Макрогетероциклы
http://macroheterocycles.isuct.ru

DOI: 10.6060/mhc2012.120359y

Synthesis of Optically Pure Macroheterocycle with Ester and Hydrazide Fragments on the Basis of *l*−Menthol

Gumer Yu. Ishmuratov, Marina P. Yakovleva,@ Galina R. Mingaleeva, Mariya A. Shutova, Rinat R. Muslukhov, Evgeny M. Viripaev, and Alexander G. Tolstikov

Institute of Organic Chemistry, Ufa Scientific Centre of RAS, 450054 Ufa, Russia
@Corresponding author E-mail: insect@anrb.ru

Based on l-menthol we have developed a synthesis method for potentially useful optically pure methyl- and isopropyl-branched 21-member macrolide with hydrazide and ester fragments via sequential [2+1]-condensation of methyl-(3R,6S)-6-hydroxy-3,7-dimethyl octanoate with glutaric acid chloranhydride and [1+1]-reaction of intermediate tetraester with hydrazine hydrate. The evidence is given for the structure of the obtained macrocycle using IR and NMR spectroscopy and mass spectrometry.

Keywords: *l*-Menthol, *O,N*-macroheterocycles, ester and hydrazide functions, synthesis.

Синтез оптически чистых макрогетероциклов со сложноэфирными и гидразидными фрагментами на основе *l*−ментола

Г. Ю. Ишмуратов, М. П. Яковлева,@ Г. Р. Мингалеева, М. А. Шутова, Р. Р. Муслухов, Е. М. Вирипаев, А. Г. Толстиков

Институт органической химии Уфимского научного центра Российской академии наук, 450054 Уфа, Российская Федерация
@E-mail: insect@anrb.ru

Разработан метод синтеза оптически чистого метил- и изо-пропил-замещенного 21-членного макролида с гидразидными и сложноэфирными фрагментами. Структура полученного соединения была подтверждена с помощью ИК и ЯМР спектроскопии и масс-спектрометрии.

Ключевые слова: *l*-Ментол, *O,N*-макрогетероциклы, сложноэфирные и гидразидные фрагменты, синтез.

Modern practical medicine successfully employs pharmaceutical preparations with oxygen and nitrogen containing macrocyclic compounds as drug substances.[1] Therefore, the development of methods for obtaining macroheterocycles containing pharmacophoric fragments presents a crucial problem for further modern pharmacology and chemical science.

This report describes a synthetic route to potentially bioactive optically pure methyl and isopropyl branched 21-member macrolide with hydrazide and ester groups fabricated from accessible natural *l*-menthol.

Experimental

IR spectra in thin layers were recorded on IR Prestige-21 Shimadzu instrument. NMR spectra were recorded in $CDCl_3$ with TMS internal standard and in MeOH+C_6D_6 with DSS internal standard on a Bruker AM-300 spectrometer (operating frequency 300.13 MHz for ^{1}H; 75.47, ^{13}C). ^{13}C NMR spectra were written down in modes with a broadband outcome on protons and in the JMOD mode. 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] instrument with He carrier gas. Column chromatography used SiO_2 (70-230, Lancaster, England).

