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Separation of Racemic Salycylaldehydes Containing Isobornyl Substituent Using (*R*)-1-Phenylethylamine

E. V. Buravlev[a], I. Yu. Chukicheva[a], F. M. Dolgushin[b], and A. V. Kuchin[a]

[a]*Institute of Chemistry, Komi Scientific Center, Ural Division, Russian Academy of Sciences, Syktyvkar167982, Russia*
e-mail: buravlev-ev@chemi.komisc.ru
[b]*Nesmeyanov Institute of Organoelemental Compounds, Russian Academy of Sciences, Moscow*

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Abstract—Racemic salicylaldehydes containing isobornyl substituent were separated by their conversion into diastereomers by the reaction with (*R*)-1-phenylethylamine. The absolute configuration of the intermediate Schiff bases and separated aldehyde eneatiomers was established by XRD analysis.

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Terpenophenol compounds are physiologically active substances of a versatile activity possessing low toxicity [1]. The antithrombogenic and antithrombocyte activity has been found in phenols possessing isobornyl substituent; they are employed as means of the local treatment of infection sources [2, 3]. Inasmuch as the enentiomers of a chiral biologically active substance sometimes differently affect the living body [4] it is urgent for revealing new qualities of terpenophenols to separate their racemates into enentiomers.

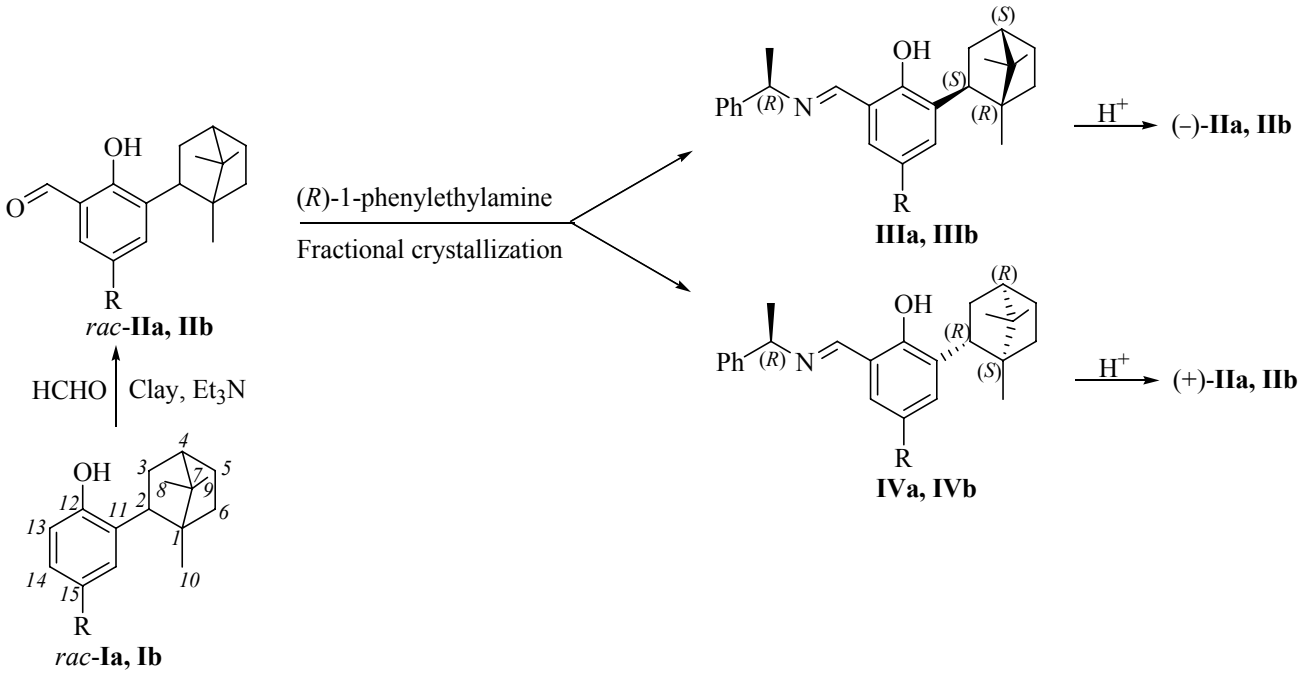
The Schiff bases prepared from the enentiomerically enriched formyl derivatives of isobornylphenol and (*S*)-*tert*-leucinol are efficient tridentate ligands in the vanadium-catalyzed asymmetrical oxidation of sulfides [5]. Therefore the physiological activity and the possibility of the application of chiral alkylphenols to the organic synthesis call for the development of the procedures of their preparation in optically active forms.

