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Heteropoly acid catalysts in the valorization of the essential oils: Acetoxylation of β-caryophyllene

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ABSTRACT

$H_3PW_{12}O_{40}$ (PW), the strongest heteropoly acid in the Keggin series, is an active and environmentally friendly catalyst for the liquid-phase conversion of β-caryophyllene (**1**) to β-caryolanyl acetate (**2**) in homogeneous and heterogeneous systems. An efficient and clean method for the synthesis of **2**, providing a mixture containing two stereoisomeric β-caryolanyl acetates **2a** and **2b**, **2a/2b** = 80/20 mol/mol, with 100% GC yield, has been developed using PW as a homogeneous catalyst under mild reaction conditions. The reaction occurs at 25 °C with a catalyst turnover number of 2000. The catalyst can be recovered without neutralization and reused without loss of activity and selectivity.

1. Introduction

Terpenes are naturally occurring substances that can be used as a renewable hydrocarbon feedstock to replace the present petroleum-based source of hydrocarbons. In particular, these compounds represent a sustainable supply of intermediates for several segments of the fine chemical industry, e.g., the manufacture of flavors and fragrances [1–4]. Various terpenic compounds used in the fine chemicals industry are produced by acid-catalyzed transformations of more abundant mono- and sesquiterpenes. In these reactions, mineral acids are used as catalysts, often in large amounts, which lead to serious environmental problems.

Heteropoly acids (HPAs), especially those of the Keggin series, are attractive acid catalysts for the clean synthesis of fine and specialty chemicals [5,6]. Recently, HPAs have been applied in various reactions of terpenoids, such as hydration, acetoxylation [7–9], and isomerization [10–15]. Due to their stronger acidity, HPAs generally exhibit higher catalytic activities compared to conventional catalysts, such as mineral acids, ion-exchange resins, mixed oxides, zeolites, etc. Furthermore, HPA catalysis lacks side reactions, such as sulfonation and chlorination, which frequently occur with mineral acids. Economic and environmental advantages of using solid acid catalysts in liquid-phase reactions are clearly apparent. It should be noted that HPAs can, in some cases, be recovered and recycled without neutralization even from homogeneous systems. Such an opportunity is provided by high solubility of HPAs in polar solvents, on the one hand, and low solubility in non-polar solvents (e.g., hydrocarbons), on the other hand, so that they can be recovered from polar organic solutions by precipitating with a non-polar solvent.

Within our program aimed at the valorization of natural ingredients of renewable essential oils, we choose to study the HPA catalyzed transformations of *β*-caryophyllene – a bicyclic sesquiterpene compound containing two olefinic bonds.

β-Caryophyllene is one of the most abundant sesquiterpenes found in many essential oils. For example, it is the main hydrocarbon component of clove (*Eugenia caryophyllata*) and copaiba (*Copaifera*) oils [4,16,17]. Various synthetic derivatives of *β*-caryophyllene find use as woody ingredients in perfumes, as aromatic additives for tobacco and food products, and as odor fixatives [4,16]. Furthermore, it is known that natural caryophyllene compounds often show a biological activity, for example, the copaiba extract is used for years in folk medicine and occupies an important place in the Brazilian pharmaceutical export [17].

The molecule of *β*-caryophyllene is highly strained and undergoes a variety of transformations with a remarkable facility. Therefore, the development of reactions which are selective for a single product is a challenging task. Probably for this reason, in spite of the industrial importance of natural and synthetic derivatives of *β*-caryophyllene, selective catalytic reactions of this compound are rare [18–21]. In particular, it has been reported that acid-catalyzed transformations of *β*-caryophyllene result in a complex mixture of polycyclic products due to the involvement of both double bonds in *trans*-annular reactions followed by a variety

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Table 1
Chemical shifts (δ, ppm), coupling constants (J, Hz, in parenthesis) and HMBC correlations for β-caryophyllene **1**, β-caryolanyl acetate **2a**, and β-caryolanol **3**.

