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Stereochemistry of terpene derivatives. Part 3: Hydrolytic kinetic resolution as a convenient approach to chiral aminohydroxyiminocaranes with local anaesthetic activity†

Stanisław Lochyński,[a,*] Bożena Frąckowiak,[a] Tadeusz Librowski,[b] Ryszard Czarnecki,[b] Jacek Grochowski,[c] Paweł Serda[c] and Marta Pasenkiewicz-Gierula[d]

[a]*Institute of Organic Chemistry, Biochemistry and Biotechnology, Wroclaw University of Technology, W. Wyspianskiego 27, 50-370 Wroclaw, Poland*

[b]*Department of Pharmacodynamics, Collegium Medicum Jagiellonian University, Kraków, Poland*

[c]*Regional Laboratory of Physicochemical Analysis, Jagiellonian University, Kraków, Poland*

[d]*Department of Biophysics, Institute of Molecular Biology, Jagiellonian University, Kraków, Poland*

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Abstract—We have developed a stereoselective hydrolytic kinetic resolution process for diastereoisomeric mixtures of epoxyiminocarene intermediates in the presence of (*R*,*R*)-(−)-(salen)Co(III)OAc catalyst, this was applied as the first step in the synthesis of novel chiral aminohydroxyiminocarane derivatives with local anaesthetic activity. The absolute configuration of the product was confirmed by X-ray crystallography.

1. Introduction

Using the naturally occurring monoterpene hydrocarbon, (+)-3-carene **1**, a major constituent of Polish turpentine, which is an inexpensive, readily available and little explored chiral raw material, we synthesized the aminohydroxyiminocarane derivative **KP-23**. Pharmacological studies showed that the hydrochloride salt of **KP-23** possesses the most efficient local anaesthetic activity in corneal infiltration anesthesia tests. It was found very promising that compound **KP-23**·HCl does not evoke any toxicodermal effects and does not induce any allergic reaction in response to its topical application.[2] The crystal structure of (2*R*,*S*)-(−)-4-[2-hydroxy-3-(*N*-isopropylamino)propoxyimino]-*cis*-carane hydrochloride (**KP-23**·HCl) revealed its presence as a dimeric form, where two molecules are diastereoisomers with opposite absolute configuration of the carbon atom bearing the hydroxyl group in the side chain.[3] Continuing our studies we present herein a significantly improved stereoselective process for the synthesis of the diastereoisomers **KP-23***R* and **KP-23***S* (epimers with *R* and *S* configuration, respectively, at the hydroxyl bearing carbon in the side chain).

2. Results and discussion

(−)-*cis*-Caran-4-one oxime **3** is readily available from (+)-3-carene **1** by a three step pathway: stereoselective borohydration–oxidation[4] followed by the Brown–Garg oxidation[5] and reaction of ketone **2** with hydroxylamine hydrochloride[6] was used as an intermediate in the stereospecific synthesis of the derived anesthetics **KP-23***R* and **KP-23***S*.

The mixture of (−)-4-[(2′,3′-epoxy)propoxyimino]-*cis*-carane diastereoisomers (*R*,*S*)-**4** was synthesized directly from oxime **3** in the reaction with racemic epichlorohydrin (Scheme 1)[2] and then subjected to the hydrolytic kinetic resolution (HKR) on reaction with water catalyzed by (salen)Co(II) complex.[7,8]

Applying (*R*,*R*)-(−)-(salen)Co(II) as precatalyst, a mixture of the 1,2-diol (*S*)-**5** (97% e.e.) and unreacted epoxide (*R*)-**4** (99% e.e.) was obtained after 7 h in 76% yield. Flash chromatography separation afforded enantiopure stereoisomers (*R*)-**4** and (*S*)-**5**. In the further course of our investigations we applied the Mitsunobu procedure,[9] in which diol (*S*)-**5** (97% e.e.) was converted to the epoxy isomer (*S*)-**4** in 71% yield in the presence of triphenylphosphine (Ph_3P) and diethylazadicarboxylate (DEAD) (Scheme 2). The course of these reactions and the enantiopurity of the diastereomeric

* Corresponding author. Fax: +48-71-328-40-64; e-mail: lochynski@kchf.ch.pwr.wroc.pl

† For Part 2, see Ref. 1.

