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# Research into the oxidation of abietic acid–derived enone with atmospheric oxygen

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**Abstract**

This work presents results of methyl 7-oxoabiet-13(14)-en-18-oate (**3**) self-oxidation with air-oxygen in the presence of various bases such as triethylamine or sodium *t*-butoxide. While under aerobic conditions, the use of sodium *t*-butoxide as a base results in the formation of four isomeric alcohols, an addition of triethylamine into reaction medium directs the enone **3** oxidation to hydroperoxides. To clarify this base dependence and to obtain more in-depth information about this reaction additional studies with cyclohexenone as a reference enone have been undertaken. Their results demonstrated the predisposition of abietane hydroperoxides to oxidize α,β-unsaturated ketones to epoxides in the presence of *t*-butoxide while reducing the hydroperoxide group to hydroxyl. This ability of hydroperoxides to epoxidize conjugated double bonds and confirmed by the present study intermolecular course allowed proposing a plausible mechanism for this reaction.

**KEYWORDS**

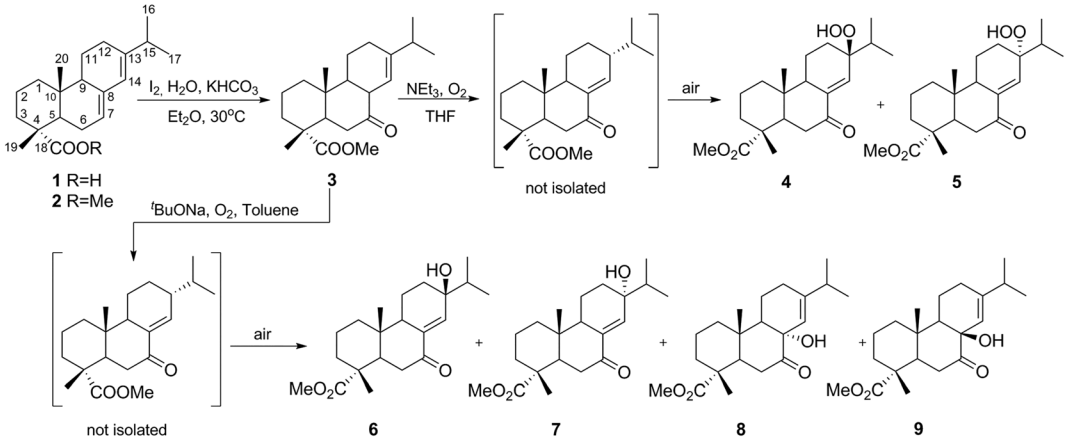
abietic acid, aerobic oxidation, autooxidation, enones, hydroperoxides

## 1 | INTRODUCTION

Abietic acid (**1**, Scheme 1), the main component of resin acids, is a natural tricyclic acid belonging to diterpenoids of a characteristic $C_{20}$ abietane carbon framework.[1,2] Scheme 1 shows, among others, numbering of compounds discussed in Section 1. Due to a large number of conifers growing on all inhabited continents, it is one of the most abundant organic acids found in nature. Its unique structural architecture and diversity, as well as virtually unlimited resources, make it an extremely convenient substrate in organic synthesis. The synthetic value of abietic acid is due to the presence of four stereogenic centers, particularly useful in enantioselective synthesis. The presence of a conjugated double bond system allows gradual molecule degradation while maintaining stereochemistry at the A and B ring junction.[3] It also creates the opportunity of an electrophilic attack on these bonds. Regioselectivity of this attack depends on the reaction conditions and reagents involved reactivity.[4,5] Thus, for example, the oxidation of abietic acid methyl ester with osmium tetroxide leads to 13β,14β-diol, whereas with *m*-chloroperbenzoic acid to the mixture of 13α,14α- and 13β,14β-epoxides.[5,6] Both of these processes occur on the more reactive double bond in the C ring, leaving the C7-C8 double bond intact. As a result of different treatments of olefinic bonds in the B and C rings, many compounds with modified scaffolding, including those with aromatic rings, can be formed. Aromatic abietane diterpenes formed by these transformations are interesting because they show a wide variety of remarkable biological activities with proven or potential pharmacological applications.[7-10] Abietic acid has also been successfully used as a substrate in the synthesis of a

Dedicated to the memory of Professor Koji Nakanishi, the world-recognized expert in the field of organic chemistry of bioactive natural products.




**SCHEME 1** Oxidation of β,γ-unsaturated ketone **3** with atmospheric oxygen in the presence of various bases

structurally complex and diverse collection of small molecules, including other terpenes, utilized in a variety of biological screens.[3,11,12] Therefore, the use of abietic acid in organic synthesis is advantageous despite the ease with which it undergoes self-oxidation under aerial exposure.[13]