The separation of phenols containing a chiral fragment is carried out using preparative HPLC that requires the application of expensive columns packed with chiral stationary phases [6, 7]. The other approach employs a preliminary preparation of therpenophenol derivatives with expensive chiral reagents, for instance, (*R*)-phenylglycinol [6]. The obtained diastereomes mixture was separated by the preparative HPLC.

Isobornyls *rac*-(**I**) were obtained by alkylation of phenol and *p*-cresol in the presence of aluminum phenolate and cresolate respectively [8]. Salicylaldehydes *rac*-(**II**) were synthesized by modified procedure [9] consisting in the formylation of isobornylphenols with paraformaldehyde in the presence of montmorillonite KSF and triethylamine. In the published procedure the formylation was carried out at high pressure. We performed the synthesis at the normal pressure by heating the reaction mixture at 100°C. Aldehydes *rac*-(**IIa, IIb**) were obtained in 60 and 71% yield, respectively.

Racemates **II** were separated after their conversion into diastereomeric imines by the reaction with the enantiomerically pure (*R*)-1-phenylethylamine. The Schiff bases were obtained in the quantitative yield as pairs of diastereomers **III** and **IV** in the ratio 1:1 (according to the data of ^{1}H NMR spectrum and GLC). Both pairs of diastereomers were separated by fractional crystallization from pentane to obtain imines enriched with diastereomers **IIIa, IVa** and **IIIb, IVb**. Diastereomeric purity of the samples in the course of separation was checked by GLC.

The slow evaporation of solutions in pentane of imines **IVa** and **IIIb** furnished single cryatls fit for the XRD analysis (see the figure). Both compounds have the *E*-configuration with respect to the C=N bond. In the



molecules an intramolecular hydrogen bond is present. The hydrogen atoms were revealed objectively, in the structure **IIIb** the position and the isotropic thermal parameter of atom H^1 were refined, in the structure **IVa** the atom H^1 was included into the refinement in the *rider* model. The parameters of the hydrogen bond are listed in Table 1, the crystallographic parameters, in Table 2.

Both compounds crystallize in the chiral space group $P2_12_12_1$. The absolute configuration of compounds **IVa** and **IIIb** was established from the data on the relative configuration found by XRD analysis and starting from the configuration of the initial (*R*)-1-phenylethylamine. The chiral centers were assigned the configurations (1*S*,2*R*,4*R*,18*R*) in compound **IVa** and (1*R*,2*S*,4*S*,19*R*) in compound **IIIb**. Thus the configurations of the terpene fragment in compounds **IVa** and **IIIb** are opposite. The chiral centers in imines **IVb** and **IIIa** have configurations (1*R*,2*S*,4*S*,18*R*) and (2*R*,4*R*,19*R*) respectively.

Enantiomerically-enriched salicylaldehydes (+)- and (–)-(**IIa, IIb**) were isolated by acid hydrolysis of each imine. The enentiomeric purity of separated aldehydes was established using analytic HPLC on columns packed with chiral stationary phases Chiralpak AD and Chiralcel OJ-H.

Table 1 Geometrical characteristics of hydrogen bonds in structures **IVa** and **IIIb**

Compd. no.	Bond D–H···A	D–H, Å	H···A, Å	D···A, Å	Angle DHA, deg
IVa	O^1–H^1···N^1	0.85	1.84	2.570(4)	144
IIIb	O^1–H^1···N^1	1.02(4)	1.66(4)	2.591(3)	150(3)

The absolute configuration of the chiral centers in the enantiomerically-enriched salicylaldehydes (+)- and (–)-(**IIa, IIb**) was established from the configuration of imines prior to hydrolysis. The data on the absolute configuration and signs of the angles of the optical rotation of (+)- and (–)- (**IIb**) enantiomers are consistent with those published in [6].

