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The Synthesis of (±)-Heliotridane and (6*S*,7*S*)-Dihydroxyheliotridane via Sequential Hydrogen Atom Abstraction and Cyclisation

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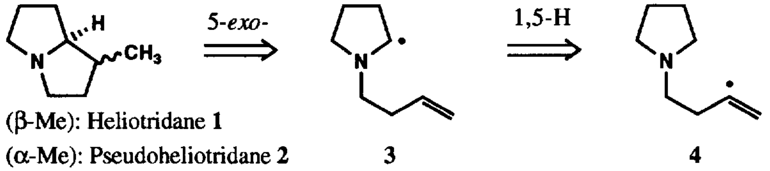
Abstract: Treatment of *N*-(3-bromo-3-butenyl)pyrrolidine derivatives with tributyltin hydride and AIBN leads to hydrogen atom transfer of the intermediate vinyl radicals to give α-amino radicals which then cyclise stereoselectively yielding pyrrolizidines **1** and **13**. Copyright © 1996 Elsevier Science Ltd

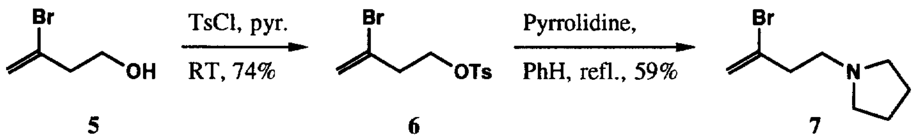
The structural diversity embodied in almost four hundred naturally occurring pyrrolizidine alkaloids[1] has attracted the continual attention of synthetic chemists as summarised in the series of reviews by Robins[2]. Synthetic routes to the necine bases that form the core of these pyrrolizidines are regularly reported and the historically important and structurally most simple compound heliotridane **1** has been a common test bed for demonstrating new methodology.

The structure of this molecule, a final reduction product of a large proportion of this class of natural products, was first confirmed[3] over fifty years ago and since then many syntheses of heliotridane **1** and its diastereoisomer pseudoheliotridane **2** have been reported. However, we recognised that the basic structure could be obtained very efficiently by a 5-*exo*-trig cyclisation of α-amino radical **3** which could, in principal, be generated by a prior 1,5-hydrogen atom transfer of vinyl radical **4** (Scheme 1)[4].



Scheme 1

This was an attractive proposal as precursors to the vinyl radical **4** were envisaged to be readily available from pyrrolidine by *N*-alkylation with an appropriate electrophile. In practice, precursor **7** was prepared in two steps from alcohol **5**[5] by tosylation (*p*-TsCl, pyr., RT, 74%) and substitution (pyrrolidine, PhH, reflux, 59%) as shown in Scheme 2.

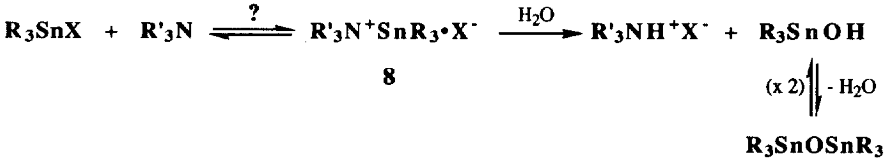


Scheme 2

Heating a mixture of compound **7** with tributyltin hydride and AIBN in benzene led to appreciable amounts of the direct reduction product, *N*-homoallylpyrrolidine, but adding the stannane slowly (syringe pump, 2-3h) to a moderately dilute solution (5 - 10 mM) of **7** and AIBN in degassed benzene at reflux circumvented this problem. Under these conditions the starting material was consumed within 3h and analysis of the crude product showed only traces of the direct reduction product.

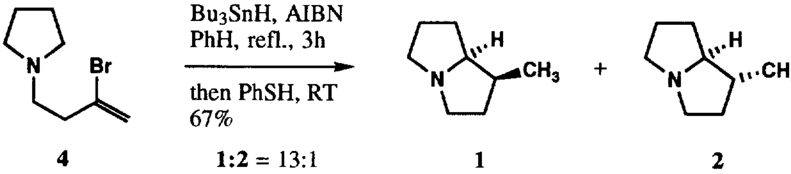
Unfortunately, attempts to isolate the products in a pure form were severely hampered by the instability to silica of the tributyltin bromide by-product. Careful column chromatography proved ineffective and application of the various work-up procedures designed to remove tin-containing materials[6] resulted in very low recovery of the cyclised products.

