Heteroatom-Assisted Isomerization of Oxiranes to Allylic Alcohols Promoted by Bases

Alessandro Mordini,*,‡ Sabina Pecchi,‡ Giuseppe Capozzi,‡ Antonella Capperucci,‡ Alessandro Degl'Innocenti,§ Gianna Reginato,‡ and Alfredo Ricci||

Centro CNR Composti Eterociclici, c/o Dipartimento di Chimica Organica "U. Schiff", via G. Capponi 9, 50121 Firenze, Italy, Dipartimento di Chimica, via N. Sauro 85, 85100 Potenza, Italy, and Dipartimento di Chimica Organica "A. Mangini", via Risorgimento 4, 40136 Bologna, Italy

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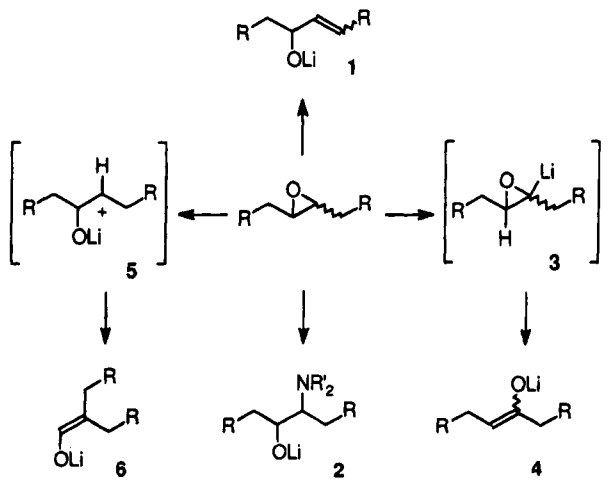
The isomerization of alkoxy-substituted oxiranes to hydroxy-substituted ene ethers promoted by mixed metal bases has been investigated. The structure of the oxirane substrate (the number, the position, and the type of alkyl substituents on the ring) plays an important role in driving the stereoselectivity of the reaction. Disubstituted oxiranes show a predictable preference for the *E*-ene ether while trisubstituted substrates give either a mixture of stereoisomers or the *E*-ene ether exclusively, depending on the location of the third alkyl substituent.

Oxiranes are versatile compounds easily isomerized both under basic[1] and acidic[2] conditions affording synthetically useful products such as allylic alcohols, aldehydes, and ketones. In order to transform a totally saturated aliphatic oxirane to the corresponding allylic alcohol, strong bases are required, such as lithium dialkylamides.[3] Even with these reagents the regio- and typoselective outcome of the oxiranes reaction is not fully controlled. Several other pathways compete with the base-promoted β-elimination leading to the allylic alcohol **1**. The base itself may act as a nucleophile giving the amino alcohol **2**,[3] particularly if a terminal epoxide is involved. The proton on the carbon adjacent to the heterocyclic oxygen atom may be abstracted in some instances. The resulting 2-oxiranyllithium intermediate **3** generally isomerizes to the ketone-derived enolate **4**.[4] Finally, in the absence of strong donor solvents, the lithium reagent may act as an electrophile, opening the oxirane to give the β-lithiooxy carbenium ion **5** which, by 1,2-alkyl migration and deprotonation, leads to the aldehyde-derived enolate **6**.[5]



In connection with our interest in the chemistry of mixed metal bases,[6] we have recently found[7] that the mixture of lithium diisopropylamide and potassium *tert*-butoxide ("LIDAKOR reagent") promotes a smooth ring opening of oxiranes to allylic alcohols with good to excellent yields. Internal epoxyalkanes and large size epoxycycloalkanes give preferentially or exclusively *trans*-alkenols. These regio- and stereocontrolled reactions have been attributed to a *syn*-periplanar elimination mechanism which has been strongly supported by studying the LIDAKOR-promoted β-elimination of both *erythro*- and *threo*-4-methoxy-3-methyl-1-nonene to the corresponding (*Z*)- and (*E*)-3-methyl-1,3-nonadiene.[8] It has been found[7] that *cis*-2,3-dipropyloxirane affords exclusively the *trans*-isomer of 5-octen-4-ol while the *trans*-substituted oxirane produces a 1:2 to 1:10 *cis/trans* mixture of the same alcohol, depending on the base concentration. This behavior has been rationalized by proposing steric effects in the transition state.

Despite the great deal of information about the base-promoted isomerization of totally saturated aliphatic oxiranes, only a few reports have been published concerning hetero-substituted substrates. Nozaki *et al.*[9] reported that the epoxides of nerol and geraniol protected with a trimethylsilyl group (**7a** and **8a**, respectively), when treated with diethylaluminum tetramethylpiperidide (DATMP), afford the unsaturated diols **9** and **10** which arise from the abstraction of the hydrogen atoms on the methyl and on the methylene far from the trimethylsilyloxy group, respectively. The same unprotected epoxides **7b** and **8b** can be treated with lithium diisopropylamide (LIDA) giving the same mixture of **9**

† Dedicated to Professor Manfred Schlosser on the occasion of his 60th birthday.
‡ Centro CNR Composti Eterociclici.
§ Dipartimento di Chimica.
|| Dipartimento di Chimica Organica "A. Mangini".
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(2) Review on the Lewis acid-mediated rearrangement of oxiranes: (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (b) Rao, A. S.; Kirtane, S. K. *Tetrahedron* **1983**, *39*, 2323.
(3) Crandall, J. K.; Chang, L. H. *J. Org. Chem.* **1967**, *32*, 435.
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(6) The most famous mixed metal base is the mixture butyllithium/potassium *tert*-butoxide discovered and largely explored by M. Schlosser: Schlosser, M. *J. Organometal. Chem.* **1967**, *8*, 9; Mordini, A. in *Advances in Carbanion Chemistry*; Snieckus, V., Ed., JAI Press: Greenwich CT, 1992; Vol. 1, 1.
(7) Mordini, A.; BenRayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2401.
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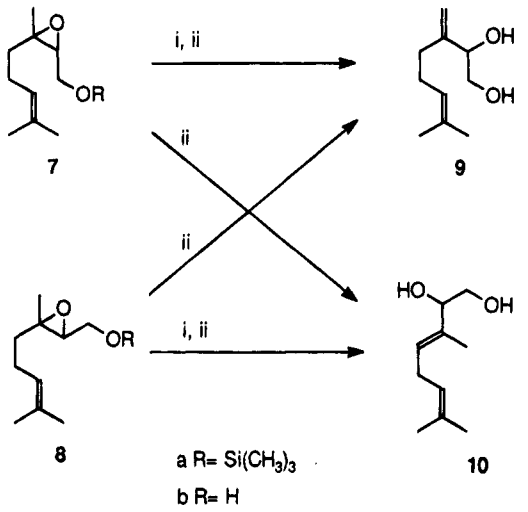
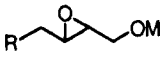
and **10** in about a 90:10 ratio.[10] The regiochemical outcome of these isomerizations has been attributed to the presence of the trimethylsilyloxy group that prevents the attack of the base on the methylene group bonded to the trimethylsilyloxy function in the first example, and we may try to attribute the behavior toward LIDA to the high electronic density on the oxygen which screens the methylene group itself.



(i) DATMP, C_6H_6, 0 °C, 2 h; (ii) LIDA, −78 to −0 °C, THF, 20 min.

The lack of data on this subject, coupled with our interest in exploiting the LIDAKOR-promoted isomerization of oxiranes, induced us to undertake a systematic study on heterosubstituted oxiranes. In this paper our first results on β-alkoxy-substituted oxiranes are reported.

Our approach to the isomerization of epoxy alcohols first began by a search for a suitable hydroxyl protective group. We found that silyloxy oxiranes **11** on treatment with lithium bases give mainly the unprotected epoxy alcohol together with starting material, the amount of which depends on the base used and the alkyl groups on the silicon.[11]



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R = C_4H_7, C_2H_5
M = $SiMe_3$, $SiEt_3$, $SiMe_2t$-Bu

This first failure prompted us to undertake a careful study in order to find the best protective group for running the isomerization to the hydroxy substituted ene ether. It was clear that the methoxymethyl (MOM) group, among several others,[12] had the requirements to be successfully employed: (1) it is easy to introduce and gives easily purifiable products; (2) the MOM—OR bond is stable to the highly basic conditions used in the isomerization reaction; (3) as explained below, the MOM-protected epoxy alcohols give a good yield together with an attractive *Z*:*E* ratio when compared to the others.

