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The iodine-assisted hydroxyselenenylation of alkenes with elemental selenium

Evgeny O. Kurkutov* and Tatyana N. Borodina

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 419 346; e-mail: kurkutov@irioch.irk.ru

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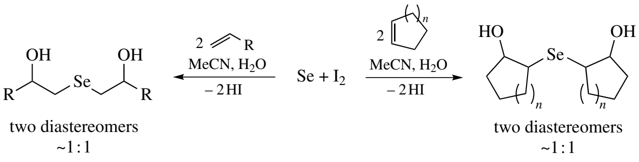
β,β′-Dihydroxy selenides are obtained by the iodine-assisted reaction of elemental selenium with alkenes in aqueous acetonitrile in up to 83% yield and ~1 : 1 diastereomeric ratio. The X-ray analysis of bis(2-hydroxycyclohex-1-yl) selenide revealed it to be the *trans,trans*-isomer indicating that the reaction occurred stereoselectively as *anti*-addition.



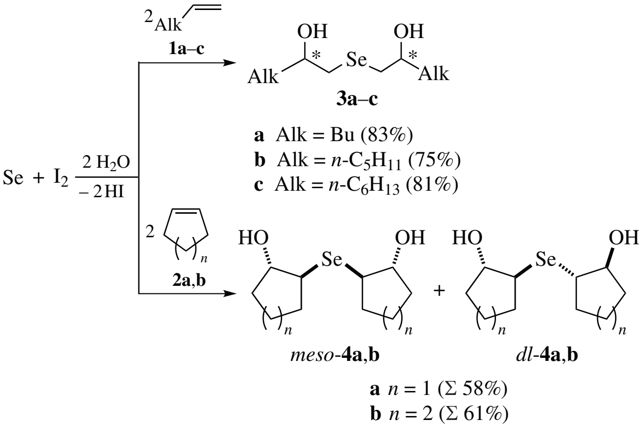
Keywords: iodine-assisted reactions, selenenylation, β-hydroxy selenides, alkenes, organoselenium compounds.

Recently much attention has been paid to the synthetic methods towards β-hydroxy selenides and studies of their biological activity.[1–8] Symmetric β-hydroxy selenides are commonly prepared by the reactions of nucleophilic selenium reagents such as sodium hydroselenide or bis(trimethylsilyl)selenide with epoxy compounds[1,4–6] and other electrophiles.[3] Electrophilic hydroxyselenenylation of alkenes is documented only for electrophilic selenyl-cation generated from diaryl diselenides. These reactions afford β-hydroxy selenides bearing only one β-positioned hydroxy group and one aryl substituent at the selenium atom.[8] It is worth noting that in only one work[7] elemental selenium was used as the starting reagent, and in another work[8] water has been used as a source of the hydroxyl function.

In addition to possible further transformations, β-hydroxy selenides attract the interest as potential catalysts for oxidation of glutathione (GSH) to glutathione disulfide (GSSG), which is a part of protective mechanisms against the harmful effects of peroxides on cells. The whole process is finalized by the glutathione reductase/NADPH-mediated reduction of GSSG to GSH.[2,3,5,9,10]

Earlier, we have performed the two-stage synthesis of β-hydroxy selenides, namely, (i) the reaction of selenium dibromide with alk-1-enes in chloroform to deliver β-bromoalkyl selenides followed by (ii) the hydrolysis in DMF.[11] Herein, we report a new convenient one-pot synthesis of novel β,β′-dihydroxy selenides *via* the reaction of the *in situ* formed electrophilic selenium reagents with alkenes, representing the first example of iodine-assisted hydroxyselenenylation of alkenes with elemental selenium and water.

As opposed to inorganic selenium chlorides or bromides, the corresponding iodides could not be isolated. However, their existence was proved spectroscopically in CS_2 solution.[12] To the best of our knowledge, inorganic selenium iodides were never employed to introduce selenium atom into an organic substrate. We have herein discovered that the reaction of an equimolar mixture of elemental selenium and iodine with an excess of alkenes **1a–c** and **2a**,**b** in aqueous acetonitrile proceeds with high chemo- and regioselectivity and affords β,β′-dihydroxy selenides **3a–c** and **4a**,**b**, respectively, in good yields (Scheme 1).[†]



Scheme 1 *Reagents and conditions*: MeCN/H_2O, room temperature, 40 h.

Double signals in the ^{13}C NMR spectra of products **3** and **4** as well as two multiplets of the CHSe protons of equal intensity are indicative of their formation as ~1 : 1 diastereomeric mixtures. Crystallization of compound **3c** allowed us to isolate a single diastereomer, which showed only one set of signals. The presence of only two sets of signals for cyclic compounds **4a**,**b** proves the formation of only isomers with the *trans* orientation of the OH and Se substituents with respect to the ring as *meso* and *dl* forms.

[†] *General procedure for the preparation of β,β′-dihydroxy selenides* **3a**–**c** *and* **4a**,**b**. An alkene **1a–c** or **2a**,**b** (3 mmol) and H_2O (0.5 ml) were added to a mixture of finely milled elemental Se (0.079 g, 1 mmol) and I_2 (0.254 g, 1 mmol) in MeCN (3.5 ml), and the mixture was stirred at room temperature for 40 h. Then, saturated solution of $Na_2S_2O_3$ (2 ml) was added, this was stirred for 10 min, the mixture was diluted with water (5 ml) and extracted with Et_2O (3×10 ml). The extract was washed with solution of $NaHCO_3$ (5 ml, 10%) and H_2O (3×5 ml), dried with $CaCl_2$ and filtered. The solvent was removed *in vacuo* to give the corresponding β,β′-dihydroxy selenide **3a**–**c** or **4a**,**b**. For details, see Online Supplementary Materials.

