chemistry proceedings

MDPI

Proceeding Paper

Synthesis of New Unsaturated Polyether Macrodiolides Based on the (7Z,11Z)-Octadeca-7,11-Diene-1,18-Dioic Acid †

Ilgiz Islamov [1,*], Ilgam Gaisin [1] and Usein Dzhemilev [2]

[1] Institute of Petrochemistry and Catalysis, Ufa Federal Research Center, Russian Academy of Sciences, 141 Prospekt Oktyabrya, Ufa 450075, Russian Federation; ilgamgaisin.ipcras@gmail.com
[2] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prospekt, 47, Moscow 119991, Russian Federation; Dzhemilev@anrb.ru
* Correspondence: iislamovi@gmail.com
† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: https://ecsoc-27.sciforum.net/.

Abstract: Stereoselective synthesis of (7Z,11Z)-octadeca-7,11-diene-1,18-dioic acid was carried out using reaction Ti-catalyzed homo-cyclomagnesiation of 2-(nona-7,8-dien-1-yloxy)tetrahydro-2*H*-pyran. By intermolecular esterification of dicarboxylic acid with polyether acetylene alcohols in the presence of DCC and DMAP, the corresponding diesters were synthesized in good yields (67–75%). Based on symmetric diesters with terminal triple bonds, polyether macrodiolides containing conjugated triple bonds and pharmacophoric 1Z,5Z-diene fragments in their structure were synthesized for the first time.

Keywords: homo-cyclomagnesiation; 1,5-dienoic compounds; oxidative coupling; 1,3-diynes; macrodiolides

Citation: Islamov, I.; Gaisin, I.; Dzhemilev, U. Synthesis of New Unsaturated Polyether Macrodiolides Based on the (7Z,11Z)-Octadeca-7,11-Diene-1,18-Dioic Acid. *Chem. Proc.* **2023**, *14*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s):

Published: 15 November 2023

1. Introduction

The chemistry of acetylenes and polyacetylenes is one of the intriguing and attractive areas of organic synthesis. This class of unsaturated compounds is widespread in nature, while various acetylene plant metabolites and semisynthetic derivatives synthesized on their basis with a wide range of biological activities are of interest for pharmaceuticals and medicinal chemistry. It is known that over the past few years, more than a thousand polyines have been isolated and studied, and for individual representatives that have successfully passed preclinical trials, original schemes for their complete synthesis have been developed [1–3].

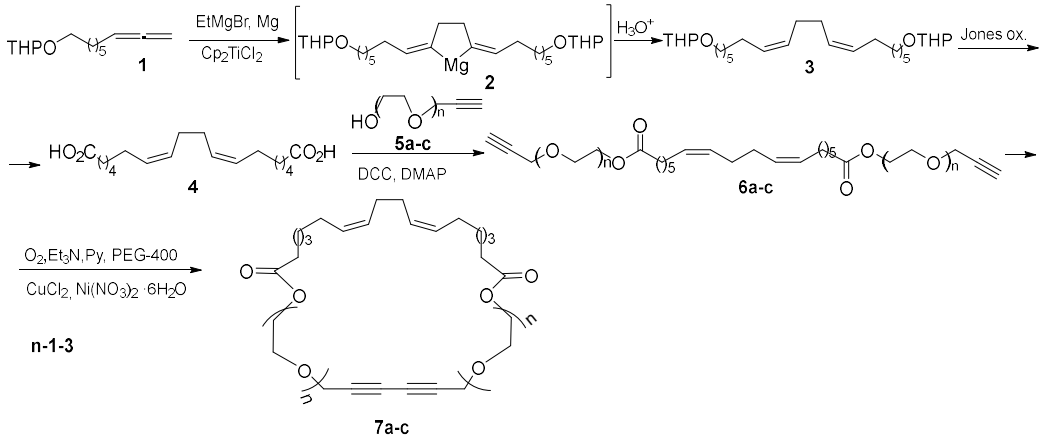
In this study, we present a scheme for the synthesis of new synthetic derivatives of unsaturated fatty acids and polyether macrodiolides containing bis-methylene separated double bonds and acetylene fragments.

