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Статья

Synthesis of Optically Pure Macroheterocycles with 2,6−Pyridinedicarboxylic and Adipic Acid Fragments from Δ³−Carene

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Based on the available natural monoterpene Δ³-carene we have developed the synthesis of four optically pure macroheterocycles with ester and dihydrazide fragments through the intermediate 1-((1S,3R)-3-(2-hydroxyethyl-2,2-dimethylcyclopropyl)propan-2-one using its [2+1]-interaction with dichloranhydrides of adipic or 2,6-pyridinedicarboxylic acids and [1+1]-condensation of the obtained α,ω-diketodiesters with dihydrazides of adipic or 2,6-pyridinedicarboxylic acids. The structure of new compounds was confirmed by IR and NMR spectroscopy and mass spectrometry.

Keywords: 3-Carenes, ozonolysis, sodium hypochlorite, macroheterocycles with ester and dihydrazide fragments, [2+1] and [1+1] condensations, synthesis.

Синтез оптически чистых макрогетероциклов со сложноэфирными и дигидразидными фрагментами адипиновой и 2,6−пиридиндикарбоновой кислот из Δ³−карена

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На основе доступного природного монотерпена Δ³-карена разработаны синтезы четырех оптически чистых макрогетероциклов со сложноэфирными и дигидразидными фрагментами через промежуточный 1-((1S,3R)-3-(2-гидроксиэтил-2,2-диметилциклопропил)пропан-2-он с использованием на ключевых стадиях [2+1]-взаимодействия последнего с дихлорангидридами адипиновой или 2,6-пиридиндикарбоновой кислот и [1+1]-конденсации образующихся α,ω-дикетодиэфиров с дигидразидами адипиновой или 2,6-пиридиндикарбоновой кислот. Структура полученных соединений установлена с помощью ИК и ЯМР спектроскопии и подтверждена хромато-масс-спектрометрией.

Ключевые слова: 3-Карены, озонолиз, гипохлорит натрия, макрогетероциклы со сложноэфирными и дигидразидными фрагментами, [2+1]- и [1+1]-конденсации, синтез.

Introduction

Δ^3-Carene was obtained using fractional distillation of turpentines from pines *Pinus roxburghii* (55–65 %), *Pinus silvestris* (20–40 %) and *Pinus ponderosa* (20–25 %).[1] This monoterpene is widely applied in the streamlined organic synthesis, including also macroheterocycles. Thus, Δ^3-carene was applied to totally synthesize 3-hexadecanoate of the diterpene ingenol from *Euphorbia ingens* and *Euphorbia lathyris* that possesses irritating and co-carcinogenic properties.[2] It was also used to synthesize a chiral pentadentate macrocyclic ligand with two carene and two nitrogen-containing (-NH-CH$_2$CH$_2$-NH- and =N-O-CH$_2$-O-N=) fragments (L),[3] and nickel(II) – [NiL](NO$_3$)$_2$ and [NiL](ClO$_4$)$_2$·2H$_2$O, cobalt(II) – CoL(NO$_3$)$_2$·H$_2$O[4] and copper(II) – [CuL](NO$_3$)$_2$·H$_2$O, [CuL](ClO$_4$)$_2$·H$_2$O, CuLCl$_2$·3H$_2$O and CuLBr$_2$·4H$_2$O complexes on its basis.[5] Such a type of metal complexes with natural chiral ligands is interesting as biologically active substances and potential catalyzers for the enantioselective synthesis of organic compounds.

We have already reported[6] about the synthesis of optically active macroheterocycles with ester nitrogen-containing (azine or hydrazide) fragments based on subsequent reactions of ozonolytic decyclization of Δ^3-carene (**1**) (*ee* 100 %) to hydroxyketone (1*R*-(1'-hydroxyethyl)-3*R*-(2''-hydroxyethyl)-2,2-dimethylcyclobutane) (**2**), its [2+1]-interaction with glutaric or adipic acid dichloranhydrides and final [1+1]-condensation of the emerged α,ω-diketodiesters with glutaric acid hydrazine or hydrazine hydrate.