Atom[a]	**1**			**2a**			**3**		
	δ (^{1}H)[b]	δ (^{13}C)	HMBC	δ (^{1}H)[b]	δ (^{13}C)	HMBC	δ (^{1}H)[b]	δ (^{13}C)	HMBC
1a	1.60–1.70 (m)	40.39	H-2, H-10, H-12, H-13	1.26–1.32 (m)	38.86	H-2, H-12, H-13	1.42–1.58 (m)	34.45	H-2, H-12, H-13
1b	1.60–1.70 (m)			1.68–1.75 (m)			1.42–1.58 (m)		
2	2.27–2.33 (m)	48.50	H-4a, H-4b, H-9a, H-9b, H-15a, H-15b	2.35 (qt, 9.3, H-1, H-10)	42.69	H-1a, H-1a, H-15a	2.28 (qt, 10.2, H-1, H-10)	39.57	H-9b, H-15a
3		154.45	H-4b, H-5a, H-5b, H-10, H-15a		83.45	H-1a, H-4b, H-15a, H-15b		71.00	H-1, H-15a, H-15b
4a	1.98–2.04 (m)	34.82	H-2, H-4a, H-4b	1.10–1.20 (m)	39.00	H-2, H-6a, H-15b	1.24–1.34 (m)	38.64	
4b	2.18–2.22 (m)		H-15a, H-15b	1.43–1.53 (m)			1.57–1.64 (m)		
5a	1.98–2.04 (m)	28.38	H-4a, H-4b	1.63–1.70 (m)	20.62		1.67–1.74 (m)	20.88	
5b	2.30–2.37 (m)			1.63–1.70 (m)			1.67–1.74 (m)		
6a	5.27–5.34 (m)	124.35	H-4a, H-4b, H-14	1.08–1.12 (m)	36.36	H-4a, H-5, H-14, H-15b	1.02–1.08 (m)	37.47	H-14
6b				1.38–1.44 (m)			1.32–1.42 (m)		
7		135.24	H-5a, H-14		34.90	H-14, H-15		34.97	H-14
8a	1.85–1.95 (m)	39.99	H-10, H-14	1.43–1.53 (m)	35.67	H-14	1.07–1.14 (m)	36.68	H-14, H-15a
8b	2.07–2.13 (m)			2.42–2.50 (m)			1.50–1.68 (m)		
9a	1.47–1.53 (m)	29.39	H-2	1.30–1.35 (m)	23.63	H-2	1.30–1.40 (m)	21.95	H-2
9b	1.47–1.53 (m)			1.43–1.53 (m)			1.42–1.48 (m)		
10	1.65–1.75 (m)	53.62	H-1, H-5b, H-12, H-13	1.78–1.86 (m)	46.52	H-1a, H-1b, H-2, H-12, H-13	1.78–1.86 (m)	44.82	H-8b, H-12, H-13
11		32.74	H-1, H-10, H-12, H-13		34.18	H-1, H-12, H-13		34.80	H-12, H-13
12	1.00 (s)	30.10	H-1, H-12	0.98 (s)	30.37	H-1a, H-13	1.01 (s)	30.54	H-1, H-13
13	0.97 (s)	22.62	H-1, H-13	0.98 (s)	20.55	H-1a, H-1b, H-12	1.00 (s)	20.83	H-1, H-12
14	1.61 (s)	16.30		0.91 (s)	34.00	H-6, H-15	0.89 (s)	33.26	H-15a
15a	4.82 (bs)	111.67	H-2, H-4a, H-4b	1.30–1.35 (m)	45.82	H-14	1.04 (d, 14.8, H-15b)	48.78	
15b	4.94 (bs)			1.92–2.00 (m)			1.70 (d, 14.8, H-15a)		
C=O					169.95				
C(O)CH_3				1.97 (s)	22.18				

[a] For carbon numbering, see Scheme 1.
[b] Resonance multiplicities, coupling constants (Hz), and coupled partners in parentheses: (s) singlet, (qt) quartet, (m) multiplet, (b) broad.

of rearrangements [4,16]. For example, the hydration of β-caryophyllene leads to the formation of up to 20 products, although in some cases, β-caryolanol is the main product (50–70% selectivity) [20–25]. The hydration of β-caryophyllene has been performed in the presence of various acid catalysts, such as sulfuric and chloroacetic acid, acidic alumina, and zeolites, which are often used in over-stoichiometric amounts [20–25].

In the present work, we report the application of $H_3PW_{12}O_{40}$ (PW), the strongest HPA in the Keggin series, as the catalyst for the liquid-phase acetoxylation of β-caryophyllene (**1**) in homogeneous and heterogeneous systems. Our aim was to achieve high selectivity towards β-caryolanyl acetate (**2**) and β-caryolanol (**3**). As a result, we developed an efficient method for the synthesis of acetate **2** with a virtually quantitative yield. To our knowledge, no attempt to use HPA catalysts for this reaction has been made so far. Moreover, none of the previous work has achieved such a high selectivity.

2. Experimental

2.1. Chemicals

All chemicals were purchased from commercial sources and used as received, unless otherwise stated. $H_3PW_{12}O_{40}$ hydrate was from Aldrich and Aerosil 300 silica from Degussa. β-Caryophyllene was kindly donated by Prof. J.C. Bayón (Universidad Autónoma de Barcelona).

2.2. Characterization techniques

^{31}P MAS NMR spectra were recorded at room temperature and 4 kHz spinning rate on a Bruker Avance DSX 400 NMR spectrometer using 85% H_3PO_4 as a reference. Powder X-ray diffraction (XRD) of the catalysts was measured using a Rigaku Geigerflex-3034 diffractometer with CuK_α radiation. Surface area and porosity of the catalysts were measured by nitrogen physisorption at 77 K on an Micromeritics ASAP 2000 instrument. Tungsten and phosphorus content in the catalysts was measured by inductively coupled plasma (ICP atomic emission spectroscopy) on a Spectro Ciros CCD spectrometer.

2.3. Catalyst preparation and characterization

The silica-supported catalysts, 20 wt% $H_3PW_{12}O_{40}/SiO_2$ (PW/SiO_2), were prepared by impregnating Aerosil 300 (S_{BET}, 300 $m^2\,g^{-1}$) with an aqueous PW solution and calcined at 130 °C/0.2–0.3 Torr for 1.5 h, as described elsewhere [26]. The PW content was determined by ICP. The BET surface area was 200 $m^2\,g^{-1}$ and average pore volume was 0.53 $cm^3\,g^{-1}$. The integrity of Keggin structure of PW was verified by ^{31}P MAS NMR; the catalysts showed only a single peak at ca. −15 ppm characteristic of $H_3PW_{12}O_{40}$ [27]. From XRD, the catalysts included crystalline phase of PW on the silica surface. The acid strength of silica-supported PW was characterized calorimetrically using ammonia and pyridine adsorption and discussed in the previous work [28].

