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Palladium catalyzed oxidation of renewable terpenes with molecular oxygen: oxidation of α-bisabolol under chloride-free conditions

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Abstract. The palladium/*p*-benzoquinone catalyzed aerobic oxidation of α-bisabolol, a bio-renewable substrate with a strong therapeutic potential available from various essential oils, has been developed. The reaction gives three main products arising from the oxidation of sterically encumbered trisubstituted double bonds of the substrate, either endocyclic or exocyclic or both together. Novel poly-functionalized sesquiterpenoids obtained with high combined selectivity at the oxidation of α-bisabolol are potentially useful as components of synthetic perfumes, cosmetics and pharmaceuticals. The system promotes an efficient dioxygen-coupled catalytic turnover in the absence of auxiliary redox-active co-catalysts under superatmospheric oxygen pressure. Alternatively, the reaction can be performed at atmospheric pressure in the presence of the catalytic amounts of cupper acetate as an electron transfer mediator for the regeneration of BQ during the catalytic cycle.

Keywords: α-Bisabolol; Oxidation; Oxygen; Palladium; Terpenoids

Introduction

Terpenes constitute a class of natural products available from essential oils of many plants and fruits. These substances represent an important renewable feedstock for flavor and fragrance and pharmaceutical industries.[1,2] For example, α-bisabolol (also known as levomenol), a monocyclic sesquiterpenic alcohol with a pleasant floral-sweet aroma, has demonstrated a strong therapeutic potential due to its biological activity including anti-inflammatory, anti-irritant, anti-bacterial, gastric-protective, analgesic and non-allergenic properties.[3–6] This compound is available from essential oils of various plants like chamomile (*Matricaria chamomilla*), candeia (*Eremanthus erythropappus*) and sage (*Salvia runcinata*) oils, which may contain up to 50, 85 and 90% of α-bisabolol, respectively.[3,4,6] However, most α-bisabolol on the market is produced synthetically from other terpenic compounds such as farnesol and nerolidol.[7–9] Although α-bisabolol is itself a fragrance and pharmacological ingredient and can be found in many fine fragrances, dermatological formulations, decorative cosmetics, shampoos and other toiletries;[5,6] the use of this compound can be significantly extended by its oxyfunctionalization. Natural and synthetic derivatives of α-bisabolol are known to present therapeutic properties also, in particular, anti-inflammatory and anti-tumor activities.[7,10,11] Therefore, the catalytic oxidation of the olefinic bonds in α-bisabolol could represent a valuable route to oxygenated bisabolane compounds potentially interesting for pharmaceutical and fragrance industries.

Palladium catalyzed oxidations of olefins with molecular oxygen represent a convenient well-established route to a variety of commercially important compounds. These reactions usually require the presence of co-oxidants for the re-oxidation of reduced palladium species, with $CuCl_2$ being the most common one (Wacker catalyst).[12] However, the Wacker system is highly corrosive because large amounts of chloride ions and acid should be used to maintain the catalytic cycle. Various alternative environmentally more friendly halide-free co-oxidants have been intensively studied to replace $CuCl_2$, such as $Cu(OAc)_2$, heteropoly acids, nitrates, and benzoquinone.[13–19] For some olefins, the use of coordinating solvents and oxidatively robust ligands allows to stabilize reduced palladium species in the solution and promote their regeneration directly by molecular oxygen without the use of co-oxidants.[20–26]

p-Benzoquinone (BQ) readily re-oxidizes zerovalent palladium and can be a valuable synthetic alternative to $CuCl_2$; however, the oxidation of *p*-hydroquinone (BQH_2) by molecular oxygen back to

BQ is a slow reaction. Various transition metal catalysts, such as cobalt and manganese salts, have been used to accelerate this process and recycle BQ in palladium catalyzed oxidations.[27–30] In particular, we have performed the aerobic oxidation of limonene using the $Pd(OAc)_2$/BQ/$Cu(OAc)_2$ catalytic system in which $Cu(OAc)_2$ acts as an electron transfer mediator in the oxidation of BQH_2 by molecular oxygen.[16] Recently, we have found that under superatmospheric oxygen pressure BQ can be recycled even in the absence of auxiliary redox-active co-catalysts allowing to obtain dioxygen-coupled turnovers with catalytic amounts of BQ.[31]

