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Lactonisation and Lactone Ether Formation of Nerol Geraniol Compounds. Use of ^{13}C to Identify the Cyclisation Process

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Abstract:
The cyclisation process leading stereoselectively to six and/or five membered ring lactones and lactone ethers from optically active epoxy or diepoxy β-hydroxyesters, or diastereoisomeric epoxy lactones obtained from nerol and geraniol has been developed. The ring closure leading to lactones mirrors the well-known iodolactonisation process while for the cyclic ether formation, Baldwin's rules are obeyed. ^{13}C NMR data are helpful for determining the relative stereochemistry of different carbon chiral centers.

Keywords: Lactonisation; Cyclisation; Etherification; Terpenes.

Tetrahydrofuran and tetrahydropyran frames are important targets for synthesis either as final products or as useful synthons. Polycyclic ether containing substances have been isolated from a variety of living sources and showed potent biological activities.[1-4] In particular 2,5-substituted tetrahydrofurans are commonly encountered in many natural products, as polyether antibiotics,[5] acetogenins.[6,7] Development of various methods for constructing cyclic ether systems have attracted much attention and has been extensively studied by many groups.[8-10]

In the course of our studies towards the synthesis of 1,3 and 1,2,3 polyhydroxylated chiral lactone synthons we developed a method for their preparation involving three key reactions: a) Sharpless asymmetric epoxidation of an allylic alcohol, b) stereocontrolled addition of tert-butyl lithioesters to an optically active α,β-epoxyaldehyde[11] and c) regio and stereospecific Lewis acid mediated lactonisation.[12] We have recently applied this methodology starting from terpenic allylic alcohols nerol and geraniol[13,14] where the alcohol generated by epoxide opening effected cyclic ether formation onto the terpenic olefin. The intramolecular cyclisation by epoxide ring opening occurred in these systems *via* activation of 6-endo over the usually favoured 5-exo process.

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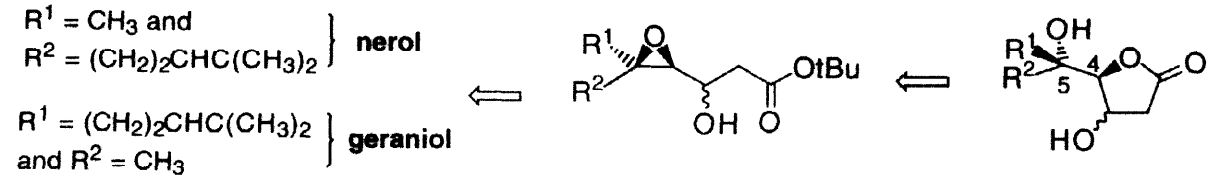
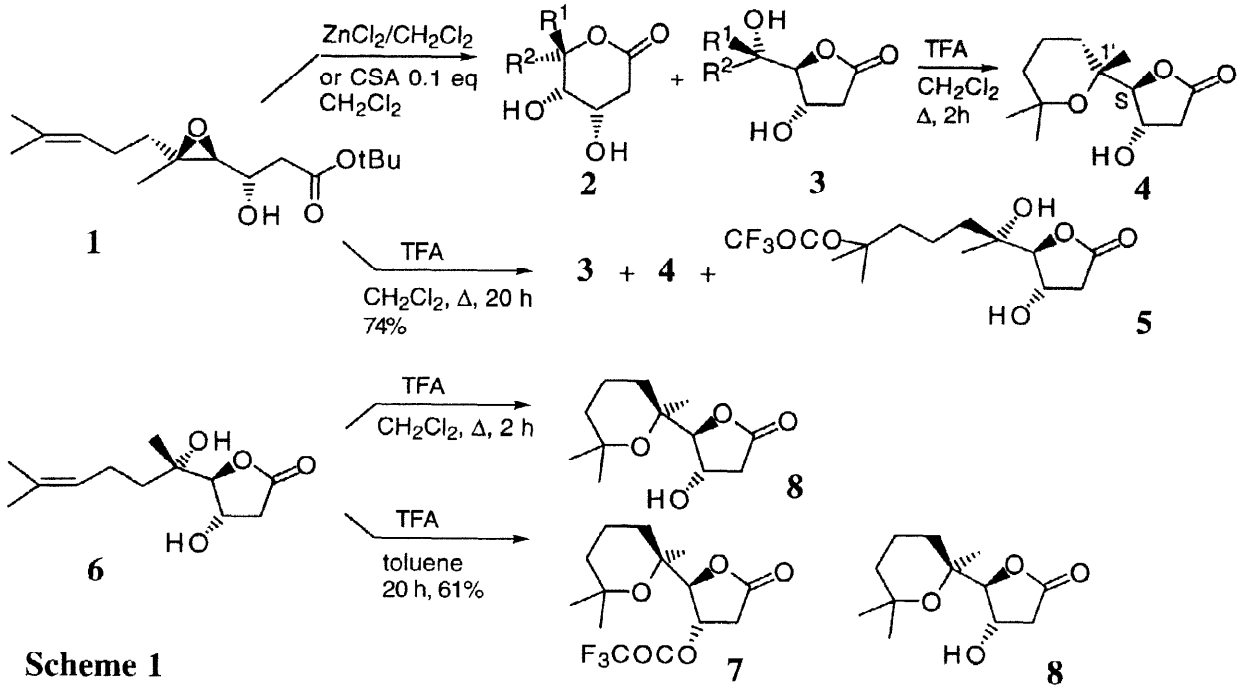


