

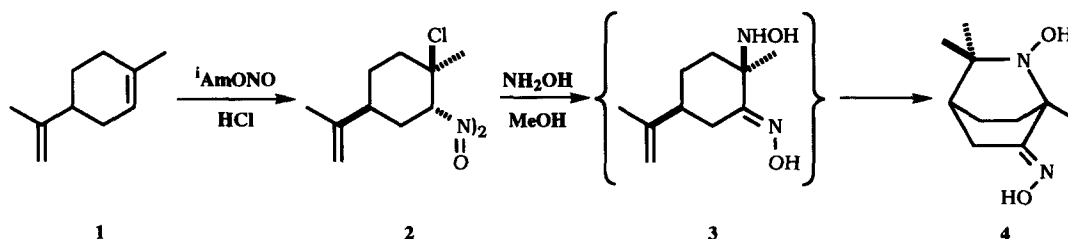
# Intramolecular Cyclisations of Hydroxylamines Derived from Limonene: Reverse-Cope or Acid-Catalysed Reactions?

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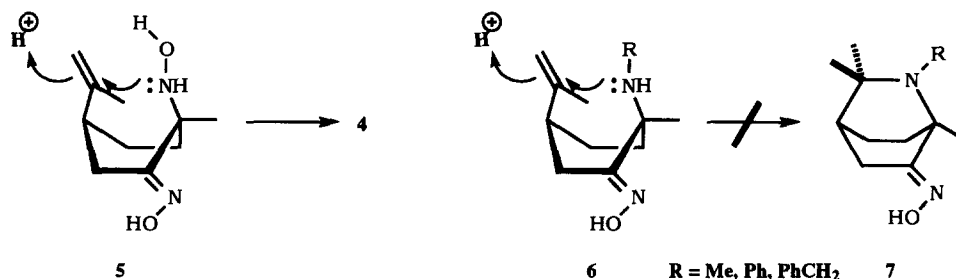
**Abstract:** Intramolecular cyclisations of *cis*-4-ethenylcyclohexyl hydroxylamines [e.g. **3** derived from limonene] proceed via a reverse-Cope mechanism rather than an acid-catalysed process, as recently reported. Copyright © 1996 Elsevier Science Ltd

In a recent publication,<sup>1</sup> Bakunov, Denisov and Tkachev reported that the structure of the product obtained by heating the nitroso-chloride dimers **2** with hydroxylamine is the isoquinuclidine derivative **4**, rather than the expected hydroxyamino oxime **3**. The formation of nitroso-chlorides from alkenes and their subsequent reactions with hydroxylamine was first reported many years ago<sup>2</sup> and, indeed, the application of this sequence to limonene **1** was first described in 1910, although the structure of the product was then thought to be a monocyclic hydroxyamino oxime,<sup>3</sup> despite some inconsistencies with its chemistry.<sup>4</sup>

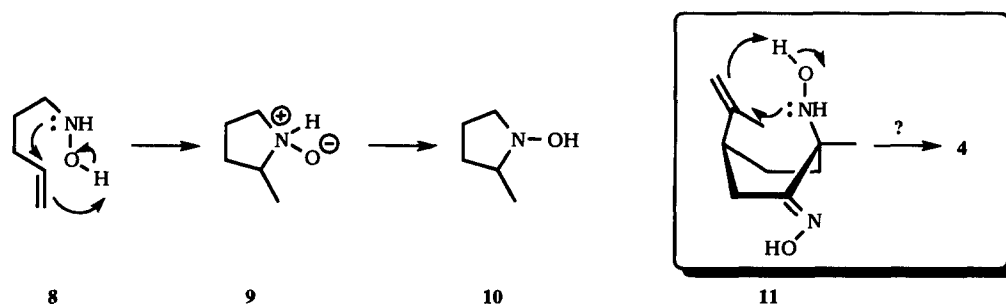


The Russian workers obtained the bicyclic product **4** when the nitroso-chloride dimers **2** (a mixture of *E*- and *Z*-isomers in solution) were heated in refluxing methanol for 4h with five equivalents of hydroxylamine and proposed that the cyclisation was catalysed by the hydrogen chloride produced as a consequence of the addition of the hydroxylamine to the nitroso-chloride **2**, as shown in structure **5**. However, rather strangely, when the nitroso-chloride **2** was treated with other amines, the resulting amino-oximes **6** [R = Me, Ph, PhCH<sub>2</sub>] failed to undergo cyclisation to the related bicyclic systems **7** under the same conditions. It was suggested<sup>1</sup> that this was due to the lower basicity of the hydroxyamino function in compound **3**, relative to the related amines **6**, which meant that the intermediate hydrochloride could be in equilibrium with the free base and hence permit cyclisation,

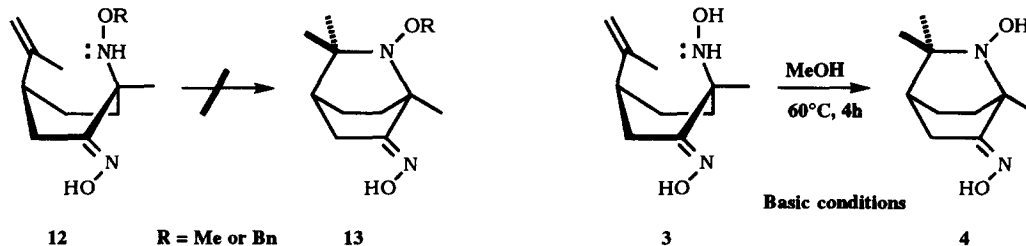
as indicated in structure 5. We were somewhat dubious of this explanation; furthermore, the juxtaposition of the hydroxylamine and alkene functions suggested that an alternative mechanism could be a reverse-Cope process, summarized in the transformation of the unsaturated hydroxylamine 8 into the pyrrolidine 10. This reaction was first reported some twenty years ago,<sup>5</sup> and has recently come to prominence as a useful route to both pyrrolidines and cyclic nitrones.<sup>6</sup> Initially, the reverse-Cope reaction was thought to involve a radical mechanism



but later studies<sup>6</sup> strongly indicate that the reaction is a pericyclic process, as indicated (8), which involves the intermediacy of an *N*-oxide 9 which undergoes proton transfer to give the observed *N*-hydroxypyrrolidine 10. We therefore wondered if the true mechanism of the cyclisation of the hydroxyamino oxime 3 was a reverse-Cope process, as indicated in formula 11.



