Synthesis of β^3-Homophenylalanine-Derived Amino Acids and Peptides by *Suzuki* Coupling in Solution and on Solid Support

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β-Peptides and, to a certain extent, also mixed α,β-peptides, are resistant to degradation by a variety of proteolytic enzymes that rapidly degrade natural α-peptides. This is one of many characteristics that make β-peptides an attractive class of compounds for drug-discovery studies. On the other hand, modern organometallic reactions such as the *Suzuki–Miyaura* cross-coupling have become standard tools in industry laboratories to derivatize side chains of α-peptidic compounds to build up libraries of unnatural peptides. Combining both features, we prepared (4-bromo)-β^3-homophenylalanine derivatives **3**–**5** and **12** as precursors for *Suzuki–Miyaura* couplings. From these bromo compounds, we synthesized biaryl-substituted β-homoamino acids **6**, and analogs **13** and **15** of the anti-AIDS drug *Saquinavir*.

Introduction. – The *Suzuki–Miyaura* cross-coupling reaction is a powerful synthetic tool for C,C-coupling reactions of borono derivatives with aryl or vinyl halides or triflates[5]), as the reaction is unaffected by the presence of H_2O, tolerates a broad range of functional groups, proceeds regio- and stereoselectively in good yields, and nontoxic inorganic side-products are easily removed. The reaction has been used with (4-borono)- [2], (4-bromo)- [3], and (4-iodo)phenylalanine [4][5], serine-derived alkylboronic acids [6], and tyrosine triflates [3][7] for the preparation of phenylalanine derivatives, which are modified in the 4-aryl position. These unnatural amino acids have been incorporated into small peptides to increase both their pharmacological potential and metabolic stability [8].

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[3]) Part of the ETH Dissertation No. 14298, Zürich 2001.

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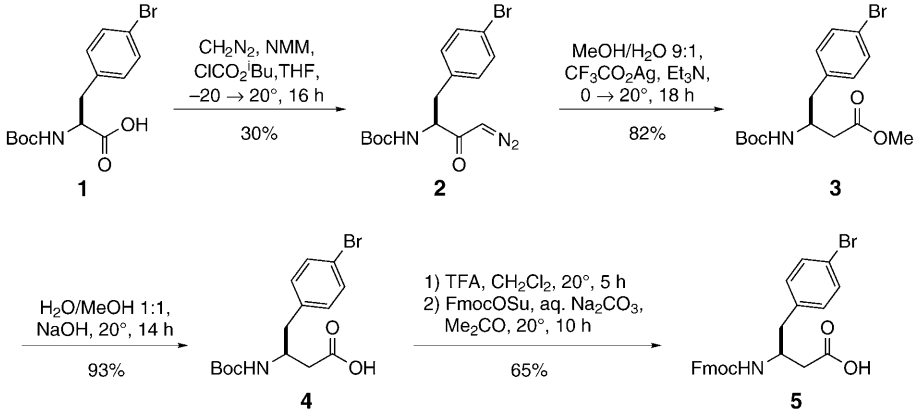
[5]) For recent reviews, see [1].

Whereas short α-peptides [5] or even α-proteins [9] bearing the above mentioned (4-aryl) phenylalanine precursors have been modified by *Suzuki–Miyaura* cross-coupling, no such operation is known for β- or mixed α,β-peptides. While α-peptides are rapidly degraded *in vivo* and *in vitro* by a multitude of peptidases, substrates with incorporated homologated α-amino acids (*i.e.*, β-amino acids) exhibit a superior stability profile [10]. To avoid a lack of recognition/inhibitory activity of these unnatural peptides resulting from the different spatial arrangements of side chains and to augment stability, peptides containing both α- and β-amino acid residues may be an ideal compromise.

Herein, we describe the preparation of 4-aryl-substituted β^3-homophenylalanine derivatives[6]) by *Suzuki–Miyaura* coupling in solution, starting from 4-bromo-β^3-homophenylalanine, which has been incorporated into a resin-bound tetrapeptide and subsequently cross-coupled on solid support to give analogs of the HIV-protease inhibitor and anti-AIDS drug *Saquinavir*. This 'late' functionalization of a peptidic substrate, combined with the advantages of solid-phase synthesis, is ideally suited for library synthesis in medicinal chemistry to create molecular diversity [11].

Results and Discussion. – 1. *Preparation of (*S*)-Boc-β^3h(4-Br)Phe-OMe and (*S*)-Fmoc-β^3h(4-Br)Phe-OH.* To test the *Suzuki* cross-coupling in solution, the appropriately protected β^3-homoamino acid **3** was prepared by *Arndt–Eistert* homologation [12], starting from commercially available (*S*)-Boc-(4-bromo)phenylalanine (**1**): its mixed anhydride, formed by treatment with isobutyl chloroformate, was allowed to react with CH_2N_2 to give diazo ketone **2** and subsequent *Wolff* rearrangement in MeOH/H_2O 9:1 provided the Boc-protected β^3-homoamino acid methyl ester **3** (*Scheme 1*).

Scheme 1. *Preparation of the Boc- and Fmoc-Protected β^3-Homo-(4-Br)phenylalanine Derivatives* **3** *and* **5** (NMM = *N*-methylmorpholine, Su = *N*-succinimido)

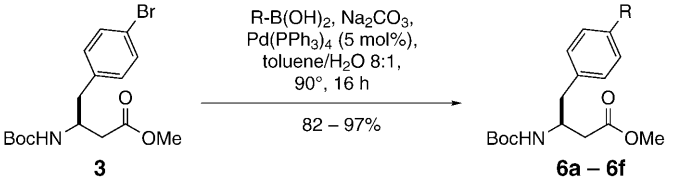


[6]) So far, our group has studied β-amino acids and β-peptides exclusively with proteinogenic side chains! See the extensive review article [10d].

Although the preparation of the Fmoc-protected derivative **5** should also be possible from the commercially available Fmoc-protected α-amino acid, we have, instead, saponified the methyl ester **3** to give the Boc-protected β^3-homoamino acid **4**, which was subjected to a protective-group interchange to give the desired Fmoc-protected β-amino acid **5**, suitable for the synthesis of peptides on solid support.

2. Suzuki *Cross-Coupling Reaction in Solution.* To test the *Suzuki* cross-coupling reaction in solution, we chose phenylboronic acid, and its 4-fluoro-, 4-methoxy-, 3-(trifluoromethyl)-, and 3-chloro derivatives, as well as naphthalen-2-ylboronic acid. It turned out that only 5 mol-% of the commercial Pd^0 source tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] was necessary to give the Boc-β^3hPhe-OMe derivatives **6a**–**6f** in yields of 82–97% (*Scheme* 2). Such enantiomerically pure protected β^3-homoamino acids have previously been obtained by employing organozinc reagents [13], which require the preparation and handling of sensitive organometallic reagents.

Scheme 2. Suzuki *Cross-Coupling Reaction with the Protected β^3-Homoamino Acid Ester* **3** *in Solution*[a]) (2-naphth : naphthalen-2-yl)



6	**a**	**b**	**c**	**d**	**e**	**f**
R	Ph	2-naphth	4-F–C_6H_4	3-Cl–C_6H_4	4-F_3C–C_6H_4	4-MeO–C_6H_4
yield [%]	97	91	82	88	86	95

[a]) The ^{13}C-NMR spectra of compounds **6a**–**6f** in $CDCl_3$ at 20°, as well as in C_6D_6 at 65°, showed extensive signal broadening, due to the presence of rotamers.

For high conversions, an elevated temperature was required (90°, 16 h), and, therefore, the reactions were carried out in sealed tubes. The progress of the reactions was monitored either by TLC or, more advantageously for the reaction on solid support, by following the evolution of CO_2. Both the Boc and the methyl-ester group turned out to be stable to the relatively harsh reaction conditions. All products were solid, and their solutions in $CHCl_3$ were levorotatory, except for the naphthyl derivative **6b**, which was dextrorotatory.

3. *Synthesis of a β-Tripeptide Analog of* Saquinavir *in Solution.* In recent years, a major research effort has been the development of pharmacologically active inhibitors of the human immunodeficiency virus protease (HIVp) [14]. In 1990, *Roche* UK reported [15][16] the subnanomolar active ($K_i = 0.12$ nM) HIVp-inhibitor *Saquinavir*, which contains a novel decahydroisoquinoline–hydroxyethylamine isostere replacement of the Phe-Pro cleavage site of the natural-substrate binding motif Leu^{165}-Asn-Phe-Pro-Ile^{169} (*Fig. 1*).

