Mixed Superbase LICKOR as a Key Reagent for the Synthesis of Conjugate Dienes from Citral and Farnesal – A New Route to a Potential Mimic Agent of Juvenile Hormones by Diels–Alder Cycloaddition[+]

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Treatment of the dimethyl acetals of citral (**1**) and farnesal (**2**) with the superbase "LICKOR" in THF at low temperatures induces regioselective metallation at the allylic methyl group at C(3). The metal–hydrogen exchange promotes immediate 1,4-elimination, yielding an (*E*)-configured conjugate alkyloxy-functionalized diene. The elimination product can be subjected to a Diels–Alder reaction, which allows further synthetic elaboration. In particular, in the case of farnesal dimethyl acetal the cycloaddition process leads to a derivative that can be transformed into a potential mimic agent of Juvenile hormones.

The chemistry of functionalized building blocks having 4- or 5-carbon atoms skeletons is a subject of increasing interest,[1] owing to their use in the synthesis of natural products. Citral and farnesol are inexpensive isoprenic derivatives, and their efficacious structural modification should be achievable according to a simple procedure that we have proposed previously[2] following our studies on the reactivity of α,β-unsaturated acetals in the presence of Schlosser's superbase LICKOR[3] (an equimolar mixture of butyllithium "LIC" and potassium *tert*-butoxide "KOR"). This polar, basic reagent selectively reacts at the γ-allylic site of the unsaturated substrate and the organometallic intermediate thus formed undergoes a 1,4-elimination reaction leading to a conjugate dienic structure. This derivative can be considered as a useful substrate for further synthetic modifications, in particular for the preparation of trienes, which have been shown to readily undergo intramolecular Diels−Alder cycloaddition.[4]

The present paper deals with the versatility of this method for obtaining 1,3-dienes, starting from the dimethyl acetals of citral (**1**) and farnesal (**2**). The acetal **1** employed was a commercial mixture of (*Z*) and (*E*) isomers, while **2** was synthesized starting from an isomeric farnesol mixture. Although for both acetals **1** and **2** our method started from a stereomeric mixture, the number of isomers ultimately formed was reduced, owing to the stereoselectivity of the elimination reaction.[5]

Farnesol was first selectively oxidized to farnesal by treatment with pyridinium chlorochromate supported on alumina.[6] The aldehyde arising from oxidation of the minor component [(*Z*,*Z*) = 0.5%] was no longer detected after filtration of the reaction mixture, probably due to adsorption of both organic reagents and products onto the insoluble inorganic phase.

Low-temperature treatment (−95 °C) of the acetals **1** and **2** with the LICKOR reagent led to regioselective metallation at the γ-allylic site adjacent to the acetal group, which was followed by immediate 1,4-elimination. This was accompanied by the appearance of a dark-red colour. Although both acetals **1** and **2** could, in principle, have undergone metallation at various acidic sites, i.e. allylic and vinylic sites, GC and ^{1}H-NMR analyses of the crude reaction mixtures confirmed that a single elimination product had been obtained.[7] Moreover, these data indicated that the metallation reaction had occurred regioselectively at the methyl group in the γ-position, and that the elimination reaction had stereoselectively afforded the (*E*)-dienes **3** and **4** (Scheme 1). Furthermore, in the case of acetal **1**, we checked the regioselectivity of the metallation by quenching the reaction with Me_3SiCl, so as to trap the possible products that might have arisen from concurrent metal−hydrogen exchange at either the allylic methyl terminus far from the acetal group or at one of the vinyl carbon atoms. No product attributable to a metallation reaction at a different site was observed. The selective metal−hydrogen exchange at the γ-methyl terminus can be attributed to the favourable interaction of the metal counterion with the adjacent oxygen atom, which stabilizes the intermediate organometallic species (see Scheme 1).[8]

The regioselective metallation of a methyl position in a substrate having both methylic and methylenic allyl hydrogens has been previously reported and discussed by Schlosser himself.[9] The selective formation of (*E*) elimination products has been described for compounds with comparable structures.[2][10]

