

# New 1Z,5Z-Diene Compounds: Stereoselective Synthesis of Tetraenoic Macrolidides †

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**Abstract:** Macrocyclic compounds, including macrolactones and macrodiolides, play a significant role in the development of supramolecular chemistry, materials science, the perfume industry, and pharmaceuticals. In previous studies conducted by our group over several years, previously undescribed macrocyclic compounds containing pharmacophoric 1Z,5Z-diene fragments in their structure were synthesized for the first time, which showed high potential in studies on cytotoxicity, apoptosis-inducing activity, effects on the cell cycle, and mitochondria in tumor cell lines (Jurkat, K562, U937). As part of the continuing research on the development of methods for synthesizing new unsaturated macrodiolides and studying their antitumor properties, this work presents, for the first time, the stereoselective synthesis of macrocyclic compounds based on 1,14-tetradeca-5Z,9Z-dienoic acid and  $\alpha,\omega$ -alka-nZ, (n + 4)Z-dienediols (1,12-dodeca-4Z,8Z-dienediol, 1,14-tetradeca-5Z,9Z-dienediol, 1,16-octadeca-6Z,10Z-dienediol) in good yields. The method for the synthesis of new macrodiolides is based on the previously well-proven reaction of direct intermolecular cyclocondensation of dienedioic acid with diene diols in the presence of 5 mol.% hafnium(IV) triflate. As a result of the experiments, it was shown that the reaction between 1,14-tetradeca-5Z,9Z-dienedioic acid and 1,16-octadeca-6Z,10Z-dienediol in toluene proceeded within 18 h with the highest yield of 76%, with the formation of previously undescribed tetraenoic macrodiolides containing two 1Z,5Z-diene fragments in their structure.

**Keywords:** homo-cyclomagnesiation; 1,5-dienoic compounds; hafnium(IV) triflate; macrodiolides



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## 1. Introduction

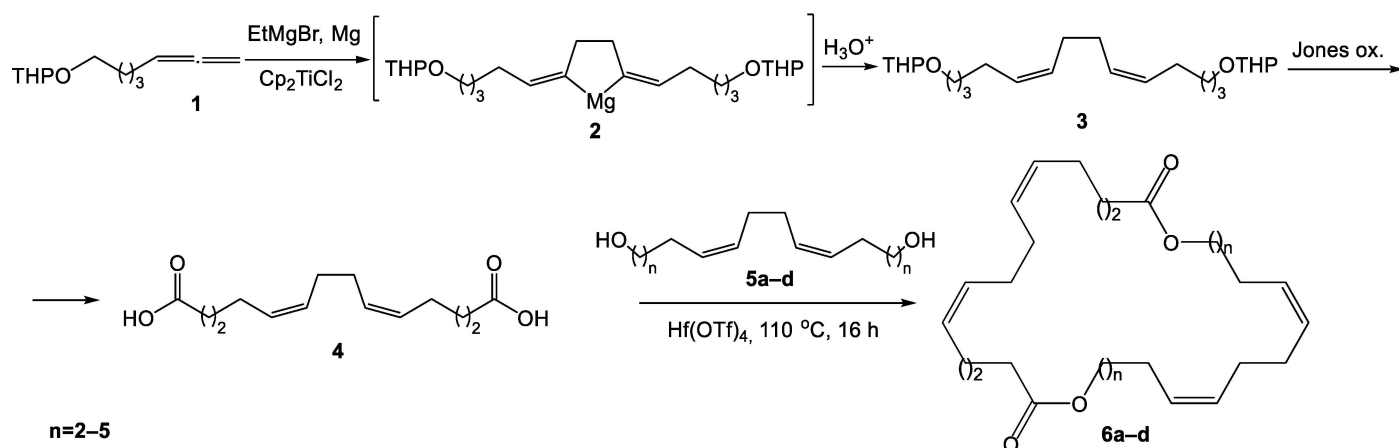
Due to their availability and diversity, natural organic biologically active compounds are often used in clinical medicine as alternative low-toxicity agents in comparison with classical synthetic drugs. Some of the most prominent representatives of the indicated compounds are polyene macrolides, on the basis of which a large number of antibacterial and antifungal drugs currently used in human therapy (spiramycin, amphotericin, nystatin, etc.) have been obtained [1–5]. A special place among this diversity of natural compounds is occupied by unsaturated macrocyclic compounds with various pharmacophoric functional groups, combined into one hybrid macrocyclic platform. The introduction of pharmacophoric fragments into the structure of the macrocyclic platform can contribute to a decrease in toxicity, an increase in affinity for the cell membrane, as well as self-association and aggregation processes, while maintaining the properties of the pharmacophores themselves [6,7].

Despite the widespread use and active application of unsaturated macrocycles in medicine, polyenes have disadvantages such as poor solubility in water, high hematotoxicity, and a number of other side effects that drive researchers to intensively search for new, less toxic, and more effective drugs [8,9].

