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Synthesis of a Hybrid Molecule Based on Biologically Active 5Z,9Z-Eicosadienoic Acid and Vanillin †

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Abstract: A hybrid compound based on (5Z,9Z)-eicosa-5,9-dienoic acid and vanillin was synthesized in high yield (94%) using a new intermolecular cross-cyclomagnesiation reaction of aliphatic and O-containing 1,2-dienes catalyzed by Cp_2TiCl_2.

Keywords: 1,2-dienes; cross-cyclomagnesiation; vanillin

1. Introduction

Vanillin (4-hydroxy-3-methoxybenzaldehyde) isolated from orchids (*Vanilla planifolia*, *V. pompona* or *V. tahitiensis*) is attracting attention for several reasons. First, vanillin as a flavoring agent is used in the food, nutraceutical, and pharmaceutical industries. Secondly, vanillin has a simple chemical structure, which can simplify its synthesis to some extent. Third, vanillin has been shown to have various biological activities, such as antitumor, antioxidant, and antimicrobial properties [1,2]. In addition, vanillin exhibited a neuroprotective effect in an experimental model of Huntington's disease and ischemia [3].

An analysis of the literature showed that vanillin derivatives also exhibit versatile biological activity. In the studies of Boiko Y. A., the analgesic and anti-inflammatory activity of vanillin and its derivatives was established, which is associated with the effect of these substances on the TRPA-1 and TRPV-1 ion channels [4]. Scipioni M. and colleagues synthesized a number of vanillin derivatives and simultaneously demonstrated that their antioxidant activity is similar to the reference antioxidant Trolox [5]. Vanillin derivatives have a high antioxidant potential and a protective effect against oxidative stress in neuroblastoma cells [6]. Li's research group reported the synthesis of a number of dendrimers from vanillin that have antioxidant properties and protective effects on fatty acids, DNA, and lipoproteins [7]. Vanillin derivatives are also used as multipurpose drugs for the treatment of atopic dermatitis with positive pharmacokinetic and pharmacodynamic results. Mourtzinos and colleagues have shown that carboxylic acid, obtained by oxidation of vanillin, increases its antibacterial effect [8].

Given the high biomedical potential of vanillin derivatives, we put forward the idea of synthesizing a hybrid compound based on 5Z,9Z-eicosa-5,9-dienoic acid and vanillin. We have previously shown that (5Z,9Z)-eicosa-5,9-dienoic acid has a high inhibitory activity of topoisomerases I (hTop1) and II (hTop2α) in vitro [9,10].

2. Results and Discussion

Using the cross-molecular cyclomagnesiation reaction of trideca-1,2-diene **1** with 2-(hepta-5,6-dien-1-yloxy)tetrahydro-2H-pyran **2** with EtMgBr in the presence of a Cp_2TiCl_2

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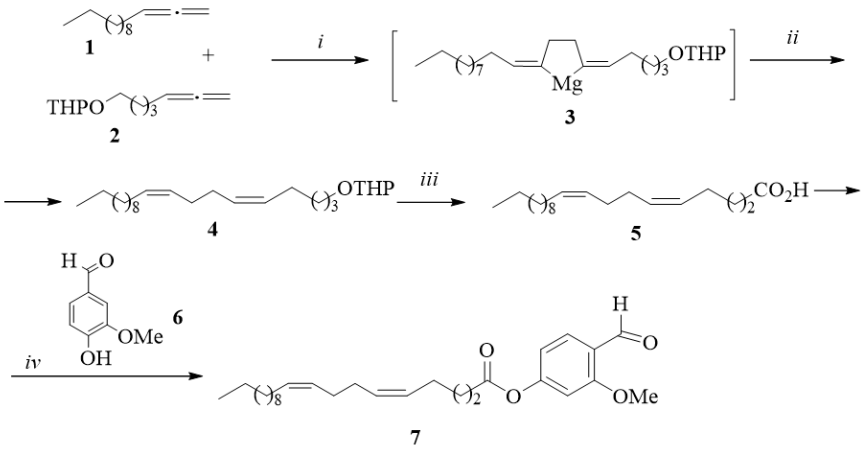
catalyst gave 2,5-dialkylidenemagnezacyclopentane **3**. Acid hydrolysis of cyclomagnesiation product **3** and oxidation of the formed tetrahydropyranyl ether 5Z with the Jones reagent, 9Z-diene **4**, leads to 5Z,9Z-eicosadienoic acid **5**. The esterification reaction of (5Z,9Z)-eicosa-5,9-dienoic acid **5** with vanillin **6** was carried out in CH_2Cl_2 at 0 °C in the presence of 4-dimethylaminopyridine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; as a result, the target product was obtained with a yield of 94% (Scheme 1).



Reagents and reaction conditions: *i*. Cp_2TiCl_2 (5 mol.%), EtMgBr (2 eq.), Mg (2 eq.), THF, 20–22 °C, 10 h; *ii*. HCl 5%, 72–86%; *iii*. Jones reagent; *iv*. DMAP, DCC, CH_2Cl_2, 2 h, 0 °C.

Scheme 1. Synthesis of a hybrid compound based on (5Z,9Z)-eicosa-5,9-dienoic acid and vanillin.

3. Conclusions

Thus, we have synthesized a hybrid compound based on natural biologically active (5Z,9Z)-eicosa-5,9-dienoic acid and vanillin with high yield (94%), using a new reaction of intermolecular cross-cyclomagnesiation of aliphatic and O-containing 1,2-dienes catalyzed by Cp_2TiCl_2 at the key stage.

4. Experimental Procedure

4-formyl-3-methoxyphenyl (5Z,9Z)-icosa-5,9-dienoate (**7**)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, *J* = 6.6 Hz, 3H), 1.45–1.28 (m, 16H), 2.03–1.77 (m, 2H), 2.22–2.12 (m, 8H), 265–2.60 (m, 2H), 3.91 (s, 3H), 5.51–5.34 (m, 4H), 7.51–7.20 (m, 3H), 9.96 (s, 1H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 191.03, 171.23, 152.01, 145.08, 135.16, 130.72, 130.60, 128.90, 128.62, 124.75, 123.42, 110.79, 56.04, 33.35, 31.92, 29.74, 29.65, 29.57, 29.50, 29.35, 29.27, 29.03, 27.42, 27.30, 24.85, 22.69, 14.12. MS (MALDI-TOF), *m*/*z*: 442 $[M]^+$. $C_{28}H_{42}O_4$. Found (%): C 75.79; H 9.41.Calcd for $C_{28}H_{42}O_4$ (%): C 75.98; H 9.56.

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