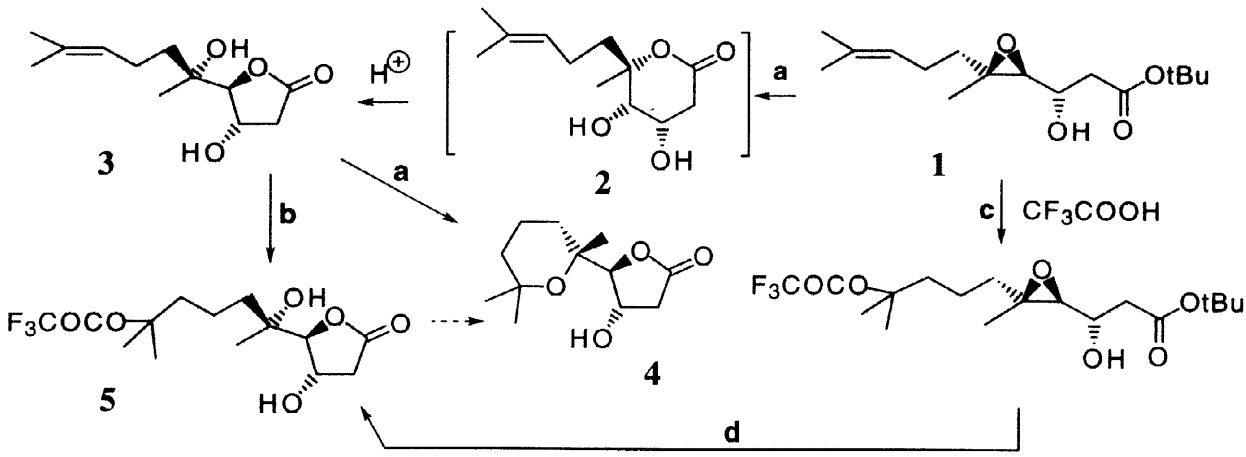
In the present paper we wish to describe studies concerning the modification of the cyclisation process and the formation of different lactone ethers from that previously described.[14] We will also show the usefulness of the ^{13}C data to identify the cyclisation process in both lactone and ether systems.

When δ,γ-epoxy β-hydroxy ester **1** issued from geraniol compound and synthesized as previously described,[13] reacts with anhydrous $ZnCl_2$ in dichloromethane two compounds were obtained **2** and **3** resulting from a C-5 ring opening of the epoxide (scheme 1). In addition, lactone **3** reacts with trifluoroacetic acid (TFA, CH_2Cl_2, 45°C, 2 h) leading to the lactone ether **4** (scheme 1).



Scheme 1

The same reaction was performed on the ester **1** by using two other Lewis acids i.e. camphorsulfonic acid (CSA) and TFA. When using a catalytic amount of CSA (0.1 eq, CH_2Cl_2) the same reaction occurred leading to products **2** and **3**. In contrast reaction of **1** with freshly distilled TFA under reflux (20 h) in CH_2Cl_2 led in 74% total yield to compounds **3**, **4** and **5** in 1:3:4 ratio. Butyrolactone **3** and lactone ether **4** are identical to those obtained previously (C-5 opening of the epoxide ring of **1**). For this latter reaction we have questioned about the role of TFA. The different possibilities leading to formation of **3**, **4** and **5** are presented in scheme 2.



Scheme 2

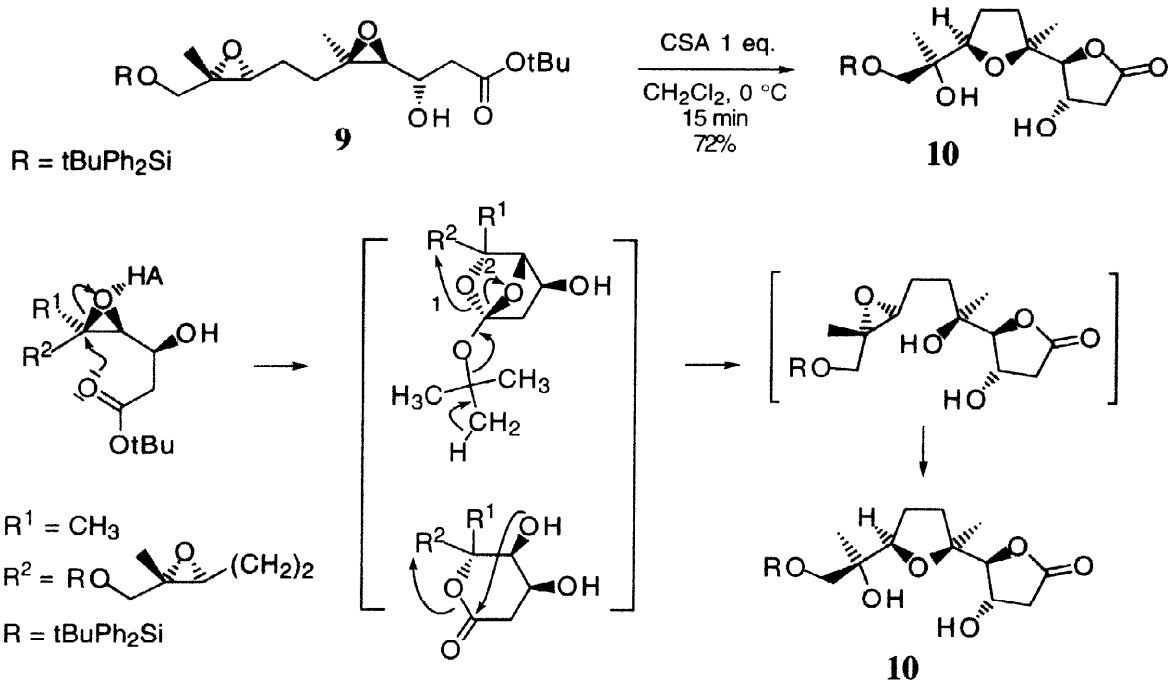
Compound **5** was isolated only when **1** was the starting material (not when synthesizing lactone ether **4** from **3** in the presence of TFA), nor was lactone **5** transformed into lactone ether **4** even after 20 h under reflux. As expected the intramolecular attack of the C-5 oxygen atom of lactone **3** to the activated double bond leading to lactone ether **4** should be faster than the intermolecular attack of CF_3COO^- at the same site of lactone **3** (path a versus b).

