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> SHORT COMMUNICATIONS

## Crystallization of Bisulfite Derivatives of Enantiomerically Enriched Verbenone

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Abstract—After separation of crystalline bisulfite derivatives of enantiomerically enriched (1S)- and (1R)-verbenones, steam distillation of the filtrates afforded (1S)- and (1R)-verbenones whose optical purity was higher by 30 and 20%, respectively, than that of the initial enantiomers.

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Verbenone 1 and some related terpene compounds exist in nature as mixtures of optical isomers. The optical purity varies over a wide range, and the natural compound may be both dextro- and levorotatory, depending on the place of its origin.

An efficient method for the isolation and purification of verbenone is based on its conversion to watersoluble bisulfite derivative which is then decomposed by steam distillation from alkaline medium [1]. It is known that under appropriate conditions bisulfite derivatives of carbonyl compounds can be isolated in the crystalline form. As a rule, crystallization of enantiomerically enriched compounds is accompanied by redistribution of enantiomers between the phases.

We have synthesized crystalline bisulfite derivatives of enantiomerically enriched verbenone isomers and studied distribution of the enantiomers between the mother liquor and crystalline bisulfite derivative. As substrates we used (1S)-(-)-verbenone [(1S)-1, Sigma-Aldrich] with 54% *ee* and  $[\alpha]_D = -147.1^{\circ}$  {cf.  $[\alpha]_D = -273^\circ$  for optically pure (1*S*)-(-)-verbenone} and dextrorotatory (1*R*)-(+)-verbenone (1*R*)-1 with 50% *ee*, which was obtained by oxidation of (+)- $\alpha$ -pinene [2].

The bisulfite derivatives were synthesized by stirring a mixture of verbenone with an aqueous solution of a  $Na_2SO_3/NaHSO_3$  mixture until it became homogeneous. The solution was cooled, and the crystalline bisulfite derivative and concomitant inorganic salts were filtered off. The crystalline bisulfite derivative was decomposed by treatment with aqueous sodium carbonate, and verbenone was isolated by steam distillation. Likewise, verbenone was isolated from the mother liquor by steam distillation after treatment with an aqueous solution of sodium carbonate.

The optical purity of verbenone before and after preparation of bisulfite derivatives was monitored by the Mosher method. For this purpose, (1S)- and (1R)-enantiomers of **1** were reduced with lithium tetrahydridoaluminate to (1S)- and (1R)-cis-verbenols



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(1*S*)-2 and (1*R*)-2 which were acylated with (*S*)-Mosher's acid chloride (3) [3] (Scheme 1). The ratio of (1*S*)-2 and (1*R*)-2 was determined from the intensities of signals of the geminal methyl groups in the <sup>1</sup>H NMR spectra. The enantiomeric purity of a commercial sample of (1*S*)-1 (Sigma-Aldrich), determined by the Mosher method, coincided with that calculated from its optical rotation value (54% *ee*), which confirmed reliability this method.

The *ee* value of (1S)-1 decreased from 54 to 40% after its conversion to bisulfite derivative and isolation from the crystalline fraction. A sample of (1R)-(+)-verbenone [(1R)-1, 50% *ee*] was converted to racemic crystalline bisulfite derivative: the methyl proton signals of the (S)-Mosher esters with the corresponding (1S)- and (1R)-enantiomers of *cis*-verbenol **2** had equal intensities.

Thus, it was impossible to isolate enantiomerically pure crystalline bisulfite derivatives and improve in this way the optical purity of commercially available verbenone. We revealed a clear tendency for precipitation of racemic bisulfite derivatives, especially when the initial substrate had lower ee value and the amount of the crystalline fraction was low. Therefore, it became possible to increase the optical purity of verbenone by separation of racemic crystalline bisulfite derivative and isolation of verbenone from the mother liquor. After separation of racemic verbenone  $(\pm)$ -1 from a sample of (1R)-1 with 50% ee, from the mother liquor we isolated (1R)-1 in 62% yield with >70% ee. Likewise, from a sample of (1S)-1 with 54% ee we isolated 1S-(-)-verbenone in 20% yield with an ee value of higher than 85%; i.e., the optical purity was improved by 31% (Scheme 2).

