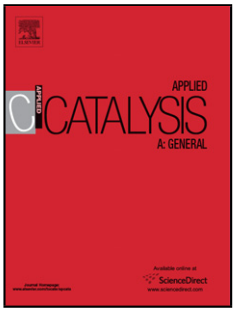

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Palladium catalyzed aerobic oxidation for the incorporation of an olfactory group on naturally occurring β-caryophyllene

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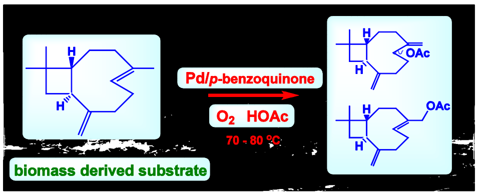
Dedicated to Prof. Martin Schmal on the occasion of his 80th birthday

Graphical abstract



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Research Highlights

- *β*-Caryophyllene is one of the most widespread sesquiterpenes, found as a main hydrocarbon component in various essential oils, e.g., copaiba oil, which is used for years in folk medicine.

- A novel selective oxidation of *β*-caryophyllene by molecular oxygen using the chloride-free $Pd(OAc)_2$/*p*-benzoquinone catalytic system has been developed.

- Poly-functionalized sesquiterpenic compounds obtained in these reactions are potentially useful as ingredients of synthetic perfumes and pharmacological compositions.

Abstract

β-Caryophyllene is one of the most widespread sesquiterpenes, found as a main hydrocarbon component in various essential oils, e.g., copaiba oil, which is used for years in folk medicine and occupies an important position in Brazilian pharmaceutical export. The novel selective oxidation of *β*-caryophyllene by molecular oxygen using the chloride-free $Pd(OAc)_2$/*p*-benzoquinone (BQ) catalytic system has been developed. The reaction gives two main products, both arising from the allylic oxidation of the sterically encumbered endocyclic double bond, whereas the terminal double bond of the substrate remains intact. The catalytic process efficiently operates under 10 atm of oxygen in the absence of auxiliary metal co-catalysts, which are commonly used in related systems. The reaction can also occur under atmospheric pressure in the presence of $Cu(OAc)_2$ to accelerate the re-oxidation of *p*-hydroquinone by molecular oxygen.

Both allylic acetates, obtained from *β*-caryophyllene in 75–85 % combined yields in both systems, are natural compounds found in essential oils of some plants and have well pronounced perfume properties. To the best of our knowledge, the present work reports the first synthesis of these functionalized sesquiterpenic compounds potentially useful as ingredients of synthetic perfumes and pharmacological compositions.

Keywords: Biorenewables; β-Caryophyllene; Oxidation; Palladium; Terpenes

1. Introduction

The involvement of bio-renewable reagents in industrial chemical processes is among the requirements of green organic synthesis along with the use of catalytic rather than stoichiometric reactions. In particular, numerous terpene hydrocarbons, the main components of essential oils of plants and flowers, represent an important feedstock for the fragrance&flavor and pharmaceutical industries [1–3]. The molecules of terpenes often contain multiple olefinic bonds and can be upgraded into more valuable compounds through a variety of chemical reactions, such as hydroformylation, oxidation, epoxidation, hydrogenation and acid-catalyzed transformations [4–9].

β-Caryophyllene is one of the most widespread sesquiterpenes found as a main hydrocarbon component in various essential oils, such as clove (*Eugenia Caryophyllata*) and copaiba (*Copaifera*) oils [9–12]. A remarkable biological activity of caryophyllanes is responsible for the well recognized therapeutic properties of copaiba oil, which is used for years in popular medicine and traditionally occupies an important position in the Brazilian export of pharmaceutical products [12]. In addition, caryophyllane derivatives usually have pleasant woody, floral or fruity scents and are widely used as aromatic ingredients in perfumes, food and tobacco products [11,12]. Therefore, the catalytic functionalization of the *β*-caryophyllene molecule, which contains two olefinic bonds, could open an access to the compounds important for the fragrance&flavor and pharmaceutical industries.

For several years our group has been involved in the catalytic upgrading of naturally occurring products [6,9], in particular, through the palladium catalyzed oxidation of their C=C bonds [13–21]. The majority of the palladium catalyzed oxidations of organic molecules by molecular oxygen require an additional redox co-catalyst in order to provide the efficient re-oxidation of reduced palladium species before their irreversible agglomeration into inactive bulk palladium metal. The original and most commonly used catalytic system for these reactions contains $CuCl_2$ as the co-catalyst and the presence of chloride ions in high concentrations is required to maintain a catalytic cycle (Wacker catalyst [22]). Many efforts were directed to search more environmentally acceptable and less corrosive alternatives for $CuCl_2$, such as *p*-benzoquinone, $Cu(OAc)_2$, heteropoly acids or special ligands, which can stabilize palladium in solutions allowing its direct re-oxidation by molecular oxygen [23–28].

