Pergamon

Tetrahedron 55 (1999) 4769–4782

TETRAHEDRON

Regiochemical Control in the Synthesis of Tetrahydrofurans by Acid-Catalyzed Cyclization of Hydroxy Selenides and Hydroxy Sulfides

Michelangelo Gruttadauria,[a*] Paolo Lo Meo,[a] and Renato Noto [a, b]

[a] Dipartimento di Chimica Organica "E. Paternò", Viale delle Scienze, 90128 Palermo, Italy

[b] Istituto di Chimica e Tecnologia dei Prodotti Naturali - Consiglio Nazionale delle Ricerche (ICTPN - CNR) (associated with National Institute for the Chemistry of Biological Systems - CNR) via Ugo La Malfa 153, 90146 Palermo, Italy

Received 19 November 1998; revised 19 January 1999; accepted 11 February 1999

Abstract: An efficient regiochemical control in the synthesis of tetrahydrofurans was achieved by acid-catalyzed cyclization of hydroxy-selenides (**10a**) and (**11a**) which cyclize in the *endo/exo* mode and by hydroxy-sulfides (**10c**) and (**11c**) which cyclize in the *exo* mode. By cyclization of the relevant hydroxy-selenides, the C15-C20 fragment of (+)-Rolliniastatin 1 was obtained. Semiempirical calculations (PM3) were used in rationalizing experimental results.

Introduction

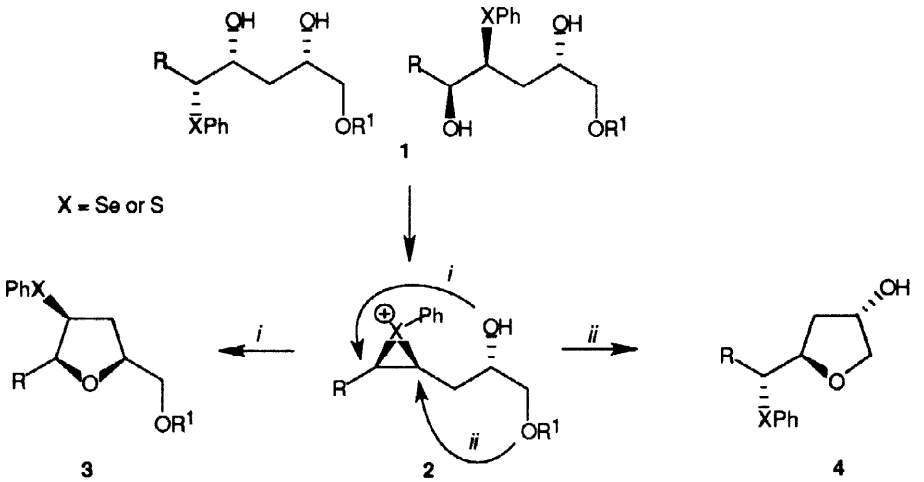
Considerable effort has been devoted to the stereoselective synthesis of tetrahydrofuran derivatives.[1] Part of the reason for this originates from the interest in biologically active naturally occurring compounds which contain one or more substituted tetrahydrofurans. In fact a particularly challenging aspect of the synthesis of polyether antibiotics[1], and more recently of the Annonaceous acetogenins[2], is the stereocontrolled synthesis of substituted tetrahydrofurans. Despite the emergence of a number of novel approaches to these structures[1,3] the development of new methodologies continues.

We were interested in exploring the possibility of constructing such tetrahydrofurans by cyclization of hydroxy-selenides[4] or hydroxy-sulfides.[3f] By acid-catalyzed cyclization of hydroxy-selenides, obtained by epoxidation of homoallylic alcohols and subsequent epoxide ring opening with sodium phenyl selenide, we realized[5] the stereoselective synthesis of the tetrahydrofuran containing fragment of (-)-nonactic acid and the pamamycins. In comparison with the hydroxy-selenides that were less investigated, the acid catalyzed cyclization of hydroxy-sulfides have been extensively studied by Warren's group.[3f,6]

Now we are interested in the behavior towards acids of the hydroxy-selenides and hydroxy-sulfides as **1** where R^1 is a protecting group labile in the reaction conditions in order to study the regiochemical outcome of the cyclization.

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00149-0

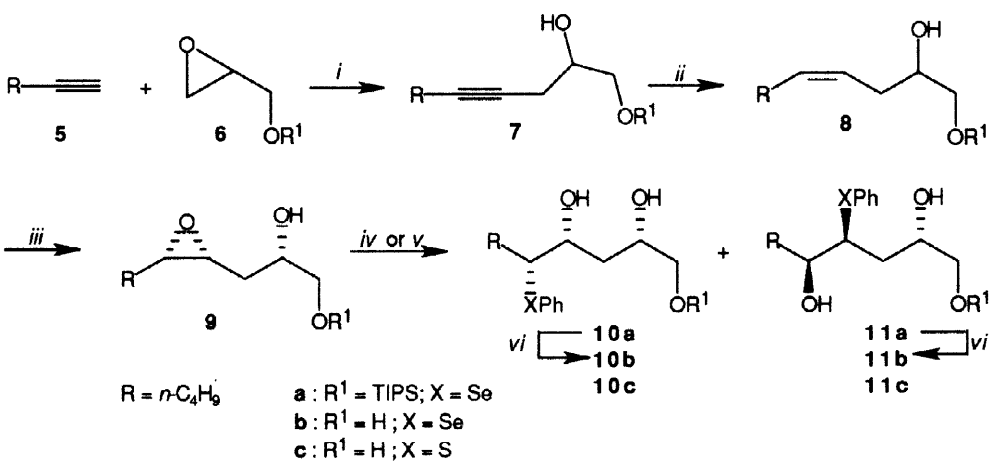
Two modes of cyclization are possible: *i*) stereoconvergent elimination of water to give **3** *via* the intermediate ion **2** (cyclization in the *endo*/*exo*[6f] mode); *ii*) stereoconvergent elimination of water to give **4** *via* **2** (cyclization in the *exo* mode) (R^1 = H).



Scheme 1

Results and Discussion

The hydroxy-selenides and the hydroxy-sulfides were prepared from the *cis*-homoallylic alcohol (**8**) which was obtained by hydrogenation of the alkyne (**7**) as showed in Scheme 2. Epoxidation using *tert*-butyl hydroperoxide and $VO(acac)_2$ gave the *syn*-hydroxy-epoxide (**9**) 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 (**10a**) and (**11a**) which were separated by column chromatography. It was not determined which was which, however, when they were treated with a catalytic amount of perchloric acid, in dichloromethane at room temperature, they gave the same mixture of products. This implies the formation of the same intermediate, perhaps the selenonium ion (**2**). Two principal products were isolated besides a small amount of the *cis*-alkene (**8**)[8] (R^1 = H).

