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Synthesis and olfactoric activity of keto-β-santalol and methoxy-β-santalol

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Abstract – In extension of structure–activity relationship investigations on β-santalol, where the shape of the molecular surface was found to be of high importance, the influence of the electrostatic properties of the molecules was investigated. Two derivatives of β-santalol with similar molecular shape but with an oxygen atom instead of carbon atoms were synthesized: keto-β-santalol and methoxy-β-santalol. These two oxygen-containing santalol analogues were synthesized by total syntheses starting from apocamphenilone. A common intermediate for both target molecules, an appropriate bicyclic ketoaldehyde, proved to be inapplicable. Therefore methoxy-β-santalol was prepared by insertion of an ethyldioxolane sidechain into apocamphenilone and completing the synthesis by five additional steps. Keto-β-santalol was prepared on a convergent route by insertion of the already prefabricated sidechain into the starting ketone, followed by one additional step. The presence of the second oxygen atom leads to the complete loss of the odour, which is the evidence that apart from the molecular shape, the electrostatic potential has to be taken into account in molecular similarity studies of this class of compounds. © Elsevier, Paris

structure–odour relationship / molecular modeling / sandalwood odorant / bicyclo[2.2.1]heptane derivative

1. Introduction

Structure–activity (= odour) relationship (SAR) studies on sandalwood odour can be started from β-santalol **1**, one of the main constituents of the precious East Indian Sandalwood oil, responsible for its strong, warm–woody–animalic, and therefore highly esteemed odour [1–4]. Changes in the sidechain as well as in the norbornane nucleus of **1** very often cause dramatic alterations of the odour character, if no odour impression can be perceived anymore at all. For example, the substitution of the 'methano' -bridge of the bicyclus with an ether bridge renders this 7-oxa-β-santalol **2** odourless [5]. Hydrogenation of all double bonds leads to tetrahydro-β-santalol **3** which lacks this precious odour too, whereas dihydro-β-santalol **4** retains the sandalwood odour even for a long time [6]. Also Brunke et al. identified the great importance of the exocyclic double bond in **1** for this special odour [1]. This rigid substituent at C-2 of the norbornane skeleton either causes a certain steric fixation of the molecule in the space, or creates a special environment with a certain steric hindrance (e.g. the double bond can also be replaced by a cyclopropane ring [1, 7]) or the higher electron density is responsible for a better contact to the hypothetic receptor site. If the latter assumption would be justified, then other functionalities with a similar electron density should be able to substitute the exocyclic double bond without a change of the sandalwood odour impression.

To get more insight in the influence of structural changes starting from β-santalol, we synthesized the title compounds, 2-*exo*-methoxy-β-santalol **5** and 2-keto-β-santalol **6** and evaluated their odour properties. In extension to conformational calculations [8, 9] with santalol analogues further molecular modeling studies were performed in order to support and to refine the theoretical model for sandalwood odour evaluated by Active Analog Approach studies [10], which were done within a series of theoretical structure–activity relationship investigations on odour molecules [11–15] (see *figure 1*).

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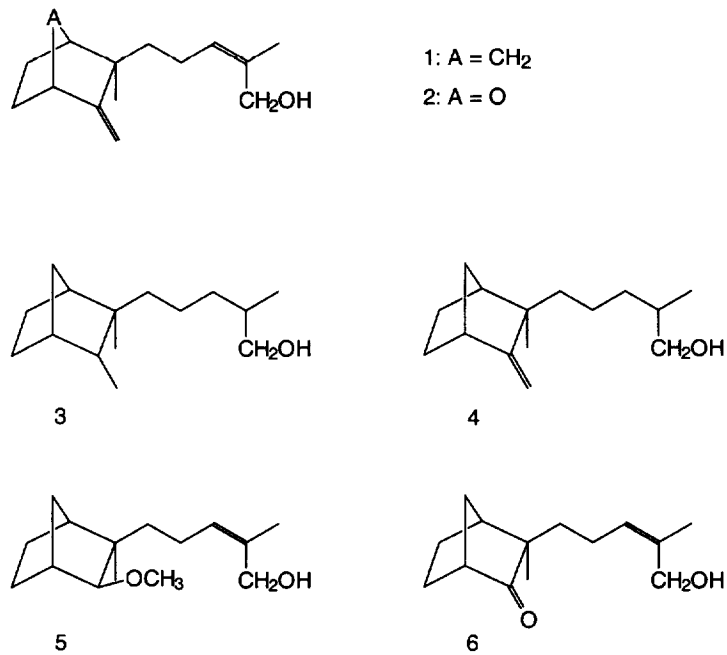

Figure 1.