As a part of our general project aiming to the valorisation of essential oils, we have recently turned our attention to the functionalization of *β*-caryophyllene (**1**). The molecule of *β*-caryophyllene has an unusual structure in which a nine-membered ring is fused in a *trans* manner with a cyclobutane ring (Scheme 1). The molecule is highly strained and enters in structural rearrangements with a remarkable facility to release this strain. This makes a great challenge the development of the selective reactions to obtain one or two particular products. Probably for this reason, only few reports on the selective catalytic transformations of *β*-caryophyllene have been described in the literature, despite the industrial importance of its derivatives [29–34]. In particular, our group has recently reported two reactions of *β*-caryophyllene: the heteropoly acid catalyzed acetoxylation to give *β*-caryolanyl compounds, i.e. the products with an isomerized carbon skeleton [32], and rhodium catalyzed hydroformylation in which the caryophyllane structure was retained [34].

To the best of our knowledge, the palladium catalyzed oxidation of *β*-caryophyllene has not been studied before. Moreover, we could find only two previously published reports on the catalytic oxidation of *β*-caryophyllene in general, both describing the reactions of epoxidation with hydrogen peroxide over titanium catalysts [29,30]. In the present work, we report the application of palladium catalytic systems for the oxidation of *β*-caryophyllene with molecular oxygen. All the reactions gave exclusively the products derived from the interaction of palladium with the endocyclic double bond of *β*-caryophyllene. The products obtained from *β*-caryophyllene in the present work and their mixtures have well pronounced perfume properties and could be used directly in perfume compositions even without the separation of individual compounds.

2. Experimental

The chemicals acquired from commercial sources were used as received, except when indicated. $CuCl_2{\cdot}2H_2O$ and LiCl were dehydrated by heating. *p*-Benzoquinone was purified by column chromatography (silica) using dichloromethane as the eluent. *β*-Caryophyllene [(-)-trans caryophyllene] was purchased from Sigma-Aldrich and glacial acetic acid used as the solvent from VETEC. The catalytic tests under 1 atm of O_2 were performed in a glass reactor, whereas those under superatmospheric pressure in a homemade stainless steel 100-mL autoclave equipped with a valve dip tube to take the samples of the reaction solution. Magnetic stirring was used in both reactors. The glass reactor was equipped by a gas burette to measure oxygen consumption during the reactions. The reaction progress was monitored by gas chromatography (GC) taking the samples without the depressurization of the reactor. In a typical catalytic test, the solution of the substrate (0.20 M), palladium salt (0.005 – 0.02 M), copper salt (if any, 0.025 – 0.05 M), BQ (if any, 0.05 – 0.20 M), and internal standard (dodecane or *p*-xylene, 0.10 M) in the indicated solvent was transferred to the reactor. The total volume of the solution was 10 mL. Reaction variables (concentrations, temperature, oxygen pressure, etc.) and reaction time are presented in the Tables. The reactor was pressurized with oxygen to 1–10 atm, heated in an oil bath and then intensive stirring was turned on to start the reaction. At the end of the run, the autoclave was cooled to room temperature and oxygen was allowed to slowly vent out. CAUTION: reactions with oxygen under elevated pressure can lead to an unforeseen explosion. It must only be performed using the appropriate equipment and under rigorous safety precautions. The samples of the reaction solutions periodically taken from the reactor were analyzed by GC on a Shimadzu GC2010 equipment using a Carbowax 20 m capillary column and a FID detector. Relative GC response factors were determined using isolated reaction products. A GC mass balance was based on the *β*-caryophyllene converted using internal standards (dodecane or *p*-xylene). The difference was attributed to the formation of high-boiling products, which were not GC determinable. Initial reaction rates were calculated at low conversions (up to 20-40%).

The product isolation was performed by a column chromatography (silica gel 60) using mixtures of hexane and CH_2Cl_2 as eluents. Before passing the reaction solution through the column, acetic acid was neutralized by sodium bicarbonate and organic components were extracted from aqueous solutions with dichloromethane. Isolated products were identified by ^{1}H and ^{13}C-NMR with TMS as an internal standard and/or GC-MS (Bruker 400 MHz spectrometer; Shimadzu QP2010-PLUS instrument, 70 eV).

