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THE USE OF SOME NON-CONVENTIONAL METHODS IN CHEMISTRY OF BICYCLOHOMOFARNESENIC METHYL ESTERS

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Abstract. The main purpose of this research was to prove the utility of some non-conventional methods in synthesis of new and known homodrimanic compounds. Three methods belonging to green chemistry were successfully used in reported transformations. As a result of microwave irradiation assisted method the formation of bicyclohomofarnesenic methyl esters versus classical Stoll and Hinder method was studied. By means of anodic oxidation and dye-sensitized photooxidation of mentioned esters series of new compounds were obtained and the mechanism of some products formation was established. In addition, new pathway for the preparation of methyl 7-oxo-13,14,15,16-tetranorlabd-6,8(8)-dien-12-oate was elaborated. The structure of all synthesized compounds was fully confirmed by spectral methods.

Keywords: bicyclohomofarnesenic methyl ester, microwave irradiation, anodic electrooxidation, dye-sensitized photooxidation.

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Introduction

The non-conventional methods of synthesis belong to green chemistry and offer many advantages. The microwave and ultrasound irradiation, as well as electrochemical and photochemical transformations often lead to desired results through non-specific mechanisms, increases yields, reduces costs and excludes the use of reagents, or the formation of toxic reaction products. Some examples of successful use of non-conventional methods in the synthesis of new compounds from various classes have been well-documented in the literature [1-12].

The transesterification-dehydration reaction of (+)-sclareolide (**1**) in the presence of sulphuric acid, known as Stoll and Hinder method, yields a mixture of isomeric bicyclohomofarnesenic methyl esters **2** and **3** [13]. Later it was found that during isomerization of lactone **1**, a mixture of three methyl esters **2-4** was obtained in 96% yield and 6:3:1 ratio (according to GS-MS and NMR data), together with a small quantity of isolactone **5** [12]. An alternative procedure for the transformation of lactone **1** into isomers **2-4** using ion-exchange resins (Amberlist 15) was reported [14]. The sulphocationite-catalysed (KU-23) transesterification of (+)-sclareolide (**1**) performed by Dragalin, I. *et al*. in methanol, after 7 h led to methyl esters **2-4** in a 12:6:1 ratio [15]. The same reaction performed in methanol/heptane mixture gave a different ratio of isomers 2:1:7 from the previously reported results [15].

The oxidation of the mixture of methyl esters **2-4** with potassium dichromate gave methyl 7-oxo-13,14,15,16-tetranorlabd-8-en-12-oate (**7**) in 38% yield, which then was decarboxylated in drim-8(9)-en-7-one (**8**) (drimenone) by the same authors [16].

Later the methyl esters **2-4** were subjected to anodic oxidation in presence of lithium perchlorate as a supporting electrolyte. The authors reported methoxy ester **6** and ketoester **7**, which yield was improved to 63% [12]. Traditionally, both compounds **7** and **8** are prepared synthetically, because no ketoester **7** and only trace amounts of drimenone **8** were detected in natural sources [17].

Until present, a large number of new synthetic compounds or natural analogues from the homodrimanic (C_{16}) or drimanic (C_{15}) series were performed based on ketoester **7** and drimenone **8** [18-25].

The present paper reports on a comparative analysis of isomeric bicyclohomofarnesenic methyl esters (**2-4)** synthesis using microwave irradiation (MW) versus Stoll and Hinder method. Also, the results of an exhaustive study of the chemical composition of anodic oxidation reaction products and the mechanism of their formation are presented.

A new method for the synthesis of methyl 7-oxo-13,14,15,16-tetranorlabd-6,8(8)-dien-12-oate (**14**) from formerly unused minor compound **13** was developed. Also, photochemical transformations of methyl esters **2-4** were performed and a series of new homodrimanic derivatives were reported.

Experimental

Generalities

The following solvents were used in the research: methanol (MeOH), chloroform ($CHCl_3$), petroleum ether (PE), ethyl acetate (EtOAc), dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), diethyl ether (Et_2O), pyridine (Py), acetic acid (AcOH), acetic anhydride (Ac_2O), tetrachloromethane (CCl_4) and deuterated chloroform ($CDCl_3$). All solvents were purified and dried by standard techniques before use. Solutions in organic solvents were dried over anhydrous Na_2SO_4, then filtered and evaporated under reduced pressure.

Melting point values were recorded on a Boetius hot stage apparatus. *Optical rotations* were determined on a Jasco DIP 370 polarimeter with a 1-dm microcell, in $CHCl_3$ and MeOH.

The *IR spectra* were registered on a Spectrum-100FT-IR Perkin-Elmer spectrometer by the ATR technique.