2. Results: syntheses and molecular similarity studies

2.1. 2-exo-Methoxy-β-santalol 5

Apocamphenilone **7** [16], obtained by α-methylation of the bicyclic ketone **8**, was used as starting material for the synthesis of the target molecules **5** and **6**. According to Corey et al. [17] it is better to insert the small methyl group into norcamphor **8** at first and then in the second step the space-demanding sidechain synthon in order to obtain the correct steric position of the two substituents at C-3 of the norbornane nucleus. **7** was alkylated with the 'Julia'-sidechain 1-bromo-4-methyl-pent-3-ene [18] to obtain keto-β-santalene **9**. After oxidizing the double bond of **9** with OsO_4/trimethyl-*N*-oxide/pyridine [19] and cleaving the corresponding glycol by $NaIO_4$ the resulting ketoaldehyde **10** seemed to be the appropriate intermediate for both target molecules **5** and **6**. The sterically unhindered and more reactive aldehyde group of **10** should undergo selectively a Wittig-reaction, followed by the transformation of the keto group into the *exo*-methylene group, a procedure which already proved successfully in the case of the synthesis of bis-homo-β-santalol [20]. But **10** could not be converted into the corresponding Wittig-product (see *figure 2*).

Therefore another strategy was developed. **7** was alkylated with 2-(2-bromoethyl)-1,3-dioxolane/sodium hexamethyldisilazanide/xylol to the keto-dioxolane **11** according to Krotz and Helmchen [21]. In comparison with the 'Julia'-procedure this alkylation proved to be advantageous and because of the shorter thermic strain we obtained the alkylation product in a purer state and thus also in a better yield. Also side products, e.g. not transformed apocamphenilone **7**, or bromo-dioxolane, could be eliminated simply by kugelrohr-distillation. $NaBH_4$ reduction of **11** furnished the alcohol **12**, which was transformed into the ether **13** by means of methyl iodide. NOE measurements with **13** showed the neighbourhood of the ether methyl group with the protons of the side-chain CH_2-group(s), but no effect with the angular methyl group at C-3, thus proving the *exo* position of the methoxy group. Cleavage of the acetal **13** provided the methoxy aldehyde **14**, which could be transformed into the Wittig-product **15** by the method of Still et al. [22] with phosphonopropionic acid triethylester/potassium bistrimethylsilyl amide/18-crown-6

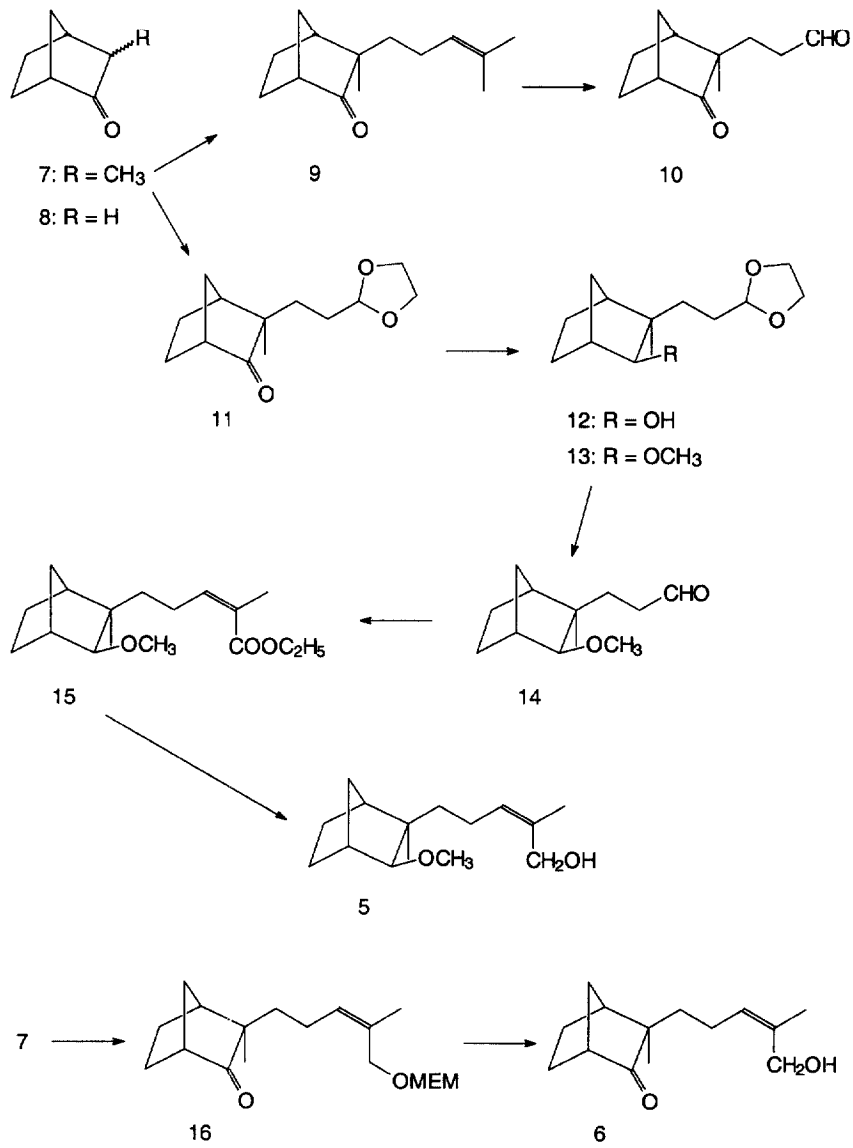

Figure 2.

