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Effect of Microwave Irradiation on the Catalytic Activity of Palladium Supported Catalysts in the One-Step Isomerisation of *Cinchona* Alkaloids to $\Delta^{3,10}$-Isobases

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Abstract Efficiency of palladium solid supported (Pd/SS) catalysts for one-step isomerisation of the side chain of four natural *Cinchona* alkaloids have been explored under controlled microwave heating in the green media (50% aqueous ethanol or ethylene glycol with HCl). Conversion progress and products purity was monitored by TLC and by ^{1}H NMR spectrometry. Final conversion is dependent on the support (Al_2O_3, C or $BaSO_4$), reaction time and temperature. Very good results: high yields and purity of (Z/E) $\Delta^{3,10}$-isomers were obtained from quinine and quinidine with 10% Pd/$BaSO_4$ as the catalyst, which is less effective for isomerisation of cinchonine and cinchonidine. Enhancing energy efficiency can be possible when the responsive support selective absorbs of microwave energy, which is translated to the palladium giving acceleration of the formation and disintegration of the transition state leading to $\Delta^{3,10}$-isomers.

Graphical Abstract
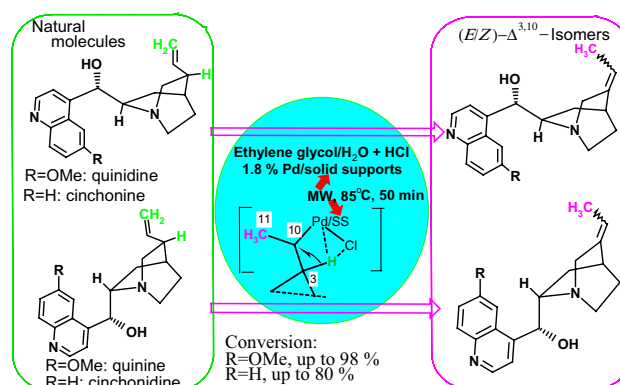
1 Introduction

The vinyl side chain plays an important role in the structure of natural molecules of *Cinchona* alkaloids [1, 2]. It is a stereo-differentiating element [3] imparting a variety their physicochemical properties and biological activity for quinidine **1a** (antiarrhythmic agent) [4] versus quinine **2a** (antimalarial activity) [5], and for cinchonine **1b** versus cinchonidine **2b**. All the four natural compounds, their derivatives and metal complexes have become more and more interesting catalysts for asymmetric syntheses [6]. Recently they play an important role in the preparation of new chiral nanomaterials [7, 8].

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The *Cinchona* $\Delta^{3,10}$-isomers **3a,b** and **4a,b** (Scheme 1) were investigated as effective chiral modifiers of solid-supported metallic catalysts for enantioselective hydrogenation of activated ketones [9–11]. $\Delta^{3,10}$-Isobases were applied also as valuable intermediates for modification of the native structure [12] including the oxidative cleavage of the double bond [13–16].

The isomerisation of the vinyl bond to the 3,10 position of *Cinchona* alkaloid molecules has been investigated for more than 100 years [17]. At the beginning, H_2SO_4 has been used, which resulted in many side processes such as the cleavage of methyl ethers in molecules **1a** and **2a** giving phenols. It was necessary to use of diazomethane for etherification [18, 19]. Two-step synthesis of the $\Delta^{3,10}$-isobases **3a,b** and **4a,b**, consisting of hydrogen halide addition and subsequent elimination by different bases has been elaborated [14–16, 20, 21]. However this way cannot be considered today as a modern preparative method by reason of poor atom economy, which is even poorer when additional stages of protection–deprotection of the hydroxy group must be performed [13, 14] for prevention of the formation of isomers possessing an intramolecular ether bond between C9 and C10.

In 1968 it was discovered that migration of double bond in natural quinidine and quinine **1a** and **1b** occurs during their commercial hydrogenation with Pd-C catalyst and furthermore that $\Delta^{3,10}$-isomers **3a** and **4a** are resistant to subsequent hydrogenation [22]. The effective isomerisation of methoxy alkaloids **1a** and **2a** to (*Z/E*)-**3a** and (*Z/E*)-**4a** was performed using rhodium solid supported catalysts (Rh/SS) in a medium of 50% EtOH in the presence of HCl under heating in water bath for a period of 24 h [23]. However, very low activity of palladium supported catalysts (Pd/SS) has been noted in this conditions. In 2005 ruthenium (III)
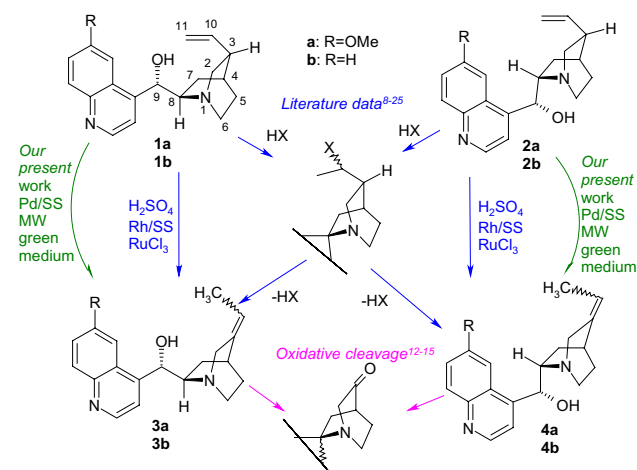
chloride trihydrate was used with addition of H_2SO_4 in ethanol for homogeneous quinine isomerisation [12]. Both those catalysts are expensive and cannot be used for large scale processes.

Microwave enhancement of many catalytic syntheses has been described [24–26]. Recently are described transformations of polar organic molecules in water with enhancing energy efficiency by microwaves with core/shell catalysts [27]. The heat generated at the core area of the support by microwave irradiation can be translated to the shell catalyst directly. Such localized heating allows maximum heat utilization and enhances the energy efficiency of catalytic reaction.

