

Proceeding Paper

Synthesis of New 1Z,5Z-Dienoic Macrololides with Benzenyl and Naphthyl Moieties [†]

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Abstract: Macrocycles represent an important class of compounds that are widespread in nature. Of particular interest to researchers are aromatic macrocyclic compounds, which, due to their rigid structure and unique physicochemical properties, can find application in many areas of science, industry and medicine. Previously, we synthesized polyether aromatic macrodiolides, which showed intriguing antitumor properties. In the work, Peyrottes S. and co-authors showed that the introduction of biphenyl or naphthyl rings, as well as triple bonds into the structure of the compounds they synthesized, not only helps to reduce the molecular flexibility of the molecule, but also increases the bioavailability after oral administration of the corresponding neutral prodrugs. Studies in mice have shown that the presence of two aromatic groups is well tolerated and has resulted in compounds with valuable properties in vitro and in vivo [1]. Based on these results, in continuation of our research on the synthesis of biologically active macrodiolides, in the framework of this work, new aromatic macrocycles were synthesized, the structure of which, along with the 1Z,5Z-diene fragment, contains phenyl or naphthyl rings. The target polyester macrodiolides were obtained by Hf-catalyzed intermolecular cyclocondensation of 1,14-tetradeca-5Z,9Z-dienedioic acid with diols synthesized from dihydroxybenzenes and naphthalenediols.

Keywords: 1,5-Dienoic compounds; homo-cyclomagnesiation; polyether macrodiolides; aromatic macrocycles

1. Introduction

Most aromatic macrocycles contain a phenyl fragment with various substituents; macrocycles with biphenyl or naphthalene functional groups are less common. At the same time, the naphthalene framework, due to its diverse biological activity, is a promising building block in the development of drugs. In particular, new derivatives of naphthalene and hybrid molecules based on it are known, which exhibit antiviral, antibacterial, fungicidal and antitumor properties [2,3].

Currently, a large number of naphthalene-based drugs, such as naphyrone, tolnafate, naftifine, nafcillin, terbinafine, propranolol, nabumetone, nafimidone, naproxen, etc., are approved by the FDA and are sold as therapeutic agents [4,5].

Over the past few years, our research group under the direction of prof. V. A. D'yakonov has been conducting research in the field of synthesis of unsaturated macrocyclic compounds that demonstrate good antitumor activity [6-14]. Recently, we have obtained polyether aromatic macrodiolides that are effective inducers of apoptosis in tumor cells [15]. In connection with the interesting properties of compounds with a naphthalene skeleton in the structure, in the development of our research within the framework of this work, the idea of synthesizing new polyether aromatic macrodiolides containing a 1Z,5Z-diene fragment, including together with a naphthalene framework, arose.

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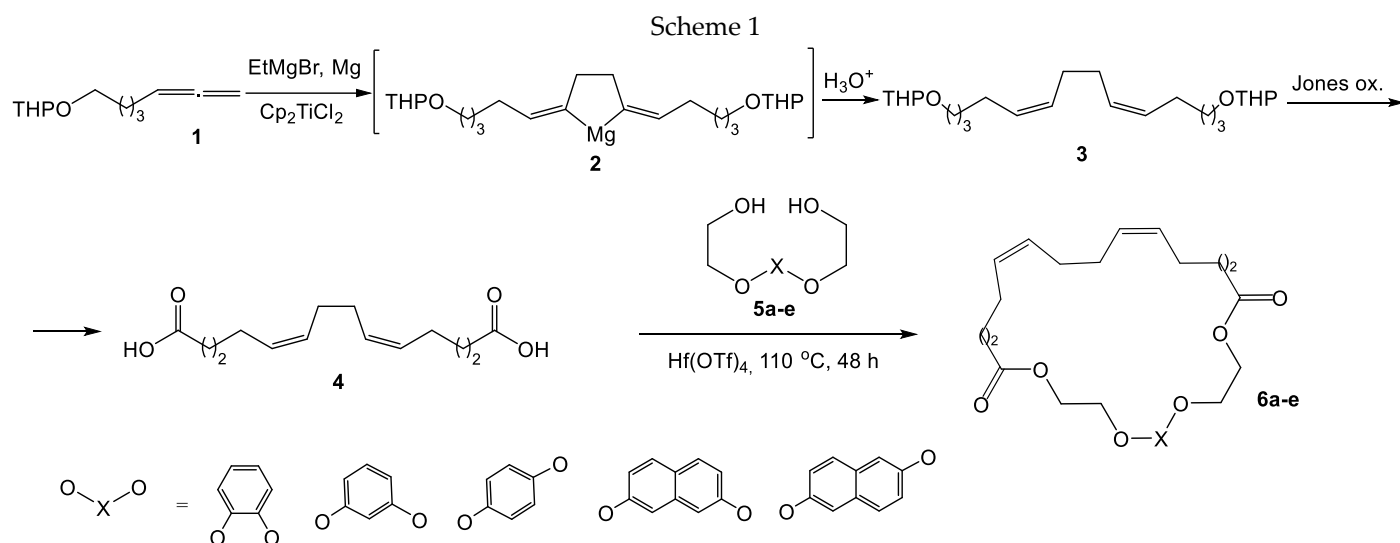
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2. Results and Discussion

Previously, we showed that direct cyclocondensation between α,ω -alka- $nZ,(n+4)Z$ -dienedioic acids and dihydroxybenzenes or naphthalenediols does not occur, however, if the hydroxyl group is located at a distance from the aromatic ring, the occurrence of these reactions becomes possible [14,15]. In connection with the above, in order to obtain new synthetic aromatic macrocycles, we synthesized diols 5a-e, obtained in two stages from dihydroxybenzenes (pyrocatechol, resorcinol, hydroquinone) and naphthalenediols (naphthalene-2,6-diol, naphthalene-2,7-diol) with ethyl bromoacetate [16]. The synthesis of the target macrodiolides was accomplished by cyclocondensation of 1,14-tetradeca-5Z,9Z-dienedioic acid 4 with aromatic diols 5a-e. (Scheme 1).



