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TETRAHEDRON: *ASYMMETRY*

Influence of a hydroxy group in the asymmetric reduction of selenides: enantioselective synthesis of naturally occurring monoterpenes

Paolo Ceccherelli,† Massimo Curini,* Francesco Epifano, Maria Carla Marcotullio and Ornelio Rosati

Istituto di Chimica Organica, Facoltà di Farmacia, Università degli Studi, Via del Liceo 1, I-06123 Perugia, Italy

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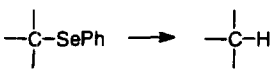
Abstract

The reductive cleavage of the benzenseleno-group in *trans*-β-hydroxyselenides, to yield a stereogenic methyne center, has been investigated. When the reaction is carried out with lithium in diethylamine, the equilibrated carbanionic intermediate traps the proton of the neighbouring hydroxy function, blocking the stereogenic center as a product with a predictable chirality. Using this strategy, several natural monoterpenes in enantiomerically pure form have been prepared.

In the last two decades there has been increasing interest in devising a variety of procedures for introducing selenium, usually as PhSe–, into organic compounds.[1] Selenides are important intermediates in that selenoxide fragmentation has been extensively utilized for double bond generation.[2] Moreover, the selenide group can be used for a variety of manipulations,[3] as well as for promoting the formation of new carbon–carbon bonds *via* selenium stabilized carbanions[4] or cyclofunctionalization processes.[5] Efficient and selective methods for removing the phenylseleno group, by reduction, are of great interest.

During a project devoted to the development of a practical synthesis of naturally occurring menthane derivatives, we needed to remove the benzenseleno-group from some β-hydroxyselenides and replace it with hydrogen (Eq. 1).



(1)

Three methods are available for reducing selenides: the carbon–selenium bond can be cleaved by Raney nickel,[6] by lithium in amine,[6] and by the use of triorganotin hydride.[7] These procedures have

* Corresponding author. E-mail: curini@unipg.it

† Deceased on 1 January 1998.

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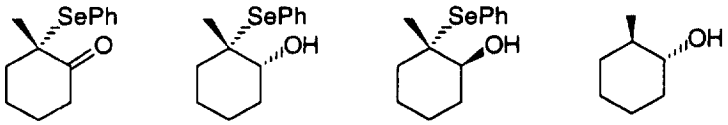
been widely used for the reduction of selenides attached to primary and secondary carbon atoms but the stereochemical outcome of these transformations was inconclusive.

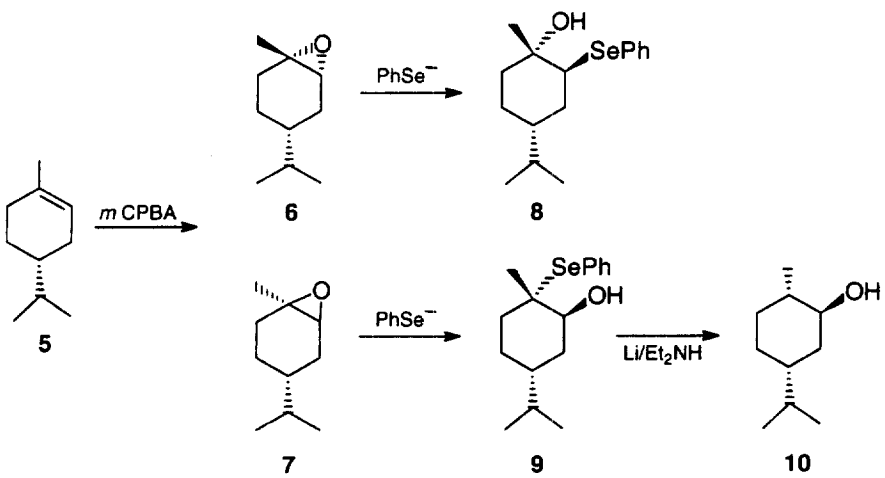
We initially studied the reduction conditions of the selenide **2**, that was prepared by $NaBH_4$ reduction of ketone (±)-**1** in 76% yield.[8] Interaction of **2** with lithium in diethylamine at room temperature, afforded a single isomer **4**[9] (94% yield) in which the $-CH_3$ and –OH groups were in a *trans* relationship.



