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Efficient Enantioselective Synthesis of Condensed and Aromatic-Ring-Substituted Tyrosine Derivatives

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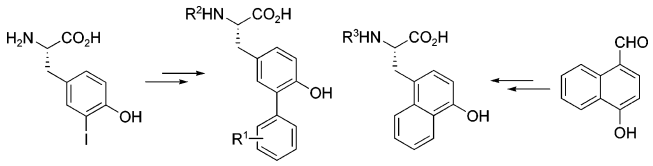

An efficient access to both condensed and conjugated tyrosine analogues of high enantiomeric purity is described. Novel ring-substituted tyrosines were synthesized by Suzuki cross couplings of appropriately protected L-3-iodotyrosine with a series of activated and deactivated boronic acid derivatives to achieve the target compounds in high yields. D- and L-4-hydroxy-1-naphthylalanines were readily prepared from the corresponding α-enamide in two different approaches, by asymmetric hydrogenation as well as by unselective hydrogenation and enzymatic resolution of the racemic mixture.

Introduction

Nonproteinogenic amino acids play an important role in drug development. While proteinogenic amino acids provide limited variation in size and shape, the introduction of unusual substituents allows a systematic study of the structure−activity relationship (SAR). Consequently, nonproteinogenic amino acids have been found to significantly improve the biological properties of numerous biologically active peptides and peptidomimetics, e.g., by limiting conformational flexibility, enhancing enzymatic stability, and improving pharmacodynamics or bioavailability.[1−3] Especially modified aromatic amino acids are important structural features in various pharmaceuticals which are currently under development or have already been introduced into the market. Among the latter are, for example, the broad-spectrum antibiotics Ampicillin and Amoxicillin, which contain a D-phenylglycine and a D-4-hydroxyphenylglycine moiety, respectively, and Nafarelin, a luteinizing hormone releasing hormone (LHRH) analogue for treatment of endometrioses comprising a D-2-naphthylalanine residue. It is evident that such unnatural aromatic amino acids are indispensable tools in pharmaceutical research. Thus, there is a great demand for methods allowing the synthesis of a variety of derivatives in a short time. In the past few years several groups have reported strategies for the synthesis of aromatic substituted phenylalanines,[4−9] tryptophans,[7,8] and naphthylalanines.[4,7,8] However, to the best of our knowledge, methods for the synthesis of the corresponding tyrosine derivatives have not been reported in the literature yet.

In contrast to phenylalanine, tyrosine provides an additional hydroxyl group in the side chain which may be crucial for the activity or selectivity of biologically active compounds, e.g., by acting as a hydrogen bond donor or acceptor. To enable systematic studies of structure−activity relationships going along with the tyrosine residue, an efficient access to a wide range of substituted tyrosine analogues is required.

In our approach toward tyrosine analogues with extended aromatic side chain residues, we focused on strategies that allow an easy and short access to a variety of compounds in a few

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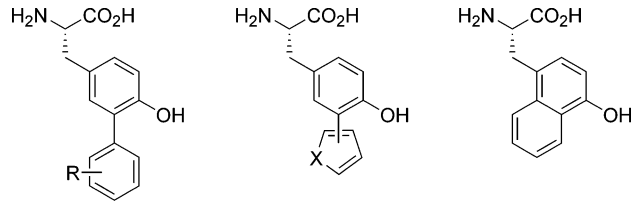

FIGURE 1. Structures of condensed and aromatic-ring-substituted tyrosine derivatives.

steps, avoiding complicated protecting group chemistry. Herein we report a general three-step procedure for the synthesis of enantiomerically pure 3-aryl-substituted L-tyrosine analogues of types **1** and **2** via a Suzuki-type cross coupling reaction (Figure 1). To extend the aromatic residue, we used a second approach in which we synthesized the condensed 2-naphthylalanine analogue of tyrosine **3** via an asymmetric hydrogenation of the corresponding α-enamide as a key step. In an alternative approach we hydrogenated the α-enamide unselectively and split the racemic mixture using acylase I.[10] This procedure provides a much cheaper approach in cases where both enantiomers are desired.

Results and Discussion

Synthesis of Aromatic-Ring-Substituted Tyrosine Derivatives. Our synthesis of 3-aryl-substituted L-tyrosine derivatives started with commercially available L-3-iodotyrosine (**4**). The amino function was protected with a *tert*-butyloxycarbonyl group (Boc) to ensure stability under Suzuki coupling conditions (Scheme 1). As expected, attempts to use compound **4** or **5** directly for Suzuki couplings failed, probably due to complexation of palladium after insertion into the carbon−iodine bond by the neighboring free phenolic hydroxyl group, which made a side chain protection necessary. Since for standard peptide coupling purposes, in both solution and the solid phase, a protection of the phenolic side chain is not crucial,[11] we protected both the phenolic side chain and the carboxylic acid in one step as a benzyl ether and a benzyl ester, respectively. This procedure avoids an additional protection and deprotection step as both groups can be removed simultaneously by hydrogenation, but offers the opportunity of a selective saponification of the benzyl ester when a side chain protection is needed. The benzyl protection was performed under mild conditions using sodium carbonate as the base to give the fully protected amino acid **6** in 93% yield and without loss of enantiomeric purity as shown below.

For Suzuki cross couplings we used $PdOAc_2/P(o\text{-tolyl})_3$ as the catalyst and sodium carbonate as the base, a system which has proven to give good results in similar systems.[4−8] Thus, a series of 3-aryl-substituted tyrosine derivatives were synthesized in moderate to high yields using a variety of activated and deactivated phenylboronic acids as well as heteroaromatic boronic acids (Table 1). The formation of the dimeric homocoupling product was generally less than 2% as measured by HPLC−MS, except for the 3-chlorophenylboronic acid, with which greater amounts of this side product were formed.

