CHEMCOMM Communication
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A novel and economical route to (±)-horsfiline using an aryl iodoazide tandem radical cyclisation strategy

Dimitrios Lizos, Régis Tripoli and John A. Murphy*

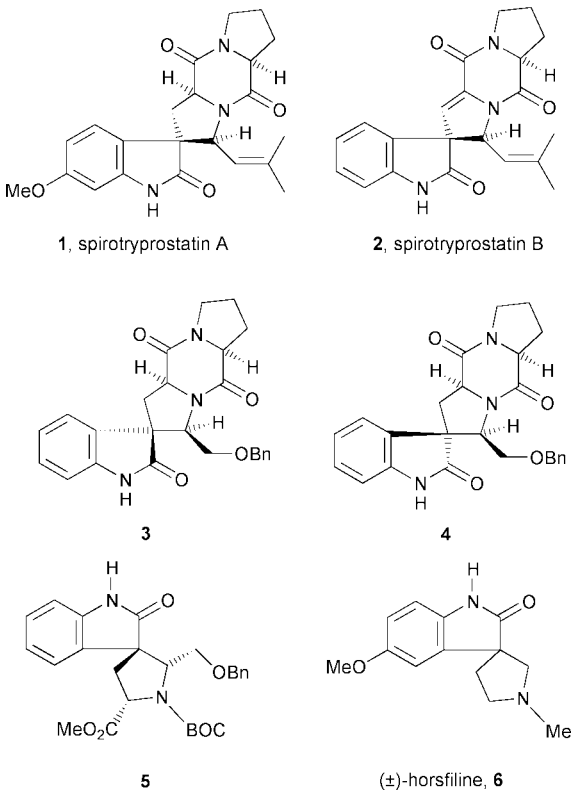
Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, UK G1 1XL. E-mail: john.murphy@strath.ac.uk; Fax: +44 141 548 4822; Tel: +44 141 548 2389

Received (in Cambridge, UK) 24th September 2001, Accepted 23rd October 2001
First published as an Advance Article on the web 29th November 2001

(±)-Horsfiline has been synthesised using a tandem radical cyclisation as the key step.

The spiropyrrolidinyloxindole nucleus is found in a number of natural products of diverse origin. However, despite their attraction as synthetic targets, the biological profile of these compounds was not exciting—until recently. The recent discovery of more members of this family such as spirotryprostatin A (**1**) and spirotryprostatin B (**2**) caused an increased interest, because they showed *mild* activity as cell-cycle inhibitors,[1] since cell-cycle inhibition frequently equates with *in vitro* anti-cancer activity. However, the crucial discovery was in 1999, when Danishefsky *et al.* showed[2] that unnatural analogues (**3**–**5**), synthesised in the laboratory, were truly potent inhibitors of at least one human breast cancer cell line [more than four orders of magnitude more powerful than spirotryprostatin A itself].

With this as background, we set ourselves the task of finding a new and flexible approach to the synthesis of the spiropyrrolidinyloxindole nucleus, and now present our route, which features a tandem radical cyclisation approach as the key step, in the synthesis of one member of the natural spiropyrrolidinyloxindoles, horsfiline (**6**). Horsfiline[3] has been synthesised by a number of research groups[4–9] using diverse methodologies; the synthesis of Jones and Wilkinson[4] deserves particular mention here since it also used a radical cyclisation approach, although very different from our own. Specifically, our approach features the aryl iodoazide[10] tandem radical cyclisation strategy, which we have recently used to prepare the complex alkaloid, (±)-aspidospermidine.[11]



1, spirotryprostatin A **2**, spirotryprostatin B

3 **4**

5 (±)-horsfiline, **6**

Scheme 1

The starting materials for our synthesis are the commercially available and economical compounds, itaconic acid and *p*-anisidine. Double deprotonation of *t*Boc-protected *p*-anisidine **7** (prepared in 91% yield from *p*-anisidine) with *t*-BuLi and reaction with 1,2-diiodoethane afforded the iodide **8** (86%).[12] Deprotection of the *t*-Boc group (89%) and reductive amination with benzaldehyde yielded the required *N*-benzyl derivative **10** (95%). Meanwhile, selective esterification of itaconic acid[13] (82%) and then conversion to the acid chloride **11**, was followed by coupling to the amine **10**, affording amide **12** in 94% yield from the mono-acid. The plan was now to convert this compound to the corresponding azide **18**. Direct reduction of **12** with DIBAL-H yielded alcohol **13**; however, this appeared to be contaminated by, and was inseparable from, the methyl derivative **14** that would result from conjugate addition of DIBAL-H at the α,β-unsaturated amide group. This complication was avoided by protecting the alkene in **12** by conjugate addition of thiophenol. The resulting sulfide **16** (96%) was then reduced to afford the alcohol **17** (55%). [Unexpectedly, this reaction also produced a small amount of amine **15**.] Oxidation of the sulfide and thermal elimination of the resulting sulfoxide yielded the desired alcohol **13** (72%), which was smoothly converted to the azide **18** (68%) with diphenylphosphoryl azide.[14] Cyclisation with tris(trimethylsilyl)silane (TTMSS) followed by *in situ* methylation afforded[15] the tricycle **20** (60% over 2 steps). Finally, this was debenzylated[7,9] to afford horsfiline **6** (87%).

