Synthesis of 3-Oxo-2,3-dihydropyrrole Amino Acids as Chiral Dipeptidomimics

Prantik Maity, Burkhard König*

Institut für Organische Chemie, Universität Regensburg, 93040 Regensburg, Germany
Fax +49(941)9431717; E-mail: Burkhard.koenig@chemie.uni-regensburg.de

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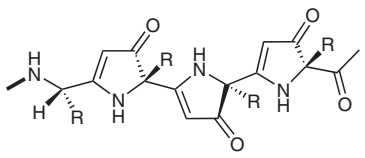
Abstract: We describe the synthesis of a novel chiral dipeptide β-sheet mimic based on aminomethyl-3-oxo-2,3-dihydropyrrole carboxylic acids. The synthesis uses a palladium-catalyzed allylation with the chiral Trost ligand as a key step for the construction of a quaternary chiral center. This allows the enantioselective conversion of 2-carboxy-3-hydroxy-pyrrole into 3-oxo-2,3-dihydropyrrole-2-allyl-2-carboxylate. The allyl group is subsequently converted into an aldehyde or ester group. Peptide coupling of the 3-oxo-2,3-dihydropyrrole amino acid leads to more extended systems with partially constrained dipeptide units.

Key words: pyrroles, 3-oxo-2,3-dihydropyrrole, allylations, amino acids, catalysis, palladium

A peptidomimic imitates peptide structures by controlled spatial disposition of functional groups and by exhibiting a generally analogous structure. Previously reported peptide mimics based on oligo-3-oxo-2,3-dihydropyrroles have been used as a protease inhibitor and ligand for hormone and protein receptors.[1] Their chiral sequence can adopt the bioactive conformation of peptide ligands while exhibiting good pharmacokinetic properties.[2] Smith and Hirschmann[3] first prepared 2,5-linked 3-oxo-2,3-dihydropyrroles **1** starting from chiral natural amino acids (Figure 1). Seebach et al.[4] have prepared α-substituted proline derivatives while retaining the chirality, which was further developed into β-turn peptide mimics **2** by Gmeiner et al.[5] We have recently reported methoxypyrrole amino acids (MOPAS), which mimic the structure of a H_2N-Gly-Δ-Ala-OEt unit with β-sheet conformation.[6] Extending this, we report here the synthesis of 2-allyl-2,3-dihydro-3-oxopyrrole amino acids by stereoselective chiral allylation using the Trost ligand[7] as the chiral control element.



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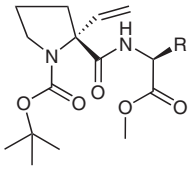

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Figure 1 Structures of 2,5-linked 3-oxo-2,3-dihydropyrroles **1** and β-turn peptide mimics **2**.

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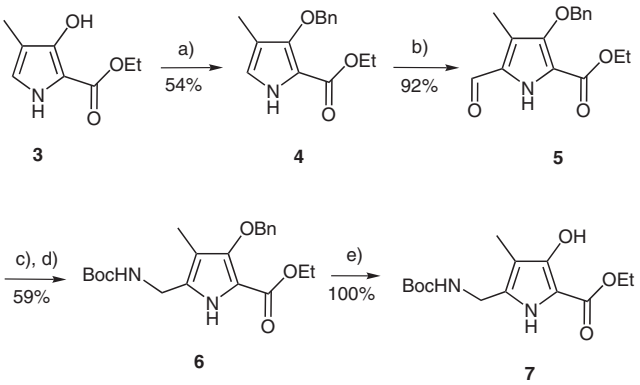
First, we prepared 3-hydroxypyrrole amino acids (HOPAS) **7** as the starting materials for the asymmetric synthesis of chiral 3-oxo-2,3-dihydropyrrole amino acids such as **8** (Scheme 1). The hydroxyl group of pyrrole **3**[8] was benzyl protected, formylated at the 5-position, converted into Boc-protected amino ester **6**, and debenzylated to give **7**.



Scheme 1 Synthesis of HOPAS **7**. *Reagents and conditions*: a) BnCl, K_2CO_3, in DMF, 85 °C, 16 h; b) $POCl_3$, DMF, DCE, reflux, 2.5 h; c) NH_2Boc, HCOOH, *p*-TsONa, THF–H_2O, r.t., 3 d; d) $NaBH_4$, THF, r.t., 2 h; e) Pd/C, H_2, MeOH, r.t., 1 d.

The basic hydrolysis of 2-ethyl-3-hydroxypyrrole carboxylates is known to be difficult. In basic media the compound exists in its two tautomeric forms (Figure 2).[9] Using this property we intended to introduce an allyl group at C-2 in a stereoselective manner via Pd-catalyzed allylation using the chiral Trost ligand.[10,11] The allylated 3-oxo-2,3-dihydropyrrole amino acid **8** was obtained, but the yield (35%) and the enantiomeric excess (28%) of the reaction were unsatisfactory (Scheme 2).

During the alkylation reaction the thermodynamically unfavorable loss of aromaticity occurs, which may explain the difficulties. Introduction of an electron-withdrawing group onto the pyrrole nitrogen, which reduces the availability of the lone pair,[12] may improve the situation.