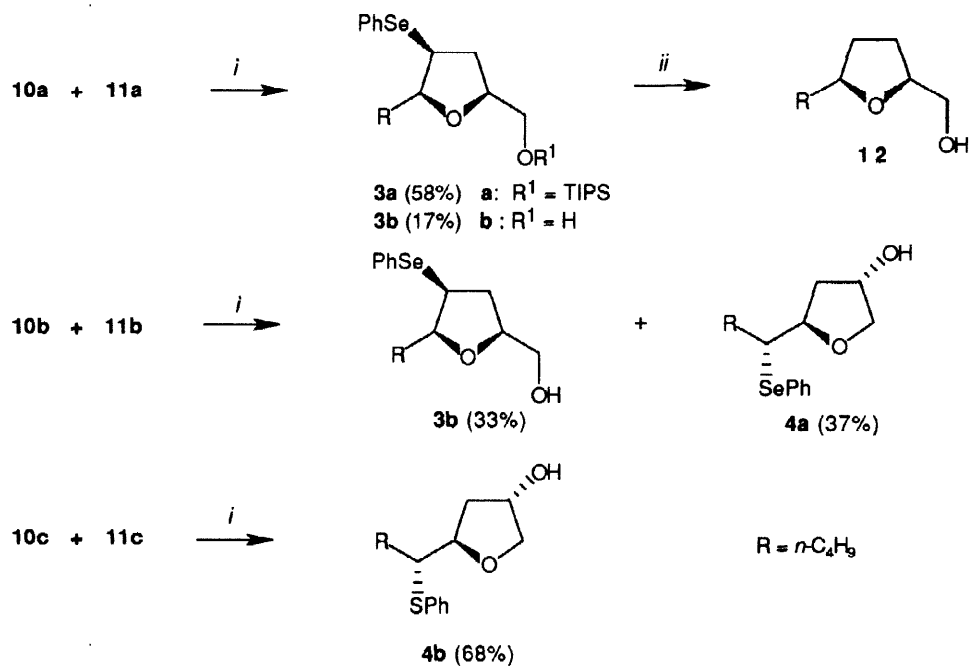


Reagents: *i*, BuLi, $BF_3.OEt_2$, THF, -78 °C, 78%; *ii*, H_2, Lindlar, EtOH, rt, 98%; *iii*, *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, rt, 76%; *iv*, $(PhSe)_2$, $NaBH_4$, EtOH, rt, 80%; *v*, PhSNa, MeOH, rt, then TBAF, THF, 93%; *vi*, TBAF, THF, 95%.

Scheme 2

These two products were identified as the 2,5-*cis*-disubstituted tetrahydrofurans (**3a**) (58%) and (**3b**) (17%); tetrahydrofuran (**4a**) was detected only in traces. Compound (**3b**) is simply formed by deprotection of **3a** in the reaction conditions. The structure of these products was proven by COSY spectrum of compound (**12**), obtained by reduction of compound (**3b**) with tributyltin hydride and AIBN, and the *cis*-geometry by NOESY spectrum. In this reaction the *endo*/*exo* attack takes place faster than the cleavage of the protecting group and the subsequent *exo* attack.

In order to investigate which of the above cyclization processes takes place faster, we removed the protecting group (R^1 = H). Having seen that both hydroxy-selenides gave the same products, we directly used the mixture of (**10b**) and (**11b**) for the reaction with the catalytic amount of perchloric acid. The reaction was very fast giving a mixture of products from which we could isolate after careful chromatography two major products that were identified as the tetrahydrofurans (**3b**) (attack in the *endo*/*exo* mode) and (**4a**) (attack in the *exo* mode) in almost the same yield. No regiocontrol was then observed.



Reagents: *i*, $HClO_4$, CH_2Cl_2, rt; *ii*, *n*-Bu_3SnH, AIBN, benzene, reflux, 90%.

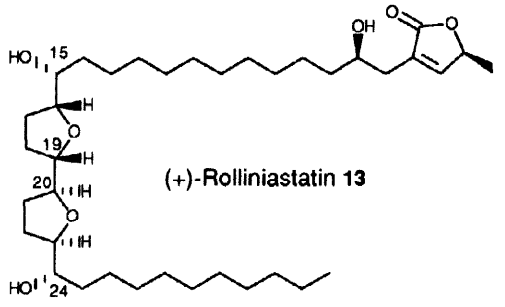
Scheme 3

The hydroxy-sulfides (**10c**) and (**11c**) were obtained by epoxide ring opening with sodium thiophenate and deprotection of the hydroxyl protecting group. Also in this case the mixture of regioisomers (*ca.* 6 : 4) was directly used for the cyclization step. The cyclization reaction was very clean giving only one product. The analytical and spectroscopic data were in accordance with the structure (**4b**).

In contrast with the cyclization of the hydroxy-selenides (**10b**) and (**11b**), in which no regiocontrol was observed, the cyclization of the hydroxy-sulfides gave an efficient regiocontrol (attack in the *exo* mode) allowing an efficient stereocontrolled synthesis of a 2,4-*trans*-tetrahydrofuran.

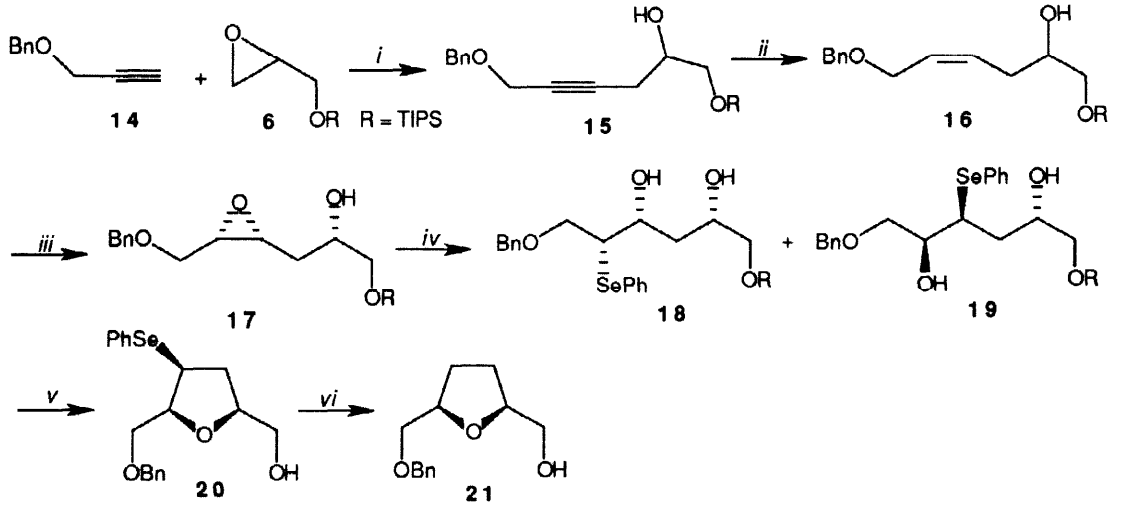
These methodologies are now under application by us with the aim of synthesizing, in a stereocontrolled way, fragments of natural products. As the first example we are now reporting the synthesis, in racemic form, of

the monobenzyl-protected C15-C20 fragment of (+)-Rolliniastatin 1 (13)[9] which belongs to the Annonaceous acetogenins, a class of natural products with remarkable antitumor and pesticidal properties.



