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Stereoselectivity of formation of monoterpene – Amino acids hybrid molecules in the reaction of monoterpene nitroso chlorides with α-amino acid derivatives

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ABSTRACT

Reaction of nitrosochlorides of natural monoterpene hydrocarbons (+)-3-carene and (−)-α-pinene with L-amino acids and their methyl esters results in stereoselective formation of terpene–amino acids hybrids, which belong to the series of α-substituted amino oximes. The reaction with an excess of racemic DL-amino acids and their derivatives induces partial resolution of the amino acid components and formation of the diastereomeric mixtures of the terpene–amino acids hybrids, with diastereomeric excess varying from 0 to 100%.

1. Introduction

Natural optically active terpenes are important starting compounds in design of chiral auxiliary [1] as well as molecular sensors [2] and host-guest complex precursors [3]. Terpenic nitrosochlorides are convenient precursors for synthesis of diverse chiral multifunctional compounds [4], and treatment of the nitrosochlorides with *N*-, *S*- or *C*-nucleophiles results in variety of chiral polyheteroatomic derivatives with terpenic mainframe, like α-amino oximes [5] α-sulfanyl oximes [6] substituted malonates [7], nitriles [8], oxime-based macrocycles [9] as well as diversity of azaheterocycles [10]. The derivatives mentioned are useful in asymmetric oxidation [11] and resolution of enantiomers [12] and have found wide application in coordination chemistry [13].

Terpene-amino acid hybrids [14] are of interest as potential biologically active molecules as well as prospective chiral ligands for coordination chemistry [15].

Herein we report on stereoselectivity of formation of the terpene-amino acid hybrids from nitrosochlorides of natural monoterpenes (+)-3-carene (**1**) and (−)-α-pinene (**2**) and a series of racemic natural amino acids.

2. Experimental

Crystalline dimeric nitroso chlorides **2** and **11** from were prepared (+)-3-carene **1** and (−)-α-pinene **10** correspondingly by passing gaseous nitrosyl chloride over a solution of terpene in dichloromethane [4]. The nitrosochlorides were purified by dissolving in chloroform followed by precipitation with pre-cold methanol. The following natural monoterpenes were used as starting compounds: (+)-3-carene with $[\alpha]^{20}_{578}$ +16.0 (d^4_{20} 0.863) and >99% *e.e.* isolated from the *Pinus sylvestris* L. oil turpentine, (−)-α-pinene from Fluka AG (Product Number 8060, 93% *e.e.*).

Aminoacids (L-alanine, L-methionine, L-phenyl glycine, L-phenyl alanine, L-histidine, L-proline, DL-histidine, and DL-phenyl glycine) were commercially available from Fluka AG. DL-Proline, DL-methionine, and DL-phenyl alanine where prepared by racemisation of the corresponding natural optically active amino acids by known procedures [16]. Hydrochlorides of amino acid esters were prepared in accordance with method [17]. All the solvents used were freshly distilled.

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions using a AV-400 (400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C) and DRX-500 (500.13 MHz for ^{1}H, 125.75 MHz for ^{13}C). Signal assignments were made based on two-dimensional ^{1}H–^{1}H and ^{13}C–^{1}H shift-correlation experiments. IR spectra were recorded

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on a Bruker TENSOR 27 spectrophotometer for solutions in $CHCl_3$ (*c* 1%) or KBr (*c* 0.25%). UV-spectra were recorded on an Agilent 8453 instrument. Optical rotation was measured on a PolAAr 3005 polarimeter. Melting points were measured on a Kofler heating stage. Mass spectra were obtained on a Termo electron DFS (electron impact ionization, EI, 70 eV) and Bruker micrOTOF-Q (electrospray ionization, ESI) mass spectrometers.

Routine monitoring of the reactions was made using analytical TLC plates *Sorbfil* (SiO_2 on a polymeric film) and visualized with iodine. Preparative column chromatography was performed on SiO_2 (Merck, 0.060–0.100 mm).

