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The question of *exo* vs *endo* cyclisation. A joint experimental and ab initio study on the stereoselective synthesis of tetrahydrofurans and tetrahydropyrans via seleniranium ions

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Abstract—The reactivity of hydroxy selenides with catalytic amounts of perchloric acid in dichloromethane was investigated. Four different cyclisation modes (4-*exo*, 5-*endo*, 5-*exo* and 6-*endo*) of the intermediate seleniranium ion could occur. The reaction of the hydroxy selenides with primary and secondary hydroxyl groups in the same side chain led first to a mixture of tetrahydrofurans from the 5-*exo* cyclisation (kinetic products), then to a 68/32 mixture of tetrahydropyrans from the 6-*endo* cyclisation (thermodynamic products) probably via two diasteromeric seleniranium ions. Both experimental and ab initio (HF/3-21G*) studies showed that the order of cyclisation of the intermediate seleniranium ion was 5-*exo-tet*<6-*endo-tet*<5-*endo-tet*<4-*exo-tet.* The factors on which regiochemistry of the 4-*exo* vs the 5-*endo* cyclisation and the 5-*exo* vs the 6-*endo* cyclisation of the seleniranium ions depend were analysed.

1. Introduction

One of the most successful routes for the stereoselective synthesis of oxygenated heterocyclic rings is the reaction between a homoallylic or bishomoallylic alcohol and an electrophilic species.[1] Common electrophiles that induce such cyclisations through formation of a three membered ring intermediate are: Br^+ or I^+, Hg(II), PhS^+ and $PhSe^+$. The above reactions involve two possible cyclisation modes, *exo* and *endo*. Moreover, these cyclisations result in the formation of two new stereogenic centres. The stereochemical factor of major interest is the relationship that the new stereogenic centres bear to that already present in the substrate.

Cyclisations by nucleophilic attack onto a three-membered ring intermediates **1** (E=halogen$^+$, $PhSe^+$ or PhS^+) can give a smaller ring **2** by a pure *exo-tet* transition state or a larger ring **3** by an *endo* cyclisation or, following Warren's nomenclature,[2] by a hybrid *endo*/*exo-tet* cyclisation (Fig. 1).

The regiochemistry of a 4-*exo* vs a 5-*endo* cyclisation ($n=1$) or a 5-*exo* vs a 6-*endo* cyclisation ($n=2$) will depend on a number of factors such as reorganisation in terms of bond angles and distances, stabilisation of an incipient positive charge on the carbon that undergoes the attack, stability of the final ring. Probably, the 4-*exo* and the 5-*endo* cyclisation experience stabilising effects more than the 5-*exo* and the 6-*endo* cyclisation, whichever is the origin of these effects.[3]

Previously[4] we have investigated the behaviour of mixtures of hydroxy selenides and hydroxy sulfides. The treatment of hydroxy selenides with a catalytic amount of perchloric acid causes a stereoconvergent elimination of water to give an intermediate seleniranium ion. The seleniranium ion can be considered as following from the corresponding alkene by treatment with the electrophilic phenylseleno species $PhSe^+$.

Recently[4e] we have discussed the kinetic and thermodynamic control of the cyclisation of the hydroxy selenides **4**. Now we would like to gain a deeper insight on the reactivity and regiochemical outcome of these cyclisations, and also performing a computational study of these reactions. We focussed our attention on a substrate that could, in principle, undergo the former four modes of cyclisation in order to investigate which cyclisation takes place faster and which is the thermodynamically favoured. As a matter of fact, four modes of cyclisation of the seleniranium ion **5** are possible: (i) cyclisation in the 5-*endo* mode to give **6**; (ii) cyclisation

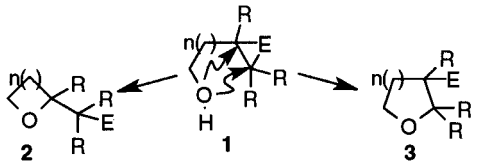

Figure 1. *exo* versus *endo* cyclisation.

Keywords: cyclisation; selenium and compounds; theoretical studies.

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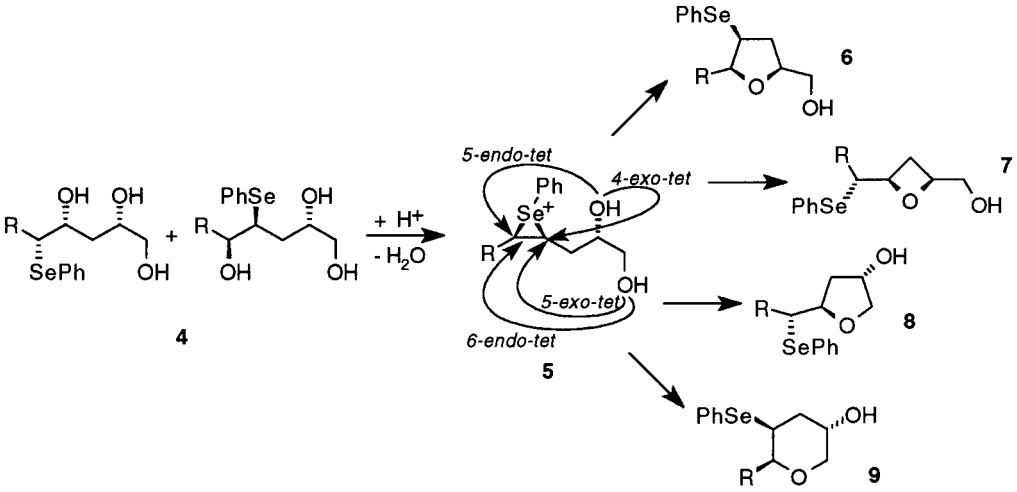


