

Article

A Practical Laboratory-Scale Synthesis of All Eight Stereoisomeric Forms of Terpene Linalool Oxide

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Abstract: In this work, we describe a user-friendly procedure for the preparation of all the isomeric forms of the terpene linalool oxide. The presented method is based on the transformation of the linalool enantiomers into the corresponding diastereoisomeric mixtures of the two furanoid oxides and two pyranoid oxides. Taking advantage of the different steric hindrance of the hydroxyl functional groups, the pyranoid forms were separated as a diastereoisomeric mixtures of their benzoate esters. Conversely, the *cis*- and *trans*-furanoid isomers were transformed in the corresponding acetates, which were directly separated by chromatography. The hydrolysis of the latter esters afforded *cis*- and *trans*-furanoid linalool oxides whereas the same reaction performed on the benzoates mixture afforded a separable mixture of *cis*- and *trans*-pyranoid linalool oxide. Overall, the method features, as a unique mandatory requirement, the availability of both linalool enantiomers, and can be conveniently performed from a milligram to a multigram scale.

Keywords: linalool; furanoid linalool oxide; pyranoid linalool oxide; terpene; stereoisomers separation; flavours; fragrances



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1. Introduction

All eight ether stereoisomers with general structure **1** and **2** (Figure 1) are naturally occurring monoterpenes, collectively called linalool oxides [1]. They comprise the two tetrahydrofuran diastereoisomers **1a** and **1b** (*cis* and *trans* furanoid linalool oxides isomers) or tetrahydropyran derivatives **2a** and **2b** (*cis* and *trans* pyranoid linalool oxides isomers). Most likely, the biosynthesis of these compounds proceeds through the regioselective monoepoxidation of the linalool trisubstituted double bond, followed by the intramolecular cyclization of the obtained epoxy-alcohol [2]. Due to the natural occurrence of both (*R*)- and (*S*)-linalool [3] as precursors, this mechanism justifies the formation of both furanoid and pyranoid isomers, as well as the presence in nature of all their possible stereoisomeric forms. Despite the differences in structure, the aromas of the different forms of linalool oxide have a strong family resemblance [4]. The furan-based linalool oxide has a floral character, somewhat reminiscent of lavender, but this is dominated by the profile of black tea. The pyran-based linalool oxide is more obviously floral, with less resemblance to tea. All these monoterpenes are important flavours and are thought to give a relevant contribute to the scent of different foods and beverages of vegetal origin such as grape [5], papaya [2,6], wine [7], and tea [8] where they are often present as glycosides derivatives [9,10] or less frequently as acetate [11]. In addition, these monoterpene isomers are important chiral building blocks for the synthesis of different bioactive natural products [12–17].