2. Results and Discussion

Previously, we developed methods for the preparation and synthesized various unsaturated macrodiolides, including those containing acetylene fragments in the structure, which showed cytotoxic activity against various tumor cell lines [4–6].

In development of these studies, the idea arose of synthesizing previously undescribed crown-like polyether macrocyclic compounds based on biologically active (7Z,11Z)-octadeca-7,11-diene-1,18-dioic acid **4** (Scheme 1). In order to obtain new derivatives of unsaturated acids, as well as polyether macrocyclic compounds similar to crown ethers, acetylene alcohols were selected in the form of ethers obtained by reacting propargyl bromide with various ethylene glycol derivatives **5a-c** (Scheme 1). By conducting a series of experiments, optimal conditions were developed for the preparation of sym-

metric diesters 6a-c by Steglich esterification with the following substrate ratio: [**4**:**5**:DCC:DMAP] = [1:2.4:2:0.2]. The target macrocyclic compounds were obtained with ring closure at terminal triple bonds using intramolecular oxidative coupling of acetylenes according to a previously developed method [6] (Scheme 1).



Scheme 1. Synthesis of polyether macrodiolides.

3. Materials and Methods

One- (^{1}H, ^{13}C) and two-dimensional heteronuclear (HSQC, HMBC) NMR spectra were recorded in $CDCl_3$ on Bruker Avance-400 ((400.13 MHz (^{1}H), 100.62 MHz (^{13}C)) instruments. 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_8 and DCTB (trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenyliden]malononitrile) were used as the matrix. (7*Z*,11*Z*)-octadeca-7,11-diene-1,18-dioic synthesized according to procedures described in literature [4].

General procedure of esterification.

A DCC (0.45 g, 2.2 mmol) solution in dry THF (10 mL) was added with stirring to a mixture of (7Z,11Z)-octadeca-7,11-diene-1,18-dioic acid **4** (0.31 g, 1 mmol), one of alcohols **5a-c** (2.4 mmol), and DMAP (0.024 g, 0.2 mmol) in dry THF (30 mL) at cooling with ice bath (~0 °C) under dry argon atmosphere. The temperature of the reaction mixture was increased to ambient (20–22 °C), and it was stirred for 12 h (TLC monitoring). Then, the reaction mixture was filtered to remove the formed precipitate. The filtrate was concentrated in vacuo. The residue was chromatographed on a column with silica gel using a petroleum ether—EtOAc mixture as an eluent to obtain products **6a–c.**

Bis [2-(prop-2-yn-1-yloxy)ethyl] (7*Z*,11*Z*)-octadeca-7,11-dienedioate (6a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.46–5.32 (m, 4H, CH=CH), 4.27–4.22 (m, 4H, CH_2O), 3.77—3.72 (m, 8H, CH_2O), 2.46 (t, 2H, CH, *J* = 2.6 Hz), 2.37–2.32 (m, 4H, CH_2), 2.11—1.99 (m, 8H, CH_2CH=), 1.76–1.61 (m, 4H, CH_2), 1.44–1.30 (m, 8H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 173.6, 130.2, 128.9, 79.3, 74.8, 67.7, 63.1, 58.3, 33.6, 29.7, 29.2, 27.3, 27.0, 24.8. HRMS (ESI-TOF): found *m*/*z* 497.2853 [M + Na]+; calculated for $C_{28}H_{42}O_6Na^+$ 497.2874. Yield 78%.