Compound **2** (two isomers): MS (70 eV, EI): *m/z* (%) first isomer (shorter GC retention time): 202 (10) [M$^+$-HOAc], 187 (22) [M$^+$-HOAc-CH$_3$], 173 (17), 159 (34), 146 (18), 145 (28), 133 (27), 132 (18), 131 (54), 120 (16), 119 (42), 118 (67), 117 (58), 107 (23), 106 (19), 105 (61), 93 (37), 92 (22), 91 (100), 81 (17), 79 (51), 77 (36), 69 (40), 67 (29), 65 (16), 60 (20), 55 (26); second isomer (longer GC retention time): 202 (9) [M$^+$-HOAc], 187 (20) [M$^+$-HOAc-CH$_3$], 173 (18), 159 (32), 146 (17), 145 (28), 133 (25), 132 (15), 131 (53), 120 (15), 119 (40), 118 (60), 117 (52), 107 (24), 106 (19), 105 (66), 93 (37), 92 (21), 91 (100), 81 (20), 79 (51), 77 (34), 69 (35), 67 (28), 65 (16), 60 (20), 55 (27). ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, Me$_4$Si): δ=0.92 (s, 6H; $C^{14}H_3$ and $C^{15}H_3$), 1.40–2.00 (m, 4H; C^2H_2 and C^6H_2), 1.50–1.70 (m, 3H; $C^{10}H_2$ and C^1H), 1.80–2.00 (m, 2H; C^3HH, and C^7HH), 1.95 and 1.96 (s, 3H; OCOCH_3), 2.20–2.45 (m, 3H; C^3HH, C^7HH and C^9H), 4.60 and 4.66 (s, 1H; $C^{13}H$H), 4.74 (s, 1H; C^{13}HH), 4.92 and 4.99 (s, 1H; $C^{12}H$H), 4.97 and 5.04 (s, 1H; C^{12}HH), 5.05–5.10 ppm (m, 1H; C^5H); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C, TMS): δ=21.20 and 22.25 (OCO*C*H$_3$), 21.82 and 22.15 (C^{14}), 29.85 and 29.91 (C^{15}), 29.96 and 30.16 (C^2 or C^6), 30.35 and 30.43 (C^2 or C^6), 30.94 and 32.48 (C^7), 33.44 and 33.48 (C^{11}), 33.79 (C^3), 36.66 and 37.73 (C^{10}), 43.41 and 43.85 (C^9), 53.03 and 54.49 (C^1), 76.65 and 76.92 (C^5), 109.35 and 109.50 (C^{13}), 115.36 and 116.35 (C^{12}), 146.26 and 147.16 (C^4), 151.54 and 152.34 (C^8), 169.85 and 170.01 ppm (O*C*OCH$_3$). For atom numbering see Scheme 1.

Compound **3**: MS (70 eV, EI): *m/z* (%) 202 (13) [M$^+$-HOAc], 187 (26) [M$^+$-HOAc-CH$_3$], 173 (24), 159 (36), 146 (21), 145 (34), 133 (30), 132 (20), 131 (63), 120 (16), 119 (39), 118 (31), 117 (48), 107 (23), 106 (20), 105 (63), 93 (39), 92 (22), 91 (100), 81 (15), 79 (51), 77 (34), 69 (39), 67 (27), 65 (16), 60 (15), 55 (24). ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, Me$_4$Si): δ=0.91 (s, 3H; $C^{14}H_3$), 0.92 (s, 3H; $C^{15}H_3$), 1.40–1.60 (m, 2H; C^2H_2), 1.50–1.70 (m, 2H; $C^{10}H_2$), 1.70–1.80 (m, 1H; C^1H), 1.99 (s, 3H; OCOCH_3), 2.05–2.15 (m, 1H; C^3HH), 2.10–2.30 (m, 5H; C^3HH, C^6H_2 and C^7H_2), 2.35–2.45 (m, 1H; C^9H), 4.40 (d, ^4J=4.0 Hz, 2H; $C^{12}H_2$), 4.68 (s, 1H; $C^{13}H$H), 4.76 (s, 1H; C^{13}HH), 5.51 ppm (t, 1H; ^3J=8.0 Hz, C^5H); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C, TMS): δ=20.93 (OCO*C*H$_3$), 22.80 (C^{14}), 25.15 (C^3), 26.13 (C^2), 27.38 (C^6), 29.85 (C^{15}), 33.06 (C^{11}), 34.65 (C^7), 40.00 (C^{10}), 40.17 (C^9), 51.62 (C^1), 68.42 (C^{12}), 110.69 (C^{13}), 130.29

(C^5), 134.55 (C^4), 155.09 (C^8), 170.78 ppm (O*C*OCH$_3$). For atom numbering see Scheme 1.

3. Results and Discussion

The molecule of *β*-caryophyllene has two olefinic bonds which could be involved in the interaction with palladium: terminal disubstituted and endocyclic trisubstituted bonds. The conventional Wacker system, $PdCl_2/CuCl_2$, was tested first for the oxidation of *β*-caryophyllene (**1**) (Table 1, run 1). The reaction was performed under typical conditions in the solution of glacial acetic acid and resulted in nearly complete *β*-caryophyllene conversion within 3 hours. More than twenty new peaks appeared in the chromatogram of the reaction solutions after this run. In a blank reaction with no palladium salt added, *β*-caryophyllene was also consumed almost completely giving nearly the same products (Table 1, run 2). The products were clearly divided in two groups on the chromatogram. The nature of these compounds was suggested based on their characteristic retention times and mass spectra. The products from the first group (ca. ten GC peaks) with retention times close to that of *β*-caryophyllene were attributed to *β*-caryophyllene isomers. The second set of GC peaks with longer retention times was suggested to belong to the products of the solvent (HOAc) addition to *β*-caryophyllene and its isomers. Thus, the Wacker catalytic system promoted almost exclusively the acid-catalyzed transformations of *β*-caryophyllene, i.e., the isomerization and solvent addition, also accompanied by the isomerization of carbenium ion intermediates. $CuCl_2$ alone promoted the same reactions of *β*-caryophyllene in acetic acid solutions. In the presence of palladium, no products which could arise from the oxidation of *β*-caryophyllene (accordingly to their mass spectra) were detected in the reaction solutions in appreciable amounts. The results of these preliminary tests clearly indicated that the attempts to oxidize *β*-caryophyllene, such a sensitive to the reaction conditions molecule, should be continued in alternative systems: preferentially with non-acidic solvents or at least free of $CuCl_2$.

