

The Stereoisomers of Nerolidol: Separation, Analysis and Olfactoric Properties

Vera Schubert, Armin Dietrich, Thomas Ulrich,
Armin Mosandl

Institut für Lebensmittelchemie, Universität Frankfurt,
Robert-Mayer-Str. 7–9, D-W-6000 Frankfurt/Main,
Bundesrepublik Deutschland

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The sesquiterpenic alcohol nerolidol was separated
into its 4 stereoisomers by MPLC of the diastereomeric
(1*S*,4*R*)-camphanoates.

An analytical GC method was found by which both
the enantiomeric pairs of (*Z*)- and (*E*)-nerolidol are re-
solved on a chiral cyclodextrin stationary phase. The ol-
factoric properties of the nerolidol stereoisomers were
investigated.

Introduction

Nerolidol (3,7,11-trimethyl-1,6,10-dodecatrien-
3-ol), a sesquiterpene analog of linalool, exists in
four stereoisomeric forms due to its asymmetric
center at C-3 and the double bond in 6-position.
Owing to its longlasting and moderately floral
odor nerolidol is appreciated as a base note in per-
fumery [1]. In addition squalene [2] and farnesol
syntheses [3] start from nerolidol and it appears as
an important intermediate in vitamin E and K₁
production.

Nerolidol is widely spread in various parts of
plants and in many essential oils. The main natural
sources of (+)-(*E*)-nerolidol are cabreuva oil from
Myrocarpus frondosus and *M. fastigiatus* Allem.
and Peru balsam from *Myroxylon pereira*
Klotzsch [4, 5]. The laevorotatory alcohol was
identified in the essential oil of clary sage (*Salvia
sclarea* L.) [6] and in an Indonesian liana (*Dalbergia
parviflora* Roxb.) [7], whereas the (*Z*)-isomer
has not yet been detected in nature.

The absolute configuration of the by far pre-
dominating (+)-(*E*)-nerolidol was elucidated by
conversion of the alcohol into (*R*)-(+)-4-methyl-
γ-hexalactone whereas (*R*)-(–)-linalool was deri-
vated to the corresponding (*S*)-(–)-lactone. Con-

sequently the (*S*)-configuration could be assigned
to the investigated (*E*)-(+)-nerolidol [8].

In this paper we report on the odor evaluation
of the four nerolidol stereoisomers separated for
the first time and on a direct GC method for their
stereodifferentiation.

Materials and Methods

Materials

Nerolidol synthetic mixture was purchased from
Merck, Darmstadt, trans-nerolidol from Roth,
Karlsruhe. Racemic (*Z*)-nerolidol, 4-dimethyl-
aminopyridine (DMAP) and (1*S*,4*R*)-camphanoic
acid chloride were purchased from Fluka, Neu-
Ulm, triethylamine (TEA) from Aldrich, Stein-
heim.

Preparation of nerolidol stereoisomers

Esterification: 500 mg (2.25 mmol) of racemic
(*Z*)- and (*E*)-nerolidol and of (+)-(*E*)-nerolidol re-
spectively were dissolved in about 5 ml of dried
CH₂Cl₂ each and 1 eq DMAP and 1.5 eq TEA
were added. The solution was cooled and 1.5 eq
camphanoic acid chloride, dissolved in *ca.* 2 ml of
dried CH₂Cl₂, was added dropwise while stirring.
After that the reaction mixture was refluxed for
4 h. After reaction had completed (TLC-control)
the mixture was subsequently washed with 2 *N*
HCl, saturated NaHCO₃- and saturated NaCl-solu-
tion. Purification on silica gel (pentane/diethyl-
ether 95:5, v/v) yielded the corresponding cam-
phanoic acid esters.

Ester hydrolysis: 105 mg (0.25 mmol) of each of
the 4 separated camphanoates were stirred with
1.5 eq of KOH in methanol (11 ml of a solution of
2 mg/ml of KOH in MeOH) for 12 h at 35 °C.
After saponification had completed (TLC-control)
20 ml of water were added, the ester extracted with
diethylether and washed with saturated NaCl solu-
tion. The organic layer was dried over Na₂SO₄ and
the solvent evaporated afterwards.

