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On the Synthesis and Odour Impression of (*Z*)-Normethyl-carvo-β-santalol

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Summary. The synthesis of the title compound is described. Starting with an α-alkylation of (*R*)-(−)-carvone in position 6 followed by a *Wittig* reaction, a *Tebbe* transformation, and a *DIBAH* ester reduction, this new santalol analogue was obtained which shows a weak woody odour with a dry note of cedrol.

Keywords. Bulky group; Monoterpene ketone; Sandalwood odorants; Structure-odour relationships; Woody odour.

Über Synthese und Geruch von (*Z*)-Normethyl-carvo-β-santalol

Zusammenfassung. Die Synthese der Titelverbindung wird beschrieben. Ausgehend von (*R*)-(−)-Carvon wurde zunächst durch α-Alkylierung in Position 6 und dann durch Carbonylolefinierung, *Tebbe*-Transformation und zuletzt durch Esterreduktion mittels *DIBAH* das neue Santalolanalogon erhalten, das einen schwachen holzigen Geruch mit einer trockenen Cedrolnote aufweist.

Introduction

In continuation of our studies on structure-odour relationships with sandalwood odorants we focused our interest on modifications of the hydrophobic part, the so-called ''bulky group'' of β-santalol (**1**). A moderate increase of the volume of the hydrophobic part of this odourous sesquiterpene alcohol does not alter the odour quality ''sandalwood'', as we were able to show recently [2, 3]. However, in these cases a somewhat spherical bulky group remained. On the other hand, many campholene aldehyde derivatives within the class of sandalwood odorants, like *e.g.* Madrol® (**2**) [3, 4], are characterized by a trimethyl-cyclopentene nucleus as a relatively flat hydrophobic part. Therefore it seemed worthwhile to synthesize further analogues of **1** with variable bulky hydrophobic groups in order to investigate the parameters responsible for the sandalwood odour. In this paper we report on the use of the cheap, naturally occurring monoterpene ketone (*R*)-(−)-carvone (**3**) as the hydrophobic residue of the new santalol analogue (*Z*)-6-normethyl carvo-β-santalol (**7**). Some structural features of **7** appear to be similar to the cyclopentene moiety of the campholene aldehyde derivatives.

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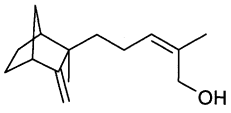

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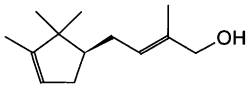

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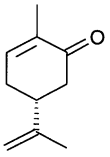

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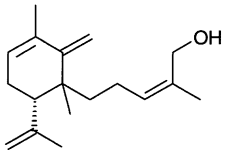

