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On the dimers of β-tocopherol

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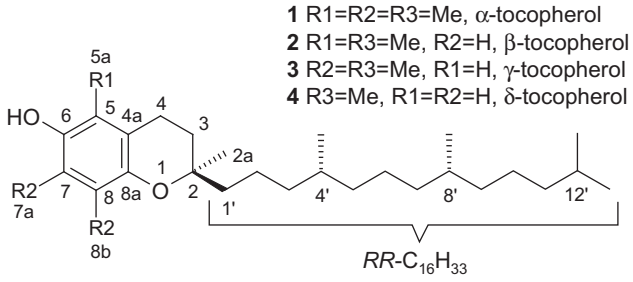
ABSTRACT

Upon oxidation in aprotic media, β-tocopherol (**2**) forms a spiro-dimer (**10**) as the main product. The reaction mechanism is a hetero-Diels–Alder process with inverse electron demand of two intermediate *ortho*-quinone methide molecules. The spiro-dimer can be reduced to the corresponding symmetric ethano-dimer (**11**). In contrast to the well-studied α-tocopherol case, spiro-dimer and ethano-dimer do not form a reversible redox pair, their interconversion is accompanied by coupling reactions at C-7 with 7a-(β-tocopher-5a-yl)-β-tocopherol (**13**) as the main byproduct besides some oligomeric material. The full NMR assignments (^{1}H, ^{13}C) of the β-tocopherol oxidation products are given.

1. Introduction

Vitamin E, a term often used synonymously (and incorrectly) for α-tocopherol (**1**), is a mixture of four tocopherols and four tocotrienols, the latter subgroup possessing an unsaturated side chain. Among the tocopherols, the α-form is the most common, it also has the highest vitamin E activity. With the recent recognition of important non-antioxidant functions of α-tocopherol,[1] the attention for the non-α-tocopherols, which offer free aromatic positions at the aromatic core, increased as well. They thus represent desmethyl derivatives of the α-congener and differ in the number and position of aromatic methyl substituents. In contrast to α-tocopherol, they are potent traps of electrophiles,[2] such as nitroxide-derived[3] or halogen-derived species.[4] The 5a-methyl group, which is critically involved in the formation of the *ortho*-quinone methide (*o*QM) intermediate and the resulting spiro-dimer in the case of α-tocopherol, is missing in the γ- and δ-counterparts (**3** and **4**), which thus show a completely different oxidation behavior.[5] β-Tocopherol (**2**), however, offers the 5a-methyl group—as does α-tocopherol—but lacks the 7a-methyl substituent. Although β-tocopherol is only a minor constituent in natural and semisynthetic vitamin E mixtures as compared to the dominant α- and γ-forms, it is certainly an integral constituent of such mixtures. In the present study, we would like to communicate the dimerization behavior of β-tocopherol in comparison to its well-studied α-counterpart and for the first time report the full NMR assignment of its spiro-dimer and ethano-dimer and the side products in this oxidation system.



2. Results and discussion

The oxidation chemistry of α-tocopherol (**1**) has been well established for quite some time.[6] When α-tocopherol (**1**),[7] the main component in vitamin E, is oxidized under aprotic conditions, it affords an *ortho*-quinone methide (*o*QM, **5**). This primary intermediate is formed quite selectively at position C-5a while formation at position C-7a is minor (97% vs 3% at rt).[6] This intermediate and the reason for its selectivity of formation have been studied in detail, also with regard to the concept of strain induced bond localization in benzo-anellated aromatics.[8] If no coreactants or trapping agents, for example, electron-rich dienophiles, are present, *o*QM **5** undergoes dimerization to the so-called spiro-dimer of α-tocopherol (**6**), an interesting compound for which a structure of two rapidly interconverting diastereomers was demonstrated and a full NMR assignment was performed[9] (see Scheme 1, path A). This dimer is one of the major tocopherol oxidation products both in vitro and in vivo. Reduction of the spiro-dimer forms the so-called 'ethano-dimer of α-tocopherol', an 1,2-bis(γ-tocopher-5-yl)ethane (**7**). This compound is quantitatively

