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Developing a Synthetic Approach to Diastereomerically Pure Sulphoxides from Pinane Series

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Abstract

A series of sulphides belonging to pinane family was obtained basing on (1*S*)-(−)-β-pinene and its oxide. The asymmetric oxidation of β-hydroxysulphide with the fragment of 2-mercaptoethanol using an oxidizing system such as $Ti(O-i-Pr)_4/R-C_6H_5CH(OH)COOH/t$-BuOOH resulted in obtaining diastereomerically pure hydroxysulphoxide with pinane structure.

Key words: (1*S*)-(−)-β-pinene, pinanyl sulphides, β-hydroxysulphoxide, asymmetric oxidation

INTRODUCTION

For the last years, searching is conducted concerning the selective oxidation methods in order to convert sulphides into sulphoxides, because the latter compounds have a wide application in various fields of human activity [1]. It is known that sulphoxides synthesized or extracted from naturally occurring raw materials exhibit a high biological activity with a wide scope of action for to be used in medicine as antibiotics, antioxidants, anti-depressants, high-efficiency antiulcer drugs [2, 3].

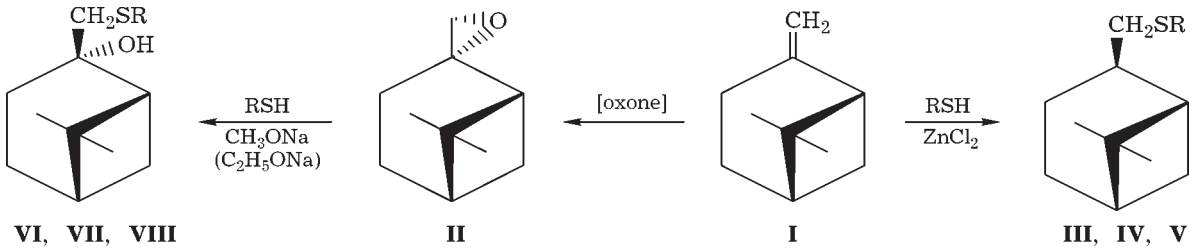
Earlier, we performed the electrophilic addition reactions consisting in 2-mercaptoethanol and mercaptoacetic acid methyl ester addition to (1*S*)-(−)-β-pinene (**I**) in the presence of zinc chloride in catalytic amounts, which resulted in the formation of sulphides **III**, **IV** with a *cis*-configuration positioning of the sulphide group with respect to the *gem*-dimethyl fragment of the molecule [4]. The reaction of mercaptoacetic acid addition to β-pinene oxide (**II**) resulted in the formation of sulphide **VIII** that underwent further dehydration and isomerization to form corresponding lactone [5].

RESULTS AND DISCUSSION

We studied earlier the (−)-β-pinene (**II**) oxide in the reactions with thiourea, ethanedithiol and di(mercaptoethyl)sulphide in the presence of a base, which resulted in the formation of corresponding products with a high yield [6].

In this work we investigated the reaction of electrophilic addition of 2-mercaptoethanol and methyl mercaptoacetate to β-pinene oxide (**II**) and that of mercaptoacetic acid to (1*S*)-(−)-β-pinene (**I**), and the reaction of the asymmetric oxidation of hydroxysulphides belonging to the pinane series.

The reaction of 2-mercaptoethanol and methyl mercaptoacetate addition to β-pinene oxide (**II**) in the presence of sodium ethylate or methylate was completed by forming the corresponding sulphides (**VI**, **VII**) those were isolated by means of column chromatography on silica gel in the form of single products. The reaction between (1*S*)-(−)-β-pinene (**I**) and mercaptoacetic acid in the presence of $ZnCl_2$ in catalytic amounts was completed by forming an addition product against the Markovnikov rule (Scheme 1).



[oxone] = $KHSO_4 \cdot 2KHSO_5 \cdot K_2SO_4$
R = CH_2CH_2OH (**III**, **VI**)
R = CH_2COOCH_3 (**IV**, **VII**)
R = CH_2COOH(**V**, **VIII**)

Scheme 1.

