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Phosphotungstic Acid as a Versatile Catalyst for the Synthesis of Fragrance Compounds by α-Pinene Oxide Isomerization: Solvent-Induced Chemoselectivity

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Abstract: The remarkable effect of the solvent on the catalytic performance of $H_3PW_{12}O_{40}$, the strongest heteropoly acid in the Keggin series, allows direction of the transformations of α-pinene oxide (**1**) to either campholenic aldehyde (**2**), *trans*-carveol (**3**), *trans*-sobrerol (**4a**), or pinol (**5**). Each of these expensive fragrance compounds was obtained in good to excellent yields by using an appropriate solvent. Solvent polarity and basicity strongly affect the reaction pathways: nonpolar nonbasic solvents favor the formation of aldehyde **2**; polar basic solvents favor the formation of alcohol **3**; whereas in polar weakly basic solvents, the major products are compounds **4a** and **5**. On the other hand, in 1,4-dioxane, which is a nonpolar basic solvent, both aldehyde **2** and alcohol **3** are formed in comparable amounts. The use of very low catalyst loading (0.005–1 mol%) and the possibility of catalyst recovery and recycling without neutralization are significant advantages of this simple, environmentally benign, and low-cost method. This method represents the first example of the synthesis of isomers from α-pinene oxide, other than campholenic aldehyde, with a selectivity that is sufficient for practical usage.

Keywords: alpha-pinene oxide · heterogeneous catalysis · isomerization · solvent effects · sustainable chemistry

Introduction

Monoterpenes are abundant naturally occurring compounds, and their epoxides are often used as important starting materials in the flavor and fragrance industry, which is essentially based on the chemistry of terpenes.[1–4] α-Pinene is particularly widely employed in the production of synthetic substitutes for natural aromas. Rearrangements of α-pinene oxide (**1**) can result in various expensive ingredients for the flavor industry, such as campholenic aldehyde (**2**), *trans*-carveol (**3**), *trans*-sobrerol (**4a**), and pinol (**5**) (see Scheme 1). For example, campholenic aldehyde is an intermediate for the manufacture of sandalwood-like fragrances[5] and is currently being investigated as a possible substitute for environmentally damaging nitro and polycyclic musks used in laundry detergents and softeners.[6] *trans*-Carveol is an important component in perfume bases and food flavor compositions; it is usually commercially available as an expensive mixture of isomers.[7]

The acid-catalyzed isomerization of α-pinene oxide can result in a large variety of products, as this substrate is highly reactive and sensitive: over 200 compounds have been found at temperatures above 100 °C.[8] Therefore, the development of the reaction, which is selective for one particular product, is a very challenging task. To the best of our knowledge, the only compound obtained up to now with a selectivity that is sufficient for practical usage is campholenic aldehyde (**2**), all other compounds are usually produced as minor products with selectivities of less than 25%. It is generally accepted that the formation of **2** is favored in the presence of Lewis acids, whereas Brønsted acids tend to produce a mixture of compounds in low yields, such as *trans*-carveol (**3**), *trans*-sobrerol (**4a**), and *p*-cymene.[6,8–10] Various solid Lewis acids have been used as catalysts for the isomerization of α-pinene oxide into aldehyde **2**;[6,8,10–14] however, most of these reactions are time-consuming and/or involve high catalyst/substrate ratios.

We have recently studied the application of silica-supported $H_3PW_{12}O_{40}$ for the liquid-phase isomerization of α-pinene oxide (**1**).[15] A nonpolar solvent, namely cyclohexane, was used to avoid $H_3PW_{12}O_{40}$ leaching. It is remarkable that in spite of the strong Brønsted acidity of $H_3PW_{12}O_{40}$,

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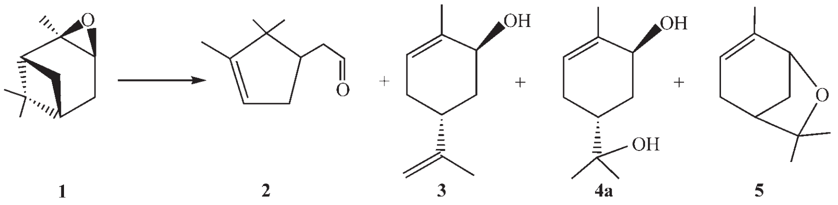
the reaction showed a 70 % selectivity to campholenic aldehyde (**2**), with the combined selectivity for products **2** and **3** being 95–98 % at a complete substrate conversion. As far as we know, this is one of the best results reported so far, and compares favorably with a 65–75 % selectivity to **2**, which is usually observed at high conversions along with the formation of numerous side products. Furthermore, the reaction proceeds very fast even with small amounts of $H_3PW_{12}O_{40}$ and under mild conditions (turnover frequency of approximately 100 min^{-1}), so that turnover numbers (TONs) of nearly 1000 can be obtained. These results encouraged us to work further with $H_3PW_{12}O_{40}$ to attempt to develop a selective synthesis of products from **1** other than **2**, in particular, **3**. The highest previously reported yield of *trans*-carveol (**3**; 45 %) was obtained by using acidic molecularly imprinted polymers as protic catalysts in amounts that are equimolar to **1**.[7] We have decided to study the isomerization of **1** in the presence of $H_3PW_{12}O_{40}$ in various solvents, as solvent effects have been reported to strongly influence the performance of both Lewis and Brønsted acid catalysts.[7,9]

