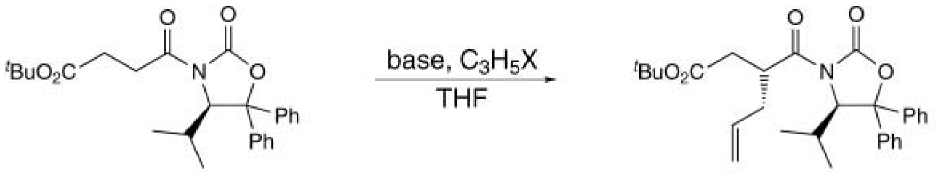
[7]) The reaction was rather messy and the formation of polymerization products were observed.

Due to the better crystallinity of compound **3** and, therefore, easier purification of its derivatives, compared to the homologue **4**, all experiments towards the construction of the amino acid backbone, according to the approaches outlined in *Scheme 1*, were performed with the former derivative. We first explored amidomethylation of the Ti-enolate from **3** with the corresponding electrophile (*N*-benzyloxycarbonyl-*N*-(methoxymethyl), $ZNHCH_2OMe$) without success; the *Lewis* acidity of Ti^{4+} caused complete deprotection of the *tert*-butyl ester and formation of an inseparable mixture of products. We then switched to an allylation/double-bond oxidation/*Curtius*-degradation strategy. An analogous stereoselective allylation reaction has been successfully applied by *Sibi* and *Deshpande* [19] on a similar substrate. Treatment of **3** with 1 equiv. of sodium hexamethyldisilazide (NHMDS) in THF at – 78° for 20 min, followed by quenching with allyl bromide, furnished, in our case, the mono alkylated derivative **5** in disappointing yields and selectivities (*Entry 1*, *Scheme 3*). Similar results were obtained when more equivalents of allyl bromide were added to the Na-enolate (*Entry 2*); however, better conversion was achieved when the more reactive iodo derivative was used as electrophile (*Entry 3*). Acceptable selectivities were realized only by running the reaction at – 50° (*Entry 4*), while complete degradation of the enolate resulted at 0° (*Entry 5*). The formation of the Li-enolate with LHMDS at – 78°,

Scheme 3. *Optimization of the Conditions for the Diastereoselective Alkylation of* **3** *with Allyl Halides*



3 **5**

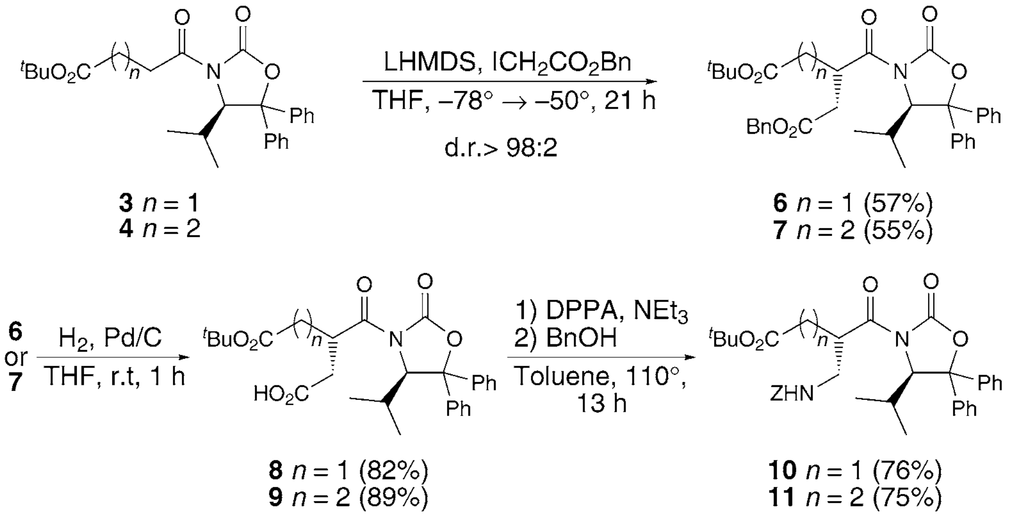
Entry	Base, equiv.	C_3H_5X, equiv.	Time [h]	Temp. [°]	Conversion [%][a])	d.r.[a])
1	NHMDS, 1.1	X = Br, 1.5	14	–78 → –48	41	75:25
2	NHMDS, 1.1	X = Br, 5	22	–78	43	84:16
3	NHMDS, 1.1	X = I, 5	6	–78	85	80:20
4	NHMDS, 1.1	X = I, 5	6	–78 → –50	88	94:6
5	NHMDS, 1.1	X = I, 5	6	–78 → 0	–[b])	–[c])
6	KHMDS, 1.1	X = I, 5	15	–78 → –50	–[b])	–[c])
7	LHMDS, 1.1	X = I, 5	23	–78 → –50	85	96:4
8	LHMDS, 1.5	X = I, 5	20	–78 → –50	81	94:6
9	LHMDS, 2	X = I, 5	20	–78 → –50	69	–[c])

[a]) Determined by ^{1}H-NMR spectroscopy of the crude product. [b]) Enolate degradation and formation of the allylated auxiliary as major product. [c]) Not determined.

followed by quenching with allyl iodide at $-50°$, gave the best result, with good conversion and 96% diastereoselectivity (*Entry 7*). Unfortunately, purification by flash chromatography was not sufficient to separate the diastereoisomers, and compound **5** was isolated in 66% yield and 96% diastereoselectivity. At this point, we thought that better separation would possibly be achieved in a later stage of the synthesis, for example, after double-bond oxidation. Ozonolysis [56] of the double bond in **5** and oxidation with periodate (catalytic $KMnO_4$ [57]) did, however, not lead to the desired carboxylic acids.

Disappointed by these results, we changed our strategy and envisaged a more direct approach of introducing the amino functionality by alkylation with benzyl iodoacetate [58] as electrophile. We were pleased to see that, upon treatment of the Li-enolates of the acyloxazolidinones **3** and **4** with this electrophile at $-78°$, the alkylated products **6** and **7**, respectively, could be isolated in *ca.* 55% yield as single diastereoisomers (*Scheme 4*).

Scheme 4. *Diastereoselective Alkylation of Succinic and Glutaric Acid Derivatives* **3** *and* **4** *with Benzyl Iodoacetate.* Note that the α-carbonyl C-atom of **6** is a stereogenic center only due to the fact that the two ester groups CO_2R carry different OR groups (^{t}Bu and Bn)! Hydrogenolysis of the benzyl esters **6** and **7**, and *Curtius* degradation leads to the Z-protected derivatives **10** and **11**.



Following hydrogenolysis of the benzyl ester and *Curtius* degradation (with DPPA (diphenylphosphoryl azide), Et_3N, and BnOH [59]), the Z-protected derivatives **10** and **11** were isolated in good yields (*Scheme 4*). Compound **10** formed single crystals suitable for structure determination by X-ray crystallography (*Fig. 3,a*): as expected, the newly created stereogenic center has (*S*)-configuration. In addition, X-ray crystal-structure determination of the fifth crop of crystals (representing less than 4% of the total yield) revealed that the unit cell contains **10** and *epi*-**10** in a 1:1 ratio (*Fig. 3,b*).

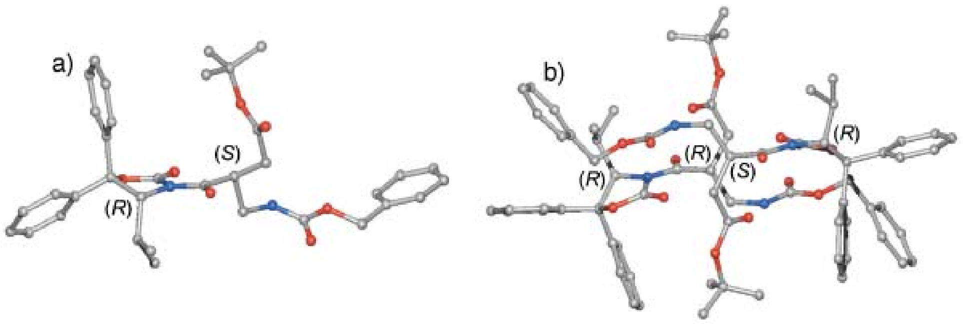
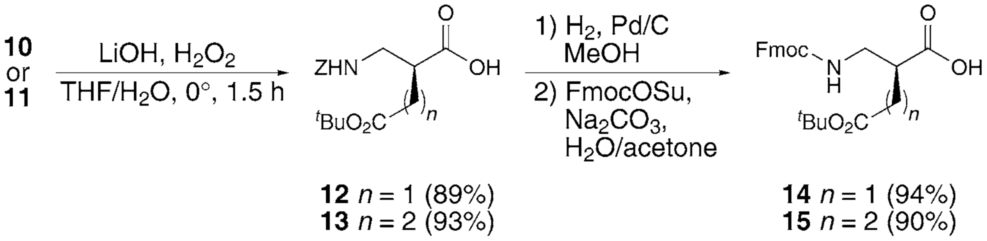


Fig. 3. *X-Ray crystal structures of* **10** (*a*) *and of a 1:1 co-crystal of* **10** *and* epi-**10** (*b*)

The next step towards the synthesis of the β^2-aspartate and β^2-glutamate derivatives involved the cleavage of (*R*)-DIOZ with LiOH/H$_2$O$_2$[8]), which gave acids **12** and **13**, as well as the recovered auxiliary, in good yields (*Scheme 5*)[9]). Following Z/Fmoc protecting-group exchange, Fmoc-β^2hAsp(O^{t}Bu)-OH (**14**) and Fmoc-β^2hGlu(O^{t}Bu)-OH (**15**) were isolated in 94 and 90% yields, respectively. In this way, the Fmoc derivatives **14** and **15** were synthesized in an overall yield of 19 and 7%[10]) over eight steps starting from the corresponding anhydrides and (*R*)-DIOZ.

