Enantioselective Synthesis of Non-Natural Aromatic α-Amino Acids

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Abstract: We present two complementary methods for the stereoselective synthesis of non-natural α-amino acids with aromatic or heteroaromatic side chains. One approach is based on the chemical transformation of methionine, whereas the other applies the stereoselective Myers alkylation of glycine. The resulting product types differ in the linker length between glycine and the aromatic substituent. Since methionine and pseudoephedrine are available in both absolute configurations, *R*- or *S*-configured enantiopure amino acids with either C_2 or C_3 linkers can be obtained on gram scales. In each case the key step of the synthesis is hydroboration of the unsaturated building blocks **9** and **17**, followed by palladium-catalyzed Suzuki cross-coupling with aryl halides. Attention must in certain cases be paid to the stereochemical integrity when basic Suzuki conditions are applied. Our initial difficulties are reported as well as the final "racemization-proof" procedures. The protecting groups chosen for the α-amino acids should be compatible with solid-phase peptide synthesis. This was confirmed by the successful synthesis of a series of tripeptides.

Keywords: amino acids · chiral auxiliaries · chiral pool · peptides · Suzuki reaction

Introduction

Over the last few years, combinatorial libraries of synthetic peptides have seen numerous applications in protein biochemistry.[1] More recently, synthetic libraries have also allowed promising peptide ligands for DNA and RNA to be identified.[2] Apart from charge effects and hydrogen bonds, molecular recognition of nucleic acids is often dominated by stacking interactions.[3] Being interested in RNA ligands and artificial nucleases,[4] we felt that, of the different classes of amino acids, those carrying positive charge or aromatic rings are the preferable building blocks. To enhance chemical diversity, it would be desirable not to restrict library design to Arg, Lys, His, Phe, Tyr, and Trp alone, but also to include non-natural aromatic or heteroaromatic amino acids.

Several methods for the synthesis of non-natural α-amino acids exist.[5] Often the complete side chain is attached to a prochiral precursor molecule in a stereoselective reaction. This approach, while successful in many cases, creates the need to determine the enantiomeric purity of each newly synthesized batch of amino acids scrupulously and, if necessary, to purify to high levels of *ee*. We preferred a different strategy, of transforming an easily accessible, enantiopure, common intermediate into a variety of final products by "racemization-proof" reactions. Derivatives of vinyl- or allylglycine should fulfil the criteria for such central intermediates, since various aryl residues could be introduced by a Suzuki cross-coupling reaction.[6–8] Allylglycine is readily available through Myers alkylation of glycine with pseudoephedrine as auxiliary.[9] The conversion of serine into derivatives of vinylglycine has also been reported.[10] For the extension of the side chain, however, the corresponding amino aldehyde is required,[11] an intermediate known for its tendency to racemize. The alternative approach described here involves methionine as starting material. This is transformed into a vinylglycine derivative ready for use in Suzuki coupling.

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Results and Discussion

Synthesis by transformation of methionine: Initially we tried to keep the oxidation level of the carboxy group unchanged. Thus, (*S*)-L-methionine (**1**) was converted into the carboxybenzoxy(Cbz)-protected methyl ester and oxidized to form sulfoxide **2** (Scheme 1). A thermal *syn* elimination then led to the vinylglycine derivative **3**.[12] This step turned out to be troublesome, temperatures around 160 °C being insufficient for complete conversion. Higher temperatures, on the other hand, produced large amounts of the achiral products **4a** and **4b**, making the purification of **3** laborious (HPLC). On larger scales, yields of **3** rarely exceeded 20 %. Performing the reaction under solvent-free conditions in a Kugelrohr[13] did not give reliable results in our hands. Even worse, the

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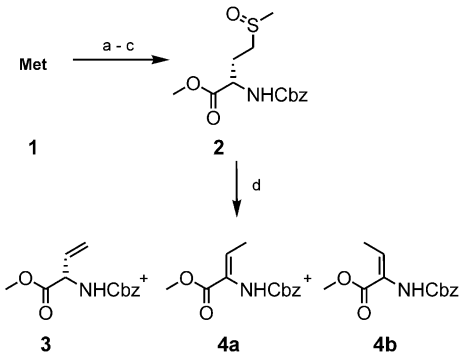


Scheme 1. a) MeOH, $SOCl_2$, 95%; b) Cbz-Cl, $KHCO_3$, 92%; c) $NaIO_4$, 84%; d) *o*-dichlorobenzene, 160°C, 20%.

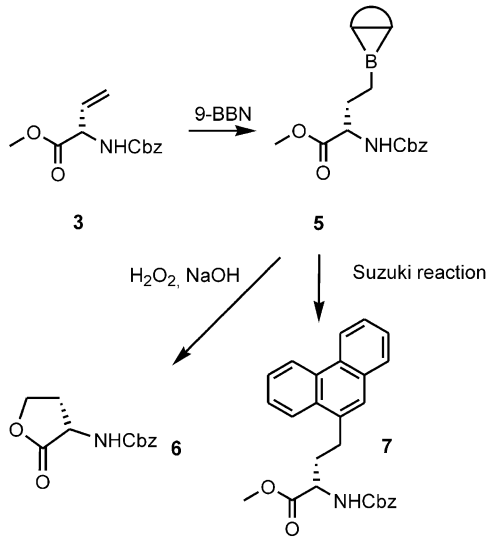
enantiomeric purity of the vinylglycine intermediate **3** dropped below 95% *ee* in the pyrolysis, incompatibly with our strategy described above. Nevertheless, cross-coupling studies were initiated with compound **3**.

Initial attempts to hydroborate **3** with 9-BBN and to cross-couple the intermediate alkyl borane under Suzuki conditions led to surprisingly low yields of compound **7** (Scheme 2; Table 1). Furthermore, the modest yield of lactone **6**, obtained by oxidation of the borane intermediate, indicated that the normal hydroboration conditions[6c] were not appropriate in this case. Attempts to improve the yield of **7** by promoting the 9-borabicyclo[3.3.1]nonane (9-BBN) addition with Wilkinson's catalyst failed.[14] The use of 1,4-dioxane as solvent and higher temperatures,[15] however, resulted in a smooth hydroboration. The cross-coupling was found to give satisfying yields (Table 1) in the presence of CsF[7] as base and $[Pd(PPh_3)_4]$ as catalyst. Further optimization of the cross-coupling conditions showed a correlation of yields with increasing strength of the base (Table 2). Unfortunately, when the *ee* of product **7** was determined, a correlation with partial racemization was also observed (Table 2), consistent with the ability of strong bases such as F^- to deprotonate the α-position of the amino acid esters.

Table 2. *ee*-Determination of compound **7**.[a]

Base [3 equiv]	Yield [%]	*ee* [%]
K_3PO_4	60	85
$CaCO_3$	6	n.d.
Cs_2CO_3	61	40
K_2CO_3	64	52
CsF	85	32

[a] Hydroboration with 1.1 equivalents of 9-BBN in 1,4-dioxane at 85°C; cross-coupling at 80°C overnight with $[Pd(PPh_3)_4]$ as catalyst.



Scheme 2. a) H_2O_2, THF; b) Suzuki reaction.

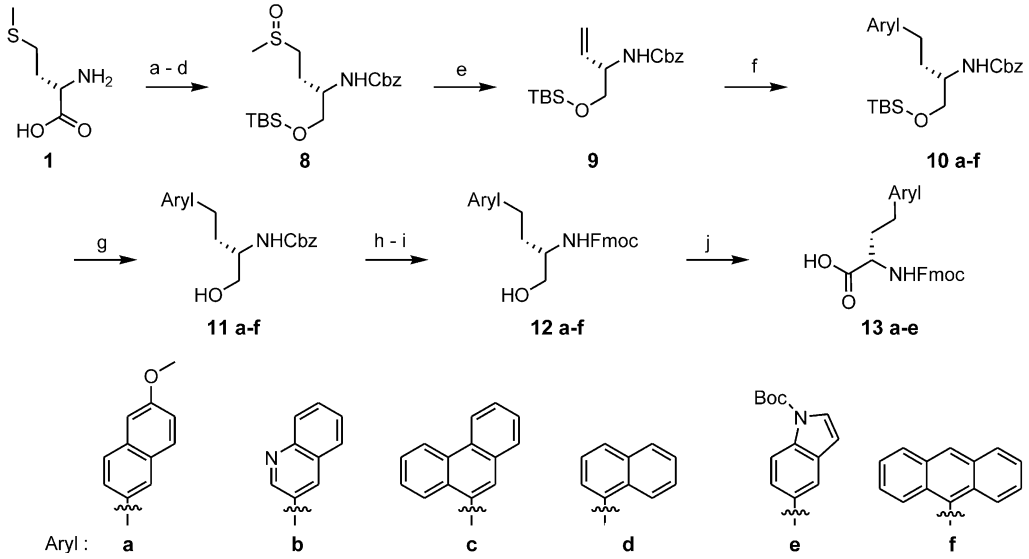
Table 1. Hydroboration of the protected vinylglycine **3**.

Solvent	9-BBN [equiv]	*T* [°C][a]	Catalyst 1 [3 mol%][b]	Catalyst 2 [3 mol%][c]	Base [3 equiv][d]	Yield [%][e]
THF	1	RT	–	[Pd(dppf)]	K_3PO_4	15
THF	2	66	–	[Pd(dppf)]	K_3PO_4	15
THF	2	RT	$[Rh(Ph_3P)_3Cl]$	[Pd(dppf)]	K_3PO_4	18
THF	2	66	$[Rh(Ph_3P)_3Cl]$	[Pd(dppf)]	K_3PO_4	18
THF	3	66	$[Rh(Ph_3P)_3Cl]$	[Pd(dppf)]	K_3PO_4	20
toluene	2	85	–	[Pd(dppf)]	K_3PO_4	30
dioxane	1.1	85	–	$[Pd(PPh_3)_4]$	K_3PO_4	60
dioxane	1.1	85	–	$[Pd(PPh_3)_4]$	CsF	85

[a] Temperature of the hydroboration step (overnight). [b] Hydroboration catalyst. [c] Cross-coupling catalyst. [d] Conditions of the cross-coupling step: THF 66°C, toluene or dioxane 80°C (each overnight). [e] Isolated yield of the Suzuki product.

