Pergamon

Tetrahedron 57 (2001) 6815–6822

TETRAHEDRON

A joint experimental and ab initio study on the reactivity of several hydroxy selenides. Stereoselective synthesis of *cis*-disubstituted tetrahydrofurans via seleniranium ions

Michelangelo Gruttadauria,* Carmela Aprile, Francesca D'Anna, Paolo Lo Meo, Serena Riela and Renato Noto

Dipartimento di Chimica Organica 'E. Paternò', Viale delle Scienze, Parco d'Orleans II, 90128 Palermo, Italy

Received 6 April 2001; revised 9 May 2001; accepted 31 May 2001

Abstract—The reactivity of several hydroxy selenides bearing an ethereal chain with catalytic amounts of perchloric acid in dichloromethane was investigated. Results showed that the position of the oxygen atom with respect to the seleniranium ring was crucial in order to get a good yield of the cyclized product. The factors on which yields of the 5-*endo* cyclization of the seleniranium ions depend were analysed by ab initio (HF/3-21G*) studies. An explanation of the different coordinating ability, towards the positively charged selenium atom, of the allylic OMe and homoallylic OH-2 groups was given. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Structurally complex tetrahydrofuran units are often found in many natural products such as polyether antibiotics and a particularly challenging aspect is the stereocontrolled synthesis of the substituted tetrahydrofuran unit, especially those in which there is a *cis* relationship between substituents at the 2 and 5 positions.[1] During the last decade several authors have prepared in a synthetically useful manner substituted tetrahydrofurans via 5-*endo*-cyclization of intermediate seleniranium,[2–8] thiiranium[9] or iodonium ions.[10,11] In the last years our efforts have been devoted to the stereoselective synthesis of oxygenated heterocyclic rings from mixtures of hydroxy selenides or by treatment of the appropriate unsaturated alcohol with a source of the electrophilic seleno species $PhSe^+$, such as PhSeCl.[12–18] Both the methods lead to oxygenated heterocyclic rings via the intermediate seleniranium ion. Recently we studied the behaviour of the intermediate seleniranium ion having two hydroxyl groups and an aliphatic R chain (Fig. 1).[17] We found that the 5-*endo-tet*[19] cyclization occurs only at high acid concentration or when the primary hydroxy group is protected.

2. Results and discussion

In order to gain deeper information about the influence of

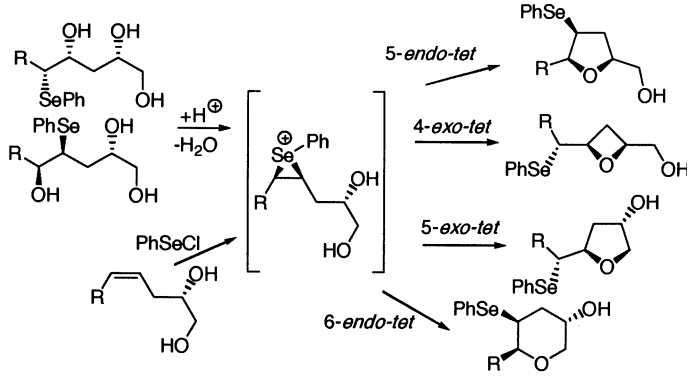
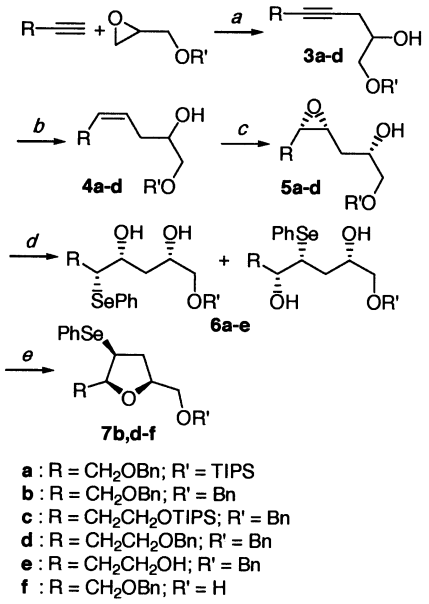


Figure 1. Different ring closure of the intermediate seleniranium ion.

Keywords: cyclizations; oxygen heterocycles; selenium; theoretical studies.

* Corresponding author. Tel.: +39-091-596919; fax: +39-091-596825; e-mail: mgrutt@unipa.it

PII: S0040-4020(01)00618-4



Scheme 1. *Reagents*: (a) BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C, 69–85%; (b) H_2, Lindlar, EtOH, rt, 89–96%; (c) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, rt, 72–84%; (d) $(PhSe)_2$, $NaBH_4$, EtOH, rt, 73–80%; (e) $HClO_4$ (cat.), CH_2Cl_2, rt, 30–72%.

the R group in the 5-*endo-tet* cyclization, we have analysed the reactivity of hydroxy selenides **6** bearing, as R group, an oxygenated aliphatic chain (R═CH_2OPG; R═CH_2CH_2OPG). These compounds were prepared as outlined in Scheme 1. Epoxidation of homoallylic alcohols **4** using *tert*-butyl-hydroperoxide and $VO(acac)_2$ gave the *syn*-epoxy-alcohols with good stereoselectivity (>93:7), the configuration of the major epoxide being assigned by analogy with the literature.[20] The hydroxy selenides were usually obtained as a ca. 80/20 mixture and we have not determined which was which. Previously we studied the cyclization of **6a**, obtaining a complex mixture of products from which we could isolate the tetrahydrofuran **7f** with low yield (27%).[14]