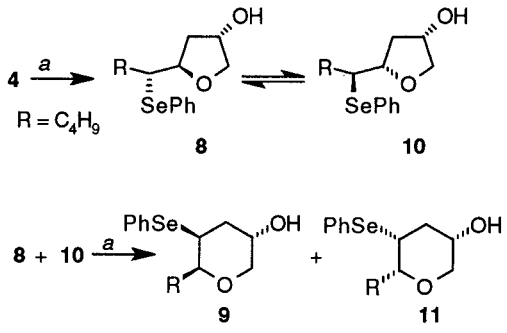
Figure 2. Different ring closure of the seleniranium ion **5**.

in the 4-*exo* mode to give **7**; (iii) cyclisation in the 5-*exo* mode to give **8**; (iv) cyclisation in the 6-*endo* mode to give **9** (Fig. 2).

2. Results and discussion

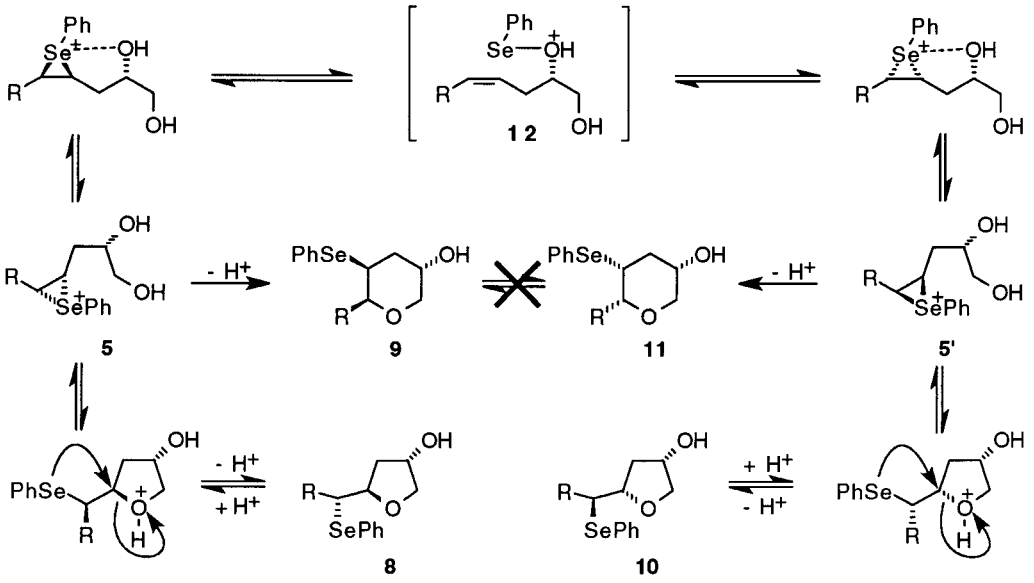
The hydroxy selenides **4** were prepared as reported[4c] and then treated with a catalytic amount of perchloric acid. First, we quenched the reaction after 1 min. No starting material was recovered and we isolated tetrahydrofurans **8** and **10** by column chromatography [5] in almost the same yield. Regiocontrol was then observed since the reaction took place exclusively in the 5-*exo* mode. Neither 4-*exo* or *endo* products were formed. However, no stereoselectivity was observed; indeed, the stereoselectivity that should follow cyclisation of the seleniranium ion **5** was lost (Scheme 1).

If the reaction was not quenched immediately we observed, by TLC, the disappearance of the two spots corresponding to the tetrahydrofurans **8** and **10** and the appearance of other two spots. The reaction was complete after 30 min. Separation by column chromatography gave the two tetrahydropyrans **9** and **11** in good overall yield (80%) and with a 68/32 ratio. The structure of these compounds was proved by the usual spectroscopic and analytical techniques. The ^{1}H NMR COSY spectrum of compound **9** in DMSO clearly showed the doublet for the OH proton that coupled with the H-5 proton at 3.91 ppm. From the HETCOR spectra, both in DMSO and $CDCl_3$, we were able to assign all the carbon and proton atoms. In particular, we assigned the multiplet at 3.50 ppm to H-3 (i.e. the proton bonded to the carbon atom that bears the phenylselanyl group). From this assignment, we deduced readily the endocyclic position of the phenylselanyl group. The very narrow multiplet of the H-3 in the ^{1}H NMR spectrum accounted for the axial position of the phenylselanyl group. Moreover, the broad multiplet at 4.18 ppm of the H-5 accounted for the equatorial position of the hydroxyl group. These findings excluded that compound **9** was in a conformation in which the phenylselanyl group was in an equatorial position and the hydroxyl group in an axial position. Indeed, in this case we had to find a broad multiplet of the H-3 and a narrow multiplet of the H-5. These considerations have also allowed us to assign the structure **9** to the major component of the reaction mixture. In addition, for compound **11** the ^{1}H NMR COSY and HETCOR spectra in $CDCl_3$ showed that the phenylselanyl group was in an endocyclic position, as a matter of fact, the multiplet at 3.42 ppm of H-3 coupled with H-4 at 2.12 and 2.30 ppm and with H-2 at 3.46 ppm which in turn coupled with the CH_2 of the side chain at 1.63 and 1.80 ppm. The very narrow multiplets of the H-3 and H-5 accounted for the axial position of the phenylselanyl and hydroxyl groups. Also in this case we were then able to exclude the conformation in which the phenylselanyl and hydroxyl groups lie in an equatorial position.