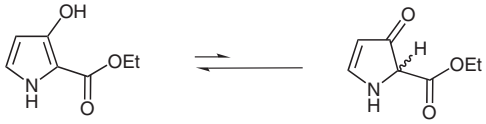
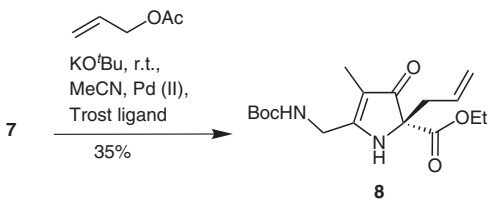
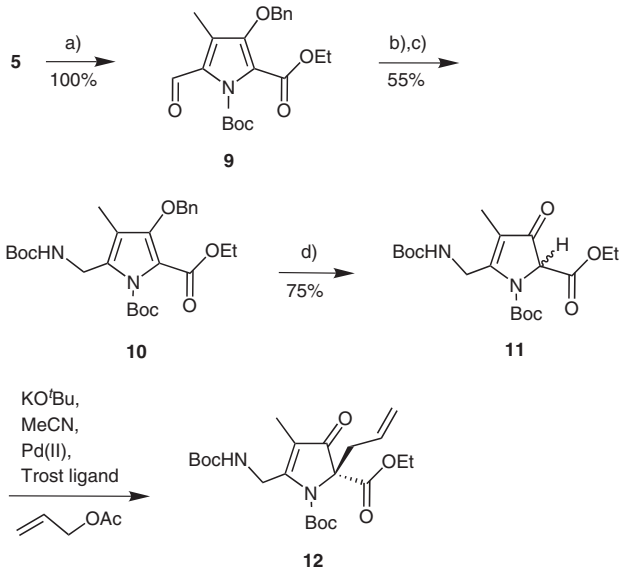


Figure 2 Tautomers of 2-ethyl-3-hydroxypyrrolecarboxylate.



Scheme 2 Synthesis of allylated 3-oxo-2,3-dihydropyrrole amino acid **8**.

Therefore, *N*-Boc protected pyrrole **10** was prepared starting from **5** (Scheme 3). The ^{1}H NMR spectrum of 3-hydroxypyrrole **11** in $CDCl_3$ reveals the presence of the keto tautomer as the only isomer, which indicates the reduced heteroaromatic character of the pyrrole ring.



Scheme 3 Synthesis of Boc-protected pyrrole **10** and its asymmetric allylic alkylation to 3-oxo-2,3-dihydropyrrole amino acid **12**. *Reagents and conditions*: a) Boc_2O, DMAP, CH_2Cl_2, r.t., 2 h; b) NH_2Boc, HCOOH, *p*-TsONa, THF–H_2O, r.t., 2 d; c) $NaBH_4$, THF, r.t., 2 h; d) Pd/C, H_2, MeOH–$CHCl_3$ (8:1).

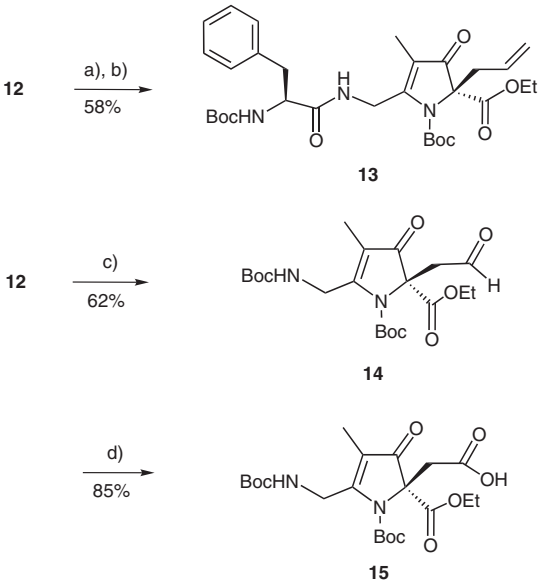
The reaction of 3-oxo-2,3-dihydropyrrole **11** with allyl acetate in the presence allyl palladium(II) chloride as catalyst and the chiral Trost ligand gave the desired compound in good yield (Table 1). An ee of 68% was observed at 0 °C with *t*-BuOK as base in MeCN. A decrease of the reaction temperature to –35 °C increased the optical purity of the isolated product to 71% ee with a chemical yield of 87%. Compound **12** was fully characterized by spectroscopic methods. The transition state model for the formation of the quaternary centre predicts an '*R*' configuration if the *R*,*R* stereoisomer of the Trost ligand is used.[12] This is supported by the optical rotation of **12**, $[\alpha]^D$ +143.8, which corresponds to $[\alpha]^D$ +22.0 reported for the structurally related compound (*R*)-2,4-dibenzyl-2-(3-methylbut-2-enyl)-1,2-dihydropyrrole-3-one.[1]

Table 1 Yield and Optical Purity of Compound **12** under Different Reaction Conditions

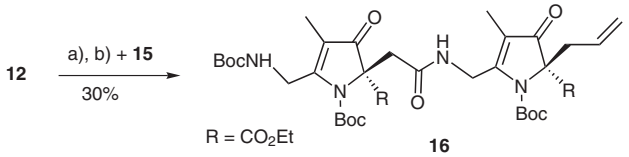
Base	Solvent	Time (h)	Temp (°C)	Yield (%)	ee (%)[a]
t-BuOK	MeCN	2	0	83	68
t-BuOK	MeCN	2.5	–22	87	71
NaH	THF	0.16	r.t.	90	17
NaH	THF	6	–15 to 0	95	31
n-BuLi	THF	1.5	–78	80	9

[a] Optical purity was determined by chiral HPLC analysis.