These observations suggest a process whereby CF_3COOH is initially added to the double bond of the epoxy ester **1** followed by the C-5 lactonisation-isomerisation reaction leading to **5** (path c, d). A competing process (path a) affords compounds **3** and **4**.

It is noteworthy that when lactone **6** issued from nerol is allowed to react in toluene in presence of TFA (90°C, 20 h) the lactone ether **7** trifluoroacetylated on the C-3 oxygen atom is obtained in 68% yield. This compound is obtained pure by recrystallisation in petroleum ether, while purification on silica yields affords quantitatively deprotected lactone ether **8** which its X-ray structure has already been established.[14]

We next performed the cyclisation reaction on an optically active diepoxyester issued from nerol. (3S,4S,5R,8S,9S)-tert-butyl-10-(tert-butyldiphenyl silyloxy)-5,9-(dimethyl)-8,9-4,5-bisepoxy-3-hydroxydecanoate **9** synthesized as previously described[13] was allowed to react with $ZnCl_2$ (2 eq., CH_2Cl_2, 3 h) or in presence of CSA (0.1 eq., CH_2Cl_2, 15 min). A sole product of the reaction was obtained that was identified to be compound **10** (scheme 3). It was crystallised in a mixture of ether / petroleum ether / benzene and its X-ray structure established (fig. 1). It confirmed unambiguously the presence of two five membered ring frames i.e the butyrolactone and tetrahydrofuran cycles. Taking into account the absolute stereochemistry of the starting ester the X-ray structure demonstrates inversion of configuration at the C-5 and C-8 carbon atoms. The proposed mechanism of the reaction is shown is scheme 3.

The lactonisation process is operating first through the formation of an intermediate six membered ring in a regio and stereospecific manner (C-5 inversion). The intermediate(s) is rapidly isomerised through orthoester formation and/or isobutene extrusion to the corresponding butyrolactone and that before the C-4 hydroxy group opens the second epoxide group at the C-8/C-9 position. Orthoester formation proceeds much more rapidly than the ether formation most likely due to energy constraints.



Scheme 3

As mentioned earlier the lactonisation process is in better agreement with the iodolactonisation reactions[15,16] than with the Baldwin's rule.[17,18] The preferential intramolecular attack is governed by the degree of substitution of the epoxide ring leading in our case to a 6-endo ring closure.

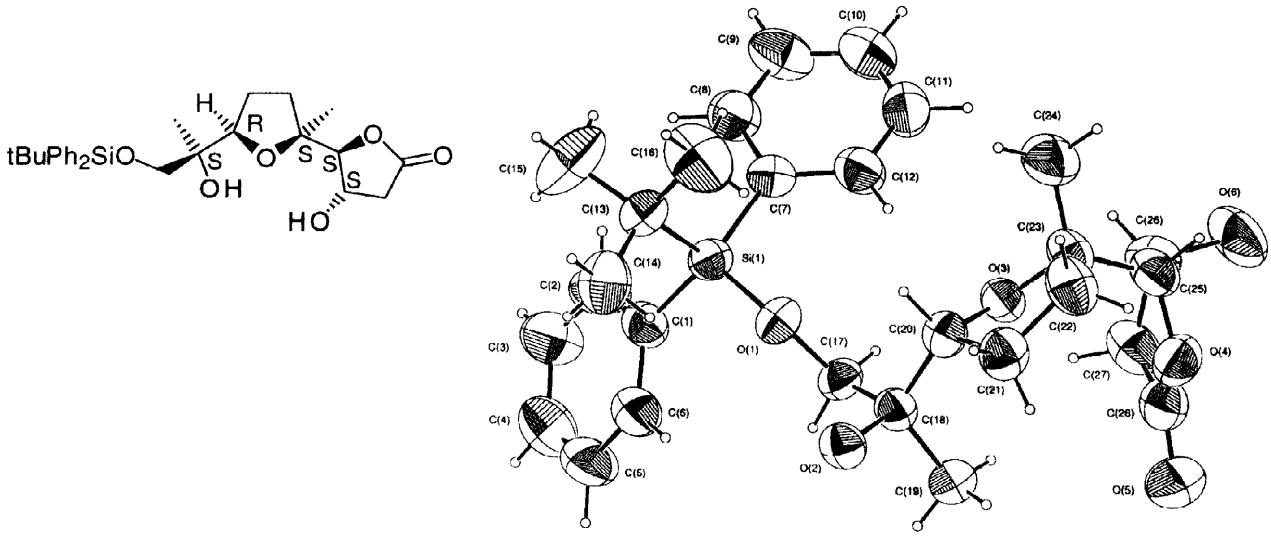
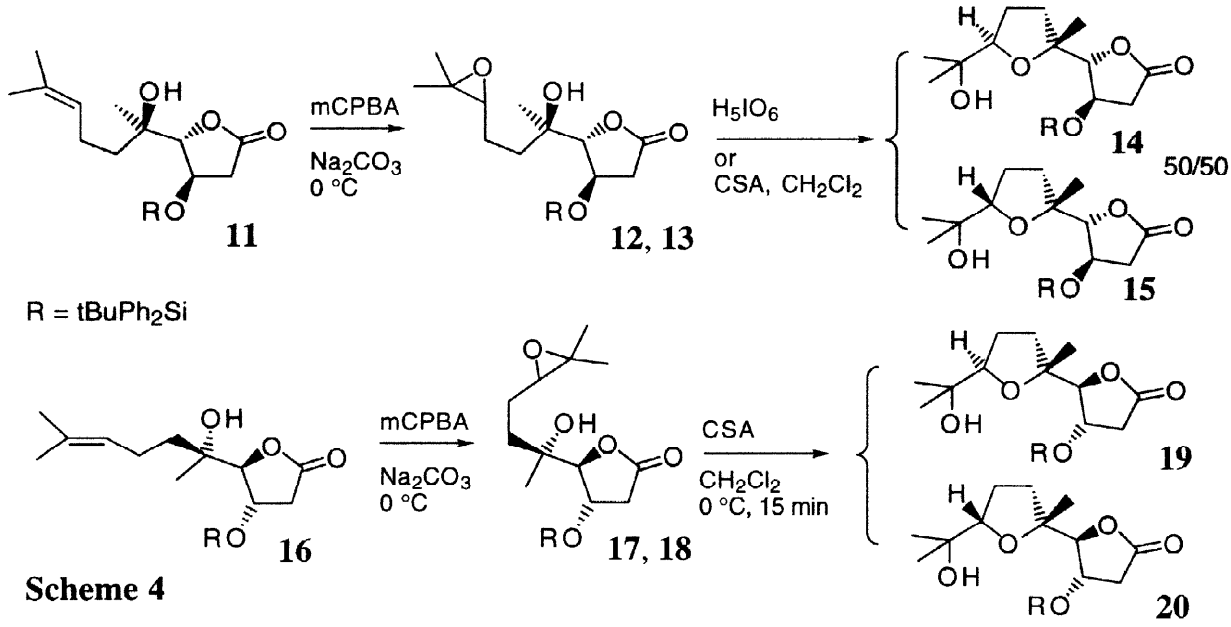