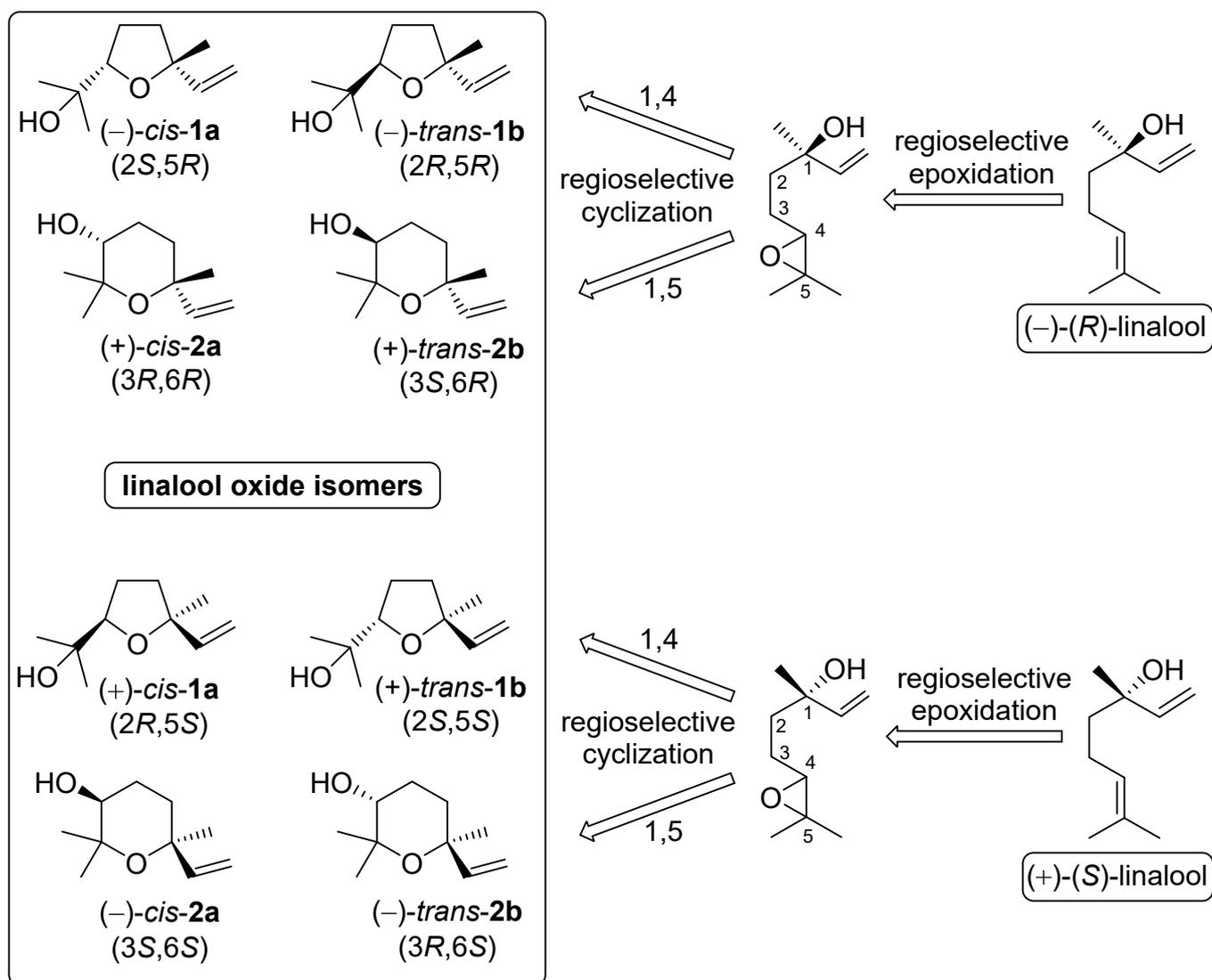


Figure 1. The eight linalool oxide isomers and their postulated biosynthesis from linalool enantiomers.

As we are involved in a number of studies focused on the stereoselective synthesis of flavors, fragrances and sesquiterpenes structurally related to the linalool and linalool oxides [18–21], we became interested in developing a synthetic method for the preparation of all the linalool oxide stereoisomers. Although a number of chemical [12,14,22–30] and chemoenzymatic syntheses [31–35] of enantioenriched linalool oxides have been previously reported, only a few [22–24] are suitable for the stereoselective preparation of all the isomeric forms of these monoterpenes. Among the latter three approaches, Klein et Al. [22] described the most direct one. Accordingly, a given linalool enantiomer was treated with peracetic acid to afford a diastereoisomeric mixture of the enantiopure furanoid and pyranoid linalool oxides. Epoxidation and cyclization steps occurred consecutively, in one pot. The first reaction was highly regioselective and the diastereoisomeric mixture of the trisubstituted epoxides was formed preferentially. Then, the acid-catalyzed cyclization step provided furanoid and pyranoid oxides in a 82:18 ratio.

Even if the above procedure appears very simple and provides all the isomers at once, their chromatographic separation is troublesome. Indeed, the linalool oxide isomers required separation by means of a two steps procedure based on fractional distillation. Accordingly, distillation of the crude reaction mixture allowed the separation of pyranoid oxides whereas furanoid oxides had to be converted into the corresponding acetates before fractionation. Moreover, as reported by Klein et al., their procedure was effective on a large

scale only, i.e., starting from five moles of linalool. On the contrary, this technique is not conveniently performable at laboratory scale where only few grams of the pure linalool oxide stereoisomers are usually required either as synthetic building blocks or as analytic standards.

Hence, in this work, we describe a user-friendly procedure for the preparation of the linalool oxide isomers starting from linalool enantiomers. Our proposed method allows the separation of all linalool oxide forms from their crude mixtures available by Klein's process. To accomplish our method, we take advantage of two additional key steps. The first step consisted of the chemoselective benzylation of the secondary alcohol functional group of the pyranoid oxides **2a** and **2b** only followed by the chromatographic separation of these esters from the unreacted furanoid oxides. The second step is the transformation of the furanoid isomers **1a** and **1b** into their corresponding acetate esters, which are separable by chromatography. Finally, the removal of the acetate functional group afforded *cis*- and *trans*-furanoid linalool oxides whereas the hydrolysis of the benzoate esters afforded a mixture of *cis*- and *trans*-pyranoid linalool oxide, which were separated by chromatography. Since the cyclization step did not involve racemization [22], the linalool oxide isomers obtained through our procedure possess the same enantiomeric purity of the starting linalool, namely 97% ee for (*R*)-linalool and 50% ee for (*S*)-linalool.

2. Materials and Methods

2.1. Materials and General Methods

All moisture and air sensitive reactions were carried out using dry solvents and under a static atmosphere of nitrogen.

All solvents and reagents were of commercial quality.

(-)-(*R*)-Linalool, extracted from *Cinnamomum camphora* (L.) and possessing 98% chemical purity by GC and 97% ee by chiral GC, $[\alpha]_D^{20} = -20.9$ (neat), lot MKBR2739V, was purchased from Sigma-Aldrich (St. Louis, MO, USA).

Coriander oil, $[\alpha]_D^{20} = +8.3$ (neat) was purchased from Sigma-Aldrich (lot MKCC6867) and was used as source of (+)-(*S*)-linalool (91% chemical purity by GC-MS analysis and 50% ee by chiral GC).

2.2. Analytical Methods and Characterization of the Chemical Compounds

¹H and ¹³C-NMR spectra and DEPT experiments (Supplementary Materials): CDCl₃ solutions at rt using a Bruker-AC-400 spectrometer (Billerica, MA, USA) at 400, 100 and 100 MHz, respectively; ¹³C spectra are proton decoupled; chemical shifts in ppm rel to internal SiMe₄ (=0 ppm).