To demonstrate the further procedure and to verify the optical purity of our products, we deprotected samples of **7a** and **7d** to apply them in solid-phase peptide synthesis. The benzyl ester in both compounds could be cleaved chemoselectively using lithium hydroxide to give the free acids **8a** and **8b** in 86% and 83% yield, respectively (Scheme 2). Alternatively, simultaneous cleavage of both benzyl groups can be achieved by hydrogenation with palladium on charcoal, yielding **9a** and **9b** in 95% and 87%, respectively.

The latter compounds were coupled to the amino free resin bound L-valine using 1.8 equiv of the amino acids **9a** and **9b**, respectively, TBTU, and HOBt in NMP for 30 min. After cleavage from the resin and deprotection, the resulting dipeptides H-*m*-(phenyl)Tyr-Val-OH (**10a)** and H-*m*-(*o*-tolyl)Tyr-Val-OH (**10b)** were isolated in high purity (Scheme 3). A formation of side products due to the free phenolic side chain was not observed.

The corresponding diastereomeric dipeptides H-*m*-(phenyl)-Tyr-D-Val-OH (**10c**) and H-*m*-(*o*-tolyl)Tyr-D-Val-OH (**10d**), respectively, were synthesized in an analogous way by coupling to D-valine. NMR and HPLC analyses of **10a**−**d** showed the formation of only one single isomer, proving that no reasonable racemization occurred during our synthesis.

Enantioselecive Synthesis of 4-Hydroxy-1-naphthylalanine Derivatives. A synthesis of 4-hydroxy-1-naphthylalanine has already been reported by Vela et al.[12] By their procedure, 4-hydroxynaphthalene-1-carbaldehyde (**11**) was condensed with hippuric acid to form the (*Z*)-oxazolone, which was subsequently opened using ethoxide and hydrogenated to give the *N*-benzoyl-protected 4-hydroxy-1-naphthylalanine ethyl ester. The cleavage of the amino protection group was accomplished by refluxing in 6 N hydrochloric acid in dioxane. Obviously, their procedure requires harsh conditions, and it is not stereoselective. Therefore, we developed a more efficient access to achieve the compound in high enantiomeric purity via Horner−Emmons olefination and hydrogenation, applying protection groups which can be cleaved under mild conditions to conserve the enantiomeric purity.

In our synthesis we also started from commercially available **11** whose hydroxy group was protected as a *tert*-butyldimethylsilyl (TBS) ether in 88% yield (Scheme 4). In our initial experiments, we used a benzyl protection group instead; however, the final cleavage by catalytic hydrogenation led to a partial hydrogenation of the naphthalene residue. This was circumvented by the use of the TBS group. The Horner−Emmons olefination of aldehyde **12** with Schmidt's Boc-α-phosphonoglycine trimethyl ester gave the dehydroamino acid **13** with the *Z*-configuration as the major product[13] (*Z*:*E* = 93:7)[14] in 91% yield.[15,16] The TBS group in this system was found to be quite acid sensible. For that reason, triethylamine had to be added to the eluent for column chromatography to avoid decomposition and great losses in yield.

For the asymmetric hydrogenation of **13** we chose Burk's [1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene](cyclooctadiene)-rhodium(I) trifluoromethanesulfonate [(*S*,*S*)-Et-DuPHOS-(COD)-Rh^{I}]OTf, which gives high yields (>95%) and high enantiomeric

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(11) Following our procedure for peptide coupling, side-chain-unprotected tyrosine and its analogues can be coupled without side reactions.

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(13) The *Z* configuration was assigned by NOESY.

(14) The *Z*:*E* ratio was determined by HPLC.

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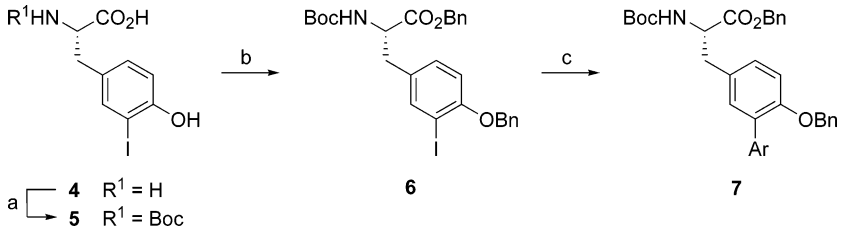
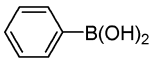
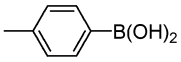
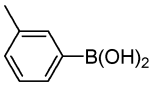
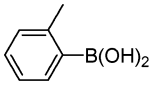
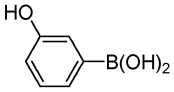
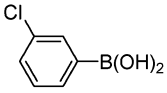
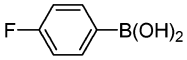
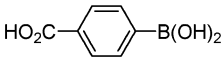
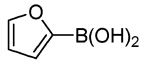
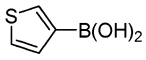
(16) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490.

