# NEW EFFECTIVE SYNTHESIS OF THE CHINCHONINIC ACIDS FROM (-)-α-PINENE

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**Abstract.** New effective synthesis of the chiral chinchoninic acids form (-)-α-pinene has been elaborated. It has been shown that, the considerable increase of the yield and purity of chiral acids is achieved applying the method of under phase transfer catalysis.

**Keywords**: chinchoninic acids, quinoline, pinonic acid, α-pinene.

## Introduction

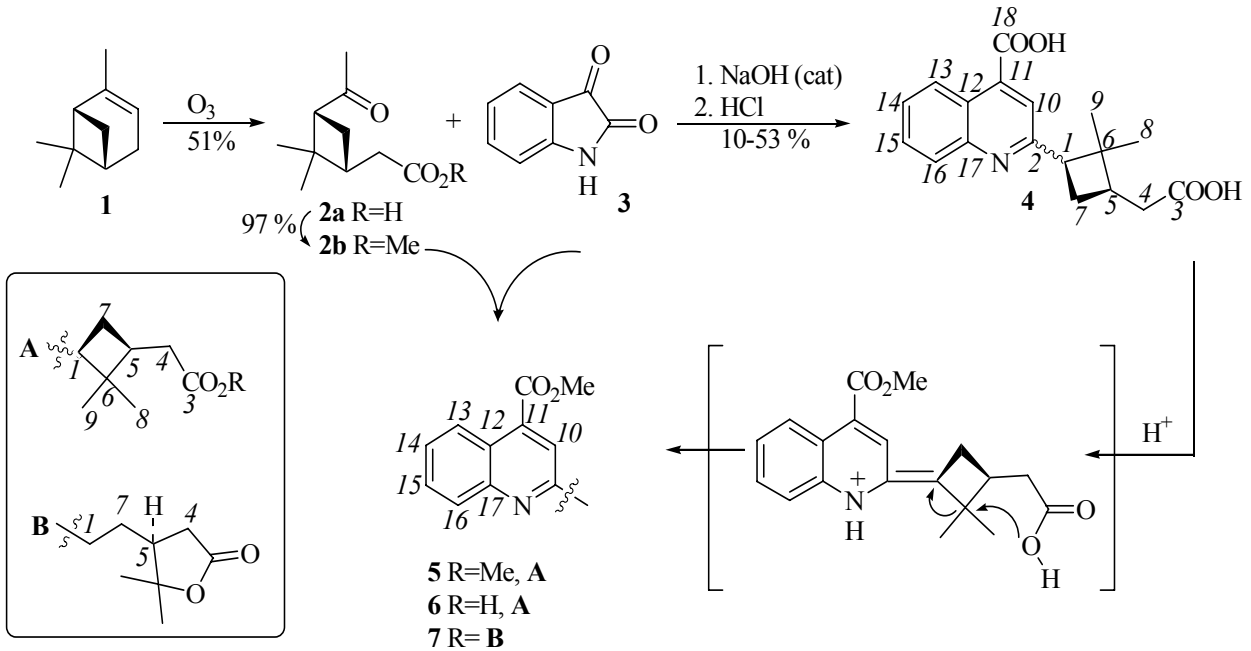
The development of pharmacological agents capable to counteract the mechanisms of drug resistance in malaria therapy has remained a major goal for the past hundred of years. When the mechanisms of multidrug resistance is identified, the hope of identifying molecules capable to simultaneously reverse the resistance to a number of unrelated drugs has to stimulate research in this field.

Early chinchoninic acids have been the main medicine for malaria treatment [1]. Nowadays a great number of analogues of this substance are known, their efficacy being three times greater than that of quinine. Recently, a novel class of optically active chiral oxindoles as specific anti HIV-1 agents from α-pinene **1** has been reported [2,3]. Therefore, these analogues are considered as promising agents for the treatment of other diseases.

This paper describes the resolution of various conditions on obtaining chiral chinchoninic acids form α-pinene **1** via pinonic acid **2**.

## Results and Discussion

The target optically active chinchoninic acids **4-7** with the substituents at C2 quinoline moiety were prepared from the keto acid **2a** and isatine **3** as outlined in Scheme 1.