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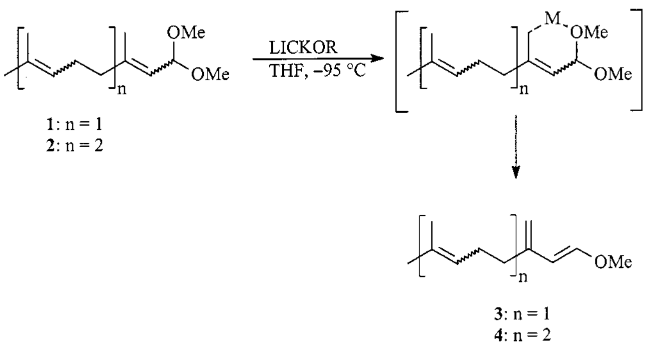


Scheme 1. Stereoselective synthesis of (*E*)-dienes promoted by the regioselective metallation of acetals

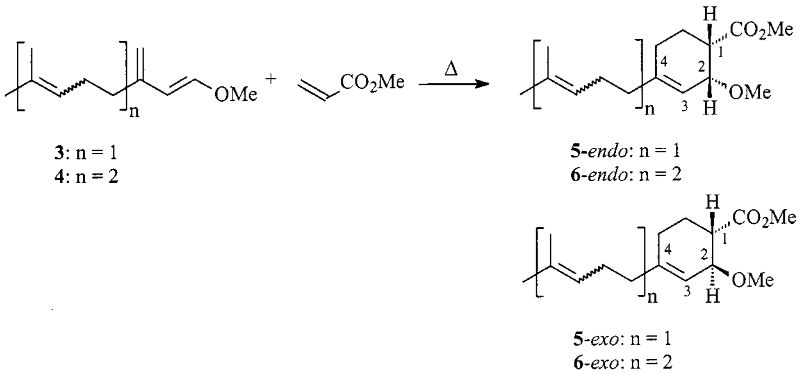
In the present case, the selectivity of the reaction results in formation of the single (*E*)-elimination product **3** starting from the mixture of (*E*)- and (*Z*)-isomeric acetals **1**, while the three isomers of acetal **2** give rise to just two elimination products **4**, namely the (1*E*,6*E*) and (1*E*,6*Z*) isomers. The ratio between the isomers [(1*E*,6*E*)/(1*E*,6*Z*) = 75:25] was established by ^{1}H-NMR analysis.

Derivatives **3** and **4** bear substituent groups that make them activated dienes, suitable for Diels–Alder cycloaddition reactions. In particular, derivative **4** may be transformed into a structure that can be considered analogous to those of Juvenile hormones. The Diels–Alder reaction proceeds with good yield under thermal conditions and affords, starting from diene **3**, the esters *endo*-**5** and *exo*-**5** (ratio 70:30), while dienes **4** gives esters *endo*-**6** and *exo*-**6** (ratio 70:30),[11] as shown in Scheme 2. Structures **3** and **4** undergo cycloaddition with methyl acrylate, selectively affording the "*ortho*" structures owing to activation of both the diene and dienophile entities.[12]

