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Short communication

Structure–activity relationships of sandalwood odorants: Total synthesis and fragrance properties of cyclopropano-β-santalol

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Abstract

The synthesis and odor properties of cyclopropano-β-santalol, a new santalol analogue, are described. The exocyclic double bond of the original molecule, β-santalol, is replaced by a cyclopropane ring. Despite the analogies in the binding properties between the double bond and cyclopropane this change in the bulky hydrophobic part of the molecule leads to the complete loss of the characteristic sandalwood odor: in an olfactory evaluation the (*Z*)-product appears spicy and sweet, the (*E*)-isomer woody, but neither of them exhibits the typical sandalwood character.

Keywords: β-Santalol; Osmophoric; Cyclopropane; Structure–odor-relationship

1. Introduction

A bicyclic sesquiterpene alcohol, (−)-(*Z*)-β-santalol (**1**), is one of the main constituents of the very appreciated and highly priced (>2000 Euro/kg, per November 2006) East Indian sandalwood oil [1–8]. The essential oil is produced by traditional steam distillation of wood obtained from trees of *Santalum album* L., which are at least about 40 years old. On account of its unique sweet, creamy, woody odor with animalic tonalities this essential oil is one of the oldest and most important ingredients for perfumery, and its character impact compound β-santalol (**1**) was and still is the target for many structure–odor-relationship studies [9–20]. Structural modifications of **1** affected, e.g. the bridge [15–17,21], or the neighborhood of the osmophoric alcohol group [9,22] or its transformation into an ester [23] or aldehyde [24]. Substitution of the exocyclic double bond, which serves as another important osmophoric group [4], by a keto- or a methoxy-group leads to a complete loss of the typical sandalwood odor [18] as this is also (and already long known) the case after its transformation into a methyl group by hydrogenation [25]. This rigid substituent at C2 of the norbornane nucleus either causes a certain steric fixation of the molecule, or creates a special environment with a certain steric hindrance. The higher electronic density could also be considered responsible for a better contact with the hypothetic receptor site [18].

On account of the ring strain cyclopropanes in many cases show olefinic behavior, they are so-called ‘‘small rings with double-bond character’’ [26,27]. By means of the ‘‘bent bonds’’ and because of analogies in the binding properties the similarities between the double bond and this three-membered ring are easy to explain, in as much regions of high electron densities in both cases lie outside the carbon–carbon-connecting line [26]. Thus, a cyclopropane ring could be a suitable substitute for the exocyclic double bond in **1** and therefore (*Z*)-cyclopropano-β-santalol (**2**) should be an alluring target molecule whose synthesis and olfactory properties are reported in this study (Fig. 1).

