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SYNTHESIS FROM *l*-MENTHOL OF OPTICALLY ACTIVE MACROHETEROCYCLES CONTAINING ESTER, AZINE, OR HYDRAZIDE GROUPS

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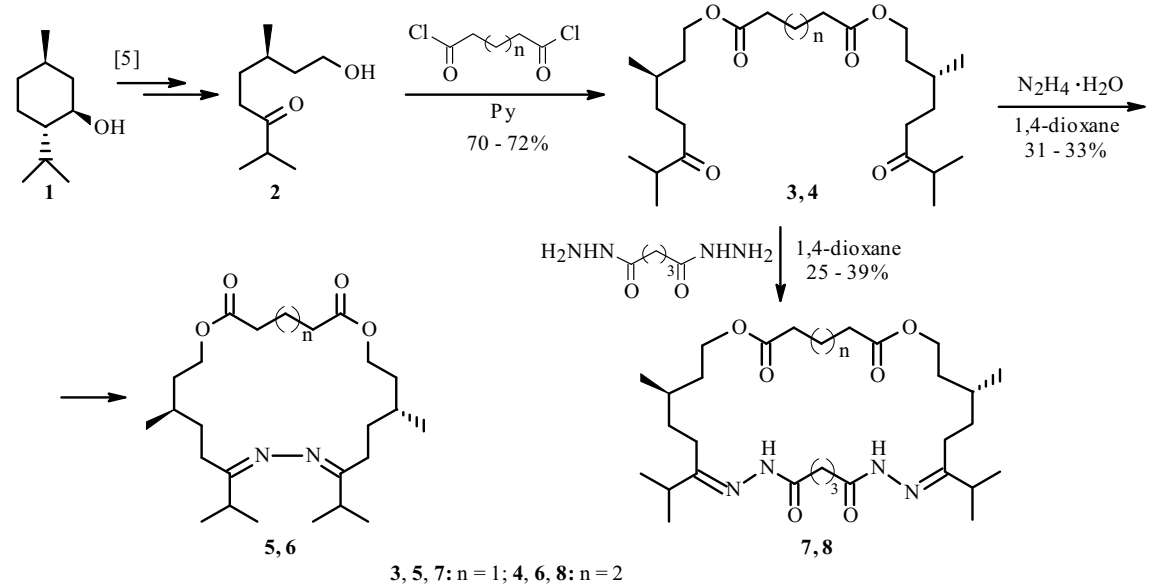
A synthesis of optically pure methyl- and isopropyl-branched 21-, 22-, 28-, and 29-membered azinodiesters and diesterdihydrazides from l-menthol using [2+1]-condensation of (6R)-8-hydroxy-2,6-dimethyloctan-3-one and glutaric and adipic acid chlorides and [1+1]-reaction of the intermediate diketodiesters with hydrazine hydrate and glutaric acid dihydrazide was developed.

Keywords: *l*-menthol, *bis*[(3′*R*)-3′,7′-dimethyl-6′-oxooctyl]pentanedioate, *bis*[(3′*R*)-3′,7′-dimethyl-6′-oxooctyl]hexanedioate, optically pure macrocyclic azinodiesters and diesterdihydrazides, synthesis.

Polyfunctional macroheterocycles are widely used as interphase transfer catalysts, extractants, analytical reagents, and materials for fabricating ion-selective electrodes. They are used to study the mechanisms of action and the creation of cardio- and psychotropic drugs and to develop antimicrobial, antiparasite, and antitumor drugs, etc. [1–4]. Therefore, the development of preparation methods of such compounds is critical for the advancement of modern chemistry and pharmacology.

Herein we report an effective synthetic pathway to optically pure methyl- and isopropyl-branched 21- (**5**), 22- (**6**), 28- (**7**), and 29-membered (**8**) macrolides with potentially complex-forming properties and biological activity that contain ester, azine, or hydrazide groups. The synthetic scheme is based on [2+1]-condensation of hydroxyketone **2**, which is accessible in three steps from natural *l*-menthol (**1**) [5], with glutaric and adipic acid dichlorides. Cyclization was effected via [1+1]-condensation of key diketodiesters **3** and **4** with hydrazine hydrate or glutaric acid dihydrazide in dioxane at room temperature with a reagent:solvent mole ratio of 1:70. Subsequent work up of the reaction products with CH_2Cl_2 and hexane in a 1:10 ratio isolated in satisfactory yields (25–39%) macrolides with azine (**5** and **6**) and hydrazide (**7** and **8**) groups.