2.4. Catalytic reactions

The reactions were carried out in a glass reactor equipped with a magnetic stirrer. In a typical run, a mixture of β-caryophyllene (0.04–0.30 M), dodecane (0.10 M, internal standard) and $H_3PW_{12}O_{40}$ (0.07–0.35 mM) or PW/SiO_2 (1.25–2.50 wt%) in a specified solvent (acetic acid or cyclohexane, 10 mL) was intensely stirred under air at a specified temperature (25–40 °C). The reaction progress was followed by gas chromatography (GC) using a Shimadzu 17 instrument fitted with a Carbowax 20 M capillary column and a flame ionization detector. In homogeneous systems, at appropriate time intervals, aliquots were taken, diluted with hexane (1/10 v/v) to separate the heteropoly acid and analyzed by GC. In heterogeneous systems, stirring was stopped and after quick catalyst settling aliquots were taken as in homogeneous systems. The mass balance, product selectivity and yield were calculated using dodecane as internal standard. Any difference in mass balance was attributed to the formation of oligomers, which were GC unobservable, and referred to as "others".

In heterogeneous systems, to control catalyst leaching and the possibility of a homogeneous reaction, the catalyst was removed by centrifugation of the reaction mixture at the reaction temperature to avoid re-adsorption of active components onto silica, then the supernatant was added with portion of substrate and allowed to react on. No further reaction was observed in such experiments, indicating absence of PW leaching.

The products were separated by a column chromatography (silica gel 60) using mixtures of hexane and CH_2Cl_2 as eluents and identified by GC–MS, ^{1}H, and ^{13}C NMR. The ^{1}H and ^{13}C NMR signals were assigned using bidimensional techniques. NMR spectra were recorded in $CDCl_3$ using a Bruker 400 MHz spectrometer, with TMS as an internal standard. Mass spectra were obtained on a Shimadzu QP2010-PLUS instrument operating at 70 eV.

Data for β-caryophyllene **1**: MS (*m*/*z*/rel.int.): 204/7 (M^+); 189/27; 161/51; 147/41; 148/27; 133/100; 121/30; 120/50; 119/46; 107/50; 106/32; 105/71; 93/100; 91/82; 81/43; 79/71; 69/83; 67/34; 59/3, 55/31. For NMR data see Table 1.

Data for β-caryolanyl acetate **2a**: MS (*m*/*z*/rel.int.): 204/17 ($[M-HOAc]^+$); 189/56; 166/35; 161/100; 148/42; 133/41; 123/39; 121/72; 119/42; 111/68; 107/33; 105/38; 95/41; 93/52; 91/34; 81/45; 79/34; 69/43; 67/34; 59/3; 55/58. For NMR data see Table 1.

Data for β-caryolanyl acetate **2b**: MS (*m*/*z*/rel.int.): 204/34 ($[M-HOAc]^+$); 189/100; 166/49; 161/98; 148/30; 135/22; 133/27; 123/26; 119/30; 107/23; 105/29; 95/26; 93/28; 91/21; 81/30; 79/23; 67/21; 55/22. ^{1}H NMR, δ_H: 0.86 (s, 3H, $C^{14}H_3$); 1.05 (s, 3H, $C^{12}H_3$); 2.03 (s, 3H, $COCH_3$). ^{13}C NMR, δ_C: 21.05 (C^5), 21.26 ($COCH_3$), 31.65 (C^{12}), 32.97 (C^{14}), 44.62 (C^{15}), 82.66 (C^3), 170.99 ($COCH_3$).

Data for β-caryolanol **3**: MS (*m*/*z*/rel.int.): 204/5 ($[M-H_2O]^+$); 161/25; 123/30; 121/18; 111/100; 95/25; 81/31; 69/21; 55/33. For NMR data see Table 1; ^{13}C NMR data are in agreement with those published previously [21,29].

Data for clovene **4**: MS (*m*/*z*/rel.int.): 204/7 (M^+); 189/43; 161/100; 133/26; 119/27; 105/34; 93/20; 91/27.

3. Results and discussion

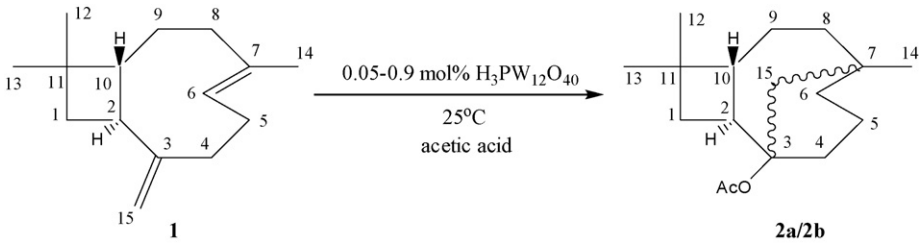
3.1. Acetoxylation of β-caryophyllene in homogeneous systems

