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TETRAHEDRON
LETTERS

An Expedient Synthesis of (±)-γ-Lycorane[†]

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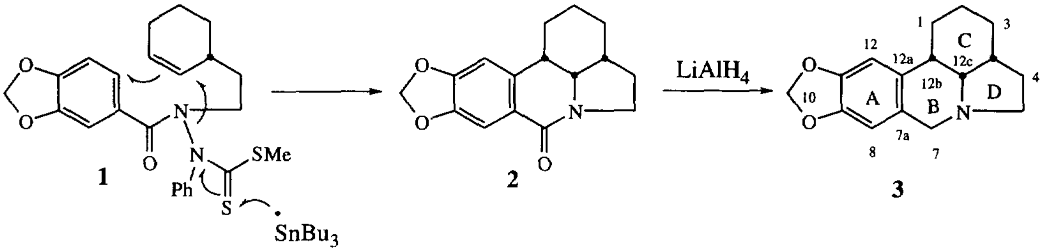
Abstract : A short synthesis of (±)-γ-lycorane is described featuring a radical cascade whereby rings B and D are formed in one step. © 1999 Elsevier Science Ltd. All rights reserved.

The development of a new reaction often results in a considerable simplification of synthetic strategies. In this respect, radical based methods have had an immense impact on organic synthesis.[1] However, most of the applications of radical processes have so far relied on the generation and capture of carbon centered radicals, to the detriment of other interesting species such as oxygen and nitrogen radicals, whose potential has by and large been neglected.[2] We have, over the past few years, devised a number of routes to a variety of nitrogen radicals[3] and, in a preliminary study aimed at the elaboration of a simple, yet general strategy towards the large group of *Amaryllidacea* alkaloids with the galanthan skeleton,[4] we have applied a new method for producing amidyl radicals[5] in an expedient approach to γ-lycorane **3**.[6]



Scheme 1

Our approach hinges on the possibility of implementing the radical cascade displayed in Scheme 1, whereby the B and D rings are created in one step. Compound **2** thus obtained is known and its conversion into γ-lycorane **3** by reduction of the lactam group with $LiAlH_4$ has been described.[6c,e]

The requisite precursor **1** was readily constructed from cyclohexenyl acetaldehyde **4**, itself prepared from commercially available 2-cyclohexen-1-ol through the Claisen rearrangement of the corresponding vinyl ether as described by Burgstahler and Nordin.[7] The two step sequence shown in Scheme 2 involves the formation of hydrazide **6** by condensation of aldehyde **4** with thiosemicarbazide **5**[8] and *in situ* reduction of the intermediate hydrazone with cyanoborohydride to give hydrazide **6**, followed by acylation with piperonoyl chloride to give **1** in 60% overall yield.

Our hope in considering this approach was that the methylenedioxy unit would direct to a certain extent the ultimate radical cyclisation onto the aromatic ring in favour of the desired regioisomer. In the event, slow addition of tributylstannane to a refluxing solution of hydrazide **1** resulted in the formation of a 6:4 mixture (by NMR and HPLC) of **2** and its isomer **7**, albeit in a quite reasonable 63% combined yield. The control of the regiochemistry is thus only moderate. One equivalent of 1,1'-azobis(cyclohexanecarbonitrile) was used in

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[†] *Dedicated with respect and affection to the memory of Dr Stéphane D. Géro.*

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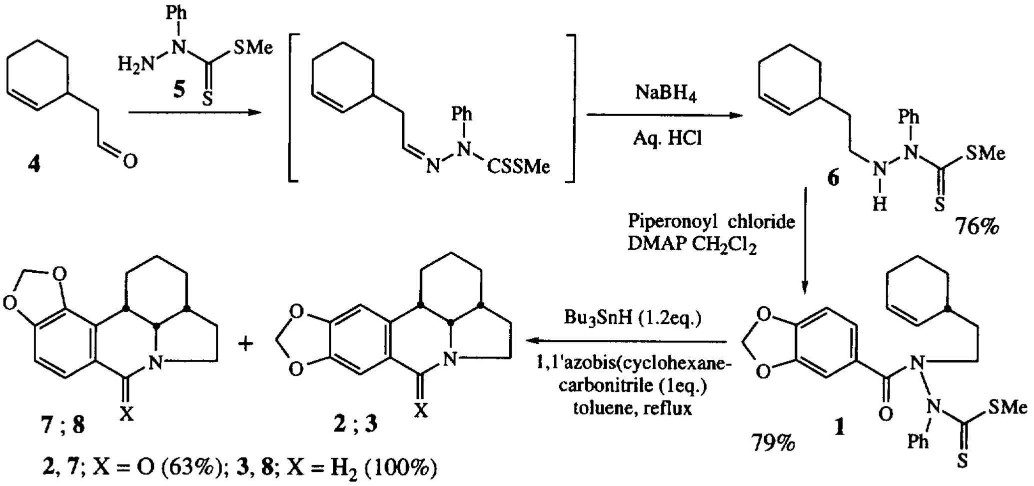
this reaction not only to initiate the radical process but also to assist with the final aromatisation. The all cis-stereochemistry was readily deduced by comparison of the NMR spectrum of **2** with that described in the literature.[6c,e] The relatively small coupling constant (4.8 Hz) for the hydrogens on C-12b and C-12c is typical of an axial-equatorial disposition and diagnostic of a cis-arrangement of the rings in such structures.[6c,e] Removal of the carbonyl group was easily accomplished on the mixture of **2** and **7** using $LiAlH_4$ to provide γ-lycorane **3** and its regioisomer **8** in quantitative yield. Final separation by HPLC finally provided pure γ-lycorane **3**.



Scheme 2

This preliminary approach represents perhaps the shortest synthesis of (±)-γ-lycorane and demonstrates the feasibility of the key radical cascade. Since 2-cyclohexenol can be easily obtained optically pure, for example by opening of cyclohexene oxide using a chiral base,[9] the present route can in principle be made enantioselective. Moreover, placing a temporary substituent at C-8 should obviate the problem of regiochemistry in the cyclisation step. Indeed, some related natural products, such as the important pancratistatine and narciclasine,[4] possess a substituent in this very same position.

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