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CHIRAL IMINES AND AMINES BASED ON 2-HYDROXYPINAN-3-ONE

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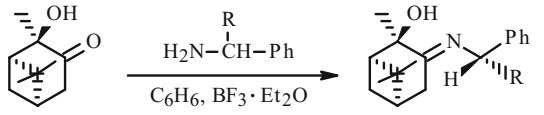
The new chiral derivatives of benzylamine and 2α-hydroxypinan-3-one (1R,2R,5R)-3-[(1S)-α-methylbenzylamino]-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (2), (1S,2S,3S,5S)-3-(benzylamino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (3), and (1R,2R,3R,5R)-3-[(1S)-α-methylbenzylamino]-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (4) were synthesized and characterized. It was shown that reduction of the benzylimines by sodium triacetoxyborohydride formed stereoselectively 3β-substituted pinanamines.

Keywords: chiral imines, amines, stereoisomers, stereoselectivity.

Chiral amines and imines are widely used as ligands and chiral promoters of asymmetric synthesis and catalysis [1, 2]. Amines and imines are key structural elements of many biologically active compounds that are used in pharmaceuticals and agrochemistry [3, 4]. For example, imines based on α-methylbenzylamine and isopinocamphone are used to combat pinewood nematodes [5]. Amines and imines are interesting as ligands for the synthesis of many transition-metal complexes [6–8].

We used the natural bicyclic monoterpene α-pinene as starting material for synthesizing chiral imines and amines. It was selected as the chiral starting material owing to the availability of the natural raw material (α-pinene occurs in pinewood resin and is the principal component of turpentine), developed isolation methods ensuring its supply, and the ability to prepare derivatives based on it that act as ligands. Oxidation of α-pinene produces 2α-hydroxypinan-3-one [9]. We used enantiomerically pure (+)- and (–)-2α-hydroxypinan-3-one and the primary amines benzylamine and optically pure (–)-(*S*)-α-methylbenzylamine to synthesize the imines.

Imines **1** and **2** were synthesized in 52–60% yields by condensation of the ketone and the corresponding amine in anhydrous benzene in the presence of a Lewis acid ($BF_3 \cdot Et_2O$) (Scheme 1).



1, 2

1: R = H; **2:** R = CH_3

Scheme 1

Mixtures of geometric isomers could form during the synthesis of **1** and **2**. The PMR spectrum of each of them showed a single set of resonances that indicated one of the geometric isomers formed. According to the literature [10–12], the thermally more stable *E*-isomer formed for their closest analogs.

Reduction of the imines could theoretically produce a mixture of two diastereomeric secondary amines. The reduction of Schiff bases of 2α-hydroxypinan-3-one and various alkyl- and arylamines was studied [13]. It was found that reduction by $LiAlH_4$ in THF formed 2α-hydroxy-3α-[*N*-alkyl(aryl)]-pinanamines. We managed to achieve exactly the opposite selectivity

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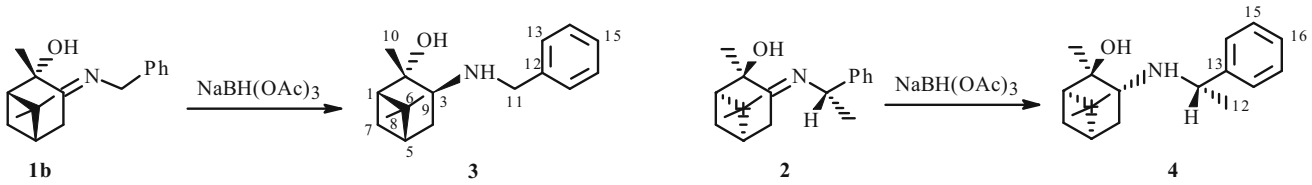
in reducing the benzylimines of 2α-hydroxypinan-3-one using $NaBH(OAc)_3$ as the reductant. This is a mild reductant with high stereoselectivity because the three acetoxy groups stabilize the B–H bond and create steric and electron-accepting effects [14]. Reduction of **1** and **2** by $NaBH(OAc)_3$ in isopropanol occurred diastereoselectively (Scheme 2) to produce amines **3** and **4** in yields of 90 and 95%, respectively, as pure diastereomers. This was confirmed by PMR and ^{13}C spectral data.



