Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2241–2251

TETRAHEDRON

Studies on the stereoselective selenolactonization, hydroxy and methoxy selenenylation of α- and β-hydroxy acids and esters. Synthesis of δ- and γ-lactones

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Received 11 November 2002; revised 15 January 2003; accepted 7 February 2003

Abstract—The diastereoselective synthesis of hydroxy substituted γ- and δ-lactones was accomplished following two approaches. A 5- or 6-*endo* cyclization promoted by electrophilic selenium reagents of α- or β-hydroxy acids and a 5- or 6-*exo* cyclization of hydroxy esters obtained through a diastereoselective hydroxy selenenylation reaction of α- or β-hydroxy esters. Moreover, the diastereoselective methoxy selenenylation of the above compounds was investigated showing a case in which the compound that was unreactive in the hydroxy selenenylation conditions gave, in the methoxy selenenylation conditions, the deprotected diol. The usefulness of the methoxy selenenylation procedure was proven by the preparation of a symmetric compound unsymmetrically functionalized. Yields and selectivities were found to depend on substituents (Ph or alkyl groups at the carbon atom that undergoes the nucleophilic attack), mode of cyclization, kinetic or thermodynamic control conditions. In the latter case, silica gel played an important role.

1. Introduction

Lactones are found in the structures of many natural products possessing important biological activities. Moreover, they constitute very useful synthetic intermediates, especially for the stereoselective synthesis of complex molecules. One of the most employed methods is the electrophile-induced ring-closure of unsaturated carboxylic acids. Halolactonization[1] and selenolactonization[2] are probably the most commonly employed methods. In recent years we have been interested in the stereoselective synthesis of oxygenated heterocycles via the intermediate formation of a seleniranium ion.[3–11] Indeed, selenium chemistry plays an important role in such synthesis and various electrophilic selenium reagents such as phenylselenenyl halides,[1,2] triflate,[12] sulfate[13] and *N*-(phenylseleno)phthalimide[14] are largely used to introduce new functional groups into organic substrates under mild experimental conditions.[15,16]

Moreover, we have also shown that the presence of the PhSe group can modify, under thermodynamic conditions, the position of equilibrium for ring interconversion. Tetrahydropyrans with an exocyclic PhSe group obtained in 33:67 ratio under kinetic conditions equilibrated to a 75:25 ratio under thermodynamic conditions (Fig. 1),[8] whereas similar tetrahydrofurans rearranged to the tetrahydropyrans having the PhSe group in an endocyclic position (Fig. 2).[6]

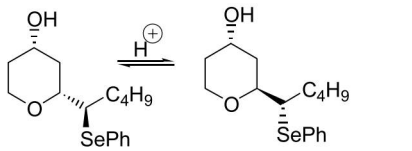

Figure 1.

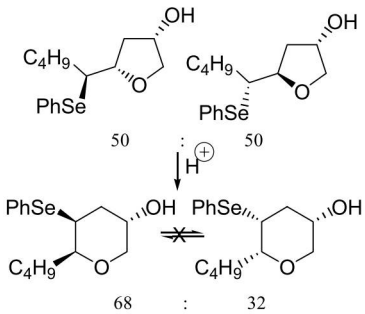

Figure 2.

Keywords: cyclization; diols; lactones; selenium and compounds.

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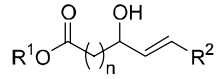
0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00206-0



1a-i

	n	R^1	R^2
a	1	H	Ph
b	1	H	Me
c	0	H	Ph
d	0	H	Pr
e	1	Et	Ph
f	1	Et	Me
g	0	Et	Ph
h	0	Et	Pr
i	0	Et	2-furyl

Scheme 1.

In order to synthesize hydroxy-substituted δ- and γ-lactones, we have investigated the behavior, towards the electrophilic $PhSe^+$ species, of substrates **1a–i** under different conditions (Scheme 1). Hydroxy acids **1a–d** were employed for cyclization reactions. Hydroxy esters **1e–i** were employed for hydroxy selenenylation reactions in order to have 1,3-diols suitable for cyclization reactions to afford lactones. Furthermore, the methoxy selenenylation reactions of hydroxy esters was investigated in order to have stable 1,3-diols for further manipulations.

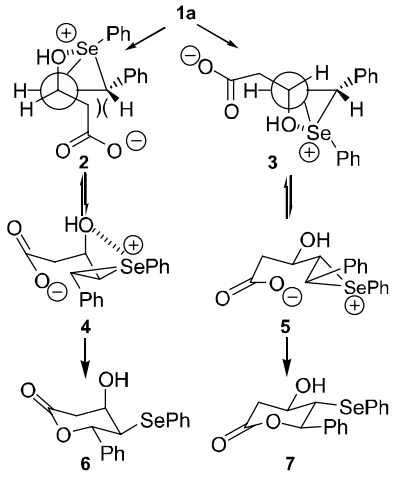
Finally, we paid attention to the behavior of δ- and γ-lactones carrying the PhSe moiety, under thermodynamic control conditions, in order to study the rearrangement of such molecules.

2. Results and discussion

2.1. Cyclizations

In this section the major points in discussion will be yields and selectivities in the 6- and 5-*endo* cyclizations and the role played by silica gel in the rearrangement of the products. In the 6-*endo* cyclization high yield, selectivity and fast rearrangement was found when R^2=Ph. In the 5-*endo* cyclization opposite selectivity was observed and, again, equilibration occurred when R^2=Ph. Moreover, a deeper insight will be given on the 6-*endo* cyclization of compound **1a**.

We started the cyclization reactions with β-hydroxy acid **1a** that was allowed to react with different amounts of PhSeX (X=Cl, Br; 1–3 equiv.) or with PhSeX (X=Cl, Br; 1–2 equiv.) and TBAX (X=Br, Cl or ClO_4; 1 equiv.). The results of these reactions, reported in our preliminary communication,[3] showed that the increasing amount of PhSeX gave, as expected, higher yields (up to 94%) and, unexpectedly, higher diastereoselectivity (up to 95:5). The combined use of PhSeX and TBAX gave lower yields, but the increased amount of X^- (from TBAX) gave higher diastereoselectivity especially with X=Br. These results were rationalized considering that the attack of the $PhSe^+$ species on both sides of the C=C double bond generates two seleniranium ions having a stabilizing interaction between the positive selenium atom and the allylic oxygen atom. In seleniranium ion **2** the unfavorable non-bonding interaction between the CH_2COO^- group and the hydrogen

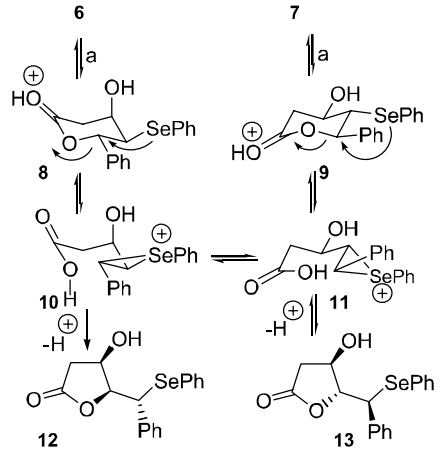


Scheme 2.

atom, should lead to a higher energy for this seleniranium ion compared with the seleniranium **3** where this interaction is absent (Scheme 2). Seleniranium **2** indicates that is possible to maintain the Se–O interaction during the cyclization process (see **4**), whereas in seleniranium **3**, when the COO^- group reaches C_6, the Se–O interaction is lost (see **5**).

Seleniranium **3** is more stable and the activation energy for its cyclization is higher, while seleniranium ion **2** is less stable with a lower transition state energy for the cyclization process. Then, seleniranium ion **3** has a long enough lifetime to undergo the intermolecular attack of the Br^- or Cl^- or ClO_4^- species at the positively charged selenium atom. As a matter of fact, by increasing the amount of X^- we increased the selectivity since seleniranium **3** is preferentially destroyed to give starting material and PhSeX. Moreover, the selenium cation, as a soft electrophile, reacts more readily with Br^- than with Cl^- or ClO_4^-. The best conditions, from a synthetic point of view, were with two equivalent of PhSeBr (94% yield; **6/7** 93:7).

