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SYNTHESIS FROM L-MENTHOL OF OPTICALLY ACTIVE MACROLIDES WITH *N*-CONTAINING (AZINE OR HYDRAZIDE) GROUPS

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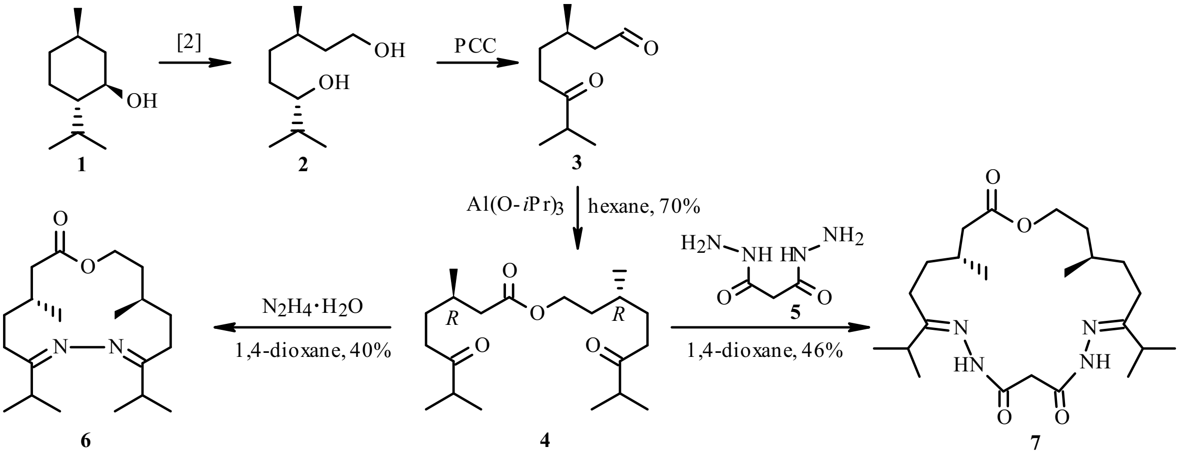
Potentially useful 15- and 20-membered macrolides containing azine or hydrazide groups were synthesized from L-menthol via [1+1]-condensation at room temperature of 3R*,7-dimethyl-6-oxooctyl-*3R*,7-dimethyl-6-oxooctanoate, which was obtained from* 3R*,7-dimethyl-6-oxooctanal via a Tishchenko reaction, with hydrazine hydrate or malonic acid dihydrazide.*

Key words: L-menthol, 3*R*,7-dimethyl-6-oxooctyl-3*R*,7-dimethyl-6-oxooctanoate, macrolide, azine, hydrazide, synthesis.

Functionalized macrocycles are widely used in organic and petrochemical syntheses, detection and separation of metals by extraction, sorption and chromatographic analytical methods, and measurements of ions [1]. Mechanisms of action and creation of cardio- and psychotropic agents have been studied. Antimicrobial, antiparasitic, antitumor, and other preparations have been developed.

Herein we report the efficient synthesis of 15- and 20-membered macrolides containing azine or hydrazide functional groups. The synthetic scheme was based on chemo- and regioselective transformations of diol **2**, which was obtained in three steps from L-menthol (**1**) [2]. Corey oxidation of **1** gave ketoaldehyde **3**, which has been used to synthesize a whole series of insect pheromones [3], and small quantities of 3*R*,7-dimethyl-6-oxooctyl-3*R*,7-dimethyl-6-oxooctanoate (**4**), the disproportionation product of **3** via a Tishchenko reaction. The yield of **3** could be increased (up to 70%) by carrying out the classical reaction in the presence of catalytic amounts of aluminium triisopropoxide. [1+1]-Condensation of resulting diketoester **4** in dioxane at high dilution and room temperature with hydrazine hydrate or malonic acid dihydrazide (**5**) and subsequent successive treatment of the reaction mixture with CH_2Cl_2 and hexane (1:10 ratio) produced in good yields (40–50%) macrolides with azine (**6**) or hydrazide (**7**) fragments, respectively.