To demonstrate the ability of compound **12** to be incorporated into peptide chains, the Boc protecting group of the primary amine was removed selectively using HCl in Et_2O. The amine was coupled using standard peptide coupling conditions with Boc-Phe-OH giving tripeptide **13** in 58% yield (Scheme 4). The allyl group of **12** allows the introduction of additional functional groups if desired; conversion to aldehyde **14** was effected using K_2OsO_4 and $NaIO_4$ in THF and H_2O.[13] The aldehyde was converted into the corresponding acid **15** using $NaClO_2$, NaH_2PO_4, and H_2O_2 in MeCN and H_2O.[14] Compound **15** resembles the structure of a partially constrained dipeptide of glycine and a β-amino acid. Acid **15** was coupled using standard peptide coupling conditions with Boc-deprotected compound **12** to give the tetrapeptide structure **16**[15] in 30% yield (Scheme 5).



Scheme 4 Synthesis of tripeptide **13**. *Reagents and conditions*: a) HCl, Et_2O; b) EDC, HOBt, DIPEA CH_2Cl_2, r.t.; c) K_2OsO_4, $NaIO_4$, THF–H_2O; d) $NaClO_2$, NaH_2PO_4, H_2O_2, MeCN–H_2O (4:1), r.t.



Scheme 5 Synthesis of compound **16**. *Reagents and conditions*: a) HCl, Et_2O; b) EDC, HOBt, DIPEA, CH_2Cl_2, r.t.

We have used the enantioselective Pd-catalyzed allylic alkylation with the Trost ligand to convert *N*-Boc protected 3-hydroxypyrrole **11** into 3-oxo-2,3-dihydropyrrole amino acid **12** breaking the heteroaromatic π-system. With *t*-BuOK as base and at low reaction temperatures an ee of 71% with a chemical yield of 87% was obtained. 3-Oxo-2,3-dihydropyrrole amino acid **12** resembles the structure of a partially constrained dipeptide, which may find use in the synthesis of more extended peptide mimics.

Melting points are uncorrected. Specific rotations were measured on a polarimeter using a 10 cm cell. NMR spectra were recorded in $CDCl_3$ at 300 MHz (^{1}H) or 75 MHz (^{13}C) unless stated otherwise. Structural assignments are based on DEPT and COSY experiments where applicable. The multiplicity of the carbon atoms is given as (+) = CH_3 or CH, (–) = CH_2 and (C_{quat}) for quaternary carbon atoms. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70–230 or 230–400 mesh) for column chromatography (CC) were purchased from Merck. Spots were visualized by UV light and/or staining with phosphomolybdate or ninhydrine in EtOH. DMF, MeCN, THF, and Et_2O were dried by standard procedures and stored over molecular sieves or Na. PE had a boiling range of 70–90 °C. All other solvents and chemicals were of reagent grade and used without further purification. The Trost ligand was prepared as described in the literature.[7,16]

Ethyl 3-Benzyloxy-4-methyl-1*H*-pyrrole-2-carboxylate (4)

To a stirred solution of hydroxypyrrole **3** (12 g, 70.9 mmol) in anhyd DMF, K_2CO_3 (9.8 g, 71 mmol) was added followed by BnCl (8.98 g, 70.9 mmol). The suspension was stirred for 14 h at 70 °C and then for 4 h at 110 °C. Then BnCl (820 mg, 6.47 mmol) was added and the solution was heated for 1 h at the same temperature. The reaction mixture was allowed to cool to r.t. and poured into H_2O (1 L). The aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with a 10% aq solution of Na_2CO_3 (100 mL), H_2O (2 × 100 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to give an oily product, which was solidified by addition of PE. The solid was recrystallized from MeOH.

Yield: 9.93 g (54%); mp 78–83 °C.

IR (KBr): 3298, 2974, 2862, 1660, 1466, 1411, 1288 cm^{-1}.

^{1}H NMR: δ = 1.35 (t, *J* = 7.14 Hz, 3 H), 1.91 (s, 3 H), 4.35 (q, *J* = 7.14 Hz, 2 H), 5.07 (s, 2 H), 6.57 (m, 1 H), 7.27–7.50 (m, 5 H), 8.45 (br s, 1 H).

^{13}C NMR: δ = 8.3 (+), 14.3 (+), 59.0 (–), 75.4 (–), 110.5 (C_{quat}), 111.4 (C_{quat}), 120.3 (+), 127.7 (+), 128.0 (+), 128.0 (+), 137.7 (C_{quat}), 149.1 (C_{quat}), 159.6 (C_{quat}).

MS (70 eV): *m*/*z* (%) = 259 (48) [M$^+$], 186 (14) [M$^+$ – $C_3H_5O_2$], 91 (100) [$C_7H_7^+$].

Anal. Calcd for $C_{15}H_{17}NO_3$ (259.31): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.26; H, 6.27; N, 5.34.

Ethyl 3-Benzyloxy-5-formyl-4-methyl-1*H*-pyrrole-2-carboxylate (5)

A solution of compound **4** (7.43 g, 28.7 mmol) in DCE (75 mL) was added dropwise to an ice-cold solution of DMF (2.3 g, 31.5 mmol) in DCE (75 mL) containing $POCl_3$ (4.83 g, 31.5 mmol). After stirring at r.t. for 1 h the mixture was heated to reflux for 2 h, then cooled to r.t. EtOAc (50 mL) and H_2O (100 mL) were added and the organic layer was separated. The aqueous layer was washed with EtOAc (2 × 100 mL), the combined organic layers were washed with a 10% aq solution of $NaCO_3$ (5 × 150 mL), and dried over $MgSO_4$. The solvent was evaporated to give 7.85 g of the crude product, which was purified by CC (PE–EtOAc, 70: 30).

Yield: 7.60 g (92%); mp 81–83 °C; R_f 0.43.

IR (KBr): 3258, 2938, 2817, 169, 1672, 1555, 1507, 1487, 1377, 1280 cm^{-1}.