Isolation of **6** and **7** was achieved by removing the unreacted **1a** with aqueous $NaHCO_3$ followed by column chromatography of the residue. However, we obtained a mixture of δ-lactones **6** and **7** and γ-lactone **12**.[17] The mixture of δ-lactones **6** and **7** was then isolated by washing the crude reaction product with light petroleum in order to remove diphenyl diselenide. Because we were interested in the study of the rearrangement of these heterocyclic rings the mixture of δ-lactones **6** and **7** was stirred in dichloromethane with silica gel and eluted to give a quantitative yield (98%) of 4,5-*syn*-γ-lactone **12** with excellent diasteromeric ratio (**12/13** >95:5) (Scheme 3). The same ratio was always obtained whichever was the starting **6/7** ratio. The acid conditions realized with silica gel caused protonation of the δ-lactones and the intramolecular Se attack at C_6 to give ring opening. This rearrangement can be ascribed to the fact that these reactions proceed via a loose S_N2 transition state. The equatorial position of the PhSe group in the δ-lactones and the exocyclic position of the PhSe group in the γ-lactones allow alignment of the selenium, carbon and oxygen atoms at the most favorable co-linear arrangement.



Scheme 3. *Reagents and conditions*: (a) SiO_2, CH_2Cl_2, rt, 98%.

The intermediate seleniranium ions **10** and **11** then cyclized to give the thermodynamically more stable γ-lactone **12** with excellent stereoselectivity. The cyclization realized under kinetic conditions afforded exclusively the δ-lactones because the phenyl group can support the partial positive charge at C_6 allowing the rupture of the C_6–Se bond, whereas the allylic OH group disfavors attack at C_5.[5]

Ab initio calculations (HF/3-21G*) performed on γ-lactones **12** and **13** showed the former to be more stable (3.06 kcal/mol, **12** −3621.48228 hartree, **13** −3621.47740 hartree). The structure of the major compound was also confirmed by T-ROESY experiments (Fig. 3). The cross-relaxation pattern clearly showed the genuine ROE dipolar couplings H_{3a}/H_4, H_{3a}/H_5 and the very weak H_{3b}/H_4 interaction. Further, the lack of interactions between H_5 and H_{3b} as well as H_5 and H_6 supports the relative configurational assignment.

Since the use of 2 equiv. of PhSeBr was found to be the best synthetic conditions for the cyclization reaction of **1a**, β-hydroxy acid **1b** was allowed to react in the same manner to give (95% yield, 58% conversion) a mixture of δ- and γ-lactones (Scheme 4). In order to ascertain the composition, the ^{1}H NMR spectrum of the crude reaction mixture was registered. We found δ-lactones **14** and **15** as major compounds but with very low diastereoselectivity (composition of the crude, **14** 64%, **15** 23%) and γ-lactone *anti* **17** (13% of the crude). Compound **1b** gave lower conversion, stereoselectivity and regioselectivity than the phenyl substituted hydroxy acid **1a**. This mixture was stirred in dichloromethane with silica gel and eluted. After column chromatography we obtained a 57% yield of lactones (calculated from **1b**). The composition of lactones **14/15/16/17** was 23:15:45:17. Lactone *syn*-**16**, absent in the crude reaction mixture, was now the major component. It showed different R_f and was obtained in pure form, whereas other lactones were recovered as an inseparable mixture. NMR investigation (T-ROESY) on *syn*-**16** confirmed its structure.

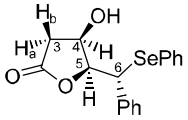
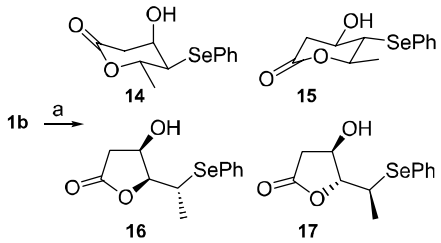


Figure 3.



Scheme 4. *Reagents and conditions*: (a) PhSeBr, K_2CO_3, CH_2Cl_2, −78°C.

In contrast to δ-lactones **6** and **7** that were completely transformed into γ-lactone **12**, lactones **14** and **15** were only partially converted into γ-lactone **16**. The high yield and regioselectivity of cyclization of **1a** and fast rearrangement of **6** and **7** compared with the poor results obtained from the corresponding reactions of the methyl substituted compounds can be easily explained by the activating nature of the phenyl group. The origin of the low diastereoselectivity for **1b** is less clear.

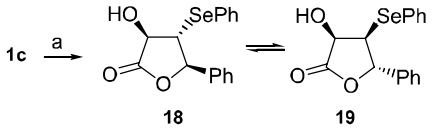
Cyclization of α-hydroxy acid **1c** under different conditions did not give satisfactory yields (see Table 1). Again, in order to have more detailed information, we registered the ^{1}H NMR spectrum of the crude reaction mixture. The selectivity **18/19** was determined as 76–80%/24–20% (Scheme 5). After treatment with silica gel of each crude the diastereoselectivity changed to 86:14. In order to confirm this observation the major compound was recovered in pure form by column chromatography then dissolved in $CDCl_3$ and its behavior monitored by ^{1}H NMR spectroscopy. After 24 h compound **18** equilibrated to a 86:14 **18/19** mixture. This result can be again ascribed to the equilibration of the phenylselenenyl-γ-lactones **18** and **19** to the more stable **18**.

Ab initio calculations realized for compounds **18** and **19** showed **18** as more stable (**18** −3222.66255 hartree; **19** −3222.66028 hartree, ΔE=1.30 kcal/mol). This difference in energy is in agreement with the selectivity found. The

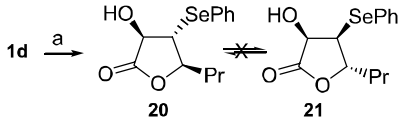
Table 1. Yields and selectivities for the 5-*endo* cyclization of compound **1c**

PhSeX (eq)	Yield[a] (%)	**18/19**[b]	**18/19**[c]
PhSeBr (1)	29	76:24	86:14
PhSeBr (2)	40	80:20	86:14
PhSeCl (1)	20	76:24	86:14
PhSeCl (1)[d]	27	76:24	86:14

[a] Recovered starting material 71, 60, 80 and 73%, respectively.
[b] Selectivity before column chromatography.
[c] Selectivity after column chromatography.
[d] Reaction carried out at rt without K_2CO_3.



Scheme 5. *Reagents and conditions*: (a) PhSeX, K_2CO_3, CH_2Cl_2, −78°C.



Scheme 6. *Reagents and conditions*: (a) PhSeBr, K_2CO_3, CH_2Cl_2, −78°C.

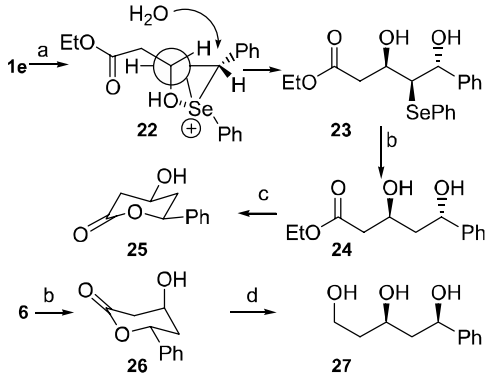
structures of the major and minor diastereoisomers were confirmed by T-ROESY experiments. It should be noted that cyclization of **1a** gave, as major diastereoisomer, δ-lactone **6** which possesses the OH, SePh and Ph groups in a *cis*,*trans* relationship, respectively, whereas the major compound of cyclization of **1c** (γ-lactone **18**) possesses a *trans*,*trans* relationship. Probably, stabilizing interactions such as intramolecular hydrogen bond or as interaction between the positively charged selenium atom and the oxygen atom or destabilizing interactions such as steric repulsion (see Scheme 2) play different roles in the 6-*endo* and in the 5-*endo* cyclization. Compound **1d** was treated with 2 equiv. of PhSeBr to give a 33% yield of lactones **20** and **21** in a 90:10 ratio. The major diastereoisomer **20** was recovered in pure form, dissolved in $CDCl_3$ and monitored by ^{1}H NMR spectroscopy. In contrast to compound **18**, γ-lactone **20** did not rearrange to **21** (Scheme 6).

2.2. Hydroxy and methoxy selenenylation

In this section yields and selectivities in the hydroxy and methoxy selenenylation and subsequent cyclization of the diols to γ- and δ-lactones will be discussed.