Bis{2-[2-(prop-2-yn-1-yloxy)ethoxy]ethyl} (7*Z*,11*Z*)-octadeca-7,11-dienedioate (6b). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.40–5.28 (m, 4H, CH=CH), 4.23–4.16 (m, 8H, CH_2O), 3.64 (dt, 8H, CH_2O, *J* = 9.4 Hz, *J* = 4.8 Hz), 3.14 (dt, 4H, CH_2O, *J* = 9.8 Hz, *J* = 5.0 Hz), 2.42 (t, 2H, CH, *J* = 2.6 Hz), 2.31 (t, 4H, CH_2, *J* = 7.3 Hz), 2.04–1.89 (m, 8H, CH_2CH=), 1.74–1.63 (m, 4H, CH_2), 1.47–1.34 (m, 8H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) =172.5, 130.2, 128.9, 79.5, 74.6, 70.3, 69.2, 69.0, 63.3, 58.4, 33.5, 29.6, 29.2, 27.2, 26.6, 24.8. HRMS (ESI-TOF): found *m*/*z* 585.3376 [M + Na]+; calculated for $C_{32}H_{50}O_8Na^+$ 585.3398. Yield 71%.

Bis{2-[2-(2-(prop-2-yn-1-yloxy)ethoxy)ethoxy]ethyl}-(7*Z*,11*Z*)-octadeca-7,11-dienedioate (6c).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.35–5.25 (m, 4H, CH=CH), 4.19–4.12 (m, 8H, CH_2O), 3.66–3.58 (m, 12H, CH_2O), 3.16–3.06 (m, 8H, CH_2O), 2.39 (s, 2H, CH), 2.27 (t, 4H, CH_2, J = 7.3 Hz), 2.02–1.81 (m, 8H, CH_2CH=), 1.73–1.62 (m, 4H, CH_2), 1.48–1.33 (m, 8H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 173.5, 130.1, 128.9, 79.5, 72.5, 70.5, 70.4, 69.1, 69.0, 63.3, 58.3, 33.3, 29.6, 29.2, 27.2, 26.5, 24.8. HRMS (ESI-TOF): found *m*/*z* 673.3901 [M + Na]+; calculated for $C_{36}H_{58}O_{10}Na^+$ 673.3922. Yield 68%.

The synthesis of polyether macrodiolides **6a–c** was carried out according to the previously described procedure [5].

(21*Z*,25*Z*)-1,4,11,14-tetraoxacyclodotriaconta-21,25-dien-6,8-diyne-15,32-dione (7a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.43–5.35 (m, 4H, CH=CH), 4.12 (t, 4H, J = 6.7 Hz, CH_2O), 3.75–3.68 (m, 8H, CH_2O), 2.43–2.36 (m, 4H, CH_2), 2.16–1.99 (m, 8H, CH_2CH=), 1.81–1.61 (m, 4H, CH_2), 1.45–1.28 (m, 8H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 173.4, 130.4, 128.8, 77.9, 74.1, 65.8, 63.2, 58.5, 33.6, 29.7, 29.2, 27.2, 26.8, 24.6. HRMS (ESI-TOF): found *m*/*z* 495.2723 [M + Na]+; calculated for $C_{28}H_{40}O_6Na^+$ 495.2717. Yield 73%.

(27*Z*,31*Z*)-1,4,7,14,17,20-hexaoxacyclooctatriaconta-27,31-dien-9,11-diyne-21,38-dione (7b). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.40–5.31 (m, 4H, CH=CH), 4.17–4.08 (m, 8H, CH_2O), 3.63–3.51 (m, 8H, CH_2O), 3.18–3.11 (m, 4H, CH_2O), 2.27 (t, 4H, CH, J = 7.3 Hz), 2.03–1.91 (m, 8H, CH_2CH=), 1.71–1.60 (m, 4H, CH_2), 1.48–1.37 (m, 8H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 172.0, 130.1, 128.7, 78.1, 72.9, 70.0, 69.2, 69.0, 63.3, 58.7, 33.5, 29.6, 29.2, 27.3, 26.7, 24.8. HRMS (ESI-TOF): found *m*/*z* 583.3258 [M + Na]+; calculated for $C_{32}H_{48}O_8Na^+$ 583.3241. Yield 71%.