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The chemical purity of **5**–**8** was established by HPLC. The structures were proved using IR, PMR, and ^{13}C NMR spectroscopy. The molecular weight was confirmed by GC/MS.

IR spectra of **5**–**8** lacked absorption bands that were characteristic of the ketones in key diketodiesters **3** (1712 cm^{-1}) and **4** (1710). The appearance in IR spectra of **5** and **6** of bands at 1635 cm^{-1} (C=N) and of **7** and **8**, at 1647 (C=N), 1660–1670 (CONH), and 3126–3420 (NH), proved that macrocycles with azine groups were formed.

NMR spectra of **5**–**8** were compared with those of the starting compounds, diketodiesters **3** and **4** and glutaric acid hydrazide. ^{13}C NMR spectra of reaction products **5**–**8** lacked resonances for the carbonyl C atoms of starting **3** (214.52 ppm) and **4** (213.99). PMR spectra of **7** and **8** did not show a resonance at 4.90 ppm for the hydrazine (NH_2NH) moiety. Therefore, the products were not linear substitution products.

The ^{13}C NMR spectra of **5** and **6** contained resonances for ester C atoms (172.82 ppm in **5** and 173.17 in **6**) in addition to singlets corresponding to the C=N group (168.89 ppm in **5** and 168.87 in **6**), which was consistent with the formation of macrocycles with an azine group in the ring.

Analogously to ^{13}C NMR spectra of **5** and **6**, those of **7** and **8** showed resonances for ester C atoms (172.87 ppm in **7** and 173.07 in **8**), the C atom of an NH–C=O group (175.48 in **7** and **8**) that was shifted compared with that of the starting dihydrazides (171.89), and singlets for the C=N group (158.50 in **7** and 158.69 in **8**). PMR spectra of these macrocycles had weak-field resonances (8.50 ppm in **7** and 8.30 in **8**), the chemical shifts and integrated intensities of which corresponded to two protons of NHC=O groups in the macrocycles.

Resonances of C atoms in NHC=O groups were noticeably broadened in the ^{13}C NMR spectra of **7** and **8** compared with those of the corresponding atoms in the starting glutaric acid dihydrazide. This was probably due to inter- and intramolecular interactions in the macrocycles. These spectral data indicated that macrocycles **7** and **8** had formed, which was also confirmed by mass spectral data. Compounds **5**–**8** were studied using atmospheric pressure chemical ionization (APCI) with detection of positive and negative ions (20 eV). The capability for protonation and solvation by H_2O is well known in the chemistry of amides and hydrazides [6], because of which the APCI method was used. Mass spectra of **3**–**8** detected very strong peaks for protonated $[MH]^+$ and deprotonated $[M - H]^-$ ions in addition to ion associates with H_2O. This could be considered proof of the existence of compounds with the corresponding molecular weights.

EXPERIMENTAL

IR spectra were recorded from thin layers on a Shimadzu Prestige-21 IR instrument. NMR spectra were recorded from $CDCl_3$ solutions with TMS internal standard on a Bruker AM-300 spectrometer (operating frequency 300.13 MHz for ^1H; 75.47, ^{13}C). Chromatographic analysis was performed in a Chrom-5 instrument [column length 1.2 m, silicone SE-30 stationary phase (5%) on Chromaton N-AW-DMCS (0.16–0.20 mm), operating temperature 50–300°C] with He carrier gas. Column chromatography used SiO_2 (70–230) (Lancaster, England). TLC monitoring used Sorbfil SiO_2 (Russia). Elemental analyses of all compounds agreed with those calculated. Mass spectra of **3**–**8** were taken in a Shimadzu LC-MS 2010EV using APCI conditions with electron energy 20 eV and detection of positive and negative ions. The liquid mobile phase was H_2O at flow rate 0.03 mL/min. HPLC analyses were carried out in a Shimadzu-LC-20AD with an SPD-M20A diode-matrix detector (Shimadzu, Japan) using a Phenomenex column (250 × 4.6 mm) and Luna C18 sorbent with particle size 5 μm. The mobile phase was H_2O:CH_3CN at flow rate 1 mL/min. The analytical wavelength was 215 nm. Petroleum ether (40–70°C), CH_2Cl_2, and Py were used for the reactions.