The reaction was complicated by the fact that in the operating conditions the labile triisopropylsilyl protecting group was removed then allowing also the cyclization in the *exo* mode and, possibly, the rearrangement.[16] The result was a complex mixture of products. In order to avoid this, we protected both the primary hydroxyl groups as benzyl ethers. The hydroxy selenides **6b** were then treated with perchloric acid, but also in this case the reaction was sluggish and after 24 h we obtained a complex mixture of

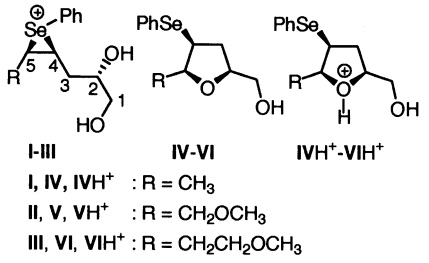


Figure 2. Models submitted to calculations.

products from which we were able to isolate the tetrahydrofuran product again in low yield (30%). In our opinion, there could be two reasons for this low yield: (i) a coordination on the positively charged phenylselenyl moiety by the oxygen atom of the benzyloxy group that stabilises the seleniranium ion, increasing in this way the activation energy of the reaction;[21] (ii) some electronically unfavourable factor(s) introduced to the carbon atom that undergoes the *endo* attack. The partial rupture of C–Se bond necessary to reach the transition state should increase the partial positive charge at the carbon atom. Then, the 5-*endo-tet* cyclization should be favoured if the partial positive charge can be supported in this position. Indeed, when the carbon atom was substituted with a phenyl[2,3] or a furan-3-yl[4,5] group the reaction took place.[22] Also with an aliphatic chain the reaction proceeded with good yield.[5–7] The CH_2OBn group, in our case, could represent the electronically unfavourable factor that does not allow the cyclization to proceed in good yield.[23] Because of the electronegativity of the oxygen atom the partial positive charge at C-5 cannot be supported.

Moreover we prepared the hydroxy selenides **6c**,**d**, in which the more distant position of the oxygen atom could play a role both in the coordination and in the stabilization of a partial positive charge. The acid treatment of **6c** gave the tetrahydrofuran ring after 30 min with a good yield (60%). It should be noticed that being the triisopropylsilyl protecting group a non-chelating group, the coordination of the positively charged phenylselenyl moiety should be hampered. However, the product obtained showed the hydroxyl function deprotected, i.e. the labile triisopropylsilyl protecting group was removed. This could occur prior to or after the cyclization step. We found that the triisopropylsilyl group was removed after the cyclization took place, indeed when we treated the hydroxy selenides **6e** with perchloric acid no reaction was observed. The inertness of **6e** may be ascribed to the existence of an effective intramolecular hydrogen bond network in the molecule.

The next step was the cyclization reaction of hydroxy selenides **6d**. Also in this case we obtained a good yield (72%). The benzyloxy, in contrast to the triisopropyloxy, is a chelating group able to coordinate the phenylselenyl moiety. Then, the good yields for **6c**,**d** should be ascribed only to the more distant position of the oxygen atom.

In order to estimate the importance of point (i) and (ii) in the cyclization of seleniranium ions we performed ab initio calculations at the HF/3-21G* level of theory on the model species **I**–**VI** and **IV**·H^+–**VI**·H^+ (Fig. 2).

In a previous paper we reported that HF/3-21G* calculations allow a detailed analysis of the behaviour of **I**.[17] Now we extended our attention to the species **II** and **III**, in order to model the seleniranium ions deriving from **6a**,**b** and **6c**,**d**, respectively. In order to save computational time we choose to replace the Bn or TIPS groups in R (see Scheme 1) with a methyl group, while the R′ groups were replaced by a hydrogen atom. A preliminary search had shown that for **I** at least six different conformations could be taken in consideration.[17] We restricted our analysis for **II** and **III** only to three possible conformers, namely *at*, *f*2 and *c*2, having respectively the chain carrying the OH groups completely

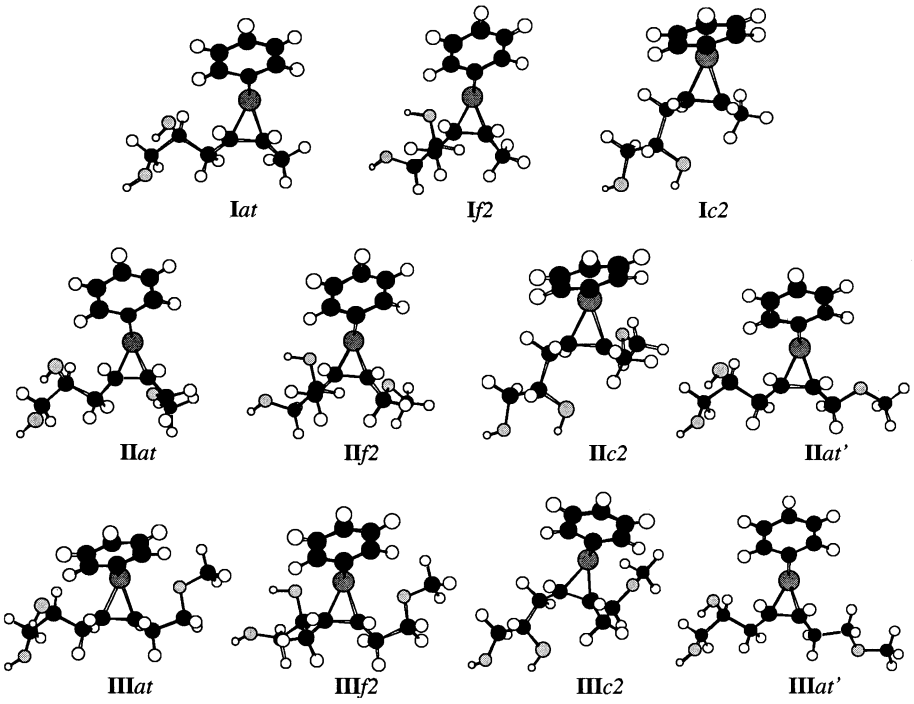


Figure 3. Conformers examined for model species **I–III** (input structures for geometry optimization).

unfolded, or folded in such a way to present the OH-2 group towards the selenium atom or towards the backside of the C–Se bonds of the seleniranium ring (see Fig. 3). At the same time in all cases the conformation of the $-CH_2OCH_3$ or $-CH_2CH_2OCH_3$ moieties was accounted to present the $-OCH_3$ group directed towards the positively charged Se atom.

