

## SYNTHESIS OF PINONIC ACID NEW DERIVATIVES

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**Abstract:** The method for synthesising new derivatives of the pinonic acid using, at the key step, the reaction of condensation with epichlorohydrin, has been elaborated. It has been shown that, in the presence of catalytic amount of tetrabutylammonium chloride, the reaction is directed towards the formation of etherchlorohydrin, which, later on, is easily transformed into epoxides as well as chloromethylketones with good overall yield.

**Keywords:** pinonic acid, chlorohydrin, epoxide.

### Introduction

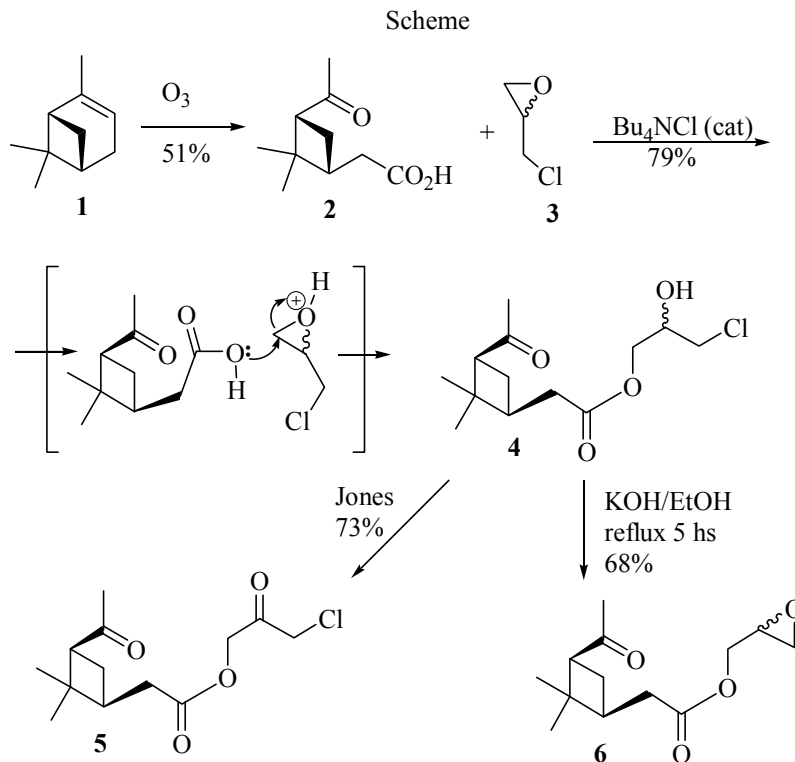
Chlorohydrins, epoxides as well as 2-chloromethylketones are widely used in synthesising various, practically important substances. One of the perspective directions towards obtaining such type compounds in an optically active form may involve the use of pinonic acid **2** [1] as chiral matrix.

### Results and discussions

To realize this approach, we have investigated the possibility of regioselective transformation of acid **2** using epichlorohydrin **3**.

Heating of **2** in **3** leads to an unidentified complex mixture of products. The probable reason of this phenomenon is the proceeding of the reaction of oxirane cycle disclosure according to both Sn2 and Sn1-mechanisms.

It has been established that the addition of catalytic quantities of tetrabutylammonium chloride directs the reaction towards the formation of chlorohydrins **4** according to the scheme.



In IR-spectrum of mixture **4** can observe characteristic bands of carbonyl group of methylketone and ester groups at  $1715$  and  $1770\text{ cm}^{-1}$ , respectively. The spectrum is added by signals at  $770\text{ cm}^{-1}$  ( $C-Cl$ ) and  $3600\text{ cm}^{-1}$  ( $OH$ ). A distinctive feature of NMR spectra of diastereomers **4** is the doubling of all peaks due to the fact that the initial epichlorohydrin **3** represented a mixture of stereo isomers.

Alcohols **4** are oxidized by Jones's reagent into ketone **5**. Its structure is confirmed by the availability of maximum of two carbonyl and carboxylic ester groups (1715, 1735  $\text{cm}^{-1}$ ) in the IR-spectrum, as well as of characteristic signals of protons of four methylene groups, of one methylketone and two methyls of *gem*-dimethyl groups in the  $^1\text{H}$  NMR-spectrum.