Chromatographic conditions

TLC: Reversed phase TLC plates (RP-18,
10 × 5 cm; Merck, Darmstadt) were used after
conditioning for 10 min at 110 °C. The eluent was
a mixture of methanol, acetonitrile and water
(5:5:1, v/v) and detection was carried out by
spraying with vanillin-sulphuric acid reagent

Reprint requests to Prof. Dr. A. Mosandl.

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(0.5% vanillin in H₂SO₄/EtOH, 4 + 1) followed by heating (10 min, 110 °C). *r_f*: nerolidol 0.54, camphanoate 0.41.

MPLC: A Perkin Elmer LC pump series 1 was used with a Rheodyne injection system no. 7125 and a Knauer UV/VIS filter photometer (cell volume 40 µl, thickness 10 mm, wavelength 220 nm). The column was made from stainless steel (20 × 250 mm, Bischoff) filled with Lichroprep Si 60, particle size 5 µm (Merck, Darmstadt).

Separation of (Z)- and (E)-nerolidol: Pentane/diethylether (85:15, v/v) was used for eluent at a flow rate of about 20 ml/min. (Z)-nerolidol is eluted prior to the (E)-isomer.

Separation of diastereomeric camphanoates: Pentane/diethylether (92:8, v/v) served as an eluent at a flow rate of about 21 ml/min. Order of elution: (R)-(Z)-, (S)-(Z)-, (R)-(E)- and (S)-(E)-camphanoates.

GC: A Carlo Erba 5160 Mega series gas chromatograph was used with on column injector and FID (230 °C). Column: duran glass capillary (Tullanox pretreated), 25 m, 0.23 mm i.d., coated with heptakis(2,3,6-tri-O-methyl-hydroxypropyl)-β-cyclodextrin (2% in pentane/dichloromethane) [9]. Carrier gas: H₂, 80 kPa; temperature program: 100 °C/5 min isothermal//1°/min//150 °C.

¹H NMR spectroscopic data

(Z)-nerolidol (300 MHz; CDCl₃/TMS): δ = 5.91 (dd; 1H, 2-H), 5.21 (dd; 1H, 1a-H), 5.16–5.09 (m; 2H, 6-H, 10-H), 5.06 (dd; 1H, 1b-H), 2.07–1.95 (m; 6H, 5-H, 8-H, 9-H), 1.68 and 1.69 (s; 3H each, 12-H, 15-H), 1.61 (s; 3H, 13-H), 1.59–1.50 (m; 3H, 4-H, –OH), 1.28 ppm (s; 3H, 14-H).

(E)-nerolidol (300 MHz; CDCl₃/TMS): δ = 5.92 (dd; 1H, 2-H), 5.22 (dd; 1H, 1a-H), 5.16–5.05 (overlapping m; 2H, 6-H, 10-H), 5.06 (dd; 1H, 1b-H), 2.10–1.95 (m; 6H, 5-H, 8-H, 9-H), 1.68 (s; 3H, 12-H), 1.60 (s; 6H, 13-H, 15-H), 1.67–1.50 (m; 3H, 4-H, –OH), 1.28 ppm (s; 3H, 14-H).

(Z)-nerolidyl(-)-camphanoate, peak 1 (300 MHz; C₆D₆/TMS): δ = 5.86 (dd; 1H, 2-H), 5.25–5.14 (overl. m; 2H, 6-H, 10-H), 5.19 (dd; 1H, 1a-H), 5.00 (dd; 1H, 1b-H), 2.13–1.96 (m; 6H, 5-H, 8-H, 9-H), 1.80–1.70 (m; 2H, 4-H), 1.70 and 1.69 (overl. s; 3H each, 12-H, 15-H), 1.58 (s; 3H, 13-H), 1.50 (s; 3H, 14-H), 1.26–1.20 (m; 4H, 5'-H, 6'-H), 0.88 and 0.85 (s; 3H, each, 8'-H, 9'-H), 0.70 ppm (s; 3H, 10'-H).