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Results and Discussion

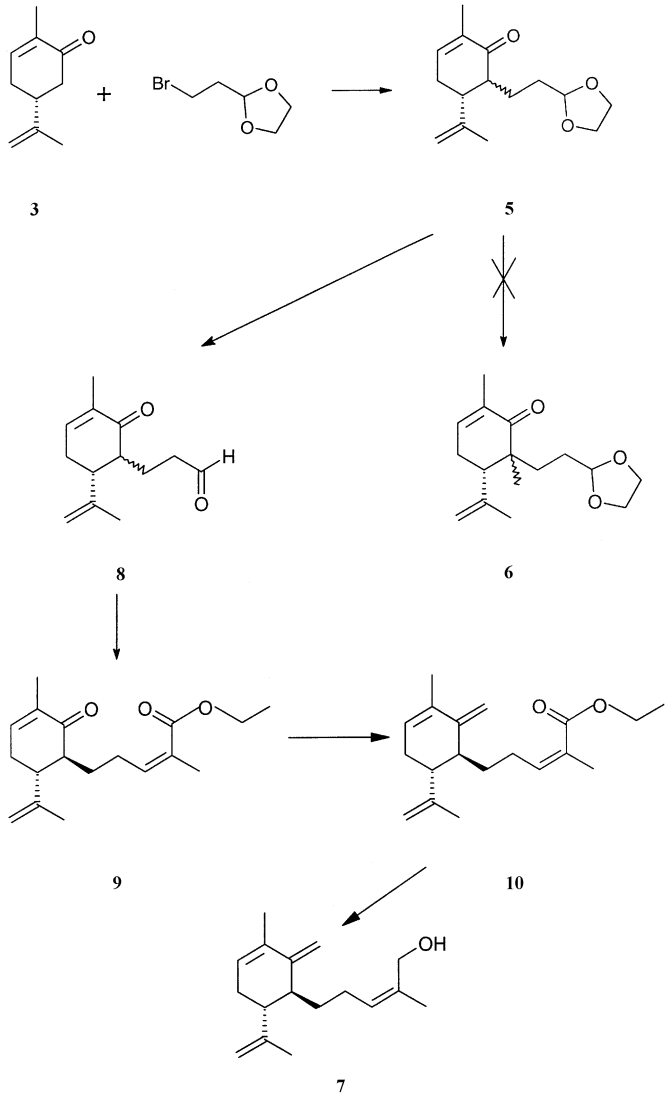
The insertion of 2-(2-bromoethyl)-1,3-dioxolane in position 6 of the carvone nucleus in order to create a suitable synthon for further functional group inversions proved to be very tedious, although this first step had been successful without greater problems in a number of cases by the method of *Krotz* and *Helmchen* [6]. Using lithium cyclohexyl isopropylamide as base [7] finally furnished **5** in mediocre yield and as a 50:50 epimeric mixture of **5**-*axial* and **5**-*equatorial*. Despite of many efforts it was not possible either to increase the yield of **5** or to separate the epimers. Therefore we tried to force the longer and space demanding side chain into the equatorial position by insertion of an angular methyl group, a procedure which has been recommended by *Corey et al.* [8] using norcamphor as starting ketone for the α-alkylation. However, the desired dialkylated carvone derivative **6** could not be obtained.

On account of the failure of the angular methylation we had to change from the primarily aspired target molecule **4** to 6-normethyl-carvo-β-santalol (**7**). Because of *Fanta et al.* having reported on the synthesis of 3-normethyl-β-santalol without any change in the odour quality [9] – obviously this angular methyl group is not necessary for the occurrence of the sandalwood odour –, we felt legitimized to regard **7** as a new santalol analogue and hence as the new target molecule.

Hydrolysis of **5** by means of diluted sulfuric acid furnished aldehyde **8**. Because of the sensitivity of the aldehyde group we refrained from a thorough purification and used crude **8** for the *Wittig* reaction (*Horner-Emmons* method) with 2-phosphonopropionic triethylester, 18-crown-6, and sodium *bis*(trimethylsilyl amide) in *THF* according to the procedure of *Still et al*. [10]. By choosing this sodium amide instead of the more frequently used potassium-*bis*-(trimethylsilyl amide), we could double the yield of the ester **9**.

The GC-MS of **9** showed 4 peaks with the same mass of $m/z = 290$ and a similar fragmentation pattern, indicating the presence of the compounds **9**-*Z-axial*, **9**-*E-axial*, **9**-*Z-equatorial*, and **9**-*E-equatorial*. By column chromatography on silica gel using petroleum ether (40–60°C):ethyl acetate = 9:1 as mobil phase we succeeded to obtain in the first fraction pure **9**-*Z-equatorial*, whereas

further fractions still consisted of inseparable mixtures. The *Z*-configuration of the side chain double bond could be established by analyzing the ^{1}H NMR spectrum. The high-field shift of the triplet of the olefinic proton to 5.90 ppm proves the desired configuration (in the ^{1}H NMR spectrum of the other fractions, this triplet could be detected at 6.61 ppm). A decision as to the epimeric status at C6 of the carvone nucleus was not yet possible, but in the ^{1}H NMR spectrum of the next reaction product we found a strong indication for the equatorial position of the side chain. Therefore, we conclude that the configuration of this ketoester fraction was already **9**-*Z-equatorial.*



Tebbe reaction of this first fraction of **9** furnished the olefinic ester **10** which could be reduced with *DIBAH* to the target molecule 6-normethyl-carvo-β-santalol (**7**) without any problems.