TLC: Merck silica gel 60 F₂₅₄ plates (Merck Millipore, Milan, Italy). Column chromatography: silica gel.

Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected.

Optical rotations were measured on a Jasco-DIP-181 digital polarimeter (Jasco, Tokyo, Japan).

Mass spectra were recorded on a Bruker ESQUIRE 3000 PLUS spectrometer (Electrospray Ionization (ESI) detector, Billerica, MA, USA or by GC-MS analyses.

GC-MS analyses: HP-6890 gas chromatograph equipped with a 5973 mass detector, using a HP-5MS column (30 m × 0.25 mm, 0.25 μm film thickness; Hewlett Packard, Palo Alto, CA, USA) with the following temp. program: 60° (1 min), then 6°/min to 150° (held 1 min), then 12°/min to 280° (held 5 min); carrier gas: He; constant flow 1ml/min; split ratio: 1/30; *t*_R given in minutes.

*t*_R(linalool) 9.19, *t*_R(**1a**) 8.88, *t*_R(**1b**) 8.50, *t*_R(**2a**) 11.14, *t*_R(**2b**) 10.99, *t*_R(**3a**) 23.90, *t*_R(**3b**) 23.79, *t*_R(**4a**) 13.13, *t*_R(**4b**) 12.71.

2.3. Procedure for the Preparation of the Linalool Oxide Isomers (2*S*,5*R*)-1*a*, (2*R*,5*R*)-1*b*, (3*R*,6*R*)-2*a* and (3*S*,6*R*)-2*b*

2.3.1. Preparation of the Mixture of the Linalool Oxide Isomers 1*a*, 1*b*, 2*a* and 2*b* from (*R*)-Linalool

m-Chloroperbenzoic acid (77% *w/w*, 40 g, 178 mmol) was added portion-wise to a mechanically stirred solution of (–)-(*R*)-linalool (25 g, 162 mmol, 98% purity, *ee* > 95%) in CH₂Cl₂ (150 mL) at 0 °C. The reaction was stirred 2 hours at 0 °C, overnight and then was treated with PTSA (1 g, 5.2 mmol) and quenched by the addition of aq. Na₂S₂O₅ (10% *w/w*, 60 mL). The reaction was stirred for one further hour and then was cooled to 0 °C. The *m*-chlorobenzoic acid formed was removed by filtration and the liquid phase was concentrated under reduced pressure. The residue was dissolved in diethyl ether (250 mL) and was washed in turn with, aq. NaOH (5% *w/v*) and brine. Then, the organic phase was dried (Na₂SO₄) and the solvent was evaporated. The obtained oil was roughly purified by filtration on an alumina column (activated, basic, Brockmann I) eluting with hexane/diethyl ether, to afford the crude mixture of the linalool oxide isomers (26.9 g, **1a** = 39%, **1b** = 42%, **2a** = 10%, **2b** = 9%).

2.3.2. Procedure for the Separation of the Linalool Oxide Isomers

The above-described mixture of the linalool oxide isomers was dissolved in a mixture of dry CH₂Cl₂ (30 mL) and dry pyridine (5 mL). The resulting solution was cooled to 0 °C and benzoyl chloride (5.4 g, 38.4 mmol) was added dropwise under stirring. The reaction was stirred at rt. for 4 hours, then was poured in crushed ice, was extracted with ethyl acetate and the organic phase was washed in turn with, aq. NaHCO₃ (saturated solution) and brine. The organic phase was dried (Na₂SO₄), was concentrated under reduced pressure and the residue was chromatographed using *n*-hexane/AcOEt (95:5–7:3) as eluent to afford the benzoate esters (6.9 g, 25.2 mmol, pyranoid/furanoid ratio 96:4) and the mixture of the furanoid linalool oxide diastereoisomers (19.6 g, 115 mmol).

The benzoate esters were dissolved in methanol (40 mL) and were heated under reflux with a solution of NaOH (3 g, 75 mmol) in methanol (30 mL). After complete hydrolysis of the esters (TLC monitoring, 3 h), the main part of the solvent was removed under reduced pressure and the reaction was quenched by the addition of crushed ice followed by the extraction with diethyl ether (3 × 70 mL). The combined organic phases were dried (Na₂SO₄), were concentrated under reduced pressure and the residue was chromatographed using *n*-hexane/AcOEt (9:1–7:3) as eluent to afford a small amount of furanoid isomers (0.1 g, 0.6 mmol) followed by the pyranose isomers. The latter compounds were eluted in the following order:

cis-linalool oxide (+)-**2a** (first eluted isomer): 1.65 g (9.7 mmol)

mixture of *cis/trans*-linalool oxide: 0.95 g (5.6 mmol)

trans-linalool oxide (+)-**2b** (second eluted isomer): 1.25 g (7.3 mmol)

pyranoid *cis*-linalool oxide (+)-**2a** = (3*R*,6*R*)-2,2,6-trimethyl-6-vinyltetrahydro-2*H*-pyran-3-ol