This simple approach to horsfiline illustrates that the aryl iodoazide tandem radical cyclisation strategy[11] is a powerful methodology for accessing the important spiropyrrolidinyloxindole nucleus.

We thank the EPSRC Mass Spectrometry Service Centre, Swansea, for mass spectra, the University of Strathclyde for University studentships (D. L. and R. T.) and the Royal Society for a Leverhulme Senior Research Fellowship (JAM).

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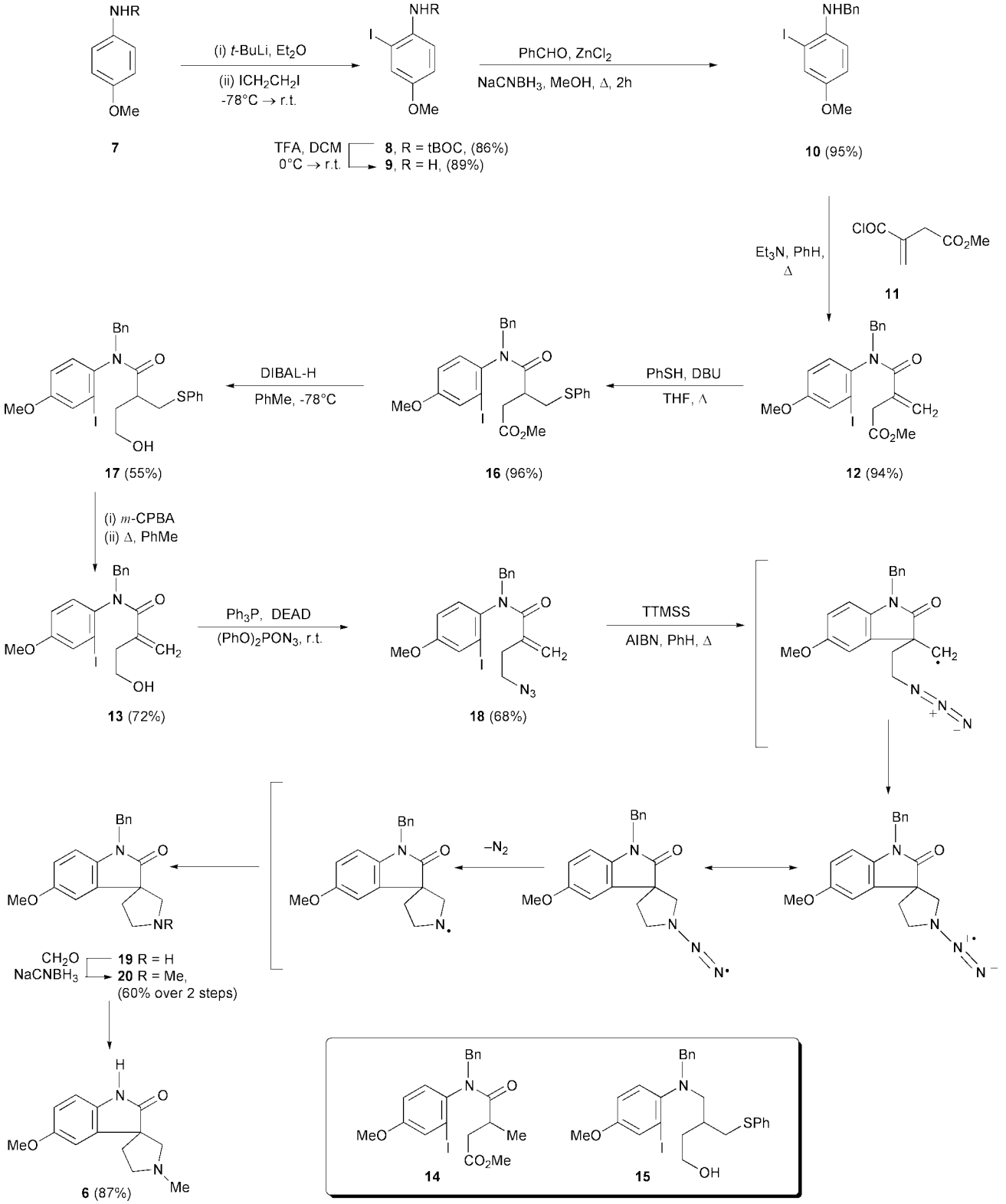

Scheme 2

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