We have established that the difficult Fischer indole synthesis can be accelerated by microwaves together with using green reagents: catalytic amounts of $ZnCl_2$ loaded on K10 clay [28] or dissolved in triethylene glycol [29]. We have recently described the results of our research on relationship structure–reactivity of natural *Cinchona* alkaloids *O*-tosyl derivatives in hydrolysis to 9-epibases. We found that replacement of conventional heating with microwave activation leads to different products [30, 31].

Our present synthetic interest concentrates on finding an effective and cheap method of transformation of four *Cinchona* alkaloids **1a,b** and **2a,b** into the corresponding $\Delta^{3,10}$-isobases **3a,b** and **4a,b**. We envisioned that heating of substrates under microwaves with palladium on solid supports (Pd/SS) together with HCl can solve this problem. This paper described our work on influence of controlled microwave heating on activity of palladium solid supported (Pd/SS) catalysts in the heterogeneous isomerisation of four natural Cinchona alkaloids. We studied also possibility of analysis and isolation of the geometric isomers Z and E in $\Delta^{3,10}$-isomers, as they will be used as chiral ligands [7, 8], catalysts and modifiers in asymmetric syntheses [9–12].

2 Results and Discussion

Four commercial *Cinchona* alkaloids **1a,b, 2a,b** were subjected to catalytic isomerisation of the side chain using tested palladium catalysts supported on various solids. We applied microwave activation instead conventional heating in water bath. Two methods regarding to reaction medium and temperature were used: method 1—controlled microwave heating at 70 °C in an aqueous ethanol [31] and method 2—heating at 85 °C in a medium of ethylene glycol (EG).

Our initial small-scale experiments under controlled microwave heating were performed with 0.5 mmol of the substrate **1a** or **2a** at 70 °C in a medium comprised of 50% EtOH with HCl aq in the presence of catalytic amount (1.8%) of 10% palladium loaded on various solid supports (method 1). This procedure was tested to find the optimal

Scheme 1 Modes of transformations of the natural Cinchona alkaloids **1a,b, 2a,b** into the $\Delta^{3,10}$-isobases **3a,b, 4a,b**

time for conversion of **1a** or **2a** to the isomers (*Z/E*)-**3a** or (*Z/E*)-**4a**. We monitored the ongoing conversion progress of substrates by taking micro-samples of the reaction mixture regularly, at 10-min intervals, which after extraction with diethyl ether in the presence of aqueous ammonia were analyzed by TLC (silica gel plates, methoxyethanol). The R_f values of the products **3a** and **4a** are higher than the R_f values of the substrates **1a** and **2a** (see Table 3). The reaction mixtures were irradiated for 30 min or after 50 min. After this times crude products were isolated and qualitatively and quantitatively analysed by ^{1}H NMR spectroscopy (Table 1).

Analysis of ^{1}H NMR spectra give the possibility to estimate the amount of product and unconverted substrate and also ratio (*Z*) to (*E*) isomers in the crude product for each experimental entry. The region of 6.10–4.00 ppm in the ^{1}H NMR spectra is useful for relative amount of components determination as is shown in the Fig. 1. The alkene protons of =HC–Me from (*Z*)- and (*E*)-$\Delta^{3,10}$-isomers give two separate signals according to the literature data [12, 13, 25]. Determination of unconverted substrates can be possible from integration of peaks: =CH$_2$ protons (two doublets at ~4.90–5.10 ppm) or –CH= (multiplet at ~6.00 ppm).

Table 1 Results of microwave-promoted isomerisation of quinidine **1a** and quinine **2a** into **3a** and **4a** (Scheme 2) with palladium supported catalysts in 50% aqueous ethanol in the presence of HCl at the controlled temperature 70 °C (method 1)

Entry	Substrate	Catalyst	Time (min)	Product	Yield[a] (%)	Conversion[b] (%)	The *Z/E* ratio in crude products[b]
1	**1a**	Pd/Al$_2$O$_3$	30	(*Z/E*)-**3a**	95	80	7.0
2	**1a**	Pd/Al$_2$O$_3$	50	(*Z/E*)-**3a**	95	85	4.7
3	**2a**	Pd/Al$_2$O$_3$	30	(*Z/E*)-**4a**	98	70	1.8
4	**2a**	Pd/Al$_2$O$_3$	50	(*Z/E*)-**4a**	98	72	1.6
5	**1a**	Pd/C	30	(*Z/E*)-**3a**	75	70	2.7
6	**1a**	Pd/C	50	(*Z/E*)-**3a**	75	75	2.7
7	**2a**	Pd/C	30	(*Z/E*)-**4a**	65	60	1.4
8	**2a**	Pd/C	50	(*Z/E*)-**4a**	60	65	1.4
9	**1a**	Pd/BaSO$_4$	30	(*Z/E*)-**3a**	96	87	6.3
10	**1a**	Pd/BaSO$_4$	50	(*Z/E*)-**3a**	96	94	5.7
11	**2a**	Pd/BaSO$_4$	30	(*Z/E*)-**4a**	97	80	3.0
12	**2a**	Pd/BaSO$_4$	50	(*Z/E*)-**4a**	97	91	2.6

[a]Isolated yields of crude product **3a** or **4a** from the reaction mixture

[b]Determined conversion of **1a** or **2a** into **3a** or **4a** and their *Z/E* ratio from ^{1}H NMR spectra of crude products

Scheme 2 One-pot isomerisation of the side chain with palladium supported catalysts under microwave activation