Several years ago Korean authors showed a new method for the preparation of 1,3-*anti*-diols via methoxy selenenylation of α,β-unsaturated alcohols.[18] The reactions were carried out in methanol at rt in the presence of a hindered nitrogen base. We thought that the hydroxy selenenylation could directly give 1,3-*anti* diols, hopefully, with good diastereoselectivity (Table 2).

Hydroxy ester **1e** was allowed to react with PhSeCl[19] in acetonitrile/water for 3 min. The 1,3-*anti* diol **23** was obtained in 80% yield and in excellent diastereomeric ratio (95:5) (Scheme 7). When the reaction was quenched after 30 min the yield was lower (65%) with almost the same selectivity. The lower yield can be ascribed to the acid



Scheme 7. *Reagents and conditions*: (a) PhSeCl, CH_3CN/H_2O, rt, 80%; (b) Bu_3SnH, AIBN, C_6H_6, reflux, 95%; (c) cat. PPTS, toluene, reflux, 70%; (d) $LiAlH_4$, Et_2O, rt, 80%.

Table 2. Yields and selectivities for the hydroxy selenenylation reactions of **1e–i**

Entry	1	d.r.	Yield (%)
1	**e**	95:5	80
2[a]	**f**	55:45	40
3	**g**	90:10	90
4	**h**	–	0
5	**i**	–	0

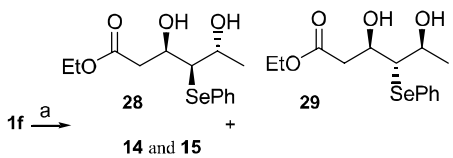
[a] Plus δ-lactones **14** and **15** (16%).

conditions realized during the reaction. Indeed, it is well known that hydroxy selenides react under these conditions.[8,9] The stereochemistry was not confirmed at this stage, but on the δ-lactone **25**. The diastereomeric ratio was better confirmed by ^{1}H NMR spectroscopy of **24** obtained after removal of the PhSe group (95% yield). The 1,3-*anti* stereochemistry is consistent with a mechanism that proceeds through the more stable seleniranium ion **22** which undergoes attack of a water molecule to give **23**. Finally, cyclization of **24** in refluxing toluene gave the δ-lactone **25** in 70% yield. This approach has allowed the synthesis of the diequatorial 4-hydroxy-6-phenyl-δ-lactone.

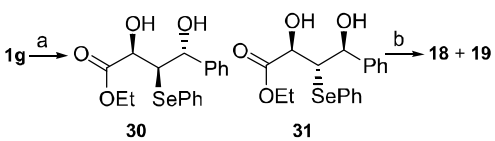
The diastereomeric structure **26** was obtained after removal of the PhSe group in compound **6**. Reduction of compound **26** gave the 1,3-*syn*-triol **27**.

The hydroxy selenenylation of **1f** gave poor results (Scheme 8). After column chromatography we obtained an inseparable mixture of diols **28** and **29** (40%) and δ-lactones **14** and **15** (16%) without selectivity (55:45). The low selectivity reflects the low selectivity found in the cyclization of **1b**. In these substrates the presence of a methyl group instead of a phenyl has a strong influence on the stereochemical outcome of the reactions.

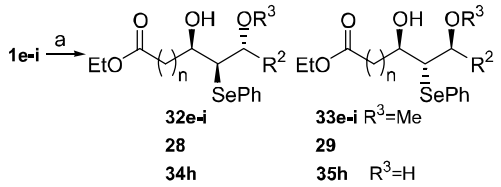
Compound **1g** gave a mixture of diols **30** and **31** in high yield (Scheme 9). However, these diols were not isolated in pure form since they readily cyclized during column chromatography. They were observed from the ^{1}H NMR spectrum of the crude reaction mixture. After stirring the mixture with silica gel and elution we obtained in 90% yield a 86:14 mixture of γ-lactones **18** and **19**. Obviously, as a



Scheme 8. *Reagents and conditions*: (a) PhSeCl, CH_3CN/H_2O, rt.



Scheme 9. *Reagents and conditions*: (a) PhSeCl, CH_3CN/H_2O, rt; (b) SiO_2, CH_2Cl_2, rt.



Scheme 10. *Reagents and conditions*: (a) PhSeCl, CH_2Cl_2/MeOH, rt or −78°C.

consequence of the silica gel, the diastereoselectivity was identical to that seen after cyclization and silica gel chromatography of compound **1c**. This approach has allowed a higher yield of γ-lactones **18** and **19**. The unfavorable 5-*endo* cyclization of **1c** has been transformed into a favorable 5-*exo* cyclization.

Treatment of **1h–i** with PhSeCl in acetonitrile/water was unsuccessful. Starting material was recovered in >95% yield.

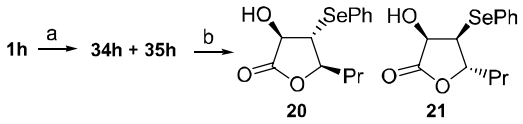
Hydroxy esters **1e–i** were also employed for methoxy selenenylation reactions. In contrast to the Korean authors, we used dichloromethane/methanol without base carrying out the reactions both at room temperature and −78°C. The reaction were quenched with a saturated aqueous solution of $NaHCO_3$ (Scheme 10).

Compound **1e** gave, at −78°C, high yield and excellent diasteromeric ratio of 1,3-*anti* diols (Table 3, entry 2). In contrast, compound **1f** gave very poor results (entry 3). The expected methoxy derivatives were detected in very low yield as a mixture with starting material. From this reaction we also isolated a 31% of the corresponding hydroxy derivatives that were present in a 1:1 ratio. Treatment of **1g** at −78°C gave **32g** and **33g** in high yield and stereoselectivity (entry 5). Methoxy selenenylation of **1h** was very intriguing. The reaction carried out at rt gave, among 27% of starting material, a low yield of the expected methoxy derivatives **32h** and **33h** (17%, d.r. not determined)[20] and a good yield of diols **34h** and **35h** (54%) with interesting d.r. (83:17) (entry 6). It should be remembered that the hydroxy selenenylation of **1h** in acetonitrile/water gave only starting material. The reaction carried out at −78°C was more interesting and synthetically useful. Indeed, we isolated an excellent yield of diols (>98% yield, 77% conversion) in good diastereomeric ratio (90:10) (entry 7). The reaction was also realized in the absence of methanol. Stirring for 30 min a dichloromethane solution of **1h** and PhSeCl and quenching at −78°C again gave the diols with high yield (>98%) but lower conversion (62%; d.r. 88:12) (entry 8). At −78°C methanol is not able to react as a nucleophile but its presence allows higher yield and selectivity. The reaction takes place only when the saturated aqueous solution of $NaHCO_3$ was added, probably via attack of the stronger nucleophile OH^-. Yields and selectivities of the last three reactions (entries 6–8) were determined from the crude reaction mixture. Indeed, purification with column chromatography afforded the γ-lactones. For instance, when the 90:10 mixture of diols **34h** and **35h** was stirred with silica gel and then chromatographed, γ-lactones **20** and **21** were obtained (60% yield from **1h**, 90:10 d.r.). Again the synthesis of γ-lactones gave better yields when realized through this two step sequence (Scheme 11).

Table 3. Yields and selectivities for the methoxy selenenylation reactions of **1e–i**

Entry	1	*anti*/*syn*	Yield (%)	R^3	*T* (°C)	React. time (min)
1	**e**	90:10	80	Me	rt	3
2	**e**	98:2	98	Me	−78	30
3[a]	**f**	n.d.	6	Me	−78	30
		50:50	31	H		
4	**g**	90:10	98	Me	rt	3
5	**g**	96:4	94	Me	−78	30
6[b]	**h**	n.d.	17	Me	rt	30
		83:17	54	H		
7[c]	**h**	–	0	Me	−78	30
		−90:10	77	H		
8[d]	**h**	88:12	62	H	−78	30
9[e]	**i**	90:10	37	Me	rt	3
10[f]	**i**	90:10	0	Me	rt	30
12[g,h]	**i**	90:10	60	Me	rt	30
13[i]	**i**	90:10	90	Me	−78	30

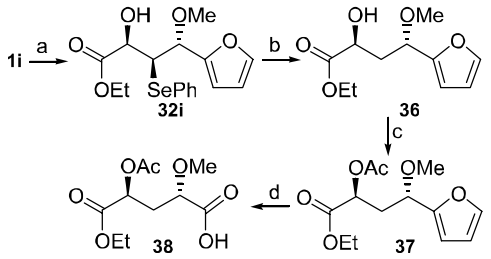
[a] **1f** 48%.
[b] **1h** 27%.
[c] **1h** 23%.
[d] Without methanol; **1h** 38%.
[e] **1i** 63%.
[f] **1i** 100%.
[g] **1i** 10%.
[h] In the presence of K_2CO_3.
[i] **1i** 40%.



