A Total Synthesis of Horsfiline *via* Aryl Radical Cyclisation

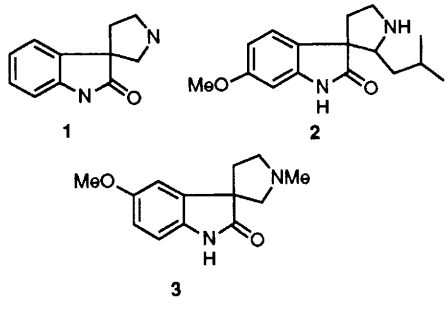
Keith Jones* and James Wilkinson

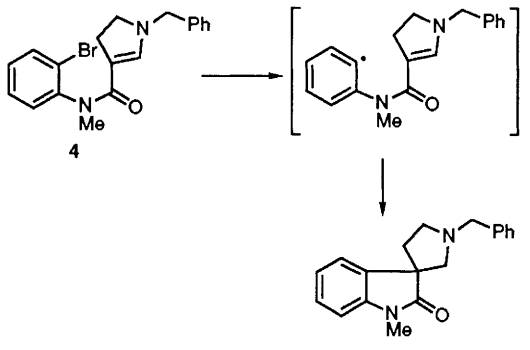
Department of Chemistry, King's College London, Strand, London WC2R 2LS, UK

Cyclisation of **15** *via* the derived aryl radical leads to spiropyrrolidinyl-oxindole **16**, which is converted in three steps into the oxindole alkaloid horsfiline **3**.

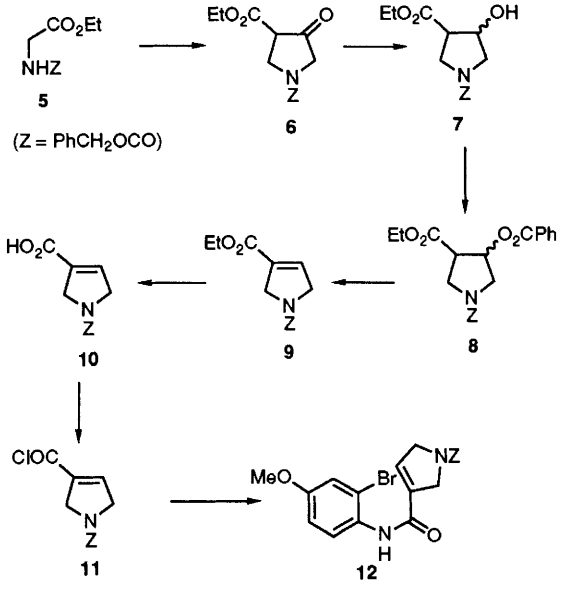
As part of an approach to indole alkaloids of the aspidosperma and strychnos type, we have been interested in using aryl radical chemistry to prepare the spiropyrrolidinyl-oxindole system **1**, which represents three of the rings of these important alkaloid skeletons.[1] Two alkaloids have been isolated that are directly based on the spiropyrrolidinyl-oxindole, an unnamed alkaloid **2** isolated by Canadian workers[2] from *Eleagnus commutata* and horsfiline **3**[3] isolated from *Horsfieldia superba*, a small Malaysian tree, extracts of which have found use in local medicine. Herein, we report the successful application of our aryl radical cyclisation approach to the total synthesis of horsfiline **3** from glycine ethyl ester hydrochloride.

Our early approach was based on the cyclisation shown in Scheme 1.[4] Surprisingly, the yield of cyclised product was, at best, poor. Although the double bond of **4** is considerably more electron-rich than that in our earlier work with acryloylanilides,[5] there are examples of the addition of aryl