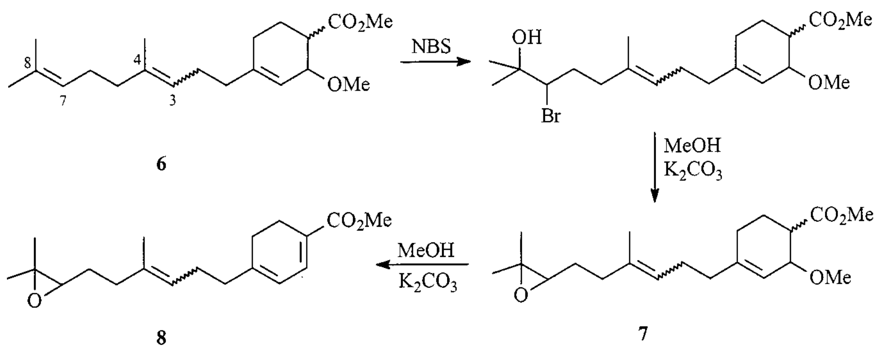
The stereochemistries of the cycloadducts **5**–**6** were established following accurate measurement of the coupling constants and a complete assignment of the NMR signals. In particular, the stereochemistry of the junction was assigned by considering the coupling pattern of C(1)–H and C(2)–H, as well as with the aid of NOE experiments.[13] The cycloadducts obtained were not separated, and the ratio between the two isomers was established by ^{1}H-NMR and GC analyses. Specifically, the integral of the signal corresponding to C(3)–H (δ = 5.72; *endo*-**5**) was compared with that of the signal assigned to C(3)–H (δ = 5.56; *exo*-**5**). Regarding the cycloadducts obtained starting from the isomeric mixture of dienes **4**, ^{1}H-NMR analysis revealed the presence of two isomers, which were characterized as *endo*-**6** (70%) and *exo*-**6** (30%).[14] The ratio between the two cycloadducts was determined on the basis of the integrals of the signals attributed to C(3)–H (δ = 5.65; *endo*-**6**) and C(3)–H (δ = 5.45; *exo*-**6**). These products show coupling patterns for C(1)–H and C(2)–H that compare well with those described[13] for the corresponding *endo*-**5** and *exo*-**5** adducts (see Experimental Section). Moreover, in the case of *endo*-**6**, irradiation of the C(2)–H signal (δ = 3.92) caused an NOE (6%) of the signal assigned to C(1)–H (δ = 2.50). On the contrary, in the case of *exo*-**6**, irradiation of C(2)–H (δ = 4.08) caused a less pronounced NOE (2%) of the signal assigned to C(1)–H (δ = 2.55).

Finally, in order to mimic the structure of Juvenile hormones, the oxirane ring was constructed. Our method, in which the intermediate bromohydrin[15] is formed selectively, gives the epoxide ring at the C(7)–C(8) positions of the isoprene chain and, moreover, it allows one to obtain, according to the experimental conditions, two different products (**7** and **8**) that can both be considered as being related to the natural derivatives (Scheme 3).[16] Thus, when the intermediate bromohydrin was treated with 4.0 equiv. of K_2CO_3 in anhydrous methanol, only the hydroxy proton was removed and the epoxide **7** was obtained as a mixture of *endo* and *exo* cycloadducts.[14] The ^{1}H-NMR spectrum of the isomeric mixture clearly indicated the formation of the epoxide ring owing to the appearance of two triplets centred at δ = 2.62 and δ = 2.63, which could be assigned to C(7)–H of the isoprene chain, corresponding to the *endo*-**7** and *exo*-**7** derivatives, respectively.[17]

On the other hand, when the same reaction was carried out using a larger excess of base (6.0 equiv.), proton abstraction also occurred at C(1) of the cyclohexene ring, leading to the cyclohexadienic structure **8** as an (*E*)/(*Z*) isomeric mixture owing to the disappearance of the *endo* and *exo* isomerism. In this case, the formation of the extended conjugate system probably plays an important role in promoting the deprotonation reaction and acts as the driving force for the elimination process. The presence of the endocyclic double bond was confirmed by the appearance of a



Scheme 2. Synthesis of cycloadducts by thermal Diels–Alder reaction



Scheme 3. Synthesis of mimic agents of Juvenile Hormones

pair of doublets ($J = 5.7$ Hz) centred at $\delta = 5.75$ [C(3)−H] and 6.95 [C(2)−H], respectively. That (*E*) and (*Z*) isomers had been formed was indicated by the splitting of the singlets attributable to the methyl groups of the isoprene chain. The ratio of the isomers [(*E*)/(*Z*) = 75:25] was determined on the basis of the integrals of the signals of the relevant methyl groups.

In conclusion, a variety of structural modifications and functionalizations can be carried out on citral and farnesal by exploiting the superbasic reagent LICKOR. Moreover, although none of the obtained derivatives have been described previously, they could turn out to be useful synthetic mimic agents of naturally occurring products.