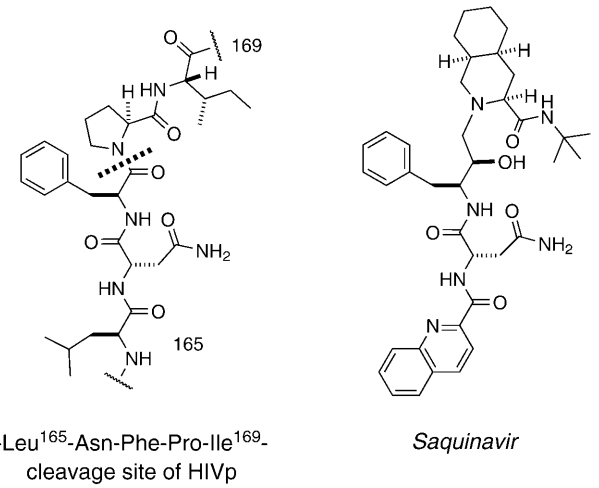
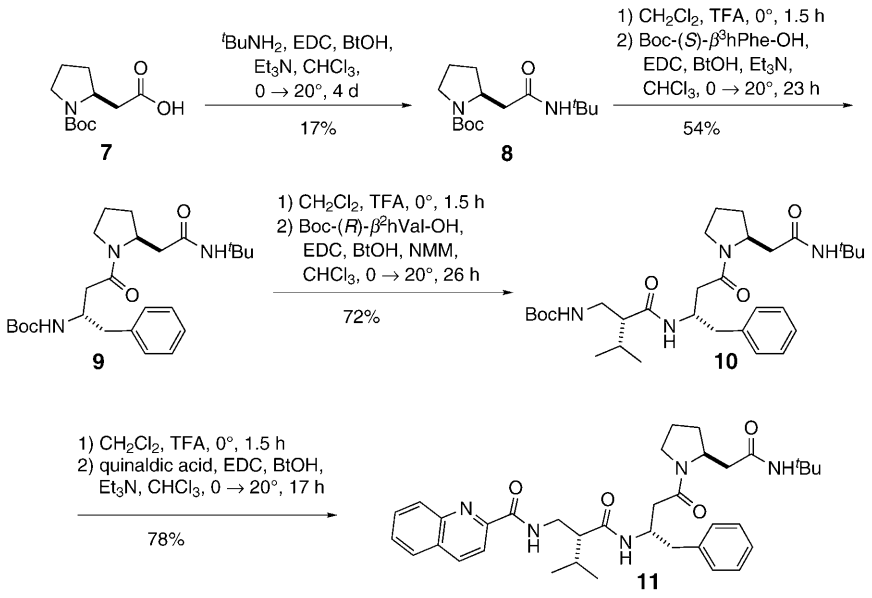


Fig. 1. *The HIVp-inhibitor* Saquinavir *and HIVps natural substrate*

Substitution of all α-amino acids by their β^2/β^3-homologs with the same absolute configuration and replacement of decahydroisochinoline by proline led to the β-tripeptidic *Saquinavir* analog[7]) **11** as a synthetic target molecule (*Scheme 3*).

Scheme 3. *Preparation of the β-Peptidic* Saquinavir *Analog* **11** *in Solution* (EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, BtOH: 1-hydroxy-1*H*-benzotriazole)



[7]) According to our experience, this compound will be absolutely stable towards peptidases [10d–g].

In a first step, ^{t}BuNH$_2$ was coupled with Boc-(*S*)-β^3hPro-OH (**7**) [17] under standard conditions (EDC, BtOH, Et_3N) to give the carboxamide **8**. Boc Deprotection and subsequent coupling with Boc-(*S*)-β^3hPhe-OH gave the dipeptide **9**, which was deprotected and coupled with Boc-(*R*)-β^2hVal-OH [18] to afford the β-tripeptide **10**. Final deprotection and coupling with quinaldic acid (= quinoline-2-carboxylic acid) furnished, after purification by normal-phase HPLC, the desired β-peptide derivative **11**, which was fully characterized (*cf. Scheme 3*, *Fig. 2*, and see *Exper. Part*). Compound **11** did, however, not inhibit HIVp at concentrations of up to 60 μM [19].

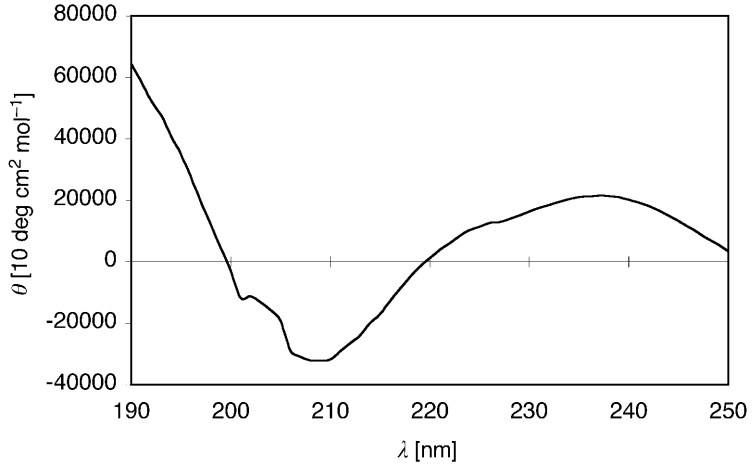


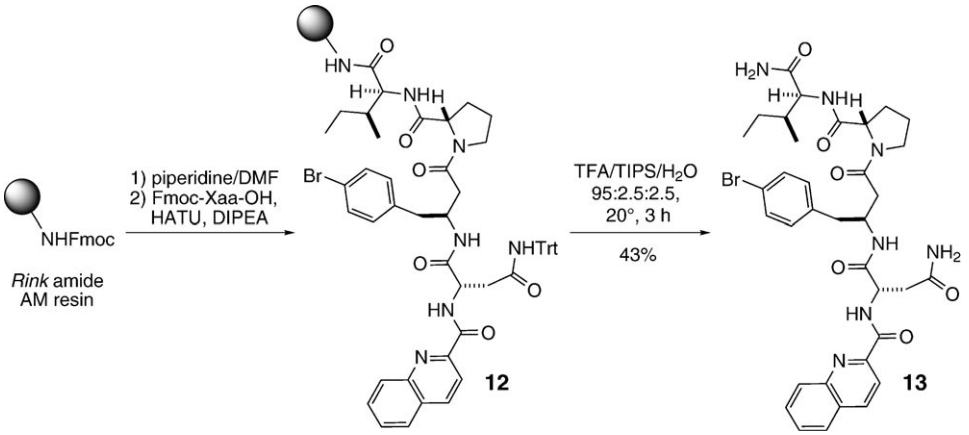
Fig. 2. *CD Spectrum of β-tripeptide derivative* **11** *at 25°* ($c = 0.2$ mM in MeOH). Due to the strong UV absorption of the quinaldyl group ($\varepsilon = 1.0 \cdot 10^4 - 1.3 \cdot 10^4$ at 200–250 nM for quinaldine in MeOH soln.) [20], the CD spectrum of **11** cannot be compared with the spectra of β-peptides bearing only proteinogenic side chains [10d].

4. Suzuki *Cross-Coupling Reaction on Solid Support.* As another *Saquinavir* analog suitable for modification by *Suzuki* coupling, we envisaged the resin-bound tetrapeptide **12**, in which the phenylalanine residue of the natural substrate-binding motif Leu^{165}-Asn-Phe-Pro-Ile^{169} is replaced by (*S*)-β^3h(4-Br)phenylalanine. Resin-bound peptide **12** was synthesized on *Rink* amide AM resin [21], as the ester bond of amino acids/peptides attached to a *Wang* resin has been reported not to be completely stable under the conditions of the *Suzuki* coupling [22]. This strategy has previously been reported for cross-coupling of resin-bound aromatic halides [23].

The Fmoc-protected amino acids were coupled in threefold excess by activation with HATU/DIPEA 0.97:2 in DMF for 1 h (*Scheme 4*). For the coupling of the valuable Fmoc-(*S*)-β^3h(4-Br)-Phe-OH (**5**) only a twofold excess was used, and the coupling time was prolonged to 2 h. Each coupling and deprotection step was monitored by the TNBS test [24] (or by the chloranil test for the secondary amino group of Pro) [25], and, if necessary, an additional coupling was performed (see *Exper. Part*).

Cleavage from the resin and deprotection were carried out with TFA/H_2O/TIPS, and the crude peptide was purified by RP-HPLC to give peptide **13** in a total yield

Scheme 4. *Solid-Phase Synthesis of the Mixed α,β-Tetrapeptide* **13**, *Containing H-(S)-β³h(4-Br)-Phe-OH* (DIPEA: $EtN(i\text{-}Pr)_2$, HATU: *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, TFA: CF_3COOH, TIPS: $(i\text{-}Pr)_3SiH$)



of 43% over eleven steps. This compound is by itself a *Saquinavir* analog, and it is ready for preparing further derivatives of this type by *Suzuki* coupling.

With the resin-bound tetrapeptide **12**, *Suzuki* coupling with 3-(trifluoromethyl)phenylboronic acid (under conditions similar to those established in solution) was actually performed in the presence of 10 mol-% Pd catalyst and EtOH as co-solvent (90°, 5 h) to give the resin-bound coupling product **14**. Subsequent cleavage from the resin and deprotection were carried out as described for the Br derivative **13**, and the crude product was purified by RP-HPLC to give the desired *Saquinavir* analog **15** in 59% yield (*Scheme 5*). As the completeness of the reaction was monitored by following the evolution of CO_2, the crude peptide turned out to be essentially pure (>95% by HPLC). Unfortunately, neither **13** nor **15** did inhibit HIVp at concentrations of up to 60 μM [19].

In summary, we have shown that the *Suzuki* coupling with a series of boronic acids in solution (six examples) as well as on solid support (one example) is a versatile tool for the derivatization of 4-(4-bromophenyl)-β^3-homophenylalanine-containing amino acids and α,β-mixed peptides. The corresponding cross-coupled products are obtained in high yields (up to 97%) and with excellent purities. This methodology was successfully applied to the synthesis of an analog of the HIV-protease inhibitor *Saquinavir*.

