

SHORT-STEP SYNTHESIS OF SOME SANTANOLIDES, DEHYDROISOERIVANIN, ISOERIVANIN, LUDOVICIN C, AND 1 α , 3 α -DIHYDROXYARBUSCULIN B BY THE USE OF THE ORGANOSELENIUM REDUCTION METHOD OF EPOXY KETONES

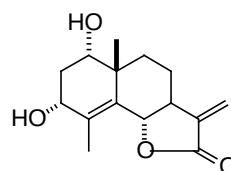
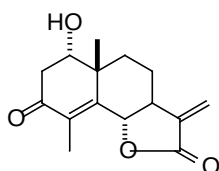
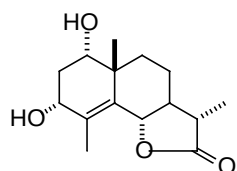
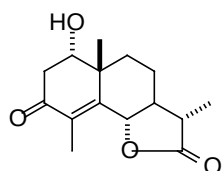
Toshio Suzukia and Masaaki Miyashita^{b*}

^aGraduate School of Science and Technology, Niigata University, Niigata 950-2102, Japan

^bDivision of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan

Abstract- Short-step synthesis of four santanolides, dehydroisoerivanin (**1**), isoerivanin (**2**), ludovicin C (**3**), and 1 α , 3 α -dihydroxyarbusculin B (**4**) is described in which the organoselenium reduction of a cross diepoxy ketone was involved as a key step.

There have been found numerous sesquiterpene lactones including β -hydroxy ketone (aldol) or 1,3-diol structure(s) in the molecule, *inter alia*, eudesmane sesquiterpene lactones (santanolides) are their representatives. The organoselenium reduction method of α,β -epoxy ketones to β -hydroxy ketones which we recently reported in full details^{1,2} provides an extremely useful methodology for the synthesis of those natural products. We describe herein the short-step synthesis of four santanolides, dehydroisoerivanin (**1**), isoerivanin (**2**), ludovicin C (**3**), and 1 α , 3 α -dihydroxyarbusculin B (**4**) which employed the organoselenium reduction method as the key step.³ The former sesquiterpenes (**1**) and (**2**) were isolated from *Balsamita major* Desf. as minor constituents,⁴ and the latter (**3**) and (**4**) were isolated from *Artemisia ludoviciana* Nutt. ssp. mexicana (Wild.) Keck.⁵ and *Schistostephium heptalobum* (DC.) Olive. et Hiern.,⁶ respectively. These sesquiterpene lactones include a common functionality, i.e., either a β -hydroxy ketone or a 1,3-diol structure as well as a γ -lactone ring.



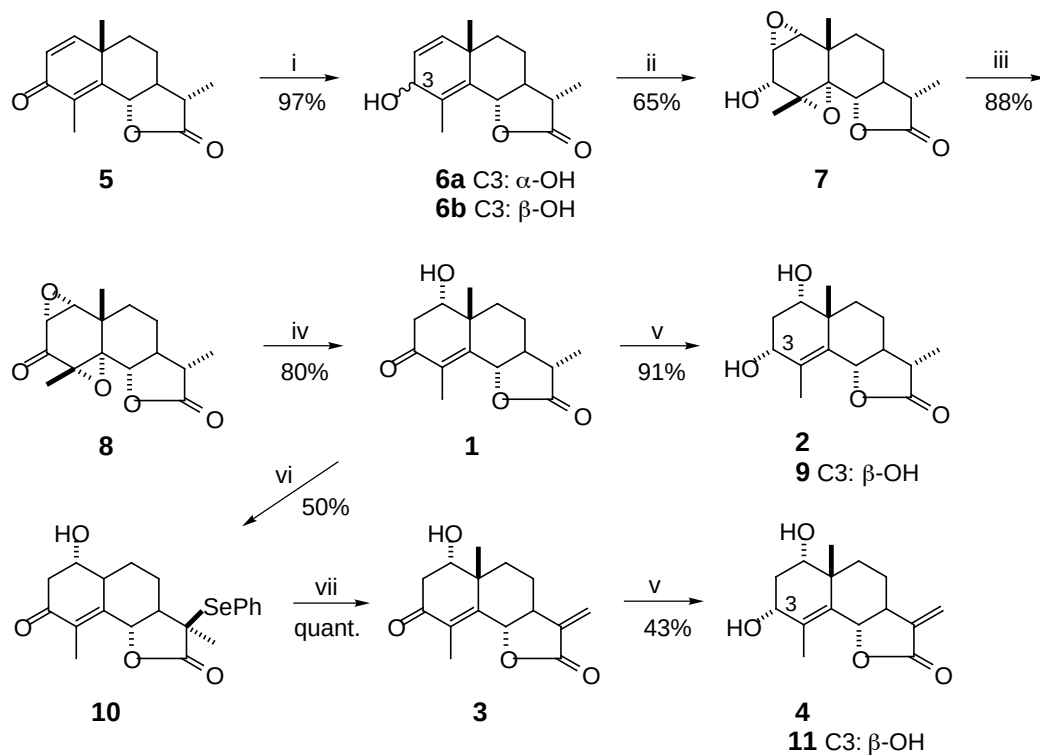
1 Dehydroisoerivanin **2** Isoerivanin **3** Ludovicin C **4** 1 α , 3 α -Dihydroxyarbusculin B

