Pd-catalysed C–C macrocyclisation of a simple tripeptide: efficient total synthesis of K-13

Manuel Pérez-González and Richard F. W. Jackson*

Department of Chemistry, Bedson Building, The University of Newcastle, Newcastle upon Tyne, UK NE1 7RU. E-mail: r.f.w.jackson@ncl.ac.uk

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The cyclic tripeptide K-13 has been prepared in 11 steps from commercially available starting materials (11% overall yield); the key step is the Pd-catalysed macrocyclisation of the zinc reagent prepared by selective insertion of zinc into the aliphatic C–I bond of the linear tripeptide 3, followed by Pd-catalysed macrocyclisation.

The conformation of peptides is a key parameter in determining their biological activity. Cyclic peptides, in which the degrees of conformational freedom are reduced, are therefore potentially important targets. Some examples of natural products falling into this class include the aminopeptidase inhibitor OF4949-III^{1a} and the ACE inhibitor K-13 (1).^{1b} There is



substantial interest in the preparation of these targets,² and analogues of these compounds have been proposed as potential



Scheme 1

therapeutic agents.³ Previous routes to these and related compounds have relied on macrocyclisation involving classical amide bond formation, or on formation of the biaryl ether. This latter approach has employed oxidative phenol coupling using thallium trinitrate, Ullmann cyclisations and the S_NAr reaction.⁴ These approaches have the advantage that the precursors for cyclisation are generally easy to prepare, with minimal reliance on protecting groups.

We have already described the palladium-catalysed reaction between aromatic iodides and the organozinc reagent derived from a protected iodolalanine derivative.⁵ The reaction has proved to be versatile and has been extended to dipeptidederived organozinc reagents.⁶ We have therefore explored whether this reaction might be applied to the synthesis of K-13,⁷ in which the key macrocyclisation step is a Negishi crosscoupling reaction of the corresponding open chain peptide **3** (Scheme 1).⁸ This approach has the benefit of requiring the synthesis of relatively simple macrocyclisation precursors, and the potential for broader application since there is no absolute requirement for a biaryl ether in the target.

It was expected that the crucial C–C bond formation could be achieved after chemoselective Zn insertion into the aliphatic C–I bond, followed by a palladium-catalyzed cross-coupling reaction of the resulting organometallic reagent. The viability of this type of coupling in an intermolecular sense had already been demonstrated.⁹ Compound **3** could be obtained by amide bond formation between the peptide **4** and the N-protected biaryl ether amino acid **5**, in which the hydroxy group of the serine residue could then be transformed into an iodide.



Scheme 2 *Reagents and conditions*: (a) 2-fluorobenzaldehyde, K_2CO_3 , DMF, 70 °C, 4 d; (b) MeI, NaHCO₃, DMF, rt, 16 h, 85% (two steps); (c) i, MCPBA, NaHCO₃, CHCl₃, 55 °C, 16 h; ii, K_2CO_3 (cat), MeOH; (d) Chloramine-T, NaI, DMF, rt, 90 min; (e) MeI, K_2CO_3 , DMF, rt, 16 h, 71% (three steps); (f) LiOH, THF–H₂O (1:4), quantitative.



Scheme 3 Reagents and conditions: (a) 4, EDCI, BtOH, iPr₂NEt, DMF, rt, 16 h, 94%; (b) (PhO)₃PMeI, DMF, rt, 20 min, 76%; (c) Zn, I₂ (cat), DMF, rt, 30 min; (d) Pd₂(dba)₃, (0.03 equiv.), P(*o*-Tol)₃, (0.12 equiv.), 3×10^{-3} M THF, 60 °C, 16 h, 35%; (e) i, TFA, thioanisole, CH₂Cl₂; ii, Ac₂O, pyridine 87%; (f) AlBr₃, EtSH, CH₂Cl₂, 85%.