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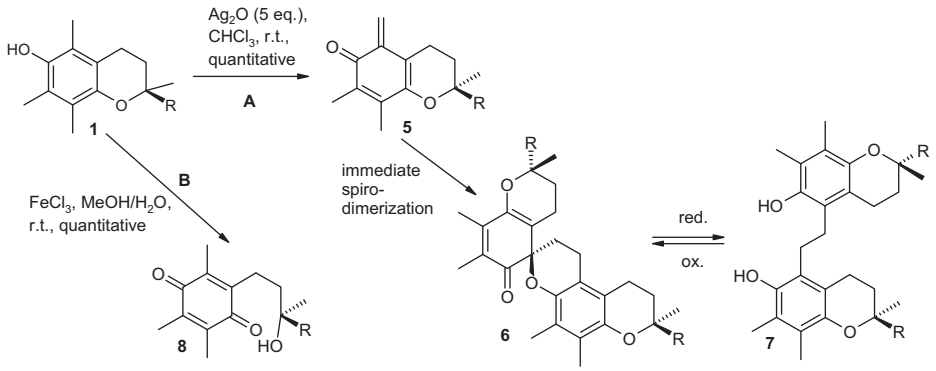


Scheme 1. Oxidation chemistry of α-tocopherol (**1**). Spiro-dimer **6** and ethano-dimer **7** form a reversible redox pair.[6]

oxidized back into spiro-dimer **6** under aprotic conditions. This happens almost independently of the oxidant used, and also in two-phase systems containing the oxidant in the aqueous phase and the tocopherol in the organic phase the reconversion of **7** into **6** is complete. Thus, spiro-dimer and ethano-dimer of α-tocopherol form a largely reversible redox pair in aprotic media, and this redox 'cycling' can be performed several times without any loss of material due to side reactions. Under protic conditions, α-tocopherol is oxidized quantitatively to α-tocopheryl quinone (**8**) (see Scheme 1, path B), and ethano-dimer **7** affords a mixture of spiro-dimer **6** and small amounts of the corresponding bis(*para*-quinone).[6]

Oxidation of β-tocopherol (**2**) in protic media, such as water or water/alcohol mixtures, provides quantitative yields of β-tocopheryl quinone (**12**), the analytical data of which we have recently described.[10] By oxidation of β-tocopherol (**2**) with excess silver oxide in aprotic media, the spiro-dimer of β-tocopherol (**10**) is formed quantitatively via the *o*QM **9**. When working in a two-phase system with the tocopherol dissolved in petroleum ether and alkaline potassium ferricyanide as the oxidant in the aqueous phase, the yields of **10** from **2** were indeed good, between 82% and 88%,[11] but not quantitative as in the α-case. As side products, β-tocopheryl quinone (**12**, 10–14%) and 7a-(β-tocopher-5a-yl)-β-tocopherol (**13**, 2–4%) were formed. This procedure, which is the 'classical' protocol for the formation of the α-tocopherol spiro-dimer from α-tocopherol,[12] is thus inferior in the β-tocopherol case and cannot be recommended, especially as **10** and **13** are difficult to separate by column chromatography. Also other oxidants gave a good to excellent, yet not a quantitative outcome. The ^{1}H NMR spectrum of **10** exhibits two characteristic singlets at 6.60 ppm and 5.78 ppm representing one aromatic and one vinylic proton, respectively. The resonances at 2.07 ppm and 1.98 ppm originate from the two 8b-methyl groups at the aromatic and quinoid moiety. In the ^{13}C NMR spectrum, resonances at 202 ppm (carbonyl carbon, C-6′), 147 ppm (phenol ether carbon, C-6), and 81 ppm (spiro carbon, C-5′) are indicative of the spiro-dimer structure, as well as the two carbons of the ethylene bridge in the central ring resonating at 18 ppm (C-5a) and 27 ppm (C-5a′). The atom numbering (see also Experimental section) is based on the numbering of tocopherols, denoting the spiro-moiety with primed numbers.

