Synthesis and Structure of Chiral Methoxypyrrole Amino Acids (MOPAS)

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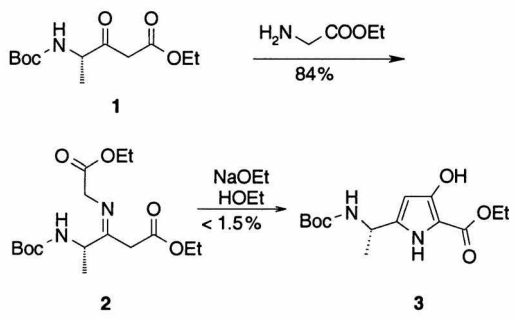
Abstract: A methoxypyrrole amino acid (MOPAS) resembling the structure of H_2N-Val-Δ-Ala-OEt in β-sheet conformation has been prepared by a chiral auxiliary approach. The X-ray structure analysis confirms the absolute configuration of the dipeptide mimic. Standard peptide coupling procedures allow coupling of the chiral MOPAS with natural amino acids or their extension by additional MOPAS units. A tight self-association of bis-MOPAS **13** in $CDCl_3$ and the affinity to Ac-Ala-Ile-OMe dipeptides illustrates the ability of the constrained dipeptide mimic MOPAS to interact with peptides.

Key words: heterocycles, amino acids, peptides, chiral auxiliaries, imines

Compounds with a molecular structure that mimic motifs of natural peptides[1] have found wide applications in medicinal chemistry[2] and protein recognition studies. Structures complementary to β-sheets are of particular interest, because of their potential to intercept protein–protein interactions,[3] inhibit protein aggregation,[4] or induce[5] or mimic peptide β-sheets.[6] We have recently reported a heterocyclic dipeptide mimic based on methoxypyrrole amino acids (MOPAS), which resembles the structure of a H_2N-Gly-Δ-Ala-OEt unit in β-sheet conformation.[7,8] We now report the extension of the concept to a chiral dipeptide mimic H_2N-Val-Δ-Ala-OEt,[9] which has been prepared using a chiral auxiliary approach.

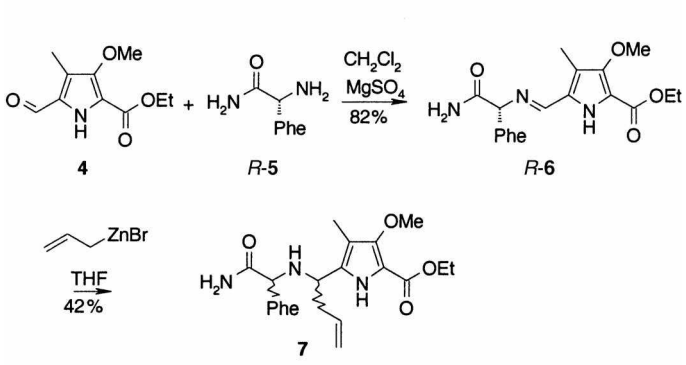
Our first attempts to prepare a chiral MOPAS unit used γ-amino-β-keto ester **1**[10] as starting material. Condensation with Gly gave amino ester **2**, unfortunately this resulted in only trace amounts of the desired cyclization product **3**.[11]



Scheme 1 Synthesis of a chiral MOPAS **3** from a natural amino acid derivative

We changed the synthetic strategy to a chiral auxiliary approach and reacted aldehyde **4** as starting material with chiral amines.[12] The initial route using (*R*)-phenyl glycineamide to form the Schiff base followed by addition of an allyl zinc reagent[13] gave only a disappointing 42% yield in the addition reaction.

