

# Structure-reactivity study of *O*-tosyl *Cinchona* alkaloids in their new synthesis and in hydrolysis to 9-epibases. Unexpected formation of cinchonine enol tosylate accelerated by microwave activation

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## Abstract

New methods for *O*-tosylation of the natural *Cinchona* alkaloids have been discovered as a biphasic processes with Bu<sub>3</sub>N as a catalyst. The optimized excess of tosyl chloride, necessary for transformation of each of the four alkaloids into *O*-tosyl derivative, decreases in the following order: quinine, quinidine, cinchonidine and cinchonine. The same decreasing order has been noticed for the hydrolysis rate of the appropriate tosylates to 9-epibases. Difficult conversion of *O*-tosylcinchonine in the hydrolytic medium of aqueous tartaric acid gives 9-epicinchonine together with parallel formation of cinchonine enol tosylate. The latter product is obtained as the main when both cinchonine and cinchonidine tosylates react in the presence of salicylic acid under controlled microwave heating. On the basis of X-ray structure of the new alkene product, the stereoselective *syn*-E2 quinuclidine ring opening process, competing to the S<sub>N</sub>2 hydrolysis is postulated for this transformation.

**Keywords:** Biphasic *O*-tosylation, conformational analysis, cinchonine, microwave enhancement, X-ray structure

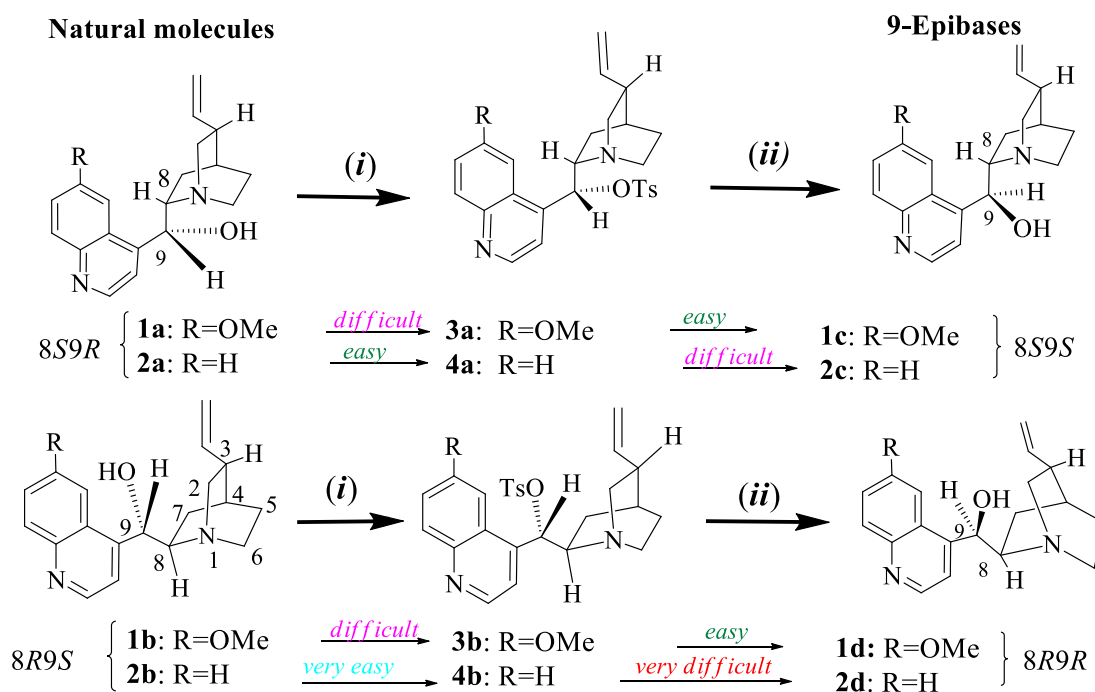
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## Introduction

Molecular diversity of the four main natural *Cinchona* alkaloids: quinine **1a**, quinidine **1b**, cinchonidine **2a** and cinchonine **2b** (Scheme 1) results in their various biological activity.<sup>1,2</sup> The *Cinchona* alkaloids and their derivatives are highly useful as chiral ligands and catalysts for a wide variety of asymmetric synthesis.<sup>3,4</sup> The natural molecules are diastereomeric *erythro*-1,2-aminoalcohols,<sup>5,6</sup> while the *Cinchona* 9-epibases **1c,d** and **2c,d**, first discovered by Rabe,<sup>7</sup> are *threo* diastereomers which do not possess medicinal value.<sup>8</sup> Steric and structural effects are

important for biological activity and chemical reactivity of *Cinchona* alkaloids and play the key role in various catalytic induction of chirality in asymmetric syntheses.<sup>9</sup>

Recently, C9-*O*-derivatives of *Cinchona* alkaloids have attracted considerable attention, as they have the functional group that introduces steric hindrance between quinuclidine and quinoline moieties and modifies polarity that is lower than in the original alkaloids.<sup>10</sup> The hydrolysis of the *O*-tosyl compounds **3a,b**, and **4a,b** as derivatives of natural *erythro*-aminoalcohols **1a,b** and **2a,b**, leads to 9-epibases **1c,d** (for **1a,b**) and **2c,d** (for **2a,b**) with inverted C9 configuration and *threo* configuration in the area of C8-C9. This reaction was first conducted by Suszko and co-workers almost eighty years ago.<sup>11-13</sup> They discovered that the weak acid was the only proper aqueous medium for hydrolysis of *O*-tosyl *Cinchona* alkaloids, however, it was not efficient for synthesis of 9-epicinchonine **2d** by this way. They described slow hydrolysis of *O*-tosyl cinchonine **4b** and incomplete conversion of its sulfonate group.<sup>13</sup> In more recent investigations of the Hoffmann group, many side processes have been observed in various conditions directed to hydrolysis of **4b**. It has been established that the efficient method for C9 epimerization of the natural *Cinchona* alkaloids is the weak acid hydrolysis of their *O*-mesyl derivatives, where steric effects lose their significance.<sup>5b,14</sup> However recently, the Mitsunobu inversion has been elaborated for preparation of *Cinchona* 9-epibases.<sup>15</sup>



**Scheme 1.** Transformation of the natural *Cinchona* alkaloids **1a,b** (8*S*,9*R*), **2a,b** (8*R*, 9*S*) into 9-epibases **1c,d**, (8*S*,9*R*), **2c,d** (8*R*,9*R*) via *O*-tosyl derivatives **3a,b**, **4a,b**: (i): retention of C9 in *O*-tosylation with TsCl, (ii): inversion of C9 configuration in hydrolysis of tosylates in the weak acid medium.

As a continuation of our work on the structure-properties relationship of *Cinchona* alkaloids,<sup>16</sup> we report here the new method of synthesis of *O*-tosyl derivatives **3a,b** and **4a,b** with the stress on research of their reactivity differences in the hydrolysis to 9-epibases **1c,d**, and **2c,d**.