The results on transformations of β-caryophyllene (**1**) in acetic acid solutions containing the dissolved PW catalyst are presented in Table 2. All experiments were performed at 25 °C due to high reactivity of the substrate in the presence of PW. In a blank reaction, with no catalyst added, only a 2% conversion of β-caryophyllene was observed in 8 h, giving mainly high-boiling products, which were not determinable by GC (run 1). The PW catalyst showed excellent performance in this reaction. With 0.1 mol% catalyst, a nearly complete conversion of β-caryophyllene was achieved in 4 h resulting in the formation of two main products, **2a** and **2b**, in an 80/20 molar ratio (run 2). These were identified as two stereoisomers of β-caryolanyl acetate (Scheme 1). Isomers **2a** and **2b** differ by the spatial position of the bridging methylene group. The total selectivity for these two products was 58%, with the rest attributed to oligomers. The determination of structures of **2a** and **2b** is described below.

Table 2
Homogeneous acetoxylation of β-caryophyllene (**1**) catalyzed by $H_3PW_{12}O_{40}$ (PW) in acetic acid solutions at 25 °C.

Run	[**1**] (M)	[PW] (10^{-4} M)	Time (h)	Conversion (%)	Selectivity for **2a**/**2b** (%)[a]	Rate (M h^{-1})[b]	TON[c]
1	0.15	None	8	2	0	–	–
2	0.30	3.5	4	98	58	0.30	840
3	0.15	3.5	0.75	97	59	0.33	420
4	0.07	3.5	0.25	100	80	–	200
5	0.04	3.5	0.25	100	90	–	114
6	0.15	1.7	4	100	70	0.18	882
7	0.15	0.7	7	100	100	0.10	2026
8	0.05	0.7	3	100	100	0.11	714
9[d]	0.07	5.3	6	30	–	–	–

[a] **2a**/**2b** ≈ 80/20 mol/mol.
[b] Initial rate of the substrate conversion.
[c] Turnover number: the number of substrate molecules converted per mol of PW.
[d] H_2SO_4 was used as catalyst (5.3×10^{-4} M).



Scheme 1. Acetoxylation of β-caryophyllene (**1**).

Further studies revealed that the substrate oligomerization can be controlled by choosing appropriate reaction conditions. With a decrease in the initial concentration of substrate, the selectivity for **2a** and **2b** gradually increased from 58 to 90% at the expense of oligomers (runs 2–5). This can be explained by a higher reaction order in substrate for oligomerization compared to the desired acetoxylation of β-caryophyllene.

The catalyst efficiency in terms of turnover number (TON) was improved significantly by decreasing the amount of PW catalyst (cf. runs 3, 6, and 7), however at the expense of reaction rate. Thus, a virtually 100% selectivity to acetate **2**, with a **2a**/**2b** molar ratio of 80/20 and a TON of more than 2000, were achieved under optimized conditions (runs 7 and 8).

3.2. Acetoxylation/hydration of β-caryophyllene in heterogeneous systems

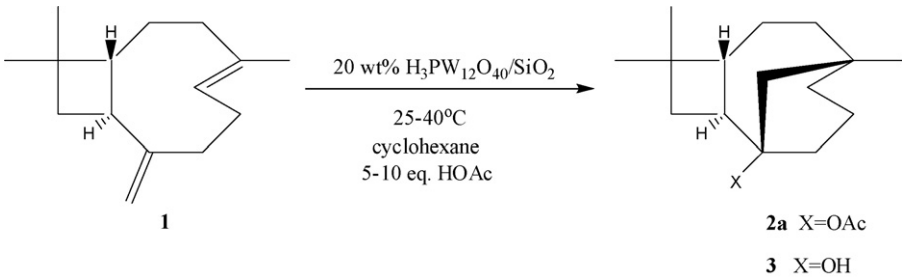
The high solubility of PW in acetic acid prevents direct use of silica-supported PW catalysts for the acetoxylation of β-caryophyllene in this solvent due to PW leaching. To avoid leaching problems, the reaction was performed in cyclohexane as a solvent with addition of small amounts of acetic acid, up to 10/1 mol/mol of substrate (Table 3).

In blank tests, with no catalyst or pure silica added, practically no reaction was observed at 25 °C (runs 1 and 2). On the other hand, a nearly complete conversion of β-caryophyllene was attained in 2 h in the presence of PW/SiO_2 catalyst (run 3). Acetate **2** and the corresponding alcohol **3** accounted for 65% of the converted substrate (Scheme 2). It is noteworthy that acetate **2** formed mainly as isomer **2a**, with only trace amount of isomer **2b** detected. This result is different from that observed for the homogeneous system, where the **2a**/**2b** molar ratio was about 80/20. Other products observed were attributed to β-caryophyllene isomers due to the characteristic GC retention times and the presence of the molecular ion peak with m/z = 204 in their mass spectra. Clovene (**4**) was identified as the predominant isomer, which amounted to more than 50% of the isomer products. A difference in the GC mass balance of 10% was observed and attributed to high-boiling products (runs 3 and 5). With increasing the concentration of acetic acid the selectivity to **2** and **3** drastically

Table 3
Transformations of β-caryophyllene (**1**) catalyzed by 20 wt% $H_3PW_{12}O_{40}$(PW)/SiO_2[a].