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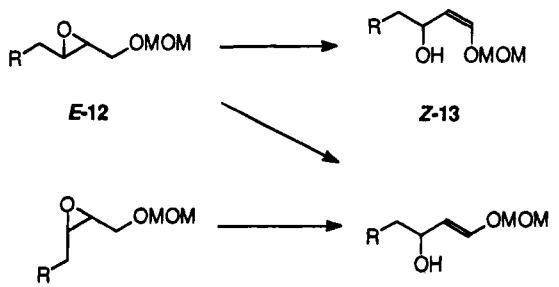
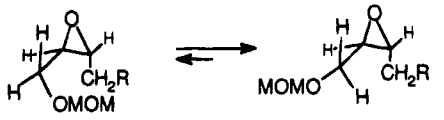
It is worthwhile to note that the unprotected 2,3-epoxyoctanol does not isomerize even in the presence of a large excess of a strong base such as LIDAKOR.

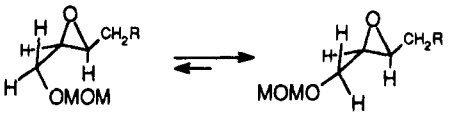
In order to test the ability of the superbasic mixture LIDAKOR to promote a clean isomerization of alkoxy-substituted oxiranes, we examined several substrates in which the alkyl substitution on the oxirane ring was varied.

2,3-Disubstituted Oxiranes. 2,3-Disubstituted oxiranes such as (*Z*)- and (*E*)-2,3-epoxy-1-(methoxymethoxy)hexane [*Z*-**12a** and *E*-**12a**] when submitted to the isomerization with LIDAKOR give the corresponding hydroxy ene ethers (*Z*)- and (*E*)-3-hydroxy-1-(methoxymethoxy)-1-hexene [*Z*-**13a** and *E*-**13a**]. The *Z* epoxide gives the *E* ene ether exclusively, whereas the *E* epoxide gives a mixture of *Z* and *E* ene ethers in a 20:80 ratio.



This behavior could have been expected on the basis of analogous results for the fully saturated epoxides. For reasons of steric repulsion, the conformation *Z*-**12** *cis*, the precursor to alcohol *Z*-**13**, is much more disfavored with respect to *Z*-**12** *trans* than is conformation *E*-**12** *cis*, again precursor to alcohol *Z*-**13**, with respect to *E*-**12** *trans*. This means that the *Z*-epoxide follows a more selective route toward the alcohol than the *E*-epoxide does.

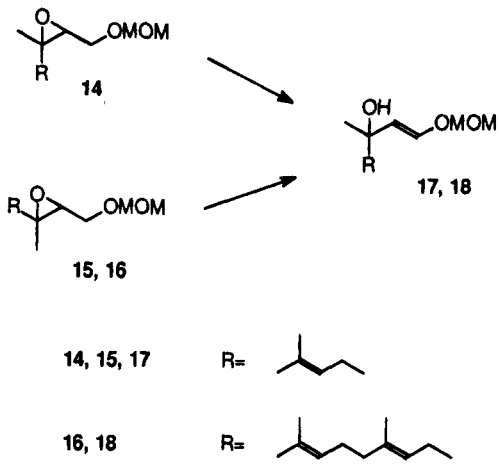




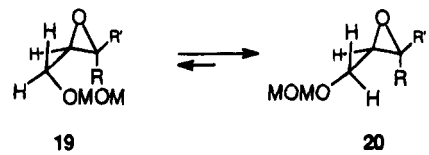
Longer alkoxy epoxides such as (*E*)-2,3-epoxy-1-(methoxymethoxy)octane *E*-**12b** and (*E*)-2,3-epoxy-1-(methoxymethoxy)tetradecane *E*-**12c** rearrange, as expected, to the corresponding (*Z*) and (*E*)-3-hydroxy-1-(methoxymethoxy)-1-octene [*Z*-**13b** and *E*-**13b**] and 3-hydroxy-1-(methoxymethoxy)-1-tetradecene [*Z*-**13c** and *E*-**13c**] respectively, both in a 78:22 ratio.

2,3,3-Trisubstituted Oxiranes. If the oxirane ring carries a third substituent in the position distant from the methoxymethoxy group, the stereochemical outcome of the isomerization reaction shows a significant change. Only the *E* ene ethers are always obtained in good yields.

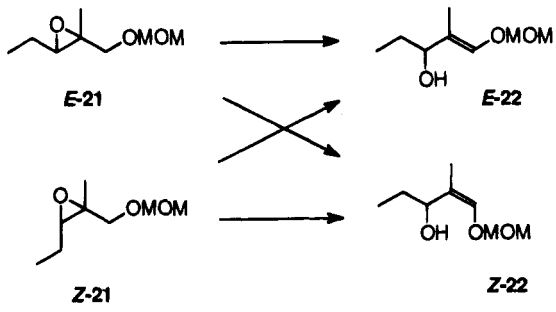
The mono epoxides of methoxymethyl-protected nerol **14**, geraniol **15**, and farnesol **16** give, upon treatment with LIDAKOR, the ene ethers **17** and **18** as unique products in a 81, 75, and 71% yield, respectively. This strict



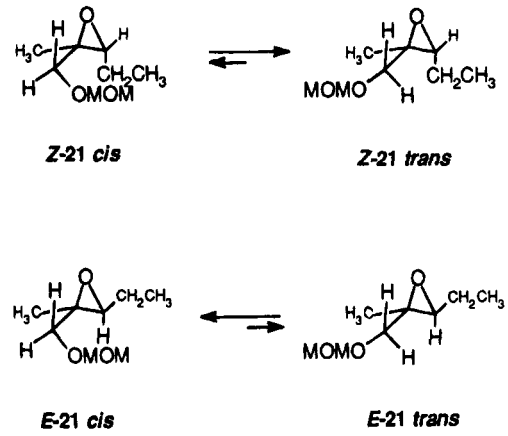
stereocontrol for both the *Z* and *E* epoxides can be explained by drawing again the transition states for the *syn*-periplanar elimination process. The steric repulsion in **19** makes this conformation disfavored compared to **20** when R = CH_3 (geraniol and farnesol) and the energy difference is even bigger when R = $(CH_3)_2C{=}CHCH_2$ (nerol).



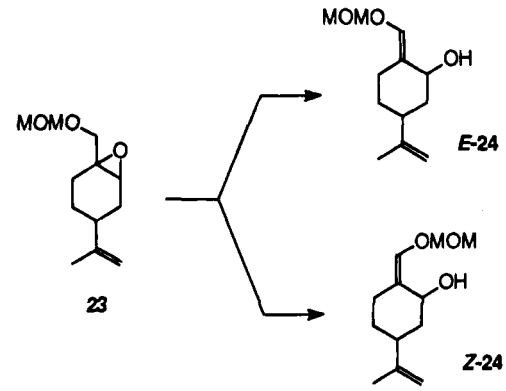
2,2,3-Trisubstituted Oxiranes. The presence of an alkyl substituent on the ring in the position proximate to the methoxymethoxy group gives a different result, still understandable by looking at the transition state model. The (*E*)-2,3-epoxy-1-(methoxymethoxy)-2-methylpentane (*E*-**21**) gives, upon treatment with LIDAKOR, a 55:45 mixture of (*Z*)- and (*E*)-3-hydroxy-1-(methoxymethoxy)-2-methyl-1-pentene, respectively [*Z*-**22** and *E*-**22**]. Base-induced isomerization of *Z*-**21** gives a 20:80 mixture of the same two stereoisomeric ene ethers.



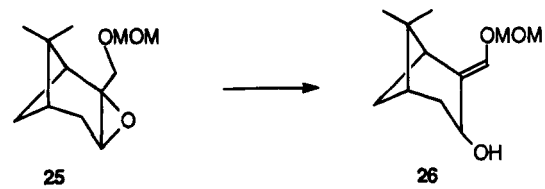
In the 2,2,3-trisubstituted substrates, the alkyl substitution in position 2 plays an important role in driving the stereochemical outcome of the isomerization process. The *Z* epoxide gives predominantly, but not exclusively as in the previous examples, the *E* ene ethers. The less strict stereocontrol is due to the interaction between the OMOM group and the methyl in position 2 experienced in *Z*-**21** *trans* and *E*-**21** *trans*. This interaction becomes very important for the *E* epoxide, where the lack of steric repulsion toward groups on position 3 makes the *cis*-conformation slightly more stable.