Hence we developed a procedure for separation of racemic salicylaldehydes containing the isobornyl substituents into enantiomers applying (*R*)-1-phenylethylamine. The method did not require the use of the preparative HPLC and expensive chiral reagents. The configuration of the chiral centers of Schiff bases and separated aldehydes was established by means of XRD analysis.

EXPERIMENTAL

IR spectra were recorded on a Fourier spectrometer Shimadzu IR Prestige 21 from pellets with KBr. ^1H and ^{13}C NMR spectra of compounds obtained were registered on a spectrometer Bruker Avance II 300 at operating frequencies 300.17 and 75.48 MHz respectively from solutions in $CDCl_3$ at room temperature. The chemical

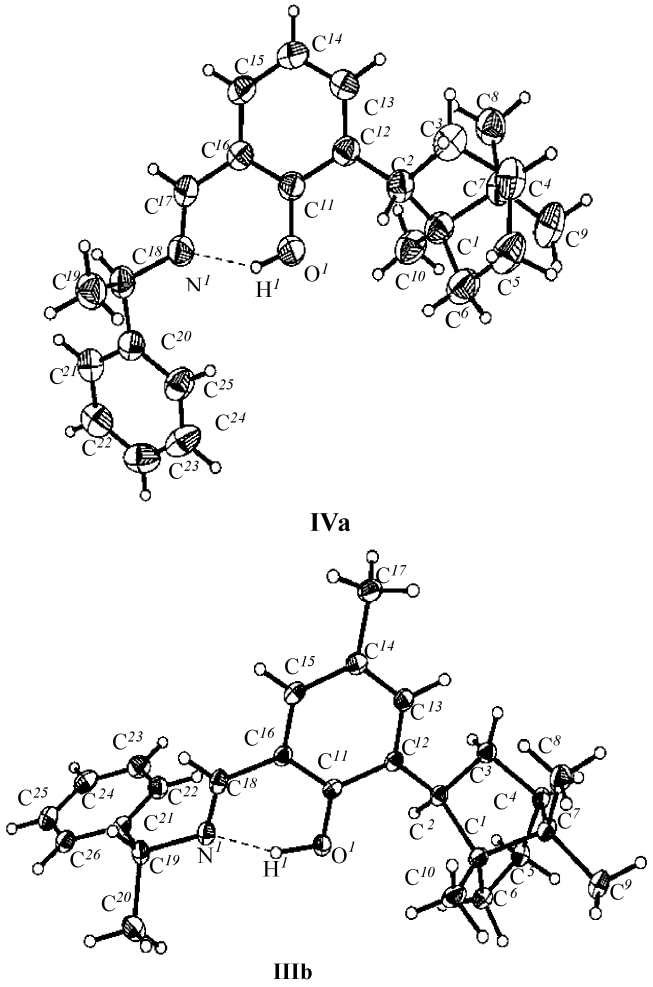
Table 2. Crystallographic data and parameters of XRD experiment for compounds **IVa** and **IIIb**

Parameter	Compound	
	IVa	**IIIb**
Empirical formula	$C_{25}H_{31}NO$	$C_{26}H_{33}NO$
Molecular weight	361.51	375.53
Crystal color	Yellow	Colorless
Crystal size, mm	0.36 × 0.26 × 0.17	0.55 × 0.35 × 0.30
Crystal system	Rhombic	Rhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Temperature, K	200(2)	120(2)
a, Å	7.408(1)	7.557(1)
b, Å	12.890(1)	11.762(2)
c, Å	22.411(2)	24.192(3)
α, deg	90	90
β, deg	90	90
γ, deg	90	90
V, Å^3	2140.0(3)	2150.5(5)
Z	4	4
d_{calc}, g·cm^{-3}	1.122	1.160
$2\theta_{max}$, deg	54	58
μ, cm^{-1}	0.67	0.69
Number of measured reflections	20538	23161
Number of independent reflections	2689	3223
R_{int}	0.0461	0.0794
Number of refined parameters	248	262
Number of reflections with $I \geq 2\sigma(I)$	1775	1814
Convergence of refinement $R_1(F)$[a] for reflections with C $I \geq 2\sigma(I)$	0.0587	0.0488
Convergence of refinement for all reflections $wR_2(F^2)$[b]	0.1629	0.1202
GOF	1.021	0.901

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma(F_o)$.