Method 1. Pd/SS, EtOH + H$_2$O, HCl, MW 70 ºC
Method 2. Pd/SS, EG + H$_2$O, HCl, MW, 85 ºC
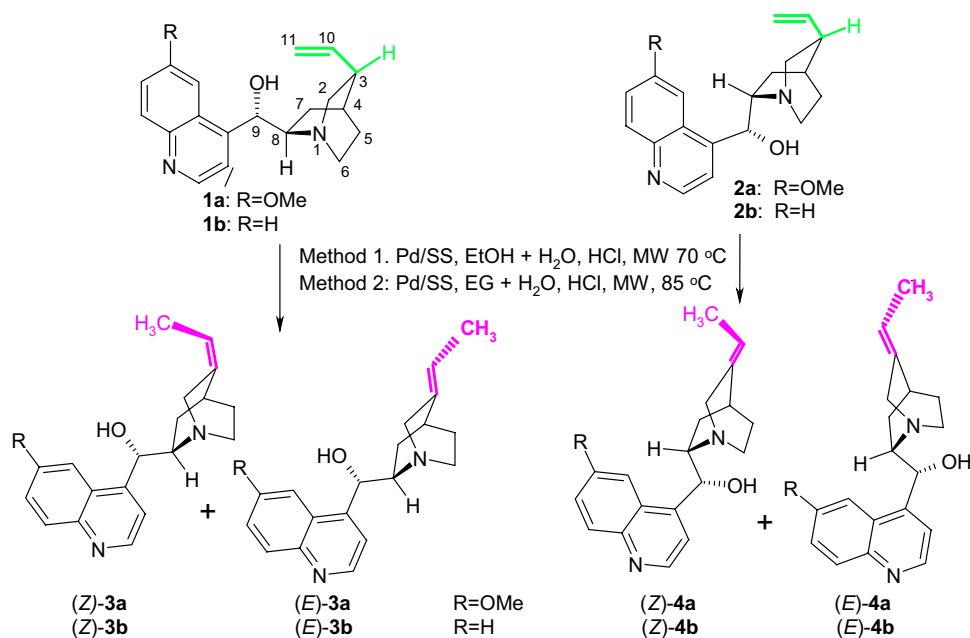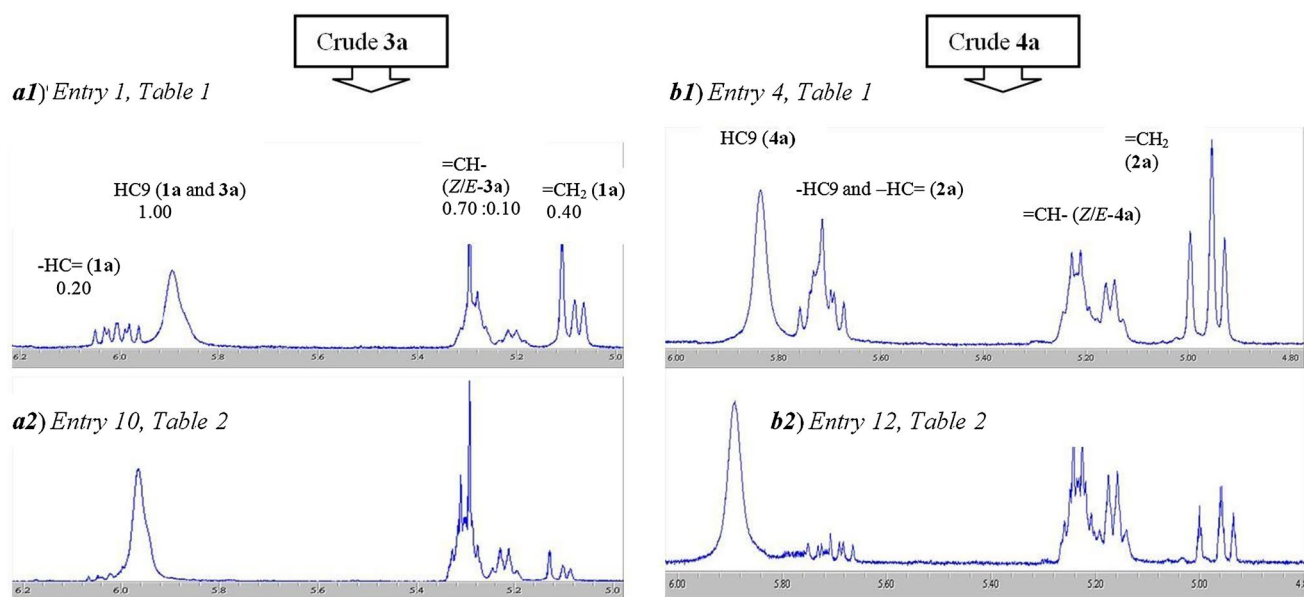
Fig. 1 Examples of fragments of ¹H NMR spectra (6.20–4.80 ppm) used for determination of the *Z/E* ratio in Δ^{3-10}-isomers **3a, 4a** and for analysis of their contamination by unconverted substrates **1a** or **2a**: crude **3a: a1** (see **Fig. S1** in Supplementary Materials–SM); **a2** (see **Fig. S3** in SM); crude **4a: b1** (see **Fig. S4** in SM); **b2** (see **Fig. S6** in SM)

The example presented in Fig. 1-a1 shows the analytical methodology for determination of the amounts of components in the crude **3a** from entry 1, Table 1 (ESM Fig. S1). The signal of the alkene proton of the isomer (*Z*)-**3a** appears as a multiplet at 5.30 ppm (integration 0.70) whereas the signal of the isomer (*E*)-**3a** is showed as a quartet at 5.33 ppm (integration 0.10) but two protons of the =CH$_2$ group from the unconverted substrate **1a** give two doublets in the region of 5.13–5.03 ppm (integration 0.40). The comparative integration of the relevant signals give the ratio of (Z)-**3a**/(E)-**3a**/unconverted substrate **1a** which is 70:10:20. The conversion progress of 80% can also be inferred from the comparative integration of HC9 proton signal summed for the substrate **1a** and the products (*Z/E*)-**3a** at 5.90 ppm (integration 1.00) and the signal of –CH= proton of the vinyl group of **1a**, which gives a multiplet (ddd) at 6.06–5.94 ppm (integration as 0.2).

The conversions of **2a** to (*Z/E*)-**4a** in our tested reactions were determined from the ¹H NMR spectra of the crude products as shown in Fig. 1-b1. The conversion in entry 4, Table 1 (see also Fig. S4 in SWM) was determined by comparison of integrations of two doublets of two protons of the =CH$_2$ group of **2a** and the summed signals of one alkene proton of (*Z/E*)-**4a** isomers. Analysis of the region revealed that the crude product contains 28% of unconverted substrate **2a** together with (*Z*)-**4a** + (*E*)-**4a** in the ratio 1,6. We can see from Table 1 that in method 1 the best conversion for quinidine **1a** into (*Z/E*)-**3a** is 94% (entry 10) and for quinine **2a** into (*Z/E*)-**4a** is 91% (entry 12) with the Pd/BaSO$_4$ catalyst when the irradiation time is prolonged to 50 min.

