Preparation of (*S*,*S*)-Fmoc-β^2hIle-OH, (*S*)-Fmoc-β^2hMet-OH, and (*S*)-Fmoc-β^2hTyr(^{t}Bu)-OH for Solid-Phase Syntheses of β^2- and β^2/β^3-Peptides[1])

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Dedicated to Professor *Duilio Arigoni* on the occasion of his 75th birthday

The preparation of three new *N*-Fmoc-protected (Fmoc = [(9*H*-fluoren-9-yl)methoxy]carbonyl) β^2-homoamino acids with proteinogenic side chains (from Ile, Tyr, and Met) is described, the key step being a diastereoselective amidomethylation of the corresponding Ti-enolates of 3-acyl-4-isopropyl-5,5-diphenyloxazolidin-2-ones with $CbzNHCH_2OMe/TiCl_4$ (Cbz = (benzyloxy)carbonyl) in yields of 60–70% and with diastereoselectivities of > 90%. Removal of the chiral auxiliary with LiOH or NaOH gives the *N*-Cbz-protected β-amino acids, which were subjected to an *N*-Cbz/*N*-Fmoc (Fmoc = [(9*H*-fluoren-9-yl)methoxy]carbonyl) protective-group exchange. The method is suitable for large-scale preparation of Fmoc-β^2hXaa-OH for solid-phase syntheses of β-peptides. The Fmoc-amino acids and all compounds leading to them have been fully characterized by melting points, optical rotations, IR, ^{1}H- and ^{13}C-NMR, and mass spectra, as well as by elemental analyses.

Introduction. – In recent years, there has been considerable interest in the design and synthesis of non-natural oligomers that form secondary structures [2]. In this class of compounds, peptides consisting exclusively of β-amino acids have emerged as a promising new class of compounds that form helices, hair-pin turns, or pleated-sheets in solution with only a few β-amino acid residues, a field that has already been reviewed [3].

Almost all β^3-amino acids with proteinogenic side chains are now commercially available[3]). Except for β^2-homoalanine and β^2-homoproline, however, no other β^2-amino acids of this type are on the market in enantiomerically pure form. In the past few years, the preparation of β^2-amino acids, mainly with simple alkyl side chains, was published by several groups [5][4]).

For our ongoing projects on the synthesis of β^2/β^3- and all-β^2-peptides, we need to have ample access to the β^2-amino acid building blocks with proteinogenic side chains and *N*-Fmoc protection. With the exceptions of β^2hLys and β^2hTrp, only Fmoc-protected β^2-amino acids with nonfunctionalized and achiral side chains have, so far, been published [7]. We describe here, in detail, the preparation of three new β^2-amino acid derivatives, with the side chains of isoleucine, tyrosine, and methionine.

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[1]) Partially published in a preliminary communication [1].

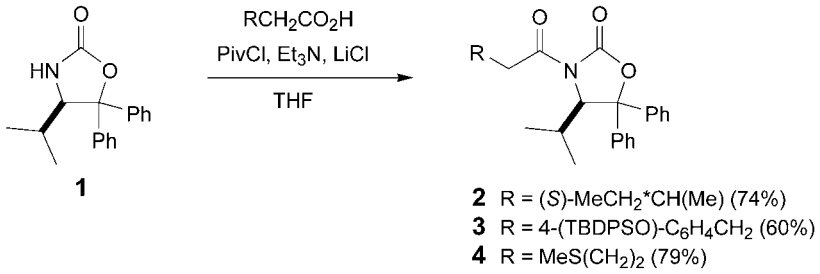
[2]) Postdoctoral fellow at ETH-Zürich, financed by the *Swiss National Science Foundation* (Grant No. 2000-58831).

[3]) For review on their synthesis, see [4].

[4]) For a recent review article on β-amino acids synthesis, see [6].

Results and Discussion. – Acylation of (*R*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**1**; DIOZ; derived from (*R*)-valine) can be achieved by two methods. The standard *Evans* procedure [8] involves reaction of lithiated **1** (generated with BuLi) with an acid chloride. The second possibility is the mixed-anhydride method introduced by *Ho* and *Mahre* [9] (*Scheme 1*), which is more convenient when the corresponding acid chloride is commercially or otherwise not available.

Scheme 1. *Acylation of* (R)*-DIOZ*



The carboxylic acid for the synthesis of β^2-homoisoleucine was actually prepared from isoleucine itself by reductive removal of the amino group with H_2NOSO_3H [10]. 3-{4-[(*tert*-Butyl)diphenylsilyl]phenyl}propanoic acid was obtained from 3-(4-hydroxyphenyl)propanoic acid by silylation of both the phenolic and the carboxylic function with (*t*-Bu)Ph_2SiCl (TBDPSCl), and subsequent deprotection of the carboxylic acid group [11]. 4-(Methylsulfanyl)butanoic acid was prepared by nucleophilic opening of γ-butyrolactone with MeSNa in DMSO [12].

Amidomethylations of Ti-enolates of acyl-DIOZ precursors **2**, **3**, and **4** were effected with benzyl (methoxymethyl)carbamate as the electrophile [13]. Amidomethylation of **2** proceeded with a high diastereoselectivity of 96%, despite the presence of two stereogenic centers in the enolate. The product **5** was freed from the auxiliary by the action of LiOH in a THF/H_2O mixture. Cbz-β^2-Homoisoleucine **6** was obtained in 66% yield after crystallization (*Scheme 2*). Use of NaOH in MeOH/THF resulted in substantial methyl ester formation. Hydrogenolysis of the Cbz group and introduction of the Fmoc group were achieved according to standard procedures [7] to give Fmoc-β^2-homoisoleucine **7** in 90% yield.

The X-ray crystal structure of Cbz-β^2hIle-OH (**6**) was determined to establish the relative configuration of the stereogenic centers as shown in *Scheme 2*, confirming that the stereochemical course of the amidomethylation is the same as with nonchiral acyl groups on DIOZ (*Fig. 1*).

For the preparation of β^2-homotyrosine, we eventually needed *t*-Bu protection of the phenolic OH group. However, it turned out that a phenolic *t*-BuO group is unstable under the condition of amidomethylation in the presence of $TiCl_4$. We, therefore, used the TBDPS group, one of the most-acid-stable protecting groups for this step. The amidomethylation proceeded smoothly, and the *Mannich* product **8** was obtained in 62% yield and with 91% diastereoselectivity. The TBDPS group was then removed with Bu_4NF (TBAF) in THF [14] to give the hydroxy derivative **9**, and the resulting OH group was protected by treatment with isobutylene/CF_3SO_3H in CH_2Cl_2 to afford the

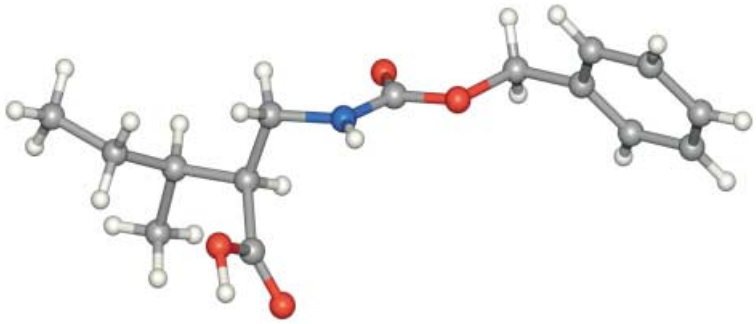
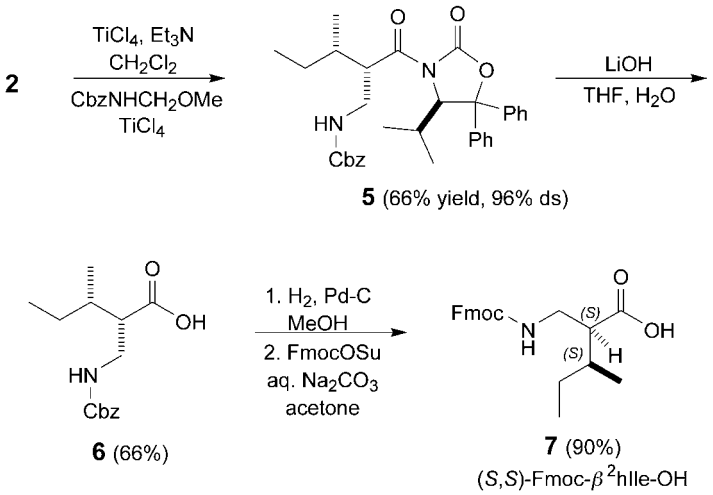


Fig. 1. *X-Ray crystal structure* (MolMol presentation) *of (*S,S*)*-N-*Cbz-β²hIle-OH* ((*S,S*)-**6**). Color code: C: grey, H: white, N: blue, O: red. The structure was determined by Dr. *B. W. Schweizer.*

Scheme 2. *Preparation of (*S,S*)*-N-*Fmoc-β²hIle-OH* (ds = diastereoselectivity)



ether **10**[5]). Cleavage of the chiral auxiliary from **10** proceeded smoothly to give the acid **11**. Deprotection of the NH_2 group and Fmoc protection afforded the desired *N*-Fmoc-β^2hTyr(^{t}Bu)-OH (**12**) in good yield (*Scheme 3*).

