A tandem radical approach to the ABCE-rings of the *Aspidosperma* and *Strychnos* alkaloids

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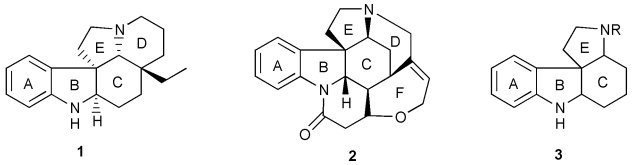
Received (in Liverpool, UK) 16th October 2000, Accepted 18th December 2000
First published as an Advance Article on the web

Reaction of indole 19 *via* the derived aryl radical gives the tetracycle 20 in 43% yield. This compound contains the ABCE-rings of both *Aspidosperma* and *Strychnos* alkaloids.

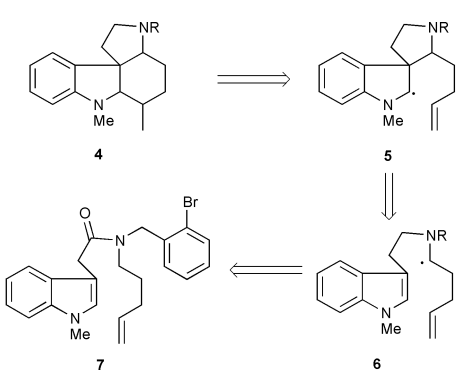
The pentacyclic *Aspidosperma* alkaloids such as aspidospermidine **1** and the heptacyclic *Strychnos* alkaloids such as



1 **2** **3**

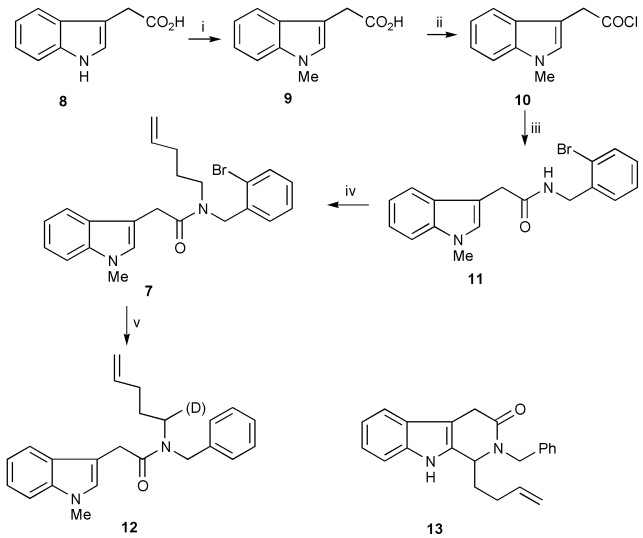
strychnine **2** remain interesting targets for synthetic chemists owing to their chemical architecture and their biological activities.[1] The tetracyclic sub-structure **3**, consisting of the ABCE-rings of both these series of natural products represents the core of these molecules and functionalised examples of this tetracycle have featured in the total synthesis of both *Strychnos* and *Aspidosperma* alkaloids.[2] Efficient approaches to **3** carrying appropriate functionality would allow not only the synthesis of these natural products but also related non-natural products. Some years ago, we commenced a programme of research based on a strategy of radical cyclisation to form oxindoles (indolin-2-ones) followed by carbanion cyclisation to create the B- and C-rings.[3] Murphy has disclosed a tandem radical cyclisation route to this tetracyclic structure in which the B- and E-rings are created by an aryl radical addition to a double bond followed by internal trapping of the resultant radical by an azide.[4] This provides an alternative to the 'radical-polar crossover' chemistry developed by the same group and utilised in a synthesis of (±)-aspidospermidine **1**.[5] Parsons has also reported a conceptually different approach to the *Aspidosperma* skeleton using aryl radicals.[6] We now wish to disclose a new route to the ABCE–tetracycle using a novel tandem radical route to create the C- and E-rings.