In recent years, there were some publications on the synthesis of macrocyclic compounds incorporating a fragment of 2,6-pyridinedicarboxylic acid. Thus, the ester function of this acid enters into the composition of cryptand molecules integrated with herbicides by paraquat and diquat and enhances their solubility in water;[7,8] the macrocyclic ring of [2]-rotaxanes;[9] crown ether macrocycles enabling the enantiomeric recognition of chiral salts;[10–12] and macroheterocycles as chiral solvating agents for the NMR enantiomeric excess determination of carbonic acids.[13] The dihydrazide fragment of 2,6-pyridinedicarboxylic acid occurs in macrocyclic hydrazone with antimicrobial activity,[14] macrocyclic peptide-calix[4]arenes and peptide-pyridines as precursors of potential molecular metal cells, chemosensors and biologically active candidates,[15] as well as tri-, tetra- and pentatopic ligands for supramolecular multinuclear complexes with manganese ions.[16]

Adipic acid dihydrazide enters into complexation reactions with nickel(II) salts. It is likely that its derivatives will possess the same properties.

The aim of this work is to study the reaction ability and propensity for the formation of macroheterocycles at the stage of dihydrazide [1+1]-condensation by adipic and 2,6-pyridinedicarboxylic acids as compared to glutaric acid hydrazide.

Experimental

Analyzes were performed on the equipment at the Center for the Collective Use «Chemistry» of the Ufa Institute of Chemistry UFRC RAS. IR spectra were recorded on the device IR Prestige-21 Shimadzu (Fourier Transform Spectrophotometer – Shimadzu) in thin layer. NMR spectra were recorded in CDCl$_3$ and D$_2$O with TMS internal standard on a Bruker AM-500 spectrometer (operating frequency 500.13 MHz for ^{1}H; 126.76 MHz for ^{13}C). Mass spectra were recorded on a LC/MS 2010 EV Shimadzu instrument (syringe input, sample solution in CH$_3$CN at flow rate 60 μL/min) using electrospray ionization (ESI) method with a simultaneous recording of positive and negative ions at capillary potentials 4.5 and –3.5 kV, respectively. The temperature of the capillary interface was 200 °C; the flow of a nebulizer gas (dry N$_2$) was 0.8 L·min^{-1}. Sorbfil SiO$_2$ (Russia) was used for TLC monitoring. For column chromatography SiO$_2$ (70–230) «Lancaster» (England) was used. Optical rotation was measured on a PerkinElmer 141 MC polarimeter.

Methanol, petroleum ether 40–70 °C, methyl-*tert*-butyl ether (*t*-BuOMe), methylene chloride, pyridine, DMF and acetonitrile purified and dried according to standard methods[9] were used for reactions and isolation of the obtained compounds. Δ^3-Carene (*ee* 100 %) was used in the work.

(3^{1}R,3^{3}S)-3^2,3^2-Dimethyl-1,5-dihydroxy-3(1,3)-cyclopropyla-hexaphane (3). An ozone–oxygen mixture was bubbled through a solution 3.00 g (22.2 mmol) of Δ^3-carene (**1**) in 24 ml of anhydrous MeOH cooled to –40 °C until 23 mmol of O$_3$ was absorbed. The mixture was then purged with argon, 2.10 g (55.2 mmol) of NaBH$_4$ was added under stirring at 15 °C, and the mixture was stirred for 48 h at room temperature (until peroxide compounds disappeared according to iodine–starch test), then a solution of 3 ml AcOH in 30 ml H$_2$O was added, stirred for 3 h. The solvent was distilled off, the residue was dissolved in 100 ml of CH$_2$Cl$_2$, and the solution was washed with brine (4×15 ml), dried over Na$_2$SO$_4$ and evaporated. Yield: 3.27 g (86 %) of diol (**3**) as mixture (1:1) of diastereomers. R$_f$ 0.2 (*t*-BuOMe). The IR, ^{1}H and ^{13}C NMR, mass spectra were identical to those reported.[18]