^{1}H NMR: δ = 1.38 (t, *J* = 7.14 Hz, 3 H), 2.12 (s, 3 H), 4.38 (q, *J* = 7.14 Hz, 2 H), 5.06 (s, 2 H), 7.30–7.47 (m, 5 H), 9.25 (br s, 1 H), 9.71 (br s, 1 H).

^{13}C NMR: δ = 6.8 (+), 14.4 (+), 61.2 (–), 77.1 (–), 117.8 (C_{quat}), 123.1 (C_{quat}), 127.7 (C_{quat}), 128.3 (+), 128.5 (+), 128.5 (+), 137.0 (C_{quat}), 148.7 (C_{quat}), 159.6 (C_{quat}), 179.1 (+).

MS (70 eV): *m*/*z* (%) = 287 (22) [M$^+$], 91 (100) [$C_7H_7^+$].

Anal. Calcd for $C_{16}H_{17}NO_4$ (287.32): C, 66.89; H, 5.96; N, 4.88. Found: C, 66.79; H, 5.95; N, 4.87.

Ethyl 3-Benzyloxy-5-(*tert*-butoxycarbonylaminomethyl)-4-methyl-1*H*-pyrrole-2-carboxylate (6)

A mixture of NH_2Boc (554 mg, 4.73 mmol), THF (1.9 mL), H_2O (2 mL), sodium *p*-toluene sulfinate (843 mg, 4.73 mmol), aldehyde **5** (1 g, 4.73 mmol), and HCOOH (1.18 mL) was stirred until the mixture became homogeneous and stirring was continued for 6 d at r.t. The solid product was suction filtered, washed successively with H_2O and PE, then dried over P_2O_5 to give 2.02 g of the tosylated intermediate, which was used in the next step without further purification. The intermediate (522 mg) was added portionwise to a suspension of $NaBH_4$ (72 mg, 1.92 mmol) in THF (5 mL), while the mixture was ice cooled. Stirring was continued for 15 min with ice cooling and then at r.t. for 2 h. The mixture was ice cooled again, quenched with a sat. solution of aq NH_4Cl (1 mL), and stirring was continued for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (15 mL), the combined layers were dried over $MgSO_4$, and concentrated. The crude product was purified by CC ($CHCl_3$–acetone, 95:5→90:10) to give 232 mg (59%) of compound **6**.

Yield: 232 mg (59%); mp 112.5–113 °C; R_f 0.68 ($CHCl_3$–acetone, 90:10).

IR (KBr): 3357, 3282, 2980, 2934, 1687, 1665, 1531, 1461, 1294, 1171, 1027 cm^{-1}.

^{1}H NMR: δ = 1.34 (t, *J* = 7.14 Hz, 3 H), 1.46 (s, 9 H), 1.86 (s, 3 H), 4.16 (m, 2 H), 4.32 (q, *J* = 7.14 Hz, 2 H), 4.98 (br s, 1 H), 5.04 (s, 2 H), 7.27–7.49 (m, 5 H), 9.08 (br s, 1 H).

^{13}C NMR: δ = 7.2 (+), 14.5 (+), 28.4 (+), 35.9 (–), 60.1 (–), 76.7 (–), 80.1 (C_{quat}), 110.4 (C_{quat}), 110.7 (C_{quat}), 127.9 (+), 128.2 (+), 128.3 (+), 129.5 (C_{quat}), 137.8 (C_{quat}), 149.7 (C_{quat}), 156.6 (C_{quat}), 160.4 (C_{quat}).

Anal. Calcd for $C_{21}H_{28}N_2O_5$ (388.47): C, 64.93; H, 7.27; N, 7.21. Found: C, 64.74; H, 7.64; N, 7.00.

Ethyl 5-(*tert*-Butoxycarbonylaminomethyl)-3-hydroxy-4-methyl-1*H*-pyrrole-2-carboxylate (7)

To a solution of compound **6** (100 mg, 257 μmol) in EtOAc (3 mL), 10% Pd/C (10 mg) was added and the mixture was transferred to an autoclave. The mixture was stirred for 48 h under H_2 (10 bar) at r.t.

The solution was filtered through celite and the solvent was evaporated in vacuo.

Yield: 76.7 mg (257 μmol, quantitative); mp 102–103 °C.

IR (KBr): 3354, 3281, 2972, 2929, 1675, 1536, 1482, 1293, 1247 cm^{-1}.

^1H NMR: δ = 1.34 (t, ^3J = 7.14 Hz, 3 H), 1.46 (s, 9 H), 1.94 (s, 3 H), 4.15 (m, 2 H), 4.31 (q, ^3J = 7.14 Hz, 2 H), 4.89 (br s, 1 H), 7.69 (br s, 1 H), 8.47 (br s, 1 H).

^{13}C NMR: δ = 6.5 (+), 14.6 (+), 28.3 (+), 59.9 (–), 77.2 (C_{quat}), 80.3 (C_{quat}), 104.2 (C_{quat}), 104.6 (C_{quat}), 131.2 (C_{quat}), 152.7 (C_{quat}), 156.7 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 299 (100) [M + H^+], 243 (13) [M + H^+ – C_4H_8].

Anal. Calcd for $C_{14}H_{22}N_2O_5$ (298.34): C, 56.36; H, 7.43; N, 9.39. Found: C, 56.17; H, 7.78; N, 9.06.