Run	Catalyst (wt%)	HOAc (M)	T (°C)	Time (h)	Conversion (%)	Selectivity (%)[b]			
						Isomers[b]	**2**[c]	**3**[d]	Others
1	None	0.70	25	6	0	–	–	–	–
2	SiO_2	0.70	25	6	2	–	–	–	100
3[e]	PW/SiO_2 (2.50)	0.35	25	2	100	25	30	35	10
4	PW/SiO_2 (2.50)	0.70	25	2	80	15	9	7	69
5	PW/SiO_2 (1.25)	0.70	40	1	97	23	42	24	11
6	PW/SiO_2 (1.25)	None	40	1	92	28	–	26	46
7	Amberlyst (0.5)	0.70	40	10	0	–	–	–	–

[a] [**1**] = 0.07 M, in cyclohexane as a solvent.
[b] Isomers of β-caryophyllene, mainly clovene (**4**).
[c] Mostly **2a**, only trace of **2b**.
[d] Oligomeric products.
[e] After reaction, the catalyst was separated by centrifugation, the supernatant was added with a fresh portion of substrate and allowed to react for 3 h, with no conversion observed thereupon. The separated catalyst was reused 2 times without loss of activity and selectivity.



Scheme 2. Acetoxylation/hydration of β-caryophyllene (**1**).

decreased due to β-caryophyllene oligomerization (run 4). In run 2, the catalyst was separated and, after washing with hexane, reused two times without any loss in its activity and selectivity.

Generally, water was not added to the reaction system. The amount of hydration water present in the PW catalyst and commercial reagents was sufficient for the formation of **3**. It should be noted that HPA crystalline hydrates could bear up to about 30 water molecules per Keggin unit. In addition, water could be present inside SiO_2 pores of the catalyst which had a pore volume of 0.53 $cm^3\ g^{-1}$.

Although PW is insoluble in non-polar solvents, the presence of acetic acid in the reaction mixture could promote PW leaching from the catalyst. To prove the absence of any contribution of homogeneous catalysis, the catalyst was removed from the reaction system after reaction completion, fresh substrate was added to the supernatant and the reaction was allowed to proceed further (run 2). No activity was observed in this experiment, which indicates that PW did not leach from silica into the reaction medium under the conditions used.

Our attempt to minimize β-caryophyllene isomerization and oligomerization by varying reaction parameters had a limited success. The best combined yield of **2** and **3** obtained was 66%, with a TON of about 100 per mol of PW (Table 3, run 5). About 15% of substrate isomerized to clovene in this run.

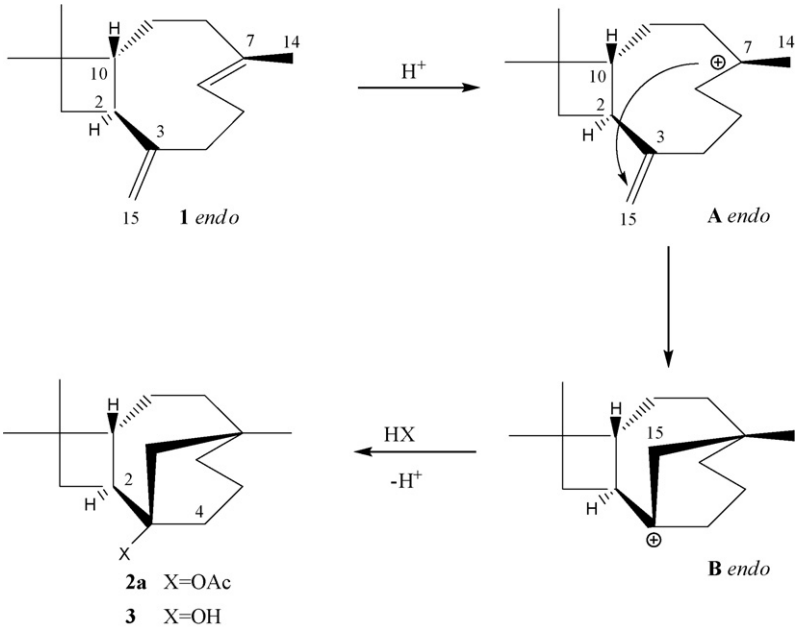
In the absence of acetic acid, the PW/SiO_2 catalyst promoted the isomerization and hydration of β-caryophyllene. However, under such conditions most of the converted substrate transformed into unidentified high-boiling products (46% of the mass balance).

Amberlyst-15 acidic resin was also tested in β-caryophyllene conversion in cyclohexane solutions of acetic acid, but no catalytic activity was observed (run 7).