(4^{1}S,4^{3}R)-4^2,4^2-Dimethyl-6-hydroxy-2-oxo-4(1,3)-cyclopropylahexaphane (2). The diol (**3**) 3.00 g (17.4 mmol) was dissolved in 15 ml of glacial acetic acid and stirred magnetically. Aqueous 1.0 M NaOCl (17.4 ml, 17.4 mmol) added dropwise at room temperature over 1 h initiated a rapid exo-thermic reaction. Stirring was continued for 1 h at room temperature, after that 15 ml of isopropanol was added to quench any remaining oxidant followed by 50 ml of water. The solution was extracted with CH$_2$Cl$_2$ (3×50 ml), washed with aqueous NaHCO$_3$ and brine (3×15 ml), dried over MgSO$_4$ and evaporated. Yield: 2.22 g (75 %) of hydroxyketone (**2**). R$_f$ 0.3 (*t*-BuOMe). [α]$_D^{20}$ –16.7° (c 0.67; MeOH), cf.[6] The IR, ^{1}H and ^{13}C NMR spectra were identical to those reported.[19]

(4^{1}S,4^{3}R,14^{1}R,14^{3}S)-4^2,4^2,14^2,14^2-Tetramethyl-2,8,10,16-tetraoxo-7,11-dioxa-9^1-aza-4,14(1,3)-dicyclopropyla-9(2,6)-pyridinaheptadecaphane (4). A solution of hydroxyketone (**2**) (2.00 g, 11.8 mmol) and 1 crystal DMAP in 2 ml of anhydrous Et$_3$N was treated with a solution of 2,6-pyridinedicarbonyl dichloride (1.20 g, 5.9 mmol) prepared as before[5] in 20 ml of anhydrous Et$_2$O. After 48 h (TLC monitoring), the mixture was diluted with 100 ml Et$_2$O, washed with 5 % HCl solution (3×15 ml) and brine (3×15 ml), dried over MgSO$_4$ and evaporated. The residue was chromatographed (SiO$_2$, petroleum ether–*t*-BuOMe, 5:1). Yield: 3.61 g (65 %) of diketodiester (**4**). R$_f$ 0.5 (*t*-BuOMe). [α]$_D^{20}$ +9.3° (c 0.04; CH$_2$Cl$_2$). *m/z* C$_{27}$H$_{37}$NO$_6$ (471) (ESI, I$_{relative}$, %): (Scan +) 472 [M+H]$^+$. IR (KBr) ν$_{max}$ cm^{-1}: 1738 (-O-C=O), 1713 (-C=O). ^{1}H NMR (CDCl$_3$) δ$_H$ ppm: 0.90 (6H, s, *cis*-CH$_3$-4^2, *cis*-CH$_3$-14^2), 0.95–1.10 (4H, m, H-4^1, H-4^3, H-14^1, H-14^3), 1.17 (6H, s, *trans*-CH$_3$-4^2, *trans*-CH$_3$-14^2), 1.60–1.70 (4H, m, H-5, H-13), 2.05 (6H, s, H-1, H-17), 2.09 (2H, d, *J* = 8.7 Hz, H$_a$-3, H$_a$-15), 2.32 (2H, d, *J* = 8.7 Hz, H$_b$-3, H$_b$-15), 4.05 (4H, t, *J* = 5.6 Hz, H-6, H-12), 8.05 (1H, t, *J* = 7.7 Hz, H-9^4), 8.45 (2H, d, *J* = 7.7 Hz, H-9^3, H-9^5). ^{13}C NMR (CDCl$_3$) δ$_C$ ppm: 17.03 (s, C-4^2,14^2), 21.21 (q, *cis*-CH$_3$-4^2, *cis*-CH$_3$-14^2), 22.69 (d, C-4^1, C-14^3), 24.40 (d, C-4^3, C-14^1), 28.74 (q, C-1, C-17), 29.64 (q, *trans*-CH$_3$-4^2, *trans*-CH$_3$-14^2), 33.92 (t, C-3, C-15), 39.32 (t, C-5, C-13), 64.45 (t, C-6, C-12), 125.98 (d, C-9^3,

C-9[5]), 139.40 (d, C-9[4]), 148.64 (C, C-9[2], C-9[6]), 173.31 (s, C-8, C-10), 208.74 (s, C-2, C-16).

