Stereoselective Preparation of the *ABCE* Tetracycle of Aspidospermidine and Related Alkaloids

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Tandem radical cyclisation affords stereoselective access to the *ABCE* tetracyclic substructure of aspidospermidine and related alkaloids.

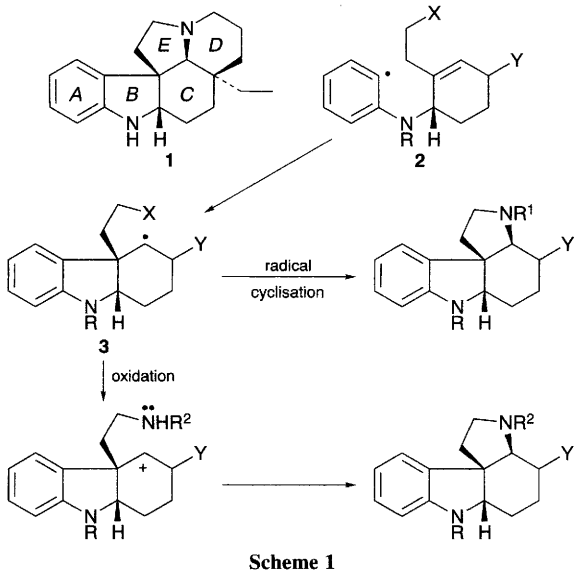
The indole alkaloids[1] feature many indoline-containing compounds with important biological activity, including strychnine and the clinically used anticancer agents vincristine and vinblastine. These compounds share as part of their structure, the [6.5.6.5] *ABCE* ring system also found in aspidospermidine **1**. The structures of these alkaloids have long attracted the attention[2] of the synthetic community, and a major focus of interest has been in finding efficient routes for the introduction of the *B/E* spirocyclic junction, shown in aspidospermidine **1**. We were attracted by the possibility of a stereocontrolled tandem cyclisation, as shown in Scheme 1. The first step, cyclisation of an aryl radical **2** to form an indoline **3**, should be extremely rapid and efficient,[3] since analogous but simpler examples proceed well and with complete stereoselectivity to afford *cis*-fused products. The second ring formation could feature attack by the carbon radical onto a functional group X, so forming a carbon–nitrogen bond,[4–7] or an oxidation of this carbon radical intermediate to a cation followed by a polar cyclisation[8] by a nitrogen nucleophile. In either case, the stereochemical disposition of the side chain will ensure that carbon–nitrogen bond-formation occurs so as to yield the desired relative stereochemistry shown in Scheme 1.

We report here on the first of these possibilities. Radical cyclisations onto azide groups have been pioneered by Kim *et al.*[5], who showed that iodoazides such as **4** react selectively at the iodo group with tributyltin or tris(trimethylsilyl)silyl radicals. However, whereas alkyl iodides[9] behave in this manner, we are not aware of any reports on the behaviour of aryl iodides. The stronger C–I bond could slow the reaction at the iodo group, allowing the azide to be attacked selectively. To investigate this question, the iodoazide **9** was prepared as shown in Scheme 2.

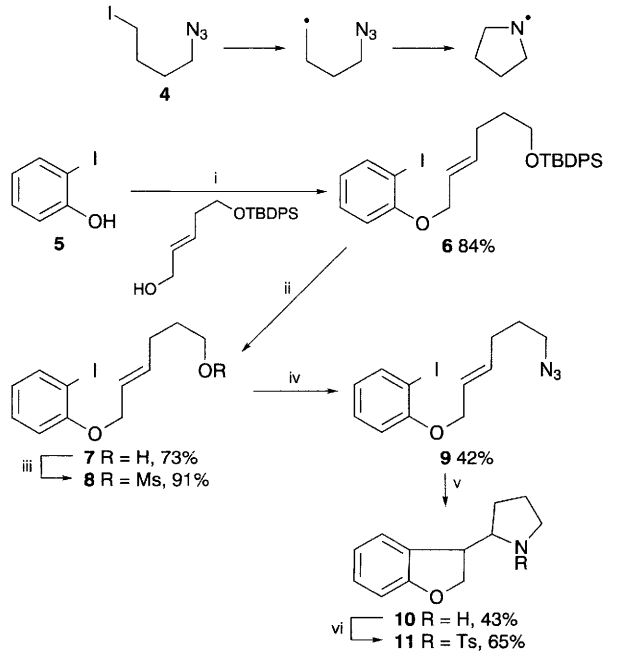
Thus, iodophenol **5** was converted to the silyl ether **6** by Mitsunobu coupling. Deprotection of the silyl group afforded the alcohol **7** and conversion to the mesylate **8** followed smoothly. The transformation to the azide **9** occurred in lower than expected yield (42%), and iodophenol **5** was produced as a by-product in 27% yield. The iodoazide **9** was then subjected to treatment with tristrimethysilylsilane (TTMS) and AIBN in benzene at 80 °C, thus affording the pyrrolidine **10**. Direct isolation led to a 43% yield, but, as suggested by Kim *et al.*, tosylation of the crude product led to isolation of 65% of the sulfonamide **11**. Encouraged by these results, we turned to the alkaloid structure.