The benzylated propargylic alcohol (**14**) was allowed to react with the triisopropylsilyl-protected glycidol to yield the alkyne (**15**) which was hydrogenated to the *cis*-homoallylic alcohol (**16**). Epoxidation using *tert*-butyl hydroperoxide and $VO(acac)_2$ gave the *syn*-hydroxy-epoxide (**17**) with good stereoselectivity (97 : 3). Ring opening with sodium phenyl selenide gave a mixture (*ca.* 6 : 4) of the hydroxy-selenides (**18**) and (**19**) which were treated with a catalytic amount of perchloric acid in dichloromethane at room temperature.

However, in this case, the reaction was slower than the cyclization of the hydroxy-selenides (**10a**) and (**11a**). A longer reaction time was necessary until the starting material disappeared giving a mixture of products from which it was possible to isolate only the deprotected tetrahydrofuran (**20**) in 27% yield. Finally reduction with tributyltin hydride and AIBN in refluxing benzene gave the expected tetrahydrofuran (**21**).

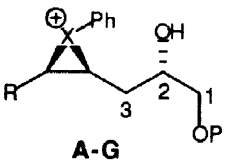


Reagents: *i*, BuLi, $BF_3.OEt_2$, THF, -78 °C, 66%; *ii*, H_2, Lindlar, EtOH, rt, 98%; *iii*, *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, rt, 75%; *iv*, $(PhSe)_2$, $NaBH_4$, EtOH, rt, 92%; *v*, $HClO_4$, CH_2Cl_2, rt, 27%; *vi*, *n*-Bu_3SnH, AIBN, benzene, reflux, 80%.

Scheme 4

In order to achieve more information about the different regiochemical control in the cyclization reaction of the hydroxy-selenides (**10b**) and (**11b**) compared with the hydroxy-sulfides (**10c**) and (**11c**), and the different yields in the cyclization reaction of the hydroxy-selenides (**10a**) and (**11a**) compared with the hydroxy-selenides

(18) and (19) we attempted to perform a quantum-mechanical study of the episulfonium or episelenonium ions **A-F** as model intermediates. Moreover we similarly studied also the episelenonium ion **G** as model for the cyclization when a branching is present in the α position to the selenonium ring in order to compare this result with our previous findings.[4a]



A-G

	P	X	R
A	H	S	Me
B	H	Se	Me
C	H	S	*n*-Bu
D	H	Se	*n*-Bu
E	TMS	Se	*n*-Bu
F	TMS	Se	CH_2OBn
G	H	Se	*i*-Pr

Owing to the complexity of the systems involved, and in particular to the presence of Si, S and Se atoms, we chose to perform semiempirical calculations at the PM3[10] level, because this method is parametrized for the requested atoms and enough short CPU time is needed for calculations.[11]

Models **A** and **B** were studied for a preliminary conformational quest. These systems can be viewed as triple rotors with regard to the hydroxylated branch C(3)-C(2)-C(1).

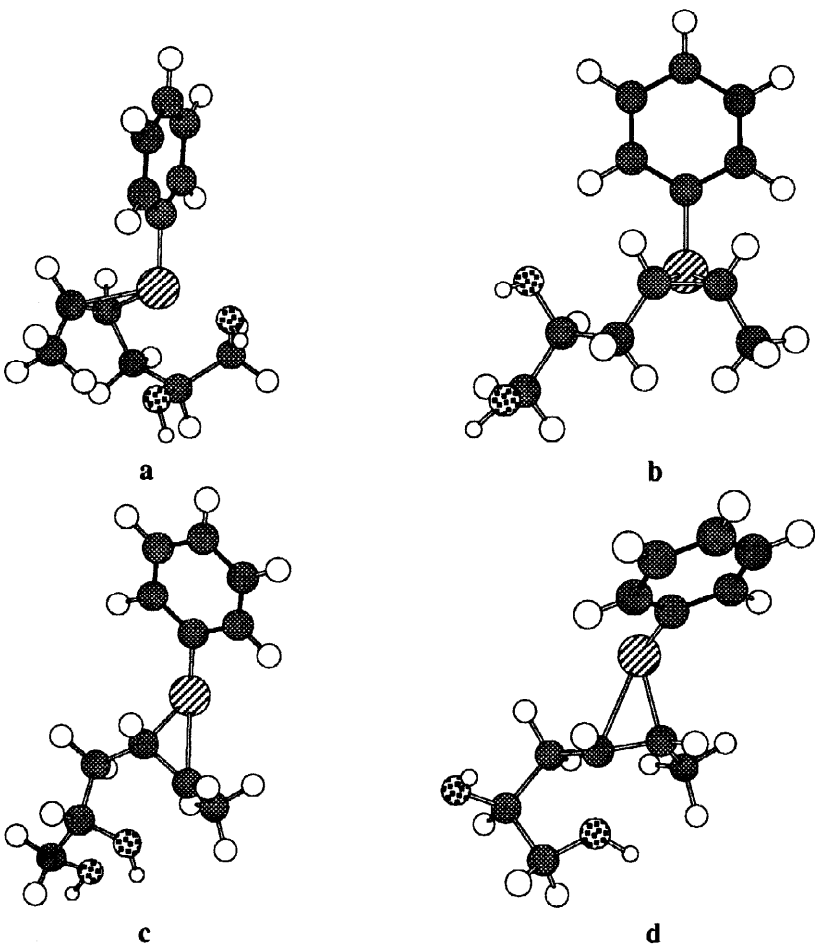


Figure - Projections of the "*all gauche*" (**a**) and "*all trans*" (**b**) conformations and of the transition state for the attack in the *endo/exo* mode (**c**) and in the *exo* mode (**d**) for model **B**, predicted on the basis of molecular modelling calculations.

For model **A**, among the other local minima, the most stable conformation is predicted to be an "*all gauche*" conformation, which is stabilized by the electrostatic interaction of the S atom with the O(1) and O(2) oxygen atoms. A conformation "*all trans*" with respect to the C-C bonds, for which steric hindrances should be minimized, is predicted only 0.6 kcal/mol higher in energy than the latter. In both the conformations the two hydroxyl groups assume a gauche position. Moreover, two "*apt for closure*" conformations are predicted, one for the *endo/exo* closure and the other for the *exo* closure, which are respectively 2.3 kcal/mol and 2.0 kcal/mol over the "*all trans*" conformation.

For model **B** the "*all gauche*" conformation is found abnormally lower (about 9.9 kcal/mol) than the "*all trans*" and a Se-O(1) distance of 1.91 Å is predicted, that is shorter than the C-Se bond distance of the episelenonium ring (about 2,02 Å). By contrast no abnormal S-O distance had been predicted for model **A**. Thus we can argue that this result is probably an artifact of the method, due to an uncorrect parametrization, and so it has to be rejected as such. Finally two "*apt for closure*" conformations are predicted, respectively 2.1 kcal/mol for *endo/exo* closure and 3.5 kcal/mol for *exo* closure over the "*all trans*" minimum.

