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Stereoselective Synthesis of Tetrahydrofurans and Tetrahydropyrans by Acid-Catalyzed Cyclization of Hydroxy Selenides and Hydroxy Sulfides

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Abstract : The behaviour in acid media of hydroxy selenides and hydroxy sulfides (**1a-c** and **1'a-c**) was investigated. The protection of the primary hydroxyl group in compounds **1a** and **1'a** allowed the stereoselective synthesis of a substituted tetrahydrofuran ring, whereas compounds **1b-c** and **1'b-c** gave an efficient regiochemical control affording substituted tetrahydropyran rings. Tetrahydropyrans containing the phenylselanyl moiety were found to be in equilibrium in the cyclization reaction conditions, whereas tetrahydropyrans containing the phenylsulfanyl moiety were not. A mechanism for the above equilibration is proposed. Semiempirical (AM1, PM3) and *ab initio* (HF/3-21G*) calculations were used in an attempt to rationalize the experimental results.

Introduction

There has been significant interest in the synthesis of natural products containing oxacyclic systems in recent years.[1] One of the most challenging aspects of the synthesis of these compounds is the stereocontrolled construction of substituted tetrahydrofuran and tetrahydropyran rings. Despite the emergence of a number of novel approaches to these structures[1,2] the development of new methodologies continues.

Recently[3] we have studied the stereocontrolled synthesis of such oxacyclic systems by acid catalyzed cyclization of hydroxy selenides and hydroxy sulfides.

β-Hydroxy selenides are interesting substrates that can be selectively transformed to a large variety of compounds including alcohols, allyl alcohols, olefins and epoxides.[4] Morever, when β-hydroxy selenides possess other hydroxyl groups they can be suitable starting materials for stereoselective synthesis of tetrahydrofurans and tetrahydropyrans.[3,5] The acid catalyzed cyclization of hydroxy-sulfides has been extensively studied by Warren's group.[2a,2g,6]

In this paper we report observations on the behaviour of hydroxy selenides and hydroxy sulfides such as **1** when treated with a catalytic amount of perchloric acid in dichloromethane at room temperature.

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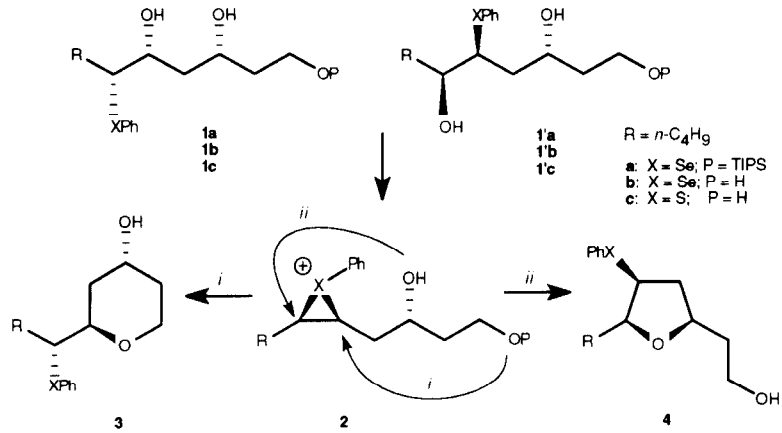
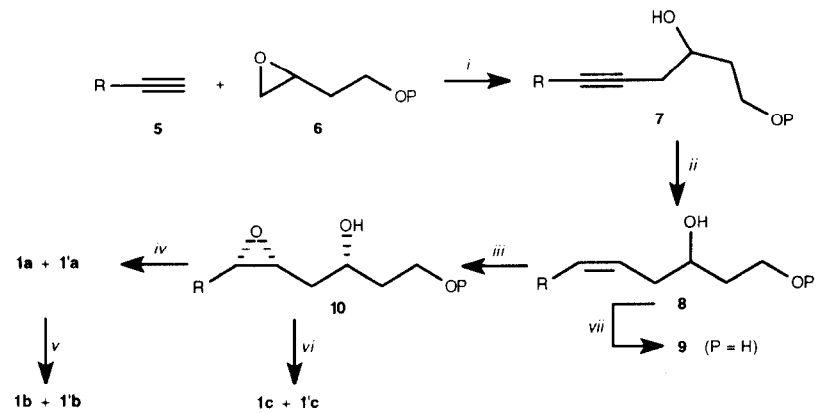
Two modes of cyclization are possible: *i*) stereoconvergent elimination of water to give **3** *via* the intermediate ion **2** (cyclization in the *exo* mode) (P = H); *ii*) stereoconvergent elimination of water to give **4** *via* **2** (cyclization in the *endo/exo*[6f] mode).



Scheme 1

Results and Discussion

In order to investigate this reaction we prepared the homoallylic alcohol (**8**) as outlined in Scheme 2. Epoxidation using *tert*-butyl hydroperoxide and $VO(acac)_2$ gave the *syn*-hydroxy-epoxide (**10**) with useful stereoselectivity (95 : 5) with the configuration of the major epoxide being assigned by analogy with the literature.[7] Ring opening with sodium phenyl selenide gave a mixture (6 : 4) of the hydroxy-selenides (**1a** and **1'a**). Deprotection of these hydroxy selenides gave the hydroxy selenides (**1b** and **1'b**). Similarly, by epoxide ring opening with sodium thiophenate and subsequent deprotection of the primary hydroxyl protecting group, we obtained the hydroxy sulfides (**1c** and **1'c**).



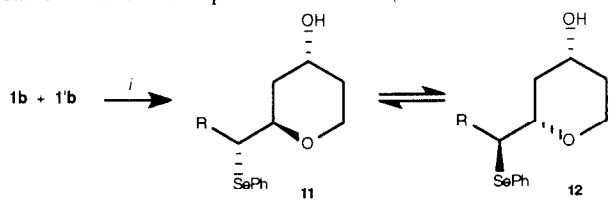
Reagents: *i*, BuLi, $BF_3.OEt_2$, THF, -78 °C, 76%; *ii*, H_2, Lindlar, EtOH, rt, 97%; *iii*, *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, rt, 80%; *iv*, $(PhSe)_2$, $NaBH_4$, EtOH, rt, 92%; *v*, TBAF, THF, 92%; *vi*, PhSNa, MeOH, rt, then TBAF, THF, 86%; *vii*, TBAF, THF, 89%.

Scheme 2

It is already known[3,5] that hydroxy selenides can be used as mixture of regioisomers avoiding their separation because, when they are treated with a catalytic amount of perchloric acid, in dichloromethane at room temperature, they give the same mixture of products. This implies the formation of the same intermediate, perhaps the seleniranium ion **2**. However, in order to confirm this behaviour also for the new substrates we separated, by column chromatography, hydroxy-selenides (**1a** and **1'a**; **1b** and **1'b**) and hydroxy sulfides (**1c** and **1'c**).