In order to obtain the diastereomerically pure sulphoxide we performed the asymmetric oxidation of β-hydroxysulphide from pinane series (**II**) with the use of the oxidizing system *tert*-butyl hydroperoxide/titanium isopropoxide/(*S*) or (*R*) BINOL. According to XRD structure analysis, the reaction resulted in the formation of β-hydroxysulphoxide from pinane series (**IX**) as a mixture of two diastereoisomers at a ratio approximately equal to 1 : 1.

In order to obtain sulphoxide (**IX**) as a single diastereomer we performed the asymmetric oxidation of sulphide **III** with the use of an oxidation system such as $Ti(O-i\text{-}Pr)_4/R-C_6H_5CH(OH)COOH/t\text{-}BuOOH$ at a molar ratio 0.025 : 0.05 : 2, respectively (Scheme 2).

The crystalline product obtained purified by means of column chromatography on silica gel, represented a diastereomerically pure β-hydroxysulphoxide of pinane structure (**IXa**), whose structure was determined using X-ray diffraction (Fig. 1).

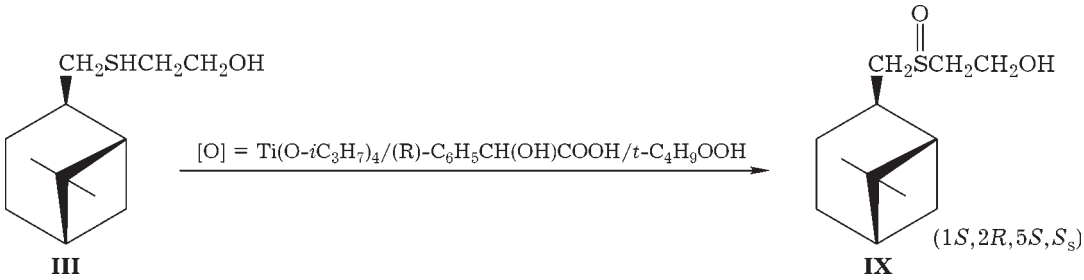
EXPERIMENTAL

In this work we used (1*S*)-(−)-β-pinene (**I**), $[\alpha]_D = -21°$ (Acros Organics, Belgium). For addition reactions we used thiols from Acros Organics.

The NMR spectra were obtained on a Bruker Advance spectrometer (Germany) with an operating frequency equal to 400.13 and 100.61 MHz for ^1H and ^{13}C nuclei, respectively, with TMS internal standard. The IR spectra were registered at the laboratory of optical studies of the Federal Multi-Access Center (Kazan) with the use of a Bruker Tensor-27 Fourier-transform spectrometer within the wavenumber range of 4000−400 cm^{-1}.

In order to isolate and purify the reaction products we used the method of adsorption chromatography on silica gel L (100/160 μ). The elution was performed using hexane/diethyl ether and methylene chloride/acetone mixtures. Monitoring the progress of reaction and quality of reaction mixture separation was carried out by means of TLC technique using Silufol plates (developers I_2 and a mixture of ethanol/sulphuric acid/anisic aldehyde = 90 : 5 : 5). Purifying and drying the solvents was carried out according to known methods described in [7].

The XRD structural investigation of the crystal of **IX** was performed with the use of a Bruker SMART Apex II diffractometer (graphite monochromator, MoK_α = 0.71073 Å).



Scheme 2.

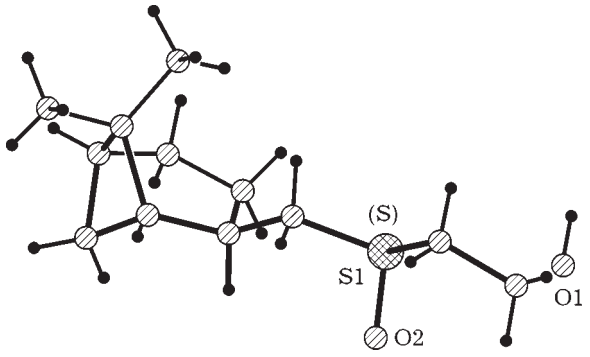


Fig. 1. Geometry of the hydroxy sulphoxide molecule of pinane structure **IX** according to XRD.

