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

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Abstract: Stereoselective synthesis of (7Z,11Z)-octadeca-7,11-diene-1,18-dioic acid was carried out using a homo-cyclomagnesiation reaction of 2-(nona-7,8-dien-1-yloxy)tetrahydro-2*H*-pyran. After Steglisch esterification of the synthesized acid and polyester acetylenes 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 *cis*,*cis*-1,5-diene fragments in their structure were synthesized for the first time.

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

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1. Introduction

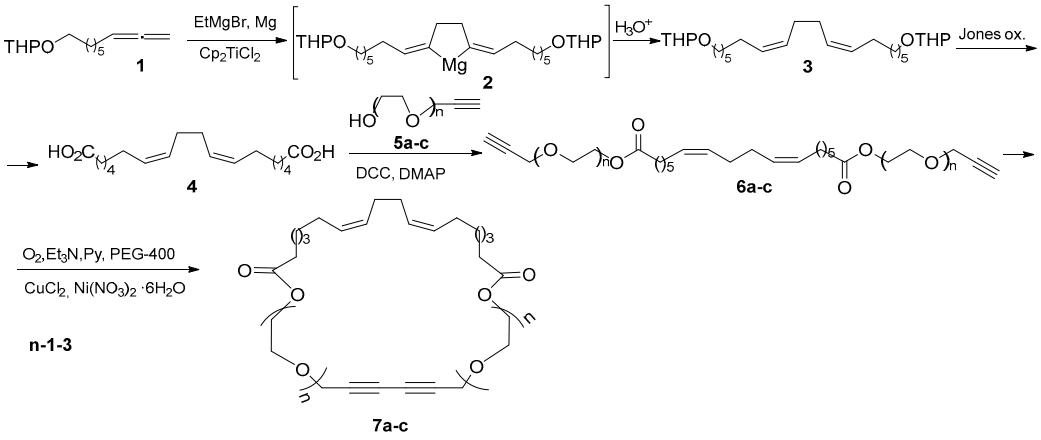
The chemistry of acetylenes and polyacetylenes is one of the intriguing and attractive areas of organic synthesis. This class of unsaturated compounds is widespread in nature, while various acetylene plant metabolites and semisynthetic derivatives synthesized on their basis, with a wide range of biological 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 synthesis of various unsaturated macrodiolides, including those containing acetylene fragments in the structure, which showed cytotoxic activity against various tumor cell lines [4–6].

In the 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 symmetric 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 the intramolecular oxidative coupling of acetylenes according to a previously developed method [6] (Scheme 1).



Scheme 1. Synthesis of polyether macrodiolides.

3. Materials and Methods

^{1}H, ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance-400 spectrometer. The mass spectra were obtained on an UltraFlex III TOF/TOF (Bruker Daltonik GmbH, Bremen, Germany). (7Z,11Z)-octadeca-7,11-diene-1,18-dioic synthesized according to procedures described in the literature [4]. Compounds **6a-c** and **7a-c** were synthesized similarly according to the procedure described in the literature [6].

Bis [2-(prop-2-yn-1-yloxy)ethyl] (7Z,11Z)-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} (7Z,11Z)-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}-(7Z,11Z)-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].

(21Z,25Z)-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%.

(27Z,31Z)-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 diester (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.

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

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