Application of 7-*endo*, 8-*endo* and 9-*endo* radical cyclisations to the synthesis of conformationally constrained amino acids and comparison with the corresponding Heck reactions

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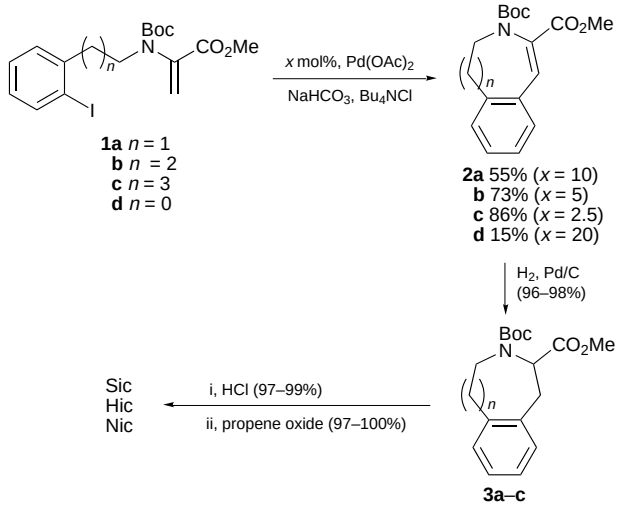
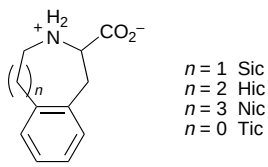
Radical cyclisation of substrates 1a–c proceeds smoothly to give seven-, eight- and nine-membered rings 3a–c in 73, 71 and 52% yield respectively; comparison of these results with those obtained using the intramolecular Heck reactions suggests that the two cyclisation methods provide complementary approaches to medium-sized rings.

The formation of seven-, eight- and nine-membered rings *via* radical cyclisation methods is generally believed to be difficult and hence of marginal synthetic use.[1] Indeed, whilst there are several hundred examples of high-yielding radical-based five- and six-membered ring-forming reactions,[1a] examples of the formation of seven-membered rings by this approach are relatively rare,[1a,2] and most of them proceed in moderate yield. A mere handful of eight-membered ring syntheses have been reported,[1a,3] and, to the best of our knowledge, there are only two reports to date of radical-mediated nine-membered ring-forming reactions.‡,[3c,4]

We recently synthesised Sic, Hic and Nic,[6] novel analogues of the well-established and readily-available conformationally constrained phenylalanine analogue Tic. Our approach to Sic, Hic and Nic utilised an intramolecular Heck reaction on substrates **1a–c** to create the required seven-, eight- and nine-membered rings in 55, 73 and 86% yield catalysed by 10, 5 and 2.5 mol% of palladium acetate respectively (Scheme 1),



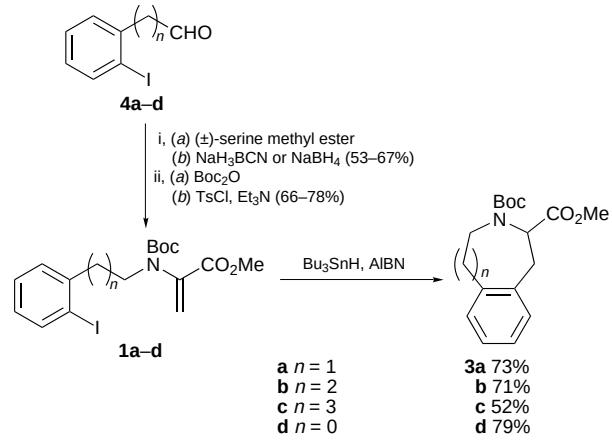
Scheme 1



reactions which represent rare examples of the use of the Heck reaction to create seven-, eight- and nine-membered rings.[7] The products of the Heck reaction (**2a–c**) were hydrogenated to **3a–c** which in turn were deprotected to give the required amino acids. Subsequent incorporation of Tic, Sic, Hic and Nic into a cholecystokinin-B/gastrin receptor antagonist revealed a significant difference in biological activity between the Nic-containing ligand and the other ligands,[8] the source of which is currently being actively pursued.

In view of the moderate yield and high catalyst loading of the reaction used to synthesise the seven-membered ring and the current interest in comparing the outcome of radical cyclisations and Heck reactions on a given substrate,[2d,9] we decided to explore the possibility of using radical reactions to create the required rings. Despite the poor precedent for the use of radical cyclisations to generate seven-, eight- and nine-membered rings, we were somewhat encouraged by the relatively high cyclisation rates observed for aryl radicals[1] and the established ability of captodative radicals to influence the *endo*/*exo* selectivity of radical reactions,[2a] and thus the radical cyclisation of substrates **1a–c** was attempted.

Substrates **1a–c** were synthesised as described previously[6] from the iodo aldehydes **4a–c** and (±)-serine methyl ester. Preliminary experiments indicated that slow addition of Bu_3SnH to the aryl iodide was the preferred experimental procedure and thus a mixture of Bu_3SnH (1.1 equiv.) and AIBN (0.1 equiv.) in nitrogen-saturated benzene was added over 1 h to a solution of **1a** and AIBN (0.1 equiv.) in nitrogen-saturated benzene maintained at 80 °C to give a reaction mixture 0.008 m in **1a**. The reaction mixture was heated under reflux for a further 1 h. Subsequent solvent removal, addition of DBU in diethyl ether, titration with etheral iodine (0.1 m), silica gel filtration[10] and column chromatography gave a colourless oil which was identified as the cyclic product **3a** by microanalysis and comparison of its ^1H and ^{13}C NMR spectra with those of a fully



Scheme 2

characterised sample of **3a** prepared previously.[6] Encouraged by the 73% yield obtained for **3a**, which represents a considerable improvement on the Heck approach to **3a**, an identical procedure was applied to substrates **1b** and **1c**. Gratifyingly, these reactions proceeded surprisingly smoothly to give the eight-membered ring **3b** in 71% yield and the nine-membered ring **3c** in 52% yield (Scheme 2).

In order to provide a fuller comparison between the intramolecular Heck reaction and the radical cyclisation method, the palladium-catalysed and the Bu_3SnH-promoted reactions of substrate **1d** were examined. As anticipated from the results described above, the Heck reaction required large quantities of palladium catalyst (20 mol%) to produce a poor yield (15%) of the six-membered ring **2d** (obtained as an inseparable 1 : 1 mixture with 1-methoxycarbonyl-1-methyl-2-(*tert*-butoxycarbonyl)-1,2,3-trihydroisoindole, a product of the *exo* mode of cyclisation), whilst the radical cyclisation proceeded much more smoothly to give a high yield (79%) of the novel Tic precursor **3d**.

In conclusion, 6-*endo*, 7-*endo*, 8-*endo* and 9-*endo* radical cyclisations have been used to synthesise precursors to conformationally constrained amino acids. Furthermore, comparison of the yields obtained and the catalyst loadings used for the conversion of **1** to **2** with the yields obtained for the conversion of **1** to **3** suggests that radical cyclisations and intramolecular Heck reactions provide complementary approaches to the synthesis of medium-sized rings.

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Footnotes

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‡ In addition, an elegant tandem 9-*endo*-5-*exo* radical cyclisation to form a 5,6-fused bicyclic ketone is of note (ref. 5).

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