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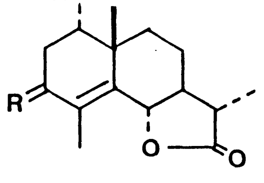
Synthesis of Dehydroisoerivanin, Isoerivanin, Ludovicin C, and 1α,3α-Dihydroxyarbusculin B Utilizing the Organoselenium-mediated Reduction of Epoxy Ketone

Masaaki MIYASHITA, Toshio SUZUKI, and Akira YOSHIKOSHI*
Chemical Research Institute of Non-Aqueous Solutions,
Tohoku University, Sendai 980

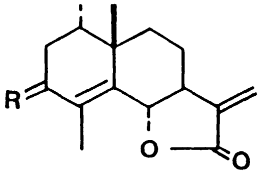
Short step synthesis of dehydroisoerivanin, isoerivanin, ludovicin C, and 1α,3α-dihydroxyarbusculin B have been achieved by employing the organoselenium-mediated reduction of α,β-epoxy ketone as the key step.

Recently we developed the organoselenium-mediated reduction of α,β-epoxy ketones to β-hydroxy ketones as a promising gateway to a wide variety of acyclic (intermolecular) and cyclic (intramolecular) aldols.1) The new method has the main advantage that it is widely applicable to complex systems containing polyfunctional groups due to its essentially neutral conditions.1) In particular, this methodology provides a powerful tool for the synthesis of natural products possessing β-hydroxy ketone units or 1,3-diol structures, e.g., prostaglandins and santanolides.

We describe herein the first syntheses of some santanolides, dehydroisoerivanin (**1**), isoerivanin (**2**), ludovicin C (**3**), and 1α,3α-dihydroxyarbusculin B (**4**) based on this strategy. Among these compounds, the formers (**1** and **2**) were isolated from Balsamita major Desf. as minor sesquiterpene lactones,2) and the latters (**3** and **4**) were isolated from Artemisia ludoviciana Nutt. ssp. mexicana (Willd.) Keck.3) and Schistostephium heptalobum (DC.) Olive. et Hiern.,4) respectively. Each compound has a common functionality either a β-hydroxy ketone unit or a 1,3-diol moiety as well as a γ-lactone ring and may be derivable from α-santonin (**5**) via the corresponding epoxide **8** (Scheme 1).



1 R=O Dehydroisoerivanin
2 R=H, α-OH Isoerivanin

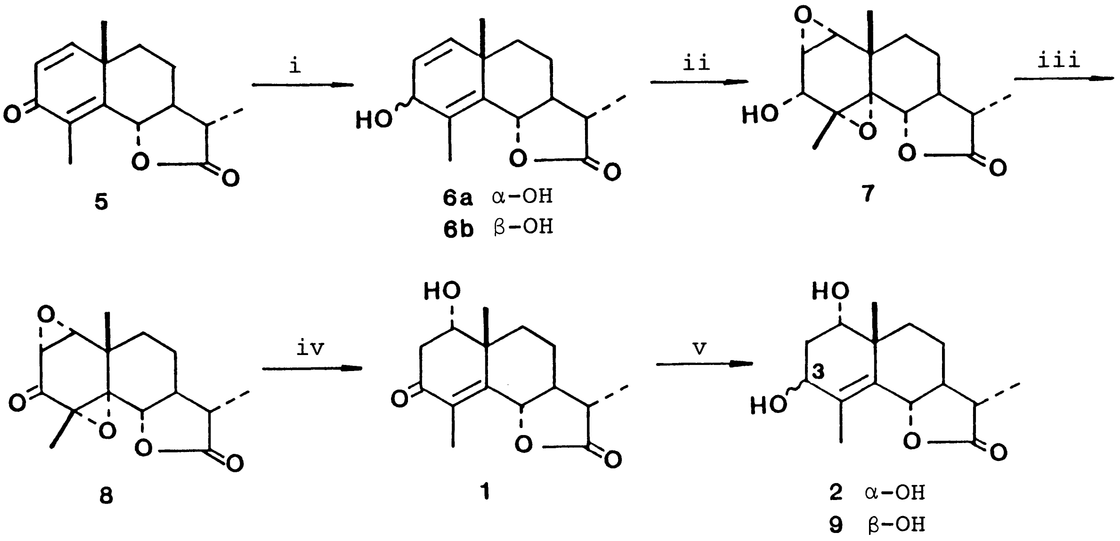


3 R=O Ludovicin C
4 R=H, α-OH 1α,3α-Dihydroxyarbusculin B

The key compound **8** was conveniently prepared as follows. α-Santonin (**5**) was reduced with diisobutylaluminum hydride at -70 °C to give an inseparable mixture of the desired α-alcohol **6a** and its β-isomer **6b** in a ratio of 3:1[5] in 97% yield.[6] Subsequent α-bis-epoxydation of **6** was successfully carried out with 1.9 equiv. of MCPBA at 0 °C in 65% yield (85% based on **6a**) due to the directive effect of the hydroxyl group.[7,8] In turn, the crystalline epoxy alcohol **7** (mp 199 °C) was oxidized with Collins reagent to produce the desired bis-epoxy ketone **8**, mp 201-202 °C, in 88% yield.

The key step in this synthesis, the organoselenium-mediated reduction, was achieved by treatment of the bis-epoxy ketone **8** with sodium benzeneselenolate[9] (5 equiv.) in the presence of AcOH (2 equiv.) in EtOH. The reaction was complete within 10 minutes at room temperature and, interestingly, the expected ring opening of two epoxides was followed by concomitant dehydration of a newly formed tertiary alcohol to give the single product, dehydroisoerivanin (**1**), mp 203-205 °C, $[\alpha]_D$ +50.1° (c, 1.0, dioxane) in 80% yield.[10] Synthetic compound was identical with the authentic specimen in all respects.[2,11] In this way, the four step synthesis of dehydroisoerivanin (**1**) was accomplished by applying the organoselenium-mediated reduction in the crucial step.

