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Original article

Structure–activity relationships of sandalwood odorants: synthesis and odor of tricyclo β-santalol

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Abstract

In a series of structure–odor relationship investigations the synthesis of a new tricyclic β-santalol derivative is described. The product of a multistep synthesis appears in an olfactive evaluation more or less odorless, may be slightly creamy but definitely with no sandalwood odor. This modification with a bulky aliphatic bridge in the neighborhood of the quaternary C_3-atom demonstrated the sensitivity of sandalwood odor on the structure of β-santalol analogues.

Keywords: Structure–odor relationship; β-Santalol; (*Z*)-2-Methyltricyclo[5.2.1.$0^{2',6'}$]dec-2′-yl-2-pentenol; Bulky group; Exocyclic double bond

1. Introduction

Sandalwood oil is one of the oldest and most important ingredients for perfumery. The essential oil is produced by traditional steam distillation of wood obtained from trees of *Santalum album* L., that are at least about 40 years old. The bicyclic sesquiterpene alcohol β-santalol (**1**) is one of the main constituents of the oil, responsible for its sweet woody odor character as well as the urineous, animalic tonality [1–3]. A series of natural and synthetic compounds with this typical sandalwood fragrance has been found and synthesized [4–7]. Structure–odor relationship studies on sandalwood odor compounds were topics of many investigations. A special challenge of these studies is the fact that only small structural modifications of a sandalwood odor molecule lead to the complete loss of the scent, whereas many substances with complete different chemical structure possess sandalwood fragrance. Many papers have been published about structure–activity relationships of sandalwood odor compounds [1–18] and it is generally accepted that special parts of the molecules, respectively, their molecular surfaces are important for the biological effect. These osmophoric points are the functional group, a methyl group closeby this position and parts of the bulky aliphatic residue [10]. Both, steric and electrostatic properties are responsible for the fragrance, as demonstrated by modifications of the parent compound (**1**) [9,10]. Moreover, optical isomers differ significantly in their odor impression [14].

In continuation of our studies on structure–odor relationship of fragrance compounds emitting the sandalwood odor, it seemed worthwhile to extend our previous investigation [9] by synthesizing the tricyclic β-santalol analogue **2** in order to study the influence of the modified ring system, the so-called "bulky group C" [10] on the sandalwood character. Already in 1979, the importance of the exocyclic double bond at C2 for this unique sandalwood scent was stressed [1,4] and we could confirm this assumption indirectly by preparing the sterically nearly identical, but odorless β-ketosantalol [18]. Therefore, it was obvious and alluring to answer the question, whether a connection of the exocyclic double bond with the angular methyl group at C3 also leads to a loss of the woody note, both present in **1** and **3**, a natural tricyclic compound found in sandalwood essential oil and which contributes to the unique total sandalwood character with a woody, ambergris odor [19], in as much as this anellated cyclopentane nucleus of **3** bears an oxygen function also in a certain distance from the quaternary C_3-atom. Furthermore, considering the fact that isomers in many cases exhibit dif-

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ferent odors, both isomers were prepared and their olfactory properties discussed (Fig. 1).

2. Results

2.1. Syntheses

The tricyclic analogue **2** of β-santalol (**1**) was achieved by connecting the methylidene function in position **2** with the methyl group in position 3 of the bicyclic system of **1** through a methylene bridge. Interestingly, a natural compound **3** has been found in sandalwood essential oil that shows the same tricyclic structure and contributes to the unique total sandalwood character with its woody, ambergris odor [19].

We started the synthetic route to the desired compound **2** from the unsaturated ester **4** [20–31]. The evidence for the *endo*-configuration of **4** was found by Herz et al. [23,24] who elucidated the relative configuration of the tricyclus by photolytic conversion. Ester **4** appeared to be rather labile, therefore it was transformed immediately after preparation [24] into the corresponding saturated ester **5** by catalytic hydrogenation.

Azeotropic transformation of **5** afforded tosylhydrazone **6** [32] as a mixture of isomers. Subsequent reduction with $LiAlH_4$ (THF) gave alcohol **7** [33] as stereochemically ho-