colorless oil which solidified on standing. Mp 95–96 °C; 98% of diastereoisomeric purity and 98% of chemical purity by GC. $[\alpha]_{\text{D}}^{20} = +3.6$ (*c* 2.3, CH₂Cl₂), Lit. [25]: $[\alpha]_{\text{D}}^{20} = +1.9$ (*c* 0.5, CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ 5.97 (dd, *J* = 17.8, 11.1 Hz, 1H), 4.99 (d, *J* = 17.8 Hz, 1H), 4.98 (d, *J* = 11.1 Hz, 1H), 3.49–3.38 (m, 1H), 2.12 (dt, *J* = 13.6, 3.7 Hz, 1H), 1.79–1.51 (m, 3H), 1.42–1.31 (m, 1H), 1.25 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 146.3 (CH), 110.6 (CH₂), 75.9 (C), 74.9 (CH), 73.4 (C), 32.5 (CH₂), 31.6 (Me), 29.5 (Me), 25.7 (CH₂), 20.8 (Me). GC-MS *m/z* (rel intensity) 155 (M⁺ – Me, 6), 143 (2), 137 (4), 125 (2), 119 (1) 109 (3), 102 (4), 94 (76), 79 (23), 68 (100), 59 (67), 43 (32).

pyranoid *trans*-linalool oxide (+)-**2b** = (3*S*,6*R*)-2,2,6-trimethyl-6-vinyltetrahydro-2*H*-pyran-3-ol.

Colorless oil. 93% of diastereoisomeric purity and 96% of chemical purity by GC. $[\alpha]_{\text{D}}^{20} = +11.4$ (*c* 2.4, CH₂Cl₂), Lit. [25]: $[\alpha]_{\text{D}}^{20} = +11.0$ (*c* 0.5, CH₂Cl₂)

^1H NMR (400 MHz, CDCl_3) δ 5.94 (dd, $J = 17.8, 11.0$ Hz, 1H), 5.03 (d, $J = 17.8$ Hz, 1H), 4.96 (d, $J = 11.0$ Hz, 1H), 3.42 (br s, 1H), 2.03–1.92 (m, 1H), 1.85–1.66 (m, 4H), 1.24 (s, 3H), 1.22 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 146.8 (CH), 110.4 (CH_2), 75.2 (C), 73.5 (C), 71.2 (CH), 30.7 (Me), 27.6 (CH_2), 27.2 (Me), 26.3 (Me), 24.2 (CH_2). GC-MS m/z (rel intensity) 155 ($\text{M}^+ - \text{Me}$, 10), 143 (3), 137 (4), 125 (2), 119 (1), 109 (4), 102 (4), 94 (74), 79 (21), 68 (100), 59 (61), 43 (30)

The diastereoisomeric mixture of furanoid linalool oxides **1a** and **1b** (19.6 g, 115 mmol) was heated at reflux, under nitrogen, with acetic anhydride (20 mL, 212 mmol) and anhydrous NaOAc (2 g, 24 mmol). The reaction was stirred until complete transformation of the starting alcohol isomers (3 h, TLC monitoring), then was cooled, and was quenched by addition of water (100 mL). The obtained mixture was extracted with diethyl ether (3 \times 100 mL) and the combined organic phases were washed in turn with water, aq. NaHCO_3 (saturated solution) and brine. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and the residue was chromatographed using *n*-hexane/ Et_2O (99:1–8:2) as eluent to afford the following fractions:

furanoid *trans*-linalool oxide acetate (–)-**4b** (first eluted isomers, $R_f = 0.23$ in hexane/diethyl ether 9:1): 5.3 g (25 mmol)

mixture of *cis/trans*-linalool oxide acetate: 11.8 g (55.7 mmol)

furanoid *cis*-linalool oxide acetate (+)-**4a** (second eluted isomers, $R_f = 0.19$ in hexane/diethyl ether 9:1): 4.4 g (20.7 mmol)

Furanoid *cis*-linalool oxide acetate (+)-**4a** = 2-((2*S*,5*R*)-5-methyl-5-vinyltetrahydrofuran-2-yl)propan-2-yl acetate. Colorless oil; $[\alpha]_{\text{D}}^{20} = +0.3$ (c 2.8, CHCl_3), Lit. [15]: $[\alpha]_{\text{D}}^{20} = -0.3$ (neat)

^1H NMR (400 MHz, CDCl_3) δ 5.97 (dd, $J = 17.5, 10.8$ Hz, 1H), 5.22 (dd, $J = 17.5, 1.6$ Hz, 1H), 4.98 (dd, $J = 10.8, 1.6$ Hz, 1H), 4.13–4.05 (m, 1H), 2.00–1.71 (m, 4H), 1.98 (s, 3H), 1.49 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 170.4 (C), 144.2 (CH), 111.3 (CH_2), 84.1 (CH), 83.1 (C), 82.9 (C), 37.7 (CH_2), 26.6 (CH_2), 25.9 (Me), 22.5 (Me), 22.4 (Me), 21.8 (Me). GC-MS m/z (rel intensity) 197 ($\text{M}^+ - \text{Me}$, 7), 185 (1), 169 (2), 152 ($\text{M}^+ - \text{AcOH}$, 29), 143 (3), 137 (27), 119 (6), 111 (100), 101 (9), 93 (63), 81 (31), 67 (32), 55 (60)