## Results and Discussion

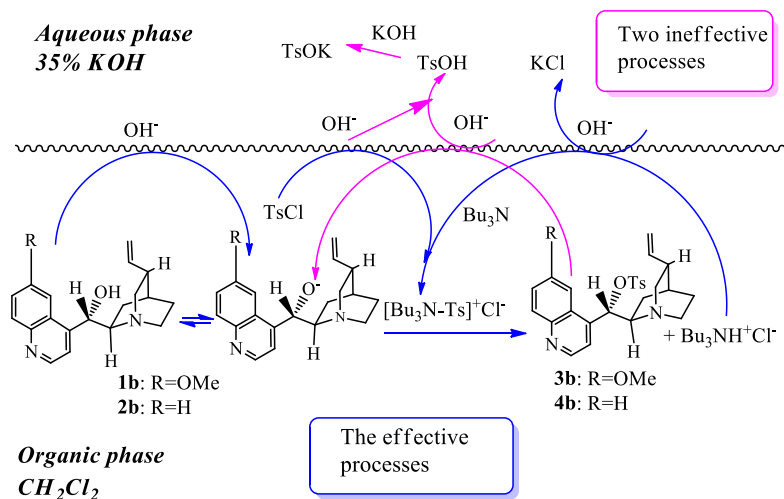
### New synthesis of *O*-tosyl *Cinchona* alkaloids

The tosylation methodologies were gradually improved. Long ago, two methods with an excess of tosyl chloride were used for *O*-tosylation of the *Cinchona* alkaloids.<sup>11-13</sup> In the first of them, alkaloid **1a** or **1b** reacted in the biphasic system of benzene-aqueous 50% KOH solution. In the second method, less soluble **2a** or **2b** reacted with TsCl in the pyridine medium. Next, *O*-tosylation was performed *via* a two-step procedure: formation of alcoholates with strong base (NaH, or BuLi), followed by reaction with tosyl chloride.<sup>16d,17</sup> Recently, *Cinchona* alkaloid tosylates have been obtained in the refluxed THF with TsCl excess, in the presence of triethylamine and DMAP.<sup>14c</sup>

In our initial experiments we tested reaction of *Cinchona* alkaloids without external tertiary amine, with an excess of tosyl chloride in the vigorously stirred biphasic system dichloromethane – aqueous KOH. We observed slow transformation to the appropriate tosylate (TLC control). Next, triethylamine was added to the reaction mixture and considerable increase in the conversion rate was noticed. Then, we chose tributylamine as an effective interface transfer agent for the room-temperature *O*-tosylation. Finally, we examined tributylamine in the catalytic quantity in two biphasic systems: liquid-liquid (dichloromethane–aqueous 35% KOH in method A); and liquid-solid (dichloromethane–solid powdered anhydrous KOH in method B).

We propose a mechanism with an inter-phase transfer of reagents in *O*-tosylation. Tosyl chloride interacts with Bu<sub>3</sub>N and gives a *N*-tosyl tributylammonium chloride, which can retain in the organic phase and acts as a tosylation agent for hydroxy function of the alkaloid (Scheme 2). Tributylamine has a role similar to pyridine in conventional acylation and sulfonylation processes of alcohols and amines in the pyridine medium, However in this case it is effective enough in the catalytic amount, since its protonation in the tosylation process can disappear in contact with the aqueous alkaline phase.

However, two ineffective phase interaction processes can run in parallel to *O*-tosylation a) tosyl chloride may be consumed when it is changed into tosylate anion and transferred from the organic phase to the aqueous phase, b) tosyl ester group of the product can be attacked by hydroxyl anion, turning back the main process of *O*-tosylation. These two side processes give excessive consumption of tosyl chloride during *O*-tosylation and therefore it must be used in excess. We have optimized the necessary excess of tosyl chloride for each alkaloid **1a,b**, and **2a,b** in order to maximize the yields of the corresponding *O*-tosylates in the experimental scale of 10 milimoles of starting materials (Table 1).



**Scheme 2.** Liquid-liquid *O*-tosylation of quinidine (R=OMe) and cinchonine (R=H) with Bu<sub>3</sub>N as a catalyst.

**Table 1.** Comparison of optimized amounts of TsCl needed for conversion of **1a,b** and **2a,b** into **3a,b** and **4a,b** by Method A<sup>a</sup>, product polarity values (as *R<sub>f</sub>* values) and yields

Started alkaloid <sup>b</sup>	TsCl (mmol)	Tosylate number	Tosylate <i>R<sub>f</sub></i> <sup>c</sup>	Tosylate yield (%) <sup>d</sup>
<b>1a</b>	40	<b>3a</b>	0.85	80
<b>1b</b>	35	<b>3b</b>	0.58	76
<b>2a</b>	25	<b>4a</b>	0.62	82
<b>2b</b>	20	<b>4b</b>	0.55	90

<sup>a</sup>Method A: substrate 10 mmol was stirred with TsCl in the medium of dichloromethane-aqueous 35 % KOH, 24 h at room temperature with 1 mmol of Bu<sub>3</sub>N). <sup>b</sup>Commercial grade. <sup>c</sup>*R<sub>f</sub>* values were measured in ethyl acetate-methanol system 10:1. <sup>d</sup>After isolation by column chromatography.

It is interesting to note that:

- The autocatalytic activity of quinuclidine nitrogen in the *Cinchona* alkaloid substrates is not sufficient for the *O*-tosylation process, which is significantly slower without tributylamine, the reaction time is noticeably longer and much higher excess of tosyl chloride is necessary.
- We found that for the synthesis of *O*-tosylcinchonine **4b** by our Method A, double excess of tosyl chloride is sufficient, whereas for the preparation of *O*-tosylquinine **3a** fourfold excess of tosyl chloride is necessary. The excess of TsCl needed for synthesis of corresponding *O*-tosyl derivatives decreases in the following sequence: quinine, quinidine, cinchonidine, cinchonine.
- As a result of our investigation of Method B, that consisted in the solid KOH-organic solvent tosylation of *Cinchona* alkaloids in the presence of Bu<sub>3</sub>N as a catalyst, we found that only the

50% excess of tosyl chloride is sufficient for each alkaloid to transform into its corresponding tosylate in yield 70-80% together with unchanged alkaloids (TLC control).

d) Both of our phase transfer methods used for *Cinchona* alkaloid *O*-tosylation are processes which can be performed at the room temperature, giving yields comparable to those obtained in refluxing THF with NEt<sub>3</sub> and DMAP.<sup>14</sup>

### Examination of *O*-tosyl *Cinchona* alkaloids' hydrolysis

The structure-reactivity relationship was observed during hydrolysis of the four tosylates in a diluted solution of tartaric acid in hot water. This is shown in Table 2, Entry 1-4, as different reaction times necessary for full conversion of compounds **3a,b** and **4a,b**. Molecules with the methoxy group, i.e. **3a** and **3b** react easily (15 min and 30 min), giving correspondingly 9-epiquinine **1c** and 9-epiquinidine **1d** as the main product, with a small amount of regenerated starting alkaloid **1a** and **1b**. Cinchonidine tosylate **4a** reacts slowly to **2c** (6 h, Entry 3), but with a good selectivity. The 9-epibases **1c**, **1d** and **2c** can be obtained by this way in the preparative scale with good yields in the purity above 98% (determined by <sup>1</sup>H NMR after isolation by the column chromatography). However, hydrolysis of cinchonine tosylate **4b** runs much slower (20 h, Entry 4), giving the mixture of three products. When we applied careful column chromatography with methoxethanol, a trace of regenerated cinchonine **2b** (*R<sub>f</sub>*=0.47) was isolated first. Then, a new compound **5** possessing lower polarity (*R<sub>f</sub>*=0.39) was collected. Next, 9-epicinchonine **2d** (*R<sub>f</sub>*=0.31) was eluted with the mixtures of 2-methoxyethanol and methanol. The new product **5** was identified by spectral data as a product of quinuclidine ring cleavage in the intramolecular piperidine elimination (Scheme 3), and can be called cinchonicine (or Pasteur's cinchotoxine) enol tosylate. Microwave enhancement of the hydrolysis of **4b** (Table 2, Entry 5) gives the equal amounts of both **2d** and **5**. We discovered that the latter compound is formed as the main product (Scheme 3) when cinchonine tosylate **4b** reacts with the excess of salicylic acid in a medium of water/ethylene glycol under controlled microwave heating (Table 3, Entry 6).