Amidomethylation of the methylsulfanyl derivative **4** resulted in two major products, the benzyl carbamate **13** (30%) and methyl carbamate **14** (33%), with 93% diastereoselectivity. From both of these compounds, the chiral auxiliary was removed easily to provide the acids **15** and **16**, respectively. Hydrogenolytic cleavage of the Cbz group from **15** is problematic; several common hydrogenation procedures were tried without success; with Me_3SiI, *S*-demethylation occured. Deprotection by removal of both the [(benzyloxy)carbonyl]amino and (method by the action of HBr in AcOH, in the presence of EtSMe to minimize formation of sulfonium salts from liberated BnBr

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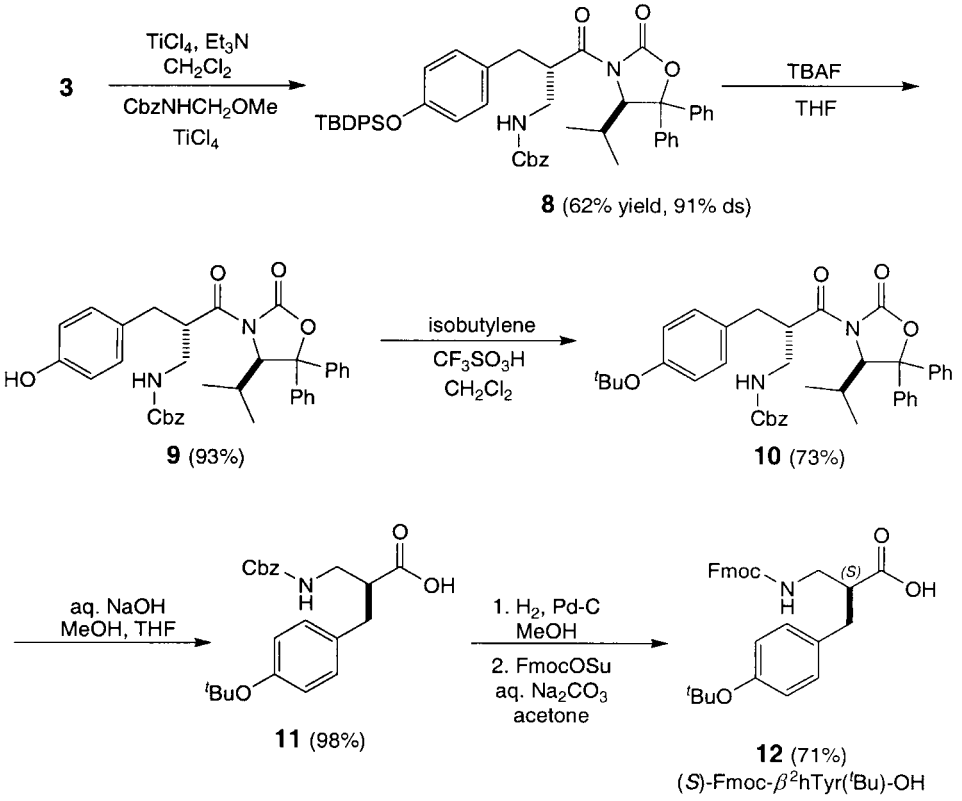
[5]) The commonly used H_2SO_4 was replaced by CF_3SO_3H to minimize side reactions [15].

Scheme 3. *Preparation of* (S)-N-*Fmoc-β²hTyr(ᵗBu)-OH*



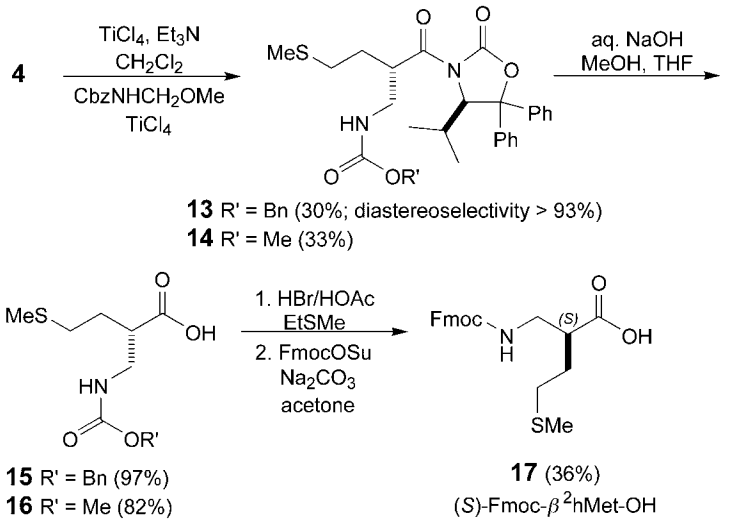
and MeBr [16]. The product (a free amino acid) could be purified by ion-exchange chromatography, and the Fmoc group was finally introduced to give *N*-Fmoc-β^2hMethionine **17** (*Scheme 4*).

The enantiomer purity of unprotected β^2hIle and β^2hTyr(^{t}Bu) was confirmed by ^{1}H-NMR spectroscopy of the diastereoisomeric Pd complexes, as shown in *Scheme 5* and *Fig. 2*. This method has been demonstrated to be reliable for determining the enantiomer purity of other β^2-, β^3-, and γ-amino acids [17].

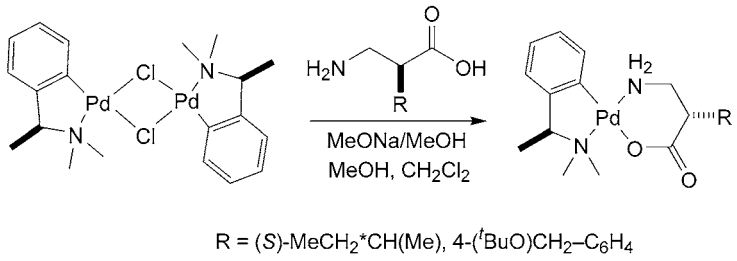
In the case of β^2hMet, it was not possible to confirm enantiomer purity by the method mentioned above (the ^{1}H-NMR spectrum was not interpretable). So, we derivatized the unprotected β^2-homomethionine for HLPC analysis on a chiral stationary phase. In two steps, (*S*)-*N*-(2,4-dinitrophenyl)-β^2-homomethionine methyl ester was prepared, and part of the compound was deliberately racemized with MeONa/MeOH. The samples thus obtained were analyzed by HPLC on a chiral stationary phase. In *Fig. 3*, the overlaid chromatograms of an enantiomerically enriched and of a racemic sample are shown.