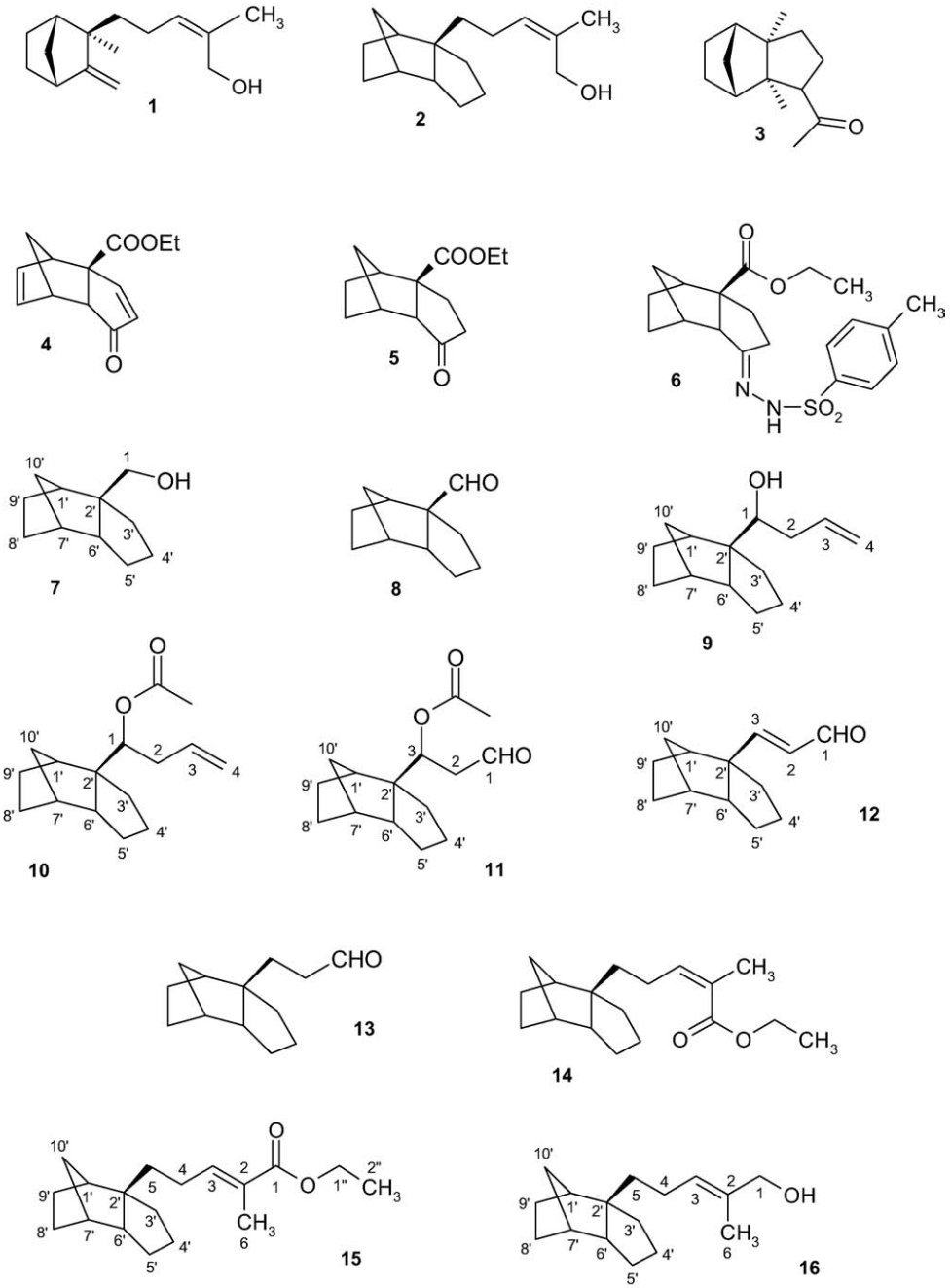

Fig. 1. Formula picture 1.

mogenous compound. Aldehyde **8** was achieved from **7** by *Swern* oxidation [34] that has been reported highly useful in the mild oxidation of alcohols to carbonyls [35,36]. Reaction of dimethyl sulfoxide (DMSO) with electrophilic "activators" such as oxalyl chloride furnishes sulfonium salts which, upon nucleophilic attack by an alcohol (such as **7**) and basification with triethylamine (TEA) results in generally high yields of the corresponding carbonyl (e.g. **8**).

Attempts of chain elongation at the CHO position of **8** by *Wittig* and related reactions failed because of steric hindrance in the tricyclic system. However, successful conversion of **8** to desired α,β-unsaturated aldehyde **12** was effected indirectly starting with a *Grignard* reaction of aldehyde **8** with allyl magnesium bromide [37,38] followed by protection of the tertiary alcohol **9** by acetylation (acetic anhydride/pyridine) [37,39] furnishing **10**. *Cis*-hydroxylation of the double bond with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMMO), the latter used as stoichiometric co-oxidant to regenerate the reagent [37,40] gave the corresponding glycol which turned out to be unstable, and therefore without further separation or purification was transformed to aldehyde **11** ($NaIO_4$) [41]. Finally, **12** was achieved in almost quantitative yield by cracking the protecting acetyl group by aqueous K_2CO_3 solution [42]. On catalytic hydrogenation in AcOEt the saturated aldehyde **13** was available [37].

The *Horner–Emmons* reaction is a well established classic method for the preparation of α,β-unsaturated esters [43]. In general, the olefination shows a preference for formation of the more stable *E*-olefins. However, under certain conditions, i.e. using strongly dissociated base systems, the *Z*-isomer can be achieved in a synthetic useful level [44]. Reaction of **13** with electrophilic triethyl 2-phosphonopropionate and Na-bis(trimethylsilyl)amid/18-crown-6 in anhydrous THF at –80 °C yielded a mixture of the *Z*/*E*-isomers **14** and **15** in a ratio 3/2, whereas the *Z* selectivity could be raised distinctively more by changing the base system to K-bis(trimethylsilyl)amid/18-crown-6, maintaining the other reaction conditions, mainly furnishing Z-ester **14** (*Z*/*E* 6/1).