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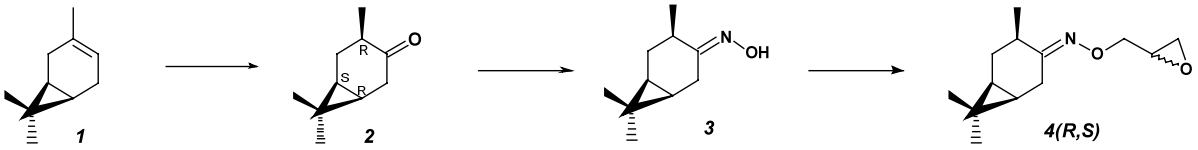
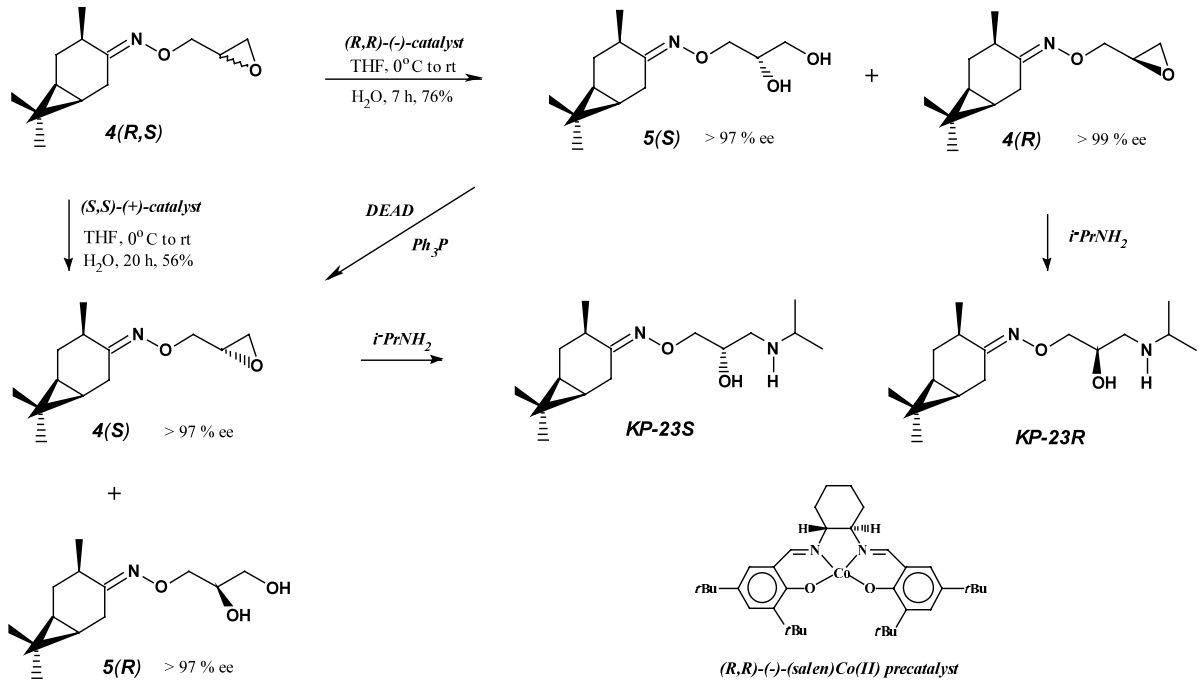


Scheme 1.



Scheme 2.

products were determined by means of chiral gas chromatography using standards synthesized directly from commercially available (Fluka) (*R*)-(−)-or (*S*)-(+)-epichlorohydrin as chiral building blocks[10] to give the isomers (1*S*,3*R*,6*R*,2′*R*)-(−)-4-[(2′,3′-epoxy)propoxyimino]-*cis*-carane (*R*)-**4**[11] and (1*S*,3*R*,6*R*,2′*S*)-(−)-4-[(2′,3′-epoxy)propoxyimino]-*cis*-carane (*S*)-**4**[12] with strictly fixed configuration of all four stereogenic centers.

We also tested the alternative pathway leading to the mixture of compounds (*S*)-**4** and (*R*)-**5** relaying on direct HKR of (*R*,*S*)-**4** by the use of (*S*,*S*)-(+)-(salen)Co(II) precatalyst. However, the moderate yield (56%) and longer reaction time (20 h) in this case made this method less favorable.