The use of amino alcohols as chiral auxiliaries and Grignard reagents for addition proved to be more efficient. Phenylglycinol and valinol gave imine **9** in quantitative yield. The compounds were characterized by X-ray structure analysis and chiral HPLC. Isopropyl magnesium chloride undergoes clean addition in THF to compound **9-Ph** yielding **10-Ph** in 77% isolated yield. Deprotection with dihydrogen and Pd/C yields the target compound *i*-Pr-MOPAS **11** nearly quantitatively.[14]



Scheme 2 Synthesis of substituted MOPAS **7** via allyl-zinc bromide addition

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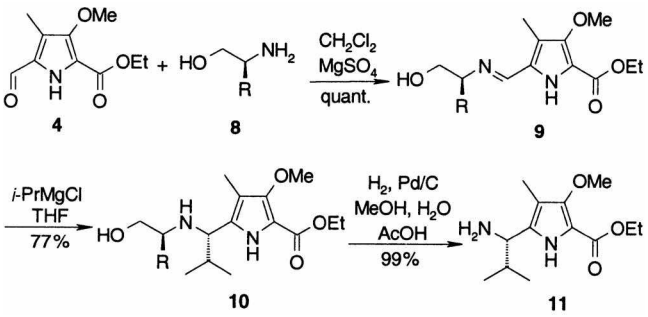


Scheme 3 Enantioselective synthesis of *i*-Pr-MOPAS **11**, R = *i*-Pr, Ph

Chiral HPLC analysis shows a diastereoselectivity of > 99:1 for the addition reaction and high optical purity of the final product. Figure 1 shows a likely mechanism of the 1,2-addition reaction. The imine alcohol is deprotonated by the first equivalent of added Grignard reagent. A six-membered chair-like conformation induced by coordination of the imine nitrogen lone pair to the magnesium alcoholate guides the second *i*-PrMgCl in its diastereoselective addition to the C=N bond. The mechanism proposes the formation of (*S*)-*i*-Pr MOPAS from imines of *S*-amino alcohols, which corresponds to the natural dipeptide sequence L-Val-Δ-Ala.

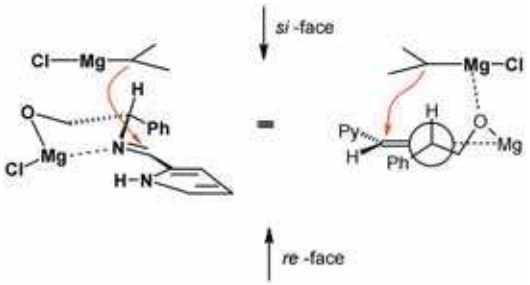


Figure 1 Proposed mechanism of the nucleophilic 1,2-addition to imine **9-Ph**

Dipeptide **14** was prepared from **11** and L-Boc-Phe-OH using standard peptide coupling conditions to confirm the predicted absolute stereochemistry. The X-ray structure analysis shows the expected *S*-configured *i*-Pr-MOPAS group (see Figure 2). Coupling of **11** with previously prepared **12** gave the constrained tetrapeptide mimic **13**.

In chloroform compound **13** shows a strong self-association of $5.2 \pm 3.7 \times 10^3$ L/mol.[15] Titration of **13** with the isomeric dipeptides Ac-Ala-Ile-OMe and Ac-Ile-Ala-OMe[16] was monitored by NMR and revealed a binding constants of $K_{11} = 293 \pm 35$ L/mol.[17]

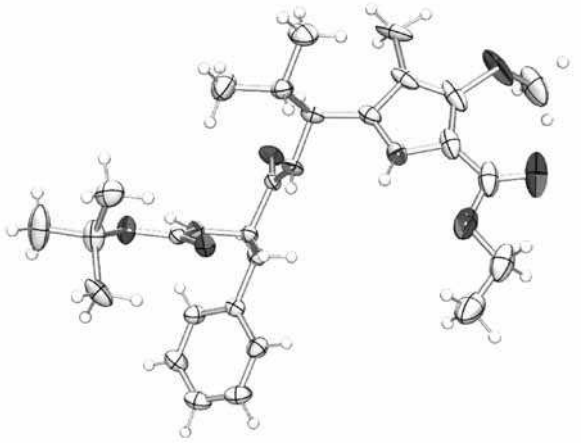
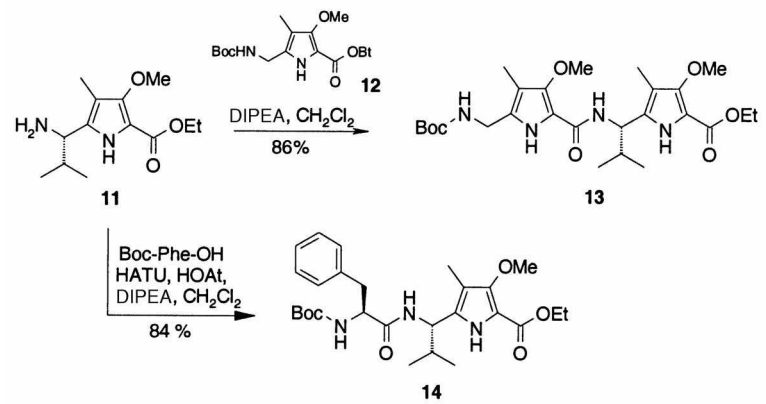