Scheme 11. *Reagents and conditions*: (a) PhSeCl, CH_2Cl_2/MeOH, $NaHCO_3$ (aq), −78°C; (b) SiO_2, CH_2Cl_2, rt.

Finally, compound **1i**[21] was treated under the usual conditions at rt. After 3 min we obtained a high yield (>95%) but low conversion (37%) of the methoxy derivative **32i** in 90:10 d.r. (entry 9). When the reaction was quenched after 30 min we isolated only starting material (entry 10). Since the reactions were carried out without the presence of a base, the acid conditions are probably able to protonate the methoxy group again to give, after attack of the nucleophilic selenium atom, the intermediate seleniranium ion that is decomposed to starting material and diphenyl diselenide. In order to confirm this idea we realized the reaction in the presence of solid K_2CO_3. We obtained, after 30 min, a 60% yield of **32i** (90:10 d.r.) (entry 11). In order to avoid decomposition of the final product we carried out the reaction at −78°C without base for 30 min.

At this temperature, even in the absence of base, the decomposition was negligible and we isolated the methoxy derivative in excellent yield (>97%, 90% conversion, 90:10 d.r.) (entry 12). This product was transformed in three high yielding steps into the useful building block **38** since all the functionality is differently protected (Scheme 12).



Scheme 12. *Reagents and conditions*: (a) PhSeCl, CH_3OH/CH_2Cl_2, −78°C; (b) Bu_3SnH, AIBN, benzene, reflux, 95%; (c) Ac_2O, pyridine, rt, 91%; (d) $RuCl_3$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$, rt, 90%.

3. Conclusions

In conclusion we have realized the stereoselective synthesis of several δ- and γ-lactones and 1,3-*anti*-diols. Two complementary approaches have been realized for the stereoselective synthesis of 4-hydroxy-6-phenyl-disubstituted δ-lactones. The first approach, which led to a 4-*axial*-6-*equatorial*-δ-lactone, is based on intramolecular selenolactonization. The second approach, which led to a 4,6-*diequatorial*-δ-lactone, is based on the intermolecular hydroxy selenenylation followed by cyclization.

The presence of a phenyl group in acid **1a** and ester **1e** was of crucial importance both for yields and selectivities (compare with **1b** and **1f**). Moreover, the presence of the phenyl group allowed a very fast rearrangment of δ- to γ-lactones.

Five membered lactones were best prepared via hydroxy selenenylation followed by ring closure. Methoxy selenenylation gave high yield and selectivity when carried out at −78°C without the need of a base. Particularly interesting was the case of **1h** that was unreactive under the hydroxy selenenylation conditions, but gave the deprotected diols under the methoxy selenenylation conditions. Again, the presence of a phenyl group allowed the equilibration of γ-lactones **18** and **19** whereas the corresponding propyl substituted lactones **20** and **21** did not equilibrate.

The usefulness of the methoxy selenenylation procedure was proven by the preparation of compound **38**.

Silica gel played an important role in phenylselenenyl derivatives. Due to the presence of the good nucleophilic selenium atom, several δ- and γ-lactones may be in equilibrium under acid conditions (e.g. silica gel) to give the more stable compounds. For this reason we believe that it is useful to check the stereoselectivity of such reactions by recording the NMR spectrum of the crude reaction mixture before the subsequent purification procedure with column chromatography.

Finally, studies realized on compound **1a** showed how electronic effects, such as a Se−O interaction as well as the nature and concentration of X^- species are important factors for the stereoselective outcome of these reactions.

4. Experimental

4.1. General

Anhydrous solvents were distilled as follows: tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium benzophenone immediately prior to use. Dichloromethane was distilled under nitrogen from calcium hydride and used immediately. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-E series 250 MHz spectrometer. IR spectra were recorded on a Perkin–Elmer infrared spectrophotometer (model 1310) using KBr cells. Flash chromatography was carried out using Macherey–Nagel silica gel (0.04–0.063 mm). Light petroleum refers to the fraction boiling in the range 40–60°C. Ab initio calculations were performed with the GAUSSIAN98 program distribuited by Gaussian Inc.[22] Full geometry optimization was performed for each model species examined. Minimum structures were confirmed by inspection of the hessian matrix eigenvalues. Compounds **1e–f** were prepared by reaction of α,β-unsaturated-aldehyde with lithium enolate of ethyl acetate. Compounds **1g–i** were prepared by sodium borohydride reduction of the corresponding α-keto-ester obtained by Wittig reaction. Compounds **1a–d** were prepared by hydrolysis of the corresponding esters. All compounds showed spectroscopic and analytical data in agreement with their structures.

All the phase sensitive T-ROESY[23–25] experiments were performed at 300 K on a Varian Unity INOVA 500 spectrometer equipped with pulse field gradient module (*Z* axis) using a 5 mm Varian inverse probe. Data were acquired using the hypercomplex method of phase cycling at a spectral width of 4400 Hz. Typically 2048 t_2 points and 256 t_1 increments were collected (recycle delay of 3 s, 16 dummy scans were acquired before each experiment, 16 transients were collected for each FID). The mixing times were 100 and 400 ms. The spin lock field strength was 1.9 kHz. Spectra were zero filled in the t_1 dimension to 2048 points prior to the Gaussian-function weighting in both dimensions and Fourier transformation. NMR data processing was performed using Varian VNMR software (version 6.1B). T-ROESY spectra of compounds **16** and **18** were registered in $CDCl_3$ solution; spectra of compound **12** in $CDCl_3$/DMSO (98:2). All chemical shifts were relative to the external TMS reference.

4.1.1. General procedure for cyclization of 1a. Synthesis of (±)-(4*RS*,5*SR*,6*SR*)-4-hydroxy-5-phenylselenenyl-6-phenyl-δ-lactone (6) and (±)-(4*RS*,5*RS*,6*RS*)-4-hydroxy-5-phenylselenenyl-6-phenyl-δ-lactone (7). To a solution of β-hydroxy acid **1a** (80 mg, 0.42 mmol) in dichloromethane (6 mL), K_2CO_3 (172 mg, 1.25 mmol) and, when the case, TBAX (X=Br, Cl or ClO_4; 1 equiv.) were added. After the mixture was cooled to −78°C a solution of PhSeX (X=Cl, Br; 1–3 equiv.) in dichloromethane (2 mL) was slowly added and stirring was continued for 1 h. The reaction was quenched by addition of water (6 mL) and the mixture was warmed to room temperature. The aqueous and organic phases were separated and aqueous layer was extracted with dichloromethane (3×). The combined organic phases were washed with a saturated solution of $NaHCO_3$, then with brine and dried with Na_2SO_4. The

solvent was removed under reduced pressure and the residue was purified by washing with petroleum ether to remove the diphenyl diselenide yielding **6** and **7**.