The structure determination of **10** and hence of **9** and **7** has been performed by studying a *Dreiding* model of **10** as well as by analyzing its ^{1}H NMR spectrum. The question of the correct substitution at C6 has not been clarified so far, but considering steric reasons, only the *bis*-equatorial position of the isopropenyl group

at C5 and the olefinic ester side chain at C6 seems plausible. In (*R*)-(−)-carvone (**3**), the isopropenyl group adopts the equatorial position despite the flexibility of the envelope part (= C4-C5-C6) of the cyclohexenone moiety. Insertion of a space demanding substituent at C6 fixes this position by a strong restriction of the flexibility of this envelope part. Rotations of both substituents at C5 and C6 are possible without hindrance only if they are oriented equatorially. Finally, another strong indication for this configuration can be found. In the ^{1}H NMR spectrum of **10** the triplet of the olefinic proton of the side chain is high-field shifted to 5.84 ppm, caused by a shielding effect of the exocyclic double bond upon this proton. Such a shift could not be detected in the ^{1}H NMR spectrum of the other epimeric mixtures mentioned above, because this proton is too far away to be influenced by the anisotropic effect of either the exocyclic double bond or the C=O double bond of the cyclohexene nucleus, thus proving the equatorial position of the side chain. With a very high probability, therefore, the configuration of the substituents can be established as (*R*)- at C5 and (*S*)- at C6.

The olfactoric evaluation of the target molecule **7** by perfumers showed the following result: **7** exerts a weak odour, a bit spicy and herbaceous at the beginning, but later on with a clear, dry woody note reminiscent of cedrol. Still woody, **7** lacks completely the warm, sweet and soft quality which renders the odour of β-santalol (**1**) so incomparable and appreciated. The relatively flat hydrophobic part of **7**, the accumulation of double bonds, and the space demanding and bulky isopropenyl group probably prevents an association of 6-normethyl-carvo-β-santalol (**7**) to the corresponding receptor site. Also, the distance of the allylic hydroxyl group oxygen from a highly substituted carbon atom of the hydrophobic part which is about 5–6 Å neither meets the necessary conditions for a sandalwood odour according to the rules of *Naipawer* [11] (about 4 Å) nor corresponds to our earlier defined postulate that the center of the bulky group should be in a distance of 6.4 Å to the allylic oxygen, a function with a strong negative electrostatic potential [12].

Experimental

For experimental details see Refs. [3] and [13].

6-((1,3-Dioxolan-2-yl)-2-ethyl)-5-isopropenyl-2-methyl-2-cyclohexen-1-one (**5**)

A solution of 8.095 g (57.14 mmol) cyclohexylisopropylamine (freshly distilled in a *Barchit* distillation flask) in 95 ml dry *THF* was mixed with 34.32 ml (54.76 mmol) *n-Bu*Li (1.6 *M* in *n*-hexane) at 0°C under argon. Upon addition of 5.0 g (33.3 mmol) carvone (**3**) to the yellow coloured mixture, the colour changed to orange. Then, 9.82 ml (83.3 mmol) 1-bromo-2-(1,3)-dioxolanyl-ethane (freshly dried by filtration through Al_2O_3 (Wölm)) were added, and the mixture was refluxed (16 h). After quenching with saturated NH_4Cl solution and extraction with diethyl ether, the organic phase was washed with 2 *N* HCl, dried over Na_2SO_4, and evaporated. The residue was distilled in a Kugelrohr apparatus (90°C/4 torr) and afforded 5.25 g (63%) of crude **5**. Further purification was performed by column chromatography (silica gel 60, mesh size 0.040–0.063 mm, petroleum ether (40–60°C):ethyl acetate = 9:1).