2.1. General procedure for the preparation of the L-alanine, L-methionine, L-phenylglycine, and L-phenylalanine derivatives

An aminoacid methyl ester hydrochloride (10 mmol) was dissolved in methanol (50 mL) followed by addition of Na_2CO_3 (1.06 g, 10 mmol). The reaction mixture was stirred for 10 min at room temperature (+20 + 23 °C), and after that crystalline dimeric nitrosochloride of (+)-3-carene or (−)-α-pinene was added (2.01 g, 5 mmol). The suspension was stirred until the nitrosochloride was completely dissolved (20–30 h), after that the reaction mixture was kept at stirring additionally for 30 min at +40 °C. The solvent was removed under reduced pressure and the residue was treated with 1 M aqueous HCl (25 mL) and ethyl acetate (25 mL). The organic phase was separated and extracted with 1 M aqueous HCl (2 × 25 mL). The combined acidic aqueous extract was treated with concentrated aqueous NH_3 to pH 10–11, the reaction products were extracted with ethyl acetate (3 × 50 mL). This combined organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to leave the crude product which was then purified by column chromatography on a SiO_2 column (light petroleum − ethyl acetate, $^v/_v$ progressing from 5:1 to 1:1) to afford the target compound.

2.1.1. (S)-2-((1S,3S,6R,E)-4-hydroxyimino-caran-3-yl)-aminopropionic acid methyl ester **3a**

Yellowish amorphous powder, 65% yield; $[\alpha]_{589}^{27}$ +98.4 (*c* 0.953, MeOH). IR (KBr, cm^{-1}): 3279, 1740, 1202, 1173, 941. MS (EI, 70 eV): *m*/*z* calcd. for $C_{14}H_{24}N_2O_3(M)^+$, 268.1781; found, 268.1778. ^{1}H NMR (400 MHz, $CDCl_3$): 8.51 (wide, 1H, =NOH), 3.68 (s, 3H, 14-H), 3.23 (q, *J* = 7.1 Hz, 1H, 11-H), 2.90 (dd, *J* = 18.9, 1.1 Hz, 1H, 5-H-*pro-S*), 2.27 (dd, *J* = 19.0, 8.7 Hz, 1H, 5-H-*pro-R*), 2.13 (dd, *J* = 15.0, 9.5 Hz, 1H, 2-H-*pro-S*), 1.30 (dd, *J* = 15.0, 5.3 Hz, 1H, 2-H-*pro-R*), 1.24 (d, *J* = 7.05 Hz, 3H, 12-H), 1.02 (s, 3H, 9-H), 1.00 (s, 3H, 10-H), 0.87 (ddd, *J* = 8.8, 8.8, 1.5 Hz, 1H, 6-H), 0.76 (ddd, *J* = 9.5, 9.5, 5.2 Hz, 1H, 1-H), 0.76 (s, 3H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.12 (13), 161.62 (4), 54.89 (3), 51.88 (14), 50.98 (11), 34.84 (2), 27.79 (9), 22.21 (6), 20.57 (12), 18.79 (7), 18.63 (1), 17.73 (5), 16.40 (8), 14.38 (10).

2.1.2. (S)-2-((1S,3S,6R,E)-4-hydroxyimino-caran-3-yl)-amino-2-phenylacetic acid methyl ester **4a**

White amorphous powder, 66% yield; $[\alpha]_{589}^{27}$ +165 (*c* 0.555, MeOH); IR (KBr, cm^{-1}): 3313, 1722, 1211, 1169, 932. MS (EI, 70 eV): *m*/*z* calcd. for $C_{19}H_{26}N_2O_3(M)^+$, 330.1938; found, 330.1937. ^{1}H NMR (400 MHz, $CDCl_3$): 8.19 (wide, 1H, =NOH), 7.40–7.23 (m, 5H, 15-H, 16-H, 17-H, 18-H, 19-H), 4.27 (s, 1H, 11-H), 3.66 (s, 3H, 13-H), 2.65 (d, *J* = 19.3 Hz, 1H, 5-H-*pro-S*), 2.21 (dd, *J* = 15.1, 9.6 Hz, 1H, 2-H-*pro-S*), 1.84 (dd, *J* = 19.2, 8.9 Hz, 1H, 5-H-*pro-R*), 1.33 (dd, *J* = 15.1, 5.6 Hz, 1H, 2-H-*pro-R*), 1.14 (s, 3H, 9-H), 0.96 (s, 3H, 10-H), 0.78–0.72 (m, 1H, 1-H), 0.74 (s, 3H, 8-H), 0.61 (dd, *J* = 10.5, 8.9 Hz, 1H, 6-H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.65 (12), 161.89 (4), 139.46 (14), 128.65 (15, 19), 127.82 (16,18), 127.32 (17), 60.00 (13), 55.09 (3), 52.19 (11), 34.80 (2), 27.72 (9), 22.50 (6), 18.68 (7), 18.29 (1), 17.70 (5), 16.47 (8), 14.47 (10).