[23]. Reduction of the methoxy ester **15** with DIBAH finally yielded the target molecule **5**, wich upon olfactoric evaluation proved itself as odourless.

2.2. 2-Keto-β-santalol ***6***

The failure to establish the ketoaldehyde **10** as intermediate also for the synthesis of **6** prompted us to use the more convergent strategy of Monti et al. [24]. By alkylating the starting ketone **7** with the appropriate, already prefabricated, but sumptuously prepared side chain [5, 24, 25] by means of LDA/THF at –78 °C and a second equivalent BuLi, the ketoether **16** was obtained. Hydrolysis of **16** with PPTS/*tert*-BuOH finally furnished the target molecule **6** with a weak camphoraceous and woody odour, but totally devoid of any sandalwood tonalities.

2.3. Molecular modelling studies on ***5*** *and* ***6***

It is known that many structurally different compounds possess sandalwood odour [2, 26–29], but

on the other hand many examples have been studied, where only small modifications of sandalwood odour molecules can lead to a strong weakening or at least to the complete lack of the odour impression. Methyl substitution in the side chain or removing of a methyl group close to the hydroxyl group causes a drastic change in the fragrance of the molecules [9]. Optical isomers also behave quite differently with respect to their scent [21, 30]. Generally the shape of parts of the molecular surface is supposed to be responsible for the sandalwood odour. The influence of the electronic properties was not investigated in detail up to now. With the help of the new synthesized substances **5** and **6** the model for Sandalwood odour can be extended and refined.

A conformational analysis of **1**, **5** and **6** was performed using molecular mechanics calculations based on Allingers MM3 parameter set [31]. As these molecules are rather flexible many different molecular conformations have to be taken into account. For the following procedures **1** has been used as reference, because it is the lead compound of the investigation and its fragrance is described as clean, pure and typical [1, 2]. For all compounds only the energetically possible conformations (with no higher deviations from the absolute conformations minimum than 5 kcal/mol) have been used for further considerations.

Molecular similarity studies of various Sandalwood odour molecules were done in order to find common structural subunits by comparison of the molecular surfaces [8, 9]. In these studies the molecules are superimposed, comparable points at the van der Waals surfaces are estimated by the intersection of a bundle of lines through the geometrical center and the individual molecular surfaces. The distance of the intersection points on one line is therefore a criterion of the agreement or the deviation of the molecular surfaces and can be used as descriptors for the molecular similarity of both considered molecules. Additionally these distances can be minimized by changing the coordinates of one molecule which leads to a matching of the molecular surfaces.

With this matching routine the reference compound **1** has been superimposed with the molecules **5** and **6**. For fitting of the molecular surfaces 3 osmophoric regions (the hydroxyl group, which is of high importance for association to the receptor complex, a lipophilic group in the neighbourhood of the hydroxyl-function and region in the lipophilc part of the molecule) evaluated by 'Active Analog Approach' investigations [10] have been taken into account. Detailed surface investigations after the fitting procedures have been done. As measurement for the agreement between reference molecule **1** and compounds **5** and **6** the distances of corresponding surface dots as descriptors of molecular similarity are registered. The results are presented in *table I.*

The agreement of compounds **5** and especially **6** is very high in the osmophoric regions, also the common volume after volume matching (79.22% for compound **5** and 92.97% for compound **6** is high. Therefore from former investigations sandalwood odour has to be proposed for these compounds. Nevertheless no sandalwood fragrance could be recognized for **5** as

Table I. Comparison of the molecular surface of **1**, **5** and **6**. Compound **1** is used as standard. The best fitting conformations were selected for the molecular matching. The distances of the intersection points are collected in the osmophoric regions (1 including the hydroxyl group, 2 close to the hydroxyl group and 3 at the hydrophobic bulky residue) between –0.3 Å and +0.3 Å (third column), negative deviations from the standard's surface less than –0.7 Å (second column) and positive deviations larger than 0.7 Å (fourth column). The given values are in percentage of the total number of intersection points.