Two other particular examples of (*E*)-2,2,3-triisubstituted-1-methoxymethyloxiranes we have examined are the MOM-protected epoxyperyllol **23** and the MOM-protected myrtenol **25**. The former, upon treatment with LIDAKOR, affords the *Z* and *E*-MOM-protected ene ethers *Z*-**24** and *E*-**24** in a 25:75 ratio. This result confirms the above findings; the slightly better stereoselectivity found here is probably due to the minor steric demand of the ring.



The MOM-protected myrtenol represents a special example in that it isomerizes to the corresponding stereochemically pure (*E*)-ene ether **26**. This can be explained by looking at the molecular model for the transition state of the elimination reaction; there is a clear interaction between the OMOM group and a methyl bonded to the methylenic bridge in the precursor of the *Z* isomer. The precursor of the *E* isomer does not suffer from the same steric hindrance.



The double bond configuration for compounds *E*-**22**, *E*-**24**, and **26** has been assigned by ^{1}H-NMR analysis. Irradiation of the olefinic hydrogen atom caused an Overhauser enhancement of the signal assigned to the hydrogen of the CHOH group. No other nuclear Overhauser effect was observed, the *E* configuration of the double bond being thus confirmed.

In conclusion, we have shown that the LIDAKOR-promoted isomerization of alkoxy-substituted oxiranes is a regiospecific reaction leading exclusively to hydroxy-substituted ene ethers and that the stereoselectivity can be predicted by looking at the steric effects in the reaction transition state, arising from the groups attached to the oxirane ring.

Experimental Section

General. Air- and moisture-sensitive compounds were stored in Schlenk tubes or in Schlenk burettes. They were protected by and handled under an atmosphere of 99.99% pure nitrogen. Ethereal extracts were dried with sodium sulfate. The temperature of dry ice–ethanol baths is consistently indicated as −78 °C, that of ice bath as 0 °C and "room temperature" as 25 °C. If no reduced pressure is specified, boiling ranges were determined under ordinary atmospheric conditions (720 ± 35 mmHg). Purifications by flash column chromatography[13] were performed using glass columns (10–50 mm wide); silica gel 230–400 mesh was chosen as stationary phase (15 cm high), with an elution rate of 5 cm/min. Nuclear magnetic resonance spectra of hydrogen nuclei were recorded at 200 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.26 ppm). Coupling constants (J) are measured in hertz. Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of a doublet), m (multiplet), bs (broad singlet), bt (broad triplet), bq (broad quartet). The nuclear Overhauser effect was measured on degassed samples using the standard Varian software package NOEDIF. Nuclear magnetic resonance spectra of carbon-13 nuclei were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 77.0 ppm). Mass spectra were obtained at a 70 eV ionization potential.

Materials. Starting materials are commercially available unless otherwise stated. All commercial reagents were used without further purification except diisopropylamine which was distilled over calcium hydride. Tetrahydrofuran was obtained anhydrous by distillation over sodium wire after the characteristic blue color of in situ-generated sodium diphenylketyl[14] was found to persist. Methylene chloride was purified by the standard procedure, dried over calcium chloride, and stored over 4-Å molecular sieves. Benzene was distilled over sodium wire. Petroleum ether, unless specified, is the 30–50 °C boiling fraction.

Epoxidation with *m*-Chloroperbenzoic acid (*m*-CPBA). General Procedure. *m*-CPBA (17.2 g, 100.0 mmol) in CH_2Cl_2 (150 mL) was added, during a period of 1 h, to a solution of the allylic alcohol (50.0 mmol) in CH_2Cl_2 (80 mL) under N_2 at 0 °C. The reaction mixture was stirred 15 h at 25 °C and then cooled to 0 °C. The precipitate of *m*-chlorobenzoic acid was rapidly filtered off and washed with cold CH_2Cl_2 (2 × 20 mL). The organic solution was then washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), saturated aqueous $Na_2S_2O_3$ (2 × 100 mL), and brine (100 mL) and dried. After evaporation of the solvent the residue was purified.

Protection of the Hydroxyl Group as Methoxymethyl Ether. General Procedure. To a solution of the epoxy alcohol (20.0 mmol) in CH_2Cl_2 (40 mL), at 0 °C, diisopropylethylamine (5.1 g, 40.0 mmol) was added, followed by chloromethyl methyl ether (MOMCl, 2.44 g, 30.0 mmol). The reaction mixture was stirred at 25 °C for 10 h, diluted with CH_2Cl_2 (25 mL), washed with 10% HCl solution (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), and dried. After evaporation of the solvent the residue was purified.

LIDAKOR Induced Isomerization of the Epoxy Ethers. General Procedure. A solution of butyllithium in hexane (20.0 mmol) was evaporated under reduced pressure and the residue dissolved at −78 °C in precooled THF (25 mL). Then diisopropylamine (2.0 g, 20.0 mmol) and potassium *tert*-butoxide (2.25 g, 20.0 mmol) were added and the mixture stirred for 15 min. After the addition of the substrate (10.0 mmol), the reaction mixture was kept 15 h at −50 °C before it was treated with H_2O (20 mL) and allowed to reach 25 °C. The aqueous phase was then extracted with ether (2 × 20 mL), and the organic solution washed with brine (2 × 20 mL) and dried. After evaporation of the solvent the residue was purified.

(*Z*)-2,3-Epoxyhexan-1-ol. (*Z*)-2-Hexen-1-ol (5.0 g, 50.0 mmol) was epoxidized with *m*-CPBA according to the general procedure. Distillation of the residue through a Vigreux column (10 cm) afforded 4.10 g (70%) of (*Z*)-2,3-epoxyhexan-1-ol.[15] bp 67–68 °C/11 mmHg; ^{1}H-NMR ($CDCl_3$): 3.79 (1 H, bd, J = 12.3 Hz), 3.50 (1 H, m), 2.93 (2 H, m), 1.83 (1 H, bs), 1.4 (4 H, m), 0.83 (3 H, t, J = 7.0 Hz).

(*Z*)-2,3-Epoxy-1-(methoxymethoxy)hexane (*Z*-12a). Protection of (*Z*)-2,3-epoxyhexan-1-ol (2.3 g, 20.0 mmol) was performed according to the general procedure. The crude product was distilled through a Vigreux column (10 cm); 2.6 g (82%) of ***Z*-12a** was obtained: bp 86–88 °C/15 mmHg; ^{1}H-NMR ($CDCl_3$) 4.66 (2 H, AB, J = 7.6 Hz), 3.71 (1 H, dd, J = 11.2, 4.5 Hz), 3.56 (1 H, dd, J = 11.2, 6.5 Hz), 3.37 (3 H, s), 3.15 (1 H, ddd, J = 6.5, 4.5, 4.3 Hz), 2.98 (1 H, dt, J = 5.8, 4.3 Hz), 1.5 (4 H, m), 0.96 (3 H, t J = 7.1 Hz). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.77; H, 10.12.

(*E*)-2,3-Epoxyhexan-1-ol. The epoxidation of (*E*)-2-hexen-1-ol (5.0 g, 50.0 mmol) was carried out according to the general procedure. The crude product was purified by distillation through a Vigreux column (10 cm); 3.9 g (67%) of (*E*)-2,3-epoxyhexan-1-ol[16] was obtained: bp 69–71 °C/13 mmHg; ^{1}H-NMR ($CDCl_3$) 3.83 (1 H, bd, J = 12.6 Hz), 3.54 (1 H, m); 2.88 (2 H, m), 1.92 (1 H, bs), 1.45 (4 H, m), 0.79 (3 H, t, J = 7.1 Hz).