The most attractive candidate would be a system recently discovered by Kaneda et al. using dimethylacetamide (DMA) solutions with $PdCl_2$ which acts as a sole catalyst [28,35]. The use of the coordinating DMA solvent in this system allows to dispense the presence of auxiliary co-oxidants because Pd(0) species stabilized by the solvent react with molecular oxygen faster than form an inactive bulk metal. We have previously applied this so called "palladium solo" system for the oxidation of several terminal and internal alkenes [20,36,37]; however, for *β*-caryophyllene the results were not promising (Table 1, runs 3–5). Under typical conditions ($PdCl_2$ - 5–10 mol %, solvent – DMA with 10–20 vol % of H_2O, 80°C, 10 atm of oxygen), only the products of the *β*-caryophyllene isomerization were detected in the reaction solutions. Varying the reaction conditions did not result in the formation of any oxidation products. The isomerization of *β*-caryophyllene was observed even in the absence of the palladium salt (Table 1, run 6).

Thus, on the one hand, both olefinic bonds of *β*-caryophyllene behave as quite resistant to the interaction with palladium and, on the other hand, the molecule is extremely sensitive to the presence of $CuCl_2$ which promotes various acid catalyzed transformations of *β*-caryophyllene. Our further attention was directed to the catalytic systems based on the use of *p*-benzoquinone (BQ), which is a valuable candidate to replace $CuCl_2$ in Wacker oxidations [23,38]. Representative results obtained are shown in Tables 2 and 3.

The strategy was to study the reactions of *β*-caryophyllene with stoichiometric amounts of BQ using $Pd(OAc)_2$ as the catalyst and then, if succeed, aim to make the reaction catalytic also in BQ. We were very pleased to observe that the reactions of *β*-caryophyllene with BQ in acetic acid solutions containing catalytic amounts of $Pd(OAc)_2$ gave only two main products (**2** and **3**) with apparently high combined selectivity (Table 2, runs 1–3). The formation of neither of these products was observed in a blank reaction performed under the same conditions without $Pd(OAc)_2$, with only BQ added.

Compounds **2** and **3** presented close GC retention times and very similar mass spectra. They were isolated from the reaction solutions by column chromatography as a mixture (with a pleasant woody-floral smell) and identified by GC-MS and NMR spectroscopy (Scheme 1). As can be seen, compounds **2** and **3** are closely related regio-isomeric allylic acetates and are both derived from the interaction of the endocyclic double bond of *β*-caryophyllene with palladium. Acetate **2** is the product of the molecule oxidation at the endocyclic carbon (C-5), whereas acetate **3** – at the terminal carbon (C-12). The oxidation of *β*-caryophyllene occurred with high site-selectivity: no products derived from the oxidation of the other double bond were detected in appreciable amounts. It is a remarkable result as the terminal double bond is expected to show higher reactivity towards the interaction with palladium than the sterically encumbered trisubstituted endocyclic bond.

Allylic acetates **2** and **3** were detected in the reactions of *β*-caryophyllene with BQ at 60–70 °C with a combined selectivity of ca. 80% (Table 2, runs 1 and 2). The major product, acetate **2**, was responsible for ca. 60% of the mass balance at high substrate conversions, whereas the selectivity for minor acetate **3** in most of the runs was 15–20%. In addition, the products of the *β*-caryophyllene isomerization were detected in small amounts (ca. 10%) along with several unidentified products with longer GC retention times (probably, over-oxidation products).

Acetate **2** was formed in all the runs as two GC-separable isomers (with virtually identical mass spectra and very similar NMR spectra) in approximately equal amounts. Judging from the structure of **2**, we suggest that the difference between the two isomers is the relative orientation of the acetate group and the hydrogens H-1 and H-9 at the carbons shared by both rings (Scheme 1). Compound **2** was previously described as a natural ingredient of the essential oil produced from the European alpine plant *Leontopodium alpinum*, commonly known as Edelweiss [39]. Acetate **3** is also a natural compound isolated from the essential oil of *Betula* species, well-known as birch tree, widely distributed in the northern hemisphere and used for years in folk medicine and cosmetic products [40]. To the best of our knowledge, the present work reports the first synthesis of these functionalized sesquiterpenic compounds, which are potentially useful as components of synthetic perfumes and pharmacological compositions.