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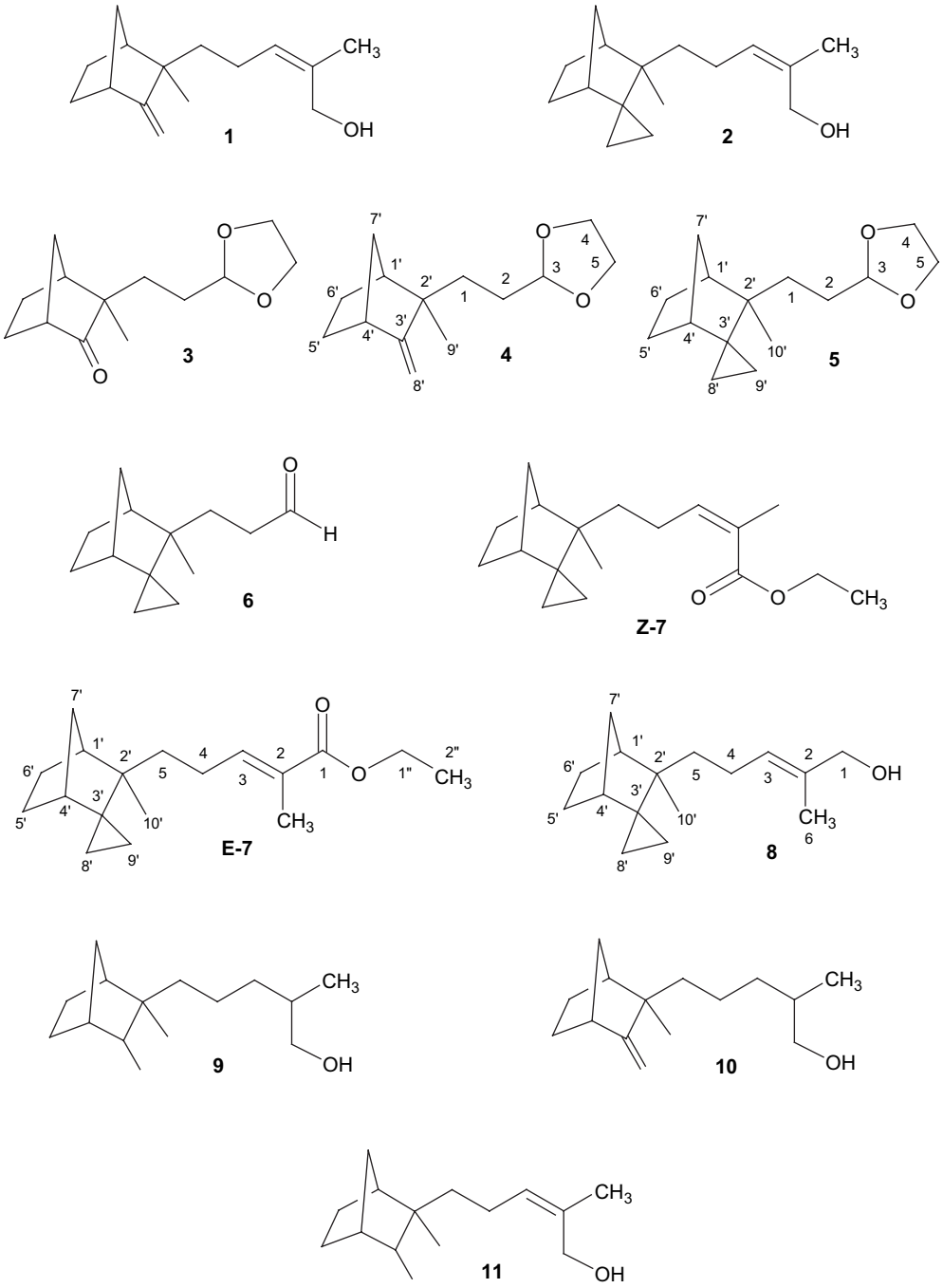

Fig. 1. Structural formulae of compounds **1**–**11**.

2. Results

2.1. Chemistry

The synthetic route to the desired compound **2** and its *trans*-isomer **8** was started from commercially available 2-norbornanone (norcamphor, Aldrich product No. N32601), which could be α-alkylated in a two-step process according to procedures described earlier [9,14,18], first with bromoethyldioxolane and subsequently with methyl iodide leading to ketone **3**.

Transformation of the ketone function of the norbornanone nucleus into an exocyclic methylene group furnishing **4** was accomplished using the *Tebbe*-reagent [20,28,29].

Access to the cyclopropane ring of **5** was provided by the *Simmons–Smith* reaction [30,31] adding methylene iodide to a stirred mixture of **4** and diethylzinc in dry methylene chloride at −10 °C.

Acidic acetal-cleavage with diluted sulfuric acid – this rather drastic condition furnished better yields and cleaner products [9,17,20] – provided aldehyde **6** which turned out

to be unstable, and therefore without further separation or purification was used for the next reaction step.