(*E*)-2,3-Epoxy-1-(methoxymethoxy)hexane (*E*-12a). Protection of (*E*)-2,3-epoxyhexan-1-ol (2.3 g, 20.0 mmol) was performed according to the general procedure. The crude product was distilled through a Vigreux column (10 cm); 2.3 g (73%) of ***E*-12a** were obtained: bp 82–83 °C/12 mmHg; ^{1}H-NMR ($CDCl_3$) 4.62 (2 H, s), 3.71 (1 H, dd, J = 11.5, 3.3 Hz), 3.50 (1 H, dd, J = 11.5, 5.5 Hz), 3.35 (3 H, s), 2.90 (1 H, ddd, J = 5.5, 3.3, 2.2 Hz), 2.81 (1 H, m), 1.5 (4 H, m) 0.96 (3 H, t, J = 7.2 Hz). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.83; H, 10.13.

Isomerization of *E*-12a. Epoxide ***E*-12a** (3.2 g, 20.0 mmol) was isomerized according to the general procedure; distillation of the residue through a Vigreux column (10 cm) afforded 2.37 g (74%) of a 25:75 mixture (bp 92–94 °C/6 mmHg) of (*Z*)- and (*E*)-1-(methoxymethoxy)-1-hexen-3-ol (***Z*-13a** and ***E*-13a**).

Isomerization of *Z*-12a. Epoxide ***Z*-12a** (1.6 g, 10.0 mmol) was isomerized according to the general procedure. Purification by distillation through a Vigreux column (10 cm) afforded 1.2 g (75%) of (*E*)-1-(methoxymethoxy)-1-hexen-3-ol (***E*-13a**).

Data for *Z*-13a. From the mixture of stereoisomers: ^{1}H-NMR ($CDCl_3$) 6.16 (1 H, d, J = 5.6 Hz), 4.79 (2 H, s), 4.77 (2 H, m), 3.38 (3 H, s), 2.64 (1 H, bs), 1.4, (4 H, m), 0.89 (3 H, t, J = 7.0 Hz). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.75; H, 10.11.

Data for *E*-13a: bp 93–94 °C/6 mmHg; ^{1}H-NMR ($CDCl_3$) 6.42 (1 H, d, J = 12.5 Hz), 5.10 (1 H, dd, J = 12.5, 8.5 Hz), 4.81 (2 H, s), 4.03 (1 H, dt, J = 8.5, 6.5 Hz), 3.40 (3 H, s), 2.03 (1 H, bs), 1.46 (4 H, m), 0.91 (3 H, t, J = 7.1). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.81; H, 10.00.

(*E*)-2-Octen-1-ol. A suspension of $LiAlH_4$ (96 mg, 25.3 mmol) in ether (70 mL) was added, during a period of 40 min, to a solution of (*E*)-2-octenal (12.6 g, 100.0 mmol) in ether (30 mL), cooled to −10 °C, and stirred. The reaction mixture was stirred at 25 °C for 1 h and then treated with H_2O (50 mL) and 10% H_2SO_4 (50 mL). The two phases were separated, the aqueous phase extracted with ether (2 × 50 mL), and the organic exctracts were collected and dried. After solvent

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removal, 12.0 g of crude (*E*)-2-octen-1-ol[17] were obtained and not submitted to further purification: ^{1}H-NMR ($CDCl_3$) 5.70 (1 H, dt, J = 15.3, 4.8 Hz), 5.60 (1 H, dt, J = 15.3, 5.3 Hz), 4.05 (2 H, d, J = 4.8 Hz), 2.04 (2 H, dt, J = 7.8, 5.3 Hz), 1.3 (7 H, m), 0.89 (3 H, t, J = 6.3 Hz).

(*E*)-2,3-Epoxyoctan-1-ol. (*E*)-2-octen-1-ol (6.4 g, 50.0 mmol) was epoxidized with *m*-CPBA according to the general procedure. Purification of the residue by flash column chromatography (petroleum ether/ether 1:2) afforded 5.8 g (81%) of (*E*)-2,3-epoxyoctan-1-ol, which directly crystallized as a white solid:[18] mp 33−34 °C; ^{1}H-NMR ($CDCl_3$): 3.90 (1 H, dd, J = 12.6, 4.4 Hz), 3.60 (1 H, dd, J = 12.6, 4.4 Hz), 2.92 (2 H, m), 2.68 (1 H, bs), 1.54 (2 H, m), 1.3 (6 H, m), 0.88 (3 H, t, J = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) 61.6, 58.6, 56.0, 31.5, 31.5, 25.6, 22.5, 14.0; MS m/z (%) 101 ($M^+ - C_3H_7$; 4), 83 (95), 71 (10), 69 (12), 61 (11), 57 (67), 56 (44), 55 (100).

(*E*)-2,3-Epoxy-1-(methoxymethoxy)octane (*E*-12b). Protection of (*E*)-2,3-epoxyoctan-1-ol (2.9 g, 20.0 mmol) was performed according to the general procedure. Bulb to bulb distillation of the crude product afforded 3.0 g (80%) of ***E*-12b**, bp 70 °C/0.03 mmHg; ^{1}H-NMR ($CDCl_3$) 4.64 (2 H, s), 3.73 (1 H, dd, J = 11.4, 3.4 Hz), 3.53 (1 H, dd, J = 11.4, 5.4 Hz), 3.37 (3 H, s), 2.92 (1 H, ddd, J = 5.4, 3.4, 2.4 Hz), 2.83 (1H, ddd, J = 6.1, 5.4, 2.4 Hz), 1.5 (2 H, m), 1.3 (6 H, m), 0.87 (3 H, t, J = 7.2 Hz); ^{13}C-NMR ($CDCl_3$): 96.5, 67.9, 56.7, 56.3, 55.3, 31.6, 31.5, 25.6, 22.5, 14.0; MS m/z (%) 143 (1), 83 (45), 71 (13), 61 (11), 58 (12), 57 (35), 55 (54), 45 (100). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.61; H, 10.77.

Isomerization of *E*-12b. Epoxide ***E*-12b** (1.9 g, 10.0 mmol) was isomerized according to the general procedure; purification of the residue by flash column chromatography (petroleum ether/ether 1:2) afforded 1.4 g (72%) of a 20:80 mixture of the two stereoisomeric ene ethers (*Z*)- and (*E*)-1-(methoxymethoxy)-1-octen-3-ol (***Z*-13b** and ***E*-13b**). A pure sample of the *E* isomer was obtained by a second flash column chromatography purification (petroleum ether/EtOAc 2:1).

Data for *Z*-13b. From the mixture of stereoisomers: ^{1}H-NMR ($CDCl_3$) 6.14 (1 H, d, J = 5.2 Hz), 4.78 (2 H, s), 4.61 (2 H, m), 3.40 (3 H, s), 1.5 (2 H, m), 1.29 (7 H, m), 0.89 (3 H, J = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) 143.4, 112.0, 96.3, 66.2, 55.8, 37.3, 31.6, 24.7, 22.6, 14.0. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.65; H, 10.78.

Data for *E*-13b: ^{1}H-NMR ($CDCl_3$) 6.43 (1 H, dd, J = 12.4, 0.7 Hz), 5.10 (1 H, dd, J = 12.4, 8.6 Hz), 4.82 (2 H, s), 4.03 (1 H, dt, J = 8.6, 6.4 Hz), 3.40 (3 H, s), 1.5 (2 H, m), 1.29 (7 H, m), 0.89 (3 H, t, J = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) 145.7, 11.4, 95.6, 70.3, 55.8, 37.7, 31.6, 25.2, 22.5, 14.0; MS m/z (%) 171 (0.4), 143 (4), 117 (38), 99 (19), 83 (33), 82 (17), 70 (37), 69 (20), 67 (11), 61 (12), 57 (21), 55 (32), 45 (100). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.65; H, 10.78.

