A Total Synthesis of Gelsemine: Oxindole Spiroannelation

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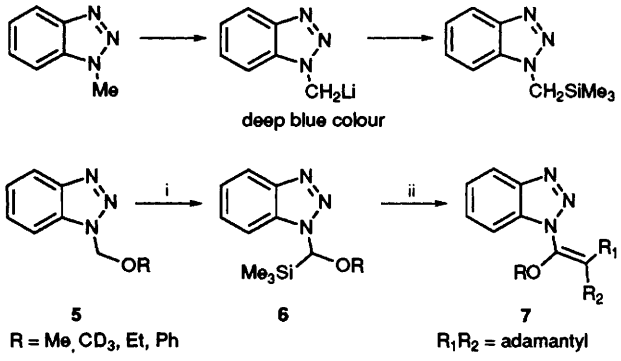
Photolysis of alkoxy-substituted-1-alkenylbenzotriazoles provides a new route to spiro-oxindoles which has been utilised in a total synthesis of gelsemine.

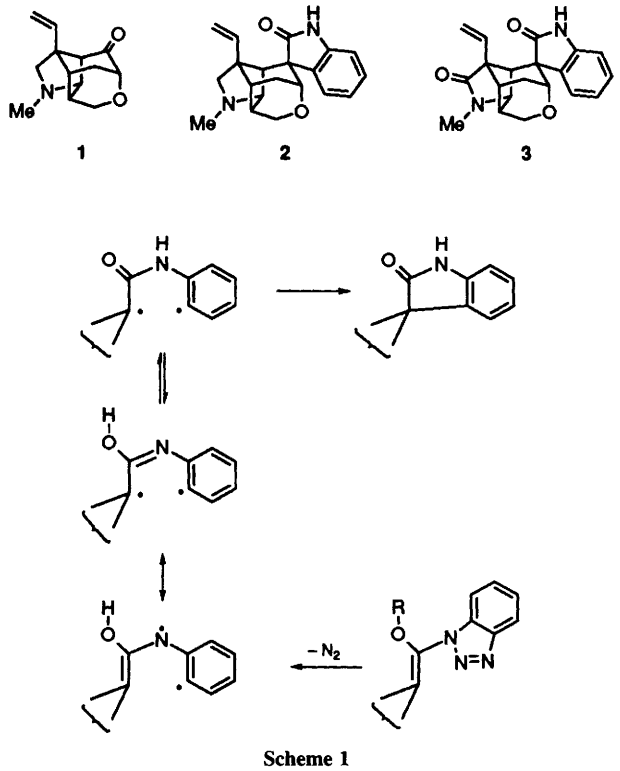
The preceding paper described the synthesis of **1**, a key intermediate in our projected synthesis of the alkaloid gelsemine **2**. Since almost all of the complex functionality which is present in gelsemine is contained in **1**, it was felt that the remaining synthetic problems were relatively straightforward in comparison to those which had already been successfully tackled. This optimism proved to be completely unfounded. The key step remaining involved the conversion of the ketone functionality in **1** to a spiro-oxindole (which would yield 21-oxogelsemine **3**, itself a natural product).[1] Extensive investigations in our laboratory and elsewhere[2] have shown that the conversion of a sterically hindered ketone, such as adamantanone (which has been used as a model for **1**) to an oxindole is not an easy process, and furthermore, that many of the methods which are successful with the model do not work in the real series. After the expenditure of very considerable effort we became convinced that the steric congestion at the reaction site was severe enough to prevent the application of most of the conventional methods for creation of a quaternary centre at this site, and that any successful method would need to be unusually insensitive to steric hindrance. In this context, a process involving C–C bond formation by combination of two radical centres was attractive becasue of the very low activation energy associated with these reactions.[3] A possible route to the required diradical is shown in Scheme 1. The generation of such diradicals from *N*-alkenylbenzotriazoles has ample precedent, including the recent photochemical synthesis of indoles developed by Wender.[4]

A particularly attractive variation of Wender's indole synthesis would involve the creation of an *N*-alkenylbenzotriazole by direct condensation of a ketone with a suitably functionalized benzotriazole. In this connection, we were greatly helped by the discovery[5] that 1-methylbenzotriazole **4**, is readily metallated by lithiumdiisopropylamide or butyllithium, and that the metallated species can be trapped with electrophiles such as chlorotrimethylsilane (Scheme 2). Application of this metallation–silylation to readily available **5** yielded **6** which could be metallated once more and the resulting species added to adamantanone to form the desired