Just the possibility of directing the abietic acid reactions to the desired product, along with its virtually unlimited availability, caused that in our recent studies, we have found it as convenient starting material for the synthesis of model *cis*-enones needed for in-depth dichroic studies.[14] While the synthesis leading to the entire range of relevant *cis*-enones was simple and consisted of a few steps at most, we encountered problems associated with abietane autoxidation. During attempts to convert β,γ-unsaturated ketone, ie, methyl 7-oxoabiet-13(14)-en-18-oate, into its conjugated counterpart under basic conditions, instead of the expected 8(14)-en-7-one derivative, we obtained a mixture of self-oxidation products depending on the base applied. Hence, a reaction performed in THF in the presence of triethylamine produced diastereomeric 13α- and 13β-hydroperoxides, whereas reaction carried out in toluene in the presence of catalytic amounts of sodium *t*-butoxide yielded a mixture of 13α-, 13β-, and 8α-alcohols in percentage 26:11:34, respectively.[14] Although the expected migration of the C13-C14 double bond to the C8-C14 position indeed occurred,[14] it immediately underwent subsequent oxidation at the allylic site by air oxygen to epimeric hydroperoxides or alcohols. Moreover, a reaction carried out in the same conditions but under argon in a strictly deoxygenated mixture of THF and triethylamine yielded the same result, thus proving that air oxidation of the allylic position in 8(14)-en-7-one derivative must be rapid and occurs spontaneously at the workup stage.

The observed selectivity of the described above oxidation leading to hydroperoxides or alcohols, depending on the base applied, may have a preparative potential. However, in order to fully benefit from this potential, the susceptibility to oxidation in aerobic conditions of 13(14)-en-7-one abietane derivative formed during the base-catalyzed isomerization of methyl 7-oxoabiet-13(14)-en-18-oate needs to be thoroughly and comprehensively examined. This necessity results from the fact that aerobic self-oxidation of abietanes is indeed a characteristic feature that has long been known but not wholly recognized due to its complexity and lack of selectivity.[15] Its exact course is also still unknown, and hydroperoxides and alcohols are not the only products.[16,17] Among the numerous self-oxidation products identified, such as peroxides, epoxides, alcohols, and ketones, there are still some unidentified ones. In this context, the possibility of running the reaction selectively in the desired direction seems to be a subject worthy of a detailed examination. Thus, the primary goal of this work is to understand better this reaction course, which could lead to establishing its mechanism by determining the full structures of products and conditions of their formation.

## 2 | MATERIALS AND METHODS

All solvents were dried and distilled before use. All reactions were monitored by thin-layer chromatography using aluminum-backed silica gel plates 60 $F_{254}$ with a thickness of 0.2 mm; visualization was accomplished with UV light at wavelength: 254 nm and a ceric molybdenum reagent. Standard flash chromatography procedures were followed using silica gel with particle size 40 to 63 μm. Melting points were recorded in a melting point stage and are not corrected. Gas chromatographs were recorded on a Clarus 689 SQ 8T (Perkin-Elmer) mass spectrometer with medium-polar column HP50+, 30 m long. Mass spectra were obtained at 70 eV on an Agilent 65040 Q-TOF MS spectrometer equipped with an

electron impact (EI) ion source and the EBE double focusing geometry mass analyzer at 70 eV. The instrument was controlled, and recorded data were processed using MassLynx 4.1 software package. Electrospray ionization (ESI) experiments were performed on a mass spectrometer equipped with an electrospray ion source and q-TOF–type mass analyzer under normal conditions. PFK solution was used as a calibrant for HRMS measurements. The instrument was controlled, and recorded data were processed using the MassLynx V4.1 software package. $^{1}$H NMR spectra were recorded on a Varian 400 MHz, Varian 600 MHz, or a Bruker 500 MHz spectrometers and $^{13}$C NMR at 125 and 150 MHz using $CDCl_3$ or $C_6D_6$ as solvents and TMS as internal standard and are reported as δ values (ppm) relative to residual $CHCl_3$ signal δ H (7.26 ppm) and $CDCl_3$ δ C (77.16 ppm), respectively.

A good-quality single-crystal of alcohol **9** was selected for the X-ray diffraction experiment at T = 100(2). Diffraction data were collected on the Agilent Technologies SuperNova Dual Source with the Cu*K*α radiation ($\lambda$ = 1.54184 Å). The lattice parameters were obtained by a least squares fit to the optimized setting angles of the reflections collected by using the CrysAlis CCD software.[18] Data were reduced using the CrysAlis RED program.[18] The multiscan empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm, was applied.[18] The structural determination procedure was carried out using the SHELX package.[19] The structure was solved with direct methods, and then successive least squares refinements were carried out based on full-matrix least squares on $F^2$ using the SHELXL program.[19] All H atoms bound to C atoms were positioned geometrically with the C–H bond length equal to 0.93, 0.96, 0.97, and 0.98 Å for the aromatic, methyl, methylene, and methine hydrogen atoms, respectively, and constrained to ride on their parent atoms with $U_{iso}(H) = xU_{eq}(C)$, where x was 1.5 for methyl H atoms and 1.2 for the aromatic, methylene, and methine H atoms respectively. The hydroxyl H atom was located on a Fourier difference map and refined as riding with $U_{iso}(H) = 1.5U_{eq}(O)$. The figure for this report were prepared using Olex2 program (see Figure 1).[20]

## 2.1 | Synthesis

Syntheses of compounds discussed herein were carried out according to the literature procedure starting from isoamylamine salt of commercial abietic acid **1** freshly purified by crystallization according to the literature procedure.[13] The pure abietic acid thus obtained was converted into methyl abietate according to a standard procedure using methyl iodide.