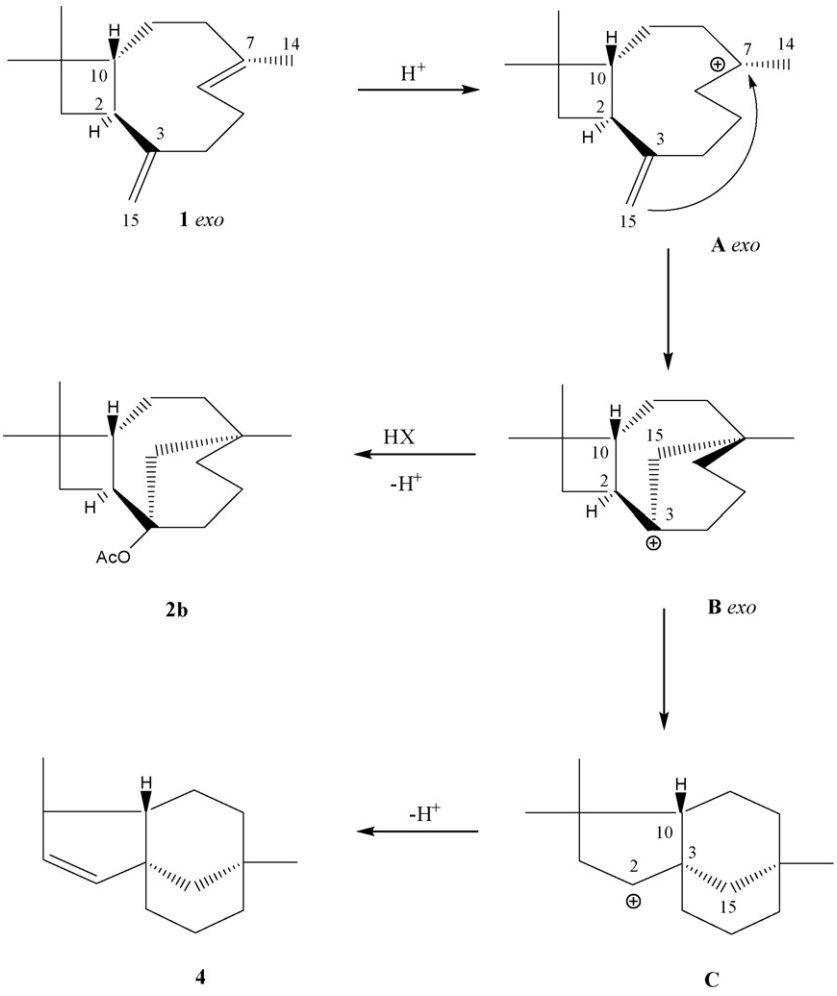
3.3. Product characterization

The chemical nature of major product **2a** has been firstly elucidated by GC–MS and then confirmed by NMR spectroscopy. In the mass spectrum of **2a**, peaks at m/e = 59, due to the formation of acetate ion, and at m/e = 204, corresponding to the loss of acetic acid molecule, are observed. This gives for the original molecule the molecular weight of 264 corresponding to the product of the addition of acetic acid to β-caryophyllene (M.M. = 204 g/mol). However, a significant difference in the relative intensities of the mass peaks of β-caryophyllene and **2a** suggests that the carbenium ion derived from the substrate molecule undergoes isomerization before the addition of the nucleophile. In the ^{1}H NMR spectrum of **2a**, a singlet at δ 1.97 corresponding to the methyl protons of the acetate group was observed, without –C*H*O– signal present. This indicates that the compound was a tertiary acetate.

Based on the ^{1}H and ^{13}C NMR spectroscopy data we suggested the structure for product **2a** is shown in Scheme 1. The stereochemistry of **2a** is shown in Scheme 3. The assignment of the hydrogen and carbon resonances (Table 1) was carried out by COSY (^{1}H, ^{1}H), HMQC (^{1}H, ^{13}C), HMBC (^{1}H, ^{13}C), and DEPT NMR. The study of the HMBC spectra was decisive for building the molecular skeleton of **2a**. It was confirmed that the cyclobutane ring of the substrate remains intact in this product. The strong cross peak



Scheme 3. Acid-catalyzed transformations of caryophyllene (**1**).



Scheme 4. Acid-catalyzed transformations of β-caryophyllene (**1**).

observed in the COSY spectrum of **2a** shows that the methine proton at C-2, which appears in the ^{1}H NMR as a quartet, is coupled with both the methine proton at C-10 and the methylene protons at C-1. On the other hand, in the HMBC spectrum, carbon C-10 correlates with both protons at C-1 via $^3J_{CH}$. Furthermore, carbon C-12 correlates with methyl protons at C-13 via $^3J_{CH}$, whereas carbon C-13 with methyl protons at C-12. This result indicates that both methyl groups C-12 and C-13 are attached to the same carbon C-11, which correlates, in its turn, with protons at C-12 and C-13 as well as with protons at C-1 via $^2J_{CH}$. Finally, both carbons C-12 and C-13 correlate with the methylene protons at C-1 via $^3J_{CH}$, whereas carbon C-10 with the methyl protons at both C-12 and C-13, also via $^3J_{CH}$.

The formation of a bridge between carbons C-3 and C-7 through carbon C-15 has been also unambiguously proved by the analysis of long-range cross signals in HMBC spectra (Table 1). One of the methylene protons at C-15 correlates via $^3J_{CH}$ with carbons C-2 and C-4, on the one hand, and with carbon C-14, on the other hand. Moreover, carbon C-15 also correlates with the protons of methyl group C-14 via $^3J_{CH}$. Formally, the formation of this new tricyclic skeleton from the bicyclic molecule of β-caryophyllene can be rationalized as the formation of the new C-7–C-15 bond and the saturation of the C-6–C-7 olefinic bond. To facilitate the discussion and signal comparison, carbon numbering used for **1** (according to [30]) is maintained for **2a**, **2b**, and **3**.

