

Stereoselective synthesis towards unnatural proline-based amino acids

Sifiso S. Makhathini,^a Sukant K. Das,^a Thishana Singh,^b Per I. Arvidsson,^{a,c} Hendrik G. Kruger,^a Hendra Gunosewoyo,^d Thavendran Govender,^{*a} and Tricia Naicker^{*a}

^a Catalysis and Peptide Research Unit, University of KwaZulu Natal, Durban, South Africa

^b T. Singh, Durban University Technology, Department of Chemistry, Durban, South Africa

^c P. I. Arvidsson, Science for Life Laboratory, Drug Discovery and Development, Platform and Division of Translational Medicine and Chemical Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet

E-mail: naickert1@ukzn.ac.za, govenderthav@ukzn.ac.za

DOI: <http://dx.doi.org/10.3998/ark.5550190.p009.462>

Abstract

A catalytic diastereoselective Mannich reaction promoted by chiral bifunctional urea-type organocatalysts has been developed. Treatment of *N*-Boc-3-ketoproline with *N*-Boc-aldimines under mild conditions afforded the corresponding unnatural proline based amino acid derivatives with excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to 97% ee). The relative configuration of the chiral reaction products was deduced by the comparison of the experimentally observed ECD spectra to that obtained theoretically.

Keywords: α,α -Disubstituted amino acid, substituted proline, organocatalysis, ECD spectra

Introduction

One major goal for synthetic chemists is to create functionalised optically active molecules from readily available starting materials via stereoselective transformations, especially those which cannot be directly attained using biosynthetic pathways or natural products.^{1,2} In particular, optically active amino acids and their derivatives play a vital role in the design of crucial building blocks required to form peptide and proteins from the twenty naturally occurring proteinogenic L-amino acids. Moreover, non-proteinogenic unnatural amino acids have increasingly become valuable target molecules for drug discovery with expanding synthetic strategies over the last decade.³⁻⁹ These essential unnatural amino acids includes β -amino acids (β^3 and β^2), homo-amino acids, proline and pyruvic acid derivatives

Unnatural proline based amino acids are used as important building blocks for pharmaceuticals, biologically active compounds and more recently as organocatalysts.^{10,11} Proline is the only amino acid to exhibit helix-inducing properties (as a result of tertiary amide bond formation) when incorporated into a peptide thereby influencing its ligand binding and overall protein activity. Chiral polysubstituted oxopyrrolidine is one example exploited in this regard based on the proline backbone in order to synthesise unnatural proline based amino acid derivatives.¹²

As a result of modification at the α -position, these molecules display unique helix-inducing potential when incorporated into peptides. This helix property promotes the restriction of conformational freedom amongst the amino acid side chains within the peptide structure which allows for resistance towards chemical and enzymatic degradation, increased hydrophobicity and metabolic stability.^{2,4}

β -Amino acids are another class of compounds that are equally important precursors leading to more complex products with biological and pharmacological activities.^{13,14} Moreover β -amino acids are precursors of β -lactams, the most important class of antibiotics. They are known to also control the conformational properties of peptides based on β -amino acids that enhance the stability towards proteases.¹⁴ This contributes to the library of a drug development tool with degradation resistance.¹⁵

In the past decade, reports and reviews have been published on this topic, highlighting the possible strategies toward asymmetric synthesis of different kinds of substituted oxopyrrolidines in the optically active form.^{5,16}

Asymmetric organocatalysed Mannich reactions emerged as a powerful strategy in the construction of these building blocks via the formation of quaternary α -amino acids.^{2,4,5,12} Some success has also been seen in direct addition of α -substituted amino acids to imines to afford these special kind of β -amino acid derivatives.^{3,17-19} The success of the reaction is highly dependent on the activation of both the nucleophile and electrophile. Non-covalent interactions such as hydrogen bonding between the organocatalysts and substrates have been successfully exploited in asymmetric catalysis and in the synthesis of β -amino acid derivatives.²⁰⁻²²