[b] $wR_2 = (\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2])^{1/2}$.

shifts were measured with respect to the signals of deuterochloroform (δ_H 7.26, δ_C 77.00 ppm). The melting points were measured on the Koeffler heating block. The angles of optical rotation were registered with an automatic digital polarimeter P3002RS Kruss Optronic (λ 589 nm).



Molecular structure of compounds **IVa** and **IIIb**.

The reaction progress was monitored by TLC on Sorbfil plates. The spots visualization was performed by treating with a solution of 15 g of $KMnO_4$, 300 ml of H_2O, and 0.5 ml of conc. H_2SO_4. The purity of initial terpenophenols **I** and aldehydes **II** was checked by GLC on a chromatograph Shimadzu GC-2010AF equipped with a flame-ionization detector (carrier gas helium), capillary column SPB-35 (Supelco, 60 m × 0.25 mm × 0.5 μm, ramp 135–255°C, heating rate 6 deg/min). Diastereomeric purity of Schiff bases was determined on a capillary column SPB-35 (Supelco, 30 m × 0.32 mm × 0.25 μm, 255°C).

Enantiomeric purity of aldehydes was measured by HPLC on a chromatograph Agilent 1100 (UV detector, λ 224 nm, 20°C), columns Chiralcel OJ-H (Daicel, 25 cm × 4.6 mm, grains 5 μm, eluent hexane–*i*-PrOH, 200 : 1, flow rate 1.0 ml/min) for enentiomers of compound **IIa**, Chiralpak AD (Daicel, 25 cm × 4.6 mm, grains 10 μm,

eluent hexane –*i*-PrOH, 200:1, flow rate 0.5 ml/min) for enentiomers of compound **IIb**.

The aldehydes were purified by column chromatography ("wet" filling) on silica gel Alfa Aesar 70/230μ. Toluene was dried with anhydrous $CaCl_2$ and distilled from metal sodium. Petroleum ether used boiled within 65–70°C. Pentane was used just after distillation. Molecular sieves (4 E) used in the synthesis of Schiff bases were activated by calcining at 140°C for 3 h; the montmorillonite clay KSF (Acros Organics) prior to the synthesis was calcined for 10 h at 130°C. Paraformaldehyde of the "chemically pure" grade was used without additional purification.

In the syntheses were used without additional purification triethylamine (Sigma-Aldrich) and (*R*)-(+)-1-phenylethylamine (Alfa Aesar, ChiPros®, enantiomeric purity over 99%).

Crystallographic data and the main refinement parameters for compounds **IVa** and **III**b obtained by XRD analysis are compiled in Table 2. The set of experimental data was obtained on a diffractometer Bruker Smart 1000 CCD [10] with a coordinate detector [graphite monochromator, λ(MoK_α) 0.71073 Å, ω-scanning]. The structures were solved by the direct method and refined in a full-matrix least-mean-squares procedure for F^2_{hkl} with anisotropic thermal parameters for all the nonhydrogen atoms. The hydrogen atoms of the hydroxy groups were revealed from the difference synthesis, the other hydrogen atoms in the structures **IVa** and **III**b were placed in the geometrically calculated locations and were refined in the *rider* model. The solving and refining of the structures was carried out using software SHELXTL [11].