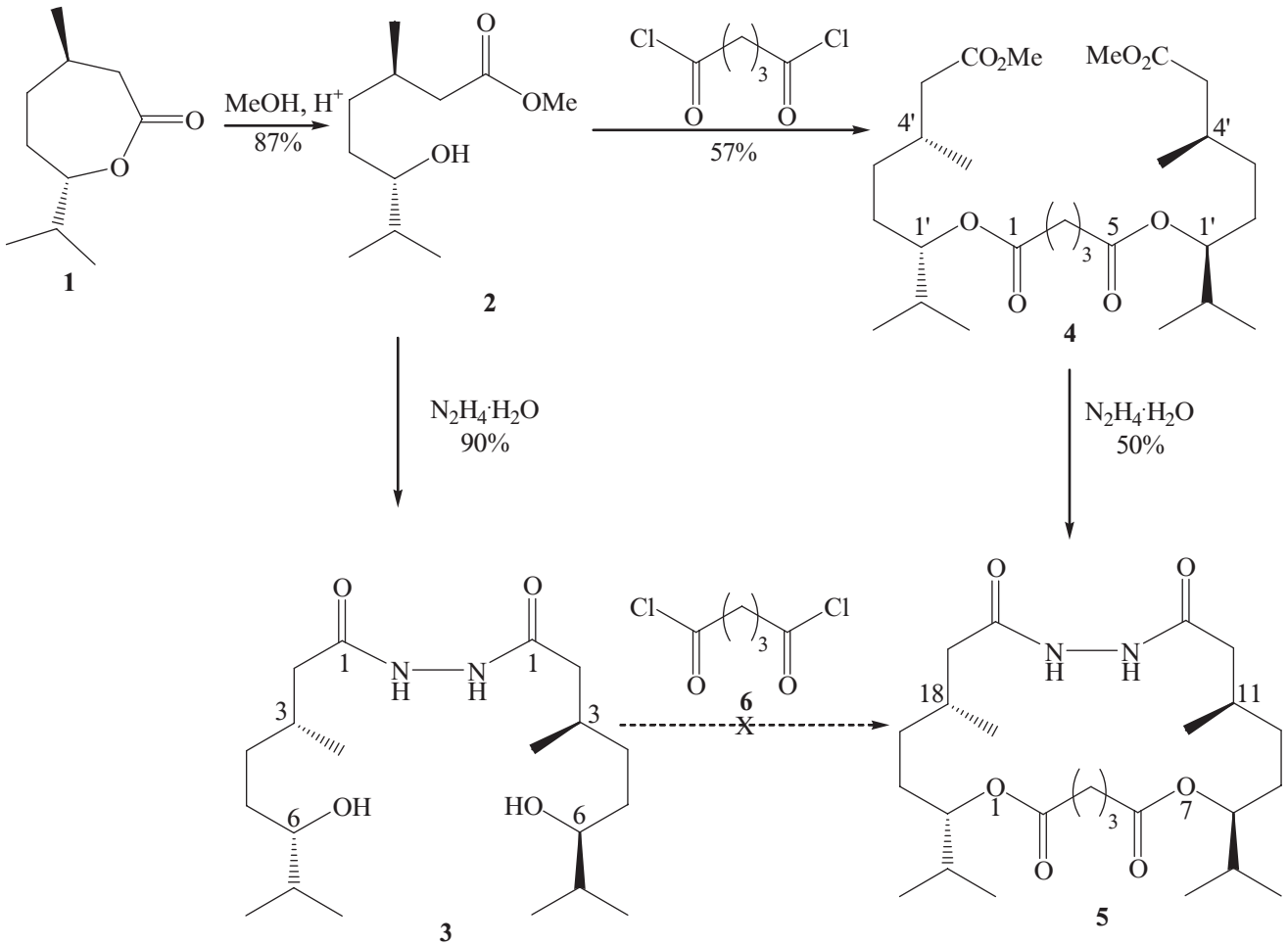
TLC monitoring used Sorbfil SiO_2 (Russia). Elemental analyses of all compounds were agreed with those calculated. Mass spectra of compounds **3**, **5** were recorded on Shimadzu LCMS 2010 EV instrument using under atmospheric pressure chemical ionization (APCI) with electron energy 20 eV and detection of positive and negative ions. The liquid mobile phase was H_2O and/or CH_3CN at flow rate 0.02 ml/min.

Methyl-(3R,6S)-6-hydroxy-3,7-dimethyloctanoate, ***2****.* To the stirred solution of mentholactone **1**[2] (10.0 g, 58.8 mmol) in 100 ml abs. methanol three drops of conc. H_2SO_4 were added and left to stand for 24 hrs (with TLC control). Thereafter, methanol was sublimed; the residue was diluted with ethyl acetate (100 ml) and sequentially rinsed with saturated NaCl, $NaHCO_3$ and NaCl solutions; the organic layer was dessicated with $MgSO_4$ and sublimed. Yield: 10.3 g (87%) by ester **3**, the IR and NMR spectral parameters were similar to those obtained previously.[2]