Compound **5**			
Osmophoric region	< –0.7 Å	–0.3 – +0.3 Å	> +0.7 Å
1	0.18	98.06	0
2	0.94	95.54	0.28
3	3.20	66.08	13.37

Compound **6**			
Osmophoric region	< –0.7 Å	–0.3 – +0.3 Å	> +0.7 Å
1	0.08	99.30	0
2	0.24	98.15	0.2
3	1.14	91.56	0.05

well as for **6**. Although the descriptors of the molecular shape have been successfully used for the explanation of rather subtle steric differences like for optical isomers [11], they appeared to be not sufficent for the explanation of the odour differences of **5** and **6** compared to **1**. The main difference between the compounds considered in the former studies and substances **5** and **6** is the existence of additional hetero atoms, which leads to changes in the electrostatic properties of the molecules only without modifying the molecular shape drastically. From the syntheses and the odour evaluation of the two compounds the conclusion has to be drawn, that the model for ideal sandalwood odour molecules has to be extended in respect to the differences of the electrostatic potentials. Therefore the electronic properties of **1**, **5** and **6** were calculated and visualized using the minimized geometries of ab initio calculations on Hartree Fock level with the 3-21G basis set included in the Gaussian 94 program package [32] and the program package Molden 3.2 [33]. First an analytical surface approximation is calculated with the algorithm described by Connolly [34] using a probe sphere of 1.4 Å rolling over the molecule and a 3.0 points per unit density. At these analytical derived points the electrostatic potential is calculated as defined by Bonaccorsi et al. [35]. $V(r)$ represents the molecular electrostatic potential (MEP), at first order pertubation, of the interaction energy between molecule M and a proton located in r, and is given by the following formula:

$$V(r) = \Sigma_A\{Z_A/|r - r_A|\} - \Sigma_\mu\Sigma_\nu P_{\mu\nu} \int [\chi_\mu(r')\chi_\nu(r')/|r - r'|]\, dr'$$

where Z_A is the nuclear charge located in r_A, $P(r')$ is the electron density, χ_μ, χ_ν are the atomic orbital basis functions and $P_{\mu\nu}$ represents the first-order density matrix. The first term of the equation corresponds to nuclear repulsion and the second term originates from electronic attraction. The sign of $V(r)$ will characterize the electrostatic potential at a given point r. Negative values will be found in molecules at regions of electron density accumulation accompanying the formation of chemical bonds, i.e. close to lone pairs of heteroatoms or to multiple bonds. The calculated values were mapped color-coded onto the 3D-surface points and displayed on screen for interactive investigation and comparison.

A comparison of the van der Waals surfaces of **1**, **5** and **6** is given in *figure 3* together with the van der Waals surfaces with the electrostatic potentials visualized in different colors.

From this figure, it can be seen that the molecular shape is more or less the same for all compounds shown, a result that has been documented quantitatively before. The corresponding electrostatic potentials