In our opinion, some of the new representatives of low-toxicity biologically active unsaturated macrolactones may be macrocyclic compounds containing bis-methylene-separated double bonds in the structure. It was previously shown that the compounds we synthesized, including macrodiolides with a 1Z,5Z-diene fragment in the structure, exhibited pronounced antitumor properties, while having low toxicity to healthy cells [10–19].

## 2. Results and Discussion

In the present work, the synthesis of new unsaturated macromolecules with several 1Z,5Z-diene fragments in the structure for subsequent study of their biological properties is realized. Taking into account the previous studies, a scheme for the preparation of new tetraene macrodiolides from 1,14-tetradeca-5Z,9Z-dienoic acid **4** and  $\alpha,\omega$ -alka-nZ, (n + 4)Z-dienediols **5a–d** was developed, the synthesis of which is based on the use of the reaction of catalytic homo-cyclomagnesiation of 1,2-dienes (Dzhe-milev reaction) [10,20]. The target macrodiolides were synthesized using Hf-catalyzed intermolecular cyclocondensation of dienic acid **4** with diols **5a–d** in yields of 67–76% (Scheme 1) [10].



**Scheme 1.** Synthesis of tetraenoic macrodiolides.

## 3. Materials and Methods

### Chemistry

NMR spectra were recorded in  $\text{CDCl}_3$  on Bruker Ascend-500 (Bruker AXS GmbH, Karlsruhe, Germany) ((500 MHz ( $^1\text{H}$ ), 126 MHz ( $^{13}\text{C}$ )) 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. Macrocyclic compounds were synthesized similarly according to the procedure described in the literature [10].

(5Z,9Z,19Z,23Z)-1,14-dioxacyclooctacos-5,9,19,23-tetraene-15,28-dione (**6a**). Yellow oil; yield 67%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.45–5.34 (m, 8H), 4.09 (t,  $J$  = 6.2 Hz, 4H), 2.33 (t,  $J$  = 7.3 Hz, 4H), 2.23–1.82 (m, 16H), 1.82–1.63 (m, 8H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.7, 130.3, 130.2, 129.0, 128.8, 63.6, 33.6, 28.6, 27.4, 27.3, 26.5, 24.8, 23.6. ESI-MS: calcd. for  $\text{C}_{26}\text{H}_{40}\text{O}_4 + \text{H}^+$   $[\text{M} + \text{H}]^+$  4,172,999; found 417.2985.

(6Z,10Z,21Z,25Z)-1,16-dioxacyclotriaconta-6,10,21,25-tetraene-2,15-dione (**6b**). Yellow oil; yield 74%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.45–5.33 (m, 8H), 4.09 (t,  $J$  = 6.6 Hz, 4H), 2.32 (t,  $J$  = 7.4 Hz, 4H), 2.12–1.94 (m, 16H), 1.74–1.57 (m, 8H), 1.47–1.38 (m, 4H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.7, 130.2, 129.7, 129.6, 129.0, 64.2, 33.6, 28.2, 27.4, 27.3, 26.7, 26.5, 26.1, 24.8. ESI-MS: calcd. for  $\text{C}_{28}\text{H}_{44}\text{O}_4 + \text{H}^+$   $[\text{M} + \text{H}]^+$  4,453,312; found 4,453,321.

(6Z,10Z,22Z,26Z)-1,16-dioxacyclodotriaconta-6,10,22,26-tetraene-2,15-dione (**6c**). Yellow oil; yield 76%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.44–5.34 (m, 8H), 4.08 (t,  $J$  = 6.4 Hz, 4H), 2.32 (t,  $J$  = 7.4 Hz, 4H), 2.12–1.95 (m, 16H), 1.73–1.62 (m, 8H), 1.40–1.32 (m, 8H).  $^{13}\text{C}$

NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 173.7, 130.2, 129.9, 129.5, 129.0, 64.3, 33.6, 29.2, 28.5, 27.5, 27.4, 26.9, 26.5, 25.6, 24.9$ . ESI-MS: calcd. for  $\text{C}_{30}\text{H}_{48}\text{O}_4 + \text{H}^+$   $[\text{M} + \text{H}]^+$  473.3625; found 473.3652. (6Z,10Z,23Z,27Z)-1,16-dioxacyclotetraconta-6,10,23,27-tetraene-2,15-dione (6d). Yellow oil; yield 74%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 5.38$  (m, 8H), 4.08 (t,  $J = 6.5$  Hz, 4H), 2.32 (t,  $J = 7.4$  Hz, 4H), 2.12–1.92 (m, 16H), 1.74–1.62 (m, 8H), 1.41–1.29 (m, 12H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 173.7, 130.2, 130.1, 129.3, 129.0, 64.4, 33.7, 29.5, 28.7, 28.6, 27.5, 27.3, 26.9, 26.5, 25.8, 24.9$ . ESI-MS: calcd. for  $\text{C}_{32}\text{H}_{52}\text{O}_4 + \text{H}^+$   $[\text{M} + \text{H}]^+$  501.3938; found 501.3953.

#### 4. Conclusions

Thus, within the framework of the presented work, a scheme for the catalytic stereoselective synthesis of previously undescribed tetraene macrodiolides with yields of 67–76% was developed.

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

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