A semi-empirical account of absorption was performed using a SADABS software package [8]. The structures were solved by a direct method according to SHELXS package [9]. Non-hydrogen atoms were refined within the framework of isotropic and further of anisotropic approximation using a SHELXL-97 package [10]. Hydrogen atoms not involved in hydrogen bonding, were placed in the positions calculated and refined by means of a "rider" model. The hydroxyl atoms of hydrogen were revealed from difference Fourier series, at the final stage of refining its position was determined in an isotropic approximation. All the calculations were performed with the help of software packages WinGX [11] and APEX2 [12], the graphic part was performed with the help a PLATON program [13].

The XRD investigation of sample **IX** was performed at the Federal Multi-Access Spectro Analytical Center for physicochemical studies of the structure, composition and properties of substances and materials (FM SAC, Kazan).

β-Pinene oxide (**II**) was obtained *via* oxidizing the initial (1*S*)-(−)-β-pinene (**I**) by oxone in the form of a mixture of two isomers at a ratio of about 16 : 1.

β-Pinene oxide (II). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 0.95 s, 1.29 s (6H, H-8,9), 1.2 m (H_e-3), 1.55 m (2H, H-1), 1.7 m (1H, H_e-7), 1.8 m (1H, H_a-3), 2.15 m (1H, H-5), 2.22−2.38 m (1H, H_a-7), 2.63, 2.80 d. AX spin system (2H, H-10, 12.7 Hz).

To 20 mmol of β-pinene oxide (**II**) was added a solution of 20 mmol of methyl mercaptoacetate in 10 mL of sodium methylate at 25 °C, then the reaction mixture was held under stirring for 4 h. The monitoring of the reaction was performed by means of TLC. The reaction mixture was washed (3 × 15 mL of CH_2Cl_2) and dried over $MgSO_4$. The solvent was evaporated; product **VII** was isolated using a column chromatography on silica gel. The yield of product **VII** was equal to 75 %.

Methyl({[(1*S*,5*S*)-6,6-dimethyl-bicyclo[3.1.1]hept-2-hydroxy-2-yl]methyl}thio) acetate (VII). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 0.92 s, 1.25 s (6H, H-8,9), 1.5−2.2 m (8H, H-1,3,4,5,7), 2.9 m (2H, H-10), 3.3 s (2H, H-11), 3.72 s (3H, H-13). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 22.5 (C-3), 23.5 (C-9), 27.6 (C-4), 27.65 (C-8), 32.4 (C-7), 35.3 (C-5), 39.7 (C-6), 41.5 (C-11), 47.3 (C-10), 51.8 (C-1), 52.1 (CH_3O), 76.5 (C-2), 171.3 (C-12). IR spectrum (ν, cm^{-1}): 1740 (C=O), 3090−3650 (O−H). $C_{12}H_{22}O_2S$. Calculation, %: C 62.61, H 9.57, O 13.91, S 13.91. Found, %: C 62.64, H 9.61, O 13.89, S 13.88.

To 20 mmol of β-pinene oxide (**II**) was added a solution of 20 mM of 2-mercaptoethanol in 10 mL of sodium ethoxide at a temperature of 25 °C, then the reaction mixture was held under stirring for 4 h. The monitoring of the reaction was performed using TLC. The reaction mixture was washed (3 × 15 mL of CH_2Cl_2) and dried over $MgSO_4$. The solvent was evaporated; product **VI** was isolated using a column chromatography on silica gel. The yield of **VI** was equal to 65 %.