SCHEME 1. Synthesis of 3-Aryl-Substituted Tyrosine Derivatives[a]



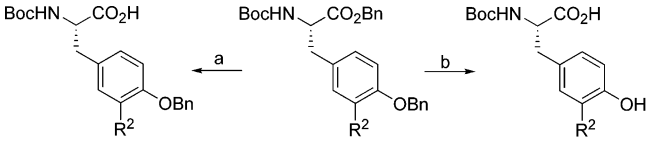
[a] Reagents and conditions: (a) Boc_2O, dioxane/H_2O, 0 °C, 18 h, 96%; (b) BnBr, Na_2CO_3, acetone, rt, 5 h, 93%; (c) $ArB(OH)_2$, Na_2CO_3, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, DME/H_2O, 80 °C, 4−6 h, 39−99%.

TABLE 1. Suzuki Cross Coupling of 6 with Arylboronic Acids

Compound	Ar-B(OH)$_2$	Yield (%)[a]
7a		95
7b		93
7c		79
7d		70
7e		80
7f		39
7g		94
7h		92
7i		99
7j		45

[a] Yields refer to isolated pure products.

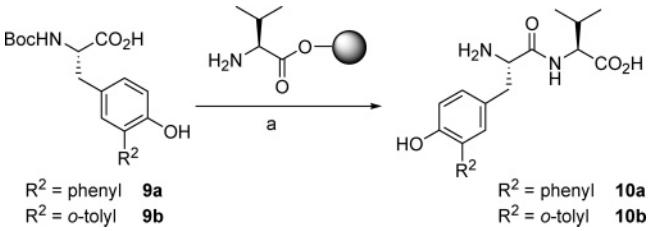
SCHEME 2. Regioselective Deprotection of 3-Aryl-Substituted Tyrosine Derivatives[a]



[a] Reagents and conditions: (a) LiOH, THF/H_2O, 0 °C → rt, 18 h, 86% (**8a**), 83% (**8b**); (b) H_2, Pd/C, MeOH/AcN(Me)$_2$, 6 h, 95% (**9a**), 87% (**9b**).

access (97% ee) when applied to hydrogenation of dehydroamino acids. Furthermore, using this type of catalyst, both diastereomers, *Z* and *E*, are hydrogenated to give the same enantiomer in similar enantiomeric purities.[5,6,17] Thus, a preceding separation of the two isomers is not essential. In our first attempts, however, working in MeOH[4−8] as solvent, we observed no conversion even at high pressures (1−50 bar). Therefore, we scanned various solvents and found the highest conversion rates when using DCM or THF (Table 2), but to our surprise, in both solvents, working at 1 bar of pressure, we were not able to reach complete conversion even at prolonged reaction times and/or by addition of fresh catalyst. Separation and analysis of the unreacted starting material gave pure *E* isomer of the dehydroamino acid **13**, indicating a much slower reaction rate for this isomer. For complete conversion of the obtained *Z*/*E* mixture of **13** the pressure had to be raised to 40 bar using DCM as the solvent. The pure *Z* isomer, which could be isolated in 75% yield from **12**, proved to react to completion at 1 bar of pressure.

SCHEME 3. Solid-Phase Peptide Synthesis Applying Side-Chain-Unprotected Tyrosine Analogues[a]

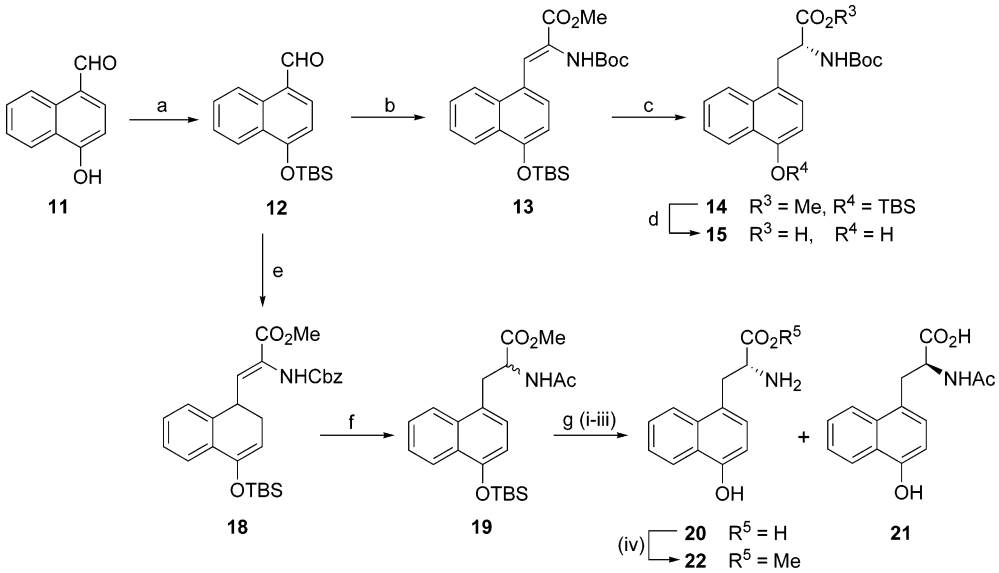


[a] Reagents and conditions: (a) (i) TBTU, HOBt, NMP, rt, 30 min; (ii) TFA/DCM/H_2O (50:40:10, v/v/v), rt, 1 h, >98% purity.