The extent of the interaction between the Se atom and the OMe group can be easily evaluated by means of the NBO population analysis,[24] a tool which has been proven effective in describing pseudo high valent Se species.[25–27] The oxygen atom is able to delocalise part of its electron density in the σ^*_{Se-Ph} antibonding orbital, with an energy gain given by the NBO deletion energy (Table 1).

Table 1. Calculated parameters for the 5-*endo*-type closure of seleniranium models **I**,**II** and **III**

	I	**II**	**III**
E_f (hartree)[a]	−2999.08971[b]	−3112.34535	−3151.16248
E_f (hartree)[c]	−2999.08268[b]	−3112.33885	−3151.15988
E_f (hartree)	−2999.08800[b,d]	−3112.33312[e]	−3151.15461[e]
E_{del} (kcal mol^{-1})[a]	–	6.90	1.82
d Se···OMe (Å)[a]	–	2.773	3.069
E_{σ^*}(C–Se) (hartree)[c]	−0.00712	+0.01887	+0.00476
$E_{LP(O)}$ (hartree)[c]	−0.94392	−0.93420	−0.92942
ΔE_{σ^*} (C–Se)–LP(O) (hartree)[c]	0.93680	0.95307	0.93418
	TS (I)	**TS (II)**	**TS (III)**
E_f (hartree)	−2999.07269[b]	−3112.31762	−3151.14683
Ring closure $\Delta H^{\neq}$ (kcal mol^{-1})	10.68	17.40	9.82
q_C (e)[f]	+0.207	+0.084	+0.210
% O···C bond formation[g]	49	46	39
% C···Se bond formation[g]	56	65	58
	IV·H$^+$	**V·H$^+$**	**VI·H$^+$**
E_f (hartree)	−2999.10882[b]	−3112.36274	−3151.20422
Ring opening $\Delta H^{\neq}$ (kcal mol^{-1})	22.67[b]	28.31	36.01
	IV	**V**	**VI**
E_f (hartree)	−2998.73751[b]	−3111.98542	−3150.80064

[a] For the *at* conformer.
[b] Values from Ref. 17.
[c] For the *c*2 conformer.
[d] For the *f*2 conformer.
[e] For conformer *at'*.
[f] Charge on the carbon atom as calculated by the NBO analysis.[28]
[g] See Ref. 29.

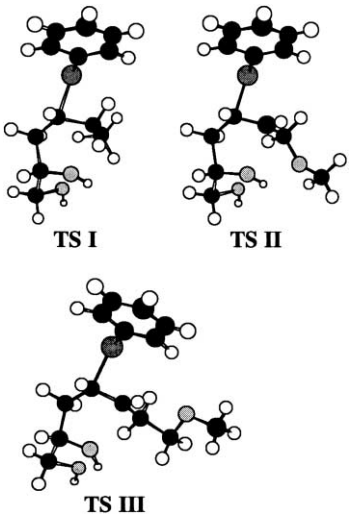


Figure 4. Optimised structures (HF/3-21G*) for transition states **TS(I)**, **TS(II)** and **TS(III)**.

Surprisingly, for both models **II** and **III** we found that the *f*2 form is not a stable minimum, but collapses to the *at* form, which is in turn the absolute energy minimum.

The collapse found by us of conformers **II***f*2 and **III***f*2 to **II***at* and **III***at*, respectively, while by contrast **I***f*2 and **I***at* are distinct minima,[17] may be attributed to the presence of Se–OMe interaction. Thus OMe group seems better coordinating than the OH-2 to the σ^*_{Se-Ph} antibonding orbital. Furthermore, the higher E_{del}(**II**) value than E_{del}(**III**) (see Table 1) shows that the formation of a pseudo-4-membered ring in **II** leads to a more favourable Se–O stabilizing interaction than the formation of a pseudo-5-membered ring in **III**, as evidenced also by the shorter Se–O distance.

It may be argued that the lack in stability for **II***f*2 and **III***f*2 is due to steric strain factors. As a matter of fact, **I***f*2, unless showing the deletion energy equal to 10.65 kcal mol^{-1} for the Se–OH-2 interaction, is less stable than **I***at* for about 1 kcal mol^{-1}.[17] So we may evaluate the strain induced by folding of the chain to be about 11.7 kcal mol^{-1}. In **II***f*2 the additional Se–OMe interaction reduces the extent of the Se–OH-2 one and makes it unable to compensate the folding strain. To get more detailed insights we studied also a further conformation, namely *at′*, for **II** and **III**, similar to *at*, but bearing the –OMe group unfolded far away from the Se atom. Model **II***at′* is found less stable than **II***at* by about 7.7 kcal mol^{-1}. Thus the Se–OMe interaction largely overwhelms the folding strain both in terms of orbitalic and coulombic interactions. Similar competing coordinations have already been recognized.[30]

This preliminary conformational search was needed in order to rationalise the behaviour of molecules **6b**,**d**, comparing the 5-*endo* cyclization of models **I**, **II** and **III**. Our calculations predict similar activation barriers for the formation of **IV** and **VI** from **I** and **III** respectively, but a higher barrier for the formation of **V** and thus a lack in reactivity for **II**, in good agreement with experimental results. NBO population analysis was very useful to rationalise these findings. Models predict that the Se–OMe interaction for **II** and **III** is lost on reaching the transition state for the ring closure process (see Fig. 4).