Although we describe herein the preparation of only a few hundred miligrams of the three *N*-Fmoc-β^2-amino acids **7**, **12**, and **17**, we know that gram amounts are accessible by the optimized procedures given in the *Exper. Part.*

Scheme 4. *Preparation of (*S*)-*N*-Fmoc-β²hMet-OH*



Scheme 5. *Preparation of Pd Complexes of β²-Amino Acids for Determination of Enantiomeric Purity*



Experimental Part

1. *General*. Abreviations: FC: flash chromatography, h.v.: high vacuum, < 50 Pa, TBDPS: (*t*-Bu)Ph_2Si. 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 and phosphomolybdic acid. FC: *Fluka* silica gel *60* (40–63 μm). HPLC: *Waters* HPLC system (pump type *515*, data module type *746*, tunable absorbance detector type *484*), *Daicel Chiralpack OD-H* column. M.p.: *Büchi 510* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter (10 cm, 1-ml cell). IR Spectra: *Perkin-Elmer 782* spectrometer. NMR Spectra: *Bruker AMX-500* (500 MHz for ^1H, 125 MHz for ^{13}C), *AMX-400* (400 MHz for ^1H, 100 MHz for ^{13}C), *Varian Gemini 2000* (300 MHz for ^1H, 75 MHz for ^{13}C); chemical shifts δ in ppm downfield from internal Me_4Si (= 0 ppm); *J* values in Hz. MS: *IonSpec Ultima-Maldi FT/ICR* mass spectrometer, matrix DHB or DCTB, 4.7 T, N_2 laser at 337 nm. Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

2. *Acylation of (*R*)-DIOZ by Mixed-Anhydride Method: General Procedure 1* (*GP 1*). To the soln. of corresponding carboxylic acid (1.05 equiv.) in THF (200 ml), Et_3N (2.6 equiv.) was added. The mixture was cooled to −30°, and pivaloyl chloride (1.05 equiv.) was added dropwise, and the resulting white suspension was stirred for 1.5 h at this temp. Anh. LiCl (1.15 equiv.) and (*R*)-DIOZ (1.0 equiv.) were added, and the mixture was then stirred overnight, allowing to warm to 25°. The mixture was diluted with Et_2O, and sat. NH_4Cl soln. was

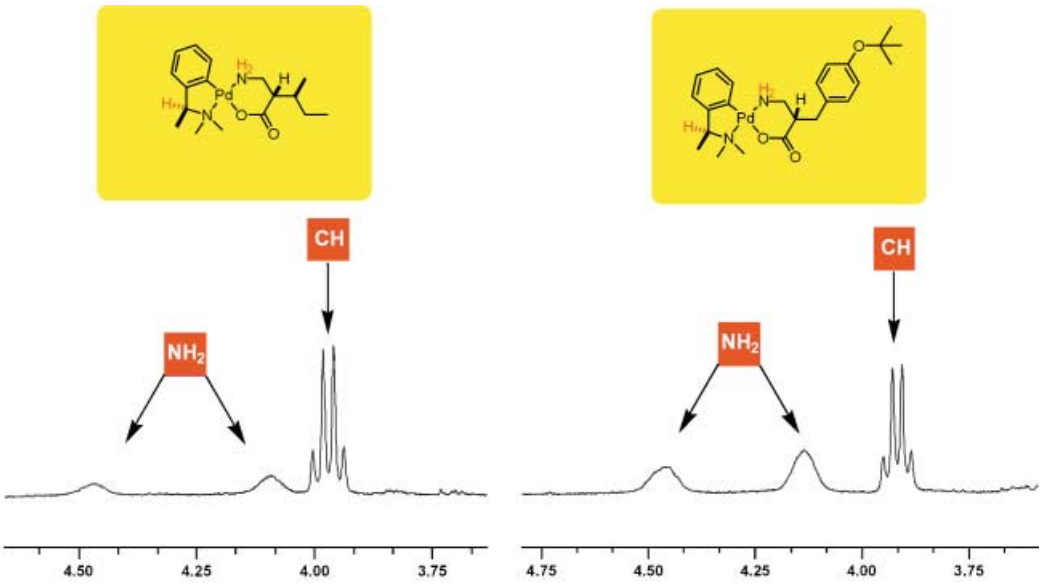


Fig. 2. *Proof of enantiomer purity of β²hIle and β²hTyr by ¹H-NMR spectra of their Pd complexes.* By analogy with already described examples [17], the signal of the enantiomer should have been observed further upfield from the *quadruplet* of the corresponding CH group.

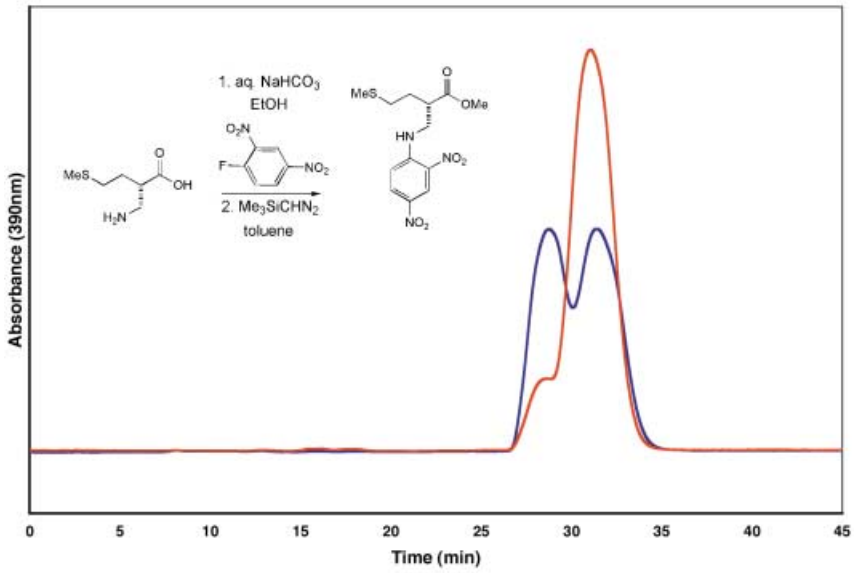


Fig. 3. *Determination of enantiomer purity of β²hMet by HPLC, by using the chiral stationary phase* Daicel Chiralpack OD-H

added. The org. phase was washed with 1N HCl (2×), 1M NaOH, and sat. NaCl, then dried ($MgSO_4$), and evaporated. The crude product was purified by FC or recrystallization.

3. *Amidoalkylation of* N-*Acyl-oxazolidin-2-ones: General Procedure 2* (*GP 2*). To a soln. of acyl (*R*)-DIOZ (1 equiv.) in CH_2Cl_2 (0.2M), $TiCl_4$ (1.05 equiv.) was added at −15° (ice/MeOH). To the yellow-orange soln., Et_3N (1.1 equiv.) was added, and the resulting dark red soln. was stirred at *ca.* −15° for 30 min. The corresponding electrophile (1.1 equiv.) was mixed with $TiCl_4$ (1.1 equiv.) in CH_2Cl_2 (0.5M) in an ice-bath, and the resulting soln. was added to the mixture *via* cannula. The mixture was stirred at 0° (ice-bath) for 3–4 h, treated with sat. NH_4Cl soln., and diluted with CH_2Cl_2. The org. phase was washed with 1N HCl (2×), 1M NaOH, and sat. NaCl soln., dried ($MgSO_4$), and evaporated. The resulting crude product was purified by FC.

4. *Cleavage of the Chiral Auxiliary: General Procedure 3* (*GP 3*). To a soln. of amidomethylated acyl DIOZ (1 equiv.) in MeOH/THF (1:1, 0.2M), 1M aq. NaOH (1.6 equiv.) was added, and the mixture was stirred for 2.5 h (in case of Ile, 24 h were required) at 25°. MeOH/THF was evaporated, Et_2O was added, and the resulting suspension was stirred for 15 min and filtered. The residue was washed with 1M NaOH soln., H_2O, Et_2O, and pentane, and dried to give the auxiliary as a white powder. The filtrate was diluted with Et_2O, the aq. phase was separated and washed with Et_2O, pH adjusted to 1–2 with 6N HCl, and extracted with AcOEt (3×). Combined org. extracts washed with sat. NaCl soln., dried ($MgSO_4$), and evaporated. The resulting Cbz-protected amino acids were used in the next steps without further purification.

5. *Cleavage of Cbz Group: General Procedure 4* (*GP 4*). The Cbz-protected amino acid (1 equiv.) was dissolved in MeOH (0.06M), the flask was purged with N_2, Pd/C (10 wt.-%) was added, then the flask was evacuated and flushed with H_2 (3×), and the mixture was stirred at 25° for 2 h under H_2 atmosphere (balloon). The catalyst was filtered off with the help of *Celite* and washed thouroughly with MeOH. The filtrate was evaporated and dried under h.v. The resulting product was pure enough for the next reaction.

6. *Fmoc Protection: General Procedure 5* (*GP 5*). The unprotected amino acid (1 equiv.) was dissolved in 0.15M aq. Na_2CO_3 soln. (2 equiv.). To this soln. was added FmocOSu (1.2 equiv.) in acetone (0.1M) at 25°. The mixture was stirred at r.t. for 2 h, acetone was evaporated, and the residue was diluted with H_2O and extracted with Et_2O (2×). The aq. phase was acidified to pH 1 with 6N HCl and extracted with AcOEt (3×). The combined org. extracts were washed with sat. NaCl soln., dried ($MgSO_4$), and evaporated. The resulting product was purified by FC (AcOEt/hexane 1:2 + 0.5% AcOH).