Working under 40 bar of hydrogen pressure in DCM, the *S*,*S* catalyst gave the amino acid derivative **14** with an absolute *S* configuration on the basis of the selectivity of the (*S*,*S*)-Et-DuPHOS ligand[5,6,17] in 95% yield. The enantiomeric purity was determined after subsequent cleavage of the TBS group and the methyl ester. The resulting free acid (*S*)-**15** was coupled to amino free resin bound L-valine using the conditions described in Scheme 3 above. Cleavage from the resin and deprotection gave the dipeptide H-(4-hydroxy)Nal-Val-OH (**16**) as a single diastereomer, as proven by HPLC and NMR analysis. As a reference, we synthesized the diastereomeric mixture H-(D/L)-(4-hydroxy)Nal-Val-OH (**17**), which was obtained by unselective hydrogenation of **13** with palladium on charcoal and subsequent deprotection and coupling to L-valine. The enantiomeric purity of **14** and (*S*)-**15** was assigned to be greater than 95%. In addition, the catalyst proved to work very efficiently (we worked with a catalyst-to-substrate ratio of 1:500), and we were able to synthesize the (*S*)-4-hydroxy-1-naphthylalanine derivative **14** in a high overall yield of 76% using three steps.

(17) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125−10138.

SCHEME 4. Enantionselective Synthesis of 4-Hydroxynaphthylalanine Derivatives[a]



[a] Reagents and conditions: (a) (TBS)Cl, imidazole, THF, 0 °C → rt, 18 h, 88%; (b) $(MeO)_2P(O)CH(NHBoc)CO_2Me$, DBU, THF, 0 °C → rt, 18 h, 91%; (c) H_2, [(*S*,*S*)-Et-DuPHOS-(COD)-Rh^I]OTf, DCM, 40 bar, 6 h, 95%; (d) (i) TBAF, THF, 0 °C, 15 min; (ii) LiOH, THF/H_2O, rt, 3 h, 89% (two steps); (e) $(MeO)_2P(O)CH(NHCbz)CO_2Me$, DBU, THF, 0 °C → rt, 18 h, 87%; (f) (i) H_2, Pd/C, MeOH, 1 bar, 2 h; (ii) Ac_2O, NEt_3, DCM, rt, 18 h, 76% (two steps); (g) (i) TBAF, THF, 0 °C, 15 min; (ii) LiOH, THF/H_2O, rt, 3 h; (iii) acylase I, H_2O (pH 7−8), 3 h, 40 °C, 46% (**21**, three steps); (iv) $SOCl_2$, MeOH, rt, 18h, 41% (**22**, four steps).

TABLE 2. Asymmetric Hydrogenation of Dehydroamino Acid 13

Z:*E* ratio of **13**	solvent	pressure (bar)	time (h)	conversion (%)	yield[a] (%)
93:7	MeOH	1	24	0	
93:7	MeOH	50	24	0	
93:7	benzene	1	24	<10	b
93:7	THF	1	24	93	b
93:7	DCM	1	24	93	91
99:1	DCM	1	24	99	b
93:7	DCM	40	4	100	95

[a] Yields refer to isolated pure products. [b] Yield not determined.

The ^1H NMR analysis of several *N*-Boc-protected compounds, e.g., **14** and **15**, showed two groups of proton signals which can be referred to the existence of two rotamers as we have already reported more than three decades ago.[19] As usual, for *N*-acetyl-protected or unprotected compounds the existence of rotamers has not been observed.

Nevertheless, the high costs for the catalyst limit this procedure, especially if both enantiomers, the L and the D forms, are needed. Therefore, we used a second approach offering a concurrent synthesis of both enantiomers. Here we condensed the aldehyde **12** in a way analogous to that described above with Cbz-α-phosphonoglycine trimethyl ester to give the (*Z*)-dehydroamino acid **18**[13] (*Z*:*E* > 95:5)[14] in 87% yield. Again, triethylamine had to be added to the eluent for column chromatography to avoid decomposition. This time, the hydrogenation was carried out using palladium on charcoal as the catalyst, leading to a simultaneous hydrogenation of the double bond and cleavage of the Cbz protection group. The reaction was monitored by TLC and mass spectroscopy and quenched after complete conversion to the saturated free amine (4 h). Prolonged reaction times (18 h) led to partial hydrogenation of the naphthalene residue. The resulting racemic mixture was directly acetylated by treatment with acetic acid anhydride in the presence of triethylamine to yield **19** in 76% yield over two steps. Applying the fully protected compound **19** to the enzymatic resolution led to an unseparable product mixture due to a partial loss of the TBS group and partial cleavage of the methyl ester. Thus, both protecting groups were removed prior to the resolution, improving the solubility in aqueous conditions. To avoid additional separation steps, a one-pot procedure was developed: the TBS ether and the methyl ester were subsequently cleaved, and the racemic mixture was resolved using acylase I to give the L isomer **20** as a free amine, while the D isomer **21** remained in the *N*-acetylated form, which was easily separated by extraction in high purity (93% by HPLC analysis).[10] As the isolation of the free L-amino acid **20** by crystallization failed, it was converted to the corresponding methyl ester **22** and also isolated by extraction (90% purity by HPLC analysis). Further purification by column chromatography gave the pure enantiomer **22**[10] and **21** (96% ee)[18] in high yields (41% over four steps and 46% over three steps, respectively).

Conclusion

The sequences described above provide high-yielding stereoselective access to a variety of tyrosine analogues. We developed a convenient route for the synthesis of aromatic-ring-substituted tyrosine derivatives via a Suzuki cross coupling reaction, thereby introducing a variety of substituted and unsubstituted aromatic as well as heteroaromatic residues in high yield. Even heavily deactivated boronic acids could be coupled in moderate yields. To provide a structural alternative, methods for the asymmetric synthesis of the ring-condensed tyrosine analogue 4-hydroxynaphthylalanine are described. For the preparation, two alternative methologies were explored to offer the most economical access if only one or both enantiomers are desired. In the latter case, the unselective hydrogenation of

(18) The enantiomeric purity of **21** was determined by chiral HPLC analyses after conversion to the corresponding methyl ester.