Figure 2 X-ray structure analysis of **14** confirming the proposed stereochemistry

In summary, we have prepared the constrained chiral dipeptide mimic **11**, which resembles the structure of H_2N-Val-Δ-Ala-OEt in β-sheet conformation. A chiral auxiliary controlled the stereochemistry during synthesis and an X-ray structure analysis confirms the structure of the final product. Standard peptide chemistry protocols allow coupling of **11** with natural amino acids or extension by additional MOPAS units. The tight self-association observed in chloroform for MOPAS **13** resembles a typical peptide β-sheet property. The binding, although rather weak, to Ac-Ile-Ala-OMe dipeptides illustrates the ability of *i*-Pr-MOPAS to interact with natural peptides. The constrained dipeptide mimic can replace amino acid residues in peptides or proteins in the investigation of structure–function relationships. The new MOPAS building block



Scheme 4 Synthesis of MOPAS dipeptides

allows issues of stereochemistry and amino acid side chain interactions in β-sheet recognition to be addressed.

NMR spectra: Bruker AC-250, Bruker Avance 300, and Bruker ARX-400. All chemical shifts δ (ppm) relative to TMS as internal standard. All assignment are based on COSY, HMQC, and HSQC spectra. Multiplicity of carbon resonances (+) = CH_3 or CH; (–) CH_2; and C_{quat} = quaternary carbon atom. Mass spectrometry: Varian CH-5 (EI), Finnigan MAT 95 (CI; FAB und FD) and Finnigan MAT TSQ 7000 (ESI). IR: Bio-Rad FT-IR FTS 155. Optical rotation: PE 241 Perkin-Elmer, Uvasol-grade solvents were used for measurements in a 10 cm cuvette at a wavelength of 589 nm. Melting points are not corrected. All solvents for synthesis were purified and dried before use by standard laboratory methods. Petroleum ether (PE) with a boiling range 60–70 °C was used.

Compounds ***R*-6**, **9-*i*-Pr**, **9-Ph**, and **14** were characterized by X-ray structure analysis. All bond length and distances are typical. Deposited data are available from the Cambridge Structural Database: CCDC 267442–267445.

Ethyl (*S*)-4-*tert*-Butoxycarbonylamino-3-ethoxycarbonylmethyliminopentanoate (2)

A mixture of keto ester (**1**; 1.27 g, 4.89 mmol) and glycine ethyl ester (504 mg, 4.89 mmol) was stirred for 14 h at 40 °C. The reaction mixture was dried under vacuum, the viscose residue was dissolved in Et_2O (20 mL), filtered, and the reaction product was precipitated, by the addition of PE, as a colorless solid. Recrystallization from PE–toluene gave 1.42 g (84%) of **2**.

$[\alpha]_D^{20}$ –5 (*c* 6.6, $CHCl_3$).

^{1}H NMR and ^{13}C NMR spectra cannot be assigned. The compound exists in solution as a mixture of tautomeric forms and *E*/*Z*-isomers.

MS (CI, NH_3): *m*/*z* (%) = 345.3 (100) [M + H^+].

Anal. Calcd for $C_{16}H_{28}N_2O_6$ (344.41): C, 55.80; H, 8.19; N, 8.13. Found: C, 56.22; H, 8.12; N, 8.02.

Ethyl 5-(*S*)-1-*tert*-Butoxycarbonylaminoethyl-3-hydroxy-1*H*-pyrrole-2-carboxylate (3)

To a solution of NaOEt [prepared from Na (67 mg, 2.9 mmol), anhyd EtOH (5 mL) under N_2] was added **3** (1 g). The reaction mixture was refluxed for 2.5 h, the solvent was removed under vacuum, the residue was dissolved in H_2O (2 mL), and neutralized by the addition of 1 N HCl. Only a trace amount (13 mg) of the desired compound was isolated.