Target compound **2** finally was available by reduction of **14** with diisobutylaluminium hydride (DIBAH) in hexane at –78 °C [45,46]; the *E*-isomer **16** was available from ester **15**. In the ^{1}H-NMR of **2** the signals due to H-1 (high resolved singlett, δ 4.10 ppm), and H-3 (triplet, δ 5.26 ppm) could easily be identified, as could the carbon signals due to C-1 (δ 61.3 ppm), C-2 (δ 133.6 ppm), C-3 (δ 129.1 ppm), C-2′ (δ 53.4 ppm), and C-6 (δ 21.1 ppm) in a simple ^{13}C-NMR experiment. The ^{1}H-NMR spectrum of *trans*-isomer **16** differed only marginally. Here the long range coupling of H-3 with H-6 (^4J = 1.01 Hz) can be noticed because of their *trans* position. Greater differences between the two isomers were found in the ^{13}C-NMR spectra: due to the *E* stereochemistry the signal of C-1 (δ 68.8 ppm) is shifted to lower field, whereas C-6 (δ 13.5 ppm) was found at higher field in **16**.

2.2. Olfactoric evaluation

The odor analysis of the last six synthesized compounds is given in Table 1. The smaller intermediates **7** and **8** possess an uncharacteristic camphoraceous odor. Even though target compound **2** is a structural combination of two pleasant smelling odorants (**1** and **3**) it was found to be almost odorless, possibly with a light pleasant creamy touch. The *E*-isomer **16** can also be considered as odorless, as can the esters **14** and **15**. The intermediates **12** and **13** on the other hand exhibit interesting intense odors: the aroma of aldehyde **12** can be described as pleasant costus- and iris-root-like with an animalic fatty tonality, whereas the odor of its saturated analog **13** can be summarized as green and woody. As to the chirality of odorants, Krotz and Helmchen [14] showed that only (*Z*)-(–)-1 exerts this appreciated, sweet woody and typical sandalwood odor, whereas its (*Z*)-(+)-enantiomer proved itself as odorless. As one enantiomer shows sandalwood odor, the racemate possesses this fragrance too, which is also documented in previous studies (see e.g. [7,47,48]). Consequently, if the racemic mixture is odorless, as is the case of **2**, also no single enantiomer exerts an odor.

2.3. Discussion

In a previous paper on the investigations of the consequences of synthetic modifications of β-santalol (**1**) on sandalwood odor, the influence of the side chain geometry on the fragrance has been shown. Moreover, a summary has been given about a series of modified β-santalol analogues and their odor impression. The presented synthesis is a significant contribution for answering the question about the importance of the stereochemistry at the carbon bond with the adjacent side chain. An overview about the importance of this position for the fragrance is given in Fig. 2.

The molecular shape around the carbon–carbon–double bond is depicted in the figure. The exocyclic carbon–carbon double bond is essential for the fragrance but omitting the methyl group at the quaternary carbon atom, where the side chain is connected, does not change the character of the fragrance impression drastically (**17**) [7,49]. A replacement of the carbon–carbon double bond by a carbonyl function leads to the complete loss of sandalwood fragrance (**18**), although the molecular shape is very similar to that of **1**. It has been postulated, that the negative charge of the oxygen

Table 1
Odor characterization of some of the newly synthesized compounds

Compounds	Odor characteristics
12	Intense pleasant odor, strong flowery, costus- and iris-root-like, animalic, erotic, fatty
13	Intense green headnote, aldehyde-like with a weak woody bynote, later reminiscent of rose odor, citronellal-like
14	Odorless
15	Odorless
2	Nearly odorless, possibly pleasant creamy
16	Nearly odorless, possibly woody