## 2.2 | Preparation of methyl abietate 2

A mixture of abietic acid **1** (14.36 g, 47.48 mmol), acetone (250 mL), anhydrous $K_2CO_3$ (33.1 g, 0.32 mol), and methyl iodide (10 mL, 160.63 mmol) was stirred at 40°C for 24 hours. Then water (200 mL) was added to the mixture and extracted with methylene chloride (2 × 200 mL). The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. The residue was chromatographed on silica gel (1% ethyl acetate in hexane) yielding 10.16 g of the methyl abietate **2** (70.75%) as a colorless oil with spectroscopic data consistent with the literature.[8,15] $^{1}$H NMR (500 MHz, $CDCl_3$): δ 5.77 (s, 1H), 5.37-5.34 (m, 1H), 3.63 (s, 3H), 2.22 (septet, $J$ = 6.8 Hz, 1H), 2.11-2.01 (m, 4H), 1.97-1.92 (m, 1H), 1.90-1.85 (m, 1H), 1.84-1.68 (m, 3H), 1.64-1.53 (m, 3H), 1.25 (, 3H), 1.25-1.10 (m, 2H), 1.01 (d, $J$ = 6.8 Hz, 3H), 1.00 (d, $J$ = 6.8 Hz, 3H), 0.82 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 179.0, 145.3, 135.6, 122.4,

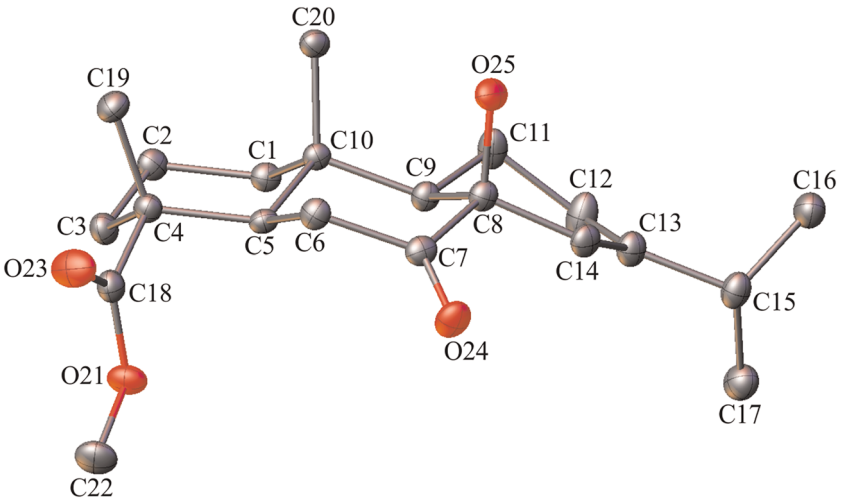



**FIGURE 1** Molecular diagram of the methyl 8β-hydroxy-7-oxoabiet-13(14)-en-18-oate (**9**) with the atom numbering scheme. The displacement ellipsoids are drawn at the 50% probability level. The H atoms are omitted for clarity

120.6, 51.8, 51.0, 46.6, 45.1, 38.3, 37.1, 34.9, 34.6, 27.5, 25.7, 22.5, 21.4, 20.8, 18.1, 17.0, 14.0.

## 2.3 | Preparation of β,γ-unsaturated ketone 3

A mixture of methyl abietate **2** (2 g; 6.3 mmol), diethyl ether (450 mL), water (12 mL), potassium bicarbonate (29.01 g; 0.3 mmol), and iodine (6.36 g; 28 mmol) was stirred at room temperature in argon atmosphere for 24 hours. Then, an excess of iodine was destroyed by washing the mixture three times with 10% aqueous sodium thiosulfate. The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. The residue was chromatographed on silica gel to yield 1.29 g (60%) of ketone **3** with melting point and spectroscopic data consistent with the literature.[14]

**3**: colorless crystals, mp 86-88°C; $^1$H NMR (500 MHz, $CDCl_3$): δ 5.81 (s, 1H), 3.64 (s, 3H), 2.88 (br d, $J$ = 10 Hz, 1H), 2.41 (t, $J$ = 14.2 Hz, 1H), 2.22 (septet, $J$ = 6.8 Hz, 1H), 2.15 (dd, $J$ = 14.2, 3.0 Hz, 1H), 2.08-1.84 (m, 5H), 1.80-1.71 (m, 1H), 1.70-1.59 (m, 3H), 1.37-1.28 (m, 2H), 1.22 (s, 3H), 1.07 (s, 3H), 1.14-1.05 (m, 1H), 1.00 (d, $J$ = 6.8 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 208.8, 177.8, 144.6, 115.2, 52.9, 52.1, 49.1, 48.8, 47.2, 40.9, 37.3, 36.8, 36.0, 34.8, 26.6, 22.5, 21.6, 21.1, 17.8, 16.0, 13.6.