We wanted to maximise yields of $\Delta^{3,10}$-isomers (*Z/E*)-**3a** and (*Z/E*)-**4a** by adopting higher temperature (85 °C) and changing the reaction medium to 50% aqueous ethylene glycol (method 2, Table 2). In the case of two catalysts, Pd/Al$_2$O$_3$ and Pd/SO$_4$ (entries 1–4 and 9–12, Table 2), an increased conversion of substrates **1a** and **2a** to the $\Delta^{3,10}$-isomers (*Z/E*)-**3a** and (*Z/E*)-**4a** was observed in comparison to method 1, (Table 1). However, in the reactions catalysed by the Pd/C catalyst, the conversion to both $\Delta^{3,10}$-isomers was lower in method 2 (entries 5–8, Table 2) in comparison to method 1 (entries 5–8, Table 1).

The differences of results obtained in both methods (method 1 and method 2) is visible by comparison of the diagnostic regions of ¹H NMR spectra of the crude product **3a** and **4a**. Figure 1-a2 (see also Fig. S3 in SM) shows the ¹H NMR spectrum of the most pure (*Z/E*)-**3a** and Fig. 1-b2 (see also Fig. S6 in SM) presents of the best crude product (*Z/E*)-**4a** (entry 12, Table 2).

We noted that the microwave promotion of vinyl bond isomerisation in both alkaloids, quinidine **1a** and quinine **2a**, is less selective at temperatures higher than 85 °C. Irradiation of the reaction mixture at 100 °C in ethylene glycol leads to the cleavage of the quinuclidine ring giving quinotoxine (quinicine). The process of the high-temperature cleavage of Cinchona alkaloids in acidic medium is well known and is described in the literature as Pasteur rearrangement [1, 17].

It is interesting to note that only traces of isomerisation products (*Z/E*)-**3a** or (*Z/E*)-**4a** were formed in experiments conducted with palladium solid supported catalysts:

Table 2 Results of microwave-promoted isomerisation of quinidine **1a** and quinine **2a** into **3a** and **4a** (Scheme 2) in 50% aqueous ethylene glycol in the presence of HCl at the controlled temperature 85 °C (method 2)

Entry	Substrate	Catalyst	Time (min)	Product	Yield[a] (%)	Conversion[b] (%)	The Z/E ratio in crude products[b]
1	**1a**	Pd/Al₂O₃	30	(Z/E)-**3a**	92	87	3.4
2	**1a**	Pd/Al₂O₃	50	(Z/E)-**3a**	90	90	5.0
3	**2a**	Pd/Al₂O₃	30	(Z/E)-**4a**	93	75	1.5
4	**2a**	Pd/Al₂O₃	50	(Z/E)-**4a**	91	80	1.5
5	**1a**	Pd/C	30	(Z/E)-**3a**	75	60	2.0
6	**1a**	Pd/C	50	(Z/E)-**3a**	74	70	6.0
7	**2a**	Pd/C	30	(Z/E)-**4a**	78	60	2.0
8	**2a**	Pd/C	50	(Z/E)-**4a**	80	56	2.3
9	**1a**	Pd/BaSO₄	30	(Z/E)-**3a**	95	95	3.8
10	**1a**	Pd/BaSO₄	50	(Z/E)-**3a**	**96**	**98**	3.9
11	**2a**	Pd/BaSO₄	30	(Z/E)-**4a**	94	90	1.6
12	**2a**	Pd/BaSO₄	50	(Z/E)-**4a**	**95**	**96**	1.7

[a]Isolated yields of crude product **3a** or **4a** from the reaction mixture

[b]Determined conversion of **1a** or **2a** into **3a** or **4a** and their Z/E ratio from ^{1}H NMR spectra of crude products
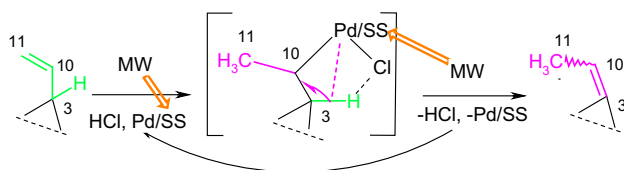
Scheme 3 Plausible mechanism of positional isomerisation of the vinyl bond in the Cinchona alkaloid molecules

a. with the use of conventional heating instead of microwave irradiation in the same reaction medium, temperature and time prolonged to 24 h as indicated in the literature [23].

b. when the alkaloids **1a** or **2a** were irradiated without hydrochloric acid with all the catalysts investigated at 70–90 °C for 50 min in EtOH/H₂O and also in EG/H₂O.

The above described results mean that hydrochloric acid not only facilitate perfect solubility of the basic reactants in the reaction mixture but also acts together with palladium leading proton addition to H_2C^{11}= and elimination from HC^3 giving positional isomerisation of the double bond (Scheme 3).

The effect of the best microwave activation of the isomerisation process of **1a** and **2a** catalysed by palladium loaded on very polar BaSO₄ can mean that the support selectively adsorbs microwave energy, which is translated to the palladium giving acceleration of the formation and disintegration of the transition state leading to more stable $\Delta^{3,10}$-isomers.

To expand the range of substrates, two effective catalysts, Pd/Al₂O₃ and Pd/BaSO₄, were evaluated in the microwave-accelerated one-step isomerisation of the double bond in the molecules of cinchonine **1b** and cinchonidine **2b** by method 2. We found out that the full conversion to the appropriate $\Delta^{3,10}$-isomers **3b** and **4b** cannot be achieved for any combination of catalyst and time. For these alkaloids the best results were obtained with Pd/Al₂O₃ catalyst. That fact can be regarded as the difference in energy of the transition state in the isomerisation process of each of alkaloids. The crude product **3b** was formed as a mixture of $\Delta^{3,10}$-isomers (Z)-**3b** and (E)-**3b** in a ratio of 2.5 containing 20% of unconverted **1b**. The crude product **4b** was prepared from **2b** as a mixture of the (Z/E) $\Delta^{3,10}$-isomers in a ratio of 2.0 with high contamination (33%) of unconverted **2b**. These data were found from the ^{1}H NMR spectra, which can be seen on Figs. S7 and S9 in SM.