For several years, we have been interested in palladium catalyzed oxidations of terpenes in attempts to add value to these cheap natural products.[16–19,31–33] The most abundant terpenes, such as limonene, camphene and myrcene, were used as substrates in our early works. Then, we began to involve in these reactions functionalized terpenic molecules, such as linalool, α-terpineol and nerolidol, to obtain oxygenated products with several functional groups, which would be hardly accessible by conventional synthetic routes.[19,31,33]

The aim of the present study was to investigate the applications of palladium(II) compounds in combination with reversible co-oxidants as catalysts for the homogeneous oxidation of α-bisabolol (**1**) with molecular oxygen. The co-oxidants used were copper(II) salts and *p*-benzoquinone. To the best of our knowledge, the palladium catalyzed oxidation of α-bisabolol has not been studied hitherto. Moreover, we could found in the literature only a few reports on the catalytic oxidation of α-bisabolol in general, with all the works using hydrogen peroxide or peroxo compounds as final oxidants to obtain bisabolol oxides or allylic ketones.[34,35] All bisabolane derivatives obtained in the present work are novel compounds and are potentially useful for cosmetic and pharmaceutical applications.

Results and Discussion

The conventional Wacker catalytic system promotes a rapid conversion of α-bisabolol (**1**) giving numerous products, none of them with appreciable selectivity. Under standard conditions ($PdCl_2$ – 5 mol %, $CuCl_2$ – 10 mol %, HOAc, 80°C, 1 atm), nearly 70% of α-bisabolol reacted for the first hour resulting in a mixture of more than ten products. Some of these products showed the same GC retention times as those formed in the absence of palladium, with $CuCl_2$ alone. The attempts to vary reaction temperature and catalyst concentrations did not bring encouraging results in terms of reaction selectivity. Due to the difficulty of separation and complex composition of the crude product, the structures of these numerous compounds were not clarified. Instead, we decided to invest in the development of $CuCl_2$-free catalysts.

Representative results on the palladium catalyzed oxidation of α-bisabolol with BQ are shown in Table 1. The reaction readily occurred at 60 °C in the presence of 5 mol% of $Pd(OAc)_2$ and 1 equiv of BQ, with a half of the substrate being converted for the first two hours (run 1 in Table 1 and Figure 1). Then the conversion became nearly stagnated with no palladium mirror being observed on the walls of the glass reactor. Two main reaction products, compounds **2** and **3**, were detected with ca. 80% combined selectivity along with a minor product, compound **4**, formed in ca. 10% selectivity. At 80 °C, the reaction was faster resulting in a 66% conversion for the first hour, then the reaction also slowed down drastically (run 2 in Table 1 and Figure 1). Products **2** and **3** accounted for ca. 80% of the mass balance after the first hour then their concentrations gradually decreased whereas the amounts of product **4** increased. The combined selectivity for products **2**, **3** and **4** was maintained at ca. 90% in the course of both runs.

Table 1. Oxidation of α-bisabolol with benzoquinone (BQ) catalyzed by $Pd(OAc)_2$.[a)]

Run	[BQ]	*T*	*t*	*C*[a)]	Selectivity for products **2**, **3** and **4**[a)] (%)			
	(M)	(°C)	(h)	(%)	**2**	**3**	**4**	Total
1	0.2	60	2	52	44	38	9	91
			5	58	46	32	12	90
2	0.2	80	1	66	44	32	16	92
			10	77	36	24	33	93
3[b)]	0.2	80	1	71	40	34	15	89
			5	95	26	20	47	93
4	0.4	80	1	75	41	29	20	90
			4	95	22	16	54	92
			10	99	13	8	72	93
5	0.2	100	1	76	37	27	23	87
			6	95	22	15	44	81

[a)] Conditions: solvent – HOAc, [α-bisabolol] = 0.20 M, [$Pd(OAc)_2$] = 0.01 M, gas phase – O_2, 1 atm. Conversion (C) and selectivity were determined by GC and calculated based on the consumed substrate. [b)] A new portion of BQ (0.2 M) was added to the reaction solution after 1 h.

Products **2**, **3** and **4** were isolated from the reaction solutions by column chromatography and identified by GC-MS and NMR spectroscopy. Their structures are shown in Scheme 1 and Figures 2–5 (Experimental Section). The major product **2** results from the oxidation of the exocyclic trisubstituted olefinic bond of the α-bisabolol molecule with the participation of the tethered hydroxyl group to give a tetrahydrofuran ring. The second product, allylic acetate **3**, arises from the allylic oxidation of the endocyclic double bond. Judging from the structure of compound **4**, it results from the oxidation of both olefinic bonds of the substrate. Product **4** accumulates in the solutions at longer reaction times at the expense of primarily formed products **2** and **3**.