^1H and *^{13}C NMR spectra* were recorded in $CDCl_3$ on a Bruker Avance DRX 400 spectrometer. Chemical shifts are given in ppm in the δ scale and referred to $CDCl_3$ (δ_H at 7.26 ppm) and to $CDCl_3$ (δ_C at 77.00 ppm), respectively. The coupling constants (*J*) are reported in Hertz (Hz). The H, H-COSY, H, C-HSQC and H, C-HMBC experiments were recorded using standard pulse sequences, in the version with *z*-gradients, as delivered by Bruker Corporation. Carbon substitution degrees were established by the DEPT pulse sequence.

The *MW-assisted* transformations were carried out using a monomode reactor (800 W, STAR SYSTEM-2, CHEM Corporation, Matthews, NC, USA), under a constant irradiation power but varying temperature. The best results were obtained when 30% of the full power of the magnetron was used.

GS-MS analyses were performed on an Agilent 7890A chromatograph with an MSD 5975C VL quadrupole MS detector and an HP-5ms capillary column (30 m × 0.25 μm).

For the *analytical thin-layer chromatography (TLC)*, Merck silica gel plates 60G in 0.25 mm layers were used. The TLC plates were sprayed with concentrated H_2SO_4 and heated at 80°C. The *column chromatography* was carried out on the Across Organics silica gel (60–200 mesh) using PE (b.p. 40-60°C) and the gradient mixture of PE with EtOAc or CH_2Cl_2 and the gradient mixture of CH_2Cl_2 and MeOH.

Synthesis of bicyclohomofarnesenic methyl esters (2-4)

Method A: by Stoll and Hinder method

Unsaturated methyl esters **2-4** were obtained in a 96% yield according to the method described by Stoll, M. and Hinder, M. [13]. The isomer structures and ratio were checked by GC-MS analysis and confirmed by NMR spectroscopy.

Method B: under MW-irradiation

Caution! It is hazardous to rapidly heat reactions under MW-irradiation. Therefore, caution should be exercised when conducting reactions of this type.

To a solution of sclareolide (**1**) (1.0 g, 4 mmol) in MeOH (20 mL), concentrated H_2SO_4 (0.7 mL) was added drop by drop and the quartz tube with resulted reaction mixture was placed in a MW cell and irradiated at 80 W for 30 minutes. Once the heating cycle was complete, the tube was cooled to ambient temperature and removed from the reactor. The 2/3 of the solvent volume were removed under reduced pressure, then the residue was diluted with H_2O (15 mL), extracted with Et_2O (3×10 mL), then the organic layer was washed with H_2O (2×20 mL) and dried. After solvent removal, the crude reaction product (1.2 g) was subjected to flash chromatography on silica gel and the mixture of methyl esters **2-4** (0.94 mg, 93%), as yellow oil, was obtained. The GC-MS and NMR analysis confirmed the ratio of isomers **2-4** depicted in Table 1. It should be mentioned that after 30 minutes of irradiation the decomposition of the reaction product begins.

Anodic oxidation of bicyclohomofarnesenic methyl esters (2-4)

A solution of methyl esters **2-4** (1.0 g, 3.8 mmol) in MeOH (100 mL) was poured in an electrolyser without diaphragm fitted with four cylindrical graphite electrodes. Then $LiClO_4$ (0.8 g, 7.4 mmol) was added and a continuous electric current (3V, 400 mA) was passed through the reaction mixture within 5 h, under stirring at room temperature. After completion of the reaction, 2/3 of the solvent were removed under reduced pressure, the residue was diluted with H_2O (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were washed with H_2O and dried. After solvent removal, the crude product (1.3 g) was purified by column chromatography on SiO_2 (13 g, eluent: PE/EtOAc 96:4) to give the compounds **10**, **11**, **12**, **6**, and **13**.

Methyl 2-((1R,2R,8aS)-2-methoxy-2,5,5,8a-tetra methyldecahydronaphthalen-1-yl)acetate (**10**). Yield 3%, colourless oil, $[\alpha]_D^{26}$= 75.1° (*c* 0.2, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 2935, 2869, 2845, 1791, 1737, 1678, 1645, 1459, 1435, 1285, 1157, 1077, 886. ^{1}H NMR: δ 3.65 (3H, s, OCH_3); 3.07 (3H, s, OCH_3); 2.57 (1H, dd, *J*= 18.2, 5.7, H-11); 2.24 (1H, dd, *J*= 17.6, 3.3, H-11); 1.69 (1H, dd, *J*= 5.7, 3.2, H-9); 0.97 (3H, s, H-17); 0.87 (3H, s, H-20); 0.86 (3H, s, H-18); 0.81 (3H, s, H-19). ^{13}C NMR: δ 176.0 (C-12); 76.1 (C-8); 55.9 (C-5); 55.6 (C-9); 51.6 (OCH_3); 48.0 (OCH_3); 41.8 (C-4); 39.1 (C-1); 38.4 (C-10); 34.5 (C-7); 33.5 (C-18); 33.2 (C-4); 29.5 (C-11); 23.8 (C-17); 21.7 (C-19); 18.3 (C-6); 18.2 (C-2); 15.4 (C-20).

