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Synthesis of Novel Optically Pure Chiral Diamine from Levopimaric Acid

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Abstract

Basing on the components of an available naturally occurring renewable raw material, a synthesis of a novel chiral optically pure diamine belonging to diterpene series was realized. The tricyclic *trans*-1,2-diamine obtained and its derivatives could be used as ligand for metal complex catalysts of asymmetric reactions.

Key words: diterpenes, chiral, *trans*-1,2-diamine

INTRODUCTION

The synthesis of substances in enantiomerically and diastereomerically pure form is of current importance, since different stereoisomers differ from each other in the effects on living organisms. The asymmetric catalysis allows one to obtain any required amount of optical isomers using only catalytic amounts of a chiral inductor.

Diamines in the form of individual stereoisomers are successfully used as ligands for homogeneous metal complex catalysis [1–3]. At the present time, their synthesis is carried out both from achiral and from chiral compounds. The disadvantages of the method for obtaining amines from achiral materials consist in multi-stage processing and the fact that there is a time-consuming and costly step of optical isomer separation involved.

An efficient method for the synthesis of chiral ligands consists in the stereospecific transformation of naturally occurring compounds; those already contain asymmetric centers in the molecule. Natural optically active compounds, in particular amino acids, carbohydrates and terpenes could be used as such raw material [4, 5].

Naturally occurring diterpenes such as abietic and levopimaric acids represent the major components of resin acids contained in the oleoresin of Pinus Silvestris. The adducts of levopimaric acid with such active dienophiles as maleic anhydride, fumaric acid, *p*-benzoquinone, *etc*., were extensively studied in the 60′s of the last century. It was found that heating the abietic acid with dienophiles results in the same products as those formed in the reaction between dienophiles and levopimaric acid [6, 7]. It should be noted that the abietic acid is a major component of gum rosin (the content being more than 50 %), a large-tonnage product of timber industry [6]. Thus, a directed functionalization of oleoresin and gum rosin with obtaining of valuable optically pure substances could become one of the ways to solve the problem concerning the complex processing of renewable raw materials, which thus would reduce the man-caused impact on the environment.

The purpose of this paper consisted in the synthesis of novel diamine belonging to diterpene series in diastereomerically pure form basing on the transformations of levopimaric acid.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of the solution of compounds synthesized were registered on a Bruker AM-400 and AV-300 spectrometers with operating frequencies equal to 400.13 and 300.13 MHz for ^1H NMR, 100.61 and 75.47 MHz for ^{13}C NMR, respectively. As an internal standard we used chloroform (δ_H 7.24 ppm, δ_C 76.90 ppm). The IR spectra were registered employing a Bruker Vector-22 IR spectrometer, in tablets with KBr for solids and in films for oil-like substances. The specific rotation value $[\alpha]_D$ was determined with the use of series PolAAr 3005 polarimeter. Mass spectra were registered on a Finnigan MAT 8200 high resolution mass spectrometer. For column chromatographing, we used silica gel L (100/160μ). Combining the individual fractions was performed basing on data obtained by thin layer chromatography (TLC). Monitoring the progress of the reaction was carried out using TLC on the plates with a fixed layer of silica gel (Sorbfil, Sorbpolymer Co., Krasnodar, Russia)); the detection was performed using a mixture of *p*-methoxybenzaldehyde (10 % vol.) and concentrated sulphuric acid (10 vol. %) dissolved in ethanol with further by heating up to 100 °C. Potassium carbonate and sodium sulphate were calcined at 250 °C during 3 h. Acetone was dried via boiling over potassium carbonate, methanol was dried through boiling over magnesium methoxide, toluene was dried *via* boiling over sodium with further distillation. Thionyl chloride was distilled over linseed oil. The other solvents and reagents were of chemical pure grade without any additional purification.

Isolation of the mixture of resin acids from oleoresin (I). The oleoresin of Pinus Silvestris (75 g in mass) was loaded into a Soxhlet extractor to extract with hexane under boiling reflux for 10 h; the solvent was evaporated [8]. As a result, we obtained 20 g of light yellow coloured oil.