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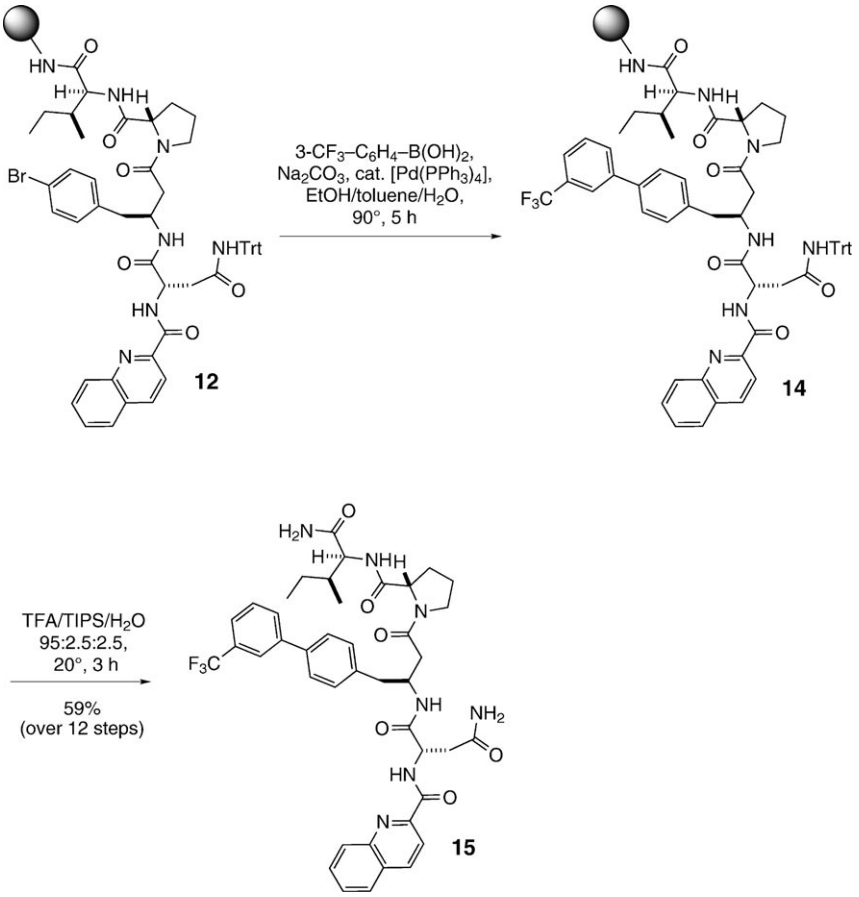
Experimental Part

1. *General.* Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*) and from KOH (Et_2O). $CHCl_3$ for optical-rotation measurements was filtered over basic Al_2O_3 (Alumina, *Woelm N*, actvity I) to remove EtOH. Et_3N and DIPEA were distilled from CaH_2 and stored over KOH. Protected Fmoc-amino acids were purchased from *Fluka*. *Rink* amide

Scheme 5. Suzuki *Cross-Coupling with the Mixed α,β-Tetrapeptide* **12** *Anchored to* Rink-*Amide Resin*



AM resin was purchased from *Novabiochem*. ***Caution:*** The generation and handling of CH_2N_2 requires special precautions [26][27]. *Abbreviations:* Boc: (*tert*-butoxy)carbonyl, DIPEA: $EtN(i\text{-}Pr)_2$, DMAP: 4-(dimethylamino)pyridine, EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, Fmoc: [(9*H*-fluoren-9-yl)methoxy]carbonyl, Fmoc-OSu: (9*H*-fluoren-9-yl)methyl *N*-succinimidyl carbonate, h.v.: high vacuum (0.01–0.1 Torr), HATU: *O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, BtOH: 1-hydroxy-1*H*-benzotriazole, *β*hXaa: *β*-homoamino acid [12][28–30], NMM: *N*-methylmorpholine, TFA: CF_3COOH, TIPS: $(i\text{-}Pr)_3SiH$, TNBS: 2,4,6-trinitrobenzenesulfonic acid. TLC: *Merck* silica-gel *60* F_{254} plates; detection under UV light at 254 nm and monitoring by solns. of ninhydrine (300 mg of ninhydrine, 3 ml of AcOH, and 100 ml of BuOH) or 'Mo-stain' (25 g of phosphomolybdic acid, 10 g of $Ce(SO_4)_2 \cdot H_2O$, 60 ml of conc. H_2SO_4, 940 ml of H_2O), followed by heating with a heat gun. FC: *Fluka* silica gel *60* (40–63 mesh). The dimensions of the columns are given as 'diameter × height of the silica column'. IR Spectra: Measured as 1–2% $CHCl_3$ soln. or KBr pellets on a *Perkin-Elmer-782* spectrophotometer, or neat on a *Perkin-Elmer 1600 FT-IR* spectrophotometer. NMR Spectra: ^{1}H-NMR Spectra were recorded on a *Bruker AMX 400* (400 MHz) or *Varian Gemini 300* (300 MHz). ^{13}C-NMR Spectra were recorded on a *Bruker AMX 400* (100 MHz) or *Varian Gemini 300* (75 MHz). Chemical shifts δ are given in ppm relative to resonances of solvent (^{1}H: 7.26 ppm for $CDCl_3$, 3.31 ppm for CD_3OD, 7.16 ppm for C_6D_6; ^{13}C: 77.0 ppm for $CDCl_3$, 49.2 ppm for CD_3OD, 128.4 ppm for

C_6D_6), coupling constants J are given in Hz; some compounds show the presence of rotamers: the chemical shifts are reported, and the intensities of rotamers were calculated where the signal of rotamers could be assigned unequivocally. The multiplicities of signals were determined by the DEPT technique: DEPT: + = primary or tertiary (positive DEPT signal), − = secondary (negative DEPT signal), C_q = quaternary C-atoms. Mass spectra: *VG Tribrid* (EI), *Bruker Reflex* (MALDI), or *IonSpec Ultima 4.7 T FT* Ion Cyclotron Resonance (ICR, HR-MALDI, in a 2,5-dihydroxybenzoic acid matrix) mass spectrometer in *m*/*z* (% of basis peak). Anal. HPLC: Analysis was performed on a *Merck* HPLC system (*LaChrom*, pump type *L-7150*, UV detector *L-7400*, Interface *D-7000*, HPLC manager *D-7000*) with a *Macherey-Nagel* C_{18} column (*Nucleosil 100–5* C_{18} (250 × 4 mm)). Linear gradient of *A*: 0.1% TFA in H_2O and *B*: MeCN at a flow rate of 1 ml/min. TFA for anal. HPLC was used as UV-grade quality (> 99% GC). Prep. HPLC: *Merck* HPLC system (*LaChrom*, pump type *L-7150*, UV detector *L-7400*, interface *D-7000*, HPLC manager *D-7000*) with *Macherey-Nagel* C_{18} column (*Nucleosil 100–7* C_{18} (250 × 21 mm)). Gradient of *A* and *B* at a flow rate of 12 ml/min. TFA for prep. HPLC was used as UV-grade quality (> 99% GC). Normal-phase HPLC analysis was performed on a *Lichrosolv Si-60*, 7-mm column (250 × 4 mm) by using an isocratic mixture or a linear gradient of i-PrOH and hexane at a flow rate of 1 ml/min with UV detection at 220 nm. Crude products were purified by prep. HPLC on a *Lichrosolv Si-60*, 7-mm column (250 × 21 mm) using an isocratic mixture or a linear gradient of i-PrOH and hexane at a flow rate of 4 ml/min with UV detection at 220 nm and then evaporated under reduced pressure. Lyophilization: *Hetosicc* cooling condenser with h.v. pump. or *GAMMA I-20* equipped with a controller *LDC-2 M* (*Christ Gefriertrocknungsanlagen*). M.p.: measured in open-end glass capillary tubes on a *Büchi 510* apparatus; uncorrected. Optical rotations $[\alpha]_D^{r.t.}$ were measured on a *Perkin-Elmer 241* polarimeter (10 cm, 1-ml cell). The solvents and concentrations (in g/100 ml) are indicated. CD Spectra: *Jasco J-710* spectropolarimeter from 190 to 250 nm with a *Jasco PTC-348 WI* peltier system at 25° in 1-mm rectangular cells. The optical system was flushed with N_2 at a flow rate of ca. 10 l/min. Parameters: band width 1.0 nm, resolution 0.2–1 nm, sensitivity 100 mdeg, response 0.5 s, speed 50 nm/min, 5 accumulations. All spectra were corrected for the corresponding solvent spectrum. Peptide concentration 0.2 mM. The molar ellipticity $[\theta]$ in 10 deg·cm^2·mol^{-1} (λ in nm) is calculated for the corresponding peptide (not normalized), taking into account the mass of TFA for each free amino group. Smoothing was done by *Jasco* software. Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich. Peptides with free amino groups form TFA salts. The molecular mass (MS) corresponds to the peptides without TFA.

2. *Synthesis of the Compounds.* *(*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-4-(4-bromophenyl)-1-diazobutan-2-one* (**2**). A soln. of (*S*)-Boc-(4-bromo)phenylalanine (**1**; 2.10 g, 6.10 mmol) in THF (35 ml) was cooled to −20°. After addition of $ClCO_2{}^tBu$ (838 µl, 6.41 mmol) and NMM (705 µl, 6.41 mmol), the mixture was stirred at −20° for 20 min. The resulting white suspension was allowed to warm to −5°, and a freshly distilled soln. of CH_2N_2 in Et_2O was added until the rich yellow color persisted, and the mixture was stirred under rewarming to r. t. for 16 h. Excess CH_2N_2 was destroyed by the addition of three drops of AcOH. The mixture was diluted with AcOEt (200 ml), washed with sat. NH_4Cl soln. (50 ml), $NaHCO_3$ (50 ml), and brine (50 ml). Drying of the org. phase ($MgSO_4$), removal of the solvent under reduced pressure, and FC (50 g of SiO_2, 3 × 20 cm; AcOEt/pentane 1:1, R_f 0.32) gave 674 mg (30%) of **2**. Pale yellow solid. M.p. 116–118°. $[\alpha]_D^{r.t.} = +13.0$ ($c = 5.50$, $CHCl_3$). IR (neat): 3336, 3076, 2985, 2933, 2864, 2169, 2113, 1902, 1739, 1688, 1626, 1519, 1485, 1445, 1383, 1329, 1249, 1199, 1120, 1068, 1024, 1010, 975, 943, 897, 857, 812, 789, 765, 734, 704, 660. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.40 (*s*, ^{t}Bu); 2.76–3.13 (*m*, CH_2); 4.27–4.49 (*m*, CH); 5.00–5.19 (*m*, CH); 5.19–5.36 (*m*, CH); 7.06 (*d*, $^3J = 8.24$, 2 arom. H); 7.41 (*d*, $^3J = 8.25$, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$, DEPT): 28.2 (+, ^{t}Bu); 37.8 (−, CH_2); 54.6 (−, CH_2); 58.1 (+, CH); 80.1 (C_q, ^{t}Bu); 120.9 (C_q, arom. C); 131.1 (+, 2 arom. C); 131.6 (+, 2 arom. C); 135.3 (C_q, arom. C); 155.0 (C_q, C=O); 192.8 (C_q, C=O). MALDI-MS: 392 (98), 390 (100), 370 (16, $[M+H]^+$), 368 (15, M^+, $C_{15}H_{18}BrN_3O_3^+$; calc. 368.2257), 286 (34), 284 (37).