7. *Preparation of Acyloxazolidinone Starting Materials* **2**–**4**. *(*R*)-4-Isopropyl-3-[(*S*)-3-methyl-1-oxopentyl]-5,5-diphenyloxazolidin-2-one* ((*R*,*S*)-**2**). Compound **2** was prepared according *GP 1*. Recrystallization from hexane yielded (*R*,*S*)-**2** (7.0 g, 74%). Colorless needles. M.p. 89–90°. R_f (AcOEt/hexane 3:7) 0.61. $[\alpha]_D^{25} = +206.4$ ($c = 0.69$, $CHCl_3$). IR ($CHCl_3$): 2966*m*, 1781*s*, 1699*s*, 1450*m*, 1366*m*, 1320*m*, 1177*m*, 1156*w*, 990*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.767 (*d*, *J* = 6.9, 3 H, Me_2CH); 0.77 (*t*, *J* = 7.2, *Me*CH_3); 0.82 (*d*, *J* = 6.9, 3 H, *Me*$_2$C); 0.89 (*d*, *J* = 6.9, *Me*CH); 1.0–1.3 (*m*, $MeCH_2$); 1.70–1.84 (*m*, MeC*H*); 1.92–2.04 (*m*, *Me*$_2$*CH*); 2.65 (*dd*, *J* = 15.6, 7.8, 1 H, CH_2CO); 2.80 (*dd*, *J* = 15.6, 6.2, 1 H, CH_2CO); 5.37 (*d*, *J* = 3.4, CHN); 7.27–7.50 (*m*, 10 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.3; 16.6; 19.1; 21.9; 29.2; 29.9; 31.6; 41.8; 64.7; 89.2; 125.5; 125.8; 127.8; 128.3; 128.4; 128.8; 138.0; 142.3; 153.0; 172.5. HR-MALDI-MS: 402.2039 ($[C_{24}H_{29}NNaO_3]^+$; calc. 402.2040). Anal. calc. for $C_{24}H_{29}NO_3$ (379.5) C 75.96, H 7.70, N 3.69; found: C 76.07, H 7.81, N 3.72.

*3-[4-[(*tert*-Butyl)diphenylsilyl]phenyl]propanoic Acid*. 3-(4-hydroxyphenyl)propanoic acid (1.66 g, 10 mmol) and 1*H*-imidazole (3.0 g, 44 mmol) were dissolved in DMF (20 ml). To this soln., TBDPSCl (6.04 g, 22 mmol, 5.64 ml) was added dropwise at 25°, and the resulting soln. was stirred for 5 h at this temp. The mixture was diluted with sat. NaCl soln. (250 ml) and extracted with Et_2O (3×). The combined extracts were washed with ice-cold 1N HCl and brine, dried ($MgSO_4$), and evaporated. The residue was redissolved in THF/MeOH (1:1; 80 ml), and 10% aq. K_2CO_3 soln. (10 ml) was added, and the mixture was stirred at 25° for 1 h, then concentrated, diluted with brine (100 ml), acidified with 1N HCl, and extracted with Et_2O (3×). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. Crude product was purified by FC (Et_2O/pentane 1:4 + 0.5% AcOH) to yield the acid (3.12 g, 77%). Colorless oil. R_f (AcOEt/hexane/AcOH 5:5:0.5) 0.55. IR ($CHCl_3$): 2933*m*, 2860*m*, 1712*s*, 1609*m*, 1510*s*, 1472*w*, 1428*m*, 1257*s*, 1114*m*, 1042*w*, 921*m*, 835*m*, 822*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.10 (*s*, *t*-Bu); 2.59 (*t*, *J* = 8.4, Ph*C*H_2); 2.83 (*t*, *J* = 8.1, $COCH_2$); 6.69 (*d*, *J* = 8.4, 2 arom. H); 6.92 (*d*, *J* = 8.7, 2 arom. H); 7.26–7.43 (*m*, 6 arom. H); 7.72 (*m*, 4 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.5; 26.6; 29.8; 35.8; 119.6; 127.6; 128.8; 129.7; 132.4; 132.9; 135.4; 153.9; 178.7. HR-MALDI-MS: 427.1703 ($[C_{25}H_{28}NaO_3Si]^+$; calc. 427.1700). Anal. calc. for $C_{25}H_{28}O_3Si$ (404.6) C 74.22, H 6.98; found: C 74.31, H 7.01.

*(*R*)-3-{3-[4-(*tert*-Butyl)diphenylsilyl)phenyl]-1-oxopropyl}-4-isopropyl-5,5-diphenyloxazolidin-2-one* ((*R*)-**3**). Compound **3** was prepared according to *GP 1*. FC (AcOEt/hexane 1:1) yielded pure (*R*)-**3** (7.5 g, 79%). White solid. M.p. 120–122°. R_f (AcOEt/hexane 3:7) 0.57. $[\alpha]_D^{25} = +106.6$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$):

2963*m*, 2932*m*, 2859*m*, 1780*s*, 1701*s*, 1510*s*, 1372*m*, 1114*m*, 921*m*, 823*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.70 (*d*, *J* = 6.8, 3 H, *Me*$_2$CH); 0.81 (*d*, *J* = 7.0, 3 H, *Me*$_2$CH); 1.08 (*s*, *t*-Bu); 1.94 (*m*, (Me$_2$C*H*); 2.68–2.82 (*m*, COCH$_2$C*H*$_2$), 2.92–2.99 (*m*, 1 H, COCH$_2$); 3.11–3.19 (*m*, 1 H, COCH$_2$); 5.34 (*d*, *J* = 3.4, NCH); 6.62 (*d*, J = 8.7, 2 arom. H); 6.84 (*d*, *J* = 8.7, 2 arom. H); 7.20–7.73 (*m*, 20 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.4; 19.5; 21.7; 26.6; 29.6; 29.8; 36.9; 64.5; 89.4; 119.5; 125.6; 127.7; 127.9; 128.4; 128.6; 128.9; 129.0; 129.8; 132.7; 133.1; 134.8; 135.5; 138.2; 142.3; 153.0; 153.9; 172.3. HR-MALDI-MS: 690.3017 ([$C_{43}H_{45}NNaO_4Si$]$^+$; calc. 690.3010). Anal. calc. for $C_{43}H_{45}NO_4Si$ (667.9) C 77.33, H 6.79, N 2.10; found: C 77.19, H 6.88, N 2.17.

*(*R*)-4-Isopropyl-3-[(*S*)-4-methylsulfanyl-1-oxobutyl]-5,5-diphenyloxazolidin-2-one* ((*R*)-**4**). Compound **1** was acylated according to *GP 1*. FC (AcOEt/hexane 1:1) yielded (*R*)-**4** (9.0 g, 86%) White solid. M.p. 71–72°. R_f (AcOEt/hexane 3:7) 0.53. $[\alpha]_D^{25} = +196.2$ (*c* = 0.78, $CHCl_3$). IR ($CHCl_3$): 2970*m*, 2923*w*, 1781*s*, 1702*s*, 1450*m*, 1366*m*, 1320*m*, 1177*m*, 1049*w*, 1002*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.76 (*d*, *J* = 6.5, 3 H, *Me*$_2$CH); 0.88 (*d*, *J* = 7.2, 3 H, *Me*$_2$CH); 1.82–2.02 (*m*, (Me$_2$C*H*, COCH$_2$C*H*$_2$); 2.04 (*s*, MeS); 2.45 (*t*, *J* = 7.2, CH$_2$S); 2.81–3.07 (*m*, COCH$_2$); 5.37 (*d*, *J* = 3.4, CHN); 7.28–7.49 (*m*, 10 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.4; 16.5; 21.9; 23.9; 30.0; 33.3; 34.1; 64.5; 89.4; 125.5; 125.8; 127.9; 128.3; 128.5; 128.8; 138.0; 142.2; 152.9; 172.3. HR-MALDI-MS: 420.1607 ([$C_{23}H_{27}NNaO_5S$]$^+$; calc. 420.1604). Anal. calc. for $C_{23}H_{27}NO_5S$ (397.5) C 69.49, H 6.85, N 3.52, S 8.07; found: C 69.60, H 6.92, N 3.61, S 8.06.