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Structures of the resulting macrocycles were elucidated using PMR and ^{13}C NMR spectroscopy. NMR spectra of **6** and **7** were analyzed by comparison with spectra of starting **4** and **5**.

^{13}C NMR spectra of **6** and **7** lacked resonances of starting **4** for carbonyl C atoms (214.13 and 214.42 ppm) and the corresponding C atoms of CH_2- and CH-groups in the α-position to the ketone (35.08 and 37.53). Furthermore, the PMR spectrum of **7** did not show a resonance for a hydrazine group (4.75 ppm). Therefore, the products were not acyclic substitution products. The ^{13}C NMR spectrum of **6** contained a singlet for a carboxyl group (170.64 ppm) and a singlet for C=N groups (169.24). This indicated that a macrocycle with an azine group had formed.

In analogy to **6**, the ^{13}C NMR spectrum of **7** exhibited a resonance for an ester C atom (170.82 ppm) and for an NH–C=O C atom (170.51) that was shifted relative to the starting dihydrazide (170.79) in addition to a singlet for C=N groups (168.80). The PMR spectrum of **7** showed a weak-field resonance (8.50 ppm), the chemical shift and integrated intensity of which corresponded to two amide protons of NHC=O groups of the macrocycles.

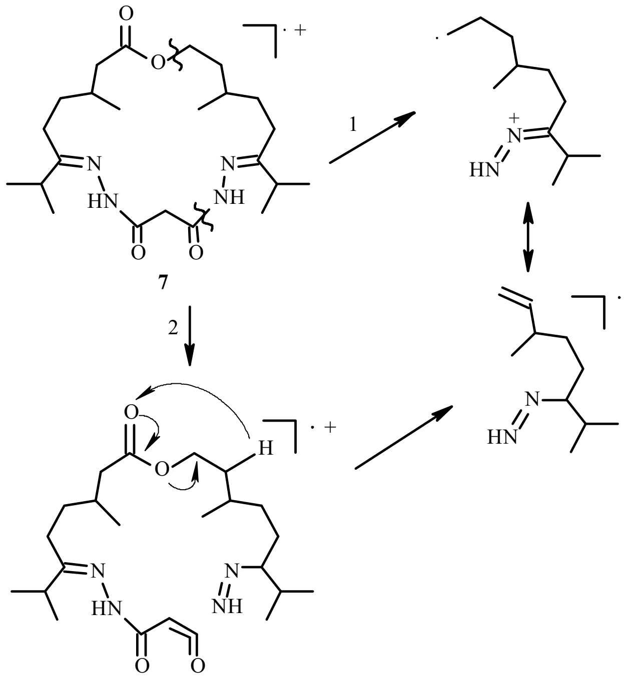
Resonances of NHC=O C atoms in the ^{13}C NMR spectrum of **7** were noticeably broadened compared with those of the corresponding C atoms of starting **5**. This was probably related to a tautomeric transition in the hydrazide group of the macrocycle.

Synthesized macrolides **6** and **7** were also studied using atmospheric pressure chemical ionization (APCI) with detection of positive and negative ions (20 eV) and using electron-impact ionization (EI, 70 eV). Because the studied compounds were extremely unstable adducts, especially under the high-vacuum conditions used for mass spectrometry, the APCI spectra were obtained first. Very strong peaks of protonated MH^+ and deprotonated $[M - H]^-$ ions and those of ionic associates with 1–2 water molecules were detected. The ability for protonation and solvation by water is well known in the chemistry of amides and hydrazides [4]. This dictated the initial study using APCI.

The EI mass spectrum of **7** was obtained in order to confirm the corresponding elemental composition and structures of **6** and **7**. Compound **7** contained an ester and two C=NNHC=O groups separated by a methylene group.