2.1.3. (S)-2-((1S,3S,6R,E)-4-hydroxyimino-caran-3-yl)-amino-3-phenylpropionic acid methyl ester **5a**

White amorphous powder, 51% yield; $[\alpha]_{589}^{26}$ +78 (*c* 0.74, EtOH). IR (KBr, cm^{-1}): 3296, 1734, 1279, 1173, 949. MS (EI, 70 eV): *m*/*z* calcd. for $C_{20}H_{28}N_2O_3(M)^+$, 344.2094; found, 344.2089. ^{1}H NMR (400 MHz, $CDCl_3$): 8.23 (wide, 1H, =NOH), 7.38–7.22 (m, 5H, 16-H, 17-H, 18-H, 19-H, 20-H), 3.74 (s, 3H, 14-H), 3.36 (dd, *J* = 10.6, 3.9 Hz, 1H, 11-H), 3.06 (dd, *J* = 13.3, 3.9 Hz, 1H, 12-H), 2.71 (dd, *J* = 13.3, 10.7 Hz, 1H, 12-H), 2.32 (d, *J* = 19.5 Hz, 1H, 5-H-*pro-S*), 2.13 (dd, *J* = 15.0, 9.5 Hz, 1H, 2-H-*pro-S*), 1.21 (dd, *J* = 19.5, 9.2 Hz, 1H, 5-H-*pro-R*), 1.15 (dd, *J* = 15.0, 5.9 Hz, 1H, 2-H-*pro-R*), 0.99 (s, 3H, 9-H), 0.89 (s, 3H, 10-H), 0.64 (s, 3H, 8-H), 0.59 (d, *J* = 9.5, 9.3, 5.8 Hz, 1H, 1-H), -0.045 (dd, *J* = 9.5, 9.0 Hz, 1H, 6-H). ^{13}C NMR (100 MHz, $CDCl_3$): 176.36 (13), 160.62 (4), 136.98 (15), 129.41 (17, 19), 128.69 (16, 20), 127.18 (18), 57.78 (14), 54.79 (3), 52.00 (11), 39.74 (12) 34.69 (2), 27.71 (9), 22.19 (6), 18.64 (7), 17.76 (1), 17.14 (5), 16.03 (8), 14.31 (10).

2.1.4. (S)-2-((1S,3S,6R,E)-4-hydroxyimino-caran-3-yl)-amino-4-methylthyobutanoic acid methyl ester **6a**

Viscid ember colored oil, 87% yield; $[\alpha]_{589}^{26}$ +58 (*c* 0.56, EtOH). IR (KBr, cm^{-1}): 1738, 939. MS (ESI^+, 4500V): *m*/*z* calcd. for $C_{16}H_{28}N_2O_3S(M+H)^+$, 329.190; found, 329.189. ^{1}H NMR (400 MHz, $CDCl_3$): 8.43 (wide, 1H, =NOH), 3.69 (s, 3H, 16-H), 3.24 (dd, *J* = 7.7, 5.8 Hz, 1H, 11-H), 2.78 (d, *J* = 19.3 Hz, 1H, 5-H-*pro-S*), 2.60–2.42 (m, 2H, 13-H), 2.35 (dd, *J* = 19.2, 8.8 Hz, 1H, 5-H-*pro-R*), 2.06 (s, 3H, 14-H), 2.05 (dd, *J* = 15.0, 9.3 Hz, 1H, 2-H-*pro-S*), 1.94–1.65 (m, 2H, 12-H), 1.29 (dd, *J* = 15.1, 5.5 Hz, 1H, 2-H-*pro-R*), 1.01 (s, 3H, 10-H), 1.00 (s, 3H, 9-H), 0.84 (ddd, *J* = 10.6, 8.9, 5.5 Hz, 1H, 6-H), 0.753 (s, 3H, 8-H), 0.75 (m, *J* = 9.2 Hz, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): 176.57 (13), 161.32 (4), 54.50 (3), 54.32 (11), 51.63 (15), 34.78 (2), 33.84 (12), 30.01 (13) 27.47 (9), 22.47 (6), 18.39 (7), 18.35 (1), 17.54 (5), 16.42 (8), 14.95 (16), 14.15 (10).