At this stage we changed our tactics and converted methionine into the amino alcohol. Through these additional reduction and oxidation steps, all the previous problems could be circumvented while not complicating the syntheses significantly (Scheme 3).

After $LiAlH_4$ reduction of the carboxy group in boiling THF overnight[16] followed by Cbz- and *tert*-butyldimethylsilyl (TBS)-protection, periodate oxidation led to the sulfoxide **8**. Successive pyrolysis afforded the desired unsaturated derivative **9** as a stable compound in scales above 30 g. Compound **9**, unlike the carbonyl analogue **3**, has no tendency towards migration of the double bond, so the elimination temperature could be increased to 180°C, improving the yield of **9** to 88% (Scheme 3). Clean hydroboration of compound **9** was observed under the previously established conditions. Replacement of $[Pd(PPh_3)_4]$ by $[Pd(dppf)Cl_2]$ in the cross-coupling step then allowed all products **10a–f** to be obtained reproducibly and in high yields. While the desilylation with TBAF in THF was a straightforward reaction, removal of Cbz under normal hydrogenolysis conditions (Pd-C/H_2) was found to cause partial reduction of some aromatic side chains. To avoid this drawback we utilized a transfer hydrogenation procedure with 1,4-cyclohexadiene and $Pd(OH)_2$ in refluxing ethanol.[17] Fmoc protection and oxidation of the hydroxy group completed the syntheses of building blocks **13a–e**, ready for peptide coupling. For amino alcohol **12f**, substituted

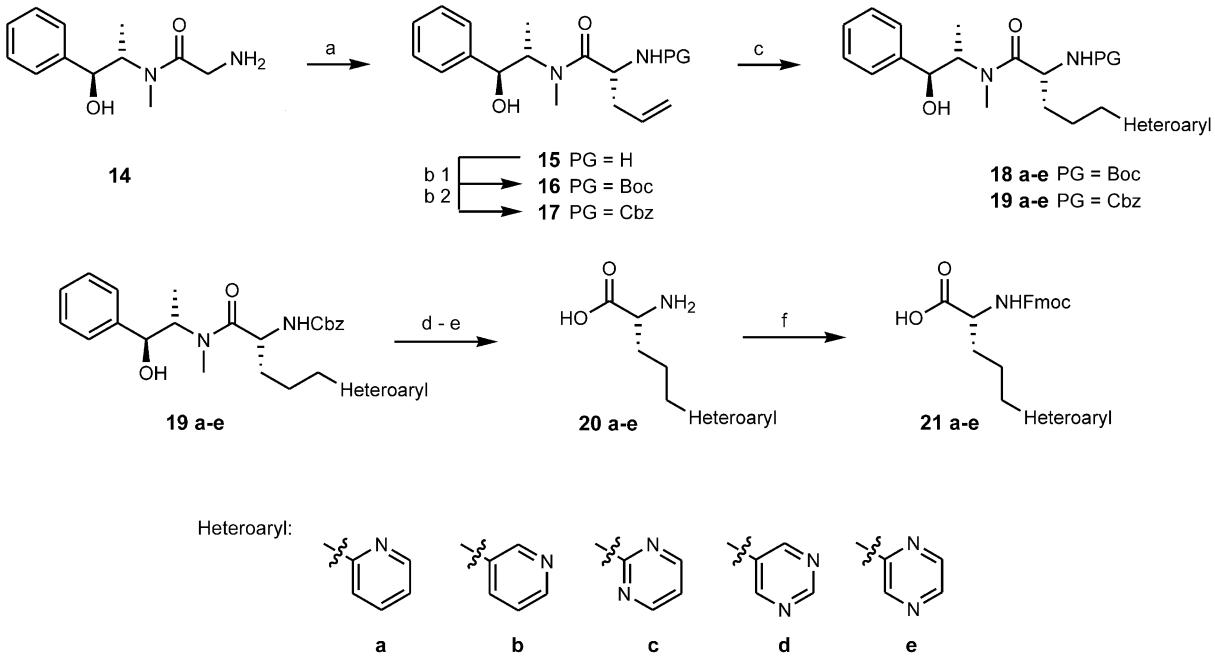


Scheme 3. a) $LiAlH_4$, THF, 76%; b) Cbz-Cl; c) TBS-Cl, imidazole; d) $NaIO_4$, 94% (over three steps); e) *o*-dichlorobenzene, 180°C, 88%; f) 1. 9-BBN, 2. Aryl-Br, CsF, $[Pd(dppf)Cl_2]$, 83–97%; g) TBAF, 68–84%; h) 1,4-cyclohexadiene, $Pd(OH)_2$; i) Fmoc-Suc, 57–84% (over two steps); j) PDC, DMF, 56–86%.

with anthracene, no sufficient oxidation to the carboxylic acid could be achieved. The starting material disappeared, but the oxidized product could not be isolated. Perhaps the poor solubility led to co-precipitation with the inorganic solid formed in the reaction.

The described approach was found to be universal for both configurations and we were able to synthesize the D derivative *ent*-**13d** by using (*R*)-D-methionine as starting material. The availability of the two enantiomers allowed the enantiomeric purity to be determined rigorously by HPLC on chiral columns. Enantiomers **13d** and *ent*-**13d** both exhibited >99% *ee*.

Synthesis by stereoselective alkylation of glycine: The chiral glycine amide **14** (Scheme 4), available from pseudoephedrine and glycine methyl ester, was introduced by Myers and applied for the synthesis of a broad scope of α-amino acids. In this procedure, a dianion of **14** is alkylated at carbon with high diastereoselectivity. We adopted the Myers protocol as a convenient route to the allyl glycine derivative



Scheme 4. a) LiCl, THF, LiHMDS, then allyl bromide, 68%; b1) Boc_2O, $NaHCO_3$, ultrasound, 85%; b2) Cbz-Cl, Et_3N, $CHCl_3$, 87%; c) 9-BBN (0.5 M THF) 2.4 equiv, 5 mol% catalyst, base, aryl halide, see Table 3; d) MeOH, Pd/C, H_2; e) H_2O, reflux, 50–60% over two steps; f) DCM, TMS-Cl, DIPEA, Fmoc-Cl, 70%.

Table 3. Suzuki coupling of the Boc- and Cbz-protected derivatives **16** and **17**.[a]

Ar-Halide	Product	Yield [%]
2-Br-pyridine	**18a/19a**	76[b]/90[c]
3-Br-pyridine	**18b/19b**	20[b]/38[c]
2-Br-pyrimidine	**18c/19c**	68[b]/88[c]
5-Br-pyrimidine	**18d/19d**	0[b]/27[c]
Cl-pyrazine	**18e/19e**	75[b]/86[c]

[a] All coupling reactions were carried out with 2.4 equivalents of 9-BBN (0.5 M in THF), $[Pd(PPh_3)_4]$ as catalyst and K_3PO_4 as base at room temperature for 16 h reaction time. [b] Boc-protected. [c] Cbz-protected.

15.[9,18] First cross-coupling experiments started from compound **16**. As described above, the unsaturated side chain was hydroborated with 9-BBN and coupled with aryl halides in a Suzuki reaction. Because of the presence of the hydroxyl group, hydroboration required at least 2 and worked best with 2.4 equivalents of 9-BBN. Three cross-coupling products (**18a**, **18c**, **18e**) could be obtained in good, and one in moderate, yield (**18b**) (Table 3). In all cases, however, the purification was found to be troublesome and required preparative HPLC. Compound **18d** remained inaccessible even after several attempts (Table 4).

Superior results were obtained with the Cbz-protected compound **17** (Scheme 4, Table 3). The Suzuki reaction was found to be highly efficient even with an aryl chloride, a species generally known for low coupling rates.[6a] We were able to synthesize pyrazine derivative **19e** (86% yield) and also the pyrimidine **19d**. Furthermore, the products could be isolated by simple column chromatography. Replacement of the catalyst $[Pd(PPh_3)_4]$ by $[Pd(dppf)Cl_2]$ did not raise the yields but again imposed the need to purify products by HPLC. After removal of Cbz, pseudoephedrine was cleaved off by boiling in neutral H_2O to avoid the risk of base-induced racemization and to isolate products not contaminated with salts. The chiral purity of the Fmoc-protected D-amino acid **21e** was determined by HPLC as 99% *ee*. Furthermore, when (*R*,*R*)-(−)-pseudoephedrine was used as auxiliary, the corresponding L derivative *ent*-**21e** could be obtained in high yield and with more than 99% *ee*.

Application in solid-phase peptide synthesis: To demonstrate the practical use of the Fmoc building blocks **13a–e** and **21a–e** for peptide synthesis, we assembled the tripeptides **22–32** by standard methods on solid support. In each compound, one of the synthetic amino acids is flanked by two D-arginines. Arginine was chosen because its deprotection is a rather critical step. Acid-induced removal of sulfonic acids such as Mtr or Pmc requires drastic conditions and forms electrophilic intermediates that might endanger aromatic rings. If the arginine-rich tripeptide could be prepared from a certain building block, we argued, its incorporation into other sequences would be less challenging. Scheme 5 summarizes the structures of tripeptides **22–32**. Two peptides, **31** and **32**, however, proved to be troublesome. After cleavage from the resin and deprotection under standard conditions (Table 5, entry 1), the mass spectra did not reveal the expected peaks, thus indicating the formation of undesirable adducts ($[M+138]^+$). To overcome this problem, various cleaving conditions for peptide **32** were tested (Table 5).

Table 5. Cleavage of tripeptide **32** under various conditions.

Entry	Cleaving conditions	Time	Result
1	TFA/$PhSCH_3$/PhOH/H_2O/EDT 82.5:5:5:5:2.5	5 h	$[M+138]^+$
2	TFA/TIS/H_2O 92.5:5:2.5	4.5 h	$[M]^+/[M+138]^+$ 1:1
3	TFA/TIS/H_2O 60:39:1	4.5 h	$[M]^+/[M+138]^+$ 1:1
4	TFA/$PhSCH_3$/PhOH/H_2O/EDT/TIS 81.5:5:5:5:2.5:1	4.5 h	$[M]^+/[M+138]^+$ 2:1
5	TFA/$PhSCH_3$/PhOH/H_2O/TIS 84:5:5:5:1	4.5 h	$[M]^+/[M+138]^+$ 1:2
6	TFA/TES/H_2O 92.5:5:2.5	4.5 h	$[M]^+/[M+138]^+$ 1:1
7	TMSBr/EDT/PhOH/H_2O 84:1:5:10	15 min	0
8[a]	CH_2Cl_2/TFA 70:30	30 min	$[M]^+/[M+61]^+$ 4:5

[a] The sample also contained protected tripeptide.