MS (EI, 70 eV): *m*/*z* (%) = 298.2 (11) [$M^{+\cdot}$], 198.1 (97) [$M^{+\cdot}$ – $C_4H_8CO_2$], 125.0 (100) [$M^{+\cdot}$ –$C_4H_8CO_2C_2H_5CO_2$].

HRMS: *m*/*z* calcd for $C_{14}H_{22}N_2O_5$ [$M^{+\cdot}$], 298.15287; found, 298.15280.

Schiff Bases from 4 and Chiral Primary Amines; General Procedure

To a solution of **4** (0.25 M) and amine (1 equiv) in CH_2Cl_2 was added $MgSO_4$ (250 mg/mmol **4**), and the reaction mixture was stirred overnight. Evaporating the filtered solution under vacuum yielded the crude product.

Ethyl 4-Methyl-3-methoxy-5-[(D-phenylglycineamidimino)methyl]-1*H*-pyrrole-2-carboxylate (*R*-6)

Compound **4** (100 mg, 473 μmol) and D-phenylglycine amide (71.1 mg, 473 μmol) were reacted according to the general procedure to give ***R*-6** (133 mg, 82%), which was recrystallized from acetone.

Mp (dec) > 158 °C; $[\alpha]_D^{20}$ +187 (*c* 1.5, $CHCl_3$).

IR (KBr): 3413 (m), 3294 (m), 2979 (m), 2933 (m), 2873 (sh), 1682 (s), 1564 (m), 1511 (m), 1473 (m), 1369 (w), 1275 (s), 1121 (w), 1028 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, ^3J = 7.14 Hz, 3 H), 2.11 (s, 3 H), 3.86 (s, 3 H), 4.39 (q, ^3J = 7.14 Hz, 2 H), 4.94 (s, 1 H), 5.56 (br s, 1 H), 6.85 (br s, 1 H), 7.27–7.48 (m, 5 H), 8.14 (s, 1 H), 9.26 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.9 (+), 14.4 (+), 60.8 (–), 62.4 (+), 77.2 (+), 114.7 (C_{quat}), 118.0 (C_{quat}), 127.3 (+), 128.1 (+, 2 C), 128.8 (+, 2 C), 139.2 (C_{quat}), 150.7 (C_{quat}), 151.3 (+,), 160.5 (C_{quat}), 174.2 (C_{quat}, 2 C).

MS [ESI, CH_2Cl_2–MeOH, NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 343.9 (100) [M + H^+], 365.9 (12) [M + Na^+], 709.4 (13) [2 M + Na^+].

Anal. Calcd for $C_{18}H_{21}N_3O_4$ (343.38): C, 62.96; H, 6.16; N, 12.29. Found: C, 62.61; H, 5.92; N, 11.83.

Ethyl 5-{1-[(Carbamoylphenylmethyl)amino]but-3-enyl}-3-methoxy-4-methyl-1*H*-pyrrole-2-carboxylate (7)

To a suspension of granulated Zn (17.5 mg, 268 μmol) in anhyd THF (2 mL) was added allylbromide (23.3 μL, 268 μmol) and the mixture was stirred for 6 h until all Zn had dissolved. Subsequently, this solution of allylzinc bromide was transferred into a solution of **6** (61.4 mg, 179 μmol, non-enantiomerically enriched) in THF (1 mL) at 0 °C and allowed to warm to r.t.; H_2O (2 mL) and EtOAc (5 mL) were added, the mixture was filtered, and the organic phase extracted with EtOAc (2 × 5 mL). The combined organic phases were dried over $MgSO_4$, the solvent was removed under vacuum and the crude product recrystallized from EtOAc–PE to give **3** (29.2 mg, 42%) as a colorless solid.

Mp 126–128 °C.