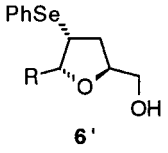


Scheme 1. *Reagents*: (a) cat $HClO_4$, CH_2Cl_2, 25°C; **9** (57%), **11** (26%).

Resubjecting compound **8** or **10** to the reaction conditions (i.e. cat. $HClO_4$) initially led to their equilibration and they then disappeared to give the two tetrahydropyrans **9** and **11** (68/32). Resubjecting compound **9** or **11** to the above conditions saw no equilibration. However, when we forced the reaction conditions increasing the acid content 10-fold in the same solvent, compound **9** gave, after 24 h, a mixture of **9** and **11** that also contained a small amount of the tetrahydrofuran ring **6** and its diasteromeric structure **6′** (as determined by ^{13}C NMR).



Scheme 2.



The loss of stereoselectivity in the cyclisation of the seleniranium ion can be reconciled with the formation of the oxonium ion intermediate **12**. The key step in this equilibration was the stabilisation of the selenium electrophile and/or the seleniranium ion by means of the hydroxyl group (Scheme 2).[6]

The equilibrium between compounds **8** and **10** and their rearrangement to compounds **9** and **11** in acid solution can be ascribed to the fact that these reactions proceed via a loose S_N2 transition state; the exocyclic position of the phenylselanyl group allows alignment of Se, C-2 and the protonated heterocyclic oxygen atom at the required 180° (see Scheme 2). Indeed, this is possible because of the free rotation around the C–C bond of the side chain, whereas the same situation is not possible when the phenylselanyl group is in endocyclic position. Similar equilibria have been observed recently.[7]

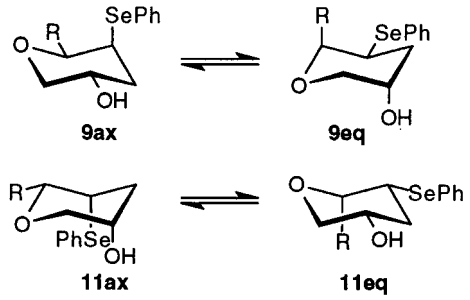
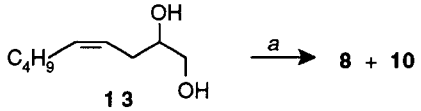


Figure 3. Chair conformations for the tetrahydropyran rings **9** and **11**.

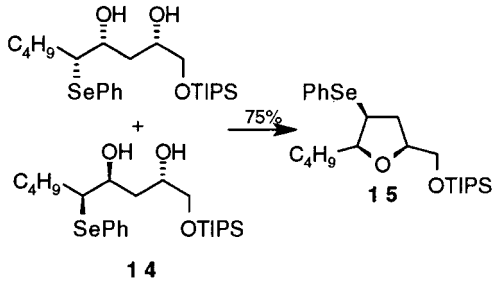
Actually, compounds **9** and **11** can exist in several conformations, and could reach a conformation in which the Se, C-2 and the protonated heterocyclic oxygen atom are almost aligned at the required 180° as in **9eq** and **11eq**. As pointed out before, the NMR analysis showed that these compounds exist in a conformation in which the phenylselanyl group lies in axial position that does not allow the alignment at the required 180° (Fig. 3).

The absence of rearrangement of these compounds, however, indicated that conformations **9eq** and **11eq** do not possess the stereoelectronic requirements that should allow the equilibration in our reaction conditions. Indeed, the intramolecular attack of the phenylselanyl group on C-2 should cause a severe distortion of the tetrahydropyran ring. This situation is certainly more stringent in the tetrahydrofuran ring **6** that bears the phenylselanyl group in endocyclic position. Then, in order to obtain the rearrangement of compounds **6**, **9** and **11**, more drastic acid conditions have to be used.

The reaction carried out in the presence of perchloric acid was then under thermodynamic control, giving the more stable compounds **9** and **11**. When we were interested in the synthesis of the tetrahydrofurans **8** and **10**, we had to perform the reaction under kinetic control. Indeed, even if we stopped the reaction under thermodynamic control after 1 min, we could isolate the tetrahydrofurans, but without selectivity. Then we performed the reaction between alkene **13** and *N*-phenylselenophthalimide (NPSP),[8] or PhSeCl as carriers of the electrophilic phenylseleno species $PhSe^+$ (Scheme 3).



Scheme 3. *Reagents*: (a) PhSeCl, K_2CO_3, CH_2Cl_2, −78°C (95%).



Scheme 4.