Experimental Section

General: Flasks and all equipment used for the generation and reaction of moisture-sensitive reagents were flame-dried under argon. The temperature of acetone/liquid nitrogen baths was −95°C; room temperature was 25°C. Anhydrous THF was distilled from sodium wire after the blue colour of in situ generated sodium diphenylketyl persisted.[18] BuLi (1.6 M solution in hexanes) was purchased from Aldrich. *t*BuOK, obtained from Merck, was sublimed in vacuo (1.0 Torr) prior to use. All commercially available chemicals were reagent-grade and were used without further purification. Products were purified by preparative column chromatography on Merck silica gel 60 using light petroleum ether (b.p. 30−60°C)/diethyl ether as eluent. ^{1}H-NMR spectra were recorded at 300 MHz (Dipartimento di Chimica Organica, Università di Pavia), 200 MHz and 400 MHz (Dipartimento di Chimica IFN, Università di Torino) in $CDCl_3$, or at 60 MHz in CCl_4, using TMS as internal standard. Coupling constants (*J*) are given in Hz. ^{13}C-NMR spectra were recorded at 100.4 or 75.5 MHz as $CDCl_3$ solutions, and chemical shifts were determined relative to the residual solvent peak ($\delta = 77.0$). GC-MS data were recorded at 70 eV ionization potential using a cross-linked methyl silicone capillary column (25 m × 0.2 mm × 0.33 mm film thickness).

Oxidation of Farnesol with Pyridinium Chlorochromate. − 3,7,11-Trimethyldodeca-2,6,10-trienal: To a solution of 2.3 g (10.0 mmol) of farnesol in 25 mL of hexanes, 26 g (25 mmol) of pyridinium chlorochromate on alumina was added, and the mixture was stirred at 25°C for 2 h. The solid was then filtered off and washed with Et_2O (3 × 10 mL). The combined filtrate and washings were concentrated to give 1.87 g of farnesal (87%) as a mixture of three isomers: (*Z*,*E*) (7%), (*E*,*Z*) (23%) and (*E*,*E*) (70%)[19] as a colourless oil. − ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.60$ (br. s, 6 H), 1.70 (br. s, 6 H), 2.2 (m, 8 H), 5.1 (m, 2 H), 5.85 (br. d, $J = 3.7$ Hz, 1 H), 9.90, 9.91 and 9.98 (d, $J = 3.7$ Hz, 1 H). − IR (film): $\tilde{\nu} = 1674$ cm^{-1} (CO), 1632 (C=C).

Synthesis of Farnesal Dimethyl Acetal. − 3,7,11-Trimethyldodeca-2,6,10-trienal Dimethyl Acetal (2): To a solution of 0.66 g (3.0 mmol) of farnesal in 30 mL of anhydrous MeOH, 0.024 g (0.1 mmol) of $LaCl_3$ and 1.30 g (12.0 mmol) of trimethyl orthoformate were consecutively added and the mixture was stirred at 25°C for 30 min. The reaction mixture was then treated with 5% aqueous $NaHCO_3$ and extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated to give 0.66 g (82%) of acetal **2** as a colourless oil, consisting of the three isomers derived from the corresponding aldehydes. The mixture was sufficiently pure for use in the following step. − ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.60$ (s, 6 H), 1.75 (s, 6 H), 2.2 (m, 8 H), 3.33 (s, 6 H), 5.0 (m, 1 H), 5.1 (m, 2 H), 5.3 (m, 1 H). − GC MS (70 ev); *m/z* (%): 235 (6) [$M^+ - OCH_3$], 83 (26), 75 (54), 69 (100).

