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Identification of carbon-centred radicals derived from linalyl hydroperoxide, a strong skin sensitizer: a possible route for protein modifications

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Abstract—Few studies are reported on the formation of reactive carbon-centred radical species from toxic xenobiotics. In this paper the formation of carbon radicals derived from the skin sensitizer linalyl hydroperoxide is described using radical trapping and EPR studies. Radical trapping used TMIO as scavenger agent and light, heat or TPP–Fe^{3+} as radical inducers. EPR spin trapping was based on the use of the parent alcohol, generating the same allyloxyl radical than the hydroperoxide by photolysis of the corresponding nitrite formed with *t*-BuONO, also playing the role of the spin trap. It is suggested that the generation of these carbon radical species could play an important role for the binding of the hydroperoxide with skin proteins to form antigenic structures, the first step of the skin sensitization mechanism.

1. Introduction

Allergic contact dermatitis (ACD) is a very common disease resulting of epidermal proteins being chemically modified by haptens.[1] The processing of such modified proteins by Langerhans cells, the main antigen-presenting cells in the epidermis, generates altered peptides that are subsequently presented, in association with major histocompatibility complex molecules, to naive T-lymphocytes in the lymph nodes. The whole process results in the selection and activation of T-lymphocyte subpopulations with T-cell receptors specific of the chemical modification.[1] Haptens are usually a low molecular weight molecules, lipophilic enough to penetrate the epidermis through the *Stratum corneum*, and with a potent chemical reactivity allowing the formation of a covalent link with protein amino acid side chains. The classical mechanism of antigen formation involved in the ACD pathology is the reaction of an electrophilic function, present on the allergen or hapten, with nucleophilic residues on proteins to form covalent bonds.[2,3] However, over the past few years, the radical mechanism, although it has never been firmly demonstrated, has gained increased interest in the discussion of the mechanism of hapten–protein binding for some specific haptens.[4]

The high sensitizing potential of allylic hydroperoxides derived from the autoxidation of terpenes is well known. It was already demonstrated, 50 years ago that several hydroperoxides derived from the autoxidation of Δ^3-carene were responsible for the allergenic potential of turpentine.[5] More recently, Karlberg and co-workers have extensively reported on the allergenic potential of allylic hydroperoxides derived from the autoxidation of D-limonene, used as a fragrance material,[6] or from the autoxidation of abietic acid, the main resin acid of colophony.[7,8]

Most of the studies reported in the literature on the decomposition of allylic hydroperoxides concern those derived from the oxidation of polyunsaturated fatty acids. By studying the mechanisms of lipid oxidation it

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has been shown that allylic hydroperoxides, when treated with a variety of radical inducers such as metal complexes, form allyloxyl radicals by easy cleavage of the peroxy bond. These unstable alkoxyl radicals readily lead to the formation of carbon-centred radicals through fragmentation, hydrogen abstraction or intramolecular cyclization that may react with molecular oxygen and then decay to hydroxy derivatives.[9,10] Fragmentation of intermediate dioxetanes, presumably derived from peroxyl radicals formed after cleavage of the peroxy-hydrogen bond, has also been described.[11,12] In the course of our studies on allergenic allylic hydroperoxides we have shown that such kind of carbon-centred radical reactions could be important for the binding of those haptens containing hydroperoxide groups with skin proteins.[13,14] In a previous study, carried out on model molecules potentially derived from the decomposition of linalyl hydroperoxide, we have shown that while hydroperoxide **1** was a very strong sensitizer, potential rearrangement products such as epoxynerol **2**, epoxygeraniol **3**, furan and pyran derivatives **4** and **5**, respectively, were not sensitizing (Fig. 1).[15] These results ruled out a possible nucleophilic–electrophilic mechanism involving epoxides as the actual sensitizers. However, the rearrangement of the allylic hydroperoxide is highly probable and, since the rearranged derivatives are not active, it may be supposed that a radical intermediate able to react with skin proteins is formed during the process.

During the last decades, much attention has been denoted to the endogenous or exogenous production of radical reactive oxygen species because of their evident link to the initiation and/or progression of many degenerative and chronic diseases. Research has been focussed on the understanding of their mechanism of action and on the development of compounds with powerful antioxidant activity. However, few studies are reported in the literature on the formation of reactive carbon-centred radical species from toxic xenobiotics that could be responsible for the chemical modification of bioorganic molecules. In this paper we report a complete identification of the carbon-centred radicals derived from the allergen linalyl hydroperoxide **1** using a radical trapping technique with the stable nitroxide 1,1,3,3-tetramethylisoindolin-2-yloxyl (TMIO) and electron paramagnetic resonance (EPR) studies. We suggest that the generation of these radical species could play an important role for the binding of the hydroperoxide with skin proteins to form antigenic structures, the first step of the ACD mechanism.

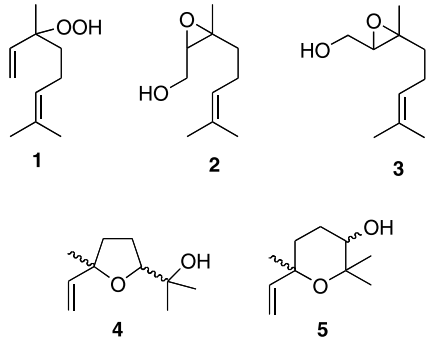


Figure 1. Potential rearrangement compounds from linalyl hydroperoxide.

2. Results

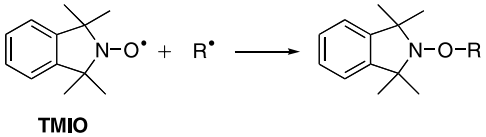
2.1. Radical trapping experiments

The radical trapping technique that we have used relies on the almost diffusion-controlled trapping of carbon-centred radicals by stable nitroxides such as TMIO to form alkoxyamine products (Scheme 1).[16] The isoindoline-based aminoxyl TMIO is known to have a variety of advantages over commercially available aminoxyls, including the commonly used pyrrolidine and piperidine species.[17] The fused aromatic moiety provides resistance to the ring-opening reactions that are known decomposition pathways for pyrrolidine and piperidine aminoxyls. In addition, TMIO is thermally and chemically stable in a wide range of chemical environments and has a suitable UV absorbing chromophore that facilitates isolation of the adducts formed, whose structures can be determined by use of classical spectroscopic techniques.

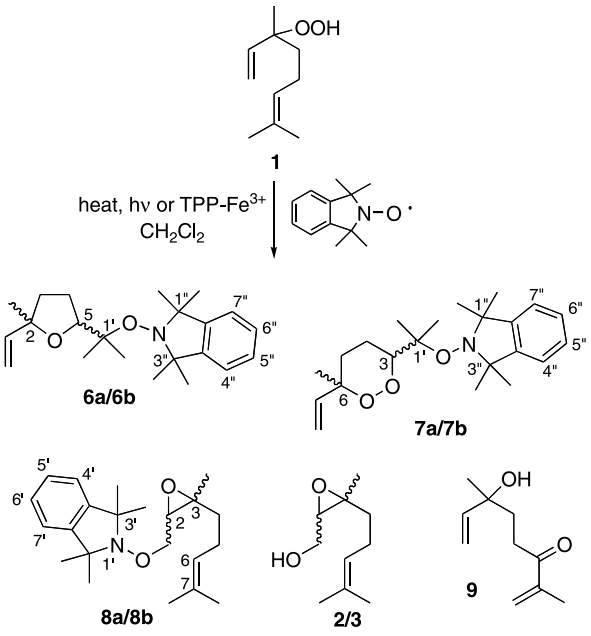
Radical formation was chemically induced by use of the *meso*-tetraphenyl-porphyrin–iron(III) chloride complex (TPP–Fe^{3+}), and by direct thermal or photochemical cleavage of **1**. Anhydrous and degassed dichloromethane was used as the reaction solvent. Structures of all isolated and identified radical trapping adducts are shown in Scheme 2.