Scheme 5. *Cleavage*[8]) *of the Auxiliary with LiOH/H$_2$O$_2$ and Subsequent Protecting-Group Exchange to Give the Fmoc-Protected Acids* **14** *and* **15**



For the preparation of the β^2hAsn and β^2hGln derivatives, the acids **12** and **13** were converted to the benzyl esters **16** and **17**, respectively, by treatment with BnBr and NaHCO$_3$ in DMF in the presence of catalytic amounts of tetrabutylammonium iodide (TBAI; *Scheme 6*). It is important to note that nucleophilic cleavage of the acyloxazolidinone **10** by BnOLi, for the direct formation of ester **16**, led to partial epimerization of the C(2)-centre (see above). Subsequent ^{t}Bu deprotection and nucleophilic addition of ammonia afforded amides **18** and **19**, which were Trt-protected

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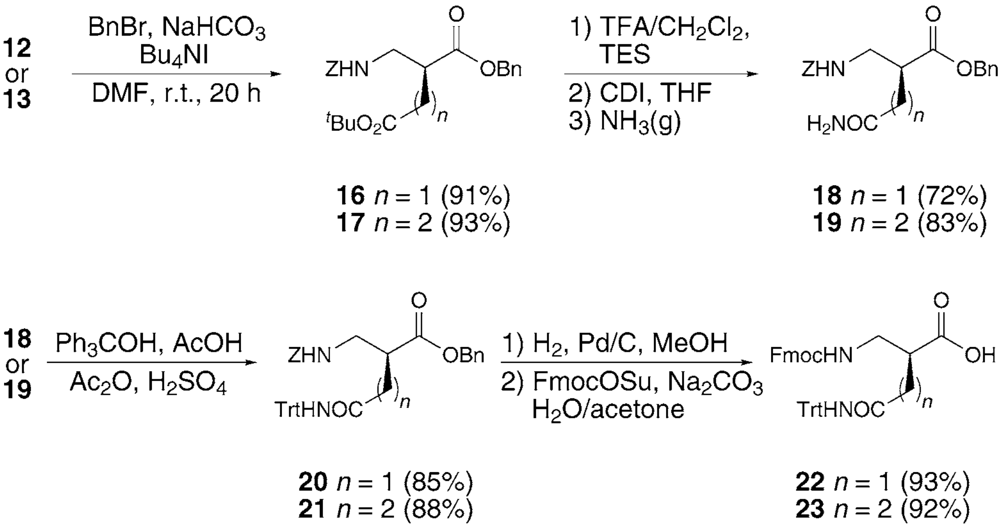
[8]) We have claimed that a major advantage of our modified *Evans* auxiliary is that it can be cleaved simply with THF/aq. NaOH and does not require LiOH/H$_2$O$_2$. This is not true for the application described here, because the substrate contains ester groups, and the hydroperoxide conditions lead to much faster cleavage.

[9]) Particular care should be taken during the workup, the *tert*-butyl ester being very sensitive to acidic conditions. For details, see *Exper. Part.*

[10]) The low overall yield for this derivative is caused 'essentially' by the disappointing yield obtained for the opening of the glutaric anhydride (not optimized).

to give the fully protected amino acids **20** and **21**, respectively, in good yields. Hydrogenolysis and Fmoc protection of the amino group led to Fmoc- and Trt-protected β^2-homoasparagine (**22**) and β^2-homoglutamine (**23**; *Scheme 6*), respectively, which have, thus, been synthesized over twelve steps with an overall yield of 10 and 4%, respectively.

Scheme 6. *Conversion of the Aspartate and Glutamate Derivatives* **12** *and* **13** *to Fmoc- and Trt-Protected β^2-Homoasparagine* (**22**) *and β^2-Homoglutamine* (**23**)



To verify the enantiomeric purity of the new β^2-amino acid derivatives, compounds **20** and **21** were injected into a chiral HPLC column (*Chiralcel OD*). For comparison, both derivatives were racemized by treatment with BnOLi at room temperature. As shown in *Fig. 4*, both derivatives show only one peak, thereby confirming the purity of all four amino acids[11]). Additionally, as previously mentioned, direct cleavage of the auxiliary from acyloxazolidinone **10** with BnOLi (1 equiv. BuLi, 0°, 4 h) gave ester **16**. This compound was further derivatized to give ester (*R*)-**20**, the enantiomeric purity of which was determined to be 66% by HPLC. Since this alternative route differs from that outlined in *Scheme 3* only in the reaction involving the removal of the auxiliary, we can conclude that the cleavage of the auxiliary with BnOLi is not always free of epimerization/racemization[8]).

In conclusion, we have shown the remarkable potential of 3-acyl-DIOZ derivatives for the preparation of β^2-amino acids carrying the side chains of Asp, Asn, Glu, and Gln. Furthermore, we have judiciously verified the enantiomeric purity of these compounds by HPLC on a chiral stationary phase in order to ensure their utility as building blocks for solid-phase peptide synthesis according to the Fmoc protocol. Our approach can easily be scaled up to produce multigram amounts of these amino acids in enantiomerically pure form.

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[11]) Interestingly, the (*S*)-form of the asparagine, but the (*R*)-form of the glutamine derivative, is eluted first.

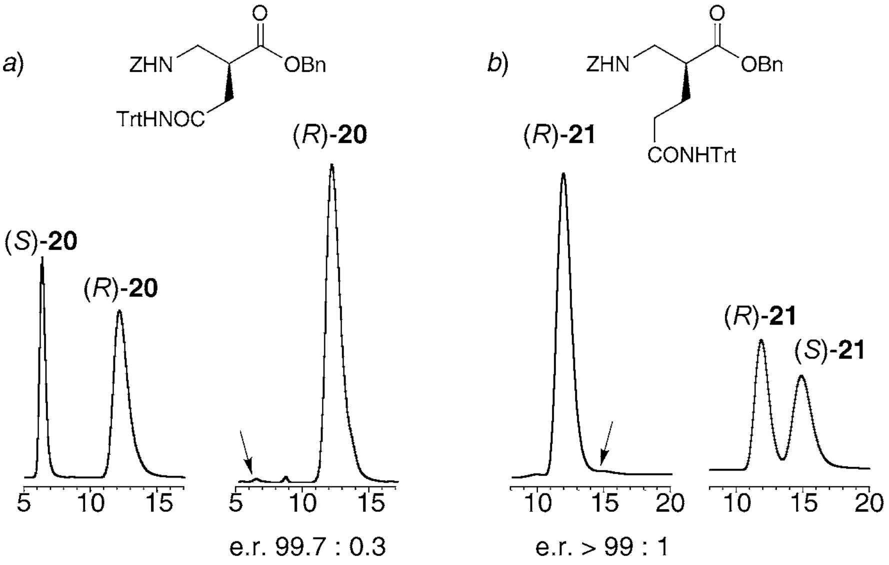

Fig. 4. *HPLC Traces of* a) *the asparagine derivative* (R)-**20** *and of* rac-**20**, *and* b) *the glutamine derivative* (R)-**21** *and* rac-**21** (*Chiralcel OD-H*, $\lambda = 220$ nm, mobile phase: ^{i}PrOH/hexane 20 : 80 for **20** and ^{i}PrOH/hexane 15 : 85 for **21**). The arrows indicate the signals of the minor enantiomers. The e.r. values were determined by integration of the corresponding peaks: (*R*)-**20**: 99.7 : 0.3; (*R*)-**21**: > 99 : 1. t_R in min.