2-Tetradecyn-1-ol. Li wire (5.2 g, 0.76 mol) and $Fe(NO_3)_3$ (304 mg) were added to liquid NH_3 (500 mL) at −78 °C. The mixture was stirred at −30 °C until formation of the $LiNH_2$, and then propargyl alcohol (21.0 g, 0.38 mol) was added. After 1 h at −30 °C, a solution of undecyl bromide (51.0 g, 0.20 mol) in THF (250 mL) was added. The reaction mixture was refluxed 9 h and then quenched with 10% HCl solution (100 mL). The aqueous layer was separated and extracted with ether (2 × 200 mL). The organic extracts were collected, washed with brine (200 mL), and dried. After evaporation of the solvent and purification by flash column chromatography (petroleum ether/EtOAc, 10:1), 29.0 g (70%) of 2-tetradecyn-1-ol[19] was obtained: ^{1}H-NMR ($CDCl_3$) 4.25 (2 H, m), 2.20 (2 H, m), 1.6 (1 H, bs), 1.5 (2 H, m), 1.26 (16 H, bs), 0.87 (3 H, t, J = 6.7 Hz); ^{13}C-NMR ($CDCl_3$) 86.7, 78.2, 51.4, 31.9, 29.6, 29.5, 29.3, 29.1, 28.9, 28.6, 22.7, 18.7, 16.0, 14.1; MS m/z (%) 210 (M^+; 19), 111 (20), 95 (28), 93 (40), 83 (29), 79 (37), 79 (36), 70 (26), 69 (21), 67 (28), 57 (21), 55 (47), 43 (67), 41 (100).

(*E*)-2-Tetradecen-1-ol. (*E*)-2-Tetradecyn-1-ol (21.0 g, 100 mmol) was added to a suspension of $LiAlH_4$ (23.8 g, 62.5 mmol) in THF (60 mL), under N_2. The reaction mixture was refluxed 2 h, then slowly cooled to 0 °C and treated with H_2O/ice mixture (200 mL) and ether (200 mL). The aqueous phase was separated, treated with 10% H_2SO_4 solution (100 mL), and extracted with ether (2 × 200 mL). The organic extracts were combined, washed with brine (400 mL), and dried. Evaporation of the solvent and purification by flash column chromatography (petroleum ether/ether 1:1) afforded 15.1 g (71%) of (*E*)-2-tetradecen-1-ol:[19] ^{1}H-NMR ($CDCl_3$) 5.57 (1 H, dt, J = 15.8, 5.4 Hz), 5.65 (1 H, dt, J = 15.8, 4.8 Hz), 4.08 (2 H, d, J = 4.8 Hz), 2.03 (3 H, m), 1.25 (18 H, bs), 0.87 (3 H, t, J = 6.2 Hz); ^{13}C-NMR ($CDCl_3$) 133.6, 128.6, 63.8, 32.2, 31.9, 29.6, 29.5, 29.3, 29.1, 28.9, 28.6, 22.7, 18.7, 14.0; MS m/z (%) 212 (M^+; 0.2), 194 (1), 83 (74), 71 (31), 70 (21), 69 (100), 67 (21), 57 (62), 43 (27).

(*E*)-2,3-Epoxytetradecan-1-ol. The epoxidation of (*E*)-2-tetradecen-1-ol (10.6 g, 50.0 mmol) with *m*-CPBA was performed following the general procedure. Evaporation of the solvent and purification by flash column chromatography (petroleum ether/ether 1:2) afforded 8.6 g (75%) of (*E*)-2,3-epoxytetradecan-1-ol:[20] ^{1}H-NMR ($CDCl_3$) 3.92 (1 H, ddd, J = 12.6, 5.4, 2.4 Hz), 3.62 (1 H, ddd, J = 12.6, 7.2, 4.2 Hz), 2.94 (2 H, m), 1.79 (1 H, bs), 1.55 (2 H, m), 1.25 (18 H, bs), 0.87 (3 H, t, J = 6.8Hz); ^{13}C-NMR ($CDCl_3$) 61.7, 58.4, 56.0, 31.9, 31.5, 29.6, 29.5, 29.4, 29.3, 25.9, 22.7, 14.1; MS m/z (%): 228 (M^+; 0.05), 197 (5), 111 (32), 97 (67), 83 (74), 71 (31), 70 (21), 69 (100), 67 (21), 57 (62), 43 (27).

(*E*)-2,3-Epoxy-1-(methoxymethoxy)tetradecane (*E*-12c). Protection of (*E*)-2,3-epoxytetradecan-1-ol (4.6 g, 20.0 mmol) was performed according to the general procedure. Purification of the residue by flash column chromatography (petroleum ether/ether 2:1) afforded 4.8 g (88%) of ***E*-12c**: ^{1}H-NMR ($CDCl_3$) 4.65 (2 H, s), 3.73 (1 H, dd, J = 11.6, 3.4 Hz), 3.53 (1 H, dd, J = 11.6, 5.6 Hz), 3.37 (3 H, s), 2.92 (1 H, ddd, J = 5.6, 3.4, 2.2 Hz), 2.83 (1 H, app td, J = 5.5, 2.2 Hz), 1.54 (2 H, m), 1.25 (18 H, bs), 0.87 (3 H, t, J = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) 96.5, 67.9, 56.7, 56.4, 55.3, 31.9, 31.6, 29.6, 29.5, 29.4, 29.3, 25.97, 22.7, 14.1; MS m/z (%) 241(M^+ − OMe; 0.3), 227 (0.4), 199 (5), 111 (21), 97 (49), 83 (52), 71 (32), 69 (53), 57 (55), 55 (44), 45 (100). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.43; H, 11.87.

Isomerization of *E*-12c. Epoxide ***E*-12c** (2.7 g, 10.0 mmol) was isomerized according to the general procedure; purification of the residue by flash column chromatography (petroleum ether/ether 1:1) afforded 1.8 g (67%) of a 22:78 mixture of the two stereoisomeric enol ethers (*Z*)- and (*E*)-1-(methoxymethoxy)-1-tetradecen-3-ol (***Z*-13c** and ***E*-13c**). A pure sample of the *E* isomer was obtained by a second flash column chromatography purification (petroleum ether/EtOAc 2:1).

Data for *Z*-13c. From the mixture of stereoisomers: ^{1}H-NMR ($CDCl_3$) 6.17 (1 H, d, J = 5.2 Hz), 4.80 (2 H, s), 4.61 (2 H, m), 3.40 (3 H, s), 1.5 (2 H, m), 1.25 (19 H, bs), 0.88 (3 H, t, J = 6.7 Hz). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.49; H, 11.85.

Data for *E*-13c: ^{1}H-NMR ($CDCl_3$) 6.42 (1 H, d, J = 12.4 Hz), 5.09 (1 H, dd, J = 12.4, 8.4 Hz), 4.82 (2 H, s), 4.02 (1 H, dt, J = 8.4, 5.9 Hz), 3.40 (3 H, s), 1.5 (2 H, m), 1.25 (19 H, bs), 0.88 (3 H, t, J = 6.7 Hz); ^{13}C-NMR ($CDCl_3$) 145.9, 111.4, 95.7, 70.4, 55.9, 37.8, 31.9, 29.6, 29.5, 29.3, 25.6, 22.7, 14.1; MS m/z (%) 211 (M^+ − OMOM, 5), 121 (14), 111 (22), 98 (32), 97 (46), 96 (34), 95 (26), 84 (30), 83 (78), 82 (43), 81 (37), 71 (24), 70 (100), 69 (46), 68 (24), 67 (32), 57 (51), 55 (43), 43 (30), 41 (26). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.38; H, 11.80.

2,3-Epoxygeraniol. A bright green solution of geraniol (10 g, 65.0 mmol) and vanadyl acetylacetonate ($VO(acac)_2$) (24 mg, 0.9 mmol) in C_6H_6 (75 mL), stirred under N_2, was heated at reflux and a 3 N *tert*-butyl hydroperoxide (*t*-BuOOH) solution in toluene (24 mL, 72.0 mmol) was added during a period of 1 h. The reaction mixture was refluxed 5 h, cooled to 25 °C, washed with saturated aqueous $Na_2S_2O_3$ (2 × 60 mL) and brine (60 mL), and dried. Evaporation of the solvent afforded 11 g of crude 2,3-epoxygeraniol,[21] not submitted to further

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purification as attempted distillation caused decomposition:[22] ^{1}H-NMR ($CDCl_3$) 5.07 (1 H, m), 3.81 (1 H, dd, J = 12.5, 4.3 Hz), 3.65 (1 H, dd, J = 12.5, 6.7 Hz), 2.96 (1 H, dd, J = 6.7, 4.3 Hz), 2.1 (3 H, m), 1.68 (3 H, s), 1.6 (2 H, m), 1.60 (3 H, s) 1.28 (3 H, s).