The different yields obtained depending on the method used to induce the radical generation are indicated in Table 1. Structures of the isolated compounds were established by a combination of ^{1}H and ^{13}C NMR data, including ^{1}H–^{13}C correlation (HSQC and HMBC) and ^{1}H–^{1}H correlation (COSY and NOESY) experiments.

2.1.1. Generation of radicals by reduction from TPP–Fe^{3+}. We have already reported, in a previous paper, our first results on radical trapping experiments of **1** using tritertiobutylphenol (TTBP) as trapping agent and TPP–Fe^{3+} as radical inducer.[15] The major reaction taking place was the formation of a furan ring by intramolecular reaction of an oxygen-centred radical with the isoprenyl double bond, forming a tertiary carbon-centred radical. Compounds **2** and **3** were also isolated. Work reported in the current paper aimed to compare those results with radical trapping using TMIO. Moreover, transition metal ions and more precisely Fe^{2+}/



Scheme 1. Formation of alkoxyamines by radical trapping with TMIO.



Scheme 2. Trapping of radicals derived from linalyl hydroperoxide **1**.

Table 1. Adduct yields obtained depending on the radical inducer used (cis/trans ratio into brackets[a])

Compound	TPP–Fe^{3+} [b]	Heat[c]	hν[d]
2/3	9% (28/72)	ND[e]	ND
6a/b	48% (46/54)	35% (43/57)	40% (44/56)
7a/b	15% (47/53)	11% (86/14)	9% (87/13)
8a/b	1%	4% (38/62)	8% (43/57)
9	ND	10%	11%

[a] Measured by ^1H integration in the NMR spectra.
[b] 1.1 equiv TPP–Fe^{3+}, 4 equiv TMIO, 90 min.
[c] Reflux, 2 equiv TMIO, 7 days.
[d] 2 equiv TMIO, 3 weeks.
[e] ND = not detected.

Fe^{3+} systems are suspected to be the most important way of peroxides degradation in vivo. Therefore, the use of TPP–Fe^{3+} needed to be studied once more. The reaction of **1** in the presence of TPP–Fe^{3+} (1.1 equiv) and an excess of TMIO was followed by thin layer chromatography until complete disappearance of the hydroperoxide. The solvent was then removed under reduced pressure and the reaction compounds were split into two fractions (polar and nonpolar) by column chromatography on silica gel. The nonpolar fraction, containing the radical trapping adducts (**6a/b**, **7a/b** and **8a/b**), was further purified by HPLC on a C18 reversed phase column. The polar fraction, containing compounds **2/3**, was purified by column chromatography on silica gel with difficulty due to the presence of multiple coloured porphyrine derivatives.

2.1.2. Generation of radicals by thermal cleavage. It is well known that peroxides undergo thermal cleavage to a pair of alkoxyl radicals.[18] However, thermolysis of pure hydroperoxides for the production of alkoxyl radicals is poorly documented. In the course of our experiments, heating to reflux of a solution of **1** in degassed and anhydrous dichloromethane and in the presence of an excess of TMIO allowed the isolation of compounds resulting from the rapid rearrangement of unstable alkoxyl and peroxyl radical intermediates. The reaction was followed as above. Once the hydroperoxide completely disappeared, the solvent was removed under reduced pressure and the crude product was split into two fractions (polar and nonpolar) by column chromatography on silica gel. The nonpolar fraction, containing the radical trapping adducts (**6a/b**, **7a/b** and **8a/b**), was further purified by column chromatography on silica gel and on aluminium oxide. The polar fraction, containing compound **9**, was purified by column chromatography on silica gel.

2.1.3. Generation of radicals by photochemical cleavage. It has been reported in the literature that photochemical cleavage of hydroperoxides is a quite facile method for alkoxyl radical production.[19] It presents the advantage of being a cleaner method that avoids the presence of metal contaminants. The formation of radical species of linalyl hydroperoxide **1** was therefore also investigated by irradiating the compound in the presence of TMIO in degassed dichloromethane. Once there was no further change in the reaction progress, the solvent was removed under reduced pressure and products were split into polar and nonpolar fractions by column chromatography on silica gel. Further purification of the nonpolar fraction by column chromatography on silica gel and on aluminium oxide afforded the radical trapping adducts (**6a/b**, **7a/b** and **8a/b**). Compound **9** was isolated from the polar fraction by column chromatography on silica gel.

2.1.4. Mechanistic interpretations. Looking at the chemical structures of the diverse compounds obtained by reaction of **1** in the presence of different radical initiators and of TMIO, it could be easily seen that several carbon-centred radical intermediates were formed (Fig. 2). First of all, homolytic cleavage of the peroxy bond produced an alkoxyl radical **10** that underwent a rapid intramolecular 5-*exo* cyclization[20] with the isoprenyl double bond, leading to the formation of a favourable five-membered ring system and a rather stable carbon-centred tertiary radical **11**. This radical was then able to react with TMIO to give diastereomers **6a/b**. As shown in Table 1, **6a/b** were the major radical trapping adducts obtained with yields ranging from 35% to 48%

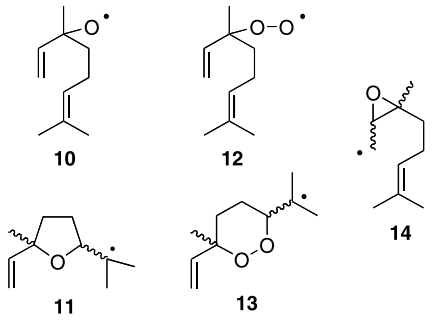


Figure 2. Radical intermediates derived from compound **1**.

depending on the radical initiation used. In all cases, the less hindered trans diastereomer was slightly preferred to the cis diastereomer. In order to validate the NMR interpretations and to confirm the conformation established for both adducts, the mixture **6a/b** was treated with an excess of zinc powder (10 equiv) and heated to reflux in a 1:1 solution of acetic acid and water. Alcohol **4** was obtained as a previously characterized mixture of diastereomers,[15] having equivalent cis/trans ratios to those of **6a/b**. The chemical structures of **6a** and **6b** were fully elucidated by NMR experiments on the diastereomeric mixture. An important NOE cross-peak between H-5 of the furan ring and H-B of the ABX vinyl system confirmed the trans conformation of adduct **6b** (Fig. 3).

In parallel, the peroxyl–hydrogen bond of **1** could be also cleaved homolytically affording the peroxyl radical **12** (Fig. 2).