IR (KBr): 3439 (m), 3319 (m), 3192 (m), 2983 (w), 2933 (w), 1675 (s), 1663 (s), 1513 (w), 1470 (m), 1447 (m), 1274 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (dd, ^3J = 7.11, 7.14 Hz, 3 H, 1-H), 1.89 (s, 3 H, 8-H), 2.44 (ddt, ^3J = 7.07, 7.05, 1.15 Hz, 2 H, 11-H), 2.58 (br s, 1 H), 3.83 (t, ^3J = 7.05 Hz, 1 H, 10-H), 3.84 (s, 3 H, 6-H) 3.99 (s, 1 H, 14-H), 4.25 (dq, ^2J = 10.75, ^3J = 7.11 Hz, 1 H, 2-$H_{a/b}$), 4.28 (dq, ^2J = 10.75, ^3J = 7.14 Hz, 1 H, 2-$H_{b/a}$), 5.10 (ddt, ^3J = 10.11, ^2J = 1.82, ^4J = 1.15 Hz, 1 H, 13-H_E), 5.11 (ddt, ^3J = 17.04, ^2J = 1.82, ^4J = 1.15 Hz, 1 H, 13-H_Z), 5.74 (ddt, ^3J = 17.04, 10.11, 7.07 Hz, 1 H, 12-H), 5.92 (br s, 1 H), 6.29 (br s, 1 H), 7.15–7.31 (m, 5 H, 16–20-H), 8.97 (br s, 1 H, 4-NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.1 (+), 14.5 (+), 40.5 (–), 53.8 (+), 59.9 (–), 62.2 (+), 64.7 (+), 109.7 (C_{quat}), 110.5 (C_{quat}), 118.3 (–), 127.3 (+, 2 C), 128.2 (+), 128.9 (+, 2 C), 133.0 (C_{quat}), 134.2 (+), 139.0 (C_{quat}), 151.2 (C_{quat}), 160.4 (C_{quat}), 174.8 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH, NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 408.0 (11) [M + Na^+], 386.0 (29), [M + H^+], 235.8 (100) [M + H^+ – $C_8H_7N_2O$].

Anal. Calcd for $C_{15}H_{17}N_1O_3$ (385.47): C, 65.44; H, 7.06; N, 10.90. Found: C, 65.21; H, 6.98; N, 10.87.

Ethly 4-Methyl-3-methoxy-5-[(L-valinolimino)methyl]-1*H*-pyrrole-2-carboxylate (*S*-9-*i*-Pr)

Compound **4** (100 mg, 473 μmol) and L-valinol (48.8 mg, 473 μmol) were allowed to react according to the general procedure to give ***S*-9-*i*-Pr** (138 mg, 99%).

Mp 105.5–106 °C; $[\alpha]_D^{20}$ +151 (*c* 2.85, $CHCl_3$).

IR (KBr): 3196 (s), 3980 (s), 2867 (sh), 1715 (s), 1628 (s), 1566 (s), 1471 (s), 1380 (s), 1283 (s), 1111 (s) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.84 (d, ^3J = 6.86 Hz, 3 H), 0.86 (d, ^3J = 6.86 Hz, 3 H), 1.29 (t, ^3J = 7.00 Hz, 3 H), 1.85 (dsept, ^3J = 5.37, 6.86 Hz, 1 H), 2.12 (s, 3 H), 2.80 (ddd, ^3J = 4.12, 8.10,

5.37 Hz, 1 H), 3.38 (dd, ^2J = 10.57, ^3J = 8.10 Hz, 1 H), 3.59 (dd, ^2J = 10.57, ^3J = 4.12, 1 H), 3.74 (s, 3 H), 4.25 (q, ^3J = 7.00 Hz, 2 H), 4.46 (br s, 1 H), 8.15 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.6 (+), 13.5 (+), 17.9 (+), 18.5 (+), 29.7 (+), 59.3 (–), 61.2 (+), 63.5 (–), 76.2 (+), 77.7 (+), 112.9 (C_{quat}), 117.0 (C_{quat}), 124.6 (C_{quat}), 149.3 (C_{quat}), 150.7 (+), 158.9 (C_{quat}).

MS (CI, NH_3): *m*/*z* (%) = 297 (100) [M + H^+].

Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.70; H, 7.71; N, 9.33.