Mixture **2a** and **3** after refluxing (6 hours) in EtOH solution NaOH lead the chinchoninic acids with 10% yield, that is in agreement with data [4] where the authors have attempted to elaborate a technological method for preparation of **4**. The yield of the target acids reaches 50-53% when the time of reaction is increased to 48-50 hours. In $^1$H NMR spectra of quinolines **4** all peaks are twinned which indicates that the reaction product is a mixture of two epimeric compounds (3:2). In spectra of the major isomer there are signals of the heminal methyl groups at 0.54 and 1.31 ppm, triplet of $^1$CH group at 3.0 ppm, duplet-duplet signal of the $^4$CH$_2$ group at 2.423 and 2.434 ppm,

multiplets of the three-protons signals of $^{7}CH_2$ and $^{5}CH$ groups at 2.19-2.34 ppm, two duplet signals of $^{10}CH$, $^{16}CH$ at 8.0 and 8.62 ppm, multiplet signals of $^{14}CH$, $^{15}CH$ at 7.61-7.79 ppm and carboxylic groups protons at 11-14 ppm. That the reaction product is a mixture of two substances also follows from the data of $^{13}C$ NMR spectrum there are doubled signals of carbons of both carboxylic groups $^{18}C$ and $^{3}C$ at 173.86, 178.05 and 167.65, 167.68 ppm, and carbon $^{2}C$ at 160.43 and 161.61 ppm. The difference in the values of the position of heminal group signals in *cis*-isomer compared with similar ones of *trans*-isomer in $^{13}C$ NMR spectra is due to the fact that the first one experience two screening effects of steric character from *cis*-located substitutors of the four-member ring, while in the *trans*-isomer it is less expressed. These data are in agreement with data for similarly constructed derivatives of 2,2-dimethylcyclobutane [5].

*Table 1*

**NMR Spectroscopic Data of Compounds 4**

| № | Groups | Method | The chemical shifts ($CDCl_3$, δ, ppm, *J*/Hz) | |
|---|---|---|---|---|
| | | | Major izomer | Minor izomer |
| 1 | CH | $^{1}H$ | 3.50, [c]t, $J = 10$ | 3.58, t, 1H, $J = 7.6$ |
| | | $^{13}C$ | 48.92 | 48.22 |
| 2 | C | $^{1}H$ | - | - |
| | | $^{13}C$ | 160.30 | 161.49 |
| 3 | $CO_2H$ | $^{1}H$ | 10.0 | 10.0 |
| | | $^{13}C$ | 172.87 | 172.67 |
| 4 | $CH_2$ | $^{1}H$ | 2.29, 2.26, [b]d d, $J_{5,4\alpha} = 6.4$, $J_{5,4\beta} = 6.8$ | 2.30, 2.28, d d, $J_{5,4\alpha} = 6.4$, $J_{5,4\beta} = 6.8$ |
| | | $^{13}C$ | 29.92 | 29.92 |
| 5 | CH | $^{1}H$ | 2.42-2.45, [d]m | 2.42-2.45, m |
| | | $^{13}C$ | 37.91 | 37.57 |
| 6 | C | $^{1}H$ | - | - |
| | | $^{13}C$ | 43.49 | 41.60 |
| 7 | $CH_2$ | $^{1}H$ | 2.53-2.64, m | 2.53-2.64, m |
| | | $^{13}C$ | 24.90 | 24.34 |
| 8 | $CH_3$ | $^{1}H$ | 0.56, [a]s | 0.64, s |
| | | $^{13}C$ | 17.52 | 17.52 |
| 9 | $CH_3$ | $^{1}H$ | 1.33, s | 1.23, s |
| | | $^{13}C$ | 30.01 | 30.01 |
| 10 | CH | $^{1}H$ | 7.63, d, $J = 8.0$ | 7.67, d, $J = 8.4$ |
| | | $^{13}C$ | 123.00 | 122.96 |
| 11 | C | $^{1}H$ | - | - |
| | | $^{13}C$ | 135.77 | 135.85 |
| 12 | C | $^{1}H$ | - | - |
| | | $^{13}C$ | 121.55 | 122.20 |
| 13 | CH | $^{1}H$ | 8.07, d , $J = 8.0$ | 8.09, d, $J = 8.0$ |
| | | $^{13}C$ | 125.32 | 125.32 |
| 14 | CH | $^{1}H$ | 7.77, 7.79, d d, $J_{13,14} = 8.0$, $J_{14,15} = 8.4$ | 7.77, 7.79, d d, $J_{13,14} = 8.0$, $J_{14,15} = 8.4$ |
| | | $^{13}C$ | 129.60 | 129.23 |
| 15 | CH | $^{1}H$ | 7.64, 7.68, d d, $J_{14,15} = 6.0$, $J_{15,16} = 4.8$ | 7.64, 7.68, d d, $J_{14,15} = 6.0$, $J_{15,16} = 4.8$ |
| | | $^{13}C$ | 126.97 | 126.97 |
| 16 | CH | $^{1}H$ | 8.63, d, $J = 8.8$ | 8.63, d, $J = 8.8$ |
| | | $^{13}C$ | 129.33 | 129.56 |
| 17 | C | $^{1}H$ | - | - |
| | | $^{13}C$ | 148.07 | 147.96 |
| 18 | $CO_2H$ | $^{1}H$ | 10.0 | 10.0 |
| | | $^{13}C$ | 167.65 | 167.68 |