2,3-Epoxy-1-(methoxymethoxy)geraniol (15). The protection of 2,3-epoxygeraniol was performed according to the general procedure. Purification of the crude product by distillation through a Vigreux column (10 cm) afforded 10.5 g (75% based on geraniol) of **15:** bp 124−125 °C/0.03 mmHg; ^{1}H-NMR ($CDCl_3$) 5.08 (1 H, bt, J = 6.6, Hz), 4.66 (2 H, AB, J = 6.7 Hz), 3.70 (1 H, dd, J = 11.6, 6.3 Hz), 3.59 (1 H, dd, J = 11.6, 6.6 Hz), 3.38 (3 H, s), 2.96 (1 H, dd, J = 6.6, 6.3 Hz), 2.08 (2 H, bq, J = 8.2 Hz), 1.68 (3 H, s), 1.60 (3 H, s), 1.53 (2 H, m), 1.28 (3 H, s); ^{13}C-NMR ($CDCl_3$) 132.0, 123.4, 96.5, 66.3, 61.0, 60.2, 55.2, 38.4, 25.6, 23.6, 17.6, 16.7; MS m/z (%) 183 (M^+ − OMe; 0.1), 169 (0.6), 145 (0.2), 109 (44), 100 (32), 95 (27), 83 (27), 82 (41), 81 (40), 73 (22), 71 (20), 69 (100), 67 (34), 45 (92), 43 (35), 41 (32). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.06; H, 10.41.

2,3-Epoxynerol. The epoxidation reaction was carried out following the procedure used in the geraniol case. The crude 2,3-epoxynerol[23] was not purified further: ^{1}H-NMR ($CDCl_3$) 5.09 (1 H, m), 3.81 (1 H, dd, J = 12.1, 4.4 Hz), 3.64 (1 H, dd, J = 12.1, 6.8 Hz), 2.96 (1 H, dd, J = 6.8, 4.4 Hz), 2.1 (3 H, m), 1.68 (3 H, s), 1.61 (3 H, s), 1.6 (2 H, m), 1.34 (3 H, s).

2,3-Epoxy-1-(methoxymethoxy)nerol (14). The protection of 2,3-epoxynerol was performed according to the general procedure. Purification of the crude product by distillation through a Vigreux column (10 cm) afforded 9.7 g (70% based on nerol) of **14**: bp 89−90 °C/0.002 mmHg; ^{1}H-NMR ($CDCl_3$) 5.08 (1 H, bt, J = 7.1 Hz), 4.66 (2 H, AB J = 6.7), 3.71 (1H, dd, J = 11.3, 4.8 Hz), 3.57 (1 H, dd, J = 11.3, 6.3 Hz), 3.38 (3 H, s), 2.96 (1 H, dd, J = 6.3, 4.8 Hz), 2.10 (2 H, bq, J = 7.5 Hz) 1.67 (3 H, d, J = 1.1 Hz), 1.60 (3 H, s), 1.54 (2 H, m), 1.33 (3 H, s); ^{13}C-NMR ($CDCl_3$) 132.2, 123.4, 96.6, 66.2, 62.3, 60.5, 55.3, 33.1, 25.6, 24.1, 22.0, 17.6; MS m/z (%) 109 (23), 69 (44), 67 (21), 45 (100), 43 (34), 41 (48). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.18; H, 10.30.

***(E,E)*-3,7-Dimethyl-1-(methoxymethoxy)-1,6-octadien-3-ol (17).** The two epoxy ether isomers **14** and **15** (2.1 g, 10.0 mmol) were submitted to the isomerization procedure. Bulb to bulb distillation of the residue afforded 1.7 g (81%) and 1.6 g (75%), respectively, of **17** as a single stereoisomer: ^{1}H-NMR ($CDCl_3$) 6.41 (1 H, d, J = 12.5 Hz), 5.17 (1 H, d, J = 12.5 Hz), 5.10 (1 H, bt, J = 7.6 Hz), 4.79 (2 H, s), 3.79 (3 H, s), 2.02 (2 H, dt, J = 9.7, 7.6 Hz), 1.68 (1 H, bs), 1.66 (3 H, d, J = 1.2 Hz), 1.59 (3 H, bs), 1.5 (2 H, m), 1.28 (3 H, s); ^{13}C-NMR ($CDCl_3$) 144.2, 132.4, 124.8, 116.0, 96.2, 72.3, 56.2, 43.6, 29.0, 26.2, 23.5, 18.1; MS m/z (%) 153 (M^+ − OMOM; 0.3), 94 (15), 84 (27), 69 (100), 67 (12). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.38; H, 10.39.

2,3-Epoxy-*trans,trans*-farnesol. A solution of *trans,trans*-farnesol (11.1 g, 50.0 mmol) and $VO(acac)_2$ (50 mg, 0.2 mmol) in benzene (100 mL) was cooled to 0 °C and a 3 N *t*-BuOOH solution in toluene (25 mL, 75 mmol) was added over 30 min. The reaction mixture, whose color changed from bright green to deep red, was allowed to reach 25 °C. After 30 min the solution was washed with saturated aqueous $Na_2S_2O_3$ (2 × 50 mL). The aqueous phase was extracted with ether (2 × 50 mL) and the organic extracts were combined, washed with brine (150 mL), and dried. After evaporation of the solvent and purification by flash column chromatography (petroleum ether/EtOAc 2:1), 9.9 g (83%) of 2,3-epoxy-*trans,trans*-farnesol[24] was obtained: ^{1}H-NMR ($CDCl_3$) 5.1 (2 H, m), 3.85 (1 H, dd, J = 11.2, 4.4 Hz), 3.67 (1 H, dd, J = 11.2, 7.2 Hz), 2.97 (1 H, dd, J = 7.2, 4.4 Hz), 2.04 (6 H, m), 1.79 (1 H, bs), 1.68 (3 H, s), 1.6 (2 H, m), 1.58 (6 H, s), 1.29 (3 H, s); ^{13}C-NMR ($CDCl_3$) 135.7, 131.3, 124.1, 123.1, 63.1, 61.3, 61.2, 39.6, 38.4, 26.5, 25.6, 23.5, 17.6, 16.7, 15.9.

2,3-Epoxy-1-(methoxymethoxy)-*trans,trans*-farnesol (16). The protection of 2,3-epoxy-*trans,trans*-farnesol (4.8 g, 20.0 mmol) was performed according to the general procedure. Purification of the crude product by flash column chromatography (petroleum ether/EtOAc 6:1) afforded 4.2 g (75%) of **16**: ^{1}H-NMR ($CDCl_3$) 5.10 (2 H, m), 4.66 (2 H, AB, J = 6.5 Hz), 3.71 (1 H, dd, J = 11.3, 4.9 Hz), 3.60 (1 H, dd, J = 11.3, 6.0 Hz), 3.38 (3 H, s), 2.98 (1 H, dd, J = 6.0, 4.9 Hz), 2.04 (6 H, m), 1.67 (3 H, s), 1.60 (2 H, m), 1.59 (6 H, s), 1.29 (3 H, s); ^{13}C-NMR ($CDCl_3$) 135.7, 131.4, 124.2, 123.2, 96.5, 66.4, 61.0, 60.3, 55.3, 39.6, 38.4, 26.6, 25.7, 23.5, 17.7, 16.8, 16.0; MS m/z (%) 282 (M^+; 0.1), 237 (2), 109 (21), 107 (21), 95 (23), 93 (31), 81 (54), 69 (100), 45 (76), 41 (39). Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.12; H, 10.68.

***(E,E,E)*-1-(Methoxymethoxy)-3,7,11-trimethyl-1,6,10-dodecatrien-3-ol (18).** Epoxide **16** (2.8 g, 10.0 mmol) was isomerized according to the general procedure. Purification by flash column chromatography (petroleum ether/EtOAc 2:1) afforded 2.0 g (71%) of **18**: ^{1}H-NMR ($CDCl_3$) 6.43 (1 H, d, J = 12.5 Hz), 5.19 (1 H, d, J = 12.5 Hz), 5.10 (2 H, m), 4.81 (2 H, s), 3.39 (3 H, s), 2.04 (6 H, m), 1.67 (3 H, d, J = 1.1 Hz), 1.60 (7 H, bs), 1.56 (2 H, m), 1.30 (3 H, s); ^{13}C-NMR ($CDCl_3$) 143.7, 135.5, 131.4, 124.2, 124.2, 115.5, 95.8, 71.9, 55.8, 43.1, 39.7, 28.6, 26.6, 25.7, 22.9, 17.7, 16.0. Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.07; H, 10.79.