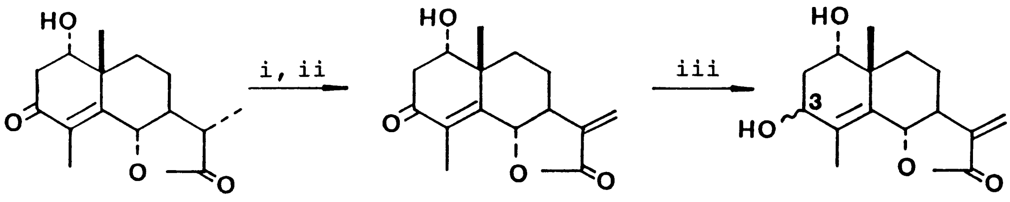
Isoerivanin (**2**) and ludovicin C (**3**) were easily derived from **1** by simple reduction of the ketone group at C_3 and by methylenation of γ-lactone ring, respectively. Thus **1** was reduced with $NaBH_4$ in the presence of cerium (III) chloride[12] to give a readily separable 5:1 mixture of the desired α-diol **2** and



Reagents: i) DIBAH, toluene-THF; ii) MCPBA, CH_2Cl_2; iii) CrO_3-2Py, CH_2Cl_2; iv) $Na^+[PhSeB(OEt)_3]^-$, AcOH, EtOH; v) $NaBH_4$, $CeCl_3$, MeOH

Scheme 1.

its β-isomer **9** in 91% yield. The major product, mp 180-184 °C and $[\alpha]_D$ +82.6° (c, 1.0, dioxane), was superimposable with the authentic isoerivanin (**2**).$^{2,13)}$ On the other hand, treatment of **1** with 3 equiv. of lithium diisopropylamide in THF at -40 °C followed by selenenylation of the resulting trianions with diphenyldiselenide yielded monoselenenylated lactone (mp 203-206 °C), which was then oxidized under the standard conditions$^{14)}$ to give α-methylene lactone **3** in 50% overall yield (94% based on the recovered **1**). Again, the product, mp 189-191 °C and $[\alpha]_D$ +85.8° (c, 0.5, $CHCl_3$), was identical with the authentic ludovicin C (**3**)$^{3,15)}$ in all respects (Scheme 2). Finally, reduction of ludovicin C (**3**) with $NaBH_4$-$CeCl_3$$^{12)}$ in MeOH produced a separable mixture of 1α,3α-dihydroxyarbusculin B (**4**) $[\alpha]_D$ +103.7° (c, 0.38, $CHCl_3$) and its isomer **10** in a ratio of 5:1 in 43% yield.$^{16)}$ The major product was unambiguously assigned to the structure **4** by comparison of its spectral data with those of the authentic sample$^{4,17)}$ (Scheme 2).



1 **3** **4** α-OH **10** β-OH

Reagents: i) LDA, $(PhSe)_2$, THF; ii) H_2O_2, AcOH, THF; iii) $NaBH_4$, $CeCl_3$, MeOH

Scheme 2.

Thus the facile syntheses of eudesmane sesquiterpene lactones (**1**, **2**, **3**, and **4**) have been achieved by introducing the organoselenium-mediated reduction of the epoxy ketone **8** and their proposed structures have been unambiguously established.

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5) The ratio was determined from the ^{1}H NMR analysis.
6) A variety of reducing agents such as $Al(i\text{-}PrO)_3$, $LiAl(t\text{-}BuO)_3H$, L-Selectride, and $NaBH_4\text{-}CeCl_3$ were also examined. These reagents, however, were found not to be effective, although $NaBH_4\text{-}CeCl_3$ reduction gave the same mixture of products in 72% yield.
7) H. B. Henbest and J. T. McCullough, Proc. Chem. Soc., 1962, 74.
8) α-Epoxidation of the tetrasubstituted $C_4\text{-}C_5$ double bond initially occurred and the disubstituted $C_1\text{-}C_2$ double bond was then epoxidized. The corresponding β-epoxide at $C_1\text{-}C_2$ was not observed unless a large excess of MCPBA was not employed owing to the steric repulsion of the angular methyl group.
9) Sodium benzeneselenolate was prepared by reduction of $(PhSe)_2$ with $NaBH_4$ in ethanol according to the procedure of Sharpless (K. B. Sharpless and R. F. Lauer, J. Am. Chem. Soc., 95, 2697 (1973)). Very recently we found that the structure of the benzeneselenolate so generated is a selenium-borane complex, $Na^+[PhSeB(OEt)_3]^-$. Details will be reported elsewhere.
10) Although a small amount of diol was detected on TLC, it was smoothly dehydrated to **1** under the reaction conditions due to the labile tertiary alcohol in an axial position.
11) Reported values (mp 189-191 °C and $[\alpha]_D$ +36.2° (dioxane)) for **1** are lower than those of the synthetic compound.
12) J. L. Luche, J. Am. Chem. Soc., 100, 2226 (1978).
13) $[\alpha]_D$ of the natural sample has not been reported.
14) P. A. Grieco and M. Miyashita, J. Org. Chem., 39, 120 (1974).
15) Mp 193-195 °C, $[\alpha]_D$ +95° ($CHCl_3$).
16) The products were soluble in water and it may be referred to the low yield of products.
17) The reported $[\alpha]_D$ value (+18° , c, 0.1, $CHCl_3$) of the authentic specimen is extremely lower in comparison with that of the synthetic material.

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