Typical Procedure for Syntheses of Dienes 3−4. − 1-Methoxy-7,11-dimethyl-3-methylenedodeca-1,6,10-triene (4): Under inert atmosphere, 4.1 mL of BuLi (1.6 M, 6.55 mmol) was added dropwise to a stirred, cooled (−95°C) solution of 0.73 g of sublimed *t*BuOK (6.55 mmol) and 0.96 g of acetal **2** (3.6 mmol) in anhydrous THF (8 mL). After a few seconds, the solution turned purple and stirring was continued at −95°C for 4 h. The reaction was then quenched with aqueous THF (1:1; 10 mL) and the colour was discharged. The two phases were separated, and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated to give crude **4** as a mixture of the (1*E*,6*E*) and (1*E*,6*Z*) isomers, which was purified by column chromatography (light petroleum ether/Et_2O, 85:15) to give a colourless oil; 0.63 g (75%). − ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.60$ (br. s, 6 H), 1.70 [s, 3 H, C(7)−CH_3; (*E*,*E*) isomer, 75%] and 1.75 [s, 3 H, C(7)−CH_3; (*E*,*Z*) isomer, 25%], 2.2 (m, 8 H), 3.35 (s, 3 H), 4.70 (br. s, 1 H), 4.80 (br. s, 1 H), 5.1 (m, 2 H), 5.55 (d, $J = 13.0$ Hz, 1 H), 6.63 [d, $J = 13.0$ Hz, 1 H, C(1)−H, (*E*,*E*) isomer] and 6.65 [d, $J = 13.0$ Hz, 1 H, C(1)−H, (*E*,*Z*) isomer]. − ^{13}C NMR ($CDCl_3$), both isomers: $\delta = 15.92$, 17.55, 17.56, 23.27, 25.60, 31.90, 32.82, 33.13, 39.60, 56.20, 107.34, 110.10, 110.15, 123.90, 124.20, 124.25, 124.70, 143.58, 148.14, 148.17. − $C_{16}H_{26}O$ (234.38): calcd. C 81.99, H 11.18; found C 82.05, H 11.06.

1-Methoxy-7-methyl-3-methyleneocta-1,6-diene (3): Purification: light petroleum ether/Et_2O, 90:10, colourless oil, 0.44 g (73%). − ^{1}H NMR (60 MHz, CCl_4): $\delta = 1.60$ (s, 3 H), 1.70 (s, 3 H), 2.5 (m, 4 H), 3.80 (s, 3 H), 4.8 (m, 2 H), 5.0 (m, 1 H), 5.60 (d, $J = 13.0$ Hz, 1 H), 6.70 (d, J = 13.0 Hz, 1 H). − $C_{11}H_{18}O$ (166.26): calcd. C 79.46, H 10.91; found C 79.15, H 11.00.

Representative Procedure for Diels−Alder Cycloaddition: A solution of 2.5 mmol of diene (corresponding to 0.42 g of **3**; 0.59 g of **4**) in 4.3 g of methyl acrylate (50.0 mmol) was degassed with argon. The solution was then refluxed in the presence of hydroquinone under inert atmosphere, while the reaction was followed by TLC (Et_2O/light petroleum ether, 15:85). After 24 h, the mixture was washed with 10% NaOH solution (5 mL). The organic phase was dried with Na_2SO_4 and the excess methyl acrylate was removed in vacuo. Column chromatography of the residue furnished the cycloadducts, which were purified by kugelrohr distillation (b.p. range 85−100°C; 0.1 Torr, in the presence of a spatula tip of hydroquinone).

Methyl 4-(4-Methylpent-3-enyl)-2-methoxycyclohex-3-ene-1-carboxylate (*endo*-5 and *exo*-5): Purification: light petroleum ether/Et_2O, 90:10, colourless oil, 0.50 g (80%). − ***endo*-5:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 3 H), 1.68 (s, 3 H), 2.0 (m, 8 H), 2.5 (m, 1 H), 3.35 (s, 3 H), 3.73 (s, 3 H), 3.95 (t, J = 4.5 Hz, 1 H), 5.09 (br. t, J = 7.0 Hz, 1 H), 5.72 (br. d, J = 4.5 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.53, 19.06, 25.51, 25.97, 28.39, 37.39, 44.19, 51.34, 55.71, 73.15, 118.57, 123.64, 131.66, 143.64, 173.59. − ***exo*-5:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 3 H), 1.68 (s, 3 H), 2.0 (m, 8 H), 2.58 (ddd, J = 11.0, 8.0, 3.0 Hz, 1 H), 3.37 (s, 3 H), 3.72 (s, 3 H), 4.14 (br. d, J = 8.0 Hz, 1 H), 5.1 (m, J = 7.0 Hz, 1 H), 5.6 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 19.06, 17.53, 24.30, 25.58, 27.41, 36.99, 45.19, 51.50, 55.91, 76.61, 120.01, 123.64, 131.62, 140.95, 175.13. − $C_{15}H_{24}O_3$ (252.35): calcd. C 71.39, H 9.59; found C 71.70, H 9.15.