***(Z)*-2,3-Epoxy-1-(methoxymethoxy)-2-methylpentane (*Z*-21).** Hydroxypropanone (7.4 g, 100.0 mmol) was submitted to the reaction with MOMCl according to the general procedure. The solvent was evaporated and the crude (methoxymethoxy)propanone was added at −78 °C, with stirring, to a red mixture of propyltriphenylphosphonium bromide (38.3 g, 100.0 mmol, previously dried under vacuum) and potassium bis(trimethylsilyl)amide (19.9 g, 100.0 mmol) in THF (100 mL) under N_2. The temperature was allowed to reach 25 °C, and the reaction mixture was stirred for 13 h. The solvent was partially evaporated under reduced pressure, and the residue diluted with petroleum ether (100 mL) and filtered. Purification of the crude product (a 90:10 mixture of *Z* and *E* isomers) by flash column chromatography (petroleum ether/EtOAc 8:1) afforded 9.4 g (65%) of (*Z*)-1-(methoxymethoxy)-2-methyl-2-pentene: ^{1}H-NMR ($CDCl_3$) 5.38 (1 H, app t, J = 8.1 Hz), 4.60 (2 H, s), 4.04 (2 H, bs), 3.37 (3 H, s), 2.06 (2 H, dqq, J = 8.1, 7.5, 1.3 Hz), 1.75 (3 H, dt, J = 1.3, 1.1 Hz), 0.94 (3 H, t, J = 7.5 Hz); MS m/z (%) 144 (M^+; 0.1), 83 (33), 82 (44), 67 (34), 55 (30), 45 (100), 41 (28).

(*Z*)-1-(Methoxymethoxy)-2-methyl-2-pentene (7.2 g, 50.0 mmol) was epoxidized with *m*-CPBA following the general procedure and the residue was purified by flash column chromatography (petroleum ether/EtOAc 8:1) affording 5.7 g (71%) of *Z*-**21**: ^{1}H-NMR ($CDCl_3$) 4.64 (2 H, AB, J = 6.6 Hz), 3.56 (2 H, AB, J = 10.5 Hz), 3.37 (3 H, s), 2.76 (1 H, t, J = 6.5 Hz), 1.58 (2 H, qd, J = 7.5, 6.5 Hz), 1.39 (3 H, s), 1.04 (3 H, t, J = 7.5 Hz); MS m/z (%) 115 (M^+ − MOM; 11), 99 (3), 73 (18), 59 (22), 57 (41), 45 (100), 43 (36). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.93; H, 10.09.

***(E)*-2-Methyl-2-pentenol.** Propanal (23.2 g, 0.4 mol) was added, over a period of 30 min, to a 1 N NaOH solution (14 mL) heated at 50 °C. The reaction mixture was stirred at 50 °C for 1 h, allowed to reach 25 °C, and extracted with ether (3 × 30 mL). The organic extracts were collected and dried. After distillation of the solvent at atmospheric pressure and purification of the crude product by distillation through a Vigreux column (10 cm), (*E*)-2-methyl-2-pentenal[25,26] was obtained as unique product (13.7 g, 70%): bp 80−81 °C/100 mmHg; ^{1}H-NMR ($CDCl_3$) 9.37 (1 H, s), 6.46 (1 H, tq, J = 7.3, 1.4 Hz), 2.35 (2 H, dqq, J = 7.5, 7.3, 08 Hz), 1.71 (3 H, dt, J = 1.3, 0.8 Hz), 1.09 (3 H, t, J = 7.5 Hz).

A solution of (*E*)-2-methyl-2-pentenal (9.8 g, 100.0 mmol) in ether (75 mL) was slowly added to a stirred suspension of $LiAlH_4$ (1.1 g, 30.0 mmol) in ether (25 mL) at such a rate as to cause a gentle reflux of the solvent. The reaction mixture was stirred 16 h at 25 °C, cooled to 0 °C, carefully treated with H_2O (50 mL), and subsequently poured into a mixture of 10%

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aqueous H_2SO_4 (50 mL) and crushed ice. The two phases were separated, and the white precipitate formed was filtered off from the aqueous phase, which was extracted with ether (3 × 100 mL). The white solid was washed with ether (3 × 30 mL). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (2 × 200 mL) and brine (2 × 200 mL), and dried. Evaporation of the solvent and purification by flash column chromatography (petroleum ether/ether 1:1) afforded 8.8 g (88%) of (*E*)-2-methyl-2-pentenol:[25] ^{1}H-NMR ($CDCl_3$) 5.40 (1 H, bt, J = 7.1 Hz), 4.00 (2 H, d, J = 5.8 Hz), 2.04 (2 H, qd, J = 7.6, 7.1 Hz), 1.66 (3 H, s), 1.38 (1 H, t, J = 5.8 Hz), 0.96 (3 H, t, J = 7.6 Hz).

(*E*)-2,3-Epoxy-1-(methoxymethoxy)-2-methylpentane (*E*-21). (*E*)-2-Methyl-2-pentenol (5.0 g, 50.0 mmol) was protected as methoxymethyl ether and subsequently epoxidized with *m*-CPBA, according to the general procedures. Solvent removal by distillation and purification of the residue by flash column chromatography (toluene/EtOAc 4:1) afforded 5.4 g (68% based on the starting alcohol) of ***E*-21**: ^{1}H-NMR ($CDCl_3$) 4.64 (2 H, s), 3.52 (2 H, s), 3.37 (3 H, s), 2.86 (1 H, t, J = 6.4 Hz), 1.58 (2 H, m), 1.32 (3 H, s), 1.04 (3 H, t, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$) 96.4, 72.0, 62.3, 59.5, 55.3, 21.6, 14.4, 10.5; MS m/z (%) 115 (M^+ − MOM; 11), 73 (19), 71 (20), 59 (26), 57 (58), 45 (100), 43 (79), 41 (41). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.85; H, 10.09.

Isomerization of *Z*-21. Epoxide ***Z*-21** (1.6 g, 10.0 mmol) was isomerized according to the general procedure. Purification by flash column chromatography (petroleum ether/EtOAc 3:1) afforded 1.1 g (67%) of a 20:80 mixture of the two stereoisomeric ene ethers (*Z*)- and (*E*)-1-(methoxymethoxy)-2-methyl-1-penten-3-ol (***Z*-22** and ***E*-22**). A pure sample of the *E* isomer was obtained by a second flash column chromatography purification (petroleum ether/EtOAc 3:1).

Isomerization of *E*-21. Epoxide ***E*-21** (1.6 g, 10.0 mmol) was isomerized according to the general procedure; purification by flash column chromatography (petroleum ether/EtOAc 2:1) afforded 1.1 g (67%) of a 55:45 mixture of (*Z*)- and (*E*)-1-(methoxymethoxy)-2-methyl-1-penten-3-ol (***Z*-22** and ***E*-22**).

Data for *Z*-22. From the mixture of stereoisomers: ^{1}H-NMR ($CDCl_3$) 6.03 (1 H, q, J = 1.4 Hz), 4.76 (2 H, s), 4.55 (1 H, td, J = 6.7, 4.6 Hz), 3.39 (3 H, s), 1.91 (1 H, bd, J = 4.6 Hz), 1.59 (2 H, qd, J = 7.4, 6.7 Hz), 1.55 (3 H, d, J = 1.4 Hz), 0.91 (3 H, t, J = 7.4 Hz); ^{13}C-NMR ($CDCl_3$) 139.2, 117.6, 96.2, 70.3, 55.8, 27.5, 12.6, 10.2; MS m/z (%) 160 (M^+; 0.3), 142 (0.2), 131 (3), 98 (26), 69 (18), 45 (100), 41 (34). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 60.11; H, 10.10.

Data for *E*-22: ^{1}H-NMR ($CDCl_3$) 6.23 (1 H, q, J = 1.3 Hz), 4.81 (2 H, s), 3.88 (1 H, t, J = 7.2 Hz), 3.39 (3 H, s), 1.62 (3 H, d, J = 1.3 Hz), 1.60 (2 H, qd, J = 7.4, 7.2 Hz), 1.45 (1 H, bs), 0.85 (3 H, t, J = 7.4 Hz); ^{13}C-NMR ($CDCl_3$) 140.6, 117.5, 96.3, 75.5, 55.6, 27.4, 9.9, 7.8; MS m/z (%) 160 (M^+; 2), 142 (1), 131 (9), 98 (42), 69 (29), 55 (20), 45 (100), 41 (66). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 60.02; H, 10.12.

