Proceeding Paper

Stereoselective Synthesis and Cytotoxic Activity of Aromatic Polyether Macrodiolides Containing 1Z,5Z-Diene Moiety †

Ilgiz Islamov *, Adelya Yusupova, Lilya U. Dzhemileva and Usein Dzhemilev

Institute of Petrochemistry and Catalysis of RAS, Ufa 450075, Russia; (A.Y.); (L.U.D.); (U.D.)
* Correspondence: iislamovi@gmail.com
† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15-30 November 2021; Available online: https://ecsoc-25.sciforum.net/

Abstract: The synthesis of previously undescribed aromatic polyether macrodiolides, containing a 1Z,5Z-diene moiety was carried out in 56–72% yields and with >98% stereoselectivity. It has been shown that the synthesized macrodiolides exhibits higher cytotoxic activity in vitro to a number of tumor cell lines (Jurkat, K562 and U937).

Keywords: 1,5-dienoic compounds; crown ethers; cyclomagnesiation; macrodiolides; cytotoxicity

1. Introduction

Polyether macrocyclic compounds, including crown ethers, since their discovery in the mid-1960s by Pedersen [1], have become an important part in the development of supramolecular chemistry (host-guest chemistry). Currently, this class of compounds is widely used in complexation, extraction, catalysis, and in various fields of industry [2]. It is known that crown ethers form stable complexes with metal ions, and at the same time, due to the presence of a hydrophobic molecular ring structure, they can freely penetrate into the lipid layer of the cell membrane, which makes them similar to natural ionophores such as gramicidin, valinomycin, etc. [3] These properties make crown ethers especially attractive and useful for biological research and medicinal chemistry. In general, a large number of pharmacological studies are associated with the use of crown ethers as carriers of medicinal substances [4–6]. At the same time, it was shown that crown ethers are able to regulate enzymatic activity, interact with DNA and break it down, and also exhibit antimicrobial, antiviral and antitumor properties [7].

In recent years, there has been an increasing interest in the synthesis and study of the biological properties of new polyether macrocyclic compounds containing various pharmacophore groups in their structure. It is expected that the combination of the beneficial properties of crown ethers and biologically active molecules will lead to compounds on the basis of which it is possible to obtain new drugs.

In view of the foregoing and to pursue our studies on the development of stereoselective syntheses of biologically active macrocyclic compounds containing 1Z,5Z-diene moieties [8–12], here we report the synthesis of new polyether macrodiolides.

2. Results and Discussion

Recently, we have developed an original scheme for the preparation of previously unknown unsaturated polyaromatic macrolactones containing 1Z,5Z-diene moiety in 48-71% yields and stereoselectivity (>98%), based on intermolecular cyclocondensation of polyether aromatic dicarboxylic acids with α,ω-alka-nZ, (n + 4) Z-dienediols. It was shown that the synthesized cyclophans exhibit cytotoxic activity in vitro against tumor cell lines Jurkat, K562, U937, HL60, Hek293. Moreover, the studies carried out to study
the effect of synthesized macrocycles on mitochondria, the ability to induce apoptosis and their influence on cell cycle have proved the antitumor activity of cyclophanes [12].

In continuation of these studies, this article presents data on the synthesis of new polyether macrocycles, which we obtained for the first time according to the following scheme (Scheme 1).

In order to implement the intended strategy for the synthesis of unsaturated macrocyclic compounds, we have initially synthesized tetradeca-5Z,9Z-diene-1,14-diol 3 by the use of the reaction of Ti-catalyzed homo-cycloalkanation of O-containing 1,2-dienes (Dzhemilev reaction) (Scheme 1) [8,9]. At the final stage of assembling the polyether macrodiolides the well-proven intermolecular cyclocondensation was employed in the presence of catalytic amounts of DMAP and EDC·HCl to obtained target macrocycles 5 in 56-72% yields (Scheme 1) [12].

The structure of the resulting macrocycles 5 has been established by combined experimental methods, which include one-dimensional (1H, 13C) and two-dimensional heteronuclear correlation NMR experiments (HSQC, HMBC), as well as mass-spectrometry (HRMS).

A preliminary assessment of the cytotoxicity of the obtained macrocyclic compounds in vitro against the Jurkat, K562, Hek293 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, Hek293 cell lines.

Currently, the Laboratory of Molecular Design and Biological Screening of Candidate Substances for the Pharmaceutical Industry at the Institute of Petrochemistry and Catalysis of RAS is conducting more detailed studies of the antitumor activity of synthesized polyether macrodiolides using a wide range of cancer cells as an example.

3. Materials and Methods

All reactions were carried out in an inert atmosphere. All solvents were dried (diethyl ether, toluene over Na, dioxane over NaOH, methanol over Mg, chloroform, dichloromethane over P2O5) and freshly distilled before use. All reactions were carried out under a dry argon atmosphere. Commercial 5-hexyn-1-ol, Cp2TiCl2 (Aldrich) were used without preliminary purification. 1,14-tetradeca-5Z,9Z-dienediol 3, was prepared from 5-hexyn-1-ol by a reported [8,9]. Individuality and purity of the synthesized compounds were controlled using of TLC on Silufol UV-254 plates; anisic aldehyde in acetic acid was used as a developer. One- (1H, 13C) and two-dimensional heteronuclear correlation (HSQC, HMBC) NMR spectra were recorded in CDCl3 on Bruker Avance-400 [(400.13 MHz (1H), 100.62 MHz (13C)] and Bruker Ascend-500 [(500 MHz (1H), 125 MHz (13C)]. 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, Bremen, Germany) operating in linear (TOF) and reflection (TOF/TOF) positive and negative ion modes. S

Scheme 1. Synthesis of polyether macrodiolides containing 1Z,5Z-diene moiety.
and DCTB (trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenyliden]malononitrile) were used as the matrix.