*(*S*)-Methyl 4-(4-Bromophenyl)-3-{[(*tert*-butoxy)carbonyl]amino}butanoate* (**3**). Compound **2** (633 mg, 1.72 mmol) was dissolved in MeOH/H_2O 9:1 (10 ml). Under exclusion of light, a soln. of $AgCO_2CF_3$ (50 mg, 172 µmol) in Et_3N (726 µl, 4.37 mmol) was added at 0°, and the resulting mixture was stirred for 18 h under rewarming to r.t. Volatiles were removed under reduced pressure, and the residue was taken up in AcOEt (200 ml). Washing of the org. phase with sat. NH_4Cl (50 ml), $NaHCO_3$ (50

ml), drying ($MgSO_4$), and FC (50 g SiO_2, 3×20 cm, AcOEt/pentane 1:1, R_f 0.48) yielded 525 mg of **3** (82%). Colorless solid. M.p. 102–103°. $[\alpha]_D^{r.t.} = -190.1$ ($c = 4.30$, $CHCl_3$). IR (neat): 3352*m*, 3087*w*, 2982*w*, 2946*w*, 2868*w*, 2650*w*, 2319*w*, 2078*w*, 1988*w*, 1901*w*, 1729*s*, 1678*s*, 1516*s*, 1442*m*, 1372*m*, 1319*m*, 1280*w*, 1255*m*, 1211*m*, 1147*s*, 1022*m*, 987*w*, 889*w*, 842*w*, 791*w*, 756*w*, 715*w*, 656*m*. ^{1}H-NMR (300 MHz, C_6D_6, 60°): 1.38 (*s*, ^{t}Bu); 2.07–2.20 (*m*, CH_2); 2.55 (*dd*, $^3J = 7.6$, $^2J = 2.4$, CH_2); 3.26 (*s*, MeO); 4.00–4.18 (*m*, CH); 4.62–4.78 (br. *s*, NH); 6.73 (*d*, $^3J = 8.1$, 2 arom. H); 7.18 (*d*, $^3J = 8.1$, 2 arom. H). ^{13}C-NMR (75 MHz, C_6D_6, 60°, DEPT): 28.2 (+, ^{t}Bu); 37.6 (–, CH_2); 39.8 (–, CH_2); 49.0 (+, CH); 50.8 (+, MeO); 78.8 (C_q, ^{t}Bu); 120.5 (C_q, arom. C); 131.1 (+, 2 arom. C); 131.6 (+, 2 arom. C); 137.1 (C_q, arom. C); 160.1 (C_q, C=O); 171.2 (C_q, C=O). MALDI-MS: 341 (7), 328 (8), 233 (9), 217 (10), 189 (9), 140 (12), 96 (9). MALDI-HR-MS: 394.0624 ($[M+Na]^+$, $C_{16}H_{22}BrNaNO_4^+$; calc. 394.0618). Anal. calc. for $C_{16}H_{22}BrNO_4$ (372.3): C 51.26, H 5.96, N 3.76; found: C 51.67, H 6.20, N 3.84.

*(S)-4-(4-Bromophenyl)-3-{[(*tert*-butoxy)carbonyl]amino}butanoic Acid* (**4**). To a soln. of **3** (1.24 g, 3.33 mmol) in MeOH/H_2O 1:1 (50 ml) was added NaOH (666 mg, 16.7 mmol), and the soln. was stirred at r.t. for 14 h. MeOH was removed under reduced pressure, the aq. phase was acidified to pH 2 with 1N HCl at 0°, and the mixture was extracted with AcOEt (3×100 ml). Drying of the org. phase ($MgSO_4$) and removal of the solvent under reduced pressure yielded 1.11 g (93%) of **4**. Colorless solid. M.p. 140–142°. $[\alpha]_D^{r.t.} = -6.65$ ($c = 6.50$, $CHCl_3$). IR (neat): 3355*m*, 2983*w*, 1686*s*, 1520*s*, 1488*m*, 1446*w*, 1366*w*, 1298*m*, 1251*m*, 1162*s*, 1054*m*, 1027*w*, 917*w*, 892*m*, 802*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.39 (*s*, ^{t}Bu); 2.50–2.67 (*m*, CH_2); 2.77–3.04 (*m*, CH_2); 3.82–4.20 (*m*, CH); 5.06 (*d*, $^3J = 7.51$, NH); 7.08 (*d*, $^3J = 8.24$, 2 arom. H); 7.42 (*d*, $^3J = 8.24$, 2 arom. H); 9.59–10.5 (br. *s*, CO_2H). ^{13}C-NMR (75 MHz, $CDCl_3$, DEPT): 28.2 (+, ^{t}Bu); 37.5 (–, CH_2); 39.6 (–, CH_2); 48.4 (+, CH); 79.7 (C_q, ^{t}Bu); 120.5 (C_q, arom. C); 131.0 (+, 2 arom. C); 131.5 (+, 2 arom. C); 136.5 (C_q, arom. C); 155.1 (C_q, C=O); 176.6 (C_q, C=O). MALDI-MS: 404 (16), 402 (17), 398 (21), 398 (10), 396 (10), 382 (40), 380 (40), 282 (9), 261 (7), 256 (8), 255 (8), 191 (11). MALDI-HR-MS: 380.0468 ($[M+Na]^+$, $C_{15}H_{20}BrNNaO_4^+$; calc. 380.0462).

*(S)-4-(4-Bromophenyl)-3-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)butanoic Acid* (**5**). To a soln. of **4** (1.13 g, 3.16 mmol) in CH_2Cl_2 (5 ml) at r.t. was added TFA (5 ml), and the soln. was stirred for 5 h. Volatiles were removed under reduced pressure, and the residue was dried in the h.v. The residue was dissolved in acetone (20 ml), and Na_2CO_3 (786 mg, 9.47 mmol), H_2O (5 ml), and Fmoc-OSu (1.17 g, 3.47 mmol) were added, and the reaction was stirred for 10 h. Dilution with H_2O (40 ml), extraction with AcOEt (5 ml), acidification of the aq. phase to pH 1 with 1N HCl at 0°, extraction of the aq. phase with AcOEt (3×100 ml), drying of the org. phase ($MgSO_4$), and FC (100 g of SiO_2, 3×40 cm; AcOEt/pentane/AcOH 1:2:0.02, R_f 0.42) yielded 990 mg (65%) of **5**. Colorless solid. M.p. 177–178°. $[\alpha]_D^{r.t.} = -16.5$ ($c = 1.00$, $CHCl_3$). IR (neat): 2480*w*, 2360*s*, 2342*s*, 2167*w*, 2051*w*, 1981*w*, 1718*m*, 1677*s*, 1560*w*, 1542*w*, 1508*w*, 1489*w*, 1468*w*, 1451*m*, 1430*m*, 1334*m*, 1225*w*, 1173*w*, 1149*w*, 1105*w*, 1085*w*, 1038*m*, 1010*w*, 831*w*, 798*m*, 770*m*, 760*m*, 731*m*, 742*w*, 668*w*, 643*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.48 (*d*, $^3J = 6.86$, CH_2); 2.71 (*dd*, $J = 6.73$, 11.0, CH); 2.84 (*dd*, $J = 6.73$, 9.48, CH); 4.09–4.31 (*m*, 2 CH_2); 7.09–7.15 (*m*, 2 arom. H); 7.25–7.40 (*m*, 6 arom. H); 7.57 (*d*, $^3J = 6.87$, 2 arom. H); 7.78 (*d*, $^3J = 7.42$, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$, DEPT): 40.0 (–, CH_2); 40.9 (–, CH_2); 51.0 (+, CH); 67.6 (–, CH_2); 120.9 (+, 2 arom. C); 121.3 (C_q, arom. C); 126.3 (+, 2 arom. C); 128.2 (+, 2 arom. C); 128.8 (+, 2 arom. C); 132.5 (+, 4 arom. C); 139.0 (C_q, arom. C); 142.7 (C_q, 2 arom. C); 145.3 (C_q, 2 arom. C); 158.1 (C_q, C=O); 174.0 (C_q, C=O). MALDI-MS: 506 (15), 505 (8), 504 (26), 503 (7), 502 (24), 500 (11), 494 (14), 491 (8), 489 (13), 480 (9), 478 (17), 464 (13), 442 (23), 440 (10), 428 (10), 423 (17), 410 (8), 398 (37). MALDI-HR-MS: 502.0627 ($[M+Na]^+$, $C_{25}H_{22}BrNNaO_4^+$; calc. 502.0624).