1,2-Bis((3R,6S)-6-hydroxy-3,7-dimethyl-1-oxooctyl)-hydrazine, ***3.*** To 3.00 g (14.9 mmol) of methyl-(3*R*,6*S*)-6-hydroxy-3,7-dimethyloctanoate (**2**) in 5 ml of dioxane 0.37 g (7.4 mmol) hydrazine monohydrate was slowly dropwise added, stirred for 4 hrs (until disappearance of **2**, with TLC control); dioxane was sublimed, and the residue was filtered through Schott filter, under rinsing with 20 ml MTBE. Yield 2.48 g (90%). $[\alpha]_D^{20}$ -5.7° (*c* 1.27, CH_3OH). *m/z* (APCI, 20 eV): 373 [$(M+H)^+$], 371 [$(M-H)^-$]. ^{1}H NMR (MeOH+C_6D_6) δ ppm: 0.80 (6H, d, *J* = 6.7 Hz, CH_3-3), 1.08 (12H, d, *J* = 6.7 Hz, CH_3-7), 1.17-1.24 (4H, m, H-4), 1.30-1.45 (2H, m, H'-5), 1.40-1.62 (2H, m, H''-5), 1.78 (2H, q, *J* = 6.8 Hz, H-7), 1.81-1.87 (2H, m, H-3), 2.06 (4H, d, *J* = 7.1 Hz, H-2), 3.51-3.82 (2H, m, H-6), 6.02 (1H, s, OH), 9.18 (2H, s, NH). ^{13}C NMR (MeOH+C_6D_6) δ ppm: 17.09, 18.81 (q, CH_3C-8), 19.46 (q, CH_3C-3), 31.24 (d, C-3), 31.66 (t, C-5), 33.53 (t, C-4), 33.99 (d, C-7), 41.73 (t, C-2), 76.82 (d, C-6), 173.66 (s, C-1). IR (KBr) ν_{max} cm^{-1}: 3285-3170 (NH, OH), 1651, 1629 (CONH).

Bis[(1'S,4'R)-1'-isopropyl-6'-methoxy-4'-methyl-6'-oxohexyl]pentane dioate, ***4.*** To the stirred solution of methyl-(3*R*,6*S*)-6-hydroxy-3,7-dimethyl octanoate (**2**) (3.00 g, 14.9 mmol) in 8 ml abs. pyridine glutaric acid chloranhydride (3.10 g, 7.4 mmol) [3] in 3 ml abs. ether was added, stirred for 24 hrs (until disappearance of **2**, TLC control). The reaction mixture was diluted with 50 ml of diethyl ester, sequentially rinsed with 5-pc HCl, saturated by NaCl solution and dessicated with $MgSO_4$; the solvent was sublimed, and the residue was chromatographed. Yield 2.10 g (57%). R_f 0.18 (SiO_2, petroleum ether - MTBE, 2:1). $[\alpha]_D^{20}$ +1.4° (c 1.88, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ ppm: 0.85 (12H, d, *J* = 6.8 Hz, CH_3-*i*-Pr), 0.92 (6H, d, *J* = 6.7 Hz, CH_3-4'), 1.12-1.35 (2H, m, H'-3'), 1.45-1.60 (2H, m, H''-3'), 1.49-1.58 (4H, m, H-3, H-4'), 1.78-1.89 (2H, m, CH-*i*-Pr), 1.88-2.21 (4H, m, H-2'), 2.11 (2H, dd, *J* = 14.4, 8.1 Hz, H'-5'), 2.29 (2H, dd, *J* = 14.4, 5.9 Hz, H''-5'), 2.38 (4H, t, *J* = 7.3 Hz, H-2, H-4), 3.64 (6H, s, CH_3-O), 4.72 (2H, dt, *J* = 8.1, 4.2 Hz, H-1'). ^{13}C NMR ($CDCl_3$) δ ppm: 17.26, 18.48 (q, CH_3-*i*-Pr), 19.60 (q, *C*H_3-C-4'), 20.35 (t, C-3), 28.30 (t, C-2'), 30.17 (d, C-4'), 30.98 (d, CH-*i*-Pr), 32.23 (t, C-3'), 33.50 (t, C-2, C-4), 41.21 (t, C-5'), 51.26 (q, CH_3-O), 78.33 (d, C-1'), 172.67 (s, C-1, C-5), 173.36 (s, C-6'). IR (KBr) ν_{max} cm^{-1}: 1732 (O=C-O).