$C_{15}H_{22}O_3$ (250.34); IR (NaCl; liquid film): $\nu = 3081$, 1669, 1452, 1376, 1143, 1044, 896 cm^{-1}; ^{1}H NMR ($CDCl_3$); $\delta = 1.40$–1.79 (m, 10H), 2.21–2.68 (m, 4H), 3.72–3.90 (m, 4H, 14-H, 15-H),

4.69–4.87 (m, 3H, 8-H, 8′-H, 13-H), 6.59 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 202.4/200.9$ (C=O), 145.4/144.7 (C-7), 143.3/142.7 (CH, C-3), 135.0/133.6 (C-2), 113.3/112.0 (CH_2, C-8), 104.7/104.2 (CH, C-13), 64.7 (CH_2 of the side chain, C-14, C-15), 48.7/48.2 (CH, C-6), 47.4 (CH, C-5), 44.8 (CH), 30.7/30.6 (CH_2, C-4), 21.9/21.8 (CH_2, C-11), 18.7 (CH_3, C-9), 16.0/15.9 (CH_3, C-10) ppm; MS: *m/z* (r.I.) = 250 (M^+), 188 (4), 173 (3), 149 (11), 99 (25), 82 (10), 73 (100), 55 (9), 45 (26), 41 (16).

3-(5-Isopropenyl-2-methyl-1-oxo-2-cyclohexen-6-yl)-propanal (**8**)

Ketone **5** (0.515 g, 2.46 mmol), dissolved in some ml of diethyl ether, was hydrolyzed with 5.7 ml 2 *N* H_2SO_4. After stirring for 48 h at room temperature, the mixture was extracted with diethyl ether. The organic phase was washed with water, dried over anhydrous $MgSO_4$, and evaporated. A brown, oily liquid of crude **8** remained (0.440 g, 86.8%).

$C_{13}H_{18}O_2$ (206.28); MS: *m/z* (r.I.) = 206 (M^+, 3), 191 (5), 173 (9), 150 (14), 135 (24), 121 (29), 109 (28), 82 (100), 41 (40).

5-(5-Isopropenyl-2-methyl-1-oxo-2-cyclohexen-6-yl)-2-methyl-2-pentenoic acid ethylester (**9**)

A solution of 0.47 ml (2.18 mmol) 2-phosphonopropionic acid triethylester and of 2.84 g (10.73 mmol) 18-Crown-6 (freshly crystallized from acetonitril) in 50 ml dry *THF* was cooled to −80°C and mixed with 2.24 ml (2.24 mmol) sodium-*bis*-(trimethylsily-amide) (1.0 *M* in *THF*). Then, aldehyde **8** (0.440 g, 2.14 mmol) in dry *THF* was added, and the mixture was stirred for 4 h at −75°C. After quenching with saturated NH_4Cl solution, the mixture was extracted with diethyl ether (3×), and the ethereal phase was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (silica gel 60, mesh size 0.040–0.063 mm, solvent system: petroleum ether:ethyl acetate = 9:1) As the first fraction, 0.065 g (15.1%) of pure **9** were obtained.

$C_{18}H_{26}O_3$ (290.40); IR (NaCl; liquid film) $\nu = 3080$, 1713, 1671, 1452, 1373, 1219, 1136, 1028, 896 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.29$ (t, $J = 7.0$ Hz, 3H, 14-H), 1.57–1.67 (m, 1H), 1.71 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.88 (s, 3H, 12-H), 2.34–2.56 (m, 6H), 2.61–2.72 (m, 1H), 4.18 (q, $J = 7.0$ Hz, 2H, 13-H), 4.80 (s, 1H, 17-H), 4.82 (s, 1H, 17′H), 5.90 (t, $J = 7.5$ Hz, 1H, 9-H), 6.64 (m, 1H, 3-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 201.0$ (C=O), 168.1 (COO*R*), 145.5 (C-16), 142.7/142.5 (C-3, C-9), 135.1 (C-2), 127.2 (C-10), 113.3 (C-17), 60.0 (C-13), 48.7/47.1 (C-7, C-8), 20.6/18.8/16.0 (3×CH_3, C-12, C-15, C-18), 14.2 (C-14) ppm; MS: *m/z* (r.I.) = 290 (M^+), 282 (1), 250 (1), 245 (5), 207 (11), 150 (4), 149 (14), 105 (11), 99 (100), 91 (16), 86 (15), 73 (84), 45 (21).