8. *Preparation of (*S,S*)-*N*-Fmoc-β²hIle-OH* (**7**). *(*R*)-3-[(2*S*,3*S*)-2-({[(Benzyloxy)carbonyl]amino}methyl)-3-methyl-1-oxopentyl]-4-isopropyl-5,5-diphenyloxazolidin-2-one* ((*R*,*S*,*S*)-**5**). Compound **2** was amidomethylated according to *GP 2*. FC (AcOEt/hexane 1:2) yielded (*R*,*S*,*S*)-**5** (5.10 g, 66%). Colorless oil. R_f (AcOEt/hexane 3:7) 0.34. $[\alpha]_D^{25} = +117.0$ (*c* = 0.53, $CHCl_3$). IR ($CHCl_3$): 3452*w*, 2969*m*, 1781*s*, 1718*s*, 1514*s*, 1451*m*, 1364*m*, 1178*m*, 1051*m*, 989*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.49 (*t*, *J* = 7.2, *Me*CH$_2$); 0.55 (*d*, *J* = 6.7, 3 H, Me$_2$CH); 0.59–0.86 (*m*, CH$_2$); 0.66 (*d*, *J* = 6.7, 3 H, *Me*$_2$CH); 0.78 (*d*, *J* = 6.9, *Me*CH); 1.38 (*m*, C*H*CH$_2$); 1.93 (*m*, Me$_2$C*H*); 3.31–3.64 (*m*, CH$_2$N); 3.74 (*m*, COCH); 5.01 (*s*, CH$_2$O); 5.06 (br. *s*, NH); 5.25 (*d*, *J* = 3.5, CHN); 7.19–7.47 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.1; 15.0; 16.5; 21.7; 27.0; 29.6; 34.9; 40.0; 47.4; 65.9; 66.6; 89.5; 125.3; 125.7; 128.0; 128.1; 128.45; 128.49; 128.6; 128.8; 128.9; 136.6; 137.7; 142.4; 153.2; 156.2; 175.1. HR-MALDI-MS: 565.2680 ([$C_{33}H_{38}N_2NaO_5$]$^+$; calc. 565.2673). Anal. calc. for $C_{24}H_{29}NO_3$ (542.7) C 73.04, H 7.06, N 5.16; found: C 73.14, H 7.02, N 5.06.

*(2*S*,3*S*)-2-{[(Benzyloxy)carbonyl]amino}methyl-3-methylpentanoic Acid* ((*S*,*S*)-**6**). Chiral auxiliary was cleaved from **5** according to *GP 3*. Recrystallization from (i-Pr)$_2$O/hexane yielded (*S*,*S*)-**6** (203 mg, 66%). Colorless needles. M.p. 74–76°. R_f (AcOEt/hexane/AcOH 5:5:0.5) 0.58. $[\alpha]_D^{25} = +25.7$ (*c* = 0.61, $CHCl_3$). IR ($CHCl_3$): 3466*w*, 2966*m*, 1714*s*, 1514*s*, 1454*w*, 1256*m*, 1141*w*, 1066*w*, 974*w*. ^{1}H-NMR (500 MHz, (D$_6$)DMSO): 0.84–0.98 (*m*, 2 Me); 1.11–1.18 (*m*, 1 H, MeC*H*$_2$); 1.36–1.44 (*m*, 1 H, MeC*H*$_2$); 1.61–1.66 (*m*, CH); 2.40–2.50 (*m*, CHCO); 3.12–3.34 (*m*, CH$_2$N); 3.57 (br. *s*, NH); 5.00 (*s*, CH$_2$O); 7.23–7.37 (*m*, 5 arom. H); 12.19 (br. *s*, OH). ^{13}C-NMR (125 MHz, (D$_6$)DMSO): 11.4; 16.0; 26.3; 34.5; 39.3; 49.6; 65.0; 127.5; 127.6; 128.2; 137.1; 156.0; 175.1. HR-MALDI-MS: 302.1360 ([$C_{15}H_{21}NNaO_4$]$^+$; calc. 302.1368). Anal. calc. for $C_{15}H_{21}NO_4$ (279.3) C 64.50, H 7.58, N 5.01; found: C 64.71, H 7.37, N 4.87.

*(2*S*,3*S*)-2-[({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)methyl]-3-methylpentanoic Acid* ((*S*,*S*)-**7**). Compound **6** was deprotected according to *GP 4* and Fmoc-protected according to *GP 5*. FC (AcOEt/hexane 1:2 +0.5% AcOH) yielded (*S*,*S*)-**7**. (279 mg, 90%). Colorless oil. R_f (AcOEt/hexane/AcOH 5:5:0.5) 0.48. $[\alpha]_D^{25} = +15.5$ (*c* = 0.42, $CHCl_3$). IR ($CHCl_3$): 3446*w*, 2964*m*, 1713*s*, 1513*s*, 1451*m*, 1144*m*, 1082*w*, 1041*w*, 990*w*. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 0.86 (*t*, *J* = 7.3, MeCH$_2$); 0.88 (*d*, *J* = 6.8, MeCH); 1.11–1.19 (*m*, 1 H, CH$_2$); 1.37–1.44 (*m*, 1 H, CH$_2$); 1.63 (*m*, MeC*H*); 2.44 (*m*, CHCO); 3.24 (*m*, CH$_2$N); 4.18–4.29 (*m*, OCHCH$_2$); 7.30–7.43 (*m*, 4 arom. H); 7.68 (*d*, *J* = 7.3, 1 arom. H); 7.69 (*d*, *J* = 7.2, 1 arom. H); 7.89 (*d*, *J* = 7.4, 2 arom. H). ^{13}C-NMR (100 MHz, (D$_6$)DMSO): 11.4; 16.1; 26.3; 34.6; 46.6; 49.6; 65.3; 120.0; 125.1; 127.0; 127.5; 140.6; 143.77; 143.81; 156.0; 175.1. HR-MALDI-MS: 390.1679 ([$C_{22}H_{25}NNaO_4$]$^+$; calc. 390.1676). Anal. calc. for $C_{22}H_{25}NO_4$ (367.4) C 71.91, H 6.86, N 3.81; found: C 72.16, H 6.81, N 3.66.

9. *Preparation of (*S*)-*N*-Fmoc-β²hTyr(*t*Bu)-OH* (**12**). *(*R*)-3-((*S*)-2-{[(Benzyloxy)carbonyl]amino})methyl-3-[4-(*tert*-butyl)diphenylsilyl)phenyl]-1-oxopropyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one* ((*R*,*S*)-**8**). Compound **3** was amidomethylated according to *GP 2*. The crude product purified by FC (AcOEt/hexane 1:4) to yield (*R*,*S*)-**8** (11.1 g, 62%). White foam. M.p. 74–77°. R_f (AcOEt/hexane 3:7) 0.35. $[\alpha]_D^{25} = +68.5$ (*c* = 0.95, $CHCl_3$). IR ($CHCl_3$): 3444*w*, 2964*w*, 2921*w*, 1779*s*, 1721*s*, 1510*s*, 1450*w*, 1363*m*, 1114*m*, 921*m*, 822*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.69 (*d*, *J* = 6.7, 3 H, *Me*$_2$CH); 0.82 (*d*, *J* = 7.0, 3 H, *Me*$_2$C); 1.09 (*s*, *t*-Bu); 1.94 (*m*, (Me$_2$C*H*); 2.36 (*m*, 1 H, CHC*H*$_2$); 2.59 (*m*, 1 H, CHC*H*$_2$); 3.33–3.67 (*m*, CH$_2$N); 4.06 (*m*, COCH); 5.05 (*s*, CH$_2$O); 5.11 (br. *s*, NH); 5.30 (*d*, *J* = 3.4, NCH); 6.48 (*d*, *J* = 8.5, 2 arom. H); 6.58 (*d*, *J* = 8.6, 2 arom. H); 7.11–7.70 (*m*, 25 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.3; 19.5; 21.7; 26.6; 29.7; 34.3; 42.2; 44.7; 65.0; 66.6; 89.5; 119.6; 125.3; 125.8; 127.7; 128.01; 128.03; 128.12; 128.4; 128.5; 128.6; 128.9; 129.4; 129.84; 129.85; 133.1; 135.53;

135.54; 137.9; 138.0; 152.9; 154.0; 173.9. HR-MALDI-MS: 853.3653 ($[C_{52}H_{54}N_2NaO_6Si]^+$; calc. 853.3643). Anal. calc. for $C_{52}H_{54}N_2O_6Si$ (831.1) C 75.15, H 6.55, N 3.37; found: C 75.15, H 6.53, N 3.49.