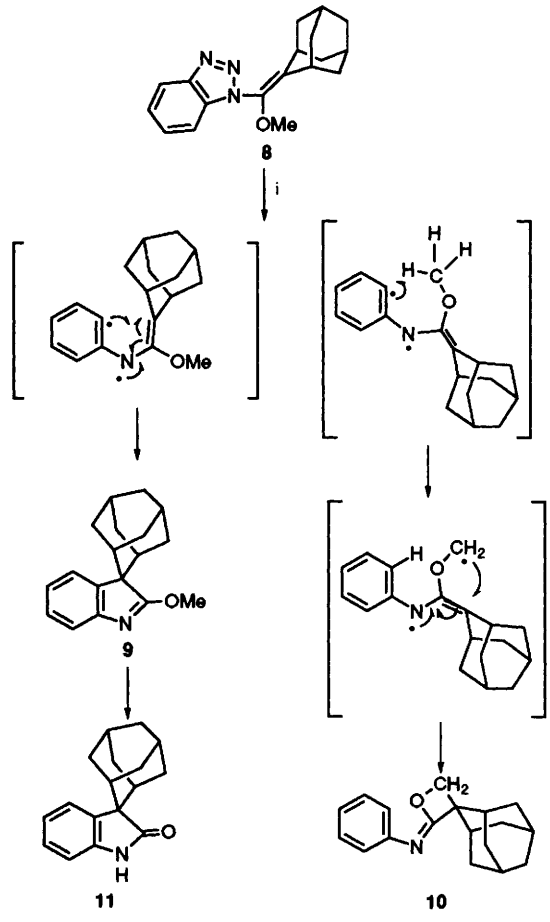


5 R = Me, CD_3, Et, Ph — **6** — **7** R_1R_2 = adamantyl

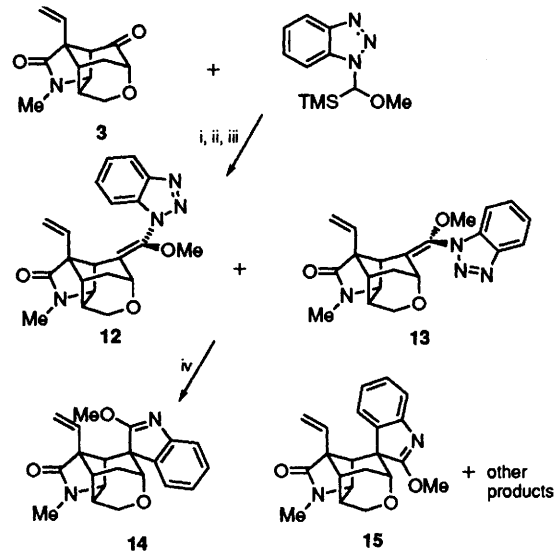
Scheme 2 *Reagents and conditions*: i, LDA, Me_3SiCl; ii, LDA R_1R_2CO



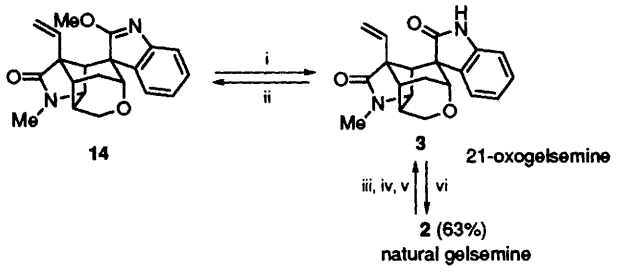
Scheme 1



Scheme 3 *Reagents and conditions*: i, *hν*, MeCN



Scheme 4 *Reagents and conditions*: i, LDA (2 equiv.); ii, Bu^nLi (2 equiv.); iii, **3**; iv, *hv*, MeCN, Pyrex



Scheme 5 *Reagents and conditions*: i, HCl, H_2O, THF; ii, Me_3OBF_4; iii, DEAD; iv, MeOH; v, CrO_3; vi, DIBALH

alkene **7** in >80% yield in a Petersen olefination. The chemistry shown in Scheme 2 is quite general, the only exception occurring when very bulky ethers (R = Bu^t or tri-isopropylsilyl) were used.[5]

Photolysis† of **8** gave a 40% yield of the desired cyclised product **9**, which unfortunately was accompanied by an equal amount of the oxetane **10**, the product of initial H-transfer, followed by cyclisation (Scheme 3). Acid hydrolysis of **9** yielded the corresponding spiro-oxindole **11**.

Given this success in the model series, ketone **3** was subjected to the same reaction sequence. Condensation of the ketone **3**, with lithiated 1-(methoxytrimethylsilylmethyl)benzotriazole gave a mixture of the (*E*)- and (*Z*)- methoxymethylene isomers **12** and **13** in a combined yield of 65% (Scheme 4). An NOE excperiment performed on the major isomer revealed it to be the (*E*)-isomer **12**.

Solutions of the two isomers **12** and **13** in acetonitrile were then irradiated separately. Each reaction gave four products, which were identical by TLC and HPLC trace, and were therefore combined. Chromatography yielded two cyclised isomers **14** and **15** in the ration 1 : 2 and a combined yield of 36%. The minor isomer **14** displayed spectral data identical to that shown by the imino-ether derived by the action of trimethyloxoniumtetrafluoroborate on synthetic 21-oxogelsemine **3**, which had been prepared by oxidation of natural gelsemine (Scheme 5). The spectral data for the major isomer are consistent with the epimeric structure **15**.

This is a formal total synthesis of gelsemine since the imino-ether **14** can be converted to gelsemine **2** by hydrolysis to 21-oxogelsemine **3**, followed by selective reduction of the tertiary amide of **3**, using DIBALH to give gelsemine **2** (Scheme 5).

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Footnote

† Photolysis reactions were carried out in Pyrex glass vessels using a medium pressure mercury UV lamp in a Rayonet reactor as the light source.

References

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