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# Organosulfur and Organoselenium Mediated Reductive Cleavage of Certain γ-Enonelactones

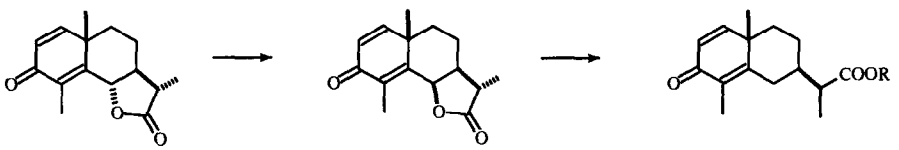
Cosme G. Francisco, Raimundo Freire, María S. Rodríguez and Ernesto Suárez*

Instituto de Productos Naturales y Agrobiología del C.S.I.C.
Carretera de la Esperanza 2, La Laguna, Tenerife, Spain

*Key Words:* organosulfur; organoselenium; reduction; lactone; γ-enonelactone

***Abstract:*** *Reduction of the alkyl-oxygen bond of several γ-enonelactones is readily accomplished in high yield with PhSeNa or PhSNa reagents. The reaction has been extended to several sesquiterpenoid lactones of the santonin and isophotosantonin groups.*

As part of our research objectives directed to the syntheses of sesquiterpenoid phytoalexins of the eudesmane group, we required dienone (**3**) on a multigram scale. This compound has been used as starting material in the syntheses of several natural products such us (+)-cyperone[1], chamaecynone and 4α-hydroxy-*iso*-chamaecynone[2], α-bulnesene[3] and (-)-occidentalol[4] , and it has been synthetized in a two step process from the well-known and readily available sesquiterpene (-)-α-santonin (**1**) with moderate overall yield (c.a. 40%). In a first step (-)-α-santonin is converted into the epimeric (-)-6-*epi*-α-santonin (**2**) following the procedure described by Ishikawa[5] (40-63% yield) and the *cis*-lactone is subsequently reduced with Zn dust in glacial acetic acid (64%)[1,6] (Scheme 1).

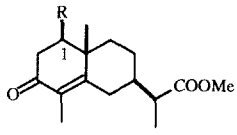



(1) (2) (3) R = H (4) R = Me

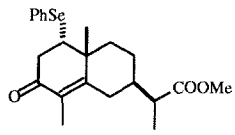
Scheme 1

We have, therefore, considered alternative methods for the preparation of (**3**) and we report in this communication its synthesis from (-)-α-santonin (**1**) in one step and >90% yield, by organosulfur- or organoselenium-mediated reduction as shown in the Table (entries 3 and 5). The generality of this method was also examined on a number of related lactones.

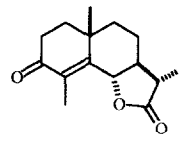
In a preliminary experiment treatment of (**1**) with an excess of ethanolic PhSNa, generated from PhSH and sodium, at reflux temperature (entry 1) gave, after methylation, the desired dienone (**4**) in low yield, while the major reaction product, originated by a Michael addition, was the phenylsulfide derivative (**5**). Encouraged by the result that the total yield of reduced lactone was 81% we developed more convenient reaction conditions to improve the yield of the dienone (**4**) using PhSH (3 mmol) and NaH (2 mmol) per mmol of



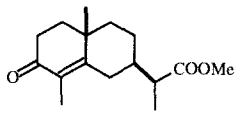
(5) R = PhS
(6) R = PhSe



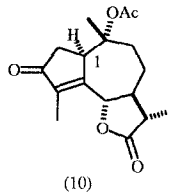
(7)



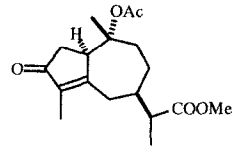
(8)



(9)



(10)

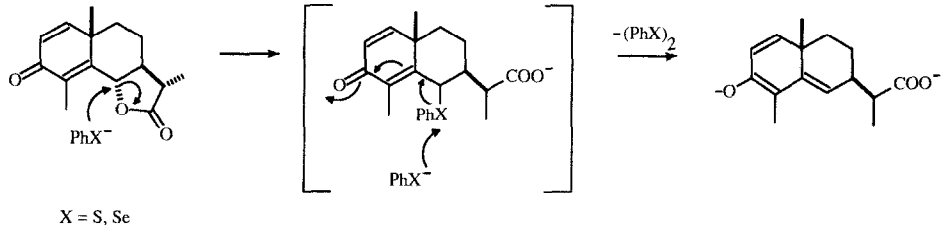


(11)

santonin in THF at 115 °C, as described in the representative experimental procedure shown below, the dienone (4) being obtained in 90% yield (entry 3). A very similar result was observed using PhSeH instead of PhSH (entry 5). In both cases, very small amounts of the respective Michael adducts (**5**) y (**6**) were obtained. The Michael adducts seem to be initially formed and then eliminated at higher temperatures, as indicated by the observed results in the experiments performed at room temperature (entries 2 and 4).