The mass spectra of **2a** and **2b** are very similar indicating that these compounds seem to be closely related isomers. Compound **2b** has been isolated from the reaction solutions only in a mixture with **2a** (**2a**/**2b** $\approx$ 2.5/1) because it is formed in the reaction as a minor product. For this reason, we could not perform a complete characterization of **2b** by NMR. In the ^{1}H NMR spectrum of the **2a**/**2b** mixture, most of the signals are overlapped and only the signals from the methyl groups could be assigned to **2b**. In the ^{13}C NMR spectrum, the signals from **2a** and **2b** are also very close or overlapped. For example, the signal from the quaternary carbon C-3 in **2a**, which is bound to the acetate group, appears at δ 83.45 and the corresponding carbon in **2b** at δ 82.66. Thus, we believe that products **2a** and **2b** are stereoisomeric acetates with the same carbon skeleton, resulting from the different possibilities for the position of the methylene C-15 bridge. The results of the NOESY experiments suggest that in a major isomer **2a** the proton at C-10 and the methylene C-15 bridge are at the same side of the nonane ring, as shown in Scheme 3, because there is a strong correlation signal between the protons at C-2 and C-4. Molecular modeling of the structures shows that the proton at C-2 is spatially proximate to protons at C-4 in **2a**, but it is not in **2b**. It should be mentioned that the butane and nonane carbon rings in natural β-caryophyllene are *trans*-linked, i.e., the protons at C-2 and C-10 are in a *trans* position, as it is shown in Schemes 1–4.

Product **3** was isolated from the reaction mixture as a pure compound and characterized by GC–MS and NMR spectroscopy. The mass spectrum of **3** also shows the heaviest peak at m/e = 204; however, it is different from the spectra of **2a** and **2b** in the relative abundance of the fragments. The data of ^{1}H and ^{13}C NMR spectroscopy (Table 1) confirm that compound **3** is a tricyclic alcohol with the same skeleton as acetate **2a** (Scheme 2). In

general, the NMR spectra of **3** are similar to those of **2a** except the absence of the signals corresponding to the acetate group and a significant difference in the chemical shift of the signals from quaternary carbons C-3 bound with the hydroxyl group in **3** (δ 71.00) and with the acetate group in **2a** (δ 83.45). Furthermore, the GC retention time of **3** is slightly longer than that of **2a** (less than 0.1 min), which is characteristic for the pair of the corresponding alcohol and acetate.

The NOESY spectrum of alcohol **3** shows a strong correlation signal between the protons at C-10 and C-15, showing their spatial proximity. Thus, we can conclude that in alcohol **3**, like in major acetate **2a**, the proton at C-10 and the methylene C-15 bridge are at the same side of the nonane ring as shown in Scheme 2.

3.4. Reaction mechanism

β-Caryophyllene is known to be one of the most remarkable and versatile of terpenoids in its variety of skeletal transformations [16]. The unusual structure of this compound contains *trans*-linked butane and nonane carbon rings and a *trans*-substituted double bond in the nonane ring. The molecule is extremely strained, therefore, it is highly reactive, undergoing a variety of *trans*-annular cyclizations to give more stable bi- and tricyclic systems. Although the reactivity of the trisubstituted double bond in β-caryophyllene is usually higher than that of the *exo*-cyclic double bond [16], the main products in acid-catalyzed reactions under certain conditions can be originated from the protonation of the *exo*-cyclic double bond [23].

At room temperature, β-caryophyllene exists as a mixture of four conformers separated by a low barrier of inversion, with two of them, $\beta\alpha$ (75%) and $\beta\beta$ (21%), amounting to 96% of the mixture [31]. Two minor conformers are found in much smaller amounts: $\alpha\alpha$ (3%) and $\alpha\beta$ (<1%). Two pairs of conformers, $\beta\alpha/\alpha\alpha$ and $\beta\beta/\alpha\beta$, differ by the relative position of the hydrogen at C-10 and the methyl group C-14 at carbon C-7. In *exo* conformers, $\beta\alpha$ and $\alpha\alpha$, they are at the opposite sides of the nine-membered ring as shown in Scheme 4, whereas in *endo* conformers, $\beta\beta$ and $\alpha\beta$, at the same side, as shown in Scheme 3. The *exo*–*endo* rearrangement occurs through the intramolecular rotation of the C-7–C-6–C-5–C-4 fragment. The difference between two conformers in each pair is the orientation of the *exo*-methylene group (C-15). In major conformers $\beta\alpha$ (*exo*) and $\beta\beta$ (*endo*), the hydrogen at C-10 and the *exo*-cyclic C-15 are at the same side of the nine-membered ring, whereas in the minor conformers $\alpha\alpha$ (*exo*) and $\alpha\beta$ (*endo*) at the opposite sides (not shown in Schemes 3 and 4). Thus, in the conformers $\beta\beta$ and $\alpha\alpha$, the *exo*-cyclic double bond C-3–C-15 and carbon C-7 are spatially proximate (carbons C-15 and C-14 are at the same side of the nonane ring), whereas in the conformers $\beta\alpha$ and $\alpha\beta$ they are not (carbons C-15 and C-14 are at the opposite sides).