Experimental Part

1. *General.* Abbreviations: CDI: 1,1′-Carbonyldi(1*H*-imidazole), DIOZ: 5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one, DMAP: 4-(dimethylamino)pyridine, DPPA: diphenylphosphoryl azide, FC: flash chromatography, h.v.: high vacuum, 0.01 – 0.1 Torr, LHMDS: lithium hexamethyldisilazide, NHMDS: sodium hexamethyldisilazide, TBAI: tetrabutylammonium iodide, TES: Et_3SiH. Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*), THF was distilled from Na, CH_2Cl_2 and Et_3N from CaH_2. LiCl was dried in h.v. at 100° for 1 h. All other reagents were used as received from *Fluka*. TLC: *Merck* silica-gel *60 F_{254}* plates; detection with UV or 'Mo-stain' soln. (25 g phosphormolybdic acid, 10 g $Ce(SO_4)_2 \cdot H_2O$, 60 ml conc. H_2SO_4, 940 ml 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. Optical rotations: *Perkin-Elmer 241* polarimeter (10 cm, 1-ml cell). IR Spectra: *Perkin-Elmer 1600 FT-IR* spectrophotometer. NMR Spectra: *Bruker AMX-400* (^{1}H 400 MHz, ^{13}C 100 MHz); chemical shifts δ in ppm downfield from internal Me_4Si (= 0 ppm); *J* values in Hz. Mass Spectra: *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. *Preparation of Diacid Mono-*tert*-butyl Esters: General Procedure 1* (*GP 1*). Similarly to the procedure reported in [54], the corresponding anhydride was suspended in toluene (1.7M) under Ar, and treated subsequently with *N*-hydroxysuccinimide (0.3 equiv.), DMAP (0.1 equiv.), dry ^{t}BuOH (3 equiv.) and Et_3N (0.3 equiv.). The mixture was stirred for 30 min at r.t., and heated at reflux for 1 d. After cooling, AcOEt was added, the org. phase washed with 10% citric acid (3 ×) and sat aq. NaCl soln. (1 ×), dried ($MgSO_4$), and concentrated under reduced pressure. FC or recrystallization yielded the pure product.

3. *Acylation of the Auxiliary by the Mixed Anhydride Method: General Procedure 2* (*GP 2*). Similarly to the procedure reported in [8], to a soln. of the corresponding carboxylic acid in THF (0.2M) under Ar, cooled at − 30°, Et_3N (2.5 equiv.) and pivaloyl chloride (1 equiv.) were added dropwise. The resulting suspension was stirred at − 30° for 2 h. At this point, LiCl (1.1 equiv.) and the auxiliary (0.95 equiv.) were added at once, stirring was continued for 1 – 2 d as the mixture was slowly allowed to warm to r.t. The mixture was diluted with Et_2O,

washed with sat. aq. NH_4Cl soln. (2 ×), 1M NaOH (2 ×), and sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure. FC of the crude product yielded the pure compound.

4. *Alkylation of Acyloxazolidinones with Benzyl Iodoacetate: General Procedure 3* (*GP 3*). To a soln. of the corresponding substrate in THF (0.3M) at −78°, LHMDS (1.1 equiv.) was slowly added, and the mixture was stirred for 1 h at this temp. At this point, a soln. of benzyl iodoacetate (1.5 equiv.) in THF (1:1, *v*/*v*) was slowly added over 1 h, and the resulting mixture was stirred for 20 h at −50°. The mixture was then diluted with Et_2O and washed with sat. aq. NH_4Cl soln., 5% $NaHSO_3$, and sat. aq. NaCl soln. The org. phase was dried (Na_2SO_4), and concentrated under reduced pressure. FC of the crude product yielded the pure compound.

5. *Selective Hydrogenolysis of the Bn Ester in the Presence of DIOZ: General Procedure 4* (*GP 4*). The corresponding substrate was dissolved in THF (0.02M) and *ca.* 10% (*w*/*w*) Pd/C (10%) was added. The apparatus was evacuated and flushed with H_2 (3 ×), and the soln. stirred under an atmosphere of H_2 (balloon) for 1.5 h (TLC control). The mixture was then filtered through *Celite* and washed thoroughly with CH_2Cl_2. The filtrate was collected and concentrated under reduced pressure. FC of the crude product yielded the pure compound.

6. Curtius *Rearrangement: General Procedure 5* (*GP 5*). The corresponding substrate was dissolved in toluene (0.15M) under Ar, and Et_3N (1.2 equiv.), followed by DPPA (1.2 equiv), was added. The resulting mixture was stirred for 30 min at r.t., and subsequently heated at reflux for 1.5 h. BnOH (2 equiv.) was then added, and the mixture was refluxed for further 16 h. After cooling, the mixture was diluted with Et_2O, washed with sat. aq. $NaHCO_3$ soln. and sat. aq. NaCl soln., dried ($NaSO_4$), and concentrated under reduced pressure. FC of the crude product yielded the pure compound.

7. *Cleavage of the Chiral Auxiliary with LiOH/H_2O_2: General Procedure 6* (*GP 6*). To a soln. of the corresponding substrate in THF/H_2O 4:1 (0.2M) at 0°, H_2O_2 (30% aq., 4.0 equiv.) and $LiOH \cdot H_2O$ (1.6 equiv.) were added, and the resulting mixture was stirred at 0° for 2 h. The mixture was diluted with H_2O, and the precipitated chiral auxiliary was removed by filtration. The THF was evaporated at 25° under reduced pressure, the soln. was cooled to 0°, and AcOEt was added to the mixture. Upon slow addition of 10% citric acid and with continuous stirring of the biphasic system at 0°, the pH of the aq. phase was adjusted to 4–5. The org. layer was separated, and the aq. phase was extracted with AcOEt (3 ×). The combined org. layers were washed with sat. aq. NaCl soln., dried (Na_2SO_4), and concentrated under reduced pressure. FC of the crude product yielded the pure compound.

8. *Hydrogenolysis of Z groups and Bn Esters: General Procedure 7* (*GP 7*). The corresponding substrate was dissolved in MeOH (0.02M), 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.

9. *Fmoc Protection: General Procedure 8* (*GP 8*). The *N*-deprotected amino acid was dissolved in 0.15M Na_2CO_3 (2–3 equiv.) and treated with a soln. of FmocOSu (1–1.2 equiv.) in acetone (0.1M). If necessary the pH was readjusted 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 with 0.6M 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 of the crude product yielded the pure compound.

10. *Preparation of Bn Esters: General Procedure 9* (*GP 9*). To a soln. of the corresponding acid in DMF (0.2M) were added $NaHCO_3$ (2.0 equiv.), TBAI (0.3 equiv.), and BnBr (5.0 equiv.). The resulting mixture was vigorously stirred at r.t. for 20 h. The mixture was diluted with Et_2O, and the org. phase was washed with H_2O and sat. aq. NaCl soln. The org. phase was dried (Na_2SO_4) and concentrated under reduced pressure. FC of the crude product yielded the pure compound.

11. *^{t}Bu Ester Deprotection: General Procedure 10 (GP 10)*. To a soln. of the corresponding substrate in CH_2Cl_2 (0.4M), TES (2.5 equiv.) and TFA (13.0 equiv.) were added dropwise, and the mixture was stirred at r.t. for 2 h. The solvent was removed under reduced pressure at 25° and residual TFA co-evaporated with toluene (3 ×). The product obtained was used in the next step without further purification.

12. *Conversion of an Acid to an Amide: General Procedure 11* (*GP 11*). The corresponding acid was dissolved in THF (0.13M), and CDI (2 equiv.) was added. After stirring for 5 h under Ar, excess NH_3 gas was bubbled through the soln. The mixture was then diluted with AcOEt, and the org. phase was washed with H_2O,

1M HCl, and sat. aq. NaCl soln. The org. phase was dried (Na_2SO_4) and concentrated under reduced pressure. Crystallization yielded the pure compound.

13. *N-Trt Protection: General Procedure 12* (*GP 12*). To a suspension of the corresponding substrate in AcOH (0.27M), solid TrtOH (2.0 equiv.) was added, followed by a soln. of Ac_2O/AcOH/H_2SO_4 100 : 200 : 3.6 (0.56 ml/mmol). The mixture was heated at 40° and stirred for 5.5 h. Et_2O was then added, and the org. phase was washed with 5% $NaHCO_3$ and sat. aq. NaCl soln. The org. phase was dried (Na_2SO_4) and concentrated under reduced pressure. FC of the crude product yielded the pure compound.

4-(tert-Butoxy)-4-oxobutanoic Acid (**1**). Transformation of succinic anhydride (30 g, 0.3 mol) according to *GP 1*, followed by recrystallization (Et_2O/pentane), afforded **1** (36.36 g, 70%). White solid. The anal. data are in agreement with the values reported in [54][60].

5-(tert-Butoxy)-5-oxopentanoic Acid (**2**). Transformation of glutaric anhydride (34.2 g, 0.3 mol) according to *GP 1*, followed by FC (Et_2O/pentane 1:1), afforded **2** (13.6 g, 24%). Colorless oil. The anal. data are in agreement with the values reported in [61].