The *Horner–Emmons* reaction [32] usually shows a preference for formation of the more stable *E*-olefins. However, reaction of **6** with electrophilic triethyl-2-phosphonopropionate and the strongly dissociated base system [33] of Na-bis(trimethylsilyl)amide/18-crown-6 at −80 °C in anhydrous THF yielded a mixture of the *Z*/*E*-isomers *Z*-**7** and *E*-**7** in a ratio approximately 1:1 which could be separated by column chromatography (CC).

Reduction of the isomeric esters *Z*-**7** and *E*-**7** with diisobutylaluminium hydride (DIBAH) in hexane at −78 °C [18–20,34] yielded target compound **2** and the *E*-isomer **8**, respectively. In the ^{1}H NMR of **2** the signals due to H-1 (high resolved singlet, δ 4.03 ppm) and H-3 (triplet, δ 5.33 ppm) could easily be identified, as could the carbon signals due to C-2 (δ 133.6 ppm), C-3 (δ 129.4 ppm), C-1 (δ 61.9 ppm), and C-6 (δ 21.5 ppm) in a simple ^{13}C NMR experiment. The ^{1}H NMR spectrum of **8** did not show any mentionable differences. Due to the *E*-stereochemistry, the signal of C-1 (69.1 ppm) was found at lower field in the ^{13}C NMR of **8**, whereas C-6 (13.6 ppm) was shifted to higher field.

2.2. Olfactory evaluation

The odor analysis of the target compound **2** and its isomer **8** is given in Table 1. The odor of *trans*-isomer **8** resembles a little the woody and medicinal characters of (*E*)-β-santalol. The fragrance of (*Z*)-**2** can be described as spicy but very volatile. The typical sandalwood odor, however, could not be found in any of the two analogues. Concerning the chirality of odor molecules, Krotz and Helmchen [14] showed that only (−)-(*Z*)-**1** exerts the typical sweet woody sandalwood odor, whereas its (+)-(*Z*)-enantiomer can be considered odorless. That means, if only one enantiomer of an odor molecule shows sandalwood odor, in most cases the racemate possesses the fragrance, too. This in mind and based on the experience of previous studies [7,9] the olfactory evaluation has been performed on the racemates only, disregarding the possibility of antagonistic effects.

2.3. Discussion

The importance of the exocyclic double bond for the olfactory capacity of β-santalol (**1**) has been shown in earlier studies [4,18,25]. A keto-group instead of this double bond, for example, leads to a complete loss of the sandalwood odor although the molecular shape of the corresponding analogue is almost identical with the standard (**1**) [18]. Nevertheless, the electronic properties, electron density, electrostatic potential and charge distribution are significantly different for the polar carbon oxygen double bond. This seems to affect the interaction between the odorant molecules and the specific receptors significantly and might also impair the molecule's transport through the mucus due to its change in polarity. To prove whether steric effects – with no mentionable changes in polarity – at this site of the molecule also influence the receptor affinity, cyclopropano-β-santalol (**2**) was synthesized.

The cyclopropane ring, in many cases showing olefinic behavior [26,27], is sometimes called "a veiled double bond" [26]. A drastic alteration in space demand at one side of the "bulky group" [10] is the result of the substitution of the exocyclic double bond by this "veiled, masked double bond". The change in the molecular shape can be seen in Fig. 2.

The complete loss of the sandalwood odor demonstrates clearly that this position of the molecular surface is a very sensitive region for the recognition of the odorant molecule by the active site of the fragrance receptors. This has also been shown by Fanta and Erman [25] by hydrogenation of the two double bonds of **1**, furnishing tetrahydro-β-santalol (**9**). This compound exerts a "chemical, earthy, musty odor" that "dies down to a very weak, neutral woody odor" [25]. On the other hand, hydrogenation of just the double bond of the side chain

Table 1
Odor characterization of the newly synthesized compounds

Compounds	Odor characteristics
2	Spicy, very weak and volatile, weak sweet bynote.
8	At the beginning camphor like, woody, rubber like, possibly sweet, rancid.