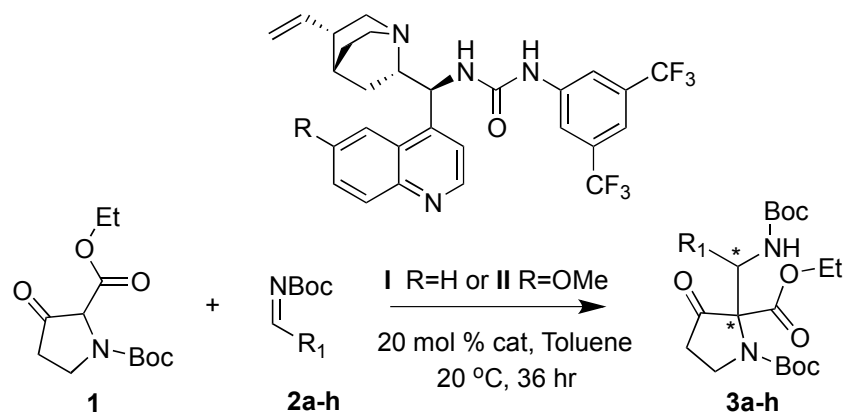
Specifically, the use of urea- and thiourea-based organic molecules as hydrogen-bond-donor organocatalysts has been reported to be compatible with various substrates and reaction conditions.²³⁻²⁵ Jacobsen and co-workers developed a collection of thiourea catalysts that promote a diverse range of reactions with excellent enantioselectivity, along with the chiral versions as efficient hydrogen-bond-donor organocatalysts.²⁶ Other groups such as; Jørgensen and Ricci and later Dixon, Takemoto, and Deng have all reported highly enantioselective Mannich reactions of β -ketoesters, catalysed by bifunctional cinchona alkaloid- derived organocatalysts.^{1,27} These catalysts are regarded as bifunctional chiral catalysts, bearing a tertiary amino group and hydrogen bond donors, which are expected to possess dual activation of both the electrophilic and nucleophilic components.^{25,28,29}

In this study, we explore the ability of a urea-type cinchonine and quinine alkaloid derivatives to catalyse the Mannich reaction between the scarcely used *N*-Boc protected 3-ketoproline

substrate with various *N*-Boc-imines in an effort to create a new route to unnatural proline based amino acids.

Results and Discussion

Several publications on the organocatalysed Mannich reactions of β -ketoesters with a range of aldimines have been reported to be successful, specifically those catalysed by bifunctional alkaloid-based urea possessing hydrogen bonding capability.³⁰ Based on our previous studies on the 3-ketoproline core for the organocatalysed Michael reaction,³¹ we started by applying these optimised conditions for Mannich reactions of *N*-Boc protected 3-ketoproline (**1**) with *N*-Boc-benzaldimine (**2**). The reactions were performed at 20 °C with 20 mol % of catalyst, cinchonine **I** or quinine derived **II** for 36 hours (Scheme 1) using toluene as the solvent.



Scheme 1: Organocatalytic asymmetric Mannich reaction on *N*-Boc protected 3-ketoproline with *N*-Boc-aldimines

Catalyst **I** provided the product **3a** in moderate isolated yield (65%), with a 70% ee and >99:1 diastereoselectivity (dr). For catalyst **II**, the product **3a** was also isolated in moderate yield (68%) and enantioselectivity (73% ee) with equally high dr of >99:1. Employing either of these catalysts in various solvents such as DCM, THF or ACN, toluene still provided the highest observed selectivity of 73% ee with up to 68% yield (see Table 1 SI).

With the optimised solvent, we then expanded the scope of the Mannich reaction (Figure 1) using both alkaloid-derived urea catalysts with a range of *para*-substituted aromatic and heteroaromatic aldimines (**2a-p**), including the electron donating and electron withdrawing heteroatoms.