In comparison with carbon spectrum of initial **4**, the signal of the carbon atom of the formed carbonyl group and the absence of the carbon atom signal at hydroxyl group in the area of 69.37 ppm, is observed in the  $^{13}\text{C}$  NMR-spectrum of product **5** in the weak field area (195.65 ppm).

Boiling of chlorohydrin **4** in KOH ethanol solution leads, with 68% yield, to oxide **6** whose structure results from spectral data. Present in its IR-spectrum are the frequencies characteristic for keto-, carboxylic ester and oxirane groups, while in the  $^1\text{H}$  NMR-spectrum available are the three protons signals of *gem*-dimethyl and acetyl groups. Besides, available in the spectrum are multiplet signals of the protons of oxirane fragment connected with carboxyl group.

## Conclusions

Thus, it has been shown that utilization of tetrabutylammonium chloride allows performing the chemo- and regioselective functionalization of pinonic acid **2** up to chlorohydrins, later converted into 2-chlorodiketone and epoxides. The utilizing the synthesized compounds for preparing the practically important optically active substances are now under investigation.

## 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.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra have been recorded for  $\text{CDCl}_3$  2-3% solution on a Bruker AC-80 (80 and 20 MHz).

**(-)- $\alpha$ -Pinene 1**— reagent from Fluka Chemical Company.  $n_D^{20}$  1.466,  $[\alpha]_D^{20}$  -58.48° (c 0.046,  $\text{CHCl}_3$ ).

**Acid 2** has been synthesized from **1** by method [1]. M.p. 64-67°C from hexane.  $[\alpha]_D^{20}$  -74.03° (c 0.0199,  $\text{CHCl}_3$ ).

### Preparation of 3-chloro-2-hydroxypropyl-2-[(1S,3R)-3-acetyl-2,2-dimethylcyclobutyl]acetate 4.

5 g (27 mmol) of acid **2** and 0.1 g of tetrabutylammonium chloride in 5 ml of epichlorohydrin **3** has been kept during 1 hour at 120°C. Then, the excess of epichlorohydrin has been distilled off in vacuum. The residue has been dissolved in 100 ml of ether, washed with saturated solution  $\text{NaCl}$  (3x20 ml), dried over  $\text{Na}_2\text{SO}_4$ , distilled off the ether and obtained 5.9 g yellowish oil-like product 7:3 mixture of diastereoisomers **4**. The yield was 79%. IR ( $\nu/\text{cm}^{-1}$ ): 770 (C-Cl), 1375, 1380  $\text{CMe}_2$ , 1715 ( $\text{COCH}_3$ ), 1740 ( $\text{COOCH}_2$ ), 3600 (OH).  $^1\text{H}$  NMR of the major isomer ( $\delta$ , ppm,  $J/\text{Hz}$ ): 0.79, 1.21 s,s(6H,  $\text{CMe}_2$ ), 1.93 s(3H,  $\text{COCH}_3$ ), 1.70-2.89 m (6H,  $^7\text{CH}_2$ ,  $^4\text{CH}_2$ ,  $^5\text{CH}$ ,  $^1\text{CH}$ ), 3.02-3.12 m (1H, OH), 3.44-4.25 m (5H,  $\text{COOCH}_2$ ,  $\text{CH-OH}$ ,  $\text{CH}_2\text{-Cl}$ ).  $^{13}\text{C}$  NMR of the major isomer ( $\delta$ , ppm): 207.62 ( $^2\text{C}$ ), 172.65 ( $^3\text{C}$ ), 69.37 (C-OH), 65.02 ( $\text{COOCH}_2$ ), 54.04 ( $^1\text{C}$ ), 45.66 (C-Cl), 43.14 ( $^6\text{C}$ ), 37.82 ( $^5\text{C}$ ), 34.76 ( $^4\text{C}$ ), 30.06 ( $^{10}\text{C}$ ), 22.91 ( $^8\text{C}$ ,  $^9\text{C}$ ), 17.22 ( $^7\text{C}$ ). Found, %: C 56.34, H 7.58.  $\text{C}_{13}\text{H}_{21}\text{ClO}_4$ . Calculated, %: C 56.42, H 7.65.