(R)-3-{3-[(tert-Butoxy)carbonyl]-1-oxopropyl}-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one (**3**). Reaction of **1** (6.0 g, 34.4 mmol) with (*R*)-DIOZ (9.21 g, 32.7 mmol) according to *GP 2*, followed by FC (Et_2O/pentane 1:5), afforded **3** (13.2 g, 92%). White solid. M.p. 149 – 151°. R_{f} (Et_2O/pentane 1:5) 0.30. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +184.0$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 2978*w*, 1782*s*, 1718*m*, 1494*w*, 1450*w*, 1368*m*, 1320*w*, 1153*m*, 1051*w*, 1001*w*, 941*w*, 845*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.77 (*d*, *J* = 6.8, Me); 0.87 (*d*, *J* = 7.0, Me); 1.40 (*s*, ^{t}Bu); 1.90 – 2.00 (*m*, Me_2CH); 2.43 – 2.59 (*m*, CH_2); 2.93 (*ddd*, *J* = 12.3, 6.8, 5.4, 1 H, CH_2); 3.26 (*ddd*, *J* = 13.9, 8.2, 6.7, 1 H, CH_2); 5.38 (*d*, *J* = 3.3, CHN); 7.26 – 7.40 (*m*, 8 arom. H); 7.45 – 7.48 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 16.32, 21.72, 28.00 (Me); 29.77 (CH_2); 30.01 (CH); 30.88 (CH_2); 64.49 (CH); 80.46, 89.46 (C); 125.68, 125.96, 128.37, 128.61, 128.92 (CH); 138.24, 142.32, 152.99, 171.32, 171.93 (C). MALDI-MS: 460.2 (44.34), 404.1 (100.00). Anal. calc. for $C_{26}H_{31}NO_5$ (437.53): C 71.37, H 7.14, N 3.20; found: C 71.40, H 7.26, N 3.15.

(R)-3-{4-[(tert-Butoxy)carbonyl]-1-oxobutyl}-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one (**4**). Reaction of **2** (6.5 g, 34.5 mmol) with (*R*)-DIOZ (9.23 g, 32.8 mmol) according to *GP 2*, followed by FC (Et_2O/pentane 1:5), afforded **4** (13.3 g, 90%). White solid. M.p. 92 – 93°. R_{f} (Et_2O/pentane 1:5) 0.30. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +173.0$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3011*w*, 2972*w*, 1781*s*, 1718*s*, 1494*w*, 1450*m*, 1368*m*, 1320*w*, 1320*m*, 1154*m*, 1050*w*, 1001*w*, 844*w*, 638*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.76 (*d*, *J* = 6.8, Me); 0.87 (*d*, *J* = 7.0, Me); 1.42 (*s*, ^{t}Bu); 1.78 – 2.01 (*m*, CH_2, Me_2CH); 2.20 (*t*, *J* = 7.4, CH_2); 2.77 (*ddd*, *J* = 17.0, 8.0, 6.6, 1 H, CH_2); 2.96 (*ddd*, *J* = 17.0, 8.2, 6.6, 1 H, CH_2); 5.37 (*d*, *J* = 3.4, CHN); 7.25 – 7.40 (*m*, 8 arom. H); 7.45 – 7.48 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.40 (Me); 19.91 (CH_2); 21.77, 28.07 (Me); 29.85 (CH); 34.31, 34.48 (CH_2); 64.47 (CH); 80.27, 89.40 (C); 125.58, 125.92, 127.94, 128.36, 128.60, 128.90 (CH); 138.14, 142.29, 152.98, 172.20, 172.42 (C). MALDI-MS: 474.2 (46.16), 418.2 (98.46). Anal. calc. for $C_{27}H_{33}NO_5$ (451.56): C 71.83, H 7.37, N 3.10; found: C 71.81, H 7.24, N 3.36.

(R)-3-((R)-2-{[(tert-Butoxy)carbonyl]methyl}-1-oxopent-4-enyl)-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one (**5**). Compound **3** (150 mg, 0.34 mmol) was dissolved in THF (0.1M) and cooled to – 78°. LHMDS (1M in THF, 0.38 ml, 1.1 equiv.) was added dropwise, and the mixture was stirred for 1.5 h at this temp. At this point, allyl iodide (0.16 ml, 5 equiv.) was added slowly over 30 min, and the resulting mixture was stirred at – 50° for 23 h. The mixture was quenched with sat. aq. NH_4Cl soln. and diluted with Et_2O. The org. phase was washed with 1M HCl, 1M NaOH, and sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure. FC (Et_2O/pentane 1:6) of the crude product yielded **5** (108 mg, 66%, d.r. 96:4). Colorless oil. R_f (Et_2O/pentane 1:6) 0.34. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.72 (*d*, *J* = 6.7, Me); 0.87 (*d*, *J* = 7.0, Me); 1.23 (*s*, ^{t}Bu); 1.93 – 2.01 (*m*, Me_2CH); 2.27 (*dd*, *J* = 16.9, 4.5, 1 H, CH_2); 2.23 – 2.30 (*m*, 1 H, CH_2); 2.54 (*dd*, *J* = 16.9, 10.5, 1 H, CH_2); 2.51 – 2.57 (*m*, 1 H, CH_2); 3.95 – 4.02 (*m*, CH_2CH); 5.06 – 5.13 (*m*, $CH_2=$); 5.45 (*d*, *J* = 2.8, CHN); 5.76 – 5.86 (*m*, CH=); 7.25 – 7.51 (*m*, 8 arom. H); 7.44 – 7.49 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.18, 22.00, 28.03 (Me); 30.63 (CH); 36.18, 36.90 (CH_2); 39.64, 64.61 (CH); 80.55, 89.52 (C); 118.09 (CH_2); 126.14, 126.33, 128.22, 128.73, 128.89, 129.25, 135.04 (CH); 139.03, 142.97, 152.97, 171.15, 175.04 (C). MALDI-MS: 500.2 (36.73), 444.2 (100.00). HR-MALDI-MS: 500.2447 ($[C_{29}H_{35}NNaO_5]^+$; calc. 500.2407).

(R)-3-((R)-2-{[(Benzyloxy)carbonyl]methyl}-3-[(tert-butoxy)carbonyl]-1-oxopropyl)-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one (**6**). Transformation of **3** (3.2 g, 7.32 mmol) according to *GP 3*, followed by FC (Et_2O/pentane 1:4) afforded, beside the recovery of unreacted starting material (0.8 g, 25%), compound **6** (2.43 g, 57%). Colorless oil. R_{f} (Et_2O/pentane 1:4) 0.24. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +124.5$ ($c = 0.80$, $CHCl_3$). IR ($CHCl_3$): 3015*w*, 2974*w*, 2933*w*, 1780*s*, 1728*s*, 1703*m*, 1451*w*, 1364*m*, 1318*w*, 1330*m*, 1159*s*, 1051*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.75 (*d*, *J* = 6.8, Me); 0.86 (*d*, *J* = 7.0, Me); 1.30 (*s*, ^{t}Bu); 1.91 – 1.99 (*m*, Me_2CH); 2.23 (*dd*, *J* = 16.5, 6.5, 1 H, CH_2); 2.37 (*dd*, *J* = 16.5, 7.8, 1 H, CH_2); 2.62 (*dd*, *J* = 16.5, 6.6, 1 H, CH_2); 2.90 (*dd*, *J* = 16.5, 7.3, 1 H, CH_2); 4.32 – 4.39 (*m*, CH_2CH); 5.11 (*d*, *J* = 7.9, $PhCH_2$); 5.38 (*d*, *J* = 2.9, CHN); 7.24 – 7.48 (*m*, 15 arom. H). ^{13}C-NMR (100 MHz,

$CDCl_3$): 16.04, 21.65, 27.92 (Me); 30.11 (CH); 35.65, 36.05 (CH_2); 64.82 (CH); 66.60 (CH_2); 80.72, 89.42 (C); 125.68, 125.80, 125.96, 127.91, 128.23, 128.25, 128.34, 128.54, 128.57, 128.85 (CH); 135.72, 138.29, 142.30, 152.59, 169.83, 170.86, 173.71 (C). MALDI-MS: 608.2 (44.44), 552.2 (100.00). Anal. calc. for $C_{35}H_{39}NO_7$ (585.70): C 71.78, H 6.71, N 2.39; found: C 71.95, H 6.62, N 2.44.

(R)*-3-((*R*)-2-{[(Benzyloxy)carbonyl]methyl}-4-[(*tert*-butoxy)carbonyl]-1-oxobutyl)-4-(1-methylethyl)-5,5-diphenyloxazolidin-2-one* (**7**). Transformation of **4** (4.3 g, 9.52 mmol) according to *GP 3*, followed by FC (Et_2O/pentane 1:4), afforded **7** (3.14 g, 55%). Colorless oil. R_f (Et_2O/pentane 1:4) 0.33. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +112.8$ ($c =$ 0.68, $CHCl_3$). IR ($CHCl_3$): 2930*w*, 1781*s*, 1727*s*, 1598*m*, 1451*w*, 1354*m*, 1313*w*, 1251*w*, 1239*m*, 1158*s*, 1149*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.74 (*d*, $J = 6.7$, Me); 0.81 (*d*, $J = 7.0$, Me); 1.31 (*s*, ^{t}Bu); 1.41–1.68 (*m*, 2 CH_2); 1.87–1.95 (*m*, Me_2CH); 2.43 (*dd*, $J = 16.9$, 4.4, 1 H, CH_2); 2.88 (*dd*, $J = 16.9$, 10.3, 1 H, CH_2); 4.14–4.21 (*m*, CH_2CH); 5.03 (*d*, $J = 10.3$, $PhCH_2$); 5.63 (*d*, $J = 3.0$, CHN); 7.15–7.38 (*m*, 11 arom. H); 7.43–7.44 (*m*, 2 arom. H); 7.45–7.46 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.02, 21.52 (Me); 27.03 (CH_2); 28.03 (Me); 30.02 (CH); 31.87, 36.37 (CH_2); 37.92, 65.29 (CH); 66.49 (CH_2); 80.20, 89.24 (C); 125.44, 125.78, 127.95, 128.18, 128.20, 128.43, 128.52, 128.70, 128.92 (CH); 135.78, 137.94, 142.46, 152.75, 171.38, 171.54, 174.71 (C). HR-MALDI-MS: 622.2775 ($[C_{36}H_{41}NNaO_7]^+$; calc. 622.2781).