## 2.4 | Preparation of hydroperoxides 4 and 5

A solution of enone **3** (500 mg; 1.5 mmol) in THF (15 mL) and triethylamine (1.5 mL; 10.76 mmol) was stirred at room temperature for 48 hours. with access to air. Then solvents were evaporated to dryness. The residue was chromatographed on silica gel to yield **4** (378 mg, 68%) and **5** (65 mg, 11%) with spectroscopic data of both consistent with the literature.[14]

**4**: colorless crystals, mp 123-125°C; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.31 (br s, 1H), 6.81-6.79 (m, 1H), 3.66 (s, 3H), 2.42-2.20 (m, 4H), 2.08-2.04 (m, 1H), 1.89-1.81 (m, 2H), 1.79-1.43 (m, 7H), 1.25 (s, 3H), 1.24-1.17 (m, 1H), 0.91 (d, $J$ = 6.9 Hz, 3H), 0.88 (s, 3H), 0.85 (d, $J$ = 6.9 Hz, 3H). $^{13}$C MNR (125 MHz, $CDCl_3$): δ 198.9, 178.1, 141.3, 136.8, 83.3, 52.2, 51.5, 46.3, 44.4, 38.7, 38.0, 36.9, 35.5, 32.7, 25.8, 18.7, 17.8, 17.2, 16.4, 16.2, 14.4.

**5**: colorless oil; $^1$H NMR (600 MHz, $CDCl_3$): δ 7.98 (br s, 1H), 6.84 (dd, $J$ = 2.3, 1.6 Hz, 1H), 3.66 (s, 3H), 2.39-2.33 (m, 2H), 2.28-2.21 (m, 2H), 1.97 (septet, $J$ = 7.0 Hz, 1H), 1.95-1.87 (m, 2H), 1.83 (qd, $J$ = 13.3, 4.0 Hz, 1H), 1.78-1.64 (m, 4H), 1.64-1.53 (m, 1H), 1.44-1.36 (m, 1H), 1.23 (s, 3H), 1.25-1.17 (m, 1H), 0.96 (d, $J$ = 6.9 Hz, 3H), 0.91 (d, $J$ = 7.1 Hz, 3H), 0.84 (s, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$): δ 199.4, 178.0, 140.6, 139.0, 84.8, 52.2, 50.5, 46.3, 44.5, 38.7, 37.5, 36.8, 35.6, 34.8, 25.8, 21.2, 17.9, 17.7, 16.8, 16.3, 14.3.

## 2.5 | Preparation of alcohols 6 to 9

A mixture of enone **3** (400 mg, 2.32 mmol), sodium *tert*-butoxide (6.0 mg, 0.06 mmol), and anhydrous toluene (20.0 mL) was stirred with access to air at room temperature for 24 hours. Then the mixture was poured into water and extracted with toluene. An organic layer was dried over sodium sulfate and evaporated to dryness. The residue was chromatographed on silica gel (10% ethyl acetate in hexane) to yield alcohols **6** (108 mg, 23%), **7** (43 mg, 9%), **8** (124 mg, 25%), and **9** (26 mg, 6.0%) with spectroscopic data of **6** to **8** consistent with the literature.[14]

**6**: colorless oil; $^1$H NMR (500 MHz, $CDCl_3$): δ 6.74 (br s, 1H), 3.66 (s, 3H), 2.40-2.24 (m, 3H), 2.10-2.05 (m, 1H), 1.86 (br d, $J$ = 13.0 Hz, 1H), 1.80-1.68 (m, 4H), 1.66-1.60 (m, 2H), 1.60-1.53 (m, 2H), 1.50-1.45 (m, 2H), 1.25 (s, 3H), 1.25-1.18 (m, 1H), 0.96 (d, $J$ = 6.8 Hz, 3H), 0.88 (s, 3H), 0.86 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.3, 178.1, 140.1, 138.4, 71.8, 52.1, 51.7, 46.3, 44.4, 38.6, 37.9, 37.8, 36.9, 35.5, 29.5, 18.3, 17.8, 17.3, 16.4, 16.1, 14.4.

**7**: colorless crystals, mp 129-130°C. $^1$H NMR (500 MHz, $CDCl_3$): δ 6.75 (br s, 1H), 3.66 (s, 3H), 2.39-2.31 (m, 2H), 2.28-2.20 (m, 2H), 2.17-2.12 (m, 1H), 1.82-1.55 (m, 7H), 1.48-1.36 (m, 3H), 1.27-1.17 (m, 1H), 1.24 (s, 3H), 0.98 (d, $J$ = 6.8 Hz, 3H), 0.94 (d, $J$ = 6.8 Hz, 3H), 0.86 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.5, 178.0, 141.3, 136.8, 72.5, 52.2, 50.7, 46.4, 45.1, 39.0, 37.4, 36.8, 36.2, 35.9, 32.8, 20.5, 17.8, 17.0, 16.7, 16.2, 14.1.

**8**: colorless crystals, mp 115-118°C. $^1$H NMR (500 MHz, $CDCl_3$): δ 5.25 (s, 1H), 3.88 (s, 1H), 3.67 (s, 3H), 2.52 (t, $J$ = 14.1 Hz, 1H), 2.26-2.16 (m, 3H), 2.14-2.04 (m, 3H), 1.94-1.92 (m, 2H), 1.77-1.70 (m, 2H), 1.67-1.56 (m, 4H), 1.22 (s, 3H), 1.11 (s, 3H), 1.01 (d, $J$ = 6.9 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 212.9, 177.8, 151.3, 118.9, 74.9, 55.1, 52.2, 47.6, 47.1. 39.8, 38.38, 38.35, 36.6, 35.2, 24.1, 21.2, 20.9, 17.5, 17.3, 16.7, 15.1.