Preparation of the mixture of the methyl esters of resin acids (II). A solution of resin acids mixture (10 g in mass, 33 mmol; for the calculation we used a gross formula for resin acids $C_{20}H_{30}O_2$) in 200 mL of absolute acetone was boiled with 2.3 g (16 mmol) of calcined potassium carbonate and 4.8 g (2.0 mL, 34 mmol) of methyl iodide during 2 h. A precipitate obtained was filtered, and the filtrate was evaporated. To the residue was added 50 mL of diethyl ether, the mixture was filtered. The solution obtained was evaporated; as the result we obtained 9.8 g of the mixture of resin acid methyl esters (94 %) in the form of yellow oil.

[1*R*-(1α,4β,5β,9α,10β,12α,13α,14β)]-5,9-dimethyl-13,14-dicarboxy-16-isopropyl-5-methyloxycarbonyltetracyclo[10.2.2.0^{1,10}0^{4,9}]-hexadecyl-15-ene (III). A mixture of the methyl esters of resin acids (9.8 g in mass, 31 mmol, for the calculation we used a gross formula for the methyl esters of resin acids $C_{21}H_{32}O_2$) and 5.5 g (47 mmol) of fumaric acid was heated in an argon atmosphere at 180–200 °C and stirred with a mechanical stirrer during 8 h. The reaction mixture was then cooled, and 40 mL of diethyl ether was added; the precipitate obtained was filtered, washed with boiling water (3×40 mL) and dried. The product was crystallized from methanol. We obtained 2 g (15 %) of compound **III** as colourless crystals, m. p. = 295–296 °C (lit. m. p. = 294–295 °C [5]). $[\alpha]_D^{21.2}$ = +36.9 (C = 0.154, C_2H_5OH), lit. $[\alpha]_D^{24.5}$ = +36 (C = 0.004, C_2H_5OH) [7]. IR spectrum (KBr): 3215, 2952, 1730, 1709, 1420, 1385, 1270, 1231, 1200, 1178, 823, 646. ^1H NMR spectrum (CD_3SOCD_3, δ, ppm, *J*, Hz): 0.53 (s, 3H, H_3C (18)), 0.98 (d, 6H, H(14), H(15), $J_{14,13} = J_{15,13}$ = 6.8), 1.04 (s, 3H, H_3C (19)), 0.80–1.82 (m, 15H, 2H(4), H(15), H(4a), 2H(5), 2H(6), 2H(7), H(8a), 2H(9), 2H(10)), 2.31 (d. septet, 1H, H(13), $J_{3,13}$ = 1.3), 2.38 (d, 1H, H(2), $J_{1,2}$ = 5.9), 2.54 (d, 1H, H(1), $J_{1,2}$ = 5.9), 2.77 (m, 1H, H(3)), 3.56 (s, 3H, H_3C (21)), 5.28 (s, 1H, H(11)). ^{13}C NMR spectrum (δ_C, ppm): singlets at 39.74 (C(4b)), 42.84 (C(10a)), 49.14 (C(8)), 149.90 (C(12)), 177.16 (C(17)), 177.44 (C(16)), 180.90 (C(20)), doublets at 56.47 (C(1)), 50.79 (C(2)), 37.81 (C(3)), 57.31 (C(4a)), 51.86 (C(8a)), 126.42 (C(11)), 34.67 (C(13)), triplets at 18.96 (C(6)), 23.88 (C(9)), 25.57 (C(4)), 37.09 (C(10)), 38.81 (C(7)), 39.92 (C(5)), quadruplets at 17.87 (C(18)), 18.55 (C(19)), 22.24 (C(14)), 22.28 (C(15)), 53.76 (C(21)).

[1*R*-(1α,4β,5β,9α,10β,12α,13α,14β)]-13,14-diamino-5,9-dimethyl-16-isopropyl-5-methyloxycarbonyltetracyclo[10.2.2.0^{1,10}0^{4,9}]-hexadec-15-ene (IV). To 1 g (2.3 mmol) of acid **III** in 0.5 mL of toluene was added 0.34 mL (0.54 g, 4.6 mmol) of thionyl chloride and one drop of dimethyl-