Although the runs with stoichiometric amounts of BQ were performed under oxygen atmosphere, no oxygen uptake was observed as expected. The re-oxidation of the reduced form of BQ, *p*-hydroquinone (BQH_2), with molecular oxygen under atmospheric pressure is known to require an auxiliary metal catalyst, such as cobalt, copper or manganese salts [24,38]. Aiming to make the reaction catalytic in BQ, $Cu(OAc)_2$ was added to the reaction solutions to accelerate the regeneration of BQ (Table 2, runs 4–13). It was verified that the presence of $Cu(OAc)_2$ did not affect negatively the reaction selectivity as well as the reaction rate (Table 2, run 4 vs. run 2). In further runs, BQ was used in sub-stoichiometric amounts and was successfully regenerated by molecular oxygen so that the reactions were catalytic not only with respect to palladium and copper but also with respect to BQ. The consumption of molecular oxygen in these runs corresponded to the amounts of β-caryophyllene converted into oxidation products.

The reactions with catalytic amounts of BQ occurred at lower rates compared to their stoichiometric counterparts (Table 2, run 5 vs. run 1; run 6 vs. runs 2 and 4; run 7 vs. run 3), suggesting that the regeneration of BQ is the slowest step of the whole process. Initial reaction rates were clearly depended on the BQ concentration (Table 2, cf. runs 6 and 8; runs 9 and 7) and also on the concentration of $Cu(OAc)_2$ (Table 2, cf. runs 10 and 8) supporting the suggestion that the rate-determining step is the oxidation of BQH_2 with molecular oxygen. Furthermore, a two-fold increase in the palladium concentration did not accelerate the reaction, suggesting nearly zero order in palladium (Table 2, run 11 vs. run 8). However, at lower palladium concentrations, the interaction of palladium with such a difficult substrate as β-caryophyllene became slower (probably, turned kinetically comparable with the BQH_2 re-oxidation) affecting the rate of the whole process (Table 2, run 12 vs. run 8; run 13 vs. run 9).

Thus, the palladium catalyzed oxidation of β-caryophyllene successfully occurs in the presence of $Cu(OAc)_2$ with an oxygen coupled catalytic turnover under atmospheric pressure. Apparently, $Cu(OAc)_2$ acts as an auxiliary catalyst accelerating the reaction of BQH_2 with molecular oxygen. The combined selectivity for allylic oxidation products **2** and **3** was 80–90% at nearly complete substrate conversions, with the major acetate **2** being responsible for 70–75% of the mass balance in most of the runs. The reactions performed at 90 ^{o}C showed slightly lower selectivity (Table 2, runs 7, 9 and 13).

We have found in our recent studies that under 5–10 atm BQ can be regenerated from BQH_2 directly by molecular oxygen in the absence of metal co-catalysts, which allowed us to create environmentally more friendly oxidation processes [17,21]. The applications of this approach to the oxidation of β-caryophyllene are presented in Table 3. The reactions were less selective as compared to their counterparts performed under atmospheric pressure due to the appearance of several unidentified minor products with longer GC retention times (probably, over-oxidation products). However, the optimization of the reaction conditions allowed to obtain allylic acetates **2** and **3** with ca. 80% selectivity at high substrate conversions (Table 3, runs 3, 4 and 7). No palladium mirror was observed on the reactor walls after the reactions with only 0.25 equiv. of BQ reflecting the efficient regeneration of Pd and BQ (Table 3, runs 5–8). The ratio between acetates **2** and **3** was slightly dependent on the reaction temperature varying from 3:1 at 80 °C to 6:1 at 50 °C; with all the reactions resulting predominantly in the endocyclic acetate **2**. The same tendency can also be seen in all the runs under atmospheric pressure (Table 2). Neither product **2** nor **3** were formed from *β*-caryophyllene under 1–10 atm of oxygen in acetic acid solutions in the absence of $Pd(OAc)_2$. At lower BQ concentrations, the reaction occurred slower, albeit with nearly the same selectivity and product distribution (Table 3, cf. runs 1 and 5; runs 2 and 6; runs 3 and 7). Therefore, the oxidation of BQH_2 by molecular oxygen seems still to be a rate controlling step at the oxidation of *β*-caryophyllene under superatmospheric oxygen pressure. On the other hand, with the increase in the $Pd(OAc)_2$ concentration the reaction occurred faster (Table 3, run 8 vs. run 6). These results could indicate that the reactions between the olefin and palladium and between BQH_2 and molecular oxygen occur at comparable rates, each one being able to control the rate of the whole process depending on the reaction conditions.