**9**: colorless crystals, mp 80-81°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.93 (dt, $J$ = 2.1, 1.0 Hz, 1H), 3.66 (d, $J$ = 1.9 Hz, 3H), 3.06 (dd, $J$ = 14.4, 13.2 Hz, 1H), 2.27-1.96 (m, 5H), 1.86-1.70 (m, 6H), 1.69-1.53 (m, 6H), 1.48 (s, 1H), 1.23 (s, 3H), 1.18-1.16 (m, 3H), 1.02 (d, $J$ = 1.7 Hz, 3H), 1.00 (d, $J$ = 1.7 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 208.2, 178.2, 150.41, 119.1, 74.2, 55.8, 52.3, 50.1, 47.8, 38.6, 38.0, 36.9, 35.0, 27.9, 21.7, 21.3, 17.6, 17.1, 16.2, 15.6. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{32}O_4Na$ 371.2198; Found 371.2201.

### 2.6 | Reaction of abietane hydroperoxide 4 with sodium *t*-butoxide

A mixture of hydroperoxide **4** (34.0 mg, 0.09 mmol) and sodium *t*-butoxide (1.2 mg, 0.01 mmol), in anhydrous toluene (1.5 mL), was stirred at room temperature under argon for 0.5 hours. The mixture was then diluted with toluene (15 mL) and washed with water (20 mL). The organic layer was dried over sodium sulfate, and the solvent was removed. The residue was chromatographed on silica gel (15% ethyl acetate in hexane) to yield epoxide **10** as an oil (29.7 mg, 87%) and alcohol **6** (2.9 mg, 9%) also in the form of an oil. An analytical sample of the alcohol **6** was purified by thin-layer chromatography (a plate 20 × 20 cm coated with a silica gel layer of 0.25 mm, eluent 30% ethyl acetate in hexane). The NMR spectrum of the pure product obtained was identical to the $^1$H NMR spectrum of the previously obtained alcohol **6**.

**10**: colorless oil; $^1$H NMR (600 MHz, $C_6D_6$): δ 3.80 (d, $J$ = 1.6 Hz, 1H), 3.21 (s, 3 H) 2.40 (dd, $J$ = 15.9, 14.2 Hz, 1H), 2.36 (br. S, 1H), 2.25 (dd, $J$ = 22.1, 3.32 Hz, 1H), 2.27 (dd, $J$ = 15.9, 3.3 Hz, 1H), 2.22 (dd, $J$ = 14.2, 3.32 Hz, 1H), 1.73 (septet, $J$ = 6.9 Hz, 1 H) 1.61(td, $J$ = 13.1, 4.2 Hz 1H), 1.48-1.48 (m, 1H), 1.35-1.31 (m, 1H), 1.31-1.16 (m, 4 H) 1.12 (dd, $J$ = 11.6, 4.0 Hz, 1H), 1.03 (d, $J$ = 0.4 Hz, 3H), 0.97-0.93 (m, 1H), 0.94 (d, $J$ = 6.8 Hz, 3H) 0.88-0.82 (m, 1H), 0.86 (s, 3H), 0.79 (d, $J$ = 6.9 Hz, 3H), 0.62 (td, $J$ = 13.4, 4.9 Hz, 1 H). $^{13}$C NMR (150 MHz, $C_6D_6$): δ 202.8, 177.0, 69.9, 63.3, 59.8, 51.3, 50.6, 47.1, 46.6, 39.7, 37.3, 37.0, 36.8, 36.6, 30.5, 17.2, 16.6, 16.0, 14.4, 13.7. HRMS: (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{32}O_5Na$ 387.2142; Found 387.2134.

### 2.7 | Cyclohexenone epoxidation with hydrogen peroxide

Cyclohexenone (0.55 g, 5.61 mmol) was dissolved in 1,4-dioxane (10 mL), and then NaOH (25.2 mg, 0.63 mmol) was added. The solution was cooled to 0°C, and 0.6 mL of 30% aqueous $H_2O_2$ was slowly added dropwise. The GC-MS analysis was used to confirm the identity of the product that turned out to be 2,3-epoxy-1-cyclohexanone.

### 2.8 | Cyclohexenone epoxidation with abietane hydroperoxide 4

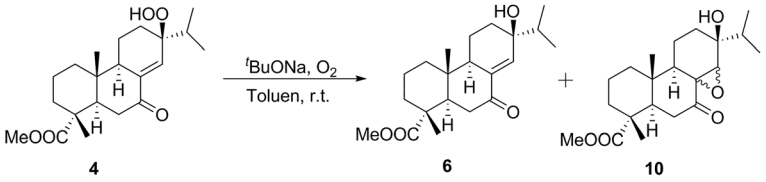
Cyclohexenone (14 mg, 0.125 mmol) was dissolved in 0.6-mL 1,4-dioxane. Subsequently, hydroperoxide **4** (45 mg, 0.125 mmol) and sodium *t*-butoxide (2 mg, 0.02 mmol) were added to the solution. The GC-MS analysis corroborated the formation of the same 2,3-epoxy-1-cyclohexanone as in the reaction with hydrogen peroxide.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Synthesis and examination of β,γ-unsaturated ketone 3 autoxidation with atmospheric oxygen in the presence of various bases

The first step of the synthesis leading to target enone **3** was an oxidation reaction of methyl abietate **2**, under an only slightly modified literature procedure (for details see Section 2).[21] As a result of this modification, the yield of **3** increased to 60% compared with 42% previously reported in the literature. This enhancement is essential as compound **3** is our starting material for further research. It is also worth noting that under the reaction conditions, the formation of 13β,14β-epoxide, competitive to unconjugated enone **3**, was negligible.