White solid mp 145–149°C (93:7 mixture). IR (nujol) ν_{max} 3380, 1705, 1455 cm^{-1}. ^1H NMR (DMSO-d_6) **6** and **7** (mixture) δ: 2.59 (1H, 3-H, **7** overlapped with DMSO-d_6 and the following signal), 2.68 (dd, J=17.6, 2.6 Hz, 1H, 3-H, **6**), 3.04 (dd, J=15.7, 4.3 Hz, 1H, 3-H, **7**), 3.24 (dd, J=17.6, 3.5 Hz, 1H, 3-H, **6**), 3.52 (dd, J=11.3, 4.3 Hz, 1H, 5-H, **7**), 3.91 (d, J=11.3 Hz, 1H, 5-H, **6**), 4.33–4.42 (m, 1H, 4-H, **7**), 4.43–4.47 (m, 1H, 4-H, **6**), 5.40 (d, J=11.3 Hz, 1H, 6-H, **7**), 5.66 (d, J=11.3 Hz, 1H, 6-H, **6**), 5.82 (d, J=3.9 Hz, 1H, OH, **7**), 6.08 (d, J=3.8 Hz, 1H, OH, **6**), 7.04–7.45 (m, 10H, ArH, **6**+**7**). ^{13}C NMR (DMSO-d_6) **6** and **7** (mixture) δ: 38.3 (**7**), 39.9 (**6**), 49.6 (**6**), 51.1 (**7**), 67.1 (**6**), 68.9 (**7**), 81.4 (**7**), 81.9 (**6**), 127.3, 127.8, 128.0, 128.1, 128.3, 128.6, 128.8, 129.2, 133.6 (**6**), 134.0 (**7**), 137.8 (**7**), 138.1 (**6**), 169.1 (**6**), 170.5 (**7**). Anal. calcd for $C_{17}H_{16}O_3Se$: C, 58.80; H, 4.64. Found: C, 58.90; H, 4.69.

4.1.2. Synthesis of (±)-(4*RS*,5*SR*,1′*RS*)-4-hydroxy-5-(1′-phenylselenenyl-benzyl)-γ-lactone (12). To a solution of compounds **6** and **7** (90 mg, 0.26 mmol) in dichloromethane (10 mL), silica gel (3 g) was added and the mixture was stirred to room temperature for 2 h. Then the solvent was removed under reduced pressure and the crude product was purified by flash chromatography using light petroleum/ethyl acetate 2:1 yielding compound **12** (89 mg). White solid mp 156–8°C. IR (nujol) ν_{max} 3360, 1755, 1455 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.41 (d, J=17.2 Hz, 1H, 3-H), 3.07 (dd, J=17.2, 4.8 Hz, 1H, 3-H), 4.73 (d, J=11.3 Hz, 1H, C*H*SePh), 4.77–4.82 (m, 1H, 4-H), 5.09 (dd, J=11.3, 3.0 Hz, 1H, 5-H), 5.79 (d, J=4.4 Hz, 1H, OH), 7.12–7.38 (m, 10H, ArH). ^{13}C NMR (DMSO-d_6) δ: 40.2, 44.3, 67.7, 83.9, 126.9, 128.0, 128.3, 128.4, 128.9, 136.1, 139.5, 176.0. Anal. calcd for $C_{17}H_{16}O_3Se$: C, 58.80; H, 4.64. Found: C, 58.88; H, 4.65.

4.1.3. Synthesis of (±)-(4*RS*,5*SR*,6*SR*)-4-hydroxy-5-phenylselenenyl-6-methyl-δ-lactone (14), (±)-(4*RS*,5*RS*,6*RS*)-4-hydroxy-5-phenylselenenyl-6-methyl-δ-lactone (15) and (±)-(4*RS*,5*RS*,1′*SR*)-4-hydroxy-5-(1′-phenylselenenyl-ethyl)-γ-lactone (17). To a solution of β-hydroxy acid **1b** (59 mg, 0.45 mmol) in dichloromethane (6.4 mL), K_2CO_3 (188 mg, 1.36 mmol) was added. After the mixture was cooled to −78°C a solution of PhSeBr (214 mg, 0.90 mmol) in dichloromethane (2.1 mL) was slowly added and stirring was continued for 1 h. The reaction was quenched by addition of water (6 mL) and the mixture was warmed to room temperature. The aqueous and organic phases were separated and aqueous layer was extracted with dichloromethane (3×). The combined organic phases were washed with a saturated solution of $NaHCO_3$, then with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure yielding a mixture of **14**, **15** and **17** (68.3 mg) and diphenyl diselenide (65.7 mg) (determined by ^1H NMR).

^1H NMR ($CDCl_3$) δ (mixture of **14**, **15** and **17**): 1.49 (d, J=7.0 Hz, 3H, CH_3, **17**), 1.56 (d, J=6.4 Hz, 3H, CH_3, **14**), 1.63 (d, J=6.2 Hz, 3H, CH_3, **15**), 2.50–2.66 (m, 3H, 3-H **14**, 3-H **15** and 3-H **17**), 2.81–2.97 (m, 4H, 3-H **14**, 3-H **15** and 3-H **17** overlapped with dd, 5-H, **15**), 3.14–3.18 (m, 1H, C*H*SePh, **17**), 3.22 (dd, J=10.9, 2.0 Hz, 1H, 5-H, **14**), 3.90–3.98 (m, 1H, 4-H, **15**), 4.14–4.18 (m, 1H, 4-H, **14**), 4.20–4.24 (m, 1H, 6-H, **15**), 4.28–4.34 (m, 1H, 5-H, **17**), 4.45–4.52 (m, 1H, 4-H, **17**), 4.74–4.86 (m, 1H, 6-H, **14**), 7.28–7.40 (m, 3H, ArH), 7.63–7.67 (m, 2H, ArH).

4.1.4. Silica gel treatment of compounds 14, 15 and 17. Synthesis of (±)-(4*RS*,5*SR*,1′*RS*)-4-hydroxy-5-(1′-phenylselenenyl-ethyl)-γ-lactone (16). To a solution of the former mixture in dichloromethane (9.2 mL), silica gel (2.8 g) was added and the mixture was stirred to room temperature for 2 h. Then the solvent was removed under reduced pressure and the crude product was purified by flash chromatography using light petroleum/ethyl acetate 2:1 yielding compound **16** (30.3 mg) and compounds **14**, **15**, and **17** (36.7 mg).

Compound **16**. IR (liquid film) ν_{max} 3440, 1760, 1575 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.63 (d, J=6.9 Hz, 3H), 2.13 (s, 1H, OH), 2.57 (d, J=17.7 Hz, 1H, 3-H), 2.79 (dd, J=10.8, 5.4 Hz, 1H, 3-H), 3.51 (dq, J=10.8, 6.9 Hz, 1H, C*H*SePh), 4.20 (dd, J=10.8, 3.2 Hz, 1H, 5-H), 4.69–4.72 (m, 1H, 4-H), 7.27–7.40 (m, 3H, ArH), 7.61–7.67 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 19.9, 38.6, 66.7, 87.7, 125.9, 128.9, 129.5, 135.9, 175.0. Anal. calcd for $C_{12}H_{14}O_3Se$: C, 50.54; H, 4.95. Found: C, 50.47; H, 5.01.

4.1.5. Synthesis of (±)-(3*RS*,4*RS*,5*RS*)-3-hydroxy-4-phenylselenenyl-5-phenyl-γ-lactone (18) and (±)-(3*RS*,4*SR*,5*SR*)-3-hydroxy-4-phenylselenenyl-5-phenyl-γ-lactone (19). To a solution of α-hydroxy acid **1c** (100 mg, 0.56 mmol) in dichloromethane (9 mL),[26] K_2CO_3 (232 mg, 1.68 mmol) was added. Then the mixture was cooled to −78°C and a solution of PhSeBr (265 mg, 1.12 mmol) in dichloromethane (6 mL) was slowly added. After stirring for 1 h at −78°C, the reaction mixture was diluted with water, warmed to room temperature and extracted with dichloromethane (3×). The combined organic phases were washed with brine. After the solvent was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography using light petroleum/diethyl ether 2:1 yielding the γ-lactones **18** and **19** (74 mg, 40%). Highly viscous yellow oil. IR (nujol) ν_{max} 3420, 1770, 1570 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.58 (dd, J=11.1, 10.4 Hz, 1H, 4-H, **18**), 4.11 (dd, J=6.6, 3.6 Hz, 1H, 4-H, **19**), 4.39 (d, J=11.1 Hz, 1H, 3-H, **18**), 4.67 (d, J=6.6 Hz, 1H, 3-H, **19**), 5.14 (d, J=10.4 Hz, 1H, 5-H, **18**), 5.14 (d, J=3.6 Hz, 1H, 5-H, **19**), 7.76 (m, 10H, ArH, **18**+**19**). ^{13}C NMR **18** ($CDCl_3$) δ: 50.8, 73.2, 83.1, 127.8, 129.4, 129.8, 130.1, 136.0, 137.3, 175.5. Anal. calcd for $C_{16}H_{14}O_3Se$: C, 57.67; H, 4.23. Found: C, 57.73; H, 4.28.