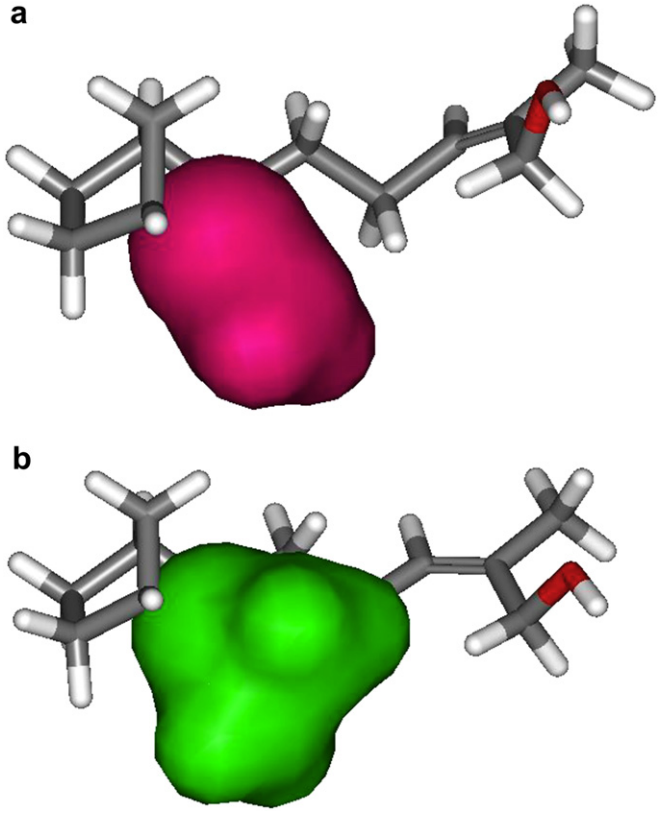

Fig. 2. Energy minimized structures of **1** (a) and **2** (b), obtained from DFT/6-31G(d,p) calculations. For the carbon–carbon double bond and the cyclopropane ring the solvent accessible surfaces are displayed.

yielding dihydro-β-santalol (**19**) does not impair the ''strong and characteristic sandalwood note'' [25]. The odor of the ''other'' dihydro-β-santalol (**11**) has not been assessed up to now, although this compound was found and characterized by spectroscopic analyses in the mixture of the reaction products upon catalytic hydrogenation of **1** [35]. The above mentioned findings show that the exocyclic double bond is essential for the interaction with the corresponding receptor sites. Moreover, such an influence of steric features on the sensory properties of sandalwood analogues has also been shown for other parts of the molecule, e.g. the alkyl substitution close to the hydroxyl group [9,10,22]. Thus, this substitution is – from a chemical point of view – a relative unspectacular alteration of a double bond in **1** into its ''bent form'' [26,27] in **2** and leads – now from a biological viewpoint – to a drastic change of the sensory properties of the new sandalwood analogue **2**.

3. Experimental protocols

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-200 NMR-spectrometer (200 MHZ, $CDCl_3$, 28 °C; Karlsruhe, Germany). Chemical shifts were given in ppm relative to tetramethylsilane (TMS) as internal standard (=0 ppm). The infrared (IR) spectrum was performed on a Perkin–Elmer FT-IR-spectrophotometer Spectrum 2000 (Oak Brook, IL) (cm^{-1}). Mass spectra were recorded on a Hewlett-Packard MSD (GC: 5890, MS: 5970, column: HP-5MS 30 mm × 0.25 mm × 0.25 μm, HPPart No. 19091S-433; Corvallis, OR). Purifications were performed either on thin layer chromatography (TLC) plates (silica gel 60 F_{254}, 0.25 mm layer thickness, No. 1.05554), or preparative thin layer chromatography (PTLC) plates (silica gel 60 F_{254}, 2 mm layer thickness, No. 5717), or with column chromatography (CC) (KG 60 F_{354}, 70–230 mesh ASTM, No. 1.07734) from Merck (Darmstadt, Germany).