The mechanistic proposal for the oxidation of *β*-caryophyllene into allylic acetates **2** and **3** is presented in Scheme 2. The accepted mechanism for the palladium catalyzed allylic oxidation involves the formation of π-allyl palladium complexes as key intermediates [14,41,42]. The structures of products **2** and **3** imply that they result from the exocyclic π-allyl palladium intermediate (**A**) formed by the abstraction of the allylic hydrogen from acyclic terminal carbon atom C-12. It is noteworthy that no products derived from endocyclic π-allyl palladium intermediates (not shown in Scheme 2), which could be formed by the hydrogen abstraction from C-3 or C-6, were observed in appreciable amounts at the oxidation of *β*-caryophyllene. The tendency in regioselectivity at the interaction of the endocyclic double bond with palladium and also such a great difference in the reactivity of allylic hydrogens in the molecule of *β*-caryophyllene are surprising. On the one hand, the formation of intermediate **A** follows a Markovnikov-type orientation; that is, involving the hydrogen allylic to the more substituted end of the olefinic bond. On the other hand, a strong preference for the hydrogen abstraction from acyclic carbon C-12 rather than from endocyclic carbon C-3 is remarkable taking into account a usually observed so-called “cyclic activation”, which is the enhanced reactivity of cyclic allylic hydrogens compared to acyclic ones. Such a “cyclic activation” has been previously observed in the palladium catalyzed allylic functionalizations of limonene [14, 43], α-bisabolol [18] and β-ionone [44] in related systems, resulting in the preferential formation of the products derived from corresponding endocyclic rather than exocyclic π-allyl palladium intermediates.

The subsequent nucleophilic attack of acetic acid on π-allyl palladium intermediate **A** results in the formation of two allylic acetates. Linear allylic acetate **3** is formed by nucleophilic addition expectedly directed to less hindered carbon C-12. However, acetate **3** is the minor product; whereas the major product is branched allylic acetate **2**, in which the acetate group bonds to more substituted endocyclic carbon C-5. In principle, the attack of acetic acid on intermediate **A** could occur on both faces of the nonane ring to give in the case of product **2** two steric isomers with different geometry at carbon C-5 with respect to the hydrogens at shared carbons C-1 and C-9. A strong effect of reaction variables on the regioselectivity at palladium catalyzed allylic oxidations is well known [42,45–47]. In particular, it was reported that terminal alkenes could be selectively oxidized to either linear or branched allylic acetates in different solvents and with different palladium catalysts [45].

Among the C-C double bonds of *β*-caryophyllene, the endocyclic one is much more reactive towards palladium species, determining the structure of the oxidation products. The products that could be derived from the oxidation of the terminal double bond were not detected in appreciable amounts. The analysis of a 3-D ball-and-stick model of β-caryophyllene reveals that its structure is highly conformationally strained and both double bonds are sterically encumbered; nevertheless, the reasons for such low reactivity of the terminal double bond compared to the endocyclic one are not straightforward. On the other hand, it is noteworthy that in most previously reported catalytic [29,30,34] and even non-catalytic [10] transformations of β-caryophyllene the endocyclic double bond reacted first; for example, in catalytic epoxidation [29,30] and hydroformylation [34] reactions. It seems reasonable to suggest that this preference is due to the weakness of the ring strain during the reactions in which the endocyclic double bond is involved [10]. The analysis of the models of caryophyllane compounds supports this suggestion showing that the structures with no double bond in the nonane ring are much less rigid than *β*-caryophyllene itself or its ring unsaturated derivatives. Thus, the high site-selectivity observed at the palladium catalyzed oxidation of *β*-caryophyllene seems to be determined by steric factors related to the attenuation of ring strain in the original molecule. We also suggest that these factors could be responsible for the regio-selectivity observed at the oxidation of the endocyclic double bond with the preferential formation of acetate **2**, which contains a saturated ring system, differently from minor acetate **3**. Moreover, all the products which could be derived from endocyclic π-allyl palladium intermediates (mentioned above) would also contain endocyclic double bonds and therefore would have much more rigid structures than acetate **2**. Probably for this reason, such products are not formed at the palladium catalyzed oxidation of β-caryophyllene in our systems. An interesting example of the site-selectivity control at the palladium catalyzed oxidation of limonene in related systems has been recently reported by Czapiewski et.al [47]. In acetic acid solutions, the products derived from the oxidation of the endocyclic olefinic bond were mainly obtained; whereas, the addition of dimethyl sulfoxide allowed for the selective oxidation of the exocyclic disubstituted terminal double bond.

4. Conclusions

The oxidation of the abundant, naturally occurring β-caryophyllene represents an attractive entry to fragrant and biologically active compounds. Herein, we developed a novel selective oxidation of *β*-caryophyllene by molecular oxygen using a chloride-free $Pd(OAc)_2$/*p*-benzoquinone catalytic system. The endocyclic double bond in the β-caryophyllene molecule unexpectedly showed much higher reactivity than the terminal one. The reaction gave two main products, both arising from the allylic oxidation of the sterically encumbered endocyclic double bond, whereas the terminal double bond of the substrate remained intact. We suppose that steric factors related to the attenuation of ring strain in the original molecule are mainly responsible not only for the high site-selectivity at the oxidation of *β*-caryophyllene, but also for the regio-selectivity observed at the oxidation of its endocyclic double bond.