For all these three examples the same mixture of products was obtained both from the pure regioisomers and the mixture of regioisomers confirming that the reactions run *via* the intermediate seleniranium or thiiranium ion **2**.

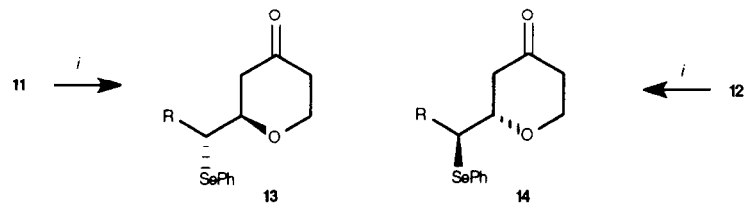
First we treated the hydroxy selenides (**1b** and **1'b**) with a catalytic amount of perchloric acid in dichloromethane at room temperature. Following the reaction by TLC we noticed that the starting material immediately disappeared giving two spots, the less polar being the major product. However, allowing the reaction to run for 110 min we noticed that the less polar spot became the minor product and the more polar spot the major one. These two products were separated by column chromatography. They were identified as the tetrahydropyran **11** (*i.e.* the product under kinetic control) in 22% yield and the tetrahydropyran **12** (*i.e.* the product under thermodynamic control) in 67% yield. The formation of these compounds was found to be reversible under the reaction conditions. As a matter of fact, resubjecting the tetrahydropyran **11** or the tetrahydropyran **12** to reaction conditions we found the same mixture of compounds **11** and **12** (25/75 as determined by ^{1}H-NMR).



Reagents: *i*, $HClO_4$, CH_2Cl_2, rt.

Scheme 3

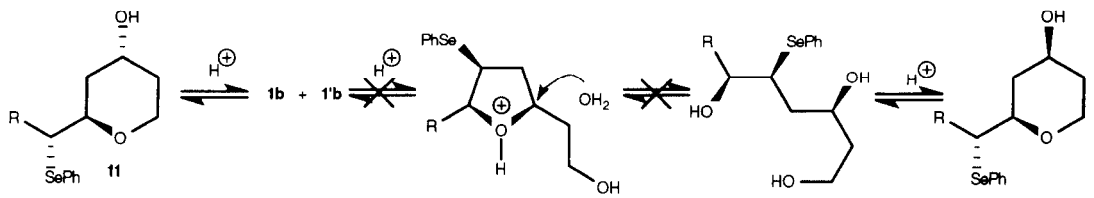
The structure of these compounds was proven by the usual spectroscopic and analytical techniques. The ^{1}H-NMR COSY spectrum of compound **11** in DMSO clearly showed the doublet for the OH proton that couples with the H-4 proton at 4.70 ppm. Finally the HETCOR and DEPT spectra indicated that the C-4 carbon atom was a secondary carbon. This observation, together with the exocyclic position of the phenylselanyl group, as deduced from COSY and HETCOR spectra, excluded the tetrahydrofuranic structure (**4**). The very narrow multiplet of the H-4 in the ^{1}H-NMR spectrum accounted for the axial position of the 4-hydroxyl group in compound **11**. Also for compound **12** the ^{1}H-NMR COSY spectrum in DMSO showed a doublet for the OH proton at 4.83 ppm that coupled with the H-4 proton at 3.65 ppm. Also in this case the HETCOR and DEPT spectra indicated that the C-4 carbon atom was a secondary carbon. The very broad multiplet of the H-4 in the ^{1}H-NMR spectrum accounted for the equatorial position of the 4-hydroxyl group in compound **12**. The tetrahydropyran structure was also confirmed by spectroscopic and analytical data of the ketone obtained by PCC oxidation of compounds **11** and **12**. Both tetrahydropyrans (**11** and **12**) gave by oxidation the same ketone as resulted by analysis of spectroscopic data (IR, ^{1}H- and ^{13}C-NMR). This result indicates that compounds **11** and **12** either differ in the configuration of the C-4 (*i.e.* the ketones are identical) or differ in the configuration of the C-2 and C-1' (*i.e.* the ketones are enantiomers). Because we performed the reactions using racemic mixtures it is not possible, at this stage, to discern between the former and the latter hypothesis.



Reagents: *i*, PCC, CH_2Cl_2, rt.

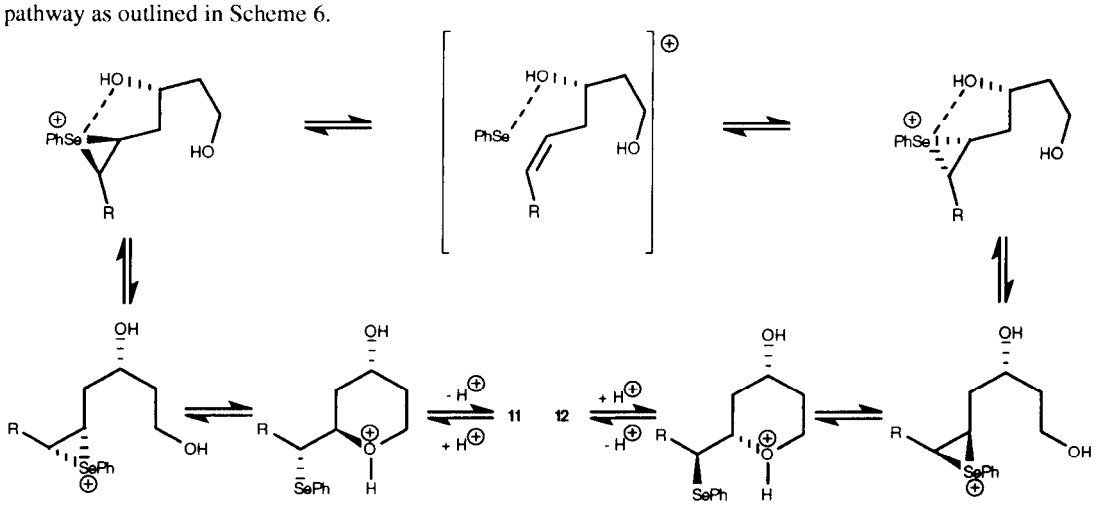
Scheme 4

Nonetheless, we strongly believe the latter hypothesis to be correct. Indeed, if compounds **11** and **12** differ only in the configuration at C-4 we could deduce that the equilibration process involves the configuration inversion of C-4 and in our opinion this could happen only in the way depicted in Scheme 5. This mechanism involves an attack of a molecule of water to the protonated tetrahydrofuran ring formed by *endo* cyclization of hydroxy selenides (**1b** and **1'b**). However, this mechanism should be rejected both because the tetrahydrofuran ring was found to be stable under the reaction conditions and because the tetrahydrofuran derivative was not detected in the cyclization reaction of compounds **1b** and **1'b** (*vide infra*).