Synthesis of macrocyclic compounds (6–9) (General method). A solution of adipic (or 2,6-pyridinedicarboxylic[20]) acid dihydrazide (1.13 mmol) in 1.0 ml of H_2O under intensive stirring to diketone (**4**) (1.13 mmol) or (4[1]S,4[3]R,17[1]R,17[3]S)-4[2],4[2],17[2],17[2]-tetramethyl-2,8,13,19-tetraoxo-7,14-dioxa-4,17(1,3)-dicyclopropylaeicosaphane (**5**)[6] in 9.0 ml of dioxane was added. The reaction mixture was stirred for 48 h at room temperature (TLC control), then dioxane was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 ml), washed with water (3×5 ml), dried with $MgSO_4$, and the solvent was evaporated. The residue was washed with 10 ml of hexane by decantation and evaporated.

(1[1]S,1[3]R,14[1]R,14[3]S,16E,26E)-1[2],1[2],16,27,14[2],14[2]-Hexamethyl-5,10,19,24-tetraoxo-4,11-dioxa-17,18,25,26-tetraaza-1,14(1,3)-dicyclopropylaoctacosaphan-16,26-diene (6). Yield: 0.73 g (68 %). $[α]_D^{20}$ +3.4° (c 0.48; CH_2Cl_2). m/z $C_{32}H_{52}N_4O_6$ (588) (ESI, $I_{relative}$, %): Scan (+) 589 [M+H]+. Scan (–) 587 [M-H]-. IR (KBr) $ν_{max}$ cm-1: 1733 (-O-C=O), 1676 (-C=O). 1H NMR (CDCl3) $δ_H$ ppm: 0.57 (2H, d.t., J = 9.1, J = 7.0 Hz, H-1[3], H-14[1]), 0.76 (2H, d.t., J = 9.1, J = 7.2 Hz, H-1[1], H-14[3]), 0.90–0.97 (4H, m, H-2, H-13), 1.07 (6H, s, cis-CH₃-1[2], cis-CH₃-14[2]), 1.18 (6H, s, trans-CH₃-1[2], trans-CH₃-14[2]), 1.51–1.60 (4H, m, H-21, H-22), 1.60–1.70 (4H, m, H-7, H-8), 1.83 (6H, s, CH₃-16, CH₃-27), 2.00 (4H, t, J = 7.3 Hz, H-20, H-23), 2.17 (2H, d.d., J = 12.7, J = 5.9 Hz, H-15ₐ, H-28ₐ), 2.24 (2H, d.d., J = 12.7, J = 6.8 Hz, H-15_B, H-28_B), 2.21 (4H, t, J = 7.3 Hz, H-6, H-9), 4.02 (4H, t, J = 7.1 Hz, H-3, H-12), 8.27 (2H, br.s., NH). 13C NMR (CDCl3) $δ_C$ ppm: 14.98 (q, cis-CH₃-1[2], cis-CH₃-14[2]), 17.04 (q, CH₃-16, CH₃-27), 17.16 (s, C-1[2], C-14[2]), 21.22 (d, C-1[1], C-14[3]), 22.70 (d, C-1[3], C-14[1]), 24.14 (t, C-21, C-22), 24.41 (t, C-7, C-8), 28.75 (q, trans-CH₃-1[2], trans-CH₃-14[2]), 28.98 (t, C-2, C-13), 32.55 (t, C-6, C-9), 34.00 (t, C-20, C-23), 39.33 (t, C-15, C-28), 64.63 (t, C-3, C-12), 154.0 (s, C-16, C-27), 173.31 (s, C-5, C-10), 175.31 (s, C-19, C-24).