Established reagents such as trimethylsilyl bromide (TMSBr) or trifluoroacetic acid/triisopropylsilane (TFA/TIS) were not successful either. Standard conditions in the presence of TIS (Table 5, entry 4) gave best results and favored the desired tripeptide peak in a ratio of 2:1 relative to the $[M+138]^+$ product. The 5-indolyl and the 5-pyrimidinyl amino acids are thus not suitable as building blocks for combinatorial libraries.

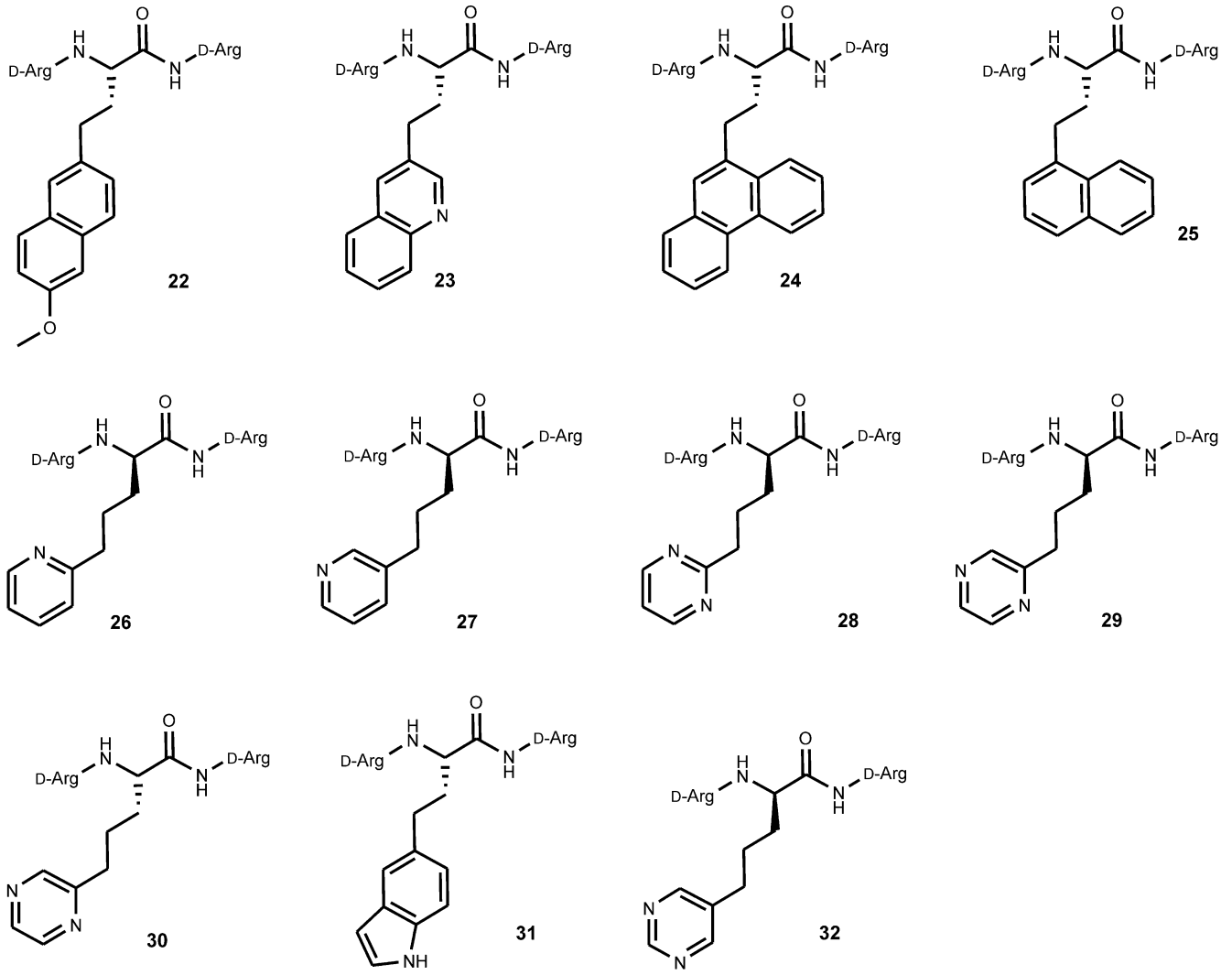
Conclusions

Here we report an efficient, easy to handle and cost-effective synthesis of non-natural aromatic amino acids, starting from vinylglycine or allylglycine as useful precursors for Suzuki couplings with aryl halides. Both configurations were accessible in 99% enantiomeric excesses after elimination of initial problems due to base-catalyzed racemization. The applicability of the new building blocks was tested in the solid-phase synthesis of tripeptides. Some aromatic systems formed

Table 4. Attempts to prepare the Boc-protected derivative **18d** (room temperature, 16 h, various catalysts and bases).

Ar halide	Catalyst	Base	Yield [%]
5-Br-Pyrimidine	$[Pd(PPh_3)_4]$, 5 mol%	NaOH (10%), 3 equiv	–
	$[Pd(PPh_3)_4]$, 5 mol%	Ag_2O, 2 equiv	–
	$Pd(OAc)_2$, 10 mol%	Na_2CO_3, 2 equiv	–
	Pd (polymer-bound)	K_3PO_4[b]	–
	$[Pd(PPh_3)_4]$, 5 mol%	CsF, 3 equiv	–
	$[Pd(dppf)Cl_2]$, 5 mol%	K_2CO_3, 3 equiv	–

[a] All coupling reactions were carried out with 2.4 equivalents of 9-BBN (0.5 M in THF). [b] 2-Propanol/H_2O 1:1.[21] [c] 9-BBN solid 1.5 equiv.



Scheme 5. Tripeptides prepared from the building blocks **13a–e**, **21a–e**, and *ent*-**21e** by standard Fmoc solid-phase synthesis (C terminus: carboxamide)[19]

by-products upon acid-induced deprotection. Isolation of pure peptides would require purification steps, and so the use of such building blocks in combinatorial libraries is not recommended. Most tripeptides, however, could easily be obtained, thus demonstrating the applicability of the new building blocks in peptide chemistry.

Experimental Section

General: Melting points: Kofler hot plate microscope, uncorrected. Optical rotations: Perkin–Elmer 241 polarimeter, temperature control by H_2O bath. ^1H NMR: Bruker Avance DPX 250 MHz, TMS as external standard; chemical shifts (δ) are given in ppm (* denotes rotamer peaks). Analytical thin layer chromatography: alumina plates precoated with silica gel 60 F254 (Merck); viewing with the aid of UV light or aqueous $KMnO_4$ solution. Flash chromatography: silica gel Merck-60 (0.040–0.063 mm). Filtration: Celite® 535 (Fluka). FT-IR: Perkin–Elmer 1600 Series. Elemental analysis: Heraeus CHN Rapid. Mass spectroscopy: low resolution: Fisons CG Platform II; high resolution: Applied Biosystems Mariner System 5033, spray voltage +700 V. All reagents were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium/benzophenone. All reactions involving LiHMDS, $LiAlH_4$ or 9-BBN were carried out in oven-dried glassware under inert argon atmosphere. DCM: dichloromethane. DIC: diisopropylcarbodiimide. DIPEA: *N*,*N*-diisopropylethylamine. EDT: ethanedithiol. HOBt: *N*-hydroxybenzotriazole. PDC: pyridinium dichromate.

Methioninol: $LiAlH_4$ (11.0 g, 290 mmol) was suspended in dry THF (400 mL), and L-methionine (20.0 g, 134 mmol) was then added in small portions. The gray suspension was heated at reflux overnight. To quench the reaction, H_2O (11 mL), NaOH (15%, 11 mL) and H_2O (33 mL) were added successively. The precipitate was filtered off and the solvent was removed in vacuo. The residual oil was further purified by distillation in the Kugelrohr (180 °C, 0.3 mbar) to give methioninol (13.75 g, 76%) as a colorless oil. R_f = 0.1 (MeOH/AcOEt 1:9) staining yellow with $KMnO_4$; $[\alpha]_D^{20}$ −16.1° (*c* = 1.2, MeOH), literature: −14° (c = 1, EtOH);[16b] ^1H NMR (250 MHz, $CDCl_3$): δ = 3.63 (dd, *J* = 10.7/3.9 Hz, 1H), 3.35 (dd, *J* = 10.7/0.7 Hz, 1H), 3.03–2.99 (m, 1H), 2.64–2.58 (m, 2H), 2.27 (br s, 3H), 2.14 (s, 3H), 1.78–1.72 (m, 1H), 1.64–1.58 (m, 1H) ppm; IR (KBr): $\tilde{\nu}$ = 3346, 2917, 2856, 2592, 1435, 1366, 1318, 1056, 958, 860, 755 cm^{-1}; elemental analysis calcd (%) for $C_5H_{13}NOS$ (135.23): C 44.41, H 9.69, N 10.36; found: C 44.22, H 9.69, N 10.15.

Benzyl [1-(*tert*-butyldimethylsilanyloxymethyl)-3-methanesulfinylpropyl]-carbamate (8): Methioninol (13.75 g, 92 mmol) was dissolved in AcOEt (300 mL). $KHCO_3$ (27.6 g, 276 mmol) in H_2O (300 mL) was added to the organic phase and the mixture was cooled to 0 °C. Small portions of Cbz-Cl (15.7 mL, 112 mmol) were added to the vigorously stirred mixture.