In the next step of our experiments we found that the same cinchonicine enol tosylate **5** can also be obtained as the main product (together with epicinchonidine **2c** and cinchonidine **2a**) from *O*-tosylcinchonidine **4a** irradiated by microwaves with an excess of salicylic acid (Table 2, Entry 7). However, in this case, it is difficult to separate pure **5** from the reaction mixture since its *R<sub>f</sub>* value (0.39) is near to the *R<sub>f</sub>* value observed for 9-epicinchonidine **2c** (0.35)

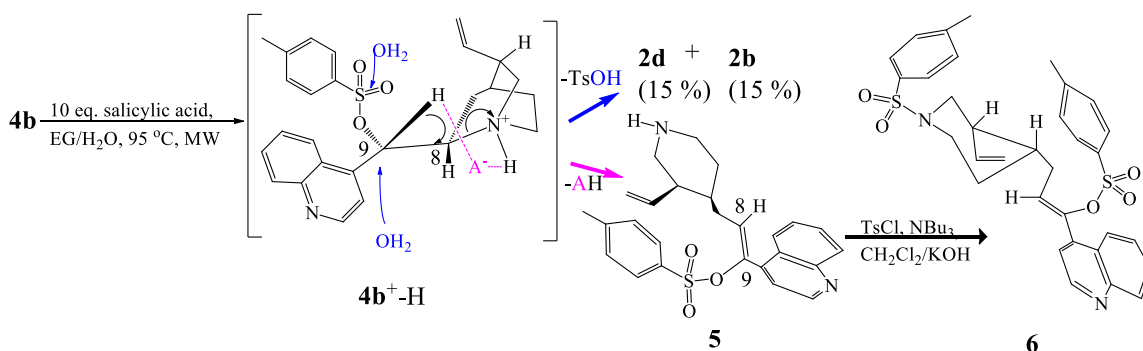
We were the first to observe that the Pasteur's type cleavage of *O*-tosylcinchonine **4b** occurs in the hydrolytical medium, leading to formation of the new compound, cinchonicine enol tosylate **5**. We have found out that this process is competing to hydrolysis of *O*-tosylcinchonine **4b** in conventional conditions (diluted aqueous tartaric acid), and that it is the main reaction under controlled microwave heating of both **4b** and **4a** with an excess of salicylic acid in the ethylene glycol-water medium. This type of transformation is similar to the Pasteur's cleavage of the natural *Cinchona* alkaloids to cinchotoxine (ketone) when they are heated with organic or mineral acids.<sup>5,6</sup> Toxine rearrangement of *Cinchona* alkaloids with acetic acid in the presence of

acetic anhydride has been investigated,<sup>18</sup> and the cinchonine enol acetate formation has been postulated. However, this compound, similar to **5**, has not been isolated so far.

**Table 2.** Yields and  $R_f$  values of 9-epibasins **1c,d** and **2c,d** obtained in different conditions from corresponding tosylates. Yields and  $R_f$  values of the new product **5** and regenerated substrates **1a,b**, **2a,b**

Entry	Substrate No / [ $R_f$ ] <sup>a</sup>	Tosylate hydrolysis		Reaction products		
		No	Time	No	$R_f$ <sup>a</sup>	Yield [%] <sup>b</sup>
1	<b>1a</b> [0.63]	<b>3a</b>	15 min <sup>c</sup>	<b>1c</b>	0.39	75
2	<b>1b</b> [0.61]	<b>3b</b>	30 min <sup>c</sup>	<b>1d</b>	0.46	65
3	<b>2a</b> [0.54]	<b>4a</b>	6 h <sup>c</sup>	<b>2c</b>	0.35	70
4	<b>2b</b> [0.47]	<b>4b</b>	20 h <sup>c</sup>	<b>5 + 2d</b>	0.39; 0.31	15; 45
5	<b>2b</b> [0.47]	<b>4b</b>	20 min <sup>d</sup>	<b>5 + 2d</b>	0.39; 0.31	30; 30
6	<b>2b</b> [0.47]	<b>4b</b>	30 min <sup>e</sup>	<b>2b+5+2d</b>	0.47; 0.39; 0.31	15; 60; 15
7	<b>2a</b> [0.54]	<b>4a</b>	15 min <sup>e</sup>	<b>2a+5+2c</b>	0.54; 0.39; 0.35	10; 40; 20

<sup>a</sup> Values of  $R_f$  were measured on silica-gel TLC plates in 2-methoxyethanol. <sup>b</sup> Yields of product isolated by column chromatography. <sup>c</sup> Procedure 1: Tosylate (10 mmol) was heated at 92-95 °C with the aqueous solution of tartaric acid (15 mmol: 0.1M, 150 ml). <sup>d</sup> Procedure 2: Tosylate **4b** (4 mmol) was added to 20 mL of water containing tartaric acid (6 mmol) and was irradiated in an open vessel (Synthewave 402 reactor, Prolabo) at the controlled temperature of 95 °C. <sup>e</sup> Procedure 3: Tosylate **4b** or **4a** (2 mmol) and salicylic acid (20 mmol) were added to 20 mL of 50 % ethylene glycol water solution and irradiated in an open vessel (Synthewave 402 reactor, Prolabo) at the controlled temperature of 95 °C.

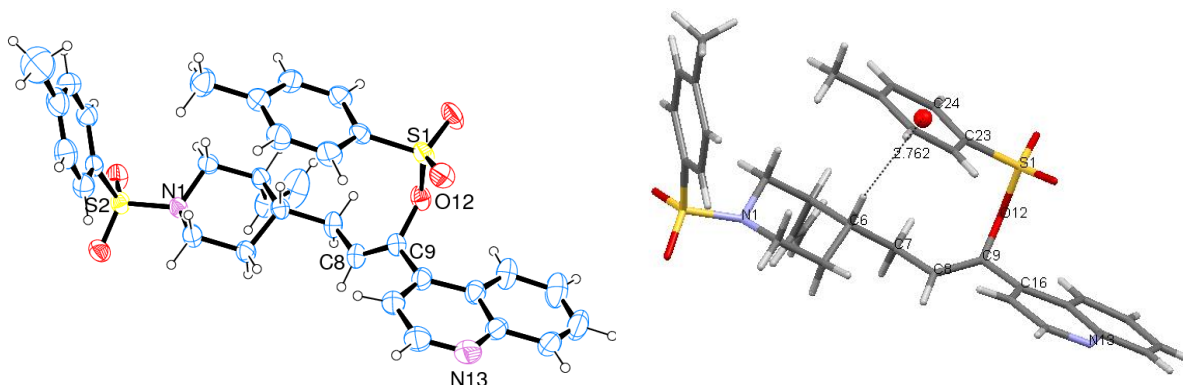


**Scheme 3.** Possible ways of transformation of **4b-H<sup>+</sup>** in the *syn-open* conformation: hydrolysis with C9 inversion to **2d** or with retention to **2b** (by H<sub>2</sub>O attack at the C9 or at the sulfur of sulfonate) *versus* H-C9 elimination together with N1-C8 bond cleavage towards the cinchonine enol tosylate **5**, which is next converted to sulfonamide **6**.

### The sulfonamide derivative **6** preparation for crystal and molecular structure determination by X-ray diffraction

The  $^1\text{H}$  NMR spectrum of the new product **5** shows a signal picture proper for four alkene protons (5.0-6.2 ppm), where three of them display the vinyl group. The signal of the new enol-alkene proton is visible as a triplet at 5.75 ppm. It is interesting that each of the four piperidine protons bonded with  $\alpha$ -carbons (2.50-3.20 ppm) gives separated signal, which means that only one conformation of piperidine can exist as dominant. Therefore, axial and equatorial protons do not give the average signals. The piperidine ring conformation with the large 4-substituent in equatorial position seems to be most probable. However, we cannot determine the enolane geometry from  $^1\text{H}$  NMR as the NOE effects were observed as unclear.