Methyl 4-(4,8-Dimethylnona-3,7-dienyl)-2-methoxycyclohex-3-ene-1-carboxylate (*endo*-6 and *exo*-6): Purification: light petroleum ether/Et_2O, 85:15, colourless oil, 0.66 g (82%). The assignment of carbon signals was only possible for the two main isomers [(E)-*endo*-**6** and (E)-*exo*-**6**] on the basis of a 2D-C,H-correlated spectrum. **−** ***endo*-6:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (br. s, 3 H), 1.61 (br. s, 6 H), 2.0 (m, 12 H), 2.5 (m, 1 H), 3.29 (s, 3 H), 3.67 (s, 3 H), 3.92 (br. t, J = 4.5 Hz, 1 H), 5.0 (m, 2 H), 5.65 (br. d, J = 4.5 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.92, 17.57, 19.10, 25.61, 25.98, 26.61, 28.44, 37.44, 39.58, 44.85, 51.30, 56.79, 73.23, 118.62, 123.56, 124.18, 131.18, 135.39, 143.70, 173.58. − ***exo*-6:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 3 H), 1.61 (s, 6 H), 2.0 (m, 12 H), 2.55 (ddd, J = 12.0, 8.0, 3.5 Hz, 1 H), 3.30 (s, 3 H), 3.68 (s, 3 H), 4.08 (br. d, J = 8.0 Hz, 1 H), 5.1 (m, 2 H), 5.45 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.92, 17.57, 19.10, 25.58, 25.84, 26.47, 27.50, 31.86, 37.79, 44.85, 51.40, 55.79, 73.21, 120.16, 123.56, 124.36, 131.44, 135.48, 141.01, 175.14. − $C_{20}H_{32}O_3$ (320.47): calcd. C 74.96, H 10.06; found C 75.20, H 9.88.

Construction of the Epoxide Ring via a Bromohydrin Derivative: To a cooled (0°C) solution of 0.77 g (2.4 mmol) of the isomeric mixture of cycloadducts **6** in THF (8.9 mL) and H_2O (2.9 mL), 0.47 g (2.6 mmol) of NBS was added under stirring. After 3 h at this temperature, the reaction mixture was treated with 5% aqueous $NaHCO_3$ and extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated to give a crude product (0.75 g, 75%), which was used directly in the following step. To 0.71 g (1.7 mmol) of the bromohydrin in 8.5 mL of anhydrous methanol, 4.0 molar equivalents of anhydrous K_2CO_3 were added under argon. The reaction mixture was stirred vigorously for 30 min., and then the solid was filtered off and washed with methanol. The organic solution was concentrated in vacuo, washed with brine, and dried. Evaporation of the solvent, followed by column chromatography (light petroleum ether/Et_2O, 90:10) of the residue furnished 0.50 g (88%) of **7** as a mixture of *endo* and *exo* isomers.