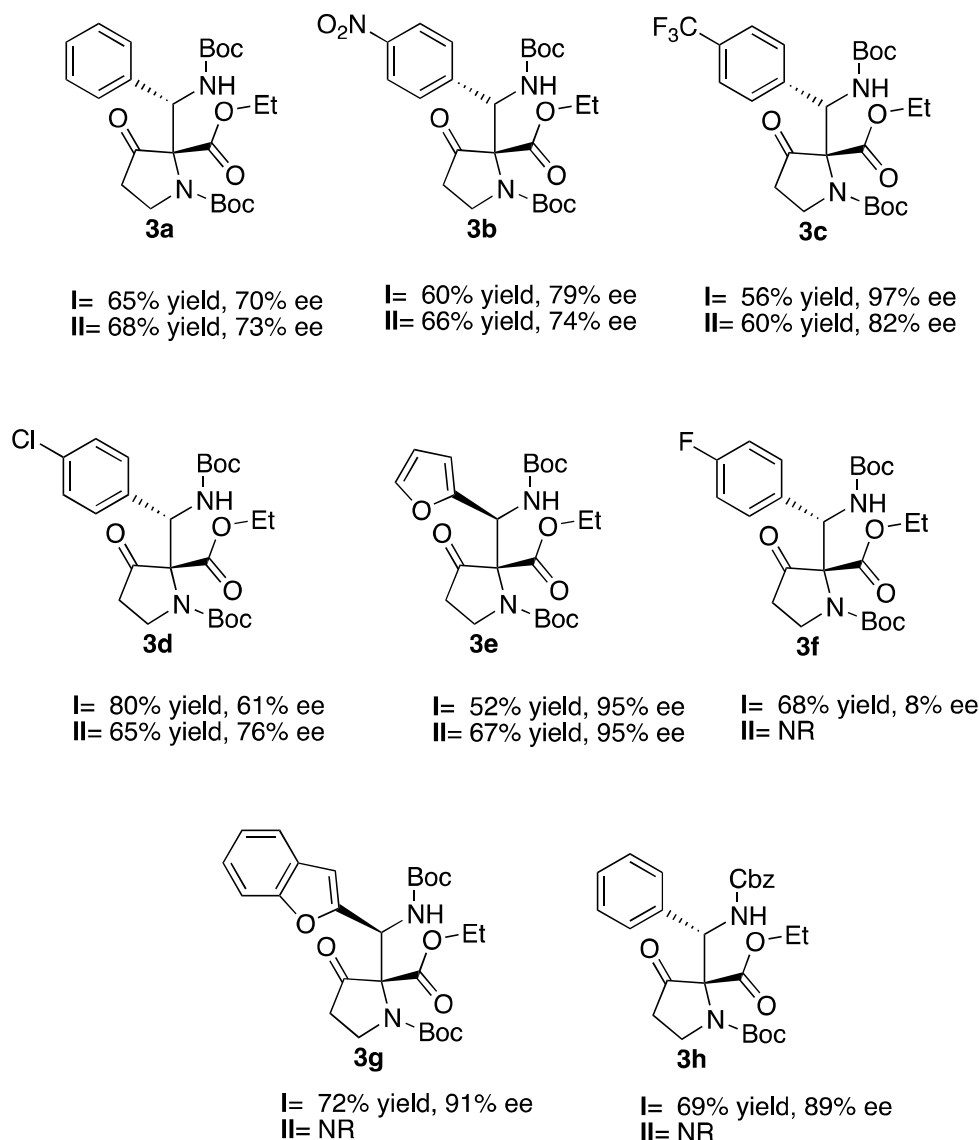


Figure 1. Unnatural proline based amino acids derivatives obtained by the Mannich reaction of 3-keto proline in the presence of catalysts **I** or **II**. All products were obtained with dr >99:1 from crude ^1H NMR.

The products (**3**) were efficiently isolated (up to 80% yield and 97% ee) and (up to 68% yield and 95% ee) for cinchonine and quinine derived urea catalysts, respectively with a dr >99:1 (Figure 1). As expected, when changing from catalyst **I** to **II**, the opposite enantiomer was obtained in all cases. It was noted that electron withdrawing substituents at the *para* position had a positive effect on the yields and stereoselectivities. Change of the protecting group on the imine component was also tolerated (**3h**) depicting the modular nature of the product adducts. Regrettably, many substrates (see Table 2 SI) showed very low reactivity, irrespective of the

catalyst used, which led to difficulties with purification. The low reactivity was a likely result of electron donating substituents increasing the nucleophilicity of the substrates thus deactivating it towards nucleophilic attack. The results obtained by either catalyst revealed that the absence of the methoxy group in catalyst **I** generally promoted better yields and selectivities. This observation was similar to previous reports for other organocatalysed reactions on β -ketoesters.^{32,33} This transformation provides a new and facile route in the formation of a new quaternary stereogenic center towards chiral α,α -disubstituted α -amino acids that are usually challenging to obtain, however desirable due to the useful properties.

In order to determine the relative absolute configuration of the reaction products, the electronic circular dichroism (ECD) was calculated for the four possible diastereoisomers of **3a** as the model using time-dependent density functional theory (TDDFT) to simulate the experimentally observed ECD spectrum.³⁴ The structures of the possible diastereoisomers were fixed at (*S,R*), (*R,S*), (*S,S*) and (*R,R*) absolute configurations and then optimized. Since the experimental measurements were carried out in methanol, the self-consistent reaction field (SCRF) with polarizable continuum model (PCM) was used for the solution state ECD spectra in methanol.³⁵ A comparison of the experimentally measured (**3a**, **3c**) and computed ECD spectra showed that the overall patterns of the solution state ECD spectrum were consistent with those of the experimental. Thus products **3a** (70% ee), and **3c** (97% ee) could be assigned to the (*S,S*) relative absolute configuration. The stereochemistry of the remaining products was assigned by analogy. It has been stated that the definition of ECD is quite clear-cut however the simulation of an ECD spectrum has not yet being clearly documented.³⁶ Nonetheless, this technique of determining the relative configuration of asymmetric adducts is slowly gaining popularity and will soon be a tool that is regularly used for the assignment of chirality. Please see computational details in the supporting information for the ECD spectra and an in depth discussion on the ECD calculations.³⁵ Based on the high degree of diastereoselection and stereochemical outcome, the following transition state was proposed in which the catalyst deprotonates the β -ketoester as well as forms a fully hydrogen-bonded intermediate with both reactants.