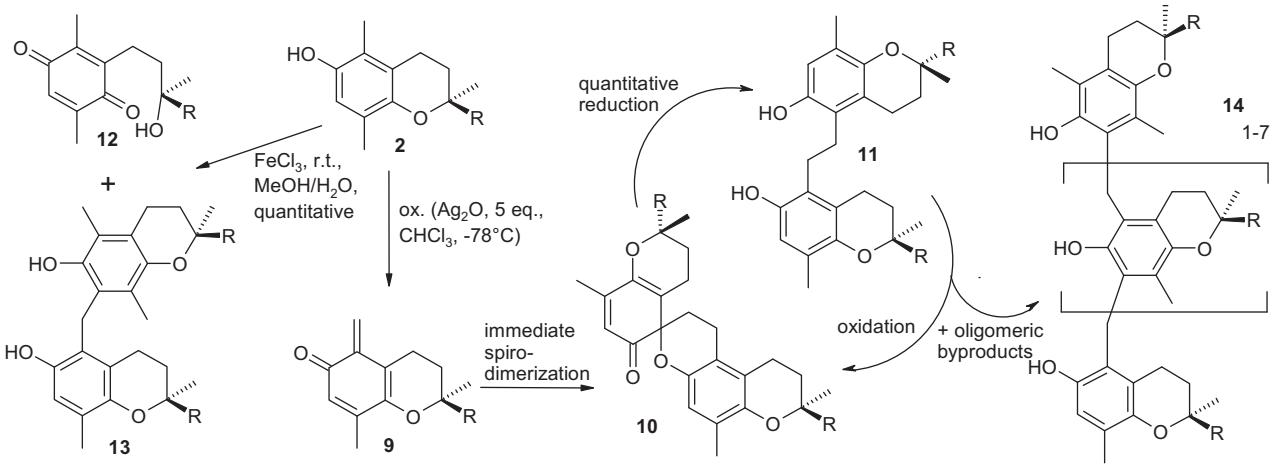
Reduction of spiro-dimer **10** to the corresponding ethano-dimer **11** proceeds quantitatively, regardless of the reductants used (sulfite, ascorbate, $NaBH_4$, ferrous sulfate), a reaction behavior, which parallels that of α-tocopherol. Though ethano-dimer **11** is very similar to β-tocopherol, it can be identified in ^{1}H NMR by the 4-methylene protons resonating at 2.73 ppm (vs 2.62 ppm in **2**) and the aromatic proton at C-7 resonating at 6.56 ppm (vs 6.39 ppm in **2**).

While re-oxidation to the spiro-dimer is quantitative in the α-tocopherol case, the oxidation of **11** back to spiro-dimer **10** was in our hands impossible to conduct in a quantitative way. Best yields were again achieved with an excess of freshly prepared silver oxide (92%), but even in this optimum case oligomeric byproducts (**14**) were formed. With other oxidants (DDQ, $Pb(OAc)_4$, Cr(VI) compounds) these oligomers even became dominant, yields of **10** dropping drastically below 20–30%. In protic media, oxidation of **11** afforded both oligomers **14** and the corresponding bis(*para*-quinone), but no **10** was produced.

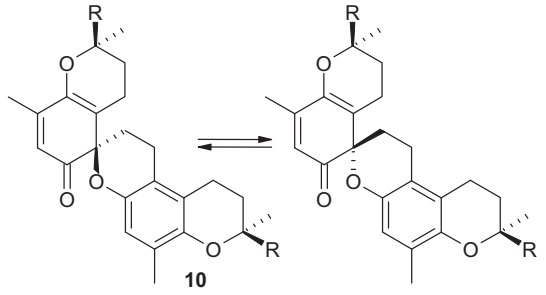
Byproduct **13**, formed upon aprotic oxidation of β-tocopherol (**2**), and the oligomeric products **14**, which resemble **13** in having 7a-(β-tocopher-5a-yl)-β-tocopheryl substructures, are also worth mentioning: compound **13** is formed by the alkylating action of *o*QM **9** toward excess β-tocopherol (**2**). It is a competitive reaction to the dimerization of two molecules of *o*QM **9** to spiro-dimer **10** (Scheme 2). Accordingly, these byproducts dominate if little excess of oxidant is used so that formed *o*QM always encounters spare β-tocopherol to react with. A large excess of oxidant generates high concentrations of *o*QM, thus spiro-dimer production is favored. MALDI analysis of **14** showed that all components were exclusively composed of β-tocopheryl units (M=414.7 g mol^{-1}), from trimer (M=1246.1 g mol^{-1}) to nonamer (M=3734.3 g mol^{-1}), the pentamer (M=2075.5 g mol^{-1}) and hexamer (M=2490.2 g mol^{-1}) being most prominent in this oligomer mixture (Scheme 2). NMR spectra confirmed a regular structure, the terminal C-7 protons distinctively resonating at 6.62 ppm (^{1}H) and the methylene bridges at 24.3 ppm (^{13}C). Due to the structural similarity of the compounds, shift differences between the β-tocopheryl units in the different oligomers are negligible in both the ^{1}H and ^{13}C domains.