The product **5** is in an oily form. We decided to transform it into sulfonamide derivative **6** in reaction with tosyl chloride in the presence of  $\text{BuEt}_3$  (Scheme 3). The crystals appropriate for the X-ray experiment were obtained after purification by column chromatography and slow evaporation of aqueous-ethanol solution.



**Figure 1.** Ortep drawing of **6** with displacement ellipsoids shown at the 30% probability level (left) and intramolecular interaction (right), where the red ball shows the center of the *O*-tosyl aromatic ring.

As shown in the projections of the molecule of the compound **6** (Figure 1), the configuration *Z* should be assigned to the double bond  $\text{C8}=\text{C9}$ . The shape of the molecule seems to be determined by the intramolecular  $\text{C-H}\cdots\pi$  interactions (e.g. the distance  $\text{C6-H}\cdots\pi = 2.762\text{\AA}$ ) which are most probably responsible for the conformation of the whole molecule.<sup>19</sup> The aromatic ring of the tosylate group and the quinoline ring are almost planar and almost parallel to each other, the angle between their planes being about  $8^\circ$ . The *N*-tosyl moiety is strongly deviated from the *O*-tosyl group (the angle between the two planes equals  $56^\circ$ ). The classical intermolecular hydrogen bonds do not exist in the crystal structure of the compound **6**, however the weak hydrogen bonds,  $\text{C-H}\cdots\text{O}$  can play a crucial part in controlling the crystal packing (see Supplementary Material).

**Comparative conformational analysis of N-1 protonated forms of 4a and 4b as a method explaining potential formation of transition states towards hydrolysis to 9-epibases versus intra-molecular elimination to 5.**

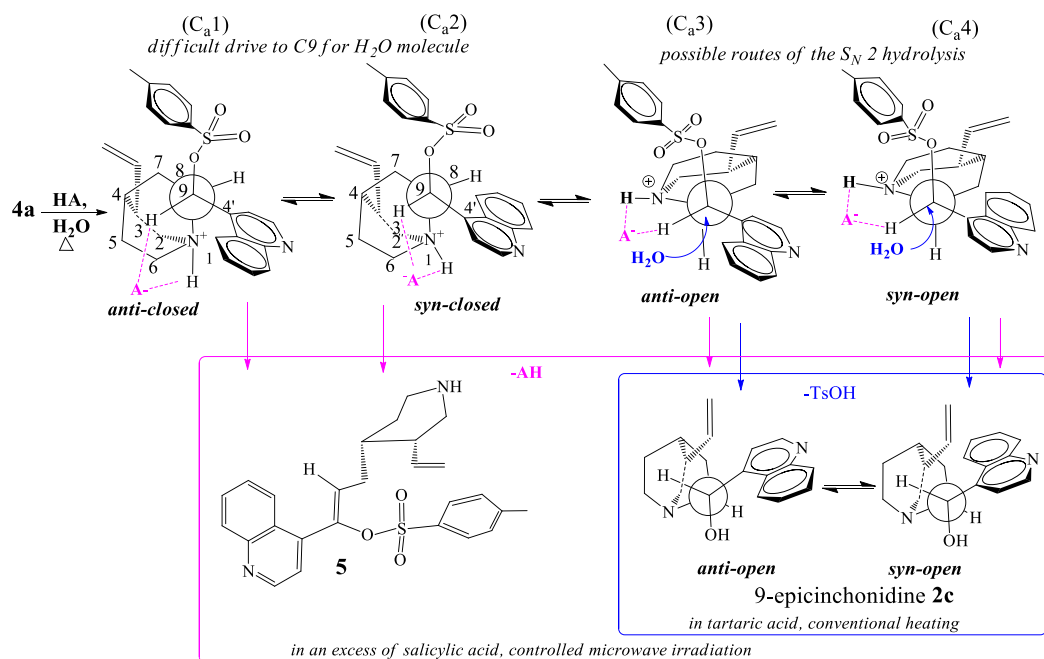
The course of hydrolysis of *O*-tosyl derivatives **4a** and **4b** with the inversion of configuration at C9 must occur as the S<sub>N</sub>2 nucleophilic attack of water molecule on the side opposite to the tosylate leaving group in the substrate protonated at the quinuclidine nitrogen. Theoretical considerations assume four energetically possible conformers of *Cinchona* alkaloid molecules:<sup>9a</sup> two *closed* (*anti* and *syn*) and two *open* (*anti* and *syn*). The *syn-open* conformation of *O*-tosyl cinchonine **4b** is the most required for 9-epicinchonine **2d** formation (see Scheme 3).

Recently, we have published results of the X-ray structure analysis and theoretical calculations of the diastereoisomeric molecules **4a** and **4b**, which were used to explain their different reactivity in the hydrolysis to the respective 9-epibases.<sup>20</sup> The differences in energetic profit during protonation on N1 atom and in propensity to the conformation change from an *anti-closed* in the crystals of both neutral molecules to a *syn-open* one, favored in their weak acid-S<sub>N</sub>2 hydrolysis process, can be correlated with the different reactivity of **4a-H**<sup>+</sup> and **4b-H**<sup>+</sup> toward 9-epibases. Now, we will try to elucidate why the competing process occurs towards the cleavage of quinuclidine ring leading to cinchonine enol tosylate **5** formation.

On the Scheme 4 can be seen the possibility of easy rotations in molecule **4a**<sup>+</sup>-H around C8-C9 bond (giving *closed* and *open* conformers), as well as around C4'-C9 bond (giving *syn* and *anti* conformers). The hydrolysis can run as the attack of water molecule at C9 atom in both *open* conformers C<sub>a3</sub> and C<sub>a4</sub>. This creates the possibility for the transition state formation that gives 9-epicinchonidine **2c**. The regioselectivity towards **2c** can be experimentally observed in the classical heating of **4a** with aqueous tartaric acid. This indicates that the S<sub>N</sub>2 process runs under kinetic control, that requires accessibility of the rotamers C<sub>a3</sub> and C<sub>a4</sub> as the energetically privileged. The experimental result shows that the microwave activation of the protonated molecule leads to the formation both of **2c** and **5**. This fact indicates that the *syn*-E2 cleavage process, competing to S<sub>N</sub>2 hydrolysis, cannot be conformationally determined. It is forced by the internal microwave activation of **4a-H**<sup>+</sup> molecule, which can react without conformational preference. In this case, high energetic demand for transition state formation requires simultaneous interaction of the anionic-base (A<sup>-</sup>) with quinuclidine cationic nitrogen (electrostatic) and the proton H-C9 (acid-base). Theoretical conformational analysis shows that this is possible in all the *open* and *closed* conformers (Scheme 4). Moreover, the experiments revealed that the preference towards elimination to **5** can be achieved under microwave irradiation of **4a-H**<sup>+</sup> with the salicylic acid in the aqueous medium.

In the view of considered ways of microwave activation in different types of organic syntheses,<sup>21</sup> the contribution of microwave catalysis through rotationally hot reactive species<sup>22</sup> is the most probable reason for the emergence of the second direction of **4a**<sup>+</sup>-H transformation towards **5** formation by the cleavage of quinuclidine ring. This none-equilibrium system can be formally described by considering of rotational temperature, which is higher than the translational temperature for the all existing *closed* and *open* conformers.