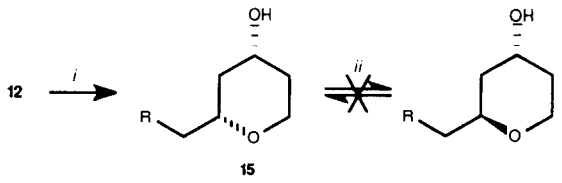
Scheme 5

It is already known[8] that two diastereomeric seleniranium ions may be in equilibrium through the alkene. Moreover the presence of at least one hydroxyl group in a suitable position is able to stabilize the selenium electrophile and/or the seleniranium ion.[8] In the light of these considerations, we propose an equilibration pathway as outlined in Scheme 6.



Scheme 6

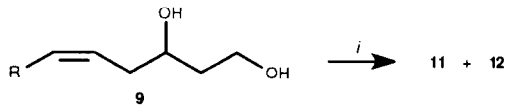
In order to demonstrate the role that the selenium atom plays in the above equilibrium, we removed the phenylselanyl group by reduction with tributyltin hydride. The tetrahydropyran (**15**) was found to be stable under the reaction conditions.



Reagents: *i*, Bu_3SnH, AIBN, C_6H_6, reflux, 92%; *ii*, $HClO_4$, CH_2Cl_2, rt.

Scheme 7

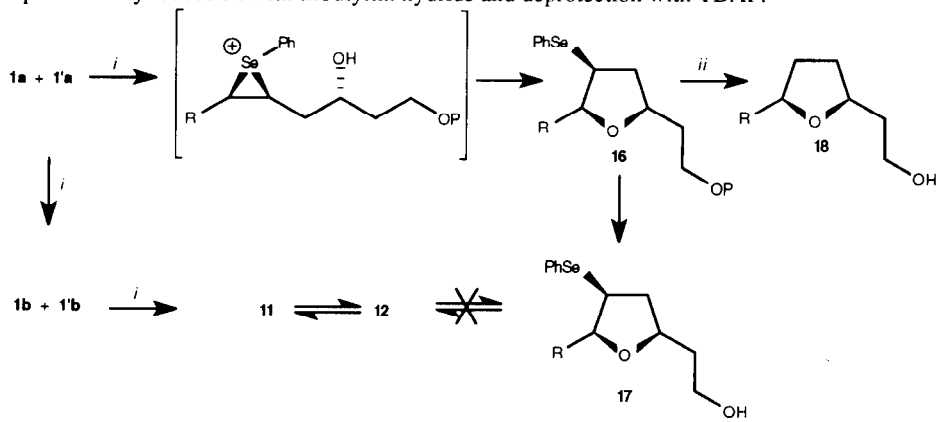
Finally, in order to gain more insight on the above mechanism, we performed the rection between the alkene (**9**) and N-phenylselenophthalimide (NPSP) as carrier of the electrophilic phenylseleno species ($PhSe^+$).[9] The reaction gave compounds **11** and **12** in 62% and 37% yield respectively. Since the reaction was not performed under the thermodynamic control conditions (cat. $HClO_4$), we found, as major product, the compound under kinetic control **11**.



Reagents: *i*, NPSP, camphorsulfonic acid (cat.), CH_2Cl_2, 0°C then rt.

Scheme 8

The hydroxy-selenides (**1a** and **1'a**) were treated with a catalytic amount of perchloric acid in dichloromethane at room temperature. The reaction was first quenched after 6 min. Besides starting material, we found the tetrahydrofuran (**16**), traces of its deprotected analogue **17** and a small amount of the *cis*-alkene (**8**).[10] The tetrahydrofuranic structure was also confirmed by analysis of spectroscopical data of compound **18** obtained from compound **16** by reduction with tributyltin hydride and deprotection with TBAF.



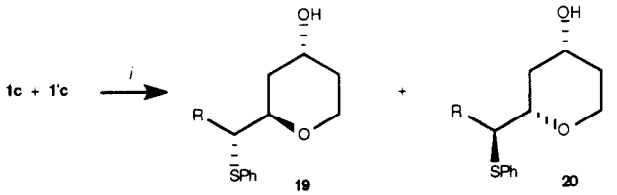
Reagents: *i*, $HClO_4$, CH_2Cl_2, rt; *ii*, Bu_3SnH, AIBN, C_6H_6, reflux then TBAF, THF, 75%.

Scheme 9

Repeating the reaction and quenching it after 30 min did not produce the protected tetrahydrofuran (**16**) but the deprotected one (58%) and small amounts of tetrahydropyrans (**11** and **12**). This implies that the *endo/exo* attack takes place faster than the cleavage of the labile protecting group and the subsequent *exo* attack that should lead to

the tetrahydropyran ring. Moreover the tetrahydrofuran was found to be stable under the reaction conditions. This means that the tetrahydropyrans are not formed from the tetrahydrofuran (**17**), but from the cyclization of the deprotected hydroxy selenides (**1b** and **1'b**) formed in the acid solution. Since tetrahydrofuran (**17**) was not detected in the cyclization reaction of the deprotected hydroxy selenides (**1b** and **1'b**) and bearing in mind the stability of compound **17**, we can argue that the cyclization of hydroxy selenides (**1b** and **1'b**) takes place only in the *exo* mode. This result again confirms that the mechanism showed in Scheme 5 does not take place.

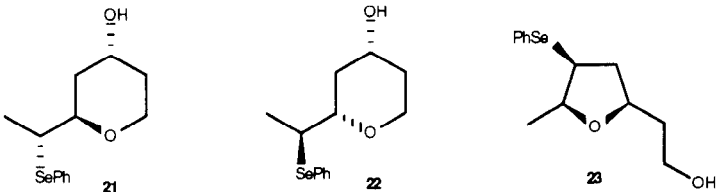
Hydroxy sulfides (**1c** and **1'c**) were allowed to react in dichloromethane with a catalytic amount of perchloric acid. Also in this case no tetrahydrofuran ring was formed and the reaction took place exclusively in the *exo* mode giving a mixture (92/8) of the tetrahydropyrans (**19** and **20**). However, in contrast to compounds **11** and **12**, the formation of compounds **19** and **20** was found to be irreversible under the reaction conditions. In this way the major product appears to be the tetrahydropyran **19** (*i.e.*, the product under kinetic control, as for **11**). Because the reversibility of the reaction is mechanistically related to a back-attack of the Se or S exocyclic atom over the C2 atom of the protonated tetrahydropyran ring (see Scheme 6), the lack of reversibility for compounds **19** and **20** may be easily related to the reduced nucleophilicity of the S atom with respect to the Se atom.[11]



Reagents: *i*, $HClO_4$, CH_2Cl_2, rt 99%.