This one could then rearrange, via an intramolecular 6-*exo* addition to the isoprenyl double bond, leading to the tertiary stable carbon-centred radical **13**, which reacted with TMIO to afford peroxides **7a/b** as a nonseparable mixture of two diastereomers. Yields, ranging from 9% to 15%, were approximately 3-fold lower than those for **6a/b**, but not insignificant. It is interesting to note the differences observed in the diastereomeric ratios obtained, depending on the experimental conditions (Table 1). In the presence of TPP–Fe^{3+}, the reaction was very fast and the trans diastereomer was slightly preferred. Thermal and photochemical reactions were slower and the cis diastereomer, thermodynamically favoured, was considerably preferred. In our previous studies on the sensitizing potential of model molecules potentially derived from the decomposition of linalyl hydroperoxide **1** we considered pyran derivative **5** (Fig. 1) but not the possibility of obtaining a cyclic peroxide by intramolecular rearrangement of a peroxyl radical. However, the formation of peroxyl radicals derived from compound **1** is not surprising.[21,22] Several reactions can be suggested for explanation (Scheme 3). The peroxy compound being considered essentially as an oxidant, it may produce RO$^{\bullet}$ and TPP–Fe^{4+}–OH in the presence of TPP–Fe^{3+} (reaction 1). Also, TPP–Fe^{4+}–OH could subsequently be reduced liberating HO$^{\bullet}$ (reaction 3). The hydroxyl (HO$^{\bullet}$) and alkoxyl (RO$^{\bullet}$) radicals could then easily perform the hydrogen abstraction affording peroxyl radicals ROO$^{\bullet}$ (reactions 2 and 4). In the experimental conditions using thermal or photochemical radical induction, reactions 2 and 4 may be produced.

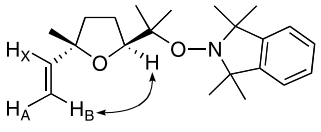
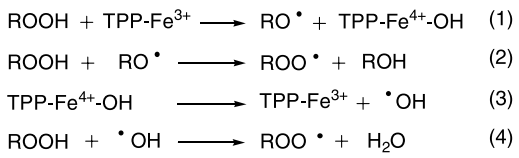


Figure 3. NOE observed in adduct **6b** confirming the trans conformation.



Scheme 3. Formation of peroxyl radicals.

Feasibility of reaction 2 could have been verified by determining the content of linalool in the crude products. Unfortunately, it was not possible to isolate linalool from the excess of TMIO. The addition of the peroxyl radical on the isoprenyl double bond was not surprising neither, even if peroxyl radicals are much more known for their aptitude to abstract hydrogen atoms from activated positions. Indeed, peroxyl radical cyclization by addition on double bonds is a property that has been used for the synthesis of cyclic peroxides with success.[23]

Finally, adducts **8a/b** were those obtained to a lower extent. Only 1% when **1** was in the presence of TPP–Fe^{3+}, 4% by thermal decomposition and 8% when exposed to irradiation. Alkoxyl radical **10** underwent a 3-*exo* cyclization with the vinyl double bond to the α-oxiranylcarbinyl radical **14**. This species was trapped by TMIO giving the nonseparable mixture of diastereomers **8a/b**. The reduction from TPP–Fe^{3+} afforded also the mixture of α-hydroxyepoxides **2/3** (28/72) with a yield of 9%. These compounds, most probably, were the result of a process taking place in the metal coordination sphere. This may explain why **2/3** were not detected during the thermal and photochemical treatment of **1**, the α-oxiranylcarbinyl radicals formed being free from TPP–Fe^{4+}–OH molecules they were easily trapped by TMIO.

In order to elucidate the chemical structures of **8a/b** NMR experiments were performed at low temperature. At room temperature, due to the high flexibility of **8a/b** compared to **6a/6b** and **7a/b**, dynamic processes associated to the 1,1,3,3-tetramethylisoindolin moiety, free to rotate rapidly, prevented good NMR resolution. The four methyl groups of the spin trap were undistinguished in the ^{1}H NMR spectra and even not observed in the ^{13}C NMR spectra (Fig. 4).

Less rapid rotation of the 1,1,3,3-tetramethylisoindolin moiety was achieved at lower temperatures. As a consequence, the four methyl groups became nonequivalent as they did not have the same time-averaged chemical environment, and could therefore be identified (Fig. 4). The **8a/b** diastereomeric ratios were calculated by ^{1}H integration of the methyl groups at carbon C-3 (Fig. 4A).

The α,β-unsaturated ketone **9** was also isolated from the thermal and photochemical experiments with a yield of 10% and 11%, respectively. A mechanism that could account for its formation, starting from radical intermediate **13** and based on the known aptitude of cyclic peroxides to be homolytically cleaved by the action of heat or light to form oxygenated biradicals,[24] is shown in Scheme 4.

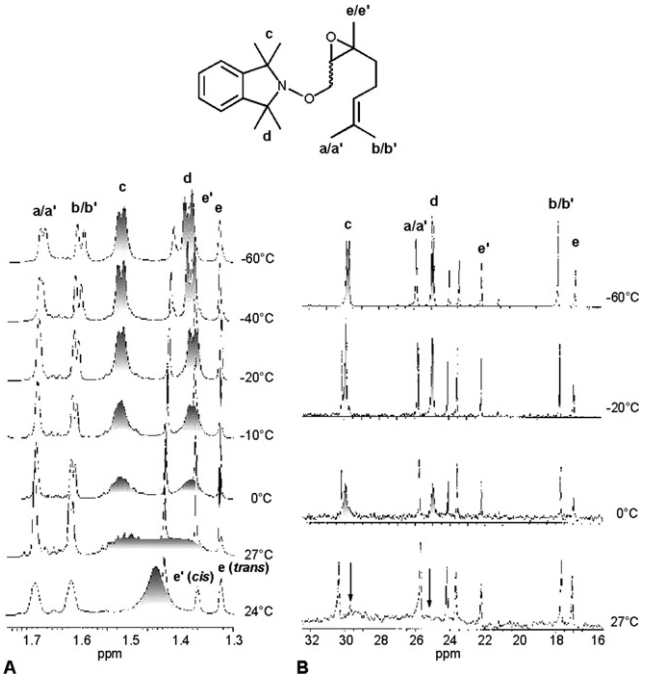
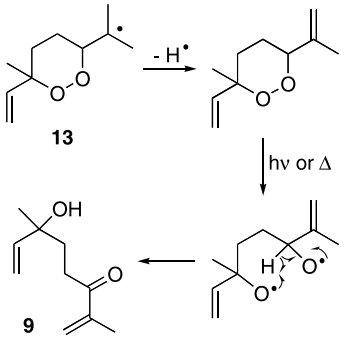


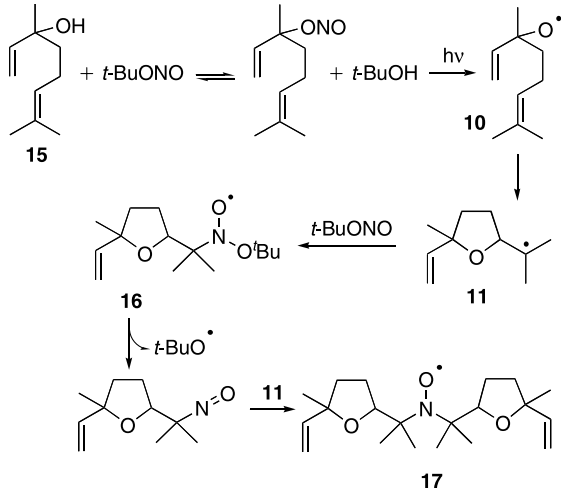
Figure 4. Identification of methyl groups in the mixture of diastereomers **8a/b** by ^{1}H (A) and ^{13}C NMR (B) at different temperatures.