RESULTS AND DISCUSSION

At the outset, we envisaged the two-step synthesis of dehydroisoerivanin (**1**) starting from santonin (**5**)

via regioselective epoxidation of the C1-C2 double bond followed by the reductive cleavage of the resulting α -epoxy ketone with organoseleniums. However, santonin (**5**) was inert to various epoxidation conditions such as alkaline hydrogen peroxide,⁷ alkaline *t*-butyl hydroperoxide,⁸ tetrabutylammonium fluoride-hydrogen peroxide,⁹ *etc.*, probably due to the facile enolization of **5** to generate an enolate species under basic conditions.

Therefore, we employed the synthetic strategy *via* a diepoxy ketone (**8**) as shown in Scheme 1. The key α -diepoxy ketone (**8**) was straightforwardly and stereoselectively synthesized as follows. Thus, santonin (**5**) was reduced with diisobutylaluminum hydride (DIBAL-H) at -70 °C to give an inseparable mixture of the desired α -allylic alcohol (**6a**) and its β -isomer (**6b**) in a ratio of 3:1 in 97% yield.¹⁰ Then, the dienol mixture was treated with 3-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 at 0 °C to furnish the crystalline α -diepoxy alcohol (**7**) in 65% yield. As anticipated, stereochemistry of two epoxides could be controlled by the directive effect of an α -hydroxyl group at the C3 position.^{11,12} The diepoxy alcohol (**7**) thus obtained was submitted to Collins oxidation¹ to give the crystalline α -diepoxy ketone (**8**), a crucial



Reagents: i. DIBAL-H, toluene; ii. MCPBA, CH_2Cl_2 ; iii. $\text{CrO}_3\cdot 2\text{Py}$, CH_2Cl_2 ; iv. $\text{Na}[\text{PhSeB}(\text{OEt})_3]$, AcOH, EtOH; v. NaBH_4 , CeCl_3 , MeOH; vi. LDA, $(\text{PhSe})_2$, THF; vii. H_2O_2 , AcOH, THF.

Scheme 1

intermediate, in 88% yield.

The organoselenium reduction of **8**, the key step in the present synthesis, was performed with 5 equiv. of a sodium phenylseleno(triethoxy)borate complex, $\text{Na}[\text{PhSeB}(\text{OEt})_3]$,¹ in the presence of AcOH in EtOH. As expected, reductive cleavage of two epoxy ketone functionalities cleanly occurred at the α -position¹ and, interestingly, a tertiary alcohol between newly formed two hydroxyl groups was smoothly dehydrated under

the conditions resulting in the direct formation of dehydroisoerivanin (**1**) in 80% yield. Spectral data of the synthetic compound were identical with those of the natural product, while the melting point (mp 203-205 °C) and $[\alpha]_D$ value (+50.1° (c, 1.0, dioxane)) of the former were considerably high in comparison with the reported values (mp 189-191 °C, $[\alpha]_D$ +36.2° (dioxane)) of a natural specimen.⁴ Thus, the four-step synthesis of dehydroisoerivanin (**1**) was accomplished by employing the organoselenium reduction of the diepoxy ketone (**8**) as a key step.