4.1.6. Synthesis of (±)-(3*RS*,4*RS*,5*RS*)-3-hydroxy-4-phenylselenenyl-5-propyl-γ-lactone (20) and (±)-(3*RS*,4*SR*,5*SR*)-3-hydroxy-4-phenylselenenyl-5-propyl-γ-lactone (21). Following the procedure for cyclization of **1b** compound **20** and a mixture **20**/**21** were obtained after flash chromatography using light petroleum/ethyl acetate 4:1 as eluent (33%). Compound **20**, colorless oil. IR (liquid film) ν_{max} 3420, 1775, 1575 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.92 (t, J=7.2 Hz, 3H, CH_3), 1.28–1.69 (m,

3H, CH*H*C*H*$_2$CH$_3$), 1.92–2.01 (m, 1H, C*H*HCH$_2$CH$_3$), 3.33 (dd, *J*=10.5, 10.5 Hz, 1H, 4-H), 4.05 (br s, 1H, OH), 4.15–4.23 (m, 1H, 5-H), 4.29 (d, *J*=10.5 Hz, 1H, 3-H), 7.31–7.44 (m, 3H, ArH), 7.61–7.69 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 13.4, 13.6, 34.6, 47.3, 72.6, 81.3, 124.9, 129.2, 129.6, 136.7, 175.0. Anal. calcd for $C_{13}H_{16}O_3Se$: C, 52.18; H, 5.39. Found: C, 52.26; H, 5.31.

4.2. General procedure for hydroxy selenenylation of 1e–i

To a solution of β-hydroxy ester **1e–i** (0.50 mmol) in acetonitrile (1.5 mL) and water (0.3 mL) was slowly added a solution of PhSeCl (0.50 mmol) in acetonitrile (1.5 mL). After the brownish red solution turned into yellow within 3 min, the reaction was quenched with a saturated solution of $NaHCO_3$ and the mixture was portioned between ether and water. The combined organic phases were washed with brine and dried with Na_2SO_4. The crude product was purified by flash chromatography.

4.2.1. Synthesis of (±)-(3*RS*,4*SR*,5*RS*)-3,5-diol-4-phenylselenenyl-5-phenyl-pentanoate ethyl ester (23). Yellow oil, from light petroleum/ethyl acetate 3:1 (156 mg, 80%). IR (liquid film) ν_{max} 3440, 1720, 1575 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, *J*=7.2 Hz, 3H), 2.58 (dd, *J*=16.4, 4.7 Hz, 1H, 2-H), 2.94 (dd, *J*=16.4, 8.5 Hz, 1H, 2-H), 3.42 (dd, *J*=5.0, 1.3 Hz, 1H, 4-H), 3.95 (s, 1H, OH), 4.06 (q, *J*=7.2 Hz, 2H), 4.41–4.47 (m, 1H, 3-H), 5.14 (d, *J*=5.0 Hz, 1H, 5-H), 7.19–7.29 (m, 8H), 7.40–7.48 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 14.0, 40.3, 59.1, 60.6, 67.2, 76.6, 126.1, 127.5, 127.6, 128.0, 128.2, 129.1, 134.5, 141.6, 172.0. Anal. calcd for $C_{19}H_{22}O_4Se$: C, 58.02; H, 5.64. Found: C, 58.10; H, 5.59.

4.2.2. Synthesis of (±)-(3*RS*,4*RS*,5*RS*)-3,5-diol-4-phenylselenenyl-hexanoate ethyl ester (28) and (±)-(3*RS*,4*SR*,5*SR*)-3,5-diol-4-phenylselenenyl-hexanoate ethyl ester (29). Column chromatography with light petroleum/ethyl acetate 3:1 gave a mixture of compounds **28** and **29** and mixture of compounds **14** and **15**.

Compounds **28** and **29**. IR (liquid film) ν_{max} 3440, 1720, 1575 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, *J*=7.6 Hz, 3H, C*H*$_3$CH$_2$O, minor diast.), 1.25 (t, *J*=7.0 Hz, 3H, C*H*$_3$CH$_2$O, major diast.), 1.36 (d, *J*=6.3 Hz, 3H, C*H*$_3$CH, minor diast.), 1.42 (d, *J*=6.4 Hz, 3H, C*H*$_3$CH, major diast.), 2.63 (dd, *J*=16.8, 8.1 Hz, 1H, 2-H, minor diast.), 2.72 (dd, *J*=16.3, 4.8 Hz, 1H, 2-H, major diast.), 2.95 (dd, *J*=16.3, 8.4 Hz, 1H, 2-H, major diast.), 3.10 (dd, *J*=16.8, 2.9 Hz, 1H, 2-H, minor diast.), 3.21 (dd, *J*=5.1, 2.1 Hz, 1H, C*H*SePh, major diast.), 3.31 (dd, *J*=8.7, 6.2 Hz, 1H, C*H*SePh, minor diast.), 3.70 (br s, 2H, OH), 4.07–4.28 (m, CH$_3$C*H*$_2$O major+minor diast, 3-H minor diast., 5-H major+minor diast.), 4.64 (ddd, *J*=8.4, 5.1, 4.8 Hz, 1H, 3-H, major diast.), 7.26–7.32 (m, 3H, ArH), 7.57–7.63 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.0, 14.1, 21.5, 21.6, 40.1 (CH_2), 40.2 (CH_2), 59.8, 60.8, 60.7 (CH_2), 60.9 (CH_2), 67.6, 68.2, 70.3, 70.4, 127.6, 127.7, 129.2, 129.3, 129.6, 133.9, 134.2, 172.1, 172.7. Anal. calcd for $C_{14}H_{20}O_4Se$: C, 50.76; H, 6.09. Found: C, 50.84; H, 6.13.

4.2.3. Synthesis of (±)-(2*RS*,3*RS*,4*RS*)-2,4-diol-3-phenylselenenyl-4-phenyl-butanoate ethyl ester (30) and (±)-(2*RS*,3*SR*,4*SR*)-2,4-diol-3-phenylselenenyl-4-phenyl-butanoate ethyl ester (31). Compounds **30** and **31** were detected prior the purification step. ^{1}H NMR of **30** from the crude reaction mixture ($CDCl_3$) δ: 1.20 (t, *J*=7.1 Hz, 3H, CH_3), 3.82 (dd, *J*=7.2, 1.6 Hz, 1H, 3-H), 3.93–4.04 (m, 1H, C*H*HCH$_3$, overlapped with br s, OH), 4.14–4.24 (m, 1H, C*H*HCH$_3$), 4.92 (d, *J*=1.6 Hz, 1H, 2-H), 5.24 (d, *J*=7.3 Hz, 1H, 4-H), 7.23–7.51 (m, 10H, ArH).

4.2.4. Synthesis of (±)-(3*RS*,4*RS*,5*RS*)-3-hydroxy-4-phenylselenenyl-5-phenyl-γ-lactone (18) and (±)-(3*RS*,4*SR*,5*SR*)-3-hydroxy-4-phenylselenenyl-5-phenyl-γ-lactone (19). Following the procedure for hydroxy selenenylation of **1g**, after the brownish red solution turned into yellow within 3 min, silica gel (1 g) was added and the mixture was stirred for 3 h. Then the solvent was removed under reduced pressure and the crude product was purified by flash chromatography using light petroleum/diethyl ether 2:1 yielding the cyclic compounds **18** and **19** (174 mg, 90%).

4.2.5. Synthesis of (±)-(3*SR*,5*SR*)-3,5-diol-5-phenylpentanoate ethyl ester (24). Compound **23** (547 mg, 1.39 mmol) was dissolved in benzene (14 mL), Bu_3SnH (0.74 mL, 2.79 mmol) and AIBN, in a catalytic amount, were added. The mixture was refluxed for 1 h and cooled to room temperature. After the solvent was evaporated under reduced pressure the residue was purified by flash chromatography using light petroleum/ethyl acetate 2:1 yielding **24** (314 mg, 95%) as a colorless oil. IR (liquid film) ν_{max} 3400, 1720, 1490 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, *J*=7.2 Hz, 3H), 1.84–1.89 (m, 2H, 4-H), 2.43–2.51 (m, 2H, 2-H), 3.72 (d, *J*=4.1 Hz, OH), 3.86 (d, *J*=4.0 Hz, OH), 4.14 (q, *J*=7.2 Hz, 2H), 4.18–4.34 (m, 1H, 3-H), 4.99–5.06 (m, 1H, 5-H), 7.25–7.36 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.1, 41.2, 44.2, 60.7, 65.4, 71.0, 126.5, 127.3, 128.4, 144.4, 172.7. Anal. calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.55; H, 7.67.