Heteropoly acids (HPAs) have attracted much interest as catalysts for the clean synthesis of fine and specialty chemicals in homogeneous and heterogeneous systems.[16–18] In particular, HPAs have been recently applied in various reactions of terpenoids, such as hydration, acetoxylation,[19–21] and isomerization.[15,22–24] Owing to their strong acidity, HPAs generally exhibit higher catalytic activities than conventional catalysts, for example, mineral acids, ion-exchange resins, mixed oxides, and zeolites; thus, very low catalyst concentrations can often promote relatively fast transformations. Economic and environmental advantages of using solid catalysts in liquid-phase reactions are clearly apparent; however, HPAs can be, in some cases, recovered and recycled without neutralization even from homogeneous systems. Such an opportunity is provided on the one hand by the high solubility of HPAs in polar solvents and on the other hand, by the very low solubility in hydrocarbons, so that they can be easily recovered from polar organic solutions by precipitating with a hydrocarbon solvent.[16]

Herein, we report a simple and efficient synthesis of several highly valuable fragrance compounds through the liquid-phase isomerization of **1** in the presence of $H_3PW_{12}O_{40}$, the strongest HPA in the Keggin series. A remarkable effect of solvent polarity and basicity on the chemoselectivity of this reaction has been found that allows control of the conversion of α-pinene oxide (**1**) towards either *trans*-carveol (**3**), *trans*-sobrerol (**4a**), or pinol (**5**) and leads to the formation of each of them in good to excellent yields.

Results and Discussion

Isomerization of α-pinene oxide (1) in dimethylformamide (DMF): In the presence of acids, α-pinene oxide (**1**) undergoes various transformations that can result in campholenic aldehyde (**2**), *trans*-carveol (**3**), *trans*-sobrerol (**4a**), and pinol (**5**; Scheme 1) as well as numerous other products, for example, *p*-cymene, isopinocamphenol, and isopinocamphone. In the present work, our efforts are directed at achieving high selectivity to any product other than campholenic aldehyde (**2**), in particular, *trans*-carveol (**3**). As the formation of **3** and other *para*-menthenic compounds is known to be favored in polar solvents and that the highest previously reported selectivity to **3** (albeit as low as 45 %) has been obtained in DMF,[7] we began our study with the $H_3PW_{12}O_{40}$ catalyst by using DMF as a solvent.



1 α– pinene oxide; **2** campholenic aldehyde; **3** *trans*-carveol; **4a** *trans*-sobrerol; **5** pinol

Scheme 1. Some products of acid-catalyzed transformations of α-pinene oxide (**1**).

In most of the runs, $H_3PW_{12}O_{40}$ showed high activity and high total selectivity towards **3** and **2**, the former being the predominant isomer (Table 1). Other possible isomers were not obtained in detectable amounts. In some cases, in addition to **2** and **3**, oligomerization products were also formed; their yields were calculated from the difference in mass bal-

Table 1. Isomerization of α-pinene oxide (**1**; 0.15 M) catalyzed by $H_3PW_{12}O_{40}$ (PW) in DMF.

Run	[PW] [mM]	*T* [°C]	Time[a] [min]	Conversion[b] [%]	Selectivity[b] [%] 2	3	2+3	TON[c]
1	7.00	25	20	56	15	75	90	12
2	7.00	40	30	100	10	85	95	21
3	7.00	60	10	100	10	78	88	21
4	3.50	40	60	60	15	85	100	26
5	3.50	60	30	80	15	85	100	34
6	3.50	100	60	100	10	90	100	43
7	1.75	60	30	50	15	85	100	43
8	1.75	100	120	95	14	86	100	81
9	0.70	100	120	60	13	86	99	129
10	0.70	120	120	100	13	87	100	214
11	0.35	120	180	94	7	93	100	403
12	0.35	140	120	100	9	91	100	429
13[d]	0.70	120	120	100	10	90	100	429
14[d]	0.35	120	90	63	13	87	100	540
15[e]	0.35	140	180	100	10	90	100	1143

[a] Time required to attain near-to-maximum conversion. [b] Selectivity and conversions determined by GC and calculated based on the reacted substrate. [c] TON = moles of the substrate converted per moles of $H_3PW_{12}O_{40}$. [d] [**1**] = 0.30 M. [e] [**1**] = 0.40 M.

ance. However, it was shown that the substrate oligomerization could be controlled by appropriate choice of reaction conditions.