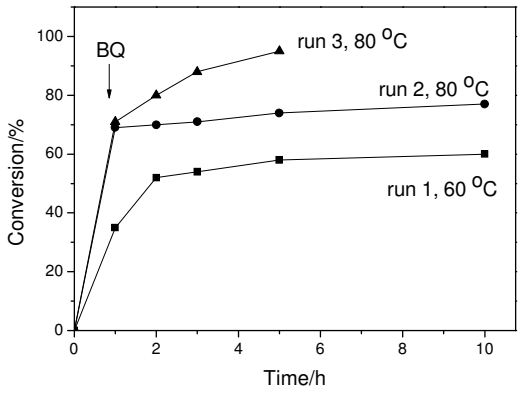
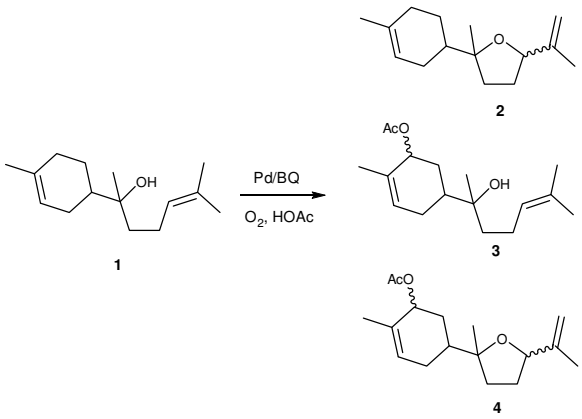


Figure 1. Palladium catalyzed oxidation of α-bisabolool with benzoquinone (BQ). Curves numbering corresponds to the runs in Table 1. Conditions: solvent – HOAc, [α-bisabolol] = 0.20 M, $[Pd(OAc)_2]$ = 0.01 M, [BQ] = 0.2 M gas phase – O_2, 1 atm. In run 3, a new portion of BQ (0.2 M) was added to the reaction solution after 1 h.



Scheme 1. The products of the palladium catalyzed oxidation of α-bisabolol.

Both compounds **2** and **3** were isolated as the mixtures of two isomers. The isomers were not separable by GC under the conditions used and showed similar NMR spectra (see Experimental Section). The isomers of compound **2** probably differ from each other by the configuration at carbon C-12 as the greatest difference in chemical shifts is observed for carbon C-12 ($\Delta \doteq 2.17$ ppm vs. ≤ 0.4 ppm for all other carbons). On the other hand, the isomers of compound **3** are expected to differ by the stereochemistry at carbon C-6.

Compound **4** was formed as a mixture of four isomers **4a**, **4b**, **4c**, and **4d**, with their ratio in most of the runs being of ca. 6:3:2:1. Isomers **4a** and **4b** were partially separable by GC under the conditions used and were isolated from the reaction solution as a mixture (**4a**:**4b** ≈ 2:1). Isomers **4c** and **4d** were not GC separable and were isolated also as a mixture (**4c**:**4d** ≈ 2:1). The attributions of the NMR signals are presented in Figures 4 and 5 (Experimental Section). Methyl hydrogens H-9 in **4c** (singlet at 1.15 ppm) give a strong NOE correlation signal with hydrogen H-12 (triplet at 4.38 ppm) suggesting for **4c** a *cis* configuration at C-12 and C-8, in which hydrogen H-12 and methyl group C-9 are at the same side of the tetrahydrofuran ring. No conclusive NOESY data were obtained on the stereochemistry at carbon C-6. We have also failed to determine the stereochemistry of isomers **4a** and **4b** due to signal overlapping in their NMR spectra. Although the same difficulty has been found in clarifying the difference between the isomers of products **2** and **3**, it seems reasonable to suggest that each pair is a couple of diastereoisomers with different configurations at new asymmetric centers which appear in the course of the reaction (C-12 in **2** and C-6 in **3**).

The identification of the reaction products revealed why the reactions with 1 equiv of BQ became stagnated at incomplete substrate conversions: as the formation of product **4** requires 2 equiv. of BQ and regeneration of BQ is not efficient, the reactions have been interrupted due to the lack of BQ. Really, the addition of BQ before the reaction stagnation allowed to complete the substrate conversion (run 3 in Table 1 and Figure 1). The combined selectivity for products **2**, **3** and **4** was 93% at a 95 % conversion, with product **4** accounting for a nearly half of the mass balance. Performing the reaction directly with 2 equiv of BQ, we were very pleased to observe that most of the primarily formed products **2** and **3** were transformed in the double-oxidation product **4** without the decrease in the total selectivity (Table 1, run 4). The reaction at 100 °C and atmospheric pressure was nearly completed with even sub-stoichiometric amounts of BQ (1 equiv); however, the selectivity for the allylic oxidation decreased to 81% (Table 1, run 5).