On the basis of these findings we decided to optimize for the model systems **C-G** only the "*all gauche*" and the "*all trans*" conformations, in order to use them for the evaluation of the activation energies to be compared with experimental data. For **F** the presence of the bulky phenyl group near the selenium atom hampers a strong interaction with the hydroxylated branch, in such a way that the "*all gauche*" conformation assumes acceptable Se-O(1) distances and differs very little in energy from the "*all trans*" conformation. Moreover, PM3 predicts for **C** the latter to be the absolute energy minimum. Also for **D**, **E** and **G** the "*all gauche*" conformation shows a Se-O(1) distance shorter than the C-Se bond. Thus, data context seem to suggest that the "*all trans*" conformation, unless not necessarily being the absolute minimum conformation, is more suitable for a comparison with transition states than the controverse "*all gauche*" conformation.

For structures **C**, **D** and **G** two transition states **I** (attack in the *endo/exo* mode) and **II** (attack in the *exo* mode) were modelled, related to the two different reaction products, while obviously only one transition state was modelled for **E** and **F**. Data are reported in the Table.

Table. Calculated energies for models **C-G** and relative transition states for *endo/exo* or *exo* cyclization.

TS	ΔH^f kcal/mol	ΔH^f_{TS} kcal/mol	$\Delta H^f_{TS} - \Delta H^f$ kcal/mol	$\Delta H_{TSI} - \Delta H_{TSII}$ kcal/mol
IC	95.72	117.34	21.62	+2.52
IIC		114.82	19.10	
ID	62.15	81.53	19.38	+0.70
IID		80.83	18.68	
IE	-4.23	12.69	16.92	
IF	-9.93	9.31	19.24	
IG	71.21	91.01	19.80	+3.68
IIG		87.33	16.12	

PM3 correctly predicts the strong preference for **IIC** over **IC** ($\Delta H_{TSI} - \Delta H_{TSII}$ = +2.52 kcal/mol); it also predicts that **IID** is only slightly favoured over **ID** ($\Delta H_{TSI} - \Delta H_{TSII}$ = +0.70 kcal/mol), in agreement with experimental product distribution. Taking the difference between the heats of formation of the "*all trans*"

conformation and of **I** or **II** as an estimate of the activation energies, values predicted by PM3 appear in fair agreement with the experimental reaction rates, even if the entropic contribution has not been evaluated. Moreover, our data show the strong preference for **IIG** over **IG** ($\Delta H_{TSI} - \Delta H_{TSII} = +3.68$ kcal/mol) in full agreement with our results,[4a] so showing that the branching in the α position of the chain plays an important role for the regiochemical control of the cyclization. Finally the comparison between **IE** and **IF** shows a higher activation energy for the latter closure and this could be the reason for the low yield and the complex mixture of products obtained.[12]

Conclusion

An efficient regiochemical control in the synthesis of tetrahydrofurans was achieved by acid-catalyzed cyclization of hydroxy-selenides or hydroxy-sulfides such as **1**. Using hydroxy-selenides (**10a**) and (**11a**) which have the primary hydroxyl group protected only the cyclization in the *endo/exo* mode occurs. On the other hand hydroxy-sulfides (**10c**) and (**11c**) cyclize only in the *exo* mode. By cyclization of the relevant hydroxy-selenides, the C15-C20 fragment of (+)-Rolliniastatin 1 was obtained, though in low yield. An explanation for this result is given. Further application of this strategy is in progress for the stereoselective synthesis of fragments of natural products. Finally, semiempirical calculations appear to have a fair predictive value and, if used with caution, may be helpful in rationalizing experimental results.

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 or 200 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. 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.

(±)(2R*)-1-(Triisopropylsilyloxy)non-4-yn-2-ol (7).

Butyllithium (1.60 M in hexane; 12.8 mL, 20.55 mmol) was added dropwise to a solution of 1-hexyne (2.31 mL, 20.55 mmol) in anhydrous tetrahydrofuran (40 mL) at -78 °C. After 20 min, BF_3-Et_2O (1.69 mL, 13.7 mmol) was added followed, after 5 min, by a solution of glycidol (**6**) (3.15 g, 13.7 mmol) in anhydrous tetrahydrofuran (7 mL). After 2 h at -78 °C, sat aq $NaHCO_3$ (15 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 and dried (Na_2SO_4). Concentration under reduced pressure gave an oil which was

separated by chromatography using light petroleum-Et_2O (20/1) as eluent to give compound **7** as an oil (3.34 g, 78%). IR (cm^{-1}): 3440, 1455, 1245, 1115, 880. ^{1}H-NMR (250 MHz) ($CDCl_3$) δ: 0.89 (t, 3H, J = 7.0 Hz), 1.06 (d, 18H, J = 4.3 Hz, overlapped with 3H), 1.34-1.48 (m, 4H), 2.11-2.19 (m, 2H), 2.37-2.43 (m, 2H), 2.56 (br s, 1H), 3.68-3.82 (m, 3H); ^{13}C-NMR δ: 11.9, 13.6, 17.9, 18.4, 22.0, 23.4, 31.1, 66.0, 70.7, 75.7, 82.6. Anal. Calcd for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61. Found: C, 69.30; H, 11.64.

(±)(Z, 2R*)-1-(Triisopropylsilyloxy)non-4-en-2-ol (8).

A suspension of Lindlar catalyst (256 mg) in a solution of the alkyne (**7**) (2.56 g, 8.19 mmol) in ethanol (40 mL) was stirred vigorously under hydrogen for 3 h. The mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was purified with a short column chromatography using light petroleum-Et_2O (20/1) as eluent to give compound (**8**) as an oil (2.52 g, 98%). IR (cm^{-1}): 3440, 1465, 1255, 1114, 837. ^{1}H-NMR (250 MHz) ($CDCl_3$) δ: 0.89 (t, 3H, J = 7.0 Hz), 1.06 (d, 18H, J = 4.5 Hz, overlapped with 3H), 1.30-1.36 (m, 4H), 2.00-2.08 (m, 2H), 2.25 (t, 2H, J = 5.8 Hz), 2.55 (d, 1H, J = 3.1 Hz), 3.54 (dd, 1H, J = 10.8 and 7.9 Hz), 3.69-3.76 (m, 2H), 5.42-5.50 (m, 2H); ^{13}C-NMR δ: 11.9, 13.9, 17.9, 22.3, 27.1, 31.0, 31.8, 67.0, 71.9, 124.6, 132.6. Anal. Calcd for $C_{18}H_{38}O_2Si$: C, 68.73; H, 12.18. Found: C, 68.68; H, 12.20.

(±)(2R*, 4S*, 5R*)-4,5-Epoxy-1-(triisopropylsilyloxy)nonan-2-ol (9).