Nonetheless NBO analysis for the *c*2 conformers, which are the actual reactive species, shows that the energy gap between the σ^*_{Se-C} antibonding orbital and the OH-2 lone pair is very similar in **I** and **III**, but strongly increases on passing to **II**.[31] The two combined effects contribute to make the activation energy for **II** much higher than that for **I** and **III**. Furthermore, calculations for the TS leading to **V** predict the development of only a small positive charge on the attacked C atom, while a higher positive charge is predicted in the TSs leading to **IV** and **VI**. At the same time bond formation percentage shows that the degree of disruption of the C–Se bond in the TS for **V** is anomalously low with respect to the contemporary formation of the C–O bond, differently from the TS leading to **IV** and **VI** that appear as pure S_N2 processes. As a final remark, data collected in table confirm that the 5-*endo* mode cyclization is an irreversible process. Indeed, activation barriers for ring opening are much higher than for closure, ranging largely over the value of 22 kcal mol^{-1}.[32]

3. Conclusion

The low yield for the cyclization of **6a**,**b** could be ascribed both to the coordination of the positively charged phenylselenyl moiety by the benzyloxy group in the seleniranium ions and to the presence of the oxygen atom (of the benzyloxy group) that hampers the development of a partial positive charge at C-5 and then the rupture of the C···Se bond. Both these factors make the activation energy of the ring closure process high. In the cyclization of **6c**,**d** both the coordination and some electronic unfavourable factors introduced to the carbon atom that undergo the *endo* attack should be negligible. These results also explain the observed regioselectivity in the hydroxyselenylation of allylic alcohols.[33] The allylic OMe group was found better coordinating than the homoallylic OMe group to the σ^*_{Se-Ph} antibonding orbital. The different coordination ability between the homoallylic OH and the allylic OMe groups is probably ascribed to the strain introduced by the chain folding. Further evidences of Se···O interaction have been recently reported by us.[18]

4. Experimental

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. ^{1}H 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.[34] Full geometry optimisation was performed for each model species examined. Minimum

and transition states structures were confirmed by inspection of the hessian matrix eigenvalues. Compounds **3**–**6a**,**7e** were described elsewhere.[14]

4.1. General procedure for the synthesis of alkynes 3b–d

Butyllithium (1.60 M in hexane; 5.7 mL, 9.12 mmol) was added dropwise to a solution of the alkyne (R=CH_2OBn, 1.34 g, 9.15 mmol) in anhydrous tetrahydrofuran (20 mL) at −78°C. After 20 min, BF_3–Et_2O (0.75 mL, 6.1 mmol) was added followed, after 5 min, by a solution of the epoxide (R′=Bn., 0.93 mL, 6.1 mmol) in anhydrous tetrahydrofuran (3.3 mL). After 2 h at −78°C, saturated aqueous $NaHCO_3$ (10 mL) was added, the mixture allowed to warm to room temperature and added to water. The mixture was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (light petroleum–Et_2O 7/1) gave **3b** (1.39 g, 73%) as an oil.

4.1.1. (±)(*SR*)-1,6-(Dibenzyloxy)-hex-4-yn-2-ol (3b). IR (liquid film) ν_{max} 3440, 1454, 1355, 1207, 1070, 738 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=2.52–2.56 (m, 2H), 2.82 (s, 1H), 3.53 (dd, 1H, *J*=9.7, 4.0 Hz), 3.64 (dd, 1H, *J*=9.7, 6.5 Hz), 3.95–4.04 (m, 1H), 4.18–4.20 (m, 2H), 4.60 (s, 4H), 7.27–7.39 (m, 10H). ^{13}C NMR ($CDCl_3$): δ= 23.9, 57.6, 66.9, 71.4, 72.9, 73.4, 78.2, 82.6, 127.7, 127.8, 128.0, 128.3, 128.4, 137.5, 137.8. Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.50; H, 7.14.

4.1.2. (±)(*SR*)-1-(Benzyloxy)-7-(triisopropylsilyloxy)-hept-4-yn-2-ol (3c). Oil, yield (85%) from light petroleum–Et_2O 9/1; IR (liquid film) ν_{max} 3420, 1455, 1380, 1100, 910, 880 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ= 1.08 (m, 21H), 2.38–2.45 (m, 4H), 2.67 (d, 1H, *J*= 5.2 Hz), 3.50 (dd, 1H, *J*=9.0, 6.3 Hz), 3.61 (dd, 1H, *J*= 9.0, 3.6 Hz), 3.77 (m, 2H), 3.89–3.96 (m, 1H), 4.57 (s, 2H), 7.27–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=11.1, 17.9, 23.1, 23.8, 62.3, 69.0, 72.9, 73.2, 76.7, 79.6, 127.6, 128.3, 137.8. Anal. Calcd for $C_{23}H_{38}O_3Si$: C, 70.72; H, 9.80. Found: C, 70.90; H, 9.85.