Thus, the palladium catalyzed oxidation of α-bisabolol in our system results in the products of the oxidation of the sterically encumbered trisubstituted exocyclic double bond and intramolecular cyclization. Simultaneously, the allylic oxidation of the endocyclic double bond occurs, albeit at a lower rate. It is important that mono-oxidation products **2** and **3** readily undergo the second oxidation to give poly-functionalized sesquiterpene compound **4**. All three novel compounds **2**, **3** and **4** still contain two carbon-carbon double bonds and can, therefore, be further involved in a variety of catalytic reactions (e.g., hydroformylation and carbonylations) to give other interesting products.

In blank reactions, with no $Pd(OAc)_2$ and BQ added or with BQ alone, no formation of products **2**, **3** and **4** was observed as expected. The reactions presented in Table 1 showed catalytic turnovers in palladium; however, they required stoichiometric amounts of BQ. Our further efforts were therefore directed to find appropriate conditions for the effective oxidation of BQH_2 by molecular oxygen to regenerate BQ and to use this reagent in catalytic amounts.

We have found that in the presence of copper acetate as additional electron transfer mediator, the reaction can be performed with a dioxygen coupled catalytic turnover under atmospheric pressure of molecular oxygen (Table 2, runs 1–6). The solutions of α-bisabolol in acetic acid containing $Pd(OAc)_2$, $Cu(OAc)_2$ and BQ in catalytic amounts readily consume molecular oxygen, which indicates the effective regeneration of BQ. At 80 °C, the combined selectivity for **2**, **3** and **4** was nearly 90% up to ca. 90% substrate conversion (Table 2, run 1). At 100 °C, the reaction was much faster; however, selectivity decreased from 90% during the first half of the reaction to 73% at the end (Table 2, runs 3 and 5). The reaction can be performed with even less amounts of $Cu(OAc)_2$ and BQ without a significant impact on the initial rate (Table 2, runs 4 and 5). However, at higher substrate conversions the reaction occurs slower at lower BQ and $Cu(OAc)_2$ concentrations (Table 2, run 1 vs. runs 3 and 4). It seems that BQ, which acts as a ligand in palladium systems,[15] influences the interaction between palladium and α-bisabolol as in all the runs with sub-stoichiometric amounts of BQ the selectivity decreases at higher substrate conversions when the BQ concentration becomes low or even negligible. The results of the run with 0.1 equiv of BQ (Table 2, run 6) collaborate with the suggestion that the presence of BQ during the whole catalytic reaction is important for the reaction selectivity. In this run, only 75% selectivity was observed from the beginning (at 25% conversion), probably, due to the lack of BQ. Palladium complexes without the coordinated BQ seem to promote the undesirable transformations of the substrate and/or over-oxidation of products **2**, **3** and **4**.

Table 2. Oxidation of α-bisabolol with molecular oxygen catalyzed by $Pd(OAc)_2$/benzoquinone (BQ).[a)]

Run	[BQ]	[$Cu(OAc)_2$]	*T*	Time	Conversion[a)]	Selectivity for products **2**, **3** and **4**[a)] (%)				TOF[a)]
	(M)	(M)	(°C)	(h)	(%)	**2**	**3**	**4**	Total	(h^{-1})
1	0.1	0.05	80	8	86	30	25	36	91	8
					93				85	
2	0.1	0.05	100	1	65	43	35	14	92	13
				2	77	35	30	19	84	
				3	93	24	19	30	73	
3	0.05	0.05	80	12	90	27	21	42	90	6
4	0.05	0.025	80	8	75	35	28	27	90	7
				12	85	30	23	27	80	
5	0.05	0.025	100	3	84	30	22	29	81	16
				5	96	18	13	45	76	
6	0.02	0.025	80	1	25	45	28	2	75	5
				4	50	39	28	22	78	
				8	70	32	24	18	74	
7[b)]	0.05	0.025	100	6	347	50	14	-	64	2
8[c)]	0.02	none	60	21	85	37	27	28	92	4
9[c)]	0.02	none	80	7	80	38	24	18	80	6

[a)] Conditions: solvent – HOAc, [α-bisabolol] = 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 rate of the α-bisabolol conversion per mol of Pd (turnover frequency, TOF) is presented. [b)] Na_2PdCl_4 was as the catalyst (0.01 M). [c)] 10 atm.