To a solution of **8** (1.00 g, 3.18 mmol) in anhydrous dichloromethane (30 mL) at 0 °C, $VO(acac)_2$ (15 mg, 0.056 mmol) was added, then *tert*-butyl hydroperoxide (5.5 M in decane; 0.87 mL, 4.77 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min then allowed to warm to room temperature. After 18 h the reaction was quenched with sat aq sodium thiosulfate. The mixture was extracted with water, washed with brine and dried (Na_2SO_4). Concentration under reduced pressure gave an oil which was separated by chromatography using light petroleum-Et_2O (5/1) as eluent to give compound (**9**) as an oil (799 mg, 76%). IR (cm^{-1}): 3440, 1465, 1255, 1105, 837, 777. ^{1}H-NMR (250 MHz) ($CDCl_3$) δ: 0.90 (t, 3H, J = 6.8 Hz), 1.05 (d, 18H, J = 4.4 Hz, overlapped with 3H), 1.34-1.54 (m, 6H), 1.62 (dt, 1H, J = 14.4 and 7.3 Hz), 1.80 (dt, 1H, J = 14.4 and 4.7 Hz), 2.71 (br s, 1H), 2.89-2.96 (m, 1H), 3.13 (dt, 1H, J = 7.3 and 4.7 Hz), 3.65 (dd, 1H, J = 9.7 and 7.0 Hz), 3.72 (dd, 1H, J = 9.7 and 4.3 Hz), 3.88-3.94 (m, 1H); ^{13}C-NMR δ: 11.8, 14.0, 17.9, 22.6, 27.5, 28.6, 31.1, 54.3, 56.5, 67.0, 70.6. Anal. Calcd for $C_{18}H_{38}O_3Si$: C, 65.40; H, 11.59. Found: C, 65.46; H, 11.61.

Preparation of the Hydroxy Selenides (10a) and (11a).

Diphenyl diselenide (384 mg, 1.23 mmol) was dissolved in absolute ethanol (3.5 mL), sodium borohydride (128 mg, 3.38 mmol) was added in batches and the mixture was stirred until the bright yellow solution turned colorless. Compound (**9**) (727 mg, 2.20 mmol) was dissolved in absolute ethanol (2.7 mL) and added *via* cannula. The reaction mixture was stirred for 16 h then concentrated under reduced pressure. Dichloromethane 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 separated by chromatography using light petroleum-

Et_2O (3/1) as eluent to give 225 mg and 460 mg as pure regioisomers and 177 mg of mixture of regioisomers as oils.

Less polar regioisomer of the mixture (**10a**) and (**11a**): IR (cm^{-1}): 3400, 1570, 1455, 1115, 880. ^1H-NMR (250 MHz) ($CDCl_3$) δ: 0.87 (t, 3H, J = 7.2 Hz), 1.04 (d, 18H, J = 4.3 Hz, overlapped with 3H), 1.24-1.86 (m, 8H), 3.13 (br s, 2H), 3.50-3.68 (m, 3H), 3.86-3.95 (m, 2H), 7.23-7.26 (m, 3H), 7.52-7.56 (m, 2H); ^{13}C-NMR δ: 11.8, 13.9, 17.9, 22.5, 30.4, 31.5, 36.4, 54.8, 67.2, 72.5, 73.6, 127.3, 129.0, 129.5, 134.3. Anal. Calcd for $C_{24}H_{44}O_3SeSi$: C, 59.11; H, 9.09. Found: C, 59.18; H, 9.11.

More polar regioisomer of the mixture (**10a**) and (**11a**): IR (cm^{-1}): 3380, 1570, 1455, 1110, 880. ^1H-NMR (250 MHz) ($CDCl_3$) δ: 0.85 (t, 3H, J = 6.8 Hz), 1.06 (d, 18H, J = 4.2 Hz, overlapped with 3H), 1.16-1.74 (m, 7H), 1.84 (ddd, 1H, J = 14.7, 9.8 and 4.9 Hz), 2.76 (br s, 2H), 3.47-3.56 (m, 2H), 3.60-3.66 (m, 1H), 3.70 (dd, 1H, J = 9.6 and 3.6 Hz), 4.06-4.13 (m, 1H), 7.25-7.29 (m, 3H), 7.59-7.63 (m, 2H); ^{13}C-NMR δ: 11.8, 13.9, 17.9, 22.6, 28.1, 34.4, 35.8, 52.2, 67.5, 70.7, 74.2, 127.5, 129.0, 129.1, 134.5. Anal. Calcd for $C_{24}H_{44}O_3SeSi$: C, 59.11; H, 9.09. Found: C, 59.20; H, 9.12.

Deprotection of the Hydroxy Selenides (10a) and (11a).

A solution of tetrabutylammonium fluoride (643 mg, 2.46 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise to a solution of the silyl ethers (**10a**) and (**11a**) (600 mg, 1.23 mmol) in tetrahydrofuran (2 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 Et_2O 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 separated by chromatography using ethyl acetate as eluent to give compounds (**10b**) and (**11b**) as oils (387 mg, 95%). IR (cm^{-1}): 3330, 1580, 1477, 1466, 1437, 1047, 738. ^1H-NMR (200 MHz) ($CDCl_3$) δ: 0.83 (t, 3H, J = 6.9 Hz), 1.13-1.95 (m, 8H), 3.18-3.48 (m, 2H), 3.51-3.72 (m, 2H), 3.76-4.00 (m, 1H), 4.57 (t, 1H, J = 4.7 Hz, OH), 4.65 (d, 1H, J = 4.2 Hz, OH), 4.86 (d, 1H, J = 4.8 Hz, OH, major regioisomer), 5.01 (br s, 1H, OH, minor regioisomer), 7.20-7.39 (m, 3H), 7.48-7.62 (m, 2H). Anal. Calcd for $C_{15}H_{24}O_3Se$: C, 54.38; H, 7.30. Found: C, 54.46; H, 7.28.

Procedure for the Cyclization of Hydroxy Selenides (10a) and (11a): (±)(2R*, 3R*, 5R*)-2-butyl-3-phenylselanyl-5-triisopropyilsilyloxymethyl-tetrahydrofuran (3a) and (±)(2R*, 3R*, 5R*)-2-butyl-5-hydroxymethyl-3-phenylselanyl-tetrahydrofuran (3b)

To a solution of hydroxy selenides (**10a**) and (**11a**) (830 mg, 1.70 mmol) in anhydrous dichloromethane (40 mL) at room temperature were added three drops (15 μL) of $HClO_4$. The reaction mixture was vigorously stirred for 15 min then quenched with sat aq $NaHCO_3$ 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 separated by chromatography using light petroleum-Et_2O (30/1, then 1/1) as eluent to give compound (**3a**) (463 mg, 58%) and compound (**3b**) (90 mg, 17%) as oils.

Compound (**3a**), IR (cm^{-1}): 1575, 1460, 1250, 1110. ^1H-NMR (250 MHz) ($CDCl_3$) δ: 0.87 (t, 3H, J = 6.4 Hz), 1.05 (d, 18H, J = 4.3 Hz, overlapped with 3H), 1.25-1.35 (m, 4H), 1.60-1.65 (m, 2H), 2.10 (dt, 1H,

J = 13.5 and 6.3 Hz), 2.43 (dt, 1H, J = 13.5 and 7.6 Hz), 3.66 (ddd, 1H, J = 10.4, 6.0 and 0.7 Hz), 3.76-3.88 (m, 2H), 3.94-4.01 (m, 2H), 7.26-7.30 (m, 3H), 7.53-7.57 (m, 2H); ^{13}C-NMR δ: 11.9, 14.0, 17.9, 22.6, 28.7, 33.1, 36.7, 45.7, 66.3, 78.7, 81.9, 127.1, 129.0, 130.2, 133.6. Anal. Calcd for $C_{24}H_{42}O_2SeSi$: C, 61.38; H, 9.01. Found: C, 61.44; H, 8.98.