In blank reactions (no catalyst added), only a 2 % conversion of **1** was observed after 20 h at 120 °C, and the major products had high boiling points and as such were mostly not detectable by GC. On the other hand, the presence of $H_3PW_{12}O_{40}$ under ambient conditions promoted a fast conversion of **1** into products **2** and **3** with a combined selectivity of 90 % (Table 1, run 1). It is remarkable that such a high selectivity to **3** (75 %) was obtained. However, a kinetic curve for this reaction (Figure 1) reveals that, in spite of the high initial reaction rate, the conversion becomes stationary at approximately 60 % after 10 min and does not increase even after keeping the mixture under the reaction conditions for more than 3 h. Fortunately, at higher temperatures (40–60 °C), the reaction can be completed (Figure 1), with an improved selectivity for alcohol **3** (78–85 %, Table 1, runs 2 and 3).

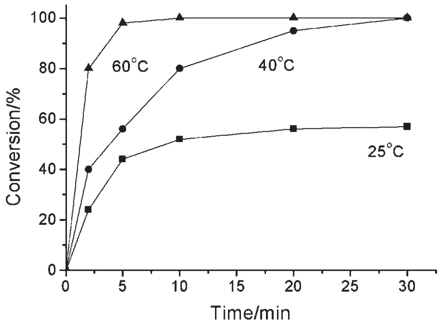


Figure 1. Isomerization of α-pinene oxide (**1**; 0.15 M) catalyzed by $H_3PW_{12}O_{40}$ (7.00 mM) in DMF at different temperatures.

A further optimization of the reaction variables allowed us to obtain excellent results in terms of activity and selectivity. For example, virtually all **1** (0.15 M) was converted into compounds **2** and **3** in the presence of only 3.5 mM of $H_3PW_{12}O_{40}$ in 60 min and at 100 °C (TON = 43). The selectivity for the desired product **3** was as high as 90 % (Table 1, run 6). It should be mentioned, however, that at lower temperatures, the reaction with this amount of catalyst becomes stagnated at incomplete conversions (Table 1, runs 4 and 5, Figure 2).

To improve the catalyst efficiency in terms of TONs, we have decreased the amounts of $H_3PW_{12}O_{40}$ and subsequently observed that the lower the concentration of the catalyst, the higher the temperature that must be used to complete substrate conversion (Table 1, runs 7–12). For example, with 1.75 mM of $H_3PW_{12}O_{40}$, a near-complete conversion was achieved at 100 °C (Table 1, run 8), whereas with 0.70 mM $H_3PW_{12}O_{40}$, complete conversion was achieved at 120 °C (Table 1, run 10) and at 140 °C with 0.35 mM $H_3PW_{12}O_{40}$ (Table 1, run 12). In the latter run, a TON of 429 per mol of $H_3PW_{12}O_{40}$ and a 91 % selectivity to **3** were obtained, with compound **2** being the only minor product. At 120 °C, such high TONs can also be achieved (Table 1, runs 11, 13, and 14); however, at a too-high substrate/catalyst ratio (approximately 800), the reaction stagnation occurs once again (Table 1, run 14).

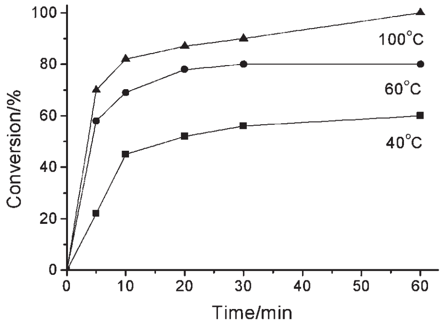


Figure 2. Isomerization of α-pinene oxide (**1**; 0.15 M) catalyzed by $H_3PW_{12}O_{40}$ (3.50 mM) in DMF at different temperatures.

Thus, in DMF solutions, $H_3PW_{12}O_{40}$ promotes the isomerization of **1** to **3** with a remarkably high selectivity, with the only minor product being **2**. In other words, the selectivity of the $H_3PW_{12}O_{40}$ catalyst in DMF is inverted from that observed in cyclohexane; where campholenic aldehyde is formed as a predominant isomer (70 %).[15] Although the reaction is more lengthy in DMF as compared with cyclohexane and occurs under homogeneous conditions, a TON of more that 1100 can be achieved (Table 1, run 15) and the catalyst solution in DMF, in principle, could be reused after the extraction of the products with hydrocarbon solvent, for example, hexane. As far as we know, this is the first example of the selective synthesis of **3** by the acid-catalyzed isomerization of **1** reported so far.