(Z)-nerolidyl(-)-camphanoate, peak 2 (300 MHz; C₆D₆/TMS): δ = 5.88 (dd; 1H, 2-H), 5.26–5.24 (m; 2H, 6-H, 10-H), 5.15 (dd; 1H, 1a-H), 4.99 (dd; 1H, 1b-H), 2.14–1.95 (m; 6H, 5-H, 8-H, 9-H), 1.85–1.78 (m; 2H, 4-H), 1.72 and 1.70 (overl. s; 3H each, 12-H, 15-H), 1.58 (s; 3H, 13-H), 1.50 (s; 3H, 14-H), 1.25–1.20 (m; 4H, 5'-H, 6'-H), 0.89 and 0.85 (s; 3H each, 8'-H, 9'-H), 0.70 ppm (s; 3H, 10'-H).

(E)-nerolidyl(-)-camphanoate, peak 1 (300 MHz; C₆D₆/TMS): δ = 5.85 (dd; 1H, 2-H), 5.25–5.17 (overl. m; 2H, 6-H, 10-H), 5.18 (dd; 1H, 1a-H), 5.00 (dd; 1H, 1b-H), 2.18–1.97 (m; 6H, 5-H, 8-H, 9-H), 1.82–1.76 (m; 2H, 4-H), 1.74 and 1.61 and 1.57 (s; 3H each, 12-H, 13-H, 15-H), 1.49 (s; 3H, 14-H), 1.26–1.20 (m; 4H, 5'-H, 6'-H), 0.87 and 0.85 (s; 3H each, 8'-H, 9'-H), 0.70 ppm (s; 3H, 10'-H).

(E)-nerolidyl(-)-camphanoate, peak 2 (300 MHz; C₆D₆/TMS): δ = 5.87 (dd; 1H, 2-H), 5.24–5.17 (overl. m; 2H, 6-H, 10-H), 5.15 (dd; 1H, 1a-H), 5.00 (dd; 1H, 1b-H), 2.17–1.95 (m; 6H, 5-H, 8-H, 9-H), 1.83–1.73 (m; 2H, 4-H), 1.68 and 1.61 and 1.57 (s; 3H each, 12-H, 13-H, 15-H), 1.49 (s; 3H, 14-H), 1.29–1.20 (m; 4H, 5'-H, 6'-H), 0.87 and 0.86 (s; 3H each, 8'-H, 9'-H), 0.70 ppm (s; 3H, 10'-H).

Results and Discussion

Since nerolidol and various of its derivatives could not be separated by HPLC using different common chiral stationary phases (Chiraspher, Chiral-2, Pirkle phase, naphthyl urea) the classical procedure *via* diastereomeric esters was pursued. Among the chiral auxiliaries tested only the (-)-camphanoates yielded four partially resolved peaks in LC on silica gel. Therefore (Z)- and (E)-nerolidol had to be esterified individually. However the commercially available (E)-nerolidol turned out to be of natural origin: its optical rotation was [α]_D²⁰ = +13.0° and the HPLC chromatogram of the corresponding camphanoates yielded the diastereomers in a ratio of about 9:1. In order to receive the racemic (E)-alcohol synthetic nerolidol, which is usually a mixture of (Z)- and (E)-isomers (2:3), was separated by MPLC on silica gel. Subsequently the (1*S*,4*R*)-camphanoates were synthesized from racemic (Z)- and (E)-nerolidol and from the (+)-(*E*)-alcohol, too. Esterification

had to be carried out by applying an excess of base to facilitate a complete reaction of the tertiary alcohol which is required due to the very similar polarities of nerolidol itself and its camphanoates.

The diastereomeric esters were separated by carefully fractionating the ascent of the first and the descent of the second peak. Determination of the diastereomeric purity proved to be rather difficult because volatility of the esters was too low for GC analysis (molecular weight >400). After all a possibility for purity estimation could be found in evaluating the ^1H NMR spectra of the separated camphanoates. The diastereomeric (*E*)- and (*Z*)-camphanoates respectively exhibit different shifts for the sharp double doublet signals of the proton

at carbon 2 (*cf.* ^1H NMR spectral data). This is sufficient to recognize the presence of remaining amounts (detection limit about 1%) of the uncompletely removed diastereomer.

The following ester hydrolysis with excess of methanolic KOH proceeds without any racemization which has been examined in case of (+)-(*E*)-nerolidol.