Suggested reaction pathways for the acid-catalyzed transformations of **1** into products **2**–**4** are presented in Schemes 3 and 4. We suppose that products **2a** and **3** are formed from one of the *endo* conformers of β-caryophyllene (Scheme 3), whereas products **2b** and **4** from one of *exo* conformers (Scheme 4), as described below. The structure of the main products **2** and **3** suggests that they arise from protonation of the internal double bond of the substrate to give carbenium ions **A** *endo* and **A** *exo* followed by a *trans*-annular ring closure to form a new C-7–C-15 bond. Two isomers of acetate **2** arise from the different stereochemistry of the nucleophilic attack of the *exo*-cyclic double bond at carbon C-7 in the intermediate carbonium ion **A**: via the top side of the nonane ring (with respect to the proton at C-10 as shown in Scheme 3) or via the bottom side (Scheme 4). In major products **2a** and **3**, the proton at C-10 and the methylene C-15 bridge are at the same side of the nonane ring, as shown in Scheme 3. Therefore, these products arise from the top attack. On the other hand, in **2b** as well as in clovene **4** the methylene bridge is oriented to the other side of the nonane and octane ring, respectively, than the proton at C-10. Therefore, these products arise from the bottom attack. A nucleophilic attack of acetic acid or water on carbenium ions **B** gives the corresponding addition products, whereas a rearrangement of carbenium ion **B** *exo* via opening the four-membered ring into carbenium ion **C** followed by the loss of a proton gives clovene **4**.

The protonation of the main $\beta\alpha$-conformer as well as $\alpha\alpha$-conformer leads to carbenium ions incapable of cyclization because of the unfavorable orientation of the *exo*-methylene group. Therefore, it should be suggested that all β-caryophyllene is pumped over to the conformers $\beta\beta$ and $\alpha\alpha$ where the *exo*-cyclic double bond and carbon C-7 are spatially proximate and, therefore, cyclization can occur. The $\beta\beta$-conformer (*endo*) originates products **2a** and **3** with the *endo*-oriented methylene bridge, while the $\alpha\alpha$-conformer (*exo*) gives products **2b** and **4** in which the methylene bridge and proton at C-10 are in a "*trans*" position. The relative amounts of the products do not correspond to the relative amounts of the conformers: $\beta\alpha$ (75%), $\beta\beta$ (21%), $\alpha\alpha$ (3%), and $\alpha\beta$ (<1%). Thus, it has to be assumed that a conformational equilibrium is shifted toward the more reactive conformers, i.e., $\beta\beta$ and $\alpha\alpha$, with the major products **2a** and **3** resulting from the more abundant conformer $\beta\beta$, as shown in Scheme 3.

It is interesting that in the homogeneous system, i.e., in pure acetic acid, both acetates **2a** and **2b** are formed in ca. 80/20 ratio, whereas the in heterogeneous system, i.e., at low acetic acid concentrations, isomer **2b** is detected only in trace amounts. On the other hand, clovene **4** is formed in the heterogeneous system instead of **2b**, in approximately the same proportion to **2a** and **3**. This can be explained suggesting that in pure acetic acid carbenium ion **B** *exo* is rapidly captured by nucleophile to give acetate **2b**, whereas at low acetic acid concentrations it has enough time to rearrange into more stable carbenium ion **C** and to lose a proton (Scheme 4).

The higher selectivities for addition products **2** and **3** in pure acetic acid, compared with those obtained in cyclohexane, can also be explained by ion-solvating ability of acetic acid. In acetic acid solution, solvated intermediate carbenium ions readily react with the abundant nucleophilic solvent rather than with another molecule of substrate, which would lead to oligomerization. In contrast, non-polar non-basic cyclohexane is less capable to prevent the nucleophilic attack of the substrate on cationic intermediates, which favors the formation of high-boiling products.

The catalytic activities of PW and H_2SO_4 are compared in Table 2 (run 4 vs. 9) under the same reaction conditions and with the same total amount of protons. Being much stronger acid, PW showed significantly higher catalytic activity and selectivity to acetate **2** than H_2SO_4. Instead, the latter promoted the formation of a variety of other products and oligomers. Besides its strong acidity, the high effectiveness of PW can be related to a weak interaction of the soft heteropoly anion with carbenium ion intermediates [6]. This makes it unlikely for the heteropoly anion to influence rearrangement of the carbenium ion intermediates. On the contrary, the anions of conventional Brønsted acids are known to affect such rearrangement, promoting side reactions.

4. Conclusions

Heteropoly acid $H_3PW_{12}O_{40}$ (PW) is an active acid catalyst for the liquid-phase acetoxylation of β-caryophyllene to give β-caryolanyl acetate (**2**) in homogeneous and heterogeneous systems. An efficient and clean method for the synthesis of **2**, providing a mixture containing two stereoisomeric β-caryolanyl

acetates **2a** and **2b**, **2a**/**2b** = 80/20 mol/mol, with 100% yield, has been developed using PW as a homogeneous catalyst under mild reaction conditions. The catalyst can be recovered without neutralization and reused without loss of activity and selectivity.

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