Methyl 4-(7,8-Epoxy-4,8-dimethylnon-3-enyl)-2-methoxycyclohex-3-ene-1-carboxylate (*endo*-7 and *exo*-7): In this case also, the assignment of carbon signals was possible only for the two main isomers [(E)-*endo*-**7** and (E)-*exo*-**7**] on the basis of a 2D-C,H-correlated spectrum. − ***endo*-7:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 3 H), 1.22 (s, 3 H), 1.55 (s, 3 H), 1.9 (m, 12 H), 2.4 (m, 1 H), 2.61 (t, J = 6.6 Hz, 1 H), 3.28 (s, 3 H), 3.68 (s, 3 H), 3.90 (br. t, J = 4.5 Hz, 1 H), 5.08 (br. t, J = 7.5 Hz, 1 H), 5.70 (br. d, J = 4.5 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.86, 18.57, 24.74, 19.04, 25.88, 27.30, 28.39, 36.13, 37.29, 44.76, 51.34, 56.76, 58.12, 63.97, 73.14, 118.67, 124.15, 134.42, 143.50, 173.52. − ***exo*-7:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 3 H), 1.23 (s, 3 H), 1.55 (s, 3 H), 1.9 (m, 12 H), 2.45 (ddd, J = 12.0, 8.0, 3.5, 1 H), 2.62 (t, J = 6.6 Hz, 1 H), 3.33 (s, 3 H), 3.65 (s, 3 H), 4.08 (br. d, J = 8.7 Hz, 1 H), 5.08 (br. t, J = 7.5 Hz, 1 H), 5.42 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.84, 18.54, 19.04, 24.72, 24.25, 25.72, 27.22, 28.37, 37.31, 45.18, 51.60, 55.37, 58.18, 63.88, 76.58, 118.73, 124.95, 134.39, 143.43, 175.07. − $C_{20}H_{32}O_4$ (336.47): calcd. C 71.39, H 9.59; found C 71.85, H 9.10.

Synthesis of Epoxides (E)-8 and (Z)-8: The syntheses were carried out under the same conditions as described above for epoxides **7**, but using 6.0 equiv. of anhydrous K_2CO_3. Purification: light petroleum ether/Et_2O, 90:10; colourless oil; 0.36 g (70%).

Methyl 4-(3E)-(7,8-Epoxy-4,8-dimethylnon-3-enyl)cyclohexa-1,3-diene-1-carboxylate [(E)-8]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3 H), 1.31 (s, 3 H), 1.62 (s, 3 H), 2.2 (m, 10 H), 2.45 (br. t, J = 9.0 Hz, 2 H), 2.70 (t, J = 6.5 Hz, 1 H), 3.75 (s, 3 H), 5.2 (m, 1 H), 5.75 (d, J = 5.7 Hz, 1 H), 6.95 (d, J = 5.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.88, 18.58, 21.46, 24.74, 25.71, 27.20, 28.40, 36.14, 37.23, 51.30, 58.13, 69.86, 118.64, 123.55, 124.68, 124.77, 134.76, 134.76, 167.83.

Methyl 4-(3Z)-(7,8-Epoxy-4,8-dimethylnon-3-enyl)cyclohexa-1,3-diene-1-carboxylate [(Z)-8]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 3 H), 1.32 (s, 3 H), 1.72 (s, 3 H), 2.2 (m, 10 H), 2.45 (br. t, J = 9.0 Hz, 2 H), 2.72 (t, J = 6.5 Hz, 1 H), 3.75 (s, 3 H), 5.2 (m, 1 H), 5.75 (d, J = 5.7 Hz, 1 H), 6.95 (d, J = 5.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 18.55, 23.13, 21.48, 24.72, 25.57, 27.23, 28.40, 36.14, 37.46, 51.30, 58.14, 69.92, 118.66, 123.57, 124.70, 124.74, 134.73, 147.96, 167.83. − $C_{19}H_{28}O_3$ (304.42): calcd. C 74.96, H 9.27; found C 75.45, H 9.75.

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[5] The commercial sample of citral dimethyl acetal used was a mixture of the acetals of geranial (70%) and neral (30%). Farnesol is sold as a mixture of (*Z*,*Z*) (0.5%), (*Z*,*E*) (12.5%), (*E*,*Z*) (37.5%) and (*E*,*E*) (49.5%) isomers. We thank Aldrich for kindly providing this information. One of the referees has suggested the use of pure isomers in order to obtain more significant findings. We will surely comply with this suggestion in future studies; in the present work, we indeed feel that a reduction in the number of isomers could be of some interest so as to stress the stereoselectivity of the elimination reaction.