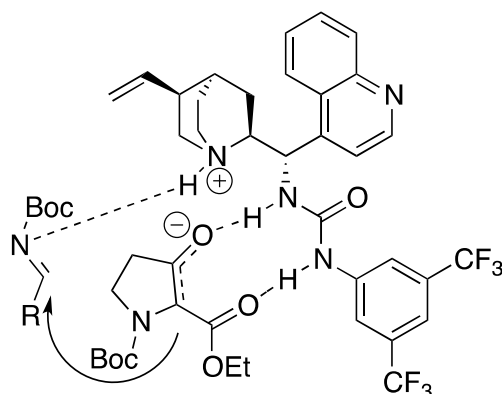


Figure 2. Proposed transition state.

Conclusions

We have developed an efficient method for the synthesis of a range of enantioenriched unnatural proline based amino acids. Diastereoselective Mannich reactions of *N*-Boc protected 3-ketoproline with a series of *N*-Boc-aldimines were achieved in good yields and enantioselectivities. Novel chiral unnatural proline based amino acids represent highly valuable building blocks for use in biomedical research, peptide/protein design and catalysis.

Experimental Section

General. Reagents and solvents were purchased from Aldrich, Merck and Fluka. All NMR spectra were recorded on the Bruker AVANCE III 400 MHz or 600 MHz instruments at room temperature. Chemical shifts are expressed in ppm and coupling constants are reported in Hz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using silica gel (60–200 mesh unless otherwise stated). All solvents were dried using standard procedures. Optical rotations were recorded on a Bellingham + Stanley Polarimeter (Model 440+). High-resolution mass spectrometric data were obtained using a Bruker micrOTOF-Q II instrument operating at ambient temperatures and a sample concentration of approximately 1.0 ppm. For HPLC analysis: Agilent 1100 HPLC equipped with a ChiralPak IA/IB column

Representative procedure for the Mannich reaction. A mixture of compound **1** (1.0 eq) and *N*-Boc-aldimines (1.2 eq) was stirred in the presence of the catalyst (0.20 eq) at 20°C. The reaction progress was monitored using TLC. On completion of the reaction, the solvent was removed under reduced pressure and the crude product mixture was purified by column chromatography.

1-tert-Butyl 2-ethyl 2-((tert-butoxycarbonylamino)(phenyl)methyl)-3-oxopyrrolidine-1,2-dicarboxylate (3a). The crude material was purified by column chromatography (ethyl acetate/hexane, 15:85, $R_f = 0.3$) to afford the product (65%) as a yellowish oil. $[\alpha]^{23}_D = +0.20$ ($c = 0.01$ in CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.22-7.17 (m, 3H), 7.11-7.04 (m, 2H), 6.63-6.26 (m, 1H), 5.74-5.56 (m, 1H), 4.30-4.03 (m, 2H); 3.92-3.69 (m, 1H), 3.62-3.44 (m, 1H), 2.64-2.58 (m, 1H), 2.54-2.45 (m, 1H), 1.49-1.33 (m, 18H), 1.22-1.16 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 166.1 (CO), 154.9 (CO), 153.1 (CO), 138.7 (C), 128.5 (2CH), 128.0 (CH), 127.3 (2CH), 79.5 (2C), 61.9 (CH₂), 55.6 (CH), 41.3 (CH₂), 36.3 (CH₂), 28.3 (6CH₃), 14.0 (CH₃); HRMS (ESI+) m/z calcd. for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_7$: 463.2439; found $[\text{M}+\text{H}]$ 463.2446; The enantiomeric excess was determined by HPLC with a Chiralpak IA-H column (hexane/2-PrOH = 97/3, 220 nm, 0.7 mL/min); $t_{\text{major}} = 11.18$ min, $t_{\text{minor}} = 13.36$ min, 70% ee.