Isoerivanin (**2**) and ludovicin C (**3**) were easily derived from **1** by simple reduction of a ketone at the C3 position and by methylenation of a γ -lactone moiety, respectively. Namely, **1** was reduced with NaBH₄ in the presence of CeCl₃·7H₂O¹⁴ to give a readily separable 5:1 mixture of the α -diol and its β -isomer (**9**) in 91% yield. The major product (mp 180-184 °C, $[\alpha]_D$ +82.6° (c, 1.0, dioxane)) was identified with isoerivanin (**2**) by comparison of its spectral data with those of natural product,⁴ though the melting point and $[\alpha]_D$ value of the latter have not been reported. On the other hand, ludovicin C (**3**) was synthesized as follows. On treatment of **1** with 3 equiv. of lithium diisopropylamide (LDA) in THF at -40 °C followed by selenenylation of the resulting trianions with diphenyldiselenide,¹⁵ the crystalline monoselenenylated lactone (**10**) was obtained as a single product in 50% (94% based on the recovered **1**) isolated yield. Then, the selenenylated lactone was subjected to oxidation with hydrogen peroxide to give the α -methylene lactone (**3**) quantitatively. Exclusive formation of the α -methylene lactone demonstrates that selenenylation of **1** occurred regio- and stereoselectively at the α -position of a γ -lactone resulting in the formation of the α -methyl- β -phenylselenolactone (**10**).¹⁵ Stereoselective selenenylation of **1** may be rationalized by the stereoelectronic effect, i.e., the preferential loss of the axial proton from a conformationally rigid *trans*-fused γ -lactone. The methylene lactone (mp 189-191 °C, $[\alpha]_D$ +85.8° (c, 0.5, CHCl₃)) thus obtained was identical with ludovicin C (**3**) (mp 193-195 °C, $[\alpha]_D$ +95° (CHCl₃)) in all respects.⁵

Finally, reduction of **3** with NaBH₄ in the presence of CeCl₃·7H₂O produced a 5:1 mixture of the 1 α ,3 α -diol and its 3 β -isomer (**11**) in 43% yield. The major product ($[\alpha]_D$ +103.7° (c, 0.4, CHCl₃)) was assigned to 1 α ,3 α -dihydroxyarbusculin B (**4**) by comparison of its spectral data with those of a natural specimen,⁶ though the $[\alpha]_D$ value (+18°, (c, 0.1, CHCl₃)) of the latter was extremely low in comparison with that of the synthetic compound.

Difference in $[\alpha]_D$ values between natural dehydroisoerivanin (**1**), 1 α ,3 α -dihydroxyarbusculin B (**4**) and the corresponding synthetic compounds may be due to a limited quantity of the natural products.

In conclusion, the short-step synthesis of four santanolides, dehydroisoerivanin (**1**), isoerivanin (**2**), ludovicin C (**3**), and 1 α ,3 α -dihydroxyarbusculin B (**4**) have been achieved by employing the organoselenium reduction as the key step and their proposed structures have been synthetically approved.

EXPERIMENTAL

Melting points were determined on a Mitamura Riken MP-A melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-3 or a Shimadzu IR-405 spectrophotometer. ¹H NMR spectra were measured at 100 MHz on a JEOL PS-100 spectrometer in CDCl₃ with tetramethylsilane as an internal standard. Merck silica gel 60 (230-400 mesh) was employed for flash chromatography.

Synthesis of allylic alcohols (6a) and (6b).

A toluene solution of DIBAL-H (1.0 M, 10.0 mL) was added dropwise to a solution of santonin (**5**) (2.0

g, 8.13 mmol) in dry toluene (20 mL) at -70 °C over 10 min under an argon atmosphere and the mixture was stirred for an additional hour at the same temperature. After the excess hydride was decomposed with a saturated NH_4Cl solution, the supernatant organic layer was decanted. Inorganic materials were washed with CH_2Cl_2 and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residual oil was purified by flash chromatography (AcOEt-hexane (1:2)) to afford an inseparable 3:1 mixture of **6a** and **6b** (1.96 g, 97%) as crystals. ^1H NMR: δ 1.15 and 1.21 (each s, 3H in total), 1.24 (d, 3H, $J=6.8$ Hz), 2.05 (br s, 3H), 1.04-2.50 (m, 7H), 4.18-4.41 (br, 1H), 4.53-4.83 (br, 1H), 5.48-5.88 (m, 2H). IR (KBr): 3200, 1770, 1455, 1240, 1140, 760 cm^{-1} .

Synthesis of α -diepoxy alcohol (7).