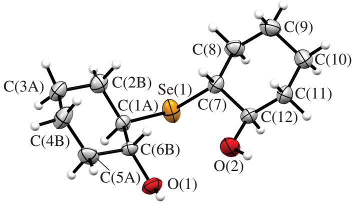
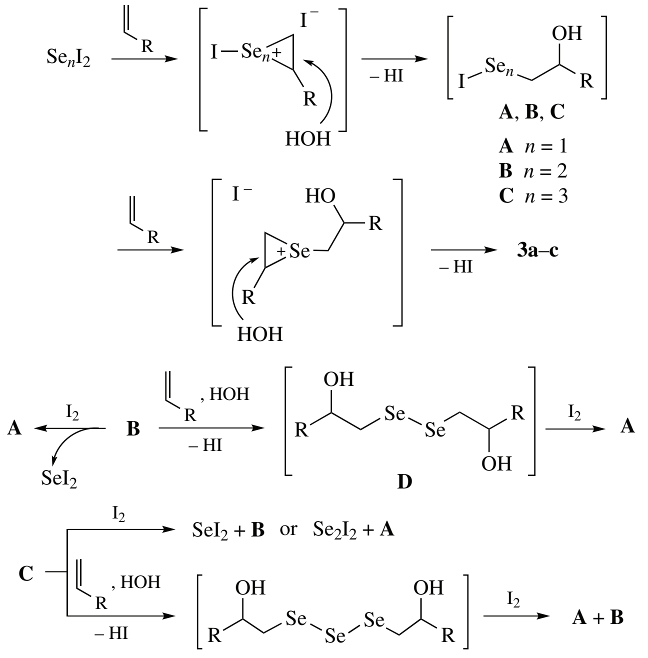


Figure 1 ORTEP plot of compound *dl*-**4b** at 25% thermal ellipsoid probability.

For selenide **4b**, suitable crystals of *dl* diastereomer were grown, and the X-ray crystal structure was obtained (Figure 1).‡ The molecule has the *trans*,*trans*-configuration with all heteroatoms in the equatorial positions, that suggests the *anti*-addition of the hydroxyl group and the organoselenium residue.

In solution, the *trans*,*trans*-configuration of **4b** was proved by NMR spectroscopy, namely, by the vicinal spin–spin coupling constants for the CHSe proton signals in both *meso* and *dl*-diastereomers with H^{6ax}, H^{2ax} and H^{6eq} equal to 13, 10 and 4 Hz, respectively. The *trans*,*trans* structure of **4a** can be concluded from a similar pattern of splitting for both the CHSe and CHOH methine protons, except that, due to fast pseudorotation of the cyclopentane ring, the lower-field CHSe signal degenerates to a doublet of triplets (see Online Supplementary Materials, Figure S9). Judging by a smaller width of the lower-field SeCH multiplet in **4a**, these signals in both **4a** and **4b** can be tentatively assigned to the more symmetric *meso* diastereomers and the higher-field SeCH signals – to *dl* ones.

Based on the established *trans* structure of the products, and the ^{77}Se NMR data proving the formation of Se_2I_2 as the major compound and SeI_2 and Se_3I_2 as minor ones in CS_2 solution,[12] the tentative mechanism for the reaction can be proposed (Scheme 2). First, selenium iodides Se_nI_2 (n = 1–3) are formed. Then, they add to the alkene to form the seleniranium ion, which undergoes ring opening by backside attack of water molecule producing the intermediate selenenyl iodides **A**–**C** and HI. Intermediate **A** reacts with the second alkene molecule in the same manner to give the final products. Intermediate **B** can react in two ways: (i) with I_2 to form SeI_2 and intermediate **A**, which reacts as above, or (ii) *via* addition to alkene to form diselenide **D,** which, by the reaction with I_2, returns the process to intermediate **A**. With Se_3I_2, a similar sequence of reactions may occur (see Scheme 2).



Scheme 2

To summarize, a facile and efficient method for the synthesis of β,β′-dihydroxy selenides *via* the iodine-assisted addition of elemental selenium to alkenes in organic-aqueous medium is developed and a tentative mechanism is proposed.

This work was performed using the equipment of the Baikal Analytical Center for Collective Use of SB RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.023.

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[‡] *Crystal data for* **4b**. $C_{12}H_{22}O_2Se$ (M = 277.26), orthorhombic, space group *Pbca* at 293(2) K: a = 10.3630(12), b = 10.6393(10) and c = 23.446(2) Å, V = 2585.0(5) Å^3, Z = 8, d_{calc} = 1.425 g cm^{-3}, μ(MoK$_\alpha$) = = 2.886 mm^{-1}, F(000) = 1152. Total of 26284 reflections were collected (3117 independent reflections, R_{int} = 0.0550) and used in the refinement, which converged to wR_2 0.1128, GOOF 1.050 for all independent reflections [R_1 = 0.0548 was calculated for 3117 reflections with $I > 2\sigma(I)$]. The X-ray diffraction analysis was carried out on a Bruker D8 Venture Photon 100 CMOS diffractometer (MoK$_\alpha$ radiation, λ = 0.71073 Å) using the φ and ω scans technique. The structures were solved and refined by direct methods using SHELX software.[13] Absorption correction was done using SADABS. All non-hydrogen atoms were refined anisotropically. The coordinates of the hydrogen atoms were calculated from geometrical positions.

CCDC 1982304 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.