General Method for Preparing Diketodiesters 3 and 4. A solution of hydroxyketone **2** (2.0 mmol) [5] in anhydrous Py (1 mL) was stirred, treated with a solution of the chloride of the appropriate dicarboxylic acid (1.0 mmol) [7] in anhydrous Et_2O (1 mL), diluted after 48 h (TLC monitoring) with CH_2Cl_2 (10 mL), washed successively with HCl solution (5%, 3 × 1.5 mL) and saturated NaCl solution (3 × 1.5 mL), dried over $MgSO_4$, and evaporated. The solid was chromatographed (SiO_2, petroleum ether:MTBE (*tert*-butyl methyl ether), 5:1) to afford the corresponding diketodiester.

***Bis*[(3′*R*)-3′,7′-dimethyl-6′-oxooctyl]pentanedioate (3).** Yield 0.15 g (70%), $[\alpha]_D^{20}$ +5.90° (*c* 0.65, CH_2Cl_2), R_f 0.80. IR spectrum (KBr, ν, cm^{-1}): 1735 (O=C—O), 1712 (C=O),

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.91 (6H, d, J = 6.1, CH_3-3′), 1.09 (12H, d, J = 6.9, H-8′), 1.35–1.72 (10H, m, H-2′, H-3′, H-4′), 1.93 (2H, t, J = 6.8, H-3), 2.35 (4H, t, J = 7.3, H-2, H-4), 2.45 (4H, t, J = 6.4, H-5′), 2.62 (2H, sept, J = 6.8, H-7′), 4.13 (4H, t, J = 6.8, H-1′).

^{13}C NMR spectrum ($CDCl_3$, δ): 18.21 (q, $\underline{C}H_3$-C-7′), 19.14 (q, $\underline{C}H_3$-C-3′), 20.03 (t, C-3), 29.42 (d, C-3′), 30.40 (t, C-4′), 33.20 (t, C-2, C-4), 35.23 (t, C-2′), 37.65 (t, C-5′), 40.68 (d, C-7′), 62.58 (t, C-1′), 172.81 (s, C-1, C-5), 214.52 (s, C-6′).

Mass spectrum (APCI, 20 eV, *m*/*z*): 441 $[M + H]^+$, 459 $[M + H + H_2O]^+$, 439 $[M - H]^-$.

***Bis*[(3′*R*)-3′,7′-dimethyl-6′-oxooctyl]hexanedioate (4).** Yield 0.16 g (72%), $[\alpha]_D^{20}$ +5.00° (*c* 0.73, CH_2Cl_2), R_f 0.82. IR spectrum (KBr, ν, cm^{-1}): 1732 (O=C—O), 1710 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.90 (6H, d, J = 6.1, CH_3-3′), 1.08 (12H, d, J = 6.8, H-8′), 1.35–1.54 (10H, m, H-2′, H-3′, H-4′), 1.55–1.71 (4H, m, H-3, H-4), 2.31 (4H, t, J = 6.6, H-2, H-5), 2.45 (4H, t, J = 7.3, H-5′), 2.62 (2H, sept, J = 6.9, H-7′), 4.13 (4H, t, J = 7.0, H-1′).

^{13}C NMR spectrum ($CDCl_3$, δ): 17.93 (q, $\underline{C}H_3$-C-7′), 18.88 (q, $\underline{C}H_3$-C-3′), 24.02 (t, C-3, C-4), 28.21 (d, C-3′), 29.16 (t, C-4′), 33.50 (t, C-2, C-5), 34.97 (t, C-2′), 37.37 (t, C-5′), 40.40 (d, C-7′), 62.18 (t, C-1′), 172.89 (s, C-1, C-6), 213.99 (s, C-6′).

Mass spectrum (APCI, 20 eV, *m*/*z*): 455 $[M + H]^+$, 473 $[M + H + H_2O]^+$, 453 $[M - H]^-$.

General Method for Preparing Macrocycles 5 and 6. The *bis*-derivative of hydroxyketone **3** or **4** (1.0 mmol) in anhydrous dioxane (6 mL) was stirred vigorously, treated slowly dropwise with hydrazine hydrate (1.0 mmol, 92%), and stirred for 24 h (TLC monitoring). The dioxane was evaporated at reduced pressure. The solid was dissolved in CH_2Cl_2 (10 mL), washed with H_2O (3 × 3 mL), dried over $MgSO_4$, and evaporated. The resulting residue was stirred and treated successively with anhydrous CH_2Cl_2 (1 mL) and hexane (10 mL) and stored until the layers separated, the upper of which was decanted. The residue was washed with hexane (3 mL) and evaporated *in vacuo*.