The specific rotation of epoxy diastereoisomers (*R*)-**4** and (*S*)-**4** obtained from hydrolytic kinetic resolution and synthesized using commercial (*R*)-(−)- and (*S*)-(+)-epichlorohydrin have identical absolute values of opposite sign. The next step of the synthesis, opening of the epoxy ring was carried out in an autoclave by heating (150°C) the appropriate enantiopure epoxy derivative (*R*)-**4** or (*S*)-**4** with excess isopropylamine used as a reactant and solvent. Attempts to isolate pure hydroxyaminocarane derivatives **KP-23***R* and **KP-23***S* from the reaction mixture failed. Subsequent reaction of the crude product with anhydrous ethereal HCl yielded the crystalline, water-soluble hydrochlorides **KP-23***R*·HCl[13] and **KP-23***S*·HCl,[14] respectively. The structures of all diastereoisomers were elucidated by IR, ^{1}H and ^{13}C NMR spectroscopy.

Structural characterization of the reaction products was done following the recent recommendations of the International Union of Crystallography,[15] covering absolute structural determination of a single grain as well as experimental proof that the single crystal sample is representative of the bulk material. Therefore, structure analysis was carried out on both single-crystal grain (using single-crystal X-ray diffraction) and the bulk material using high-resolution powder diffraction. This precaution is also in compliance with European and US medical products evaluation agencies' recommendations with respect to chiral drugs, especially in relation to the stability and equilibria of the enantiomeric forms.[16,17]

The crystal structure of homochiral **KP-23***S* (possessing (*S*)-absolute configuration at the stereogenic center in the side chain) is similar to the epimeric **KP-23**, where