Figure 1: X-ray structure of compound **10**: crystal data $C_{28}H_{38}O_6Si$ M = 498.69, colourless crystal monoclinic, space group $P2_1$ a = 9.552, b = 12.775, c = 11.151 Å,V = 1360.4 Å^3, Z = 2, F (000) = 532. Data collected on a Kappa-CCD diffractometer at r.t. using graphite monochromator (Mo-Kα radiation). 3418 unique reflections were collected in the range $0 \leq 0 \leq 27°$. The structure was solved by direct methods and refined using 2588 reflections with $I > 3\ \sigma(I)$. The final residuals were R = 0.042 and Rw = 0.052. Atomic coordinates bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Concerning the formation of the cyclic ether system differences arise between the cyclisation process on a double bond (leading to **4** or **8**) or on a epoxide ring. In the former a tetrahydropyran system is formed while in the latter a tetrahydrofuran one is obtained. Tetrahydrofuran system also arises in the following reactions. Lactones **11** and **16** issued from nerol and geraniol respectively, were epoxidized (mCPBA, Na_2CO_3, $CHCl_3$/ether 0°C 4 h) leading in 90% to the diastereoisomeric epoxides **12**, **13**, and **17**, **18** (scheme 4). Epoxides **12**, **13** can be obtained in 90% purity (each contaminated with the other diastereoisomer) after silica gel purification, and **17**, **18** are obtained as an inseparable mixture. These compounds were subjected to cyclisation in presence of different acids or Lewis acids (H_5IO_6,TFA, CSA). In each case the five membered lactone ethers **14**, **15** and **19**, **20** were obtained.



Scheme 4

The acid catalysed cyclisation of epoxyalcohols is one of the most effective methods for constructing cyclic ethers. The cyclisation process as described by many groups when there are no electronic directing effects,[19,20] proceeds in the exo mode giving cyclic ethers (tetrahydrofuran in our case) having a hydroxy group in the side chain. The regioselectivity of the cyclisation is predicted by the Baldwin's rule.

The formation of ethers by interaction of a hydroxy group with a double bond are less studied. We can note first that tetrahydropyran formation is predicted by the Baldwin's rule in which the 6-endo process in trigonal systems is favored. In alkenol systems, tetrahydropyran formation has also been reported by Whittaker[21] to occur almost exclusively (> 75% yield) in presence of a superacid (fluorosulfuric acid). In ion radical chemistry, 4-pentenyl-oxy radical obtained *in situ* from N-alkyloxy pyridine-2 (1H) thiones are shown to undergo fast ring closure reactions leading to tetrahydrofuran frames almost exclusively.[22] Finally while oxidative cyclisation of 5-hydroxy alkenes with rhenium oxide in presence of an oxidant leads to tetrahydrofuran systems,[23] rhenium oxide alone provides non oxidative cyclisation to tetrahydropyran rings.[24]

^{13}C NMR data. In many polycyclic tetrahydrofurans containing substances like annonaceous acetogenins who do not produce crystals for an adequate X-ray crystallographic analysis the determination of absolute stereochemistry represents the major problem in the elucidation of their structures.[25] The comparison of ^{13}C data of our compounds may help to elucidate some of the problems arised.

In a previous publication[14] we have shown how ^{13}C NMR chemical shifts of furanone can be linked to the relative configuration threo/erythro of C3/C4 carbon atoms. We have also demonstrated that these relative configurations are closely connected to the lactonisation process especially to the endo over exo cyclisation.

