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Natural and Synthetic Dienoic and Trienoic Acids—An Original Method for the Synthesis and Antitumor Activity †

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Abstract: The report contains the recent data about our research on the synthesis and study of the properties of unique natural and synthetic Z,Z-dienoic and Z,Z,Z-trienoic fatty acids exhibiting a wide range of biological activities (antiviral, antibacterial, neuritogenic, antitumor, antiparasitic, fungicidal). All the methods and approaches for the synthesis of the above-mentioned unsaturated carboxylic acids presented in the report are based on the using at the key stage of the synthesis of the catalytic cross-cyclomagnesiation of 1,2-dienes developed by the main co-authors.

Keywords: Z,Z-dienoic and Z,Z,Z-trienoic fatty acids; cross-cyclomagnesiation; anti-cancer activity

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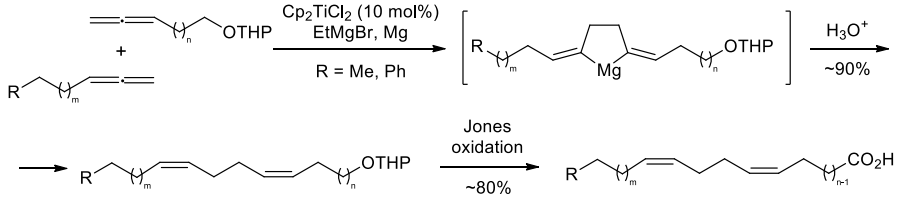
1. Introduction

5Z,9Z-Dienoic acids with a long hydrocarbon chain from C16 to C34, belonging to the class of non-methylene-interrupted fatty acids, are found in trace amounts in molluscs, sea sponges [1] and seeds of gymnosperms [2,3]. It is known that some representatives of these acids exhibit antimalarial, antimicrobial [4], antibacterial, antileishmania, anti-tuberculosis, and antitumor activity [5]. Earlier, several scientific groups have shown that 5Z,9Z-dienoic acids are inhibitors of cell cycle enzymes–topoisomerases, catalyzing DNA relaxation reactions during replication, regulating processes that are essential for cell life [6–9]. In the world literature, there are no general, universal methods for the synthesis of 1Z,5Z-diene compounds of high stereochemical purity, in addition, the known methods for the synthesis of 1Z,5Z-dienes are multistage and the yields of the final compounds vary within 5–15% [10]. Meanwhile, the low content, the complexity of the isolation of individual 5Z,9Z-dienoic acids and the lack of effective methods for their synthesis significantly hampered studies on identifying the patterns of the effect of the structure on the manifested biological activity.

Recently, using a new reaction of catalytic cross-cyclomagnesiation of aliphatic and O-containing 1,2-dienes at the key stage of the synthesis, we have developed an original, stereoselective method for obtaining fatty acids containing 1Z,5Z-diene fragment in a given position relative to the carboxyl group (Scheme 1) [7].

The developed approach made it possible to synthesize a line of 5Z,9Z-diene acids of various lengths of the hydrocarbon chain and an acid with different positions of the 1Z,5Z-diene fragment relative to the carboxyl group. As a result, it was shown that the chain length, the nature of the substituent and the position of the 1Z,5Z-diene group have a significant effect on the inhibitory activity against topoisomerases. Thus, among the synthesized acids, selective inhibitors of topoisomerase I and topoisomerase IIα were found, as well as acids exhibiting dual inhibitory activity against topoisomerases [7–9,11,12].

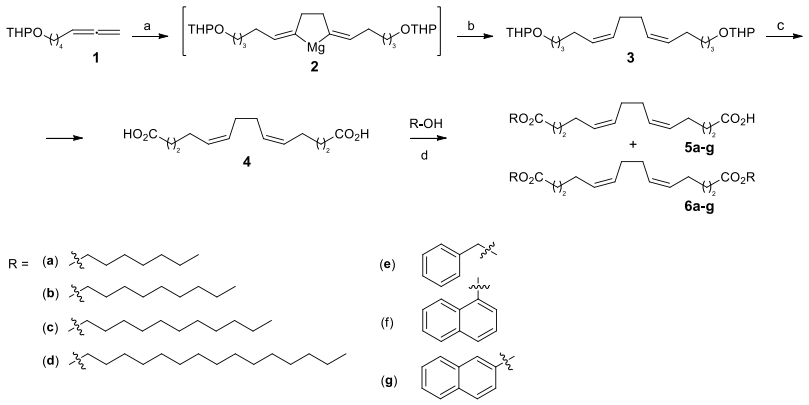


Scheme 1. Ti-Catalyzed cross-cyclomagnesiation of aliphatic and oxygenated 1,2-dienes in the synthesis of n*Z*,(n + 4)*Z*-dienoic acids.