Scheme 4. Mechanism suggested for the obtention of **9**.

2.2. EPR experiments

In order to get more detailed information on the evolution of radical intermediate **10**, a spin trapping EPR technique described in preliminary communications was employed.[25] The technique is based on the known ability of alkyl nitrites, in particular of *tert*-butyl nitrite (*t*-BuONO), to act as a spin trap for short-lived alkyl radicals.[26] More precisely, the allyloxyl radical **10** can be generated by photolysis of the corresponding nitrite prepared via the facile exchange reaction between the parent alcohol and *t*-BuONO. The alkyl radicals formed by rapid decay of the allyloxyl radical are then trapped by the excess of *t*-BuONO in the reaction medium to give stable nitroxides detectable by EPR. This method affords the same allyloxyl radical obtained by homolytic cleavage of the O–O bond of the hydroperoxide chemical function. Moreover, hydroperoxides are often unstable species difficult to handle. Linalool **15**, the stable tertiary alcohol precursor of linalyl hydroperoxide **1**, was therefore used to carry out these studies.



Scheme 5. Spin trapping of alkyl radicals derived from linalool **15**.

The experiments were conducted under continuous flow (1–2 mL/h) of acetonitrile solutions of **15** in the presence of an excess of *t*-BuONO. The solutions were photolyzed with a laser tuned for UV light (334–364 nm) directly in the EPR spectrometer cavity thermostated at 240 K. The analysis of all EPR spectra allowed the identification of nitroxide radicals derived from the trapping of tertiary carbon-centred radicals (Scheme 5). Nitroxide **16** was formed by *t*-BuONO trapping of the five-membered ring system and stable carbon-centred tertiary radical **11**, formed via 5-*exo* cyclization of allyloxyl radical **10**. The hyperfine splitting constant of the nitrogen atom (a_N = 25.00 G) was characteristic of an R–N(O•)–O′Bu nitroxide type (25–28 G) as well as the *g* value (2.0052–2.0053).[25] This radical was observed when using more concentrated linalool solutions, at low flow rate, under a full power laser irradiation (Fig. 5A). Nitroxides derived from the coupling of species generated in situ could also be observed, as **17**. The loss of the *tert*-butoxide group from **16** afforded a nitroso derivative, which acted as a spin trap of carbon-centred radical **11** to give nitroxide **17**. Its a_N hyperfine splitting constant value (14.60 G) was indeed comparable to those of R–N(O•)–R′ systems, as well as the *g* value of 2.0057.

Nitroxide radical **17** was observed under the same conditions as **16**. However, it was the only radical observed when less concentrated solutions of linalool were used, at low power laser irradiation, but higher flow conditions (Fig. 5B). EPR studies confirmed thus the formation of the carbon-centred radical **11**, via the favoured 5-*exo* cyclization of the parent allyloxyl radical. However, spin adducts formed by trapping of radicals of the oxiranylcarbinyl type could not be identified, as no β-proton hyperfine couplings were observed.

3. Discussion

The results presented in this paper, coming from a combination of radical trapping and EPR studies, confirmed the formation of reactive carbon-centred radicals from

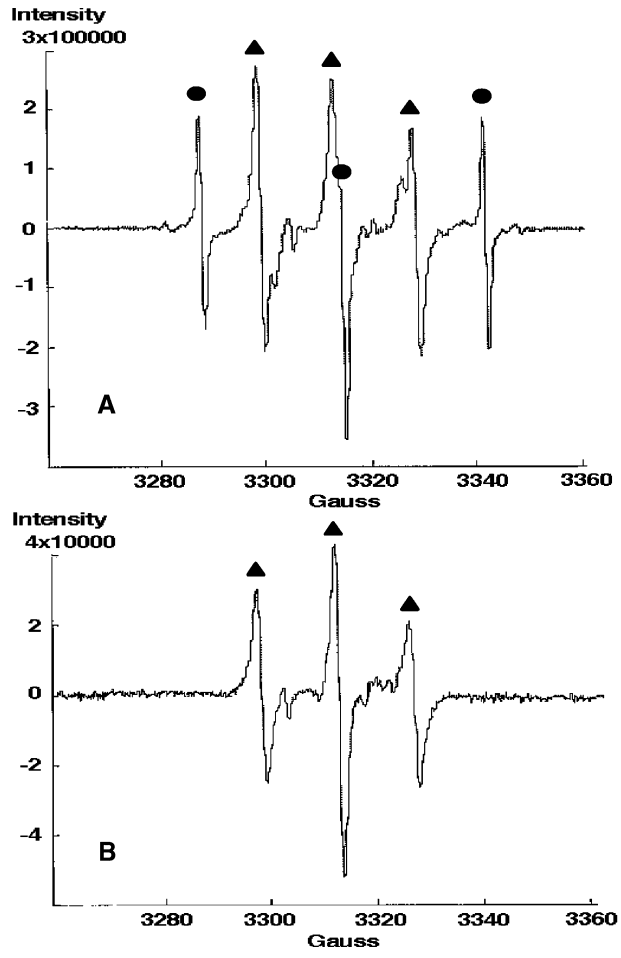


Figure 5. A) EPR spectrum obtained in the photolysis of an acetonitrile solution of **15**, 104 mM and *t*-BuONO, 224 mM, at 240 K (flow rate 1 mL/h; laser at 50 mW power), showing radicals **16** (●) and **17** (▲). (B) EPR spectrum obtained in the photolysis of an acetonitrile solution of **15**, 50 mM, and *t*-BuONO, 110 mM, at 240 K (flow rate 2 mL/h; laser at 5 mW power), showing radical **17** (▲).

linalyl hydroperoxide **1**. The easy cleavage of the hydroperoxide chemical function afforded unstable oxygenated radicals that readily rearranged to form stable carbon radicals. An intramolecular 5-*exo* cyclization of the alkoxyl radical **10** with the isoprenyl double bond led to the formation of the furan derivative **11** (35–48% yield). Radical **10** could also rearrange via a 3-*exo* cyclization with the vinyl double bond to form the α-oxiranylcarbinyl radical **14** (4–10% yield). Finally, the peroxyl radical **12** followed an intramolecular 6-*exo* addition to the isoprenyl double bond to form the peroxide **13** (9–15%). The results presented in this paper were in accordance with our previous studies on the allergenic activity of compounds suggested as a result of the linalyl hydroperoxide decomposition (Fig. 1). However, in the present study we did not observe the pyran derivative **5** derived from the 6-*endo* ring closure of intermediate **10**, neither trapped by TMIO or by HO•, but the formation of the peroxide **13** as well as of compound **9**. We cannot therefore exclude the presence of these intermediates in vivo and their implication in the allergenic activity of linalyl hydroperoxide should be also evaluated.