MCPBA (85%, 1.07 g, 5.28 mmol) was added to a solution of the mixture of **6a** and **6b** (874 mg, 3.52 mmol) in CH_2Cl_2 (70 mL) at 0 °C. After it was stirred for 3 h in the cold, the mixture was successively washed with a 10% NaHCO_3 solution containing a small amount of sodium thiosulfate, water, and saturated brine. The aqueous washes were extracted once with CH_2Cl_2 (30 mL). The combined organic layers were concentrated *in vacuo* and a crystalline residue was purified by flash chromatography. Elution with AcOEt-hexane (1:2) afforded 4,5- α -monoepoxy alcohol (353 mg) as crystals and further elution with AcOEt-hexane (3:1) gave the α -diepoxy alcohol (**7**) (414 mg) as crystals. The former compound was again treated with MCPBA (258 mg, 1.27 mmol) in CH_2Cl_2 (30 mL) at 0 °C for 16 h giving rise to 230 mg of **7**. In total, 644 mg (65%) of the α -diepoxy alcohol (**7**) was obtained. **7**: mp 199 °C (acetone-hexane); ^1H NMR: δ 1.22 (s, 3H), 1.24 (d, 3H, $J=6.6$ Hz), 1.68 (s, 3H), 2.35 (d, 1H, $J=12.1$ Hz), 1.50-2.44 (m, 6H), 2.97 (d, 1H, $J=4.3$ Hz), 3.37 (dd, 1H, $J=4.3, 3.2$ Hz), 4.00 (dd, 1H, $J=12.1, 3.2$ Hz), 4.31 (d, 1H, $J=10.1$ Hz). IR (KBr): 3420, 1800, 1780, 1380, 1270, 1030 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_5$: C, 64.27; H, 7.41. Found: C, 64.15; H, 7.41.

Synthesis of α -diepoxy ketone (8).

The Collins reagent¹³ (2.28 g, 8.87 mmol) was added in small portions to a solution of the diepoxy alcohol (**7**) (414 mg, 1.48 mmol) in dry CH_2Cl_2 (30 mL) under argon and the whole mixture was stirred for 30 min at rt. The reaction mixture was diluted with AcOEt (100 mL) and passed through a short silica gel column by the aid of AcOEt. Evaporation of the solvents from the eluate left crystalline residue which was recrystallized from acetone-hexane to afford pure α -diepoxy ketone (**8**) (361 mg, 88%): mp 201-202 °C; ^1H NMR: δ 1.22 (s, 3H), 1.24 (s, 3H), 1.65 (s, 3H), 1.52-2.54 (m, 6H), 3.24 (d, 1H, $J=4.3$ Hz), 3.57 (d, 1H, $J=4.3$ Hz), 4.34 (d, 1H, $J=10.4$ Hz). IR (KBr): 1785, 1708, 1382, 1145, 1035 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_5$: C, 64.73; H, 6.52. Found: C, 64.69; H, 6.77.

Synthesis of dehydroisoerivanin (1).

AcOH (4.1×10^{-2} mL, 0.73 mmol) was added to an ethanolic solution of $\text{Na}[\text{PhSeB}(\text{OEt})_3]$ (1.82 mmol), which was prepared by the reduction of $(\text{PhSe})_2$ (283 mg, 0.91 mmol) with NaBH_4 (90%, 77 mg, 1.82 mmol) in EtOH (4.5 mL) under an argon atmosphere,¹ and the mixture was stirred for a few minutes at rt. Then, the mixture was added at once to a solution of the diepoxy ketone (**8**) (101 mg, 0.36 mmol) in EtOH (5.5 mL) and THF (1.5 mL) and stirring was continued for 5 min at rt. The reaction mixture was diluted with AcOEt- CH_2Cl_2 (1:1, 60 mL) and washed twice with saturated brine. The aqueous washes were extracted three times with CH_2Cl_2 (20 mL). The combined organic layers were dried over MgSO_4 and

concentrated *in vacuo*. The oily residue was purified by preparative thin layer chromatography (TLC) (AcOEt-hexane (2:1)) to give **1** (76.5 mg, 80%) as colorless crystals: mp 203-204 °C (acetone-hexane); $[\alpha]_D^{25} +50.1$ °(c, 1.0, dioxane). The IR and ¹H NMR spectra of the synthetic compound were superimposable with those of natural dehydroisoerivanin.⁴

Synthesis of isoerivanin (**2**).