4.1.3. (±)(*SR*)-1,7-(Dibenzyloxy)-hept-4-yn-2-ol (3d). Oil, yield (69%) from light petroleum–Et_2O 7/1; IR (liquid film) ν_{max} 3440, 1450, 1360, 1100, 740 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=2.39–2.48 (m, 4H), 2.83 (d, 1H, *J*=3.9 Hz, OH), 3.43–3.56 (m, 4H), 3.85–3.97 (m, 1H), 4.50–4.53 (s, 4H), 7.26–7.34 (m, 10H). ^{13}C NMR ($CDCl_3$): δ=20.0, 23.7, 68.4, 68.9, 72.7, 72.8, 73.1, 76.8, 79.1, 127.4, 127.5, 128.2, 137.8, 137.9. Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.60; H, 7.50.

4.2. General procedure for the synthesis of alkenes 4b–d

A suspension of Lindlar catalyst (126 mg) in a solution of the alkyne **3b** (1.26 g, 4.06 mmol) in ethanol (20 mL) was stirred vigorously under hydrogen for 210 min. The mixture was filtered through Celite and the filtrate evaporated in vacuo. Purification of the crude product by flash chromatography (light petroleum–Et_2O 7/1) gave **4b** (1.22 g, 96%) as an oil.

4.2.1. (±)(*Z*,*SR*)-1,6-(Dibenzyloxy)-hex-4-en-2-ol (4b). IR (liquid film) ν_{max} 3448, 1445, 1205, 1072, 736 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=2.28–2.33 (m, 2H), 2.74 (s, 1H), 3.40 (dd, 1H, *J*=9.6, 5.0 Hz), 3.48 (dd, 1H, *J*=9.6, 3.6 Hz), 3.81–3.90 (m, 1H), 4.08–4.17 (m, 2H), 4.53–4.59 (m, 4H), 5.67–5.82 (m, 2H), 7.27–7.39 (m, 10H). ^{13}C NMR ($CDCl_3$): δ=31.7, 65.4, 69.7, 72.2, 73.3, 73.7, 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 128.6, 129.0, 137.8, 138.0. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.90; H, 7.74.

4.2.2. (±)(*Z*,*SR*)-1-(Benzyloxy)-7-(triisopropylsilyloxy)-hept-4-en-2-ol (4c). Oil, yield (89%) from light petroleum–Et_2O 7/1; IR (liquid film) ν_{max} 3440, 1450, 1380, 1245, 1100, 880 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ= 1.08 (m, 21H), 2.28–2.38 (m, 4H), 2.56 (d, 1H, *J*= 3.3 Hz), 3.40 (dd, 1H, *J*=9.3, 7.2 Hz), 3.52 (dd, 1H, *J*= 9.3, 3.6 Hz), 3.71 (t, 2H, *J*=6.8 Hz), 3.84–3.91 (m, 1H), 4.57 (s, 2H), 5.49–5.65 (m, 2H), 7.27–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=11.9, 17.9, 31.2, 31.4, 62.9, 70.1, 73.3, 73.9, 126.3, 127.6, 128.3, 129.0, 138.0. Anal. Calcd for $C_{23}H_{40}O_3Si$: C, 70.36; H, 10.27. Found: C, 70.50; H, 10.35.

4.2.3. (±)(*Z*,*SR*)-1,7-(Dibenzyloxy)-hept-4-en-2-ol (4d). Oil, yield (92%) from light petroleum–Et_2O 7/1; IR (liquid film) ν_{max} 3440, 1450, 1365, 1100, 740 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=2.31–2.48 (m, 4H), 2.81 (s, 1H), 3.39–3.53 (m, 4H), 3.84–3.92 (m, 1H), 4.54 (s, 2H), 4.57 (s, 2H), 5.56–5.61 (m, 2H), 7.28–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$): δ=27.9, 31.4, 69.3, 70.0, 72.8, 73.2, 73.9, 126.8, 127.4, 127.5, 127.6, 128.2, 128.3, 128.6, 138.0, 138.2. Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.30; H, 8.10.

4.3. General procedure for the synthesis of epoxides 5b–d

To a solution of **4b** (1.12 g, 3.6 mmol) in anhydrous dichloromethane (34 mL) at 0°C, $VO(acac)_2$ (17 mg, 0.064 mmol) was added, then *tert*-butyl hydroperoxide (5.5 M in decane; 0.98 mL, 5.40 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 10 min then allowed to warm to room temperature. After 20 h the reaction was quenched with saturated aqueous sodium thiosulfate. The mixture was washed with water, brine, dried (Na_2SO_4) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (light petroleum–ethyl acetate 3/1) gave **5b** (855 mg, 72%) as an oil.

4.3.1. (±)(2*SR*,4*RS*, 5*SR*)-1,6-(Dibenzyloxy)-4,5-epoxy-hexan-2-ol (5b). IR (liquid film) ν_{max} 3446, 1496, 1454, 1365, 1205, 1100 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ= 1.64–1.86 (m, 2H), 2.80 (s, 1H), 3.16–3.25 (m, 2H), 3.44–3.61 (m, 3H), 3.68 (dd, 1H, *J*=11, 4.4 Hz), 4.02–4.13 (m, 1H), 4.53 and 4.63 (d, each 1H, *J*=11.8 Hz), 4.56 (s, 2H), 7.27–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$): δ=31.6, 53.3, 54.4, 68.0, 68.9, 73.3, 73.4, 73.7, 127.7, 127.8, 128.4, 137.7, 137.8. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.25; H, 7.44.