(8S,11R,18R,21S)-8,21-Diisopropyl-11,18-dimethyl-1,7-dioxa-14,15-diazacyclogeneicosane-2,6,13,16-tetron, ***5.*** To the solution of tetraester **4** (1.35 g, 2.7 mmol) in 10 ml abs. dioxane hydrazine hydrate (0.14 g, 2.7 mmol) was slowly added dropwise under intense stirring and it was stirred for 6 hrs (until disappearance of **4**, with TLC control); dioxane was sublimed. The residue was diluted in 20 ml CH_2Cl_2, rinsed with water (3×5 ml), dessicated with $MgSO_4$ and sublimed. To the resulting residue we sequentially



Scheme 1.

added 1 ml of dry CH_2Cl_2 and 10 ml hexane under stirring and left to stand until the layers separated, the upper one being decanted. The residue was rinsed with 5 ml hexane and sublimed. The yield was 0.46 g (50%) of the compound **5**. $[\alpha]_D^{20}$ +0.6° (c 2.23, CH_2Cl_2). *m/z* (APCI, 20 eV): 487 $[(M+H+H_2O)^+]$, 485 $[(M-H+H_2O)^-]$. ^1H NMR ($CDCl_3$) δ ppm: 0.89 (12H, d, *J* = 6.8 Hz, CH_3-*i*-Pr), 0.91 (6H, d, *J* = 6.7 Hz, CH_3-11, CH_3-18), 1.01-1.25 (2H, m, H-11, H-18), 1.38-1.55 (4H, m, H-10, H-19), 1.41-1.56 (2H, m, H-4), 1.75-1.98 (4H, m, H-9, H-20), 1.78-1.92 (2H, m, CH-*i*-Pr), 2.05 (2H, dd, *J* = 14.0, 5.7 Hz, H'-12, H'-17), 2.23 (2H, dd, *J* = 14.0, 7.9 Hz, H''-12, H''-17), 2.32 (4H, t, *J* = 7.1 Hz, H-3, H-5), 4.67 (2H, dt, *J* = 8.0, 4.7 Hz, H-8, H-21), 8.06 (2H, s, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 17.12, 18.34 (q, CH_3-*i*-Pr), 19.47 (q, *C*H_3-C-11, *C*H_3-C-18), 20.21 (t, C-4), 28.30 (t, C-9, C-20), 30.00 (d, C-11, C-18), 30.84 (d, CH-*i*-Pr), 32.08 (t, C-10, C-19), 33.30 (t, C-3, C-5), 41.56 (t, C-12, C-17), 78.13 (d, C-8, C-21), 172.43 (s, C-2, C-6), 173.07 (s, C-13, C-16). IR (KBr) ν_{max} cm^{-1}: 3292 (NH), 1735 (O=C-O), 1635, 1701 (CONH).

Results and Discussion

The synthesis scheme (Scheme 1) is based on chemo- and regioselective transformations of mentholactone **1** obtained from natural *l*-menthol in two stages.[2] Re-esterification of cyclic ether **1** with methanol in presence of H_2SO_4 gave methyl-(3*R*,6*S*)-6-hydroxy-3,7-dimethyl octanoate (**2**), [2+1]-condensation of which with absolute glutaric acid chloranhydride resulted in *bis*[(1*S*,4*R*)-1-isopropyl-6-methoxy-4-methyl-6-oxyhexyl]pentane dioate (**4**).

Involvement of the latter into the [1+1]-condensation reaction with hydrazine hydrate made it possible to get the target macroheterocycle **5** containing hydrazide and ester groups.

An alternative attempt to synthesize the macrocycle **5** via [2+1]-condensation of methyl-(3*R*,6*S*)-6-hydroxy-3,7-dimethyl octanoate (**2**) with hydrazine hydrate followed by [1+1]-condensation of the resulting 1,2-*bis*((3*R*,6*S*)-6-hydroxy-3,7-dimethyl-1-oxooctyl)hydrazine (**3**) with glutaric acid chloranhydride failed at the second stage, even with another solvent (CCl_4 was changed for 1,4-dioxane) plus the $CoCl_2$ catalyst previously used in [4].