3.1. 2-[2-(2-Methyl-3-methylenebicyclo[2.2.1]hept-2-yl)ethyl]-1,3-dioxolane (*4*)

In an argon atmosphere **3** (0.50 mg, 2.26 mmol) [9,14,18] dissolved in absolute THF (25 ml) was cooled down to 0 °C, mixed drop-wise with *Tebbe*-reagent (5.38 ml, 0.5 M in toluene) and stirred at 0 °C for 3 h. After quenching with a 1:1-mixture of ether/CH_3OH the solution was filtered through a layer of Celite®/Al_2O_3 (1:1) and washed with ether. The solvent then was evaporated. Bulb-to-bulb distillation followed by CC (petroleum ether/ethyl acetate 90:10) furnished 219 mg (44%) of light yellow oil (**4**). MS: *m/z* (%) = 222 (M^+, 1), 147 (1), 145 (1), 134 (3), 105 (7), 99 (100), 73 (70), 45 (28). ^{1}H NMR: $\delta = 0.98$ (s, 3H, CH_3), 1.28–1.62 (m, 10H, 5 × CH_2), 1.95 (bs, 1H, 1′-H), 2.65–2.66 (m, 1H, 4′-H), 3.82–3.94 (m, 4H, 4-H, 5-H), 4.48 (s, 1H, 8′-H), 4.70 (s, 1H, 8′-H), 4.80–4.82 (m, 1H, 3-H). ^{13}C NMR: $\delta = 166.3$ (C-3′), 104.9 (C-3), 99.5 (C-8′), 64.8 (C-4, C-5), 46.7/45.0 (C-4′, C-1′), 44.3 (C-2′), 37.0/32.7/29.8/29.0 (4 × CH_2), 25.2 (CH_3), 23.5 (CH_2). $C_{14}H_{22}O_2$ (222.33).

3.2. 2-[2-(3-Methylspiro[bicyclo[2.2.1]heptane-2,1′-cyclopropan]-3-yl)ethyl]-1,3-dioxolane (*5*)

A solution of diethylzinc (10.76 ml, 1 M in hexane) was cooled to −10 °C in an argon atmosphere. Under heavy stirring and cooling iodomethane (1.39 ml, 16.14 mmol, freshly cleaned over Al_2O_3) was injected very slowly. Compound **4** (597 mg, 2.69 mmol) in absolute CH_2Cl_2 (15 ml) was added, the reaction mixture was stirred for 30 min at −10 °C, then allowed to warm to RT within 1.5 h. The deposit was hydrolyzed with saturated NH_4Cl, and extracted with ether. The combined organic layers were washed (sat. $Na_2S_2O_3$), dried ($MgSO_4$), evaporated, and purified by bulb-to-bulb distillation and PTLC (CH_2Cl_2/petroleum ether 95:5; twice developed) yielding 362 mg (43%) of slight yellow oil (**5**). IR (NaCl, liquid film): $\nu = 3405$, 3066, 2939, 1713, 949. MS: *m/z* (%) = 236 (M^+, 1), 221 (2), 208 (2), 174 (10), 135 (16), 99 (92), 86 (49), 72 (100), 45 (38). ^{1}H NMR: $\delta = 0.20$–0.48 (m, 4H, 8′-H, 9′-H), 0.75 (s, 3H, CH_3), 0.81–1.68 (m, 10H, 5 × CH_2), 1.81–1.97 (m, 2H, 4′-H, 1′-H), 3.78–3.99 (m, 4H, 4-H, 5-H), 4.78 (t, $J = 4.8$ Hz, 1H, 3-H). ^{13}C NMR: $\delta = 105.2$ (C-3), 64.8 (C-4, C-5), 48.5/46.9 (C-1′, C-4′), 39.0/36.9 (C-2′, C-3′), 36.1/31.9/29.7 (3 × CH_2), 27.0 (CH_3), 24.5/24.0 (2 × CH_2), 10.7/6.2 (C-8′, C-9′). $C_{15}H_{24}O_2$ (236.36).

