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# Synthesis and X-Ray Structure of a 1,2,3,6-Tetrahydropyridine-based Phenylalanine Mimetic

**Andrew D. Abell*, James Gardiner, Andrew J. Phillips, Ward T. Robinson**

*Department of Chemistry, University of Canterbury, Christchurch, New Zealand*

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***Abstract:*** A ring-closing metathesis reaction on methyl (2*R*)-(*N*-allyl-*N*-benzoylamino)-2-benzylpent-4-enoate **5**, prepared as a single isomer from L-phenylalanine, gave a conformationally restricted 1,2,3,6-tetrahydropyridine-based phenylalanine mimetic **6** in good yield. The solid state conformation of which was determined by X-ray crystallography. 

Peptides are highly flexible molecules that are capable of adopting multiple conformations, many of which are biologically unimportant. The conformation of a peptide is, therefore, critical to its biological activity and function.[1,2] As a consequence, much effort has been invested into the design and synthesis of amino acid mimetics which possess well defined conformational restriction.[1,2] These mimetics can be incorporated into peptides to provide probes to study the conformational requirements for activity and also to provide analogues with improved potency, stability, bioselectivity, and bioavailability. Freidinger lactams, peptidomimetics in which the α-carbon of an amino acid residue in a peptide is cyclised onto the nitrogen of the adjacent C-terminal amino acid, have been extensively studied in this context.[2b,3] Another classic example of conformationally restricted peptidomimetics can be found in the myriad of cyclic β-turn mimics that have been reported.[2,4,5] There has also been much recent interest in constructing biopolymers, or foldamers, based on simple cyclic peptidomimetics such as pyrrolin-4-ones[6] and cyclic β-peptides.[7] The resulting compounds possess well defined and stable secondary structures. An important natural example of the link between conformation and biological function is evidenced by the ability of proline, and its derivatives, to induce secondary structure in peptides and proteins.[8]

A definite need exists to identify new, readily available, and general classes of amino acid mimetics possessing a well defined and documented configuration and conformation.[9] We, like others,[10] were attracted to the pioneering work of Grubbs *et al*,[11] whereby dienic substrates can be efficiently cyclised in a ring-closing metathesis reaction (RCM) to give ring structures of varying size, as a means to address this need. To this end, we report the synthesis and solid state conformation, as determined by X-ray crystallography, of a 1,2,3,6-tetrahydropyridine-based phenylalanine mimetic.

The synthesis (Scheme 1) began with the preparation of the *anti* oxazolidinone **2** from L-phenylalanine.[12,13] This was then deprotonated at C4 with lithium hexamethyldisilazide (LiHMDS) in THF at -78°C, and the resulting anion was reacted with allyl bromide (1.5 equiv) to give the alkylated oxazolidinone **3** as a single isomer (by $^1$H NMR) in 93% yield. Hydrolysis of the oxazolidinone ring of **3**, followed by the addition of an excess of diazomethane, gave the α-allyl phenylalanine analogue **4** in 91% yield. Allylation on nitrogen then gave the dienic derivative **5** in 30% yield† which was cyclised using

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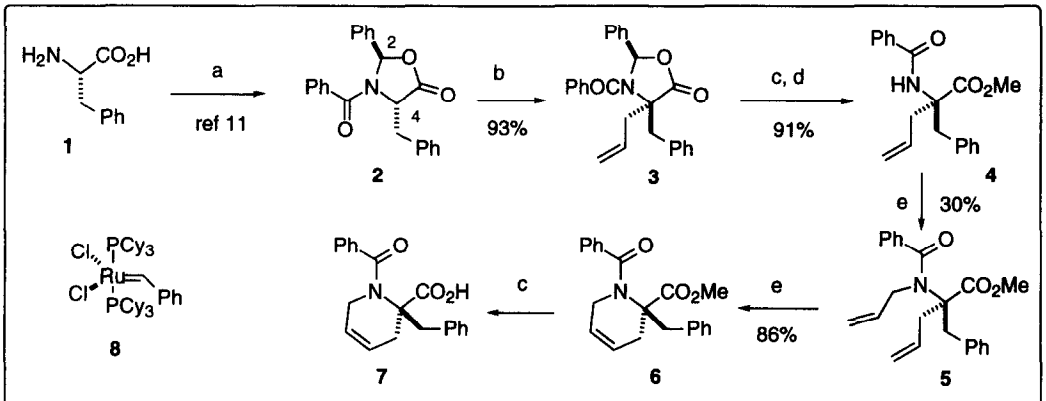


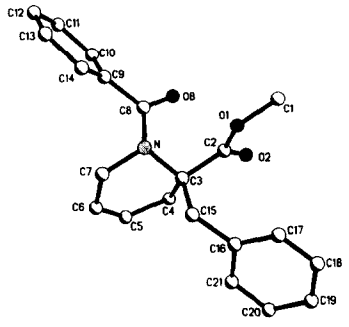

**Scheme 1.** *Reagents and conditions:* (a) 1M aq NaOH then PhCHO, 1,2-DCE, reflux then PhCOCl, -20 °C to 4 °C; (b) LiHMDS, THF, -78 °C then allyl bromide, warm to rt; (c) NaOH, MeOH/$H_2O$ (5:1), reflux; (d) $CH_2N_2$, diethyl ether; (e) NaH, DMF, 0 °C then allyl bromide; (e) **8**, $CH_2Cl_2$, rt, 2 h.