Scheme 10

Further insight on the reaction mechanism was achieved by performing quantum-mechanical calculations at both semiempirical (AM1[12], PM3[13]) and *ab initio* (HF/3-21G*) levels of theory on the model molecules **21**, **22** and **23** (simplified analogues of **11**, **12** and **17**, where a methyl group replaces the butyl group). In general semiempirical calculations take great advantage from the short CPU time needed, with respect to the complexity of the system examined, for their performance. Nonetheless owing to the presence of the heavy and polarizable Se atom, *ab initio* methods should be of choice for the study of such systems.[14]



Scheme 11

A careful preliminary conformational analysis was performed for the three models by means of the AM1 method. For **21** and **22** several chair-like and boat-like conformations were considered, but in both cases the chair-like conformation bearing the bulky MeCHSePh group in an equatorial position was found as the most stable (Fig. **a**, **b**), as reasonably expected. In **23** the ring is quite rigid, but the hydroxylated branch prefers a folded conformation allowing an intramolecular hydrogen-bond (Fig. **c**). These conformations were further optimized with PM3[15] and 3-21G*.[16] Data are reported in the Table and show clearly that the three systems have similar

energies, thus if their formation were thermodynamically controlled, they should all be found in comparable amounts in the reaction mixture, in contrast with the experimental finding of the lack of formation of the tetrahydrofuran ring. Noticeably the energy difference between **21** and **22** is in fair agreement with the product distribution found.

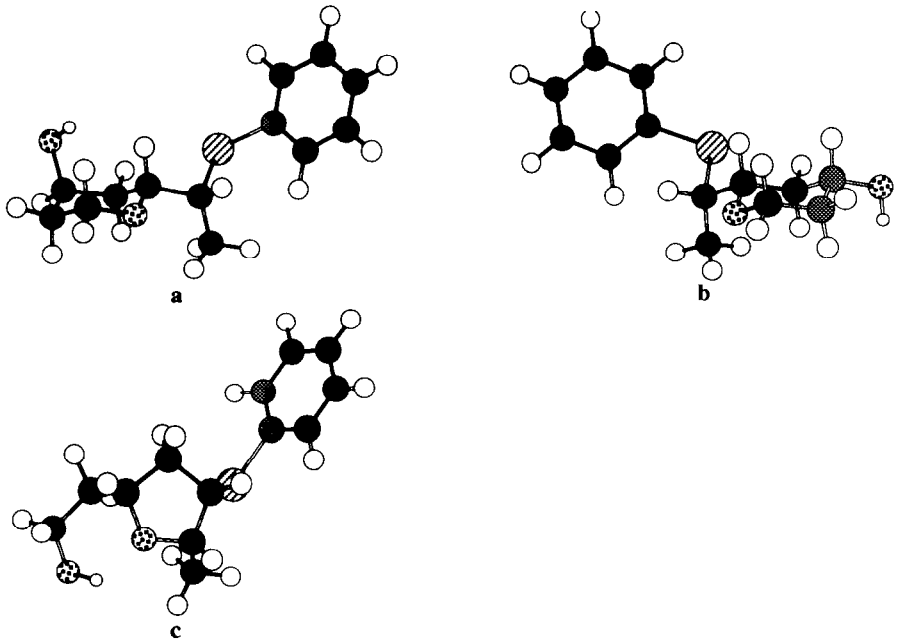


Figure - Projections of the lowest energy conformation for model molecules **21** (**a**), **22** (**b**) and **23** (**c**).

Table. Calculated energies for model molecules **21**, **22** and **23**.

Model	AM1 ΔHf (kcal/mol) [a]	PM3 ΔHf (kcal/mol) [a]	3-21G* Ef (Hartree) [b]
21	-74.69	-96.09	-3037.5600619
22	-75.31	-96.33	-3037.5619513
23	-74.38	-97.68	-3037.5610201

[a] from the elements at 298 K; [b] absolute energy at 0 K.

Conclusion

In conclusion we have demonstrated the behaviour of some hydroxy selenides and sulfides **1** in acid solution. When the primary hydroxyl group is protected the cyclization easily proceeds in the *endo* mode. However, when the primary hydroxyl group is deprotected the cyclization takes place only in the *exo* mode giving initially the (±)(2R*,4R*,1'R*)-tetrahydropyran (**11**) (*i.e.* the product under kinetic control) that assumes a 2-equatorial-4-axial conformation as confirmed by quantum-mechanical calculations, then, predominantly (25/75), the (±)(2S*,4R*,1'S*)-tetrahydropyran (**12**) (*i.e.* the product under thermodynamic control) that assumes a 2,4-

diequatorial conformation as confirmed by quantum-mechanical calculations. Whereas the formation of compounds **11** and **12** was found to be reversible, the corresponding sulfur derivatives **19** and **20** were found to be stable in the reaction conditions giving predominantly the kinetic product. These results allow us to broaden the knowledge about the behaviour of the hydroxy selenides and hydroxy sulfides and are useful for the stereoselective synthesis of oxygenated heterocyclic compounds.

Experimental Section

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-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. AM1 and PM3 calculations were performed with the MOPAC93 program available from the CS Chem3D Pro™ package version 3.5 for MacIntosh distribuited by Cambridge Soft Corporation. *Ab initio* calculations were performed with the GAUSSIAN98 program distribuited by Gaussian Inc.[17]

(±)(3R*)-1-(Triisopropylsilyloxy)dec-5-yn-3-ol (7).

Butyllithium (1.60 M in hexane; 20.6 mL, 33 mmol) was added dropwise to a solution of 1-hexyne (3.70 mL, 33 mmol) in anhydrous tetrahydrofuran (70 mL) at -78 °C. After 20 min, BF_3-Et_2O (2.71 mL, 22 mmol) was added followed, after 5 min, by a solution of the epoxide (**6**) (5.5 g, 22 mmol) in anhydrous tetrahydrofuran (12 mL). After 4 h at -78 °C, sat aq $NaHCO_3$ (22 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 30/1-10/1) gave the *title compound* **7** (5.49 g, 76%) as an oil; [Found: C, 69.60; H, 11.75. $C_{19}H_{38}O_2Si$ requires C, 69.88; H, 11.73%]; ν_{max}(liquid film) 3420, 1455, 1095, 885 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.90 (t, 3H, *J* 6.7 Hz), 1.06 (d, 18H, *J* 4.3 Hz, overlapped with 3H), 1.31-1.52 (m, 4H), 1.71-1.89 (m, 2H), 2.12-2.18 (m, 2H), 2.34-2.40 (m, 2H), 3.58 (s br, 1H), 3.86-4.04 (m, 3H); δ_C (63 MHz, $CDCl_3$) 11.7, 13.6, 17.9, 18.4, 21.9, 27.4, 31.1, 37.4, 62.8, 70.8, 76.4, 82.4.

(±)(Z, 3R*)-1-(Triisopropylsilyloxy)dec-5-en-3-ol (8).