After 30 min the ice bath was removed, the mixture was stirred for a further 3 h at room temperature, and the basic aqueous phase was separated. The organic phase was then washed with HCl (1 N), H_2O and brine. After the mixture had been dried over $MgSO_4$ the solvent was evaporated in vacuo. The crude product was dissolved in DCM (400 mL) containing imidazole (7.61 g, 112 mmol). The solution was cooled to 0 °C and *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (16.85 g, 112 mmol) was added in small portions. After 30 min the ice bath was removed. The reaction mixture was stirred at room temperature overnight. The organic phase was extracted several times with H_2O. After evaporation of the organic solvent, the crude protected amino alcohol was dissolved in MeOH (300 mL). An aqueous solution (300 mL) of $NaIO_4$ (23.9 g, 112 mmol) was added dropwise to the MeOH solution over a period of 30 min. A thick, colorless precipitate was produced. After the mixture had been stirred for 2 h at room temperature all starting material was consumed. The solid was filtered off, and after evaporation of MeOH the aqueous solution was extracted three times with DCM. Finally the organic solvent was removed, and the remaining oil was purified by column chromatography (AcOEt) to give **8** (38.04 g, 94 % over three steps) as a colorless oil. R_f = 0.4 (AcOEt); $[\alpha]_D^{20}$ −21.6° (c = 0.9, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.27 (s, 5H), 7.12 (d, J = 7.9 Hz, 1H), 4.98 (s, 2H), 3.54–3.45 (m, 2H), 2.70–2.60 (m, 2H), 2.47 (s, 3H), 1.91–1.82 (m, 1H), 1.67–1.58 (m, 1H), 0.83 (s, 9H), 0.00 (s, 6H) ppm; IR (KBr): $\tilde{\nu}$ = 3252, 3067, 2954, 2856, 1714, 1561, 1472, 1250, 1122, 1022, 837, 699 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{33}NO_4SSi$ (399.62): C 57.11, H 8.32, N 3.51; found: C 56.95, H 8.35, N 3.65.

Benzyl [1-(*tert*-butyldimethylsilanyloxymethyl)allyl]carbamate (9): The sulfoxide **8** (45.18 g, 113 mmol) was dissolved in *o*-dichlorobenzene (300 mL). After addition of powdered $CaCO_3$ (28.6 g, 268 mmol) the stirred mixture was heated to reflux at 180 °C until total consumption of the starting material (4 h). The reaction mixture was cooled to room temperature and filtered over celite, and the solvent was removed by vacuum distillation (50 °C, 4 mbar). The yellow, viscous residue was purified by column chromatography (AcOEt/hex 1:10) to give **9** (33.54 g, 88 %) as a colorless oil. R_f = 0.5 (AcOEt/hex 1:10); $[\alpha]_D^{20}$ −31.7° (c = 3.2, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.32–7.24 (brs, 6H), 5.15 (d, J = 20.6 Hz, 1H), 5.07 (d, J = 12.5 Hz, 1H), 5.00 (s, 2H), 4.09–3.97 (m, 1H), 3.49 (d, J = 6.3 Hz, 2H), 0.82 (s, 9H), 0.00 (s, 6H) ppm; IR (KBr): $\tilde{\nu}$ = 3445, 3332, 2956, 2857, 1716, 1646, 1505, 1471, 1256, 1115, 992, 921, 836, 778, 696, 699 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{29}NO_3Si$ (335.51): C 64.44, H 8.71, N 4.17; found: C 64.18 H 8.78 N 4.38.

General procedure for the synthesis of Suzuki products 10a–f: **preparation of Suzuki product 10a**: Compound **9** (1.5 g, 4.5 mmol) was dissolved in dry 1,4-dioxane (15 mL). After addition of 9-BBN (0.6 g, 5.0 mmol), the stirred mixture was heated to 80 °C and kept at this temperature for about 20 min until TLC showed complete hydroboration. After the addition of CsF (2.04 g, 13.4 mmol), Pd[dppf]Cl$_2$ (110 mg, 0.13 mmol) and 2-bromo-6-methoxy-naphthalene (1.33 g, 5.6 mmol), the resulting heterogeneous mixture was stirred overnight at 80 °C. For the isolation of the coupling product the mixture was extracted with H_2O and AcOEt. The organic phase was then evaporated and the residue was adsorbed on SiO_2. The crude product was purified by chromatography (AcOEt/hex 1:10) to give **10a** (2.14 g, 97 %) as a colorless oil. R_f = 0.4 (AcOEt/hex 1:10); $[\alpha]_D^{20}$ −26.2° (c = 0.9, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.94–7.71 (m, 2H), 7.61 (s, 1H), 7.56–7.26 (m, 7H), 7.17–7.10 (m, 2H), 5.04 (s, 2H), 3.87 (s, 3H), 3.57–3.46 (m, 3H), 2.79–2.66 (m, 2H), 1.99–1.87 (m, 1H), 1.70–1.67 (m, 1H), 0.86 (s, 9H), 0.00 (s, 6H) ppm; IR (KBr): $\tilde{\nu}$ = 2954, 2857, 1728, 1714, 1607, 1505, 1470, 1470, 1392, 1229, 1118, 836, 777 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{39}NO_4Si$ (493.71): C 70.55, H 7.96, N 2.84; found: C 70.31, N 8.03, H 3.04.

Compound 10b: yield: 88 %; R_f = 0.2 (AcOEt/hex 1:3); $[\alpha]_D^{20}$ −28.8° (c = 1.1, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.92 (s, 1H), 8.08 (s, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.70 (t, J = 6.8/1.4 Hz, 1H), 7.54 (t, J = 7.9/7.0 Hz, 1H), 7.36 (brs, 5H), 7.22 (d, J = 8.6 Hz, 1H), 5.03 (s, 2H), 3.56–3.51 (m, 3H), 2.88–2.70 (m, 2H), 2.00–1.74 (m, 2H), 0.82 (s, 9H), 0.00 (s, 6H) ppm; IR (KBr): $\tilde{\nu}$ = 3326, 3034, 2953, 2857, 1716, 1540, 1497, 1463, 1388, 1330, 1251, 1116, 1058, 836, 778, 752, 697 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{36}N_2O_3Si$ (464.67): C 69.79, H 7.81, N 6.03; found: C 69.52, H 7.98, N 5.96.

Compound 10c: yield: 95 %; R_f = 0.5 (AcOEt/hex 1:10); $[\alpha]_D^{20}$ −16.0° (c = 1.1, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.86 (d, J = 7.8 Hz, 1H), 8.80 (d, J = 5.8 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H), 7.86 (d, J = 6.3 Hz, 1H), 7.72–7.61 (m, 5H), 7.41–7.30 (m, 6H), 5.09 (s, 2H), 3.64–3.51 (m, 3H), 2.36–2.31 (m, 1H), 2.05–2.00 (m, 1H), 1.78–1.73 (m, 2H), 0.83 (s, 9H), 0.00 (s, 6H) ppm; IR (KBr): $\tilde{\nu}$ = 3338, 3066, 3032, 2926, 2855, 2366, 1698, 1506, 1453, 1252, 1064, 838, 778, 778, 747, 726, 696 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{39}NO_3Si$ (513.74): C 74.81, H 7.65, N 2.73; found: C 74.68, H 7.92, N 2.78.

Compound 10d: yield: 95 %; R_f = 0.2 (AcOEt/hex 1:10); $[\alpha]_D^{20}$ −25.0° (c = 0.9, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.06 (d, J = 6.2 Hz, 1H), 7.94–7.90 (m, 1H), 7.76 (d, J = 7.9 Hz, 2H), 7.54–7.50 (m, 2H), 7.42–7.28 (m, 7H), 5.05 (s, 2H), 3.61–3.45 (m, 3H), 3.25–2.92 (m, 2H), 1.74–1.50 (m, 2H), 0.87 (s, 9H), 0.00 (s, 6H) ppm; IR (KBr): $\tilde{\nu}$ = 3341, 2954, 2857, 1715, 1635, 1607, 1506, 1464, 1390, 1262, 1230, 1120, 878, 778 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{37}NO_3Si$ (463.68): C 72.53, H 8.04, N 3.02; found: C 72.26, H 8.14, N 3.14.

Compound 10e: yield: 93 %; R_f = 0.1 (AcOEt/hex 1:10); $[\alpha]_D^{20}$ −23.4° (c = 0.9, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.91 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 3.7 Hz, 2H), 7.37–7.35 (brs, 5H), 7.12 (m, 2H), 6.61 (d, J = 3.6 Hz, 1H), 5.03 (s, 2H), 3.57–3.44 (m, 3H), 2.75–2.63 (m, 2H), 1.87–1.72 (m, 2H), 1.62 (s, 9H), 0.83 (s, 9H), 0.00 (s, 6H) ppm; IR (KBr): $\tilde{\nu}$ = 3358, 2956, 2856, 1706, 1506, 1470, 1348, 1250, 1160, 847, 766, 670 cm^{-1}; elemental analysis calcd (%) for $C_{31}H_{44}N_2O_5Si$ (552.78): C 67.36, H 8.02, N 5.07; found: C 67.33, H 8.27, N 4.96.

Compound 10f: yield: 83 %; R_f = 0.5 (AcOEt/hex 1:10); $[\alpha]_D^{20}$ +1.7° (c = 1.1, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.45 (s, 1H), 8.30 (d, J = 6.7 Hz, 2H), 8.06 (d, J = 4.4 Hz, 2H), 7.50–7.28 (m, 10H), 5.09 (s, 2H), 3.69–3.54 (m, 3H), 2.33–2.28 (m, 1H), 2.00–1.92 (m, 1H), 1.83–1.73 (m, 2H), 0.83 (s, 9H), 0.00 (s, 6H) ppm; IR (KBr): $\tilde{\nu}$ = 3315, 3059, 2952, 2855, 2366, 1693, 1542, 1470, 1290, 1249, 1122, 1060, 836, 776, 726 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{39}NO_3Si$ (513.74): C 74.81, H 7.65, N 2.73; found: C 74.56, H 7.74, N 2.71.

