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Targeted Synthesis and Antitumor Activity In Vitro of Macrodiolides Containing 1*Z*,5*Z*-Diene and 1,3-Diyne Moieties †

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Abstract: An efficient methods have been developed for synthesizing previously unknown macrodiolides incorporating 1*Z*,5*Z*-diene and 1,3-diyne moieties in 54–84% yields and with >98% stereoselectivity by intermolecular cyclocondesation of (7*Z*,11*Z*)-octadeca-7,11-dienedioic acid with α,ω-diols catalyzed by hafnium triflate $Hf(OTf)_4$, as well as by oxidative coupling of α,ω-diynes obtained by esterification of (7*Z*,11*Z*)-octadeca-7,11-dienedioic acid with alkynols. The macrodiolides synthesized exhibit in vitro cytotoxic activity toward Jurkat, K562, U937, HL-60, HeLa and Hek293 cell lines.

Keywords: macrodiolides; 1,5-dienoic compounds; 1,3-diynes; 1,2-dienes; cyclomagnesiation; homogeneous catalysis

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1. Introduction

Macrocyclic compounds are widespread in nature and have a huge range of useful properties, therefore, they are the object of close attention from researchers. A large number of macrocycles currently used in pharmaceuticals, materials science, supramolecular and medicinal chemistry. Drugs based on macrolactones are highly effective and, at the same time, are considered one of the safest groups of antibacterial drugs. They do not have a high toxic effect on organs and tissues and less often, in comparison with many other antibiotics, cause allergic reactions [1,2].

In this regard, interest is steadily growing in the synthesis of new polyfunctional macrolactones containing various pharmacophore groups in the structure, as well as in the study of their biological properties. One of the active pharmacophore groups is the 1,3-diyne fragment, which is found in the structure of a large number of natural biologically active compounds with antitumor, anti-HIV, antifungal, antibacterial and antiviral activity [3–9].

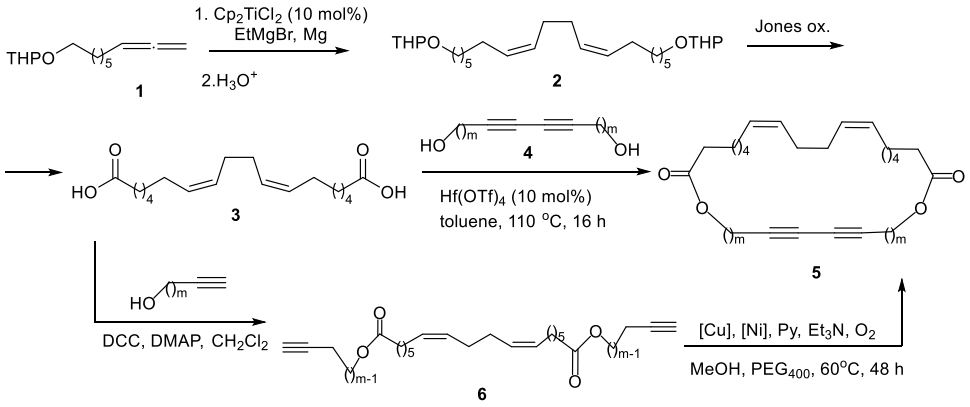
Natural 1,3-diyne macrolactones, which exhibit high biological activity are known. For example, in 2012 by Yue et al. were isolated from trees of the genus *Khaya Ivorenesis A*. new macrocyclic lactones Ivorenolide A and Ivorenolide B containing a 1,3-diyne fragment in their structure [10,11]. Crude extracts of the stem bark of this tree are used in traditional medicine to treat malaria and other tropical diseases. Biological studies have revealed the anti-plasmodial and anti-inflammatory properties of these extracts. Recently, biological studies of isolated macrocycles have demonstrated high immunosuppressive activity and surprisingly high inhibition of Con A-induced T-cell proliferation [12–15].

In view of the foregoing and a continuation of our research on the development of original methods for the synthesis of biologically active macrocyclic compounds [16–18], within the framework of this work, we put forward the idea of the possibility of obtaining new macrodiolides containing in their structure, along with the 1*Z*,5*Z*-diene group, a 1,3-diyne fragment.

2. Results and Discussion

Recently, we have developed two original methods for the synthesis of macrodiolides containing 1*Z*,5*Z*-diene and 1,3-diyne moieties in the structure in 55-79% yields and stereoselectivity (>98%). We found that the synthesized unsaturated macrolactones exhibit high in vitro cytotoxic activity against Jurkat, K562, U937, HL-60 and Hek293 cell lines [19].

In this work, we present data on the synthesis of new macrodiolides obtained by us for the first time according to the following scheme (Scheme 1).