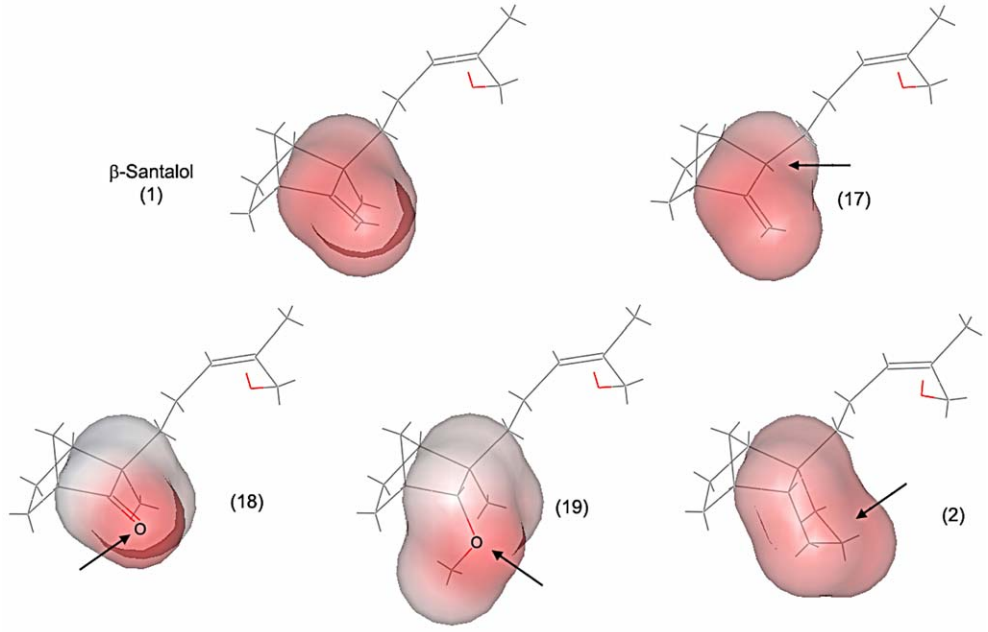

Fig. 2. β-santalol (1).

atom of the polarized double bond is now responsible for the changed odor [18]. The same argument is valid in the case of the methoxy-substituted compound (**19**) [18]. Furthermore, it has been found that hydrogenation of the carbon–carbon double bond again destroys the sandalwood odor [50]. The synthesis of compound **2** together with the olfactoric evaluation shows that an increase of the size of the molecular shape around both carbon atoms 2′ and 6′ by introducing one more carbon atom as well as the absence of the exocyclic double bond leads to the loss of sandalwood fragrance.

3. Experimental protocols

Melting points were investigated on a *Kofler* apparatus and are uncorrected. 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) or on a Varian Unityplus 300 NMR-spectrometer (300 MHz, $CDCl_3$, 28 °C; Palo Alto, CA). Chemical shifts are given in ppm relative to tetramethylsilane (TMS) as internal standard (= 0 ppm). Infrared (IR) spectra were 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 m × 0.25 mm × 0.25 μm, HPPart No. 19091S-433; Corvallis, OR) or on a Shimadzu DI-QP5000 instrument (Kyoto, Japan). Purifications were performed either on preparative thin layer chromatography (PTLC) plates (silica gel 60 F_{254}, 2 mm layer thickness, No. 5717), on thin layer chromatography (TLC) plates (silica gel 60 F_{254}, 0.25 mm layer thickness, No. 5554), or with column chromatography (CC) (KG 60 F 354, 70–230 mesh ASTM, No. 7734) from Merck (Darmstadt, Germany).

3.1. Ethyl tricyclo[5.2.1.$0^{2,6}$]decan-5-one-2-carboxylate (*5*)

Three grams (13.75 mmol) of **4** were diluted in 30 ml ethanol and hydrogenated by stirring with a Pd/C-catalyst until hydrogen saturation was completed. The product was extracted with ether, washed, dried over anhydrous $MgSO_4$, and evaporated. Yield: 2.7 g (88.4%) of a yellowish oil. $C_{13}H_{18}0_3$ (222.29).

3.2. 2-Carbethoxy-tricyclo[5.2.1.$0^{2,6}$]decan-5-one p-tosyl hydrazone (*6*)

Eleven grams (60 mmol) of *p*-toluenesulfonyl hydrazide (pTSH) were added to a solution of 11.90 g (53.50 mmol) of **5** in benzene and heated under reflux for 16 h on a water separator. After extraction with ether the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Yield: 20.17 g (97%) of a highly viscous brown substance. Eight hundred twenty milligrams of the crude product were purified for spectroscopic analyses by TLC (petroleum ether/ethyl acetate 60:40) yielding 235 mg (29%) of yellowish crystals of a mixture of isomers. M.p. interval 165–180 °C. IR (KBr): ν = 3206, 2966, 1721, 1342, 1167. MS: *m/z* (%) = 391 (M^+, 10), 317 (31), 235 (100), 163 (26), 133 (49), 105 (28), 93 (24), 91 (94), 79 (22), 67 (52). ^{1}H-NMR: δ = 0.72–2.61 (m, 18H), 3.34 (m, 1H, N–H), 4.03 (q, J = 7.06 Hz, 2H, O–CH_2), 7.20–7.77 (m, 5H). ^{13}C-NMR

($CDCl_3$): δ = 176.9/176.6 (C=O), 168.1/166.8 (C=N), 143.75/143.72 (C-1′), 135.4 (C-4′), 129.4/129.3/127.7 (Ar–CH), 61.3/60.9/60.7/59.2 (O–CH_2, C-2), 54.0/49.5/45.2/44.9/42.6/39.5 (C-1, C-6, C-7), 40.6/40.4 (C-10), 35.1/30.4/28.3/27.6/24. 1/23.5/23.2/22.8 (4 × CH_2), 21.41/21.39 (Ar–CH_3), 14.0/13.9 (O–CH_2–CH_3). $C_{20}H_{26}N_2O_4S$ (390.50).