Having at hand the optimized protocol, we performed microwave-promoted syntheses in the scale of 10 mmol [32]. The reaction scale is limited due to the microwave apparatus used in the research. The results were compatible with those obtained in analytical quantities. We checked out that the purification of the crude products **3a,b** and **4a,b** can be achieved by careful recrystallization with aqueous ethanol, which accomplishes separation of starting materials. However, the ratio of the geometric isomers in the recrystallized products is not reproducible and depends on dilution of ethanol and time of cooling.

Pure $\Delta^{3,10}$-isobases **3a,b** and **4a,b** can be isolated by column chromatography because they have the lowest polarity (the highest R_f values, see Table 3) in comparison to the R_f values of the starting alkaloids **1a,b** and **2a,b**. We isolated the mixture of geometric isomers: (Z/E)-**3a** in the ratio of four from crude **3a** in 88.0% yield. The $\Delta^{3,10}$-isocinchonine has been separated in yield of 55.0% as the (Z/E)-**3b** in a ratio 4.5.

Table 3 Values of R_f on silica gel TLC plates of the substrates **1a,b, 2a,b** and main products **3a,b, 4a,b** together with their yields and the ratio of components of Z/E geometric isomers

Substrate/R_f[a]	$\Delta^{3,10}$-Isomer/R_f[a]	Yield[b] of product and its component[c]
Quinidine **1a**: 0.44	(Z/E)-**3a**: 0.65	80%: Z/E = 4.0
Cinchonine **1b**: 0.41	(Z/E)-**3b**: 0.56	55%: Z/E = 4.5
Quinnie **2a**: 0.42	(Z)-**4a**: 0.63 and (E)-**4a** 0.59	16.2%: pure (Z) + 62.5%: Z/E = 1.0
Cinchonidine **2b**: 0.40	(Z)-**4b**: 0.59 and (E)-**4b** 0.55	18.5%: pure (Z) + 41.7%: Z/E = 1.0

[a]2-Methoxyethanol was used as a mobile phase

[b]Yields of products isolated by column chromatography

[c]Analyses of products purity and their components by TLC (during column chromatography) and by ^{1}H NMR spectroscopy

The geometric isomers (E)- and (Z)-$\Delta^{3,10}$-isoquinine **4a** as well as (E)- and (Z)-$\Delta^{3,10}$-isocinchonidine **4b** are visible on the TLC plates as separated spots (R_f values are done in the Table 3). The geometric isomer with the higher R_f value can be partially isolated in pure form. We obtained from the crude **4a** the sample of the single geometric isomer (Z)-**4a** (16.2%) as the first fraction and next, an equimolar mixture of (Z/E)-**4a** isomers (62.5% yield). From the crude **4b**, at first the pure isomer (Z)-**4b** (its ^{1}HNMR spectrum is given on Fig. S10 in SM) was collected (yield 18.5%), and next a 1:1 mixture of (Z/E)-**4b** in yield of 41.7%.

Our experiments provide a new look at the reason of the differences in physicochemical properties of $\Delta^{3,10}$-isobases *Cinchona* alkaloids obtained long ago when not existed possibilities to control molecular composition, which is depended on methods of isomerisation process and also on method of products isolation. Their data in the old literature [18, 19 and ref. givens in 17] have been given probably for $\Delta^{3,10}$-isomeric alkaloids **3a,b, 4a,b** with different ratio of (E)/(Z) geometric isomers.

To the best of our knowledge, the results we obtained are similar to those presented in the literature for expensive heterogeneous (rhodium) and homogenous (ruthenium) catalysts used in this one-step reaction. $\Delta^{3,10}$-Isomers of natural *Cinchona* alkaloids will be applied in material and medicinal chemistry as reactants for preparation of organometallic catalysts and organocatalysts for asymmetric synthesis.

3 Conclusion

We elaborated the microwave-accelerated one-step catalytic isomerisation of the vinyl double bond, the side chain of *Cinchona* alkaloids, using inexpensive palladium solid supported catalyst, which was ineffective for this process under conventional heating. Mixture of ethylene glycol with hydrochloric acid was found as green reaction media. The reaction proved to be tolerant towards other functional groups present in natural molecules of *Cinchona* alkaloids. The conversion is depended on the kind of support, and on time and temperature of reaction.

We used the small analytical scale to choose the best catalyst and the reaction medium under controlled microwave irradiation. Next, the method was developed for the scale of 10 mmoles, which can be expanded to higher preparative scale. Especially good effects of almost complete conversion were obtained with Pd/BaSO$_4$ for quinidine **1a** and quinine **2a** transformations to appropriate $\Delta^{3,10}$-isomers: (Z/E)-**3a** and (Z/E)-**4a**, which were isolated by us in high yields (80% and 79%). The scope of application of our method was extended to the transformation of alkaloids without methoxy groups, **1b** and **2b**, into (Z/E)-**3b** and (Z/E)-**4b** by using Pd/Al$_2$O$_3$ catalyst. Nevertheless, we developed two easy separation methods: the crystallisation with aqueous ethanol and the column chromatography, leading to 55–60% yields of pure $\Delta^{3,10}$-isobases (Z/E)-**3b** and (Z/E)-**4b**. Furthermore, the pure (Z)-$\Delta^{3,10}$-isomers **4a** and **4b** were isolated.

Diversity of the structure and stereochemistry of the natural Cinchona alkaloids results in divergence in conversion degree to $\Delta^{3,10}$-isomers with the each palladium supported catalyst. The fact that Pd/BaSO$_4$ is very effective in the cases of quinine and quinidine, but Pd//Al$_2$O$_3$ is the most effective for cinchonidine and cinchonine can be regarded as the difference in energy of the transition state in the isomerisation processes of both type of alkaloids. So, specific microwave interaction can be postulated in the formation and disintegration of the catalytic transition state: double bond of substrate–palladium-support in irradiated polar reaction mixture for each alkaloid. Our results show opportunity to enhance energy efficiency by the microwave irradiation in heterogenous catalytic reactions in polar reaction media.