2.1.5. (S)-2-[(1R,2R,3E,5R)-3-hydroxyimino-pinan-2-yl] aminopropionic acid methyl ester **12a**

Yellowish amorphous powder, 70% yield; $[\alpha]_{589}^{26}$ −70.0 (*c* 0.869, MeOH). IR (KBr, cm^{-1}): 3329, 1734, 1215, 1178, 957. MS (EI, 70 eV): *m*/*z* calcd. for $C_{14}H_{24}N_2O_3(M)^+$, 268.1781; found, 268.1783. ^{1}H NMR (400 MHz, $CDCl_3$): 8.36 (wide, 1H, =NOH), 3.66 (s, 3H, 14-H), 3.62 (q, *J* = 18.3 Hz, 1H, 11-H), 2.80 (ddd, *J* = 18.3, 3.1, 3.1 Hz, 1H, 4-H-*pro-R*), 2.35 (dd, *J* = 18.4, 2.4 Hz, 1H, 4-H-*pro-S*), 2.30 (dddd, *J* = 10.7, 6.0, 6.0, 2.8 Hz, 1H, 7-H-*pro-S*), 1.99 (dd, *J* = 6.0, 5.6 Hz, 1H, 1-H), 1.94 (dddd, *J* = 6.0, 5.6, 3.1, 2.4 Hz, 1H, 5-H), 1.62 (d, *J* = 10.8 Hz, 1H, 7-H-*pro-R*), 1.30 (s, 3H, 10-H), 1.27 (s, 3H, 9-H), 1.21 (d, *J* = 7.2 Hz, 3H, 12-H), 0.85 (s, 3H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 178.14 (13), 161.3 (3), 59.86 (2), 52.03 (14), 51.87 (1), 50.07 (11), 39.22 (6), 38.07 (5), 29.77 (4), 28.21 (7), 27.53 (9), 24.95 (10), 22.49 (8), 20.94 (12).

2.1.6. (S)-2-[(1R,2R,3E,5R)-3-hydroxyimino-pinan-2-yl]amino-2-phenylacetic acid methyl ester **13a**

White amorphous powder, 75% yield; $[\alpha]_{589}^{28}$ −29.0 (*c* 0.773, EtOH). IR (KBr, cm^{-1}): 3340, 1730, 1211, 1167, 1105, 962, 766, 898. MS (ESI^+, 4500V): *m*/*z* calcd. for $C_{19}H_{24}N_2O_3(M+H)^+$, 331.20217; found, 331.202. ^{1}H NMR (400 MHz, $CDCl_3$): 7.41 (s, 1H, =NOH), 7.35–7.20 (m, 5H, 15-H, 16-H, 17-H, 18-H, 19-H), 4.70 (s, 1H, 11-H), 3.66 (s, 3H, 13-H), 2.85 (ddd, *J* = 18.5, 2.9, 2.9 Hz, 1H, 4-H-*pro-R*), 2.44 (dd, *J* = 18.5, 2.1 Hz, 1H, 4-H-*pro-S*), 2.28 (dddd, *J* = 10.7, 6.0, 6.0, 2.7 Hz, 1H, 7-H-*pro-S*), 2.01–1.93 (m, 2H, 1-H, 5-H), 1.68 (d, *J* = 10.8, 1H, 7-H-*pro-R*), 1.38 (s, 3H, 9-H), 1.28 (s, 3H, 10-H), 0.89 (s, 3H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$):