Two-dimensional ROESY experiments proved that **10** consisted of a mixture of two interconverting diastereomers (Scheme 3), similar to the spiro-dimer of α-tocopherol (**6**) examined by Schröder and Netscher.[13] A fluxional nature was thus confirmed for both spiro-dimers, the interconversion rate of the β-compounds being slightly slower than that of the α-compound as shown by temperature-dependent NMR measurements. A rough approximation of the relative rates gave an activation energy difference of 25 kJ mol^{-1}, so that at rt the interconversion of the α-dimer would be 3.2 times faster than that of the β-counterpart.

Establishing the analytical data of the oxidation products of β-tocopherol will help in the analysis of the complex in vivo reaction mixtures of vitamin E, since the minor constituents of these mixtures derived from β-tocopherol and γ-tocopherol are rather difficult to analyze. We hope that this study will help to improve the data situation for β-tocopherol oxidation products and render it similarly satisfying as that of the well-studied α- and γ-constituents.



Scheme 2. Oxidation chemistry of β-tocopherol (**2**). Under protic conditions, β-tocopheryl quinone (**12**) is formed. Spiro-dimer **10** is formed quantitatively only under carefully controlled conditions. Reduction of **10** to the ethano-dimer **11** is quantitative, but re-oxidation is not, precluding full redox reversibility between **10** and **12**.



Scheme 3. Interconversion process in spiro-dimer **10**.

3. Experimental

3.1. General

(all-*R*)-β-Tocopherol (**2**) was used as the starting material.[14] The β-tocopherol model compound **2a** was available from previous work.[3] All other chemicals were obtained from commercial suppliers (Sigma–Aldrich). Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Column chromatography was performed on silica gel G_{60} (40–63 μm).

^{1}H NMR spectra were recorded at 400.13 MHz for ^{1}H and at 100.13 MHz for ^{13}C NMR in $CDCl_3$ if not otherwise stated. Chemical shifts, relative to TMS as internal standard, are given in δ values, coupling constants in hertz. ^{13}C peaks were assigned by means of APT, HMQC, and HMBC spectra, which were acquired according to standard pulse programmes.[15] Two-dimensional ROESY experiments used the following parameters: 1024 t_1 data points, 2048 t_2 data points, zero filling, mixing time 0.5 s, resolution f_1: 4 Hz (^{1}H) and 16 Hz (^{13}C) and f_2: 2 Hz. Resonances of the isoprenoid side chain, denoted by the letter s followed by the numbering, are only negligibly affected (<0.1 ppm for ^{13}C) by modifications of the chroman skeleton, the corresponding side chain resonances are thus very similar for all four tocopherols. An asterisk (*) denotes assignment that can be exchanged.