Scheme 1. Synthesis of aromatic polyether macrodiolides.

Based on our previous studies [14,15], macrocyclization using carbodiimides (DCC, EDCI) catalyzed by 4-dimethylaminopyridine (DMAP) was studied, but in these reactions it was not possible to achieve acceptable yields of the target products. At the same time, intermolecular cyclocondensation catalyzed by Hf(OTf)₄ allows the synthesis of target macrocycles with good yields (64–75%).

3. Materials and Methods

Chemistry

NMR spectra were recorded in CDCl₃ on Bruker Ascend 500 ((500 MHz (¹H), 126 MHz (¹³C)) 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. Macrocylic compounds were synthesized similarly according to the procedure described in the literature [10].

(9Z,13Z)-2,3,6,7,8,11,12,15,16,17,20,21-dodecahydrobenzo[e][1,4,7,10]tetraoxacyclopentacosine-5,18-dione (6a). White waxy solid; yield 72%. ¹H NMR (500 MHz, CDCl₃): δ = 6.94–6.86 (m, 4H), 5.48–5.31 (m, 4H), 4.56–4.48 (m, 4H), 4.36–4.28 (m, 4H), 2.34–2.23 (m, 4H), 2.11–1.95 (m, 8H), 1.71–1.64 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ = 173.6, 149.7, 130.1, 129.2, 122.3, 116.8, 66.7, 62.5, 33.3, 27.6, 26.7, 24.7. ESI-MS: calcd. for C₂₄H₃₂O₆ + H⁺ [M + H]⁺ 417.2272; found 417.2281

(10Z,14Z)-2,5,20,23-tetraoxa-1(1,3)-benzenacyclotricosaphane-10,14-diene-6,19-dione (6b). White waxy solid; yield 75%. ¹H NMR (500 MHz, CDCl₃): δ = 7.21 (t, J = 7,8 Hz, 1H), 6.57–6.50 (m, 3H), 5.46–5.32 (m, 4H), 4.52–4.46 (m, 4H), 4.36–4.24 (m, 4H), 2.33–2.19 (m, 4H), 2.11–1.94 (m, 8H), 1.70–1.62 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ = 173.5, 159.6,

130.1, 130.0, 129.2, 107.2, 101.9, 68.2, 64.1, 33.4, 27.7, 26.6, 24.8. ESI-MS: calcd. for $C_{24}H_{32}O_6 + Na^+ [M + Na]^+$ 439.2091; found 439.2082

(10Z,14Z)-2,5,20,23-tetraoxa-1(1,4)-benzenacyclotricosaphane-10,14-diene-6,19-dione (6c). White waxy solid; yield 71%. 1H NMR (500 MHz, $CDCl_3$): δ = 6.86 (s, 4H), 5.45–5.32 (m, 4H), 4.51–4.40(m, 4H), 4.37–4.27 (m, 4H), 2.35–2.22 (m, 4H), 2.12–1.91 (m, 8H), 1.74–1.68 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.5, 152.5, 130.2, 129.1, 115.4, 66.5, 62.4, 33.4, 27.5, 26.8, 24.8. ESI-MS: calcd. for $C_{24}H_{32}O_6 + H^+ [M + H]^+$ 417.2272; found 417.2279

(10Z,14Z)-2,5,20,23-tetraoxa-1(2,7)-naphthalenacyclotricosaphane-10,14-diene-6,19-dione (6d). White waxy solid; yield 67%. 1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.3 Hz, 2H), 7.13–7.04 (m, 4H), 5.29–5.17 (m, 4H), 4.60–4.48 (m, 4H), 4.36–4.24 (m, 4H), 2.44–2.30 (m, 4H), 2.14–1.87 (m, 8H), 1.70–1.62 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.6, 157.2, 135.7, 131.9, 130.4, 129.2, 124.8, 116.2, 107.4, 66.4, 62.8, 33.5, 27.2, 26.9, 24.7. ESI-MS: calcd. for $C_{28}H_{34}O_6 + H^+ [M + H]^+$ 467.2428; found 467.2439

(10Z,14Z)-2,5,20,23-tetraoxa-1(2,6)-naphthalenacyclotricosaphane-10,14-diene-6,19-dione (6e). White waxy solid; yield 64%. 1H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, J = 5.8 Hz, 2H), 7.17–7.07 (m, 4H), 5.35–5.16 (m, 4H), 4.55–4.46 (m, 4H), 4.36–4.25 (m, 4H), 2.39–2.21 (m, 4H), 2.06–1.92 (m, 8H), 1.76–1.65 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.6, 155.5, 131.2, 130.2, 129.9, 128.2, 125.0, 119.3, 66.5, 63.2, 33.6, 27.2, 26.4, 24.7. ESI-MS: calcd. for $C_{28}H_{34}O_6 + H^+ [M + H]^+$ 467.2428; found 467.2431

4. Conclusions

As a result of the conducted research, stereoselective synthesis of polyether aromatic macrodiolides containing pharmacophoric 1Z,5Z-diene, phenyl and naphthyl fragments was carried out for the first time with yields of 64–75%.

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

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