General Procedure for the Suzuki *Coupling in Solution* (*GP*). To a suspension of Na_2CO_3 (2 equiv., 86 mg, 806 μmol), the corresponding boronic acid derivative (1.5 equiv., 605 μmol), and **3** (1 equiv., 150 mg, 403 μmol) in a degassed mixture of toluene (2 ml) and H_2O (250 μl) was added $[Pd(PPh_3)_4]$ (0.05 equiv., 24 mg, 20 μmol), and the suspension was heated in a *Schlenck* tube, sealed with a rubber septum, at 90° for 15 h. The course of the reaction was followed by penetrating the rubber septum with a fine needle to see whether there is still CO_2 formation (foaming of the reaction mixture!). Dilution of the mixture with AcOEt (150 ml), extraction with sat. $NaHCO_3$ soln. (50 ml) and brine (50 ml), drying of the org. phase (Na_2SO_4), and FC on SiO_2 (Et_2O/pentane 1:2 → 1:1) yielded the coupling products **6a**–**6f** as colorless solids.

*(S)-Methyl 4-[1,1′-Biphenyl-4-yl]-3-{[(*tert*-butoxy)carbonyl]amino}butanoate* (**6a**). Yield: 144 mg (97%). Colorless solid. M.p. 97–98°. R_f (Et_2O/pentane 1:1) 0.52. $[\alpha]_D^{r.t.} = -11.8$ ($c = 2.50$, $CHCl_3$). IR (neat): 3367*w*, 2980*w*, 1727*s*, 1682*s*, 1515*s*, 1486*m*, 1438*m*, 1391*w*, 1305*w*, 1266*w*, 1250*m*, 1076*w*, 918*w*, 837*m*. ^{1}H-NMR (300 MHz, $CDCl_3$; rotamers A/B *ca.* 5:3): 1.41 (*s*, ^{t}Bu, rotamer A); 1.42 (*s*, ^{t}Bu, rotamer B); 2.32–2.70 (*m*, 2 CH_2, rotamer A + B); 2.73–3.15 (*m*, 2 CH_2, rotamer A + B); 3.70 (*s*, MeO, rotamer A); 3.71 (*s*, MeO, rotamer B); 4.04–4.38 (*m*, 2 CH, rotamer A + B); 4.92–5.28 (br. *s*, 2 CH, rotamer A + B); 7.11–7.77 (*m*, 10 arom. H, rotamer A + B). ^{13}C-NMR (75 MHz, $CDCl_3$, DEPT; rotamers A/B *ca.* 5:3): 28.4 (+, ^{t}Bu); 36.8 (–, CH_2); 40.0 (–, CH_2); 49.5 (+, CH); 51.8 (+, MeO); 78.8 (C_q, ^{t}Bu); 126.8 (+, arom. C); 126.9 (+, 2 arom. C); 127.1 (+, 2 arom. C); 128.6 (+, 2 arom. C); 129.7 (+, 2 arom. C); 133.3 (C_q, arom. C); 136.6 (C_q, arom. C); 161.7 (C_q, C=O); 172.0 (C_q, C=O). MALDI-MS: 444 (8), 442 (8), 409 (16), 408 (70), 393 (21), 392 (88), 370 (13), 340 (8), 339 (29), 336 (10), 331 (7), 328 (7), 315 (7), 314 (11), 314 (35), 303 (26), 301 (7), 271 (9), 270 (58), 261 (11), 217 (30), 216 (9), 215 (8), 200 (8), 189 (12), 183 (12), 162 (14), 140 (15), 96 (29). MALDI-HR-MS: 392.1832 ($[M+Na]^+$, $C_{22}H_{27}NNaO_4^+$; calc. 392.1825).

*(S)-Methyl 3-{[(*tert*-Butoxy)carbonyl]amino}-4-[4-(naphthalen-2-yl)phenyl]butanoate* (**6b**). Yield: 154 mg (91%). Colorless solid. M.p. 115–117°. R_f (Et_2O/pentane 1:1) 0.48. $[\alpha]_D^{r.t.} = +107.9$ ($c = 5.35$, $CHCl_3$). IR (neat): 3371*m*, 2941*m*, 2861*w*, 2750*w*, 2651*w*, 2585*w*, 2328*w*, 2041*w*, 1990*w*, 1916*w*, 1733*s*, 1686*s*, 1608*w*, 1515*s*, 1443*m*, 1364*m*, 1315*w*, 1248*m*, 1213*w*, 1158*s*, 1044*m*, 1013*m*, 958*w*, 889*w*, 811*s*, 752*m*, 614*m*. ^{1}H-NMR (300 MHz, C_6D_6, 65°): 1.42 (*s*, ^{t}Bu); 2.35 (*d*, $^3J = 7.5$, CH_2); 2.81 (*dd*, $^3J = 7.5$, $^2J = 2.6$, CH_2); 3.31 (*s*, MeO); 4.20–4.45 (*m*, CH); 4.72–4.98 (br. *s*, CH); 7.12–7.19 (*m*, 2 arom. H); 7.20–7.38 (*m*, 2 arom. H); 7.43–7.56 (*m*, 2 arom. H); 7.56–7.80 (*m*, 4 arom. H); 7.86–7.99 (*m*, 1 arom. H). ^{13}C-NMR (75 MHz, C_6D_6, 65°, DEPT): 28.3 (+, ^{t}Bu); 37.9 (–, CH_2); 40.2 (–, CH_2); 49.4 (+, CH); 50.8 (+, MeO); 78.8 (C_q, ^{t}Bu); 125.6 (C_q, arom. C); 125.8 (+, arom. C); 126.1 (+, arom. C); 127.6 (+, 2 arom. C); 127.7 (+, arom. C); 128.0 (+, arom. C); 128.3, 128.5, 129.9, 133.0 (C_q, arom. C); 134.2 (C_q, arom. C); 137.3 (+, arom. C); 138.6 (C_q, arom. C); 139.7 (C_q, arom. C); 155.0 (C_q, C=O); 171.4 (C_q, C=O). MALDI-MS: 458 (13), 443 (14), 442 (51), 420 (17), 398 (8), 365 (16), 364 (68), 328 (14), 321 (22), 320 (100), 314 (7), 303 (17), 302 (9), 284 (11), 242 (8), 242 (8), 234 (11), 233 (14), 217 (14), 189 (14), 140 (12), 96 (16). MALDI-HR-MS: 442.1970 ($[M+Na]^+$, $C_{22}H_{29}NNaO_4^+$; calc. 442.1989).

*(S)-Methyl 3-{[(*tert*-Butoxy)carbonyl]amino}-4-(4′-fluoro[1,1′–biphenyl]-4-yl)butanoate* (**6c**). Yield: 128 mg (82%). Colorless solid. M.p. 104–106°. R_f (Et_2O/pentane 1:1) 0.45. $[\alpha]_D^{r.t.} = -92.0$ ($c = 4.70$, $CHCl_3$). IR (neat): 3361*m*, 2942*w*, 2859*w*, 2180*w*, 2108*w*, 1904*w*, 1734*s*, 1682*s*, 1605*w*, 1522*s*, 1444*m*, 1362*w*, 1324*w*, 1245*m*, 1214*w*, 1164*s*, 1098*w*, 1043*w*, 1017*w*, 949*w*, 813*s*, 677*w*, 631*m*. ^{1}H-NMR (300 MHz, C_6D_6, 65°): 1.40 (*s*, ^{t}Bu); 2.25 (*d*, $^3J = 7.5$, CH_2); 2.76 (*dd*, $^3J = 7.8$, $^2J = 2.3$, CH_2); 3.30 (*s*, MeO); 4.20–4.35 (*m*, CH); 4.58–4.82 (br. *s*, NH); 6.83 (*t*, $^3J = 8.1$, 2 arom. H); 7.02–7.35 (*m*, 6 arom. H). ^{13}C-NMR (75 MHz, C_6D_6, 65°, DEPT): 28.2 (+, ^{t}Bu); 37.8 (–, CH_2); 40.1 (–, CH_2); 49.3 (+, CH); 50.8 (+, MeO); 78.8 (C_q, ^{t}Bu); 115.3 (C_q, arom. C); 115.6 (C_q, arom. C); 127.1 (+, 2 arom. C); 128.5 (+, 2 arom. C); 128.6 (+, 2 arom. C); 129.8 (+, 2 arom. C); 137.3 (C_q, arom. C); 138.7 (C_q, arom. C); 154.9 (C_q, arom. C); 164.3 (C_q, C=O); 171.3 (C_q, C=O). MALDI-MS: 410 (12), 357 (8), 339 (19), 332 (13), 328 (8), 234 (8), 233 (8), 217 (10), 189 (8), 140 (11), 96 (13). MALDI-HR-MS: 410.1728 ($[M+Na]^+$, $C_{22}H_{26}FNNaO_4^+$; calc. 410.1758).