3.3. Tricyclo[5.2.1.$0^{2',6'}$]dec-2′-yl-methanol (7)

Forty-three milliliters (43 mmol) of lithium aluminum hydride ($LiAlH_4$) (1 M in THF) were carefully added to a suspension of 5.6 g (14.34 mmol) of crude **6** in 57 ml absolute tetrahydrofurane (THF) in argon atmosphere. The mixture was then stirred for 30 min at room temperature and 1 h under reflux. Afterwards, the reaction mixture was cooled with ice, mixed with ice water until no more hydrogen was developed, and stirred for another 30 min. The deposit was dissolved in H_2SO_4 (10%), and extracted with ether (5×). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated, furnishing 4.34 g of a dark brown, highly viscous substance. The crude product was submitted to CC (petroleum ether/ethyl acetate 60:40) yielding 1.35 g (31%) of yellowish semi-crystals. IR (KBr): ν = 3338, 2949, 2876, 1467, 1054. MS: *m/z* (%) = 136 (11), 135 (100), 107 (11), 93 (24), 91 (18), 81 (14), 79 (33), 77 (17), 67 (56), 53 (8). ^{1}H-NMR ($CDCl_3$): δ = 1.20–1.82 (m, 13H), 1.92 (bs, 1H, OH), 2.06–2.08 (m, 2H), 3.22 (d, ^2J = 10.53 Hz, 1H, 1-H), 3.51 (d, ^2J = 10.53 Hz, 1H, 1-H). ^{13}C-NMR ($CDCl_3$): δ = 70.6 (C-1), 55.8 (C-2′), 48.6/42.9/41.9 (3 × CH), 40.1 (C-10′), 31.1/28.5/27.1/23.9/23.3 (5 × CH_2). Analysis CH: $C_{11}H_{18}O$ (166.26).

3.4. Tricyclo[5.2.1.$0^{2,6}$]dec-2-ylal (8)

A mixture of 2 ml (22.93 mmol) of freshly distilled oxalyl chloride in 20 ml of anhydrous methylene chloride (CH_2Cl_2) was cooled to –78 °C in argon atmosphere. 3.1 ml (43.68 mmol) of distilled DMSO were very slowly injected. After 5 min, 2.64 g (15.88 mmol) of **7** dissolved in anhydrous CH_2Cl_2 and 10 ml (71.75 mmol) of distilled trimethylamine (TEA) were added. After another 5 min the reaction mixture was allowed to warm to room temperature, and stirred for additional 20 min. It then was extracted with H_2O/CH_2Cl_2, dried ($MgSO_4$), and evaporated to give 3.2 g of a brown viscous raw product. Purification by CC (petroleum ether/ethyl acetate 80:20) yielded 2.85 g (89%) of light yellow semi-crystals. IR (NaCl, liquid film): ν = 2943, 2690, 1718, 1460. MS: *m/z* (%) = 165 (M + 1, 1), 164 (M^+, 4), 135 (100), 107 (17), 97 (10), 93 (37), 91 (26), 79 (46), 77 (28), 67 (95). ^{1}H-NMR ($CDCl_3$): δ = 1.24–2.60 (m, 15H), 9.44 (s, 1H, CHO). ^{13}C-NMR ($CDCl_3$): δ = 204.1 (C=O), 65.4 (C-2), 48.2/41.7/41.6 (3 × CH), 41.57/28.6/28.5/27.6/23.3/23.1 (6 × CH_2). $C_{11}H_{16}O$ (164.25).

3.5. Tricyclo[5.2.1.$0^{2',6'}$]dec-2′-yl-3-butenol (9) [37,38]

A solution of 2.37 g (14.43 mmol) of **8** in 5 ml of absol. THF was cooled to –78 °C in argon atmosphere, and treated with 8.7 ml (17.4 mmol) of allyl magnesium bromide (2 M in THF). After stirring for 15 min at –78 °C the reaction mixture was allowed to warm to room temperature, and stirring was continued for 45 min. The mixture then was poured on ice water, the deposit dissolved in saturated NH_4Cl, and extracted into ether. The combined organic layers were washed with saturated solutions of sodium bicarbonate ($NaHCO_3$) and sodium bisulphite ($NaHSO_3$), respectively, dried ($MgSO_4$), and concentrated in vacuo. Yield: 2.75 g (93%) of a mixture of two isomers (1:1). For spectroscopic analyses 230 mg of the crude product were submitted to PTLC (petroleum ether/ethyl acetate 80:20) furnishing 179 mg (77%) of light pink flat crystals. M.p: 65–68 °C.

IR (KBr): ν = 3367, 2935, 2876, 1639, 906. MS: *m/z* (%) = 166 (12), 165 (100), 147 (61), 135 (62), 119 (63), 105 (29), 95 (21), 93 (36), 91 (60), 77 (28). ^{1}H-NMR ($CDCl_3$): δ = 1.22–2.42 (m, 18H), 3.53 (m, 1H, 1-H), 5.07 (m, 1H, 4a-H), 5.14 (m, 1H, 4b-H), 5.86 (m, 1H, 3-H). ^{13}C-NMR ($CDCl_3$): δ = 136.6 (C-3), 117.4 (C-4), 76.0 (C-1), 58.5 (C-2′), 49.4/44.1/43.0 (3 × CH), 40.6/38.4/28.3/28.0/27.0/24.0/23.7 (7 × CH_2). $C_{14}H_{22}O$ (206.33).