[Cu] = $CuCl_2$;
[Ni] = $Ni(NO)_3 \cdot 6H_2O$;
m = 1-4

Scheme 1. Synthesis of macrodiolides containing 1*Z*,5*Z*-diene and 1,3-diyne moieties.

The key precursor, (7*Z*,11*Z*)-octadeca-7,11-dienedioic acid **3**, was synthesized according to the previously developed scheme in 3 stages, using the original reaction of catalytic homo-cyclomagnesiation of O-containing 1,2-dienes (Dzhemilev reaction) with a total yield 47% and stereoselectivity >98% [18]. Target macrolactones were obtained by Hf-catalyzed cyclocondensation of acid **3** with 1,3-diyne α,ω-diols **4** in 54–72% yields. In addition, an alternative two-step approach to the preparation of macrodiolides using an intramolecular oxidative coupling reaction with a total yield of 67–84% is shown (Scheme 1).

A preliminary assessment of the cytotoxicity of the obtained macrocyclic compounds in vitro against the Jurkat, K562, Hek293, HeLa, U937 cell lines and fibroblasts was carried out, including determination of IC50 by flow cytometry with the Guava ViaCount reagent kits (Millipore). The macrodiolides synthesized were found to exhibit in vitro cytotoxic activity toward Jurkat, K562, U937, HL-60 and Hek293 cell lines (IC50 = 0.05–0.76 μM).

Currently, in the Laboratory of Molecular Design and Biological Screening of Candidate Substances for the Pharmaceutical Industry at the Institute of Petrochemistry and Catalysis of RAS, more detailed studies of the antitumor activity of synthesized macrodiolides are being carried out to study the effect of this class of compounds on the cell cycle and the ability to induce apoptosis.

3. Materials and Methods

All reactions were carried out in an inert atmosphere. The ethereal and aromatic solvents were dried over Na. Commercial 2-propyn-1-ol, 3-butyn-1-ol, 4-pentyn-1-ol, 5-hexyn-1-ol, $Hf(OTf)_4$ and Cp_2TiCl_2 (Aldrich) were used without preliminary purification. (7*Z*,11*Z*)-octadeca-7,11-dienedioic acid **3**, was prepared from oct-7-yn-1-ol by a reported [18]. One- (^1H, ^{13}C) and two-dimensional heteronuclear (HSQC, HMBC) NMR spectra were recorded in $CDCl_3$ on Bruker Avance-400 [(400.13 MHz (^1H), 100.62 MHz (^{13}C)] and Bruker Ascend-500 [(500 MHz (^1H), 125 MHz (^{13}C)]. IR spectra were recorded on Bruker VERTEX 70V using KBr discs over the range of 400–4000 cm^{-1}. Mass spectra were obtained on MALDI TOF/TOF spectrometer in a sinapic acid matrix. The mass spectra were obtained on an UltraFlex III TOF/TOF (Bruker Daltonik GmbH, Germany) operating in linear (TOF) and reflection (TOF/TOF) positive and negative ion modes. S_8 and DCTB (trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenyliden]malononitrile) were used as the matrix.

General procedure synthesis of macrodiolides.

Method 1. (7*Z*,11*Z*)-octadeca-7,11-dienedioic acid **3** (0.2 mmol, 1.0 equiv.) and diol (0.2 mmol, 1.0 equiv.) were dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (0.02 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 16–18 h. After cooling to room temperature, silica gel (~1 mL) was added and the slurry was concentrated under reduced pressure and purified by column chromatography (elution with petroleum ether/EtOAc (15/1)) to afford the desired product as a colorless oil.

Method 2. To a vial equipped with a stirring bar was added $CuCl_2$ (5.0 mg, 0.44 mmol, 25 mol.%) and $Ni(NO_3)_2{\cdot}6H_2O$ (8.5 mg, 0.44 mmol, 25 mol.%). Polyethylene glycol 400 (3.05 mL), triethylamine (0.046 mL, 0.33 mmol, 3 equiv.) and pyridine (0.046 mL, 0.55 mmol, 5 equiv.) were added and the mixture was stirred at room temperature for 15 min or until the metals were solubilized. The diyne (**6**) (0.11 mmol) was added to the homogenous mixture as a methanol solution (1.5 mL) in one portion. Oxygen was bubbled in the solution for 5 min and the vial was then closed with a screw cap. The reaction was warmed to 60 °C and monitored by TLC for consumption of the starting material (oxygen was bubbled again through the solution every 12 h). When the starting material was completely consumed (TLC), the reaction was cooled to room temperature and the crude mixture was loaded directly on a silica column. Purification by chromatography (elution with petroleum ether/EtOAc (15/1)) to afford the desired product as a colorless oil.