*(S)-Methyl 3-{[(*tert*-Butoxy)carbonyl]amino}-4-(3′-chloro[1,1′-biphenyl]-4-yl)butanoate* (**6d**). Yield: 143 mg (88%). Colorless solid. M.p. 92–94°. R_f (Et_2O/pentane 1:1) 0.58. $[\alpha]_D^{r.t.} = -65.6$ ($c = 4.30$, $CHCl_3$). IR (neat): 3365*m*, 2955*w*, 2928*w*, 2862*w*, 2360*w*, 2076*w*, 1990*w*, 1931*w*, 1726*s*, 1687*s*, 1590*w*, 1553*w*, 1515*s*, 1467*m*, 1436*m*, 1362*m*, 1255*s*, 1162*s*, 1090*w*, 1039*s*, 961*w*, 902*w*, 869*w*, 833*w*, 776*s*, 749*w*, 674*w*, 642*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.49 (*s*, ^{t}Bu); 2.44–2.59 (*m*, CH_2); 2.85 (*dd*, $^3J = 7.4$, 7.4, CH); 2.98 (*dd*, $^3J = 6.3$, 5.8, CH); 3.69 (*s*, MeO); 4.16 (*quint.*, $^3J = 7.3$, CH); 5.09 (*d*, $^3J = 7.1$, NH); 7.25–7.55 (*m*, 8 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$, DEPT): 28.3 (+, ^{t}Bu); 37.5 (–, CH_2); 39.9 (–, CH_2); 48.7 (+, CH); 51.7 (+, MeO); 79.4 (C_q, ^{t}Bu); 125.1 (+, arom. C); 127.1 (+, arom. C, 2 C); 127.2 (+, 2 arom. C); 129.90 (+, 2 arom. C); 129.94 (+, arom. C); 134.6 (C_q, arom. C); 137.5 (C_q, arom. C); 138.1 (C_q, arom. C); 142.7 (C_q, arom. C); 155.1 (C_q, C=O); 172.1 (C_q, C=O). MALDI-MS: 442 (11), 428 (12), 427 (10), 426 (41), 404 (12), 350 (10), 348 (35), 328 (12), 306 (14), 304 (44), 303 (10), 284 (10), 279 (7), 264 (7), 242 (19), 236 (7), 234 (16), 233 (18), 184 (7). MALDI-HR-MS: 426.1428 ($[M+Na]^+$, $C_{22}H_{26}ClNNaO_4^+$; calc. 426.1443).

*(S)-Methyl 3-{[(*tert*-Butoxy)carbonyl]amino}-4-(3′-methyl[1,1′-biphenyl]-4-yl)butanoate* (**6e**). Yield: 152 mg (86%). Colorless solid. M.p. 88–90°. R_f (Et_2O/pentane 1:1) 0.45. $[\alpha]_D^{r.t.} = -10.8$ ($c = 4.50$, $CHCl_3$). IR (neat): 3367*m*, 3064*w*, 3028*w*, 2983*w*, 2962*w*, 2851*w*, 2359*w*, 1725*s*, 1687*s*, 1672*w*, 1595*m*, 1518*s*, 1446*m*, 1395*m*, 1364*m*, 1334*s*, 1265*w*, 1155*s*, 1115*s*, 1076*m*, 1035*m*, 1046*m*, 998*m*, 196*m*, 827*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.32 (*s*, ^{t}Bu); 2.50 (*dd*, $^3J = 5.77$, $^2J = 3.03$, CH_2); 2.63–3.01 (*m*, CH_2); 3.62 (*s*, MeO); 4.11 (*m*, CH); 7.33 (*d*, $^3J = 8.24$, 2 arom. H); 7.60–7.65 (*m*, 4 arom. H); 7.86–7.91 (*m*, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$, DEPT): 28.2 (+, ^{t}Bu); 39.7 (–, CH_2); 40.6 (–, CH_2); 50.1 (+, CH); 51.9 (MeO); 79.0 (C_q, ^{t}Bu); 124.5 (+, 2 arom. C); 127.7 (+, 2 arom. C); 130.4 (+, 2 arom. C); 130.8 (+, 2 arom. C); 131.3 (C_q, arom. C); 138.0 (C_q, arom. C); 139.6 (C_q, arom. C); 142.4 (C_q, arom. C); 154.9 (C_q, C=O); 171.3 (C_q, C=O). MALDI-MS: 477 (8), 476 (32), 461 (25), 460 (100), 438 (17), 404 (9), 383 (14), 382 (69), 345 (7), 339 (7), 338 (33), 303 (9), 235 (27), 234 (10), 233 (11), 217 (7), 184 (11), 162 (11), 140 (13), 96 (8). MALDI-HR-MS: 460.1698 ($[M+Na]^+$, $C_{23}H_{26}F_3NNaO_4^+$; calc. 460.1706).

*(S)-Methyl 3-{[(*tert*-Butoxy)carbonyl]amino}-4-(4′-methoxy[1,1′-biphenyl]-4-yl)butanoate* (**6f**). Yield: 153 mg (95%). Colorless solid. M.p. 136–137°. R_f (Et_2O/pentane 1:1) 0.56. $[\alpha]_D^{r.t.} = -102.2$ ($c = 4.55$, $CHCl_3$). IR (neat): 3385*m*, 2981*w*, 2942*w*, 2849*w*, 2643*w*, 2357*w*, 2077*w*, 2043*w*, 1990*w*, 1914*w*, 1734*s*, 1684*s*, 1609*w*, 1503*s*, 1444*m*, 1364*w*, 1251*s*, 1217*w*, 1160*s*, 1120*w*, 1033*s*, 807*s*, 756*w*, 721*w*, 679*w*, 639*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.41 (*s*, ^{t}Bu); 2.40–2.62 (*m*, CH_2); 2.91 (*dd*, $^3J = 7.9$, $^2J = 2.2$, CH_2); 3.70 (*s*, MeO); 3.85 (*s*, MeO); 4.15–4.25 (*m*, CH); 5.00–5.15 (br. *s*, NH); 6.99 (*d*, $^3J = 8.0$, 2 arom. H); 7.22 (*d*, $^3J = 8.0$, 2 arom. H); 7.492 (*d*, $^3J = 7.5$, 2 arom. H); 7.495 (*d*, $^3J = 7.5$, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$, DEPT): 28.3 (+, ^{t}Bu); 37.8 (–, CH_2); 40.2 (–, CH_2); 49.4 (+, CH); 50.7 (+, MeO); 54.7 (+, MeO); 78.7 (C_q, ^{t}Bu); 114.5 (+, 2 arom. C); 126.9 (+, 2 arom. C); 129.8 (+, 2 arom. C); 133.8 (C_q, arom. C); 136.5 (C_q, arom. C); 139.5 (C_q, arom. C); 159.6 (C_q, C=O); 171.4 (C_q, C=O). MALDI-MS: 438 (10), 423 (10), 422 (45), 400 (19), 369 (14), 345 (11), 344 (58), 328 (11), 301 (18), 300 (100), 284 (10), 282 (9), 263 (45), 242 (9), 241 (97), 235 (32), 234 (8), 233 (11), 217 (10), 189 (17), 140 (13), 96 (11). MALDI-HR-MS: 422.1928 ($[M+Na]^+$, $C_{23}H_{29}NNaO_5^+$; calc. 422.1938).

Boc-(S)-β^{3}hPro-NH^{t}Bu (**8**). To a soln. of Boc-(*S*)-β^{3}hPro-OH (57 mg, 440 μmol) in $CHCl_3$ (1.8 ml) at 0° were added ^{t}BuNH$_2$ (47 μl, 440 μmol), Et_3N (61 μl, 440 μmol), BtOH (81 mg, 530 μmol), and EDC (10 mg, 540 μmol). The mixture was allowed to warm to r.t., and stirring was continued for 4 d. Subsequent dilution with $CHCl_3$, washing with 1N HCl, aq. sat. $NaHCO_3$, and brine, drying of the org. phase ($MgSO_4$), removal of the solvent under reduced pressure, and FC (SiO_2; MeOH/CH_2Cl_2 2:98, R_f 0.23) yielded 22 mg (17%) of **8**. Colorless solid. M.p. 74.5–75.5°. $[\alpha]_D^{r.t.} = -44.9$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3436*w*, 3007*m*, 2982*m*, 1673*s*, 1511*m*, 1477*w*, 1454*m*, 1403*s*, 1366*s*, 1306*w*, 1169*m*, 1123*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.33 (*s*, ^{t}Bu); 1.47 (*s*, ^{t}Bu); 1.76–1.88 (*m*, 2 CH); 1.95–2.05 (*m*, 2 CH); 2.21–2.32 (*m*, CH); 2.54 (*dd*, $J = 13.6$, 3.4, 1 H, CH_2); 3.31–3.34 (*m*, 2 CH); 3.98–4.04 (*m*, CHN); 5.21 (br. *s*, NH, rotamer); 5.94 (br. *s*, NH, rotamer). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.5 (CH_2); 28.6, 28.8 (Me); 30.7, 42.1, 46.8 (CH_2); 51.0 (C); 55.3 (CH); 79.5 (C); 170.4 (C). EI-MS: 183 (27), 127 (29), 115 (15), 110 (34), 100 (10), 84 (23), 83 (32), 82 (12), 70 (100), 69 (14), 68 (16), 58 (49), 57 (25), 56 (29), 55 (12), 44 (17), 42 (11), 41 (38), 39 (14), 28 (12). Anal. calc. for $C_{15}H_{28}N_2O_3$ (284.40): C 63.35, H 9.92, N 9.85; found: C 63.37, H 9.73, N 9.72.