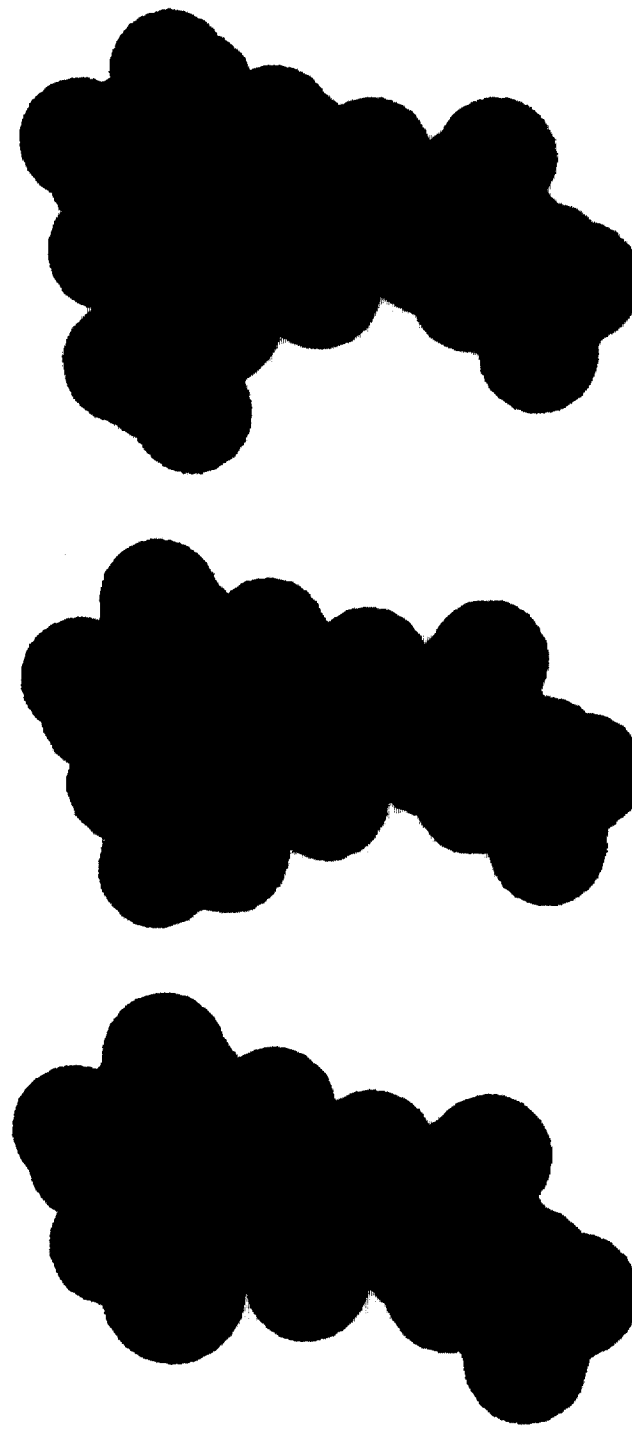

Figure 3. Van der Waals surfaces of Methoxy-β-santalol **5** (top), β-santalol **1** (middle), keto-β-santalol **6** (bottom) with electrostatic potentials projected on the surface.

differ drastically according to the influence of the electron-withdrawing oxygen atoms in **5** and **6**.

The association of the odour molecule at the receptor protein depends on the steric interaction in the osmophoric regions; additionally changes in the electrostatic properties are just as important for the association process.

3. Discussion

Many aspects have to be considered for giving prognoses on the properties of nonexisting molecules created by molecular modelling and for the calculations on newly synthesized compounds with the goal to get more information about the olfactory mechanism and receptors. One of the most important question for studies on odourous compounds is, which conditions such a biologically active molecule has to follow. The class of sandalwood odour compounds seems to be somewhat inhomogenous, which makes it difficult to find common structural elements which are responsible for this typical odour impression and could give more information about the nature of the responsible receptors.

After a series of investigations it turned out, that for many types of compounds the biological effect is extremely sensitive to small changes of the structure, although also many different substances with same fragrance are known. In a detailed analysis first of all some physicochemical parameters, like vapour pressure, hydrophilicity, etc. as well as structural parameters have to have to be in a proper range so that the substance can reach the olfactory receptor site. If these conditions are given, detailed information about energetical relevant conformations (considering the Boltzmann distribution, conformations with energies higher than 5 kcal/mol as the minimum do not have to be taken into account), then about the nature of the molecular surface and also the electron density are necessary. The sensitivity of the fragrance on steric effects has been shown previously extensively. From the synthesis of compounds **5** and **6** it is evident, that also electronic properties have to be taken into account.

4. Experimental protocols

Experimental procedures are described in detail elsewhere as well as spectroscopic and chromatographic techniques [5, 20].

4.1. 3-Methyl-3-(4-methyl-3-pentenyl)-bicyclo[2.2.1]heptan-2-one ***9*** *('2-keto-β-santalene')*

To diisopropylamine (8.64 mL, 61.6 mmol) in dry THF (30 mL) a solution of BuLi in hexane (1.6 N, 42.35 mL, 67.7 mmol) was added dropwise at –78 °C and under argon atmosphere. This mixture was stirred at 0 °C for 30 min and afterwards cooled down to –78 °C again. **7** (5.1 g, 41.12 mmol) in 10 mL of dry THF was added dropwise and stirred for 2 h. Then, 1-bromo-4-methylpent-3-ene, prepared according to Julia et al. [18] (8.64 g, 41.1 mmol), dissolved in 10 mL of dry THF, was added dropwise. Upon warming up to room temperature the mixture was refluxed for 18 h. Upon hydrolysis with a solution of NH_4Cl the water phase was extracted with diethyl ether. The combined ethereal phases were washed with 2 N HCl, then with $NaHCO_3$-solution and dried with $MgSO_4$. Evaporation of the solvent and kugelrohr distillation (70 °C, 0.3 Torr) finally furnished 3.37 g (39.8 %) of a colourless, oily liquid. $C_{14}H_{22}O$ (206.33). MS (*m/z*; r.I.): 206 (M^+, 1),124 (39), 96 (100), 81 (7), 69 (22), 67 (20), 55 (11), 41 (34).

4.2. 3-(2-Methyl-3-oxo-bicyclo[2.2.1]heptan-2-yl)-propanal ***10*** *('2-keto-ekasantalal')*

Method A: To a mixture of *N*-methylmorpholino-*N*-oxide (586 mg, 4.34 mmol) and osmiumtetroxide (7.92 mg, 0.03 mmol), both dissolved in 4 mL of *tert*-butanol, a solution of **9** (800 mg, 3.88 mmol) was added dropwise and stirred for 8 h at room temperature. Upon adding a solution of 200 mg $NaHSO_3$ in 1 mL water the mixture was filtered through Celite® and the solvent evaporated. The residue was mixed with brine and extracted with diethyl ether. Usual work up followed by a kugelrohr distillation (175 °C, 0.001 torr) yielded a colourless, viscious oil (723 mg, 77.6%). IR (NaCl; liquid film): 3450, 1740; ^{1}H-NMR ($CDCl_3$): 1.00 (s, 3 H), 1.16 and 1.21 (2 s, 6 H), 2.34 (m, 2 H), 2.56 (m, 2 H), 3.26 (m, 1 H); MS (*m/z*; r.I.): 222 (46), 181 (68), 164 (60), 124 (74), 96 (76), 95 (77), 67 (88), 59 (100).