The synthesis of fragment 5 started from commercially available N-Boc protected tyrosine 6. Thus, nucleophilic aromatic substitution reaction between N-Boc protected tyrosine 6 and 2-fluorobenzaldehyde afforded the diaryl ether 7, which was directly transformed into the corresponding methyl ester 8 in 85% overall yield (Scheme 2). Perkin reaction on the aromatic aldehyde 8, using MCPBA in CHCl₃, followed by treatment of the formate intermediate with a catalytic amount of K_2CO_3 in MeOH, provided the phenol 9 in quantitative yield, which was used in the next step without further purification. This compound had already been synthesised by Jung using a different route in 30% yield over three steps.9 At this stage, the enantiomeric purity of compound 9 was checked by removal of the Boc protecting group and Mosher's amide formation using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The enantiomeric purity of 9 was found to be >95% by ¹H-NMR spectroscopy. The use of the free carboxylic acid derivative of tyrosine 6 in the reaction with 2-fluorobenzaldehyde is crucial to ensure high enantiomeric purity; use of the corresponding methyl ester derivative afforded racemic mixtures under a wide variety of conditions. Compound 9 was treated without further purification, following Jung's conditions,9 with one equivalent of Chloramine-T hydrate (sodium salt of N-chlorotoluene-p-sulfonamide)-NaI to produce a mixture of 5-iodo 10 and 3,5-diiodo derivatives in a 90:10 ratio. This mixture was submitted to methylation (MeI, K₂CO₃, DMF) to give 11 (71% from 8 over three steps). This procedure allowed the synthesis of compound 11 on a multigram scale in 60% overall yield from commercially available N-Boc-tyrosine and 2-fluorobenzaldehyde. Finally, acid 5 was obtained in quantitative yield by saponification.

With the key intermediate 5 in hand, the synthesis of the crucial precursor 3 proved straightforward (Scheme 3). Thus,

condensation of compound **5** and HCl·**4**¹⁰ gave the dipeptide **12** (94%), which was transformed into the iodide **3** (76%) using (PhO)₃PMeI in DMF.¹¹ Treatment of iodide **3** with zinc dust in DMF gave a solution of the organometallic intermediate **13**, which was added dropwise to a dilute solution of a catalyst prepared from Pd₂(dba)₃ and P(*o*-Tol)₃ in THF (maximum conc. of **13**, 3×10^{-3} M at 60 °C, and the solution was then stirred overnight. After extractive work up, cyclic dipeptide **2** was isolated by flash chromatography (35%). Compound **2** was transformed into K-13 following the experimental procedure published by Evans and Ellman⁷ in good overall yield (74%). Synthetic K-13 exhibited physical and spectroscopic properties in close agreement with those reported.¹²

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- 12 Synthetic K-13 (1): mp (MeOH–diethyl ether) 265–270 °C (decomp.); lit.^{1b} mp 260–270 °C (decomp.); $[\alpha]_D = -6.6 (c \ 1.4, MeOH)$; lit.⁷ $[\alpha]_D = -6.5 (c \ 0.46, MeOH)$, natural^{1b} $[\alpha]_D = -3.4 (c \ 0.6, MeOH)$; ^{1H–}NMR (500 MHz, CD₃OD) δ 7.29 (dd, J 8.0, 2.0, 1 H), 7.04 (dd, J 8.5, 2.5, 1 H), 6.99–6.93 (m, 3 H), 6.80 (dd, J 8.0, 1 H), 6.73 (dd, J 8.0, 2.0, 1 H), 6.66 (dd, J 8.0, 2.5, 1 H), 6.62–6.57 (BB', 2 H), 6.38 (d, J 2.0, 1 H), 4.48–4.40 (m, 2 H), 4.17 (t, J 5.5, 1 H), 3.17 (dd, J 15.5, 2.0, 1 H), 3.01 (dd, J 12.5, 5.5, 1 H), 2.95 (dd, J 13.0, 6.0, 1 H), 2.91 (dd, J 15.5, 9.0, 1 H), 2.85 (dd, J 13.5, 5.0, 1 H), 2.77 (t, J 12.0, H), 2.03 (s, 3 H); ¹³C-NMR (125.7 MHz, CD₃OD) δ 175.5, 172.9, 172.2, 171.5, 158.2. 157.0, 147.8, 147.5, 132.8, 132.0 (3C), 131.2, 130.7, 128.2, 125.4, 122.1, 120.8, 118.8, 117.5, 115.8 (2C), 57.3, 55.9, 54.3, 39.1, 38.7, 36.6, 22.4.