Methyl 2-((1R,2S,3R,8aS)-2,3-dimethoxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl) acetate (**11**). Yield 3%, colourless oil, $[\alpha]_D^{26}$= 70.8° (*c* 1.1, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 2928, 2869, 1737, 1461, 1435, 1364, 1276, 1163, 1141, 1099, 993, 848. ^{1}H NMR: δ 3.63 (3H, s, OCH_3); 3.29 (3H, s, OCH_3); 3.12 (3H, s, OCH_3); 2.46 (1H, dd, *J*= 17.1, 6.5, H-11); 2.18 (1H, dd, *J*= 17.2, 3.1, H-11); 1.05 (3H, s, H-17); 0.86 (3H, s, H-20); 0.85 (3H, s, H-18); 0.80 (3H, s, H-19). ^{13}C NMR: δ 175.6 (C-12); 78.5 (C-7); 78.4 (C-8); 56.4 (C-5); 51.5 (C-9); 51.3 (OCH_3); 48.9 (OCH_3); 46.1 (OCH_3); 41.8 (C-3); 39.0 (C-1); 38.3 (C-10); 33.2 (C-18); 32.7 (C-4); 29.7 (C-11); 21.7 (C-19); 20.2 (C-17); 20.1 (C-6); 18.3 (C-2); 15.2 (C-20).

Methyl 2-((1R,2R,8aS)-2-methoxy-2,5,5,8a-tetra methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate (**12**). Yield 2%, colourless oil, $[\alpha]_D^{26}$= 72.6° (*c* 0.2, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 3675, 2925, 1738, 1460, 1435, 1369, 1252, 1165, 1076, 870, 706. ^{1}H NMR: δ 5.87 (1H, dd, *J*= 10.2, 2.4, H-7); 5.82 (1H, dd, *J*= 10.5, 0.9, H-6); 3.69 (3H, s, OCH_3); 3.17 (3H, s, OCH_3); 2.64 (1H, dd, *J*= 17.7, 2.8, H-11); 2.33 (1H, dd, *J*= 17.5, 7.2, H-11); 1.17 (3H, s, H-17); 0.94 (3H, s, H-20); 0.87 (3H, s, H-18); 0.84 (3H, s, H-19). ^{13}C NMR: δ 176.1 (C-12); 129.1 (C-7, C-6); 73.1 (C-8); 55.1 (C-5); 54.6 (C-9); 51.6 (OCH_3); 48.9 (OCH_3); 41.1 (C-3); 37.1 (C-10); 36.1 (C-1); 32.7 (C-4); 32.6 (C-18); 29.1 (C-11); 24.1 (C-17); 21.9 (C-19); 18.3 (C-2); 13.9 (C-20).

Methyl 2-((1R,3R,8aS)-3-methoxy-5,5,8a-tri methyl-2-methylenedecahydronaphthalen-1-yl) acetate (**6**). Yield 6%, colourless oil, $[\alpha]_D^{26}$= 89.4° (*c* 0.2, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 3675, 2926, 2817, 1738, 1649, 1457, 1435, 1378, 1327, 1269, 1205, 1156, 1081, 902. ^{1}H NMR: δ 4.92 (1H, s, H-17); 4.70 (1H, s, H-17); 3.69 (1H, t, *J*= 3.4, 2.1, H-7); 3.59 (3H, s, OCH_3); 3.13 (3H, s, OCH_3); 2.63 (1H, dd, *J*= 11.5, 3.6, H-11); 2.47 (1H, dd, *J*= 15.6, 3.5, H-11); 0.85 (3H, s, H-20); 0.76 (3H, s, H-18); 0.64 (3H, s, H-19). ^{13}C NMR: δ 173.8 (C-12); 147.5 (C-8); 110.8 (C-17); 82.2 (C-7); 55.0 (C-5); 51.4 (C-9); 47.9 (OCH_3); 41.7 (OCH_3); 41.9 (C-3); 38.9 (C-10); 38.5 (C-1); 33.2 (C-18); 32.9 (C-4); 30.2 (C-11); 29.9 (C-6); 21.4 (C-19); 19.2 (C-2); 13.6 (C-20).

Methyl 2-((3R,8aS)-3-methoxy-2,5,5,8a-tetra methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate (**13**). Yield 25%, colourless oil, $[\alpha]_D^{26}$= 34.9° (*c* 30.1, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 2980, 2952, 2868, 1738, 1668, 1613, 1458, 1436, 1381, 1267, 1157, 1116, 1076, 843, 735. ^{1}H NMR: δ 3.63 (3H, s, OCH_3); 3.45 (1H, s, H-7); 3.34 (3H, s, OCH_3); 3.03 (2H, d, *J*= 8.1, H-11); 1.65 (3H, s, H-17); 0.89 (3H, s, H-18); 0.88 (3H, s, H-20); 0.83 (3H, s, H-19). ^{13}C NMR: δ 172.6 (C-12); 139.0 (C-9); 130.2 (C-8); 79.1 (C-7); 56.6 (C-5); 51.7 (OCH_3); 45.8 (OCH_3); 41.1 (C-3); 39.4 (C-10); 36.0 (C-1); 32.9 (C-11); 32.8 (C-4); 32.8 (C-18); 22.5 (C-6); 21.6 (C-19); 18.8 (C-2); 17.9 (C-20); 17.8 (C-17).

