# Indole Alkaloid Synthesis; a Stereospecific Preparation of Functionalised *cis*-Hexahydrocarbazoles

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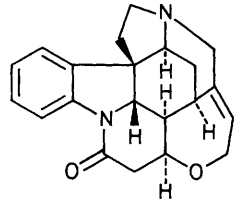
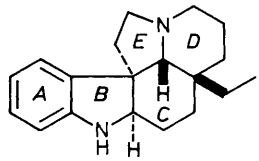
Treatment of oxindole bromides (**4**) and (**6**) with t-butyl-lithium followed by reduction with lithium aluminium hydride gave the *cis*-4a-methylhexahydrocarbazoles (**11**) and (**13**).

The synthesis of indole alkaloids by efficient stereospecific routes remains a considerable challenge. With few exceptions, syntheses of these compounds proceed through indole intermediates.[1] However, the pioneering work of Ban[2] and Levy[3] has shown that oxindoles are viable precursors to some indole alkaloids. We have recently reported the radical cyclisation of 2'-bromoacryloylanilides to give oxindoles as part of a programme to synthesise a range of indole-derived alkaloids.[4] In order to utilise these readily available oxindoles in syntheses of alkaloids such as strychnine (**1**) and aspidospermidine (**2**), we needed an intramolecular reaction to form the *C*-ring. We now report the preparation of model hexahydrocarbazoles[5] with the correct *B*/*C*-ring junction stereochemistry by an organolithium cyclisation of suitable oxindoles.

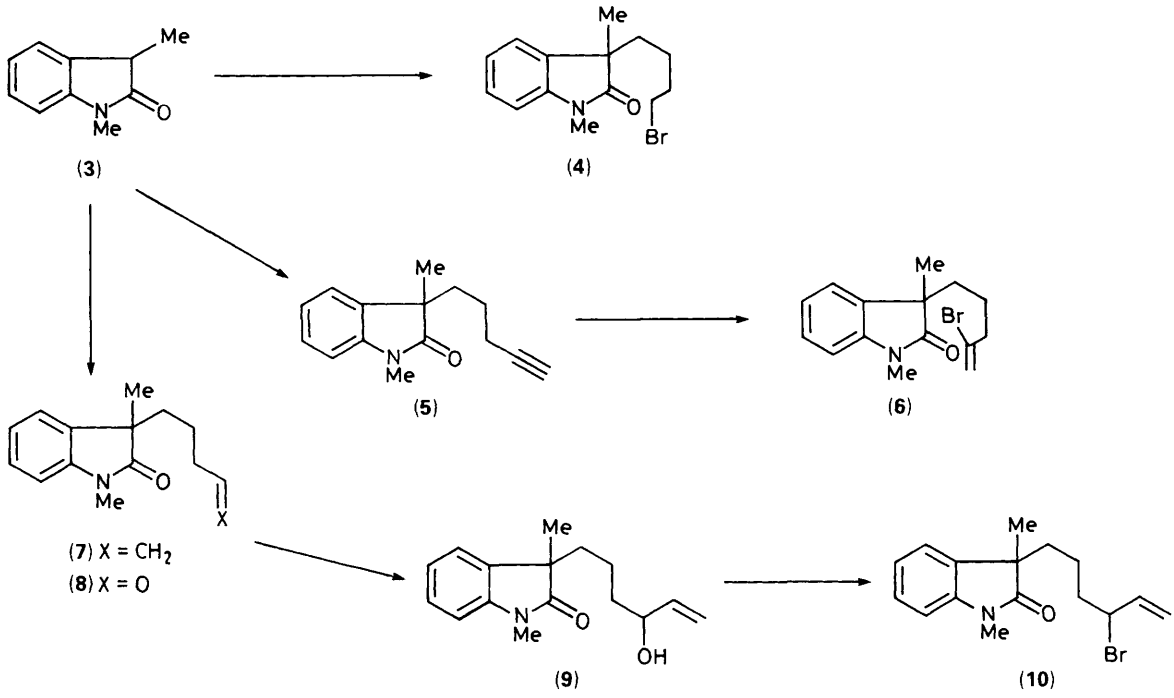
The reactions of carbon nucleophiles with amides or lactams have been the subject of few reports. However, Fowler has reported the intermolecular reaction of organolithiums with various lactams followed by reduction to give α-substituted amines.[6] We have extended this reaction to intramolecular additions to oxindoles to give hexahydrocarbazoles. Three cyclisations have been studied with the primary bromide (**4**), the vinyl bromide (**6**), and the allyl bromide (**10**).