4.2.6. Synthesis of (±)-(4*SR*,6*SR*)-4-hydroxy-6-phenyl-δ-lactone (25). To a solution of **24** (209 mg, 0.88 mmol), in toluene (32 mL), PPTS (44 mg, 0.18 mmol) was added. The reaction mixture was refluxed for 2 h, then cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using light petroleum/ethyl acetate 1:1 yielding the δ-lactone **25** (118 mg, 70%) as a colorless oil. IR (liquid film) ν_{max} 3440, 1725, 1490 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.96 (ddd, *J*=21.2, 12.2, 9.1 Hz, 1H, 5-H$_{ax}$), 2.39–2.48 (m, 1H, 5-H$_{eq}$), 2.54 (dd, *J*=17.1, 7.6 Hz, 1H, 3-H$_{ax}$), 2.98 (ddd, *J*=17.1, 5.9, 1.1 Hz, 1H, 3-H$_{eq}$), 3.20 (br s 1H, OH), 4.28–4.39 (m, 1H, 4-H), 5.14 (dd, *J*=12.2, 3.1 Hz, 1H, 6-H), 7.25–7.39 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$) δ: 39.4, 40.0, 63.6, 78.7, 125.9, 128.6, 128.7, 138.5, 171.1. Anal. calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.80; H, 6.34.

4.2.7. Synthesis of (±)-(4*SR*,6*RS*)-4-hydroxy-6-phenyl-δ-lactone (26). To a solution of δ- lactones **4** and **5** (100 mg, 0.29 mmol) in benzene (3 mL) Bu_3SnH (152 μl, 0.58 mmol) and AIBN, in a catalytic amount, were added. The mixture was refluxed for 1 h and cooled to room temperature. After the solvent was evaporated under reduced pressure the residue was purified by flash chromatography using light petroleum/ethyl acetate 1:1

yielding **26** (53 mg, 95%) as a white solid, mp 108–111°C. IR (nujol) ν_{max} 3400, 1720, 1490 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.93–2.05 (m, 1H, 5-H_{ax}), 2.15–2.22 (m, 1H, 5-H_{eq}), 2.66–2.75 (m, 2H, 3-H, overlapped with br s 1H, OH), 4.36–4.40 (m, 1H, 4-H), 5.73 (dd, J=11.3, 3.2 Hz, 1H, 6-H), 7.24–7.38 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$) δ: 38.2, 38.6, 62.5, 77.3, 125.7, 128.3, 128.6, 139.2, 170.7. Anal. calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.80; H, 6.24.

4.2.8. Synthesis of (±)-(3*RS*,5*RS*)-5-phenyl-pentan-1,3,5-triol (27). To a solution of **26** (80 mg, 0.42 mmol) in diethyl ether (4 mL), $LiAlH_4$ (16 mg, 0.42 mmol) was slowly added. The mixture was stirred for 15 min at 0°C then warmed to room temperature. After additional stirring for 30 min at room temperature the reaction mixture was diluted with water (4 mL). The aqueous and organic phases were separated and aqueous layer was extracted with ether (3×). The combined organic phases were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using light petroleum/ethyl acetate 1:4 yielding **27** (108 mg, 66%) as a colorless oil. IR (liquid film) ν_{max} 3300 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.63–1.55 (m, 3H, 4-H_2+2-H), 1.90 (ddd, J=19.9, 9.9, 9.9 Hz, 1H, 2-H), 3.71–3.90 (m, 2H, 5-H overlapped with br s, 3H, OH), 4.11–4.19 (m, 1H, 3-H), 4.90 (dd, J=9.9, 2.9 Hz, 1H, 1-H), 7.24–7.34 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$) δ: 38.3, 38.8, 45.4, 60.8, 72.01, 75.0, 125.7, 127.6, 128.5, 144.3. Anal. calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.39; H, 8.30.

4.3. General procedure for methoxy selenenylation of 1e–i

Hydroxy esters **1e–i** (0.39 mmol) were dissolved in dichloromethane (1.15 mL) and methanol (0.52 mL, 17.8 mmol). After the mixture was cooled to −78°C, a solution of PhSeCl (79 mg, 0.41 mmol) in dichloromethane (1.1 mL) was slowly added. The mixture was stirred for 30 min, then was diluted with aqueous $NaHCO_3$, warmed to room temperature and extracted with dichloromethane (3×). The residue was purified by flash chromatography. The reactions carried out at rt were quenched after 3 min.

4.3.1. Synthesis of (±)-(3*RS*,4*SR*,5*RS*)-3-hydroxy-4-phenylselenenyl-5-methoxy-5-phenyl-pentanoate ethyl ester (32e). Colorless oil from light petroleum/ethyl acetate 5:1. IR (liquid film) ν_{max} 3490, 1725, 1575 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.20 (t, J=7.2 Hz; 3H), 2.70 (dd, J=15.8, 5.2 Hz, 1H, 2-H), 2.93 (dd, J=15.8, 8.1 Hz, 1H, 2-H), 3.34 (s, 3H, OMe), 3.36 (dd, J=6.4, 1.4 Hz, 1H, 4-H), 3.61 (br s, 1H, OH), 4.09 (q, J=7.2 Hz, 2H), 4.57–4.61 (m, 1H, 3-H), 4.66 (d, J=6.4 Hz, 1H, 5-H), 7.16–7.37 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.0, 40.3, 57.8, 58.8, 60.4, 66.9, 86.3, 127.1, 127.4, 127.9, 128.3, 128.9, 129.6, 134.5, 139.0, 171.6. Anal. calcd for $C_{20}H_{24}O_4Se$: C, 58.97; H, 5.94. Found: C, 59.10; H, 5.59.

4.3.2. Synthesis of (±)-(3*RS*,4*RS*,5*RS*)-3-hydroxy-4-phenylselenenyl-5-methoxy-hexanoate ethyl ester (32f) and (±)-(3*RS*,4*SR*,5*SR*)-3-hydroxy-4-phenylselenenyl-5-methoxy-hexanoate ethyl ester (33f). Column chromatography using light petroleum/ethyl acetate 4:1 gave a less polar fraction containing starting material and **32f/33f**,[27] and a more polar fraction containing hydroxy selenenylated compounds **28** and **29**.

4.3.3. Synthesis of (±)-(2*RS*,3*RS*,4*RS*)-2-hydroxy-3-phenylselenenyl-4-methoxy-4-phenyl-butanoate ethyl ester (32g). Colorless oil from light petroleum/ethyl acetate 5:1. IR (liquid film) ν_{max} 3480, 1730, 1575 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.17 (t, J=7.0 Hz, 3H), 3.24 (s, 3H, OMe), 3.51 (d, J=5.0 Hz, 1H, OH), 3.62 (dd, J=9.9, 1.7 Hz, 1H, 3-H), 3.99–4.06 (m, 1H, C*H*HCH_3), 4.17–4.24 (m, 1H, CH*H*CH_3), 4.48 (d, J=9.9 Hz, 1H, 4-H), 5.09 (dd, J=5.0, 1.7 Hz, 1H, 2-H), 6.94–7.29 (m, 10H, ArH,). ^{13}C NMR ($CDCl_3$) δ: 13.9, 56.0, 57.1, 61.8, 70.2, 84.2, 127.2, 127.9, 128.0, 128.2, 128.4, 134.2, 139.0, 173.3. Anal. calcd for $C_{19}H_{22}O_4Se$: C, 58.02; H, 5.64. Found: C, 58.11; H, 5.70.

4.3.4. Synthesis of (±)-(2*RS*,3*RS*,4*RS*)-2,4-diol-3-phenylselenenyl-heptanoate ethyl ester (34h) and (±)-(2*RS*,3*SR*,4*SR*)-2,4-diol-3-phenylselenenyl-heptanoate ethyl ester (35h). Hydroxy ester **1h** (89 mg, 0.52 mmol) was dissolved in dichloromethane (1.5 mL) and methanol (0.69 mL, 17.1 mmol). After the mixture was cooled to −78°C, a solution of PhSeCl (104 mg, 0.54 mmol) in dichloromethane (1.5 mL) was slowly added. The mixture was stirred for 30 min and then was diluted with aqueous $NaHCO_3$ and extracted with dichloromethane (3×). The ^1H NMR of the residue showed the hydroxy selenenylated compounds **34h** and **35h** (77%) and starting material (23%).