The catalytic process efficiently operates under 10 atm of oxygen in the absence of auxiliary metal co-catalysts, which are conventionally used in related systems. The reaction can also occur under atmospheric pressure in the presence of $Cu(OAc)_2$ to accelerate the re-oxidation of *p*-hydroquinone by molecular oxygen. Both allylic acetates obtained from *β*-caryophyllene are natural compounds found in essential oils of some plants and have well pronounced perfume properties. To the best of our knowledge, the present work reports the first synthesis of these functionalized sesquiterpenic compounds potentially useful as components of synthetic perfumes and pharmacological compositions.

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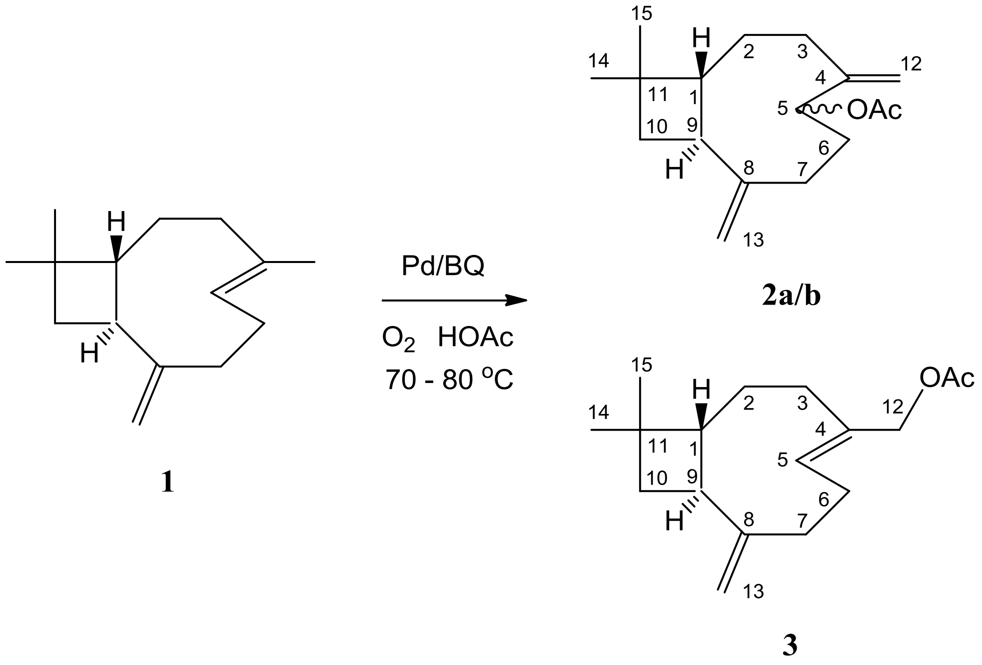
Scheme and Table captions

Scheme 1. Oxidation of *β*-caryophyllene.

Scheme 2. Proposed mechanistic scheme for the palladium catalyzed oxidation of *β*-caryophyllene.



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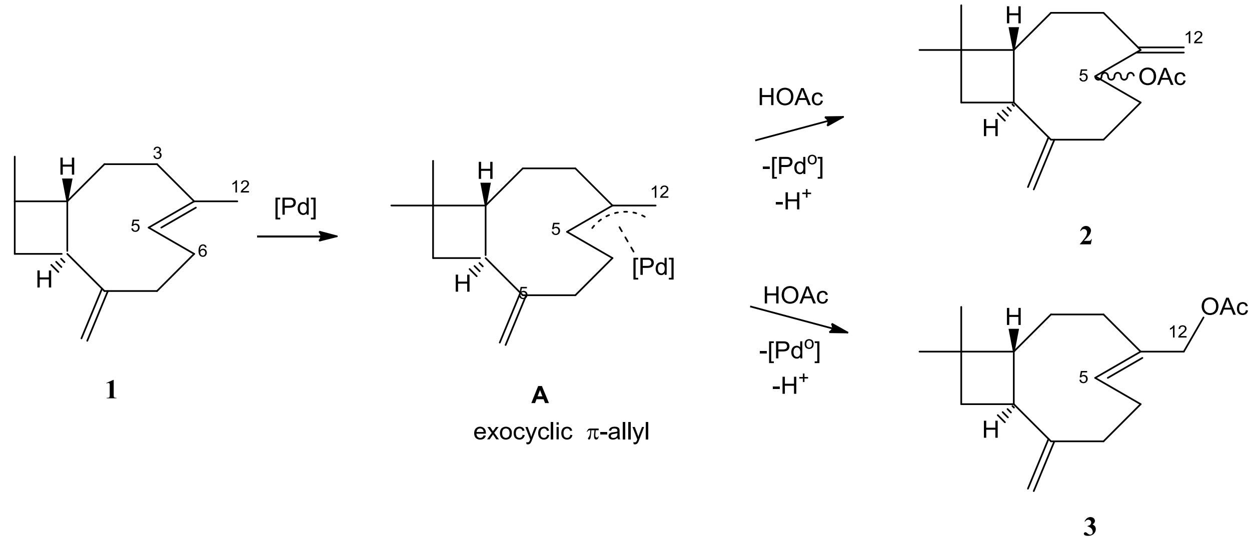

Scheme 2. Proposed mechanistic scheme for the palladium catalyzed oxidation of *β*-caryophyllene.