(R)*-3-{(*R*)-[(*tert*-Butoxy)carbonyl]methyl}-4-[4-(1-methylethyl)-2-oxo-5,5-diphenyloxazolidin-3-yl]-4-oxobutanoic acid* (**8**). Transformation of **6** (2.4 g, 4.1 mmol) according to *GP 4*, followed by FC (Et_2O/pentane/AcOH 10:20:0.1), afforded **8** (1.67 g, 82%). White foam. R_f (Et_2O/pentane/AcOH 10:20:0.1) 0.31. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +148.0$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 2980*w*, 1780*s*, 1725*s*, 1601*w*, 1494*w*, 1450*w*, 1368*m*, 13196*m*, 1176*m*, 1153*m*, 1052*w*, 990*w*, 942*w*, 844*w*, 638*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.75 (*d*, $J = 6.7$, Me); 0.86 (*d*, $J = 7.0$, Me); 1.30 (*s*, ^{t}Bu); 1.91–1.99 (*m*, Me_2CH); 2.24 (*dd*, $J = 16.4$, 6.5, 1 H, CH_2); 2.36 (*dd*, $J = 16.4$, 7.6, 1 H, CH_2); 2.57 (*dd*, $J = 16.7$, 6.6, 1 H, CH_2); 2.86 (*dd*, $J = 16.7$, 7.0, 1 H, CH_2); 4.25–4.32 (*m*, CH_2CH); 5.38 (*d*, $J = 3.0$, CHN); 7.24–7.46 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.05, 21.63, 27.91 (Me); 30.08 (CH); 36.00 (CH_2); 36.55, 64.81 (CH); 80.88, 89.51 (C); 125.82, 125.99, 127.91, 128.34, 128.57, 128.85 (CH); 138.24, 142.25, 152.65, 170.07, 173.72, 176.64 (C). MALDI-MS: 518.2 (68.93), 462.1 (100.00). Anal. calc. for $C_{28}H_{33}NO_7$ (495.57): C 67.86, H 6.71, N 2.83; found: C 67.74, H 6.54, N 2.76.

(R)*-5-[(*tert*-Butoxy)carbonyl]-3-[(*R*)-4-(1-methylethyl)-2-oxo-5,5-diphenyloxazolidine-3-carbonyl]pentanoic Acid* (**9**). Transformation of **7** (2.67 g, 4.45 mmol) according to *GP 4*, followed by FC (Et_2O/pentane/AcOH 10:20:0.1), afforded **9** (2.02 g, 89%). White foam. R_f (Et_2O/pentane/AcOH 10:20:0.1) 0.22. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +121.5$ ($c = 0.95$, $CHCl_3$). IR ($CHCl_3$): 3015*w*, 2974*m*, 2933*w*, 1779*s*, 1718*s*, 1451*w*, 1390*w*, 1364*m*, 1318*w*, 1256*w*, 1236*w*, 1174*m*, 1149*w*. ^{1}H-NMR (400 MHz, CD_3OD): 0.78 (*d*, $J = 6.7$, Me); 0.92 (*d*, $J = 7.0$, Me); 1.39 (*s*, ^{t}Bu); 1.39–1.46 (*m*, CH_2); 1.60–1.65 (*m*, CH_2); 2.01–2.08 (*m*, Me_2CH); 2.45 (*dd*, $J = 17.0$, 4.4, 1 H, CH_2); 2.78 (*dd*, $J = 17.0$, 10.6, 1 H, CH_2); 4.14–4.21 (*m*, CH_2CH); 5.52 (*d*, $J = 2.7$, CHN); 7.25–7.31 (*m*, 2 arom. H); 7.34–7.39 (*m*, 4 arom. H); 7.48–7.52 (*m*, 2 arom. H); 7.57-7.60 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.34, 21.93 (Me); 28.30 (CH_2); 28.36 (Me); 31.46 (CH); 32.98, 37.13 (CH_2); 39.29, 66.74 (CH); 81.64, 90.57 (C); 126.48, 126.82, 129.08, 129.80, 130.05 (CH); 139.54, 144.44, 154.39, 173.48, 174.99, 176.44 (C). HR-MALDI-MS: 532.2306 ($[C_{29}H_{35}NNaO_7]^+$; calc. 532.2312).

tert-*Butyl (*S*)-3-({[(Benzyloxy)carbonyl]amino}methyl)-4-[(*R*)-4-(1-methylethyl)-2-oxo-5,5-diphenyloxazolidin-3-yl]-4-oxobutanoate* (**10**). Transformation of **8** (2.0 g, 4.0 mmol) according to *GP 5*, followed by FC (Et_2O/pentane 1:3 → 1:2), afforded **10** (1.84 g, 76%). White solid. M.p. 132–134°. R_f (Et_2O/pentane 1:2) 0.28. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +123.0$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3438*w*, 3008*w*, 2966*w*, 2992*w*, 1777*s*, 1722*s*, 1516*m*, 1450*m*, 1394*w*, 1368*m*, 1248*m*, 1154*m*, 1052*w*, 990*w*, 845*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.69 (*d*, $J = 6.7$, Me); 0.84 (*d*, $J = 7.0$, Me); 1.26 (*s*, ^{t}Bu); 1.91–1.99 (*m*, Me_2CH); 2.30 (*dd*, $J = 16.8$, 4.6, 1 H, CH_2); 2.65 (*dd*, $J = 16.8$, 9.9, 1 H, CH_2); 3.44–4.60 (*m*, CH_2); 4.09–4.13 (*m*, CH_2CH); 5.07 (*s*, $PhCH_2$); 5.23 (br. *s*, NH); 5.40 (*d*, $J = 3.0$, CHN); 7.23–7.46 (*m*, 15 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.01, 21.79, 27.90 (Me); 30.01 (CH); 34.81 (CH_2); 40.07 (CH); 42.80 (CH_2); 64.87 (CH); 66.81 (CH_2); 80.69, 89.67 (C); 125.79, 125.82, 127.93, 128.09, 128.16, 128.36, 128.48, 128.54, 128.85 (CH); 136.42, 138.25, 142.08, 153.18, 156.26, 170.13, 173.36 (C). MALDI-MS: 639.2 (3.07), 623.3 (20.11), 567.2 (100.00), 286.1 (44.30). Anal. calc. for $C_{35}H_{40}N_2O_7$ (600.70): C 69.98, H 6.71, N 4.66; found: C 69.94, H 6.80, N 4.56.

tert-*Butyl (*S*)-4-({[(Benzyloxy)carbonyl]amino}methyl)-5-[(*R*)-4-(1-methylethyl)-2-oxo-5,5-diphenyloxazolidin-3-yl)-5-oxopentanoate* (**11**). Transformation of **9** (5.94 g, 11.6 mmol) according to *GP 5*, followed by FC (Et_2O/pentane 1:3 → 1:2), afforded **11** (5.4 g, 75%). Colorless oil. R_f (Et_2O/pentane 1:2) 0.32. $[\alpha]_{\mathrm{D}}^{\mathrm{r.t.}} = +75.8$ ($c = 0.85$, $CHCl_3$). IR ($CHCl_3$): 3015*m*, 2974*w*, 2933*w*, 1780*s*, 1718*s*, 1513*m*, 1451*m*, 1364*m*, 1313*m*, 1231*s*, 1176*s*, 1154*s*, 1050*w*, 990*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.61 (*d*, $J = 6.7$, Me); 0.85 (*d*, $J = 7.0$, Me); 1.32 (*s*, ^{t}Bu); 1.37–1.48 (*m*, 4 H, 2 CH_2); 2.00–2.08 (*m*, Me_2CH); 3.22–3.29 (*m*, CH_2N); 3.78–3.82 (*m*, CH_2CH); 4.93–5.02 (*m*, $PhCH_2$); 5.58 (*d*, $J = 2.4$, CHN); 7.24–7.41 (*m*, 12 H, 11 arom. H, NH); 7.57 (*d*, $J = 7.2$, 2 arom. H), 7.64 (*d*,

$J = 7.4$, 2 arom. H). ^{13}C-NMR (100 MHz, (D$_6$)DMSO): 15.27, 20.90 (Me); 24.48 (CH$_2$); 27.56 (Me); 29.21 (CH); 31.01 (CH$_2$); 41.62 (CH); 41.99 (CH$_2$); 64.80 (CH); 65.11 (CH$_2$); 79.39, 88.65 (C); 124.74, 125.16, 127.54, 127.61, 127.71, 128.17, 128.26, 128.36, 128.63 (CH); 136.99, 137.80, 142.86, 152.35, 156.01, 170.87, 173.14 (C). HR-MALDI-MS: 637.2884 ([$C_{36}H_{42}N_2NaO_7$]$^+$; calc. 637.2890). Anal. calc. for $C_{36}H_{42}N_2O_7$ (614.73): C 70.34, H 6.89, N 4.56; found: C 70.30, H 6.75, N 4.62.