(10*R*,19*R*)-13,16-Diisopropyl-10,19-dimethyl-1,7-dioxo-14,15-diazacycloheneicosa-13,15-dien-2,6-dione (5). Yield 0.14 g (33%), $[\alpha]_D^{20}$ +5.00° (*c* 1.83, CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 1730 (O=C—O), 1635 (C=N).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.92 (6H, d, J = 6.5, CH_3-10, CH_3-19), 1.12 [12H, d, J = 6.8, CH_3-(i-Pr)], 1.35–1.64 (6H, m, H-10, H-11, H-18, H-19), 1.63–1.74 (4H, m, H-9, H-20), 1.95 (2H, pent, J = 7.4, H-4), 2.15–2.32 (4H, m, H-12, H-17), 2.36 (4H, t, J = 7.4, H-3, H-5), 2.51 [2H, sept, J = 6.8, CH-(i-Pr)], 4.09 (4H, t, J = 6.9, H-8, H-21).

^{13}C NMR spectrum ($CDCl_3$, δ): 19.08 (q, $\underline{C}H_3$-C-10, $\underline{C}H_3$-C-19), 19.95 (t, C-4), 20.17 [q, CH_3-(*i*-Pr)], 27.11 (t, C-12, C-17), 30.31 (d, C-10, C-19), 32.65 (t, C-11, C-18), 33.12 (t, C-3, C-5), 35.01 (t, C-9, C-20), 35.14 [d, CH-(*i*-Pr)], 62.65 (t, C-8, C-21), 168.89 (s, C-13, C-16), 172.82 (s, C-2, C-6).

Mass spectrum (APCI, 20 eV, *m*/*z*): 437 $[M + H]^+$, 455 $[M + H + H_2O]^+$, 435 $[M - H]^-$.

(11*R*,20*R*)-14,17-Diisopropyl-11,20-dimethyl-1,8-dioxo-15,16-diazacyclodocosa-14,17-dien-2,7-dione (6). Yield 0.13 g (31%), $[\alpha]_D^{20}$ +5.10° (*c* 0.23, CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 1732 (O=C–O), 1635 (C=N).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.91 (6H, d, J = 6.1, CH_3-11, CH_3-20), 1.12 [12H, d, J = 6.7, CH_3-(i-Pr)], 1.36-1.62 (10H, m, H-10, H-11, H-12, H-19, H-20, H-21), 1.61-1.69 (4H, m, H-4, H-5), 2.14-2.26 (4H, m, H-13, H-18), 2.31 (4H, t, J = 7.0, H-3, H-6), 2.51 [2H, sept, J = 6.9, CH-(i-Pr)], 4.08 (4H, t, J = 6.9, H-9, H-22).

^{13}C NMR spectrum ($CDCl_3$, δ): 18.98 (q, $\underline{C}H_3$-C-11, $\underline{C}H_3$-C-20), 20.14 [q, CH_3-(*i*-Pr)], 24.18 (d, C-4, C-5), 27.09 (t, C-13, C-18), 30.30 (d, C-11, C-20), 32.64 (t, C-12, C-19), 33.69 (t, C-3, C-6), 34.92 (t, C-10, C-21), 35.10 [d, CH-(*i*-Pr)], 62.54 (t, C-9, C-22), 168.87 (s, C-14, C-17), 173.17 (s, C-2, C-7).

Mass spectrum (APCI, 20 eV, *m*/*z*): 451 $[M + H]^+$, 469 $[M + H + H_2O]^+$, 449 $[M - H]^-$.

General Method for Preparing Macrocycles 7 and 8. Diketodiester (**3** or **4**, 1.0 mmol) in anhydrous dioxane (6 mL) was stirred vigorously, treated slowly with glutaric acid dihydrazide (0.16 g, 1.0 mmol) [7], and stirred for 48 h (TLC monitoring). The dioxane was evaporated. The residue was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (3 × 5 mL), dried over $MgSO_4$, and evaporated. The resulting residue was stirred, treated successively with anhydrous CH_2Cl_2 (1 mL) and hexane (10 mL), and stored until the layers separated, the upper of which was decanted. The residue was washed with hexane (5 mL) and evaporated.