Compound (**3b**), IR (cm^{-1}): 3380, 1575, 1470, 1430. ^{1}H-NMR (250 MHz) ($CDCl_3$) δ: 1.17 (t, 3H, J = 6.8 Hz), 1.53-1.75 (m, 4H), 1.92-2.00 (m, 2H), 2.29 (ddd, 1H, J = 13.7, 6.7 and 4.3 Hz), 2.55 (br s, 1H), 2.75 (dt, 1H, J = 13.7 and 7.5 Hz), 3.90 (dd, 1H, J = 11.6 and 5.3 Hz), 4.04 (dd, 1H, J = 11.6 and 2.8 Hz), 4.13-4.26 (m, 2H), 4.31-4.40 (m, 1H), 7.54-7.57 (m, 3H), 7.81-7.85 (m, 2H); ^{13}C-NMR δ: 14.0, 22.6, 28.7, 32.8, 35.6, 46.2, 64.8, 78.4, 82.3, 127.4, 129.1, 129.6, 134.0. Anal. Calcd for $C_{15}H_{22}O_2Se$: C, 57.51; H, 7.08. Found: C, 57.57; H, 7.11.

(±)(2R*, 3R*, 5R*)-2-butyl-5-hydroxymethyl-3-phenylselanyl-tetrahydrofuran (3b) and (±)(2S*, 4R*, 1'S*)-4-hydroxy-2-(1'-phenylselanylpentyl)-tetrahydrofuran (4a)

Following the procedure used to cyclize the compounds (**10a**) and (**11a**), hydroxy selenides (**10b**) and (**11b**) (364 mg, 1.10 mmol) in dichloromethane (54 mL) and $HClO_4$ (3 drops) gave after careful chromatography, using light petroleum-Et_2O (2/1) as eluent, compound (**3b**) (115 mg, 33%) and compound (**4a**) (128 mg, 37%) as oils. Compound (**4a**): IR (cm^{-1}): 3400, 1580, 1477, 1465, 1435, 1070, 738. ^{1}H-NMR (250 MHz) ($CDCl_3$) δ: 0.88 (t, 3H, J = 7.2 Hz), 1.25-2.10 (m, 9H), 3.16-3.23 (m, 1H), 3.77 (d, 1H, J = 9.8 Hz), 4.06 (dd, 1H, J = 9.8 and 4.1 Hz), 4.37 (ddd, 1H, J = 9.8, 6.2 and 3.8 Hz), 4.55 (m, 1H), 7.23-7.28 (m, 3H), 7.53-7.57 (m, 2H); ^{13}C-NMR δ: 13.9, 22.5, 30.2, 32.8, 39.3, 51.4, 72.7, 76.2, 80.3, 127.1, 128.9, 130.1, 134.0. Anal. Calcd for $C_{15}H_{22}O_2Se$: C, 57.51; H, 7.08. Found: C, 57.45; H, 7.10.

(±)(2R*, 5R*)-2-butyl-5-hydroxymethyl-tetrahydrofuran (12).

A solution of compound (**3b**) (60 mg, 0.19 mmol) dissolved in anhydrous benzene (2 mL) was degassed for 15 min with argon, then tributyltin hydride (111 mg, 0.38 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 (1/1 plus 1% triethylamine) to give **12** as an oil (27 mg, 90%). IR (cm^{-1}): 3390, 1466, 1380, 1043, 883. ^{1}H-NMR (250 MHz) ($CDCl_3$) δ: 1.19 (t, 3H J = 6.7 Hz), 1.55-2.02 (m, 8H), 2.12-2.32 (m, 2H), 3.04 (t, 1H, J = 6.3 Hz, OH), 3.78 (dt, 1H, J = 11.3 and 5.9 Hz, CH_2OH), 3.96 (ddd, 1H, J = 11.3, 6.3 and 3.5 Hz, CH_2OH), 4.15 (m, 1H, H-5), 4.28 (m, 1H, H-2); ^{13}C-NMR δ: 13.9, 22.6, 26.9, 28.2, 31.1, 35.4, 65.1, 79.2, 80.1. Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: 68.35; H, 11.48.

Preparation of the Hydroxy Sulfides (10c) and (11c).

To a solution of the epoxide (**9**) (984 mg, 2.98 mmol) in anhydrous methanol (1.8 mL) was added *via* cannula a solution of thiophenol/ sodium thiophenate (1/1, 2.98 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 (1.31 g) was dissolved in anhydrous tetrahydrofuran (10 mL) and added *via* cannula to a solution of tetrabutylammonium fluoride (1.55 g, 5.96 mmol) in anhydrous 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 Et_2O and extracted with water. The organic phase was washed with brine and dried (Na_2SO_4). Concentration under reduced pressure gave a solid which was purified by chromatography using ethyl acetate as eluent to give compounds (**10c**) and (**11c**) as white cristals (788 mg, 93%); m.p.77-79 °C. IR (cm^{-1}): 3300, 1585, 1481, 1464, 1456, 1377, 1089, 1039,1012. ^{1}H-NMR (250 MHz) (DMSO-d_6) δ: 0.86 (t, 3H, J = 6.9 Hz, major regioisomer), 0.99 (t, 3H, J = 7.2 Hz, minor regioisomer), 1.17-1.45 (m, 5H), 1.56-1.78 (m, 3H), 3.20-3.46 (m, 2H), 3.53-3.65 (m, 2H), 3.78-3.86 (m, 1H), 4.60 (t, 1H, J = 5.7 Hz, OH), 4.65 (d, 1H, J = 5.3 Hz, OH), 4.84 (d, 1H, J = 5.0 Hz, OH), 7.20-7.26 (m, 3H, minor regioisomer), 7.31-7.38 (m, 3H, major regioisomer), 7.42-7.49 (m, 2H). Anal. Calcd for $C_{15}H_{24}O_3S$: C, 63.35; H, 8.51. Found: C, 63.40; H, 8.54.

Cyclization of the Hydroxy Sulfides (10c) and (11c): (±)(2S*, 4R*, 1'S*)-4-hydroxy-2-(1'-phenylsulfanylpentyl)-tetrahydrofuran (4b).

To a solution of hydroxy sulfides (**10c**) and (**11c**) (316 mg, 1.11 mmol) in anhydrous dichloromethane (54 mL) at room temperature were added three drops of $HClO_4$. The reaction mixture was vigorously stirred for 15 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 and dried (Na_2SO_4). Concentration under reduced pressure gave an oil which was separated by chromatography using light petroleum-Et_2O (5/1, then 1/1, then ethyl acetate) as eluent to give compound (**4b**) as an oil (202 mg, 68%) and 44 mg of starting material. IR (cm^{-1}): 3400, 1583, 1479, 1466, 1438, 1090, 1068, 742. ^{1}H-NMR (250 MHz) ($CDCl_3$) δ: 0.87 (t, 3H, J = 7.2 Hz), 1.26-1.76 (m, 6H), 1.96-2.02 (m, 2H), 3.08 (br s 1H, OH, overlapped with 1H), 3.71, (d, 1H, J = 9.6 Hz), 3.97 (dd, 1H, J = 9.6 and 4.1 Hz), 4.31-4.39 (m, 1H), 4.42-4.46 (m, 1H), 7.16-7.28 (m, 3H), 7.37-7.41 (m, 2H); ^{13}C-NMR δ: 13.8, 22.4, 29.2, 31.2, 38.0, 53.0, 72.1, 75.9, 79.7, 126.3, 128.7, 130.9, 135.9. Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.45; H, 8.34.