Grubbs' ruthenium alkylidene conditions[11] to provide the doubly protected, phenylalanine mimetic **6**, as a single isomer in 86% yield.‡ Sodium hydroxide catalysed hydrolysis of the methyl ester of **6** gave the free acid **7**. It should be noted that the cyclic peptidomimetics **6** and **7** possess the opposite relative configuration as natural amino acids, eg L-proline. The configuration of **6** is set by the absolute configuration at C2 of **2**, ie this centre governs which face of the planar C4 enolate, derived from **2** on treatment with LiHMDS, is allylated (Scheme 1, conditions b). This configuration is in turn determined by the configuration of the starting amino acid.[12,13] The synthetic method detailed in Scheme 1 should, however, provide a convenient and general synthesis of 1,2,3,6-tetrahydropyridine-based amino acid mimetics from a range of oxazolidinones derived from both natural and non-natural amino acids.[12,13]

The factors which govern the ease of RCM reactions of peptide-based dienes are only now beginning to be explored.[10] For example, it has recently been shown that the nature of the *N*-protecting group of the diene is critical to the success of RCM reactions such that BOC-protected *N*-allyl glycines do not undergo reaction while the corresponding *N*-trityl derivatives do. This observation was originally attributed to the presence of an acidic proton at Cα,[11] however, it is now thought to be due to a conformationally dependent electronic effect which deactivates the vinyl double bond in the BOC case.[10a] α,α-Disubstitution of an amino acid-based diene substrate would also seem to favour the ease of RCM cyclisations. The present study whereby **5** is readily cyclised to give **6**, while the *N*-allyl allylglycine derivative is inert under the same conditions,[11] supports this proposal.

Finally, the solid state structure of **6** was determined, by X-ray crystallography, in order to define the conformation of the backbone of the amino acid mimetic. The asymmetric unit for compound **6** contained two independent molecules which differed slightly in conformation, principally about the benzyl group. A perspective drawing of one molecule of **6**, with atom labelling, is presented in Figure 1. A proline-like N to Cα cyclization, as in **6**, results in significant restriction about the C8-N-C3-C2 (peptide-backbone) torsion which also narrows the conformational space explorable by the adjacent torsion angles. In the current crystal structure of **6**, this torsion angle# is 38.7(2) / 40.2(2)° a value significantly shorter than that reported for proline.[9] The adjacent N-C3-C2-O1, C8-N-C3-C15 and C9-C8-N-C3 torsion angles are 53.24(18) / 50.60(18)°, 155.51(15) / 157.20(15)° and 175.97(15) / 177.90(15)°, respectively. The

**Figure 1.** ORTEP diagram of **6** showing crystallographic numbering scheme




magnitude of the C9-C8-N-C3 and C8-N-C3-C15 torsion angles are consistent with a *Z* amide bond and *anti* relationship between the benzoyl and benzyl groups, respectively. The C4, C5, C6 and C7 ring atoms are approximately in the same plane with N and C3 deviating from the least squares plane defined by the other four ring atoms by -0.2970 / -0.2739 Å and 0.4698 / 0.4904 Å , respectively. Some pyramidalisation of the amide nitrogen is evident with the angles at N summing to 351.14° / 350.17°.

In conclusion, we present a convenient synthesis of a 1,2,3,6-tetrahydropyridine-based phenylalanine mimetic using a combination of Grubbs' RCM chemistry to give the cycle and Seebach oxazolidinone chemistry to establish the absolute stereochemistry. This sequence of reactions should be amenable to the preparation of a range 1,2,3,6-tetrahydropyridine-based amino acid mimetics using oxazolidinones based on both natural and non-natural amino acids. The solid state conformation of the new mimetic has also been determined by X-ray crystallography. Ongoing work is centred on incorporating the procedure into solid phase protocols to provide ready access to peptides whose secondary structure will be studied.

## Acknowledgment

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## References and Footnotes

† Yield not optimised. Starting material (17%) also recovered.

‡ To a solution of **5** (100 mg, 0.3 mmol) in degassed dichloromethane (5 mL) was added bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride (Grubbs' catalyst) (23 mg, 0.03 mmol) and the initially purple solution was stirred at room temperature under $N_2$ for 2 h. The brown reaction mixture was concentrated and the residue was purified by flash chromatography on silica, eluting with 2:3 ethyl acetate/petroleum ether, to give **6** (79 mg, 86%).

# torsion angles, throughout, are given for both molecules in the asymmetric unit.

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