The ligand effect became even more pronounced when $Pd(OAc)_2$ was substituted by Na_2PdCl_4: much lower selectivity for products **2** and **3** was obtained in the reaction with Na_2PdCl_4 (Table 2, run 7 vs. run 5). In addition, the reaction with Na_2PdCl_4 occurred at a much lower rate than that with $Pd(OAc)_2$. A possible explanation could be a lower reactivity of α-bisabolol towards palladium in the presence of strongly coordinating chloride ligands and higher stability of π-allyl palladium chlorides compared to π-allyl palladium acetates, which are known to be much more prone to collapse to allylically substituted products.[36]

Thus, it became clear that to maintain the high selectivity in the reaction with sub-stoichiometric amounts of BQ, the reaction should be performed under the conditions allowing the fast re-oxidation of BQH_2. In previous works we have found that under superatmospheric oxygen pressure (5–10 atm) BQH_2 can be rapidly oxidized back to BQ in the absence of auxiliary redox-active co-catalysts.[31,37] These results were successfully applied to the oxidation of α-bisabolol (Table 2, runs 8 and 9). In the reaction with only 0.1 equiv of BQ, the selectivity of 80–90% was maintained up to 80–85% substrate conversion suggesting the effective regeneration of BQ. The reactions in runs 8 and 9 were catalytic in both palladium and BQ and showed a dioxygen-coupled catalytic turnover, with no palladium mirror being observed on the walls of the autoclave. This result could also be explained by the stabilization of Pd(0) species towards aggregation by the BQ ligand and their re-oxidation directly by molecular oxygen. However, the hypothesis that the catalytic cycle is

maintained due to the re-oxidation of BQH_2 seems for us more reasonable as we have previously found that the reaction of the oxidative aromatization of some monoterpenes by molecular oxygen can be catalyzed by BQ alone in the absence of palladium.[37] In other words, in that process under the conditions similar to those used in the present work, BQ was effectively regenerated by molecular oxygen.

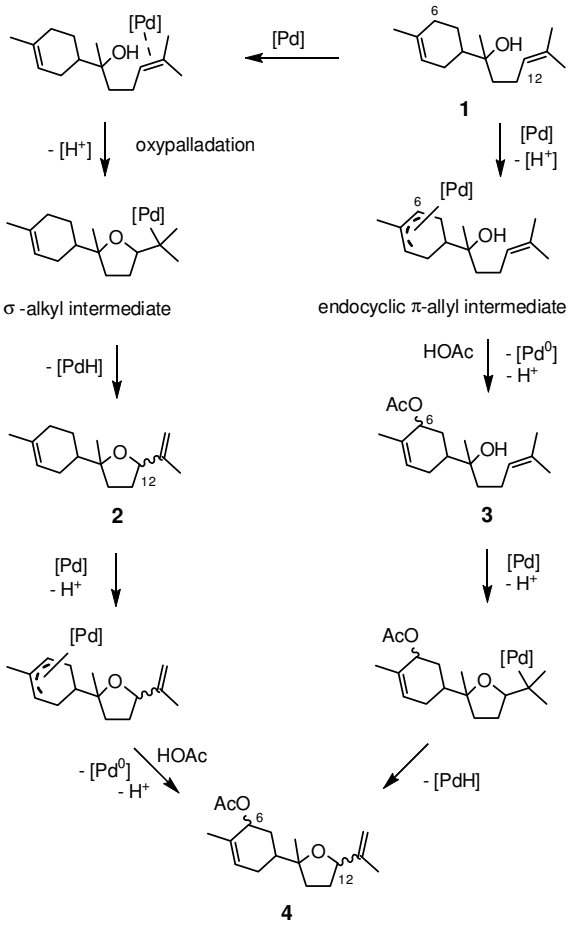
The formation of main reaction products can be rationalized within a mechanistic scheme presented in Scheme 2. The structure of major product **2** implies that this compound arises from the interaction of the exocyclic internal double bond with palladium followed by the cyclization of the molecule. Product **3** is the result of the allylic oxidation of the endocyclic double bond and product **4** arises from the oxidation of both olefinic bonds in the α-bisabolol molecule.