NaBH₄ (96%, 4.5 mg, 0.11 mmol) was added to a solution of **1** (30 mg, 0.11 mmol) and CeCl₃·7H₂O (42 mg, 0.11 mmol) in MeOH (2 mL) at 0 °C under argon. After 10 min, the reaction was quenched with AcOH (3.2x10⁻² mL). The mixture was concentrated *in vacuo* to leave an oil which was purified by preparative TLC (AcOEt) to afford **2** (23 mg, 76%) as colorless crystals along with its 3β-isomer (5 mg, 16%). **2**: mp 180-184 °C (acetone-hexane); $[\alpha]_D^{24} +82.6$ °(c, 1.0, dioxane). The IR and ¹H NMR spectra of the synthetic compound were identical with those of natural isoerivanin.⁴

Synthesis of selenolactone (**10**).

To a solution of LDA in THF, prepared from diisopropylamide (5.6x10⁻² mL, 0.40 mmol) and BuLi (1.6 M in hexane, 0.25 mL, 0.40 mmol) in dry THF (1 mL), was added dropwise a solution of **1** (30 mg, 0.11 mmol) in dry THF (1.5 mL) at -65 °C under an argon atmosphere. The mixture was warmed to -50 °C over 1.5 h to which was added a solution of (PhSe)₂ (71 mg, 0.23 mmol) in THF (1 mL). The mixture was warmed to -40 °C over 1.5 h and stirring was continued for an additional hour. After the reaction was quenched with AcOH (2.5x10⁻² mL), the mixture was diluted with AcOEt-CH₂Cl₂ (1:1, 20 mL) and successively washed with 5% HCl, water, and saturated brine. The aqueous washes were extracted once with CH₂Cl₂ (20 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The oily residue was purified by preparative TLC (AcOEt-hexane (4:1)) to give the selenolactone (**10**) (24 mg, 50%) along with starting material (14 mg, 47%). **10**: mp 203-206 °C (acetone-hexane); ¹H NMR: δ 1.35 (s, 3H), 1.59 (s, 3H), 2.02 (d, 3H, *J*=1.8 Hz), 1.40-2.48 (m, 6H), 2.64 (dd, 1H, *J*=16.4, 4.3 Hz), 2.88 (dd, 1H, *J*=16.4, 3.1 Hz), 3.80 (dd, 1H, *J*=4.3, 3.1 Hz), 5.15 (dd, 1H, *J*=10.8, 1.8 Hz), 7.20-7.48 (m, 3H), 7.48-7.70 (m, 2H); IR (KBr): 3400, 1770, 1668, 1440, 1380, 1030, 740, 693 cm⁻¹. Anal. Calcd for C₂₁H₂₄O₄Se: C, 60.14; H, 5.77. Found: C, 60.29; H, 5.89.

Synthesis of ludovicin C (**3**).

Hydrogen peroxide (30%, 4.4x10⁻² mL, 0.40 mmol) was added dropwise to a solution of **10** (24 mg, 0.06 mmol) and AcOH (1.0x10⁻² mL, 0.17 mmol) in THF (1 mL) and the mixture was stirred for 30 min at rt. A 10% NaHCO₃ solution was added to the reaction mixture and the product was thoroughly extracted with AcOEt-CH₂Cl₂ (1:1). The combined extracts were dried over MgSO₄ and concentrated *in vacuo*. The crystalline residue was purified by preparative TLC (AcOEt-CH₂Cl₂ (4:1)) to afford **3** (15 mg, 100%). The IR and ¹H NMR spectra of the synthetic compound were superimposable with those of natural ludovicin C.⁵

Synthesis of 1a,3a-dihydroxyarbusculin B (**4**).

NaBH₄ (96%, 3.5 mg, 0.09 mmol) was added to a solution of **3** (23 mg, 0.09 mmol) and CeCl₃·7H₂O (33 mg, 0.09 mmol) in MeOH (1.5 mL) at 0 °C under argon. After 15 min, the excess hydride was decomposed with a saturated NH₄Cl solution and the mixture was extracted with CH₂Cl₂. The combined extracts were dried (MgSO₄) and concentrated *in vacuo*. The oily residue was purified by preparative

TLC (AcOEt) to give **4** (9 mg, 38%) as an oil along with its 3 β -isomer (1 mg, 5%). **4**: $[\alpha]_D^{24} +103.7^\circ$ (c, 0.38, CHCl₃). The IR and ¹H NMR spectra of the synthetic compound were identical with those of natural 1 α ,3 α -dihydroxyarbusculin B (**4**).⁶

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