A suspension of Lindlar catalyst (300 mg) in a solution of the alkyne (**7**) (3.00 g, 9.18 mmol) in ethanol (45 mL) was stirred vigorously under hydrogen for 105 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 10/1) gave the *title compound* **8** (2.92 g, 97%) as an oil; [Found: C, 69.68; H, 12.20. $C_{19}H_{40}O_2Si$ requires C, 69.45; H, 12.27%]; ν_{max}(liquid film) 3430, 1460, 1090, 880 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.87 (t, 3H, *J* 6.8 Hz), 1.06 (d, 18H, *J* 4.5 Hz, overlapped with 3H), 1.27-1.33 (m, 4H), 1.62-1.70 (m, 2H), 2.00-2.05 (m, 2H), 2.17-2.28 (m, 2H), 3.54 (s, 1H), 3.82-4.00 (m, 3H), 5.38-5.47 (m, 2H); δ_C (63 MHz, $CDCl_3$) 11.7, 14.0, 17.9, 22.3, 27.2, 31.8, 35.3, 37.7, 63.3, 72.2, 125.3, 132.4.

(±)(3R*, 5S*, 6R*)-5,6-Epoxy-1-(triisopropylsilyloxy)decan-3-ol (10).

To a solution of **8** (2.85 g, 8.76 mmol) in anhydrous dichloromethane (80 mL) at 0 °C, $VO(acac)_2$ (36 mg, 0.13 mmol) was added, then *tert*-butyl hydroperoxide (5.5 M in decane; 2.40 mL, 13.2 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 sat aq 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-Et_2O 5/1) gave the *title compound* **10** (2.43 g, 80%) as an oil; [Found: C, 66.30; H, 11.65. $C_{19}H_{40}O_3Si$ requires C, 66.22; H, 11.70%]; ν_{max}(liquid film) 3480, 1460, 1100, 890 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.91 (t, 3H, *J* 7.1 Hz), 1.07 (d, 18H, *J* 4.4 Hz, overlapped with 3H), 1.35-1.52 (m, 6H), 1.63-1.85 (m, 4H), 2.88-2.96 (m, 1H), 3.10-3.17 (m, 1H), 3.75 (d, 1H, *J* 1.6 Hz), 3.82-4.05 (m, 2H), 4.08-4.16 (m, 1H); δ_C (63 MHz, $CDCl_3$) 11.7, 13.9, 17.9, 22.5, 27.6, 28.6, 35.2, 38.2, 54.3, 56.4, 63.0, 70.6.

Preparation of the Hydroxy Selenides (1a and 1'a).

Diphenyl diselenide (1.21 g, 3.88 mmol) was dissolved in absolute ethanol (6 mL), sodium borohydride (402 mg, 10.62 mmol) was added in batches and the mixture was stirred until the bright yellow solution turned colorless. Compound **10** (2.38 g, 6.91 mmol) was dissolved in absolute ethanol (6 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-Et_2O 5/1 then 1/1) gave the *title compounds* (**1a** and **1'a**) (3.20 g, 92%). A portion of this mixture was separated by flash chromatography (light petroleum-ethyl acetate 9/1-4/1).

Less polar regioisomer of the mixture **1a** and **1'a**: pale yellow oil; [Found: C, 59.48; H, 9.11. $C_{25}H_{46}O_3SeSi$ requires C, 59.85; H, 9.24%]; ν_{max}(liquid film) 3400, 1575, 1455, 1095, 880 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.89 (t, 3H, *J* 7.2 Hz), 1.04 (d, 18H, *J* 4.3 Hz, overlapped with 3H), 1.25-1.81 (m, 10H), 3.10-3.20 (m, 1H), 3.90-4.10 (m, 4H), 4.20 (s br, 2H), 7.23-7.28 (m, 3H), 7.54-7.58 (m, 2H); δ_C (63 MHz, $CDCl_3$) 11.7, 14.0, 17.9, 22.5, 30.6, 31.4, 38.7, 40.4, 54.4, 63.0, 73.0, 74.1, 127.1, 129.0, 129.8, 134.1.

More polar regioisomer of the mixture **1a** and **1'a**: pale yellow oil; [Found: C, 59.38; H, 9.13. $C_{25}H_{46}O_3SeSi$ requires C, 59.85; H, 9.24%]; ν_{max}(liquid film) 3380, 1575, 1455, 1090, 880 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.84 (t, 3H, *J* 7.3 Hz), 1.08 (d, 18H, *J* 4.2 Hz, overlapped with 3H), 1.16-2.00 (m, 10H), 3.00 (s br, 2H), 3.50-3.65 (m, 2H), 3.88-4.04 (m, 2H), 4.22.4.30 (m, 1H), 7.23-7.27 (m, 3H), 7.59-7.63 (m, 2H); δ_C (63 MHz, $CDCl_3$) 11.7, 14.0, 17.9, 22.6, 28.3, 34.4, 38.7, 40.5, 52.2, 63.3, 71.0, 74.2, 127.3, 129.0, 129.5, 134.4.

Deprotection of the Hydroxy Selenides (1a and 1'a).

A solution of tetrabutylammonium fluoride (2.20 g, 6.98 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise to a solution of the silyl ethers (**1a** and **1'a**) (1.75 g, 3.49 mmol) in tetrahydrofuran (10 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 compounds* **1b** and **1'b** (1.10 g, 92%) as oils. A portion of this mixture was carefully separated by chromatography using ethyl acetate as eluent.

Less polar regioisomer of the mixture **1b** and **1'b**: colourless oil; [Found: C, 55.38; H, 7.67. $C_{16}H_{26}O_3Se$ requires C, 55.65; H, 7.59%]; ν_{max}(liquid film) 3350, 1577, 1477, 1437, 1056, 738 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 0.86 (t, 3H, *J* 7.0 Hz), 1.26-1.92 (m, 10H), 3.20-3.30 (m, 1H), 3.45-3.62 (m, 2H), 3.70-3.80 (m,

1H), 3.85-3.97 (m, 1H), 4.38 (t, 1H, *J* 5.0 Hz, OH), 4.56 (d, 1H, *J* 4.8 Hz, OH), 5.03 (d, 1H, *J* 3.5 Hz, OH), 7.30-7.35 (m, 3H), 7.53-7.58 (m, 2H); δ_C (63 MHz, $CDCl_3$) 13.9, 22.4, 30.3, 31.1, 38.7, 40.3, 55.7, 61.1, 72.3, 74.2, 127.5, 129.1, 129.5, 134.7.