The palladium catalyzed oxidative cyclization of alkenes bearing a hydroxyl group at an appropriate distance from the C=C bond is generally accepted to proceed through an oxypalladation step.[38-43] The intramolecular nucleophilic attack of the hydroxyl group on the palladium coordinated alkene gives a σ-alkyl palladium intermediate having a tetrahydrofuran ring (Scheme 2). A subsequent β-hydrogen elimination results in two isomers of compound **2**, probably, with different geometry at carbon C-12.

On the other hand, the pathway leading to allyl acetate **3** more probably occurs through the formation an endocyclic η^3-allyl palladium intermediate due to the hydrogen removal from the CH_2 group (Scheme 2). Palladium is usually considered to be the catalyst of choice for the allylic oxidation of olefins and dienes.[29] The accepted mechanism of these reactions involves π-allyl palladium complexes as key intermediates; thus, it seems reasonable to suggest their formation in the case of α-bisabolol. The nucleophilic attack of the acetate group on the π-allyl intermediate gives allyl acetate **3**. In principle, this attack could occur on both faces of the cyclohexane ring resulting in two steric isomers of acetate **3** with different geometry at carbon C-6. The allylic hydrogen could be also removed from the CH_3 group forming in this case an exocyclic π-allyl intermediate. However, no products derived from the nucleophilic attack on the acyclic terminal carbon atom have been detected in appreciable amounts. The acetalylation of α-bisabolol occurred regioselectively at the endocyclic position.

In a further reaction, both products **2** and **3** undergo a second oxidation through the corresponding η^3-allyl or σ-alkyl palladium intermediates shown in Scheme 2 to give the double oxidation product – compound **4**.

It is noteworthy that the trisubstituted exocyclic double bond of the α-bisabolol molecule exhibited higher reactivity than the endocyclic bond as in all the runs product **2** was formed in larger amounts than product **3**. Although the endocyclic double bond is trisubstituted as well, it is expected to be more reactive due to a so-called "cyclic activation", which is the enhanced reactivity of cyclic allyl hydrogens compared to acyclic ones. Internal acyclic non-functionalized olefins usually show extremely low reactivity and selectivity in Wacker-type oxidations with only few successful examples being published so far.[24] The presence of the hydroxyl group in γ-position in the α-bisabolol molecule allowed to involve the internal exocyclic double bond in the interaction with palladium leading to heterocyclic compounds **3** and **4**.



Scheme 2. Proposed mechanism of the palladium catalyzed oxidation of α-bisabolol.

In attempts to extend the reaction scope, we have tested the reactivity of citronellol under the conditions used for α-bisabolol in run 5 in Table 2 (Scheme 3). Citronellol (3,7-dimethyloct-6-en-1-ol) is a monoterpenic alcohol having a fragment with a trisubstituted exocyclic double bond similar to that of α-bisabilalol and also a hydroxyl group, albeit at a longer distance from the C=C bond. However, no oxidation of citronellol was observed revealing the importance of the other part of the α-bisabolol molecule (most probably, the position of the hydroxyl tether) for the activation of the exocyclic double bond.

Conclusion

In summary, a novel selective Pd^{2+}/BQ catalyzed oxidation of α-bisabolol by molecular oxygen under chloride-free conditions has been developed. α-Bisabolol is a bio-renewable substrate with a strong therapeutic potential available from various essential oils. The reaction is highly selective and gives the products arising from the oxidation of sterically encumbered internal exocyclic or endocyclic double bonds of the substrate or both double bonds together. The trisubstituted exocyclic double bond of the α-bisabolol molecule undergoes the oxidation due to the presence of the hydroxyl group in γ-position and shows even higher reactivity than the endocyclic double bond.

Novel poly-functionalized sesquiterpenoids obtained at the oxidation of α-bisabolol are potentially useful as components of synthetic perfumes, cosmetics and pharmaceuticals. At 10 atm of oxygen pressure, dioxygen-coupled catalytic turnovers can be achieved in the absence of auxiliary redox-active co-catalysts, which are usually applied in conventional palladium-based catalytic systems. Alternatively, the reaction can be performed under atmospheric pressure in the presence of catalytic amounts of cupper acetate as an electron transfer mediator for the effective regeneration of BQ during the catalytic cycle. We suppose that the results obtained herein can open new possibilities to convert stoichiometric synthetic procedures in which benzoquinones are used as oxidants into catalytic processes with molecular oxygen being used as a final oxidant.