1-tert-Butyl 2-ethyl 2-((tert-butoxycarbonylamino)(4-nitrophenyl)methyl)-3-oxopyrrolidine-1,2-dicarboxylate (3b). The crude material was purified by column chromatography (ethyl

acetate/hexane, 15:85, $R_f = 0.3$) to afford the product (60%) as a yellowish oil. $[\alpha]^{23}_D = +0.04$ ($c = 0.01$ in CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.28-8.06 (m, 2H), 7.52-7.31 (m, 2H), 6.61-6.41 (m, 1H), 5.92-5.77 (m, 1H), 4.38-4.17 (m, 2H), 4.14-4.09 (m, 2H), 3.74-3.52 (m, 1H), 2.70-2.54 (m, 1H), 1.59-1.36 (m, 18H), 1.27-1.22 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 210.5 (CO), 166.2 (CO), 155.1 (CO), 153.0 (CO), 148.7 (C), 147.9 (C), 124.6 (2CH), 123.6 (2CH), 80.1 (2C), 62.8 (CH₂), 56.3 (CH), 48.1 (CH₂), 32.0 (CH₂), 28.4 (6CH₃), 13.9 (CH₃); HRMS (ESI+) m/z calcd. For $\text{C}_{24}\text{H}_{34}\text{N}_3\text{O}_9$: 508.2290; found $[\text{M}+\text{H}]$ 508.2292; The enantiomeric excess was determined by HPLC with a Chiralpak IA-H column (hexane/2-PrOH = 97/3, 254 nm, 0.7 mL/min); $t_{\text{major}} = 22.65$ min, $t_{\text{minor}} = 25.61$ min, 79% ee.

1-tert-Butyl 2-ethyl 2-((tert-butoxycarbonylamino)(4-(trifluoromethyl)phenyl)methyl)-3-oxopyrrolidine-1,2-dicarboxylate (3c). The crude material was purified by column chromatography (ethyl acetate/hexane, 15:85, $R_f = 0.5$) to afford the product (56%) as a yellowish oil. $[\alpha]^{23}_D = +0.28$ ($c = 0.01$ in CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.55-7.51 (m, 2H), 7.29-7.25 (m, 2H), 6.47-6.42 (m, 1H), 5.85-5.78 (m, 1H), 4.28-4.16 (m, 2H), 3.73-3.69 (m, 2H), 2.68-2.46 (m, 2H), 1.59-1.32 (m, 18H), 1.29-1.21 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 174.6 (CO), 163.2 (CO), 154.9 (CO), 151.2 (CO), 129.8 (C), 127.9 (2CH), 125.4 (2CH), 123.1 (CF), 105 (CH), 85 (2C), 62.4 (CH₂), 55.3 (CH), 38.7 (CH₂), 32.1 (CH₂), 28.4 (6 CH₃), 14.1 (CH₃); HRMS (ESI+) m/z calcd. For $\text{C}_{24}\text{H}_{34}\text{F}_3\text{N}_2\text{O}_7$: 531.2313; found $[\text{M}+\text{H}]$ 531.2316; The enantiomeric excess was determined by HPLC with a Chiralpak IA-H column (hexane/2-PrOH = 97/3, 254 nm, 0.7 mL/min); $t_{\text{major}} = 8.07$ min, $t_{\text{minor}} = 10.40$ min, 97% ee.

1-tert-Butyl 2-ethyl 2-((tert-butoxycarbonylamino)(4-chlorophenyl)methyl)-3-oxopyrrolidine-1,2-dicarboxylate (3d). The crude material was purified by column chromatography (ethyl acetate/hexane, 15:85, $R_f = 0.4$) to afford the product (80%) as a yellowish oil. $[\alpha]^{23}_D = +0.24$ ($c = 0.01$ in CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.22-7.14 (m, 2H), 7.06-7.00 (m, 2H), 6.34-6.27 (m, 1H), 5.72-5.60 (m, 1H), 4.34-4.03 (m, 2H), 3.95-3.48 (m, 1H), 3.62-3.44 (m, 1H), 2.63-2.42 (m, 2H), 1.65-1.27 (m, 18H), 1.20-1.15 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 205.0 (CO), 166.2 (CO), 155.2 (CO), 153.2 (CO), 137.5 (C), 133.7 (C), 128.7 (2CH), 128.4 (2CH), 104.2 (C), 79.6 (2C), 62.3 (CH₂), 55.2 (CH), 41.7 (CH₂), 36.5 (CH₂), 28.5 (6CH₃), 14.0 (CH₃); HRMS (ESI+) m/z calcd. for $\text{C}_{24}\text{H}_{34}\text{ClN}_2\text{O}_7$: 497.2049 $[\text{M}+\text{H}]$ 497.2050; The enantiomeric excess was determined by HPLC with a Chiralpak IA-H column (hexane/2-PrOH = 97/3, 254 nm, 0.7 mL/min); $t_{\text{major}} = 12.70$ min, $t_{\text{minor}} = 14.83$ min, 61% ee