More polar regioisomer of the mixture **1b** and **1'b**: mp 64-5° C, white crystals; [Found: C, 55.42; H, 7.65. $C_{16}H_{26}O_3Se$ requires C, 55.65; H, 7.59%]; ν_{max}(Nujol) 3350, 1575, 1460, 1437, 1056, 738 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 0.86 (t, 3H, *J* 7.2 Hz), 1.12-1.71 (m, 9H), 1.80-1.95 (m, 1H), 3.51-3.60 (m, 4H), 3.91-3.98 (m, 1H), 4.41 (t, 1H, *J* 4.9 Hz, OH), 4.51 (d, 1H, *J* 5.9 Hz, OH), 4.87 (d, 1H, *J* 4.9 Hz, OH), 7.27-7.36 (m, 3H), 7.59-7.63 (m, 2H); δ_C (63 MHz, $CDCl_3$) 13.9, 22.5, 28.3, 33.4, 38.9, 39.6, 51.0, 61.0, 70.1, 74.0, 127.5, 129.1, 129.3, 134.3.

Procedure for the Cyclization of Hydroxy Selenides (1b and 1'b):

(±)(2R*, 4R*, 1'R*)-2-[(1'-Phenylselanyl)-pentyl]-tetrahydropyran-4-ol (11).
(±)(2S*, 4R*, 1'S*)-2-[(1'-Phenylselanyl)-pentyl]-tetrahydropyran-4-ol (12).

To a solution of hydroxy selenides (**1b** and **1'b**) (360 mg, 1.02 mmol) in anhydrous dichloromethane (51 mL) at room temperature were added three drops (15 μL) of $HClO_4$ (70%). The reaction mixture was vigorously stirred for 110 min then quenched with sat aq $NaHCO_3$ 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, then 4/1) gave the *title compound* **11** (72 mg, 22%) as an oil and the *title compound* **12** (223 mg, 67%) as white crystals.

Compound **11**, [Found: C, 58.44; H, 7.55. $C_{16}H_{24}O_2Se$ requires C, 58.71; H, 7.39%]; ν_{max}(liquid film) 3410, 1575, 1470, 1460, 1430, 1250, 1070, 740 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.85 (t, 3H, *J* 7.2 Hz), 1.20-1.95 (m, 9H), 2.01 (ddd, 1H, *J* 11.7, 11.0 and 2.7 Hz), 3.05-3.11 (m, 1H, 1'-H), 3.77-3.96 (m, 3H, 2-H and 6-H_2), 4.27-4.30 (m, 1H, 4-H), 7.23-7.30 (m, 3H), 7.53-7.57 (m, 2H); δ_H (250 MHz, DMSO-d_6) 0.85 (t, 3H, *J* 7.2 Hz), 1.20-1.30 (m, 2H), 1.37-1.52 (m, 3H), 1.62-1.70 (m, 3H), 1.75- 1.92 (m, 2H), 3.15-3.24 (m, 1H), 3.68-3.93 (m, 3H), 4.10-4.13 (m, 1H), 4.70 (d, *J* 3.6 Hz), 7.30-7.37 (m, 3H), 7.52-7.58 (m, 2H); δ_C (63 MHz, $CDCl_3$) 13.9, 22.4, 30.2, 32.5, 32.7, 36.4, 51.9, 62.7, 64.1, 73.5, 126.9, 128.9, 130.6, 133.9.

Compound **12**, mp 50-1 °C; [Found: C, 58.55; H, 7.46. $C_{16}H_{24}O_2Se$ requires C, 58.71; H, 7.39%]; ν_{max}(Nujol) 3240, 1578, 1460, 1375, 1080, 730 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.87 (t, 3H, *J* 7.1 Hz), 1.24-1.69 (m, 8H), 1.81-1.91 (m, 2H), 2.09 (ddd, 1H, *J* 12.1, 2.3 and 2.3 Hz), 3.12-3.19 (m, 1H, 1'H), 3.34 (ddd, *J* 11.0, 2.1 and 2.1 Hz, 6-H), 3.39-3.46 (m, 1H, 2-H), 3.74-3.86 (m, 1H, 4-H), 4.04 (ddd, *J* 11, 4.6 and 1.2 Hz, 6-H'), 7.24-7.28 (m, 3H), 7.53-7.58 (m, 2H); δ_H (250 MHz, DMSO-d_6) 0.85 (t, 3H, *J* 7.3 Hz), 1.20-1.93 (m, 10H), 3.23-3.48 (m, 3H), 3.60-3.75 (m, 1H), 3.91 (ddd, *J* 11.4, 4.9 and 2.8 Hz), 4.83 (d, 1H, *J* 4.6 Hz, OH), 7.30-7.37 (m, 3H), 7.54-7.58 (m, 2H); δ_C (63 MHz, $CDCl_3$) 14.0, 22.5, 30.3, 32.0, 35.6, 38.5, 51.1, 66.1, 68.3, 78.3, 127.1, 128.9, 130.3, 134.1.

(±)(2S*, 3S*, 5R*)-2-Butyl-5-triisopropylsilyloxyethyl-3-phenylselanyl-tetrahydrofuran (16).

A solution of hydroxy selenides (**1a** and **1'a**) (290 mg, 0.58 mmol) in anhydrous dichloromethane (25 mL) containing *ca.* 7μL of $HClO_4$ (70%) was vigorously stirred for 6 min at room temperature then quenched with sat aq $NaHCO_3$ 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 then light petroleum-ethyl acetate 7/1, then 4/1) gave the *title compound* **16** (62 mg, 22%) as an oil, hydroxy selenides (**1a** and **1'a**) (174 mg, 60%), alkene (**8**) (13 mg, 6%) and other minor unidentified products.

Compound **16**, colourless oil; [Found: C, 62.30; H, 9.30. $C_{25}H_{44}O_2SeSi$ requires C, 62.08; H, 9.17%]; ν_{max}(liquid film) 1575, 1470, 1460, 1430, 1095, 880 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.89 (t, 3H, *J* 7.0 Hz), 1.06 (d, 18H, *J* 4.1 Hz, overlapped with 3H), 1.27-1.49 (m, 4H), 1.62-1.99 (m, 5H), 2.51-2.62 (m, 1H), 3.76-4.06 (m, 5H), 7.24-7.30 (m, 3H), 7.53-7.57 (m, 2H); δ_C (63 MHz, $CDCl_3$) 11.9, 14.0, 18.0, 22.7, 28.8, 33.3, 39.6, 40.4, 46.0, 60.7, 75.5, 81.4, 127.0, 129.0, 130.4, 133.5.

(±)(2S*, 3S*, 5R*)-2-Butyl-5-hydroxyethyl-3-phenylselanyl-tetrahydrofuran (17).

To a solution of hydroxy selenides (**1a** and **1'a**) (590 mg, 1.18 mmol) in anhydrous dichloromethane (55 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 sat aq $NaHCO_3$ 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 then light petroleum-ethyl acetate 7/1, then 4/1) gave compound **11** (36 mg, 9%) and a mixture (260 mg) of compounds **17** and **12** (58% and 8% respectively as determined by ^{1}H-NMR) as oils. A small amount of the *title compound* **17** was separated after repeated column chromatography.