After obtaining our substrate for self-oxidation studies, ie, β,γ-unsaturated ketone **3**, the next step was the isomerization of **3** to the conjugated enone **i** using triethylamine as a base (Scheme 1). Although enone **i** was not isolated, we have evidence of specified stereochemistry of **i** from our earlier work.[14] This reaction carried out under the described conditions (in THF in the presence of triethylamine at room temperature for 24 h) led to two hydroperoxides **4** and **5** in 68% and 11% yields, respectively, and was consistent with reported results. To determine the rate and quantity of oxygen consumed in the course of this reaction, we measured the amount of gas absorbed by a vigorously stirred solution of enone **3** (150 mg) in THF (4.5 mL) containing triethylamine (1.5 mL) in an apparatus equipped with a gas burette and filled with air. Although within the first 2 hours, the oxygen consumption was not observed, however, after 24 hours, the total volume of oxygen absorbed was 20.1 $cm^3$, far beyond the calculated stoichiometric amount of 15.4 $cm^3$. Even at this stage, the oxygen absorption did not cease entirely, but slowly continued at a rate of approximately 0.2 mL/h. Based on the obtained result, two conclusions can be drawn. Firstly, the autoxidation reaction has most probably an autocatalytic character. Secondly, the reaction does not stop at the hydroperoxides **4** and **5** stages but proceeds further to form other yet unidentified products of further oxidation. This assumption is confirmed by a TLC analysis, which shows that the final reaction mixture, although predominantly consisting of hydroperoxides **4** and **5**, also contains



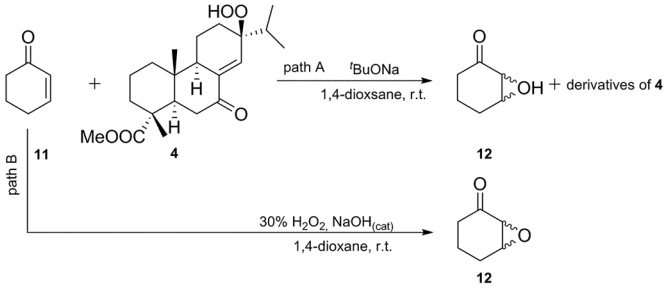

**SCHEME 2** Reaction of abietic hydroperoxide **4** with *t*-BuONa

tars and small amounts of number of various more polar components.

The question needed to be answered was whether enone **3** oxidizes to hydroperoxides in direct reaction with oxygen or whether some form of oxidized tetrahydrofuran is involved in the reaction as an oxygen transporter. The answer came from a blank experiment in which tetrahydrofuran containing triethylamine was stirred in an apparatus with a gas burette in an air atmosphere. After 48 hours of mixing, the gas volume in the burette did not decrease, which led to a plausible conclusion that the oxidizing agent in the studied reaction is atmospheric oxygen alone. We obtained the same result using toluene instead of THF in a blank experiment.

Then we performed the same isomerization reaction of enone **3** but using sodium *t*-butoxide instead of triethylamine as a base and anhydrous toluene as a solvent. In the beginning, we used 0.1 eq. sodium *t*-butoxide, according to the literature procedure.[14] Next, we gradually diminished the amount of added base starting from 0.05 eq. to 0.025 equivalent. In all cases, we received alcohols **6** to **9** (Scheme 1) with the same yields of 23%, 9%, 25%, and 6%, respectively, in ascending order. Among the alcohols **6** to **9** formed in the course of this reaction, alcohols **6** to **8** proved to be already described in the literature. The structure of the new, not yet described alcohol **9**, including the (*R*) absolute configuration of the C-8 carbon atom, was fully characterized by spectroscopic methods and single-crystal X-ray diffraction analysis. The molecular diagram showing the atom numbering scheme for this compound is shown on Figure 1.

The performed experiments proved the catalytic role played by sodium *t*-butoxide in the oxidation process. In




**SCHEME 3** Epoxidation of cyclohexenone (**11**) with hydroperoxide **4** and with hydrogen peroxide in dioxane

one experiment in which we measured the oxygen consumption during the reaction discussed above, we found that the situation was very similar to the oxidation in THF with triethylamine. Like in the previous case, the oxygen consumption started very slowly, exceeding the calculated volume of oxygen absorbed for equimolar oxidation after 24 hours.