We were concerned that the products were capable of reacting with the tin bromide thus impeding our purification procedures. This property of tertiary amines was implied in a published procedure for removing tin halides from radical reactions by salt formation and hydrolysis[7]. Adventitious water was shown to be required to mediate this process and it is therefore unclear whether an intermediate such as **8** is actually formed or whether the base simply aids direct hydrolysis of the tin halide[8].



$$\begin{array}{r} R_3SnX + R'_3N \overset{?}{\rightleftharpoons} \underset{\mathbf{8}}{R'_3N^+SnR_3{\cdot}X^-} \xrightarrow{H_2O} R'_3NH^+X^- + R_3SnOH \\ (x\,2)\big\downarrow\big\uparrow -H_2O \\ R_3SnOSnR_3 \end{array}$$

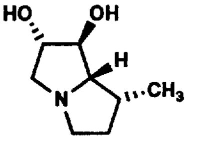
We proposed that if an intermediate such as **8** *were* to form we ought to be able to displace the amine by a more effective ligand for tin. Thus, at the end of the radical reaction, a slight excess of thiophenol was added to the cooled solution to liberate the amine (as its hydrobromide salt) and generate thiophenyltributyl stannane. The choice of thiophenol proved advantageous as the resulting tin sulphide is easily removed by chromatography, being relatively stable on silica. Using this method we were able to readily purify the products to obtain a mixture of the hydrobromide salts of heliotridane **1** and pseudoheliotridane **2** in a 13:1 ratio (Scheme 3).



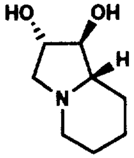
Scheme 3

Formation of the *endo*-methyl isomer **1** during the cyclisation of radical **3** accords with the all-carbon analogue which has been shown to cyclise to give an 8:1 mixture of the two methylbicyclo[2.2.0]octane diasteroisomers[9]. Additionally, Pandey has shown that a photolytically generated radical cation analogous to **3** afforded **1** and **2** in a 97:3 ratio[10] and Hart demonstrated that the pyrrolidinone analogue of **3** cyclised to give a 10:1 ratio of the bicyclic lactams[11]. These results have been explained using the Beckwith model for radical cyclisations[12] but interestingly the stereoselectivity of these processes is much higher than that predicted using Houk's force field model for intramolecular radical additions[13,14].

This sequence effectively established the methodology but we subsequently extended this chemistry to provide an enantiospecific synthesis of the previously unreported 6,7-dihydroxyheliotridane **9**[15] which is a close structural isomer of lentiginosine **10**, a potent amyloglucosidase inhibitor[16]. The relative stereochemistry in **9** was predicted on the basis that cyclisation should occur from the face opposite to the proximal alkoxy function but still with the *endo-* disposition of the methyl group.

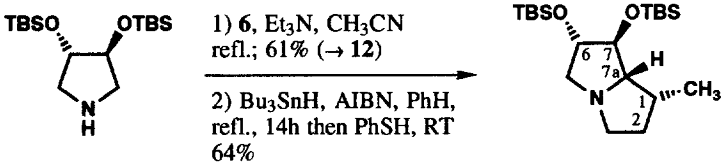


9



(+)-Lentiginosine, **10**

The synthesis initiated with the C_2-symmetric protected pyrrolidine diol **11** which is easily obtained in four steps from L-tartaric acid[17]. *N*-alkylation of **11** proved to be troublesome under the earlier conditions however treatment of a mixture of this compound, tosylate **6** and an excess of triethylamine, as a concentrated solution in boiling acetonitrile, resulted in a clean reaction to give precursor **12** in 61% yield. The lower than expected yield in these alkylation reactions appears to be due to competing elimination of the tosylate giving bromobutadiene with a corresponding recovery of the pyrrolidine derivative. Subjecting compound **12** to the conditions previously found to be successful for **7**, again using thiophenol to aid the purification process, resulted in a 64% isolated yield of the *bis*-silyloxyheliotridane **13** (Scheme 4) whose relative stereochemistry was determined through n.O.e. experiments[18].



11 **13**

Scheme 4

Finally, (6*S*, 7*S*)-Dihydroxyheliotridane **9** was obtained in 71% yield as the freebase by desilylation of **13** using fluorosilicic acid[19] (2 equiv. H_2SiF_6, aq. acetonitrile, 80°C, 16h) followed by ion exchange chromatography[20]. Full details of this and our other results in this area will be reported in due course.

ACKNOWLEDGEMENTS

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18.

	Enhancement					
Irradiate	H1	H2α	H2β	H7	H7a	CH_3
H1 (2.70 ppm)	—	—	3.8%	—	8.7%	5.6%
H7a (4.05 ppm)	7%	—	—	—	—	—
CH_3 (1.20 ppm)	10.7%	2.1%	—	14%	—	—

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20. All new compounds exhibited the expected spectroscopic and analytical or accurate mass data.

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