Compound **17**: colourless oil; [Found: C, 58.54; H, 7.49. $C_{16}H_{24}O_2Se$ requires C, 58.71; H, 7.39%]; ν_{max}(liquid film) 3400, 1580, 1477, 1465, 1437, 1064, 737 692 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.89 (t, 3H, *J* 6.8 Hz), 1.20-1.48 (m, 5H), 1.60-1.70 (m, 2H), 1.71-1.99 (m, 2H), 2.56 (ddd, *J* 13.5, 13.5 and 7.3 Hz, 1H), 2.78 (br s, 1H), 3.77-4.10 (m, 5H), 7.24-7.30 (m, 3H), 7.52-7.57 (m, 2H); δ_C (63 MHz, $CDCl_3$) 14.0, 22.6, 28.8, 33.3, 37.9, 40.4, 45.4, 61.4, 78.1, 82.2, 127.2, 129.1, 130.1, 133.7.

(±)(2S*, 5S*)-2-Butyl-5-hydroxyethyl-tetrahydrofuran (18).

A solution of compound **16** (60 mg, 0.12 mmol) dissolved in anhydrous benzene (2 mL) was degassed for 15 min with argon, then tributyltin hydride (64 μL, 0.24 mmol) and 2,2'-azobisisobutyronitrile (cat.) were added and the mixture heated under reflux for 1 h before being cooled and concentrated under reduced pressure. The residue was chromatographed with light petroleum-Et_2O (10/1 plus 1% triethylamine) to give the reduced tetrahydrofuran as an oil (34 mg, 83%). A solution of tetrabutylammonium fluoride (44 mg, 0.14 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise to a solution of the latter silyl ether (34 mg, 0.07 mmol) in tetrahydrofuran (2 mL) at 0 °C, and the mixture allowed to warm to room temperature and stirred for 20 h. The solvent was evaporated *in vacuo*. Purification of the crude product by flash chromatography (light petroleum-ethyl acetate 4/1) gave the *title compound* **18** (11 mg, 91%) as an oil. [Found: C, 69.50; H, 11.59. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70%]; ν_{max}(liquid film) 3400, 1465, 1058 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 0.90 (t, 3H, *J* 6.9 Hz), 1.23-1.71 (m, 10H), 1.89-1.99 (m, 2H), 3.45-3.52 (m, 2H), 3.68-3.72 (m, 1H), 3.79-3.84 (m, 1H), 4.37 (t, *J* 5.2 Hz, 1H, OH). δ_C (63 MHz, DMSO-d_6) 14.1, 22.4, 28.1, 30.8, 30.9, 35.6, 39.3, 58.4, 75.9, 78.5.

(±)(2R*, 1'R*)-2-[(1'-Phenylselanyl)-pentyl]-tetrahydropyran-4-one (13).

(±)(2S*, 1'S*)-2-[(1'-Phenylselanyl)-pentyl]-tetrahydropyran-4-one (14).

To a solution of compound **11** or **12** (72 mg, 0.22 mmol) in anhydrous dichloromethane (5 mL) pyridinium chlorochromate (95 mg, 0.44 mmol) was added under argon. The suspension was stirred for 60 min then filtered through Celite and the filtrate evaporated *in vacuo*. Purification of the crude product by flash chromatography (light petroleum-ethyl acetate 5/1) gave the *title compound* **13** or **14** (43 mg, 60%) as an oil. [Found: C, 59.38; H, 6.72. $C_{16}H_{22}O_2Se$ requires C, 59.07; H, 6.82%]; ν_{max}(liquid film) 1720, 1577, 1254, 740 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.88 (t, 3H, *J* 7.3 Hz), 1.23-1.61 (m, 4H), 1.74-1.93 (m, 2H), 2.29-2.35 (m, 1H, 5-H), 2.45 (dd, 1H, *J* 14.3 and 2.1 Hz, 3-H), 2.63 (m, 1H, 5-H'), 2.92 (dd, 1H, *J* 14.3 and 11.8

Hz, 3-H'), 3.06-3.13 (m, 1H, 1'-H), 3.61 (ddd, 1H, *J* 12.2, 2.6 and 2.6 Hz, 6-H), 3.73 (ddd, 1H, *J* 11.3, 2.7 and 2.7 Hz, 2-H), 4.32 (ddd, 1H, *J* 12.2, 7.5 and 7.2 Hz, 6-H'), 7.25-7.30 (m, 3H), 7.54-7.58 (m, 2H); δ_C (63 MHz, $CDCl_3$) 13.9, 22.4, 30.3, 32.7, 42.1, 46.5, 51.9, 66.5, 79.8, 127.4, 129.1, 130.0, 134.2, 207.0.

(±)(2R*, 4R*)-2-(Pentyl)-tetrahydropyran-4-ol (15).

A solution of compound **12** (74 mg, 0.23 mmol) dissolved in anhydrous benzene (3 mL) was degassed for 15 min with argon, then tributyltin hydride (120 μL, 0.46 mmol) and 2,2'-azobisisobutyronitrile (cat.) were added and the mixture heated under reflux for 1 h before being cooled and evaporated *in vacuo*. Purification of the crude product by flash chromatography (light petroleum-ethyl acetate 4/1 plus 1% triethylamine) gave the *title compound* **15** (36 mg, 92%) as an oil. C, 69.80; H, 11.60. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70%]; ν_{max}(liquid film) 3360, 1464, 1377, 1363, 1251, 1085 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.87 (t, 3H, *J* 7.3 Hz), 1.10-1.56 (m, 10H), 1.83-1.97 (m, 2H), 2.03 (br s, 1H), 3.19-3.28 (m, 1H), 3.32-3.41 (m, 1H), 3.68-3.81 (m, 1H), 3.99 (dd, *J* 11.7 and 4.8 Hz, 1H); δ_C (63 MHz, $CDCl_3$) 14.0, 22.5, 25.1, 31.8, 35.7, 36.1, 41.5, 65.8, 68.1, 76.2.

(±)(Z, 3R*)-Dec-5-en-1,3-diol (9).

A solution of tetrabutylammonium fluoride (1.75 g, 5.56 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise to a solution of the alkene (**8**) (913 mg, 2.78 mmol) in tetrahydrofuran (10 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 5/1 then 3/1) gave the *title compound* **9** (427 g, 89%) as an oil. [Found: C, 69.64; H, 11.61. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70%]; ν_{max}(liquid film) 3332, 1460, 1058 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 0.90 (t, 3H, *J* 7.0 Hz), 1.27-1.40 (m, 4H), 1.42-1.63 (m, 2H), 2.01-2.10 (m, 2H), 2.13-2.18 (m, 2H), 3.50-3.67 (m, 3H), 4.39 (t, *J* 5.0 Hz, 1H), 4.49 (d, *J* 5.1 Hz, 1H), 5.39-5.47 (m, 2H); δ_C (63 MHz, DMSO-d_6) 14.0, 22.0, 26.8, 31.6, 35.7, 39.4, 58.5, 67.8, 126.8, 130.8.