By using NPSP and camphorsulfonic acid in CH_2Cl_2 a 63/37 ratio was obtained, whereas a 86/14 ratio was obtained with PhSeCl and K_2CO_3 in CH_2Cl_2. The poor stereoselectivity with NPSP may be attributed to camphorsulfonic acid that provide partly thermodynamic conditions during the cyclisation process with respect to the more strictly kinetic conditions that were realized using PhSeCl and potassium carbonate.

In the cyclisation of hydroxy selenides **4** the tetrahydrofuran ring **6** was observed, as minor product, only at higher acid concentration, whereas the oxetane **7** was never observed. In order to allow the 5-*endo-tet* cyclisation, the primary hydroxyl group should be protected.[3d,e,4a,c] For example, compounds **14** gave the tetrahydrofuran ring **15** (Scheme 4).[4c]

Also in this case the 4-*exo-tet* cyclisation was not observed. Since the reaction was performed under thermodynamic control conditions (i.e. cat. $HClO_4$) the more stable 5-*endo* product was obtained. The formation of the 5-*endo* product over the 4-*exo* product could be explained in two different ways: (i) the 4-*exo* product, due to the exocyclic position of the phenylselanyl group, readily rearranged under reaction conditions; (ii) the 4-*exo-tet* cyclisation, though an *exo* cyclisation, could have an higher activation energy. The point (i) easily explains the experimental findings of the cyclisation under thermodynamic conditions, however, our results (see before) and the literature[9] revealed that when the reaction was performed under kinetic conditions (i.e. by reacting the alkene with PhSeCl or NPSP or TIPPSe–Br) the 4-*exo-tet* product was not observed. Then, point (ii) should be important also.

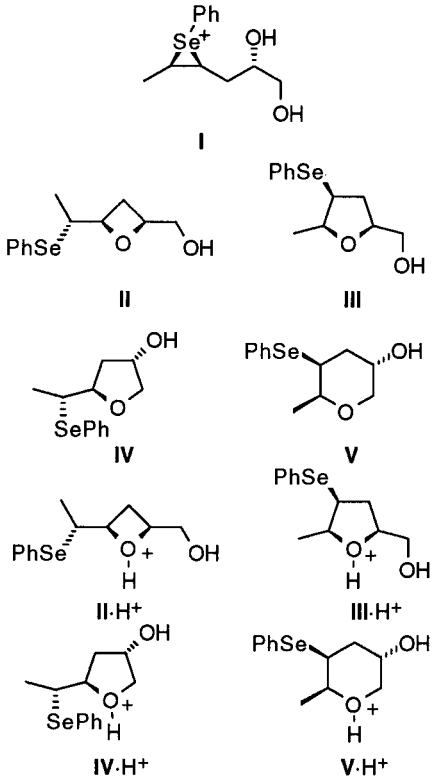


Figure 4. Models submitted to calculations.

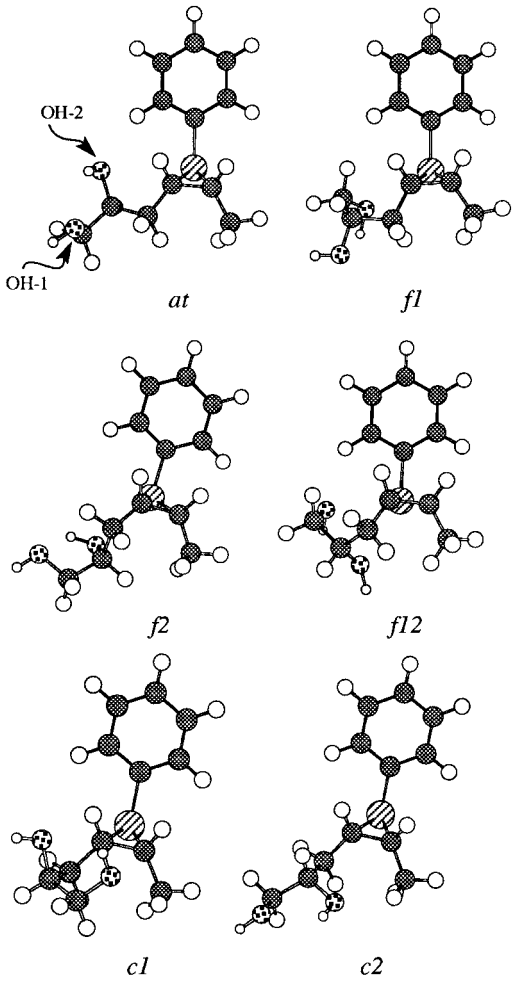


Figure 5. Conformers for seleniranium ion **I**.

3. Calculations

Further rationalization of experimental data was achieved by performing ab initio calculations at the HF/3-21G* level of theory on the model species **I**–**V** and **II**·H^+–**V**·H^+, as shown in Fig. 4, in order to get a detailed explanation of the observed regioselectivity as well as the characteristics of reversibility or irreversibility found for the different cyclisation modes.