(19) Kessler, H.; Molter, M. *Angew. Chem., Int Ed. Engl.* **1973**, *12*, 1011−1012.

the corresponding dehydroamino acid and enzymatic separation of the racemic mixture is the most cost efficient access, as acylase I is cheap and both enantiomers are obtained simultaneously. In contrast, if only one single enantiomer is required, the racemic synthesis is associated with 50% loss of substance due to the undesired second enantiomer. The asymmetric hydrogenation of the dehydroamino acid provides a high-yielding access to a single enantiomer. Although the catalyst is quite expensive, its great efficiency and the high yields make this procedure the most economic when only one enatiomer is desired.

Experimental Section

(*S*)-*N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*O*-benzyl-*m*-iodotyrosine Benzyl Ester (6). To a solution of **5** (2.74 g, 6.73 mmol, 1.0 equiv) in acetone (20 mL) were added K_2CO_3 (2.90 g, 21.0 mmol, 3.0 equiv) and benzyl bromide (1.38 mL, 14.4 mmol, 2.2 equiv), and the mixture was heated under reflux for 5 h. After the solvent was evaporated, the residue was taken up in $CHCl_3$ (240 mL), washed with saturated aqueous $NaHCO_3$ (3 × 80 mL), dried over Na_2SO_4, and evaporated. Flash chromatography on silica gel (EtOAc/hexane, 1:4) yielded **6** (3.30 g, 83%) as a colorless solid: R_f = 0.20 (EtOAc/hexane, 1:4); $[\alpha]^{23}_D$ +2.4 (*c* 6.1, $CHCl_3$); mp 68−70 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.55 (d, *J* = 1.1 Hz, 1H), 7.51 (m, 2H), 7.36 (m, 8H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 5.10 (s, 2H), 5.02 (d, *J* = 7.6 Hz, 1H), 4.57 (m, 1H), 3.08−2.88 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.4, 156.3, 154.9, 140.2, 136.5, 135.1, 130.5, 130.2, 128.6, 128.52, 128.49, 128.47, 127.9, 126.9, 112.5, 86.8, 80.0, 70.9, 67.2, 54.5, 36.9, 28.3; HRMS (EI) *m*/*z* calcd for $C_{28}H_{30}INO_5$ 587.11687, found 587.11707.

(*S*)-*N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*O*-benzyl-*m*-phenyltyrosine Benzyl Ester (7a). To a solution of **6** (3.30 g, 5.62 mmol, 1.0 equiv) in degassed DME/H_2O (6:1, 40 mL) were added the appropriate phenylboronic acid (1.03 g, 8.43 mmol, 1.5 equiv) and Na_2CO_3 (1.20 g, 11.2 mmol, 2.0 equiv). After five vacuum/argon cycles $Pd(OAc)_2$ (63 mg, 281 μmol, 5 mol %) and P(*o*-tolyl)$_3$ (171 mg, 562 μmol, 10 mol %) were added, and the mixture was heated to 80 °C until complete conversion (3−8 h). After the reaction mixture was cooled to room temperature, it was passed through a short column with a bottom layer of silica gel (40−63 μm) and a top layer of $NaHCO_3$ using EtOAc as the eluent. The solvent was removed under reduce pressure and the crude product purified by flash chromatography (EtOAc/hexane, 1:4) to achieve **7a** (2.75 g, 91%) as a pale yellow solid: R_f = 0.25 (EtOAc/hexane, 1:4); $[\alpha]^{23}_D$ +2.6 (*c* 0.6, $CHCl_3$); mp 111−113 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.5 Hz, 2H), 7.40 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.38−7.26 (m, 11H), 7.09 (s, 1H), 6.94 (d, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 5.15 (d, *J* = 12.3, 1H), 5.10 (d, *J* = 12.3, 1H), 5.06−5.00 (m, 3H), 4.67−4.61 (m, 1H), 3.13−3.02 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.7, 155.1, 154.6, 138.1, 137.1, 135.0, 132.0, 131.2, 130.3, 129.5, 129.2, 128.5, 128.43, 128.40, 128.37, 127.8, 127.5, 126.9, 126.7, 113.4, 80.0, 70.4, 67.1, 54.5, 37.3, 28.2; HRMS (EI) *m*/*z* calcd for $C_{34}H_{35}NO_5$ 537.25153, found 537.25207.

(*S*)-*N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*O*-benzyl-*m*-phenyltyrosine (8a). A solution of lithium hydroxide (1.8 mg, 74 μmol, 1.0 equiv) in H_2O (0.11 mL) was added to a solution of **7a** (40 mg, 74 μmol, 1.0 equiv) in 2 mL of THF at 0 °C. After the resulting solution was stirred for 18 h, a 10% aqueous solution of citric acid (50 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue purified by flash chromatography on silica gel (EtOAc/hexane, 1:1; 1% AcOH), yielding **8a** (28.6 mg, 86%) as a colorless solid: R_f = 0.30 (EtOAc/hexane, 1:1; 1% AcOH); $[\alpha]^{23}_D$ +11.3 (*c* 1.7, MeOH); mp 108−110 °C; ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.53 (d, *J* = 7.0 Hz, 2H), 7.35 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.31−7.22 (m, 6H), 7.22−7.10 (m, 2H), 7.02 (d, *J* = 8.3 Hz, 1H), 5.02 (s, 2H), 4.36 (dd, *J* = 8.2, 5.1 Hz, 1H), 3.15 (dd, *J* = 13.9, 4.8 Hz, 1H), 2.91 (dd, *J* = 13.8, 8.7 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (90 MHz, MeOH-d_4) δ 175.4, 157.7, 155.9, 140.0, 138.8, 132.9, 132.5, 131.3, 130.7, 130.4, 129.3, 128.8, 128.6, 128.2, 127.8, 114.8, 80.5, 71.7, 56.3, 37.9, 28.7; HRMS (EI) *m*/*z* calcd for $C_{27}H_{29}NO_5$ 447.20456, found 447.20400.