Table 1

Oxidation of β-caryophyllene (**1**) with various catalytic systems[a]

Run	Pd catalyst (M)	Co-catalyst (M)	Solvent	T (°C)	P (atm)	Time (h)	C (%)	Selectivity for the products of (%)		
								oxidation	isomerization	addition
1[b]	$PdCl_2$ (0.02)	$CuCl_2$ (0.05)	HOAc	70	1	3	96	traces	38	62
2[b]	none	$CuCl_2$ (0.05)	HOAc	70	1	3	92	0	40	60
3[c]	$PdCl_2$ (0.01)	none	DMA	80	10	6	15	0	100	0
4[c]	$PdCl_2$ (0.02)	none	DMA	80	10	6	28	0	100	0
5[d]	$PdCl_2$ (0.02)	none	DMA	80	10	6	20	0	100	0
6[c]	none	none	DMA	80	10	6	5	0	100	0

[a] Conditions: [β-caryophyllene] = 0.20 M, gas phase – O_2. Conversion (C) and selectivity were determined by GC and calculated based on the consumed β-caryophyllene; [b] [LiCl] = 0.17 M. [c] DMA – dimethylacetamide; 20 vol% of water was added. [d] 10 vol% of water was added.

Table 2

Oxidation of β-caryophyllene (**1**) catalyzed by $Pd(OAc)_2$ [a]

Run	[BQ]	$Cu(OAc)_2$	*T*	*t*	Conversion	Selectivity (%)		Initial rate
	(M)	(M)	(°C)	(h)	(%)	**2**	**3**	($M\ h^{-1}$)
1	0.20	none	70	3	75	70	15	0.08
				7	95	65	16	
2	0.20	none	80	3	94	62	18	0.12
				4	98	60	20	
3	0.20	none	90	3	95	60	16	0.14
				5	98	48	14	
4	0.20	0.05	80	3	92	69	21	0.12
				4	99	59	23	
5	0.10	0.05	70	3	55	80	10	0.04
				10	78	71	13	
6	0.10	0.05	80	3	60	72	10	0.06
				8	80	68	14	
7	0.10	0.05	90	4	94	60	20	0.10
				6	100	50	25	
8	0.05	0.05	80	3	60	72	10	0.04
				10	95	65	15	
9	0.05	0.05	90	4	88	61	18	0.07
				6	96	54	20	
10	0.05	0.025	80	3	37	75	10	0.02
				10	82	66	14	
11[b]	0.05	0.05	80	3	62	83	12	0.04
				10	96	75	15	
12[c]	0.05	0.05	80	3	25	75	7	0.02
				10	64	65	11	
13[c]	0.05	0.05	90	4	60	65	15	0.04
				8	92	50	20	

[a] Conditions: solvent – HOAc, [β-caryophyllene] = 0.20 M, [$Pd(OAc)_2$] = 0.01 M, gas phase – O_2, 1 atm. Conversion and selectivity were determined by GC and calculated based on the consumed substrate. Initial reaction rates were calculated at low conversions (up to 20–40%). [b] [$Pd(OAc)_2$] = 0.02 M.

[c] $Pd(OAc)_2$] = 0.005 M.

Table 3

Oxidation of *β*-caryophyllene (**1**) with molecular oxygen catalyzed by Pd(OAc)$_2$/*p*-benzoquinone (BQ)[a]

Run	[BQ] (M)	*T* (°C)	*t* (h)	Conversion (%)	Selectivity (%)		Initial rate (M h^{-1})
					2	**3**	
1	0.10	80	3	77	50	17	0.06
			4	96	45	15	
2	0.10	70	3	53	65	11	0.04
			8	100	56	16	
3	0.10	60	3	45	70	11	0.03
			24	100	66	11	
4	0.10	50	3	27	72	10	0.02
			24	85	70	11	
5	0.05	80	3	62	50	17	0.04
			6	96	47	15	
6	0.05	70	3	45	63	9	0.03
			8	90	59	11	
7	0.05	60	3	35	72	13	0.02
			10	85	68	12	
8[b]	0.05	70	3	60	65	10	0.05
			6	95	55	15	

[a] Conditions: solvent – HOAc, [*β*-caryophyllene] = 0.20 M, [Pd(OAc)$_2$] = 0.01 M, gas phase – O$_2$, 10 atm. Conversion and selectivity were determined by GC and calculated based on the consumed substrate. Initial reaction rates were calculated at low conversions (up to 20–40%). [b] [Pd(OAc)$_2$] = 0.02 M.