In order to confirm the participation of such kind of radicals in the reaction of **1** with proteins, studies were started on its reactivity towards a synthetic model peptide. We used an analogue of the N-terminal chain of the globine protein: H_2N-Val-Leu-Ser-Pro-Ala-Asp-Lys-Thr-Asn-Trp-Gly-His-Glu-Tyr-Arg-Met-Phe-Gln-Ile-Gly-CO_2H. This peptide was reacted by irradiation with compound **1** ^{13}C labelled at the isoprenyl double bond, which is involved in the formation of carbon-centred radicals **11** and **13**. The peptide was then analyzed by ^{13}C NMR in order to identify peaks corresponding to potential adducts. New ^{13}C signals were observed that could correspond, up to the chemical shifts, to the formation of ^{13}C–O bonds between the two entities. This suggested that **11** or **13**, now ^{13}C-centred radicals, could react with peptide chemical functions containing the oxygen heteroatom. These preliminary studies need further development and are a preface for future analysis. However, they reinforced the hypothesis that the in situ generation of such reactive radicals in the epidermis could lead to the formation of antigenic structures explaining the sensitizing potential of **1**.

4. Conclusion

Few studies are reported in the literature on the formation of reactive carbon-centred radical species from toxic xenobiotics. We have demonstrated the formation of carbon radicals from the skin sensitizer linalyl hydroperoxide by using radical trapping and EPR studies. The generation of these carbon radical species could play an important role for the binding of the hydroperoxide with skin proteins to form antigenic structures, the first step of the skin sensitization mechanism. Moreover, these radical intermediates could be responsible for the modification of amino acids that are not usually considered in the mechanism of ACD, going further into the mechanism of hapten–protein interactions.

5. Experimental

Caution: Skin contact with hydroperoxides must be avoided. Since these compounds are skin sensitizing substances, they must be handled with care.

Elemental microanalyses were performed by the microanalytical laboratory of the CRM (Centre de Recherche sur les Macromolécules), Strasbourg, France. IR spectra were recorded on a Perkin–Elmer 1600 Series Fourier Transform spectrophotometer (cm^{-1} scale) and refer to thin films of liquids (neat). ^1H NMR spectra were recorded at 200 MHz on a Bruker AC-200 spectrometer and at 500 MHz on a Bruker ARX-500 spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and are indirectly referenced to tetramethylsilane via the solvent signal ($CDCl_3$, 7.26 ppm). Multiplicities are denoted as s (singlet), d (doublet), t (triplet), sept (septuplet), m (multiplet) and br (broad). ^{13}C NMR spectra were recorded at 50 MHz on a Bruker AC-200 spectrometer and at 125 MHz on a Bruker ARX-500 spectrometer. ^{13}C chemical shifts (δ) are

reported in ppm and are indirectly referenced to tetramethylsilane via the ^{13}C isotope signal of the solvent, used as internal reference ($CDCl_3$, 77.03 ppm; C_6D_6, 128.60 ppm). The different types of carbon in the structures (quaternary, methine, methylene and methyl) were identified by the DEPT-135 technique. The two-dimensional phase-sensitive ^1H–^1H COSY (correlation spectroscopy) spectra were collected using a standard pulse sequence with a 254 ms acquisition time, a sweep width of 12.25 ppm, 512 complete t_1 data points, and 8 scans per increment. The two-dimensional phase-sensitive ^1H–^1H NOESY (nuclear Overhauser effect spectroscopy) were collected using a 800 ms mixing time and a 254 ms acquisition time, a sweep width of 12.25 ppm, 512 complete t_1 data points, and 16 scans per increment. The two-dimensional ^1H–^{13}C HSQC (heteronuclear single-quantum correlation) spectra and ^1H–^{13}C HMBC (heteronuclear multiple-bond correlation) spectra were collected using a standard pulse sequence, with a 254 ms acquisition time, 512 complete t_1 data points, 16 (HSQC) or 32 (HMBC) scans per increment, and a spectral width in the f_1 dimension of 209.23 ppm. The data were processed using XWINNMR software. The HPLC analyses were performed on a Waters Associates apparatus equipped with a model M680 automated gradient controller and two M510 pumps. The solutions were analyzed and compounds separated on reverse-phase columns (C18, Nucleosil 5 μm, Interchrom, 4.6 mm; C18, Rsil 5 μm, Interchrom, 10 mm), and the effluent absorption was monitored by a M686 tunable absorbance detector at 250 nm. All radical trapping experiments were conducted in flame-dried glassware under an inert atmosphere of argon. The generation of radicals by photochemical cleavage was achieved using a Philips 150 W tungsten filament lamp. EPR spectra were recorded on a Bruker ESP 300 spectrometer equipped with a X-band microwave bridge, 100 KHz modulation, and a variable temperature apparatus Bruker BVT 2000. Irradiation of the solutions inside the EPR cavity was performed with a laser Spectra Physics Stabilite 2018-RM tuned for UV light (334–364 nm). Hyperfine splitting assignments were obtained by means of computer simulation using WINEPR SimFonia.

TLC analyses were performed on 0.25 mm Merck silica gel plates ($60F_{254}$). After elution, the TLC plates were inspected under ultraviolet light (254 nm) or sprayed with a solution of phosphomolybdic acid in ethanol (5% w/v) or with a solution of *m*-anisaldehyde (0.5 mL) and *p*-anisaldehyde (0.5 mL) in glacial acetic acid (100 mL), ethanol (85 mL) and concentrated sulfuric acid (5 mL), followed by heating. Compounds were purified by column chromatography on silica gel (Merck 60, 230–400 mesh) or on aluminium oxide (Merck 90, standardized). Linalyl hydroperoxide **1** and TMIO were synthesized as previously reported in the literature.[15,27] Linalool **15** was purchased from Sigma–Aldrich (St Quentin Fallavier, France), TPP–Fe^{3+} and *t*-BuONO were purchased from Fluka (St Quentin Fallavier, France), and all used without further purification. Acetonitrile (99.8%, spectrophotometric grade), diethyl ether (99.8%), ethyl acetate (99.8%) and dichloromethane (99.5%) were purchased from Carlo Erba (Val de Reuil, France). Dichloromethane was dried over Sicapent® (Merck, Nogent-sur-Marne, France) before distillation. Hexane (99%) was obtained from SDS (Peypin, France). Aqueous solutions were prepared with deionized water. All other chemicals were obtained from Sigma Aldrich (St Quentin de Fallavier, France).

5.1. Radical trapping experiments

5.1.1. Generation of radicals by reduction from TPP–Fe^{3+}. To a solution of linalyl hydroperoxide **1** (200 mg, 1.17 mmol) in anhydrous dichloromethane (25 mL) were added TMIO (894 mg, 4.70 mmol) and TPP–Fe^{3+} (910 mg, 1.29 mmol). The reaction mixture was stirred at room temperature until complete disappearance of **1** followed by TLC (90 min). The mixture was then concentrated under reduced pressure, taken up with the minimum amount of dichloromethane, and firstly purified by column chromatography on silica gel (diethyl ether/hexane, 16/84; followed by ethyl acetate/hexane, 35/65) to fractionate the crude product into a nonpolar fraction of compounds and a mixture of **2/3** as a colourless oil (19 mg, 9% yield). The nonpolar fraction was purified by HPLC (C18 reversed-phase; water/acetonitrile, 30/70) to give the different adducts as yellowish oils, which were further purified by column chromatography on aluminium oxide (hexane) to obtain the mixtures of diastereomers **6a/b** (195 mg, 48% yield), **7a/b** (65 mg, 15% yield) and **8a/b** (4 mg, 1% yield) as colourless oils.