We believe that the use of the described procedure for enhancement of the optical purity of verbenone by crystallization and separation of its racemic bisulfite derivative for preparative purposes is expedient only when crystalline racemate seeds are available and conditions are created for its preferential crystallization from the solution.

Crystalline bisulfite derivative of (1*R*)-(+)-verbenone and isolation of racemic verbenone therefrom. Sulfur dioxide was passed through a mixture of 37.8 g (0.3 mol) of sodium sulfite and 115 mL of water until a weight gain of 20 g was attained and the solution turned slightly yellowish. Sodium hydrogen carbonate, 2 g, and (1R)-(+)-verbenone, 1.3 g (8.2 mmol), were added to 20 mL of the resulting solution, and the mixture was stirred for 24 h at room temperature until it became homogeneous, cooled to 3°C, and kept for 24 h at that temperature. The precipitate was filtered off and washed with a small amount of a saturated solution of Na<sub>2</sub>SO<sub>3</sub>. The crystals of bisulfite derivative were added to 50 mL of a 10% solution of sodium carbonate, and the mixture was steam-distilled to separate racemic verbenone  $(\pm)$ -1. The distillate was saturated with sodium chloride and extracted with diethyl ether  $(3 \times 10 \text{ mL})$ . The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue, 0.34 g (26%), was pure racemic verbenone  $(\pm)$ -1 (according to the <sup>1</sup>H NMR data).

Enantiomerically enriched (1R)-(+)-verbenone from the mother liquor. After separation of the crystalline bisulfite derivative of (1R)-1, the mother liquor was added to 50 mL of a 15% aqueous solution of sodium carbonate, and the mixture was steam-distilled. The distillate was saturated with sodium chloride and extracted with diethyl ether  $(3 \times 10 \text{ mL})$ , and the combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residue, 0.80 g (62%) was (1R)-(+)-verbenone with >70% ee (<sup>1</sup>H NMR). **Crystalline bisulfite derivative of 1***S***-(–)-verbe-none** was obtained as described above for (1*R*)-1 from 1.3 g (8.2 mmol) of (1*S*)-1 and was then decomposed to isolate 0.87 g (67%) of (1*S*)-1 with 40% *ee*.

Enantiomerically enriched 1S-(-)-verbenone was isolated from the mother liquor as described above for (1*R*)-1. Yield 0.26 g (20%), >85% *ee*.

Determination of the optical purity of (1R)-(+)and 1S-(-)-verbenone. A suspension of 0.1 g (2.6 mmol) of LiAlH<sub>4</sub> in 4 mL of THF was cooled with ice water, and 200 mg (1.3 mmol) of (1R)-1 or (1S)-1 was added with stirring. The mixture was stirred for 1 h at room temperature and treated in succession with 0.1 mL of water, 0.1 mL of 20% aqueous sodium hydroxide, and 0.2 mL of water. The mixture was filtered, and the filtrate was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. A 10-mg portion of the residue was dissolved in 0.5 mL of methylene chloride, 0.1 mL of pyridine and 35 mg (0.14 mmol) of (S)-Mosher's acid chloride were added, and the mixture was kept for 18 h at room temperature. It was then diluted with 5 mL of diethyl ether, washed in succession with saturated solutions of NaHCO<sub>3</sub> and NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure. The residue was analyzed by <sup>1</sup>H NMR. The intensities of the methyl proton signals at  $\delta$  0.72 (1*R*) and 0.84 ppm (1*S*), as well as at  $\delta$  1.26 (1*R*) and 1.34 ppm (1*S*), were compared [3].

The <sup>1</sup>H NMR spectra were recorded on a Bruker Avance 500 spectrometer at 500 MHz using CDCl<sub>3</sub> as solvent. The solvents used were dried according to standard procedures and distilled.

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