Method B: To a solution of sodium periodate (438 mg, 2.05 mmol) in 22 mL of a water/methanol (1:1) mixture a solution of the above obtained oxidation product (300 mg, 1.25 mmol) in 3 mL methanol was added dropwise and stirred for 2 h. Upon filtration and evaporation of the solvent the residue was extracted with diethyl ether. The combined ethereal phases were washed with 2 N NaOH and dried with anhydrous $MgSO_4$. Upon evaporation of the solvent 128 mg (56.9%) of a colourless, oily liquid were obtained. $C_{11}H_{16}O_2$ (180.25).Calc.: C 73.29, H 8.95; found: C 73.43, H 8.80. IR (NaCl; liquid film): 2740, 1740; ^{1}H-NMR ($CDCl_3$): 0.98 (s, 3 H), 1.25–2.63 (m, 12 H), 9.77 (m, 1 H); MS (*m/z*; r.I.): 180 (M^+, 6), 152 (37), 124 (27), 111 (21), 93 (100), 85 (48), 67 (93), 55 (89).

4.3. 3-[2-(1,3-Dioxolan-2-yl)-ethyl]-3-methyl-bicyclo[2.2.1]-heptan-2-one ***11***

The mixture of sodium amide (1.17 g, 30 mmol) and hexamethyldisilazane (6.3 mL, 30 mmol) dissolved in 30 mL of dry xylene was refluxed for a period of 5 h, then **7** (3.1 g, 25 mmol) was added and stirred for another 2 h at room temperature. Upon addition of 2-(2-bromo ethyl)-1,3-dioxolane (5.9 mL, 50 mmol) the mixture was refluxed for 4 h. Afterwards it was cooled down and quenched with water. Ether-extraction followed and the combined extracts were dried with magnesium sulfate. Upon evaporation of the solvent, the residue was distilled (kugelrohr, 70 °C, 0.3 torr). Yield: 3.15 g (56.2 %) of a colourless oil. $C_{13}H_{20}O_3$ (224.30). Calc.: C 69.91, H 8.99; found: C 69.83, H 9.07. IR (NaCl; liquid film): 1740, 1140; ^{1}H-NMR ($CDCl_3$): 0.99 (s, 3 H), 2.33 (m, 1 H), 2.56 (m, 1 H), 3.91 (m, 4 H), 4.83 (m, 1 H); MS (*m/z*; r.I.): 224 (M^+, 9), 196 (2), 124 (2), 99 (100), 86 (30), 73 (99), 67 (16), 45 (22).

4.4. 3-[2-(1,3-Dioxolan-2-yl)-ethyl]-3-methyl-bicyclo[2.2.1]-heptan-2-ol ***12***

Ketone **11** (3.1 g, 13.84 mmol) was dissolved in methanol and mixed with $NaBH_4$ (220 mg, 6.92 mmol) in small portions. Upon stirring at room temperature and GC-monitoring of the outcome of this reduction the mixture was hydrolyzed with water and worked up as usual. Yield: 3.07 mg (99%). $C_{13}H_{22}O_3$ (226.32). IR (NaCl; liquid film): 3460, 1150; ^{1}H-NMR ($CDCl_3$): 0.58 (s, 3 H), 1.65 (m, 1 H), 2.02 (m, 1 H), 3.42 (m, 1 H), 3.68 (m, 4 H), 4.60 (m, 1 H); ^{13}C-NMR ($CDCl_3$): 16.38, 18.46, 24.66, 28.67, 33.60, 36.09, 40.48, 43.68, 46.46, 64.75, 78.99, 104.96; MS (*m/z*; r.I.): 226 (M^+, 4), 208 (4), 164 (18), 146 (10), 136 (12), 88 (39), 73 (100), 45 (69).

