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Conformationally Constrained Amino Acids: Synthesis of Novel 3,4-Cyclised Tryptophans.

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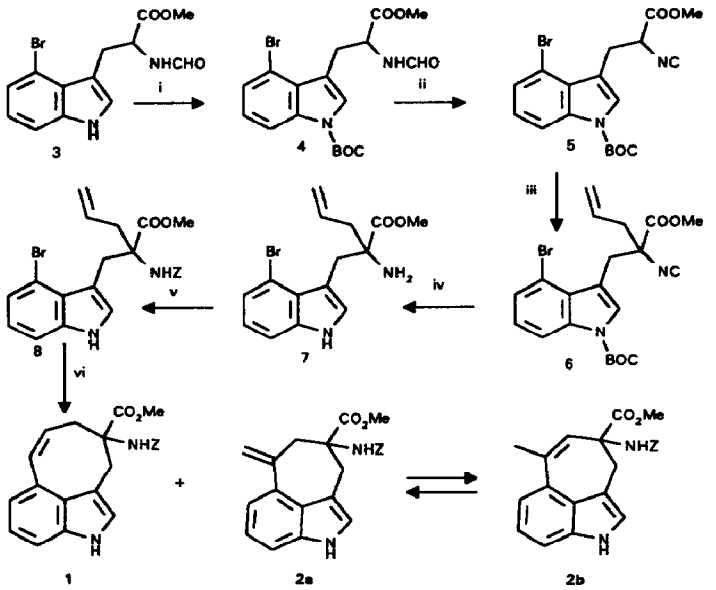
Abstract: The synthesis of novel conformationally constrained tryptophan derivatives via a Heck-type cyclisation of an unusual α-substituted amino acid is described.

The development of potential therapeutic agents based on the structure of peptides has stimulated a keen interest in the design and synthesis of unusual and unnatural amino acids.[1-5] When incorporated into the peptide of interest, these surrogates may infer conformational constraint as well as increasing biostability making them non-peptidic, rather peptoidic, and suitable for potential use as drug candidates.[6] Many cyclic amino acid analogues have been reported in the literature which include a number of cyclic tryptophan derivatives.[7,8]

Cyclic derivatives that have the α-nitrogen incorporated into the constraining ring cannot be included into peptides without perturbing the global conformation of the peptide through *cis- trans-* amide bond isomerism and the removal of any possible hydrogen bond formation between the nitrogen and a suitable partner. It was the intention of the present project to minimise as much as possible these effects. As a consequence, a set of target molecules was considered (**1**, **2**) in which both the amino and carboxylic acid groups on the α-carbon were exocyclic to the 3,4- ring. One cyclisation strategy to such compounds we considered was a Heck-type coupling. This would involve the synthesis of 4-bromo-α-allyl-tryptophan **8**.

This was achieved according to the synthetic scheme. The 4-bromo-Nα-formyltryptophan **3** was prepared according to standard procedures.[10] The indole nitrogen was protected as the Boc derivative. Dehydration of the formamide using triphosgene yielded the isonitrile **5** ready for α-alkylation. This α-alkylation was realised by the use of lithium diisopropylamide then allyl bromide in 45% yield. The protection of the α-nitrogen was changed from the isonitrile group to the benzyloxycarbonyl (Z) group. This enabled the palladium catalysed cyclisation to proceed without interference from the isonitrile. Treatment of **6** with methanolic HCl both removed the indole Boc group and generated the amine. Protection of the free amine with benzyloxycarbonylchloride gave the required precursor **8**, ready to attempt the cyclisation. The cyclisation proceeded using standard Heck methodology. A 2:1 mixture of compounds which were identified as **1** and **2** respectively after being separated by medium pressure liquid chromatography (MPLC) over reverse phase silica. Detailed NOESY and COSY experiments, coupled with mass spectrometry, UV, IR, and elemental analysis were used to assign the structural formulae to the compounds (supplemental material).



Reagents and Conditions: i) Di-t-butyl carbonate, DMAP (cat.), DMF, RT, 18h, 94%; ii) Triphosgene, Et_3N, CH_2Cl_2, 0°C,18h, 87%; iii) LDA, THF, -78°C, 0.5h, then allyl bromide, RT,45%; iv) MeOH.HCl, 0°C to RT, 4h, >95%; v) Benzyl chloroformate, THF, pyridine, 18h, 70%; vi) Palladium acetate, Et_3N, tri-o-tolylphosphine, acetonitrile,Δ, 6h, 88%

These data also revealed that **2** was a mixture of two isomers in equilibrium, designated **2a** and **2b** in which the double bond has migrated. Compounds **1**, **2a** and **2b** can act as surrogates for tryptophan in tryptophan-containing peptides. These derivatives and their biological activities will be reported elsewhere.

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