(*S*)-*N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*m*-phenyltyrosine (9a). Palladium on charcoal (5% Pd/C, 0.23 g, 10 mol % Pd) was added to a degassed solution of **7a** (0.60 g, 1.11 mmol) in *N*,*N*-dimethylacetamide/MeOH (1:1, 30 mL). Hydrogenation was carried out at 1 bar of hydrogen pressure for 6 h. The catalyst was removed by filtration, the solvent removed under reduced pressure, and the residue purified by flash chromatography on silica gel (EtOAc/hexane, 1:2; 1% AcOH), yielding **9a** (373 mg, 95%) as a colorless solid: R_f = 0.26 (EtOAc/hexane, 1:1; 1% AcOH); $[\alpha]^{23}_D$ +17.9 (*c* 10.5, MeOH); mp 80−82 °C; ^{1}H NMR (360 MHz, acetone-d_6) δ 7.61 (dd, *J* = 8.1, 1.0 Hz, 2H), 7.39 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.29 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.22 (d, *J* = 1.6 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 4.43 (m, 1H), 3.17 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.99 (dd, *J* = 13.8, 8.4 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (90 MHz, acetone-d_6) δ 174.5, 157.1, 154.7, 140.7, 133.5, 131.1, 130.5, 129.9, 129.8, 129.7, 128.4, 117.8, 80.2, 56.6, 38.3, 21.4; HRMS (EI) *m*/*z* calcd for $C_{20}H_{23}NO_5$ 357,15762, found 357.15622.

(*Z*)-Methyl 2-(*tert*-Butyloxycarbonyl)amino-3-(1-(*tert*-butyldimethylsilyloxy)naphthalen-4 -yl)acrylate (13). To a solution of $(MeO)_2P(O)CH(NHBoc)CO_2Me$[15] (1.47 g, 4.95 mmol, 1.5 equiv) in dry CH_2Cl_2 (3 mL) was added DBU (583 μL, 3.9 mmol, 1.3 equiv), and the mixture was stirred for 10 min at 0 °C. A solution of **12** (945 mg, 3.30 mmol, 1.0 equiv) in dry CH_2Cl_2 (3 mL) was added slowly via syringe, and the reaction mixture was warmed to room temperature over 18 h. After the solvent was removed under reduced pressure, the residue was dissolved in EtOAc (50 mL), quickly washed with saturated aqueous NH_4Cl (2 × 20 mL) and brine (20 mL), and dried over Na_2SO_4. The solvent was evaporated and the crude product purified by flash chromatography on silica gel (EtOAc/hexane, 1:4; 1% NEt_3), yielding **13** (*Z*:*E* > 90:10, 1.37 g, 91%) as a pale yellow solid. Pure *Z* isomer was separated under the same conditions as the pale yellow solid (75% yield): R_f = 0.43 (EtOAc/hexane, 1:2); mp 116−120 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.95 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.69 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.56−7.46 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.08 (s, 1H), 3.90 (s, 3H), 1.31 (s, 9H), 1.10 (s, 9H), 0.31 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 152.7, 132.9, 127.8, 127.1, 126.9, 126.1, 125.8, 125.3, 124.0, 123.7, 123.1, 112.0, 80.7, 52.4, 27.9, 25.8, 18.4, −4.2; HRMS (EI) *m*/*z* calcd for $C_{25}H_{35}NO_5Si$ 457.22845, found 457.22828.

(*S*)-*N*$^{\alpha}$-*tert*-Butyloxycarbonyl-1-(4-*tert*-butyldimethylsilyloxy)-naphthylalanine Methyl Ester (14). [(*S*,*S*)-Et-DuPHOS-(COD)-Rh^I]OTf (0.38 mg, 0.52 μmol) was added to a solution of **13** (120 mg, 262 μmol, 1.0 equiv) in degassed DCM (3 mL). Hydrogenation was carried out at 40 bar of hydrogen pressure for 4 h. The catalyst was removed by flash chromatography on silica gel (EtOAc/hexane, 1:10), yielding **14** (114 mg, 95%) as a colorless oil: two rotamers (ca. 4:1 ratio); R_f = 0.31 (EtOAc/hexane, 1:4); $[\alpha]^{23}_D$ +20.5 (*c* 3.7, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.54 (ddd, *J* = 7.0, 6.8, 1.3 Hz, 1H), 7.48 (ddd, *J* = 7.3, 7.0, 0.8 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 5.06 (d, *J* = 7.3 Hz, 1H (80%)), 4.86 (s, 1H (20%)), 4.68 (d, *J* = 6.9 Hz, 1H (80%)), 4.57 (s, 1H (20%)), 3.66 (s, 3H (20%)), 3.61 (s, 3H (80%)), 3.50 (dd, *J* = 14.0, 6.3 Hz, 1H), 3.39 (dd, *J* = 13.7, 6.6 Hz, 1H), 3.15 (s, 1H), 1.41 (s, 9H (80%)), 1.17 (s, 9H (20%)), 1.10 (s, 9H), 0.29 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.7, 154.9, 151.2, 133.4, 128.2, 127.3, 126.4, 124.9, 124.8, 123.4, 123.2, 111.8, 79.7, 54.4, 52.0, 35.3, 28.2, 25.8, 18.4, −4.2; HRMS (EI) *m*/*z* calcd for $C_{25}H_{37}NO_5Si$ 459.24411, found 459.24438.