The structures of the resulting acyclic compounds **3, 4** and macrolide **5** were established by IR, ^1H and ^{13}C NMR spectroscopic techniques; the molecular mass was measured using chromatic mass spectrometry.

The IR spectra of the acyclic compound **3** and macrolide **5** do not have an absorption band in the region of 1735 cm^{-1} characteristic of the carboxylic function of the compound **2**. The presence of signals corresponding to the CONH fragment (1627 and 1651 cm^{-1} for **3**; 1635 and 1701 cm^{-1} for **5**) and N-H bond (3284 cm^{-1} for **3** and 3292 cm^{-1} for **5**) evidences for the formation of a hydrazide group. The IR spectrum of the acyclic compound **4** does not have the absorption bands at 3300-3600 and 1099 cm^{-1} for the hydroxyl group, and the presence of the absorption bands at 1732 and 1728 cm^{-1} indicates the formation of tetraester **4**.

NMR data analysis of the compound **5** was performed through comparison of those known for acyclic tetraester **4**. The carbon signal of the COOMe grouping in the ^{13}C NMR spectrum of the product **5** (173.36 ppm), obtained from the initial **4**, and proton signals of the hydrazide (NH_2NHCO) residue (~ 4.90 ppm) in the ^1H NMR spectrum are absent. This indicates that the compound **5** is not an acyclic product.

Besides a carbon signal of the ester groups (172.43 ppm), we can observe a singlet of NHC=O groups (173.07 ppm) in the ^{13}C NMR spectrum of the compound **5**. Proton spectrum displays a downfield signal (8.06 ppm), the chemical shift value and integral intensity of which correspond to the two protons of NHC=O groups. This is testimony to the formation of a hydrazide [-C(O)NHNHC(O)-] fragment. All these spectral data point out to the formation of the macrocycle **5** with ester and hydrazide functions, that being additionally supported by mass spectrometry data.

Acyclic tetraester **3** and macroheterocycle **5** were investigated under atmospheric pressure chemical ionization (APCI) with recording positive and negative ions (20 eV). In this case we noted very intense peaks of protonated MH^+ and deprotonated $(M-H)^-$ ions as well as their ionic associates with water molecules, since protonation and water solvatization capabilities are well-known facts in the chemistry of amides and hydrazides.[5]

Conclusions

On the basis of *l*-menthol we have developed a synthetic method for the optically active macrocycle **5** with two ester and hydrazide functions using [2+1]-condensation of methyl-(3*R*,6*S*)-6-hydroxy-3,7-dimethyloctanoate with glutaric acid chloranhydride and [1+1]-reaction of intermediate tetraester with hydrazine hydrate at key stages. The structure of the macrolide **5** was established by IR, ^1H and ^{13}C NMR spectroscopic techniques and chromatic mass spectrometry.

References

1. Ovchinnikov Yu.A. *Bioorganicheskaya Khimiya* [*Bioorganic Chemistry*]. Moskva: Prosveshcheniye, **1987**. 816 p.
2. Ishmuratov G.Yu., Yakovleva M.P., Ganieva V.A., Muslukhov R.R., Tolstikov G.A. *Chem. Nat. Compd.* **2005***, 41,* 41-44 *[Khimiya Prirodnykh Soedinenii* **2005**, 33-36 (in Russ.)].
3. Weygand-Hilgetag. *Organisch-Chemische Experimentierkunst*. Leipzig: Verlag, **1968**. 944 p.
4. Kataev V.E., Militsina O.I., Strobykina I.Yu., Kovylyaeva G.I., Musin R.Z., Fedorova O.V., Rusinov G.L., Zueva M.N., Mordovskoi G.G., Tolstikov A.G. *Pharm. Chem. J.* **2006**, *40*, 473-475 [*Khimiko-Farmatsevticheskii Zh.* **2006**, *40*, 12-13 (in Russ.)].
5. *Obshchaya Organicheskaya Khimiya.* Moskva: Khimiya, **1983**, Vol 4. 438 p. (Russ. transl. of *Comprehensive Organic Chemistry: The Synthesis and Reactions of Organic Compounds* [Barton D., Ollis W.D., Eds.]. Vol. 4: *Heterocyclic Compounds.* Oxford: Pergamon Press, **1979**).

Received 11.03.2012
Accepted 25.04.2012