Racemic salicylaldehydes with isobornyl substituent II. Into a three-neck flask equipped with a thermometer and a reflux condenser was charged 10.0 mmol of phenol *rac*-(**I**) dissolved in 20 ml of toluene, 40.0 mmol of paraformaldehyde, 3.2 g of montmorillonite KSF, and 10.0 mmol of Et_3N. The reaction mixture was heated at reflux in an argon flow for 15 h. The reaction progress was monitored by TLC (eluent petroleum ether–Et_2O, 10 : 1) and GLC. On completing the reaction the catalyst was filtered off, washed with Et_2O, and the solution was evaporated at a reduced pressure. The reaction products were separated by column chromatography (graduent elution with petroleum ether–Et_2O with growing content of the latter). The spectral characteristics of aldehydes obtained were in agreement with those described in [6, 12].

2-Hydroxy-3-(1,7,7-trimethylbicyclo[2.2.1]-hept-*exo*-2-yl)benzaldehyde *rac*-(IIa). Yield 60%. Light yellow powder, mp 67–68°C (75–78°C [12]). Found, %: C 79.06; H 8.56. $C_{17}H_{22}O_2$. Calculated, %: C 79.03; H 8.58.

2-Hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo-[2.2.1]hept-*exo*-2-yl)benzaldehyde *rac*-(IIb). Yellow powder, mp 100–101°C (103°C [6]). Found, %: C 79.44; H 8.93. $C_{18}H_{24}O_2$. Calculated, %: C 79.36; H 8.87.

Schiff bases III, IV. Into a two-neck round-bottom flask equipped with a reflux condenser was charged 7.74 mmol of racemic aldehyde **II** dissolved in 30 ml of anhydrous toluene, 0.95 ml (7.74 mmol) of (*R*)-(+)-1-phenylethylamine, and 8.5 g of molecular sieves. The reaction mixture was heated at reflux in an argon flow for 3.5 h. On completing the reaction the solution was filtered through a glass frit, molecular sieves were washed with Et_2O, and the solution was evaporated at a reduced pressure. The mixture of diastereomers was separated by fractional crystallization from pentane. The course of separation was checked by GLC.

2-{(*E*)-[(*R*)-1-phenylethylimino]methyl}-6-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl}phenol (IIIa). Yield 58%, diastereomeric purity 98%. Retention time 20.7 min. Yellow powder, mp 92–93°C. IR spectrum, ν, cm^{-1}: 3437 (OH), 1628 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.84 s (3H, C^{10}H$_3$), 0.87 s (3H, C^{9}H$_3$), 0.93 s (3H, C^{8}H$_3$), 1.34–1.43 m (1H, H^5), 1.56–1.68 m (6H, H^3, C^{6}H$_2$, C^{19}H$_3$), 1.79–1.92 m (2H, H^{4,5}), 2.11–2.18 m (1H, H^3), 3.41 t (1H, H^2, *J* 9.0 Hz), 4.56 q (1H, H^{18}, *J* 6.6 Hz), 6.84 m (1H, H^{14}), 7.08 d (1H, H^{16}, *J* 7.2 Hz), 7.25–7.40 m (6H, H$^{15,21,21',22,22',23}$), 8.41 br.s (1H, H^{17}), 13.87 br.s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 12.34 (C^{10}), 20.45 (C^9), 21.44 (C^8), 24.90 (C^{19}), 27.52 (C^5), 34.18 (C^3), 39.77 (C^6), 44.54 (C^2), 45.74 (C^4), 47.96 (C^7), 49.86 (C^1), 68.48 (C^{18}), 118.05 (C^{13}), 117.53, 126.44, 127.16, 128.61, 128.87 (C$^{14,15,16,21,21',22,22'}$), 130.78 (C^{23}), 131.93 (C^{11}), 143.96 (C^{20}), 160.49 (C^{12}), 163.93 (C^{17}). Found, %: C 83.02; H 8.71; N 3.88. $C_{25}H_{31}NO$. Calculated, %: C 83.06; H 8.64; N 3.87.