4.3.2. (±)(2*SR*,4*RS*, 5*SR*)-1-(Benzyloxy)-7-(triisopropylsilyloxy)-4,5-epoxy-heptan-2-ol (5c). Oil, yield (75%) from light petroleum–ethyl acetate 7/1; IR (liquid film) ν_{max} 3420, 1460, 1100, 880 cm^{-1}. ^1H NMR (250 MHz,

$CDCl_3$): δ=1.08 (m, 21H), 1.58–1.93 (m, 4H), 2.77 (d, 1H, J=3.2 Hz), 3.10–3.20 (m, 2H), 3.46–3.56 (m, 2H), 3.85–3.90 (m, 2H), 4.07–4.11 (m, 1H), 4.57 (s, 2H), 7.27–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=11.8, 17.9, 31.4, 31.6, 54.0, 54.2, 60.6, 69.1, 73.3, 73.8, 127.6, 127.7, 128.4, 137.8. Anal. Calcd for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87. Found: C, 67.70; H, 9.85.

4.3.3. (±)(2*SR*,4*RS*,5*SR*)-1,7-(Dibenzyloxy)-4,5-epoxy-heptan-2-ol (5d). Oil, yield (84%) from light petroleum–ethyl acetate 3/1; IR (liquid film) ν_{max} 3440, 1450, 1365, 1100, 740 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.65–1.90 (m, 4H), 2.99 (s, 1H), 3.09–3.20 (m, 2H), 3.48–3.52 (m, 2H), 3.62–3.67 (m, 2H), 4.10–4.20 (m, 1H), 4.54 (s, 2H), 4.56 (s, 2H), 7.29–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$): δ=28.4, 31.4, 53.9, 54.0, 67.2, 68.7, 72.9, 73.1, 73.7, 127.4, 127.5, 127.6, 128.2, 128.3, 137.7, 137.9. Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.60; H, 7.60.

4.4. General procedure for the synthesis of hydroxy selenides 6b–d

Diphenyl diselenide (189 mg, 0.61 mmol) was dissolved in absolute ethanol (1.8 mL), sodium borohydride (67 mg, 1.77 mmol) was added in batches and the mixture was stirred until the bright yellow solution turned colourless. Compound **5b** (361 mg, 1.10 mmol) was dissolved in absolute ethanol (1.4 mL) and added via cannula. The reaction mixture was stirred for 16 h then concentrated under reduced pressure. Dichloromethane was added and the mixture was washed 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 4/1) gave the title compounds **6b** (427 mg, 80%) as pale-yellow oil.

4.4.1. (±)(2*SR*,3*SR*,4*SR*)-1,6-(Dibenzyloxy)-3-phenylselenyl-hexan-2,5-diol and (±)(2*RS*,3*RS*,4*SR*)-1,6-(Dibenzyloxy)-2-phenylselenyl-hexan-3,5-diol (6b). Regioisomers ratio ca. 85/15 (determined by ^{1}H NMR); IR (liquid film, mixture of isomers) ν_{max} 3418, 1577, 1454, 1075 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.75–1.87 (m, 1H), 1.92–2.06 (m, 1H), 3.32–3.54 (m, 3H), 3.64–3.78 (m, 2H), 3.85–3.94 (m, 1H), 3.98–4.10 (m, 1H), 4.35 and 4.43 (d, each 1H, J=12 Hz), 4.51 (s, 2H), 4.77 (d, 1H, J=5.6 Hz, OH, major regioisomer), 4.10 (d, 1H, J=4.0 Hz, OH, minor regioisomer), 5.25 (d, 1H, J=4.6 Hz, OH, major regioisomer), 5.40 (d, 1H, J=4.1 Hz, OH, minor regioisomer), 7.23–7.42 (m, 13H), 7.58–7.63 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=major regioisomer 36.5, 47.8, 68.9, 72.5, 73.0, 73.2, 73.3, 74.4, 127.4, 127.6, 127.7, 128.3, 128.4, 129.1, 129.4, 134.1, 137.8. Anal. Calcd for $C_{26}H_{30}O_4Se$: C, 64.32; H, 6.23. Found: C, 64.40; H, 6.32.

4.4.2. (±)(2*SR*,4*SR*,5*SR*)-1-(Benzyloxy)-7-(triisopropylsilyloxy)-4-phenylselenyl-heptan-2,5-diol and (±)(2*SR*,4*RS*,5*RS*)-1-(Benzyloxy)-7-(triisopropylsilyloxy)-5-phenylselenyl-heptan-2,4-diol (6c). Pale-yellow oil, yield (79%) from light petroleum–ethyl acetate 5/1; regioisomers ratio ca. 80/20 (determined by ^{1}H NMR); IR (liquid film, mixture of isomers) ν_{max} 3400, 1578, 1470, 1460, 1100, 880, 738 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.02–1.09 (m, 21H), 1.70–1.90 (m, 4H), 3.34–3.49 (m, 2H), 3.54–3.62 (m, 1H), 3.72–3.78 (m, 2H), 3.81–3.93 (m, 1H), 4.00–4.07 (m, 1H), 4.50 (s, 2H, minor regioisomer), 4.53 (s, 2H, major regioisomer), 4.82 (d, 1H, J=4.7 Hz, minor regioisomer), 4.86 (d, 1H, J=5.4 Hz, major regioisomer), 4.94 (d, 1H, J=4.9 Hz, major regioisomer), 5.09 (d, 1H, J=4.1 Hz, minor regioisomer), 7.26–7.41 (m, 8H), 7.55–7.61 (m, 2H). ^{13}C NMR (DMSO-d_6): δ=major regioisomer 11.6, 18.0, 36.3, 37.3, 50.6, 60.5, 67.5, 69.8, 72.4, 75.1, 126.6, 127.5, 127.6, 128.3, 129.1, 131.0, 132.7, 138.7. Anal. Calcd for $C_{29}H_{46}O_4SeSi$: C, 61.57; H, 8.20. Found: C, 61.70; H, 8.30.