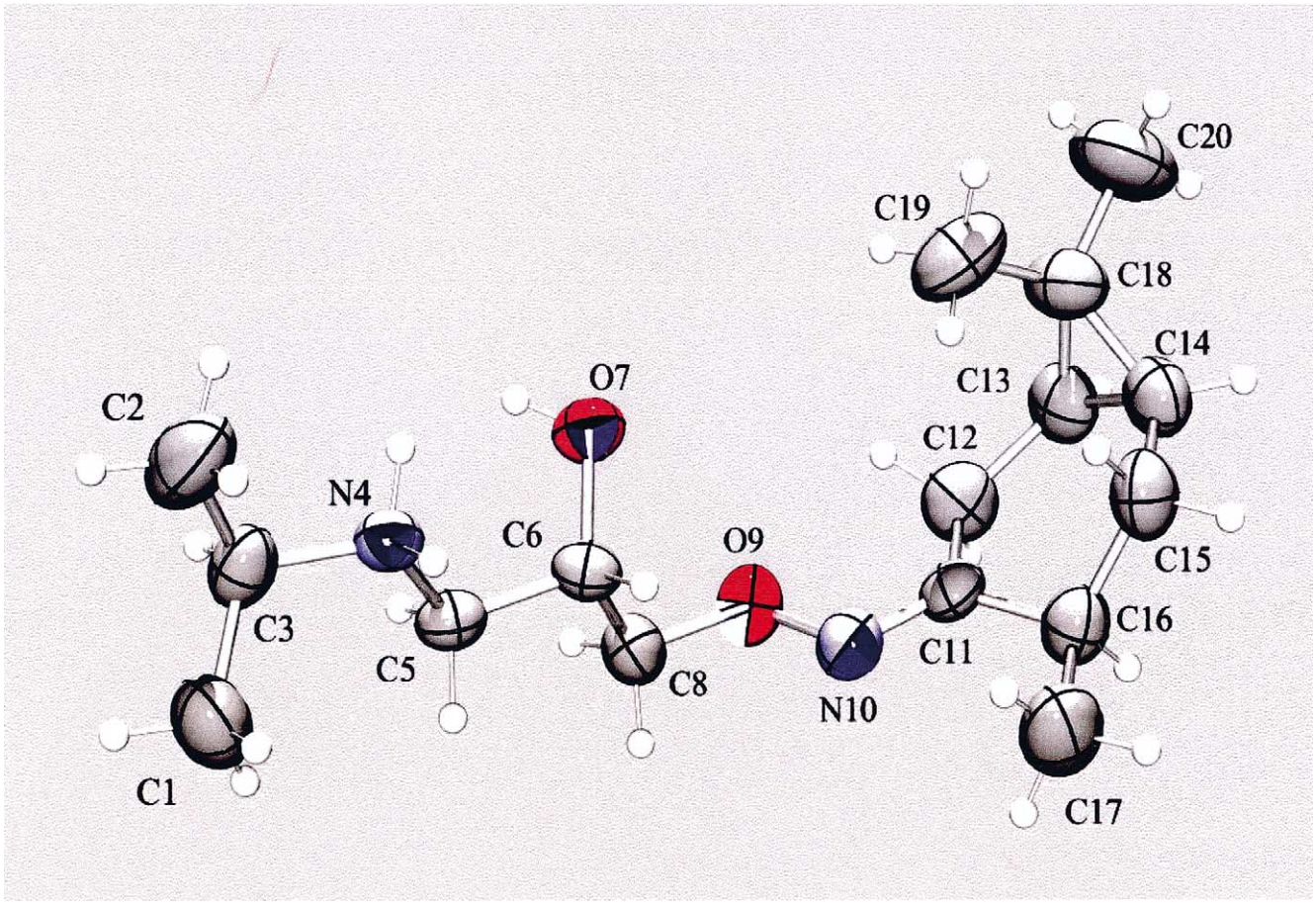


Figure 1. ORTEP-III[20] view of molecular structure of **KP-23***S*. Thermal ellipsoids are drawn at the 50% probability level. The H atoms are shown as spheres with fixed radius. The crystallographic numbering shown differs from the systematic numbering.

50% of molecules have opposite absolute configuration in the side chain.[3] Fig. 1 presents a perspective view of the molecule and the absolute configurations at four stereogenic centers.

A diffraction experiment was carried out on CAD4 single-crystal diffractometer and CuKα radiation. The absolute structure was assigned using azimuthal scan statistics on selected Bijvoet pairs.[18] Details of the single-crystal structure analysis have been deposited at the Cambridge Crystallographic Data Centre, methodological aspects are discussed.[19]

The morphology of the bulk material shows far from perfect crystallinity, as seen in the SEM image of the polycrystalline sample (Fig. 2). A high-resolution powder diffraction pattern recorded at B2 beamLine at the Hamburger Synchrotronstrahlungslabor HASYLAB (Hamburg) was successfully indexed giving lattice parameters close to those determined from single-crystal data.

Subtraction of experimental and calculated powder pattern did not reveal the presence of any other phase, proving phase homogeneity of the sample. Experimental details are reported elsewhere.[21]

The local anaesthetic activity of the hydrochloride salt of **KP-23** and its (*R*)- and (*S*)-diastereomers versus the known anaesthetic lidocaine were the subject of comparative pharmacological investigations, which were completed according to Bülbring and Wajda.[22] The details are published as a preliminary communication.[23]

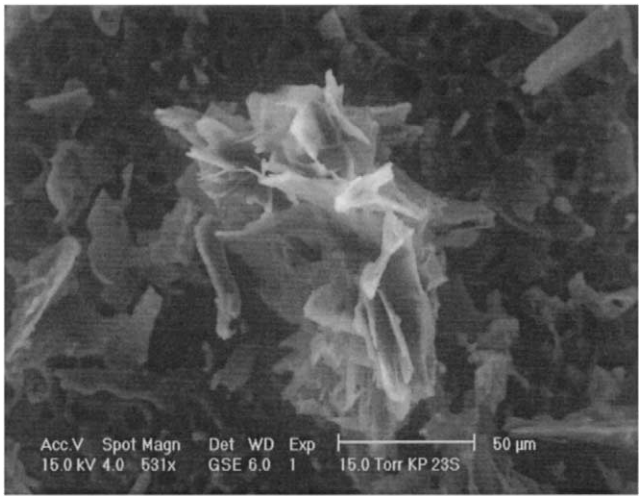


Figure 2.

3. Experimental

The course of all reactions and purity of intermediates the products were checked by means of thin-layer chromatography (TLC) and gas chromatography (GC). TLC was carried out on Silica gel DC-Alufolien Kieselgel 60 F_{254} (Merck). Chromatograms were developed with mixtures of hexane, acetone and ethyl acetate applied in various ratios and detected with 20% ethanolic H_2SO_4 with a mixture of 0.1% of anisaldehyde. GC analyses were performed on a Hewlett Packard 5890 (seria II) instrument using the following capillary columns: HP-1 (length 25 m, temperature: 120–280°C), Chirasil-Val-L (length 25 m, temperature 120–200°C) IR spectra were taken for liquid films or KBr disks on a Perkin–Elmer 621 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded for $CDCl_3$ or D_2O solutions on a Bruker Avance DRX 300 apparatus, with TMS as the internal standard. Melting points (uncorrected) were determined on a Boetius apparatus. Optical rotation measurements were obtained on an Autopol IV automatic polarimeter (Rudolph) in chloroform or ethanol, the concentrations are denoted in g/100 mL.