Cyclization of alkene (9) with N-phenylselenophtalimide (NPSP)

To a solution of compound **9** (122 mg, 0.71 mmol) in anhydrous dichloromethane (7 mL) stirred under argon was added camphorsulfonic acid (15 mg, 0.065 mmol). The mixture was cooled at 0°C and after adding NPSP (250 mg, 0.83 mmol), it was allowed to reach room temperature over a period of 30 min then stirred for further 150 min. Direct flash chromatography of the mixture with light petroleum-ethyl acetate (5/1) gave compounds **11** (144 mg, 62%) and **12** (87 mg, 37%)

Preparation of the Hydroxy Sulfides (1c and 1'c).

To a solution of the epoxide (**10**) (962 mg, 2.79 mmol) in anhydrous methanol (1.8 mL) was added *via* cannula a solution of thiophenol/ sodium thiophenate (1/1, 2.79 mmol) in anhydrous methanol (1.8 mL). The reaction mixture was stirred for 24 h then concentrated under reduced pressure. Dichloromethane (20 mL) was added and extracted with water. The organic phase was washed with brine and dried (Na_2SO_4). Concentration under reduced pressure gave an oil which was used for the deprotection without purification. The residue was dissolved in anhydrous tetrahydrofuran (8 mL) and added *via* cannula to a solution of tetrabutylammonium fluoride (1.76 g, 5.58 mmol) in anhydrous tetrahydrofuran (10 mL) at 0 °C, and the mixture allowed to warm to room temperature and stirred for 20 h. The solution was concentrated under reduced pressure, then dissolved in

Et_2O 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 compounds* **1c** and **1'c** (714 mg, 86%). A portion of this mixture was carefully separated by chromatography using ethyl acetate as eluent.

Less polar regioisomer of the mixture **1c** and **1'c**: mp 70-1 °C, white crystals; [Found: C, 64.50; H, 8.58. $C_{16}H_{26}O_3S$ requires C, 64.39; H, 8.78%]; ν_{max}(Nujol) 3354, 1585, 1479, 1438, 1066, 746 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 0.89 (t, 3H, *J* 7.0 Hz), 1.30-1.93 (m, 10H), 3.17-3.26 (m, 1H), 3.49-3.57 (m, 2H), 3.71-3.81 (m, 1H), 3.85-3.97 (m, 1H), 4.36 (t, 1H, *J* 5.1 Hz, OH), 4.56 (d, 1H, *J* 4.6 Hz, OH), 4.98 (d, 1H, *J* 3.9 Hz, OH), 7.23-7.44 (m, 5H); δ_C (63 MHz, $CDCl_3$) 13.9, 22.5, 29.6, 30.0, 38.7, 39.4, 56.9, 61.2, 72.5, 74.0, 127.1, 129.0, 131.9, 134.7.

More polar regioisomer of the mixture **1c** and **1'c**: mp 48-50 °C, white crystals; [Found: C, 64.53; H, 8.62. $C_{16}H_{26}O_3S$ requires C, 64.39; H, 8.78%]; ν_{max}(Nujol) 3330, 1583, 1479, 1438, 1055, 744 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 0.85 (t, 3H, *J* 6.7 Hz), 1.15-1.62 (m, 9H), 1.76-1.87 (m, 1H), 3.53-3.58 (m, 4H), 3.90-4.04 (m, 1H), 4.41 (t, 1H, *J* 4.9 Hz, OH), 4.56 (d, 1H, *J* 5.9 Hz, OH), 4.83 (d, 1H, *J* 4.8 Hz, OH), 7.19-7.49 (m, 5H); δ_C (63 MHz, $CDCl_3$) 13.9, 22.5, 28.3, 32.2, 38.4, 39.0, 52.3, 60.7, 69.1, 73.5, 126.8, 128.9, 131.4, 135.2.

Cyclization of the Hydroxy Sulfides (1c and 1'c):
(±)(2R*, 4R*, 1'R*)-2-[(1'-Phenylsulfanyl)-pentyl]-tetrahydropyran-4-ol (19).
(±)(2S*, 4R*, 1'S*)-2-[(1'-Phenylsulfanyl)-pentyl]-tetrahydropyran-4-ol (20).

To a solution of hydroxy sulfides (**1c** and **1'c**) (385 mg, 1.29 mmol) in anhydrous dichloromethane (51 mL) at room temperature were added three drops of $HClO_4$ (70%). The reaction mixture was vigorously stirred for 80 min then quenched with sat aq $NaHCO_3$ and extracted with water. The aqueous phase was extracted with ethyl acetate and the combined organic phase were 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 compound* **19** (330 mg, 91%) as an oil and the *title compound* **20** (30 mg, 8%) as an oil.

Compound **19**, [Found: C, 68.45; H, 8.74. $C_{16}H_{24}O_2S$ requires C, 68.53; H, 8.63%]; ν_{max}(liquid film) 3420, 1583, 1479, 1466, 1438, 1068, 738 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.85 (t, 3H, *J* 7.1 Hz), 1.21-1.56 (m, 6H), 1.68-1.99 (m, 4H), 2.61 (br s 1H, OH), 3.00-3.08 (m, 1H), 3.77-3.96 (m, 3H), 4.18-4.21 (m, 1H), 7.11-7.26 (m, 3H), 7.35-7.38 (m, 2H); δ_C (63 MHz, $CDCl_3$) 13.7, 22.3, 29.4, 30.8, 32.4, 34.7, 53.4, 62.6, 63.5, 72.8, 126.0, 128.6, 130.5, 136.2.

Compound **20**, [Found: C, C, 68.40; H, 8.52. $C_{16}H_{24}O_2S$ requires C, 68.53; H, 8.63%]; ν_{max}(liquid film) 3390, 1583, 1479, 1466, 1438, 1080, 740 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.89 (t, 3H, *J* 7.2 Hz), 1.26-1.90 (m, 9H), 2.08-2.16 (m, 1H), 3.12-3.19 (m, 1H), 3.31-3.46 (m, 2H), 3.72-3.83 (m, 1H), 4.04 (ddd, 1H, *J* 11.6, 4.8 and 1.5 Hz), 7.19-7.31 (m, 3H), 7.36-7.44 (m, 2H); δ_C (63 MHz, $CDCl_3$) 14.0, 22.6, 29.7, 30.4, 35.6, 37.0, 53.1, 66.1, 68.4, 77.6, 126.4, 128.9, 131.0, 136.2.

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REFERENCES AND NOTES

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