Ethyl 2-Allyl-5-(*tert*-butoxycarbonylaminomethyl)-4-methyl-3-oxo-2,3-dihydro-1*H*-pyrrole-2-carboxylate (8)

To a flask containing a solution of compound **7** (2 g, 6.5 mmol) in anhyd MeCN (25 mL), *t*-BuOK (0.73 g, 6.5 mmol) was added under nitrogen. The mixture was stirred for 15 min at 0 °C. Meanwhile, the palladium complex (η^3-$C_3H_5PdCl)_2$ (36.5 mg, 100 μmol) and (*R*,*R*)-Trost ligand (69.2 mg, 100 μmol) were dissolved in anhyd MeCN and stirred for 15 min at r.t. before allyl acetate (2.10 mL, 19.54 mmol) was added and stirring was continued at r.t. for an additional 5 min. The catalyst solution was cooled to 0 °C, then transferred via syringe into the enolate solution at 0 °C. The mixture was stirred for 1 d. The reaction was quenched with a sat. aq solution of NH_4Cl (10 mL), stirred vigorously for 10 min, and then H_2O (20 mL) was added to dissolve the precipitate. The solution was extracted with Et_2O (3 × 30 mL), the organic phase was dried over $MgSO_4$, and the solvent removed in vacuo. The crude product was purified by CC (PE–EtOAc; 1:1).

Yield: 768 mg (35%); colorless oil; R_f 0.32.

IR (NaCl): 3327, 2983, 2933, 1772, 1729 cm^{-1}.

^1H NMR: δ = 1.27 (m, 3 H), 1.46 (s, 9 H), 1.66 (s, 3 H), 2.43 (m, 1 H), 2.93 (m, 1 H), 4.16 (m, 1 H), 4.19 (m, 2 H), 4.24 (m, 1 H), 4.98 (m, 1 H), 5.10 (m, 1 H), 5.15 (m, 1 H), 5.67 (m, 1 H), 5.81 (m, 1 H).

^{13}C NMR: δ = 6.0 (+), 14.2 (+), 28.3 (+), 38.0 (–), 39.9 (–), 62.4 (–), 72.6 (C_{quat}), 105.5 (C_{quat}), 119.8 (–), 131.6 (+), 156.4 (C_{quat}), 167.4 (C_{quat}), 173.7 (C_{quat}), 196.1 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 339.1 (100) [M + H^+], 283.0 (15) [M + H^+ – C_4H_8].

1-*tert*-Butyl-2-ethyl-3-benzyloxy-5-formyl-4-methylpyrrole-1,2-dicarboxylate (9)

To a solution of compound **5** (5 g, 17.42 mmol) in anhyd CH_2Cl_2 (100 mL) at r.t., DMAP (2.2 g, 18.0 mmol) was added and the mixture was stirred for 10 min under nitrogen. $(Boc)_2O$ (3.93 g, 18.0 mmol) was added and the resulting mixture was stirred for 30 min. The solution was washed with H_2O (4 × 100 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was purified by CC (PE–EtOAc, 2:1).

Yield: 6.7 g (quantitative yield); colorless oil; R_f 0.60 (EtOAc–PE, 1:4).

IR (NaCl): 3444, 3145, 3005, 2977, 2933, 2875, 2200, 1729, 1754, 1603, 1500, 1462, 1432, 1389 cm^{-1}.

^1H NMR: δ = 1.35 (t, *J* = 7.14 Hz, 3 H), 1.69 (s, 9 H), 2.20 (s, 3 H,), 4.35 (q, *J* = 7.14 Hz, 2 H), 5.00 (s, 2 H), 7.27–7.50 (m, 5 H), 10.05 (s, 1 H).

^{13}C NMR: δ = 8.3 (+), 14.2 (+), 27.5 (+), 61.6 (–), 77.4 (–), 86.4 (C_{quat}), 118.9 (C_{quat}), 125.1 (C_{quat}), 128.3 (+), 128.4 (+), 128.6 (+), 136.60 (+), 148.23 (C_{quat}), 148.81 (C_{quat}), 160.05 (C_{quat}), 181.55 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 388.2 (95) [M + H^+], 288.1 (100) [M + H^+ – C_4H_8].

Anal. Calcd for $C_{21}H_{25}NO_6$ (387.44): C, 65.10; H, 6.50; N, 3.62. Found: C, 64.92; H, 6.57; N, 3.52.

1-*tert*-Butyl-2-ethyl-3-benzyloxy-5-(*tert*-butoxycarbonylaminomethyl)-4-methylpyrrole-1,2-dicarboxylate (10)

A mixture of NH_2Boc (302 mg, 2.58 mmol), THF (1.9 mL), H_2O (2 mL), sodium *p*-toluene sulfinate (459.8 mg, 2.58 mmol), aldehyde **9** (1 g, 4.73 mmol), and HCOOH (1.18 mL) was stirred until a homogeneous mixture was obtained, then stirring was continued for 2 d at r.t. The solid product was removed by suction filtration, washed successively with H_2O, PE, and dried over P_2O_5 to give 1.50 g of 1-*tert*-butyl-2-ethyl-3-benzyloxy-5-[*tert*-butoxycarbonylamino(toluene-4-sulfinyloxy)methyl]-4-methyl-pyrrole-1,2-dicarboxylate, which was used in the next step without further purification.

To a suspension of $NaBH_4$ (72 mg, 1.92 mmol) in THF (5 mL), 1-*tert*-butyl-2-ethyl-3-benzyloxy-5-[*tert*-butoxycarbonylamino(toluene-4-sulfinyloxy)methyl]-4-methyl-pyrrole-1,2-dicarboxylate (522 mg) was added portionwise while the mixture was ice cooled. Stirring was continued for 15 min with ice cooling and then the mixture was stirred for 2 h at r.t. The mixture was ice cooled again, quenched with a sat. aq solution of NH_4Cl (1 mL) and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined layers were dried over $MgSO_4$ and concentrated. The crude product was purified by CC (EtOAc–PE, 1:4) and then recrystallized from Et_2O.