2. Synthesis of Synthetic Analogs of 5Z,9Z-Diene Acids

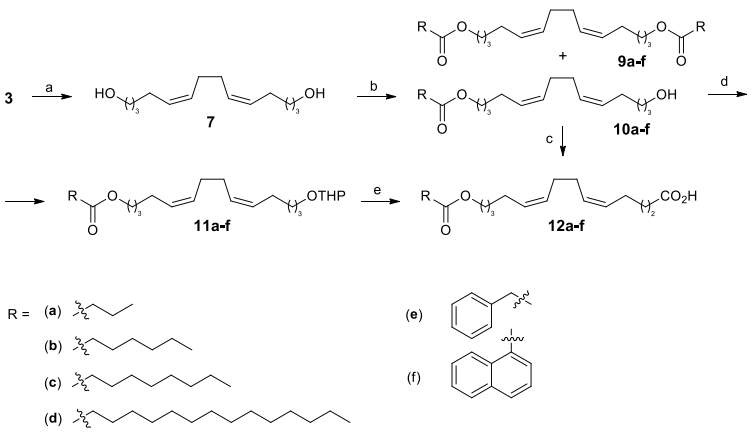
We have synthesized new derivatives of 5Z,9Z-dienoic acids by esterification reactions of aliphatic and aromatic alcohols and carboxylic acids with (5Z,9Z)-1,14-undeca-5,9-dienedicarboxylic acid or (5Z,9Z)-1,14-undeca-5,9-dienediol obtained using the reaction of Ti-catalyzed homo-cyclomagnesiation of tetrahydropyran ether of hepta-5,6-diene-1-ol using Grignard reagents [13].

So, for the synthesis of the first line of 5Z,9Z-dienoic acids, at the first stage, we carried out the homo-cyclomagnesiation of tetrahydropyran ester 5,6-hepta-5,6-dien-1-ol 1 using EtMgBr in the presence of magnesium and the catalyst Cp_2TiCl_2 (5 mol%). Acid hydrolysis of the in situ formed magnesacyclopentane **2** gives 1,14-bis-tetrahydropyranyl-5Z,9Z-diene-1,14-diol **3** in 76% yield. The latter, as a result of oxidation with the Jones reagent, leads to (5Z,9Z)-tetradeca-5,9-dienedioic acid **4** with a yield of 57% (Scheme 3). Subsequently, by the reaction of catalytic esterification of aliphatic and aromatic alcohols with (5Z,9Z)-tetradeca-5,9-dienedioic acid **4** using DCC/DMAP, the target 5Z,9Z-dienoic acids **5a-g** were obtained in 69–81% yields, along with symmetric dimers **6a-g**, the yield of which does not exceed 15% (Scheme 2).



Scheme 2. Ti-Catalyzed homo-cyclomagnesiation of oxygenated 1,2-dienes in the synthesis of 5*Z*,9*Z*-dienoic acids. (**a**): EtMgBr, Mg, Cp_2TiCl_2 (5 mol%), Et_2O; (**b**):H_3O^+; (**c**):H_2CrO_4/H_2SO_4, acetone, CH_2Cl_2; (**d**) DCC/DMAP.

In continuation of studies in the chosen direction, we also thought it interesting to study the influence of the orientation of the ester group in a series of synthesized analogs of natural 5Z,9Z-diene acids on their cytotoxicity towards tumor cell lines. Therefore, an original scheme for the synthesis of 5Z,9Z-dienoic acids was developed, including the esterification of carboxylic acids with (5Z,9Z)-1,14-undeca-5,9-dienediol, obtained by removing the tetrahydropyran protection from ester **3** using p-TSA, CHCl3 / CH3OH, at the first stage to obtain mono-**10a-f** and diesters **9a-f** of diol **7**. Further, target acids **12a-f** can be obtained in two ways—direct oxidation of alcohols **10a-f** with pyridinium dichromate (PDC) or oxidation of tetrahydropyran esters **11a-f** corresponding to alcohols **10a-f** with Jones reagent (Scheme 3).



