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

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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 during research of cytotoxicity, apoptosis-inducing activity, effects on the cell cycle and mitochondria in tumors cell lines (Jurkat, K562, U937). As part of continuing research on the development of methods for the synthesis of new unsaturated macrodiolides and the study of their antitumor properties, in this work, for the first time, stereoselective synthesis of macrocyclic compounds based on 1,14-tetradeca-5Z,9Z-dienoic acid and α,ω-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 proceeds within 18 hours 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-toxic agents in comparison with classical synthetic drugs. Some of the brightest 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 [1,2]. 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 [3].

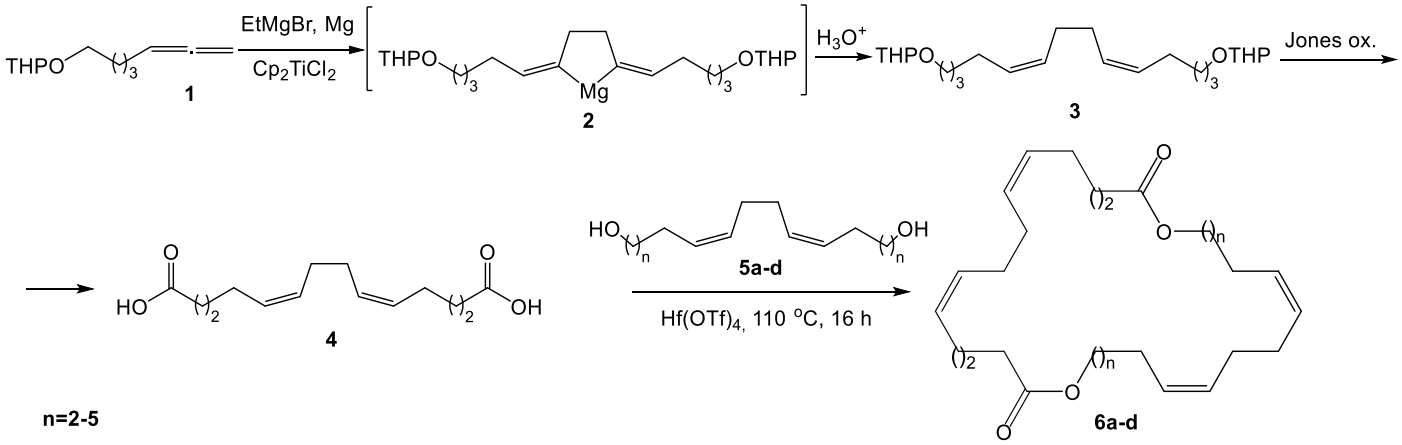
Despite the widespread use and active application of unsaturated macrocycles in medicine, polyenes have such disadvantages as poor solubility in water, high hematotoxicity, and a number of other side effects that stimulate researchers to intensively search for new, less toxic, and more effective drugs [4].

In our opinion, some of the new representatives of low-toxic 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 1*Z*,5*Z*-diene fragment in the structure, exhibit pronounced antitumor properties, while being low toxic to healthy cells [5-15].

2. Results and Discussion

In the present work, the synthesis of new unsaturated macromolecules with several 1*Z*,5*Z*-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-5*Z*,9*Z*-dienoic acid **4** and α,ω-alka-n*Z*, (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 (Dzhemilev reaction) [5,6,16]. 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) [5,6].

Схема 1



Scheme 1. Synthesis of tetraenoic macrodiolides.

3. Materials and Methods

Chemistry

NMR spectra were recorded in $CDCl_3$ on Bruker Ascend-500 ((500 MHz (^{1}H), 126 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. Macrocyclic compounds were synthesized similarly according to the procedure described in the literature [5,6].

(5Z,9Z,19Z,23Z)-1,14-dioxacyclooctacosa-5,9,19,23-tetraene-15,28-dione (6a). Yellow oil; yield 67%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 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}C NMR (126 MHz, $CDCl_3$): δ = 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 $C_{26}H_{40}O_4$ + H^+ $[M + H]^+$ 417,2999; found 417.2985

(6Z,10Z,21Z,25Z)-1,16-dioxacyclotriaconta-6,10,21,25-tetraene-2,15-dione (6b). Yellow oil; yield 74%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 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}C NMR (126 MHz, $CDCl_3$): δ = 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 $C_{28}H_{44}O_4$ + H^+ $[M + H]^+$ 4,453,312; found 4,453,321

(6Z,10Z,22Z,26Z)-1,16-dioxacyclododotriaconta-6,10,22,26-tetraene-2,15-dione (6c). Yellow oil; yield 76%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 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}C NMR (126 MHz, $CDCl_3$): δ = 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 $C_{30}H_{48}O_4$ + H^+ $[M + H]^+$ 473.3625; found 473.3652

(6Z,10Z,23Z,27Z)-1,16-dioxacyclotetratriaconta-6,10,23,27-tetraene-2,15-dione (6d). Yellow oil; yield 74%. ^{1}H NMR (500 MHz, $CDCl_3$): δ =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}C NMR (126 MHz, $CDCl_3$): δ = 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 $C_{32}H_{52}O_4$ + H^+ $[M + H]^+$ 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.