Yield: 232 mg (55%); R_f 0.59; mp 103–105 °C.

IR (KBr): 3448, 3245, 3035, 2977, 2933, 2875, 2200, 1739, 1714, 1603, 1500, 1462, 1432, 1389, 1336, 1302, 1238 cm^{-1}.

^1H NMR: δ = 1.34 (t, *J* = 7.14 Hz, 3 H), 1.47 (s, 9 H), 1.63 (s, 9 H), 2.06 (s, 3 H), 4.25 (m, 4 H), 5.05 (s, 2 H), 5.51 (br s, 1 H), 7.27–7.49 (m, 5 H).

^{13}C NMR: δ = 7.6 (+), 14.6 (+), 15.3 (+), 27.6 (+), 28.4 (+), 35.1 (–), 60.8 (–), 60.8 (+), 77.1 (–), 85.3 (C_{quat}), 114.1 (C_{quat}), 115.3 (C_{quat}), 128.1 (+), 128.1 (+), 128.4 (+), 132.1 (+), 137.6 (+), 149.6 (C_{quat}), 151.6 (C_{quat}), 155.6 (C_{quat}), 160.7 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 489.3 (100) [M + H^+], 433.1 (10) [M + H^+ – C_4H_8], 389.2 (20) [M + H^+ – $2C_4H_8$].

Anal. Calcd for $C_{26}H_{36}N_2O_7$ (488.59): C, 63.92; H, 7.43; N, 5.73. Found: C, 63.83; H, 7.71; N, 5.64.

1-*tert*-Butyl-2-ethyl-5-(*tert*-butoxycarbonylaminomethyl)-4-methyl-3-oxo-2,3-dihydropyrrole-1,2-dicarboxylate (11)

Compound **10** (2 g, 4.1 mmol) was dissolved in $CHCl_3$ (2 mL) and MeOH (10 mL), 10% Pd/C (200 mg) was added and the mixture was transferred to an autoclave. The mixture was stirred for 2 h under H_2 (8 bar) at r.t. The solution was filtered through celite and the solvent was evaporated in vacuo to give the crude product, which was purified by CC (PE–EtOAc, 4:1). The product decomposed at r.t. and therefore was stored in a refrigerator.

Yield: 1.2 g (75%); colorless oil; R_f 0.32.

IR (NaCl): 3453, 3412, 3101, 2973, 2943, 1763, 1724, 1698, 1623, 1489, 1367 cm^{-1}.

^1H NMR: δ = 1.34 (t, ^3J = 7.14 Hz, 3 H), 1.43 (s, 9 H), 1.53 (s, 9 H), 1.86 (s, 3 H), 4.31 (q, ^3J = 7.14 Hz, 2 H), 4.54 (m, 2 H), 4.79 (s, 1 H), 5.56 (br s, 1 H).

^{13}C NMR: δ = 6.6 (+), 14.2 (+), 28.0 (+), 28.4 (+), 36.5 (–), 62.0 (–), 67.0 (+), 79.3 (C_{quat}), 83.7 (C_{quat}), 117.7 (C_{quat}), 149.2 (C_{quat}), 155.5 (C_{quat}), 164.1 (C_{quat}), 165.5 (C_{quat}), 192.3 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 399 (100) [M + H$^+$], 343.1 (17) [M + H$^+$ – C_4H_8].

Anal. Calcd for $C_{19}H_{30}N_2O_7$ (398.46): C, 57.27; H, 7.59; N, 7.03. Found: C, 55.28; H, 7.31; N, 6.65.

1-*tert*-Butyl-2-ethyl-2-allyl-5-(*tert*-butoxycarbonylaminomethyl)-4-methyl-3-oxo-2,3-dihydropyrrole-1,2-dicarboxylate (12)

To a flask containing a solution of compound **11** (0.3 g, 0.8 mmol) in anhyd MeCN (15 mL), *t*-BuOK (0.09 g, 0.8 mmol) was added under nitrogen. The mixture was stirred for 15 min at –22 °C. Meanwhile the palladium catalyst (η^3-$C_3H_5PdCl)_2$ (27.6 mg, 75 μmol) and (*R*,*R*)-Trost ligand (52.2 mg, 75 μmol) were dissolved in anhyd MeCN (5 mL) and stirred for 15 min at r.t. before allyl acetate (0.4 mL, 3.8 mmol) was added. Stirring was continued at r.t. for an additional 5 min. The catalyst solution was cooled to –22 °C before the enolate solution was transferred via syringe at –22 °C. The resulting mixture was stirred for 2.5 h at –22 °C. The reaction was quenched with a sat. aq solution of NH_4Cl (5 mL) and the mixture was stirred vigorously for 10 min. H_2O (10 mL) was then added to dissolve the precipitate. The solution was extracted with Et_2O (3 × 15 mL) and the organic phase was dried over $MgSO_4$. The solvent was removed in vacuo to give the crude product, which was purified by CC (PE–EtOAc; 1:4).

Yield: 305 mg (87%); colorless oil; R_f 0.37; [α]^D +143.8 (*c* 0.2, $CHCl_3$).

IR (NaCl): 3454, 3402, 3081, 2980, 2933, 1753, 1716, 1698, 1622, 1489, 1367, 1285, 1246, 1166, 1115, 1068 cm^{-1}.