(±)(5R*)-1-Benzyloxy-6-(triisopropylsilyloxy)hex-2-yn-5-ol (15).

Butyllithium (1.60 M in hexane; 3.9 mL, 6.24 mmol) was added dropwise to a solution of the alkyne (**14**) (904 mg, 6.18 mmol) in anhydrous tetrahydrofuran (10 mL) at -78 °C. After 20 min, BF_3-Et_2O (0.76 mL, 6.18 mmol) was added followed, after 5 min, by a solution of glycidol (**6**) (950 g, 4.12 mmol) in anhydrous tetrahydrofuran (10 mL). After 2 h at -78 °C, sat aq $NaHCO_3$ (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 and dried (Na_2SO_4). Concentration under reduced pressure gave an oil which was separated by chromatography using light petroleum-Et_2O (5/1) as eluent to give compound (**15**) as an oil (1.02 g, 66%). IR (cm^{-1}): 3440, 1462, 1354, 1118, 1070, 883. ^{1}H-NMR (200 MHz) ($CDCl_3$) δ: 1.09 (d, 18H, J = 4.5 Hz, overlapped with 3H), 2.46-2.55 (m, 2H), 3.00 (br s, 1H), 3.62 (dd, 1H, J = 10.0 and 5.8 Hz), 3.69-3.85 (m, 2H), 4.17 (s, 2H), 4.59 (s, 2H), 7.30-7.36 (m, 5H); ^{13}C-NMR δ: 12.0, 18.0, 23.5, 57.7, 66.0, 70.4,

71.5, 78.1, 89.1, 127.8, 128.0, 128.4, 137.7. Anal. Calcd for $C_{22}H_{36}O_3Si$: C, 70.16; H, 9.63. Found: C, 70.30; H, 9.64.

(±)(Z, 5R*)-1-Benzyloxy-6-(triisopropylsilyloxy)hex-2-en-5-ol (16).

A suspension of Lindlar catalyst (100 mg) in a solution of the alkyne (**15**) (920 mg, 2.44 mmol) in ethanol (25 mL) was stirred vigorously under hydrogen for 100 min. The mixture filtered through Celite and the filtrate concentrated under reduced pressure. The residue was purified with a short column chromatography using light petroleum-Et_2O (5/1) as eluent to give compound (**16**) as an oil (905 mg, 98%). IR (cm^{-1}): 3450, 1462, 1382, 1112, 1070, 883. ^{1}H-NMR (200 MHz) ($CDCl_3$) δ: 1.06 (d, 18H, J = 4.5 Hz, overlapped with 3H), 2.26 (t, 2H, J = 6.1 Hz), 2.58 (d, 1H, 3.9 Hz, OH), 3.46 (dd, 1H, J = 9.7 and 6.6 Hz), 3.61 (dd, 1H, J = 9.7 and 3.9 Hz), 3.60-3.70 (m, 1H), 4.07-4.09 (m, 2H), 4.53 (s, 2H), 5.66-5.79 (m, 2H), 7.30-7.36 (m, 5H); ^{13}C-NMR δ: 12.0, 18.0, 31.5, 65.6, 66.9, 71.5, 72.3, 127.6, 127.8, 128.3, 128.5, 129.2, 138.2. Anal. Calcd for $C_{22}H_{38}O_3Si$: C, 69.79; H, 10.12. Found: C, 69.81; H, 10.14.

(±)(2R*, 3S*, 5R*)-1-Benzyloxy-2,3-epoxy-6-(triisopropylsilyloxy)hexan-5-ol (17).

To a solution of **16** (830 mg, 2.19 mmol) in anhydrous dichloromethane (20 mL) at 0 °C, $VO(acac)_2$ (15 mg, 0.056 mmol) was added, then *tert*-butyl hydroperoxide (5.5 M in decane; 0.60 mL, 3.30 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 extracted with water, washed with brine and dried (Na_2SO_4). Concentration under reduced pressure gave an oil which was separated by chromatography using light petroleum-Et_2O (5/1) as eluent to give compound (**17**) as an oil (648 mg, 75%). IR (cm^{-1}): 3455, 1462, 1382, 1101, 1072, 883. ^{1}H-NMR (200 MHz) ($CDCl_3$) δ: 1.09 (d, 18H, J = 4.3 Hz, overlapped with 3H), 1.64-1.75 (m, 2H), 2.26 (br s, 1H), 3.19-3.25 (m, 2H), 3.49-3.88 (m, 4H), 3.80-3.95 (m, 1H), 4.53 and 4.64 (d, each 1H, J = 12 Hz), 7.30-7.40 (m, 5H); ^{13}C-NMR δ: 11.9, 17.9, 31.3, 53.3, 54.5, 66.9, 68.2, 70.4, 73.4, 127.6, 127.8, 128.4, 137.8. Anal. Calcd for $C_{22}H_{38}O_4Si$: C, 66.96; H, 9.71. Found: C, 67.12; H, 9.75.

Preparation of the Hydroxy Selenides (18) and (19).

Diphenyl diselenide (247 mg, 0.79 mmol) was dissolved in absolute ethanol (3.5 mL), sodium borohydride (77 mg, 2.03 mmol) was added in batches and the mixture was stirred until the bright yellow solution turned colorless. Compound (**17**) (510 mg, 1.29 mmol) was dissolved in absolute ethanol (2.5 mL) and added *via* cannula. The reaction mixture was stirred for 16 h then concentrated under reduced pressure. Dichloromethane 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 separated by chromatography using light petroleum-Et_2O (2/1) as eluent to give compounds (**18**) and (**19**) (656 mg, 92%) as oil. IR (cm^{-1}): 3420, 1580, 1462, 1103, 1070, 883. ^{1}H-NMR (200 MHz) ($CDCl_3$) δ: 1.06 (d, 18H, J = 4.1 Hz, overlapped with 3H), 1.77-1.88 (m, 2H), 2.70 (br s, 1H), 3.02 (br s, 1H), 3.47-3.74 (m, 5H), 3.90-4.00 (m, 1H), 4.01-4.13 (m, 1H), 4.43

(m, 2H), 7.20-7.30 (m, 8H), 7.53-7.65 (m, 2H). Anal. Calcd for $C_{28}H_{44}O_4SeSi$: C, 60.96; H, 8.04. Found: C, 61.18; H, 8.08.

(±)(2R*, 3R*, 5R*)-2-Benzyloxymethyl-5-hydroxymethyl-3-phenylselanyl-tetrahydrofuran (20).