The ^{13}C data concerning the C3, C4, C5 carbon atoms of lactones and C3, C4, C5, C8, C9 for epoxidized lactones and lactone ethers are presented in table 1. These results show the following trends. The C4 chemical shift for all compounds listed is well defined between the region 90-94 ppm. This is in accordance with our previous result where a C3/C4 threo configuration leads to C4 chemical shifts of ~92 ppm and an erythro one to δ = 84-85 ppm (compounds **21, 22,** table 1). This is also confirmed by the X-ray structure of compound **10** (δC4 = 90.3 ppm) where a C3/C4 threo configuration is observed.

Table 1 - Relevant ^{13}C NMR chemical shifts for C3, C4, C5, C8, C9 carbon atoms

	3	**4**	**5**	**6**	**7**	**8**	**9**[a]	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**[a]	**22**[a]
C3	67.6	68.4	67.5	67.8	75.8	68.4	66.4	68.5	70.0	70.2	70.1	70.2	70.4	69.7	69.7	69.9	70.0	70.1	69.7	69.5
C4	92.3	94.2	92.0	92.1	90.0	93.2	65.5	90.3	92.6	93.0	93.3	91.8	92.7	93.5	93.4	93.8	92.5	93.3	84.6	85.8
C5	73.2	72.1	72.9	73.0	72.7	72.3	61.5	82.5	73.1	72.5	72.5	82.6	82.6	73.1	72.6	72.6	82.7	83.0	74.3	74.2
C8							61.0	81.0		64.3	64.2	85.5	88.4		64.3	64.3	85.0	87.8		
C9		74.1			74.3	74.0	61.8	73.4		59.6	58.7	71.4	69.9		59.2	59.5	71.1	69.9		

a: Lactones **21** and **22** are obtained from the minor aldol adducts issued from nerol and geraniol respectively and are described in ref. 14 (ref. 14, compounds **13a** and **13b**). Compound **9** is described in ref. 13.

The C5 carbon atom resonates at two different frequencies based on its structural context. When it is not engaged in a heterocycle or when is part of a tetrahydropyran ring it resonates between δ = 72.1-73.2 ppm. In the contrary when it is engaged in a tetrahydrofuran ring it is shifted downfield to almost 10 ppm (δ ≈ 82 ppm). We can also remark that in the tetrahydrofuran system the variation of C5 chemical shift is too weak for the different compounds studied that it cannot be helpful for the determination of absolute configuration of this quaternary carbon atom.

The chemical shift of C8 carbon atom possess more relevant informations. We can observe first that the substitution of a methyl group by $CH_2OSitBuPh_2$ in the C9 position of the terminal epoxide affects the chemical shift of the C8 carbon atom. In fact, when comparing epoxide **9** (δC8 = 61.0 ppm)[13] with epoxide lactones **12, 13, 17, 18,** a 3.2 ppm upfield chemical shift is observed for **9** due to the substituent modification. When these

compounds are cyclised to give the tetrahydrofuranic lactones **10** and **14**, **15**, **19** **20**, except for a value of δC8 = 81.0 ppm for **10**, two couples of values are observed i.e. δC8 ≈ 85 ppm and δC8 ≈ 88 ppm. If we apply the same difference of chemical shift due to substituent modification on **10** (δ = 81.0 + 3.2 = 84.2 ppm) we find a value analogous to that of compounds **14** and **19**. Taking into account the X-ray structure of compound **10** we thus can say that the 2,5 substitution in the tetrahydrofuran ring is *cis* for compounds **10, 14** and **19** and consequently *trans* for compounds **15** and **20**. This is also in agreement with data from the literature[26,27] where for a *cis* disposition on 2,5 substituted tetrahydrofuran rings the tertiary carbon atom adjacent to the isopropyl alcohol group resonates at 84 ppm. For the C9 chemical shifts we observe the same trends concerning the substituent modification. In diepoxyde **9** C9 resonates at δ = 61.8 ppm ($CH_2OSitBuPh_2$ substitution) and in epoxides **12** and **18** at δ = 59.6 and 59.5 ppm respectively (Δδ ≈ 2.3 ppm). This difference remains the same between C9 of compound **10** and that of compounds **14** and **19** (δC9 = 73.4 ppm (**10**) and 71.4, 71.1 ppm for **14** and **19** respectively).

According to all these data we can assign the absolute configurations of C8 carbon atom of epoxides **12, 13** and **17, 18** and also that of the tetrahydrofuran systems (C8 (R) for compounds **13, 14, 18, 19** and (S) for compounds **12, 15, 17, 20**).

In conclusion we have studied the lactonisation and cyclic ether formation of compounds issued from nerol and geraniol. Using an X-ray structure and the appropriate ^{13}C chemical shifts of compounds synthesized we were able to assign most of the absolute configurations of the lactone and tetrahydrofuran systems.

EXPERIMENTAL SECTION

Commercially available reagents were used as supplied $ZnCl_2$ was dried at 150°C/0.1 torr for 2 h. All solvents were distilled prior to use. HPLC chromatography was carried out on a Jobin-Yvon or a Prochrom apparatus using Merck 15 μm or Amicon silica (6-35 μm). Infrared spectra were recorded in a Perkin-Elmer 883 spectrophotometer. ^1H (250 MHz) and ^{13}C (62.9 MHz) NMR spectra were recorded in $CDCl_3$ using Bruker AC250 instrument with TMS as internal reference. Mass spectra were obtained on a Nermag R10-10 mass spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Compounds **1**, **9**[13] and **2**, **3**, **6**, **8**, **11** and **16**[14] have already been described.