1b **3** **2** **4**

Scheme 2

The stereochemistry of the products was determined using PMR spectral data. The 2α,3α- and 2α,3β-stereoisomers should have different spin–spin coupling constants (SSCCs) for the H3–H4α and H3–H4β protons. These values in **3** were 8.7 and 9.2 Hz, respectively. The dihedral angles H3–C3–C4–H4α and H3–C3–C4–H4β were calculated for the 3α- and 3β-isomers using molecular mechanics. The values were $\tau = 25°$ and 142° for the β-isomer and 137° and 21° for the α-isomer. Based on these values and handbook data [15], the SSCCs for H3–H4α and H3–H4β were determined for the β-isomer (both J = 9 Hz) and the α-isomer (J = 11 and J = 7 Hz, respectively). Thus, a comparison of the experimental and calculated data suggested that the 2α,3β-isomer was produced. Analogous calculations were performed for **4** and were consistent with the 3β-isomer. These results were in agreement with those published [13]. The researchers prepared 2α-hydroxy-3α-(*N*-butyl)pinanamine, the structure of which was confirmed by an x-ray structure analysis. They reported PMR data, according to which the SSCCs for the H3–H4α and H3–H4β protons were 6.5 and 11.0 Hz, respectively.

EXPERIMENTAL

IR spectra were recorded as thin layers or KBr pellets on an IR Prestige 21 instrument (Shimadzu). PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance-II-300 instrument at operating frequency 300 MHz (^1H) and 75 MHz (^{13}C) using $CDCl_3$ resonances (δ_H 7.27 ppm, δ_C 77.00 ppm) as internal standards. Resonances were assigned using ^{13}C NMR spectra recorded using J-modulation and 2D ^1H–^1H (COSY) and ^1H–^{13}C (HSQC) correlation spectra. Melting points were determined using a TP heater. Refractive indices were measured on an IRF-454BM instrument; optical rotation, on a Kruss automated P3002RS polarimeter (Germany). Elemental analysis was performed on an EA 1110 element analyzer (CHNSO). The course of reactions was monitored using TLC on Silufol and Sorbfil plates using C_6H_{14}:Et_2O and $CHCl_3$:MeOH:NH_3 (25%) (100:10:1) as solvents. Compounds on plates were detected using iodine vapor and ninhydrin or vanillin solution with subsequent heating to 100–120°C. Column chromatography used silica gel (70–230 mesh, Lancaster). (*S*)-α-methylbenzylamine (*ee* 99.5%, Lancaster) was used without further purification.

(+)-(1*R*,2*R*,5*R*)-2-Hydroxypinan-3-one, $[\alpha]_D^{20}$ +39° (*c* 0.9, $CHCl_3$), mp 39–40°C and (–)-(1*S*,2*S*,5*S*)-2-hydroxypinan-3-one, $[\alpha]_D^{20}$ –38° (*c* 1.0, $CHCl_3$), mp 39–40°C were prepared by oxidation of α-pinene using $KMnO_4$ and the literature method [9] ($[\alpha]_D^{20}$ –42.7° and $[\alpha]_D^{20}$ +42°, respectively).

(1*R*,2*R*,5*R*)-3-(Benzylimino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (1a). A solution of (+)-2α-hydroxypinan-3-one (2.9 g, 0.02 mmol) and benzylamine (1.93 g, 0.02 mmol) in anhydrous benzene (60 mL) was refluxed for 21 h in the presence of $BF_3 \cdot Et_2O$ (0.9 g, 0.01 mmol) and calcined 4-Å molecular sieves (20 g). The mixture was filtered. The molecular sieves were rinsed with benzene. Solvent was vacuum distilled. The solid was dissolved in Et_2O and purified by chromatography [SiO_2, petroleum ether (PE):EtOAc, 2:1]. Solvent was removed to afford a thick yellow oil that contained according to TLC (Sorbfil, PE:EtOAc, 2:1, iodine vapor) a product with R_f 0.8, yield 2.4 g, 52%, $[\alpha]_D^{20}$ +11.7° (*c* 0.7, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3396 (OH), 1651 (C=N).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, s, CH_3-9), 1.37 (3H, s, CH_3-8), 1.57 (3H, s, CH_3-10), 1.62 (1H, d, $J_{7\alpha,7\beta}$ = 10.6, H_α-7), 2.06–2.16 (2H, m, H-1, H-5), 2.39 (1H, ddd, $J_{7\beta,1}$ = 1.9, $J_{7\beta,5}$ = 5.9, $J_{7\beta,7\alpha}$ = 10.6, H_β-7), 2.56–2.71 (2H, m, H-4), 4.56 (2H, s, H-11), 7.25–7.39 (5H, m, H_{arom}).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 22.94 (C-9), 27.40 (C-8), 28.23 (C-7), 28.48 (C-10), 33.69 (C-4), 38.41 (C-5), 38.53 (C-6), 50.28 (C-1), 54.15 (C-11), 76.63 (C-2), 126.62 (C-15), 127.52 (C-14), 128.41 (C-13), 140.12 (C-12), 176.79 (C-3).