Boc-(S)-β^{3}hPhe-(S)-β^{3}hPro-NH^{t}Bu (**9**). To a soln. of **8** (48 mg, 170 μmol) in CH_2Cl_2 (500 μl) at 0° was added TFA (500 μl), and the soln. was stirred at r.t. for 1.5 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (1 ml). At 0° were added Et_3N (90 μl, 650 μmol), Boc-(*S*)-β^3*h*Phe-OH (71 mg, 250 μmol), BtOH (38 mg, 250 μmol), and EDC (48 mg, 250 μmol), and the soln. was stirred under rewarming to r.t. for 23 h. Dilution with $CHCl_3$, washing with 1N HCl, aq. sat. $NaHCO_3$, and brine, drying of the org. phase ($MgSO_4$), removal of the solvent under reduced pressure, and twofold FC (SiO_2; MeOH/CH_2Cl_2 3:97 then AcOEt, R_f 0.45) and recrystallization from CH_2Cl_2/hexane yielded 38 mg (51%) of **9**. Colorless solid. M.p. 151–152°. $[\alpha]_D^{r.t.} = -19.3$ ($c = 1.1$, $CHCl_3$). IR ($CHCl_3$): 3433*m*, 3007*s*, 2979*s*, 2877*w*, 1701*s*, 1671*s*, 1625*s*, 1496*s*, 1453*s*, 1392*m*, 1366*s*, 1308*m*, 1286*m*, 1168*s*, 1050*w*, 1029*w*, 928*w*, 850*w*, 639*w*, 619*w*, 607*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; rotamers A/B *ca.* 8:1): 1.33 (*s*, ^{t}Bu, rotamer B); 1.35 (*s*, ^{t}Bu, rotamer A); 1.40 (*s*, ^{t}Bu, rotamer B); 1.41 (*s*, ^{t}Bu, rotamer A); 1.81–2.07 (*m*, 4 CH); 2.14 (*dd*, $J = 13.7$, 9.0, 1 H, CH_2); 2.38 (*d*, $J = 5.0$, CH_2); 2.71 (*dd*, $J = 13.7$, 3.3, 1 H, CH_2); 2.86 (*dd*, $J = 13.4$, 8.3, 1 H, CH_2); 3.00–3.08 (*m*, CH); 3.18–3.26 (*m*, 2 CH); 4.08–4.16 (*m*, CHN); 4.24–4.30 (*m*, CHN); 5.48 (br. *s*, NH, rotamer B); 5.71 (br. *s*, NH, rotamer A);

6.05 (br. *s*, NH); 7.17–7.23 (*m*, 3 arom. H); 7.27–7.31 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; signals of rotamers in italics): *21.6*, *23.7* (CH_2); 28.4, 28.8 (Me), 30.1 (CH_2); *31.0*, *36.8*, *40.2*, *41.8*, *42.3*, *45.4*, 47.1 (CH_2); 49.3 (CH); 51.1 (C); 55.5 (CH); 79.1 (C); 126.5, 128.5, 129.2 (CH); 138.6, 155.4, 168.9, 170.1 (C). MALDI-HR-MS: 368.2307 (100, $[M-Boc+Na]^+$, $C_{20}H_{31}N_3NaO_2^+$; calc. 368.2314), 346.2491 (41, $[M-Boc+H]^+$, $C_{20}H_{32}N_3O_2^+$; calc. 346.2495).

*Boc-(*R*)-β²hVal-(*S*)-β³hPhe-(*S*)-β³hPro-NH^{t}Bu* (**10**). To a soln. of **9** (39 mg, 870 μmol) in CH_2Cl_2 (1 ml), at 0° was added TFA (1 ml), and the soln. was stirred at r.t. for 1.5 h. The solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$ (860 μl), and NMM (27 μl, 240 μmol), Boc-(*R*)-β²hVal-OH (41 mg, 180 μmol), BtOH (25 mg, 190 μmol), and EDC (33 mg, 170 μmol) were added at 0°. The soln. was stirred for 1 h at 0°, then for 26 h at r.t. Dilution with $CHCl_3$, washing with 1N HCl, aq. sat. $NaHCO_3$, and brine, drying of the org. phase ($MgSO_4$), removal of the solvent under reduced pressure and FC (SiO_2; MeOH/CH_2Cl_2 2:98, R_f 0.43) yielded 35 mg (72%) of **10**. Colorless, highly viscous oil. ^{1}H-NMR (400 MHz, $CDCl_3$; rotamers A/B *ca.* 3:1; all other rotamers are given in italics): 0.88 (*d*, *J* = 6.7, Me, rotamer A); 0.94 (*d*, *J* = 6.7, Me, rotamer A); 1.25 (*s*, ^{t}Bu, rotamer B); 1.28 (*s*, ^{t}Bu, rotamer A); 1.31 (*s*, ^{t}Bu, rotamer B); 1.33 (*s*, ^{t}Bu, rotamer A); *1.36* (*s*, ^{t}Bu); *1.37* (*s*, ^{t}Bu); *1.43* (*s*, ^{t}Bu); 1.85–2.23 (*m*, 7 CH); 2.38–2.46 (*m*, 2 CH); 2.71–2.79 (*m*, CH); 2.84 (*dd*, *J* = 13.5, 8.4, 1 H, CH_2); 3.02 (*dd*, *J* = 13.5, 7.1, 1 H, CH_2); 3.13–3.23 (*m*, 2 CH); 3.31–3.40 (*m*, CH); 4.21–4.32 (*m*, CH); 4.40–4.58 (*m*, CH); 4.90–4.98 (*m*, CH); *5.46* (*s*, NH); *5.97* (*s*, NH); 7.04 (*d*, *J* = 8.6, NH); 7.17–7.25 (*m*, 3 arom. H); 7.28–7.32 (*m*, 2 arom. H); 8.59 (*d*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$; signals of rotamers in italics): 20.1, 20.8 (Me); 23.7 (CH_2); *28.4*, *28.5*, *28.6*, *28.8* (Me); *29.7*, *30.1*, *30.2*, *34.5*, *36.5*, *39.3*, *40.1*, *40.6*, *41.6*, *47.2* (CH_2); *47.4*, *47.6*, *48.7* (CH); 51.2 (C); *54.1*, *55.4*, *55.5*, *55.6* (CH); 62.8 (CH_2); 79.1, *126.7*, *126.8*, *127.0*, *128.6*, *128.8*, *129.1*, *129.1*, *129.6*, *129.8* (CH); 138.2, 156.1, 170.0, 170.2, 173.5 (C). MALDI-HR-MS: 582.3716 (17), 581.3680 (49, $[M+Na]^+$, $C_{31}H_{50}N_4NaO_5^+$; calc. 581.3679), 482.3190 (29), 481.3155 (100, $[M-Boc+Na]^+$, $C_{26}H_{42}N_4NaO_3^+$; calc. 481.3155), 459.3343 (16, $[M-Boc+H]^+$, $C_{26}H_{43}N_4O_3^+$; calc. 459.3335), 386.2446 (11), 185.1657 (22).

*(Quinoline-2-carbonyl)-(*R*)-β²hVal-(*S*)-β³hPhe-(*S*)-β³hPro-NH^{t}Bu* (**11**). To a soln. of **10** (35 mg, 620 μmol) in CH_2Cl_2 (1 ml) at 0° was added TFA (1 ml), and the soln. was stirred at r.t. for 1.5 h. The solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$ (0.6 ml) and Et_3N (35 μl, 250 μmol), quinaldic acid (= quinoline-2-carboxylic acid; 27 mg, 160 μmol), BtOH (26 mg, 190 μmol), and EDC (36 mg, 190 μmol) were added at 0°, and the soln. was stirred under rewarming to r.t. for 17 h. Dilution with $CHCl_3$, washing with 1N HCl, aq. sat. $NaHCO_3$, and brine, drying of the org. phase ($MgSO_4$), removal of the solvent under reduced pressure and purification by normal-phase HPLC (*Merck* system: the column was first loaded using an isocratic mixture of 2% ^{i}PrOH and was then washed with a linear gradient of 2–50% ^{i}PrOH within 15 min) yielded 30 mg (78%) of **11**. White powder. M.p. 79.0° (sint.). HPLC (*Merck* system, ^{i}PrOH/hexane 25:75): t_R 4.2 min, purity > 99%. CD (0.2 mM in MeOH): $+2.1\cdot10^4$ (237 nm), 0 (220 nm), $-3.2\cdot10^4$ (209 nm), 0 (200 nm). IR (KBr): 3314*m*, 3063*w*, 2965*m*, 1647*s*, 1534*s*, 1500*s*, 1452*s*, 1390*m*, 1364*m*, 1310*w*, 1226*m*, 1172*w*, 848*w*, 777*m*, 742*w*, 701*m*, 625*w*. ^{1}H-NMR (400 MHz, CD_3OD; rotamer A/B 3:2): 0.92 (*d*, *J* = 6.7, Me, rotamer B); 0.94 (*d*, *J* = 6.7, Me, rotamer A); 1.02 (*d*, *J* = 6.7, Me, rotamer B); 1.02 (*d*, *J* = 6.7, Me, rotamer A); *1.26* (*s*, ^{t}Bu, rotamer A); *1.28* (*s*, ^{t}Bu, rotamer B); *1.29* (*s*, ^{t}Bu, rotamer B); *1.30* (*s*, ^{t}Bu, rotamer A); 1.77–1.95 (*m*, 4 CH); 1.99 (*dd*, *J* = 13.5, 10.0, 1 H, CH_2); 2.17–2.40 (*m*, 2 CH); 2.43 (*d*, *J* = 6.7, CH); 2.65 (*dd*, *J* = 13.4, 3.8, 1 H, CH_2); 2.74 (*dd*, *J* = 13.7, 6.8, 1 H, CH_2); 2.86 (*dd*, *J* = 13.6, 7.2, 1 H, CH_2); 3.28–3.39 (*m*, 2 CH); 3.54–3.67 (*m*, 2 CH); 4.15–4.27 (*m*, CHN); *4.53–4.59* (*m*, CHN, rotamer A); *4.62–4.69* (*m*, CHN, rotamer B); 6.81–6.87 (*m*, 1 H); 6.95–7.01 (*m*, 2 H); 7.08–7.12 (*m*, 2 H); 7.20–7.25 (*m*, 1 H); 7.63–7.69 (*m*, 1 H); 7.71–7.78 (*m*, 1 H); *7.98* (*d*, *J* = 8.1, 0.5 H, rotamer A); *7.98* (*d*, *J* = 8.1, 0.5 H, rotamer B); 8.07 (*d*, *J* = 8.5, 1 H); 8.18 (*d*, *J* = 8.5, 1 H); 8.46 (*d*, *J* = 8.1, 1 H). ^{13}C-NMR (100 MHz, CD_3OD; signals of rotamers in italics): 20.6, 21.4 (Me); 22.4, 24.5 (CH_2); 28.9 (Me); 30.1 (CH); *30.1*, *31.6*, *39.5*, *40.8*, *40.9*, *41.4*, *42.4*, *46.8*, *48.0*, *48.3* (CH_2); 49.0 (CH); 51.9 (C); *54.5*, *54.7*, *56.7*, *56.9* (CH); 119.5, 127.3, 129.0, 129.2, 129.3, 129.4, 130.3, 130.3, 130.9, 131.5 (CH); 139.0 (C); 139.5 (CH); 148.0, 150.7, 166.6, 171.3, 172.0, 172.7, 175.9 (C). MALDI-HR-MS: 636.3520 (100, $[M+Na]^+$, $C_{36}H_{47}N_5NaO_4^+$; calc. 636.3526), 614.3716 (4, $[M+H]^+$, $C_{36}H_{48}N_5O_4^+$; calc. 614.3706).