4 Experimental Section

4.1 General Information

Commercial *Cinchona* alkaloids from Fluka were used. Catalysts and other reagents and solvents were purchased from commercial suppliers (Sigma-Aldrich) and used without further purification. Microwave heating at the controlled temperature was performed with SYNTHEWAVE 402 reactor

(Prolabo, open system, external IR detector for temperature monitoring, connected with the software of computer for online temperature regulation). The course of reactions was monitored by thin-layer chromatography (aliquots were taken and extracted by ethyl ether in the presence of ammonia), which was carried out on 0.25 mm Merck silica gel (60 F254) plates on aluminum. Pure products were isolated by column chromatography with the Merck silica gel 60 (230–400 mesh). The column output was monitored with TLC. Melting points (uncorrected) were determined on the Bëthius apparatus. The optical rotations were measured on a Perkin Elmer 241 polarimeter. High resolution mass spectra were measured on AMD 604 Inectra GmbH spectrometer (EI) or on GC/MSQP 5050 Shimadzu spectrometer (ESI). IR spectra (KBr pellets) were recorded on FT-IR MAGNA 769 (Nicolet). The ^{1}H and ^{13}C NMR spectra were recorded with VARIAN 400MR spectrometer (^{1}H; 400 MHz, ^{13}C: 100 MHz). Chemical shifts are given relative to TMS ($\delta = 0$) in ppm and refer to residual solvent CDCl$_3$ as internal standard. Examples of analytical ^{1}H NMR spectra are given in Supplementary Material (SM).

4.2 General Procedure for Small Scale Catalytic Isomerisation of *Cinchona* Alkaloids by Method 1 and by Method 2 (Results in the Tables 1, 2)

To a quartz cylindrical vial (volume 10 mL) was loaded with 0.5 mmol of *Cinchona* alkaloid (162 mg **1a** or **2a** versus 147 mg of **1b** or **2b**), 0.75 mL of 50% ethanol (method 1) or 0.75 mL of 50% ethylene glycol (method 2), 0.15 ml (1.8 mmol, 350% mol) of concentrated HCl and 10 mg (1 mg = 0.009 mmol Pd, 1.8% mol) of 10% palladium catalyst (Pd/Al$_2$O$_3$ or Pd/C or Pd/BaSO$_4$). The reaction mixture was irradiated in the Synthewave 402, Prolabo microwave reactor (open system) at the programmed temperature 70 °C (method 1) or 85 °C (method 2). The conversion of substrate was monitored by taking of micro-samples of the reaction mixtures regularly, in the interval of each 10 min, which after extraction with diethyl ether in the presence of aqueous ammonia were analyzed by TLC (silica gel plates, 2-methoxyethanol, R_f values are shown in the Table 3).The irradiation was stopped after 30 min or after 50 min. The reaction mixture was filtered by Celite and added to the cold aqueous ammonia (5 mL). The white solid was filtered off, washed with water and dried. The obtained crude product was analyzed by ^{1}H NMR to determine of the conversion degree and the ratio of geometric isomers. The results of analysis are given in Table 1 (method 1) and in Table 2 (method 2). The examples of spectra of crude products are given in Supporting Material.

4.3 Preparative Scale Isomerisation and Purification of Crude Products

To a quartz cylindrical vial (volume 50 mL) was added 10 mmol of *Cinchona* alkaloid (3.24 g **1a** or **2a** vs2.94 g of **1b** or **2b**), 15.0 mL of 50% ethylene glycol, 3.0 mL 36 mmol, 350% mol of concentrated HCl and 200 mg, of 10% Pd/BaSO$_4$ (20 mg, 0.18 mmol Pd, 1.8% mol). The reaction mixture was irradiated in the Synthewave 402 microwave reactor (open system) at the programmed temperature or 85 °C for a period 50 min. The reaction mixture was filtered by Celite and added to the excess of cold aqueous ammonia. The white solid was filtered off, washed with water and dried. Separation by column chromatography of (Z/E)-$\Delta^{3,10}$-isomers from crude products was performed using 200 g of silica gel and a mixture of ethyl acetate:methanol in the ratio 20:1 as eluent.

4.3.1 The Mixture of Geometric Isomers (Z/E)-(S)-[(2R,4S)-5-Ethylidenequinuclidin-2-yl] (6-methoxyquinolin-4-yl)methanol, (Z/E)-3a in the Ratio 4

The crude $\Delta^{3,10}$-isoquinidine **3a** (3.20 g, 96.0%) was obtained according to entry 10. Table 2 and its purity was determined by ^{1}H NMR spectroscopy (SM, Fig. S3): the conversion 98%, the ratio (Z/E) = (78:20). The crude product was purified by column chromatography and the product as the mixture $\Delta^{3,10}$-isomer (Z/E)-**3a** in the ratio 4:1 was obtained as possessing the most higher R_f value (Table 3). Yield 2.84 g, 88.0%, mp 191.0–192.5 °C, $[\alpha]_D^{22}$ +181.0º (c1 in EtOH); {lit, [13]: mp 178–180 °C, $[\alpha]_D^{15}$ +193.2 (c 1, EtOH) called as an apoquinidine methyl ether}. ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 8.68 (d, $J = 4.4$ Hz, 1H, 2′-H), 7.90 (d, $J = 8.8$ Hz, 1H, 8′-H), 7.54 (d, $J = 4.4$ Hz, 1H, 3′-H), 7.23 (dd, $J = 8.9$, 2.4 Hz, 1H, 7′-H), 7.13 (d, $J = 2.4$ Hz, 1H, 5′-H), 5.97 (br s, 1H, 9-H), 5.33–5.27 (m, 0.8H, 10-H of (Z)-**3a**), 5.27–5.18 (m, 0.2H 10-H of (E)-**3a**), 4.43 (d, $J = 15.6$ Hz, 1H, 2-H), 3.88 (s, 3H, MeO), 3.50 (d, $J = 15.6$, 1H, 2-H), 3.28 (m, 1H, 8-H), 3.06 (m, 1H, 6-H) 2,87 (m, 1H, 6-H), 2.44 (br s, 1H, 4-H), 2.06 (m, 1H, 5-H), 1.68 (m, 2H, 5-H, 7-H), 1.62 (d, $J = 6.4$ Hz, 0.6H (E)–CH$_3$CH=), 1.54 (d, $J = 6.4$ Hz, 2.4H (Z)–CH$_3$CH=), 1.40 (m, 1H, 7-H); ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 157.4 (C6′), 148.2 (C4′), 147.3 (C2′), 144.0 (C9′), 141.8 (C3), 131.3 (C8′), 126.5 (C10′), 121.5 (C3′), 118.6 (C7′), 113.1 (C10), 101.3 (C5′), 71.4 (C9), 59.6 (C8), 55.6 (MeO), 51.2 (C2), 50.0 (C6), 33.5 (C4), 22.5 (C5), 22.3 (C7), 12.3 (C11); IR (KBr), cm^{-1}: 3419. 3160, 2936, 1509, 1432, 1366, 1240, 1120, 1096, 1077, 1054, 1027; MS (EI), m/e (%): 324 (M$^+$, 100%), 309 (16), 189 (45), 136 (95), 108 (20); HRMS (EI): founded 324.18372, for M$^+$, calculated for C$_{20}$H$_{24}$N$_2$O$_2$: 324.18378.