Next compound eluted from the chromatographic column was the ketoester **7** (0.66 g, 63%), as white crystals, m.p. 101-102°C (PE). Its spectral data are in accordance with those reported before [12].

Synthesis of methyl 7-oxo-13,14,15,16-tetranorlabd-6,8(8)-dien-12-oate (14)

The solution of concentrated H_2SO_4 (0.18 mL) in THF (1 mL) was added to the solution of methoxy ester **13** (294 mg, 1 mmol) in THF (4 mL), and the obtained mixture was stirred at 20°C for 24 h, diluted with H_2O (10 mL), and extracted with Et_2O (3×10 mL). The organic layer was washed with H_2O (2×10 mL) and dried. The removal of the solvent afforded the crude reaction product (270 mg), which was purified by column chromatography on silica gel (4 g). Elution with *n*-pentane yielded dieneester **14** (224 mg, 86%), as white crystals, m.p. 55-56°C (PE). Its spectral data correspond to those reported before [26].

***Dye-sensitized photooxygenation of methyl esters* 2-4**

meso-Tetraphenylporphyrin (TPP, 20 mg) was added to a stirred solution of mixture of methyl esters **2-4** (1.0 g, 3.8 mmol) in dry CH_2Cl_2 (100 mL). The resulting mixture was kept for 7 h at 5°C and irradiated with three bulb lamps (60 W each) while oxygen was passing through the solution. After solvent removal at reduced pressure, the residue (1.06 g) was separated by chromatography on SiO_2 (15 g, eluent: PE) to give (90 mg, 9.7%) of the recovered initial mixture of methyl esters **2-4**, then compound **15** was eluted.

Methyl 2-((1R,3R,8aS)-3-hydroperoxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl) acetate (**15**) (285 mg, 76.9%), m.p. 106-107°C; $[\alpha]_D^{26}$= 56.5° (*c* 1.3, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 3389, 2997, 2843, 1813, 1712, 1657, 1456, 1441, 1407, 1379, 1339, 1121, 1043. ^{1}H NMR: δ 8.61 (1H, br. s, OOH); 5.09 (1H, s, H-17); 4.74 (1H, d, *J*= 1.4, H-17); 4.54 (1H, d, *J*= 3.5, H-7); 3.66 (3H, s, OCH_3); 2.79 (1H, d, *J*= 10.5, H-9); 2.54 (1H, dd, *J*= 16.9, 3.6, H-11); 2.42 (1H, dd, *J*= 16.9, 12.2, H-11); 1.98 (1H, dd, *J*= 11.2, 2.9, H-6); 1.61 (1H, dd, *J*= 13.1, 3.2, H-6); 1.55 (1H, br. s, H-5); 0.84 (3H, s, H-18); 0.77 (3H, s, H-19); 0,68 (3H, s, H-20). ^{13}C NMR: δ 174.7 (C-12); 146.4 (C-8); 112.1 (C-17); 85.9 (C-7); 51.9 (OCH_3); 48.8 (C-9); 46.6 (C-5); 41.9 (C-6); 38.6 (C-10); 38.3 (C-1); 33.1 (C-4); 33.0 (C-19); 29.3 (C-11); 27.5 (C-3); 20.9 (C-18); 19.2 (C-2); 13.9 (C-20).

The next compound that eluted from the chromatographic column with the same eluent was **16**.

Methyl 2-((3R,8aS)-3-hydroperoxy-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate (**16**) (40 mg, 9.2%), as colourless oil, $[\alpha]_D^{26}$= 81.2° (*c* 1.1, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 3392, 2934, 2873, 1735, 1665, 1456, 1456, 1435, 1391, 1367, 1338, 1163, 1046. ^{1}H NMR: δ 8.24 (1H, br. s, OOH); 4.26 (1H, br. s, H-7); 3.64 (3H, s, OCH_3); 3.06 (2H, dd, *J*= 28.5, 16.4, H-11); 1.69 (3H, s, H-17); 1.48 (1H, s, H-5); 0.94 (3H, s, H-18); 0.89 (3H, s, H-19); 0.85 (3H, s, H-20). ^{13}C NMR: δ 172.4 (C-12); 142.9 (C-8); 126.6 (C-9); 83.8 (C-7); 51.9 (OCH_3); 45.5 (C-5); 41.2 (C-6); 35.6 (C-1); 32.9 (C-19); 23.1 (C-3); 21.6 (C-18); 18.7 (C-2); 18.1 (C-20); 18.0 (C-17).