General procedure synthesis of macrodiolides.
To a mixture of 1,14-tetradeca-5Z,9Z-dienediol (0.2 mmol, 1 eq), aromatic dicarboxylic acid (0.2 mmol, 1 eq) and 4-dimethylaminopyridine (12 mg, 0.1 mmol, 0.5 eq) in dichloromethane (35 mL) at 0°C was added a solution of EDCHCl (62 mg, 0.4 mmol, 2 eq) in 5 mL of dichloromethane under argon. The mixture was warmed-up to room temperature and stirred for 12 h. After the reaction mixture was treated with a 5% solution of HCl in H₂O (2 × 10 mL). The products were extracted with dichloromethane (2 × 30 mL), the extracts were dried with MgSO₄, the solvent was evaporated, and the residue was chromatographed on a column (SiO₂, elution with petroleum ether/EtOAc (10/1–3/1)).

(11Z,15Z)-7,8,9,10,13,14,17,18,19,20,28,29-dodecahydro-5H,22H-dibenzo[e,y][1,4,8,23]tetraoxacyclohexacosine
White waxy solid. ¹H NMR (500 MHz, CDCl₃): δ = 7.38–7.32 (m, 4H), 7.04–6.95 (m, 4H), 5.43–5.29 (m, 4H), 4.37–4.29 (m, 8H), 2.11–1.90 (m, 8H), 1.77–1.68 (m, 4H), 1.49–1.38 (m, 4H); ¹³C NMR (126 MHz, CDCl₃): δ = 167.4, 157.1, 132.0, 131.1, 129.7, 129.1, 125.7, 121.6, 113.7, 67.6, 62.1, 31.2, 27.4, 26.8, 24.9. HRMS (MALDI TOF) [M]⁺ for C₄₃H₃₆O₇ found 536.2771. Yield 68%. Rᵣ = 0.46, hexane/EtOAc 3:1.

(11Z,15Z)-7,8,9,10,13,14,17,18,19,20,28,29,31,32-tetradecahydro-5H,22H-dibenzo[b1,h][4,7,11,26]pentaoxacyclononacosine
Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.36–7.29 (m, 4H), 7.01–6.91 (m, 4H), 5.40–5.31 (m, 4H), 4.24–4.19 (m, 8H), 3.99–3.91 (m, 4H), 2.09–1.91 (m, 8H), 1.79–1.65 (m, 4H), 1.47–1.36 (m, 4H); ¹³C NMR (126 MHz, CDCl₃): δ = 167.3, 157.2, 131.8, 131.1, 129.8, 129.0, 125.8, 121.8, 112.9, 69.8, 68.7, 61.9, 31.1, 27.3, 26.7, 24.6. HRMS (MALDI TOF) [M]⁺ for C₅₄H₄₆O₇ found 536.2774; found 536.2771. Yield 68%. Rᵣ = 0.46, hexane/EtOAc 3:1.

(11Z,15Z)-7,8,9,10,13,14,17,18,19,20,28,29,31,32,34,35-hexadecahydro-5H,22H-dibenzo[e1,k][1,4,7,10,14,29]hexaoxacyclodotriacontine-5,22-dione
Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.35–7.27 (m, 4H), 7.00–6.89 (m, 4H), 5.39–5.32 (m, 4H), 4.21–4.18 (m, 8H), 3.91–3.87 (m, 4H), 3.68 (s, 4H), 2.36–2.31 (m, 8H), 2.10–1.97 (m, 4H), 1.73–1.66 (m, 4H); ¹³C NMR (126 MHz, CDCl₃): δ = 167.2, 157.1, 131.4, 131.1, 129.7, 129.2, 124.8, 121.3, 121.2, 71.2, 69.9, 67.6, 61.8, 31.0, 27.4, 26.8, 24.8. HRMS (MALDI TOF) [M]⁺ for C₅₄H₄₆O₇ found 580.3036; found 580.3024. Yield 72%. Rᵣ = 0.34, hexane/EtOAc 3:1.

4. Conclusions
Thus, we developed an original method for stereoselective synthesis, providing 56–72% yields and >98% stereoselectivity, of previously unreported biologically active macrodiolides containing an 1Z,5Z-diene moiety in the molecules. Preliminary studies of the antitumor activity of synthesized macrocyclic compounds have shown high cytotoxicity in vitro against the cell lines Jurkat, K562 and Hek293.

Author Contributions: Conceptualization, Data curation, Synthetic investigation, Writing—original draft, and review and editing, I.I., A.Y. and L.D. Supervision: U.D. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data available on request.

Acknowledgments: The work was done within approved plans for research projects at the IPC RAS State Registration No. AAAA-A19-119022290008-6 (2019–2021) and AAAA-A19-119022290007-9 (2019-2021) and Grants of Russian Foundation for Basic Research 20-03-00694, 18-29-09068.

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