4.3.2 Pure (Z)-4a and the Mixture 1:1 (Z/E)-4a

The crude $\Delta^{3,10}$-isoquinine **4a** (3.08 g, 95.0%) was obtained according to the entry 12, Table 2 and its purity was determined by ^{1}H NMR spectrum (Fig. S6: conversion 96%, Z/E = 6.1/3.5). The crude product was purified by column chromatography. At the beginning the pure $\Delta^{3,10}$-isomer (Z)-**4a** was obtained{0.52 g, 16.2%, mp 180–181 °C, $[\alpha]_D^{22}$ −158.6° (c1 in EtOH)} and next the mixture 1:1 of (Z/E)-**4a** $\Delta^{3,10}$-isomers was collected: yield 0.51 g, 62.5%, mp 184–185 °C, $[\alpha]_D^{22}$ −172.4° (c1 in EtOH). Lit [18, 19]: β-isoquinine or apoquinine methyl ether, mp 183–185 °C, $[\alpha]_D^{15}$ −201.9° (c1 in EtOH) and α-isoquinine or isoapoquinine methyl ether: mp 192–194 $[\alpha]_D^{22}$ −253.4° (c 0.811, EtOH). Spectral data for the $\Delta^{3,10}$-isoquinine as Z:E mixture in ratio 1:1 **(Z/E)-4a, (Z/E)-R-[(2S,4S,)-5-ethylidenequinuclidin-2-yl](6methoxyquinolin-4-yl)methanol**: ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 8.71 (d, J = 4.4 Hz, 1H, 2′-H), 7.92 (d, J = 9.2 Hz, 1H, 8′-H), 7.60 (d, J = 4.4 Hz, 1H, 3′-H), 7.24 (d, J = 2.4 Hz, 1H, 5′-H), 7.14 (dd, J = 9.2, 2.4 Hz, 1H, 7′-H), 5.89 (br s, 1H, 9-H), 5.27–5.20 (m, 0,5 H, 10-H from (Z)-**4a**), 5.20–5.13 (m, 0.5 H, 10-H from (E)-**4a**), 3,84 and 3.82 (2 × s 3H, MeO from (Z/E)-**4a**), 3.60–3.45 (m, 2H, 2-H), 3.24–3.16 (m, 1H, 8-H), 2.94–2.80 (m, 2H, 6-H), 2.42–2.38 (m, 1H, 4-H), 2.08–2.00 (m, 1H, 5-H), 1.92–1.84 (m, 1H, 7-H), 1.70–1.60 (m, 1H, 5-H), 1.52 (d, J = 7.6 Hz, 1,5 H, 11-H from (Z)-**4a**), 1.45 (d, J = 5.8 Hz, 1.5 H, 11-H from (E)-**4a**), 1.42–138 (m, 1H, 7-H);^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 157.4 (C6′), 147.9 (C4′), 147.2 (C2′), 143.2 (C9′), 139.1 (C3), 131.1 (C8′), 126.4 (C10′), 121.3 (C3′), 118.5 (C7′), 113.1 (C10), 101.3 (C5′), 70.9 (C9), 60.8 (C8), 56.5 (C2), 55.7 (MeO), 44.0 (C6), 33.1 (C4), 27.4 (C5, C7), 12.3 (C11); IR (KBr), cm^{-1}: 3200 br, 2990, 1622, 1591, 1566, 1511, 1459, 1384, 1340, 1262, 1190, 1171, 1124, 1090, 1079, 1035. MS (EI), m/e (%): 324 (M$^+$, 85%), 309 (18), 189 (75), 136 (100), 108 (25); HRMS (EI): M$^+$ founded 324.18381, calculated for C$_{20}$H$_{24}$N$_2$O$_2$ 324.18378.