General procedure of hydroperoxides 15 and 16 reduction

The reduction of hydroperoxides **15** and **16** was performed in accordance with the method described in reference [21]. After workup and column chromatography corresponding alcohols **17** and **19** were obtained.

Methyl 2-((1R,3R,8aS)-3-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl) acetate (**17**) (96%), as a colourless oil, $[\alpha]_D^{26}$= 45.7° (*c* 0.47, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 3464, 3081, 2925, 2869, 2849, 1732, 1647, 1435, 1222, 1157, 1036, 901. ^{1}H NMR: δ 4.97 (1H, s, H-17); 4.60 (1H, d, *J*= 1.4, H-17); 4.35 (1H, t, *J*= 2.8, H-7); 3.63 (3H, s, OCH_3); 2.82 (1H, t, *J*= 1.4, H-9); 2.49 (1H, dd, *J*= 15.9, 3.7, H-11); 2.35 (1H, dd, *J*= 14.8, 10.6, H-11); 2.14 (1H, br. s, OH); 1.87 (1H, dt, *J*= 13.9, 2.7, H-6); 1.72 (1H, dd, *J*= 13.2, 2.6, H-6); 0.89 (3H, s, H-18); 0.79 (3H, s, H-19); 0.65 (3H, s, H-20). ^{13}C NMR: δ 174.1 (C-12); 150.3 (C-8); 109.4 (C-17); 73.5 (C-7); 51.6 (OCH_3); 47.2 (C-9); 47.0 (C-5); 41.9 (C-6); 39.1 (C-10); 38.5 (C-1); 33.2 (C-19); 33.0 (C-4); 30.4 (C-11); 30.2 (C-3); 21.5 (C-18); 19.2 (C-2); 13.4 (C-20).

Methyl 2-((3R,8aS)-3-hydroxy-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate (**19**) (94%), as a colourless oil, $[\alpha]_D^{26}$= 106.9° (*c* 0.8, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 3517, 3376, 3222, 3000, 2921, 2864, 1762, 1727, 1663, 1459, 1433, 1338, 1200, 1167, 1129, 1057, 967. ^{1}H NMR: δ 3.92 (1H, d, *J*= 4.2, H-7); 3.66 (3H, s, OCH_3); 3.08 (1H, d, *J*= 16.9, H-11); 3.0 (1H, d, *J*= 16.9, H-11); 2.14 (1H, br. s, OH); 1.82 (1H, d, *J*= 13.7, H-6); 1.67 (1H, d, *J*= 4.7, H-6); 1.69 (3H, s, H-17); 0.91 (3H, s, H-18); 0.88 (3H, s, H-19); 0.83 (3H, s, H-20). ^{13}C NMR: δ 172.8 (C-17); 138.5 (C-8); 131.5 (C-9); 69.9 (C-7); 51.8 (OCH_3); 45.5 (C-5); 41.3 (C-6); 39.3 (C-10); 35.7 (C-1); 32.9 (C-19); 32.8 (C-4); 32.8 (C-11); 28.5 (C-3); 21.6 (C-18); 18.8 (C-2); 18.0 (C-20); 17.8 (C-17).

General procedure of alcohols 17 and 19 acetylation

The acetylation of alcohols **17** and **19** was performed by the standard method described in reference [21]. After workup and column chromatography corresponding acetates **18** and **20** were obtained.

Methyl 2-((1R,3R,8aS)-3-acetoxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl) acetate (**18**) (98%), as a colourless oil, $[\alpha]_D^{26}$= 6.5° (*c* 2.1, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 3676, 3085, 2950, 2926, 2869, 1734, 1652, 1435, 1368, 1234, 1204, 1157, 1023, 918. ^{1}H NMR: δ 5.38 (1H, t, *J*= 2.6, H-7); 5.08 (1H, d, *J*= 1.0, H-17); 4.72 (1H, d, *J*= 1.6, H-17); 3.62 (3H, s, OCH_3); 2.73 (1H, d, *J*= 6.1, H-6); 2.47 (1H, dd, *J*= 15.8, 4.2, H-11); 2.32 (1H, dd, *J*= 15.8, 14.3, H-11); 2.05 (3H, s, OAc); 1.90 (1H, dd, *J*= 12.2, 2.6, H-6); 0.83 (3H, s, H-19); 0.78 (3H, s, H-19); 0.67 (3H, s, H-20). ^{13}C NMR: δ 173.7 (C-12); 170.3 (OAc); 145.6 (C-8); 112.1 (C-17); 75.6 (C-7); 51.6 (OCH_3); 48.3 (C-9); 48.1 (C-5); 41.8 (C-6); 38.7 (C-10); 38.5 (C-1); 33.2 (C-19); 32.6 (C-4); 30.3 (C-11); 28.6 (C-3); 21.5 (OAc); 21.3 (C-18); 19.1 (C-2); 13.5 (C-20).