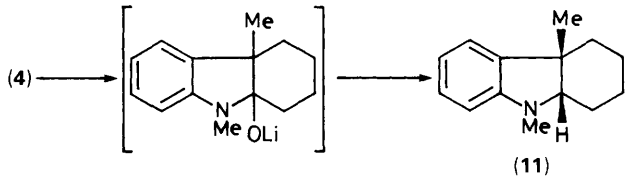

(**1**)




(**2**)




Scheme 1




Scheme 2

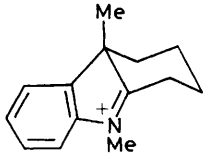
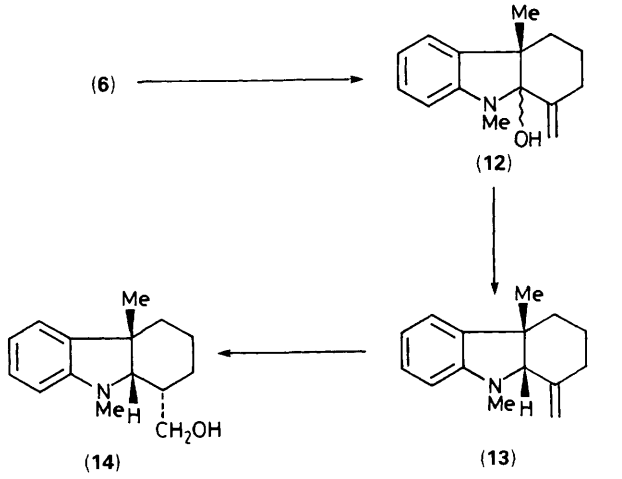



Figure 1




Scheme 3

The syntheses of the bromides (**4**), (**6**), and (**10**) are shown in Scheme 1.† Alkylation of 1,3-dimethyloxindole (**3**) with 1,4-dibromobutane [$LiN(SiMe_3)_2$, tetrahydrofuran (THF), 0 °C] gave the primary bromide (**4**)† in 62% yield. The vinyl bromide (**6**)† was prepared by alkylation of (**3**) with 1-bromopent-4-yne [$LiN(SiMe_3)_2$, THF, 0 °C] to give acetylene (**5**)† in 64% yield. Treament of (**5**) with HBr in dichloromethane at 20 °C for 2 h gave the vinyl bromide (**6**) in 95% yield. Finally, the allyl bromide (**10**)† was prepared by alkylation of (**3**) with 1-bromopent-4-ene followed by ozonolysis ($O_3$, MeOH, −78 °C, then $PPh_3$) to give aldehyde (**8**)† in 50% yield. Reaction with vinylmagnesium bromide (0 °C, ether) gave allyl alcohol (**9**)† which was brominated ($CBr_4$, $PPh_3$) to give (**10**) in 26% yield from (**8**).

Cyclisation of (**4**) was accomplished by treatment with $Bu^tLi$ (1.5 equiv.) in THF at −78 °C under argon followed, after 30 min, by addition of $LiAlH_4$ (1 M in ether, 5 equiv., 0 °C, then reflux overnight). Hexahydrocarbazole (**11**) was isolated in 76% yield after chromatography and the ring junction stereochemistry was assigned by comparison with published $^1H$ NMR data (the *N*-methyl group resonates at δ 2.7 in the *cis*-isomer and δ 2.47 in the *trans*-isomer[7]). This reaction presumably proceeds through the intermediacy of the lithiated carbinolamine, reduction of which involves the iminium ion, finally leading to the hexahydrocarbazole (Scheme 2). Fowler reported[6] that the reducing agent used affects the stereochemistry of intermolecular reactions and we briefly explored other reducing agents in the cyclisation process. Use of $BH_3$, catalytic hydrogenation, and $NaBH_4$ all gave the same *cis*-isomer (**11**), whilst lithium in liquid ammonia led to some reduction of the aromatic ring. It would appear that the conformation of the intermediate iminium ion is as shown in Figure 1 and attack by the reducing agent occurs preferentially from the more open, convex face to give the *cis*-ring junction.

In a similar manner, cyclisation of (**6**) proceeded to give (**13**)† in 85% yield (Scheme 3). Hexahydrocarbazole (**13**) was

† All new compounds gave satisfactory spectroscopic and analytical data.

again assigned the *cis*-stereochemistry on the basis of NMR shifts and by analogy to the cyclisation of (**4**). On a large scale, a small quantity (4%) of a compound tentatively assigned the *trans*-stereochemistry was isolated. In this vinyl-lithium cyclisation, the carbinolamine (**12**) could be isolated by quenching the reaction before addition of $LiAlH_4$. The alkene (**13**) was treated with $BH_3$ followed by $H_2O_2$ to give the alcohol (**14**)† as shown in Scheme 3. The stereochemistry of (**14**) was confirmed by nuclear Overhauser enhancement (NOE) studies. This alcohol was designed to study the feasibility of introducing the aldehyde required at this position for the synthesis of strychnine. Although (**14**) has the correct ring junction stereochemistry, the hydroxymethyl substituent has the incorrect stereochemistry. However, it seems likely that this could be oxidised and epimerised at a suitable stage in the synthesis.

Attempts to cyclise the allyl bromide (**10**) using this methodology failed. Interestingly, the oxindole (**3**) failed to react with allyl-lithium although it cleanly reacted with vinyl-lithium (reaction with vinyl magnesium bromide also failed). It would appear that the extra stability of the allyl-lithium is sufficient to disfavour initial addition to the oxindole carbonyl group.

In summary, we have developed the intramolecular addition of organolithiums to oxindoles as a stereospecific route to substituted *cis*-hexahydrocarbazoles and we believe that this approach has potential in the synthesis of complex indole alkaloids.

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