[a]s-singlet, [b]d-doublet, [c]t-triplet, [d]m-multiplet

We have shown that the considerable increase of the yield and purity of chiral acids is achieved applying the method of under phase transfer catalysis. In this method, a catalyst is used to carry the nucleophile from the aqueous into the organic phase. As an example, 18-crown-6·CN is added and the product **4** is formed with 81% yield. It is worth noting that not all catalysts, as well as ketones **2a,b,** work equally well in our situations. Experimentation is

required to find benzyltriethylammonium chloride as optimum catalyst under condensation of ester **2b** with **3**. In last case the product **4** has been obtained with yield up to 95%.

Esterification of acids **4** has been investigated, also. There are many ways of performing this reaction. It has been established that treatment of **4** with MeOH in the presence of catalytic amounts of $H_3PO_4$, $HClO_4$ or $H_2SO_4$ at room temperature results in the formation of esters **5**, while at high temperature (reflux), the lactone **7** has been isolated.

It's $^1$H NMR-spectrum is characterized by the presence of the singlet six-proton signal of the hem-dimethyl group at 1.35 ppm, the three-proton signal of the ester group at 3.60 ppm, the multiplet four-proton signals of $^1CH_2$, $^7CH_2$ at 0.59-1.43, 3.38-4.15 ppm, the multiplet three-proton signals of two groups: $^4CH_2$ and $^5CH$ at 1.05-2.58 ppm and of multiplet signals of quinoline fragment's protons at 7.54-8.74 ppm. Elemental analysis data in combination with characteristic bands of ester, lactone and quinoline groups in the IR-spectrum supplement the spectral characteristics of substance **7.** It should be mentioned that the transformation of the pinonic acid **2** into such types of lactones has been described earlier [5], while the registered signals of the dimethyl-tetrahydrofuran fragment are in good agreement with data for 3-(3'-oxobutyl)-4,4-dimethylbutyrolactone [6].

By action of solution $CH_2N_2$ in 1.4-dioxane upon **2a,** diesters **5** have been obtained (50% yield). In the $^1$H NMR spectrum of **5**, all peaks are doubled and one of the products in the mixture predominates. Present in its NMR-spectrum are the characteristic singlet signals of the hem-dimethyl group at 0.52 ppm, 1.28 ppm and esters ones at 3.38 ppm and 3.97 ppm. That the reaction product is a mixture of two substances also results from data of $^{13}$C NMR spectrum. In the area of the weak field there are doubled signals of carboxy groups' carbons at 172.60 ppm and 172.58 ppm, as well as the appearance, at 51.06 ppm and 52.66 ppm, of the methyl ester's carbon signal in comparison with the spectrum of the initial **4.**

## Conclusions

This report describes new effective synthesis of the chiral chinchoninic acids form (-)-α-pinene. Because of the reactive pinonic acid is a reactive chemical undergoing many reactions of a methyl ketone, carboxyl groups as well as cyclobutane ring. Moreover, in those instances where rupture of the cyclobutane ring has been shown as well as a new methods for liquid/solid phase transfer/catalyst conditions proposed.

## Experimental

All the used solvents were of reagent quality, and all commercial reagents have been used without additional purification. Removal of all solvents has been carried out under reduced pressure. Analytical TLC plates were Silufol® UV-254 (Silpearl on aluminium foil, Czecho-Slovakia). Melting points has been determined on the heating table "Boetius" and not corrected. IR spectra have been recorded on a Specord 75 IR instrument. $^1$H and $^{13}$C NMR spectra have been recorded for $CDCl_3$ 2-3% solution on a Bruker AC-80 (80 and 20 MHz) and "Bruker AC-E400" (200.13 and 50.32 MHz). The specific rotation has been recorded on "Jasco-P-2000".

**(-)-α-Pinene 1**– reagent from Fluka Chemical Company. $n_D^{20}$ 1.466, $[\alpha]_D^{20}$-58.48° (c 0.046, $CHCl_3$).

**Acid 2a** and **ester 2b** have been prepared according to previously published method [2].

**Preparation of (+)-2-[(1*S*)-3(4-carboxy-2-quinoline)-2.2-dimethylclobutyl] acetic acid 4** has been obtained by three methods.