The requisite iodoazide **16** was prepared as shown in Scheme 3. Modified Mitsunobu coupling[10] of the methanesulfonamide **12** with the cyclohexenol **13** afforded the diene **14**, which was smoothly transformed into the desired azide **16** *via* the aldehyde **15**.[11] Formation of the azide **16** occurred in high yield with no by-products, unlike in the case of the oxygen-linked substrate above. Cyclisation afforded a very clean crude product **17**; this was washed with dilute acid to afford the amine **18** in 95% yield from **16**. Intriguingly, the spectrum of the crude reaction product differs from that of the subsequently purified amine; the ^{1}H NMR spectrum of the amine featured many broad resonances, in line with our experience of other related aromatic amines. We assume that this is due to intermolecular association of the amine. The crude reaction product, on the other hand, afforded a very well-resolved spectrum. We suggest that the crude spectrum in fact contains not the amine but the tris(trimethylsilyl)silyl derivative **17** [formed by reaction of the amine with tris(trimethylsilyl)silyl iodide] which is hydrolysed on treatment with aqueous acid.

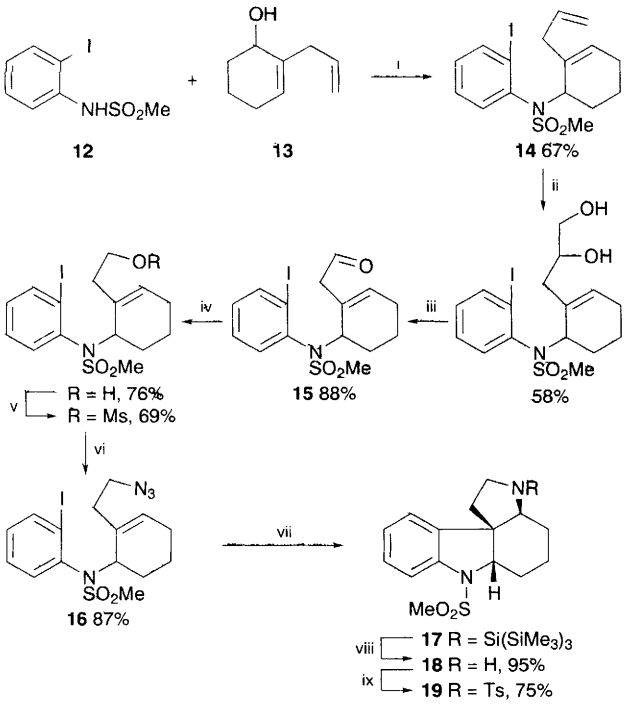
To confirm that the amine was in fact formed, it was converted into the toluenesulfonamide **19**. This sequence shows that the complicated *ABCE* ring system of indoline-containing alkaloids such as aspidospermidine can be assembled by a tandem radical cyclisation sequence. The efficiency of the route



Scheme 1



Scheme 2 *Reagents and conditions*: i, DEAD, PPh_3, THF, room temp., 48 h; ii, TBAF, THF, 12 h; iii, $MeSO_2Cl$, NEt_3, CH_2Cl_2, DMAP, room temp., 5 h; iv, NaN_3, DMF, 60 °C, 5 h; v, TTMS, AIBN, 80 °C, benzene, 5 h; vi, *p*-TsCl, pyridine, DMAP, 110 °C, 12 h



Scheme 3 *Reagents and conditions*: i, DEAD, PPh_3, THF, room temp., 48 h; ii, OsO_4, NMO, acetone–water (9 : 1), room temp., 12 h; iii, $NaIO_4$, Et_2O, H_2O, room temp., 12 h; iv, $NaBH_4$, MeOH, 10 min; v, $MeSO_2Cl$, NEt_3, CH_2Cl_2, DMAP, room temp., 5 h; vi, NaN_3, DMF, 60 °C, 6 h; vii, TTMS, AIBN, 80 °C, benzene, 5 h; viii, H_2O; ix, *p*-TsCl, pyridine, DMAP, 110 °C, 12 h

suggests that the method may be developed in the future to afford high-yielding syntheses of complex alkaloids.

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