The new disconnection sequence is shown in detail in Scheme 1. The key features of this plan involve the addition of radical **6** to the indole 3-position to create the E-ring. The α-amino radical generated in this step can then be captured in a 6-*exo* manner to create the C-ring. In order to generate radical **6**, it was decided to take advantage of the well-known ability of aryl radicals to abstract hydrogen atoms *via* a 6-membered ring transition state.[7] This analysis led back to the tertiary amide **7** as the substrate for a series of radical reaction steps under the usual conditions of tributyltin hydride (TBTH) and a suitable initiator.



Scheme 1

The synthesis of radical precursor **7** commenced with indole-3-acetic acid **8** (Scheme 2). Treatment with sodium hydride and methyl iodide gave the *N*-methylindole-3-acetic acid **9** in 93% yield. Reaction of **9** with oxalyl chloride in THF at 0 °C gave the acid chloride **10** which was reacted immediately with 2-bromobenzylamine hydrochloride in the presence of excess diisopropylethylamine to give amide **11** in overall 86% yield. Alkylation of **11** with 5-bromopentene using potassium hydride as base in THF and tetrabutylammonium iodide as catalyst proceeded smoothly resulting in tertiary amide **7** in 73% yield. The ^{1}H NMR spectrum of **7** showed clearly the presence of two rotamers caused by restricted rotation about the amide bond. The minor rotamer possessed a singlet resonance at δ 4.72 assigned to the benzyl group in **7a** (Fig. 1) whilst the major rotamer displayed a singlet at δ 4.56 assigned to the benzyl group in **7b**. Integration of these signals revealed a ratio of 6:5 favouring **7b**. It is well known that the timescale for amide bond rotation to occur is considerably longer than the lifetime of radical intermediates which means that cyclisation of the translocated radical derived from major rotamer **7b** is unlikely.[8]



Scheme 2 *Reagents and conditions*: i, NaH, THF, 0 °C, then MeI warm to 20 °C, 12 h, 93%; ii, oxalyl chloride, THF, 0 °C to 20 °C, 20 h; iii, 2-bromobenzylamine hydrochloride, *N*,*N*-diisopropylethylamine, dichloromethane, 0 °C, 2 h, 86%; iv, KH, THF, 0 °C, then 5-bromopentene, tetrabutylammonium iodide, warm to 20 °C for 20 h, 73%, v, TBTH (or TBTD), AIBN, xylene, reflux, 10 h.

DOI: 10.1039/b008465o

With this problem in mind, reaction of **7** with TBTH at reflux in xylene under dilute conditions (0.02 M) was carried out. A complex mixture of products was obtained and to help determine the nature of the products, the reaction was repeated using tributyltin deuteride (TBTD). Extensive spectroscopy on the isolated products allowed assignment of the structure **12** (both rotamers) to the major product (50%) and structure **13** to one of the minor products (18%). Both products contained the intact alkene unit indicating that tetracycle formation had not occurred whilst the product **12** from reaction with TBTD contained deuterium adjacent to the nitrogen indicating successful radical translocation. Addition of the intermediate α-amido radical to the indole C-2 followed by rearomatisation to give **13** is not unreasonable given the results of Moody[9] and related work by Bowman[10] in other heteroaromatic systems. Product **12** could simply be arising from the major rotamer **7b** which cannot cyclise. However, the isolation of **13** indicates that the rather nucleophilic α-amido radical prefers to add to the indole ring at the C-2 position.