Methyl 2-((3R,8aS)-3-acetoxy-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate (**20**) (97%), as a colourless oil, $[\alpha]_D^{26}$= 108.9° (*c* 0.5, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 2929, 2871, 1746, 1665, 1623, 1457, 1378, 1259, 1189, 1165, 1134, 1019, 957. ^{1}H NMR: δ 5.18 (1H, d, *J*= 4.1, H-7); 3.68 (3H, s, OCH_3); 3.08 (2H, dd, *J*= 27.9, 16.7, H-11); 2.07 (3H, s, OAc); 1.58 (3H, s, H-17); 0.91 (3H, s, H-19); 0.85 (3H, s, H-19); 0.82 (3H, s, H-20). ^{13}C NMR: δ 172.3

(C-12); 171.2 (OAc); 141.2 (C-8); 127.9 (C-9); 72.7 (C-7); 51.8 (OCH_3); 46.2 (C-5); 41.5 (C-6); 39.2 (C-10); 35.8 (C-1); 32.9 (C-11); 32.7 (C-19); 32.7 (C-4); 25.7 (C-3); 21.4 (OAc); 21.4 (C-17), 18.7 (C-2); 18.0 (C-18); 17.4 (C-20).

General procedure of alcohols 17 and 19 oxidation

The oxidation of alcohols **17** and **19** was performed by the standard method described in reference [21]. After workup and column chromatography corresponding ketones **7** and **21** were obtained.

The ketoester **7** was obtained (98%), as white crystals, m.p. 101-102°C (PE). Its spectral data are in accordance with those previously reported [12].

Methyl 2-((1R,8aS)-5,5,8a-trimethyl-2-methylene-3-oxodecahydronaphthalen-1-yl)acetate (**21**) (98%), as a colourless oil, $[\alpha]_D^{26}$= 149.1° (*c* 0.5, $CHCl_3$). IR (ATR) (*v*, cm^{-1}) 3676, 2960, 2926, 1736, 1695, 1635, 1608, 1436, 1393, 1260, 1230, 1162, 1066, 915. ^{1}H NMR: δ 5.90 (1H, s, H-17); 5.08 (1H, s, H-17); 3.66 (3H, s, OCH_3); 2.73 (1H, dd, *J*= 9.5, 2.6, H-11); 2.66 (1H, t, *J*= 3.4, H-9); 2.62 (1H, dd, *J*= 5.5, 3.2, H-11); 2.35 (1H, dd, *J*= 13.2, 9.7, H-6); 2.29 (1H, dd, *J*= 14.3, 9.4, H-6); 0.90 (3H, s, H-19); 0.87 (3H, s, H-19); 0.81 (3H, s, H-20). ^{13}C NMR: δ 202.1 (C-7); 173.5 (C-12); 147.8 (C-8); 119.3 (C-17); 51.9 (OCH_3); 51.3 (C-9), 51.1 (C-5); 41.5 (C-6); 38.6 (C-1); 38.2 (C-11); 37.3 (C-10); 33.5 (C-4); 32.5 (C-19); 31.5 (C-3); 20.8 (C-18), 18.8 (C-2); 14.0 (C-20).

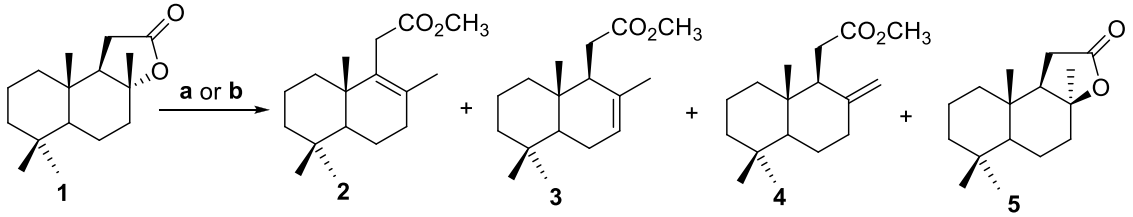
Results and discussion

As was mentioned before, during decades, bicyclohomofarnesenic methyl esters (**2-4**) have been prepared using Stoll and Hinder procedure [13]. It implies a multi-hour reflux of acidulated (+)-sclareolide (**1**) methanolic solution, which is the main disadvantage (Scheme 1).

Using microwave irradiation, the transesterification-dehydration reaction of (+)-sclareolide (**1**) into compounds **2-4**, was performed in just 30 minutes (Scheme 1), with a 95% yield and co-ratio of the products depicted in Table 1. In this study, the dynamics of ester **2-4** formation was analysed using GC-MS method during their preparation by the Stoll and Hinder procedure and compared the data with those of MW assisted method (Table 1).