## 3.2 | Examination of methyl 8β-hydroxy-7-oxoabiet-13(14)-en-18-oate autooxidation in the presence of catalytic amounts of sodium *t*-butoxide

In the literature, the air oxidation of enones, including resin acid derivatives, to form peroxides is known and well documented.[22-25] Since in our case, the only significant difference between the peroxides or alcohols formation was the type of base used in the reaction, we decided to check whether the hydroperoxide **4** formed in the reaction with triethylamine could be converted to alcohol **6** by sodium *t*-butoxide. To that end, we carried out the reaction between abietic hydroperoxide **4** and sodium *t*-butoxide under the same conditions as the one using enone **3**, ie, in anhydrous toluene, under argon and in the presence of a catalytic amount of base. Admittedly, alcohol **6** (9%) was among the reaction products, but the main component of the reaction mixture was epoxide **10** (87%) (Scheme 2). Its structure was determined based on NMR spectra; nevertheless, stereochemical assignments of C8 and C14 carbon atoms were not possible due to the epoxide oiliness precluding the use of X-ray diffraction analysis.

Regardless of the stereochemistry of epoxide **10**, its formation in the above experiment indicates that the double bond present in the hydroperoxide molecules acts in the alkaline medium as a reducing agent for hydroperoxide groups and epoxides might be intermediates in the alcohols formation process. The reduction of hydroperoxides to alcohols and the oxidation of double bonds to epoxides can be explained based on the commonly accepted mechanism of α,β-unsaturated ketones epoxidation.[26] Although the formation of epoxide **10** can be assumed as an intramolecular process, the formation of alcohol **6** as a by-product indicates that epoxidation is rather intermolecular. This indication confirms the

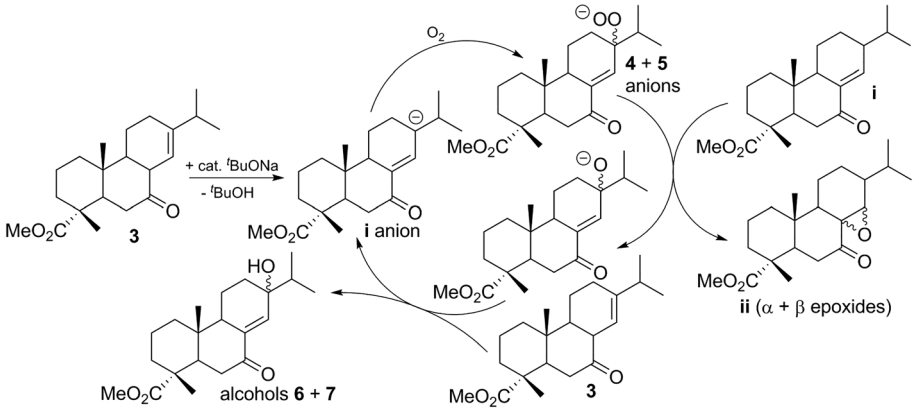
formation of epoxide **12** in the reaction of cyclohexenone (**11**) with hydroperoxide **4**, which acts as an oxidizing agent (Scheme 3). Due to the volatility of both cyclohexenone (**11**) and its epoxidation product **12**, the reaction course was monitored by gas chromatography. Epoxycyclohexanone **12** needed as a reference to track the reaction progress in gas chromatography was synthesized in separate epoxidation of cyclohexenone with 30% hydrogen peroxide and a catalytic amount of sodium hydroxide in a dioxane solution (Scheme 3).

The aforementioned epoxidation reaction of cyclohexenone with hydroperoxide **4** was carried out in dioxane at room temperature in the presence of a catalytic amount of sodium *t*-butoxide. After 1.5 hours, gas chromatography analysis of the crude reaction mixture revealed the formation of a significant amount (26%) of 2,3-epoxycyclohexanone **12**, and a TLC analysis showed the formation of alcohol **6**. Thus, the demonstrated ability of the hydroperoxide group in enone **4** to act as an oxidant for α,β-unsaturated ketones with a simultaneous reduction of the hydroperoxide to hydroxyl derivatives indicates that we are dealing here with intermolecular epoxidation.

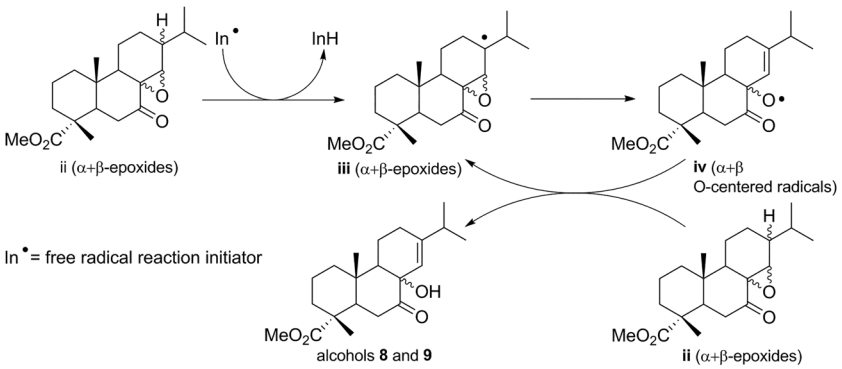
This proven ability of hydroperoxides to epoxidize conjugated double bonds in the presence of a catalytic amount of sodium *t*-butoxide, ultimately resulting in the formation of four alcohols **6** to **9**, has provided sufficient information to propose a plausible mechanism of this reaction, which is presented in Schemes 4 and 5. In the first reaction stage, under the influence of a base, an unconjugated enone **3** is converted into a conjugated, nonisolable enone **i**. Afterward, under aerial exposure, the oxidation of the enone **i** begins, and a mixture of 13α- and 13β-hydroperoxides, **4** and **5**, respectively, is formed. Thus, at the early stage of the process, the reaction mixture must contain a vulnerable to epoxidation, but a still unreacted enone **i**, besides a mixture of its oxidation products just formed, ie, hydroperoxides **4** and **5**. In the presence of sodium *t*-butoxide, these components react with each other to form mixtures of 13β- and 13α-alcohols **6** and **7**, respectively, as well as epoxyketones **ii** with 8α,14α- or 8β,14β-oxirane ring (Scheme 4).