The mass spectrum of **7** showed a peak for M^+ at 436.3016, exact mass measurement of which agreed with the proposed empirical formula $C_{23}H_{40}N_4O_4$ (calc. 436.3050). The peak for the molecular ion (MI) was rather strong (17.2% of the base peak). This indicated that the opened species made a small contribution. Apparently the isopropyl substituents have a negative effect on transangular interactions in the MI (steric effect).

Peaks for *N*-containing fragments were most numerous in the spectrum of **7**. Series of ions $[C_nH_{2n}N_2]^+$, $[C_nH_{2n-1}N_2]^+$, and $[C_nH_{2n-2}N_2]$+ were observed. Fragmentation of the MI of **7** typically involved C(=O)–NH and C–C (and/or O–C) bonds in the β-position to double bonds. Therefore, the base peak was $[C_{10}H_{20}N_2]^+$ with *m/z* 168.1591 (calc. 168.1626), which was produced either through two simple β-cleavages of O–C and C(=O)–NH bonds (direction 1) [5] or alternatively (direction 2) through two successive MacLafferty rearrangements with opening of the macrocycle in an intermediate step [6].



Introduction of methyl substituents in the β- and γ-positions relative to the ester CO and O groups, respectively, opened fragmentation pathways of M^+ through cleavage of C–C bonds of tertiary C atoms. Fragments $[M - C_6H_9O]^+$, $[M - C_6H_{11}O_2]^+$, and $[M - C_6H_{12}O_2]^+$ were observed. The resulting peaks with *m/z* 253 and 125 were obviously due to cleavages of isopropyl groups from fragments with *m/z* 296 and 168, respectively.

Thus, the mass spectrometric study of **6** and **7** led to the following conclusions.

Because peaks of protonated positive MH^+ and deprotonated negative $[M - H]^-$ ions were detected in APCI spectra of **6** and **7**, the appearance of this tendency could be considered proof of the existence of compounds with the corresponding molecular weights. Analysis of structurally specific ions allowed the EI mass spectrum of **7** to be interpreted as that of a 20-membered macrolide with a hydrazide group.

EXPERIMENTAL

IR spectra in thin layers were recorded on a UR-20 instrument. NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 with TMS internal standard and in D_2O with DSS internal standard on a Bruker AM-300 spectrometer (operating frequency 300.13 MHz for ^1H; 75.47, ^{13}C). Chromatography was carried out in Chrom-5 [column length 1.2 m, stationary phase SE-30 (5%) silicone on Chromaton N-AW-DMCS (0.16–0.20 mm), 50–300°C] and Chrom-41 [column length 2.4 m, stationary phase PEG-6000, 50–200°C] instruments with He carrier gas. HPLC was performed on a Shimadzu-LC-20AD liquid chromatograph with an SPD-M20A diode-array detector (Shimadzu, Japan) using a Phenomenex column (250 × 4.6 mm) with Luna C18 sorbent (5 μm). The mobile phase was $H_2O:CH_3CN$ at flow rate 1 mL/min. The analytical wavelength was 215 nm. 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. The mass spectrum of **7** was obtained in a Finnigan MAT 95 XP instrument with a DEC Alpha Station 433 au data processing system at source temperature 250°C and ionizing electron energy 70 eV. Direct sample introduction into the ion source was used. Exact masses of ions were determined in the range 1–3500 D with 10,000 resolution for all significant ions using peak overlap methods. Perfluorokerosene was used as a standard. Mass spectra of compounds were recorded on a Shimadzu LCMS 2010 EV instrument using APCI with electron energy 20 eV and detection of positive and negative ions. The liquid mobile phase was H_2O and/or CH_3CN at flow rate 0.02 mL/min.