4.5. 3-[2-(1,3-dioxolan-2-yl)-ethyl]-2-methoxy-3-methyl-bicyclo[2.2.1]heptane ***13***

To a suspension of sodium hydride (272 mg, 11.35 mmol) in 7.5 mL of dry diethyl ether, alcohol **12** (2325 mg, 10.3 mmol) was added dropwise and under argon atmosphere in such a manner, that the evolution of hydrogen was under control. After stirring for 24 h at room temperature the ether was removed by distillation and the residue mixed with methyl iodide (2.24 mL, 36 mmol). Afterwards the mixture was stirred for another 1.5 h and diluted with 5 mL of dry diethyl ether. Upon hydrolyzing with water, extraction with diethyl ether, the combined ethereal extracts were dried with $MgSO_4$. Evaporation of the solvent furnished 2100 mg (84.9%) **13** as an oily, colourless liquid. $C_{14}H_{24}O_3$ (240.34). Calc.: C 69.96, H 10.06; C 69.82, H 9.96. IR (NaCl; liquid film): 2815, 1140; ^{1}H-NMR ($CDCl_3$): 0.76 (s, 3 H), 1.78 (m, 1 H), 2.35 (m, 1 H), 3.03 (m, 1 H), 3.15 (s, 3 H), 3.85 (m, 4 H), 4.75 (m, 1 H); ^{13}C-NMR ($CDCl_3$): 16.61, 18.54, 24.72, 28.72, 33.59, 36.54, 40.03, 40.68, 46.38, 57.25, 64.82, 64.84, 88.21, 105.11; MS (*m/z*; r.I.): 240 (M^+, 4), 225 (3), 120 (8), 107 (10), 99 (50), 86 (20), 73 (100), 55 (14).

4.6. 3-[3-Methoxy-2-methyl-bicyclo[2.2.1]heptan-2-yl]-propanal ***14***

A mixture of the ether acetal **13** (2.1 g, 8.75 mmol) in a small amount of diethyl ether and 20 mL of a 2 N H_2SO_4 solution was stirred overnight. Upon extraction with diethyl ether the organic phases were washed with water and freed from the solvent by evaporation. On account of the incomplete cleavage of the ether acetal **13** the procedure was repeated and furnished finally 1.676 g (97.7%) of the ether aldehyde **14**. $C_{12}H_{20}O_2$ (196.29). Calc.: C 73.42, H 10.27; found: C 73.61, H 10.14. IR (NaCl; liquid film): 2815, 1720; ^{1}H-NMR ($CDCl_3$): 0.75 (s, 3 H), 1.77 (m, 1 H), 2.37 (m, 3 H), 3.01 (m, 1 H), 3.18 (s, 3 H), 9.75 (s, 1 H); ^{13}C-NMR ($CDCl_3$): 16.71, 18.39, 24.73, 33.54, 34.15, 39.51, 39.94, 40.89, 46.24, 57.20, 88.02, 202.90; MS (*m/z*; r.I.): 196 (M^+, 4), 164 (6), 146 (5), 121 (30), 107 (21), 95 (30), 71 (100),41 (48).

4.7. 5-[3-Methoxy-2-methyl-bicyclo[2.2.1]heptan-2-yl]-2-methyl-2-pentenoic acid ethyl ester ***15***

A solution of 2-phosphonopropionic acid triethyl ester (0.59 mL, 2.75 mmol) and freshly recrystallized 18-Crown-6 (3.3 g, 12.5 mmol) in 50 mL THF was cooled down to –80 °C and mixed with potassium-bis-(trimethylsilyl)-amide (0.5 M in toluene) (5.25 mL, 2.63 mmol). Afterwards a solution of the ether aldehyde **14** (490 mg, 2.5 mmol) in THF was added dropwise and the mixture stirred for 4 h at –80 °C. Upon quenching with a saturated NH_4Cl solution, extraction with diethyl ether followed. Afterwards the combined ethereal extracts were dried with $MgSO_4$ and freed from the solvent by evaporation. The residue was distilled (kugelrohr) and yielded 753 mg of the raw Wittig-product which was purified by preparative TLC with pentane/aceton = 99:1. $C_{17}H_{28}O_3$ (280.41). IR (NaCl; liquid film): 2815, 1720, 1640, 1215; ^{1}H-NMR ($CDCl_3$): 0.85 (s, 3 H), 1.90 (m, 4 H), 2.40 (m, 3 H), 3.11 (m, 1 H), 3.25 (s, 3 H), 4.22 (m, 2 H), 5.90 (m, 1 H); ^{13}C-NMR ($CDCl_3$): 14.35, 16.68, 18.62, 20.75, 24.74, 33.65, 40.13, 41.37, 42.50, 46.23, 57.34, 60.06, 88.42, 126.90, 143.12, 168.22; MS (*m/z*; r.I.): 280 (M^+, 18), 248 (36), 175 (28), 134 (25), 121 (58), 108 (33), 93 (46), 71 (100).