(1[1]S,1[2]R,13[1]S,13[2]R,3E,10E)-1[3],1[3],3,11,13[3],13[3]-Hexamethyl-16,23-dioxa-4,5,9,10-tetraaza-7(2,6)-pyridine-1,13(1,2)-dicyclopropancyclopentacosaphane-3,10-diene-6,8,17,22-tetraone (7). Yield: 0.55 g (43 %). $[α]_D^{20}$ +8.7° (c 0.02; CH_2Cl_2). m/z $C_{33}H_{47}N_5O_6$ (588) (ESI, $I_{relative}$, %): Scan (+): 610 [M+H]+ 628 [M+H+H₂O]+. IR (KBr) $ν_{max}$ cm-1: 1737 (-O-C=O), 1676 (-C=O). 1H NMR (CDCl3) $δ_H$ ppm: 0.59 (2H, d.t., J = 9.0, J = 7.1 Hz, H-1[2], H-13[2]), 0.83 (2H, d.t., J = 9.1, J = 7.2 Hz, H-1[1], H-13[1]), 0.92–0.97 (4H, m, H-14, H-25), 1.08 (6H, s, cis-CH₃-1[2], cis-CH₃-13[2]), 1.25 (6H, s, trans-CH₃-1[2], trans-CH₃-13[2]), 1.51–1.61 (4H, m, H-19, H-20), 2.00 (6H, s, CH₃-3, CH₃-11), 2.02 (6H, s, CH₃-3, CH₃-11), 2.10 (2H, d.d., J = 12.8, J = 6.0 Hz, H-2A, H-12A), 2.20 (2H, d.d., J = 12.7, J = 6.7 Hz, H-2B, H-12B), 2.29 (4H, t, J = 17.1 Hz, H-18, H-21), 4.05 (4H, t, J = 7.1 Hz, H-15, H-24), 8.05 (1H, d, J = 6.6 Hz, H-7[4]), 8.43 (2H, d, J = 7.6 Hz, H-7[3], H-7[5]), 10.31 (2H, s, H-5, H-9). 13C NMR (CDCl3) $δ_C$ ppm: 14.97 (q, cis-CH₃-1[2], cis-CH₃-13[2]), 17.03 (q, CH₃-3, CH₃-11), 17.49 (s, C-1[2], C-13[2]), 22.69 (d, C-1[1], C-13[1]), 24.41 (t, C-19, C-20), 28.74 (q, trans-CH₃-1[3], trans-CH₃-13[3]), 29.04 (t, C-14, C-15), 33.92 (t, C-18, C-21), 39.32 (d, C-2, C-12), 64.45 (t, C-15, C-24), 125.98 (d, C-7[3], C-7[5]), 139.40 (d, C-7[4]), 148.64 (s, C-7[2], C-7[6]), 158.91 (s, C-3, C-11), 161.04 (s, C-6, C-8), 173.31 (s, C-17, C-22).

(1[1]R,1[2]S,11[1]R,11[2]S,13E,23E)-1[3],1[3],11[3],11[3],13,24-Hexamethyl-4,8-dioxa-14,15,22,23-tetraaza-6(2,6)-pyridina-1,11(1,2)-dicyclopropanacyclopentacosaphane-13,23-diene-5,7,16,21-tetraone (8). Yield 0.41 g (60 %). $[α]_D^{20}$ +9.3° (c 0.03; CH_2Cl_2). m/z $C_{33}H_{47}N_5O_6$ (609) (ESI, $I_{relative}$, %): Scan (+) 610 [M+H]+, 618 [M+H+H₂O]+. IR (KBr) $ν_{max}$ cm-1: 1733 (-O-C=O), 1677 (-C=O), 1586 (Aryl). 1H NMR (CDCl3) $δ_H$ ppm: 0.89 (6H, s, cis-CH₃-1[2], cis-CH₃-11[2]), 1.01 (6H, s, trans-CH₃-1[2], trans-CH₃-11[2]), 1.17 (2H, t, J = 16.9 Hz, H-1[1], H-11[1]), 1.34 (2H, t, J = 17.1 Hz, H-1[3], H-11[3]), 1.55 (4H, t, J = 14.5 Hz, H-18, H-19), 1.62–1.72 (2H, m, H-2, H-10), 1.92 (4H, d, J = 7.3 Hz, H-12, H-25), 1.94 (6H, s, CH₃-13, CH₃-24), 2.16 (4H, t, J = 17.1 Hz, H-17, H-20), 4.23 (4H, t, J = 17.0 Hz, H-3, H-9), 8.40 (1H, d, J = 7.2 Hz, H-6[4]), 8.53 (2H, d, J = 7.3 Hz, H-6[3], H-6[5]), 12.60 (2H, br.s., H-15, H-22). 13C NMR (CDCl3) $δ_C$ ppm: 14.52

(q, CH₃-13, CH₃-24), 18.00 (s, C-1[2], C-11[2]), 19.41 (d, C-1[1], C-11[1]), 21.21 (q, cis-CH₃-1[3], cis-CH₃-11[3]), 21.50 (d, C-1[3], C-11[3]), 28.74 (t, trans-CH₃-1[3], trans-CH₃-11[3]), 30.70 (t, C-18, C-19), 31.53 (t, C-2, C-10), 34.61 (t, C-12, C-25), 40.94 (t, C-17, C-20), 63.10 (t, C-3,C-9), 127.90 (d, C-6[3], C-6[5]), 139.82 (d, C-6[4]), 147.63 (s, C-6[2], C-6[4]), 155.62 (s, C-13, C-24), 167.01 (s, C-5, C-7), 173.20 (s, C-16, C-21).