4.4.3. (±)(2*SR*,4*SR*,5*SR*)-1,7-(Dibenzyloxy)-4-phenylselenyl-heptan-2,5-diol and (±)(2*SR*,4*RS*,5*RS*)-1,7-(dibenzyloxy)-5-phenylselenyl-heptan-2,4-diol (6d). Pale-yellow oil, yield (73%) from light petroleum–ethyl acetate 3/1; regioisomers ratio ca. 80/20 (determined by ^{1}H NMR); IR (liquid film, mixture of isomers) ν_{max} 3410, 1575, 1490, 1450, 1360, 1090, 740 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.72–2.03 (m, 4H), 3.35–3.70 (m, 5H), 3.85–3.93 (m, 1H), 4.02–4.10 (m, 1H), 4.46 (s, 2H), 4.54 (s, 2H), 4.87 (d, 1H, J=5.5 Hz, OH, major regioisomer), 5.06 (d, 1H, J=4.9 Hz, OH, major regioisomer), 5.12 (d, 1H, J=4.5 Hz, OH, minor regioisomer), 7.27–7.41 (m, 13H), 7.58–7.65 (m, 2H). ^{13}C NMR (DMSO-d_6): δ=major regioisomer: 34.4, 36.8, 50.8, 67.3, 67.6, 70.2, 72.0, 72.4, 75.1, 126.7, 127.4, 127.5, 127.6, 128.4, 129.2, 131.1, 132.8, 138.7, 138.8. Anal. Calcd for $C_{27}H_{32}O_4Se$: C, 64.92; H, 6.46. Found: C, 65.05; H, 6.50.

4.4.4. (±)(2*SR*,4*SR*,5*SR*)-1-(Benzyloxy)-4-phenylselenyl-heptan-2,5,7-triol and (±)(2*SR*,4*RS*,5*RS*)-1-(benzyloxy)-5-phenylselenyl-heptan-2,4,7-triol (6e). A solution of tetrabutylammonium fluoride (1.03 g, 3.28 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise to a solution of the silyl ethers **6c** (927 mg, 1.64 mmol) in tetrahydrofuran (5 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 (light petroleum–ethyl acetate 1/1) gave the title compounds **6e** (648 mg, 95%) as oil. Regioisomers ratio ca. 80/20 (determined by ^{1}H NMR); IR (liquid film, mixture of isomers) ν_{max} 3370, 1475, 1490, 1475, 1450, 1180, 740 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.70–1.95 (m, 4H), 3.35–3.65 (m, 4H), 3.69–3.97 (m, 1H), 4.01–4.10 (m, 1H), 4.41–4.47 (m, 1H, major regioisomer), 4.50 (s, 2H, minor regioisomer), 4.52 (s, 2H, major regioisomer), 4.61–4.70 (m, 1H, minor regioisomer), 4.96 (d, 1H, J=5.2 Hz, OH, major regioisomer), 5.10 (d, 1H, J=4.6 Hz, OH, major regioisomer), 7.26–7.41 (m, 8H), 7.56–7.63 (m, 2H). ^{13}C NMR (DMSO-d_6): δ=major regioisomer 37.2, 37.7, 51.1, 58.5, 67.6, 70.6, 72.4, 75.1, 126.6, 127.5, 127.6, 128.4, 129.2, 131.2, 132.6, 138.72. Anal. Calcd for $C_{20}H_{26}O_4Se$: C, 58.68; H, 6.40. Found: C, 58.75; H, 6.32.

4.5. General procedure for the synthesis of tetrahydrofurans 7b,d,e

To a solution of hydroxy selenides **6c** (566 mg, 1.00 mmol)

in anhydrous dichloromethane (50 mL) 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 5/1) gave **7e** (228 mg 60%) as an oil.

4.5.1. (±)(2*SR*,3*SR*,5*SR*)-2-Hydroxyethyl-3-phenylselenyl-5-benzyloxymethyl-tetrahydrofuran (7e). IR (liquid film) ν_{max} 3340, 1575, 1480, 1455, 1100 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=1.82–2.02 (m, 3H), 2.47 (ddd, 1H, J=13.4, 7.4 and 7.4 Hz), 3.00 (s, 1H, OH), 3.50–3.62 (m, 2H), 3.77 (t, 3H, J=5.6 Hz), 3.50–3.90 (m, 1H), 4.06–4.15 (m, 1H), 4.18–4.26 (m, 1H), 4.53 and 4.59 (d, each 1H, J=12.1 Hz), 7.22–7.36 (m, 8H), 7.49–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=35.5, 36.2, 44.8, 60.6, 72.3, 73.1, 77.1, 80.5, 127.1, 127.4, 127.5, 128.1, 128.9, 129.6, 133.3, 137.7. Anal. Calcd for $C_{20}H_{24}O_3Se$: C, 61.38; H, 6.18. Found: C, 61.40; H, 6.22.

4.5.2. (±)(2*SR*,3*SR*,5*SR*)-2-Benzyloxyethyl-3-phenylselenyl-5-benzyloxymethyl-tetrahydrofuran (7d). Oil, yield (72%) from light petroleum–ethyl acetate 7/1; IR (liquid film) ν_{max} 1575, 1490, 1470, 1450, 1360, 1100 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=1.97–2.11 (m, 3H), 2.57 (ddd, 1H, J=13.5, 7.6, 7.6 Hz), 3.54–3.70 (m, 4H), 3.87 (ddd, 1H, J=7.5, 5.6, 5.6 Hz), 4.14–4.22 (m, 2H), 4.51 and 4.56 (d, each 1H, J=11.9 Hz), 4.60 and 4.66 (d, each 1H, J=12.2 Hz), 7.28–7.41 (m, 13H), 7.53–7.57 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=33.5, 36.8, 45.4, 67.5, 72.8, 73.2, 77.0, 78.8, 127.1, 127.4, 127.5, 127.6, 127.7, 128.2, 129.0, 133.5, 138.1, 138.4. Anal. Calcd for $C_{27}H_{30}O_3Se$: C, 67.35; H, 6.28. Found: C, 67.35; H, 6.30.