(10*R*,26*R*)-13,23-Diisopropyl-10,26-dimethyl-1,7-dioxo-14,15,21,22-tetraazacyclooctacosa-13,22-dien-2,6,16,20-tetraone (7). Yield 0.22 g (39%), $[\alpha]_D^{20}$ +4.86° (*c* 0.33, CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 3420 (NH), 1660 (CONH), 1647 (C=N).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.89 (6H, d, J = 6.5, CH_3-10, CH_3-26), 1.09 [12H, d, J = 6.8, CH_3-(i-Pr)], 1.35–1.55 (6H, m, H-10, H-11, H-25, H-26), 1.55–1.70 (4H, m, H-9, H-27), 1.92 (2H, pent, J = 6.9, H-4), 2.03 (2H, m, H-18), 2.12–2.30 (4H, m, H-17, H-19), 2.34 (4H, t, J = 6.9, H-3, H-5), 2.40–2.48 (4H, m, H-12, H-24), 2.58 [2H, sept, J = 6.8, CH-(i-Pr)], 4.09 (4H, t, J = 6.9, H-8, H-28), 8.50 (2H, br.s, N$\underline{H}$).

^{13}C NMR spectrum ($CDCl_3$, δ): 18.23 [q, CH_3-(*i*-Pr)], 20.06 (d, C-4), 20.15 (q, $\underline{C}H_3$-C-10, $\underline{C}H_3$-C-26), 25.43 (t, C-18), 29.47 (d, C-10, C-26), 30.45 (t, C-12, C-24), 32.33 (t, C-11, C-25), 33.24 (t, C-3, C-5), 35.25 (t, C-17, C-19), 35.55 [d, CH-(*i*-Pr)], 37.69 (t, C-9, C-27), 62.65 (t, C-8, C-28), 158.50 (s, C-13, C-23), 172.87 (s, C-2, C-6), 175.48 (s, C-16, C-20).

Mass spectrum (APCI, 20 eV, *m*/*z*): 565 $[M + H]^+$, 583 $[M + H + H_2O]^+$, 563 $[M - H]^-$.

(4*R*,20*R*)-7,17-Diisopropyl-4,20-dimethyl-1,23-dioxo-8,9,15,16-tetraazacyclononacosa-7,16-dien-10,14,24,29-tetraone (8). Yield 0.14 g (25%), $[\alpha]_D^{20}$ +4.90° (*c* 0.30, CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 3126 (NH), 1670 (CONH), 1647 (C=N).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.89 (6H, d, J = 6.7, CH_3-11, CH_3-27), 1.06 [12H, d, J = 6.8, CH_3-(i-Pr)], 1.35–1.52 (6H, m, H-11, H-12, H-26, H-27), 1.52–1.70 (4H, m, H-10, H-28), 1.95–2.08 (6H, m, H-4, H-5, H-19), 2.09 [2H, sept, J = 6.8, CH-(i-Pr)], 2.25–2.33 (4H, m, H-18, H-20), 2.33 (4H, t, J = 6.9, H-3, H-6), 2.40–2.48 (4H, m, H-13, H-25), 4.08 (4H, t, J = 6.9, H-9, H-29), 8.30 (2H, br.s, N$\underline{H}$).

^{13}C NMR spectrum ($CDCl_3$, δ): 18.20 [q, CH_3-(*i*-Pr)], 19.90 (q, $\underline{C}H_3$-C-11, $\underline{C}H_3$-C-27), 24.12 (t, C-4, C-5), 25.18 (t, C-19), 29.27 (d, C-11, C-27), 30.26 (t, C-13, C-25), 32.12 (t, C-12, C-26), 33.63 (t, C-3, C-6), 35.05 (t, C-18, C-20), 35.49 [d, CH-(*i*-Pr)], 37.51 (t, C-10, C-28), 62.37 (t, C-9, C-29), 158.69 (s, C-14, C-24), 173.07 (s, C-2, C-7), 175.48 (s, C-17, C-21).

Mass spectrum (APCI, 20 eV, *m*/*z*): 579 $[M + H]^+$, 597 $[M + H + H_2O]^+$, 577 $[M - H]^-$.

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