(4S,5S,1'R)-5-[1',3',3'-trimethyl-2'-oxacyclohexyl]-4-hydroxy-2-oxo-1-oxacyclopentane **4**. To a stirred solution of 0.115 g (0.5 mmol) of lactone **3** in 7 mL of anhydrous CH_2Cl_2 under N_2 atmosphere, 2 mL of freshly distilled TFA is added and heated under reflux (45°C) for 2 h. The reaction mixture is evaporated and purified on silica gel eluting with petroleum ether (PE)/ethyl acetate (EA) 5/5 to yield 98 mg (85% yield) of lactone ether **4** (Rf = 0.25). F = 114°C. IR: (film), ν cm^{-1}: 3613-3531 (O-H); 2978-2946 (C-H); 1780 (C=O); 1046 (C-O). ^1H NMR δ ppm: 4.57 (ddd, J = 7.3; 4.2; 3.5 Hz, 1H); 3.97 (d, J = 3.5 Hz, 1H); 2.87 (dd, J = 18; 7.3 Hz, 1H); 2.43 (dd, J = 18; 4.2 Hz, 1H); 1.89-1.40 (m, 6H); 1.25; 1.20; 1.12 (3s, 9H). ^{13}C NMR δ ppm: 175.9; 94.2; 74.1; 72.1; 68.4; 38.2; 36.3; 32.9; 32.0; 27.2; 21.6; 15.6. Analysis (calc./found): %C 63.14 (63.13); %H 8.83 (8.91).

(4R,5S,1'R)-5-[1',5'-dimethyl-5'-trifluoroacetoxy-1'-hydroxyhexyl]-4-hydroxy-2-oxo-1-oxacyclopentane **5**. A stirred solution of 500 mg (1.76 mmol) of epoxyester **1** and 0.5 mL of TFA in anhydrous CH_2Cl_2 (13 mL) is heated under reflux for 20 h. The reaction mixture is quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer is separated and extracted three times (3x10 mL) with ether. All organic phases are dried over $MgSO_4$ and solvent evaporated. The crude product was purified on silica gel eluting with PE/EA (4/6) to yield 104 mg (26% yield) of compound **4** (Rf = 0.33), 37 mg (10%) of **3** (Rf = 0.24) and 231 mg (39%) of compound **5** (Rf = 0.19).
Compound **5**: IR (film), ν cm^{-1}: 3428 (O-H); 2982 (C-H); 1777-1664 (C=O); 1167 (C-O). ^1H NMR δ ppm: 4.63 (ddd, J = 7.6; 4.3; 3.5 Hz, 1H); 4.16 (d, J = 3.5 Hz, 1H); 2.92 (dd, J = 18.2; 7.6 Hz, 1H) ; 2.73 (s, 2H); 2.54 (dd, J = 18.2; 4.3 Hz, 1H); 1.86-1.51 (m, 6H); 1.56; 1.54 (2s, 6H); 1.26 (s, 3H). ^{13}C NMR δ ppm: 175.9; 92.0; 89.1; 72.9; 67.5; 40.6; 38.6; 37.9; 25.7; 25.5; 22.8; 17.4. Analysis (calc./found): %C 49.40 (49.12); %H 6.20 (6.18).

(4S,5S,1'S)-5-[1',3',3'-trimethyl-2'-oxacyclohexyl]-4-trifluoroacetoxy-2-oxo-1-oxacyclopentane **7**. A solution of lactone **6** (100 mg, 0.44 mmol) and TFA (2 mL) in toluene (7 mL) is heated under reflux for 20 h. The solution is quenched at r.t. with saturated aq. $NaHCO_3$ (5 mL) and extracted three times (3x20 mL) with ether. The organic phases are dried over $MgSO_4$ solvent evaporated and the crude product is recrystallised in ether to leave 89 mg (61%) of compound **7**. IR: (film), ν cm^{-1}: 3016-2979 (C-H); 1782 (C=O); 1124 (C-O). ^1H NMR δ ppm: 5.70 (d, J = 6.80 Hz, 1H); 4.12 (s, 1H); 3.10 (dd, J = 19.1; 6.80 Hz, 1H); 2.48 (dd, J = 19.1 Hz, 1H); 1.80-1.66-1.33 (m, 6H); 1.37-1.21-1.10 (3s, 9H). ^{13}C NMR δ ppm: 174.0; 90.0; 75.8; 74.3; 72.7; 35.7; 35.5; 29.0; 15.3; 32.6; 27.1; 23.2. MS (DCI/NH_3): 347 (M+23, 14%); 325 (M+1, 100%); 211 (M-113, 24%). Analysis (calc./found): %C 51.62 (51.85); %H 6.02 (5.91).

(4S,5S,1'S,3'R,1"S)-5-[3'-(1"-hydroxy-1"-methyl)tert-butyldiphenylsilyloxyethyl-1'-methyl-2'-oxacyclopentyl]-4-hydroxy-2-oxo-1-oxacyclopentane **10**. To a solution of diepoxyester **9** (964 mg, 1.74 mmol) in anhydrous CH_2Cl_2 (25 mL) under stirring, N_2 and at 0°C, CSA (400 mg, 1.74 mmol) is added. After 15 min of stirring the reaction mixture is quenched with sat. aqueous $NaHCO_3$ (5 mL). The aqueous phase is extracted three times with ether (3x10 mL) and all organic phases are dried over $MgSO_4$ and solvent evaporated. The crude product was purified over silica gel eluting with PE/EA (5/5) to yield 620 mg (72%) of compound **10** (Rf = 0.26). IR (film), ν cm^{-1}: 3516-3342 (O-H); 3028-2937 (C-H); 1768 (C=O); 1111 (C-O). ^1H NMR δ ppm: 7.66-7.43 (m, 10H); 4.47 (ddd, J = 7.3; 5.2; 4 Hz, 1H); 4.16 (d, J = 4 Hz, 1H); 3.96 (t, J = 8.7 Hz, 1H); 3.52 and 3.41 (2d, J = 9.8 Hz, 2H); 2.72 (dd, J = 18; 7.3 Hz, 1H); 2.42 (dd, J = 18; 5.2 Hz, 1H); 2.10 (m, 1H), 1.87 (m, 2H); 1.65 (m, 1H); 1.30-1.15 (2s, 6H); 1.07 (s, 9H). ^{13}C NMR δ ppm: 175.1; 135.6; 130.0; 127.7; 127.6; 132.8; 132.7; 90.3; 82.5; 81.0; 73.4; 68.8; 68.5; 38.2; 33.3; 26.3; 26.9; 24.5; 20.4; 19.3. $[\alpha]_D^{25}$ = + 8.0° (c = 1.4, $CHCl_3$). MS (DCI/NH_3): 516 (M+18, 100%); 499 (M+1, 0,39%).