3*R*,7-Dimethyl-6-oxooctanal (3) and 3′*R*,7′-Dimethyl-6′-oxooctyl-3*R*,7-dimethyl-6-oxooctanoate (4). a). A suspension of pyridinium chlorochromate (PCC, 5.31 g, 24.4 mmol) in anhydrous CH_2Cl_2 (66 mL) was stirred (20°C, Ar), treated with a solution of **2** (1.70 g, 9.8 mmol) that was obtained from L-menthol (**1**) [2] in CH_2Cl_2 (24 mL), stirred for 2 h at room temperature, diluted with Et_2O (125 mL), and filtered through a layer of SiO_2. The filtrate was evaporated to afford a mixture of **4** (1.26 g, 15% by GC) and **3** (85%), which was chromatographed (SiO_2, petroleum ether:EtOAc, 7:3) to afford **3** (1.07 g, 65%, R_f 0.44) and **4** (0.33 g, 10%, R_f 0.57). The IR and NMR spectra of **3** and **4** were identical to those published previously [2].

b). A solution of **3** (1.00 g, 5.9 mmol) in petroleum ether (10 mL) was treated at room temperature with aluminium triisopropoxide (0.05 g, 0.2 mmol) and stirred for 48 h. Solvent was evaporated. The solid was chromatographed (SiO_2, petroleum ether:Et_2O, 7:3) to afford **4** (0.56 g, 70%), $[\alpha]_D^{20}$ +2.0° (*c* 1.40, CH_2Cl_2).

7,10-Diisopropyl-4*R*,13*R*-dimethyl-1-oxa-8,9-diaza-7,9-cyclopentadecadien-2-one (6). A solution of **4** (0.34 g, 1.0 mmol) in anhydrous dioxane (30 mL) was stirred vigorously, treated dropwise with hydrazine hydrate (0.51 g, 1.0 mmol), and stirred for 48 h until **4** disappeared (TLC monitoring). Dioxane was evaporated at reduced pressure. The solid was dissolved in CH_2Cl_2 (20 mL), washed with water (3 × 5 mL), and dried over $MgSO_4$. The solvent was evaporated. The resulting solid was treated with stirring successively with anhydrous CH_2Cl_2 (1 mL) and hexane (10 mL). The layers were allowed to separate. The upper layer was decanted. The remainder was washed with hexane (5 mL) and evaporated in vacuo to afford **6** (0.13 g, 40%), $[\alpha]_D^{20}$ +5.0° (*c* 1.96, CH_2Cl_2). IR spectrum (ν, cm^{-1}): 1735 (O=C–O), 1639 (C=N), 1030 (C–O–C).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.89, 1.13 (each 3H, both d, J = 6.7, CH_3), 1.03 [12H, d, J = 6.7, $(C\mathbf{H}_3)_2CH$], 1.30–2.55, 1.90–2.25 (each 1H, m, $CH_3C\mathbf{H}$), 1.30–1.52, 1.50–1.65 (each 2H, m, CH_2), 2.08 (2H, dd, ^2J = –14.8, ^3J = 6.7, $C\mathbf{H}_2COO$), 2.42–2.53 (4H, m, $CH_2C=N$), 4.05 (2H, t, J = 7.8, CH_2O), 2.50–2.68 [2H, m, $(CH_3)_2C\mathbf{H}$].

^{13}C NMR spectrum ($CDCl_3$): 19.88, 20.70 (both q, CH_3), 20.41 [q, $(\mathbf{C}H_3)_2CH$], 27.03 [d, $(CH_3)_2\mathbf{C}H$], 33.35, 34.62 (t, CH_2), 34.92 (t, $\mathbf{C}H_2COO$), 30.15, 35.03 (both d, CH_3CH), 35.03 (t, $\mathbf{C}H_2C=N$), 62.63 (t, CH_2O), 169.24 (s, C=N), 170.64 (s, COO).

APCI mass spectrum (20 eV, MW, ion type, *m/z*): MW 336. MH^+ 337, $[MH + H_2O]^+$ 355, $[MH + 2H_2O]^+$ 373; $[M – H]^-$ 335, $[M + H_2O – H]^-$ 353.