Method a) Solution of 6.72g (120 mmol) KOH in 5 ml of water was added to the solution of 2.4g (16.6mmol) of isatine **3** in 25 ml of EtOH. The mixture was boiled during 5 minutes and then cooled. The obtained solution was supplemented (drop-by-drop) with the solution of 3g (16 mmol) of pinonic acid **2a** in 25ml of EtOH and boiled for 48 hours. The solvent was distilled; water (25ml) was added with following acidification to pH 1 by HCl conc. The solid was filtered out, washed with water, EtOH and dried. 2.13g (53%) of creamy-colored crystals were obtained. M.p. 248-250° (EtOH). $[\alpha]_D^{20}$+6.33° (c 0.016, MeOH). IR-spectrum (ν/cm$^{-1}$): 1380, 1385 ($CMe_2$), 1720-1760, 2560-3000 (COOH). It was found %: C 69.03, H 6.09, N 4.44. $C_{18}H_{19}NO_4$. It was calculated, %: C 68.99, H 6.11, N 4.47. The major isomer was isolated for analytical purposes. M.p. 253-254° (EtOH). $[\alpha]_D^{20}$+19.55° (c 0.005, MeOH). IR-spectrum (ν/см$^{-1}$): 1373, 1388 ($C(CH_3)_2$), 1716, 2600-3000 (COOH), 3432 (C=N).

Method b) The solution of 0.8g (0.02 mol) NaOH in 5ml of EtOH has been added to the suspension of 1.47g (0.01 mol) **3** in 30 ml of dry benzene. After 2 hours of stirring the solution of 1.84g (0.01 mol) **2a** in 20 ml of benzene has been added followed by 0.4g (0.01 mol) of NaOH and 0.15g (0.0005 mol) of 18-crown-6·$CH_3CN$ catalyst. The reaction mixture was boiled for 7 hours. The organic phase was separated. The residue was dissolved in 20ml of water and acidified up to pH 2 by conc. HCl. The solid was filtered, washed with water, dried in open air then over NaOH. In result, we have obtained 2.54g (81%) of mixture of isomers similar to those described in point a).

Method c) 20 ml of diethyl ether followed by 1.47g (0.01 mol) **3** were added to the solution of 0.8g (0.02 mol) of NaOH in 6 ml of EtOH. The formed violet suspension was mixed during 1.5 hours and then boiled during 3 hours. At room temperature and while mixing, the solution of 1.98g (0.01 mol) of ester **2b** in 20 ml of ether, 0.4g(0.01 mol) of NaOH and 0.114g (0.005 mol) of benzyltriethylammonium chloride was gradually added to the reaction mixture.

The suspension was boiled during 6 hours under mixing, the ester was distilled, and the residue was dissolved in a minimum quantity of water, acidified to pH2 by conc. HCl. The solid was filtered, washed with water, dried in open air then over NaOH. We obtained 2.98g (95%) of substance **4** in the form of isomers mixture.

**Preparation of methyl 2-[2,2-dimethyl-3-(methyl 2-quinoline-4-carboxylate)cyclobutyl] acetate 5.**

The solution of diazomethane, obtained from 0.08g (7.8 mmol) of NMU and 2g (36 mmol) of KOH in 15 ml of diethyl ether, was added to the solution of 0.94g (3mmol) of acid **2a** in 10 ml of 1,4-dioxane drop by drop during 30 minutes under mixing. After that, the mixture was stirred for another half an hour, washed by saturated solution of $NaHCO_3$ (3 X 10 ml) and with water (10 ml), dried over $Na_2SO_4$, steamed in vacuum, and the obtained oily residue (1g) was chromatographed on the column (silica gel 100/400, petroleum ester/ethyl-acetate 2:1). We obtained 0.51g of oily light-yellow product **5**. The yield was 50%. IR-spectrum (ν/cm$^{-1}$): 1370, 1383 ($C(CH_3)_2$), 1733 ($COOCH_3$), 3444 (C=N). Spectrum NMR $^1$H of major isomer ($CDCl_3$, δ, ppm, *J*/Hz): 0.52, 1.28 s, s (6H, $CMe_2$), 2.2-2.52 m (5H, $^4CH_2$, $^5CH$,$^7CH_2$), 3.40 t (1H, $^1CH$, *J*=7.94), 3.58, 3.97 s, s (6H, $2CO_2Me$), 7.62-8.12 m (3H, $^{13}CH$, $^{14}CH$, $^{15}CH$), 8.47-8.59 m (2H, $^{10}CH$, $^{16}CH$). Spectrum NMR $^{13}$C of the prevailing isomer ($CDCl_3$, δ, ppm): 172.58 ($^3C$), 166.26 ($^{18}C$), 160.18 ($^2C$), 148.06 ($^{17}C$), 134.45 ($^{11}C$), 129.62 ($^{14}C$), 129.39 ($^{16}C$), 127.11 ($^{15}C$), 124.71 ($^{13}C$), 122.25 ($^{10}C$), 121.58 ($^{12}C$), 52.66, 51.06 2($CO_2$Me), 48.97 ($^1C$), 43.46 ($^6C$), 37.51 ($^5C$), 35.15 ($^9C$), 29.84 ($^4C$), 24.89 ($^7C$), 17.41 ($^8C$). It was found,%: C 70.52, H 7.67, N 3.88. $C_{21}H_{27}NO_4$. It was calculated, % C 70.56, H 7.61, N 3.92.