(1*S*,2*S*,5*S*)-3-(Benzylimino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (1b) was prepared from (–)-(1*S*,2*S*,5*S*)-2α-hydroxypinan-3-one by an analogous method to give a thick yellow oil, yield 60%, $[\alpha]_D^{20}$ –11.9° (*c* 0.7, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3421 (OH), 1649 (C=N).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, s, CH_3-9), 1.37 (3H, s, CH_3-8), 1.57 (3H, s, CH_3-10), 1.62 (1H, d, $J_{7\alpha,7\beta}$ = 10.6, H_α-7), 2.06–2.15 (2H, m, H-1, H-5), 2.39 (1H, ddd, $J_{7\beta,1}$ = 1.6, $J_{7\beta,5}$ = 5.9, $J_{7\beta,7\alpha}$ = 10.6, H_β-7), 2.57–2.70 (2H, m, H-4), 4.56 (2H, s, H-11), 7.25–7.39 (5H, m, H_{arom}).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 22.95 (C-9), 27.39 (C-8), 28.22 (C-7), 28.48 (C-10), 33.70 (C-4), 38.39 (C-5), 38.53 (C-6), 50.25 (C-1), 54.15 (C-11), 76.63 (C-2), 126.64 (C-15), 127.52 (C-14), 128.42 (C-13), 140.11 (C-12), 176.83 (C-3).

(1*R*,2*R*,5*R*)-3-[(1*S*)-α-Methylbenzylimino]-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (2). Light-yellow oil, yield 55%, n_D^{23} 1.5333, $[\alpha]_D^{23}$ –34.4° (*c* 0.25, $CHCl_3$). Hydrochloride HL_3·HCl, white needle-like crystals, mp 176–177°C. IR spectrum (hydrochloride) (ν, cm^{-1}): 3232 (OH), 1662 (C=N). $C_{18}H_{25}NO$·HCl.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.94 (3H, s, CH_3-9), 1.36 (3H, s, CH_3-8), 1.48 (3H, d, $J_{12,11}$ = 6.5, CH_3-12), 1.51 (1H, d, $J_{7\alpha,7\beta}$ = 10.2, H_α-7), 1.57 (3H, s, CH_3-10), 2.04 (1H, ddd, $J_{5,4\beta}$ = 2.6, $J_{5,4\alpha}$ = 3.0, $J_{5,1}$ = 5.9, H-5), 2.11 (1H, dd, $J_{1,5}$ = 5.9, $J_{1,7\beta}$ = 6.0, H-1), 2.32 (1H, ddd, $J_{7\beta,4\beta}$ = 2.4, $J_{7\beta,1}$ = 6.0, $J_{7\beta,7\alpha}$ = 10.2, H_β-7), 2.57 (1H, dd, $J_{4\alpha,5}$ = 3.0, $J_{4\alpha,4\beta}$ = 17.9, H_α-4), 2.69 (1H, ddd, $J_{4\beta,7\beta}$ = 2.4, $J_{4\beta,5}$ = 2.6, $J_{4\beta,4\alpha}$ = 17.9, H_β-4), 3.65 (br, OH), 4.73 (1H, q, $J_{11,12}$ = 6.5, H-11), 7.27 (1H, dd, $J_{16,14}$ = 1.4, $J_{16,15}$ = 7.1, H-16), 7.35 (2H, dd, $J_{15,16}$ = 7.1, $J_{15,14}$ = 7.8, H-15), 7.40 (2H, dd, $J_{14,16}$ = 1.4, $J_{14,15}$ = 7.8, H-14).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 23.00 (C-9), 24.00 (C-12), 27.39 (C-8), 28.06 (C-7), 28.53 (C-10), 32.96 (C-4), 38.37 (C-6), 38.42 (C-5), 50.27 (C-1), 58.06 (C-11), 76.53 (C-2), 126.50 (C-15), 126.68 (C-16), 128.42 (C-14), 145.13 (C-13), 174.47 (C-3).