^1H NMR **34h** ($CDCl_3$) δ: 0.84 (t, J=7.2 Hz, 3H, 7-H), 1.22 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.38–1.50 (m, 2H, 6-H), 1.67–1.74 (m, 1H, 5-H), 2.30–2.42 (m, 1H, 5-H), 2.92 (br s, 2H, OH), 3.63 (dd, J=11.0, 1.6 Hz, 1H, 3-H), 4.07–4.38 (m, 2H, CH_3CH_2O overlapped with m 1H, 4-H), 5.11 (d, J=1.6 Hz, 1H, 2-H), 7.25–7.63 (m, 10H, ArH). ^{13}C NMR **34h** ($CDCl_3$) δ: 13.2, 13.9, 19.3, 38.2, 55.8, 62.3, 64.5, 67.3, 71.7, 127.7, 128.2, 131.5, 134.4, 135.4, 172.9.

4.3.5. Synthesis of (±)-(3*RS*,4*RS*,5*RS*)-3-hydroxy-4-phenylselenenyl-5-propyl-γ-lactone (20) and (±)-(3*RS*,4*SR*,5*SR*)-3-hydroxy-4-phenylselenenyl-5-propyl-γ-lactone (21). Hydroxy selenenylated compounds **34h** and **35h** (120 mg, 0.35 mmol) were dissolved in dichloromethane (5.7 mL) and silica gel (820 mg) was added to the solution. The mixture was stirred for 2 h, then the solvent was removed under reduced pressure and the crude product was purified by flash chromatography using light petroleum/ethyl acetate 4:1 yielding the cyclic compounds **20** and **21** (83 mg, 84%).

4.3.6. Synthesis of (±)-(2*RS*,3*RS*,4*RS*)-2-hydroxy-3-phenylselenenyl-4-methoxy-4-(2′-furyl)-butanoate ethyl ester (32i). Pale yellow oil from light petroleum/ethyl acetate 5:1. IR (liquid film) ν_{max} 3420, 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.18 (t, J=7.2 Hz, 3H), 3.30 (s, 3H, OMe), 3.38 (d, J=5.2 Hz; 1H, OH), 3.94 (dd, J=10.6, 1.6 Hz, 1H, 3-H, overlapped with m, 1H, OCH*H*CH_3), 4.15–4.25 (m, 1H, OC*H*HCH_3), 4.48 (d, J=10.6 Hz, 1H, 4-H), 5.04 (dd, J=5.2, 1.6 Hz, 1H, 2-H), 6.29 (dd, J=3.3, 1.7 Hz, 1H, ArH), 6.38 (d, J=3.3 Hz, 1H, ArH), 7.13–7.26 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$) δ: 13.8, 52.6, 56.8, 61.7, 69.8, 76.8, 109.9, 110.8,

127.3, 128.4, 128.6, 134.2, 142.1, 151.2, 173.2. Anal. calcd for $C_{17}H_{20}O_5Se$: C, 53.27; H, 5.26. Found: C, 53.35; H, 5.31.

4.3.7. Synthesis of (±)-(2*SR*,4*SR*)-2-hydroxy-4-methoxy-4-(2′-furyl)-butanoate ethyl ester (36). To a solution of **32i** (564 mg, 1.47 mmol) in toluene (15.5 mL), Bu_3SnH (0.78 mL, 2.93 mmol) and AIBN, in a catalytic amount, were added. The reaction mixture was refluxed for 2 h and then cooled to room temperature. After the solvent was removed under reduced pressure and the crude oil was purified by flash chromatography using light petroleum/ethyl acetate 6:1 yielding compound **36** (329 mg, 90%) as a yellow oil. IR (liquid film) ν_{max} 3460, 1730, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.24 (t, J=7.2 Hz, 3H), 1.90 (ddd, J=14.0, 9.3, 3.5 Hz, 1H, 3-H), 2.38 (ddd, J=14.0, 10.4, 3.3 Hz, 1H, 3-H), 3.23 (s, 3H, OMe), 3.45 (d, J=6.2 Hz, 1H, OH), 4.09–4.21 (m, 2H, 4-H and OC*H*HCH$_3$), 4.38–4.48 (m, 2H, 2-H and OCH*H*CH$_3$), 6.25–6.31 (m, 2H, ArH), 7.35 (d, J=1.5 Hz, 1H, ArH). ^3C NMR ($CDCl_3$) δ: 13.9, 38.6, 56.3, 61.2, 67.5, 72.3, 107.9, 109.8, 142.2, 153.4, 174.7. Anal. calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.82; H, 7.12.

4.3.8. Synthesis of (±)-(2*SR*,4*SR*)-2-acetoxy-4-methoxy-4-(2′-furyl)-butanoate ethyl ester (37). To a solution of **36** (100 mg, 0.44 mmol) in pyridine (4 mL) acetic anhydride (2 mL) was slowly added. After stirring at room temperature for 24 h, the mixture was diluted with ether (5 mL). The mixture was washed with an aqueous solution of HCl (5%), then with a saturated solution of $CuSO_4$ and finally with water. Then the organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure to afford compound **37** (108 mg, 91%, oil). IR (liquid film) ν_{max} 1740, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.25 (t, J=7.2 Hz, 3H, OCH$_2$C*H*$_3$), 2.11 (s, 3H, COCH$_3$), 2.14 (ddd, J=14.4, 10.5, 4.0 Hz, 1H, 3-H), 2.47 (ddd, J=14.4, 9.7, 3.3 Hz, 1H, 3-H), 3.20 (s, 3H, OMe), 4.16 (q, J=7.2 Hz, 2H, OC*H*$_2$CH$_3$), 4.30 (dd, J=9.7, 4.0 Hz, 1H, 4-H), 5.22 (dd, J=10.4, 3.3 Hz, 1H), 6.29 (dd, J=3.2, 0.7 Hz, 1H, ArH), 6.33 (dd, J=3.2, 1.8 Hz, 1H, ArH), 7.39 (dd, J=1.8, 0.7 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.1, 20.5, 35.6, 56.4, 61.3, 69.3, 71.9, 108.3, 110.0, 142.6, 153.0, 170.0, 170.2. Anal. calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.83; H, 6.77.

4.3.9. Synthesis of (±)-(2*SR*,4*SR*)-2-methoxy-4-acetoxy-5-ethoxy-5-oxopentanoic acid (38). To a solution of **37** (50 mg, 0.185 mmol) in carbon tetrachloride (0.29 mL), acetonitrile (0.29 mL) and water (0.45 mL), $NaIO_4$ (596 mg, 2.78 mmol) and $RuCl_3$, in a catalytic amount, were added. After stirring for 40 min at room temperature the mixture was filtered through celite. Then the solvent was dried with $MgSO_4$ and evaporated under reduced pressure to afford compound **38** (41 mg, 90%). IR (liquid film) ν_{max} 3500–2500, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.25 (t, J=7.2 Hz, 3H, OCH$_2$C*H*$_3$), 2.15 (s, 3H, COCH$_3$), 2.30 (dd, J=6.8, 6.4 Hz, 2H, 3-H), 3.42 (s, 3H, OMe), 3.87 (dd, J=6.8, 6.8 Hz, 1H, 2-H), 4.18 (q, J=7.2 Hz, 2H, OC*H*$_2$CH$_3$), 5.2 (dd, J=6.4, 6.4 Hz, 1H, 4-H), 7.20 (br s 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 13.9, 20.4, 33.9, 58.7, 61.6, 68.6, 76.0, 169.7, 170.2, 176.0. Anal. calcd for $C_{10}H_{16}O_7$: C, 48.39; H, 6.50. Found: C, 48.45; H, 6.45.

Acknowledgements

Financial support from the University of Palermo (funds for selected research topics) and Italian MIUR within the National Research Project 'Non-aromatic heterocycles in stereocontrolled processes' is gratefully acknowledged.

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