Furanoid *trans*-linalool oxide acetate (–)-**4b** = 2-((2*R*,5*R*)-5-methyl-5-vinyltetrahydrofuran-2-yl)propan-2-yl acetate. Colorless oil; $[\alpha]_{\text{D}}^{20} = -8.2$ (c 2.9, CHCl_3), Lit. [15]: $[\alpha]_{\text{D}}^{20} = -5.0$ (neat)

^1H NMR (400 MHz, CDCl_3) δ 5.86 (dd, $J = 17.2, 10.6$ Hz, 1H), 5.18 (dd, $J = 17.2, 1.2$ Hz, 1H), 4.99 (dd, $J = 10.6, 1.2$ Hz, 1H), 4.07 (t, $J = 6.5$ Hz, 1H), 1.99 (s, 3H), 1.94–1.79 (m, 3H), 1.77–1.67 (m, 1H), 1.48 (s, 6H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 170.4 (C), 143.6 (CH), 111.3 (CH_2), 83.9 (CH), 83.3 (C), 83.0 (C), 37.1 (CH_2), 26.6 (Me), 26.4 (CH_2), 22.4 (Me), 22.4 (Me), 21.5 (Me). GC-MS m/z (rel intensity) 197 ($\text{M}^+ - \text{Me}$, 2), 185 (2), 169 (3), 152 ($\text{M}^+ - \text{AcOH}$, 26), 143 (3), 137 (21), 119 (5), 111 (100), 101 (8), 93 (56), 81 (29), 67 (33), 55 (49)

A sample of the ester (+)-**4a** or (–)-**4b** (1 g, 4.7 mmol) was dissolved in dry diethyl ether (30 mL) and treated under stirring with LiAlH_4 (0.2 g, 5.3 mmol). As soon as the starting ester was no longer detectable by TLC analysis (1 hour), the reaction was diluted with diethyl ether (70 mL), was quenched with crushed ice and was acidify with aq. HCl (3% w/v). The separated organic phase was dried (Na_2SO_4), concentrated under reduced pressure and the residue was purified by bulb-to-bulb distillation to afford linalool oxide (–)-**1a** (0.71 g, 88% yield) or linalool oxide (–)-**1b** (0.73 g, 91% yield), respectively.

Furanoid *cis*-linalool oxide (–)-**1a** = 2-((2*S*,5*R*)-5-methyl-5-vinyltetrahydrofuran-2-yl)propan-2-ol. Colorless oil; $[\alpha]_{\text{D}}^{20} = -4.1$ (c 2.1, CHCl_3), Lit. [13]: $[\alpha]_{\text{D}}^{23} = -3.8$ (c 0.72, CHCl_3)

^1H NMR (400 MHz, CDCl_3) δ 5.98 (dd, $J = 17.5, 10.8$ Hz, 1H), 5.19 (dd, $J = 17.5, 1.3$ Hz, 1H), 5.00 (dd, $J = 10.8, 1.3$ Hz, 1H), 3.85 (t, $J = 7.1$, 1H), 2.12–2.04 (m, 1H), 1.96–1.72 (m, 4H), 1.31 (s, 3H), 1.22 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 144.3 (CH), 111.5 (CH_2), 85.5 (CH), 82.7 (C), 71.2 (C), 37.9 (CH_2), 27.3 (Me), 26.4 (CH_2), 26.0 (Me), 24.3 (Me). GC-MS m/z (rel intensity) 155 ($\text{M}^+ - \text{Me}$, 11), 137 (9), 125 (1), 119 (2), 111 (43), 102 (3), 94 (62), 81 (24), 68 (36), 59 (100)

Furanoid *trans*-linalool oxide (–)-**1b** = 2-((2*R*,5*R*)-5-methyl-5-vinyltetrahydrofuran-2-yl)propan-2-ol. Colorless oil; $[\alpha]_{\text{D}}^{20} = -6.5$ (c 2.4, CHCl₃), Lit. [13] for the (2*S*,5*S*) enantiomer: $[\alpha]_{\text{D}}^{23} = +5.7$ (c 0.95, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 5.86 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.17 (dd, *J* = 17.4, 1.5 Hz, 1H), 4.98 (dd, *J* = 10.8, 1.5 Hz, 1H), 3.78 (t, *J* = 7.1, 1H), 2.16 (s, 1H), 1.93–1.77 (m, 3H), 1.75–1.66 (m, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 1.12 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 143.7 (CH), 111.3 (CH₂), 85.5 (CH), 83.0 (C), 71.1 (C), 37.4 (CH₂), 27.1 (Me), 26.8 (Me), 26.3 (CH₂), 24.1 (Me). GC-MS *m/z* (rel intensity) 155 (M⁺ – Me, 6), 137 (7), 125 (2), 111 (39), 102 (3), 94 (55), 81 (23), 68 (34), 59 (100)

2.4. Procedure for the Preparation of the Linalool Oxide Isomers (2*R*,5*S*)-**1a**, (2*S*,5*S*)-**1b**, (3*S*,6*S*)-**2a** and (3*R*,6*S*)-**2b**

The procedure described above (paragraph 2.3) was repeated using (*S*)-linalool as starting material (obtained by rectification of coriander oil, 50% e.e.). The obtained linalool oxide isomers (2*R*,5*S*)-**1a**, (2*S*,5*S*)-**1b**, (3*S*,6*S*)-**2a** and (3*R*,6*S*)-**2b** showed the same analytical data of their corresponding enantiomers with the exception of the sign and magnitude of their optical rotation values. Below are reported the measured optical rotation values:

(2*R*,5*S*)-**1a**: $[\alpha]_{\text{D}}^{20} = +1.8$ (c 2.1, CHCl₃)

(2*S*,5*S*)-**1b**: $[\alpha]_{\text{D}}^{20} = +3.0$ (c 2.4, CHCl₃)

(3*S*,6*S*)-**2a**: $[\alpha]_{\text{D}}^{20} = -1.5$ (c 2.3, CH₂Cl₂)

(3*R*,6*S*)-**2b**: $[\alpha]_{\text{D}}^{20} = -6.3$ (c 2.3, CH₂Cl₂)

3. Results and Discussion

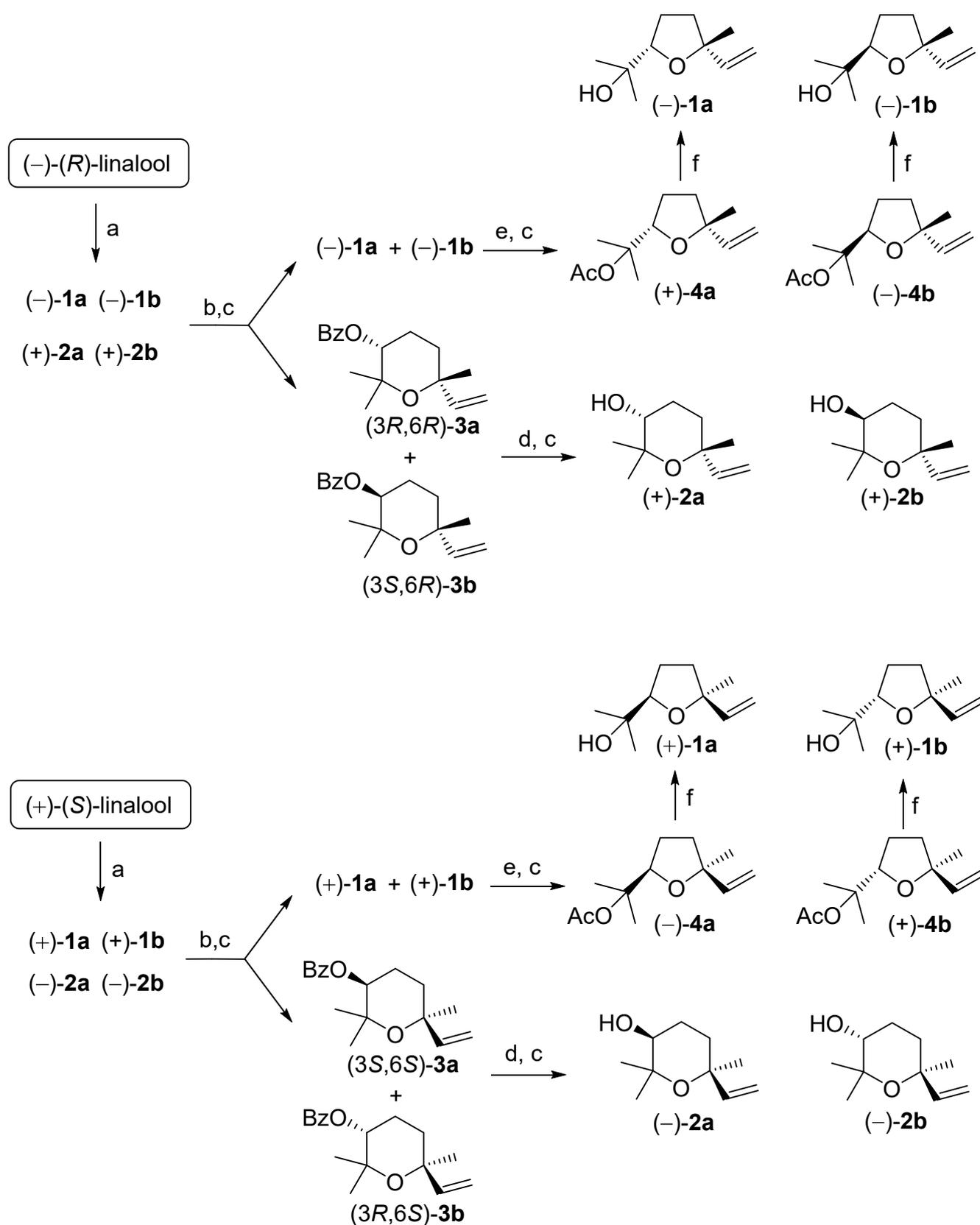
The first step of our procedure followed closely the process reported by Klein et al. [22]. The only difference lies in the use of *m*-chloroperbenzoic acid (MCPBA) as reagent of choice for linalool epoxidation instead of peracetic acid.

Accordingly, the reaction of (*R*)-linalool (Scheme 1) with an equimolar amount of MCPBA at 0 °C, afforded the corresponding mono-epoxide derivative. The reaction was highly regioselective since only the trisubstituted double bond was converted in the corresponding epoxide. The latter compound was not isolated because of its high instability to acid environment. In fact, the cyclization reaction started during the epoxidation reaction and proceeded rapidly with the work-up procedure, making unnecessary the epoxide isolation. Therefore, the completion of the cyclization step was warranted by adding to the reaction mixture a catalytic amount of *p*-toluenesulfonic acid (PTSA) as soon as the starting linalool was completely transformed. The obtained crude linalool oxides mixture consisted of a combination of furanoid linalool oxide isomers (81% of the mixture, of which **1a** = 39% and **1b** = 42%) and pyranoid isomers (19% of the mixture, of which **2a** = 10% and **2b** = 9%).