(*S*)-*N*$^{\alpha}$-*tert*-Butyloxycarbonyl-1-(4-hydroxy)naphthylalanine (15). To a solution of **14** (50.0 mg, 109 μmol, 1.0 equiv) in dry THF at 0 °C was added tetrabutylammonium fluoride (36.1 mg, 114 μmol, 1.05 equiv). After the resulting solution was stirred for 15 min, a solution of lithium hydroxide (5.04 mg, 120 μmol, 1.1 equiv) in water (182 μL) was added, and the mixture was stirred for an additional 3 h at room temperature. The solution was acidified by addition of a 10% aqueous solution of citric acid (20 mL) and extracted with EtOAc (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by flash chromatography on silica gel (MeOH/$CHCl_3$, 1:9; 1% AcOH), yielding **15** (32 mg, 89%) as a colorless solid: two rotamers (ca. 2.5:1 ratio); R_f = 0.18 (MeOH/$CHCl_3$, 1:9; 1% AcOH); $[\alpha]^{23}_D$ −25.9 (*c* 1.6, MeOH); mp 88−92 °C; ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.24 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 7.5, 7.5 Hz, 1H), 7.42 (dd, J = 7.4, 7.4 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 6.73 (d, J = 7.7 Hz, 1H), 4.44 (dd, J = 8.8, 5.1 Hz, 1H), 3.68 (dd, J = 12.2, 2.9 Hz, 1H (30%)), 3.59 (dd, J = 14.3, 4.9 Hz, 1H (70%)), 3.17 (dd, J = 14.2, 9.1 Hz, 1H (70%)), 2.99 (dd, J = 12.0, 12.0 Hz, 1H (30%)), 1.34 (s, 9H (70%)), 0.98 (s, 9H (30%)); ^{13}C NMR (125 MHz, MeOH-d_4) δ 175.9, 157.8, 154.0, 134.4, 129.4, 129.0, 127.4, 126.9, 125.26, 125.20, 124.4, 124.23, 124.19, 124.0, 108.3, 80.5, 56.8, 56.1, 37.4, 35.8, 28.7, 28.1; HRMS (EI) *m*/*z* calcd for $C_{18}H_{21}NO_5$ 331.14197, found 331.14097.

(*Z*)-Methyl 2-(Benzyloxycarbonyl)amino-3-(1-(*tert*-butyldimethylsilyloxy)naphthalen-4-yl)acrylate (18). To a solution of $(MeO)_2P(O)CH(NHCbz)CO_2Me$[15] (1.10 g, 3.33 mmol, 1.5 equiv) in dry CH_2Cl_2 (3 mL) was added DBU (432 μL, 2.89 mmol, 1.3 equiv), and the mixture was stirred for 10 min at 0 °C. A solution of **12** (635 mg, 2.22 mmol, 1.0 equiv) in dry CH_2Cl_2 (3 mL) was added slowly via syringe, and the reaction mixture was warmed to room temperature over 18 h. After the solvent was removed under reduced pressure, the residue was dissolved in EtOAc (50 mL), quickly washed with saturated aqueous NH_4Cl (2 × 20 mL) and brine (20 mL), and dried over Na_2SO_4. The solvent was evaporated and the crude product purified by flash chromatography on silica gel (EtOAc/hexane, 1:4; 1% NEt_3), yielding **16** (948 mg, 87%) as a pale yellow oil: R_f = 0.33 (EtOAc/hexane, 1:2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.28−8.20 (m, 1H), 7.95−7.88 (m, 1H), 7.81 (s, 1H), 7.56−7.47 (m, 3H), 7.34−7.27 (m, 3H), 7.27−7.20 (m, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.25 (s, 1H), 5.06 (s, 2H), 3.86 (s, 3H), 1.11 (s, 9H), 0.32 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.6, 153.9, 153.0, 135.85, 133.0, 128.4, 128.1, 128.1, 128.1, 127.9, 127.3, 127.0, 125.5, 125.4, 123.9, 123.2, 123.2, 111.9, 67.3, 52.6, 25.8, 18.4, −4.2; HRMS (EI) *m*/*z* calcd for $C_{28}H_{33}NO_5Si$ 491.21280, found 491.21264.