*3.1.1. β-Tocopherol spiro-dimer (**10**).* β-Tocopherol (**2**, 0.83 g, 2 mmol) was dissolved in MeCN (20 ml) and freshly precipitated and pulverized Ag_2O (10 mmol, 2.32 g) was added at once. The mixture was stirred at rt for 10 min, solids were filtered off, and the solvent was removed in vacuo. The oily residue was purified by flash chromatography (*n*-hexane/ethyl acetate, v/v=19:1) to provide **10** as colorless oil solidifying to a wax below 15 °C (0.82 g, 99%). TLC: R_f=0.64 (*n*-hexane/ethyl acetate, v/v=19:1). ^{1}H NMR δ: 0.80–0.91 (24H, H-s13, H-s12a, H-s8a, H-s4a; H-s13′, H-s12a′, H-s8a′, H-s4a′), 1.00–1.18, 1.20–1.46 (16H, H-s3, H-s5, H-s7, H-s9; H-s3′, H-s5′, H-s7′, H-s9′), 1.06–1.39 (8H, H-s6, H-s10; H-s6′, H-s10′), 1.12–1.17 (4H, H-s11, H-s11′), 1.24 (3H, H-2a*), 1.24–1.48 (4H, H-s2, H-s2′), 1.25 (3H, H-2a′*), 1.32–1.46 (4H, H-s4, H-s8; H-s4′, H-s8′), 1.52 (4H, H-s1, H-s1′), 1.52–1.55 (2H, H-s12, H-s12′), 1.60–1.78 (4H, H-3, H-3′), 1.92 and 2.02 (4H, 5a, 5a′), 1.98 (3H, H-8a′), 2.05 and 2.42 (2H, H-4a and H-4a′), 2.07 (3H, H-8a), 2.32, 2.48, 2.54, 2.60 (2H, H-4b and H-4b′), 5.78 (1H, H-7′), 6.60 (1H, H-7). ^{13}C NMR δ: 16.0 (C-8b), 16.5 (C-4′), 17.6 (C-8b′), 18.0 (C-5a), 18.6 (C-4), 19.7, 19.8 (C-s8a, C-s4a), 20.9 (C-s2), 22.3 (C-2a), 22.6 (C-2a′), 22.6, 22.7 (C-s13, C-s12a), 24.5 (C-s6), 24.8 (C-s10), 27.3 (C-5a′), 27.9 (C-s12), 29.9 (C-3), 30.3 (C-3′), 32.6, 32.7 (C-s4, C-s8), 37.2–37.5 (C-s3, C-s5, C-s7, C-s9), 39.1 (C-s11), 40.2, 40.25 (C-s1), 73.4 (C-2), 74.7 (C-2′), 81.4 (C-5′), 115.6 (C-7), 115.9 (C-4a*), 117.7 (C-4a′*), 118.4 (C-5*), 121.3 (C-7), 125.1 (C-8), 143.1 (C-8a′), 145.6 (C-8a), 147.1 (C-6), 152.4 (C-8′), 202.1 (C-6′). Calcd for $C_{56}H_{92}O_4$: C 81.10, H 11.18. Found: C 81.02, H 11.28.

*3.1.2. β-Tocopherol ethano-dimer (**11**).* β-Tocopherol spiro-dimer (**10**, 0.50 g, 0.60 mmol) was dissolved in *iso*-propanol (20 ml) and sodium borohydride (2 mmol) was added. The mixture was stirred at 40 °C for 2 h, neutralized by slow addition of 1 N HCl and extracted three times with *n*-hexane. The combined extracts were washed with water and dried over Na_2SO_4. The residue obtained after separation of the solids and evaporation of the solvent was purified by flash chromatography (*n*-hexane/ethyl acetate, v/v=9:1). TLC: R_f=0.33 (*n*-hexane/ethyl acetate, v/v=9:1), white wax (0.50 g, 99%). ^{1}H NMR δ: 0.80–0.91 (24H, H-s13, H-s12a, H-s8a, H-s4a), 1.00–1.46 (16H, H-s3, H-s5, H-s7, H-s9), 1.06–1.39 (8H, H-s6, H-s10), 1.10–1.19 (4H, H-s11), 1.24–1.42 (4H, H-s2), 1.26 (6H, H-2a), 1.32–1.44 (4H, H-s4, H-s8), 1.51–1.56 (2H, H-s12), 1.52 (4H, H-s1), 1.64–1.82 (4H, H-3), 2.12 (6H, H-8a), 2.71 (4H, s, H-5a), 2.73 (4H, t, $J_{H,H}$=7.1 Hz, H-4), 5.46 (2H, s, OH), 6.56 (2H, H-7). ^{13}C NMR δ: 16.0 (C-8b), 19.7, 19.8 (C-s4a, C-s8a), 20.5 (C-4), 20.7 (C-s2), 22.6, 22.8 (C-s13, C-s12a), 23.8 (C-2a), 24.5 (C-s6), 24.7 (C-s10), 26.7 (C-5a), 27.9 (C-s12), 31.4 (C-3), 32.6, 32.7 (C-s4, C-s8), 37.2–37.5 (C-s3, C-s5, C-s7, C-s9), 39.1 (C-s11), 40.2 (C-s1), 74.4 (C-2), 115.8 (C-7), 118.9 (C-5), 123.3 (C-4a), 124.9 (C-8), 146.0 (C-6*), 146.1 (C-8a*). Calcd for $C_{56}H_{94}O_4$: C 80.91, H 11.40. Found: C 80.87, H 11.52.