The chromatographic separation of these isomers is very complex. Furanoid linalool oxides **1a** and **1b** show the same retention factor (*R_f*) and are not separable.

On the contrary, pyranoid linalool oxides have different *R_f* but although the *cis*-isomer **2a** is separable from the *trans*-isomer **2b**, their partial co-elution with furanoid oxide isomers result in the difficult isolation of the isomeric pure forms. Overall, the purification of the linalool oxide isomers by direct chromatographic separation is not a feasible procedure.

Therefore, we investigated the possibility of derivatize selectively the oxides **2a** and **2b** in presence of the oxides **1a** and **1b**. The obtained new compounds, possibly possessing *R_f* very different from the starting alcohols, should be easier separable. Then, the removal of the derivatizing moiety should give oxides **2a** and **2b** free of the furanoid isomers. Following this reasoning, we took advantage of the different steric hindrance of the hydroxyl functional groups present in the linalool oxide framework.



Scheme 1. Experimental procedure for the preparation of all the isomeric forms of linalool oxide starting from (*R*)-linalool and (*S*)-linalool. Reagents and conditions: (a) *m*CPBA, CH₂Cl₂, 0 °C, PTSA cat.; (b) BzCl, Py, CH₂Cl₂, 0 °C; (c) chromatographic separation; (d) NaOH/MeOH, reflux, 3 h; (e) NaOAc, Ac₂O, reflux, 3 h; (f) LiAlH₄, dry Et₂O, r.t. 1 h.

Thus, the secondary alcohol functional group of the pyranoid isomers we expected to be transformed into the corresponding esters easier than the tertiary alcohol present in the furanoid oxides. To this end, we selected benzoyl chloride (BzCl) as derivatizing agent. Indeed, the obtained benzoate esters were stable, easily separable from the linalool oxides mixture and straightforwardly hydrolysable by alkali treatment. Accordingly, we tested the benzoylation reaction using different experimental conditions and employing the crude linalool oxides mixture as substrate (Table 1). It is worth noting that only the 19% of the latter mixture had to be esterified. Therefore, the reaction should proceed with high chemoselectivity.

Table 1. Study of the chemoselective benzoylation of the crude mixture of the linalool oxide isomers obtained from linalool.

Entry	Experimental Conditions ¹	Conversion of Linalool Oxide (Pyranoid) % ⁴	Benzoate Ester (Pyranoid) % ^{2,4}	Benzoate Ester (Furanoid) % ^{3,4}	Benzoate Esters Ratio (Pyranoid/Furanoid)
1	BzCl (3 eq.); DMAP cat.; rt; 4 h	>99	55	45	1.2
2	BzCl (3 eq.); rt; 4 h	>99	73	27	2.7
3	BzCl (1.2 eq.); from 0 °C to rt; 4 h	96	97	3	32.3

¹ Reaction conditions: Each experiment was performed using 10 mMol of a mixture of linalool oxide isomers (81:19 ratio of furanoid/pyranoid isomers). The alcohols mixture, in dry CH₂Cl₂ (4 mL) was treated under stirring with 1 mL of pyridine followed by the addition of BzCl, according to the experimental conditions indicated in the table. The molar equivalents of BzCl were calculated in relation to the starting amount of pyranoid linalool oxide. ² Percentage of the pyranoid benzoate esters in relation to the sum of all the linalool oxide benzoate ester isomers. ³ Percentage of the furanoid benzoate esters in relation to the sum of all the linalool oxide benzoate ester isomers. ⁴ Compounds concentrations were determined by GC-MS analysis.

The addition of an excess of BzCl (three equivalents in relation to the starting amount of pyranoid linalool oxide) and of a catalytic amount of dimethylaminopyridine (DMAP) at room temperature, lead to the complete esterification of the pyranoid oxides although with the concomitant formation of a considerable quantity of furanoid esters (entry 1). Since DMAP strongly catalyzes the acylation reactions, we further ran the reaction in the same experimental conditions but without any DMAP addition. Indeed, with this experiment, we observed that the pyranoid oxides were completely esterified whereas the furanoid esters were yet formed, although in minor amount (entry 2).

In order to increase further the selectivity of this transformation, we reduced both the equivalent of BzCl (1.2) and the temperature (0 °C). These new experimental conditions (entry 3) allowed the formation of the pyranoid benzoate ester in high yield (96% of conversion) and with very high chemoselectivity (the formed esters contained only 3% of furanoid isomers).