Experimental Section

All reagents were purchased from commercial sources and used as received. $CuCl_2 \cdot 2H_2O$ and LiCl were dehydrated by heating. Glacial acetic acid was used as a solvent. *p*-Benzoquinone was purified by column chromatography (silica) using dichloromethane as the eluent. Natural α-(-)-bisabolol extracted from candeia (*Eremanthus erythropappus*) was used as the substrate (from CITROLEO Ind. Com. Oleos Essenciais).

The reactions at atmospheric pressure were carried out in a magnetically stirred glass reactor equipped with a condenser and followed by measuring the oxygen uptake (if any) and by gas chromatography (GC). The reactions at higher pressures were carried out in a magnetically stirred stainless steel 100-mL autoclave and followed by GC using a sampling system. In a typical run, the solution of the substrate, palladium and copper (if any) complexes, BQ (if any), and dodecane (internal standard, 0.10 M) in acetic acid (20 mL) was transferred in the reactor. The concentrations of the components are given in the Tables. The autoclave was pressurized with oxygen to a total pressure indicated in the Tables. The reactor was placed in an oil bath; then, the solutions were stirred at a specified temperature. At appropriate time intervals, aliquots were taken via a special sampling system without depressurization of the reactor and analyzed by GC using a Shimadzu 17A instrument fitted with a Carbowax 20 m capillary column and a flame ionization detector. After carrying out the reaction and cooling to room temperature, the excess of oxygen was slowly vented from the reactor. Relative GC response factors were determined using isolated reaction products. A GC mass balance was based on the substrate charged using dodecane as the internal standard. The difference was attributed to the formation of high-boiling products, which were not GC determinable.

The products were isolated by a column chromatography (silica gel 60) using mixtures of hexane and CH_2Cl_2 as eluents and identified by ^1H and ^{13}C-NMR and/or GC-MS (Supplementary information, Figures S1–S5). NMR spectra were recorded in $CDCl_3$ using a Bruker 400 MHz spectrometer, with TMS as an internal standard (DEPT, COSY, HMQC, HMBC and NOESY experiments). Mass spectra were obtained on a Shimadzu QP2010-PLUS instrument operating at 70 eV.

Compound **2** (new compound): MS (70 eV, EI): *m/z* (%): 220 (1) [M^+], 187 (1) [M^+–H_2O–CH_3], 132 (17), 125 (100), 107 (50), 95 (14), 93 (13), 67 (17). For NMR data see Figure 2. Two isomers (not GC separable) were observed in the NMR spectra.

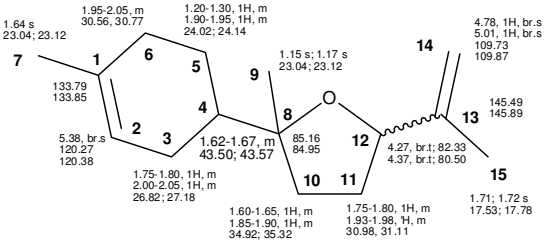


Figure 2. NMR data for product **2** (two isomers).

Compound **3** (new compound): MS (70 eV, EI): m/z (%): 220 (13) [M^+–HOAc], 202 (3) [M^+–HOAc–H_2O], 187 (4) [M+–HOAc–H_2O–CH_3], 109 (100), 94 (65), 93 (55), 79 (57), 69 (95), 44 (73). For NMR data see Figure 3. Two isomers (not GC separable) were observed in the NMR spectra.

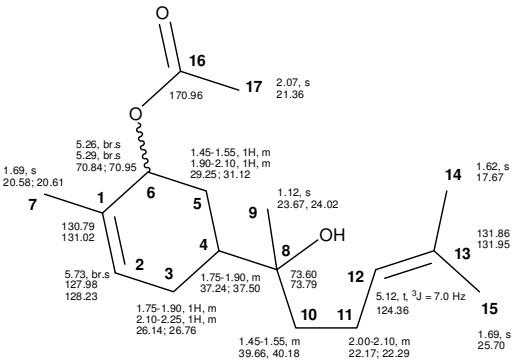


Figure 3. NMR data for product **3** (two isomers).

Compound **4** (new compound, four isomers **4a**–**4d**): **4a**: MS (70 eV, EI): *m/z* (%): 278 (1) [M^+], 132 (25), 125 (100), 107 (41), 93 (16); **4b** (longer retention time than **4a**): MS (70 eV, EI): *m/z* (%):278 (1) [M^+], 132 (16), 125 (100), 107 (43), 93 (11); **4c** and **4d** (not CG separable, longer retention time than **4b**): MS (70 eV, EI): *m/z* (%):132 (22), 125 (100), 107 (40), 93 (12). For NMR data of **4a** and **4b** isolated as a mixture see Figure 4. For NMR data of **4c** and **4d** isolated as a mixture see Figure 5.