(1*S*,2*S*,3*S*,5*S*)-3-(Benzylamino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (3). A solution of **1b** (2.2 g, 0.009 mol) in isopropanol (100 mL) was stirred under an Ar atmosphere at room temperature, treated over an hour with $NaBH(OAc)_3$ (2.8 g, 0.013 mol), stirred for 6 h at room temperature, and treated with stirring with NaOH solution (30 mL, 10%). The products were separated by extraction with EtOAc (3×). The organic extract was dried over anhydrous $MgSO_4$. Solvent was removed to afford **3** as a bright yellow oil that contained according to TLC (Sorbfil, PE:EtOAc, 1:1, iodine vapor) a single product, R_f 0.2, yield 1.9 g (90%), n_D^{23} 1.5340, $[\alpha]_D^{20}$ +36.5° (*c* 0.4, EtOH). IR spectrum (ν, cm^{-1}): 3404 (OH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.94 (3H, s, CH_3-9), 1.27 (3H, s, CH_3-8), 1.43 (3H, s, CH_3-10), 1.51 (1H, dd, $J_{4\alpha,3}$ = 8.7, $J_{4\alpha,4\beta}$ = 13.7, H_α-4), 1.57 (1H, d, $J_{7\alpha,7\beta}$ = 10.3, H_α-7), 1.88–2.00 (2H, m, H-1, H-5), 2.14 (1H, ddd, $J_{7\beta,1}$ = 1.4, $J_{7\beta,5}$ = 5.6, $J_{7\beta,7\alpha}$ = 10.3, H_β-7), 2.34 (1H, ddd, $J_{4\beta,5}$ = 5.0, $J_{4\beta,3}$ = 9.2, $J_{4\beta,4\alpha}$ = 13.7, H_β-4), 3.18 (1H, dd, $J_{3,4\alpha}$ = 8.7, $J_{3,4\beta}$ = 9.2, H-3), 3.88 (1H, d, $J_{11\alpha,11\beta}$ = 13.3, H_α-11), 3.94 (1H, d, $J_{11\beta,11\alpha}$ = 13.3, H_β-11), 7.40 (5H, m, H_{arom}).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 23.11 (C-9), 24.76 (C-7), 24.81 (C-10), 27.70 (C-8), 33.01 (C-4), 39.17 (C-6), 40.34 (C-5), 52.76 (C-11), 55.80 (C-1), 60.20 (C-3), 76.62 (C-2), 126.91 (C-15), 128.12 (C-14), 128.38 (C-13), 140.72 (C-12).

(1*R*,2*R*,3*R*,5*R*)-3-[(1*S*)-α-Methylbenzylamino]-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (4). Thick yellow oil that gradually crystallized, yield 95%, $[\alpha]_D^{20}$ –51.1° (*c* 0.3, EtOH), mp 67–68°C. IR spectrum (ν, cm^{-1}): 3458 (OH), 3340 (NH). $C_{18}H_{27}NO$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.93 (3H, s, CH_3-9), 1.25 (3H, s, CH_3-8), 1.37 (3H, s, CH_3-10), 1.39 (3H, d, $J_{12,11}$ = 6.6, CH_3-12), 1.42 (1H, d, $J_{7\alpha,7\beta}$ = 15.6, H_α-7), 1.48 (1H, dd, $J_{4\alpha,3}$ = 9.0, $J_{4\alpha,4\beta}$ = 13.2, H_α-4), 1.88 (1H, dd, $J_{1,5}$ = 5.8, $J_{1,7\beta}$ = 10.6, H-1), 1.94 (1H, ddd, $J_{5,7\beta}$ = 5.1, $J_{5,4\beta}$ = 5.1, $J_{5,1}$ = 5.8, H-5), 2.05 (1H, ddd, $J_{7\beta,5}$ = 5.1, $J_{7\beta,1}$ = 10.6, $J_{7\beta,7\alpha}$ = 15.6, H_β-7), 2.30 (1H, ddd, $J_{4\beta,5}$ = 5.1, $J_{4\beta,3}$ = 9.0, $J_{4\beta,4\alpha}$ = 13.2, H_β-4), 2.93 (1H, dd, $J_{3,4\alpha}$ = 9.0, $J_{3,4\beta}$ = 9.0, H-3), 3.99 (1H, q, $J_{11,12}$ = 6.6, H-11), 7.4 (5H, m, H_{arom}).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 23.23 (C-9), 24.63 (C-7), 24.95 (C-10), 25.01 (C-12), 27.77 (C-8), 32.98 (C-4), 39.11 (C-6), 40.39 (C-5), 55.08 (C-1), 55.23 (C-11), 57.57 (C-3), 77.63 (C-2), 126.66 (C-15), 126.92 (C-16), 128.46 (C-14), 145.79 (C-13).

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