3.3. 3-(3-Methylspiro[bicyclo[2.2.1]heptane-2,1′-cyclopropan]-3-yl)propanal (*6*)

Compound **5** (189 mg, 0.80 mmol) in toluene (10 ml) was treated with 2 N H_2SO_4 (22 ml) and heated under reflux for 24 h. The solution was extracted with ether, washed with water, dried ($MgSO_4$), and evaporated. The resulting dark yellow oil (0.14 g crude product) was directly used for the next reaction in order to avoid decomposition on the stationary phase of PTLC. Aldehyde **6** was confirmed by mass spectrometer analysis. MS: *m/z* (%) = 192 (M^+, 1), 177 (15), 164 (11), 148 (11), 136 (32), 119 (21), 94 (100). $C_{13}H_{20}O$ (192.30).

3.4. Ethyl((2Z)/(2E)-2-methylspiro[bicyclo[2.2.1]heptane-2,1′-cyclopropan]-3-yl)pent-2-enoate (*Z*-**7**/*E*-**7**)

A solution of triethyl-2-phosphonopropionate (0.15 ml, 0.69 mmol) and recrystallized 18-crown-6-ether (0.90 g, 3.41 mmol) in absolute THF (20 ml) was cooled to −80 °C in an argon atmosphere. The mixture was then carefully treated with Na-bis(trimethylsilyl)amide ($NaN(TMS)_2$) (0.71 ml, 1.0 M in THF). The crude product containing aldehyde **6** (0.14 g) in absol. THF (2.5 ml) was added, and stirring was continued for 4 h at −80 °C. After quenching with saturated NH_4Cl solution the product was extracted into ether. The combined ether layers were dried and evaporated, furnishing 175 mg of a mixture of the *Z*/*E*-isomers *Z*-**7** and *E*-**7** in a ratio 8:8.5. Purification and separation by CC (CH_2Cl_2/petroleum ether 70:30) yielded 20 mg of *Z*-**7** and 22 mg of *E*-**7**, a total of 42 mg (19%). MS: *m/z* (%) *Z*-**7** = 276 (M^+, 5) 261 (1), 248 (13), 231 (15), 149 (23), 136 (29), 121 (76), 107 (42), 93 (100), 79 (45). *E*-**7** = 276 (M^+, 3) 261 (1), 248 (10), 231 (12), 149 (20), 136

(27), 121 (98), 107 (42), 93 (100), 79 (57). ^{1}H NMR: δ *Z*-**7** = 0.08–0.38 (m, 4H, H-8′, H-9′), 0.78 (s, 3H, 10′-H), 1.08–1.76 (m, 11H, 4 × CH_2, 2″-H), 1.79–1.95 (m, 4H, 6-H, CH), 2.03 (bs, 1H, CH), 2.21–2.37 (m, 2H, 4-H), 4.13 (q, J = 6.95 Hz, 2H, 1″-H), 5.78–5.85 (t, J = 6.94 Hz, 1H, 3-H). *E*-**7** = 0.07–0.49 (m, 4H, H-8′, H-9′), 0.85 (s, 3H, 10′-H), 1.06–1.71 (m, 11H, 4 × CH_2, 2″-H), 1.76–2.20 (m, 7H, 1′-H, 4′-H, 4-H, 6-H), 4.13 (q, J = 6.94 Hz, 2H, 1″-H), 6.72 (t, J = 6.94 Hz, 1H, 3-H). ^{13}C NMR: δ *Z*-**7** = 178.5 (C=O), 143.4 (C-3), 126.6 (C-2), 60.0 (C-1″), 48.5/47.0 (C-1′, C-4′), 39.5 (C_q), 37.7 (CH_2), 36.9 (C_q), 36.1/27.1/25.6 (3 × CH_2), 24.6 (CH_3), 24.1 (CH_2), 20.7/14.3 (2 × CH_3), 10.7/6.1 (C-8′, C-9′). *E*-**7** = 177.9 (C=O), 143.3 (C-3), 127.2 (C-2), 60.4 (C-1″), 48.4/46.9 (C-1′, C-4′), 39.5/36.9 (2 × C_q), 36.8/36.1/27.1/24.7 (4 × CH_2), 24.5 (CH_3), 24.2 (CH_2), 14.3/12.2 (2 × CH_3), 10.7/6.2 (C-8′, C-9′). $C_{18}H_{28}O_2$ (276.42).