General procedure for the synthesis of the alcohols 11a–f: **preparation of alcohol 11a**: The protected amino alcohol **10a** (2.13 g, 4.3 mmol) was dissolved in TBAF in THF (1 M, 10 mL, 10 mmol) and the mixture was stirred for 4 h at room temperature. After addition of H_2O, the mixture was extracted with AcOEt. The crude product was isolated from the organic phase and purified by column chromatography (AcOEt/hex 1:1) to give **11a** (1.26 g, 77 %) as a colorless solid. R_f = 0.2 (AcOEt/hex 1:1); m.p. 101–103 °C; $[\alpha]_D^{20}$ −17.4° (c = 0.5, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.73 (d, J = 7.1 Hz, 2H), 7.59 (s, 1H), 7.39–7.27 (m, 7H), 7.12 (d, J = 6.4 Hz, 2H), 5.05 (s, 2H), 4.66 (t, J = 5.5 Hz, 1H), 3.87 (s, 3H), 3.50–3.25 (m, 3H), 2.84–2.60 (m, 2H), 1.93–1.89 (m, 1H), 1.71–1.66 (m, 1H) ppm; IR (KBr): $\tilde{\nu}$ = 3449, 3311, 3061, 2939, 2911, 2370, 1684, 1606, 1541, 1483, 1389, 1265, 1232, 1175, 852, 697 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{25}NO_4$ (379.45): C 72.80, H 6.64, N 3.69; found: C 72.88, H 6.68, N 3.71.

Compound 11b: yield: 84 %; R_f = 0.3 (AcOEt); m.p. 102–104 °C; $[\alpha]_D^{20}$ −20.3° (c = 0.6, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.81 (s, 1H), 8.13 (s, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 5.4/1.5 Hz, 1H), 7.61 (t, J = 6.9 Hz, 1H), 7.42–7.35 (brs, 5H), 7.20 (d, J = 8.3 Hz, 1H), 5.07 (s, 2H), 4.74 (t, J = 5.5 Hz, 1H), 3.54–3.32 (m, 3H), 2.90–2.78 (m, 2H), 2.03–1.73 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3322, 3206, 3035, 2953, 1959, 1680, 1528, 1467, 1331, 1308, 1253, 1073, 1051, 961, 880, 782, 732 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{22}N_2O_3$ (350.41): C 71.98, H 6.33, N 7.99; found: C 71.72, H 6.32, N 7.82.

Compound 11c: yield: 75 %; R_f = 0.6 (AcOEt/hex 1:1); m.p. 156 °C; $[\alpha]_D^{20}$ −6.7° (c = 0.7, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.89 (d, J = 7.1 Hz, 1H), 8.81 (d, J = 6.7 Hz, 1H), 8.18 (d, J = 6.9 Hz, 1H), 7.92–7.88 (m, 1H), 7.76–7.64 (m, 5H), 7.43–7.28 (m, 6H), 5.11 (s, 2H), 4.73 (t, J = 5.5 Hz, 1H), 3.66 (m, 1H), 3.52–3.38 (m, 2H), 3.22–3.06 (m, 2H), 2.06–1.86 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3328, 3063, 2851, 1685, 1534, 1451, 1258, 1069, 1025, 959, 869, 744, 722 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{25}NO_3$ (399.48): C 78.17, H 6.31, N 3.51; found: C 77.98, H 6.31, N 3.70.

Compound 11d: yield: 69 %; R_f = 0.4 (AcOEt/hex 1:1); m.p. 96–105 °C; $[\alpha]_D^{20}$ −6.2° (c = 0.9, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.11 (t, J = 5.1/4.0 Hz, 1H), 7.95 (m, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.55 (m, 2H), 7.48–7.33 (m, 7H), 7.27 (d, J = 8.5 Hz, 1H), 5.10 (s, 2H), 4.71 (t, J = 5.5 Hz, 1H), 3.61–3.49 (m, 1H), 3.47–3.39 (m, 2H), 3.20–3.00 (m,

2H), 1.95–1.78 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3293, 3061, 2934, 1953, 1730, 1596, 1509, 1478, 1454, 1411, 1244, 1026, 940, 800, 737 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{23}NO_3$ (349.42): C 75.62, H 6.63, N 4.01; found 75.39, H 6.86, N 4.21.

Compound 11e: yield: 83%; R_f = 0.2 (AcOEt/hex 1:1); m.p. 101–103°C; $[\alpha]_D^{20}$ −16.1° (c = 1.2, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.94 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 3.7 Hz, 1H), 7.40–7.32 (brs, 6H), 7.13 (t, J = 10.3/9.0 Hz, 1H), 6.64 (d, J = 3.6 Hz, 1H), 5.04 (s, 2H), 4.65 (t, J = 5.5 Hz, 1H), 3.46–3.23 (m, 2H), 2.77–2.55 (m, 2H), 1.88–1.84 (m, 2H), 1.80–1.70 (brs, 10H) ppm; IR (KBr): $\tilde{\nu}$ = 3332, 2959, 2860, 1949, 1732, 1690, 1534, 1470, 1384, 1328, 1257, 1130, 1054, 891, 841, 765, 726, 697 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{30}N_2O_5 \cdot 0.5\,H_2O$ (447.53): C 67.10, H 6.98, N 6.26; found: C 67.17, H 6.79, N 6.38.

Compound 11f: yield: 68%; R_f = 0.4 (AcOEt/hex 1:1); m.p. 135°C; $[\alpha]_D^{20}$ +19.7° (c = 0.8, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.50 (s, 1H), 8.38–8.34 (m, 2H), 8.13–8.09 (m, 2H), 7.59–7.35 (m, 10H), 5.20 (s, 2H), 4.77 (t, J = 5.6, 1H), 3.80 (brs, 1H), 3.67–3.41 (m, 4H), 2.02–1.95 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3319, 3057, 2946, 1694, 1540, 1452, 1349, 1286, 1243, 1149, 1067, 1038, 879, 836, 729, 696 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{25}NO_3$ (399.48): C 78.17, H 6.31, N 3.51; found: C 77.97, H 6.42, N 3.70.

General procedure for the synthesis of the alcohols 12a–f: preparation of alcohol 12a: The Cbz-protected alcohol **11a** (707.8 mg, 1.9 mmol), 1.4-cyclohexadiene (873 µL, 9.3 mmol) and Pd(OH)$_2$ (53 mg, 0.38 mmol) were heated at reflux in ethanol (25 mL). After complete conversion of the starting material (TLC monitoring), the catalyst was removed by filtration over celite. The filtrate was concentrated in vacuo and redissolved in AcOEt (25 mL) and EtOH (15 mL). The addition of Fmoc-Suc (705 mg, 2.1 mmol) followed and the clear solution was stirred at room temperature. After 30 min a colorless precipitate of **12a** was produced. The solid was isolated by filtration to give the Fmoc-protected amino alcohol **12a** (699.7 mg, 80%). R_f = 0.3 (AcOEt/hex 1:1); m.p. 196–197°C; $[\alpha]_D^{20}$ −10.5° (c = 0.7, DMF); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.93 (d, J = 7.3 Hz, 2H), 7.79–7.73 (m, 4H), 7.62 (s, 1H), 7.48–7.29 (m, 6H), 7.16 (t, J = 6.5/2.4 Hz, 2H), 4.69 (t, J = 5.5 Hz, 1H), 4.41–4.27 (m, 3H), 3.89 (s, 3H), 3.51–3.31 (m, 3H), 2.80–2.68 (m, 2H), 1.94–1.73 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3327, 3052, 2933, 1957, 1913, 1689, 1607, 1538, 1451, 1390, 1291, 1264, 1158, 1087, 1032, 966, 901, 851, 760 cm^{-1}; elemental analysis calcd (%) for $C_{30}H_{29}NO_4$ (467.56): C 77.06, H 6.25, N 3.00; found: C 76.92, H 6.22, N 3.21.

Compound 12b: yield: 84%; R_f = 0.3 (AcOEt), m.p. 158–159°C; $[\alpha]_D^{20}$ −11.3° (c = 0.7, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.78 (s, 1H), 8.11–7.18 (m, 15H), 4.70 (brs, 1H), 4.42–4.21 (m, 3H), 3.43–3.39 (m, 2H), 2.85–2.67 (m, 2H), 1.95–1.71 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3333, 2931, 1959, 1702, 1676, 1531, 1450, 1254, 1048, 739 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{26}N_2O_3 \cdot 0.3$ AcOEt (464.95): C 75.43, H 6.16, N 6.02; found: C 75.20, H 6.18, N 6.20.

Compound 12c: yield: 74%; R_f = 0.3 (AcOEt/hex 1:1); m.p. 195–196°C; $[\alpha]_D^{20}$ +5.9° (c = 0.5, DMF); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.73 (d, J = 7.3 Hz, 1H), 8.64 (d, J = 6.8 Hz, 1H), 8.03 (d, J = 7.0 Hz, 1H), 7.78–7.72 (m, 3H), 7.64–7.46 (m, 7H), 7.29–7.15 (5H), 4.55 (brs, 1H), 4.28–4.13 (m, 4H), 3.48–2.87 (m, 4H), 1.88–1.85 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3313, 3063, 2947, 2870, 2364, 1918, 1692, 1542, 1450, 1334, 1291, 1246, 886, 738 cm^{-1}; elemental analysis calcd (%) for $C_{33}H_{29}NO_3$ (487.59): C 81.29, H 5.99, N 2.87; found: C 81.04, H 5.95, N 3.05.

Compound 12d: yield: 57%; R_f = 0.3 (AcOEt/hex 1:1); m.p. 196–197°C; $[\alpha]_D^{20}$ +0.7° (c = 0.8, MeOH/AcOEt 1:9); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.11–8.08 (m, 1H), 7.94–7.89 (m, 3H), 7.77 (d, J = 7.5 Hz, 3H), 7.56–7.27 (m, 9H), 4.68 (t, J = 5.5 Hz, 1H), 4.42–4.27 (m, 3H), 3.60 (brs, 1H), 3.48–3.33 (m, 2H), 3.13–2.98 (m, 2H), 1.92–1.76 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3482, 3336, 3066, 2947, 2873, 2366, 1677, 1546, 1451, 1399, 1342, 1286, 1259, 1286, 1259, 1142, 1088, 1070, 779, 739 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{27}NO_3 \times 0.5\,H_2O$ (446.53): C 78.00, H 6.32, N 3.14; found: C 78.12, H 6.25, N 3.13.