^{1}H NMR: δ = 1.27 (m, ^3J = 7.14 Hz, 3 H), 1.43 (s, 9 H), 1.49 (s, 9 H), 1.66 (s, 3 H), 3.05 (d, 2 H), 4.16 (q, ^3J = 7.14 Hz, 2 H), 4.36–4.54 (m, 2 H), 4.96–5.10 (m, 2 H), 5.23–5.37 (m, 1 H), 5.50–5.60 (br s, 1 H).

^{13}C NMR: δ = 6.0 (+), 14.2 (+), 28.3 (+), 38.0 (–), 39.9 (–), 62.4 (–), 72.6 (C_{quat}), 105.5 (C_{quat}), 119.8 (–), 131.6 (+), 156.4 (C_{quat}), 167.4 (C_{quat}), 173.7 (C_{quat}), 196.1 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 339.1 (100) [M + H$^+$], 283.0 (15) [M + H$^+$ – C_4H_8].

Anal. Calcd for $C_{22}H_{34}N_2O_7$ (438.53): C, 60.26; H, 7.82; N, 6.39. Found: C, 59.71; H, 7.64; N, 6.09.

1-*tert*-Butyl-2-ethyl-2-allyl-5-[(2-*tert*-butoxycarbonylamino-3-phenylpropinoylamino)methyl]-4-methyl-3-oxo-2,3-dihydropyrrole-1,2-dicarboxylate (13)

Compound **12** (100 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (4 mL), a solution of Et_2O saturated with HCl (4 mL) was added and the resulting mixture was stirred at r.t. overnight. The resulting ammonium salt (90 mg, 0.24 mmol) was dissolved in a solution of *N*-Boc-phenylalanine (82.7 mg, 0.312 mmol), EDC (60 μL, 0.312 mmol), HOBt (42.1 mg, 0.312 mg), and DIPEA (0.09 mL, 0.528 mmol) in CH_2Cl_2 (5 mL) and the resulting solution was stirred for 4 h at r.t. Then the reaction mixture was washed with H_2O (2 × 5 mL), a 5% aq solution of $KHSO_4$ (5 mL), and a sat. aq solution of $NaHCO_3$ (2 mL). The resulting solution was dried over $MgSO_4$ and the solvent was evaporated.

Yield: 52%; white solid; mp 58–60 °C; [α]^D –110.3 (*c* 0.007, $CHCl_3$).

IR (KBr): 3424, 3365, 2978, 2933, 2872, 2362, 2199, 1944, 1753, 1702, 1620, 1498, 1454, 1367, 1280 cm^{-1}.

^{1}H NMR: δ = 1.25 (t, ^3J = 7.14 Hz, 3 H), 1.43 (s, 9 H), 1.53 (s, 9 H), 1.86 (s, 3 H), 2.85–3.14 (m, 4 H), 4.19 (q, ^3J = 7.14 Hz, 2 H), 4.29–4.51 (m, 2 H), 4.61–4.72 (m, 1 H), 4.75–5.10 (m, 3 H), 5.16–5.27 (m, 1 H), 6.90 (br s, 1 H), 7.13–7.37 (m, 5 H).

^{13}C NMR: δ = 6.6 (+), 14.1 (+), 28.1 (+), 28.2 (+), 35.3 (–), 38.3 (–), 38.8 (–), 55.5 (+), 62.4 (–), 73.7 (C_{quat}), 84.0 (C_{quat}), 83.7 (C_{quat}), 117.7 (C_{quat}), 119.9 (–), 120.0 (+), 128.6 (+), 129.4 (+), 129.8 (+), 136.4 (C_{quat}), 149.2 (C_{quat}), 164.7 (C_{quat}), 165.5 (C_{quat}), 170.7(C_{quat}), 195.6 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 586.5 (100) [M + H$^+$], 530.5 (21) [M + H$^+$ – C_4H_8], 630.6 (25) [M + NH_4^+].

Anal. Calcd for $C_{31}H_{43}N_3O_8$ (585.70): C, 63.57; H 7.40; N, 7.17. Found: C, 63.80; H, 7.21; N, 7.54.

***1-tert*-Butyl-2-ethyl-5-(*tert*-butoxycarbonylaminomethyl)-4-methyl-3-oxo-2-(2-oxoethyl)-2,3-dihydropyrrole-1,2-dicarboxylate (14)**

Compound **12** (200 mg, 0.46 mmol) was dissolved in THF–H_2O (4:1, 12 mL). This solution was stirred under nitrogen, and $K_2OsO_4{\cdot}2H_2O$ (20 mg) was added, which turned the reaction dark brown. After 5 min $NaIO_4$ (312 mg) was added in three batches over a 10 min period. The reaction turned light green and stirring was continued for 5 h. The reaction was diluted with Et_2O (10 mL) and H_2O (5 mL). The aqueous layer was extracted with Et_2O (2 × 12 mL), the combined ethereal layers were washed with brine (5 mL), and dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by CC (EtOAc–PE, 1:3).

Yield: 150 mg (75%); colorless oil; R_f 0.4; [α]^D +17.7 (*c* 0.007, $CHCl_3$).

IR (NaCl): 3453, 2980, 2930, 2728, 2199, 2097, 1789, 1698, 1622, 1492, 1365, 1284, 1247, 1167 cm^{-1}.

^{1}H NMR: δ = 1.27 (t, ^3J = 7.14 Hz, 3 H), 1.43 (s, 9 H), 1.47 (s, 9 H), 1.90 (s, 3 H), 3.20–3.42 (m, 2 H), 4.15–4.23 (q, ^3J = 7.14 Hz, 2 H), 4.45–4.51 (d, 2 H), 5.40–5.55 (br s, 1 H), 9.55 (s, 1 H).