(33Z,37Z)-1,4,7,10,17,20,23,26-octaoxacyclotetratetraconta-33,37-dien-12,14-diyne-27,44-dione (7c).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.43–5.32 (m, 4H, CH=CH), 4.12–4.07 (m, 8H, CH_2O), 3.54–3.42 (m, 12H, CH_2O), 3.12–3.01 (m, 8H, CH_2O), 2.24 (t, 4H, CH_2, J = 7.1 Hz), 2.06–1.89 (m, 8H, CH_2CH=), 1.69–1.62 (m, 4H, CH_2), 1.47–1.32 (m, 8H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) =173.0, 130.0, 128.8, 78.0, 73.9, 71.9, 70.1, 69.9, 69.2, 63.4, 58.5, 33.4, 29.7, 29.2, 27.3, 26.7, 24.7. HRMS (ESI-TOF): found *m*/*z* 671.3754 [M + Na]+; calculated for $C_{36}H_{56}O_{10}Na^+$ 671.3766. Yield 70%.

4. Conclusions

Thus, we were the first to carry out the stereoselective synthesis of new acetylene derivatives of fatty acids in the form of diesters (7Z,11Z)-octadeca-7,11-diene-1,18-dioic acid in good yields (68–78%). Based on symmetric diesters with terminal triple bonds, the synthesis of polyether macrodiolides containing conjugated triple bonds and pharmacophoric 1Z,5Z-diene fragments in the structure was carried out for the first time.

Author Contributions: Conceptualization, U.D. and I.I.; methodology, validation, and execution of chemistry experiments, I.G. and I.I.; manuscript preparation, I.G. and I.I. All authors have read and agreed to the published version of the manuscript.

Funding: This work was performed under financial support of the Russian Science Foundation, project number 22-73-10164.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data available on request.

Acknowledgments: The structural studies of the synthesized compounds were performed with the use of Collective Usage Centre "Agidel" at the Institute of Petrochemistry and Catalysis of RAS.

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

References

1. Minto, R.E.; Blacklock, B.J. Biosynthesis and function of polyacetylenes and allied natural products. *Prog. Lipid Res.* **2008**, *47*, 233–306.
2. Zhou, Z-F.; Menna, M.; Cai, Y.-S.; Guoet, Y.-W. Polyacetylenes of Marine Origin: Chemistry and Bioactivity. *Chem. Rev.* **2015**, *115*, 1543–1596.
3. Lee, Y.-J.; Cho, Y.; Tran, H.N.K. Secondary Metabolites from the Marine Sponges of the Genus Petrosia: A Literature Review of 43 Years of Research. *Mar. Drugs* **2021**, *19*, 122.
4. Dzhemileva, L.U.; D'yakonov, V.A.; Islamov, I.I.; Yunusbaeva, M.M.; Dzhemilev, U.M. New 1Z,5Z-diene macrodiolides: Catalytic synthesis, anticancer activity, induction of mitochondrial apoptosis, and effect on the cell cycle. *Bioorganic Chem.* **2020**, *99*, 103832.
5. Islamov, I.I.; Makarov, A.A.; Makarova, E. Kh.; Yusupova, A.V.; D′yakonov, V.A.; Dzhemilev, U.M. Synthesis of macrocyclic and linear compounds with 1Z,5Z-diene and alkynylcarbinol fragments based on (5Z,9Z)-tetradeca-5,9-diene-1,14-diol. *Russ. Chem. Bull*. **2023**, *72*, 925–931.
6. D'yakonov, V.A.; Islamov, I.I.; Dzhemileva, L.U.; Yunusbaeva, M.M.; Dzhemilev, U.M. Stereoselective synthesis and antitumor activity of macrodiolides containing 1*Z*,5*Z*-diene and 1,3-diyne moieties. *Mend. Commun.* **2019**, *29*, 613–615.