7,15-Diisopropyl-4*R*,18*R*-dimethyl-1-oxa-8,9-13,14-tetraaza-7,14-cycloeicosadien-2,10,12-trione (7). A solution of **4** (0.34 g, 1.0 mmol) in anhydrous dioxane (30 mL) was stirred vigorously, treated slowly with dicarboxylic acid dihydrazide (**5**, 0.13 g, 1.0 mmol) obtained as before [6], and stirred for 48 h until **4** disappeared (TLC monitoring). Dioxane was evaporated at reduced pressure. The solid was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (3 × 5 mL), and dried over $MgSO_4$. Solvent was evaporated. The resulting solid was treated with stirring successively with anhydrous CH_2Cl_2 (1 mL) and hexane (10 mL). The layers were allowed to separate. The upper layer was decanted. The remainder was washed with hexane (5 mL) and evaporated in vacuo to afford **7** (0.17 g, 46%), $[\alpha]_D^{20}$ +7.5° (*c* 0.63, CH_2Cl_2). IR spectrum (ν, cm^{-1}): 3400 (NH), 1735 (O=C–O), 1675 (CONH), 1639 (C=N), 1030 (C–O–C).

^{13}C NMR spectrum ($CDCl_3$): 18.91, 20.70 (both q, CH_3), 20.05 [q, $(\mathbf{C}H_3)_2CH$], 28.89 [d, $(CH_3)_2\mathbf{C}H$], 30.16, 35.15 (both d, $CH_3\mathbf{C}H$), 32.53, 34.62 (t, CH_2), 34.93 (t, $\mathbf{C}H_2C{=}N$), 35.03 (t, $\mathbf{C}H_2COO$), 37.42 (t, $O{=}C\mathbf{C}H_2C{=}O$), 62.46 (t, CH_2O), 168.80 (s, C=N), 170.51 (s, NHC=O), 170.82 (s, COO).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.89, 0.95 (each 3H, both d, J = 6.8, CH_3), 1.02 [12H, d, J = 6.6, $(C\mathbf{H}_3)_2CH$], 1.25–1.50, 1.50–1.75 (each 2H, m, CH_2), 2.09–2.20 (4H, m, CH_2COO, $2CH_3C\mathbf{H}$), 2.30–2.50 [2H, m, $(CH_3)_2C\mathbf{H}$], 2.30–2.55 (4H, m, $CH_2C{=}N$), 3.60 (2H, s, $O{=}CCH_2C{=}O$), 4.06 (2H, t, J = 7.6, CH_2O), 8.50 (2H, br.s, NH).

APCI mass spectrum (20 eV, ion type, *m/z*): MH^+ 437, $[M – H]^-$ 435, $[M + H_2O – H]^-$ 453.

EI mass spectrum (ion type, measured exact mass, I_{rel}, %, elemental formula, calc. exact mass): M^+ 436.3016 (17.2, $C_{23}H_{40}N_4O_4$, 436.3050), $[M – C_6H_9O]^+$ 339.2463 (6.8, $C_{17}H_{31}N_4O_3$, 339.2447), $[M – C_6H_{11}O_2]^+$ 321.2399 (18.9, $C_{17}H_{29}N_4O_2$ 321.2369), $[M – C_8H_{12}O_2]^+$ 296.2327 (35.1, $C_{15}H_{28}N_4O_2$, 296.2212), 253.1785 (69.2, $C_{12}H_{21}N_4O_2$, 251.1665), 212.1553 (33.1, $C_{11}H_{20}O_2$, 212.1525), 181.1623 (34.3, $C_{11}H_{21}N_2$, 181.1705), 168.1537 (100, $C_{10}H_{20}N_2$, 168.1626), 125.1034 (30.2, $C_7H_{13}N_2$, 125.1079), 55 (41.5).

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