2-({[(1*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-hydroxy-2-yl]methyl}thio) ethanol (VI). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 0.92 s, 1.25 s (6H, H-8,9), 1.5−2.3 m (8H, H-1,3,4,5,7), 2.7−2.9 m (4H, H-10,11), 3.1 s (1H, OH), 3.78 s (2H, H-12). IR spectrum (ν, cm^{-1}): 3030−3650 (O−H). $C_{13}H_{22}O_3S$. Calculation, %: C 60.47, H 8.53, O 18.60, S 12.40. Found, %: C 60.51, H 8.52, O 18.58, S 12.46.

To 35 mmol of (1*S*)-(−)-β-pinene (**I**) was added a solution of 35 mmol of mercaptoacetic acid in 15 mL of CH_2Cl_2 at a temperature of 25 °C then the reaction mixture was held under stirring for 7 h. The monitoring of the reaction was performed by means of TLC. The reaction mixture was washed (3 × 20 mL of CH_2Cl_2) and dried over $MgSO_4$. The solvent was evaporated; product **V** was isolated using a column chromatography on silica gel. The yield of product **VI** was equal to 58 %.

Methyl({[(1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl}thio)acetic acid (V). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.0 s, 1.2 s (6H, H-8,9), 1.5–1.8 m (8H, H-1,3,4,5,7), 2.6–2.8 m (4H, H-10,11), 3.3 s (1H, OH). IR (ν, cm^{-1}): 3030–3650 (O–H). $C_{12}H_{20}O_2S$. Calculation, %: C 63.16, H 8.77, O 14.04, S 14.04. Found, %: C 63.15, H 8.75, O 14.07, S 14.05.

To 0.0125 mmol of $Ti(O-i-Pr)_4$ was added 0.025 mmol of $R-C_6H_5CH(OH)COOH$ in 5 mL of CCl_4, under stirring. After 1 h of stirring, was added 2 mmol of pinane structure hydroxysulphide **V**. After stirring for 30 min, was added 4 mM of *t*-BuOOH. The reaction mixture was stirred during 14 h till obtaining a complete conversion level of initial hydroxysulphide **V**. The monitoring of the reaction was performed by means of TLC. The solvent was evaporated using a water-jet air pump; product was **IX** was isolated using a column chromatography on silica gel. The yield was equal to 91 %.

The crystals of product **IX** ($C_{12}H_{22}O_2S$) are monoclinic. At 20 °C a = 6.534(3), b = 7.020(3), c = 14.258(6) Å, β = 99.548(5)°, V = 644.9(5) Å^3, Z = 2, d_{calc} = 1.186 g/cm^3, space group $P2_1$, μMo 2.32 cm^{-1}. We measured the intensities of 2433 independent reflexes, 2139 thereof exhibit $I \geq 2\sigma$. The absolute configuration was determined basing on Flack parameter value (−0.08(8)), which corresponds to the configuration of (−)-β-pinene. The final values of the divergence factors are as it follows: R = 0.035, R_w = 0.092.

2-({[(1*S*,2*R*,5*S*,*S*$_s$)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl}sulphinyl) ethanol (IX). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.20 s (9H, H-7,9,10); 3.0 m (4H, CH_2S, SCH_2); 3.7 s (3H, OCH_3); 5.2 s (1H, H-1). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 22.85 (C-3); 23.91, 23.93 (C-9); 26.53, 26.65 (C-4); 28.42, 28.46 (C-8); 33.58, 33.77 (C-7); 35.46, 35.87 (C-5); 39.26, 39.34 (C-6); 41.54, 41.57 (C-1); 45.60, 47.31 (C-2); 54.34, 54.70 (C-10); 57.27 ($\underline{C}H_2OH$); 61.48, 62.19 ($SO\underline{C}H_2$). Mass spectrum, m/z (I_{rel}, %): 230 (M^+, 1), 213 (62), 185 (26), 169 (8), 137 (26), 121 (27), 107 (17), 93 (71), 81 (100), 69 (80), 55 (54), 41 (53), 29 (12).

CONCLUSION

Thus, we obtained novel sulphur-containing derivatives belonging to pinane series; a convenient preparative method was developed for the synthesis of diastereomerically pure в-hydroxysulphoxide of pinane series.

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