Compound 12e: yield: 58%; R_f = 0.3 (AcOEt/hex 1:1); m.p. 64°C; $[\alpha]_D^{20}$ −4.9° (c = 0.4, AcOEt); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.96 (t, J = 9.2/8.8 Hz, 3H), 7.77 (d, J = 7.0 Hz, 2H), 7.65 (d, J = 3.6 Hz, 1H), 7.48–7.34 (m, 5H), 7.17 (t, J = 8.2/7.4 Hz, 2H), 6.66 (d, J = 3.6 Hz, 1H), 4.67 (t, J = 5.5/5.1 Hz, 1H), 4.40–4.28 (m, 3H), 3.46–3.26 (m, 3H), 2.75–2.66 (m, 2H), 2.02–1.90 (m, 11H) ppm; IR (KBr): $\tilde{\nu}$ = 3329, 2977, 2928, 2863, 2364, 1813, 1793, 1734, 1689, 1541, 1472, 1374, 1350, 1257, 1220, 1165, 1131, 1085, 1032, 760, 739 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{34}N_2O_5 \cdot 1\,H_2O$ (544.64): C 70.57, H 6.66, N 5.14; found: C 70.57, H 6.69, N 5.20.

Compound 12f: yield: 68%; R_f = 0.3 (AcOEt/hex 1:1); m.p. 221°C; $[\alpha]_D^{20}$ −30.7° (c = 0.4, DMF); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.48 (s, 1H), 8.36–8.32 (m, 2H), 8.10–8.07 (m, 2H), 7.93–7.88 (m, 2H), 7.82 (d, J = 7.2 Hz, 2H), 7.54–7.50 (m, 4H), 7.45–7.29 (m, 5H), 4.75 (t, J = 5.5 Hz, 1H), 4.50–4.28 (m, 3H), 3.79 (brs, 1H), 3.60–3.38 (m, 4H), 2.00–1.82 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3307, 3060, 2955, 2372, 1695, 1547, 1450, 1286, 1249, 1149, 1039, 879, 736 cm^{-1}; elemental analysis calcd (%) for $C_{33}H_{29}NO_3 \cdot 0.75\,H_2O$ (501.11): C 79.04, H 6.13, N 2.80; found 78.94, H 6.09, N 2.80.

General procedure for the synthesis of the carboxylic acids 13a–f: preparation of acid 13a: The Fmoc-protected alcohol **12a** (649.4 mg, 1.4 mmol) was dissolved in DMF (20 mL). PDC (3.13 g, 8.3 mmol) was added to this clear solution, which was stirred overnight at room temperature. After completion of the reaction the dark solution was extracted with H_2O and AcOEt. The combined organic phases were washed with aqueous $Na_2S_2O_5$. The organic phase was evaporated and the residue was adsorbed onto SiO_2. The crude product was purified by column chromatography (MeOH/AcOEt 1:9) to give **13a** (390 mg, 58%) as a solid. R_f = 0.3 (MeOH/AcOEt 1:9); m.p. 190–195°C; $[\alpha]_D^{20}$ +19.5° (c = 0.6, DMF/MeOH/AcOEt 1:3:6); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.91 (d, J = 6.2 Hz, 2H), 7.71–7.67 (m, 4H), 7.55 (s, 1H), 7.41–7.32 (m, 6H), 7.10 (m, 2H), 4.35–4.23 (m, 4H), 3.85 (s, 3H), 2.2–1.9 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3422, 3062, 2934, 2370, 1701, 1607, 1578, 1543, 1508, 1458, 1450, 1420, 1390, 1340, 1264, 1229, 1081, 1033, 740 cm^{-1}; MS (ESI) m/z (%): 480.3 (100) $[M-H]^+$, 227.8 (83) $[M-H-Fmoc]^+$; $C_{30}H_{27}NO_5$ calcd 481.54; elemental analysis calcd (%) for $C_{30}H_{27}NO_5 \cdot 1.75\,H_2O$ (513.04): C 70.23, H 5.99, N 2.73; found 69.94, H 5.70, N 3.03.

Compound 13b: yield: 79%; R_f = 0.3 (MeOH/AcOEt 1:2); m.p. 181–184°C; $[\alpha]_D^{20}$ +11.8° (c = 0.3, MeOH/AcOEt 1:2); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.19 (s, 1H), 8.89 (s, 1H), 8.38 (m, 2H), 8.22 (d, J = 7.7 Hz, 1H), 8.03 (m, 1H), 7.92–7.74 (m, 5H), 7.42–7.34 (m, 4H), 4.32–4.22 (m, 3H), 4.02 (m, 1H), 3.17 (m, 2H), 2.21–1.99 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3400, 3062, 2947, 2368, 1702, 1604, 1498, 1450, 1420, 1332, 1254, 1130, 1053, 740, 670 cm^{-1}; MS (ESI) m/z (%): 453.3 (100) $[M+H]^+$; $C_{28}H_{24}N_2O_4$ calcd 452.2.

Compound 13c: yield: 86%; R_f = 0.3 (MeOH/AcOEt 1:9); m.p. 135–140°C; $[\alpha]_D^{20}$ +16.6° (c = 0.7, MeOH/AcOEt 1:2); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.88 (d, J = 9.3 Hz, 1H), 8.80 (d, J = 8.7 Hz, 1H), 8.20 (d, J = 9.2 Hz, 1H), 7.96–7.87 (m, 6H), 7.81–7.59 (m, 5H), 7.46–7.35 (m, 4H), 4.37–4.32 (m, 3H), 4.13 (m, 1H), 3.24–3.17 (m, 2H), 2.16 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3403, 3063, 2931, 2372, 1953, 1718, 1663, 1596, 1496, 1449, 1414, 1330, 1246, 1146, 1050, 741 cm^{-1}; MS (ESI) m/z = 524.1896 $[M+Na]^+$; $C_{33}H_{27}NO_4Na$ calcd 524.1838.

Compound 13d: yield: 56%; R_f = 0.3 (AcOEt); m.p. 156–157°C; $[\alpha]_D^{20}$ +19.4° (c = 0.2, MeOH/AcOEt 1:4); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.10 (s, 1H), 7.96 (s, 1H), 7.91 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.51–7.31 (m, 10H), 4.38–4.26 (m, 3H), 3.95 (m, 1H), 3.06 (m, 2H), 2.07 (m, 2H) ppm; IR (KBr): $\tilde{\nu}$ = 3407, 3063, 2934, 2368, 1718, 1664, 1596, 1510, 1450, 1417, 1334, 1247, 1080, 1054, 740 cm^{-1}; MS (ESI) m/z (%): 450.3 (50) $[M-H]^+$, 227.8 (100) $[M-H-Fmoc]^+$; $C_{29}H_{25}NO_4$ calcd 451.2; elemental analysis calcd (%) for $C_{29}H_{25}NO_4 \cdot 1.25\,H_2O \cdot 0.25$ DMF (492.28): C 72.58, H 5.99, N 3.56; found 72.53, H 5.62, N 3.71.

Compound *ent*-13d: yield: 53%; R_f = 0.3 (AcOEt); m.p. 154–155°C; $[\alpha]_D^{20}$ −19.1° (c = 0.4, MeOH/AcOEt 1:4); NMR and IR spectra are identical with those of compound **13d**.

Determination of *ee*: Column: Daicel Chiralcel OJ-R 150×4.6 mm; eluent: aqueous 0.1% trifluoroacetic acid/acetonitrile 40:60, flow rate 0.5 mL min^{-1}; detection: UV, 254 nm; Rt **13d**: 9.03 min, Rt *ent*-**13d** : 11.52 min.

Compound 13e: yield: 79%; R_f = 0.3 (AcOEt); m.p. 158–160°C; $[\alpha]_D^{20}$ +18.6° (c = 1, MeOH/AcOEt 1:4); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.96–7.90 (m, 4H), 7.70 (s, 1H), 7.57 (d, J = 3.3 Hz, 2H), 7.39–7.33 (m, 5H), 7.11–7.08 (d, J = 7.9 Hz, 4H), 6.57 (s, 1H), 4.34–4.21 (m, 3H), 3.85 (m, 1H), 2.64 (m, 2H), 1.92 (m, 2H), 1.59 (9H) ppm; IR (KBr): $\tilde{\nu}$ = 3405, 2977, 2931, 1729, 1665, 1590, 1508, 1450, 1374, 1256, 1164, 1131, 1023, 740 cm^{-1}; MS (ESI) m/z (%): 539.2 (50) $[M-H]^+$, 317.3 (100)

$[M-H-Fmoc]^+$; $C_{32}H_{32}N_2O_6$ calcd 540.2; elemental analysis calcd (%) for $C_{32}H_{32}N_2O_6 \cdot 1.2\,H_2O \cdot 0.4\,DMF$ (591.44): C 67.42, H 6.34, N 5.68; found 67.25, H 5.94, N 6.00.

N-Cbz-(*S,S*)-Pseudoephedrine-allylglycine compound (17): Et_3N (9.56 mL, 69 mmol) was added dropwise by syringe to a solution of the allylglycine derivative **15**[9b] (15.0 g, 57 mmol) in $CHCl_3$ (250 mL, argon atmosphere). After the mixture had been stirred at room temperature for 30 min, Cbz-Cl (9.67 mL, 69 mmol) was added slowly at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 18 h. At this point saturated aqueous $NaHCO_3$ solution was added (100 mL) and the mixture was stirred for 20 min. The organic phase was separated and washed with saturated $NaHCO_3$ solution (100 mL). After reextraction of the combined aqueous layers (twice with 100 mL DCM), the combined organic layers were evaporated in vacuo. The resulting yellow oil was purified by gradient column chromatography (AcOEt/hex 1:1, AcOEt), providing **17** as a pale yellow oil in 96% yield (21.68 g). R_f = 0.5 (AcOEt/hex 1:1); $[\alpha]_D^{20}$ +53.9° (c = 0.3, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.54 (d, J = 8.8 Hz, 1H), 7.53–7.23 (m, 10H), 5.91–5.69 (m, 1H), 5.26–4.94 (m, 4H), 4.69–4.46 (m, 2H), 4.17–4.00 (m, 1H), 2.82 (s*, 3H), 2.46–2.24 (m, 2H), 0.83 (d*, J = 6.6 Hz, 3H) ppm; IR (KBr): $\tilde{\nu}$ = 3416, 3032, 1717, 1630, 1508, 1455, 1411, 1253, 1112, 1049, 919, 756, 700 cm^{-1}; elemental analysis calcd: (%) for $C_{23}H_{28}N_2O_4$ (396.47): C 69.67, H 7.12, N 7.07; found: C 69.42, H 7.01, N 6.92.