4-Methyl-2-{(*E*)-[(*R*)-1-phenylethylimino]-methyl}-6-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo-[2.2.1]hept-*exo*-2-yl}phenol (IIIb). Yield 76%, diastereomeric purity 91%. Retention time 23.1 min. Light yellow powder, mp 111–113°C (from pentane). IR spectrum, ν, cm^{-1}: 3422 (OH), 1632 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.83 s (3H, C^{10}H$_3$), 0.87 s (3H, C^{9}H$_3$),

0.93 s (3H, $C^{8}H_3$), 1.33–1.42 m (1H, H^{5}), 1.56–1.66 m (6H, H^{3}, $C^{6}H_2$, $C^{20}H_3$), 1.81–1.93 m (2H, $H^{4,5}$), 2.07–2.19 m (1H, H^{3}), 2.29 s (3H, $C^{17}H_3$), 3.38 t (1H, H^{2}, *J* 9.2 Hz), 4.55 q (1H, H^{19}, *J* 6.6 Hz), 6.87 d, 7.19 d (1H each, $H^{14,16}$, *J* 1.8, *J* 1.8 Hz), 7.22–7.39 m (5H, $H^{22,22',23,23',24}$), 8.36 br.s (1H, H^{18}), 13.61 br.s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 12.34 (C^{10}), 20.45 (C^{9}), 20.78 (C^{17}), 21.46 (C^{8}), 24.91 (C^{20}), 27.51 (C^{5}), 34.10 (C^{3}), 39.73 (C^{6}), 44.50 (C^{2}), 45.73 (C^{4}), 47.98 (C^{7}), 49.85 (C^{1}), 68.48 (C^{19}), 117.62 (C^{13}), 126.27 (C^{15}), 126.45, 127.11 ($C^{22,22',23,23'}$), 128.58, 128.84 ($C^{14,16}$), 131.59 (C^{11}), 131.82 (C^{24}), 144.05 (C^{21}), 158.22 (C^{12}), 163.93 (C^{18}). Found, %: C 83.11; H 8.90; N 3.69. $C_{26}H_{33}NO$. Calculated, %: C 83.15; H 8.86; N 3.73.

2-{(*E*)-[(*R*)-1-Phenylethylimino]methyl}-6-{(1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl}phenol (IVa). Yield 60%, diastereomeric purity 74%. Retention time 21.6 min. Light yellow powder, mp 118–119°C. IR spectrum, ν, cm^{-1}: 3439 (OH), 1626 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.79 s (3H, $C^{10}H_3$), 0.85 s (3H, $C^{9}H_3$), 0.92 s (3H, $C^{8}H_3$), 1.33–1.43 m (1H, H^{5}), 1.56–1.68 m (6H, H^{3}, $C^{6}H_2$, $C^{19}H_3$), 1.81–1.93 m (2H, $H^{4,5}$), 2.10–2.19 m (1H, H^{3}), 3.40 t (1H, H^{2}, *J* 9.0 Hz), 4.56 q (1H, H^{18}, *J* 6.6 Hz), 6.84 m (1H, H^{14}), 7.08 d (1H, H^{16}, *J* 7.2 Hz), 7.25–7.42 m (6H, $H^{15,21,21',22,22',23}$), 8.42 br.s (1H, H^{17}), 13.90 br.s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 12.39 (C^{10}), 20.49 (C^{9}), 21.41 (C^{8}), 25.03 (C^{19}), 27.53 (C^{5}), 34.25 (C^{3}), 39.83 (C^{6}), 44.63 (C^{2}), 45.74 (C^{4}), 47.94 (C^{7}), 49.85 (C^{1}), 68.43 (C^{18}), 117.98 (C^{13}), 117.55, 126.43, 127.17, 128.64, 128.87 ($C^{14,15,16,21,21',22,22'}$), 130.78 ($C^{23}$), 132.00 ($C^{11}$), 144.02 ($C^{20}$), 160.48 ($C^{12}$), 163.86 ($C^{17}$). Found, %: C 83.03; H 8.66; N 3.90. $C_{25}H_{31}NO$. Calculated, %: C 83.06; H 8.64; N 3.87.