The reaction stagnation observed in some runs deserves special attention. It can not be related to a thermodynamic equilibrium because at any given temperature, the increase in the catalyst amount allows completion of the conversion as illustrated in Figure 3. This result suggests that a possible reason for this should be a partial deactivation of the catalyst in the course of the reaction. However, at any given catalyst concentration, the reaction can be completed by increasing the temperature (Figure 1 and 2). At 140 °C, even

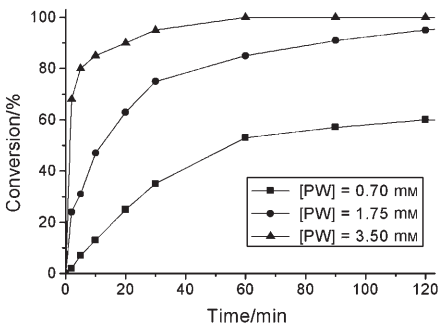
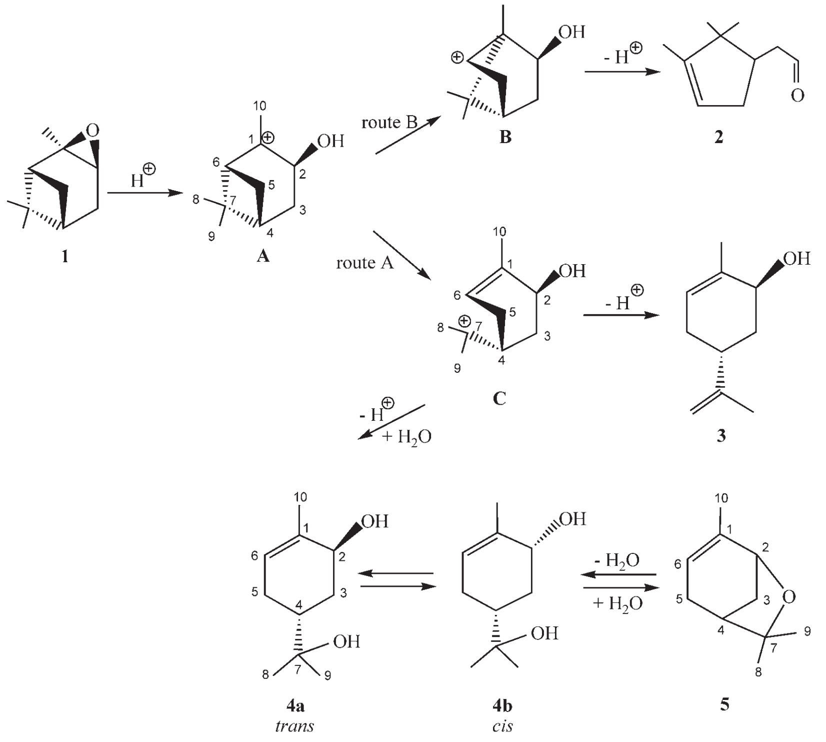


Figure 3. Isomerization of α-pinene oxide (**1**; 0.15 M) catalyzed by $H_3PW_{12}O_{40}$ (PW) in DMF at 100 °C. The effect of the catalyst concentration is shown.

very small amounts of $H_3PW_{12}O_{40}$ convert all the substrate with a TON of 1143 (Table 1, run 15). Thus, the deactivation, if any, is reversible and the catalyst can be re-activated by the temperature increase. Consideration of the nature of the solvent allowed us to suggest an explanation for the observations described.

Suggested reaction pathways for the acid-catalyzed transformations of **1** into products **2**–**5** are presented in Scheme 2. Protonation of the oxygen atom in **1** induces opening of the epoxy ring and initially gives carbenium ion **A**. The latter rearranges into carbenium ions **B** and **C** through the movement of the pair of electrons from the same carbon–carbon σ bond to either C7 or C6. Then, both cations **B** and **C** can loose protons to give aldehyde **2** and alcohol **3**, respectively. Considering the relatively high basicity of DMF ($pK_a \approx -0.5$ for DMF·H^{+}[25]), a competition between solvent oxygen atoms and the epoxide oxygen for the protons of $H_3PW_{12}O_{40}$ should be expected. At high conversion levels, the situation becomes less favorable for the substrate and the reaction can become stagnated because most of the protons are captured by the basic solvent, that is, the catalyst is deactivated. A specific catalysis does not seem to contribute significantly under these conditions, probably owing to the difficulties associated with the approach of DMF·H^{+} to a sterically encumbered oxygen in the bicyclic substrate. The increase in temperature should favor the deprotonation of both the solvent and the substrate; however, the latter can undergo isomerization before the proton is lost and this isomerization should also be accelerated by heating so that *trans*-carveol (**3**) becomes the main product of the substrate deprotonation in DMF. Thus, to achieve high TONs, relatively high reaction temperatures have to be used. In this regard, the high boiling point of DMF (152 °C) is an important advantage of this solvent.