*(*R*)-3-[(*S*)-2-({[(Benzyloxy)carbonyl]amino}methyl)-3-(4-hydroxyphenyl)-1-oxopropyl]-4-isopropyl-5,5-diphenyloxazolidin-2-one* ((*R,S*)-**9**). Compound ((*R,S*)-**8** (1.63 g, 1.96 mmol) was dissolved in THF (15 ml), and TBAF (682 mg, 2.16 mmol, 1.1 equiv.) in THF (10 ml) was added, and the mixture was stirred at 25° for 4 h. The soln. was diluted with AcOEt (120 ml), and washed with H_2O and sat. NaCl soln. Aq. phases were extracted with AcOEt. Combined org. extracts were dried ($MgSO_4$) and evaporated. FC (AcOEt/hexane 1:2) yielded (*R,S*)-**9** (1.08 g, 93%). For anal. purposes, a sample was recrystallized from AcOEt/hexane. Colorless needles. M.p. 153–154°. R_f (AcOEt/hexane 3:7) 0.10. $[\alpha]_D^{25} = +95.5$ ($c = 0.78$, $CHCl_3$). IR ($CHCl_3$): 3599*m*, 3443*m*, 3008*m*, 2971*m*, 1779*s*, 1717*s*, 1515*s*, 1450*m*, 1364*m*, 1318*m*, 1149*m*, 1051*m*, 990*m*, 826*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.71 (*d*, $J = 6.7$, 3 H, Me_2CH); 0.84 (*d*, $J = 7.0$, 3 H, Me_2CH); 1.99 (*m*, (Me_2CH); 2.41 (*m*, 1 H, $CHCH_2$); 2.58 (*m*, 1 H, $CHCH_2$); 3.38–3.50 (*m*, CH_2N); 4.16 (*m*, COCH); 5.07 (*s*, CH_2O); 5.26 (br. *s*, NH); 5.32 (*d*, $J =$ 3.3, NCH); 5.62 (*s*, OH); 6.52 (*d*, $J = 8.3$, 2 arom. H); 6.75 (*d*, $J = 8.3$, 2 arom. H); 7.25–7.38 (*m*, 15 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.3; 21.7; 29.7; 34.4; 42.1; 44.8; 65.1; 66.8; 89.6; 115.3; 125.3; 125.8; 128.0; 128.1; 128.2; 128.4; 128.5; 128.6; 129.0; 129.1; 129.8; 136.4; 138.8; 141.9; 153.1; 154.4; 156.3; 174.2. HR-MALDI-MS: 615.2461 ($[C_{36}H_{36}N_2NaO_6]^+$; calc. 615.2466). Anal. calc. for $C_{36}H_{36}N_2O_6$ (592.7) C 72.95, H 6.12, N 4.73; found: C 72.93, H 6.13, N 4.64.

*(*R*)-3-[(*S*)-2-({[(Benzyloxy)carbonyl]amino}methyl-3-[4-(*tert*-butoxy)phenyl]-1-oxopropyl]-4-is opropyl-5,5-diphenyloxazolidin-2-one* ((*R,S*)-**10**). Isobutylene (15 ml) was dissolved in CH_2Cl_2 (10 ml) at −78°. At −30°, CF_3SO_3H (0.11 ml, 1.25 mmol, 10 mol-%) was added to this soln. followed by **9** (7.4 g, 12.5 mmol) in CH_2Cl_2 (50 ml). The resulting red soln. was stirred for 5 h at −30°. Et_3N (0.17 ml, 1.25 mmol) was added, and the mixture was allowed to warm slowly to 25°, the solvent was then evaporated, and the crude product was purified by FC (AcOEt/hexane 3:7), and then recrystallized from Et_2O/pentane to give the (*R,S*)-**10** (5.88 g, 73%). White amorphous solid. M.p. 97–99°. R_f (AcOEt/hexane 3:7) 0.32. $[\alpha]_D^{25} = +94.4$ ($c = 0.64$, $CHCl_3$). IR ($CHCl_3$): 3444*w*, 2980*m*, 1779*s*, 1719*s*, 1507*s*, 1450*m*, 1366*m*, 1177*m*, 1180*m*, 1016*m*, 895*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.71 (*d*, $J = 6.7$, 3 H, Me_2CH); 0.84 (*d*, $J = 7.0$, 3 H, Me_2CH); 1.29 (*s*, *t*-Bu); 1.97 (*m*, Me_2CH); 2.45 (*dd*, $J = 14.0$, 7.6, 1 H, $CHCH_2$); 2.65 (*dd*, $J = 14.2$, 6.2, 1 H, $CHCH_2$); 3.39 (*m*, 1 H, CH_2NH); 3.49 (*m*, 1 H, CH_2NH); 4.13 (*m*, COCH); 5.06 (*s*, CH_2O); 5.15 (br. *s*, NH); 5.35 (*d*, $J = 3.3$, NCH); 6.71 (*d*, $J = 8.2$, 2 arom. H); 6.80 (*d*, $J = 8.5$, 2 arom. H); 7.25–7.41 (*m*, 15 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.3; 21.7; 28.9; 29.7; 34.5; 42.2; 44.7; 65.0; 66.7; 78.1; 89.6; 124.0; 124.2; 125.4; 125.8; 128.03; 128.05; 128.1; 128.4; 128.5; 128.7; 128.96; 129.05; 136.5; 137.9; 142.0; 153.0; 153.9; 156.1; 174.0. HR-MALDI-MS: 671.3099 ($[C_{40}H_{44}N_2NaO_6]^+$; calc. 671.3092). Anal. calc. for $C_{40}H_{44}N_2O_6$ (648.8) C 74.05, H 6.84, N 4.32; found: C 74.22, H 6.86, N 4.32.

*(*S*)-2-({[(Benzyloxy)carbonyl]amino}methyl)-3-[4 -(*tert*-butoxy)phenyl]propanoic Acid* ((*S*)-**11**). The chiral auxiliary was cleaved from **10** according to *GP 3*. The resulting product (*S*)-**11** (376 mg, 94%) was pure enough for next reaction. White solid. For anal. purposes, a sample was recrystallized from Et_2O/pentane. M.p. 112–113°. R_f (AcOEt/hexane/AcOH 5:5:0.5) 0.46. $[\alpha]_D^{25} = +3.3$ ($c = 0.43$, $CHCl_3$). IR ($CHCl_3$): 3444*w*, 2980*m*, 1719*s*, 1507*s*, 1455*m*, 1367*m*, 1160*m*, 895*m*. ^{1}H-NMR (400 MHz, CD_3OD): 1.30 (*s*, *t*-Bu); 2.74–2.91 (*m*, $CHCH_2$); 3.28–3.47 (*m*, CH_2NH); 5.06 (*s*, CH_2O); 6.88 (*d*, $J = 8.4$, 2 arom. H); 7.11 (*d*, $J = 8.4$, 2 arom. H); 7.27–7.34 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, CD_3OD): 29.2; 36.2; 43.5; 67.5; 79.5; 125.2; 128.8; 129.0; 129.5; 130.5; 135.4; 138.4; 155.0; 158.9; 177.5. HR-MALDI-MS: 408.1787 ($[C_{22}H_{27}NNaO_5]^+$; calc. 408.1781). Anal. calc. for $C_{22}H_{27}NO_5$ (385.5) C 68.55, H 7.06, N 3.63; found: C 68.45, H 6.99, N 3.61.