General procedure for Suzuki cross-coupling reactions of compound 17: **preparation of the 2-pyridyl derivative (19a)**: A three-necked, round-bottomed flask was charged with **17** (2.0 g, 5.1 mmol) under argon atmosphere. 9-BBN (24.3 mL of 0.5 M in THF, 12.2 mmol) was added and the mixture was stirred at room temperature. After total consumption of the starting material (15 min), $[Pd(PPh_3)_4]$ (291 mg, 5 mol%) was added, followed by aqueous K_3PO_4 solution (3 M, 5 mL) and 2-bromopyridine (517 μL, 5.3 mmol). The resulting mixture was stirred for another 16 h at room temperature. The mixture was diluted with Et_2O (10 mL) and extracted four times with saturated $NaHCO_3$ solution. The combined aqueous solutions were extracted twice with Et_2O (20 mL). The organic layers were combined and concentrated in vacuo. The resulting viscous residue was purified by column chromatography on silica gel eluting with a gradient (AcOEt/hex 1:1, AcOEt) to afford product **19a** as a colorless foam (2.16 g, 90%). R_f = 0.5 (DCM/MeOH 20:1); $[\alpha]_D^{20}$ +56.5° (c = 0.1, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.5–7.2 (m, 15H), 5.50 (d, 1H, J = 3.7 Hz), 5.07–4.93 (m, 2H), 4.58–4.47 (m, 2H), 4.14–4.05 (m, 1H), 2.84–2.65 (m, 5H), 1.77–1.44 (m, 4H), 0.82 (d*, 3H, J = 6.4 Hz) ppm; IR (KBr): $\tilde{\nu}$ = 3402, 3287, 3062, 3031, 2935, 2863, 1715, 1630, 1528, 1496, 1477, 1454, 1436, 1409, 1247, 1119, 1050, 1027, 911, 838, 753, 700, 612 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{33}N_3O_4 \cdot 0.3\,H_2O$ (480.65): C 69.92, H 7.04, N 8.74; found: C 69.97, H 7.11, N 8.39.

Compound 19b: yield: 38%; R_f = 0.5 (DCM/MeOH 20:1); $[\alpha]_D^{20}$ +53.3° (c = 0.6, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.48–8.37 (m, 1H), 7.66–7.18 (m, 13H), 5.51 (d, 1H, J = 3.7 Hz), 5.09–4.91 (m, 2H), 4.62–4.37 (m, 2H), 4.19–4.07 (m, 1H), 2.88–2.52 (m, 5H), 1.66–1.35 (m, 4H), 0.83 (d*, J = 6.3 Hz, 3H) ppm; IR (KBr): $\tilde{\nu}$ = 3406, 2933, 1718, 1629, 1528, 1456, 1412, 1351, 1245, 1116, 1049, 755, 700, 611 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{33}N_3O_4 \cdot 0.95\,AcOEt$ (558.95): C 68.29, H 7.32, N 7.51; found: C 68.02, H 7.02, N 7.77.

Compound 19c: yield: 88%; R_f = 0.5 (DCM/MeOH 20:1); $[\alpha]_D^{20}$ +58.1° (c = 0.5, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.72 (dd, 2H, J = 4.9/4.1 Hz), 7.55–7.27 (m, 12H, J = 4.9 Hz), 5.48 (d, 1H, J = 3.7 Hz), 5.07–4.93 (m, 2H), 4.75–4.65 (m, 2H), 4.18–4.00 (m, 1H), 2.90–2.78 (m, 5H,), 1.85–1.50 (m, 4H), 0.83 (d*, 3H, J = 6.5 Hz) ppm; IR (KBr): $\tilde{\nu}$ = 3336, 3063, 2936, 1711, 1639, 1561, 1529, 1491, 1453, 1423, 1376, 1249, 1199, 1101, 1046, 912, 818, 754, 698, 636, 582 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{32}N_4O_4 \cdot 0.50\,H_2O$ (485.24): C 66.79, H 6.85, N 11.54; found: C 66.95, H 6.87, N 11.21.

Compound 19d: yield: 27%; R_f = 0.5 (DCM/MeOH 20:1); $[\alpha]_D^{20}$ +61.2° (c = 0.5, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.04 (d, 1H, J = 1.9 Hz), 8.66 (m, 2H), 7.42–7.24 (m, 11H), 5.57 (d, 1H, J = 4.1 Hz), 5.08–4.93 (m, 2H), 4.62–4.41 (m, 2H), 4.18–4.00 (m, 1H), 2.88–2.52 (m, 5H), 1.69–1.41 (m, 4H), 0.83 (d*, 3H, J = 6.6 Hz) ppm; IR (KBr): $\tilde{\nu}$ = 3396, 3291, 3031, 2936, 2866, 1713, 1632, 1563, 1530, 1496, 1454, 1410, 1375, 1250, 1122, 1049, 911, 838, 756, 728, 701, 635, 612 cm^{-1}; MS (ESI) m/z = 477.2345 $[M+H]^+$; $C_{27}H_{33}N_4O_4$ calcd 477.2502.

Compound 19e: yield: 86%; R_f = 0.5 (DCM/MeOH 20:1); $[\alpha]_D^{20}$ +58.2° (c = 0.5, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.60–8.50 (m, 2H, J = 2.5 Hz), 8.48 (d, 1H, J = 2.5 Hz), 7.60–7.25 (m, 12H), 5.50 (d, 1H, J = 3.7 Hz), 5.35–4.90 (m, 2H), 4.75–4.45 (m, 2H), 4.20–4.05 (m, 1H), 2.90–2.65 (m, 5H), 1.85–1.40 (m, 4H), 0.83 (d*, 3H, J = 6.5 Hz) ppm; IR (KBr): $\tilde{\nu}$ = 3407, 3062, 2934, 1718, 1636, 1526, 1497, 1476, 1456, 1405, 1245, 1120, 1050, 1017, 912, 836, 757, 700, 610 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{32}N_4O_4 \cdot 0.45\,H_2O$ (484.34): C 66.91, H 6.84, N 11.56; found: C 66.95, H 6.75, N 11.36.

General procedure for the deprotection of amino acids: **preparation of 20a**: A flask filled with argon was charged with MeOH (20 mL), **19a** (5.9 g, 12.4 mmol) and Pd/C (10%, 700 mg). After replacement of argon by hydrogen (normal pressure), the mixture was vigorously stirred for 16–24 h (depending on the activity of the catalyst) at room temperature until total consumption of the starting material. The reaction mixture was then filtrated over celite® and washed with MeOH, and the resulting organic layer was concentrated in vacuo. The oily residue was suspended in H_2O (40 mL) and heated at reflux for 24 h to remove the chiral auxiliary. After cooling to room temperature, the mixture was extracted five times with DCM. The aqueous solution was concentrated in vacuo and the resulting oily residue crystallized from MeOH/AcOEt/hexanes/Et_2O to yield a colorless solid (1.5 g, 62% over two steps). R_f = 0.2 (H_2O); m.p. 192 °C; $[\alpha]_D^{20}$ +7.0° (c = 0.4, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.39–8.33 (m, 1H), 7.76–7.69 (m, 1H), 7.39–7.19 (m, 2H), 3.73–3.64 (m, 1H), 2.84–2.70 (m, 2H), 1.87–1.66 (m, 4H) ppm; IR (KBr): $\tilde{\nu}$ = 3017, 2934, 2862, 2594, 2112, 1631, 1587, 1520, 1477, 1459, 1439, 1406, 1352, 1308, 1232, 1201, 1157, 1129, 1065, 1050, 1015, 998, 882, 846, 827, 784, 755, 737, 671, 634, 605 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{14}N_2O_2 \cdot 0.3\,MeOH$ (203.72): C 60.69, H 7.52, N 13.74; found: C 60.81, H 6.75, N 13.68.

Compound 20e: yield: 63% (over two steps); R_f = 0.4 (H_2O); m.p. 246 °C; $[\alpha]_D^{20}$ +3.9° (c = 0.3, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.49 (d, J = 3.6H, 2H), 8.41 (d, J = 2.6 Hz, 1H), 3.40–3.35 (m, 1H), 2.79–2.74 (m, 2H), 1.80–1.61 (m, 4H) ppm; IR (KBr): $\tilde{\nu}$ = 3444, 3042, 2956, 2602, 2133, 1584, 1519, 1407, 1355, 1355, 1327, 1161, 1134, 1062, 1019, 828, 670 cm^{-1}; elemental analysis calcd (%) for $C_9H_{13}N_3O_2$ (195.10): C 55.37, H 6.71, N 21.52; found: C 55.41, H 6.72, N 21.33.

First procedure for Fmoc-protection: **preparation of 21a**: Compound **20a** (500 mg, 2.57 mmol) was suspended in DCM (15 mL) under argon and TMS-Cl (651 μL, 5.15 mmol) was added dropwise. Within 30 min the suspension dissolved to form a pale yellow solution. At that point DIPEA (761 μL, 4.45 mmol) and Fmoc-Cl (665 mg, 2.57 mmol) were added and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with aqueous $NaHCO_3$ solution (2.5%, 15 mL) and Et_2O (15 mL). The aqueous layer was extracted four times with Et_2O. The combined organic layers were extracted with aqueous $NaHCO_3$ solution (2.5%, 20 mL) followed by H_2O (20 mL). All aqueous layers were combined and acidified to pH 1 with HCl (1 M). Upon acidification, the solution became turbid. It was then extracted eight times with AcOEt (50 mL). After concentration in vacuo a slightly brownish foam remained. It was dissolved in AcOEt with heating. The organic layer was separated from the brown precipitate. After concentration in vacuo the resulting foam was recrystallized with AcOEt/MeOH/hexanes/Et_2O to yield a tan-colored powder (860 mg; 80%). R_f = 0.5 (MeOH); m.p. 108–110 °C; $[\alpha]_D^{20}$ +1.7° (c = 0.2, methanol); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.8–12.2 (br s, 1H), 8.49 (d, 1H, J = 4.1 Hz), 7.91–7.20 (m, 12H), 4.31–4.23 (m, 3H), 4.15–3.95 (m, 1H), 2.74 (d, 2H, J = 5.9 Hz), 1.50–1.81 (m, 4H) ppm; IR (KBr): $\tilde{\nu}$ = 3556, 2959, 2490, 1960, 1697, 1599, 1538, 1449, 1334, 1301, 1235, 1155, 1110, 1082, 1055, 1012 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{24}N_2O_4 \cdot 1.3\,H_2O$ (440.57): C 68.26, H 6.09, N 6.37; found: C 68.21, H 5.83, N 6.55.