Ethyl 4-Methyl-3-methoxy-5-[(L-phenylglycinolimino)methyl]-1*H*-pyrrole-2-carboxylate (*S*-9-Ph)

Compound **4** (1.03 g, 4.90 mmol) and L-phenylglycinole (672 mg, 4.90 mmol) were allowed to react according to the general procedure to give ***S*-9-Ph** in quantitative yield.

Mp 88–90 °C; $[\alpha]_D^{20}$ –129 (*c* 2.0, $CHCl_3$).

IR (KBr): 3240 (s), 2980 (s), 2933 (s), 2870 (sh), 1710 (s), 1630 (s), 1564 (s), 1510 (s), 1474 (s), 1381 (s), 1163 (s), 1028 (s) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.30 (t, ^3J = 7.14 Hz, 3 H), 2.19 (s, 3 H), 3.58 (m, 2 H), 7.75 (s, 3 H), 4.22 (m, 1 H), 4.26 (q, ^3J = 7.14 Hz, 2 H), 4.88 (br s, 1 H), 7.16–7.52 (m, 5 H), 8.30 (s, 1 H), 11.49 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 8.1 (+), 14.2 (+), 59.5 (–), 61.6 (+), 66.8 (–), 76.9 (+), 112.1 (C_{quat}), 113.7 (C_{quat}), 126.8 (+), 127.1 (+, 2 C), 127.8 (C_{quat}), 128.1 (+, 2 C), 141.7 (C_{quat}), 150.7 (C_{quat}), 152.5 (+), 159.3 (C_{quat}).

MS (CI, NH_3): *m*/*z* (%) = 331.2 (100) [M + H^+], 211.1 (11) [144 + H^+].

Anal. Calcd for $C_{18}H_{22}N_2O_4$ (330.39): C, 65.44; H, 6.71; N, 8.48. Found: C, 65.23; H, 6.52; N, 8.45.

Ethyl 5-{(*S*)-1-[(*S*)-2-Hydroxy-1-phenylethylamino]-2-methylpropyl}-3-methoxy-4-methyl-1*H*-pyrrole-2-carboxylate (*S*,*S*-10-Ph)

A solution of ***S*-9-Ph** (59.8 mg, 181 μmol) in THF (2 mL) was cooled to –5 °C and *i*-PrMgCl (400 μL, 2 M in Et_2O) was added via cannula. The reaction mixture was stirred for 1.5 h at 0 to –5 °C (a blue color slowly developed), and subsequently was allowed to warm to r.t. and then stirred overnight. Aq NH_4Cl (1 mL) and 1 N HCl (1 mL) were added to quench the reaction. The solution was diluted with EtOAc (2 mL) and aq 1 N NaOH was added until pH > 13. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 2 mL), the combined organic phases were dried over $MgSO_4$ and the solvent removed under vacuum to give 69 mg of the crude product, which was purified by column chromatography (SiO_2, $CHCl_3$–EtOAc, 80:20→50:50) to give ***S*,*S*-10-Ph** (52.4 mg, 77%) as a colorless oil.

$[\alpha]_D^{20}$ –71 (*c* 2.9, MeCN); R_f 0.46 ($CHCl_3$–EtOAc, 50:50).

IR (neat): 3458 (s), 3323 (s), 2960 (s), 2933 (sh), 2871 (sh), 1675 (s), 1463 (s), 1270 (s) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.64 (d, ^3J = 6.50 Hz, 3 H, 12-H or 13-H), 1.02 (d, 6.50 Hz, 3 H, 13-H or 12-H), 1.26 (t, ^3J = 7.15 Hz, 3 H, 1-H), 1.70 (s, 3 H, 8-H), 1.92 (dsept, ^3J = 8.31, 6.50 Hz , 1 H, 11-H), 2.56 (br s, 1 H, 10-NH or 21-OH), 3.37 (d, ^3J = 8.31 Hz, 1 H, 10-H), 3.46 (m, 2 H, 21-H), 3.49 (m, 1 H, 14-H), 3.64 (s, 3 H, 6-H), 4.18 (q, ^3J = 7.15 Hz, 2 H,), 4.59 (br s, 1 H, 21-OH or 10-NH), 7.09–7.21 (m, 5 H, 16–20-H), 10.37 (br s, 1 H, 4-NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.1 (1 C, 8-C), 14.4 (1 C, 1-C), 19.3 (1 C, 12-C or 13-C), 20.4 (1 C, 13-C or 12-C), 32.8 (1 C, 11-C), 58.7 (1 C, 2-C), 59.3 (1 C, 10-C), 61.2 (1 C, 6-C), 63.0 (1 C, 14-C), 65.6 (1 C, 21-C), 108.4 (1 C, 4-C), 109.1 (1 C, 7-C), 126.4 (1 C, 18-C), 127.2 (2 C, 16-C, 20-C or 17-C, 19-C), 127.5 (2 C, 17-C, 19-C or 16-C, 20-C), 135.3 (1 C, 9-C), 142.9 (1 C, 15-C), 150.3 (1 C, 5-C), 159.5 (1 C, 3-C).