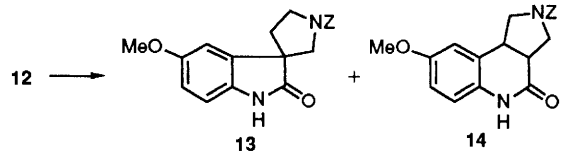
Scheme 1



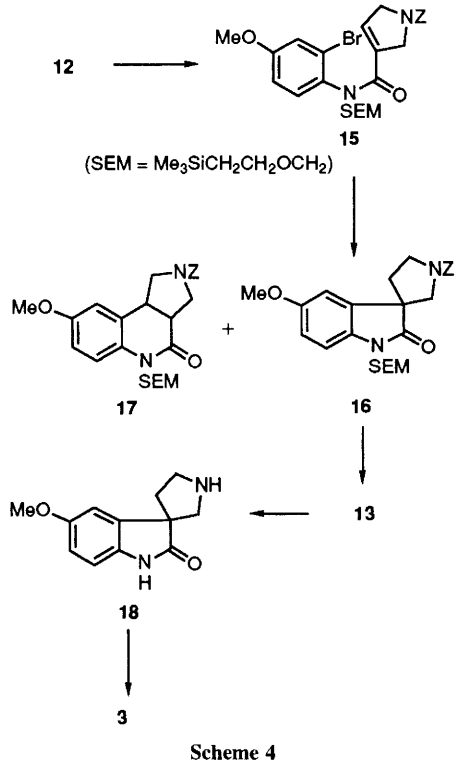
Scheme 2

radicals to electron-rich double bonds.[6] We, therefore, turned our attention to the cyclisation of an aryl radical onto a 2,5-dihydropyrrole unit. After initial unsuccessful attempts to prepare the required 2,5-dihydropyrrole *via* intramolecular aldol chemistry, we developed the synthesis outlined in Scheme 2.[7] Protection of the amino function in ethyl glycine hydrochloride with the benzyloxycarbonyl (Z) group under standard conditions gave **5** in 65% yield. This was treated with ethyl acrylate in toluene containing sodium wire to give **6**† in 83% yield *via* Michael addition followed by Dieckman cyclisation.[8] Reduction of the ketone was achieved using $NaCNBH_3$[9] in methanol at pH 3–4 to give **7**† as a mixture of diastereoisomers (6:1) in 85% yield. Elimination of the hydroxy group to give the α,β-unsaturated ester **9**† was attempted in a variety of ways. Mesylation followed by elimination gave variable yields and we found the most reliable method involved benzoylation (benzoyl chloride, pyridine, 4-dimethylaminopyridine) followed by elimination achieved by heating the benzoates **8**† at 80 °C in toluene in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This reliably gave the α,β-unsaturated ester **9**† in 53% overall yield. Hydrolysis of the ester (KOH, dioxane–water, 50 °C, 45 min) proceeded smoothly to give the acid **10**† in 89% yield. The best conditions for the preparation of the acid chloride **11**† were found to be formation of the triethylammonium salt [NEt_3, 1,2-dimethoxyethane (DME)] and reaction of this with thionyl chloride in DME at 0 °C,[10] which gave the required acid chloride **11**. Reaction of freshly prepared **11** with 2-bromo-4-methoxyaniline in the presence of diisopropylethylamine gave the α,β-unsaturated amide **12**† in an overall yield of 79% from acid **10**.

† All new compounds gave satisfactory spectral and analytical data.



Scheme 3



Scheme 4

Owing to the conformation of the amide bond, treatment of *N*-unsubstituted amides such as **12** with a radical initiator and tributyltin hydride (TBTH) leads only to reduction.[5] Consequently, an alkyl group has to be introduced on to the nitrogen in order to change the conformation of the amide bond. With amide **12** in hand, we decided to try and use a 'one-pot' procedure utilising a trimethylsilyl group as a temporary *N*-substituent, which would be readily removed on work-up.[11] To this end, **12** was treated with one equivalent of lithium hexamethyldisilazide in toluene at 0 °C followed by one equivalent of trimethylsilyl chloride to generate the *N*-trimethylsilylamide (Scheme 3). Introduction of TBTH and azoisobutyronitrile (AIBN) into the reaction solution and heating at 80 °C for 1 h followed by a simple aqueous work-up led to a mixture of two products. The required spiropyrrolidine **13**† was isolated in 29% yield while the pyrrolidinylquinolone **14**† was isolated in 26% yield. In our experience, this is a very high ratio of 6-*endo* cyclisation to 5-*exo* cyclisation for such a system and provides a potential procedure for the synthesis of *N*-unsubstituted oxindoles and dihydroquinolones *via* aryl radical cyclisation. However, in the context of the synthesis of horsfiline this ratio is rather poor. The strategy shown in Scheme 4 was adopted successfully. Reaction of amide **12** with KH in tetrahydrofuran (THF) at room temp. followed by the addition of trimethylsilylethoxymethyl chloride (SEMCl)[12] gave the *N*-SEM amide **15**† in 94% yield. Radical cyclisation (TBTH, AIBN, toluene, reflux, 3 h) gave spiropyrrolidine **16**† in 70% yield along with only 5% of the product of 6-*endo* cyclisation **17**.† This is a far more favourable ratio of 5-*exo* to 6-*endo* cyclisation than that observed in similar systems and is presumably due, at least in

part, to the conformation of the substrate **15**. Spiropyrrolidine **16** was treated with Bu_4NF in dimethylformamide (DMF)–ethylenediamine at 80 °C to remove the SEM group[12] (81%) followed by transfer hydrogenation[13] (cyclohexa-1,4-diene, Pd–C, EtOH, 1 h) to remove the Z group and give desmethylhorsfiline **18**† (85%). The synthesis was completed by treatment of **18** under Eschweiler–Clarke conditions[14] (HCO_2H, HCHO, reflux, 1 h) to achieve *N*-methylation giving horsfiline **3** in 75% yield. The synthetic sample proved to be identical in all spectral details to the natural product.[3]

We thank the SERC for a research studentship (J. W.).

Received, 27th July 1992; Com. 2/04016F

References

1 C. McCarthy and K. Jones, *J. Chem. Soc., Chem. Commun.*, 1989, 1717.
2 M. N. G. James and G. J. B. Williams, *Can. J. Chem.*, 1972, **50**, 2407.
3 A. Jossang, P. Jossang, H. A. Hadi, T. Sévenet and B. Bodo, *J. Org. Chem.*, 1991, **56**, 6527.
4 C. McCarthy, J. Wilkinson and K. Jones, upublished work.
5 K. Jones, M. Thompson and C. Wright, *J. Chem. Soc., Chem. Commun.*, 1986, 115.
6 D. J. Hart and S. C. Wu, *Tetrahedron Lett.*, 1991, **32**, 4099.
7 T. L. MacDonald and B. A. Narayanan, *J. Org. Chem.*, 1983, **48**, 1129.
8 R. Kuhn and G. Osswald, *Chem. Ber.*, 1956, **89**, 1423.
9 R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897.
10 R. J. Boatman and H. W. Whitlock, *J. Org. Chem.*, 1976, **41**, 3050.
11 D. H. Hua, S. W. Miao, S. N. Bharathi, T. Katsuhira and A. A. Bravo, *J. Org. Chem.*, 1990, **55**, 3682.
12 J. M. Muchowski and D. R. Solas, *J. Org. Chem.*, 1984, **49**, 203.
13 J. S. Bajwa, *Tetrahedron Lett.*, 1992, **33**, 2299.
14 M. L. Moore, *Org. React.*, NY, 1949, **5**, 301.