*3.1.3. β-Tocopheryl quinone (**12**).* β-Tocopherol (**2**, 0.83 g, 2 mmol) was dissolved in 50 ml of methanol and a solution of $FeCl_3$ hexahydrate (12 mmol, 3.25 g) in 100 ml of water was added. The

mixture was stirred for 10 min at rt and extracted three times with *n*-hexane (50 ml each). The combined organic extracts were washed with diluted acetic acid (1 N, 50 ml) and two times with water (50 ml each) and dried over Na_2SO_4. The solids were filtered off and the solvent was evaporated in vacuo at rt. Purification by flash chromatography (*n*-hexane/diethyl ether, v/v=9:1) afforded a colorless oil (0.79 g, 92%). TLC: R_f=0.39 (*n*-hexane/diethyl ether, v/v=9:1). ^{1}H NMR δ: 1.29 (s, 6H, H-2a), 1.52 (m, 2H, H-3), 1.74 (br s, 1H, −OH), 2.03 (s, 6H, H-5a, H-8b), 2.57 (m, 2H, H-4), 6.55 (q, 1H, $^4J_{H,H}$=1.3 Hz, H-6), numbering of tocopherols maintained, data of isoprenoid side chain not given. ^{13}C NMR δ: 11.6 (C-5a), 15.8 (C-8b), 21.6 (C-4), 26.0 (C-2a), 41.9 (C-3), 70.7 (C-2), 133.1 (CH in quinone), 140.6, 144.9, 145.4 (C in quinone), 187.7, 187.8 (C=O in quinone), isoprenoid side chain: 19.76 (C-4a′), 19.84 (C-8a′), 21.1 (C-2′), 22.67 (C-13′), 22.74 (C-12a′), 24.5 (C-6′), 24.6 (C-10′), 28.0 (C-12′), 32.64 (C-8′), 32.75 (C-4′), 37.3 (C-7′), 37.46 (C-5′), 37.47 (C-9′), 37.52 (C-3′), 39.3 (C-11′), 39.7 (C-1′). Calcd for $C_{28}H_{48}O_3$: C 77.73, H 11.18. Found: C 77.65, H 11.30.

*3.1.4. 7a-(β-Tocopher-5a-yl)-β-tocopherol (**13**).* β-Tocopherol (**2**, 0.83 g, 2 mmol) was dissolved in MeCN (20 ml) and freshly precipitated and pulverized Ag_2O (2 mmol, 0.46 g) was added slowly during 10 min. The mixture was stirred at rt for another 10 min, solids were filtered off, and the solvent was removed in vacuo. The oily residue was purified by flash chromatography (*n*-hexane/ethyl acetate, v/v=19:1) eluting first spiro-dimer **10** (see above, 36%), followed by **13** (colorless oil, 47%) and by unchanged starting material. TLC: R_f=0.22 (*n*-hexane/ethyl acetate, v/v=19:1). ^{1}H NMR δ: 1.28 (s, 6H, CH_3), 1.80 (m, 4H, H-3′, H-3), 1.98, 2.02, 2.16 (s, 9H, Ar−CH_3), 2.62 (t, 1H, H-4, $J_{H,H}$=7.1 Hz), 2.70 (t, 2H, H-4, $J_{H,H}$=7.1 Hz), 5.00 (s, 1H, −OH), 6.62 (s, 1H, H-7). ^{13}C NMR δ: 11.6 (C-5a), 15.8,15.9 (C-8b, C-8b′), 21.6, 21.65 (C-4, C-4′), 23.6, 23.8 (C-2a, C-2a′), 24.3 (C-5a′), 31.4, 31.5 (C-3, C-3′), 74.4, 74.5 (C-2, C-2′), 116.0 (C-7′), 117.3 (C-4a), 118.9 (C-5), 119.6 (C-4a′), 121.5 (C-7), 121.8 (C-8), 124.0 (C-5′), 124.4 (C-8′), 144.1 (C-6), 144.9 (C-6′), 145.1 (C-8a), 146.1 (C-8a′). Calcd for $C_{56}H_{94}O_4$: C 80.91, H 11.40. Found: C 81.02, H 11.42. Resonances of the isoprenoid side chain are identical (±0.05 ppm) to those of ethano-dimer **11**.

Acknowledgements

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