4.8. 5-[3-Methoxy-2-methyl-bicyclo[2.2.1]heptan-2-yl]-2-methyl-pent-2-enol ***5*** *('2-methoxy-β-santalol')*

A solution of 38 mg (0.14 mmol) of the methoxy ester **15** in dry methylene chloride was cooled down to –78 °C and mixed with a 20% solution of diisobutylaluminiumhydride (0.35 mL, 0.34 mmol) in *n*-hexane. Stirring overnight caused a warming up of the reaction mixture to room temperature and afforded another cooling, but this time only to –20 °C. Then 5 mL of a methanol/water (1:1) mixture was added and stirring proceeded for another 3 h, this time at room temperature, as long as the precipitation of a thick, white sediment could be noticed, which was filtered through Celite®. The residue was washed with ethyl acetate and the filtrate freed from the solvent by evaporation. Purification of the residue was performed by preparative TLC (ligroin/ethyl acetate = 70:30). Yield: 30 mg (90%). $C_{15}H_{26}O_2$ (238.37). Calc.: C 75.57, H 10.99; found: C 75.71, H 11.17. IR (NaCl; liquid film): 3360, 2810; ^{1}H-NMR ($CDCl_3$): 0.84 (s, 3 H), 1.80 (s, 3 H), 1.84 (m, 1 H), 2.04 (m, 2 H), 2.43 (m, 1 H), 3.12 (m, 1 H), 3.23 (s, 3 H), 4.14 (m, 2 H), 5.30 (m, 1 H); ^{13}C-NMR ($CDCl_3$): 16.63, 18.49, 21.35, 22.64, 24.75, 33.58, 39.95, 41.32, 43.07, 46.67, 57.12, 61.53, 88.08, 129.15, 133.88; MS (*m/z*; r.I.): 238 (M^+, 1), 220 (3), 178 (14), 121 (35), 107 (40), 93 (46), 71 (100), 41 (50).

4.9. 3-(5-Methoxyethoxymethoxy-4-methyl-pent-3-enyl)-3-methyl-bicyclo[2.2.1]heptan-2-one ***16***

To a cold solution (–78 °C) of diisopropyl amide (0.56 mL, 4 mmol) in 5 mL dry THF was added a 1.6 M solution of *n*-butyl lithium in hexane (2.75 mL, 4.4 mmol) and proceeded the stirring for 30 min at 0 °C. Upon cooling down to –78 °C, **7** (330 mg, 2.66 mmol) was added dropwise. The mixture was stirred for 30 min, mixed with a second equivalent of *n*-butyl lithium (1.6 molar in *n*-hexane) (2.75 mL, 4.4 mmol) and proceeded the stirring for another 2 h at –78 °C. Afterwards the reaction mixture was warmed up to room temperature and cooled down again to –78 °C. Now 1000 mg 'side chain' (5-iodo-2-methyl-pent-2-enyl-(2-methoxyethoxymethyl)-ether), prepared according to [5], was added and the mixture stirred for 16 h at room temperature. Upon quenching with saturated NH_4Cl-solution the mixture was extracted with diethyl ether. The combined ethereal phases were washed with 2 N HCl and water and dried with $MgSO_4$. Evaporation of the solvent furnished 320 mg (38.8%) of a colourless oil. $C_{18}H_{30}O_4$ (310.43). IR (NaCl; liquid film): 1740; ^{1}H-NMR ($CDCl_3$): 1.00 (s, 3 H), 1.75 (s, 3 H), 2.36 (m, 1 H), 2.55 (m, 1 H), 3.40 (s, 3 H), 3.56 (m, 2 H), 3.72 (m, 2 H), 4.05 (m, 2 H), 5.71 (s, 2 H), 5.32 (m, 1 H); MS (*m/z*; r.I.): 204 (M^+ – 106, 67), 189 (46), 176 (18), 161 (17), 137 (29), 96 (61), 81 (71), 59 (100).

4.10. 3-Methyl-3-(4-hydroxymethyl-3-pentenyl)-bicyclo[2.2.1]-heptan-2-one ***6*** *('(Z)-2-keto-β-santalol')*

A mixture of 270 mg (0.87 mmol) of the 'MEM-ether' **16** and of 2.5 g (10 mmol) dry PPTS in 10 mL *tert*-butanol was

refluxed in an argon atmosphere for 9 h. Upon cooling and addition of 10 mL water, the mixture was extracted with diethyl ether. Then the combined ethereal phases were washed with water in order to remove most of the solvent. The residue was dried with $MgSO_4$, freed from the last parts of the solvent and this raw material (220 mg) finally purified by preparative TLC with ether/pentane = 70:30. $C_{14}H_{22}O_2$ (222.33). Calc.: C 75.63, H 9.97; found: C 75.81, H 10.13. IR (NaCl; liquid film): 3440, 1740; ^{1}H-NMR ($CDCl_3$): 1.01 (s, 3 H), 1.77 (m, 3 H), 2.35 (m, 1 H), 2.58 (m, 1 H), 4.11 (m, 2 H), 5.25 (m, 1 H); MS (*m/z*; r.I.): 204 (M^+ – 18, 54), 189 (40), 176 (15), 124 (36), 107 (30), 96 (100), 81 (68), 41 (58).

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