MS [ESI, CH_2Cl_2–MeOH, NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 375 (100) [M + H^+], 238 (36) [M + H^+ –$C_8H_{11}NO$].

HRMS: *m*/*z* calcd for $C_{21}H_{30}N_2O_4$, 374.2206 [$M^{+\cdot}$]; found, 374.2209.

Ethyl 5-[(*S*)-1-Amino-2-methylpropyl)]-3-methoxy-4-methyl-1*H*-pyrrole-2-carboxylate [H-(S)-*i*-PrMOPAS-OEt (*S*-11)]

To a solution of ***S*,*S*-10-Ph** (645 mg, 1.72 mmol) in MeOH–H_2O–AcOH (10 mL; 20:2:1), Pd/C (10%, 60 mg) was added and the reaction mixture was stirred for 48 h under H_2 (1 MPa). The mixture was filtered through celite, the solvent was removed under vacuum, the residue was dissolved in EtOAc (50 mL), and extracted with aq $KHSO_4$ (5%; 5 × 10 mL). The pH of the combined aqueous phases were adjusted to >12 by addition of 2 N NaOH and then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under vacuum to give ***S*-11** (433 mg, 99%) as a colorless oil.

$[\alpha]_D^{20}$ +33 (*c* 3.7, $CHCl_3$).

IR (neat): 3348 (s), 2964 (s), 2937 (sh), 2871 (sh), 1683 (s), 1513 (w), 1470 (s), 1274 (s) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.68 (d, ^3J = 6.68 Hz, 3 H), 0.91 (d, ^3J = 6.68 Hz, 3 H), 1.27 (t, ^3J = 7.00 Hz, 3 H), 1.76 (dsept, ^3J = 7.72, 6.68 Hz, 1 H), 1.84 (s, 3 H), 3.42 (d, *J* = 7.72 Hz, 1 H), 3.71 (s, 3 H), 4.20 (q, ^3J = 7.00 Hz, 2 H), 10.56 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 7.3 (+), 14.4 (+), 19.3 (+), 19.5 (+), 33.1 (+), 54.1 (+), 58.7 (–), 61.3 (+), 107.4 (C_{quat}), 108.0 (C_{quat}), 137.7 (C_{quat}), 150.6 (C_{quat}), 159.5 (C_{quat}).

HRMS: *m*/*z* calcd for $C_{13}H_{22}N_2O_3$ [$M^{+\cdot}$], 254.1630; found, 254.1633.

Anal. Calcd for $C_{13}H_{22}N_2O_3$ (254.22): C, 61.39; H, 8.72; N, 11.01. Found: C, 60.59; H, 8.32; N, 10.51.

Boc-MOPAS-(*S*)-*i*-PrMOPAS-OEt (*S*-13)

A solution of ***S*-11** (100 mg, 393 μmol), Boc-MOPAS-OBt (158 mg, 393 μmol), and *i*-Pr_2EtN (82.0 μL, 60.7 mg, 469 μmol) in CH_2Cl_2 (5 mL) was stirred for 2 h at r.t. The solution was diluted with CH_2Cl_2 (3 mL), extracted with aq $KHSO_4$ (5 × 3 mL), aq $NaHCO_3$ (4 × 3 mL), and H_2O (3 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum to yield 210 mg of the crude product, which was recrystallized from $CHCl_3$–PE (60:40) to give 176 mg (86%) of ***S*-13** as a colorless solid.