*(Quinoline-2-carbonyl)-Asn-(*S*)-(4-Br)-β³hPhe-Pro-Ile-NH$_2$* (**13**). In a reactor, *Rink* amide AM resin (280 mg, 199 μmol, 200–400 mesh, 0.71 mmol/g) was swollen in DMF (5 ml) for 30 min. After filtration,

the resin was deprotected with piperidine/DMF (20%, 5 ml, 3×10 min) and washed with DMF (5×5 ml, 1 min). The free resin was coupled with the corresponding amino acid (3 equiv.), HATU (2.9 equiv.) and DIPEA (6 equiv.) for 1 h, *i.e.*, Fmoc-Ile-OH (212 mg, 600 μmol, 1×60 min and 1×45 min), Fmoc-Pro-OH (202 mg, 600 μmol), Fmoc-β^3hPhe-OH (212 mg, 400 μmol), Fmoc-Asn(Trt)-OH (358 mg, 600 μmol), and quinoline-2-carboxylic acid (173 mg, 1.0 mmol). The resin was washed with DMF (5×5 ml, 1 min) and CH_2Cl_2 (5×5 ml, 1 min), and dried in the h.v. The resin was split into three parts, and 144 mg (200 μmol) were cleaved with TFA/H_2O/TIPS 95:2.5:2.5 for 3 h. Removal of volatiles under reduced pressure, precipitation of the peptides with Et_2O, centrifugation, and purification by prep. RP-HPLC (30–40% *B* in 5 min, 40–95% *B* in 40 min, 95–99% *B* in 10 min, t_R 47.61 min) yielded 21 mg of **13** (43%). Colorless solid. Anal. RP-HPLC (5–8% *B* in 9 min, 8–60% *B* in 41 min, 60–99% *B* in 10 min): t_R 42.21 min, purity > 97%. ^{1}H-NMR (400 MHz, CD_3OD; signals of rotamers in italics): 0.84–0.96 (*m*, 6 H); 1.10–1.37 (*m*, 1 H); 1.49–1.59 (*m*, 1 H); 1.76–2.06 (*m*, 4 H); 2.12–2.34 (*m*, 1 H); 2.52–2.67 (*m*, 2 H); 2.73–2.93 (*m*, 4 H); 3.44–3.63 (*m*, 2 H); 4.20–4.25 (*m*, 1 H); 4.37–4.51 (*m*, 2 H); 4.84–4.91 (*m*, 1 H); *7.08* (*d*, ^3J = 8.5, 2 arom. H); 7.15 (*d*, ^3J = 8.5, 2 arom. H); *7.19* (*d*, ^3J = 8.5, 2 arom. H); 7.24 (*d*, ^3J = 8.5, 2 arom. H); 7.68–7.72 (*m*, 1 arom. H); 7.82–7.86 (*m*, 1 arom. H); 8.00 (*d*, ^3J = 8.5, 1 arom. H); 8.17–8.20 (*m*, 2 arom. H); 8.49 (*d*, ^3J = 8.6, 1 arom. H). ^{13}C-NMR (100 MHz, CD_3OD; DEPT; signals of rotamers in italics): *11.4* (+, Me); 11.6 (+, Me); 16.0 (+, Me); *16.1* (+, Me); *23.7* (–, CH_2); 25.8 (–, CH_2); 26.0 (–, CH_2); 26.1 (–, CH_2); 30.8 (–, CH_2); *33.2* (–, CH_2); *37.7* (–, CH_2); 38.0 (–, CH_2); 38.1 (+, CH); 39.1 (–, CH_2); *39.3* (–, CH_2); *40.1* (–, CH_2); 40.2 (–, CH_2); *48.1* (–, CH_2); 48.4, 49.7 (–, CH_2); *50.0*, *50.4*, *51.7* (+, CH); 52.1 (+, CH); 59.0 (+, CH); 61.6 (+, CH); *61.9* (+, CH); 119.6 (+, arom. C); *119.7* (+, arom. C); 121.2 (C_q, arom. C); 129.1 (+, arom. C); 129.5 (+, arom. C); 130.9 (C_q, arom. C); 131.0 (+, arom. C); 131.6 (+, arom. C); *131.7* (+, arom. C); 132.4 (+, 2 arom. C); 132.5 (+, arom. C); 132.6 (+, 2 arom. C); 138.7 (+, arom. C); 139.1 (C_q, arom. C); 148.1 (C_q, arom. C); 150.4 (C_q, arom. C); 166.4 (C_q, C=O); 172.0 (C_q, C=O); *172.1* (C_q, C=O); 172.3 (C_q, C=O); *172.5* (C_q, C=O); *174.2* (C_q, C=O); 174.6 (C_q, C=O); 175.2 (C_q, C=O); 176.4 (C_q, C=O). MALDI-MS: 776 (22, 775 (8), 774 (20), 762 (8), 761 (40), 760 (100), 759 (39), 758 (95), 738 (7), 722 (21), 721 (57), 720 (22), 719 (55), 703 (8), 693 (19), 691 (18), 676 (12), 674 (10), 608 (13), 606 (15), 591 (11), 589 (11). MALDI-HR-MS: 758.2259 ($[M+Na]^+$, $C_{35}H_{42}BrN_7NaO_6^+$; calc. 758.2272).

(Quinoline-2-carbonyl)-Asn-(S)*-4-(3-trifluoromethyl)-β^3hPhe-Pro-Ile-NH$_2$* (**15**). To a suspension of **12** (144 mg, 70 μmol) in degassed EtOH (300 μl) were added 3-(trifluoromethyl)phenylboronic acid (25 mg, 130 μmol), Na_2CO_3 (28 mg, 260 μmol), [$Pd(PPh_3)_4$] (8 mg, 7.00 μmol), degassed H_2O (130 μl), and degassed toluene/EtOH 7:3 (1 ml). The tube was sealed and heated under shaking to 90° for 5 h. The cold suspension was filtered, the resin was washed with EtOH/H_2O (5×5 ml, 1 min), DMF (5×5 ml, 1 min), and CH_2Cl_2 (5×5 ml, 1 min), and dried in h.v. Cleavage with TFA/H_2O/TIPS 95:2.5:2.5 for 3 h, removal of volatiles under reduced pressure, precipitation of the peptide with cold Et_2O, centrifugation, and purification by prep. RP-HPLC (30–40% *B* in 5 min, 40–95% *B* in 35 min, 95–99% *B* in 10 min, t_R 27.03 min) yielded 33 mg of **15** (59%). Colorless solid. Anal. RP-HPLC (5–8% *B* in 8 min, 8–60% *B* in 52 min, 60–99% *B* in 10 min): t_R 48.55 min, purity > 97%. ^{1}H-NMR (300 MHz, CD_3OD): 0.85–1.10 (*m*, 6 H); 1.16–1.28 (*m*, 1 H); 1.51–1.60 (*m*, 1 H); 1.77–2.37 (*m*, 5 H); 2.56–3.07 (*m*, 5 H); 3.48–3.68 (*m*, 2 H); 4.20–4.28 (*m*, 1 H); 4.41–4.54 (*m*, 2 H); 4.81–4.94 (*m*, 2 H); 7.29–7.51 (*m*, 5 arom. H); 7.51–7.79 (*m*, 3 arom. H); 7.90–8.19 (*m*, 4 arom. H); 8.35–8.41 (*m*, 2 arom. H). ^{13}C-NMR (75 MHz, CD_3OD, DEPT): 11.4 (+, Me); 16.9 (+, Me); 26.1 (–, CH_2); 30.8 (–, CH_2); 38.0 (–, CH_2); 38.2 (+, CH); 39.2 (–, CH_2); 40.2 (–, CH_2); 48.8 (–, CH_2); 52.3 (+, CH); 59.2 (+, CH); 61.7 (+, CH); 119.7 (+, arom. C); 123.2 (C_q, arom. C); 124.0 (C_q, arom. C); 127.8 (+, 2 arom. C); 129.0 (+, arom. C); 129.6 (+, arom. C); 130.6 (C_q, arom. C); 130.7 (+, arom. C); 131.4 (+, 2 arom. C); 131.5 (+, arom. C); 131.7 (+, arom. C); 132.4 (+, arom. C); 132.5 (+, arom. C); 132.6 (+, arom. C); 139.2 (+, arom. C); 139.3 (C_q, arom. C); 143.1 (C_q, arom. C); 148.1 (C_q, arom. C); 150.4 (C_q, arom. C); 166.3 (C_q, C=O); 172.3 (C_q, C=O); 174.6 (C_q, C=O); 175.3 (C_q, C=O); 176.6 (C_q, C=O). MALDI-MS: 841 (10). 840 (23), 826 (13), 825 (47), 824 (100), 803 (20), 802 (38), 787 (8), 786 (31), 785 (67), 757 (9), 633 (8), 533 (8), 456 (14), 235 (11). MALDI-HR-MS: 824.3366 ($[M+Na]^+$, $C_{42}H_{46}F_3N_7NaO_6^+$; calc. 824.3354).

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