### Preparation of (-)-3-chloro-2-oxopropyl-2-[(1S,3R)-3-acetyl-2,2-dimethylcyclobutyl]acetate 5.

Jones's reagent prepared from 7 g  $\text{CrO}_3$ , 6 ml  $\text{H}_2\text{SO}_4$  and 10 ml  $\text{H}_2\text{O}$  has been added to solution of 2.8 g (10 mmol) of **4** in 15 ml acetone at by drops stirring, and has been stirred for 3 hours. Then, 30 ml of *i*-propyl alcohol has been added and left overnight. The following day, the mixture has been extracted by means of diethyl ether (5x50 ml), the extract has been washed with  $\text{NaHCO}_3$  solution (2x30ml) and with saturated  $\text{NaCl}$  solution (2x30 ml), dried over  $\text{Na}_2\text{SO}_4$ , distilled off the ether and have obtained 2.01 g yellow oil-like product **5**. The yield was 73%.  $[\alpha]_D^{20}$  -14.09° (c 0.1,  $\text{CHCl}_3$ ). IR ( $\nu/\text{cm}^{-1}$ ): 760 (C-Cl), 1380, 1385  $\text{CMe}_2$ , 1715 (C=O), 1735 ( $\text{COOCH}_2$ ).  $^1\text{H}$  NMR ( $\delta$ , ppm,  $J/\text{Hz}$ ): 1.16, 1.24 s,s (6H,  $\text{CMe}_2$ ), 2.05 s (3H,  $\text{COCH}_3$ ), 1.33-2.90 m (6H,  $^7\text{CH}_2$ ,  $^4\text{CH}_2$ ,  $^5\text{CH}$ ,  $^1\text{CH}$ ), 4.18 m (2H,  $\text{CH}_2\text{Cl}$ ), 4.89 m (2H,  $\text{COOCH}_2$ ).  $^{13}\text{C}$  NMR ( $\delta$ , ppm): 208.33 ( $^2\text{C}$ ), 195.65 ( $\text{O=C-CH}_2$ ), 172.87 ( $^3\text{C}$ ), 64.24 ( $\text{COOCH}_2$ ), 53.87 ( $^1\text{C}$ ), 46.01 (C-Cl), 43.14 ( $^6\text{C}$ ), 37.64 ( $^5\text{C}$ ), 34.33 ( $^4\text{C}$ ), 29.99 ( $^{10}\text{C}$ ), 22.83 ( $^8\text{C}$ ,  $^9\text{C}$ ), 17.11 ( $^7\text{C}$ ). Found, %: C 56.80, H 7.02.  $\text{C}_{13}\text{H}_{19}\text{ClO}_4$ . Calculated, %: C 56.83, H 6.97.

### Preparation of 2-oxiranylmethyl-2-[(1S,3R)-3-acetyl-2,2-dimethylcyclobutyl]acetate 6.

Solution of 1.35 g (4.9 mmol) of **5** and 0.41 g (7.3 mmol) of KOH in 20 ml of EtOH have been boiled under refluxing during 5 hours. Then, the ethanol has been distilled off, the residue has been diluted with 20 ml of water and extracted with  $\text{CHCl}_3$  (5x10 ml). The extract has been washed with 10 ml of saturated  $\text{NaCl}$  solution, dried over  $\text{Na}_2\text{SO}_4$ , chloroform has been distilled off and 0.8 g of yellow oil-like 7:3 mixture of diastereoisomers **6** have been obtained. The yield was 68%. IR ( $\nu/\text{cm}^{-1}$ ): 1380, 1385 ( $\text{CMe}_2$ ), 1710 ( $\text{COCH}_3$ ), 1735 ( $\text{COOCH}_2$ ), 3040 (epoxi).  $^1\text{H}$  NMR of major isomer ( $\delta$ , ppm,  $J/\text{Hz}$ ): 1.05, 1.14 s,s (6H,  $\text{CMe}_2$ ), 1.90 s (3H,  $\text{COCH}_3$ ), 1.79-2.74 m (8H,  $^7\text{CH}_2$ ,  $^4\text{CH}_2$ ,  $^5\text{CH}$ ,  $^1\text{CH}$ ,  $\text{CH}_2$  epoxi), 3.35-3.44 m (1H, CH epoxi), 3.83-4.10 m (2H,  $\text{CO}_2\text{CH}_2$ ). Found, %: C 64.83, H 8.42.  $\text{C}_{13}\text{H}_{20}\text{O}_4$ . Calculated, %: C 64.98, H 8.39.

## References

- [1]. Gudima, A. Research in chemistry: achievements and prospects. Chişinău, 2003, V.II, p. 103-105.