3.6. Tricyclo[5.2.1.$0^{2',6'}$]dec-2′-yl-3-butenyl acetate (10)

A solution of 2.87 g (13.92 mmol) of **9** in 19 ml of dry pyridine was cooled to 0 °C, and mixed with 9.5 ml of acetic anhydride under in atmosphere. After stirring for 12 h at room temperature the reaction mixture was then poured into ether, washed subsequently with 20% HCl, 5% $NaHCO_3$, and water, and dried ($MgSO_4$). The solvent was removed by rotary evaporation yielding 3.36 g (97%) of a light yellow oil of a mixture of two isomers (1:1). IR (NaCl, liquid film): ν = 2948, 1739, 1642, 1241, 1020. MS: *m/z* (%) = 207 (3/2), 165 (100), 147 (75/94), 135 (43/64), 119 (71/58), 107 (10/14), 105(16/17), 93 (21/30), 91 (39/48), 67 (40/53). ^{1}H-NMR ($CDCl_3$): δ = 1.27–2.46 (m, 20H), 4.99–5.11 (m, 3H, 1-H, 4-H), 5.78 (m, 1H, 3-H). ^{13}C-NMR ($CDCl_3$): δ = 171.1/171.0 (C–O), 135.4 (C-3), 116.7/116.6 (C–4), 78.6/78.5 (C-1), 57.9/57.7 (C-2′), 49.3/49.2/44.7/44.2/42.9/42.6 (CH) 40.5/40.4/36.6/34.3/28. 4/28.2/27.9/27.8/27.4/23.8/23.5 (CH_2), 21.2/21.0 (CH_3). $C_{16}H_{24}O_2$ (248.37).

3.7. 3-Oxo-tricyclo[5.2.1.$0^{2',6'}$]dec-2′-ylpropyl acetate (11)

To a mixture of 0.36 ml of osmium tetroxide (OsO_4) (2.5% w/w in *tert*-butyl alcohol), 0.97 g (8.28 mmol) *N*-methylmorpholine-*N*-oxide in 3 ml of water, and 4.5 ml of acetone at 0 °C was added 1 g (4.03 mmol) of **10** dissolved in acetone. The solution was allowed to warm to room temperature and stirred for 16 h. After adding ether the reaction mixture was subsequently washed with 1 N HCl and H_2O.

MS: *m/z* (%) = 251 (1/0), 222 (2/1), 173 (27/24), 147 (23/25), 135 (100), 119 (17), 107 (15), 93 (26/27), 79 (28/30), 67 (39). $C_{16}H_{26}O_4$ (282.38).

The ether solution of the glycol was cooled to 0 °C, and 2 g of sodium periodate ($NaIO_4$) in 2 N aqueous H_2SO_4 were added. After stirring for 10 min the reaction mixture was allowed to warm to room temperature, and was stirred for 2 h. Afterward, it was extracted with ether and the combined organic layers were washed with water and sodium thiosulfate ($Na_2S_2O_3$, to eliminate traces of I_2). Concentration in vacuo yielded 876 mg (87%) of a mixture of isomers.

IR (NaCl, liquid film): *v* = 2947, 2880, 2732, 1738, 1241. MS: *m/z* (%) = 208 (0/1), 190 (13/5), 147 (15/5), 135 (100), 119 (27/9), 107 (17/12), 93 (34/25), 91 (33/24), 79 (39/27), 67 (47/36). ^{1}H-NMR ($CDCl_3$): δ = 1.18–2.10 (m, 18H), 2.50 (m, 2H, 2-H), 5.30 (m, 1H, 3-H), 9.65 (m, 1H, 1-H). ^{13}C-NMR ($CDCl_3$): δ = 200.0 (C-1), 170.8 (acetyl–C=O), 74.1/73.9 (C-3), 57.6/57.5 (C-2′), 49.1/48.9 (CH), 46.7/44.7 (CH_2), 44.4/44.1/42.8/42.5 (2 × CH), 40.3/40.1/28.7/28.1/27.8/27.7/27.3/23.5/23.2/23.2 (6 × CH_2), 20.8/20.7 (CH_3). $C_{15}H_{22}O_3$ (250.34).

3.8. (E)-3-tricyclo[5.2.1.0$^{2',6'}$]dec-2′-yl-2-propenal (**12**)

To a solution of 6.19 g (24.72 mmol) of **11** in 100 ml of methanol, 90 ml of aqueous K_2CO_3 solution (5%) were added under ice cooling. After stirring for 3 h at room temperature, followed by extraction with ether, the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. Yield: 4.59 g (97%) of yellowish oil. Purification for spectroscopic analyses: PTLC (methylene chloride/petroleum ether 90:10).

