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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 9545–9547

A tandem metathesis–hydrogenation route to dicarba analogues of cystine-containing cyclic peptides

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Received 27 September 2004; revised 19 October 2004; accepted 28 October 2004
Available online 13 November 2004

Abstract—Dicarba cyclic peptide analogues of the cyclic peptide octreotide have been synthesised in good yields using a single pot, on resin, tandem homogeneous metal-catalysed metathesis–hydrogenation sequence.
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The cyclic peptide octreotide **1**[1] is a synthetic analogue of the tetradecapeptide somatostatin and when labelled with ^{111}In is marketed as OctreoScan®,[2] an imaging agent for neuroendocrine tumours.[3] The limited availability, high cost and sub-optimal imaging characteristics of this analogue have led to a search for other useful radioisotopic derivatives of **1**.[4] Particular attention is being focussed on ^{99m}Tc and ^{188}Re radiolabelled analogues[5] but the incorporation of these isotopes into cystine-containing peptides is often complicated by the need for a reduction step for the generation of Tc and Re in the (III)–(V) oxidation states required for complexation to the ligand.[6] This reduction step leads to concomitant reduction of the disulfide bridge in octreotide and other cyclic peptides containing cystine bridges resulting in loss of receptor binding affinity.[7]

In octreotide and in many other cases, the cystine bridge serves only a skeletal, structural role and does not act as a reactive functional group and can be replaced with a non-reducible structural mimic without significantly affecting biological activity.[8] Thioether (–S–CH_2–)[9] and the all carbon (–CH_2–CH_2–) bridge[10] have both been used as cystine (–S–S–) isosteres without loss of activity. The synthesis of a dicarba analogue of octreotide **2** involving a generic, on-resin, tandem-homogeneous catalyst strategy is now reported.

The linear peptide sequence was synthesised on Rink amide resin using a modified solid-phase protocol described by Hsieh et al.[11] The resin was functionalised with a *p*-carboxybenzaldehyde linker and the first residue, Fmoc-threoninol, was attached via formation of its acetal **3** (Scheme 1). The next residue, Fmoc-protected allylglycine, was then coupled using HBTU/HOBt reagents. We have previously reported that nonproteinaceous allylglycine can be conveniently generated, in both enantiomeric forms, via Rh(I)-catalysed hydrogenation of α-*N*-acyl dienamides with excellent stereoselectivity (95% ee) and yield (90%).[12] It is also commercially available, albeit at high cost. The remaining sequence was constructed and intermediates were carried through without purification or characterisation up to the octapeptide **4**. A resin aliquot was then removed and the peptide was cleaved from the resin with aqueous trifluoroacetic acid containing ethanedithiol, phenol and thioanisole with simultaneous removal of side-chain protecting groups. The linear peptide **5** was determined to be of >95% purity by reverse-phase preparative chromatography and the structure was confirmed by mass spectral analysis (*m*/*z* 1009.4, $M+H^+$) (Scheme 1).

Carbocycle formation was performed on the solid phase resin to eliminate any potential problems arising from dimerisation and/or poor peptide solubility. Exposure of the fully protected peptide sequence **4** to the