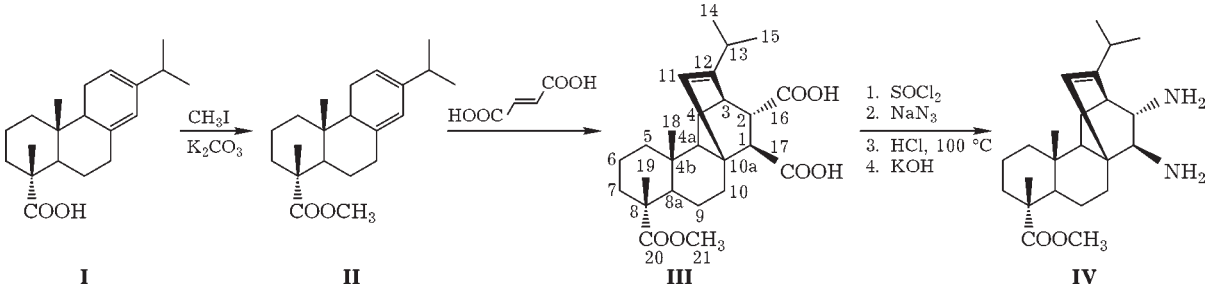
formamide. The reaction mixture was stirred at 80 °C during 1 h. The solvent was evaporated, and then 5 mL of toluene was added to the residue. The obtained solution of the acid **III** chloride in toluene was dropwise added to a solution of 0.75 g (11.6 mmol) of sodium azide in 15 mL of water during 10 min. The reaction mixture was stirred at 0 °C during 30 min. The organic layer obtained was separated, washed with water (2×10 mL) and dried then with Na_2SO_4. The resulting solution was boiled for 2 h. Then to the reaction mixture was added 2.38 g (65 mmol, 2 mL) of 35 % hydrochloric acid with further heating for 3 h. The formed precipitate of amine **IV** hydrochloride was filtered, washed with water (2×10 mL) and dried then in air. To a solution of 0.123 g (2.2 mmol) KOH in 5 mL of absolute methanol was added amine hydrochloride **IV**. The precipitate of potassium chloride was filtered; the solution was evaporated with further adding 50 mL of ethyl acetate, washed with water (2×10 mL), dried with Na_2SO_4. The solution was evaporated; the product was crystallized from diethyl ether. We obtained 0.63 g (73 %) of diamine **IV** as colourless crystals, m. p. = 110−112 °C. $[\alpha]_D^{24.5}$ = +2.54 (C = 0.340, $CHCl_3$). IR spectrum (KBr): 3308, 2953, 1725, 1461, 1386, 1245, 1195, 1139. Found: *m/z* 374.29310 [M^+], $C_{23}H_{38}N_2O_2$. Calculated: M = 374.29331. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 0.58 (s, 3H, H_3C (18)), 1.02 (d, 6H, H(14), H(15), $J_{14,13} = J_{15,13}$ = 6.8), 1.11 (s, 3H, H_3C (19)), 0.80−1.82 (m, 15H, 2H(4), H(15), H(4a), 2H(5), 2H(6), 2H(7), H(8a), 2H(9), 2H(10)), 2.33 (septet, 1H, H(13), $J_{13,14} = J_{13,15}$ = 6.8), 2.13 (d, 1H, H(2), $J_{1,2}$ = 2.0), 2.37 (d, 1H, H(1), $J_{1,2}$ = 2.3), 2.38 (m, 1H, H(3)), 3.63 (s, 3H, H_3C (21)), 5.27 (s, 1H, H(11)). ^{13}C NMR spectrum (δ_C, ppm): singlets at 37.54 (C(4b)), 42.77 (C(10a)), 47.40 (C(8)), 150.05 (C(12)), 179.50 (C(20)), doublets at 66.33 (C(1)), 59.07 (C(2)), 39.07 (C(3)), 53.16 C(4a)), 49.62 (C(8a)), 123.03 (C(11)), 32.75 (C(13)), triplets at 17.28 (C(6)), 20.88 (C(9)), 21.88 (C(4)), 33.61 (C(10)), 36.97 (C(7)), 38.07 (C(5)), quadruplets at 16.25 (C(18)), 16.93 (C(19)), 20.72 (C(14)), 20.75 (C(15)), 52.12 (C(21)).

RESULTS AND DISCUSSION

Earlier basing on the transformations of levopimaric acid adducts with maleic anhydride and fumaric acid, we developed methods for the synthesis of diastereomerically pure bisphosphines, ureas and Schiff bases belonging to diterpene series [9, 10]. The derivatives obtained were used as ligands for asymmetric reaction catalysts. In this paper we continued the study of fumaropimaric acid derivatives to obtain novel chiral 1,2-diamine, using naturally occurring optically pure levopimaric acid as a precursor.