(15*Z*,19*Z*)-1,8-dioxacyclohexacosa-15,19-dien-3,5-diyne-9,26-dione **5a**
Colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.59–5.26 (4H, m, =C<u>H</u>), 4.76 (4H, s, O-C<u>H</u>$_2$), 2.42–2.32 (4H, m, C<u>H</u>$_2$), 2.23–1.95 (8H, m), 1.77–1.69 (4H, m, C<u>H</u>$_2$), 1.37–1.32 (m, 8H, C<u>H</u>$_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 172.6, 130.8, 128.6, 76.8, 73.7, 51.6, 32.8, 28.6, 27.1, 26.8, 26.0, 24.5). IR (ν/cm^{-1}): 1735 (C=O), 1238, 1155 (C–O). HRMS (MALDI TOF) $[M]^-$ calcd. for $C_{24}H_{32}O_4$ 384.2301; Found 384.2309. Yield (method 1/method 2): 54%/62%.

(17*Z*,21*Z*)-1,10-dioxacyclooctacosa-17,21-dien-4,6-diyne-11,28-dione **5b**
Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.58–5.25 (4H, m, =C<u>H</u>), 4.16 (4H, t, *J* = 5.4 Hz, O-C<u>H</u>$_2$), 2.60 (4H, t, *J* = 5.4 Hz, C<u>H</u>$_2$), 2.34 (4H, t, *J* = 7.3 Hz, C<u>H</u>$_2$), 2.22–1.94 (8H, m, C<u>H</u>$_2$), 1.83–1.67 (4H, m, C<u>H</u>$_2$), 1.37–1.32 (m, 8H, C<u>H</u>$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 170.4, 130.2, 128.9, 74.1, 66.5, 61.6, 33.4, 28.5, 27.3, 26.9, 26.4, 24.7, 19.8. IR (ν/cm^{-1}): 1741 (C=O), 1245, 1165 (C–O). HRMS (MALDI TOF) $[M]^-$ calcd. for $C_{26}H_{36}O_4$ 412.2614; Found 412.2618. Yield (method 1/method 2): 59%/66%.

(19*Z*,23*Z*)-1,12-dioxacyclotriaconta-19,23-dien-5,7-diyne-13,30-dione **5c**
Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.58–5.25 (4H, m, =C<u>H</u>), 4.16 (4H, t, *J* = 5.4 Hz, O-C<u>H</u>$_2$), 2.60 (4H, t, *J* = 5.4 Hz, C<u>H</u>$_2$), 2.44–2.33 (8H, m), 2.22–1.96 (8H, m, C<u>H</u>$_2$),

1.89–1.71 (4H, m, C<u>H</u>$_2$), 1.37–1.32 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 173.4, 130.2, 128.9, 76.1, 66.1, 62.6, 33.5, 28.3, 27.3, 27.1, 26.7, 26.4, 24.6, 16.8. IR (ν/cm^{-1}): 1733 (C=O), 1240, 1170 (C–O). HRMS (MALDI TOF) $[M]^-$ calcd. for $C_{28}H_{40}O_4$ 440.2927; Found 440.2919. Yield (method 1/method 2): 65%/72%.

(21*Z*,25*Z*)-1,14-dioxacyclodotriaconta-21,25-dien-6,8-diyne-15,32-dione **5d**
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.56–5.29 (4H, m, =C<u>H</u>), 4.10 (4H, t, *J* = 5.4 Hz, O-C<u>H</u>$_2$), 2.41–2.31 (8H, m), 2.21–2.01 (8H, m, C<u>H</u>$_2$), 1.87–1.51 (12H, m, C<u>H</u>$_2$), 1.39–1.31 (m, 8H, C<u>H</u>$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 173.6, 130.4, 128.9, 76.7, 65.9, 63.6, 33.8, 28.4, 27.6, 27.2, 26.8, 26.6, 25.2, 24.7, 18.9. IR (ν/cm^{-1}): 1727 (C=O), 1239, 1177 (C–O). HRMS (MALDI TOF) $[M]^-$ calcd. for $C_{30}H_{44}O_4$ 468.3240; Found 468.3247. Yield (method 1/method 2): 75%/84%.

4. Conclusions

Thus, the synthesis of previously undescribed biologically active macrodiolides with good yields and high stereoselectivity (>98%) was carried out. Preliminary studies of the antitumor activity of synthesized macrocyclic compounds have shown high cytotoxicity in vitro against the cell lines Jurkat, K562, U937, HL-60, HeLa and Hek293.

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Conflicts of Interest: The authors declare no conflicts of interest.

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