1,2-Epoxy-1-(hydroxymethyl)-4-isopropenylcyclohexane. *S*-(−)-Peryllil alcohol (7.6 g, 50.0 mmol) was epoxidized[27] with *t*-BuOOH according to the procedure followed in the *trans-trans*-farnesol case. The epoxide was obtained as a 65:35 mixture of diasteroisomers (7.4 g). Major diasteroisomer: ^{1}H-NMR ($CDCl_3$) 4.67 (2 H, m), 3.70 (1 H, d, J = 4.6 Hz), 3.65 (1 H, d, J = 4.6 Hz), 3.36 (1 H, m), 2.1 (3 H, m), 1.8 (3 H, m), 1.7 (3 H, m), 1.6 (2 H, m). Minor diasteroisomer: ^{1}H-NMR ($CDCl_3$) 4.73 (2 H, m), 3.60 (1 H, d, J = 8.6 Hz), 3.54 (1 H, d, J = 8.6 Hz), 3.29 (1 H, d, J = 5.4 Hz), 2.1 (3 H, m), 1.8 (3 H, m), 1.7 (3 H, m), 1.6 (2 H, m).

1,2-Epoxy-4-isopropenyl-1-[(methoxymethoxy)methyl]-cyclohexane (23). Protection of the crude 1,2-epoxy-1-(hydroxymethyl)-4-isopropenylcyclohexane was performed according to the general procedure. The crude product was purified by flash column chromatography (petroleum ether/ether 2:1) affording 7.7 g (73%, based on the starting alcohol) of **23**[28] as a 65:35 mixture of diasteroisomers. Major diasteroisomer: ^{1}H-NMR ($CDCl_3$) 4.66 (2 H, m), 4.62 (2 H, s), 3.51 (2 H, s), 3.36 (3 H, s), 3.20 (1 H, m), 2.1 (3 H, m), 1.8 (2 H, m), 1.68 (3 H, s), 1.6 (2 H, m); MS m/z (%) 181 (M^+ − OMe; 1), 167 (1), 119 (16), 109 (14), 107 (20), 93 (33), 91 (26), 79 (20), 45 (100). Minor diasteroisomer: ^{1}H-NMR ($CDCl_3$) 4.71 (2 H, m), 4.62 (2 H, s), 3.56 (2 H, s), 3.36 (3 H, s), 3.15 (1 H, d, J = 5.2 Hz), 2.1 (3 H, m), 1.8 (2 H, m), 1.68 (3 H, s), 1.6 (2 H, m); MS m/z (%) 181 (M^+ − OMe; 2), 167 (2), 151 (17), 135 (22), 121 (34), 119 (35), 109 (38), 106 (23), 105 (26), 95 (33), 94 (26), 93 (75), 91 (48), 81 (32), 79 (51), 67 (48), 55 (36), 45 (100).

Isomerization of 23. Epoxide **23** (4.2 g, 20.0 mmol) was isomerized according to the general procedure; a four diasteroisomers mixture was obtained, the *Z*:*E* ratio being 25:75. Only the two *E* isomers have been isolated (2.41 g, 57%) after purification by flash column chromatography (petroleum ether/ether 10:1) as a 50:50 mixture. Pure samples of both *E* isomers were obtained by a second flash column chromatography (petroleum ether/ether 10:1). First diasteroisomer: ^{1}H-NMR ($CDCl_3$) 6.00 (1 H, d, J = 1.9 Hz), 5.05 (1 H, m), 4.77 (2 H, s), 4.69 (2 H, bs), 3.40 (3 H, s), 2.45 (2 H, m), 1.98 (2 H, m), 1.71 (3 H, s), 1.44 (2 H, m), 1.24 (2 H, m); ^{13}C-NMR ($CDCl_3$) 149.9, 137.4, 120.0, 108.6, 96.3, 63.0, 55.8, 38.7, 38.3, 32.6, 25.7, 20.9; MS m/z (%) 150 (M^+ − MOMOH; 16), 135 (27), 122 (27), 93 (31), 91 (30), 77 (36), 68 (100), 67 (92), 53 (29). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.85; H, 9.57. Second diasteroisomer: ^{1}H-NMR ($CDCl_3$) 6.21 (1 H, d, J = 2.0 Hz), 4.79 (2 H, s), 4.69 (2 H, bs), 4.25 (1 H, m), 3.39 (3 H, s), 2.71 (1 H, m), 2.54 (1 H, m), 2.02 (2 H, m), 1.71 (3 H, s), 1.41 (2 H, m), 1.22 (2 H, m); ^{13}C-NMR ($CDCl_3$) 149.9, 138.6, 120.2, 108.6, 96.3, 69.6, 55.7, 39.0, 31.5, 25.7, 20.9, 20.9; MS m/z (%) 150 (M^+ − MOMOH; 29), 135 (40), 122 (38), 121 (25), 108 (23), 107 (61), 106 (23), 105 (22), 95 (23), 93 (52), 91 (56), 79 (100), 68 (69), 67 (70). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.75; H, 9.54.

6,6-Dimethyl-3-oxatricyclo[4.1.1.0^{2,4}]octane-2-methanol (25). Myrtenol (3.04 g, 20.0 mmol) was epoxidized[29] with *m*-CPBA and subsequently protected as methoxymethyl ether, according to the general procedures. Purification of the residue by flash column chromatography (petroleum ether/ether 2:1) afforded 2.8 g (66%) of **25**: bp 100−101 °C/0.03 mmHg; ^{1}H-NMR ($CDCl_3$, 300 MHz) 4.62 (2 H, s), 3.77 (1 H, d, J = 11.8 Hz), 3.51 (1 H, d, J = 11.8 Hz), 3.35 (3 H, s), 3.30 (1 H, dd, J = 4.0, 1.4 Hz), 2.06 (1 H, dd, J = 12.2, 5.9 Hz), 2.03 (1 H, dd, J = 14.8, 4.0 Hz), 2.02 (1 H, ddd, J = 12.2, 9.6, 2.6 Hz), 1.85 (1 H, ddd, J = 14.8, 3.5, 1.4 Hz), 1.76 (1 H, m), 1.66 (1 H, d, J = 9.6 Hz), 1.29 (3 H, s), 0.93 (3 H, s); ^{13}C-NMR ($CDCl_3$) 96.4, 68.5, 62.0, 55.2, 53.1, 40.6, 40.6, 40.0, 27.2, 26.6, 25.4, 20.1; MS m/z (%) 135 (11), 109 (28), 108 (21), 107 (43), 106 (28), 95 (30), 93 (42), 82 (21), 81 (56), 79 (71), 69 (58), 67 (82), 65 (30), 55 (100), 54 (23), 53 (98), 51 (38). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.68; H, 9.45.

(*E*)-6,6-Dimethyl-2-[(methoxymethoxy)methylene]-bicyclo[3.1.1]heptan-3-ol (26). Epoxide **25** (2.1 g, 10.0 mmol) was isomerized according to the general procedure; purification by flash column chromatography (petroleum ether/ether 10:1) afforded 1.5 g (70%) of **26**: ^{1}H-NMR ($CDCl_3$) 5.96 (1 H, d, J = 1.5 Hz), 4.84 (1 H, d, J = 6.4 Hz), 4.82 (1 H, m), 4.78 (1 H, d, J = 6.4 Hz), 3.41 (3 H, s), 2.4 (2 H, m), 2.3 (2 H, m), 1.98 (1 H, m), 1.82 (1 H, ddd, J = 14.4, 3.8, 1.4 Hz), 1.57 (1 H, d, J = 9.7 Hz), 1.24 (3 H, s), 0.67 (3 H, s); ^{13}C-NMR ($CDCl_3$) 138.5, 127.4, 96.3, 61.5, 55.9, 45.6, 40.4, 40.1, 34.2, 28.9, 25.7, 22.2; MS m/z (%) 212 (M^+; 0.01), 143 (22), 111 (23), 107 (37), 79 (28), 45 (100), 41 (24). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.78; H, 9.47.

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