Scheme 2. Proposed mechanism of acid-catalyzed transformations of α-pinene oxide (**1**).

Comparative data on the catalytic activity of $H_3PW_{12}O_{40}$ and conventional Brønsted acid catalysts, for example, H_2SO_4 and Amberlyst-15, are presented in Table 2. A comparison was performed under the same reaction conditions and, in the case of H_2SO_4, with the same total amount of protons. Amberlyst-15 was used with the same weight amounts as $H_3PW_{12}O_{40}$ (0.2 wt %). $H_3PW_{12}O_{40}$ showed a significantly higher catalytic activity and selectivity to **3** than H_2SO_4 (Table 2, run 1 vs. run 2) and Amberlyst-15 (Table 2, run 3 vs. run 4). Moreover, both H_2SO_4 and Amberlyst-15 promote the formation of a wide variety of products; thus, a combined selectivity to compounds **2** and **3** does not exceed 70–75 % at high conversions.

The advantage of using $H_3PW_{12}O_{40}$ as the catalyst for the isomerization of **1** in terms of selectivity can be related to the weak interaction of its anion, which is a very soft base, with the cationic intermediates formed in the course of the reaction. The heteropoly anion is not expected to influence the rearrangements of the intermediate carbocations differently from conjugated bases of conventional Brønsted acids, which usually strongly affect the nature of the products by

Table 2. Isomerization of α-pinene oxide (**1**) in DMF: A comparative performance of various acid catalysts.

Run	Catalyst	Time [min]	Conversion[a] [%]	Selectivity[a] [%] **2**	**3**	others
1[b]	$H_3PW_{12}O_{40}$ (2.50 mM)	20	80	12	88	–
		100	100	13	87	–
2[b]	H_2SO_4 (3.75 mM)	20	31	13	66	21
		300	74	4	69	27
3[c]	$H_3PW_{12}O_{40}$ (0.70 mM)	20	50	15	85	–
		120	100	10	90	-
4[c]	Amberlyst-15 (0.2 wt %)	20	36	16	43	41
		300	95	19	54	27

[a] Selectivity and conversions determined by GC and calculated based on the reacted substrate. [b] [**1**] = 0.15 M, 100 °C. [c] [**1**] = 0.30 M, 120 °C.

promoting side reactions.[9] In this regard, the strong acidity of HPAs, which is responsible for their high catalytic activity, is also attributed to a weak interaction between the protons and the anion owing to the delocalization of surface charge density throughout the large-sized polyanion, which favors the acid dissociation.[26]

Isomerization of α-pinene oxide (1) in dimethylacetamide (DMA): We have tested another amidic solvent, DMA, in the isomerization of **1** catalyzed by $H_3PW_{12}O_{40}$ (Table 3).

Table 3. Isomerization of α-pinene oxide (**1**; 0.15 M) catalyzed by $H_3PW_{12}O_{40}$ (PW) in DMA.

Run	[PW] [mM]	*T* [°C]	Time[a] [min]	Conversion[b] [%]	Selectivity[b] [%] 2	3	2+3	TON[c]
1	3.50	25	30	100	17	83	100	43
2	1.75	25	20	51	16	84	100	43
3	0.70	120	60	100	15	85	100	429
4[d]	0.35	140	30	100	15	85	100	1143
5[e]	0.35	140	180	100	14	86	100	2285

[a] Time necessary to attain near-to-maximum conversion. [b] Selectivity and conversions determined by GC and calculated based on the reacted substrate. [c] TON = moles of the substrate converted/moles of $H_3PW_{12}O_{40}$. [d] [**1**] = 0.40 M. [e] [**1**] = 0.80 M.

The reaction proceeds similarly to that in DMF, giving aldehyde **2** and alcohol **3** in a quantitative total yield and with the selectivity for the latter being as high as 86%. Notably, the stagnation phenomenon was less pronounced in DMA: at room temperature with 3.50 mM $H_3PW_{12}O_{40}$, a near-complete conversion was achieved (Table 3, run 1), whereas in DMF, the reaction became stagnated even at a higher catalyst concentrations (see Table 1, run 1). This advantage allowed us to obtain higher TONs (up to 2285, Table 3, run 5) in DMA than in DMF. Moreover, the reaction in DMA is much faster than in DMF (compare Table 1, run 10 and Table 3, run 3; Table 1, run 15 and Table 3, run 4).