According to this, at the beginning of transesterification-dehydration reaction of (+)-sclareolide (**1)** by Stoll and Hinder procedure the formation of trisubstituted isomer **3** is favoured. The tetrasubstituted **2** and exocyclic **4** isomers are obtained in lower yields. Then, in the course of the reaction their ratio changes to 15:5:3, the yield of isomer **2** increases and that of isomer **3** decreases, more than twice, respectively. The isomer **4** is a minor product of the reaction and its yield varies from 7.10% to 1.53%. It should be noted, that in this case only trace amounts of isolactone **5** were detected.

In the case of MW assisted transesterification of (+)-sclareolide (**1**) the ratio of the mixture of methyl esters **2-4** is 3:11:5, quite different from the previously reported.



Reagents and conditions: a) H_2SO_4, MeOH, Δ, 96 h; b) H_2SO_4, MeOH, MW, 30 min.

Scheme 1. Syntheses of bicyclohomofarnesenic methyl esters 2-4 from (+)-sclareolide (1).

Table 1

The results of GC-MS analysis of bicyclohomofarnesenic methyl esters 2-4 mixtures.

Time, (h) Stoll & Hinder	Compounds, ratio (%)			Time, (min) MW	Compounds, ratio (%)		
	2	**3**	**4**		**2**	**3**	**4**
8	36.43	51.49	7.10	10	14.45	56.69	24.49
24	56.92	40.97	2.11	20	14.05	52.73	26.85
48	60.03	38.87	1.09	30	14.78	55.79	24.32
72	70.17	28.20	1.63	40	Decomposition		
96	73.67	24.39	1.53				

According to GC-MS analysis, in 30 minutes the major isomer is trisubstituted **3** (55.79%), followed by exocyclic **4** (24.32%) and tetrasubstituted **2** (14.78%) ends the series. After this time the decomposition of the reaction products starts.

As it was mentioned before, the compounds **7** and **8** are key intermediates in the synthesis of new polyfunctionalized homodrimanic and drimanic derivatives. The use of microwave irradiation allowed improving the preparation method of drimenone **8**, in 92% overall yield, by faster decarboxylation of ketoester **7** (Scheme 2) in comparison with reported before [23].

Chromatographic analysis (analytical TLC and GC-MS) of the electrooxidation reaction product of methyl esters **2-4** showed a complex mixture of compounds. For this reason, it was decided to realize an exhaustive study of its chemical composition. As result, additionally to previously reported compounds **6** and **7** a series of minor compounds **10-13** were isolated and characterized (Scheme 3).

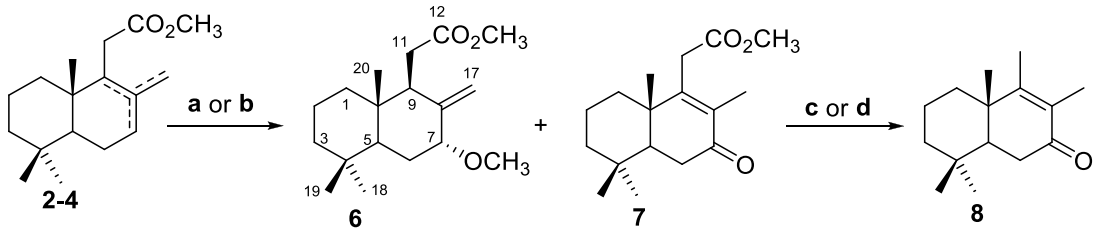
It is well known that the anodic oxidation of olefins, including terpenes, occurs by cation radical intermediate generated by anodic one-electron elimination from the olefinic π-electron system [27-30]. The olefins bearing at least one allylic hydrogen undergo an allylic substitution reaction in which the solvent is a nucleophile.

In this study, at the first step mixture of methyl esters **2-4** loses an electron and generates cation radical **9** as a reactive species. Next, its interaction with methanol as a nucleophile is accompanied by a series of electrons, radicals or ions addition/elimination, and leads to the allylic substitution products **10-13**, which were isolated and characterized (Scheme 3).

With reference to the ketoester **7**, it can be assumed that this is a product of allylic oxidation of isomer **2**. Lithium perchlorate is a strong oxidizing agent and in these conditions, its reduction takes place according to Eq.(1) with the formation of atomic oxygen.