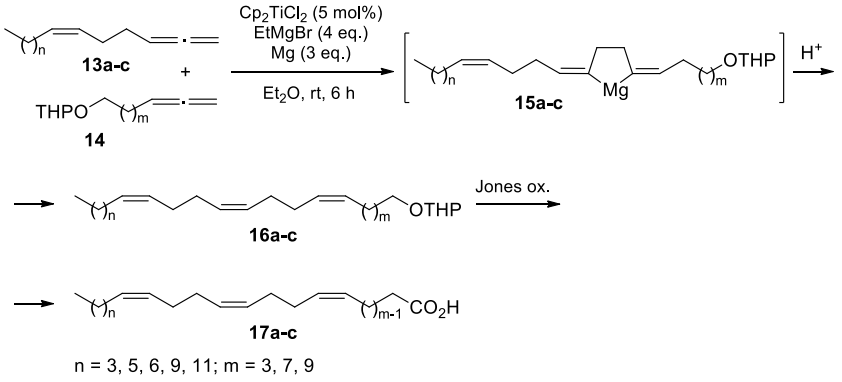
Scheme 3. Ti-Catalyzed homo-cyclomagnesiation of oxygenated 1,2-dienes in the synthesis of 5Z,9Z-dienoic acids. (**a**): p-TSA, $CHCl_3/CH_3OH$; (**b**):DCC/DMAP; (**c**): PDC; (**d**): 3,4-dihydro-2H-pyran, HCl; (**e**) H_2CrO_4/H_2SO_4, acetone, CH_2Cl_2.

In the development of these studies, we have developed a method for the preparation of synthetic analogs of 5Z,9Z-diene acids based on steroids, fullerene C60 [14–19].

3. Synthesis of Natural and Synthetic Trienoic Acids Containing Bis-Methylene Separated Z-Double Bonds

A new effective method has been developed for the synthesis of unique trienoic acids containing in their structure 1Z,5Z,9Z-triene fragment [20], including natural ones found in the composition of phospholipids of the sea anemone *Stoichactis helianthus* [21]. The negligible content of these acids in natural objects and the difficulty of their isolation are the main limiting factors for the study of their biomedical potential.

At the next stage, according to the scheme for the complete synthesis of 1Z,5Z,9Z-trienoic acids developed on the basis of the retrosynthetic analysis, we carried out the reactions of intermolecular cross-cyclomagnesiation of (6Z)-alk-1,2,6-trienes **13a-c** with tetrahydropyran ether 1,2-dienol **14** using EtMgBr in the presence of Mg (powder) and catalytic amounts of Cp_2TiCl_2 (**13a-c**: **14**: EtMgBr: Mg: [Ti] = 12: 10: 36: 24: 0.1, Et2O, 20–22 °C, 10 h), which, after acidic hydrolysis of the in situ formed magnesacyclopentanes **15a-c**, led to tetrahydropyran esters **16a-c** containing 1Z,5Z,9Z-triene fragments in 81–89% yields. At the final stage, the target acids 17a-c were obtained by oxidation of esters **16a-c** with Jones reagent in 61–64% yields (Scheme 4).



Scheme 4. (*Z*,*Z*,*Z*)- Stereoselective synthesis of trienoic acids.

Using the developed ideology, we have implemented original approaches to the synthesis of natural and synthetic di- and triene acids, as well as studied their antitumor activity using modern methods of flow cytometry and multiplex analysis.

Experimental section, 1H and 13C NMR spectra and general procedure for all synthesized compounds are presented in previously published articles [7–9,11–19].

4. Conclusions

Thus, we have developed new effective methods for the synthesis of natural and synthetic di- and trienoic acids using at the key stage of the reaction Ti-catalyzed cross-cyclomagnesiation of terminal allenes (Dzhemilev reaction) with high yields and stereoselectivity, possessing antiviral, antitumor and antifungal activity. For the synthesized acids, the in vitro antitumor activity was assessed on Jurkat, K562, HL-60, U937 cell lines and fibroblasts, including the determination of IC50 using flow cytometry and multiplex analysis.

Author Contributions: Conceptualization, U.M.D. and L.U.D.; methodology, A.A.M.; validation, E.K.M.; resources, E.K.M.; data curation, U.M.D.; writing—original draft preparation, E.K.M.; A.A.M.; writing—review and editing, U.M.D. and L.U.D.; visualization, E.K.M.; supervision, U.M.D.; project administration, A.A.M.; funding acquisition, A.A.M. 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.

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