We could not find in the literature precise values of pK_a for DMF·H^+ and DMA·H^+; however, DMA is expected to be more basic than DMF owing to the electron-donating effect of the additional methyl group. Therefore, the results obtained are surprising: in DMA, the competition between the solvent oxygen atoms and the epoxide oxygen for the protons of $H_3PW_{12}O_{40}$ should be stronger than in DMF. A possible explanation for the difference in catalyst performance in these two solvents might be the greater acid strength of $H_3PW_{12}O_{40}$ in DMA compared with that in DMF, resulting in higher proton concentrations. In any case, the use of DMA as the solvent for the $H_3PW_{12}O_{40}$-catalyzed isomerization of **1** to synthesize **3** is an excellent practical proposition for industrial applications (even better than DMF) owing to the advantage of higher boiling point of this solvent (166 °C) and the possibility to obtain high product yields at very low catalyst loading, that is, to obtain higher TONs.

Isomerization of α-pinene oxide (1) in other solvents: The data on the $H_3PW_{12}O_{40}$-catalyzed transformations of **1** in various solvents are presented in Table 4. These results showed that the nature of the solvent can profoundly affect the reaction pathways and product composition, which allowed us to develop efficient syntheses of compounds **2**–**5** in good to excellent yields through the appropriate choice of the solvent.

Table 4. Isomerization of α-pinene oxide (**1**; 0.15 M) catalyzed by $H_3PW_{12}O_{40}$ (PW) in various solvents.

Run	Solvent	[PW] [mM]	*T* [°C]	Time [min]	Yield[a] [%] 2	3	4a	4b	5	TON[b]
1[c]	cyclohexane	PW/SiO_2	15	60	70	24	–	–	–	920
2[c]	cyclohexane	PW/SiO_2	25	5	70	28	–	–	–	460
3	1,4-dioxane	0.35	25	5	40	48	9	–	–	429
4	$PhNO_2$	0.35	25	5	30	16	6	6	24	429
5	MeCN	7.00	60	180	22	20	38	–	4	22
6[d]	DMF	0.35	140	180	10	90	–	–	–	1143
7[e]	DMA	0.35	140	180	14	86	–	–	–	2285
8	acetone	1.50	5	15	17	9	–	–	70	100
9	acetone	0.0075	25	10	15	12	71	–	–	20000
10	acetone	0.35	5	5	17	11	53	14	5	429
				30	17	9	26	20	27	429

[a] Yield by GC; conversions were 100% in all runs. [b] TON = moles of the substrate converted/moles of $H_3PW_{12}O_{40}$. [c] 20% PW/SiO_2 was used as a heterogeneous catalyst: 0.30 wt% in run 1 and 0.60 wt% in run 2.[15] [d] [**1**] = 0.40 M. [e] [**1**] = 0.80 M.

As can be seen in Scheme 2, the relative amounts of aldehyde **2**, on the one hand, and *para*-menthenic compounds **3**–**5**, on the other hand, which are formed from epoxide **1**, depend on the balance between the two types of isomerization of carbenium ion **A**: 1) into cyclopentanic cation **B** (route B) and 2) into *para*-menthenic cation **C** (route A). Tertiary carbenium ion **C** is expected to be more thermodynamically stable than secondary carbenium ion **B**; therefore, the formation of aldehyde **2** should be kinetically controlled. Carbenium ion **C**, in its turn, can undergo either a direct deprotonation to give **3** or a nucleophilic attack by water to give **4a**, whose further acid-catalyzed dehydration can give **5**. It has been shown (see below) that the latter reaction proceeds through the intermediate isomerization of *trans*-sobrerol (**4a**) into *cis*-sobrerol (**4b**), which is not an unexpected result. It should be mentioned that, generally, water was not added to the reaction system. The amount of hydration water that is present in the $H_3PW_{12}O_{40}$ catalyst and commercial α-pinene oxide (**1**) and solvents was sufficient for the formation of sobrerol.

The data on polarity (dielectric constants) for the solvents used in the present work and approximate pK_a values for corresponding conjugated acids are given in Table 5. We have observed remarkable effects of these solvent characteristics on the transformations of **1** in the presence of $H_3PW_{12}O_{40}$. First, the increase in both solvent basicity and polarity strongly prejudices route B to form aldehyde **2**, whereas it favors route A to form *para*-menthenic compounds **3**–**5**. Second, the distribution between the latter

Table 5. Dielectric constants (ε) for the solvents and pK_a values for corresponding conjugated acids.

Solvent	ε	Conjugated acid	Approximate pK_a (relative to water)[25]
DMA	37.8	$DMA\cdot H^+$	−0.5
MeCN	37.5	$MeCNH^+$	−10
DMF	36.7	$DMF\cdot H^+$	−0.5
$PhNO_2$	34.8	$PhNO_2H^+$	−11
acetone	20.7	$(CH_3)_2COH^+$	−7
1,4-dioxane	2.2	$C_4H_8O_2H^+$	−3.5
cyclohexane	2.0	–	–

compounds depends on solvent basicity rather than on its polarity: in more basic solvents, the direct deprotonation of cation **C** to give **3** is much more preferable than the formation of compounds **4** and **5**.