(*R*/*S*)-*N*$^{\alpha}$-Acetyl-1-(4-*tert*-butyldimethylsilyloxy)naphthylalanine Methyl Ester (19). To a solution of **18** (0.28 g, 0.57 mmol, 1 equiv) in degassed MeOH (30 mL) was added palladium on charcoal (5% Pd/C, 0.12 g, 10 mol % Pd). Hydrogenation was carried out at 1 bar of hydrogen pressure for 2 h. After the catalyst was removed by filtration, the solvent was removed under reduced pressure and the residue dissolved in dry DCM (10 mL). Ac_2O (60 μL, 0.68 mmol, 1.2 equiv) and NEt_3 (0.12 mL, 0.85 mmol, 1.5 equiv) were added, and the mixture was stirred for an additional 18 h. The solvent was removed under reduced pressure and the residue taken up with EtOAc (50 mL), subsequently washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (50 mL), and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by flash chromatography on silica gel (EtOAc/hexane, 1:1; 1% NEt_3), yielding **18** (194 mg, 76%) as a colorless solid: R_f = 0.16 (EtOAc/hexane, 1:1; 1% NEt_3); mp 50−55 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.24 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.57−7.43 (m, 2H), 7.08 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 5.99 (d, J = 7.7 Hz, 1H), 4.97 (m, 1H), 3.61 (s, 3H), 3.45 (dd, J = 13.9, 6.8 Hz, 1H), 3.45 (dd, J = 14.4, 6.1 Hz, 1H), 1.93 (s, 3H), 1.09 (s, 9H), 0.28 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.4, 169.6, 151.2, 133.4, 128.1, 127.2, 126.4, 124.9, 124.7, 123.4, 123.2, 111.8, 53.2, 52.1, 34.6, 25.8, 23.0, 18.4, −4.2; HRMS (EI) *m*/*z* calcd for $C_{20}H_{23}NO_5$ 357.15762, found 357.15622.

(*R*)-*N*$^{\alpha}$-Acetyl-1-(4-hydroxy)naphthylalanine (21) and (*S*)-1-(4-Hydroxy)naphthylalanine Methyl Ester (22). To a solution of **19** (100 mg, 249 μmol, 1.0 equiv) in dry THF (7 mL) at 0 °C was added tetrabutylammonium fluoride (82.5 mg, 261 μmol, 1.05 equiv). After the resulting solution was stirred for 15 min, a solution of lithium hydroxide (41.8 mg, 996 μmol, 4 equiv) in water (1.5 mL) was added, and stirring was continued for an additional 2 h at room temperature until complete conversion (TLC control). Thereafter, the solvent was removed under reduced pressure and the residue dissolved in water (10 mL) and adjusted to pH 7−8 by addition of 1 N HCl. Acylase I (50 mg) was added, and the mixture was stirred at 37 °C until no further conversion was observed (2−3 h, HPLC monitoring). Additional acylase I (50 mg) was added and stirring continued for 1 h. The mixture was diluted with water (20 mL), acidified to pH 1 by addition of 1 N HCl, and extracted with EtOAc (5 × 20 mL).

The organic phase was dried over Na_2SO_4, the solvent removed under reduced pressure, and the residue further purified by a short column of silica (MeOH/$CHCl_3$, 1:3; 1% AcOH) to give **21** (31 mg, 46%) as a colorless solid.

The aqueous phase was concentrated under reduced pressure and dried. The residue was suspended in dry MeOH (30 mL), and $SOCl_2$ (1 mL) was added dropwise at 0 °C. After being stirred for 24 h at room temperature, the mixture was concentrated under reduced pressure, diluted with 1 N NaOH (30 mL), and extracted with EtOAc (5 × 20 mL). The organic phase was dried over Na_2SO_4, the solvent removed under reduced pressure, and the residue further purified by a short column of silica (MeOH/$CHCl_3$, 1:9; 1% NEt_3) to obtain a pale yellow oil which was dissolved in Et_2O and a minimum volume of dioxane. Addition of a 1 M solution of HCl in ether (2 mL) gave **22** as a colorless solid which was filtered off and dried in vacuo.

Data for 21: R_f = 0.31 (MeOH/$CHCl_3$, 1:1; 0.1% TFA); $[\alpha]^{23}_D$ −1.7 (*c* 0.5, MeOH); mp 130−134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 7.6, 7.6 Hz, 1H), 7.42 (dd, J = 7.5, 7.5 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 6.73 (d, J = 7.7 Hz, 1H), 4.74 (dd, J = 8.9, 5.2 Hz, 1H), 3.63 (dd, J = 14.3, 5.1 Hz, 1H), 3.21 (dd, J = 14.3, 9.0 Hz, 1H), 1.85 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 173.1, 154.0, 134.4, 128.8, 127.3, 126.8, 125.2, 125.1, 124.3, 124.0, 108.2, 55.0, 35.5, 22.3; HRMS (EI) *m*/*z* calcd for $C_{15}H_{15}NO_4$ 273.10010, found 273.10083.

Data for 22: R_f = 0.50 (MeOH/$CHCl_3$, 1:9; 1% NEt_3); $[\alpha]^{23}_D$ +5.2 (*c* 0.6, MeOH); mp(**22**·HCl) > 240 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.30 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.59 (dd, J = 7.5, 7.5 Hz, 1H), 7.48 (dd, J = 7.4, 7.4 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 4.31 (dd, J = 7.4, 7.4 Hz, 1H), 3.80−3.63 (m, 4H), 3.41 (dd, J = 14.5, 8.5 Hz, 1H); ^{13}C NMR (226 MHz, $CDCl_3$) δ 175.8, 154.4, 134.3, 129.2, 127.5, 125.5, 124.2, 108.3, 56.1, 52.6, 38.3; HRMS (EI) *m*/*z* calcd for $C_{14}H_{15}NO_3$ 245.10519, found 245.10519.

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Supporting Information Available: Synthesis and compound characterization of **5**, **8b**, **9b**, and **12**, general procedure for the synthesis of 3-aryl-substituted tyrosine analogues **7b**−**j** by Suzuki cross coupling, compound characterization of **7b**−**j**, general procedure for the synthesis of dipeptides **10a**−**d**, **16**, and **17**, ^{1}H and ^{13}C NMR spectra of all synthesized compounds, NOESY spectra of **13** and **18**, and HPLC analyses of **10a**−**d**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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