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[7] In the case of acetal **1**, the ^{1}H-NMR spectrum of the elimination product shows the appearance of two well-defined AB systems: the first (centred at $\delta = 6.15$) characterized by a *trans* coupling constant ($J = 13.5$ Hz), attributable to C(1)−H ($\delta = 6.70$) and C(2)−H ($\delta = 5.60$), and the second (centred at $\delta = 4.80$) distinguished by a geminal coupling constant ($J = 1.5$ Hz), due to the methylene group bonded to C(3). The ^{1}H-NMR spectrum of the elimination product derived from farnesal dimethyl acetal shows an analogous pattern.

[8] Such an interaction could also account for the facile 1,4-elimination reaction, since metal−oxygen interaction makes the alkyloxy group a more effective leaving group (as regards the importance of metal−oxygen interactions, see for example: K. S. Y. Lau, M. Schlosser, *J. Org. Chem.* **1978**, *43*, 1595−1598). We intend to carry out some experiments on the acetals of pure neral and geranial, in order to compare relative rates of 1,4-elimination as a function of the stereochemistry. This study might clarify the role of the interactions of the metal cation with the alkyloxy leaving group in a concerted process.

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[11] Modified experimental conditions, such as exploiting the catalytic effect of Lewis acids, proved not to be advantageous since they preferentially accelerated the hydrolysis of the vinyl ether function, resulting in loss of the dienic unit.

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[13] In the case of the *endo*-**5** adduct, C(1)−H and C(2)−H have a *cis* relationship since C(2)−H ($\delta = 3.95$) shows a broad triplet ($J = 4.5$ Hz) suggesting an axial−equatorial relationship with C(1)−H ($\delta = 2.53$). On the other hand, in the *exo*-**5** adduct both C(1)−H and C(2)−H are axial, as C(2)−H ($\delta = 4.14$) shows a relatively large coupling constant ($J = 8.0$ Hz) suggesting a *trans* relationship with C(1)−H ($\delta = 2.58$).

[14] In the ^{1}H-NMR spectra, we were able to characterize the two isomers corresponding to the *endo* and *exo* approaches. It was impossible to single out useful signals that would have allowed discrimination of the (*E*) and (*Z*) isomers as regards the C(3)−C(4) double bond in the isoprene chain. However, GC, GC-MS, and ^{13}C-NMR analyses indicated the presence of four isomers (ratio ca. 55:25:15:5 by GC analysis). On the basis of the ratio of the two isomers of diene **4** [(1*E*,6*E*)/(1*E*,6*Z*) = 75:25], and of the *endo* and *exo* cycloadducts **6**, we can reasonably deduce the following assignments: (*E*)-*endo* (55%), (*E*)-*exo* (25%), (*Z*)-*endo* (15%), and (*Z*)-*exo* (5%).

[15] R. J. Anderson, C. A. Henrick, J. B. Siddall, R. Zurflüh, *J. Am. Chem. Soc.* **1972**, *94*, 5379−5386.

[16] *m*-CPBA promotes the formation of the oxirane ring at both the terminal and the endocyclic C−C double bonds.

[17] That an epoxidation reaction had occurred was confirmed by the following observations: (i) The integral of the broad triplet centred at $\delta = 5.08$ (1 H) attributable to C(3)−H of the isoprene chain was smaller than that of the multiplet attributable to C(3)−H and C(7)−H in the spectra of compounds *endo*-**6** and *exo*-**6** ($\delta = 5.0$, and 5.1, respectively); (ii) the singlets attributable to the geminal C(8)-$(CH_3)_2$ were high-field shifted owing to the loss of the C(7)−C(8) double bond.

[18] W. Schlenk, E. Bergmann, *Justus Liebigs Ann. Chem.* **1928**, *464*, 1−42.

[19] The ratio of the isomers was been established on the basis of the integrals of the signals attributable to the aldehydic protons centred at $\delta = 9.90$ (*Z*,*E*), 9.91 (*E*,*Z*) and 9.98 (*E*,*E*), respectively.

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