*(*S*)-2-({[(Benzyloxy)carbonyl]amino}methyl)-3-[(*tert*-butoxy)carbonyl]propanoic Acid* (Z-β^2hAsp(O^{t}Bu)-OH; **12**). Transformation of **10** (3.0 g, 5.0 mmol) according to *GP 6*, followed by FC (Et$_2$O/pentane/AcOH 20 : 10 : 0.1), afforded **12** (1.5 g, 89%). Colorless oil. R_f (Et$_2$O/pentane/AcOH 20 : 10 : 0.1) 0.40. $[\alpha]_D^{r.t.} = +35.4$ ($c = 0.85$, CHCl$_3$). IR (CHCl$_3$): 3436*m*, 3036*m*, 2974*m*, 1718*s*, 1513*s*, 1451*m*, 1364*m*, 1148*s*. ^{1}H-NMR (400 MHz, CD$_3$OD): 1.43 (*s*, ^{t}Bu); 2.43 (*dd*, $J = 16.6, 5.2$, 1 H, CH$_2$); 2.55 (*dd*, $J = 16.6, 8.8$, 1 H, CH$_2$); 2.90 – 2.96 (*m*, CH$_2$C*H*); 3.28 – 3.38 (*m*, 1 H, CH$_2$N); 3.43 (*dd*, $J = 13.9, 6.3$, 1 H, CH$_2$N); 5.07 (*s*, PhC*H*$_2$); 7.27 – 7.34 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, CD$_3$OD): 28.32 (Me); 36.04, 43.00 (CH$_2$); 43.41 (CH); 67.55 (CH$_2$); 82.07 (C), 128.82, 129.00, 129.49 (CH); 138.38, 158.93, 172.75, 176.56 (C). HR-MALDI-MS: 360.1418 ([$C_{17}H_{23}NNaO_6$]$^+$; calc. 360.1423).

*(*S*)-2-({[(Benzyloxy)carbonyl]amino}methyl)-4-[(*tert*-butoxy)carbonyl]butanoic Acid* (Z-β^2hGlu(O^{t}Bu)-OH; **13**). Transformation of **11** (2.7 g, 4.39 mmol) according to *GP 6*, followed by FC (Et$_2$O/pentane/AcOH 20 : 10 : 0.1), afforded acid **13** (1.5 g, 93%). Colorless oil. R_f (Et$_2$O/pentane/AcOH 20 : 10 : 0.1) 0.35. $[\alpha]_D^{r.t.} = +2.3$ ($c = 1.03$, CHCl$_3$). IR (CHCl$_3$): 3446*w*, 2974*w*, 1718*s*, 1513*m*, 1451*w*, 1369*m*, 1149*m*. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 1.31 (*s*, ^{t}Bu); 1.52 – 1.66 (*m*, CH$_2$); 2.04 – 2.21 (*m*, CH$_2$CO); 2.36 – 2.40 (*m*, CH$_2$C*H*); 2.96 – 3.03 (*m*, 1 H, CH$_2$N); 3.11 – 3.18 (*m*, 1 H, CH$_2$N); 4.94 (*s*, PhC*H*$_2$); 7.21 – 7.31 (*m*, 5 arom. H); 12.25 (br. *s*, CO$_2$H). ^{13}C-NMR (100 MHz, (D$_6$)DMSO): 24.26 (CH$_2$); 27.63 (Me); 32.28, 41.82 (CH$_2$); 44.26 (CH); 65.12 (CH$_2$); 79.53 (C); 127.54, 127.63, 128.23 (CH); 137.06, 156.07, 171.54, 174.77 (C). HR-MALDI-MS: 374.1574 ([$C_{18}H_{25}NNaO_6$]$^+$; calc. 374.1580). Anal. calc. for $C_{18}H_{25}NO_6$ (351.39): C 61.53, H 7.17, N 3.99; found: C 61.32, H 7.13, N 4.00.

*(*S*)-3-[(*tert*-Butoxy)carbonyl]-2-({[(9*H*-fluoren-9-yl)carbonyl]amino}methyl)propanoic Acid* (Fmoc-β^2hAsp(O^{t}Bu)-OH; **14**). The Z-protected acid **12** (1 g, 2.96 mmol) in MeOH (0.02M) was hydrogenated according to *GP 7*. The resulting product was Fmoc-protected according to *GP 8*. FC (Et$_2$O/pentane/AcOH 20 : 10 : 0.1) of the crude product afforded **14** (1.18 g, 94%). White solid. M.p. 109 – 113°. R_f (Et$_2$O/pentane/AcOH 20 : 10 : 0.1) 0.19. $[\alpha]_D^{r.t.} = +1.4$ ($c = 1.20$, CHCl$_3$). IR (CHCl$_3$): 3450*w*, 3015*m*, 2981*m*, 1723*s*, 1515*s*, 1450*m*, 1369*m*, 1236*s*, 1153*s*. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 1.38 (*s*, ^{t}Bu); 2.30 – 2.45 (*m*, COCH$_2$); 2.73 – 2.80 (*m*, C*H*CH$_2$N); 3.08 – 3.15 (*m*, 1 H, CH$_2$N); 3.25 – 3.30 (*m*, 1 H, CH$_2$N); 4.21 (*t*, $J = 7.0$, C*H*CH$_2$O); 4.30 (*d*, $J = 7.3$, CHC*H*$_2$O); 7.31 – 7.44 (*m*, 4 arom. H, NH); 7.68 (*d*, $J = 7.4$, 2 arom. H), 7.88 (*d*, $J = 7.5$, 2 arom. H); 12.38 (br. *s*, CO$_2$H). ^{13}C-NMR (100 MHz, (D$_6$)DMSO): 27.60 (Me); 34.40, 41.41 (CH$_2$); 41.62, 46.64 (CH); 65.28 (CH$_2$); 79.76 (C); 120.01, 125.08, 126.94, 127.50 (CH); 140.63, 143.76, 156.09, 170.53, 173.97 (C). HR-MALDI-MS: 448.1731 ([$C_{24}H_{27}NNaO_6$]$^+$; calc. 448.1736). Anal. calc. for $C_{24}H_{27}NO_6$ (425.47): C 67.75, H 6.40, N 3.29; found: C 67.84, H 6.39, N 3.34.

*(*S*)-4-[(*tert*-Butoxy)carbonyl]-2-({[(9*H*-fluoren-9-yl)carbonyl]amino}methyl)butanoic Acid* (Fmoc-β^2hGlu(O^{t}Bu)-OH; **15**). The Z-protected acid **13** (0.2 g, 0.57 mmol) in MeOH (0.02M) was hydrogenated according to *GP 7*. The resulting product was Fmoc-protected according to *GP 8*. FC (Et$_2$O/pentane/AcOH 20 : 10 : 0.1) of the crude product afforded **15** (225 mg, 90%). Colorless oil. R_f (Et$_2$O/pentane/AcOH 20 : 10 : 0.1) 0.18. $[\alpha]_D^{r.t.} = +1.8$ ($c = 0.85$, CHCl$_3$). IR (CHCl$_3$): 3445*w*, 3010*m*, 2977*w*, 1720*s*, 1514*m*, 1448*m*, 1369*m*, 1225*m*, 1150*s*. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 1.38 (*s*, ^{t}Bu); 1.63 – 1.73 (*m*, COCH$_2$C*H*$_2$); 2.13 – 2.27 (*m*, COCH$_2$); 2.44 – 2.49 (*m*, CH$_2$C*H*); 3.06-3.10 (*m*, 1 H, CH$_2$N); 3.20 – 3.25 (*m*, 1 H, CH$_2$N); 4.20 (*t*, $J = 5.5$, C*H*CH$_2$O); 4.27 (*d*, $J = 4.7$, CHC*H*$_2$O); 7.31 – 7.45 (*m*, 4 arom. H, NH); 7.69 (*d*, $J = 6.0$, 2 arom. H), 7.88 (*d*, $J = 6.0$, 2 arom. H); 12.32 (br. *s*, CO$_2$H). ^{13}C-NMR (100 MHz, (D$_6$)DMSO): 24.25 (CH$_2$); 27.64 (Me); 32.29, 41.78 (CH$_2$); 44.24, 46.62 (CH); 65.33 (CH$_2$); 79.54 (C); 119.99, 125.10, 126.95, 127.50 (CH); 140.62, 143.78, 156.05, 171.55, 174.79 (C). HR-MALDI-MS: 462.1887 ([$C_{25}H_{29}NNaO_6$]$^+$; calc. 462.1893). Anal. calc. for $C_{25}H_{29}NO_6$ (439.50): C 68.32, H 6.65, N 3.19; found: C 68.33, H 6.81, N 3.19.