5.1.2. Generation of radicals by thermal cleavage. Linalyl hydroperoxide **1** (200 mg, 1.17 mmol) was dissolved in anhydrous dichloromethane (25 mL), together with TMIO (447 mg, 2.35 mmol). The solution was heated to reflux and the reaction followed by TLC until complete disappearance of the hydroperoxide. After 7 days stirring under reflux, the solution was cooled to room temperature and concentrated under reduced pressure. The crude product was fractionated into polar and nonpolar compounds by silica gel column chromatography (diethyl ether/hexane, 8/92; followed by ethyl acetate/hexane, 40/60). Further purification of the nonpolar fraction was carried out by column chromatography on silica gel (diethyl ether/hexane, 5/95) to give the different adducts as yellowish oils, which were afterwards purified by column chromatography on aluminium oxide (hexane) to obtain the mixtures of diastereomers **6a/6b** (140 mg, 35% yield), **7a/b** (46 mg, 11% yield) and **8a/b** (15 mg, 4% yield) as colourless oils. The polar fraction was purified by column chromatography on silica gel (ethyl acetate/hexane, 20/80) and was found to contain compound **9** (20 mg, 10% yield) as a yellow oil.

5.1.3. Generation of radicals by photochemical cleavage. Linalyl hydroperoxide **1** (200 mg, 1.17 mmol) was dissolved in anhydrous dichloromethane (25 mL). TMIO (447 mg, 2.35 mmol) was added to the solution and the stirred reaction mixture was irradiated for 3 weeks with a 150 W tungsten filament lamp at a distance of 30 cm. The evolution of the reaction was followed by TLC until complete disappearance of the hydroperoxide. The mixture was concentrated under reduced

pressure and fractionated into polar and nonpolar compounds by silica gel column chromatography (diethyl ether/hexane, 8/92; followed by ethyl acetate/hexane, 40/60). Further purification of the nonpolar fraction was carried out by column chromatography on silica gel (diethyl ether/hexane, 5/95) to give the different adducts as yellowish oils, which were afterwards purified by column chromatography on aluminium oxide (hexane) to obtain the mixtures of diastereomers **6a/b** (160 mg, 40% yield), **7a/b** (38 mg, 9% yield) and **8a/b** (32 mg, 8% yield) as colourless oils. The polar fraction was purified by column chromatography on silica gel (ethyl acetate/hexane, 20/80) to obtain compound **9** (22 mg, 11% yield) as a yellow oil.

5.2. Characterization data for radical trapping adducts

5.2.1. Mixture of diastereomers 2 and 3. Anal. Calcd for $C_{10}H_{18}O_2$ (170.25): C, 70.55; H, 10.66. Found: C, 70.28; H, 10.71. IR (neat) ν_{max} 3420 (O–H), 2969, 2866 (C–H), 1454, 1380 (C–H), 1035 (C–O) cm^{-1}.

5.2.1.1. 2,3-Epoxynerol (2). Minor isomer (28% yield, ^1H integration); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32 (s, 3H, C*H*$_3$–C–O–), 1.37–1.74 (m, 2H, –CH$_2$–C*H*$_2$–C–O–), 1.60 (br s, 3H, C*H*$_3$–C=CH–), 1.67 (br s, 3H, C*H*$_3$–C=CH–), 1.96–2.17 (m, 2H, –C*H*$_2$–CH$_2$–C–O–), 2.18–2.30 (m, 1H, –O*H*), 2.95 (X part of an ABX system, J = 6.9, 4.4 Hz, 1H, –O–C*H*–CH$_2$–OH), 3.63 (B part of an ABX system, J = 12.1, 6.9 Hz, 1H, –O–CH–C*H*–OH), 3.80 (A part of an ABX system, J = 12.1, 4.4 Hz, 1H, –O–CH–C*H*–OH), 5.08 (tsept, J = 7.1, 1.5 Hz, 1H, (CH$_3$)$_2$C=C*H*–); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.6, 22.2, 24.2, 25.6, 33.1, 61.2, 61.5, 64.2, 123.3, 132.5.

5.2.1.2. 2,3-Epoxygeraniol (3). Major isomer (72% yield, ^1H integration); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.28 (s, 3H, C*H*$_3$–C–O–), 1.36–1.75 (m, 2H, –CH$_2$–C*H*$_2$–C–O–), 1.59 (br s, 3H, C*H*$_3$–C=CH–), 1.67 (br s, 3H, C*H*$_3$–C=CH–), 1.94–2.16 (m, 2H, –C*H*$_2$–CH$_2$–C–O–), 2.19–2.41 (m, 1H, –O*H*), 2.96 (X part of an ABX system, J = 6.6, 4.2 Hz, 1H, –O–C*H*–CH$_2$–OH), 3.65 (B part of an ABX system, J = 12.1, 6.6 Hz, 1H, –O–CH–C*H*–OH), 3.81 (A part of an ABX system, J = 12.1, 4.2 Hz, 1H, –O–CH–C*H*–OH), 5.06 (tsept, J = 7.1, 1.5 Hz, 1H, (CH$_3$)$_2$C=C*H*–); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 16.7, 17.6, 23.7, 25.6, 38.5, 61.2, 61.4, 63.0, 123.3, 132.1.

5.2.2. Mixture of diastereomers 6a and 6b. Anal. Calcd for $C_{22}H_{33}NO_2$ (343.51): C, 76.92; H, 9.68. Found: C, 76.92; H, 9.89. IR (neat) ν_{max} 3076 (Ar C–H), 2975, 2870 (C–H), 1644 (C=C), 1486, 1362 (C–H), 1154, 1033 (C–O) cm^{-1}.

5.2.2.1. *cis*-2-Methyl-5-[1′-methyl-1′-(1′,1″,3″,3″-tetramethyl-1″,3″-dihydroisoindol-2″-yloxy)ethyl]-2-vinyltetrahydrofuran (6a). Minor isomer (44% yield, ^1H integration); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.26 (s, 3H, –C*H*$_3$), 1.32 (s, 6H, 2×–C*H*$_3$), 1.34 (s, 3H, –C*H*$_3$), 1.35 (s, 3H, –C*H*$_3$), 1.50 (s, 3H, C*H*$_3$-1″ or C*H*$_3$-3″), 1.52 (s, 3H, C*H*$_3$-1″ or C*H*$_3$-3″), 1.70–2.10 (m, 4H, –CH–C*H*$_2$–C*H*$_2$–), 4.04 (t, J = 7.0 Hz, 1H, –C*H*–CH$_2$–CH$_2$–), 4.99 (A part of an ABX system, J = 10.8, 1.5 Hz, 1H, –C*H*=CH–C–O–), 5.22 (B part of an ABX system, J = 17.5, 1.5 Hz, 1H, –C*H*=CH–C–O–), 6.02 (X part of an ABX system, J = 17.5, 10.8 Hz, 1H, CH$_2$=C*H*–C–O–), 7.03–7.16 (m, 2H, *H*-4″, *H*-7″), 7.17–7.30 (m, 2H, *H*-5″, *H*-6″); ^{13}C NMR (C_6D_6, 50 MHz): δ 23.6, 24.2, 26.0, 26.1, 26.2, 27.6, 30.6 (2C), 38.0, 68.6 (2C), 80.5, 82.7, 84.7, 111.1, 122.0 (2C), 127.5 (2C), 145.2, 145.9, 146.0.