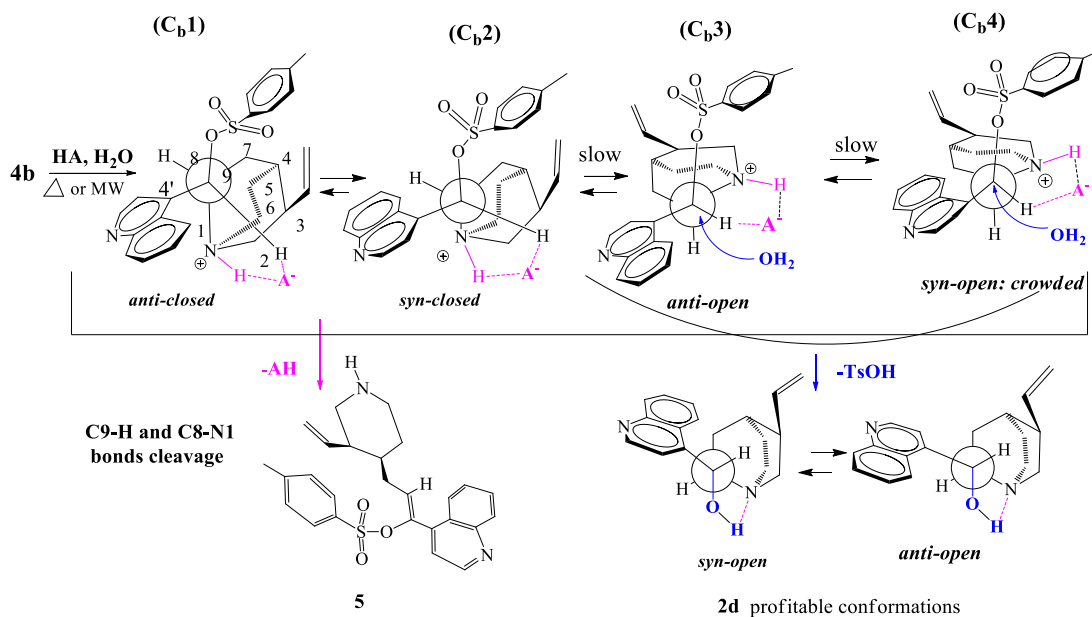
**Scheme 4.** Hypothetical ways of  $4a^+-H$  hydrolysis towards formation of **2c** and **5**.

In the case of the protonated molecule of *O*-tosyl cinchonine  $4b^+-H$  (Scheme 5), the vinyl group is a tethered element that determines possible rotations. There are difficulties in the rotation around bond C8-C9 that change the *closed* conformers ( $C_{b1}$  and  $C_{b2}$ ) into more hindered *open* conformers ( $C_{b3}$  and  $C_{b4}$ ). Due to high energetic barrier of rotations, the transition state for the attack of the water molecule on the carbon atom C9 in  $S_N2$  hydrolysis that leads to 9-epicinchonine **2d**, is difficult to achieve. This is the reason for *O*-tosyl cinchonine **4b** hydrolytic stability in the weak acid medium.

The discussion of conformations leads to the conclusion that in this case a competing reaction with the acid anion as a base can lead to the intramolecular *syn*-E2 elimination to the alkene **5** possessing the same geometry as that obtained from  $4a-H^+$ . This product can form without conformational preference and was observed both in the prolonged conventional heating of  $4b-H^+$  (Entry 4, Table 2) and under short microwave irradiation at the temperature of 95°C. The excess of the salicylic acid with the microwave activation leads to prevailing conversion into the cleavage product **5**. However, in this case, considerable amount of cinchonine **2b** with the retention of C9 configuration is parallel formed in the course of hydrolysis. It is possible in result of the O-SO<sub>2</sub> bond cleavage after water molecule attack on the sulfonate group of  $4b^+-H$ .

The stereoselectivity that we observed, lead to formation of *Z*-alkene **5** from tosylates **4a** and **4b**, which confirms that this is the second type of mechanism (three types are mentioned in the literature: ref<sup>4</sup> pp. 361-363) for the Pasteur cleavage of natural *Cinchona* alkaloids giving ketone *via* enol. The fact that the intramolecular piperidine elimination is more plausible when

the planar salicylate anion ( $A^-$ ) takes part as a base, instead of the tartrate anion, can be interpreted as a stereoelectronic factor.



**Scheme 5.** Conformational analysis of **4b** in the aspect of the two routes of its transformation: intramolecular elimination to **5** and the difficult  $S_N2$  hydrolysis to **2d**.

## Conclusions

We have developed the new methods for the effective and selective transformation of the four natural *Cinchona* alkaloids into appropriate *O*-tosyl derivatives at room-temperature in biphasic systems using tributylamine as the catalyst. The tosyl esters has been carefully reinvestigated in the hydrolysis-inversion process leading to 9-epibases **1c,d** and **2c,d**. We confirm that the molecules with the methoxy group **3a,b** are significantly more reactive than cinchonidine and cinchonine tosylates **4a** and **4b**. The latter one is the most hydrolytically stable in the substitution process by the water molecule in the weak-acid aqueous medium. Comparative conformational analysis for cinchonidine and cinchonine tosylates **4a** and **4b** has been employed for the explanation of this phenomenon. We have found that the vinyl group can take part in the tethering effect inside molecule **4b**<sup>+</sup>-H and it can prevent rotation that leads to conformation necessary for hydrolysis in the aqueous acid medium. Therefore, this molecule is less prone to  $S_N2$  hydrolysis and it reacts in the Pasteur-type quinuclidine ring cleavage process leading to the new derivative, cinchonicine enol tosylate **5**. (*Z*)-Alkene geometry is determined on the basis of the X-ray structure of the sulfonamide **6** as derivative of **5**. Therefore the stereoselective *syn*-E2

of quinuclidine ring-opening process, competing to the  $S_N2$  hydrolysis is postulated for the formation of the product **5**. This product is almost selectively formed from cinchonidine or cinchonine tosylates (**4a** or **4b**) with salicylic acid solution under controlled microwave irradiation and can be synthesized by this route in the preparative scale. The new compound is the chiral alkene and can be used as building block<sup>23</sup> for asymmetric synthesis, including chiral self-organized nanopolymers, similar to those we have just started to obtain.<sup>24</sup>

## Experimental Section

**General.** Commercial *Cinchona* alkaloids from Fluka were used. Other reagents and solvents were purchased from commercial suppliers (Sigma-Aldrich) and used without further purification. 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 aluminium. Pure products were isolated by CC over Merck silica gel 60 (230-400 mesh). The column output was monitored with TLC (on aluminium sheets precoated with silica gel 60<sub>254</sub>, Merck). 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. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with MERCURY 400 BB or VARIAN 400MR spectrometer (<sup>1</sup>H; 400 MHz, <sup>13</sup>C: 100 MHz). Chemical shifts are given relative to TMS ( $\delta=0$ ) in ppm and refer to residual solvent as internal standard. All compounds were determined to be > 96 % pure by <sup>1</sup>H NMR analysis. IR spectra (KBr pellets) were recorded on FT-IR MAGNA 769 (Nicolet).

### General procedure for the Method A tosylation exemplified by the synthesis of **4b**

Tosyl chloride (3.81 g, 20 mmol), tributylamine (0.25 mL, 1 mmol) and 35% potassium hydroxide aqueous solution (50 mL) were added to a stirred solution of cinchonine **2b** (2.94 g, 10 mmol) in dichloromethane (150 mL). The resulting mixture was stirred at 20°C for 24 h (the monitoring of cinchonine conversion on silica gel TLC plates with a mixture of ethyl acetate and methanol 10:1). Then water (100 mL) was added and stirred for 10 min. The organic phase was separated and washed by water (3 x 50 mL) and extracted with cold 1M hydrochloric acid (5 x 25 mL). The aqueous phase was washed with diethyl ether (3 x 25 mL) and then 2N NaOH was added until pH > 10. The mixture was extracted with dichloromethane (4 x 50 mL) and the combined organic extracts were washed with water (2 x 30 mL) and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure and crude product **4b**; 4.25 g, 95.0 % (containing a trace amount of starting alkaloid **2b**, TLC indicated), as white precipitate was obtained. After column chromatography with ethyl acetate-methanol 20:1, pure **4b** 4.03g, 90 % was obtained.