1-tert-Butyl 2-ethyl 2-((tert-butoxycarbonylamino)(furan-2-yl)methyl)-3-oxopyrrolidine-1,2-dicarboxylate (3e). The crude material was purified by column chromatography (ethyl acetate/hexane, 15:85, $R_f = 0.3$) to afford the product (52%) as a yellowish oil. $[\alpha]^{23}_D = -0.040$ ($c = 0.01$ in CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.30-7.28 (m, 1H), 6.32-6.30 (m, 1H), 6.23-6.05 (m, 2H), 5.90-5.85 (m, 1H), 4.31-4.12 (m, 2H), 3.82-3.70 (m, 1H), 2.91-2.83 (m, 1H), 2.77-2.72 (m, 1H), 2.58-2.49 (m, 1H), 1.59-1.43 (m, 18H), 1.30-1.25 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 209.9 (CO), 166.5 (CO), 154.9 (CO), 153.0 (CO), 151.2 (C), 142.2 (CH), 113.2 (CH), 110.9 (CH), 108.3 (CH), 79.6 (2C), 62.5 (CH₂), 50.4 (CH), 47.8 (CH₂), 36.4 (CH₂), 28.7 (6CH₃), 14.2 (CH₃); HRMS (ESI+) m/z calcd. For $\text{C}_{22}\text{H}_{33}\text{N}_2\text{O}_8$: 453.2231; found $[\text{M}+\text{H}]$

453.2252; The enantiomeric excess was determined by HPLC with a Chiralpak IA-H column (hexane/2-PrOH = 97/3, 254 nm, 0.7 mL/min); $t_{\text{major}} = 14.91$ min, $t_{\text{minor}} = 15.87$ min, 95% ee

1-tert-Butyl 2-ethyl 2-((tert-butoxycarbonylamino)(4-fluorophenyl)methyl)-3-oxopyrrolidine-1,2-dicarboxylate (3f). The crude material was purified by column chromatography (ethyl acetate/hexane, 15:85, $R_f = 0.4$) to afford the product (68%) as a yellowish oil. $[\alpha]^{23}_D = +0.040$ ($c = 0.01$ in CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.22-7.14 (m, 2H), 7.06-7.00 (m, 2H), 6.34-6.27 (m, 1H), 5.72-5.60 (m, 1H), 4.34-4.09 (m, 2H), 4.03-3.48 (m, 2H), 2.63-2.42 (m, 2H), 1.46-1.32 (m, 18H), 1.27-1.18 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 208 (CO), 166 (CO), 163 (C), 155 (CO), 153 (CO), 134 (C), 129 (2CH), 115 (2CH), 105 (CH), 79.6 (2C), 62.3 (CH_2), 55 (CH), 41.7 (CH_2), 36.5 (CH_2), 28.3 (6 CH_3), 14.0 (CH_3); HRMS (ESI+) m/z calcd. For $\text{C}_{24}\text{H}_{34}\text{FN}_2\text{O}_7$: 481.2345; found $[\text{M}+\text{H}]$ 481.2343; The enantiomeric excess was determined by HPLC with a Chiralpak IA-H column (hexane/2-PrOH = 93/7, 254 nm, 0.7 mL/min); $t_{\text{major}} = 13.98$ min, $t_{\text{minor}} = 15.79$ min, 7.5% ee.

1-tert-Butyl 2-ethyl 2-(benzofuran-2-yl(tert-butoxycarbonylamino)methyl)-3-oxopyrrolidine-1,2-dicarboxylate (3g). The crude material was purified by column chromatography (ethyl acetate/hexane, 15:85, $R_f = 0.4$) to afford the product (72%) as a yellowish oil. $[\alpha]^{23}_D = +0.040$ ($c = 0.01$ in CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.51-7.49 (m, 1H), 7.39-7.33 (m, 1H), 7.25-7.19 (m, 2H), 6.66-6.58 (m, 1H), 6.25-6.15 (m, 1H), 6.10-6.00 (m, 1H), 4.28-4.08 (m, 2H), 2.93-2.88 (m, 1H), 2.82-2.75 (m, 1H), 2.66-2.60 (m, 1H); 2.18-2.07 (m, 1H), 1.60-1.32 (m, 18H), 1.29-1.23 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 209.7 (CO), 166.4 (CO), 156.8 (C), 154.8 (CO), 154.1 (C), 153.2 (C), 152.2 (CO), 128.1 (C), 124.6 (CH), 123.8 (CH), 121.4 (CH), 105.4 (CH), 103.6 (CH), 79.8 (2C), 62.4 (CH_2), 50.9 (CH), 41.4 (CH_2), 35.9 (CH_2), 28.4 (3 CH_3), 14.4 (CH_3); HRMS (ESI+) m/z calcd. For $\text{C}_{26}\text{H}_{35}\text{N}_2\text{O}_8$: 503.2388; found $[\text{M}+\text{H}]$ 503.2387; The enantiomeric excess was determined by HPLC with a Chiralpak IA-H column (hexane/2-PrOH = 97/3, 254 nm, 0.7 mL/min); $t_{\text{major}} = 13.57$ min, $t_{\text{minor}} = 15.34$ min, 91% ee.