5.2.2.2. *trans*-2-Methyl-5-[1′-methyl-1′-(1″,1″,3″,3″-tetramethyl-1″,3″-dihydroisoindol-2″-yloxy)ethyl]-2-vinyltetrahydrofuran (6b). Major isomer (56% yield, ^1H integration); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29 (s, 3H, –C*H*$_3$), 1.34 (s, 6H, 2×–C*H*$_3$), 1.35 (s, 3H, –C*H*$_3$), 1.37 (s, 3H, –C*H*$_3$), 1.51 (s, 3H, C*H*$_3$-1″ or C*H*$_3$-3″), 1.53 (s, 3H, C*H*$_3$-1″ or C*H*$_3$-3″), 1.60–2.10 (m, 4H, –CH–C*H*$_2$–C*H*$_2$–), 3.97 (t, J = 6.9 Hz, 1H, –C*H*–CH$_2$–CH$_2$–), 5.02 (A part of an ABX system, J = 10.6, 1.7 Hz, 1H, –C*H*=CH–C–O–), 5.23 (B part of an ABX system, J=17.2, 1.7 Hz, 1H, –C*H*=CH–C–O–), 5.91 (X part of an ABX system, J = 17.2, 10.6 Hz, 1H, CH$_2$=C*H*–C–O–), 7.03–7.16 (m, 2H, *H*-4″, *H*-7″), 7.17–7.30 (m, 2H, *H*-5″, *H*-6″); ^{13}C NMR (C_6D_6, 50 MHz): δ 23.4, 24.3, 26.2 (2C), 27.2, 27.3, 30.6 (2C), 37.4, 68.6 (2C), 80.4, 83.0, 85.1, 111.2, 122.0 (2C), 127.5 (2C), 144.5, 145.9 (2C).

5.2.3. Mixture of diastereomers 7a and 7b. Anal. Calcd for $C_{22}H_{33}NO_3$ (359.51): C, 73.50; H, 9.25. Found: C, 73.10; H, 9.58. IR (neat) ν_{max} 3082 (Ar C–H), 2973, 2857 (C–H), 1486, 1461, 1375, 1363 (C–H), 1144, 1018 (C–O) cm^{-1}.

5.2.3.1. *cis*-6-Methyl-3-[1′-methyl-1′-(1″,1″,3″,3″-tetramethyl-1″,3″-dihydroisoindol-2″-yloxy)ethyl]-6-vinyl-1, 2-dioxane (7a). Major isomer (87% yield, ^1H integration); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.21 (s, 3H, –C*H*$_3$), 1.25 (s, 3H, –C*H*$_3$), 1.29 (s, 3H, –C*H*$_3$), 1.32 (s, 3H, –C*H*$_3$), 1.33 (s, 3H, –C*H*$_3$), 1.48 (s, 3H, –C*H*$_3$), 1.49 (s, 3H, –C*H*$_3$), 1.65–2.12 (m, 4H, –CH–C*H*$_2$–C*H*$_2$–), 4.08 (dd, J = 10.7, 2.1 Hz, 1H, –C*H*–CH$_2$–CH$_2$–), 5.18 (A part of an ABX system, J = 10.8, 1.2 Hz, 1H, –C*H*=CH–C–O–), 5.19 (B part of an ABX system, J = 18.0, 1.2 Hz, 1H, –C*H*=CH–C–O–), 6.14 (X part of an ABX system, J = 18.0, 10.8 Hz, 1H, CH$_2$=C*H*–C–O–), 7.01–7.15 (m, 2H, *H*-4″, *H*-7″), 7.16–7.33 (m, 2H, *H*-5″, *H*-6″); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.1, 23.4, 24.1, 26.5, 25.8, 25.9, 30.2, 30.5, 33.4, 68.2, 68.4, 79.4, 80.9, 86.7, 114.0, 121.7 (2C), 127.1 (2C), 141.9, 145.4, 145.6.

5.2.3.2. *trans*-6-Methyl-3-[1′-methyl-1′-(1″,1″,3″,3″-tetramethyl-1″,3″-dihydroisoindol-2″-yloxy)ethyl]-6-vinyl-1,2-dioxane (7b). Minor isomer (13% yield, ^1H integration); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32 (s, 3H, –C*H*$_3$), 1.34 (s, 6H, 2×–C*H*$_3$), 1.36 (s, 3H, –C*H*$_3$), 1.49 (s, 6H, 2×–C*H*$_3$), 1.51 (s, 3H, –C*H*$_3$), 1.65–2.12 (m, 4H, –CH–C*H*$_2$–C*H*$_2$–), 4.07 (dd, J = 10.7, 2.1 Hz, 1H, –C*H*–CH$_2$–CH$_2$–), 5.15 (A part of an ABX system, J = 10.8, 1.1 Hz, 1H, –C*H*=CH–C–O–), 5.26 (B part of an ABX system, J = 17.7, 1.1 Hz, 1H, –C*H*=CH–C–O–), 5.83 (X part of an ABX system, J = 17.7,

10.8 Hz, 1H, CH_2=C*H*–C–O–), 7.017.15 (m, 2H, *H*-4″, *H*-7″), 7.167.33 (m, 2H, *H*-5″, *H*-6″); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.6, 21.0, 23.5, 24.2, 25.9, 26.0, 30.3, 30.6, 32.8, 68.3, 68.5, 79.4, 79.8, 86.9, 114.7, 121.7 (2C), 127.1 (2C), 141.4, 145.3, 145.6.

5.2.4. Mixture of diastereomers 8a and 8b. Anal. Calcd for $C_{22}H_{33}NO_2$ (343.51): C, 76.92; H, 9.68. Found: C, 76.91; H, 9.83. IR (neat) ν_{max} 3047 (Ar C–H), 2972, 2859 (C–H), 1484, 1455, 1376, 1361 (C–H), 1143 (C–O) cm^{-1}.