*3.5. (2Z)-2-Methyl-5-(3-methylspiro[bicyclo[2.2.1] heptane-2,1′-cyclopropan]-3-yl)pent-2-en-1-ol (**2**)*

Z-**7** (52 mg, 0.19 mmol) was dissolved in anhydrous CH_2Cl_2 (1.2 ml) and cooled to −78 °C in an argon atmosphere. A 20% solution of DIBAH in *n*-hexane (0.82 ml, equals 1 M) was added, and the resulting mixture was stirred for 16 h at RT. It then was cooled to −20 °C, hydrolyzed with a mixture of MeOH/H_2O (2 ml, 1:1), and stirred for another 3 h at RT. Afterwards, the solution was mixed with Celite®, filtered over Celite®, washed with ethyl acetate, and evaporated, yielding 34.2 mg of brownish oil. Purification by TLC (toluene/ethyl acetate 80:20; twice developed) furnished 17 mg (33%) of colorless oil (**2**). MS: *m/z* (%) = 234 (M^+, 6), 203 (11), 187 (8), 176 (15), 161 (10), 147 (20), 121 (100), 93 (96). ^{1}H NMR: δ = 0.08–0.38 (m, 4H, H-8′, H-9′), 0.65–2.09 (m, 19H), 4.12 (s, 2H, 1-H), 5.23 (t, J = 4.43 Hz, 1H, 3-H). ^{13}C NMR: δ = 133.6 (C-2), 129.4 (C-3), 61.9 (C-1), 48.5/47.0 (C-1′, C-4′), 39.1/36.4/30.02/27.9 (3 × CH_2, C-2′, C-3′), 24.3 (C-10′), 24.1/23.5 (2 × CH_2), 21.5 (C-6), 10.7/6.2 (C-8′, C-9′). $C_{16}H_{26}O$ (234.39).

*3.6. (2E)-2-Methyl-5-(3-methylspiro[bicyclo[2.2.1] heptane-2,1′-cyclopropan]-3-yl)-pent-2-en-1-ol (**8**)*

E-**7** (52 mg, 0.19 mmol) was treated as described above yielding 34.2 mg of crude product. Purification furnished 14 mg (27%) of almost colorless oil (**8**). MS: *m/z* (%) = 234 (M^+, 3), 203 (14), 187 (2), 175 (6), 161 (3), 147 (12), 121 (100), 93 (79). ^{1}H NMR: δ = 0.06–0.45 (m, 4H, H-8′, H-9′), 0.73–0.89 (s, 3H, 10′-H), 1.13–2.09 (m, 6H), 3.93 (s, 2H, 1-H), 5.33 (t, J = 4.45 Hz, 1H, 3-H). ^{13}C NMR: δ = 134.1 (C-2), 127.1 (C-3), 69.1 (C-1), 48.5/47.1 (C-1′, C-4′), 37.9/36.8/36.1/29.8/27.1 (3 × CH_2, C-2′, C-3′), 24.6 (C-10′), 24.2/23.5 (2 × CH_2), 13.6 (C-6), 10.1/6.2 (C-8′, C-9′). $C_{16}H_{26}O$ (234.39).

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