^{13}C NMR: δ = 6.0 (+), 14.2 (+), 28.3 (+), 38.0 (–), 39.9 (–), 62.4 (–), 72.6 (C_{quat}), 105.5 (C_{quat}), 119.8 (–), 131.6 (+), 156.4 (C_{quat}), 167.4 (C_{quat}), 173.7 (C_{quat}), 196.1 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 441.2 (100) [M + H$^+$], 385.1 (30) [M + H$^+$ – C_4H_8], 285.0 (30) [M + H$^+$ – 2 C_4H_8 – CO_2].

Anal. Calcd for $C_{21}H_{32}N_2O_8$ (440.50): C, 57.26; H, 7.32; N, 6.36. Found: C, 57.28; H, 7.51; N, 6.65

***1-tert*-Butyl-2-ethyl-5-(*tert*-butoxycarbonylaminomethyl)-2-carboxyethyl-4-methyl-3-oxo-2,3-dihydropyrrole-1,2-dicarboxylate (15)**

Aldehyde **14** (40 mg, 0.09 mmol) and $NaH_2PO_4{\cdot}H_2O$ (21 mg, 0.17 mmol) were dissolved in MeCN–H_2O (4:1, 2.5 mL). H_2O_2 (1.5 mL) and $NaClO_2$ (32 mg, 0.35 mmol) were added and the resulting mixture was stirred for another 30 min. H_2O (1 mL) was added and the aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, and concentrated.

Yield: 35 mg (85%); R_f 0.12 (EtOAc–PE, 1:1); [α]^D +15.4 (*c* 0.015, $CHCl_3$).

IR (NaCl): 3435, 2982, 2913, 2728, 2200, 2097, 1698, 1650, 1622, 1492, 1365, 1284, 1247, 1167 cm^{-1}.

^{1}H NMR: δ = 1.27 (t, ^3J = 7.14 Hz, 3 H), 1.43 (s, 9 H), 1.47 (s, 9 H), 1.90 (s, 3 H), 3.20–3.42 (m, 2 H), 4.15–4.23 (q, ^3J = 7.14 Hz, 2 H), 4.45–4.51 (d, 2 H), 5.40–5.55 (br s, 1 H), 9.55 (s, 1 H).

^{13}C NMR: δ = 6.0 (+), 14.2 (+), 28.3 (+), 38.0 (–), 39.9 (–), 62.4 (–), 72.6 (C_{quat}), 105.5 (C_{quat}), 119.8 (–), 131.6 (+), 156.4 (C_{quat}), 167.4 (C_{quat}), 173.7 (C_{quat}), 196.1 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 457.3 (100) [M + H^+], 474.3 (75) [M + NH_4^+].

HRMS: *m*/*z* calcd for $C_{21}H_{33}N_2O_9$ [M + H^+], 457.2186; found: 457.2188 ± 0.42.

Compound 16

Compound **12** (28 mg, 0.06 mmol) was dissolved in CH_2Cl_2 (2 mL), a solution of Et_2O saturated with HCl (2 mL) was added and the reaction mixture was stirred at r.t. overnight. The resulting ammonium salt (24 mg, 0.06 mmol) was dissolved in a solution of compound **15** (30 mg, 0.065 mmol), EDC (0.01 mL, 0.065 mmol), HOBt (10.0 mg, 0.065 mmol), and DIPEA (0.03 mL, 0.15 mmol) in CH_2Cl_2 (2 mL) and the resulting solution was stirred for 4 h at r.t. The reaction mixture was washed with H_2O (2 × 1 mL), a 5% aq solution of $KHSO_4$ (1 mL), and a sat. aq solution of $NaHCO_3$ (1 mL). The resulting solution was dried over $MgSO_4$, the solvent was evaporated, and the crude product was purified by CC (EtOAc–PE, 1:3).

Yield: 12 mg (30%); colorless oil; R_f 0.15.

^{1}H NMR: δ = 1.26 (m, 6 H), 1.45 (s, 9 H), 1.51 (s, 9 H), 1.54 (s, 9 H), 1.80 (s, 3 H), 1.90 (s, 3 H), 3.05 (m, 2 H), 3.20 (m, 2 H), 4.18 (m, 4 H), 4.30 (dd, ^3J = 5.88 Hz, ^2J = 14.75 Hz, 1 H, C*H*H), 4.48 (m, 2 H), 4.58 (dd, ^3J = 5.88 Hz, ^2J = 14.75 Hz, 1 H, CH*H*), 5.05–5.07 (m, 2 H), 5.23–5.26 (m, 1 H), 5.58 (br s, 1 H), 6.60 (br s, 1 H).

^{13}C NMR: δ = 6.5 (+), 6.7 (+), 14.3 (+), 14.2 (+), 28.3 (+), 28.4 (+), 29.0 (+), 34.9 (–), 36.7 (–), 38.2 (–), 40.6 (–), 62.2 (–), 62.6 (–), 71.8 (C_{quat}), 73.8 (C_{quat}), 79.5 (C_{quat}), 84.0 (C_{quat}), 117.5 (C_{quat}), 119.9 (–), 120.2 (C_{quat}), 129.5 (+), 129.7 (+), 148.9 (C_{quat}), 149.3 (C_{quat}), 155.5 (C_{quat}), 164.7 (C_{quat}), 165.3 (C_{quat}), 165.4 (C_{quat}), 166.0 (C_{quat}), 166.4 (C_{quat}), 195.0 (C_{quat}), 195.5 (C_{quat}).

MS [ESI, CH_2Cl_2–MeOH–NH_4Ac (10 mmol/L)]: *m*/*z* (%) = 777.6 (100) [M + H^+], 794 (20) [M + NH_4^+].

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