IR (NaCl, liquid film): *v* = 2954, 2879, 2725, 1688, 1625. MS: *m/z* (%) = 191 (M + 1, 3), 190 (M^+, 19), 161 (25), 147 (35), 133 (33), 123 (21), 105 (34), 91 (100), 77 (63), 67 (44). ^{1}H-NMR ($CDCl_3$): δ = 1.19–1.85 (12H), 2.10–2.28 (m, 3H), 5.97 (dd, *J* = 7.5, 15.8 Hz, 1H, 2-H), 6.82 (d, *J* = 15.8 Hz, 1H, 3-H), 9.43 (d, *J* = 7.5 Hz, 1H, 1-H). ^{13}C-NMR ($CDCl_3$): δ = 194.5 (C-1), 169.5 (C-3), 127.4 (C-2), 56.9 (C-2′), 52.5/45.3/42.1 (3 × CH), 41.4/33.9/28.6/27.2/23.7/22.6 (6 × CH_2). $C_{13}H_{18}O$ (190.29).

3.9. 3-Tricyclo[5.2.1.0$^{2',6'}$]dec-2′-ylpropanal (**13**)

Four hundred eighteen milligrams (2.17 mmol) of **12** were diluted in 5 ml of ethyl acetate and hydrogenated by stirring with a Pd/C-catalyst, until the end of hydrogen uptake. The saturated product was extracted into ether, washed with water, dried ($MgSO_4$), and evaporated, yielding 310 mg (74%) of a yellowish oil. Purification for spectroscopic analyses: PTLC (petroleum ether/ethyl acetate 90:10).

IR (NaCl, liquid film): *v* = 2941, 2879, 2714, 1727, 1461. MS: *m/z* (%) = 193 (M + 1, 1), 192 (M^+, 4), 174 (12), 163 (5), 148 (70), 135 (63), 107 (42), 105 (30), 91 (74), 79 (100). ^{1}H-NMR ($CDCl_3$): δ = 1.07–2.10 (m, 17H), 2.21–2.54 (m, 2H), 9.77 (t, *J* = 1.88 Hz, 1H, 1-H). ^{13}C-NMR ($CDCl_3$): δ = 203.1 (C-1), 52.9 (C-2′), 52.4/45.0/42.5 (3 × CH), 40.8/40.7/34.0/33.1/28.5/27.2/ 24.1/23.1 (8 × CH_2). $C_{13}H_{20}O$ (192.30).

3.10. Ethyl-(Z)-2-methyl-5-tricyclo[5.2.1.0$^{2',6'}$]dec-2′-yl-2-pentenoate (**14**)

A solution of 2.13 g (8.05 mmol) recrystallized 18-crown-6-ether and 0.37 ml (1.73 mmol) triethyl 2-phosphonopropionate in 34 ml absol. THF was cooled to –80 °C in argon atmosphere. The resulting mixture was carefully treated with 3.34 ml (1.67 mmol) K-bis(trimethylsilyl)amid ($KN(TMS)_2$) (0.5 M in toluene), and stirred for 15 min at –80 °C. Three hundred ten milligrams (1.61 mmol) of **13** diluted in absol. THF were then added, and stirring was continued for 4 h at –80 °C. Saturated NH_4Cl solution was added, and the product was extracted into ether. The combined ether extracts were dried and evaporated, furnishing 476 mg of a mixture of the *Z*/*E*-isomers in a ratio of 6/1. Purification and separation were carried out on PTLC (petroleum ether/ethyl acetate 90:10; twice developed) furnishing 197 mg of *Z*-isomer (and 26 mg of *E*-isomer, a total of 223 mg (50%)).

IR (NaCl, liquid film): *v* = 2945, 2878, 1715, 1647, 1458. MS: *m/z* (%) = 278 (M + 2, 1), 277 (M + 1, 4), 276 (M^+, 17), 203 (12), 149 (63), 141 (95), 135 (45), 113 (38), 91 (60), 67 (100). ^{1}H-NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7.10 Hz, 3H, 2″-H), 1.86 (ds, ^4J = 1.26 Hz, 3H, 6-H), 1.17–2.07 (m, 17H), 2.29–2.51 (m, 2H), 4.18 (q, *J* = 7.10 Hz, 2H, 1″-H), 5.90 (dt, *J* = 7.65 Hz, ^4J = 1.26 Hz, 1H, 3-H). ^{13}C-NMR ($CDCl_3$): δ = 168.1 (C-1), 143.6 (C-3), 126.5 (C-2), 59.9 (C-1″), 53.4 (C-2′), 52.4/45.0/42.5 (3 × CH), 42.3/40.8/33.0/28.6/27.2/25.9/24.1/23.3 (8 × CH_2), 20.7 (C-6), 14.3 (C-2″). Analysis CH: $C_{18}H_{28}O_2$ (276.42).

3.11. Ethyl-(E)-2-methyl-5-tricyclo[5.2.1.0$^{2',6'}$]dec-2′-yl-2-pentenoate (**15**)

A solution of 8.72 g (33 mmol) recrystallized 18-crown-6-ether and 1.5 ml (7 mmol) of triethyl 2-phosphonopropionate in 130 ml of absol. THF was cooled to –80 °C. The mixture was carefully treated with 7 ml (7 mmol) Na-bis(trimethylsilyl)amid ($NaN(TMS)_2$) (1 M in absol. THF) and stirred for 15 min at –80 °C. 1.27 g (6.60 mmol) of **13** diluted in the same solvent were added, and the resulting mixture was stirred for another 4 h at –80 °C. Saturated NH_4Cl solution was added, the product was extracted into ether (3×), the combined ether extracts were dried ($MgSO_4$), and evaporated. Yield: 2.25 g of crude product of the *Z*/*E*-isomers in a ratio of 2/3.