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

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

References

1. Caffrey, P.; Hogan, M.; Song, Y. New Glycosylated Polyene Macrolides: Refining the Ore from Genome Mining. *Antibiotics* **2022**, *11*, 334.
2. Qiao, L.; Dong, Y.; Zhou, H.; Cui, H. Effect of Post–Polyketide Synthase Modification Groups on Property and Activity of Polyene Macrolides. *Antibiotics* **2023**, *12*, 119.
3. Shurpik, D.N.; Akhmedov, A.A.; Cragg, P.J.; Plemenkov, V.V.; Stoikov, I.I. Progress in the Chemistry of Macrocyclic Meroterpenoids. *Plants* **2020**, *9*, 1582.
4. Olsufyeva, E.N.; Yankovskaya, V.S. Main trends in the design of semi-synthetic antibiotics of a new generation. *Russ. Chem. Rev.* **2020**, *89*, 339–378.
5. D'yakonov, V.A.; Islamov, I.I.; Dzhemileva, L.U.; Khusainova, E.M.; Yunusbaeva, M.; Dzhemilev, U.M. Targeted synthesis of macrodiolides containing bis-methylene-separated Z-double bonds and their antitumor activity in vitro. *Tetrahedron* **2018**, *74*, 4606–4612.
6. 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. *Bioorg. Chem.* **2020**, *99*, 103832.
7. D'yakonov, V.A.; Islamov, I.I.; Dzhemileva, L.U.; Makarova, E.K.; Dzhemilev, U.M. Direct synthesis of polyaromatic cyclophanes containing bis-methylene-interrupted *Z*-double bonds and study of their antitumor activity in vitro. *Int. J. Mol. Sci*. **2021**, *22*, 8787.
8. Islamov, I.I.; Dzhemileva, L.U.; Gaisin, I.V.; Dzhemilev, U.M.; D' yakonov, V.A. New Polyether Macrocycles as Promising Antitumor Agents─ Targeted Synthesis and Induction of Mitochondrial Apoptosis. *ACS Omega* **2024**, *9*, 19923–19931.
9. D'yakonov, V.A.; Makarov, A.A.; Dzhemileva, L.U.; Makarova, E.K.; Khusnutdinova, E.K.; Dzhemilev, U.M. The facile synthesis of the 5Z,9Z-dienoic acids and their topoisomerase I inhibitory activity. *Chem. Commun.* **2013**, *49*, 8401–8403.
10. D'yakonov, V.A.; Dzhemileva, L.U.; Makarov, A.A.; Mulyukova, A.R.; Baev, D.S.; Khusnutdinova, E.K.; Tolstikova, T.G.; Dzhemilev, U.M. nZ,(n + 4)Z-Dienoic fatty acids: A new method for the synthesis and inhibitory action on topoisomerase I and IIα. *Med. Chem. Res.* **2016**, *25*, 30.
11. D'yakonov, V.A.; Dzhemileva, L.U.; Dzhemilev, U.M. Natural compounds with bis-methylene-interrupted Z-double bonds: Plant sources, strategies of total synthesis, biological activity, and perspectives. *Phytochem. Rev.* **2021**, *20*, 325–342.
12. D'yakonov, V.A.; Makarov, A.A.; Dzhemileva, L.U.; Ramazanov, I.R.; Makarova, E.K.; Dzhemilev, U.M. Natural Trienoic Acids as Anticancer Agents: First Stereoselective Synthesis, Cell Cycle Analysis, Induction of Apoptosis, Cell Signaling and Mitochondrial Targeting Studies. *Cancers* **2021**, *13*, 1808.

13. Islamov, I.I.; Yusupova, A.V.; D'yakonov, V.A.; Dzhemilev, U.M. Synthesis of polyether macrodiolides based on acetylenic derivatives of (5*Z*, 9*Z*)-tetradeca-5, 9-diene-1, 14-dioic acid. *Russ. Chem. Bulletin.* **2023**, *72*, 2473–2483.
14. Islamov, I.I.; Makarov, A.A.; Makarova, E.K.; Yusupova, A.V.; D'yakonov, V.A.; Dzhemilev, U.M. Synthesis of macrocyclic and linear compounds with 1 Z, 5 Z-diene and alkynylcarbinol fragments based on (5 Z, 9 Z)-tetradeca-5, 9-diene-1, 14-diol. *Russ. Chem. Bulletin.* **2023**, *72*, 925–931.
15. Islamov, I.I.; Gaisin, I.V.; Dzhemilev, U.M.; D'yakonov, V.A. Synthesis of macrocyclic mono-and diolides based on new ω-hydroxyalkadienoic acids with (Z, Z)-1, 5-diene moiety. *Russ. Chem. Bulletin*. **2024**, *73*, 1623–1630.
16. D'yakonov, V.A.; Makarov, A.A.; Makarova, E.K.; Dzhemilev, U.M. Novel organomagnesium reagents in synthesis. Catalytic cyclomagnesiation of allenes in the synthesis of N-, O-, and Si-substituted 1Z, 5Z-dienes. *Tetrahedron* **2013**, *69*, 8516–8526.