We assume that in the epoxy ketone **ii**, the ability to form tertiary radicals at C13 carbon in aerobic conditions may be as significant as is the case of abietane allylic systems. Thus, the abstraction of a hydrogen atom from **ii** will proceed smoothly with the formation of carbon-centered radical **iii** (Scheme 5). Once the radical **iii** is formed, a chain reaction begins. As is well known, free radicals located at the α-carbon atom to any three-membered ring (including epoxides) undergo very fast rearrangement with the ring opening and a double bond formation.[27] In our case, this rearrangement leads to the allyl alkoxy radical **iv**, which subsequently abstracts a hydrogen atom from epoxide **ii** to afford two alcohols **8** and **9** together with new alkoxy radical **iv**. At this point, the next reaction chain can be initiated.

The natural consequence of the mechanism shown above is that the sum of the yields of alcohols **6** and **7** should be equal to the sum of the yields of alcohols **8** and **9**. In our experiments, the average total yields of **6** and **7** were found as 32%, and the average total yields of **8** and **9** were found as 31%. These results perfectly fit the presented reaction pattern and support the proposed mechanism. At this point, a few additional comments concerning the reaction shown in Scheme 2 must be given. Reciprocal epoxidation of hydroperoxide molecule **4** in the presence of catalytic amounts of sodium *t*-butoxide affords an epoxide **10** accompanied by a small amount of alcohol **6**. The formation of alcohol **6** in such an epoxidation process might change the ratio of alcohol **6** to alcohol **7** presented in Scheme 1 in favor of alcohol **6**. Such a situation, however, does not occur since a total yield of **6** + **7** and a total yield of **8** + **9** are almost the same. That means that the reciprocal epoxidation of hydroperoxide **4** molecules plays only a marginal role, if any, in the formation of alcohols **6** to **9** in the air oxidation reaction catalyzed by sodium *t*-butoxide. Moreover,




**SCHEME 4** Proposed mechanism of the formation of alcohols **6** and **7** from enone **3** by oxidation with atmospheric oxygen in the presence of catalytic amount of *t*-BuONa




**SCHEME 5** Proposed mechanism of the formation of alcohols **8** and **9** from epoxyketone **ii** by oxidation with atmospheric oxygen in the presence of catalytic amont of *t*-BuONa. In the above scheme, the word "radicals" has been added to the description of compound **iii**

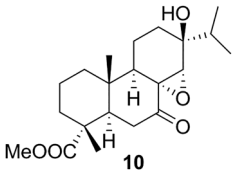



**FIGURE 2** Structure of methyl 8α,14α-epoxy-7-oxoabiet-13β-hydroxy-18-oate (**10**)

assuming that the initial aerobic hydroperoxide formation in the presence of sodium *t*-butoxide takes the same course as in the reaction in the presence of triethylamine and where the axial β-hydroperoxide **4** is the dominant product, we can state with high probability that the epoxide ring in epoxyalcohol **10** is oriented towards α-face of the molecule (Figure 2).

As shown in Scheme 1, alcohol **8** with an equatorial hydroxy group, apart from alcohol **6**, is the main component of the *t*-butoxide catalyzed oxidation products. According to the mechanism presented in Scheme 5, alcohols with hydroxyl groups located at carbon atom C-8 originate from an epoxide ring opening initiated by a radical formed at C-13. Thus, since α-alcohol **8** can be formed only from α-epoxide **ii**, we conclude that an hydroperoxide attack on 8(14)-en-7-on system in the abietane skeleton is privileged from the α-side of the molecule.

## 4 | CONCLUSION

In this work, we presented the dependence of the direction of the self-oxidation reaction of methyl 7-oxoabiet-13(14)-ene-18-oate (**3**) on the base used, resulting finally in various products. As stated, the oxidation of enone **3** to hydroperoxides **4** and **5** occurred under aerobic conditions in the presence of triethylamine. The use of sodium *t*-butoxide as a base, in turn, leads to four easily separable tertiary alcohols **6** to **9**. The alcohols thus formed are not primary oxidation products but originate from more complex processes that involve the epoxidation of conjugated double bonds by hydroperoxides and the rearrangement of radical epoxides.

Considering the steady interest in abietane derivatives resulting from their potential pharmacological properties along with the low price and virtually unlimited abietic acid resources, the possibility of directing the air oxidation reaction of abietane enones on demand towards hydroperoxides or tertiary alcohols through the use of an appropriate base makes the reaction discussed in this work a valuable tool in medical chemistry.

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