(4R,5R,1'R,4'S) and (4R,5R,1'R,4'R)-5-(1'-hydroxy-1',5'-dimethyl-4',5'-epoxyhexyl]-4-tert-butyldiphenylsilyloxy-2-oxo-1-oxacyclopentane **12** *and* **13**. A suspension of 533 mg of lactone **11** (1.14 mmol) and 243 mg (2.29 mmol) of Na_2CO_3 in 5 mL of 2:1 (v/v) mixture of $CHCl_3$ and ether was cooled to -78°C before the addition of 370 mg (1.49 mmol) of m-chloroperbenzoic acid (70%) in 3 mL of $CHCl_3$ over a period of 8 min. The mixture was kept at -78°C under stirring for 5 h then allowed to warm at 0°C and then quenched with 8 mL of 10% $NaHSO_3$ solution. After stirring for a further 15 min the mixture was diluted with CH_2Cl_2 (20 mL) and washed with 50% aq. $NaHCO_3$. The organic phase was dried over Na_2SO_4 and

solvent evaporated. The crude product was purified on silica gel eluting with PE/CH_2Cl_2/EA to leave yield a 80/20 mixture of compounds **12, 13** (495 mg, total yield 90%).
Compound **12**. IR (film) ν cm^{-1}: 3480 (O-H); 3050-2980 (C-H); 1785 (C=O); 1124 (C-O). ^1H NMR δ ppm: 7.61-7.38 (m, 10H); 4.54 (td, J = 1.0; 6.1 Hz, 1H); 4.25 (s, 1H); 3.58 (t, J = 7.3 Hz, 1H); 2.71 (dd, J = 6.1; 17.8 Hz, 1H); 2.37 (dd, J = 1; 17.8 Hz, 1H); 1.73 (m, 2H); 2.05 (ddd, J = 6.5; 9.3; 12.3 Hz, 1H); 1.46 (ddd, J = 6.7; 8.5; 12.3 Hz, 1H); 1.04 (s, 3H); 1.02 (s, 9H); 1.00 (s, 3H); 0.7 (s, 3H). ^{13}C NMR δ ppm: 178.5; 135.9; 132.9; 130.2; 93.0; 72.5; 70.2; 64.3; 59.6; 39.2; 35.3; 26.9; 24.8; 23.3; 21.8; 19.7; 19.1.
Compound **13**. IR (film) ν cm^{-1}: 3480 (O-H); 3050-2980 (C-H); 1785 (C=O); 1124 (C-O). ^1H NMR δ ppm: 7.63-7.40 (m, 10H); 4.51 (dd, J = 0.8; 5.9 Hz, 1H); 4.22 (s, 1H); 3.54 (t, J = 8.2 Hz, 1H); 2.70 (dd, J = 5.9; 17.8 Hz, 1H); 2.35 (dd, J = 0.8; 7.8 Hz, 1H); 1.75 (m, 2H); 2.18 (ddd, J = 8.9; 10.0; 13.3 Hz, 1H); 1.50 (ddd, J = 5.8; 10.4; 13.3 Hz, 1H); 1.09 (s, 9H); 1.05 (s, 3H); 0.97 (s, 3H); 0.65 (s, 3H). ^{13}C NMR δ ppm: 178.3; 135.8; 132.8; 128.0; 93.3; 72.5; 70.1; 64.2; 58.7; 39.3; 35.40; 3.7; 25.0; 23.6; 22.1; 19.1; 18.7. Analysis (calc./found): %C 69.98 (69.67); %H 8.02 (7.94).