Keywords: Metathesis; Hydrogenation; Octreotide; Tandem reactions.
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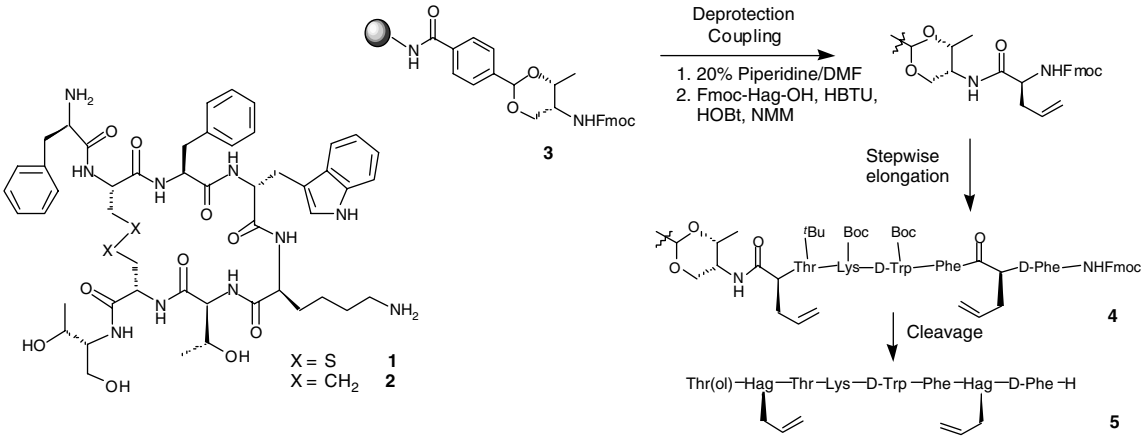
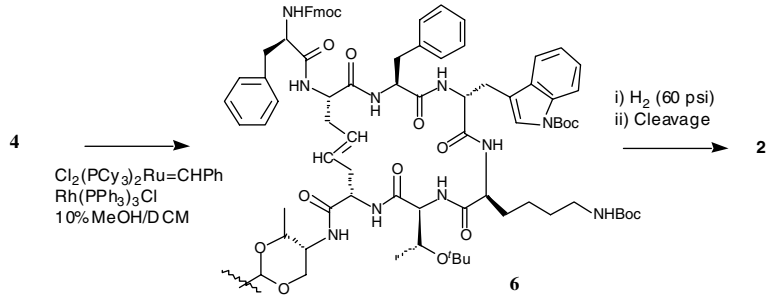
doi:10.1016/j.tetlet.2004.10.165



Scheme 1.



Scheme 2.

ruthenium benzylidene complex $Cl_2(PCy_3)_2Ru{=}CHPh$ (Grubbs' catalyst)[13] resulted in quantitative formation of the carbocycle **6** (Scheme 2). Notably, no oligomerisation or dimerisation via acyclic diene metathesis polymerisation was observed. Exposed amino and carboxylate groups were found to prevent the metathesis reaction.[14] LCMS analysis of the cleaved material showed one major product with molecular mass consistent with the expected product. ^{1}H NMR analysis strongly suggests that this product represents the *cis*-isomer of the carbocycle **6**. Rh(I)-catalysed homogeneous hydrogenation using Wilkinson's catalyst in 10% MeOH–DCM affected quantitative reduction of the resin-attached alkene at room temperature and mild hydrogen pressure (60 psi). The peptide **2** was cleaved from the resin, purified using reverse-phase preparative chromatography (>98.9% purity) and characterised using mass and ^{1}H NMR spectroscopy. Fully deprotected and purified material was obtained from resin-bound **2** and **6** in 23% and 46% yields, respectively.

Grubbs' catalysts[13] have been previously used to facilitate the formation of cyclic peptides via metathesis,[15] but only Vederas and co-workers, in a recent paper targeting oxytocin,[15h] specifically used bis-allylglycine-containing peptides to form dicarba mimics of the cystine bridge. However, the protocol outlined in this publication minimises the number of isolation steps, allows the homogeneous hydrogenation to be carried out on the resin-attached side-chain protected peptide minimising the chances of reduction of liberated functional groups and enables the catalyst to be easily separated from the resin-bound peptide. No solubility problems are encountered with the resin-bound peptide, mild hydrogenation conditions are used and high conversions are obtained.

The methodology developed above is a highly efficient, on-resin route to carbon-based cystine mimics which could find widespread use in peptidomimetic research. Molecular modelling studies of carbocycle **2**,[16] based on X-ray diffraction data of octreotide **1**,[17] suggests that the structural modification should not significantly perturb the Phe^7-D-Trp^8-Lys^9-Thr^{10} binding domain and hence somatostatin receptor affinity. Receptor binding and radiolabelling of carbocycle **2** and deprotected intermediate **6** are currently being assessed.

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