3.1. Substrates

(+)-3-Carene **1** (Industrial Chemistry Research Institute Warsaw), bp 79°C/28 mmHg, $n_D^{20}=1.4732$, $\alpha_D^{20}=+14.7$ (neat), was transformed, via (−)-*cis*-caran-4-one **2** (bp 74–76/4.5 mmHg, $n_D^{20}=1.4680$, $\alpha_D^{20}=-135.8$ (neat); lit.:[24] bp 98–99°C/19 mmHg, $\alpha_D^{20}=1.4703$, $\alpha_D^{20}=-133.2$ (neat)), to the crystalline (−)-*cis*-caran-4-one oxime **3** mp 42°C, bp 95–102°C/4 mmHg, $[\alpha]_D^{20}=-45.1$ ($c=1.8$, MeOH); lit.:[6] mp 40–43°C, $\alpha_D^{20}=-6.8$ (neat) according to the known procedure.[4–6] The (*R*,*R*)-(−)-(salen)Co(II) and (*S*,*S*)-(+)-(salen)Co(II) precatalysts were prepared according to the literature procedure.[25]

3.2. Hydrolytic kinetic resolution: general procedure

A mixture of (salen)Co(II) precatalyst (61 mg, 0.1 mmol), epoxyiminocarane derivative (*S*,*R*)-**4** (4.47 g, 20.0 mmol) and acetic acid (23 μL, 0.4 mmol)) was stirred under air at room temperature. After the red reaction mixture turned to a dark brown solution, the flask was cooled to 0°C and dry THF (0.2 mL) and H_2O (0.2 mL) were added. After 2 h the reaction was allowed to warm to room temperature and was stirred for 6 h. The solution of crude products was purified by vacuum chromatography using as eluents: hexane:ethyl acetate (20:1) for unreacted epoxyiminocarane isolation and hexane:acetone (4:1) for diol isolation.

3.2.1. (1*S*,3*R*,6*R*,2′*R*)-(−)-4-[(2′,3′-epoxy)propoxyimino]-*cis*-carane (*R*)-4. (1.70 g, 7.6 mmol, 76% yield, 99% e.e.), $[\alpha]_D^{25}=-34.6$ ($c=2.0$, $CHCl_3$); IR (KBr, cm^{-1}): 3051 (w), 2930 (vs), 1712 (w), 1630 (w), 1456 (m), 1376 (m), 1048 (s), 1037 (s), 912 (s); ^{1}H NMR ($CDCl_3$), δ: 0.75 (t/d, $J=8.8/1.8$ Hz, 1H at C-1); 0.82 (s, 3H, *gem*-Me, C-8 or C-9); 0.88 (t/d, $J=9.0/3.6$ Hz, 1H at C-6); 1.00 (s, 3H, *gem*-Me C-8 or C-9); 1.02 (d, $J=6.4$ Hz, 3H at C-10); 1.01–1.10 (m, 1H at C-3); 2.09–2.25 (m, 2H at C-2); 2.36 (d/d, $J=18.5/8.5$ Hz, $1H_{ax}$ at C-5); 2.62 (d/d, $J=5.0/2.7$ Hz, $1H_{eq}$ at C-5); 2.79–2.86 (m, 2H at C-13); 3.19–3.22 (m, 1H at C-12); 3.99 (d/d, $J=12.3/5.8$ Hz, 1H at C-11); 4.19 (d/d, $J=12.3/3.7$ Hz, 1H at C-11); ^{13}C NMR (δ): 14.56 (C-9), 16.18 (C-8), 18.37 (C-7), 19.42 (C-1), 20.38 (C-6), 20.77 (C-2), 28.07 (C-10), 29.48 (C-5), 34.34 (C-3), 44.91 (C-13), 50.30 (C-12), 74.05 (C-11), 163.88 (C-4). Elemental analysis: calcd for $C_{13}H_{21}NO_2$ (223.32) C, 69.92; H, 9.48; N, 6.27. Found:, C, 69.78; H, 9.57; N, 6.32%.