To a solution of hydroxy selenides (**18**) and (**19**) (600 mg, 1.08 mmol) in anhydrous dichloromethane (54 mL) at room temperature were added three drops of $HClO_4$. The reaction mixture was vigorously stirred for 80 min then quenched with sat aq $NaHCO_3$ 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 separated by chromatography using light petroleum-ethyl acetate (4/1) as eluent to give compound (**20**) (110 mg, 27%) as an oil. IR (cm^{-1}): 3425, 1577, 1477, 1454, 1437, 1091, 1072, 736. ^{1}H-NMR (250 MHz) ($CDCl_3$) δ: 2.14-2.41 (m, 2H), 2.77 (br s, 1H), 3.57 (dd, 1H, J = 11.9 and 3.8 Hz), 3.74 (d, 2H, J = 4.1 Hz), 3.79-3.92 (m, 2H), 4.03-4.12 (m, 1H), 4.29-4.39 (m, 1H), 4.52 and 4.59 (d, each 1H, J = 11.7 Hz), 7.26-7.38 (m, 8H), 7.51-7.56 (m, 2H); ^{13}C-NMR δ: 35.2, 43.3, 63.9, 72.2, 73.4, 79.2, 79.9, 127.3, 127.7, 128.0, 128.3, 129.1, 133.4, 133.7, 137.5. Anal. Calcd for $C_{19}H_{22}O_3Se$: C, 60.48; H, 5.88. Found: C, 60.36; H, 5.90.

(±)(2R*, 5R*)-2-Benzyloxymethyl-5-hydroxymethyl-tetrahydrofuran (21).

A solution of compound (**20**) (100 mg, 0.26 mmol) dissolved in anhydrous benzene (1.5 mL) was degassed for 15 min with argon, then tributyltin hydride (154 mg, 0.53 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-ethyl acetate (2/1 plus 1% triethylamine) to give **21** as an oil (46 mg, 80%). IR (cm^{-1}): 3425, 1500, 1454, 1365, 1076, 738, 698. ^{1}H-NMR (250 MHz) ($CDCl_3$) δ: 1.80-2.00 (m, 4H), 2.61 (m, 1H, OH), 3.46 (dd, J = 10.0 and 4.8 Hz, 1H overlapped with 3.42-3.51 m, 1H), 3.60 (dd, J = 10.0 and 3.7 Hz, 1H), 3.75 (ddd, J = 11.7, 4.7 and 3.0 Hz, 1H), 4.05-4.12 (m, 1H), 4.12-4.19 (m, 1H), 4.56 (s, 2H), 7.25-7.35 (m, 5H); ^{13}C-NMR δ: 27.2, 28.2, 65.3, 72.4, 73.3, 78.6, 80.1, 127.6, 128.2, 128.3, 137.8. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.35; H, 8.14.

Acknowledgments - We are grateful to MURST (Rome) for financial support.

REFERENCES AND NOTES

1. (a) Harmange J. C.; Figadere B. *Tetrahedron: Asymmetry*, **1993**, 4, 1711-1754; (b) Bovin T. L. B. *Tetrahedron*, **1987**, 43, 3309-3362; (c) Bartlett P. A. *Tetrahedron*, **1980**, 36, 2-72; (d) Bartlett P. A. *Asymetric Synthesis*, Vol. III, Chap. 6, Academic Press: Florida, 1984; 411-454; (e) Semple J. E.; Jouillie M. *Heterocycles*, **1980**, 14, 1825-1870.
2. (a) Koert U.; Stein M.; Wagner H. *Chem. Eur. J.*, **1997**, 3, 1170-1180; (b) Hoppe R.; Scharf H.-D. *Synthesis*, **1995**, 1447-1464.
3. For representative recent example of tetrahydrofuran synthesis see: (a) Kang S. H.; Lee S. B. *Tetrahedron Lett.*, **1993**, 34, 7579-7582; (b) Banks J. M.; Knight D. W.; Seaman C. J.; Weingarten G. G. *Tetrahedron Lett.*, **1994**, 35, 7259-7262; (c) Walkup R. D.; Kim S. W. *J. Org. Chem.*, **1994**, 59, 3433-3441; (d) Lipshutz B. H.; Gross T. *J. Org. Chem.*, **1995**, 60, 3572-3573; (e) Bratt K.; Garavelas A.; Perlmutter P.; Westman G. *J. Org. Chem.*, **1996**, 61, 2109-2117; (f) Eames J.; Jones R. V. H.; Warren S. *Tetrahedron Lett.*, **1996**, 37, 4823-4826; (g) Andrey O.; Glanzmann C.; Landais Y.; Parra-Rapado L. *Tetrahedron*, **1997**, 53, 2835-2854 and pertinent references within these articles.
4. (a) Arista L.; Gruttadauria M.; Noto R. *Heterocycles*, **1998**, 48, 1325-1330; (b) Mihelich E. D. *J. Am. Chem. Soc.*, **1990**, 112, 8995-8997.
5. Arista L.; Gruttadauria M.; Thomas E. J. *Synlett*, **1997**, 627-628.
6. (a) Eames J.; de las Heras M. A.; Jones R. V. H.; Warren S. *Tetrahedron Lett.*, **1996**, 37, 4581-4584; (b) Eames J.; Warren S. *Tetrahedron Lett.*, **1996**, 37, 3525-3528; (c) Bird P.; Eames J.; Fallis A. G.; Jones R. V. H.; Roddis M.; Sturino C. F.; O'Sullivan S.; Warren S.; Westwell M. S.; Worrall J. *Tetrahedron Lett.*, **1995**, 36, 1909-1912; (d) Djakovitch L.; Eames J.; Jones R. V. H.; McIntyre S.; Warren S. *Tetrahedron Lett.*, **1995**, 36, 1723-1726; (e) Sansbury F. H.; Warren S. *Tetrahedron Lett.*, **1992**, 33, 539-542; (f) McIntyre S.; Warren S. *Tetrahedron Lett.*, **1990**, 31, 3457-3460.
7. Mihelich E. D.; Daniels K.; Eickhoff D. J. *J. Am. Chem. Soc.*, **1981**, 103, 7690-7692.
8. Rémion J.; Dumont W.; Krief A. *Tetrahedron Lett.*, **1976**, 1385-1388.
9. Koert U. *Tetrahedron Lett.*, **1994**, 35, 2517-2520.
10. Stewart J. J. P. *J. Comput. Chem.*, **1989**, 10, 210-220; *J. Comput. Chem.*, **1991**, 12, 320-341.
11. Semiempirical calculations with the AM1 method were also performed, but results are unsatisfactory. In fact, conformational analysis does not predict any stable *"apt for closure"* conformation corresponding to the *endo/exo* product; moreover the method fails in the prediction of transition states energies, which do not match the experimental reactivity.
12. Comparison between models **D** and **E** shows that the TMS group lowers the activation energy. Nonetheless such an effect seems overestimated. As a matter of fact, the predicted activation energy for **F**, which is comparable with that for **D**, seems low in front of the experimental reactivity trend. Noticeably, calculations performed on the non-silylated analogue of **F** predict for the "*endo/exo*" closure an activation energy of about 23 kcal/mol. For **F** and its non-silylated analogue, the predicted higher activation energy than **E** and **D** respectively, may be accounted for by a stabilizing effect of the benzyloxy group upon the positively charged episelenonium framework in the intermediate species.