*(*S*)-2-[({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)methyl]-3-[4-(*tert*-butoxy)phenyl]propanoic Acid* ((*S*)-**12**). Compound **11** was deprotected according to *GP 4* and the resulting product was Fmoc-protected according to *GP 5*. The crude product was purified by FC (AcOEt/hexane 1:2 + 0.5% AcOH) to give final compound (*S*)-**12** (203 mg, 71%). White foam. M.p 58–60°. R_f (AcOEt/hexane/AcOH 5:5:0.5) 0.48. $[\alpha]_D^{25} =$ +5.4 ($c = 0.37$, $CHCl_3$). IR ($CHCl_3$): 3466*w*, 3008*m*, 2979*m*, 1719*s*, 1507*s*, 1450*m*, 1367*m*, 1160*m*, 1082*w*, 1041*w*, 894*m*. ^{1}H-NMR (400 MHz, CD_3OD): 1.30 (*s*, *t*-Bu); 2.73–2.91 (*m*, $CHCH_2$); 3.31 (*m*, CH_2N); 4.20 (*t*, $J = 6.8$, CH); 4.33 (*d*, $J = 6.1$, CH_2); 6.89 (*d*, $J = 8.4$, 2 arom. H); 7.11 (*d*, $J = 8.4$, 2 arom. H); 7.27–7.39 (*m*, 4 arom. H); 7.63 (*d*, $J = 7.5$, 2 arom. H); 7.78 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (100 MHz, CD_3OD): 29.2; 36.1; 43.4; 48.5; 49.1; 67.8; 79.4; 120.9; 125.2; 126.2; 128.1; 128.8; 130.5; 135.4; 142.6; 145.3; 155.0; 158.8; 177.5. HR-MALDI-MS: 496.2099 ($[C_{29}H_{31}NNaO_5]^+$; calc. 496.2094). Anal. calc. for $C_{29}H_{31}NO_5$ (473.6) C 73.55, H 6.60, N 2.96; found: C 73.38, H 6.64, N 2.77.

10. *Preparation of (*S*)-N-Fmoc-β²hMet-OH* (**17**). *(*R*)-3-[(*S*)-2-{[(Benzyloxy)carbonyl]amino}methyl)-4-(methylsulfanyl)-1-oxobutyl]-4-isopropyl-5,5-diphenyloxazolidin-2-one* ((*R,S*)-**13**) *and (*R*)-4-Isopropyl-3-((*S*)-2-[[(methoxycarbonyl)amino]methyl]-4-(methylsulfanyl)-1-oxobutyl)-5,5-diphenyloxazolidin-2-one* ((*R,S*)-

14). Amidomethylation of (*R*)-**4** was carried out according to *GP 2*. Two major products, (*R*,*S*)-**13** and (*R*,*S*)-**14**, were separated by FC (Et_2O/pentane 1:1).

*Data for (*R,S*)-***13***: 0.70 g, 30%. White solid. M.p. 130–131°. R_f (AcOEt/hexane 3:7) 0.24. $[\alpha]_D^{25} = +99.6$ ($c = 0.83$, $CHCl_3$). IR ($CHCl_3$): 3446*w*, 2968*m*, 2921*m*, 1779*s*, 1719*s*, 1515*s*, 1450*m*, 1364*m*, 1181*m*, 1145*m*, 1052*m*, 1002*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.71 (*d*, *J* = 6.7, 3 H, Me_2CH); 0.83 (*d*, *J* = 6.9, 3 H, Me_2CH); 1.53 (*m*, Me_2CH); 1.74 (*m*, 1 H, $CHCH_2$); 1.79 (*s*, MeS); 1.99 (*m*, 3 H, CH_2S, $CHCH_2$); 3.39 (*m*, 1 H, CH_2N); 3.74 (*m*, 1 H, CH_2N); 3.95 (*m*, COCH); 5.07 (*s*, CH_2O); 5.17 (br. *s*, NH); 5.35 (*d*, *J* = 3.4, CHN); 7.26–7.50 (*m*, 15 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.1; 16.3; 21.6; 28.8; 29.7; 31.0; 42.3; 43.0; 65.4; 66.8; 89.7; 125.4; 125.7; 128.06; 128.09; 128.2; 128.3; 128.5; 128.8; 128.9; 136.5; 137.7; 142.3; 153.2; 156.2; 174.1. HR-MALDI-MS: 583.2244 ($[C_{32}H_{36}N_2NaO_5S]^+$; calc. 583.2237). Anal. calc. for $C_{32}H_{36}N_2O_5S$ (560.7) C 68.55, H 6.47, N 5.00, S 5.72; found: C 68.51, H 6.53, N 4.99, S 5.71.

Data for **14**: 0.68 g, 33%. White solid. M.p. 103–104°. R_f (AcOEt/hexane 3:7) 0.18. $[\alpha]_D^{25} = +114.8$ (c = 0.40, $CHCl_3$). IR ($CHCl_3$): 3446*w*, 2964*w*, 1780*s*, 1718*s*, 1518*s*, 1451*m*, 1364*m*, 1318*m*, 1051*w*, 990*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.76 (*d*, *J* = 6.8, 3 H, Me_2CH); 0.86 (*d*, *J* = 7.0, 3 H, Me_2CH); 1.51 (*m*, 1 H, $CHCH_2$); 1.70 (*m*, 1 H, $CHCH_2$); 1.80 (*s*, MeS); 2.03 (*m*, CH_2S, Me_2CH); 3.34–3.56 (*m*, CH_2N); 3.63 (*s*, MeO); 3.93 (*m*, COCH); 5.16 (br. *s*, NH); 5.36 (*d*, *J* = 3.5, NCH); 7.26–7.51 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.1; 16.3; 21.6; 28.8; 29.7; 31.1; 42.4; 43.0; 52.1; 65.4; 89.7; 125.4; 125.7; 128.1; 128.5; 128.8; 128.9; 137.7; 142.3; 153.2; 156.9; 174.2. HR-MALDI-MS: 507.1919 ($[C_{26}H_{32}N_2NaO_5S]^+$; calc. 507.1924). Anal. calc. for $C_{26}H_{32}N_2O_5S$ (484.6) C 64.44, H 6.66, N 5.78, S 6.62; found: C 64.45, H 6.79, N 5.86, S 6.47.

*(*S*)-2-([[(Benzyloxy)carbonyl]amino]methyl)-4-(methylsulfanyl)butanoic Acid* ((*S*)-**15**). The chiral auxiliary was cleaved from **13** according to *GP 3*. Compound **15** (2.05 g, 97%) was pure enough for the next reaction. A sample was recrystallized from Et_2O/pentane. White solid. M.p. 77–79°. R_f (AcOEt/hexane/AcOH 5:5:0.5) 0.50. $[\alpha]_D^{25} = +0.3$ ($c = 0.74$, $CHCl_3$). IR ($CHCl_3$): 3448*m*, 3025*m*, 2920*m*, 1717*s*, 1515*s*, 1454*m*, 1260*m*, 1142*m*, 1089*w*, 1040*m*, 980*w*, 913*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.63–1.84 (*m*, $CHCH_2$); 2.01 (*s*, MeS); 2.37–2.60 (*m*, CH_2S, CH); 3.08–3.25 (*m*, CH_2N); 3.27 (br. *s*, NH); 5.02 (*s*, CH_2O); 7.28–7.38 (*m*, 5 arom. H); 12.3 (br. *s*, OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 14.4; 28.5; 30.7; 41.8; 44.2; 65.1; 127.5; 127.6; 128.2; 137.1; 156.1; 174.8. HR-MALDI-MS: 320.0930 ($[C_{14}H_{19}NNaO_4S]^+$; calc. 320.0927). Anal. calc. for $C_{14}H_{19}NO_4S$ (297.4) C 56.55, H 6.44, N 4.71; found: C 56.58, H 6.30, N 4.79.

*(*S*)-2-[[(Methoxycarbonyl)amino]methyl]-4-(methylsulfanyl)butanoic Acid* ((*S*)-**16**). The chiral auxiliary was cleaved from **14** according to *GP 3*. FC (AcOEt/hexane 1:1 +0.5% AcOH) yielded **16** (1.16 g, 82%). Colorless oil. R_f (AcOEt/hexane/AcOH 5:5:0.5) 0.25. $[\alpha]_D^{25} = -4.5$ ($c = 0.42$, $CHCl_3$). IR ($CHCl_3$): 3682*w*, 3446*m*, 3005*m*, 2923*m*, 1718*s*, 1518*s*, 1446*m*, 1144*m*, 1087*m*, 1041*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.29–1.93 (*m*, $CHCH_2$); 2.07 (*s*, MeS); 2.47–2.59 (*m*, CH_2S); 2.71 (*m*, CH); 3.24–3.38 (*m*, CH_2N); 3.62 (*s*, MeO). ^{13}C-NMR (100 MHz, CD_3OD): 15.1; 30.1; 32.5; 43.2; 46.0; 52.5; 159.6; 177.5. HR-MALDI-MS: 244.0617 ($[C_8H_{15}NNaO_4S]^+$; calc. 244.0614). Anal. calc. for $C_8H_{15}NO_4S$ (221.3) C 43.42, H 6.83, N 6.33; found: C 43.71, H 6.98, N 6.16.