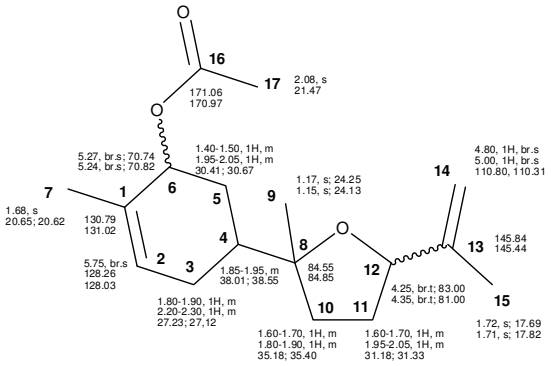


Figure 4. NMR data for compound **4** (isomers **4a** and **4b**).

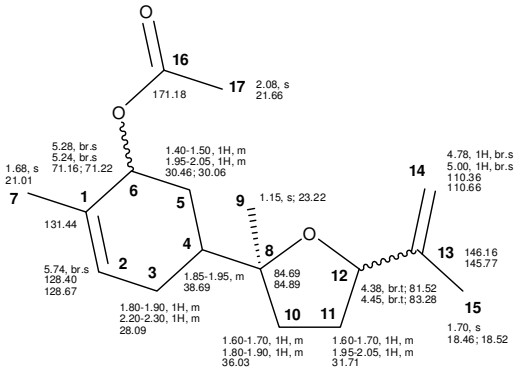


Figure 5. NMR data for compound **4** (isomers **4c** and **4d**).

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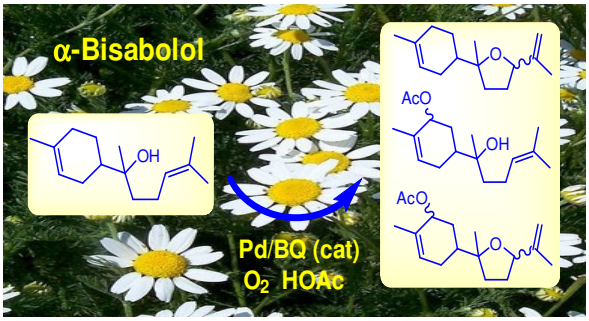
FULL PAPER

Palladium catalyzed oxidation of renewable terpenes with molecular oxygen: oxidation of α-bisabolol under chloride-free conditions

Catal. Sci. Technol. **Year**, *Volume*, Page – Page

Luciana A. Parreira, Luciano Menini, Elena V. Gusevskaya*



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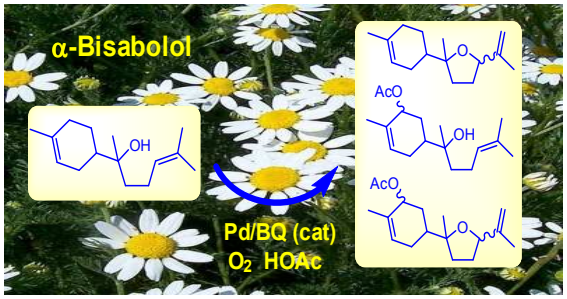

Several novel compounds potentially useful as components of synthetic perfumes and cosmetics were obtained from α-bisabolol via palladium-catalyzed aerobic oxidation.

Abstract. The palladium/*p*-benzoquinone catalyzed aerobic oxidation of α-bisabolol, a bio-renewable substrate with a strong therapeutic potential available from various essential oils, has been developed. The reaction gives three main products arising from the oxidation of sterically encumbered trisubstituted double bonds of the substrate, either endocycic or exocyclic or both together. Novel poly-functionalized sesquiterpenoids obtained with high combined selectivity at the oxidation of α-bisabolol are potentially useful as components of synthetic perfumes, cosmetics and pharmaceuticals. The system promotes an efficient dioxygen-coupled catalytic turnover in the absence of auxiliary redox-active co-catalysts under superatmospheric oxygen pressure. Alternatively, the reaction can be performed at atmospheric pressure in the presence of the catalytic amounts of cupper acetate as an electron transfer mediator for the regeneration of BQ during the catalytic cycle.

Keywords: α-Bisabolol; Oxidation; Oxygen; Palladium; Terpenoids