4.3.3 The Mixture of Geometric Isomers (Z/E)-3b in the Ratio 4.5

The crude $\Delta^{3,10}$-isocinchonine **3b** was obtained by method 2 from 10 mmol (2.94 g) **1b** with 200 mg Pd/Al$_2$O$_3$ in yield 95%. Its analysis by ^{1}H NMR (Fig. S7 in SM) was showed 70% containing of (Z/E)-**3b** in the ratio 2.5 and 20% of unconverted substrate **1b**. The crude product (2.80 g) was purified by column chromatography 1.60 g (55.0%) of the pure $\Delta^{3,10}$-isomer (Z/E)-**3b** in the ratio 4.5:1 was collected (^{1}H NMR spectrum see Fig. S8 in SM), mp 210.0–212.0 °C, $[\alpha]_D^{22}$ +157.8 ° (c1 in EtOH). Literature data for apocinchonine [22, 23]:: mp 214–216 °C, $[\alpha]_D^{22}$ +158.8° (c0.510 in EtOH).Spectral data for **(Z/E)-(S)-[(2R,4S)-5-ethylidenequinuclidin-2-yl](quinolin-4-yl)methanol, (Z/E)-3b in**

the ratio 4.5:1: ^{1}H NMR (see, Fig. S8 in SM): (400 MHz, CDCl$_3$, δ, ppm): 8.75 (d, J = 4.8 Hz, 1H, 2′-H), 8.05 (d, J = 8.3 Hz, 1H, 8′-H), 7.84 (d, J = 8.6 Hz, 1H, 5′-H), 7.58 (t, J = 8.3 Hz, 1H, 7′-H), 7.56 (d, J = 4.8 Hz, 1H, 3′-H), 7.20 (t, J = 8.3 Hz, 1H, 6′-H), 5.71 and 5.68 (d, J = 3.6 Hz and d, J = 4.0 Hz, Σ 1H, 9-H in Z/E-**3b**), 5.34 (br s, 1H, OH), 5.23–5.15 (m, 0,82 H, 10-H in (Z)-**3b**), 5.15–5.08 (m, 0.18 H, 10-H in (E)-**3b**), 4.14 (d, J = 16,4 Hz, 1H, 2-H), 3.21 (d, J = 16,4 Hz, 1H, 2-H), 3.14–296 (m, 1H, 8-H), 2.88–2.78 (m, 2H, 6-H), 2.72–2.62 (m, 1H, 6-H), 2.32 (br s, 1H, 4-H), 2.00–1.92 (m, 1H, 5-H), 1.61–1.45 (m, Σ 5H = m, 2H, from 5-H and 7-H + 2 × d, 3H 10-H$_3$ at 1.58 and 1.48, J = 6.4 Hz, for H$_3$C–CH= in (Z/E)-**3b**), 1.41–133 (m, 1H, 7-H);^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 150.4, 149.7, 148.3, 141.9, 130.5, 129.3, 126.8, 125.8, 123.2, 118.6, 113.4, 72.0, 60.2, 51.4, 51.1, 33.7, 27.7, 27,5, 12.6; IR (KBr, cm^{-1}); 3416 (br), 3068, 2917, 2975, 2716 (br), 1620, 1590, 1569, 1509, 1459, 1383, 1333, 1299, 1235, 1209, 1168, 1119, 1099, 1054, 1028, 993, 951, 885, 864, 832, 798, 759, 689; HR MS (ESI) [M + H]$^+$: founded: 295.1811, calculated for C$_{19}$H$_{23}$N$_2$O: 295.1810.

4.3.4 Pure (Z)-4b and Mixture 1:1 (Z/E)-4b

The crude $\Delta^{3,10}$-isocinchonidine **4b** was obtained by method 2 from 10 mmol (2.94 g) **2b** with 200 mg Pd/Al$_2$O$_3$ in yield 92%. Its analysis by ^{1}H NMR (spectrum, Fig. S9 in SM) was showed 65% containing of (Z/E)-**4b** in the ratio 42:23 and 35% of unconverted substrate **2b**. The crude product (2.68 g) was purified by column chromatography. At the beginning the pure $\Delta^{3,10}$-isomer (Z)-**4b** 0.56 g, (18.5%) was separated (^{1}H NMR spectrum—Fig. S10 in SM), m.p. 230.0–232.0 °C, $[\alpha]_D^{22}$ −95.5° (c1 in EtOH), and next was collected 1.24 g, (41.7%) of the mixture 1:1 (Z/E)-**4b** $\Delta^{3,10}$-isomers $[\alpha]_D^{22}$ −172.4° (c1 in EtOH). Spectral data for pure **(R)-[(2S,4S,Z)-5-ethylidenequinuclidin-2-yl](quinolin-4-yl)methanol, (Z)-4b**: ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 8.87 (d, J = 4.6 Hz, 1H, 2′-H), 8.09 (dd, J = 7.8, 1.2 Hz, 1H, 6′-H), 7.99 (dd, J = 8.2, 1.2 Hz, 8′-H), 7.66 (ddd J = 8.2, 7.0, 1.2 Hz, 1H, 7′-H), 7.59 (d, J = 4.6 Hz, 1H, 3′-H), 7.43 (ddd, J = 7.8. 7.0, 1.2 Hz, 1H, 6′-H), 5.80 (d, J = 3.2 Hz, 1H, 9-H), 5.18 (qt, J = 6.8, 2.4 Hz, 1H, 10-H), 3.67–3.58 (m, 1H, 8-H), 3.50 (d, J = 16.4 Hz, 1H, 2-H), 3.37 (d, J = 16.4 Hz, 1H, 2-H), 3.14 (ddd, J = 14.4, 12.2. 4.8 Hz, 1H, 6-β-H), 2,74 (ddd, J = 12.2, 8.7, 4.8 Hz, 6-α-H), 2.35 (d, J = 2.4 Hz, 1H, 4-H), 1.97 (ddd, J = 12.7, 8.7, 1.5 Hz, 5-α-H), 1.79 (tt, J = 11,3,4.3 Hz, 1H, 7-β-H), 1.64–1.54 (m, 1H, 5-β-H), 1.48–1.38 (m, 1H, 7-α-H), 1.42 (d, 3H, J = 6.8 Hz, 11-H);^{13}C NMR, (100 MHz, CDCl$_3$, δ, ppm): 150.8, 150.5, 150.0, 149.1, 148.5, 130.7, 129.4, 127.0, 123.3, 118.5, 115.3, 72.1, 61.5, 57.0, 44.4, 33.6, 26.1, 25.8, 13.1; IR (KBr, cm^{-1}): 3428 (br), 3018, 2929, 2859, 2715 (br), 1622, 1590, 1569, 1508, 1446, 1381, 1345, 1302, 1236,

1160, 1122, 1093, 1079, 1031, 977, 941, 880, 806, 790, 759, 640; HR MS (ESI) [M + H]$^+$ founded: 295.1813, calculated for $C_{19}H_{23}N_2O$: 295.1810.

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