Following the precedent in the work of Fang,[11] we decided to introduce an electron-withdrawing group at the 2-position of indole **7** to encourage addition of the nucleophilic α-amido radical to C-3 of the indole. Reaction of 3-methylindole with triphenylphosphine–thiocyanogen has been reported to give 2-cyano-3-methylindole in 85% yield.[12] Treatment of **7** under these conditions led only to starting material. A variety of other studies to introduce a cyano-group at the 2-position were undertaken but eventually it was decided to develop a new route to the desired radical precursor (Scheme 2). The required secondary amine was prepared following the chemistry of Fukuyama and Bowman.[13] Reaction of 2-bromobenzylamine hydrochloride with sulfonyl chloride **14** gave sulfonamide **15** in 86% yield (Scheme 3). Alkylation using 5-bromopentene and caesium carbonate as base gave **16** in 93% yield and removal of the 2-nitrosulfonamide group was achieved in high yield using potassium carbonate and benzenethiol yielding secondary amine **17**. Reaction of **17** with the acid chloride **18** (derived from the acid[14] by reaction with oxalyl chloride in THF at 0 °C) gave the radical precursor **19** in 83% yield. Again the NMR revealed the presence of rotamers in a ratio of 1.1 : 1. Reaction of **19** with TBTH in refluxing 5-*tert*-butyl-*m*-xylene (*ca.* 200 °C) under syringe pump conditions gave some 50% of reduced product (**19** with Br = H) and 43% of **20** which had undergone the desired translocation–cyclisation–cyclisation sequence. Tetracycle **20** was isolated as a mixture of 4 diastereoisomers in a ratio of 8 : 3 : 2 : 1. The relative stereochemistry of the four diastereoisomers obtained cannot be assigned from their NMR spectra owing to the contiguous quaternary centres at the BC- and CE-ring junctions. Calculations show the *trans,trans* stereochemistry at these ring junctions to be of very high energy leaving 6 possible diastereoisomers, four of which possess the natural *cis* CE-ring junction stereochemistry and two of which possess the *trans* CE-ring junction stereochemistry. Although the transition state for the addition of the α-amido radical to the 3-position of the indole would seem to favour creation of a *cis* CE-ring junction, we cannot rule out the formation of isomers containing the *trans*-CE, *cis*-BC stereochemistry.

In summary, we have shown that the sequence of radical reaction steps shown in Scheme 1 is successful if a cyano group is present at the indole C-2. This short sequence to tetracycles such as **20** may provide a rapid entry into indole alkaloid natural products and related compounds and is under active investigation.

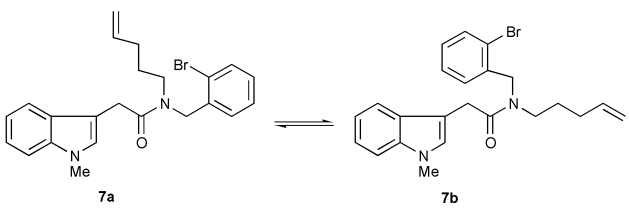
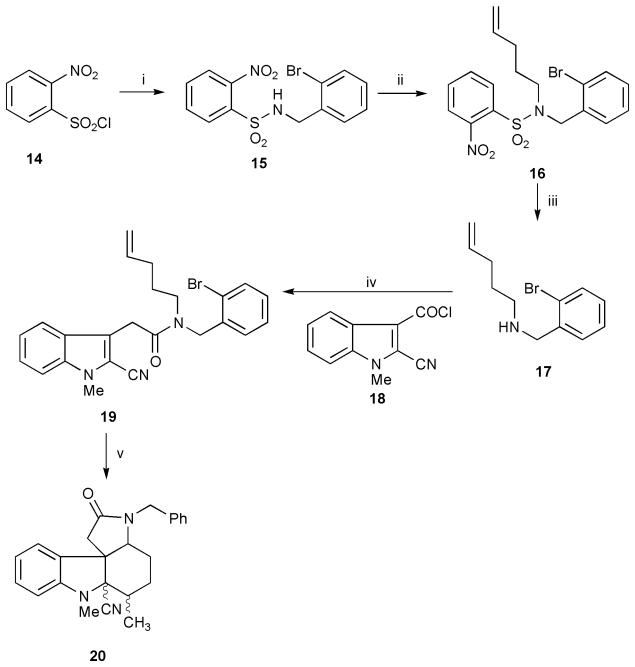


Fig. 1



Scheme 3 *Reagents and conditions*: i, 2-bromobenzylamine hydrochloride, triethylamine, dichloromethane, 0 °C, 86%; ii, caesium carbonate, DMF, 80 °C, 30 min, then 5-bromopentene, 75 °C, 3 h, 93%; iii, potassium carbonate, PhSH, MeCN, 80 °C, 86%; iv, dichloromethane, diisopropylethylamine, 0 °C, 12 h, 83%; v, TBTH, 5-*tert*-butyl-*m*-xylene, syringe pump, reflux, 6 h, 43%.

We should like to acknowledge financial support from Kingston University (S. T. H.), King's College London (T. C. T. H.) and the EU (G. P. and M. S.).

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