3.2.2. (1*S*,3*R*,6*R*,2′*S*)-(−)-4-[(2′,3′-dihydroxy)propoxyimino]-*cis*-carane (*S*)-5. (1.80 g, 7.5 mmol, 75% yield, 97% e.e.), $[\alpha]_D^{20}=-28.3$ ($c=2.0$, $CHCl_3$); IR (film, cm^{-1}): 3387 (vs), 2932 (vs), 1708 (w), 1630 (w), 1456 (m), 1376 (m), 1048 (vs), 930 (m); ^{1}H NMR ($CDCl_3$), δ: 0.75–0.82 (m, 1H at C-1); 0.80 (s, 3H, *gem*-Me, C-8 or C-9); 0.89 (t/d, $J=9.1/5.1$ Hz, 1H at C-6); 1.01 (s, 3H, *gem*-Me C-8 or C-9); 1.02 (d, $J=4.5$ Hz, 3H at C-10); 1.00–1.07 (m, 1H at C-3); 2.11–2.26 (m, 2H at C-2); 2.32 (d/d, $J=18.5/8.5$ Hz, $1H_{ax}$ at C-5); 2.59 (bs, 2H, -OH at C-12 and C-13) 2.85 (d, $J=18.5.0$ Hz, $1H_{eq}$ at C-5); 3.58–3.70 (m, 2H at C-11); 3.93–3.99 (m, 1H at C-12); 4.13 (d, $J=3.6$ Hz, 1H at C-13); ^{13}C NMR (δ): 14.61 (C-9), 16.09 (C-8), 18.42 (C-7), 19.31 (C-1), 20.34 (C-6), 20.75 (C-2), 28.01 (C-10), 29.39 (C-5), 34.39 (C-3), 63.58 (C-11), 72.19 (C-12), 73.64 (C-13), 164.75 (C-4). Elemental analysis: calculated for $C_{13}H_{23}NO_3$ (241.33) C, 64.70; H, 9.61; N, 5.80. Found: C, 64.38; H, 9.67; N, 5.82%.

3.2.3. (1*S*,3*R*,6*R*,2′*R*)-(−)-4-[(2′,3′-dihydroxy)propoxyimino]-*cis*-carane (*R*)-5. (56% yield, 97% e.e.), $[\alpha]_D^{20}=-50.7$ ($c=2.5$, $CHCl_3$); IR (film, cm^{-1}): 3388 (vs), 2932 (vs), 1708 (w), 1630 (w), 1455 (m), 1376 (m), 1048 (vs), 930 (m); ^{1}H NMR ($CDCl_3$), δ: 0.75–0.82 (m, 1H at C-1); 0.80 (s, 3H, *gem*-Me, C-8 or C-9); 0.89 (t/d, $J=9.1/5.1$ Hz, 1H at C-6); 1.01 (s, 3H, *gem*-Me C-8 or C-9); 1.02 (d, $J=4.5$ Hz, 3H at C-10); 1.00–1.07 (m, 1H at C-3); 2.11–2.26 (m, 2H at C-2); 2.32 (d/d, $J=18.5/8.5$ Hz, $1H_{axi}$ at C-5); 2.59 (bs, 2H, -OH at C-12 and C-13) 2.85 (d, $J=18.5.0$ Hz, $1H_{eq}$ at C-5); 3.58–3.70 (m, 2H at C-11); 3.93–3.99 (m, 1H at C-12); 4.13 (d, $J=3.6$ Hz, 1H at C-13); ^{13}C NMR (δ): 14.49 (C-9), 16.02 (C-8), 18.41 (C-7), 19.29 (C-1), 20.27 (C-6), 20.76 (C-2), 27.96 (C-10), 29.37 (C-5), 34.40 (C-3), 63.58 (C-11), 72.41 (C-12), 73.59 (C-13), 165.07 (C-4). Elemental analysis: calcd for $C_{13}H_{23}NO_3$ (241.33) C, 64.70; H, 9.61; N, 5.80. Found: C, 64.41; H, 9.66; N, 5.83%.