**Preparation of 2-[-2,2-Dimethyl-3-(methyl 2-quinoline-4-carboxylate)cyclobutyl] acetic acid 6.**

Method a). The solution of 0.63g (0.002 mol) of acid **IV** and 0.1 ml of conc. $H_2SO_4$ in 30 ml of MeOH was stirred at room temperature during 3 days. Then the MeOH was removed and the residue was dissolved in water. The mixture was neutralized by NaOH solution up to pH 6. The white solid was filtered, washed with water, dried and in result has been obtained 0.58g (88%) of product **6**. M.p. 98-99°. The spectrum $^1$H NMR of the major isomer ($CDCl_3$, δ, ppm, *J*/Hz): 0.72, 1.46 s, s (6H, $CMe_2$), 2.3-2.60 m (5H, $^4CH_2$, $^5CH$,$^7CH_2$), 3.41 m (1H, $^1CH$), 3.70 s (3H, $CO_2Me$), 7.49-8.18 m (3H, $^{13}CH$, $^{14}CH$, $^{15}CH$), 8.83-8.96 m (2H, $^{10}CH$, $^{16}CH$), 10.0 s (1H, $CO_2H$). The spectrum $^{13}$C NMR of the major isomer ($CDCl_3$, δ, ppm): 171.95 ($^3C$), 167.65 ($^{18}C$), 160.95 ($^2C$), 148.63 ($^{17}C$), 135.25 ($^{11}C$), 129.54 ($^{14}C$), 128.65 ($^{16}C$), 126.28 ($^{15}C$), 125.83($^{13}C$), 122.54 ($^{10}C$), 122.07 ($^{12}C$), 50.77 ($CO_2$Me), 49.61 ($^1C$), 38.22 ($^6C$), 34.71 ($^5C$), 30.31 ($^9C$), 29.42 ($^4C$), 25.18 ($^7C$), 17.66 ($^8C$).

Method b).Out of 0.63g (0.002 mol) of acid **2a** and 0.22ml of $HClO_4$ (60%), similar to method a), we obtained 0.28g (43%) of product **6**.

**Preparation of methyl 2-{2-[(3S)-2.2-dimethyl-5-oxotetra-hydro-3-furanile] ethyl} 2-quinoline-4-carboxylate 7.**

One drop of $H_2SO_4$ (98% concentration) was added to the solution of 0.47g (1.5 mmol) of acid **2a** in 5ml of MeOH and was refluxed during 12 hours. After that the methanol was distilled and the residue was recrystallized from water. We obtained 0.42g (86%) of crystalline cream-colored product with 205-208°C m.p. IR-spectrum (ν/см$^{-1}$): 1375, 1380 ($C(CH_3)_2$), 1735 ($COOCH_3$), 1760 (COOH), 3400 (C=N). $^1$H NMR spectrum ($CDCl_3$, δ, ppm, *J*/Hz): 0.75 d (1H, $^5CH$, *J*=7.79), 0.94 d (1H, $^4CH_\beta$, *J*=7.79), 1.32, 1.43 s, s (6H, $CMe_2$), 2.25-3.58 m (5H, $^4CH_\alpha$, $^6CH_2$, $^7CH_2$), 3.68 s (3H, $CO_2Me$), 7.54-7.72 m (3H, $^{13}CH$, $^{14}CH$, $^{15}CH$), 8.04-8.94 m (2H, $^{10}CH$, $^{16}CH$). It was found, %: C 69.79, H 6.55, N 4.37. $C_{19}H_{21}NO_4$. It was calculated, %: C 69.71, H 6.47, N 4.28.

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