Purification and separation of 840 mg of the crude mixture on PTLC plates (petroleum ether/ethyl acetate 90:10; twice developed) furnished 235 mg *E*-isomer (as well as 98 mg *Z*-isomer, and 150 mg of the mixture; a total of 483 mg (71%)).

IR (NaCl, liquid film): *v* = 2942, 2879, 1712, 1650, 1462. MS: *m/z* (%) = 278 (M + 2, 1), 277 (M + 1, 4), 276 (M^+, 18),

203 (13), 149 (58), 141 (32), 135 (49), 113 (11), 91 (56), 67 (100). ^{1}H-NMR ($CDCl_3$): δ = 7.25 (t, J = 7.13 Hz, 3H, 2″-H), 1.17–1.70 (m, 15H), 1.80 (ds, ^4J = 1.0 Hz, 3H, 6-H), 1.98–2.18 (m, 4H), 4.15 (q, J = 7.13 Hz, 2H, 1″-H), 6.73 (dt, J = 7.53 Hz, ^4J = 1.0 Hz, 1H, 3-H). ^{13}C-NMR ($CDCl_3$): δ = 168.2 (C-1), 142.8 (C-3), 127.1 (C-2), 60.2 (C-1″), 53.4 (C-2′), 52.5/44.8/42.4 (3 × CH), 41.3/40.7/33.1/28.6/27.1/24.9/24.1/23.2 (8 × CH_2), 14.2 (C-2″), 12.1 (C-6). Analysis CH: $C_{18}H_{28}O_2$ (276.42).

*3.12. (Z)-2-Methyl-5-tricyclo[5.2.1.0$^{2',6'}$]dec-2′-yl-2-pentenol (**2**)*

One hundred ninety milligrams (0.69 mmol) of **14** were dissolved in 5 ml anhydrous CH_2Cl_2 and cooled to –78 °C in argon atmosphere. Three milliliters of a 20% (equals 1 M) solution of DIBAH in *n*-hexane were injected, and the resulting mixture was stirred for 16 h at room temperature. The mixture then was cooled to –20 °C, hydrolyzed with 2 ml of a mixture of MeOH/H_2O (1:1), and stirred for another 3 h room temperature. Afterwards, the solution was mixed with Celite®, filtered over Celite®, washed with ethyl acetate, and evaporated, yielding 164 mg of a yellowish oil. The crude product was purified by PTLC (petroleum ether/ethyl acetate 80:20) furnishing 135 mg (83%) of an almost colorless oil.

IR (NaCl, liquid film): ν = 3325, 2942, 2878, 1459, 1006. MS: m/z (%) = 235 (M + 1, 1), 234 (M^+, 6), 149 (63), 135 (100), 133 (28), 119 (17), 107 (35), 91 (47), 79 (66), 67 (90). ^{1}H-NMR ($CDCl_3$): δ = 1.76 (s, 3H, 6-H), 1.09-2.06 (m, 20H), 4.10 (s, 2H, 1-H), 5.26 (t, J = 7.15 Hz, 1H, 3-H). ^{13}C-NMR ($CDCl_3$): δ = 133.6 (C-2), 129.1 (C-3), 61.3 (C-1), 53.4 (C-2′) 52.4/44.9 (2 × CH), 43.2 (CH_2), 42.4 (CH), 40.7/33.1/28.6/27.2/24.1/23.6/23.2 (7 × CH_2), 21.1 (C-6). Analysis CH: $C_{16}H_{26}O$ (234.38).

*3.13. (E)-2-Methyl-5-tricyclo[5.2.1.0$^{2',6'}$]dec-2′-yl-2-pentenol (**16**)*

One hundred fifty-two milligrams (0.55 mmol) of **15** were treated as described above yielding 130 mg of crude product. Purification furnished 109 mg (85%) of a yellowish oil.

IR (NaCl, liquid film): ν = 3326, 2939, 1461, 1010. MS: m/z (%) = 235 (M + 1, 1), 234 (M^+, 6), 149 (67), 135 (82), 133 (29), 119 (15), 107 (34), 91 (46), 79 (65), 67 (100). ^{1}H-NMR ($CDCl_3$): δ = 1.11–2.07 (m, 23H), 3.95 (s, 2H, 1-H), 5.37 (dt, J = 7.03 Hz, ^4J = 1.01 Hz, 1H, 3-H). ^{13}C-NMR ($CDCl_3$): δ = 134.1 (C-2), 127.0 (C-3), 68.8 (C-1), 53.4 (C-2′) 52.4/44.9 (2 × CH), 42.5 (CH_2), 42.4 (CH), 40.7/33.1/28.6/27.2/24.1/23.7/23.2 (7 × CH_2), 13.5 (C-6). Analysis CH: $C_{16}H_{26}O$ (234.38).

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