*1-Benzyl 4-(*tert*-Butyl) (*S*)-2-({[(Benzyloxy)carbonyl]amino}methyl)butanedioate* (Z-β^2hAsp(O^{t}Bu)-OBn; **16**). Transformation of **12** (2.7 g, 8.0 mmol) according to *GP 9*, followed by FC (Et$_2$O/pentane 1 : 2), afforded **16** (3.11 g, 91%). Colorless oil. R_f (Et$_2$O/pentane 2 : 1) 0.34. $[\alpha]_D^{r.t.} = +1.6$ ($c = 1.03$, CHCl$_3$). IR (CHCl$_3$): 3446*w*, 3015*m*, 2974*w*, 1723*s*, 1513*m*, 1456*w*, 1364*m*, 1251*m*, 1149*s*. ^{1}H-NMR (400 MHz, CD$_3$OD): 1.37 (*s*, ^{t}Bu); 2.45 (*dd*, $J = 16.8, 4.8$, 1 H, COCH$_2$); 2.60 (*dd*, $J = 16.8, 9.4$, 1 H, COCH$_2$); 2.97 – 3.03 (*m*, CH$_2$C*H*); 3.33 – 3.43 (*m*, CH$_2$N); 5.04 – 5.13 (*m*, 2 PhC*H*$_2$); 7.27 – 7.36 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, CD$_3$OD): 28.25 (Me); 35.85, 43.03 (CH$_2$); 45.58 (CH); 67.53, 67.75 (CH$_2$); 82.13 (C); 128.80, 128.97, 129.17, 129.24, 129.45, 129.51 (CH); 138.28, 137.39, 158.83, 172.44, 174.56 (C). HR-MALDI-MS: 450.1887 ($[C_{24}H_{29}NNaO_6]^+$; calc. 450.1893). Anal. calc. for $C_{24}H_{29}NO_6$ (427.49): C 67.43, H 6.84, N 3.28; found: C 67.18, H 6.84, N 3.53.

*1-Benzyl 5-(*tert*-Butyl) (*S*)-2-([{(Benzyloxy)carbonyl]amino}methyl)pentanedioate* (Z-β^2hGlu(O^{t}Bu)-OBn; **17**). Transformation of **13** (3.0 g, 8.5 mmol) according to *GP 9*, followed by FC (Et_2O/pentane 1:2), afforded **17** (3.5 g, 93%). Colorless oil. R_f (Et_2O/pentane 2:1) 0.26. $[\alpha]_D^{r.t.} = +5.7$ ($c = 0.58$, $CHCl_3$). IR ($CHCl_3$): 3446*w*, 3026*w*, 2995*w*, 1718*s*, 1513*m*, 1456*w*, 1364*w*, 1236*m*, 1149*m*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.37 (*s*, ^{t}Bu); 1.67–1.73 (*m*, $COCH_2CH_2$); 2.10–2.25 (*m*, $COCH_2$); 2.57–2.65 (*m*, CH_2CH); 3.11–3.18 (*m*, 1 H, CH_2N); 3.22–3.29 (*m*, 1 H, CH_2N); 5.00–5.10 (*m*, 2 $PhCH_2$); 7.28–7.36 (*m*, 10 arom. H); 7.44 (*t*, $J = 5.9$, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 24.24 (CH_2); 27.61 (Me); 32.04, 41.90 (CH_2); 44.33 (CH); 65.20, 65.64 (CH_2); 79.53 (C); 127.56, 127.65, 127.75, 127.87, 128.21, 128.27 (CH); 136.01, 137.00, 156.08, 171.42, 173.07 (C). HR-MALDI-MS: 464.2044 ($[C_{25}H_{31}NNaO_6]^+$; calc. 464.2049). Anal. calc. for $C_{25}H_{31}NO_6$ (441.52): C 68.01, H 7.08, N 3.17; found: C 61.12, H 6.97, N 3.29.

*Benzyl (*S*)-3-(Aminocarbonyl)-2-([{(benzyloxy)carbonyl]amino}methyl)propanoate* (Z-β^2hAsn-OBn; **18**). The diester **16** (0.55 g, 1.29 mmol) was ^{t}Bu deprotected according to *GP 10*. The acid obtained was then converted to **18** according to *GP 11*. Recrystallization of the crude product yielded **18** (345 mg, 72%). White solid. M.p. 130–131°. R_f (AcOEt/Et_2O 2:1) 0.2. $[\alpha]_D^{r.t.} = -18.7$ ($c = 0.92$, $CHCl_3$). IR ($CHCl_3$): 3518*w*, 3426*w*, 3405*w*, 3015*w*, 2954*w*, 1723*s*, 1682*s*, 1595*w*, 1513*m*, 1451*w*, 1226*s*, 1174*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.28 (*dd*, $J = 15.8, 5.1$, 1 H, $COCH_2$); 2.44 (*dd*, $J = 15.8, 9.0$, 1 H, $COCH_2$); 2.90–2.97 (*m*, CH_2CH); 3.16–3.29 (*m*, CH_2N); 4.97–5.07 (*m*, 2 $PhCH_2$); 6.82 (br. *s*, 1 H, NH_2); 7.28–7.37 (*m*, 11 H, 10 arom. H, NH_2); 7.42 (*t*, $J = 6.0$, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 34.17, 41.64 (CH_2); 41.83 (CH); 65.23, 65.50 (CH_2); 127.51, 127.59, 127.67, 127.70, 128.21, 128.23 (CH); 136.11, 136.97, 156.09, 171.92, 172.90 (C). HR-MALDI-MS: 393.1421 ($[C_{20}H_{22}N_2NaO_5]^+$; calc. 393.1427). Anal. calc. for $C_{20}H_{22}N_2O_5$ (370.40): C 64.85, H 5.99, N 7.56; found: C 64.83, H 5.95, N 7.43.

*Benzyl (*S*)-4-(Aminocarbonyl)-2-([{(benzyloxy)carbonyl]amino}methyl)butanoate* (Z-β^2hGln-OBn; **19**). The diester **17** (3.5 g, 7.93 mmol) was ^{t}Bu deprotected according to *GP 10*. The acid obtained was then converted to **19** according to *GP 11*. Recrystallization of the crude product yielded **19** (2.63 g, 83%). White solid. M.p. 112–113°. R_f (EtOAc/Et_2O 2:1) 0.28. $[\alpha]_D^{r.t.} = +2.5$ ($c = 0.95$, $CHCl_3$). IR ($CHCl_3$): 3528*w*, 3446*w*, 3405*w*, 3036*w*, 3005*w*, 2964*w*, 1718*s*, 1682*s*, 1590*w*, 1513*m*, 1451*w*, 1226*m*, 1164*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.66–1.73 (*m*, $COCH_2CH_2$); 1.99–2.12 (*m*, $COCH_2$); 2.56–2.63 (*m*, CH_2CH); 3.13–3.29 (*m*, CH_2N); 5.00 (*s*, $PhCH_2$); 5.06 (s, $PhCH_2$); 6.73 (*s*, 1 H, NH_2); 7.23 (*s*, 1 H, NH_2); 7.27–7.37 (*m*, 10 arom. H); 7.42 (*t*, $J = 5.9$, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 24.75, 32.20, 42.01 (CH_2); 44.79 (CH); 65.18, 65.58 (CH_2); 127.56, 127.65, 127.71, 127.83, 128.23, 128.28 (CH); 136.02, 137.00, 156.06, 173.27 (C). HR-MALDI-MS: 407.1577 ($[C_{21}H_{24}N_2NaO_5]^+$; calc. 407.1583). Anal. calc. for $C_{21}H_{24}N_2O_5$ (384.43): C 65.61, H 6.29, N 7.29; found: C 65.67, H 6.50, N 7.37.