**O-tosylcinchonine (4b)** M.p. 174-175 °C,  $[\alpha]_D^{27} +35.9^\circ$  (*c* 1.00, in EtOH anhyd.); (lit.<sup>11a</sup> m.p. 173 °C,  $[\alpha]_D^{20} +51^\circ$  (*c* 1 in 96 % EtOH); IR (KBr)  $\text{cm}^{-1}$ : 3069, 2939 2867, 1635, 1592, 1511, 1454, 1363 (SO<sub>2</sub>), 1242, 1189, 1174 (SO<sub>2</sub>), 1095, 1058, 1021, 987, 935, 870, 811, 760, 667, 555; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 8.68 (d, <sup>3</sup>*J* = 4.4 Hz, 1H, H-2'), 7.98 (d, <sup>3</sup>*J* = 7.6 Hz, 1H, H-8'), 7.97 (bs, 1H, H-5'), 7.67 (t, <sup>3</sup>*J* = 7.6 Hz., 1H, H-7'), 7.51 (t, <sup>3</sup>*J* = 7.6 Hz, 1H, H-6'), 7.33 (d, <sup>3</sup>*J* = 7.2 Hz, 2H, H-2'', H-6''), 7.21 (bs, 1H, H-3'), 6.78 (d, 2H, <sup>3</sup>*J* = 7.2 Hz, H-3'', H-5''), 6.10 (bs, 1H, H-9), 5.98 (ddd, <sup>3</sup>*J* = 17.6, 10.6, 7.7 Hz, 1H, H-10), 5.12-5.05 (m, 2H, H<sub>2</sub>-11), 3.30 (s-br, 1H, H-8), 2.82-2.76 (m, 2H, H-2, H-6), 2.64-2.56 (m, 2H, H-2, H-6), 2.28-2.18 (m, 1H, H-3), 2.16 (s, 3H, H<sub>3</sub>C<sub>Ar</sub>), 1.92-1.84 (m, 1H H-5), 1.84-1.78 (m, 1H, H-7), 1.76-1.65, m, 1H, H-4), 1.54-1.48 (m, 2H, H-5, H-7); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 149.4 (C-2'), 148.1, (C-4'), 144.5 (C-9'), 143.9 (C-4''), 139.9 (C-10), 132.9 (C-1''), 130.2 (C-3'', C-5''), 129.0 (C-8'), 128.8 (C-7'), 127.5 (C-2'' and C-6''), 126.7, (C-6') 125.5 (C-10'), 122.9 (C-5'), 119.5 (C-3'), 114.9 (C-11), 76.2 (C-9), 60.3 (C-8), 49.6 (C-2), 48.7 (C-6), 39.7 (C-3), 27.6 (C-7), 26.2 (C-5), 24.5 (C-4), 21.3 (H<sub>3</sub>C<sub>Ar</sub>).

The products **3a**, **3b** and **4a** are obtained from **1a**, **1b** and **2a** with tosyl chloride in the excess given in Table 1 (together with *R<sub>f</sub>* values of products). Their physicochemical and spectral data are reported below.

**O-tosylquinine (3a)**. Crude (92 %), an oily form; pure (80 %), m.p. 58-60 °C,  $[\alpha]_D^{27} +11.7^\circ$  (*c* 1.00 in 99.8 % EtOH); (lit.<sup>12</sup> oil,  $[\alpha]_D^{21} +9.8^\circ$  (*c* 1.02 in 96.0 % EtOH); IR (KBr),  $\text{cm}^{-1}$ : 3071, 2938, 2867, 1621, 1596, 1508, 1475, 1453, 1362 (SO<sub>2</sub>), 1304, 1263, 1226, 1186, 1175 (SO<sub>2</sub>), 1091, 1029, 989, 930, 919, 862, 811, 766, 668, 569, 550; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 8.51 (d, <sup>3</sup>*J* = 4.4 Hz, 1H, H-2'), 7.86 (d, <sup>3</sup>*J* = 9.2 Hz, 1H, H-8'), 7.31-7.25 (m, 3H, H-7', H-2'', H-6''), 7.15 (bs, 2H, H-3', H-5'), 6.76 (d, <sup>3</sup>*J* = 7.2 Hz, 2H, H-3'', H-5''), 6.10 (bs, 1H, H-9) 5.81 (ddd, <sup>3</sup>*J* = 17.2, 9.8 7.4 Hz, 1H, H-10), 5.02-4.95 (m, 2H, H<sub>2</sub>-11), 3.93 (s, 3H, MeO), 3.30 (bs, 1H, H-8), 3.14-3.05 (m, 1H, H-6), 2.98-2.90 (m, 1H, H-2), 2.64-2.56 (m, 1H, H-2), 2.54-2.46 (m, 1H, H-6), 2.28-2.20 (m, 1H, H-3), 2.15 (s, 3H, Me-Ar), 1.92-1.86 (m, 1H, H-4), 1.79-1.60 (m, 2H, H-5, H-7), 1.58-1.42 (m, 2H, H-5, H-7). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 157.8 (C-6'), 146.9 (C-2'), 144.5 (C-4'), 1.44.3 (C-4''), 141.9 (C-9'), 141.6 (C-10), 133.7 (C-1''), 133.0 (H-8'). 131.6 (H-3'', H-5''), 128.8 (H-8'), 127.4 (C-2'', C-6''), 126.5 (C-10'), 121.6 (H-3'), 118.8 (H-7'), 114.4 (C-12), 100.4 (C-5'), 79.7 (C-9), 60.3 (C-8), 56.3 (C-6), 55.9 (H<sub>3</sub>C-O), 42.3 (C-2), 39.5 (C-3), 27.4 (C-5), 27.2 (C-7), 25.0 (C-4), 21.3 (H<sub>3</sub>C<sub>Ar</sub>).

**O-tosylquinidine (3b)**. Crude; (85 %), oily; pure (76 %), m.p. 119-120 °C;  $[\alpha]_D^{27} +23.5^\circ$  (*c* 1.00 in 99.8 % EtOH); (lit.<sup>12</sup> m.p. 116-118 °C  $[\alpha]_D^{21} +28.3^\circ$  (*c* 1.02 in 96.0 % EtOH); IR (KBr),  $\text{cm}^{-1}$ , 3072, 3011, 2935, 2869, 1621, 1596, 1509, 1475, 1454, 1364 (SO<sub>2</sub>), 1302, 1225, 1189, 1176 (SO<sub>2</sub>), 1090, 1027, 989, 918, 856, 818, 764, 666, 570, 550; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.53 (d, <sup>3</sup>*J* = 4.4 Hz, 1H, H-2'), 7.88 (d, <sup>3</sup>*J* = 9.2 Hz, 1H, H-8'), 7.40-7.32 (m, 2H, H-3', H-5'), 7.30 (dd, <sup>3</sup>*J* = 9.2 Hz, <sup>4</sup>*J* = 2.0 Hz, 1H, H-7'), 7.15 (d, <sup>3</sup>*J* = 7.6 Hz, 2H, H-2'', H-6''), 6.82 (d, <sup>3</sup>*J* = 7.6 Hz, 2H, H-3'', H-5''), 6.13 (bs, 1H, H-9), 5.97 (ddd, <sup>3</sup>*J* = 17.2, 10.8, 7.2 Hz, 1H, H-10), 5.12-5.05 (m, 2H, H<sub>2</sub>-11), 3.93 (s, 3H, H<sub>3</sub>C-O), 3.20 (bs, 1H, H-8), 2.87-2.77 (m, 2H, H-2, H-6), 2.68-2.57

(m, 2H, H-2, H-6), 2.29-2.19 (m, 1H, H-3), 2.17 (s, 3H,  $\text{H}_3\text{C}\text{Ar}$ ), 1.96-1.85 (m, 1H, H-4), 1.83-1.78 (m, 1H, H-5), 1.72-1.58 (m, 1H, H-7), 1.54-1.47 (m, 2H, H-5, H-7);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 157.7 (C-6'), 146.9 (C-4'), 144.6 (C-2'), 144.3 (C-1'), 142.5 (C-9'), 140.0 (C-10), 133.0 (C4''), 131.6 (C3'', C5''), 128.9 (C8'), 127.5 (C2'', C6''), 126.6 (C10'), 121.6 (C3') 118.7 (C-7') 115.0 (C-11), 100.4 (C-5'), 79.4 (C-9), 60.5 (C-8), 55.4 ( $\text{H}_3\text{C}\text{O}$ ), 49.7 (C-2), 49.0 (C-6), 39.7 (C-3), 27.6 (C-5), 26.22 (C-7), 23.9 (C-4), 21.3 ( $\text{H}_3\text{C}\text{Ar}$ ).