1-tert-Butyl 2-ethyl 2-((benzyloxycarbonylamino)(phenyl)methyl)-3-oxopyrrolidine-1,2-dicarboxylate (3h). The crude material was purified by column chromatography (ethyl acetate/hexane, 15:85, $R_f = 0.3$) to afford the product (69%) as a yellowish oil. $[\alpha]^{23}_D = +0.12$ ($c = 0.01$ in CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.27-7.726 (m, 2H), 7.24-7.14 (m, 6H), 6.64-6.61 (m, 2H), 5.79-5.67 (m, 1H), 5.0 (m, 2H), 4.20-4.0 (m, 2H), 2.53-2.46 (m, 1H), 2.32-2.26 (m, 1H), 2.19-2.12 (m, 2H); 1.51-1.44 (m, 9H), 1.30-1.25 (m, 3H), $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 211 (CO), 166 (CO), 155 (CO), 153 (CO), 138 (C), 138 (C), 128.6 (4 CH), 128.1 (2CH), 127 (4CH), 82.6 (2C), 67.0 (CH_2), 62.3 (CH_2), 56.2 (CH), 41.4 (CH_2), 36.5 (CH_2), 28.3 (3 CH_3), 14.0 (CH_3); HRMS (ESI+) m/z calcd. For $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_7$: 497.2282; found $[\text{M}+\text{H}]$ 497.2270; The enantiomeric excess was determined by HPLC with a Chiralpak IA-H column (hexane/2-PrOH = 97/3, 254 nm, 0.7 mL/min); $t_{\text{major}} = 30.72$ min, $t_{\text{minor}} = 32.39$ min, 89% ee.

Acknowledgements

The authors wish to thank Prof. Adolf Gogoll and Mr Magnus Blom at Uppsala University, Sweden for their assistance with the ECD experiments. All computations were carried out using the computational cluster resources at the National Supercomputer Center based at Linköping University, Sweden.

References

1. Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E., *J. Am. Chem. Soc.* **2005**, *127*, 11256-11257.
<http://dx.doi.org/10.1021/ja0537373>
2. Tanaka, M., *Chem. Pharm. Bull.* **2007**, *55*, 349-358.
<http://dx.doi.org/10.1248/cpb.55.349>
3. Córdova, A., *Acc. Chem. Res.* **2004**, *37*, 102-112.
<http://dx.doi.org/10.1021/ar030231l>
4. Vogt, H.; Bräse, S., *Org. Biomol. Chem.* **2007**, *5*, 406-430.
<http://dx.doi.org/10.1039/B611091F>
5. Williams, R. M.; Im, M. N., *J. Am. Chem. Soc.* **1991**, *113*, 9276-9286.
<http://dx.doi.org/10.1021/ja00024a038>
6. Huang, H.; Xu, Y.; Mao, F.; Zhu, J.; Jiang, H.; Li, J., *Tetrahedron Lett.* **2015**, *56*, 586-589.
<http://dx.doi.org/10.1016/j.tetlet.2014.12.011>
(7) Fanelli, R.; Jeanne-Julien, L.; René, A.; Martinez, J.; Cavelier, F., *Amino Acids* **2015**, *47*, 1107-1115.
<http://dx.doi.org/10.1007/s00726-015-1934-0>
8. Perdih, A.; Sollner Dolenc, M., *Current Organic Chemistry* **2011**, *15*, 3750-3799.
<http://dx.doi.org/10.2174/138527211797884566>
9. Rammeloo, T.; Stevens, C. V., *Chem. Commun.* **2002**, 250-251.
<http://dx.doi.org/10.1039/b110765h>
10. Calaza, M. I.; Cativiela, C., *Eur. J. Org. Chem.* **2008**, *2008*, 3427-3448.
<http://dx.doi.org/10.1002/ejoc.200800225>
11. He, J.; Li, S.; Deng, Y.; Laforteza, B. N.; Spangler, J. E.; Yu, J.-Q., *Science (New York, N.Y.)* **2014**, *343*, 1216-1220.
<http://dx.doi.org/10.1126/science.1249198>
12. Han, M.-Y.; Jia, J.-Y.; Wang, W., *Tetrahedron Lett.* **2014**, *55*, 784-794.
<http://dx.doi.org/10.1016/j.tetlet.2013.11.048>
13. Ballerini, E.; Curini, M.; Gelman, D.; Lanari, D.; Piermatti, O.; Pizzo, F.; Santoro, S.; Vaccaro, L., *ACS Sus. Chem. Eng.* **2015**.
14. Weiner, B.; Szymański, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L., *Chem. Soc. Rev.* **2010**, *39*, 1656-1691.