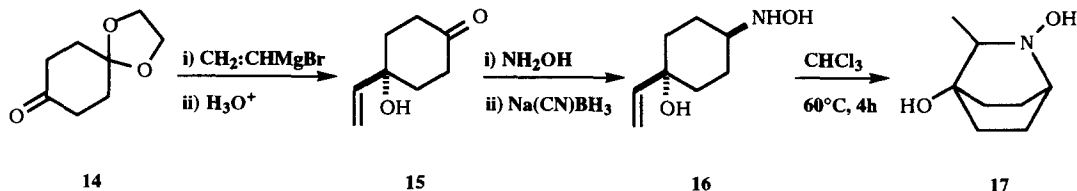
Our first experiments indicated that this could be the case. When either *O*-methyl or *O*-benzylhydroxylamine was reacted with the nitroso-chloride dimers 2, only the oximes 12 [R = Me or Bn] were



isolated and these could not be induced to cyclise to the isoquinuclidine skeleton 13, despite prolonged heating in the presence of acid.<sup>1</sup> It seems reasonable to presume that these substrates would have electronic properties more closely related to the corresponding hydroxylamine 3, rather than the alkylamines 6 and would therefore be expected<sup>1</sup> to undergo cyclisation, if this were truly acid-catalysed. Subsequently, we treated the nitroso-chloride

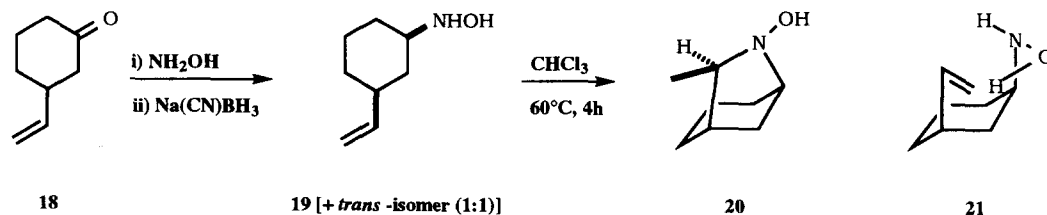
dimers **2** with 2.1 equivalents of hydroxylamine hydrochloride in refluxing methanol containing 10 equivalents of sodium hydroxide and were pleased to isolate an essentially quantitative yield of the isoquinuclidine oxime **4** after a reaction time of 4h. It therefore seems clear that a reverse-Cope process is involved in the transformation of the presumed hydroxylamine oxime **3** into the product **4** as, in the presence of an excess of base, acid-catalysed cyclisation should not be possible.

This single example suggested that this type of reverse-Cope process could represent a valuable new approach to the isoquinuclidine skeleton. However, we were concerned that the highly substituted and relatively distorted nature of the intermediate **3** could mean that cyclisation of the latter was a rather special case. We therefore elected to examine similar 'transannular' cyclisations of much simpler alkenyl hydroxylamines. Thus, treatment of the commercially available mono-protected cyclohexane-1,4-dione **14** with vinylmagnesium bromide followed by acidic hydrolysis of the dioxolane group gave a good yield of the hydroxy-ketone **15**; oxime formation, followed by reduction using sodium cyanoborohydride then gave the desired hydroxylamine **16**, along with the corresponding stereoisomer [vinyl and hydroxylamine *trans*].



We were delighted to find that the *cis*-hydroxylamine **16** underwent a smooth and essentially quantitative conversion into the isoquinuclidine **17** when heated in chloroform for 4h.<sup>7</sup>

This type of 'transannular' reverse-Cope cyclisation is also not restricted to 1,4-disubstituted cyclohexanes. Copper-catalysed Michael addition of vinylmagnesium bromide to cyclohex-2-en-1-one gave the ketone **18**, which was converted into the corresponding oxime and thence into the *cis*-hydroxylamine **19** by a non-stereoselective reduction by cyanoborohydride. Once again, heating this material in chloroform gave a quantitative yield of the cyclised product **20**, as a single diastereoisomer.<sup>7</sup> We presume that the latter arises from the conformation **21**, wherein the vinyl group points away from the cyclohexane ring in order to avoid steric interaction with the axial proton ( $A^{1,3}$  strain).



We therefore conclude that these types of cyclisation proceed *via* reverse-Cope mechanisms and that they represent viable approaches to the two ring systems **17** and **21** which should be of some generality; the likely

transition state conformations strongly suggest that other ring sizes will also be able to act as templates. Clearly, further work is needed to define more stereoselective and efficient approaches to the precursor hydroxylamines, as well as to better understand some of the seemingly peculiar stereochemical features of the initial transformations of limonene **1** into the hydroxyamino oxime **3**; studies in these directions are in progress.

### Acknowledgements

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7. Spectroscopic and analytical data fully support all the structures reported herein.

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