4-Methyl-2-{(*E*)-[(*R*)-1-phenylethylimino]-methyl}-6-{(1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]hept-*exo*-2-yl}phenol (IVb). Yield 68%, diastereomeric purity 98%. Retention time 22.1 min. Light yellow powder, mp 110–112°C. IR spectrum, ν, cm^{-1}: 3420 (OH), 1632 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.79 s (3H, $C^{10}H_3$), 0.86 s (3H, $C^{9}H_3$), 0.92 s (3H, $C^{8}H_3$), 1.27–1.42 m (1H, H^{5}), 1.55–1.66 m (6H, H^{3}, $C^{6}H_2$, $C^{20}H_3$), 1.81–1.93 m (2H, $H^{4,5}$), 2.11–2.20 m (1H, H^{3}), 2.29 s (3H, $C^{17}H_3$), 3.38 t (1H, H^{2}, *J* 9.0 Hz), 4.55 q (1H, H^{19}, *J* 6.6 Hz), 6.88 d, 7.19 d (1H each, $H^{14,16}$, *J* 0.9, *J* 1.2 Hz), 7.27–7.41 m (5H, $H^{22,22',23,23',24}$), 8.37 br.s (1H, H^{18}), 13.65 br.s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 12.35 (C^{10}), 20.48 (C^{9}), 20.79 (C^{17}), 21.43 (C^{8}), 25.07 (C^{20}), 27.52 (C^{5}), 34.15 (C^{3}), 39.78 (C^{6}), 44.59 (C^{2}), 45.74 (C^{4}), 47.96 (C^{7}), 49.84 (C^{1}), 68.45 (C^{19}), 117.63 (C^{13}), 126.28 (C^{15}), 126.46, 127.13 ($C^{22,22',23,23'}$), 128.83, 128.62 ($C^{14,16}$), 131.66 (C^{11}), 131.84 (C^{24}), 144.12 (C^{21}), 158.20 (C^{12}), 163.86 (C^{18}). Found, %: C 83.20; H 8.88; N 3.70. $C_{26}H_{33}NO$. Calculated, %: C 83.15; H 8.86; N 3.73.

Enantiomerically enriched aldehydes IIa, IIb. To a solution of 0.5 g of each of separated imines **IIIa**, **IIIb**, **IVa**, **IVb** in 5 ml of EtOH was added 7 ml of 37% HCl. The solution was stirred for 6 h at room temperature. Excess solvent was removed at a reduced pressure, to the residue 75 ml of dichloromethane was added, the organic layer was washed with water from acid (3 × 30 ml) till pH 7, dried with anhydrous Na_2SO_4, evaporated, the product was purified by column chromatography (eluent petroleum ether–Et_2O) and recrystallization from pentane.

2-Hydroxy-3-{(1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]hept-*exo*-2-yl}benzaldehyde (+)-(IIa). Yield 96%, enantiomeric purity 72%. Retention time 6.08 min. Light yellow powder, mp 84–87°C, $[\alpha]_D^{22}$ +55.1° (*c* 0.5, $CHCl_3$).

2-Hydroxy-3-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo-[2.2.1]hept-*exo*-2-yl}benzaldehyde (–)-(IIa). Yield 97%, enantiomeric purity 98%. Retention time 4.54 min. Light yellow powder, mp 89–90°C, $[\alpha]_D^{22}$ –87.6° (*c* 0.6, $CHCl_3$).

2-Hydroxy-5-methyl-3-{(1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl}benzaldehyde (+)-(IIα). Yield 97%, enantiomeric purity 96%. Retention time 9.02 min. Light yellow powder, mp 109–110°C (109°C [6]), $[\alpha]_D^{22}$ +41.0° (*c* 0.6, $CHCl_3$) {$[\alpha]_D^{20}$ +42.7° (*c* 0.3, $CHCl_3$), *ee* >99% [6]}.

2-Hydroxy-5-methyl-3-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl}benzaldehyde [(–)-IIα]. Yield 98%, enantiomeric purity 92%. Retention time 8.22 min. Light yellow powder, mp 108–110°C (108–109°C [6]), $[\alpha]_D^{22}$ –40.9° (*c* 0.6, $CHCl_3$) {$[\alpha]_D^{20}$ –42.3° (*c* 0.07, $CHCl_3$), *ee* >99% [6]}.

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