Taking advantage of the latter successful derivatization procedure, we checked its applicability for the large-scale separation of the linalool oxide isomers (150 mmol scale). Accordingly, (–)-(R)-linalool was treated with *m*CPBA and was transformed in the mixture of the linalool oxide isomers (–)-**1a**, (–)-**1b**, (+)-**2a** and (+)-**2b** (Scheme 1). The following reaction with BzCl, using the previously selected experimental conditions, afforded an equimolar mixture of the benzoate (3*R*,6*R*)-**3a** and (3*S*,6*R*)-**3b**, which was easily separated from the furanoid isomers (–)-**1a**, (–)-**1b** by chromatography. Hence, the purified esters were hydrolyzed using NaOH in methanol and the obtained linalool oxides were chromatographed to afford *cis*-pyranoid isomer (+)-**2a** (first eluted isomer) and *trans*-pyranoid isomers (+)-**2b** (second eluted isomer).

As mentioned before, the diastereoisomers (–)-**1a** and (–)-**1b** could not be separated by chromatography because they possess the same retention factor (R_f). This problem has been previously resolved through transformation of the *cis*- and *trans*-furanoid oxides mixture in the corresponding acetate esters followed by fractional distillation [15,22]. In our work, we observed that these diastereomerically related acetates, **4a** and **4b** (Scheme 1) can be, however, separated in pure stereoisomeric form by chromatographic separation.

Accordingly, we treated the mixture of compounds (–)-**1a** and (–)-**1b** with acetic anhydride in the presence of sodium acetate to give the expected acetates (+)-**4a** and (–)-**4b**

in almost quantitative yield. The subsequent chromatographic separation afforded isomers (–)-**4b** (first eluted) and (+)-**4a** (second eluted), both in diastereoisomerically pure form. Finally, the cleavage of the acetate functional group was performed by reduction using LiAlH_4 , to give pure *trans*- and *cis*-furanoid linalool oxides (–)-**1b** and (–)-**1a**, respectively.

Overall, we obtained the pyranoid isomers (3*R*,6*R*)-**2a**, (3*S*,6*R*)-**2b** and the furanoid isomers (2*S*,5*R*)-**1a**, (2*R*,5*R*)-**1b** in isomerically pure forms. Since our synthesis starts from (*R*)-linalool, all these compounds possess configuration *R* in position 6 (for tetrahydropyran ring) or position 5 (for tetrahydrofuran ring) of their framework. In order to prepare the lacking four linalool oxides enantiomers, we applied the same reaction sequence starting from (*S*)-linalool. The linalool enantiomers are available from many plant essential oils where they are present in different enantiomeric purity. Differently from (*R*)-linalool, which occurred in rosewood and in ho leaf in almost enantiopure form, the most relevant source of (*S*)-linalool is coriander oil, where the enantiomeric excess of the terpene is rather modest (40–60%).

Thus, we purified commercially available coriander oil and the obtained (*S*)-linalool, possessing about 50% ee. was employed for the synthesis of the linalool oxide isomers. Accordingly, the application of our procedure afforded the pyranoid isomers (3*S*,6*S*)-(–)-**2a**, (3*R*,6*S*)-(–)-**2b** and the furanoid isomers (2*R*,5*S*)-(+)-**1a**, (2*S*,5*S*)-(+)-**1b**, which showed optical rotation values of opposite sign and inferior magnitude of the corresponding enantiomeric forms.

In conclusion, we present a user-friendly procedure for the preparation of all the isomeric forms of the terpene linalool oxide. The method features, as a unique mandatory requirement, the availability of both linalool enantiomers and can be conveniently performed from a milligram to a multigram scale. The linalool oxide isomers obtained through our procedure possess the same enantiomeric purity of the starting linalool and could be employed both as chiral building blocks for stereoselective synthesis and as reference standards in F&F formulation and essential oils analysis.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/chemistry3040090/s1>. Study of the benzoylation of the crude mixture of the linalool oxide isomers obtained from linalool; Figure S1: $^1\text{H-NMR}$ of the *cis* linalool oxide (pyranoid); Figure S2: $^{13}\text{C-NMR}$ of the *cis* linalool oxide (pyranoid); Figure S3: DEPT experiment of the *cis* linalool oxide (pyranoid); Figure S4: $^1\text{H-NMR}$ of the *trans* linalool oxide (pyranoid); Figure S5: $^{13}\text{C-NMR}$ of the *trans* linalool oxide (pyranoid); Figure S6: DEPT experiment of the *trans* linalool oxide (pyranoid); Figure S7: $^1\text{H-NMR}$ of the *cis* linalool oxide (furanoid); Figure S8: $^{13}\text{C-NMR}$ of the *cis* linalool oxide (furanoid); Figure S9: DEPT experiment of the *cis* linalool oxide (furanoid); Figure S10: $^1\text{H-NMR}$ of the *trans* linalool oxide (furanoid); Figure S11: $^{13}\text{C-NMR}$ of the *trans* linalool oxide (furanoid); Figure S12: DEPT experiment of the *trans* linalool oxide (furanoid); Figure S13: $^1\text{H-NMR}$ of the *cis* linalool oxide acetate (furanoid); Figure S14: $^{13}\text{C-NMR}$ of the *cis* linalool oxide acetate (furanoid); Figure S15: DEPT experiment of the *cis* linalool oxide acetate (furanoid); Figure S16: $^1\text{H-NMR}$ of the *trans* linalool oxide acetate (furanoid); Figure S17: $^{13}\text{C-NMR}$ of the *trans* linalool oxide acetate (furanoid); Figure S18: DEPT experiment of the *trans* linalool oxide acetate (furanoid).

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