5.2.4.1. *cis*-2,3-Epoxy-3,7-dimethyl-1-(1′,1′,3′,3′-tetramethyl-1′,3′-dihydroisoindol-2′-yloxy)-6-octene (8a). Minor isomer (43% yield, ^{1}H integration); ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K): δ 1.37 (s, 3H, C*H*$_3$–C–O–), 1.45–1.73 (m, 2H, –CH_2–C*H*$_2$–C–O–), 1.34–1.58 (m, 12H, 2 × C*H*$_3$-1′, 2 × C*H*$_3$-3′), 1.62 (s, 3H, C*H*$_3$–C=CH–), 1.69 (s, 3H, C*H*$_3$–C=CH–), 2.06–2.20 (m, 2H, –C*H*$_2$–CH_2–C–O–), 3.12 (X part of an ABX system, J = 6.3, 4.8 Hz, 1H, –O–C*H*–CH_2–), 3.99 (B part of an ABX system, J = 11.4, 6.3 Hz, 1H, –O–CH–C*H*–O–N–), 4.09 (A part of an ABX system, J = 11.4, 4.8 Hz, 1H, –O–CH–C*H*–O–N–), 5.11 (tsept, J = 6.9, 1.4 Hz, 1H, $(CH_3)_2$=C*H*–), 7.11 (AA′ part of an AA′XX′ system, J = 7.6, 7.4, 1.1 Hz, 2H, *H*-4′, *H*-7′), 7.24 (XX′ part of an AA′XX′ system, J = 7.6, 1.1, 0.6 Hz, 2H, *H*-5′, *H*-6′); ^{1}H NMR ($CDCl_3$, 500 MHz, 213 K): δ 1.38 (s, 3H, C*H*$_3$–C–O–), 1.40–1.70 (m, 2H, –CH_2–C*H*$_2$–C–O–), 1.38 (s, 3H, C*H*$_3$-1′ or C*H*$_3$-3′), 1.39 (s, 3H, C*H*$_3$-1′ or C*H*$_3$-3′), 1.51 (s, 3H, C*H*$_3$-1′ or C*H*$_3$-3′), 1.52 (s, 3H, C*H*$_3$-1′ or C*H*$_3$-3′), 1.59 (s, 3H, C*H*$_3$–C=CH–), 1.67 (s, 3H, C*H*$_3$–C=CH–), 2.06–2.20 (m, 2H, –C*H*$_2$–CH_2–C–O–), 3.10–3.20 (m, 1H, –O–C*H*–CH_2–), 3.91–4.19 (m, 2H, –O–CH–C*H*$_2$–O–N–), 5.02–5.14 (m, 1H, $(CH_3)_2$=C*H*–), 7.10–7.20 (m, 2H, *H*-4′, *H*-7′), 7.22–7.36 (m, 2H, *H*-5′, *H*-6′); ^{13}C NMR ($CDCl_3$, 50 MHz, 300 K): δ 17.7, 22.2, 24.2, 25.7, 33.4, 60.2, 62.1, 67.4 (2C), 75.7, 121.5 (2C), 123.6, 127.2 (2C), 132.2, 145.0 (2C); ^{13}C NMR ($CDCl_3$, 125 MHz, 213 K): δ 17.7, 22.1, 23.9, 25.8, 24.8, 25.0, 29.7, 29.9, 33.0, 60.5, 61.9, 67.0 (2C), 75.2, 121.5 (2C), 122.9, 127.2 (2C), 132.5, 144.4 (2C).

5.2.4.2. *trans*-2,3-Epoxy-3,7-dimethyl-1-(1′,1′,3′,3′-tetramethyl-1′,3′-dihydroisoindol-2′-yloxy)-6-octene (8b). Major isomer (57% yield, ^{1}H integration); ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K): δ 1.33 (s, 3H, C*H*$_3$–C–O–), 1.45–1.73 (m, 2H, –CH_2–C*H*$_2$–C–O–), 1.34–1.58 (m, 12H, 2 × C*H*$_3$-1′, 2 × C*H*$_3$-3′), 1.63 (s, 3H, C*H*$_3$–C=CH–), 1.69 (s, 3H, C*H*$_3$–C=CH–), 2.06–2.20 (m, 2H, –C*H*$_2$–CH_2–C–O–), 3.11 (X part of an ABX system, J = 6.3, 4.8 Hz, 1H, –O–C*H*–CH_2–), 4.02 (B part of an ABX system, J = 11.3, 6.3 Hz, 1H, –O–CH–C*H*–O–N–), 4.12 (A part of an ABX system, J = 11.3, 4.8 Hz, 1H, –O–CH–C*H*–O–N–), 5.12 (tsept, J = 7.1, 1.4 Hz, 1H, $(CH_3)_2$=C*H*–), 7.11 (AA′ part of an AA′XX′ system, J = 7.6, 7.4, 1.1 Hz, 2H, *H*-4′, *H*-7′), 7.24 (XX′ part of an AA′XX′ system, J = 7.6, 1.1, 0.6 Hz, 2H, *H*-5′, *H*-6′); ^{1}H NMR ($CDCl_3$, 500 MHz, 213 K): δ 1.32 (s, 3H, C*H*$_3$–C–O–), 1.40–1.70 (m, 2H, –CH_2–C*H*$_2$–C–O–), 1.38 (s, 3H, C*H*$_3$-1′ or C*H*$_3$-3′), 1.39 (s, 3H, C*H*$_3$-1′ or C*H*$_3$-3′), 1.51 (s, 3H, C*H*$_3$-1′ or C*H*$_3$-3′), 1.52 (s, 3H, C*H*$_3$-1′ or C*H*$_3$-3′), 1.61 (s, 3H, C*H*$_3$–C=CH–), 1.68 (s, 3H, C*H*$_3$–C=CH–), 2.06–2.20 (m, 2H, –C*H*$_2$–CH_2–C–O–), 3.10–3.20 (m, 1H, –O–C*H*–CH_2–), 3.91–4.19 (m, 2H, –O–CH–C*H*$_2$–O–N–), 5.02–5.14 (m, 1H, $(CH_3)_2$=C*H*–), 7.10–7.20 (m, 2H, *H*-4′, *H*-7′), 7.22–7.36 (m, 2H, *H*-5′, *H*-6′); ^{13}C NMR ($CDCl_3$, 50 MHz, 300 K): δ 17.0, 17.7, 23.7, 25.7, 38.5, 60.6, 60.7, 67.4 (2C), 76.0, 121.5 (2C), 123.6, 127.2 (2C), 132.0, 145.0 (2C); ^{13}C NMR ($CDCl_3$, 125 MHz, 213 K): δ 16.8, 17.7, 23.4, 25.9, 24.8, 25.0, 29.7, 29.9, 38.1, 60.9 (2C), 67.1 (2C), 75.7, 121.5 (2C), 122.9, 127.2 (2C), 132.4, 144.2 (2C).

5.2.5. 6-Hydroxy-2,6-dimethylocta-1,7-dien-3-one (9). CAS registry number [56698-54-5]; IR (neat) ν_{max} 3462 (O–H), 2960, 2859 (C–H), 1676 (C=O), 1631 (C=C), 1453, 1373 (C–H), 1087 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30 (s, 3H, C*H*$_3$–C–OH), 1.73–1.99 (m, 5H, –C*H*$_2$–CH_2–CO–, CH_2=C–C*H*$_3$), 2.70–2.86 (m, 2H, –CH_2–C*H*$_2$–CO–), 5.06 (A part of an ABX system, J = 10.7, 1.4 Hz, 1H, –C*H*=CH–C–OH), 5.23 (B part of an ABX system, J = 17.3, 1.4 Hz, 1H, –C*H*=CH–C–OH), 5.72–5.78 (m, 1H, –C*H*=C–CH_3), 5.96–6.01 (m, 1H, –C*H*=C–CH_3), 5.85 (X part of an ABX system, J = 17.3, 10.7 Hz, 1H, CH_2=C*H*–C–OH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.7, 28.7, 32.3, 35.7, 72.7, 112.2, 124.7, 144.5 (2C), 202.6.

5.3. EPR experiments

An oxygen free acetonitrile solution containing linalool **15** (104 mM) and *t*-BuONO in excess (224 mM) was continuously flowed (flow rate 1 mL/h) through a flat quartz cell inside the EPR cavity and directly irradiated with a laser Spectra Physics Stabilite 2018-RM, tuned for UV light (334–364 nm), at 240 K. The solutions were deaerated prior to use by purging with N_2-gas for 30 min.

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