4.5.3. (±)(2*SR*,3*SR*,5*SR*)-2,5-Dibenzyloxymethyl-3-phenylselenyl-tetrahydrofuran (7b). To the solution of hydroxy selenides **6b** were added 20 μL of $HClO_4$ (70%). The reaction mixture was vigorously stirred for 20 h. Oil, yield (30%) from light petroleum–ethyl acetate 8/1; IR (liquid film) ν_{max} 1577, 1477, 1454, 1205, 1074 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ=2.06 (ddd, 1H, J=8.5, 8.0, 8.0 Hz), 2.48 (ddd, 1H, J=12.8, 7.1, 7.1 Hz), 3.55 (dd, 1H, J=10.1, 4.6 Hz), 3.65 (dd, 1H, 10.1 and 5.9 Hz), 3.73–3.77 (m, 2H), 3.82–3.91 (m, 1H), 4.13–4.19 (m, 1H), 4.30–4.37 (m, 1H), 4.52 and 4.58 (d, each 1H, J=12 Hz), 4.58 and 4.67 (d, each 1H, J=9.8 Hz), 7.27–7.41 (m, 13H), 7.54–7.58 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=37.2, 43.0, 72.1, 72.5, 73.2, 77.6, 80.3, 126.8, 127.4, 127.5, 127.6, 127.7, 128.2, 128.3, 128.4, 129.0, 130.9, 133.4, 138.0, 138.1. Anal. Calcd for $C_{26}H_{28}O_3Se$: C, 66.80; H, 6.04. Found: C, 66.76; H, 6.02.

Acknowledgements

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

References

1. Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754.
2. Andrey, O.; Ducry, L.; Landais, Y.; Planchenault, D.; Weber, V. *Tetrahedron* **1997**, *53*, 4339–4352.
3. Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Tetrahedron Lett.* **1991**, *32*, 4015–4018.
4. Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1993**, *34*, 1955–1958.
5. Lipshutz, B. H.; Gross, T. *J. Org. Chem.* **1995**, *60*, 3572–3573.
6. Mihelich, E. D.; Hite, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7318–7319.
7. Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995–8997.
8. Bravo, F.; Castillon, S. *Eur. J. Org. Chem.* **2001**, 507–516.
9. House, D.; Kerr, F.; Warren, S. *J. Chem. Soc., Chem. Commun.* **2000**, 1779–1780.
10. Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1993**, *34*, 7579–7582.
11. Barks, J. M.; Weingarten, G. G.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3469–3476.
12. Arista, L.; Gruttadauria, M.; Thomas, E. J. *Synlett* **1997**, 627–628.
13. Arista, L.; Gruttadauria, M.; Noto, R. *Heterocycles* **1998**, *48*, 1325–1330.
14. Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron* **1999**, *55*, 4769–4782.
15. Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron* **1999**, *55*, 14097–14110.
16. Gruttadauria, M.; Noto, R. *Tetrahedron Lett.* **1999**, *40*, 8477–8481.
17. Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron* **2001**, *57*, 1819–1826.
18. Gruttadauria, M.; Aprile, C.; Riela, S.; Noto, R. *Tetrahedron Lett.* **2001**, *42*, 2213–2215.
19. Following Warren's nomenclature this should be a 6-*endo*/5-*exo* cyclization: McIntyre, S.; Warren, S. *Tetrahedron Lett.* **1990**, *31*, 3457–3460.
20. Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690–7692.
21. Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1987**, *52*, 2018–2026.
22. However in these cases the reaction should be considered as a 5-*exo* cyclization.
23. For a similar case see: Haraguchi, K.; Hosoe, M.; Tanaka, H.; Tsuruoka, S.; Kanmuri, K.; Miyasaka, T. *Tetrahedron Lett* **1998**, *39*, 5517–5520.
24. Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746.
25. Iwaoka, M.; Tomoda, S. *J. Org. Chem.* **1995**, *60*, 5299–5302.
26. Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc.* **1996**, *118*, 8077–8084.
27. Komatsu, H.; Iwaoka, M.; Tomoda, S. *J. Chem. Soc., Chem. Commun.* **1999**, 205–206.
28. We choose to calculate charges by NBO analysis rather than by Mulliken population analysis, as proposed by Reed et al., see Ref. 24.
29. The percentage of bond formation in the TS for the C···Se bond may be evaluated as the ratio100 $(d_P-d_{TS})/(d_P-d_I)$ where d_I, d_{TS} and d_P are the C···Se distances in the seleniranium ions **I**–**III**, in the TSs and in the related cyclization

products (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**–**III**, in the TSs and in the related products respectively. The values for d_I and d'_I were deduced from the 'apt for closure *c*2' conformers.

30. Spichty, M.; Fragale, G.; Wirth, T. *J. Am. Chem. Soc.* **2000**, *122*, 10914–10916.
31. From the frontier orbitals interaction point of view, reactivity should have an inverse dependence from such an energy gap.
32. In order to calculate the ΔH^0 for the proton exchange process the following values of E_f were used. For H_2O: −75.58596 hartree.[17] For H_3O^+: −75.89123.
33. Cooper, M. A.; Ward, A. D. *Tetrahedron Lett.* **1995**, *36*, 2327–2330.
34. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A.6*; Gaussian Inc: Pittsburgh, PA, (1998).