Indeed, in cyclohexane, a nonpolar nonbasic solvent, the main reaction product is aldehyde **2** (70 % yield as determined by GC), with **3** being the only minor product (approximately 25 % yield; Table 4, runs 1 and 2). No trace amounts of compounds **4** and **5** are detected in this solvent. On the other hand, in 1,4-dioxane, which is also a nonpolar, albeit basic, solvent, compounds **3** and **4a** derived from cation **C** account for as much as 57 % of the mass balance (Table 4, run 3). The yield for aldehyde **2** in this solvent was only 40 %, whereas the yield for alcohol **3** was 48 %.

In polar solvents with similar dielectric constants, the yield of aldehyde **2** decreases with the increase in solvent basicity: $PhNO_2$ (30 %) > MeCN (22 %) > DMF(10 %) ≈ DMA (14 %) (Table 4, runs 4–7). On the other hand, a combined yield of *para*-menthenic products **3**–**5** increases in the same order from 52 % ($PhNO_2$) to approximately 90 % (DMF and DMA). To evaluate the role of solvent polarity in this reaction, the results obtained in acetone can be compared with those in dioxane (Table 4, runs 8–10 vs. run 3). The weaker basicity of acetone should favor the formation of aldehyde **2**; however, only 15–17 % yield was obtained in acetone versus 40 % in dioxane. This appears to occur owing to the much higher polarity of acetone; therefore, it can be concluded that the increase in solvent polarity clearly favors the isomerization of cation **A** to cation **C** at the expense of route B (Scheme 2).

Thus, in the polar solvents studied herein, the $H_3PW_{12}O_{40}$ catalyst transforms **1** mainly into the products that are derived from intermediate **C**, that is, compounds **3**, **4**, and **5**. Moreover, the higher the solvent basicity is, the higher the combined yield of these products. A possible explanation for these results might be a stabilization of cation **A** by the interaction with polar solvents owing to their increased ion-solvating ability, which favors the rearrangement of **A** into the thermodynamically more stable tertiary carbenium ion **C**. It is expected that the isomerization pathways of the initially formed cation **A** should be very sensitive to the degree of solvation and bonding with the nucleophilic species present in the reaction solutions, including anions.

It is remarkable that the individual selectivities for the products **3**, **4**, and **5** can also be controlled by the choice of solvent characteristics. Basic solvents, that is, DMA and DMF, favor the direct deprotonation of cation **C** owing to their relatively strong proton–acceptor properties. As a result, **3** is formed in these solvents as the only *para*-menthenic product with a chemoselectivity of up to 93 % (see Tables 1 and 3). On the other hand, in weakly basic polar solvents, such as acetone, nitrobenzene, and acetonitrile, alcohol **3** becomes the minor product (selectivity of 10–20 %), whereas compounds **4** and **5** become the major products. As the selectivities are higher in acetone, we have optimized the reaction conditions in this solvent and obtained compounds **4a** and **5**, each in a 70 % yield, which is a synthetically valuable result (Table 4, runs 8 and 9).

Although **5** can be formed directly from cation **C** by the intramolecular nucleophilic attack of the hydroxy group on C7, this route looks unlikely, at least, in acetone. We have shown that in acetone, **5** is formed by the acid-catalyzed dehydration of **4b**, which arises from the acid-catalyzed isomerization of the primarily formed, **4a**. At a very high substrate/catalyst ratio ([**1**]/[$H_3PW_{12}O_{40}$] = 20000; Table 4, run 9), a 71 % yield of **4a** can be obtained, without any trace amounts of the isomer **4b** and pinol **5**. The reaction is very fast: at room temperature, a complete conversion occurs within 10 min. When the reaction mixture was allowed in contact with the catalyst for more 3 h, the product distribution remained roughly the same, except for the trace appearance of **4b**. On the other hand, the addition of more $H_3PW_{12}O_{40}$ to the reaction solution resulted in the appreciable conversion of **4a** into **4b** and then into **5**. Such behavior is illustrated by the data in Table 4, run 10 ([**1**]/[$H_3PW_{12}O_{40}$] = 429). Only small amounts of **4b** and **5** are detected after reacting for 5 min upon which complete conversion of the substrate has been already achieved, with **4a** accounting for as much as 53 % of the mass balance. At longer reaction times, the concentration of **4a** starts to decrease, whereas those of **4b** and **5** begin to increase.