Seleniranium ion **I** is an interesting system because it is a

Table 1. Formation energies and Se···O of the conformers of seleniranium model **I**

	at	*f*1	*f*2
E_f (hartree)	−2999.08971	−2999.07507	−2999.08800
$d_{Se\cdots OH\text{-}1}$ (Å)	5.557	3.036	4.450
$d_{Se\cdots OH\text{-}2}$ (Å)	3.672	4.822	2.746
E_{del} (kcal mol^{-1})		3.44	10.65
	*f*12	*c*1	*c*2
E_f (hartree)	−2999.08645	−2.999.08380	−2999.08268
$d_{Se\cdots OH\text{-}1}$ (Å)	4.205	2.739	6.631
$d_{Se\cdots OH\text{-}2}$ (Å)	2.997	2.696	4.552
$d_{C4\cdots Se}$ (Å)		2.065	2.051
$d_{C5\cdots Se}$ (Å)		2.066	2.072
$d_{C4\cdots OH\text{-}1}$ (Å)		2.739	
$d_{C5\cdots OH\text{-}1}$ (Å)		2.804	
$d_{C4\cdots OH\text{-}2}$ (Å)			2.658
$d_{C5\cdots OH\text{-}2}$ (Å)			2.927

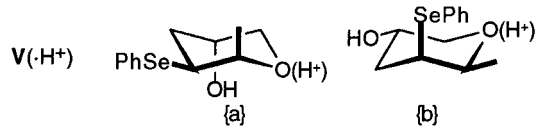


Figure 6. Chair conformations for the tetrahydropyran models **V** and **V**·H$^+$.

potential pseudo-high-valent selenium species (vide infra), a topic which has received attention in recent years.[10] Furthermore, recently[4c,11] semiempirical PM3 calculations have been reported to be predictive on the regiochemistry of cyclisation for similar systems. Nonetheless they have been found unsuitable in describing pseudo-high-valent selenium species, while the HF/3-21G* basis set is considered as the minimum one in order to perform reasonable ab initio calculations.[10a]

A preliminary conformational search was performed firstly on the seleniranium ion **I**, model of the species **5**. For **I** at least six main conformers may be considered (Fig. 5). The first one (*at*) presents an '*a*ll *t*rans'-type conformation with respect to the hydroxylated carbon chain; it should have minimal steric hindrances and a remarkable intramolecular interaction between the OH groups but no interaction between them and the selenium centre. Nonetheless, it is well known[10a,b] that interaction between divalent selenium and donor atoms (such as N or O) is very stabilising and leads to the formation of a pseudo-high-valent species with a three-centre-four-electron-type bond. Thus three other *f*olded conformers, named as *f*1, *f*2 and *f*12, were also examined, having the OH-1, the OH-2 or both the hydroxyl groups, respectively, directed towards the selenium atom. Finally, two further 'apt for closure' conformers, *c*1 and *c*2, having the OH-1 and the OH-2 groups, respectively, near the backside of the seleniranium C–Se bond were considered. The results are reported in Table 1. Calculations find *at* as the more stable conformer, followed by *f*2, *f*12, *c*1, *c*2 and *f*1, with differences in energy of about 1.1, 2.0, 3.7, 4.4 and 9.2 kcal mol^{-1}, respectively.

NBO population analysis,[12] which has been reported to be a very useful tool for investigation of pseudo-high-valent selenium species,[10] was also performed on the optimised models *f*1 and *f*2. Results show that the hydroxyl groups of the carbon chain, when approaching the positively charged Se atom, are able to delocalise electron density mainly into the σ^*_{Se-Ph} antibonding orbital. The energy gain associated with this interaction is evaluated by the NBO deletion energy (E_{del}). The values found (Table 1), which are roughly a function of the O···Se distance, are comparable to those reported for similar cases.[10] Thus, the calculations suggest that for the folded conformations examined such an energy gain is de facto not sufficient to compensate the strain and steric hindrances induced by folding, such that the *at* conformer is the more stable one.

Models of the cyclic products **II**–**V** and of their conjugate acids (protonated on the annular oxygen atom) **II**·H$^+$–**V**·H$^+$, possible derivatives from species **I**, were also studied. In particular, the six-membered systems **V** and **V**·H$^+$ were also subjected to a conformational analysis owing to the non-rigidity of the ring. Ab initio calculations predict, as an absolute minimum, a chair conformation. In **V**, the phenylselanyl group is found to prefer the axial position in agreement with NMR data. In contrast, in the protonated model **V**·H$^+$ the phenylselanyl group is found to prefer the equatorial position. Noticeably this conformation corresponds to the best activated complex for the 6-*endo*-type cyclisation (vide infra), so we can argue that stereoelectronic effects may play an important role here. It should be reminded that when the acid content was increased, compound **9** (**V**·H$^+$) rearranged partly (Fig. 6).

An individuation of the more stable conformers of the seleniranium ions and of the cyclized products was needed in order to evaluate the activation energies for the cyclisation processes. Thus, we studied the competition between the different cyclisation modes determining the regiochemistry of the reaction. The activated complexes of the four possible cyclisation modes for **I** were modelled and activation energies were compared (Table 2). As different activated complexes could be obtained for the formation of **V** (each corresponding to one of the possible conformers of

Table 2. Formation energies, E_f (hartrees) of the model products **II**–**V**, **II**·H$^+$–**V**·H$^+$ and of the related TSs, and activation energies for the ring closure/opening processes

Transition states	Protonated model products	Model products	Activation energy $\Delta H^{\neq}$	
			Closure	Opening
TS 4-*exo* −2999.07014	**II**·*H*$^+$ −2999.07524	**II** −2998.70184	12.28	3.20
TS 5-*endo* −2999.07269	**III**·H$^+$ −2999.10882	**III** −2998.73751	10.68	22.67
TS 5-*exo* −2999.08000	**IV**·H$^+$ −2999.09731	**IV** −2998.73525	6.09	10.86
TS 6-*endo* −2999.07806	**V**·H^{+a} −2999.10400 {a}	**V**^{a} −2998.74008 {b}	7.31	16.28

[a] The letters in brackets {a} or {b} refer to the conformers depicted in Fig. 6.