**O-tosylcinchonidine (4a).** Crude (91 %) m.p. 125-127 °C, pure (82.0 %), m.p. 134-135 °C,  $[\alpha]_{\text{D}}^{27} +3.8^\circ$  (c 1.00 in 99.8 % EtOH); (lit.<sup>12</sup>  $[\alpha]_{\text{D}}^{20} +3.1^\circ$  (c 0.03, 96.0 % EtOH); IR (KBr)  $\text{cm}^{-1}$ : 3071, 2968, 2941, 2870. 1621, 1596, 1511, 1455, 1433, 1361 ( $\text{SO}_2$ ), 1263, 1190, 1173 ( $\text{SO}_2$ ), 1096, 1030, 1018, 989, 930, 868, 804, 759, 672, 572;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.66 (d,  $^3J = 4.0$  Hz, 1H, H-2'), 7.98 (d,  $^3J = 8.0$  Hz, 2H, H-5', H-8'), 7.67 (t,  $^3J = 8.3$  Hz, 1H, H-7'), 7.56-7.48 (m, 1H, H-6'), 7.29 (d, 2H,  $^3J = 7.7$  Hz, H-2'', H-6''), 7.19 (bs, 1H, H-3'), 6.73 (d,  $^3J = 7.7$  Hz, 2H, H-3'', H-5''), 6.08 (bs, H-9), 5.83 (ddd,  $^3J = 17.6$ , 10.4, 7.4 Hz, 1H, HC10), 5.02-4.96 (m, 2H, H<sub>2</sub>-11), 3.35 (bs, 1H, H-8), 3.12-3.00 (m, 1H, H-6), 2.92 (dd, 1H,  $^2J = 13.6$ ,  $^3J = 9.4$  Hz, H-2), 2.56 (ddd,  $^2J = 12.6$ ,  $^3J = 10.8$ , 4.4 Hz, 1H, H-6), 2.51-2.42 (m, 1H, H-2), 2.28-2.20 (m, 1H, H-3), 2.14 (s, 3H,  $\text{H}_3\text{C}\text{Ar}$ ), 2.14-2.0 (m, 1H, H-4), 1.91-1.87 (m, 1H, H-7), 1.78-1.62 (m, 1H, H-5), 1.56-1.48 (m, 2H, H-5, H-7);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 150.3 (C-4'), 149.5 (C-2'), 148.1 (C-9'), 144.5 (C-4''), 141.6 (C-10), 133.0 (C-1'), 130.3 (C-3'', C-5''), 129.1 (C-8'), 128.8 (C-7'), 127.5 (C-2'', C-6''), 126.7 (C-6'), 125.8 (C-10'), 123.1 (C-5'), 117.5 (C-3'), 114.5 (C-11), 76.2 (C-9), 60.3 (C-8), 49.6 (C-2), 48.7 (C-6), 39.7 (C-3), 27.6 (C-7), 26.2 (C-5), 24.5 (C-4), 21.3  $\text{H}_3\text{C}\text{Ar}$ ).

**Method B: Solid-liquid phase O-tosylation: is given in the Supplementary Material.**

**Hydrolysis of O-tosyl derivatives by conventional Procedure 1 to 9-eipibases 1c, 1d, 2c, 2d** and their  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are given in the Supplementary Material.

General characterization data: for obtained 9-eipibases **1c,d, 2c,d** are given below.

**9-Epiquinine (1c).** Oil,  $[\alpha]_{\text{D}}^{27} +42.5^\circ$  (c 1.24, 99.8 % EtOH); {lit.<sup>12</sup> oil,  $[\alpha]_{\text{D}}^{20} +50.4^\circ$  (c 0.442, 99.0 % EtOH), lit.<sup>17b</sup>  $[\alpha]_{\text{D}}^{28} +39.9^\circ$  (c 1.13 in EtOH)}.

**9-Epiquinidine (1d).** M.p. 114-115 °C,  $[\alpha]_{\text{D}}^{27} +105.5^\circ$  (c 1.00, 99.8% EtOH); {lit.<sup>12</sup> m.p. 112-113 °C, ,  $[\alpha]_{\text{D}}^{27} +103.7^\circ$  (c 1.05 in EtOH anhydrous), lit.<sup>17b</sup>  $[\alpha]_{\text{D}}^{26} +96.3^\circ$  (c 1.15 in EtOH)}.

**9-Epicinchonidine (2c).** M.p. 109-110 °C,  $[\alpha]_{\text{D}}^{27} + 60.8^\circ$  (c 1.00, 99.8 % EtOH), {lit.<sup>12</sup> m.p. 101-104 °C,  $[\alpha]_{\text{D}}^{19} +69.7^\circ$  (c 0.80, EtOH 99.5 %) lit.<sup>17b</sup>  $[\alpha]_{\text{D}}^{28} + 56.9^\circ$  (c 1.15 in EtOH)}.

**9-Epicinchonine (2d).** M.p. 89-90 °C,  $[\alpha]_{\text{D}}^{27} +116.4^\circ$  (c 1.00, 99.8 % EtOH); {lit.<sup>12</sup> m.p.85-87 °C,  $[\alpha]_{\text{D}}^{27} +122.0^\circ$  (c 1.00, 99.5 % EtOH) lit.<sup>17b</sup>  $[\alpha]_{\text{D}}^{26} +114.5^\circ$  (c 1.07 in EtOH)}.

**Procedure 2. Hydrolysis of tosylate 4b under microwave irradiation in the medium of tartaric acid is given in the Supplementary Material.**

**Procedure 3. Hydrolysis of tosylates 4a and 4b under controlled microwave irradiation in the medium of salicylic acid toward cinchonine enol tosylate 5 formation: Tosylate 4b (or**

**4a**) (0.90 g, 2 mmol) and salicylic acid (20 mmol) were placed in a Pyrex cylindrical vessel and 20 mL of 50 % ethylene glycol was added. The reaction mixture was subjected to microwave irradiation at 95 °C. The full conversion of substrate **4b** was observed (TLC, EtOAc-EtOH=10:1) after 30 minutes (**4a** after 15 min). The reaction mixture was extracted with dichloromethane in the presence of an excess of cold sodium hydroxide 20 % solution. The organic phase was dried with anhydrous sodium sulfate and the organic solvent was removed under reduced pressure. The yields and  $R_f$  values of products obtained from **4b** after CC separation are given in Table 2, entry 6. Product **5** (0.54 g, 60 %) was isolated using the mixture methoxyethanol/methanol 5:1) as a colorless oil substance:  $[\alpha]_D^{20} +33.2^\circ$  ( $c$  1.08 in 99.8% EtOH).