Compound 21e: yield: 68%; R_f = 0.5 (MeOH); m.p. 89–90 °C; $[\alpha]_D^{20}$ + 1.5° (c = 0.3, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.53 (br s, 1H), 8.56 (s, 2H), 8.49 (d, J = 2.2 Hz, 1H), 7.91–7.29 (m, 10H), 4.32–4.20 (3H), 4.15–3.85 (m, 1H), 2.85–2.70 (m, 2H), 1.85–1.61 (m, 4H) ppm; IR (KBr): $\tilde{\nu}$ = 3320, 3064, 2926, 2863, 2519.4, 1924, 1718, 1691, 1608, 1542, 1476, 1450, 1404, 1372, 1258, 1160, 1050, 9889, 861, 758, 733, 660, 621 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{23}N_3O_4$ (416.17): C 69.05, H 5.55, N 10.07; found: C 68.84, H 5.76, N 9.82.

Compound *ent*-21e: yield: 67%; R_f = 0.5 (MeOH); m.p. 87–90°C; $[\alpha]_D^{20}$ −1.4° (c = 0.4, MeOH); NMR and IR spectra are identical with those of compound **21e**; elemental analysis calcd (%) for $C_{24}H_{23}N_3O_4 \cdot 0.5\,AcOEt$ (460.23): C 67.67, H 5.90, N 9.10; found: C 67.60, H 5.86, N 9.35.

Determination of *ee*: Column: Daicel Chiralcel OJ-R 150×4.6 mm; eluent: aqueous 0.1% trifluoroacetic acid/acetonitrile 73:27; flow rate 0.5 mL min^{-1}; detection: UV, 254 nm; Rt *ent*-**21e**: 42.19 min, Rt **21e**: 47.73 min.

Second procedure for Cbz removal and Fmoc protection: **preparation of compound 21b**: The Cbz group of **19b** (2.1 g, 4.39 mmol) was removed by hydrogenolysis with Pd/C (10%, 300 mg) as described above. The remaining oil was suspended in H_2O (30 mL) and heated at reflux until removal of the auxiliary was complete (24 h). Pseudoephedrine was isolated by extraction with DCM. Evaporation of the aqueous phase to dryness gave the amino acid **20b**. It was used for Fmoc protection without further purification according to the general procedure with TMS-Cl (1.04 mL, 8.24 mmol), DIPEA (1.22 mL, 7.13 mmol) and Fmoc-Cl (451 mg, 4.12 mmol) to yield a colorless foam (906 mg, 50% over three steps): R_f = 0.5 (MeOH); $[\alpha]_D^{20}$ +3.4° (c = 0.3, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.8–12.2 (br s, 1H), 8.48 (dd, J = 7.2/2.2 Hz, 1H), 7.90 (br d, 2H), 7.76–7.26 (m, 9H), 4.35–4.18 (m, 3H), 4.05–3.93 (m, 1H), 2.73–2.57 (m, 2H), 1.82–1.52 (m, 4H) ppm; IR (KBr): $\tilde{\nu}$ = 3323, 3063, 2937, 1718, 1534, 1450, 1400, 1332, 1245, 1048, 761, 740 cm^{-1}; MS (ESI) *m/z*: 417.1677 $[M+H]^+$; $C_{25}H_{25}N_2O_4$ calcd 417.1814.

Compound 21c (second procedure): yield 32% (over three steps); R_f = 0.5 (MeOH); m.p. 60–64°C; $[\alpha]_D^{20}$ +1.9° (c = 0.3, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.9–12.2 (br s, 1H), 8.73 (d, 2H, J = 5.1 Hz), 7.92–7.30 (m, 11H), 4.33–4.20 (m, 3H), 4.08–3.93 (m, 1H), 2.92–2.86 (m, 2H), 1.92–1.57 (m, 4H) ppm; IR (KBr): $\tilde{\nu}$ = 3405, 3039, 2950, 1718, 1561, 1540, 1527, 1450, 1424, 1340, 1247, 1106, 1052, 760, 741 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{23}N_3O_4 \cdot 1\,AcOEt$ (505.56): C 66.52, H 6.18, N 8.31; found: C 66.57, H 6.12, N 8.46.

Compound 21d (second procedure): yield: 40% (over three steps); R_f = 0.5 (MeOH); m.p. 78–80°C; $[\alpha]_D^{20}$ +3.5 ° (c = 0.3, MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.5–12.2 (br s, 1H), 9.05 (s, 1H), 8.68 (s, 2H), 7.93–7.25 (m, 10H), 4.34–4.18 (m, 3H), 4.06–3.92 (m, 1H), 2.68–2.56 (m, 2H), 1.76–1.57 (m, 4H) ppm; IR (KBr): $\tilde{\nu}$ = 3396, 3040, 2948, 2368, 1718, 1522, 1449, 1410, 1321, 1218, 1052, 760, 740, 646 cm^{-1}; MS (ESI) *m/z* = 418.1716 $[M+H]^+$; $C_{25}H_{24}N_2O_4$ calcd 418.1767.

General procedures for solid-phase peptide synthesis: Attachment of N-Fmoc-amino acids to Rink amide MBHA resin: After swelling of the resin (150 mg, theoretical loading 0.78 mmol g^{-1}, 0.19 mmol) twice with DCM (2 mL) for 20 min, the solvent was changed to DMF. The Fmoc-protected resin was then treated three times with a solution of piperidine in DMF (25%) to liberate the amine (15 min/5 min/2 min). Subsequently, the resin was washed with DMF (five times). For coupling, the Fmoc-protected amino acid (2 equiv, 0.38 mmol) was dissolved in DMF (2 mL) together with HOBt (3 equiv) and DIC (3 equiv). This mixture was added to the resin. After 3 h of gentle agitation, the resin was again washed with DMF and tested for complete coupling by the Kaiser test.[20] The Fmoc-amine was liberated by treatment with piperidine in DMF as described before. After washing with DMF (5 times) the following Fmoc-amino acids were coupled in identical fashion.

Cleavage of the resin and protecting groups: After removal of the last Fmoc group, the resin was washed with DCM and dried in vacuo. The resin was then treated with TFA (1650 μL), thioanisole (100 μL), H_2O (100 μL), phenol (50 mg) and EDT (50 μL). The resin turned red and after 5 h of gentle agitation it was filtered off. Upon trituration with Et_2O, the peptide precipitated from the filtrate. The precipitate was several times suspended in Et_2O and spun down in a centrifuge. After removal of the organic solvent, the pellet was dissolved in H_2O, concentrated by use of a speedvac to eliminate volatile impurities and finally dissolved in H_2O.

Preparation of compound NH$_2$-D-Arg-L-NaphtOMe-D-Arg-CONH$_2$ (22) from 13a: yield: 74%; MS (ESI) *m/z* (%): 571.4 (5) $[M+H]^+$, 286.1 (100) $[M+2H]^+$; $C_{27}H_{42}N_{10}O_4$ calcd 570.3.

Preparation of compound NH$_2$-D-Arg-L-Quino-D-Arg-CONH$_2$ (23) from 13b: yield: 87%; MS (ESI) *m/z* (%): 542.5 (9) $[M+H]^+$, 271.7 (100) $[M+2H]^+$; $C_{25}H_{39}N_{11}O_3$ calcd 541.3.

Preparation of compound NH$_2$-D-Arg-L-Phenan-D-Arg-CONH$_2$ (24) from 13c: yield: 99%; MS (ESI) *m/z* (%): 591.5 (4) $[M+H]^+$, 296.2 (100) $[M+2H]^+$; $C_{30}H_{42}N_{10}O_3$ calcd 590.3.

Preparation of compound NH$_2$-D-Arg-L-Napht-D-Arg-CONH$_2$ (25) from 13d: yield: 94%; MS (ESI) *m/z* (%): 541.5 (8) $[M+H]^+$, 271.1 (100) $[M+2H]^+$; $C_{26}H_{40}N_{10}O_3$ calcd 540.3.

Preparation of compound NH$_2$-D-Arg-D-2-Pyridyl-D-Arg-CONH$_2$ (26) from 21a: yield: 74%; MS (ESI) *m/z* (%): 506.5 (8) $[M+H]^+$, 253.7 (100) $[M+2H]^+$; $C_{22}H_{39}N_{11}O_3$ calcd 505.3.

Preparation of compound NH$_2$-D-Arg-D-3-Pyridyl-D-Arg-CONH$_2$ (27) from 21b: yield: 92%; MS (ESI) *m/z* (%): 506.5 (10) $[M+H]^+$, 253.6 (100) $[M+2H]^+$; $C_{22}H_{39}N_{11}O_3$ calcd 505.3.

Preparation of compound NH$_2$-D-Arg-D-2-Pyrimidinyl-D-Arg-CONH$_2$ (28) from 21c: yield: 78; MS (ESI) *m/z* (%): 507.4 (100) $[M+H]^+$ %; $C_{21}H_{38}N_{12}O_3$ calcd 506.3.

Preparation of compound NH$_2$-D-Arg-D-Pyrazinyl-D-Arg-CONH$_2$ (29) from 21e: yield: 73%; MS (ESI) *m/z* (%): 507.4 (3) $[M+H]^+$, 254.2 (100) $[M+2H]^+$; $C_{21}H_{38}N_{12}O_3$ calcd 506.3.

Preparation of compound NH$_2$-D-Arg-L-Pyrazinyl-D-Arg-CONH$_2$ (30) from *ent*-21e: yield: 99%; MS (ESI) *m/z* (%): 507.3 (8) $[M+H]^+$, 254.1 (100) $[M+2H]^+$; $C_{21}H_{38}N_{12}O_3$ calcd 506.3.

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