*(*S*)-2-(Aminomethyl)-4-(methylsulfanyl)butanoic Acid*. Compound **16** (1.07 g, 4.84 mmol) (or **15**) was mixed with EtSMe (1.84 g, 2.18 ml, 24.2 mmol, 5 equiv.), and HBr/HOAc (5.7M, 5 ml) was added at 25°, and the mixture was stirred for 18 h (2 h in case of **15**), protected from moisture with $CaCl_2$ drying tube. Et_2O (20 ml) was added, and the oily residue was separated and triturated with Et_2O (3×), and dried in h.v. The resulting crude product was used directly in the next step.

*(*S*)-2-[([(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)methyl]-4-(methylsulfanyl)butanoic Acid* ((*S*)-**17**). Crude product from the previous reaction was Fmoc-protected according *GP 5*. FC (AcOEt/hexane 3:7 + 0.5% AcOH) yielded **17** (337 mg, 36%). White solid. M.p. 138–140°. R_f (AcOEt/hexane/AcOH 5:5:0.5) 0.52. $[\alpha]_D^{25} = +3.8$ ($c = 0.40$, $CHCl_3$). IR ($CHCl_3$): 3446*w*, 3005*m*, 2923*w*, 1718*s*, 1513*s*, 1451*m*, 1144*m*, 1087*w*, 1041*w*, 985*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.72–1.93 (*m*, $CHCH_2$); 2.05 (*s*, MeS); 2.48–2.58 (*m*, CH_2S); 2.73 (*m*, COCH); 3.25–3.40 (*m*, CH_2N); 4.20 (*t*, *J* = 6.9, CH); 4.33 (*d*, *J* = 7.0, CH_2O); 7.17 (br. *s*, NH); 7.28–7.40 (*m*, 4 arom. H); 7.64 (*d*, *J* = 6.7, 2 arom. H); 7.78 (*d*, *J* = 7.5, 2 arom. H). ^{13}C-NMR (100 MHz, CD_3OD): 15.2; 30.1; 32.5; 43.2; 46.0; 48.5; 67.8; 121.0; 126.2; 128.2; 128.8; 142.6; 145.4; 158.9; 177.6. HR-MALDI-MS: 408.1242 ($[C_{21}H_{23}NNaO_4S]^+$; calc. 408.1240). Anal. calc. for $C_{21}H_{23}NO_4S$ (385.5) C 65.43, H 6.01, N 3.63, S 8.32; found: C 65.48, H 5.98, N 3.66, S 8.18.

11. *Determination of Enantiomer Purity of β²-Homoamino Acids. Preparation of Pd Complexes for Determination of Enantiomer Purity of β²hIle and β²hTyr*. Unprotected amino acid (0.1 mmol) was dissolved in MeOH (10 ml); to this soln. 1M MeONa in MeOH (0.2 mmol, 0.2 ml) was added dropwise, and the mixture was stirred for 15 min at r.t. To the resulting solution, di-μ-chlorobis{2-[1-(dimethylamino)-χN-ethyl]phenyl-χC}palladium (58 mg, 0.1 mmol) in CH_2Cl_2 (3 ml) was added, and the mixture was stirred for 1.5 h at r.t. The

org. solvents were then evaporated, and the residue was redissolved in $CHCl_3$ and washed with H_2O, sat. aq. $NaHCO_3$ soln., and again with H_2O. $CHCl_3$ was then evaporated *in vacuo*, and the residue was analyzed by ^{1}H-NMR.

*{(2*S*,3*S*)-2-[(Amino-*χ*N)methyl]-(3-methylpentanoato-*χ*O} {(1*S*)-2-[1-(dimethylamino-*χ*N)ethyl]phenyl-*χ*C}palladium*. ^{1}H-NMR (300 MHz, CD_3OD): 0.92 (*d*, *J* = 6.7, $MeCH_2$); 0.99 (*t*, *J* = 7.3, Me); 1.30 (*m*, 1 H, CH_2); 1.48 (*d*, *J* = 6.6, Me); 1.55 (*m*, 1 H, CH_2); 2.24 (*m*, MeC*H*); 2.42–2.55 (*m*, CHCO); 2.52 (*s*, MeN); 2.75–2.89 (*m*, NH_2CH_2); 2.80 (*s*, MeN); 3.97 (*q*, *J* = 6.6, CHN); 4.09 (br. *s*, 1 H, NH_2); 4.47 (br. *s*, 1 H, NH_2); 6.74–7.00 (*m*, 4 arom. H).

*{(2*S*)-2-[(Amino-*χ*N)methyl]-3-[4-(*tert*-butoxy)phenyl]propanoato-*χ*O} {(1*S*)-2-[1-(dimethylamino-*χ*N)-ethyl]phenyl-*χ*C}palladium*. ^{1}H-NMR (300 MHz, CD_3OD): 1.30 (*s*, *t*-Bu); 1.51 (*d*, *J* = 6.6, *Me*CH); 2.53 (*s*, MeN); 2.70 (*m*, CH_2); 2.77–2.87 (*m*, CH_2N); 2.82 (*s*, MeN); 3.37 (*m*, CHCO); 3.92 (*q*, *J* = 6.5, NCH); 4.14 (br. *s*, 1 H, NH_2); 4.46 (br. *s*, NH_2); 6.67–7.21 (*m*, 8 arom. H).

Preparation of N-*(2,4-dinitrophenyl)-β²homomethion ine Methyl Ester for Determination of Enantiomer Purity of β²hMet by HPLC.* β^2-Homomethionine (1.74 mmol) was dissolved in sat. aq. $NaHCO_3$ soln. (10 ml), the resulting soln. was cooled in an ice-bath, and 2,4-dinitrofluorobenzene (389 mg, 2.09 mmol) in EtOH (10 ml) was added. The mixture was stirred for 3 h at 0°. The soln. was diluted with Et_2O, washed with 1N HCl and sat. aq. NH_4Cl soln., dried, and evaporated. The residue was dissolved in toluene (20 ml) and Me_3SiCHN_2 (2M soln. in hexane, 1.29 ml, 2.58 mmol) was added dropwise and the resulting mixure stirred for 15 min at r.t. At this point, AcOH (2 ml) was added slowly. Org. solvents were evaporated, and the residue was purified by FC (AcOEt/hexane 3 : 7) to give the product as yellow solid (153 mg, 26%). Part of this material was racemized by treating it with 1M MeONa in MeOH overnight at r.t. HPLC (hexane/i-PrOH 4 : 1, flow 0.8 ml/min): t_R 28.8 and 31.3 min. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.88 (*m*, 1 H, CH_2); 2.12 (*s*, MeS); 2.18 (*m*, 1 H, CH_2); 2.59 (*m*, CH_2S); 3.05 (*m*, CH); 3.64 (*m*, CH_2N); 3.77 (*s*, MeO); 6.97 (*d*, *J* = 9.5, 1 arom. H); 8.30 (*dd*, *J* = 9.6, 2.8, 1 arom. H); 8.82 (br. *s*, NH); 9.15 (*d*, *J* = 2.7, 1 arom. H).

X-Ray Crystal-Structure Determination of **6**[6]). The intensities were collected on *Nonius KappaCCD* diffractometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71073$). The structure was solved by direct methods with SIR 97 [18] and refined by full-matrix least-squares refinement on F^2 with SHELXL-97 [19]. The H-atoms were fixed at calculated positions. Crystallization from $(i\text{-Pr})_2O$/hexane, colorless needles, $C_{15}H_{21}NO_4$, $M_r = 279.336$, $a = 6.7708$ (3), $b = 16.0378$ (9), $c = 28.379$ (2) Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 3081.7$ (3) Å^3, orthorhombic space group $P2_12_12_1$, $Z = 8$, $D_x = 1.204$ g cm^{-3}, θ Range 0.998–22.986°, $\mu = 0.087$ mm^{-1}; 4286 reflections measured, 4260 independent, 3368 reflections observed ($I > 2\sigma(I)$), 362 parameters, 0 restraints, $R(F) = 0.0625$, $wR(F^2) = 0.1581$, $S(\text{ref}) = 1.193$, $\Delta\rho_{max} = 0.155$ e Å^3, $\Delta\rho_{min} = -0.166$ e Å^3.

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6) CCDC 217729 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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