As the main method for the synthesis of diamine from fumaropimaric acid we chose the Curtius reaction. An important feature of this reaction consists in the fact that resulting from the rearrangement there is no inversion of chiral centres configuration [11]. In addition, this method allows one to obtain 1.2-diamine from 1,2-dicarboxylic acid, wherein in the case of fumaropimaric acid, both nitrogen atoms are located directly at the asymmetric centre of the molecule. In order that the target product was diamine the levopimaric acid was previously converted into the ester **II** using the Claisen methylation with 94 % yield (Scheme 1).

The esterification was performed with a mixture of resin acids containing levopimaric acid, which mixture was isolated from oleoresin. The adduct of the diene synthesis was obtained *via* heating the fumaric acid with methyl levopimarate which was used in a mixture



Scheme 1.

with the methyl esters of isomeric acids. The diastereomerically pure fumaropimaric acid was isolated from the reaction mixture via crystallization from methanol. Thus, the levopimaric acid was used for the Diels–Alder reaction in our experiments without isolating this substance from the naturally occurring mixture; in this case the yield of fumaropimaric acid from the feedstock was equal to 15 %. The diastereomeric purity of the compound obtained was confirmed by ^{1}H and ^{13}C NMR spectroscopy, where a single set of signals for hydrogen and carbon atoms is observed.

The transformation of the monomethyl ester of fumaropimaric acid **III** into **IV** diamine was realized with no isolation and purification of intermediates. With this purpose, the reaction between fumaropimaric acid **III** and thionyl chloride was performed resulted in obtaining fumaropimaric acid chloride. The formation of the chloride was confirmed by the presence of the absorption band chloride groups (1790 cm^{-1}) in the IR spectrum of the reaction product alongside with the absorption band of the ester group (1727 cm^{-1}). The interaction of crude chloride with sodium azide in the two-phase system resulted in the formation of intermediate fumaropimaric acid diazide. The thermal decomposition of crude diazide resulted in the formation of diisocyanate *via* the Curtius rearrangement, whose formation was confirmed by the presence of the absorption band of the isocyanate groups in the IR spectrum of the reaction product at 2251 cm^{-1}. Diisocyanate hydrolysis in concentrated hydrochloric acid resulted in the formation of diamine dihydrochloride, wherefrom we further obtained free diamine **IV**.

The structure of the diamine **IV** is confirmed by IR and NMR spectroscopic data as well as by elemental analysis. The results obtained demonstrate that heating the isocyanate in concentrated hydrochloric acid during 3 h did not result in the hydrolysis of the ester group at C(20). The presence of the ester group in the compound **IV** is confirmed by the presence of an absorption band of the ester group at 1725 cm^{-1} in the IR spectrum and by the presence of a singlet of the methyl ester group at 3.63 ppm in the ^{1}H NMR spectrum.

The presence of amino groups at C(1) and C(2) is indicated by shifting the signal of the mentioned atoms towards weak field in the ^{13}C NMR spectrum of compound **IV** (66.33 ppm for C(1), 59.07 ppm for C(2)) comparing to the spectrum of acid **III** (56.47 ppm for C(1) and 50.79 ppm for C(2)). In addition, the spectrum of diamine **IV** exhibits no characteristic signals inherent in carboxyl groups observed in the spectrum of the acid at 177.16 (C(17)) and 177.44 ppm (C(16)). The IR spectrum of diamine **IV** also demonstrate the bands characteristic for the stretching (3308 cm^{-1}) and bending (1600 cm^{-1}) vibrations of free amino groups.

CONCLUSION

Thus, for the first time we demonstrated the possibility of using levopimaric acids for the synthesis of optically pure 1,2-*trans*-diamine, basing on that one could obtain chiral catalysts for asymmetric reactions. The advantage of the synthetic method developed consists in the fact that the feedstock represents a mixture of resin acids without isolating the initial acid **I** there from. In addition, the synthetic scheme developed for the conversion of acid **III** to diamine **IV** allows one to provide a high yield of the reaction product with no isolation and purification of intermediates, which minimizes the overall costs of the process.

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