Table 3. Calculated structural parameters of the transition states and related products derived from seleniranium ion **I**

Structural parameters	Transition states	Related products	Difference	% of bond formation in the TS[a]
	TS 4-*exo*	**II**·H$^+$		
$d_{O\cdots C}$ (Å)	1.976	1.628	0.348	66
$d_{C\cdots Se}$ (Å)	2.498	2.746	0.248	36
Se–C–O angle (°)	164.1	158.3	6.2	
C–C–Se angle (°)	77.7	103.3	25.6	
q_C (e)[b]	+0.166			
	TS 5-*endo*	**III**·H$^+$		
$d_{O\cdots C}$ (Å)	2.238	1.523	0.715	49
$d_{C\cdots Se}$ (Å)	2.454	2.940	0.486	56
Se–C–O angle (°)	134.8	101.0	33.8	
C–C–Se angle (°)	89.2	113.0	23.8	
q_C (e)[b]	+0.207			
	TS 5-*exo*	**IV**·H$^+$		
$d_{O\cdots C}$ (Å)	2.236	1.587	0.649	44
$d_{C\cdots Se}$ (Å)	2.354	2.798	0.444	61
Se–C–O angle (°)	156.5	150.3	6.2	
C–C–Se angle (°)	84.0	106.1	21.1	
q_C (e)[b]	+0.136			
	TS 6-*endo*	**V**·H$^+$		
$d_{O\cdots C}$ (Å)	2.257	1.570	0.687	38
$d_{C\cdots Se}$ (Å)	2.382	2.875	0.493	63
Se–C–O angle (°)	146.7	145.1	1.6	
C–C–Se angle (°)	85.7	110.2	24.5	
q_C (e)[b]	+0.105			

[a] See Ref. 14.
[b] Charge on the C atom in the TS as calculated by the NBO analysis.

the protonated product), we referred only to the more stable one in Table 2.

A much higher energy is predicted for the transition state (TS) leading to the 4-*exo*-type cyclisation of **I**. Regarding the other modes of cyclisation, calculations predict the following order of decreasing activation energy: 5-*endo*>6-*endo*>5-*exo*. Moreover, the second step for the formation of the cyclic products is the exchange of a proton with a suitable base; if this base is, as reasonable, a water molecule it may be easily shown from data reported in Table 2 that this process should be endothermic.[13] This means that the activation energies for the reverse reactions of ring opening are actually given by the differences in energy between each protonated product and the related transition state. Ring opening is predicted easier than ring closure for the 4-*exo* product only.

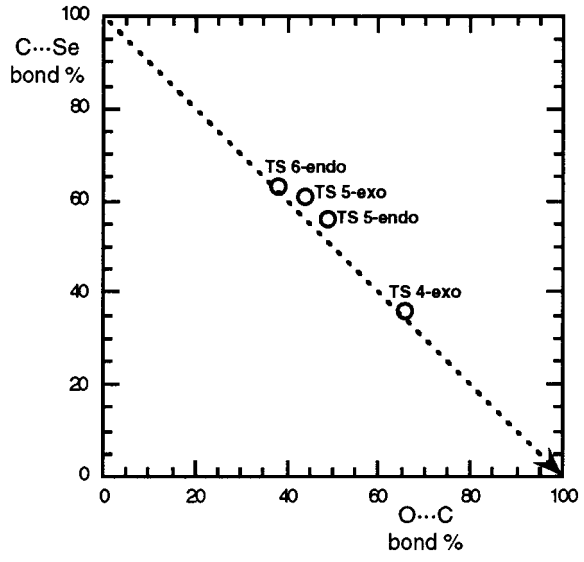


Figure 7. Jencks–More O'Ferral-type diagram.

A comparison with experimental results is very interesting, especially if structural parameters (Table 3) are also taken in account. Keeping in mind that the reaction is assimilable to a simple S_N2 process, we can notice that the two *exo*-type activated complexes show the O···C···Se attack angle closer to 180° than the two *endo*-type activated complexes, allowing consequently a better orbital superimposition. Nonetheless the 4-*exo* TS suffers for severe annular strain, and presents an O···C distance shorter by about 0.3 Å with respect to the TSs for the other modes. Assuming that from bond distances and their differences, we can get an evaluation of how many O···C and the C···Se bonds are formed/disrupted in the TSs,[14] and building the related Jenks–More O'Ferral-type diagram (Fig. 7), we can easily deduce that for seleniranium **I** the 4-*exo* mode has the latest TS.