3.3. Mitsunobu reaction. (1*S*,3*R*,6*R*,2′*S*)-(−)-4-[(2′,3′-epoxy)propoxyimino]-*cis*-carane (*S*)-4

A mixture of (*S*)-diol (*S*)-**5** (0.80 g, 3.3 mmol), Ph_3P (1.30 g, 5.0 mmol) and diethylazadicarboxylate (DEAD, 0.8 mL, 5.0 mmol) in benzene (40 mL) was heated 3 h under reflux. After completion of the reaction (as detected by TLC) solvent was removed under reduced pressure and diethyl ether was added to the residue of precipitated Ph_3PO and filtered. The extract was concentrated and crude product was purified by flash chromatography (eluent hexane:ethyl acetate,

10:1) giving (0.54 g, 2.4 mmol, 71% yield) enantiopure (97% e.e.) epoxyiminocarene derivative **4**(*S*): $[\alpha]_D^{25} = -53.6$ ($c = 2.0$, $CHCl_3$); IR (film, cm^{-1}): 3051 (w), 2930 (vs), 1712 (w), 1630 (w), 1456 (m), 1376 (m), 1048 (s), 1037 (s), 912 (s); ^1H NMR ($CDCl_3$), δ: 0.72 (t/d, $J = 8.7/1.9$ Hz, 1H at C-1); 0.79 (s, 3H, *gem*-Me C-8 or C-9); 0.86 (t/d, $J = 8.9/3.4$ Hz, 1H at C-6); 0.98 (s, 3H, *gem*-Me C-8 or C-9); 1.00 (d, $J = 6.4$ Hz, 3H at C-10); 1.02–1.08 (m, 1H at C-2); 2.05–2.25 (m, 1H at C-2 and 1H at C-3); 2.34 (d/d, $J = 18.5/8.5$ Hz, $1H_{ax}$ at C-5); 2.60 (d/d, $J = 5.0/2.7$ Hz, $1H_{eq}$ at C-5); 2.77–2.84 (m, 2H at C-13); 3.19–3.22 (m, 1H at C-12); 3.98 (d/d, $J = 12.3/5.6$ Hz, 1H at C-11); 4.16 (d/d, $J = 12.3/3.7$ Hz, 1H at C-11); ^{13}C NMR (δ): 14.64 (C-9), 16.20 (C-8), 18.38 (C-7), 19.37 (C-1), 20.44 (C-6), 20.75 (C-2), 28.08 (C-10), 29.44 (C-5), 34.37 (C-3), 44.91 (C-13), 50.39 (C-12), 73.96 (C-11), 163.82 (C-4). Elemental analysis: calcd for $C_{13}H_{21}NO_2$ (223.32) C, 69.92; H, 9.48; N, 6.27. Found: C, 69.79; H, 9.59; N, 6.31%.

3.4. Epoxy ring opening of (*R*)-4 and (*S*)-4: general procedure

The opening of the epoxy ring was carried out in an autoclave by heating epoxyiminoether (2.23 g, 10.0 mmol) with isopropylamine (2.36 g, 40.0 mmol) as a reagent and solvent at 150°C for 18 h. After evaporation of the excess of isopropylamine under reduced pressure, the residue was dissolved in diethyl ether and shaken with a 5% solution of sulphuric acid to remove organic impurities. The obtained aqueous layer was alkalized whit saturated solution of $NaHCO_3$ and again extracted with diethyl ether. After drying with $MgSO_4$ and solvent evaporation crude product was purified by flash chromatography (eluent:hexane:acetone:diethyl ether:propanol, 40:1:1:3). Dry diethyl ether saturated with hydrochloric acid (prepared by extraction of diethyl ether with concentrated hydrochloric acid in ratio 10:1 and dried with $CaCl_2$) was slowly added dropwise to the mixture of purified product under pH control. The white crystalline hydrochloride was precipitated and after filtered off was recrystallized from acetone.