**(Z)-1-(Quinolin-4-yl)-3-((3R,4R)-3-vinylpiperidin-4-yl)prop-1-enyl 4-methylbenzene sulfonate (5)**. IR (KBr)  $\text{cm}^{-1}$  (m-middle, s-strong): 3066 (m), 3030 (m), 2922 (s), 2854 (m) 2802 (m), 2733 (m), 1693 (m), 1637 (m), 1586 (m), 1506 (s), 1444 (m), 1373 (s, SO<sub>2</sub>), 1268 (m), 1188 (s, SO<sub>2</sub>), 1177 (s), 1092 (m); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.51 (d, <sup>3</sup>J = 4.5 Hz, 1H, H-2'), 7.95 (dd, <sup>3</sup>J = 7.8, <sup>4</sup>J = 1.6 Hz, 1H, H-8'), 7.93 (dd, <sup>3</sup>J = 7.8, <sup>4</sup>J = 1.2 Hz, 1H, H-5'), 7.62 (ddd, 1H, <sup>3</sup>J = 8.2, 7.8, <sup>4</sup>J = 1.2, 1H, H-7'), 7.45 (ddd, <sup>3</sup>J = 8.2, 7.8, <sup>4</sup>J = 1.6 Hz, 1H, H-6'), 7.27 (d, <sup>3</sup>J = 8.2 Hz, 2H-*o*-SO<sub>2</sub>Ar), 7.21 (d, <sup>3</sup>J = 4.5 Hz, 1H, H-3'), 6.78 (d, <sup>3</sup>J = 8.2 Hz, 2H- *m*-SO<sub>2</sub>Ar), 6.10 (ddd, <sup>3</sup>J = 17.0, 10.3, 7.6 Hz, 1H, HC10), 5.75 (t, <sup>3</sup>J = 7.6 Hz, 1H, H-8), 5.17 (dd, <sup>3</sup>J = 10.3, <sup>2</sup>J = 2.0 Hz, 1H, H-11), 5.09 (dd, <sup>3</sup>J = 17.0, <sup>3</sup>J = 2.0 Hz, 1H, H-11), 3.09 (ddd, <sup>2</sup>J = 12.4 Hz, <sup>3</sup>J = 3.6 Hz, <sup>3</sup>J = 3.4 Hz, 1H, H<sub>eqat</sub>-6), 2.97 (dd, <sup>2</sup>J = 14.8 Hz, <sup>3</sup>J = 3.4 Hz, 1H, H<sub>eqat</sub>-2), 2.83 (dd, <sup>2</sup>J = 14.8 Hz, 3.6 Hz, 1H, H<sub>axial</sub>-2), 2.65 (ddd, <sup>2</sup>J = 12.4 Hz, <sup>3</sup>J = 10.8 Hz, <sup>3</sup>J = 3.6 Hz, 1H, H<sub>axial</sub>-6), 2.36-2.20 (m, 3H, H-3, H<sub>2</sub>-7), 2.17, s, H<sub>3</sub>CAr 3H), 1.82-1.73 (m, 1H, H-4) 1.68-1.44 (m, 2H, H<sub>2</sub>-5), <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 162.3 (C-9), 150.2 (C-2'), 148.2 (C-9'), 145.6 (C-1''), 144.8 (C-4'), 141.0 (C-4''), 137.3 (C-11), 130.2 (C-3'', C-5''), 129.9 (C-8'), 129.6 (C-7'), 127.9 (C-6'), 127.5 (C-2'', C-6''), 126.0 (C-10'), 125.7 (C-5'), 121.8 (C-11), 117.7 (C-2'), 116.5 (C-8), 51.0 (C-2), 46.7 (C-6), 43.1 (C-3), 39.6 (C-4), 35.1 (C-5), 28.5 (C-7), 21.4 (H<sub>3</sub>CAr<sub>3</sub>); HRMS (ESI, [M+H]<sup>+</sup>) found: 449.1905, calcd for C<sub>26</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub>S: 449.1899.

**Synthesis of sulfonamide (60)**. To the solution of **5** (224 mg, 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) tosyl chloride 143.0 mg, 0.75 mmol), tributylamine (0.012 mL, 0.05 mmol) and 35 % KOH solution (10 mL) were added. Substrate was disappeared in reaction mixture (TLC control) after 15 min stirring at room temperature. The organic phase was separated and washed by water, dried and evaporated. White solid was obtained (283 mg, 94.0 %). After column chromatography with using of the ethyl acetate as eluent, pure **6** was obtained (260 mg, 86.4%), m.p. 154-155 °C. Solid was dissolved in the mixture 1:1 hexane-ethyl ether and was stored to crystallization. White crystals were obtained, m.p. 156.0-156.5 °C which were used for X-ray measurements.

**(Z)-1-(quinolin-4-yl)-3-((3R,4R)-1-tosyl-3-vinylpiperidin-4-yl)prop-1-enyl 4-methylbenzenesulfonate (6)**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.70, (d, <sup>3</sup>J = 4.1 Hz, 1H, H-2'), 7.94 (d, <sup>3</sup>J = 8.6 Hz, 1H, H-8'), 7.86 (d, <sup>3</sup>J = 8.6 Hz, 1H, H-5'), 7.63-7.59 (m, 3H, H-7' + 2 x H-*o*-OSO<sub>2</sub>Ar), 7.43 (dd, <sup>3</sup>J = 8.6, 8.2 Hz, 1H, H-6'), 7.30 (d, <sup>3</sup>J = 8.1 Hz, 2H, 2H-*o*-NHOSO<sub>2</sub>Ar),

7.21 (d,  $^3J = 8.1$  Hz, 2H, 2H-*m*-NH<sub>2</sub>SO<sub>2</sub>Ar), 7.17 (d,  $^3J = 4.1$  Hz, 1H, H-3'), 6.74 (d,  $^3J = 8.1$  Hz, 2H, 2H-*m*-SO<sub>2</sub>Ar), 6.17 (ddd,  $^3J = 17.2, 10.2, 8.8$  Hz, 1H, H-10), 5.65 (t,  $^3J = 7.7$  Hz, 1H, H-8), 5.22 (d,  $^3J = 10.2$  Hz, 1H, H-11), 5.18 (d,  $^3J = 17.2$  Hz, 1H, H-11), 3.69 (dd,  $^2J = 11.2, ^3J = 2.1$  Hz, 1H, H<sub>equat.</sub>-2), 3.58 - 3.55 (m, 1H, H<sub>equat.</sub>-6), 2.53 (dd,  $^2J = 11.2, ^3J = 3.0$  Hz, 1H, H<sub>axial</sub>-2), 3.44-3.38 (m, 2H, H-3, H<sub>axial</sub>-6), 3.40 (s, 3H, CH<sub>3</sub>Ar), 2.26 (dd,  $^3J = 17.4, 7.7$  Hz, 2H, H<sub>2</sub>-7), 2.15 (s, 3H, H<sub>3</sub>CAr), 1.68 - 1.56 (m, 3H, H-4, H<sub>2</sub>-5). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 163.2 (C-9), 149.2 (C-2'), 147.9 (C-9'), 144.9 (C-1''), 144.3 (HC-4'), 143.4 (C-1'''), 140.2 (C-10), 138.2 (C-4''), 137.5 (C-4'''), 134.9 (2xC-*m*-Ar''), 132.9 (2xC-*m*-Ar'''), 129.5 (2xC-*o*-Ar''), 129.3 (C-8'), 128.7 (C7'), 127.5 (2xC-*o*-Ar'''), 126.9 (C-6'), 126.1 (C-10'), 125.4 (C-5'), 125.2 (C-8), 121.2 (C-3'), 118.0 (C-11), 50.7 (C-2), 46.0 (C-6), 42.0 (C-4), 38.4 (C-3), 29.3 (C-5), 27.1 (C-7), 21.5 (Ar''-CH<sub>3</sub>), 21.2 (Ar'''-CH<sub>3</sub>).

**Supplementary Materials:** Additional experimental procedures, X-ray data, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra.

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