(4R,5R,1'R,3'R) and (4R,5R,1'R,3'S)-5-[3'-(1''-hydroxy-1''-methyl)ethyl-1'-methyl-2'-oxacyclopentyl]-4-tert-butyldiphenylsilyloxy 2-oxo-1-oxacyclopentane **14** *and* **15**. A solution of 150 mg (0.31 mmol) of each of the precedent 80/20 mixture of compounds **12, 13** in THF/H_2O (v/v 3/1) was treated at 0°C with 106 mg (0.46 mmol) of periodic acid. After stirring for 12 h leaving the mixture gradually to reach the r.t., it is diluted with ether and washed with sat. $NaHCO_3$, then aq. NaCl. The organic phase is dried over $MgSO_4$ and solvent evaporated. The crude mixture purified on silica eluting with pentane/THF/CH_2Cl_2 (3.5/0.5/6) to yield compounds **14, 15** (110 mg, 73% yield). Rf(**14**) = 0.17, Rf(**15**) = 0.24.
Compound **14**. IR (film), ν cm^{-1}: 3484 (O-H); 3074-2971 (C-H); 1788 (C=O); 111 (C-O). ^1H NMR δ ppm: 7.65-7.44 (m, 10H); 4.57 (d, J = 6.0; 0.7 Hz, 1H); 4.28 (s, 1H); 3.63 (t, J = 7.4 Hz, 1H); 2.73 (dd, J = 17.5; 6.0 Hz, 1H); 2.41 (dd, J = 17.5; 0.7 Hz, 1H); 2.15 (m, 1H); 1.72 (m, 2H); 1.42 (m, 1H); 1.07; 1.01; 0.73 (3s, 9H); 1.03 (s, 9H). ^{13}C NMR δ ppm: 176.7; 135.8-130.2-128.0; 132.8; 91.8; 85.5; 82.6; 71.4; 70.2; 39.3; 34.3-26.0; 26.8; 26.7-24.9-22.0; 19.1. $[\alpha]_D^{25}$ = + 1.9° (c = 1.0 , $CHCl_3$). MS (DCI/NH_3): 500 (M+18, 100%).
Compound **15**. IR (film), ν cm^{-1}: 3503 (C-H); 3074-2971 (C-H); 1785 (C=O); 1109 (C-O). ^1H NMR δ ppm: 7.65-7.44 (m, 10H); 4.54 (d, 1H, J = 6.0 Hz); 4.25 (s, 1H); 3.58 (t, J = 7.8 Hz, 1H); 2.74 (dd, J = 17.7; 6.0 Hz, 1H); 2.39 (d, J = 17.7 Hz, 1H); 2.20 (m, 1H); 1.75 (m, 2H); 1.30 (m, 1H); 1.08; 1.00; 0.68 (3s, 9H); 1.05 (s, 9H). ^{13}C NMR δ ppm: 176.4; 135.8; 130.2; 132.9; 132.7; 128.0; 92.7; 88.4; 82.6; 70.4; 69.9; 39.0; 34.2; 27.8; 26.8; 25.5; 24.2; 23.6; 19.1. $[\alpha]_D^{25}$ = + 6.2° (c = 0.8 , $CHCl_3$). MS (DCI/NH_3): 500 (M+18, 100%); 483 (M+1, 0.67%).

(4S,5S,1'R,3'R) and (4S,5S,1'R,3'S)-5-[3'-(1''-hydroxy-1''-methyl)ethyl-1'-methyl-2'-oxacyclopentyl]-4-tert-butyldiphenylsilyloxy 2-oxo-1-oxacyclopentane **19** *and* **20**. Synthesis was carried out as for compounds **12** and **13** starting from 300 mg (0.64 mmol) of lactone **16** we obtained 247 mg (80% yield) of an inseparable mixture of compounds **17** and **18** was obtained. A solution of 200 mg (0.41 mmol) of compounds **17** and **18** in anhydrous CH_2Cl_2 (8 mL) under stirring and N_2 was treated at 0°C with CSA (96 mg, 0.41 mmol) for 2 h. The reaction mixture was then quenched with aq. $NaHCO_3$ (4 mL). The aqueous phase was extracted three times with ether (3x10 mL) and all organic phases were dried over $MgSO_4$ and solvent evaporated. The crude product was purified over silica eluting with PE/CH_2Cl_2/EA (56/14/30) to yield **19** (80 mg) and **20** (80 mg) in a total yield of 80%.

Compound **19**. ^{1}H NMR δ ppm: 7.68-7.61 (m, 4H); 7.46-7.37 (m, 6H); 4.43 (td, J = 2.0; 7.5 Hz, 1H); 4.39 (d, J = 2 Hz, 1H); 3.70 (dd, J = 6.5; 8.0 Hz, 1H); 2.56 (dd, J = 6.5; 18.0 Hz, 1H); 2.40 (dd, J = 2.5; 18.0 Hz, 1H); 1.74 (m, 2H); 1.48 (m, 3H); 1.10 (s, 3H); 1.09 (s, 3H); 1.04 (s, 9H); 0.95 (s, 3H). ^{13}C NMR δ ppm: 175.6; 135.8; 133.0; 132.6; 130.2; 128.0; 92.5; 85.0; 82.7; 71.1; 70.0; 38.9; 33.8; 26.8; 25.7; 24.9; 22.1; 19.0. Analysis (calc./found): %C 69.53 (69.67); %H 7.90 (7.94).
Compound **20**. ^{1}H NMR (400 MHz) δ ppm: 7.65-7.59 (m, 4H); 7.43-7.38 (m, 6H); 4.36 (td, J = 1.5; 6.5 Hz, 1H); 4.28 (d, J = 1.2 Hz, 1H); 3.20 (dd, J = 5.5; 10.3 Hz, 1H); 2.55 (dd, J = 6.5; 17.9 Hz, 1H); 2.41 (dd, J = 1.7; 17.9 Hz, 1H); 1.76 (sb, 1H); 1.72 (dddd, J = 7.9; 10.4; 11.8; 12.7 Hz, 1H); 1.49 (dddd, J = 1.7; 5.5; 7.4; 12.7 Hz, 1H); 1.45 (ddd, J = 1.7; 7.9; 9.6 Hz, 1H); 1.27 (ddd, J = 7.6; 9.8; 11.9 Hz, 1H); 1.06 (s, 3H); 1.04 (s, 3H); 1.03 (s, 9H); 0.97 (s, 3H). ^{13}C NMR δ ppm: 176.1; 136.0; 132.9; 130.4; 128.1; 93.4; 87.8; 70.2; 70.0; 53.1; 39.0; 34.1; 27.53; 26.95; 25.80; 24.15; 23.92; 19.26. Analysis (calc./found): %C 69.43 (69.67); %H 7.98 (7.94).

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