Looking for a possibility of controlling the optical purity of the nerolidol stereoisomers received by the presented method a large number of chiral stationary GC phases were tested. The best results could be achieved using a capillary column coated with heptakis(2,3,6-tri-*O*-methyl-hydroxypropyl)- β -cyclodextrin [9] which permits a nearly complete

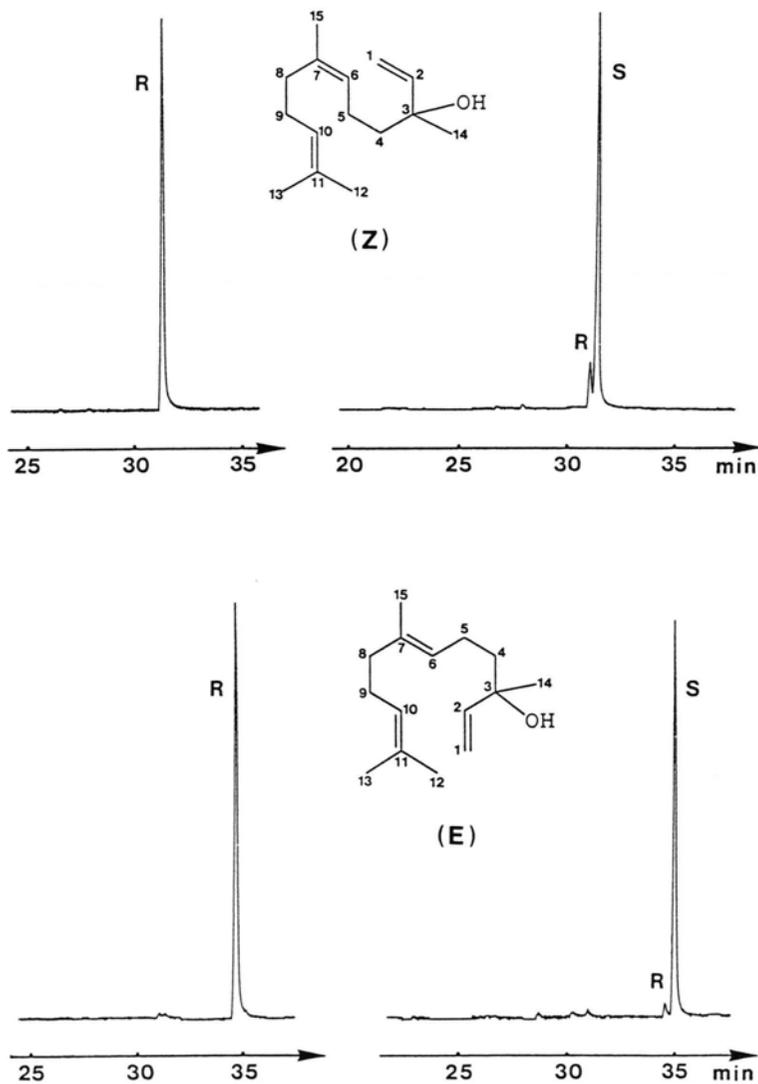


Fig. 1. Enantiomeric purity control of nerolidol stereoisomers; chromatographic conditions see experimental section.

resolution of the 4 isomers. Assignment of the absolute configuration was carried out by correlation with the optical rotation: the first eluting (*Z*)-nerolidol enantiomer had a rotatory power of $[\alpha]_D^{20} = -13.2^\circ$ ($c = 6.28$, MeOH) whereas the purchased (+)-(*E*)-alcohol eluted at last. For both the enantiomeric pairs the order of elution therefore has to be (*R*) prior to (*S*). Very recently heptakis(2,3-di-*O*-pentyl-6-acetyl- β -cyclodextrin also has been applied for enantioseparation of nerolidol [10].

The optical purity of the four stereoisomers obtained above is shown in Fig. 1.

Synthetic nerolidol is described to have a tenacious mild flowery fragrance [1]. Odor evaluation of the individual stereoisomers (out of etherial solutions) demonstrates that each of them exhibits

Table I. Olfactoric properties of stereoisomeric nerolidols.

	(-)-(<i>R</i>)	(+)-(<i>S</i>)
(<i>Z</i>)	intensive, flowery, sweet, fresh	woody, green, like fresh bark
(<i>E</i>)	pleasant, woody, warm, musty	slightly sweet, mild, soft, flowery; different to (<i>Z</i>)-(-), less intensive

distinct and characteristic olfactoric properties which are listed in Table I.

At this point further investigations should be focused on the natural occurrence of nerolidol stereoisomers.

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