Comparing the 6-*endo* and 5-*exo* closures we also notice an increase of the cationic character of the C centre in the TS (see Table 3).[15] This is in agreement with the observation that the 6-*endo* closure is favoured by a higher charge stabilisation.[3g] In contrast, the same does not seem true when we compare the 4-*exo* and the 5-*endo* modes. We may argue that such a result is a consequence of a prevailing 'product-control' for the 4-*exo* mode in the sense that, owing to the late character of its TS, the formation of the oxetane ring should be mostly driven by product stability. Further comparison with structural parameters for the

protonated products shows that opening involves a minor reorganisation of the molecular structure for the 4-*exo* product, but a wider reorganisation for the 5-*endo* product, both in terms of bond angles and distances. As a first consequence, the lack in observation of any 4-*exo* product may be attributed to kinetic as well as thermodynamic factors, because the product is intrinsically more difficult to obtain (the related TS is too high in energy), easier to open, and less stable. The experimental finding of a rapid formation of the 5-*exo* product from **4** followed by its slow and irreversible transformation to the 6-*endo* one—while the 5-*endo* closure is observed only if the OH-1 group is protected, and the product is not opened in the reaction conditions—involves that the activation energies for the formation of the three products should increase in the order 5-*exo*<6-*endo*<5-*endo* and also that the activation energy for opening should be low for the 5-*exo* product and high for the 5-*endo* and 6-*endo* products. The calculations are in full agreement with this picture.

Finally we conclude that the cyclisation of hydroxy selenides **4** is an interesting way for the stereoselective synthesis of tetrahydropyrans and that they are governed by both kinetic and thermodynamic factors: (a) the order of cyclisation of **5** is 5-*exo-tet*<6-*endo-tet*<5-*endo-tet*<4-*exo-tet*; (b) the oxetanes **7** derived from the 4-*exo* cyclisation were never observed probably for both kinetic and thermodynamic reasons; (c) the tetrahydrofurans **8** and **10** coming from the pure 5-*exo-tet* cyclisation are the kinetic products; (d) the tetrahydropyrans **9** and **11** derived from the 6-*endo-tet* cyclisation are the thermodynamic products of the acid catalysed cyclisation; (e) the tetrahydrofuran **6** is observed only at high acid concentration or if the primary hydroxyl group is protected; (f) the hydroxy selenides **4** gave a ca. 50/50 mixture of **8** and **10** and then a 68/32 mixture of **9** and **11** via the intermediate species **12**; (g) the 6-*endo-tet* cyclisation should be favoured by a higher charge stabilization of the carbon atom that undergo the attack compared with the 5-*exo-tet* cyclisation, whereas the 4-*exo-tet* cyclisation is probably driven by the stability of the oxetane ring. Similar experimental observation involving thiiranium ions have been reported recently by Warren.[16]

4. Experimental

4.1. General

Anhydrous solvents were distilled as follows: tetrahydrofuran was distilled under nitrogen from sodium benzophenone immediately prior to use. Dichloromethane was distilled under nitrogen from calcium hydride and used immediately. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-E series 250 MHz spectrometer. 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. Melting points were determined with a Kofler hot stage and are uncorrected. Ab initio calculations were performed with the GAUSSIAN 98 program distributed by Gaussian Inc.[17] Full geometry optimisation was performed for each model species examined.

4.1.1. (±)(2*SR*,3*SR*,5*SR*)-2-Butyl-3-phenylselanyl-tetrahydropyran-5-ol (9) and (±)(2*RS*,3*RS*,5*SR*)-2-butyl-3-phenylselanyl-tetrahydropyran-5-ol (11). To a solution of hydroxy selenides **4** (348 mg, 1.05 mol) in anhydrous dichloromethane (50 mol) at room temperature were added three drops (15 μL) of $HClO_4$ (70%). The reaction mixture was vigorously stirred for 30 min then quenched with saturated aqueous $NaHCO_3$ and extracted with water. The organic phase was washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (light petroleum–ethyl acetate 7/1) gave the *title compound* **11** (87 mg, 26%) as white crystals and the *title compound* **9** (187 mg, 57%) as white crystals. Compound **9**: mp 64–66°C; IR (nujol) ν_{max} 3420, 1575, 1455, 1433, 1050, 740 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J=6.8 Hz, CH_3), 1.23–1.38 (m, 4H, $CH_3CH_2CH_2$), 1.55–1.92 (m, 3H, $CH_3CH_2CH_2CH_2$+H-4$_{ax}$), 2.20 (br s, 1H), 2.40–2.46 (m, 1H, H-4$_{eq}$), 3.19 (dd, 1H, J=10.7 and 9.9 Hz, H-6$_{ax}$), 3.37–3.44 (m, 1H, H-2), 3.49–3.52 (m, 1H, H-3), 4.05 (ddd, 1H, J=10.7, 4.9 and 1.9 Hz, H-6$_{eq}$), 4.12–4.24 (m, 1H, H-5), 7.25–7.28 (m, 3H, ArH), 7.52–7.60 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 22.5 (CH_2), 27.9 (CH_2), 33.6 (CH_2), 39.5 (C-4), 47.1 (C-3), 63.7 (C-5), 72.7 (C-6), 80.1 (C-2), 127.4, 129.1, 129.9, 134.2. Anal. Calcd for $C_{15}H_{22}O_2Se$: C, 57.51; H, 7.08. Found: C, 57.90, H, 7.14.