1 **2** **3** **4**

The stereoselective protonation process yielding **4** turned out to be faster than the expected equilibration of these species.[10] To get more information on the stereochemical course of the β-hydroxyselenide reduction, we exposed the diastereomeric mixture (2:3) of selenides **2** and **3**, obtained by $Al(iPrO)_3$ reduction of ketone **1**, to lithium in diethylamine. Even in this transformation, only the alcohol **4** (95% yield) was detected. Thus, while the reduction of **2** proceeds with retention of configuration, **3** is converted into **4** by inversion at the center involved in the reductive process.

For the preparation of compounds of biological interest, we examined the lithium–diethylamine reduction of selenide **9** prepared from the (+)-*p*-menth-1-ene **5**, following the sequence earlier applied to limonene and reported in Scheme 1.[11]

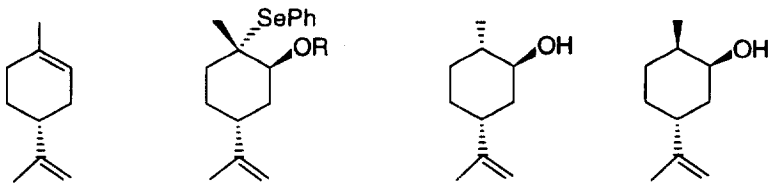


5 **6** **8** **7** **9** **10**

Scheme 1.

Compound **9** was transformed in 89% yield into the alcohol **10**, as the only reaction product. **9** exhibits the same reductive behaviour as **3**. Thus the protonation of the carbanion is once again *syn* in relation to the hydroxy function. Since the rigid conformation of **10** imposes an *anti* relationship between the methyl and hydroxy functions, **10** was generated by a contrathermodynamic process. Compound **10** shows spectroscopic properties consistent with the proposed structure and the analytical and specific rotation data agree with those reported for the naturally occurring (−)-isocarvomenthol.[12]

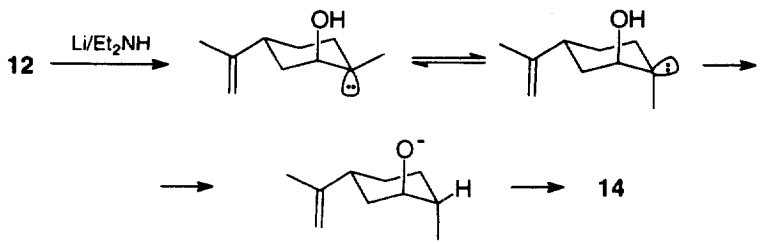
Similarly, the β-hydroxyselenide **12**, prepared from (*R*)-(+)-limonene **11**,[11] yielded (−)-isodihydrocarveol[12] **14** in 86% yields.



11 **12** R = H **14** **15**
13 R = Ac

It is interesting to point out that Bu_3SnH or Raney nickel reduction of **12** afforded a quasi equimolar mixture of **14** and its epimer at C(2) **15**.[13,14]

The reported data clearly suggest participation of the –OH function in orienting the stereochemistry of the reduction. It is reasonable to predict an intramolecular acid–base process, in which the initially formed carbanion abstracts the proton of the neighbouring hydroxy group during the equilibration, generating an alkoxide (Scheme 2).



Scheme 2.

We were unable to prepare deuterated precursors to prove the proposed mechanism. However, **13**, in which the hydroxy function is protected as acetate, afforded a 1:2 mixture of **14** and **15** by lithium–diethylamine reduction.

In summary, the lithium–diethylamine reduction of β-hydroxyselenides shows that the hydroxy group exerts a significant stereochemical influence leading to products of predictable chirality.

Acknowledgements

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