*Benzyl (*S*)-2-([{(Benzyloxy)carbonyl]amino}methyl)-3-{[triphenylmethyl)amino]carbonyl}propanoate* (Z-β^2hAsn(Trt)-OBn; **20**). Treatment of **18** (0.3 g, 0.81 mmol) according to *GP 12*, followed by FC (Et_2O/pentane 3:1), afforded **20** (421 mg, 85%). White solid. M.p. 104–105°. R_f (Et_2O/pentane 3:1) 0.29. $[\alpha]_D^{r.t.} = -20.8$ ($c = 1.15$, $CHCl_3$). IR ($CHCl_3$): 3434*w*, 3028*w*, 3020*w*, 1721*s*, 1513*s*, 1492*s*, 1446*w*, 1236*m*, 1195*w*, 1169*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.45 (*dd*, $J = 15.6, 5.2$, 1 H, $COCH_2$); 2.75 (*dd*, $J = 15.6, 8.9$, 1 H, $COCH_2$); 2.83–2.90 (*m*, CH_2CH); 3.12–3.26 (*m*, CH_2N); 4.96–5.05 (*m*, 2 $PhCH_2$); 7.14–7.34 (*m*, 25 arom. H); 7.38 (*t*, $J = 6.1$, NH); 8.69 (*s*, NHTrt). ^{13}C-NMR (100 MHz, (D_6)DMSO): 35.20, 41.71 (CH_2); 41.88 (CH); 65.25, 65.60 (CH_2); 69.24 (C); 126.21, 127.30, 127.56, 127.62, 127.68, 127.72, 128.03, 128.22, 128.42 (CH); 136.01, 136.95, 144.69, 156.08, 169.75, 172.79 (C). HR-MALDI-MS: 635.2516 ($[C_{39}H_{36}N_2NaO_5]^+$; calc. 635.2522). Anal. calc. for $C_{39}H_{36}N_2O_5$ (612.71): C 76.45, H 5.92, N 4.57; found: C 76.27, H 6.02, N 4.57.

*Benzyl (*S*)-2-([{(Benzyloxy)carbonyl]amino}methyl)-4-{[(triphenylmethyl)amino]carbonyl}butanoate* (Z-β^2hGln(Trt)-OBn; **21**). Treatment of **19** (2.66 g, 6.9 mmol) according to *GP 12*, followed by FC (Et_2O/pentane 3:1), afforded **21** (3.81 g, 88%). White solid. M.p. 91–92°. R_f (Et_2O/pentane 3:1) 0.3. $[\alpha]_D^{r.t.} = -4.6$ ($c = 0.90$, $CHCl_3$). IR ($CHCl_3$): 3536*w*, 3067*w*, 3035*w*, 3005*w*, 1718*s*, 1682*m*, 1512*s*, 1492*s*, 1446*w*, 1235*m*, 1164*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.63–1.68 (*m*, $COCH_2CH_2$); 2.27–2.30 (*m*, $COCH_2$); 2.52–2.59 (*m*, CH_2CH); 3.12–3.25 (*m*, CH_2N); 4.99 (*s*, $PhCH_2$); 5.07 (s, $PhCH_2$); 7.14-7.32 (*m*, 25 arom. H); 7.33 (*t*, $J = 2.4$, NH) 7.23 (*s*, NHTrt). ^{13}C-NMR (100 MHz, (D_6)DMSO): 24.89, 33.09, 41.91 (CH_2); 44.73 (CH); 65.18, 65.56 (CH_2); 69.10 (C); 126.19, 127.32, 127.56, 127.64, 127.67, 127.81, 128.22, 128.27 (CH); 136.04, 136.98, 144.79, 156.07, 171.09, 173.29 (C). HR-MALDI-MS: 649.2673 ($[C_{40}H_{38}N_2NaO_5]^+$; calc. 649.2679). Anal. calc. for $C_{40}H_{38}N_2O_5$ (626.74): C 76.66, H 6.11, N 4.47; found: C 76.65, H 6.16, N 4.41.

*(*S*)-2-({[(9*H*-Fluoren-9-yl)carbonyl]amino}methyl)-3-{[(triphenylmethyl)amino]carbonyl}propanoic Acid* (Fmoc-β^2hAsn(Trt)-OH; **22**). Hydrogenation of **20** (0.39 g, 0.64 mmol) in MeOH (0.02M) according to *GP 7* afforded the crude H-β^2hAsn(Trt)-OH, which was Fmoc-protected according to *GP 8* to give, after FC (AcOEt/

pentane/AcOH 20 : 10 : 0.1), the acid **22** (0.36 g, 93%). White foam. R_f (AcOEt/pentane/AcOH 20 : 10 : 0.1) 0.4. $[\alpha]_D^{\mathrm{r.t.}} = -29.6$ ($c = 1.35$, $\mathrm{CHCl_3}$). IR ($\mathrm{CHCl_3}$): 3436*w*, 3056*w*, 3005*w*, 2995*w*, 1718*s*, 1672*m*, 1625*w*, 1513*s*, 1492*s*, 1446*m*, 1231*m*. ^{1}H-NMR (400 MHz, ($\mathrm{D_6}$)DMSO): 2.36 (*dd*, $J = 15.2$, 4.8, 1 H, $\mathrm{COCH_2}$); 2.67 (*dd*, $J = 15.2$, 9.1, 1 H, $\mathrm{COCH_2}$); 2.72 – 2.75 (*m*, $\mathrm{CH_2C}H$); 3.06 – 3.13 (*m*, 1 H, $\mathrm{CH_2N}$); 3.18 – 3.26 (*m*, 1 H, $\mathrm{CH_2N}$); 4.19 – 4.22 (*m*, $\mathrm{C}H\mathrm{CH_2O}$); 4.26 – 4.28 (*m*, $\mathrm{CH_2O}$); 5.01 (*d*, $J = 1.8$, $\mathrm{N}H\mathrm{CH_2}$); 7.15 – 7.21 (*m*, 9 arom. H); 7.23 – 7.42 (*m*, 10 arom. H); 7.68 (*d*, $J = 7.4$, 2 arom. H); 7.88 (*d*, $J = 7.5$, 2 arom. H); 8.64 (*s*, NHTrt); 12.27 (br. *s*, $\mathrm{CO_2H}$). ^{13}C-NMR (100 MHz, ($\mathrm{D_6}$)DMSO): 34.43, 41.66 ($\mathrm{CH_2}$); 41.80, 46.60 (CH); 65.36 ($\mathrm{CH_2}$); 69.20 (C); 120.00, 125.10, 126.20, 126.97, 127.30, 127.51, 127.60, 127.65, 128.23, 128.46 (CH); 137.03, 140.60, 143.74, 143.79, 144.79, 156.05, 170.07, 174.53, 174.56 (C). HR-MALDI-MS: 633.2366 ($[\mathrm{C_{39}H_{34}N_2NaO_5}]^+$; calc. 633.2360).

(S)-2-({[(9H-Fluoren-9-yl)carbonyl]amino}methyl)-4-{[(triphenylmethyl)amino]carbonyl}butanoic Acid (Fmoc-β^2hGln(Trt)-OH; **23**). Hydrogenation of **21** (0.25 g, 0.4 mmol) in MeOH (0.02M) according to *GP 7* afforded the crude H-β^2hGln(Trt)-OH, which was Fmoc-protected according to *GP 8* to give, after FC (AcOEt/pentane/AcOH 20 : 10 : 0.1), the acid **23** (0.23 g, 92%). White foam. R_f (AcOEt/pentane/AcOH 20 : 10 : 0.1) 0.22. $[\alpha]_D^{\mathrm{r.t.}} = -10$ ($c = 0.95$, $\mathrm{CHCl_3}$). IR ($\mathrm{CHCl_3}$): 3436*w*, 3024*w*, 2974*w*, 1713*s*, 1513*s*, 1492*s*, 1446*m*, 1236*m*, 1149*w*, 1103*w*. ^{1}H-NMR (400 MHz, ($\mathrm{D_6}$)DMSO): 1.59 – 1.66 (*m*, $\mathrm{COCH_2C}H_2$); 2.27 – 2.32 (*m*, $\mathrm{COCH_2}$); 2.41 – 2.45 (*m*, $\mathrm{CH_2C}H$); 3.04 – 3.11 (*m*, 1 H, $\mathrm{CH_2N}$); 3.16 – 3.23 (*m*, 1 H, $\mathrm{CH_2N}$); 4.18 – 4.21 (*m*, $\mathrm{C}H\mathrm{CH_2O}$); 4.24 – 4.26 (*m*, $\mathrm{CH_2O}$); 7.15 – 7.34 (*m*, 17 arom. H, NH); 7.40 (*t*, $J = 7.4$, 3 arom. H); 7.67 (*d*, $J = 7.4$, 2 arom. H); 7.88 (*d*, $J = 7.5$, 2 arom. H); 8.57 (*s*, NHTrt); 12.26 (br. *s*, $\mathrm{CO_2H}$). ^{13}C-NMR (100 MHz, ($\mathrm{D_6}$)DMSO): 25.00, 33.36, 41.81 ($\mathrm{CH_2}$); 44.67, 46.59 (CH); 65.35 ($\mathrm{CH_2}$); 69.08 (C); 119.98, 125.11, 126.17, 126.96, 127.32, 127.50, 128.23, 128.41 (CH); 140.60, 143.77, 144.83, 156.04, 171.29, 175.02 (C). HR-MALDI-MS: 647.2523 ($[\mathrm{C_{40}H_{36}N_2NaO_5}]^+$; calc. 647.2516).

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