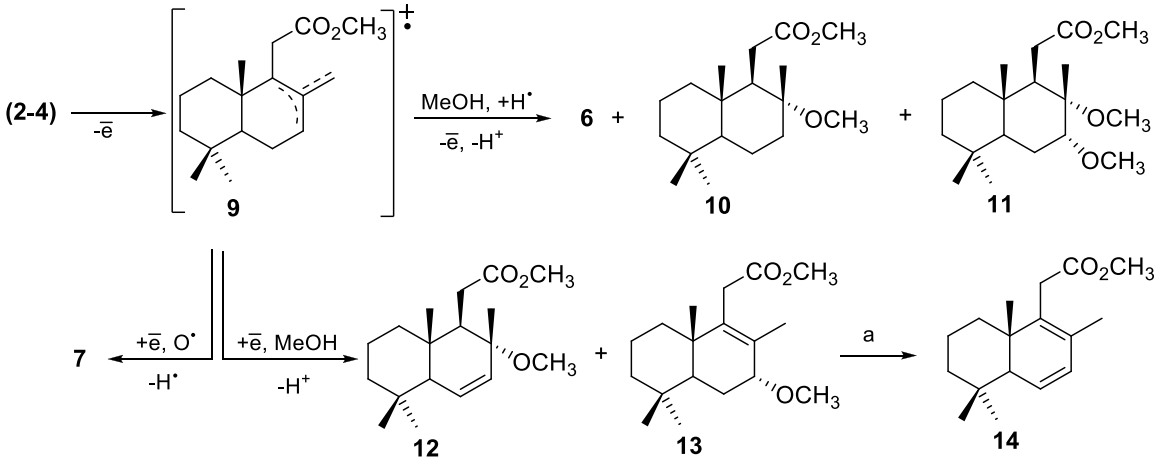
$$LiClO_4 \xrightarrow{-e} LiCl + 4O^{\bullet} \quad (1)$$

The lifetime of this highly reactive species is enough to attack the allylic position of cation radical **9** and to cause its oxidation through several intermediate states (Scheme 3).



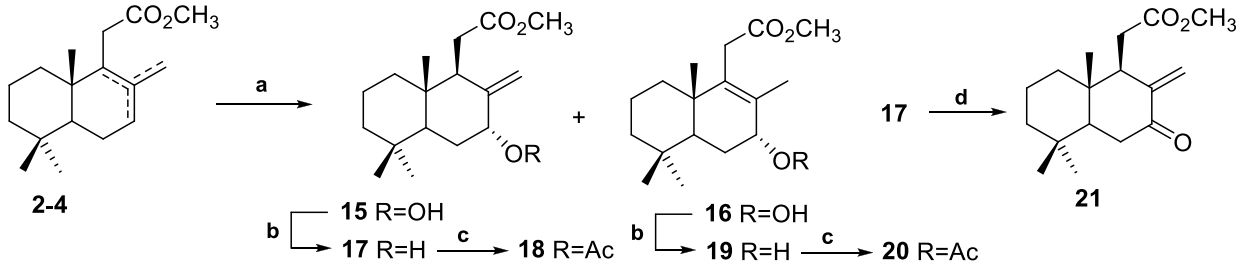
Reagents and conditions: a) $K_2Cr_2O_7$, MeOH, Δ, 96 h; b) $LiClO_4$, MeOH, ē, 15 min; c) KOH, EtOH, Δ, 96 h; d) KOH, EtOH, MW, 96 h.

Scheme 2. Syntheses of ketoester 7 and drimenone 8.



Reagents and conditions: a) H_2SO_4, THF, r.t., 24 h.

Scheme 3. Minor compounds from anodic oxidation of mixture of methyl esters 2-4.



Reagents and conditions: a) O_2, TPP, hν, CCl_4, r.t.; b) thiourea, MeOH, 0°C to r.t.; c) Py, Ac_2O, r.t.; d) PCC, CH_2Cl_2, AcOH (gl.), r.t., 3 Å sieves.

Scheme 4. Dye-sensitized photooxidation of mixture of methyl esters 2-4.

Due to the high content of metoxyester **13** it was decided to employ it for the synthesis of dienester **14**, an important intermediate used before for the synthesis of polyfunctional homodrimanic compounds [24]. The attempt was successful and compound **14** was obtained in 86% yield.

The dye-sensitized photooxidation of methyl esters **2-4** leads to new isomeric hydroperoxydes **15** and **16**, in 76.9% and 9.2% yield, respectively, calculated based on the conversion of methyl esters **2-4**. In continuation, by means of standard methods [21], these compounds were converted in corresponding alcohols **17** and **19** (96 and 94%) and acetates **18** and **20** (98 and 97%).

The oxidation of alcohols **17** and **19**, assisted by pyridinium chlorochromate (PCC), in conditions described before [21] led to known ketoesters **7** and **21**, both with the same 98% yield. It should be noted that compound **21** has not been described previously (Scheme 4).

The structures of all synthesized compounds were fully confirmed by spectral methods of analysis.

Conclusions

This article is a recent contribution to the chemistry of (-)-sclareol. As a result of the present study, the dynamics of bicyclohomofarnesenic methyl esters (**2-4)** formation during transesterification reaction of (+)-sclareolide (**1**) by Stoll-Hinder and MW-assisted methods was established and compared.

An exhaustive study of the products from anodic oxidation of methyl esters **2-4** and the mechanism of their formation was described. In addition, the photochemical transformation of the mentioned esters allowed a series of new homodrimanic derivatives.

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