(1[1]R,1[2]S,11[1]R,11[2]S,13E,20E)-1[3],1[3],11[3],11[3],13,21-Hexamethyl-4,8-dioxa-14,15,19,20-tetraaza-6,17(2,6)-dipyridina-1,11(1,2)-dicyclopropanacyclodocosaphane-13,20-diene-5,7,16,18-tetraone (9). Yield 0.22 g (31 %). $[α]_D^{20}$ +5.7° (c 0.07; CH_2Cl_2). m/z $C_{34}H_{42}N_6O_6$ (630) (ESI, $I_{relative}$, %): Scan (+) 631 [M+H]+, 649 [M+H+H₂O]+. IR (KBr) $ν_{max}$ cm-1: 1740 (-O-C=O), 1679 (-C=O). 1H NMR (CDCl3) $δ_H$ ppm: 0.89 (6H, s, cis-CH₃-1[2], cis-CH₃-11[2]), 1.01 (6H, s, trans-CH₃-1[2], trans-CH₃-11[2]), 1.17 (2H, t, J = 17.1 Hz, H-1[1], H-11[1]), 1.34 (2H, t, J = 17.1 Hz, H-1[3], H-11[3]), 1.62–1.72 (2H, m, H-2, H-10), 1.92 (4H, d, J = 13.3 Hz, H-12, H-22), 1.94 (6H, s, CH₃-13, CH₃-24), 4.23 (4H, t, J = 17.0 Hz, H-3, H-9), 8.40 (1H, d, J = 7.3 Hz, H-6[4]), 8.53 (2H, d, J = 7.2 Hz, H-6[3], H-6[5]), 8.56 (1H, d, J = 7.3 Hz, H-17[4]), 8.80 (2H, d, J = 7.1 Hz, H-17[3], H-17[5]), 12.60 (2H, br.s., H-15, H-19). 13C NMR (CDCl3) $δ_C$ ppm: 14.51 (q, CH₃-13, CH₃-21), 18.00 (s, C-1[2], C-11[2]), 19.40 (d, C-1[1], C-11[1]), 21.21 (q, cis-CH₃-1[3], cis-CH₃-11[3]), 21.50 (d, C-1[3], C-11[3]), 28.74 (q, trans-CH₃-1[3], trans-CH₃-11[3]), 31.52 (t, C-2, C-10), 34.60 (t, C-12, C-22), 63.14 (t, C-3, C-9), 127.90 (d, C-6[3], C-6[5]), 139.82 (d, C-6[4]), 147.61 (s, C-6[2], C-6[4]), 155.60 (s, C-13, C-21), 167.10 (s, C-5, C-7), 173.25 (s, C-16, C-21).

Results and Discussion

The authors of the paper propose a new method for the synthesis of hydroxyketone **2** based on ozonolytic transformation of parent cycloolefin **1** into diol **3** and its chemoselective oxidation with a mixture of sodium hypochlorite and acetic acid. The total yield in this two-stage process is 82 %, this being commensurable to the yield (85 %) previously achieved during the reduction of peroxidation products of olefin **1** ozonolysis by sodium *tris*-acetoxyborohydride.[19] α,ω-Diketodiester **4** is synthesized using general method[6] with the yield of 67 %. The reaction of keto alcohol **2** [2+1]-condensation with dichloranhydride aromatic (2,6-pyridinedicarboxylic) acid gives α,ω-diketodiester **4** with a yield of 65 %. A slight decrease in the yield of ester **4** as compared to **5** is probably due to the nature of aromatic chloranhydride.