Compound **11**: mp 59–61°C; IR (nujol) ν_{max} 3410, 1575, 1455, 1370, 1090, 1035, 745 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.91 (t, 3H, J=6.7 Hz, CH_3), 1.28–1.42 (m, 4H, $CH_3CH_2CH_2$), 1.60–1.67 (m, 1H, $CH_3CH_2CH_2CH_2$), 1.76–1.83 (m, 1H, $CH_3CH_2CH_2CH_2$), 2.12 (ddd, 1H, J=15.0, 4.1 and 3.8 Hz, H-4), 2.30 (ddd, 1H, J=15.0, 5.5 and 3 Hz, H-4), 2.50 (br s, 1H, OH), 3.40–3.44 (m, 1H, H-3), 3.40–3.51 (m, 1H, H-2, partly overlapped with H-3), 3.66 (dd, 1H, J=12.1 and 1.6 Hz, H-6$_{ax}$), 3.78–3.81 (m, 1H, H-5), 4.00–4.06 (m, 1H, H-6$_{eq}$), 7.27–7.32 (m, 3H, ArH), 7.59–7.66 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 22.5 (CH_2), 27.7 (CH_2), 34.1 (CH_2), 34.3 (C-4), 43.9 (C-3), 66.0 (C-5), 73.7 (C-6), 80.4 (C-2), 127.9, 128.5, 129.2, 135.2. Anal. Calcd for $C_{15}H_{22}O_2Se$: C, 57.51; H, 7.08. Found: C, 57.88, H, 7.16.

4.1.2. (±)(2*RS*,4*SR*,1′*RS*)-4-Hydroxy-2-(1′-phenylsulfanylpentyl)-tetrahydrofuran (8) and (±)(2*SR*,4*SR*,1′*SR*)-4-hydroxy-2-(1′-phenylsulfanylpentyl)-tetrahydrofuran (10). A solution of phenylselenenyl chloride (383 mg, 2.00 mmol) in anhydrous dichloromethane (4 mL) was added dropwise to a solution of compound **13** (316 mg, 2.00 mmol) in anhydrous dichloromethane (6 mL) containing potassium carbonate (276 mg, 2.00 mmol) at −78°C. The reaction was stirred for 20 min then warmed at room temperature and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (light petroleum–ethyl acetate 7/1) gave the *title compounds* **8**[4c] (512 mg, 82%) and **10** (83 mg, 13%) as oils.

Compound **10**: IR (liquid film) ν_{max} 3420, 1577, 1477, 1466, 1437, 1090, 739 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=7.2 Hz, CH_3), 1.24–1.70 (m, 4H, $CH_3CH_2CH_2CH_2$), 1.80–1.92 (m, 3H, $CH_3CH_2CH_2CH_2$+H-3), 2.37 (ddd, 1H, J=14.1, 8.7 and 3.1 Hz, H-3), 3.10–3.17 (m, 1H, C*H*SePh, overlapped with br s 1H, OH), 3.61 (dd, 1H, J=9.7 and

3.6 Hz, H-5), 3.93 (d, 1H, J=9.7 Hz, H-5), 4.06–4.13 (m, 1H, H-2), 4.35–4.39 (m, 1H, H-4), 7.24–7.29 (m, 3H, ArH), 7.56–7.61 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 22.4 (CH_2), 30.4 (CH_2), 34.5 (CH_2), 39.9 (C-3), 53.9 (C–Se), 72.1 (C-4), 75.6 (C-5), 81.0 (C-2), 127.4, 129.0, 130.0, 134.2. Anal. Calcd for $C_{15}H_{22}O_2Se$: C, 57.51; H, 7.08. Found: C, 57.60, H, 7.11.

4.1.3. (±)(*Z*,2*SR*)-Non-4-en-1,2-diol (13). A solution of tetrabutylammonium fluoride (1.39 g, 4.40 mmol) in anhydrous tetrahydrofuran (7 mL) was added dropwise to a solution of the silyl ether[4c] (600 mg, 2.20 mmol) in tetrahydrofuran (8 mL) at 0°C, and the mixture allowed to warm to room temperature and stirred for 18 h. The solution was concentrated under reduced pressure, then dissolved in ethyl acetate and extracted with water. The organic phase was washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (ethyl acetate) gave the *title compound* **13** (322 mg, 92%) as oil. IR (liquid film) ν_{max} 3350, 1455, 1370, 1082, 1040, 860 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.91 (t, 3H, J=7.1 Hz), 1.25–1.40 (m, 4H), 1.98–2.09 (m, 3H), 2.25 (ddd, 1H, J=13.8, 5.3 and 5.3 Hz), 3.28–3.33 (m, 2H), 3.41–3.51 (m, 1H), 4.52 (t, 1H, J=4.5 Hz, OH, overlapped with d, 1H, OH), 5.37–5.54 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 14.0, 21.9, 26.6, 31.4, 31.7, 65.6, 71.5, 126.7, 130.6. Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.20, H, 11.41.

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14. The percentage of bond formation in the TS for the C···Se bond may be evaluated as the ratio $100(d_P - d_{TS})/(d_P - d_I)$, where d_I, d_{TS} and d_P are the C···Se distances in the seleniranium ion **I**, in the TS and in the related cyclisation product (the conjugate acid form), respectively. In the same way the percentage of formation for the O···C bond may be estimated as $100(d'_I - d'_{TS})/(d'_I - d'_P)$ where d'_I, d'_{TS} and d'_P are the O···C distances in I, in the TS and in the related product, respectively. The values for d_I and d'_I were desumed from the 'apt for closure' c1 and c2 conformers.
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