Under appropriate conditions, pinol **5** was obtained from **1** in a 70 % yield and TON = 100 (Table 4, run 8). As can be seen from Table 4, not only the nature of the solvent but also the changes in other reaction variables, such as temperature, reaction time, and $H_3PW_{12}O_{40}$ loading, significantly affect the product composition. However, it should be mentioned that such changes only affect the relative amounts of products **4a**, **4b**, and **5**, whereas the amounts of aldehyde **2** and alcohol **3** remain virtually the same (Table 4, runs 8–10). In other words, the balance between the reaction pathways (i.e., route B versus route A and deprotonation of intermediate **C** versus nucleophilic attack by water) is mostly determined by the nature of the solvent rather than by other reaction conditions.

Conclusion

Heteropoly acid $H_3PW_{12}O_{40}$ is a very efficient, environmentally benign and versatile catalyst for the liquid-phase isomerization of α-pinene oxide (**1**). Good control of chemoselectivity can be achieved through the choice of the solvent, whose polarity and basicity strongly affect the reaction pathways. This simple and low-cost method provides a new attractive entry point to the synthesis of several high-priced low-volume ingredients for the fragrance industry with good to excellent yields and remarkable atom economy and selectivity. The catalyst shows high turnover numbers (100–20000) and, in principle, could be recycled. To the best of our knowledge, this work represents the first example of the synthesis of isomers from α-pinene oxide (**1**) (other than campholenic aldehyde (**2**)) with a selectivity that is sufficient for practical usage. Further studies are targeted towards the development of solid heteropoly acid catalysts that are resistant to leaching in polar solvents to facilitate catalyst separation.

Experimental Section

Chemicals were purchased from commercial sources and used as received, unless otherwise stated. $H_3PW_{12}O_{40}$ hydrate and α-pinene oxide were purchased from Aldrich.

The reactions were carried out in a glass reactor equipped with a magnetic stirrer at 5–140 °C. In a typical run, a mixture of α-pinene oxide (**1**; 0.228–1.216 g, 1.5–8.0 mmol, 0.15–0.80 M), dodecane (225 μL, 1.0 mmol, 0.10 M, internal standard) and $H_3PW_{12}O_{40}$ (0.01–0.2 g, 3.5–70 μmol, 0.35–7.00 mM) in a specified solvent (10 mL) was intensively stirred under air at a specified temperature. The reaction progress was monitored by GC by using a Shimadzu 17 instrument fitted with a Carbowax 20 M capillary column and a flame ionization detector. At appropriate time intervals, aliquots were taken, diluted with hexane (1:10 v/v) to separate the heteropoly acid and then analyzed by GC. The GC mass balance, product selectivities, and yields were calculated based on the substrate (dodecane was used as the internal standard). The difference was attributed to the formation of oligomers, which were not GC determinable.

Products were isolated by column chromatography (silica) and identified by ^{1}H and ^{13}C NMR spectroscopy (Bruker DRX-400, tetramethylsilane, $CDCl_3$, COSY, HMQC, DEPT and NOESY experiments).Spectroscopic data for campholenic aldehyde (**2**) and *trans*-carveol (**3**) were reported in our previous work.[15] Spectroscopic data for *trans*-sobrerol (**4a**): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.08$ (s, 3H; C9-H_3), 1.14 (s, 3H; C8-H_3), 1.26–1.32 (m, 1H; C3-*H*H), 1.62–1.68 (m, 1H; C5-*H*H), 1.71 (s, 3H; C10-H_3), 1.68–1.73 (m, 1H; C4-H), 1.96–2.05 (m, 2H; C3-H*H* and C5-H*H*), 3.96 (brs, 1H; C2-H), 5.44–5.49 ppm (m, 1H; C6-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 20.82$ (C10), 25.44 (C9), 27.38 (C5), 27.83 (C8), 32.49 (C3), 38.79 (C4), 68.43 (C2), 72.24 (C7), 125.08 (C6), 134.42 ppm (C1). Spectroscopic data for pinol (**5**): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta ? = 1.19$ (s, 3H; C9-H_3), 1.31 (s, 3H; C8-H_3), 1.70 (d, ^{4}J(H,H) = 2.0 Hz, 3H; C10-H_3), 1.84 (d, ^{2}J(H,H) = 10.6 Hz, 1H; C3-HH), 2.08–2.13 (brm, 1H; C4-H), 2.19–2.24 (m, 1H; C3-H*H*), 2.24–2.66 (m, 2H; C5-H_2), 3.98 (d, ^{3}J(H,H) = 5.0 Hz, 1H; C2-H), 5.18–5.20 ppm (m, 1H; C6-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 21.48$ (C10), 25.49 (C8), 30.43 (C5), 30.52 (C9), 34.66 (C3), 41.90 (C4), 76.71 (C2), 82.83 (C7), 120.29 (C6), 139.62 ppm (C1).

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