Previously, diketodiester **4** condensation was performed[6] with glutaric acid dihydrazide and the corresponding macroheterocycle **6** was obtained with a yield of 64 %. We have found that the interaction of this diketodiester **4** with adipic acid dihydrazide occurs with the formation of macrocycle **7** with a yield of 68 %, and consequently the reaction ability and propensity for the formation of macroheterocycles did not essentially depend on the length of the aliphatic dihydrazide carbon chain. During the interaction of diketodiester **4** with dihydrazide of aromatic (2,6-pyridinedicarboxylic) acid the yield of macroheterocycle **8** was only 43 %. This can be explained by the fact that the hydrazide has lower reaction ability as compared to adipic acid dihydrazide on account of conjugation between the undivided pairs of nitrogen atoms and the pyridine ring that decreases the basicity and nucleophilicity of NH_2 groups. One more reason for the lower yield of macroheterocycle **8** can be associated with the formation of a higher number of linear condensation products as compared to macrocyclic ones. The same tendency is observed during the [1+1]-condensation of α,ω-
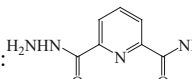
diketodiesters **5** with adipic or 2,6-pyridinedicarboxylic acid dihydrazides. The yield of macroheterocycle **9** is 60 %. It is somewhat lower than the yield of macroheterocycle **7** (68 %), which fact is probably associated with the influence of the ester fragment of 2,6-pyridinedicarboxylic acid either decreasing the activity of α,ω-diketodiester **4** or increasing

the propensity for the formation of linear condensation products. The lowest yield (31 %) is recorded for macroheterocycle (**10**), in which case both ester and dihydrazide fragments of 2,6-pyridinedicarboxylic acid exert their effects.

The structure of diketodiesters **4**, **5** and macroheterocycles **7–10** was determined using IR, ^{1}H and ^{13}C NMR
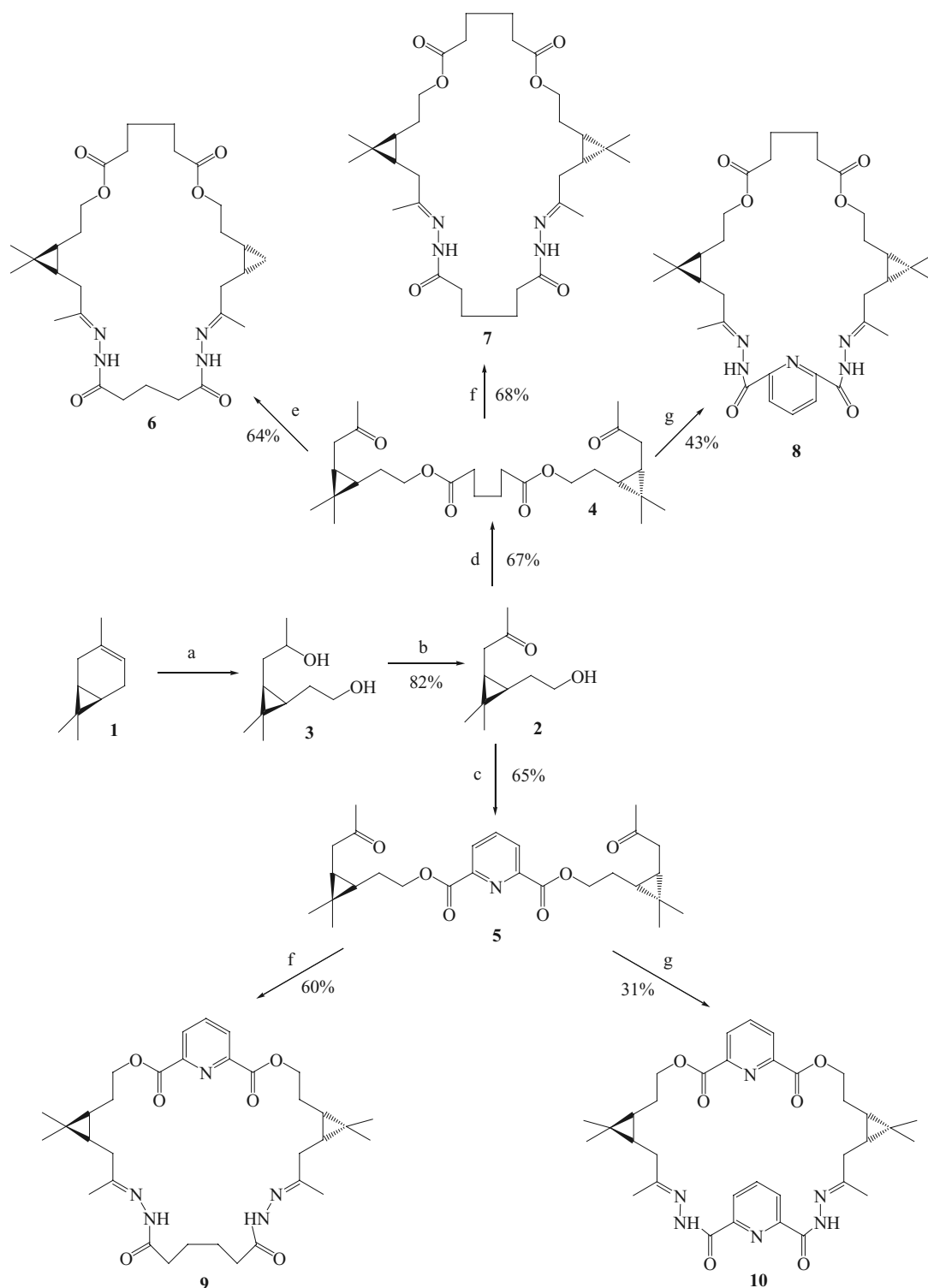
a: O$_3$ / MeOH, -40 °C; b: NaClO / AcOH; c: [structure], DMAP, CH$_2$Cl$_2$; d[8]; e: H$_2$NHNC(O)(CH$_2$)$_3$C(O)NHNH$_2$, dioxane-H$_2$O; f:

H$_2$NHNC(O)(CH$_2$)$_4$C(O)NHNH$_2$, dioxane-H$_2$O; g: [structure], dioxane-H$_2$O.

spectroscopy. The analysis of NMR spectra for compounds (**7–10**) was performed through comparison with those for parent diketoesters **4** and **5** and dicarboxylic acid hydrazides.

The ^{13}C NMR spectra of reaction products (**7–10**) have no signals of carbonyl carbon atoms [208.73 and 208.74 ppm], and the ^{1}H NMR spectrum has no signals [~4.8 ppm] of the hydrazine (NH_2NH) residue. These facts show that the obtained compounds are not the linear substitution products. Along with the signals of the carbon atom of the ester groups [173.31 ppm in (**7**) and (**8**), 173.20 ppm in (**9**) and 173.25 ppm in (**10**)] and those of the nitrogen atoms of the NH-C=O groups [175.31 ppm in (**7**), 161.04 ppm in (**8**), 167.01 ppm in (**9**) and 167.20 ppm in (**10**)], the ^{13}C NMR spectra of compounds (**7–10**) have singlet signals of the C=N group [154.00 ppm in (**7**), 155.91 ppm in (**8**), 155.62 ppm in (**9**) and 155.60 ppm in (**1**)] and two quartets of the CH_3 groups [17.04 ppm in (**7**), 17.03 ppm in (**8**), 14.52 ppm in (**9**) and 14.51 ppm in (**10**)]. Their chemical shift values correspond to the nitrogen atoms of two magnetically equivalent CH_3-C=N groups, this confirming the formation of the hydrazide ($CH_2C=N-NH-C=O$) grouping. The PMR spectra of macrocycles (**10–13**) have no proton signals of the hydrazine (NH_2NH) residue [~4.8 ppm]. Yet there are downfield signals [8.27 ppm in (**7**), 10.31 ppm in (**8**), 12.60 ppm in (**9**) and (**10**)], which correspond by their chemical shift values and integral intensities to two protons of the NHC=O macrocyclic groups. All these spectral data attest to the formation of macrocycles (**7–10**), this being additionally confirmed by the data of APCI mass spectra, where protonated and deprotonated ions and their water-molecule associates were clearly recorded.

Conclusions

Thus, this paper presents the research on the reaction ability and propensity for the formation of macroheterocycles of adipic and 2,6-pyridinedicarboxylic acid chloranhydrides and dihydrazides. It is revealed that the aromatic fragment reduces the yields of macrocycles due to a decrease in the reaction ability and an increase in the propensity for the formation of linear products. Since the optically active centres in molecules remain unaffected, the optical purity of all compounds corresponds to that of the parent carene (100 %).

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