Mp 91–93 °C; $[\alpha]_D^{20}$ +34 (*c* 2.1, $CHCl_3$).

IR (KBr): 3385 (s), 3296 (s), 2972 (m), 2933 (sh), 2875 (sh), 1663 (s), 1640 (s), 1532 (s), 1459 (m) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.88 (m, 3 H), 1.42 (m, 3 H), 1.32–1.54 (m, 12 H), 2.10 (s, 3 H), 2.12–2.22 (m, 4 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.28 (m, 2 H), 4.37 (m, 2 H), 5.54 (m, 1 H), 5.60 (m, 1 H), 7.56 (m, 1 H), 10.79 (br s, 1 H), 11.47 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 7.8 (+), 8.1 (+), 14.4 (+), 19.8 (+), 20.0 (+), 28.4 (+), 34.0 (+), 35.5 (–), 53.4 (+), 60.4 (–), 61.4 (+), 62.4 (+), 79.2 (C_{quat}), 108.1 (C_{quat}), 108.7 (C_{quat}), 112.4 (C_{quat}), 128.4 (C_{quat}), 134.5 (C_{quat}), 146.9 (C_{quat}), 152.4 (C_{quat}), 155.6 (C_{quat}), 160.3 (C_{quat}), 162.3 (C_{quat}).

HRMS: *m*/*z* calcd for $C_{26}H_{40}N_4O_7$ [$M^{+\cdot}$], 520.2897; found, 520.2895.

Anal. Calcd for $C_{26}H_{40}N_4O_7$: C, 59.98; H, 7.74; N, 10.76. Found: C, 59.31; H, 7.67; N, 10.45.

Boc-Phe-(*S*)-*i*-PrMOPAS-OEt (*S*,*S*-14)

A mixture of ***S*-11** (22.0 mg, 86.5 μmol), *S*-Boc-Phe-OH (22.9 mg, 86.5 μmol), HATU (32.9 mg, 86.5 μmol), HOAt (11.8 mg, 86.5 μmol), and *i*-Pr_2NH (14.7 μL, 11.2 mg, 86.5 μmol) in CH_2Cl_2 (3 mL) was stirred for 6 h at r.t. The reaction mixture was diluted with of CH_2Cl_2 (10 mL), washed with aq $KHSO_4$ (5%, 5 × 10 mL), aq $NaHCO_3$ (0.5 M; 3 × 10 mL), the organic phase was dried over $MgSO_4$, and the solvent was removed under vacuum. The crude product was recrystallized from EtOAc–PE to give ***S*,*S*-14** (36.3 mg, 84%) as a colorless solid.

Mp 159.5–161 °C; $[\alpha]_D^{20}$ –90 (*c* 2.2, MeCN).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.69 (m, 3 H), 0.84 (m, 3 H), 1.18–1.46 (m, 12 H), 1.88 (s, 3 H), 1.89–2.06 (m, 1 H), 2.97 (m, 2 H), 3.81 (s, 3 H), 4.15–4.39 (m, 3 H), 4.62 (m, 1 H), 5.29 (m, 1 H), 6.63 (m, 1 H), 6.96–7.17 (m, 5 H), 9.12 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.4 (+), 14.6 (+), 19.2 (+), 19.4 (+), 28.3 (+, 3 C), 32.4 (+), 38.1 (–), 52.6 (+), 56.5 (+), 60.1 (–), 62.2 (+), 80.3 (C_{quat}), 109.7 (C_{quat}), 110.2 (C_{quat}), 126.9 (+), 128.6 (+, 2 C), 129.1 (+, 2 C), 132.1 (C_{quat}), 136.4 (C_{quat}), 151.2 (C_{quat}), 155.7 (C_{quat}), 160.8 (C_{quat}), 171.0 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH, NH_4Ac (10 mmol/L]: *m*/*z* (%) = 502 (100) [M + H^+], 446 (12) [M + H^+ –C_4H_8].

Anal. Calcd for $C_{27}H_{39}N_3O_6$ (501.62): C, 64.65; H, 7.84; N, 8.38. Found: C, 64.39; H, 7.27; N, 8.12.

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