- <http://dx.doi.org/10.1039/b919599h>
15. Bea, H.-S.; Park, H.-J.; Lee, S.-H.; Yun, H., *Chem. Commun.* **2011**, 47, 5894-5896.
<http://dx.doi.org/10.1039/c1cc11528f>
16. Curto, J. M.; Dickstein, J. S.; Berritt, S.; Kozlowski, M. C., *Org. Lett.* **2014**, 16, 1948-1951.
<http://dx.doi.org/10.1021/ol500506t>
17. Song, J.; Wang, Y.; Deng, L., *J. Am. Chem. Soc.* **2006**, 128, 6048-6049.
<http://dx.doi.org/10.1021/ja060716f>
18. Zhang, H.; Syed, S.; Barbas III, C. F., *Org. Lett.* **2010**, 12, 708-711.
<http://dx.doi.org/10.1021/ol902722y>
19. Tillman, A. L.; Ye, J.; Dixon, D. J., *Chem. Commun.* **2006**, 1191-1193.
<http://dx.doi.org/10.1039/b515725k>
20. Auvil, T. J.; Schafer, A. G.; Mattson, A. E., *Eur. J. Org. Chem.* **2014**, 2014, 2633-2646.
<http://dx.doi.org/10.1002/ejoc.201400035>
21. Schreiner, P. R., *Chem. Soc. Rev.* **2003**, 32, 289-296.
<http://dx.doi.org/10.1039/b107298f>
22. Yu, X.; Wang, W., *Chem. Asian J.* **2008**, 3, 516-532.
<http://dx.doi.org/10.1002/asia.200700415>
23. Han, X.; Zhong, F.; Lu, Y., *Adv. Synth. Catal.* **2010**, 352, 2778-2782.
<http://dx.doi.org/10.1002/adsc.201000562>
24. Takemoto, Y., *Org. Biomol. Chem.* **2005**, 3, 4299-4306.
<http://dx.doi.org/10.1039/b511216h>
25. Takemoto, Y., *Chem. Pharm. Bull.* **2010**, 58, 593-601.
<http://dx.doi.org/10.1248/cpb.58.593>
26. McCooey, S. H.; Connon, S. J., *Angew. Chem.* **2005**, 117, 6525-6528.
<http://dx.doi.org/10.1002/ange.200501721>
27. Kang, Y. K.; Kim, D. Y., *J. Org. Chem.* **2009**, 74, 5734-5737.
<http://dx.doi.org/10.1021/jo900880t>
28. Albrecht, L.; Jiang, H.; Jørgensen, K. A., *Chem. Eur. J.* **2014**, 20, 358-368.
<http://dx.doi.org/10.1002/chem.201303982>
29. Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L., *Acc. Chem. Res.* **2004**, 37, 621-631.
<http://dx.doi.org/10.1021/ar030048s>
30. Cai, X.-h.; Xie, B., *Arkivoc* **2013**, 1, 264-293.
31. Das, S. K.; Mujahid, M.; Arvidsson, P. I.; Kruger, H. G.; Naicker, T.; Govender, T., *Tetrahedron Lett.* **2015**.
32. Szollosi, G.; Bartok, M., *Chirality* **2001**, 13, 614-618.
<http://dx.doi.org/10.1002/chir.10000>
33. Pihko, P. M.; Pohjakallio, A., *Synlett* **2004**, 2115-2118.
<http://dx.doi.org/10.1055/s-2004-831326>

34. Trani, F.; Scalmani, G.; Zheng, G.; Carnimeo, I.; Frisch, M. J.; Barone, V., *J. Chem. Theory Comput.* **2011**, *7*, 3304-3313.
<http://dx.doi.org/10.1021/ct200461y>
35. Scalmani, G.; Frisch, M. J.; Mennucci, B.; Tomasi, J.; Cammi, R.; Barone, V., *J. Chem. Phys.* **2006**, *124*, 094107.
<http://dx.doi.org/10.1063/1.2173258>
36. Zhu, H. J., *Organic Stereochemistry: Experimental and Computational Methods*, 163-204.