3.4.1. (1*S*,3*R*,6*R*,2′*R*)-(−)-4-[2′-Hydroxy-3′-(*N*-isopropylamino)propoxyimino]-*cis*-carane hydrochloride KP-23*R*. (2.35 g, 8.3 mmol, 83.0% yield); mp 159–163°C, $[\alpha]_D^{25} = -33.7$ ($c = 5.0$, EtOH); IR (KBr, cm^{-1}): 3323 (s), 2969 (vs), 1578 (m), 1551 (w), 1457 (m), 1375 (m), 1108 (m), 1094 (m), 1059 (m), 1042 (m), 897 (w); ^1H NMR (D_2O, δ): 0.72 (d/d/d, $J = 8.8/8.6/1.7$ Hz, 1H at C-6); 0.76 (s, 3H at C-8 or C-9); 0.84 (d/d/d, $J = 9.0/9.0/5.5$ Hz, 1H at C-1); 0.95 (s, 3H at C-9 or C-8); 0.97 (d, $J = 3.5$ Hz, 3H at C-10); 0.972–1.080 (m, 1H at C-2); 1.42 (d, $J = 6.4$ Hz, 3H at C-15 or C-16); 1.44 (d, $J = 6.4$ Hz, 3H at C-16 or C-15);2.01–2.22 (m, 1H at C-2 i 1H at C-3); 2.30 (d/d, $J = 18.6/8.5$ Hz, $1H_{ax}$ at C-5); 2.75 (d/d, $J = 18.6/1.7$ Hz, $1H_{eq}$ at C-5); 2.967 (d/d, $J = 12.5/10.0$ Hz, 1H at C-13); 3.15 (d/d, $J = 12.5/2.2$ Hz, 1H at C-13); 3.33–3.46 (m, 1H at C-14); 4.01 (d/d, $J = 11.9/5.9$ Hz, 1H at C-11); 4.12 (d/d, $J = 11.9/4.4$ Hz, 1H at C-11); 4.35–4.47 (m, 1H at C-12); ^{13}C NMR (δ): 14.40 (C-9 or C-8); 16.00 (C-8 or C-9); 17.92 (C-16); 18.16 (C-7); 18.35 (C-15); 19.33 (C-1); 20.25 (C-6); 20.84 (C-2); 27.78 (C-10); 29.27 (C-5); 34.24 (C-3); 46.92 (C-13); 50.81 (C-12); 65.85 (C-14); 74.08 (C-11); 166.44 (C-4). Elemental analysis: calcd for $C_{16}H_{30}N_2O_2 \cdot HCl$ (318.85) C, 60.27; H, 9.80; Cl, 11.11; N, 8.78. Found: C, 59.99; H, 10.06; Cl, 10.70; N, 9.00%.

3.4.2. (1*S*,3*R*,6*R*,2′*S*)-(−)-4-[2′-Hydroxy-3′-(*N*-isopropylamino)propoxyimino]-*cis*-carane hydrochloride KP-23*S*. (1.51 g, 4.6 mmol, 67% yield), mp 151–155°C; $[\alpha]_D^{25} = -7.2$ ($c = 5.0$, EtOH); IR (KBr, cm^{-1}): 3282 (s), 2968 (vs), 1631 (w), 1551 (m), 1458 (m), 1374 (m), 1107 (s), 1088 (m), 1065 (s), 945 (m), 908 (m); ^1H NMR (D_2O, δ): 0.72 (d/d/d, $J = 9.0/9.0/1.7$ Hz, 1H at C-6); 0.77 (s, 3H at C-8 or C-9); 0.83 (d/d/d, $J = 9.0/9.0/5.4$ Hz, 1H at C-1); 0.96 (s, 3H at C-9 or C-8); 0.98 (d, $J = 4.0$ Hz, 3H at C-10); 0.98–1.09 (m, 1H at C-2); 1.43 (d, $J = 6.5$ Hz, 3H at C-15 or C-16); 1.44 (d, $J = 6.5$ Hz, 3H at C-16 or C-15); 2.04–2.2 (m, 1H at C-2 i 1H or C-3); 2.31 (d/d, $J = 18.6/8.5$ Hz, $1H_{ax}$ at C-5); 2.75 (d/d, $J = 18.6/1.7$ Hz, $1H_{eq}$ at C-5); 2.97 (d/d, $J = 12.5/10.0$ Hz, 1H at C-13); 3.16 (d/d, $J = 12.5/2.5$ Hz, 1H at C-13); 3.33–3.47 (m, 1H at C-14); 4.03 (d/d, $J = 11.9/5.6$ Hz, 1H at C-11); 4.12 (d/d, $J = 11.9/4.4$ Hz, 1H at C-11); 4.35–4.46 (m, 1H at C-12); ^{13}C NMR (δ): 14.37 (C-9); 15.90 (C-8); 17.90 (C-16); 18.13 (C-7); 18.33 (C-15); 19.30 (C-1); 20.17 (C-6); 20.90 (C-2); 27.65 (C-10); 29.24 (C-5); 34.25 (C-3); 46.75 (C-13); 50.81 (C-12); 65.76 (C-14); 74.07 (C-11); 167.04 (C-4). Elemental analysis: calcd for $C_{16}H_{30}N_2O_2 \cdot HCl$ (318.85) C, 60.27%; H, 9.80; Cl, 11.11; N, 8.78. Found: C, 60.01; H, 10.00, Cl, 10.82, N, 9.04%.

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