The reaction behaviour does not seem to be especially dependent on the lactone stereochemistry since (-)-6-*epi*-α-santonin (**2**) was analogously reduced in almost identical yield (entries 6-9), nor on the enone type since the reaction also proceeds with enone (**8**) (entries 10 and 11) and with cyclopentenone (**10**) (entries 12 and 13). With the latter, when PhSNa was used as reagent several non-identified products were formed and (**11**) was obtained in lower yield (entry 12).

A possible mechanism for this reaction is shown in Scheme 2. The proposed intermediate is very plausible since it is well known that a non-complexed selenolate anion cleaves the C-O bond in esters and lactones by a preferential nucleophilic attack on the carbinol carbon.[13] Nucleophilic attack by a second molecule of selenolate anion on a selenium atom has been proposed previously to explain the organoselenium-mediated reduction of α-β-epoxyketones to β-hydroxyketones.[14] An analogous mechanism is proposed for the reaction with PhSNa. Although the thiophenoxide anion has not been used for the alkyl-oxygen cleavage of lactones, the thiomethoxide anion is an excellent reagent for this reaction.[15] The isolation of one equivalent of diphenyldiselenide and diphenyldisulfide from the reduction with PhSeNa and PhSNa respectively is a good support for the proposed mechanism.[16]



X = S, Se

Scheme 2

Table. Reduction of Lactones

| Entry | Lactone | Reagent | Conditions[d] | | Products[e] |
|---|---|---|---|---|---|
| | | | Temp.(°C) | Time(h) | (yield %) |
| 1 | **1** | PhSH/Na/EtOH[a] | reflux | 20 | **4**(13)[7]; **5**(68)[8] |
| 2 | **1** | PhSH/NaH/THF[b] | r.t. | 70 | **4**(37); **5**(43); **1**(20) |
| 3 | **1** | PhSH/NaH/THF[b] | 115 | 6 | **4**(90); **5**(9) |
| 4 | **1** | PhSeH/NaH/THF[c] | r.t. | 80 | **4**(10); **6**(50)[9];**1**(30) |
| 5 | **1** | PhSeH/NaH/THF[c] | 115 | 6 | **4**(91); **6**(7) |
| 6 | **2** | PhSH/NaH/THF[b] | r.t | 88 | **4**(60); **5**(15); **2**(16) |
| 7 | **2** | PhSH/NaH/THF[b] | 115 | 6 | **4**(90) |
| 8 | **2** | PhSeH/NaH/THF[c] | r.t. | 66 | **4**(60); **6**(16); **7**(17)[10] |
| 9 | **2** | PhSeH/NaH/THF[c] | 115 | 6 | **4**(90); **6**(2); **7**(2) |
| 10 | **8** | PhSH/NaH/THF[b] | 115 | 6 | **9**(85)[11] |
| 11 | **8** | PhSeH/NaH/THF[c] | 115 | 6 | **9**(91) |
| 12 | **10** | PhSH/NaH/THF[b] | 115 | 4 | **11**(36)[12] |
| 13 | **10** | PhSeH/NaH/THF[c] | 115 | 6 | **11**(95) |

[a] PhSH (35 mmol)/Na (4 mmol)/EtOH (45 ml) per mmol of lactone; [b] PhSH (3 mmol)/NaH (2mmol)/THF (5 ml) per mmol of lactone; [c] PhSeH (3 mmol)/NaH (2 mmol)/THF (5 ml) per mmol of lactone; [d] All reactions under argon in a hydrolysis tube (Kontes-896860); [e] After methylation with excess of ethereal diazomethane.

Representative Experimental Procedure

To a suspension of NaH (20 mg, 0.8 mmol) in dry THF (1 ml) was added slowly benzeneselenol (130 µl, 1.2 mmol) at r.t. under argon in a 5 ml heavy wall hydrolysis tube with a high vacuum teflon valve (Kontes-896860).[17] After stirring for five minutes a solution of lactone (**1**) (100 mg, 0.4 mmol) in THF (1.5 ml) was added, the valve was tightly closed and the tube immersed in a preheated silicon bath at 115 °C for 6 h. The mixture was poured into aqueous hydrochloric acid (10%) and extracted with ethyl acetate. The organic layer was concentrated under vacuo and the residue was dissolved in ether (10 ml) and treated with an excess of ethereal diazomethane. The solution was then evaporated and the crude purified by silica gel chromatography (90:10 hexane-ethyl acetate) to give compound (**4**) (97 mg, 91%), a small amount of the phenylselenium derivative (**6**) (13 mg, 7%) and diphenyldiselenide (126 mg, 0.4 mmol). An analogous procedure was used with thiophenol to give (**4**) (90%), (**5**) (9%) and diphenyldisulfide (86 mg, 0.4mmol).

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7. Compound (**4**): oil; IR (KBr) $\nu_{max}$ 1730, 1660, 1630, 1610 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.20 (3H, s, 10-Me), 1.20 (3H, d, J 7 Hz, 11-Me), 1.87 (3H, s, 4-Me), 3.71 (3H, s, 13-OMe), 6.21, 6.72 (2H, AB, J 9.8 Hz, 2-H, 1-H); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) δ *inter alia* 186.24 (3-C), 175.93 (13-C), 158.95 (5-C), 156.36 (1-C), 129.27 (4-C), 126.29 (2-C); MS m/z 262.1578 ($M^+$, 23%).
8. Compound (**5**): m.p. 114.5-115.5 °C (acetone-n-pentane); $[\alpha]_D$ -70° ($CHCl_3$); IR ($CHCl_3$) $\nu_{max}$ 1740, 1650 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 249 nm (ε 17250); $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.19 (3H, d, J 7 Hz, 11-Me), 1.26 (3H, s, 10-Me), 1.74 (3H, s, 4-Me), 3.32 (1H, apparent t, 1α-H), 3.70 (3H, s, 13-OMe), 7.34 (5H, m, 1β-S-Ar); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) δ *inter alia* 197.03 (3-C), 176.13 (13-C), 161.83 (5-C), 134.77 (4-C), 56.73 (1-C); MS m/z 372.1730 ($M^+$, 23%), 175.1145 (100%).
9. Compound (**6**): m.p. 114.7-115.7 °C (n-pentane); $[\alpha]_D$ -28° ($CHCl_3$); IR (KBr) $\nu_{max}$ 1730, 1650, 1605 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 247 nm (ε 15800), 220 nm (ε 13600);$^1H$ NMR (200 MHz, $CDCl_3$) δ 1.19 (3H, d, J 7 Hz, 11-Me), 1.26 (3H, s, 10-Me), 1.73 (3H, br s, 4-Me), 3.41 (1H, dd, 1α-H), 3.70 (3H, s, 13-OMe), 7.28, 7.57 (5H, m, m, 1β-Se-Ar);$^{13}C$ NMR (50.3 MHz, $CDCl_3$) δ *inter alia* 197.07 (3-C), 175.93 (13-C), 161.31 (5-C), 129.45 or 128.81 (4-C), 53.07 (1-C); MS m/z 420.1183 ($M^+$, $C_{22}H_{28}O_3{}^{80}Se$, 14%), 263.1644 (100%).
10. Compound (**7**): m.p. 115-116 °C (n-hexane); $[\alpha]_D$ +64° ($CHCl_3$); IR (KBr) $\nu_{max}$ 1730, 1670, 1615 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 248 nm (ε 11600), 219 nm (ε 11500); $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.20 (3H, d, J 7Hz, 11-Me), 1.41 (3H, s, 10-Me), 1.78 (3H, br s, 4-Me), 2.77, 2.95 (2H, AMX, $J_{AM}$ 16.6, $J_{AX}$ 8.3, $J_{MX}$ 4.2 Hz, 2-$H_2$), 3.47 (1H, AMX, 1β-H), 3.71 (3H, s, 13-OMe), 7.27, 7.54 (5H, m, m, 1α-Se-Ar); $^{13}C$ NMR (20.1 MHz, $CDCl_3$) δ *inter alia* 196.39 (3-C), 175.82 (13-C), 159.41 (5-C), 129.19 or 129.03 (4-C), 52.90 (1-C); MS m/z 420.1196 ($M^+$, $C_{22}H_{28}O_3{}^{80}Se$, 21%), 263.1656 (100%).
11. Compound (**9**): oil; IR ($CHCl_3$) $\nu_{max}$ 1735, 1665, 1610 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.18 (3H, d, J 7 Hz, 11-Me), 1.17 (3H, s, 10-Me), 1.73 (3H, br s, 4-Me), 3.70 (3H, s, 13-OMe); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) δ *inter alia* 198.68 (3-C), 175.91 (13-C), 161.13 (5-C), 128.70 (4-C); MS m/z 264.1730 ($M^+$, 31%), 177.1273 (100%).
12. Compound (**11**): low melting solid, 50-52 °C ; IR (KBr) $\nu_{max}$ 1730, 1700, 1630 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.01 (3H, s, 10-Me), 1.15 (3H, d, J 7.3 Hz, 11-Me), 1.63 (3H, br s, 4-Me), 1.95 (3H, s, 13-OMe), 4.03 (1H, m, 1α-H); $^{13}C$ NMR (20.1 MHz, $CDCl_3$) δ *inter alia* 206.93 (3-C), 175.39 (13-C), 170.38 or 170.09 (5-C or $OCOCH_3$), 139.56 (C-4), 86.16 (10-C); MS m/z 322.1779 ($M^+$, <1%), 262.1570 (50%).
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16. Nevertheless, attempts to trap the dianion intermediate by adding to the reactions of (**1**) and (**8**) an excess of methyl iodide were unsuccessful, the only products observed being the corresponding methyl esters (**4**) and (**9**).
17. Despite the fact that no incidents have been observed, the use of a protective shield and a good hood is recommended.


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