5-(5(R)-Isopropylen-1-methyliden-2-methyl-2-cyclohexen-6(S)-yl)-2-methyl-2-(Z)-pentenoic acid ethylester (**10**)

A solution of 0.120 g (0.41 mmol) **9** in 4 ml dry *THF* was cooled to 0°C. Then, 1.02 ml (0.51 mmol) of the *Tebbe* reagent (0.5 *M* in toluene) were added slowly at this temperature which was maintained for at least 1 hour. After stirring for 17 h under an argon atmosphere, 15 ml of diethyl ether and 12 drops of methanol were added. This mixture was mixed with celite, filtered through another layer of celite, and this layer was washed with 150 ml of diethyl ether. After evaporation of the solvent, the yellow solution was roughly purified by column chromatography (sationary phase: Al_2O_3). The final purification was performed by preparative TLC (DC-Alu-foil, Merck, Art.Nr. 5554, silica gel 60 F_{254}, 20×20 cm, 0.2 mm, solvent system petroleum ether:ethyl acetate = 9:1). The desired ester could be found in the second fraction from above; yield: 0.036 g (29.8%) of **10**.

$C_{19}H_{28}O_2$ (288.43); IR (NaCl; liquid film): $\nu = 3081$, 1715, 1646, 1441, 1374, 1187, 1128, 886 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.22$ (m, 3H, 14-H), 1.43–1.51 (m, 3H), 1.64 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.82 (s, 3H, CH_3, 12-H), 2.25–2.35 (m, 3H), 2.38–2.47 (m, 2H), 4.12 (q, $J = 7.2$ Hz, 2H,

13-H), 4.63/4.67/4.69 (3×s, 3H, 17-H, 17′-H, 19-H), 4.91 (s, 1H, 19′-H) 5.47 (m, 1H, 3-H), 5.84 (t, $J = 7.4$ Hz, 1H, 9-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 168.2$ (COO*R*, C-11), 147.9 (C-1), 145.7 (C-16), 142.8 (C-9), 131.2 (C-2), 127.2 (C-10), 124.8 (C-3), 110.1/109.8 (C-17, C-19), 60.0 (C-13), 44.2/44.0 (C-5, C-6), 33.6 (C-4), 27.4/27.1 (C-7, C-8), 21.4/20.7/19.8 (3×CH_3, C-12, C-15, C-18), 14.3 (C-14) ppm; MS: *m/z* (r.I.) = 288 (M^+, 6), 273 (1), 259 (1), 242 (2), 214 (2), 201 (2), 199 (6), 187 (11), 171 (16), 161 (18), 148 (30), 133 (100), 119 (60), 105 (70), 91 (76), 41 (71).

5-(5(R)-Isopropylen-1-methyliden-2-methyl-2-cyclohexen-6(S)-yl)-2-methyl-2-(Z)-pentenol (**7**, *(Z)-6-Normethyl-carvo-β-santalol)*

A solution of **10** (0.036 g, 0.12 mmol) in dry CH_2Cl_2 was cooled to −78°C and mixed with 0.54 ml (0.77 mmol) of a 20% solution of *DIBAH* in *n*-hexane. After stiring overnight (the mixture warmed up to room temperature) and renewed cooling to −20°C, 0.15 ml methanol/water (1:1) were added and the mixture was stirred for another 3 hours. The white muddy solution was mixed with celite, filtered through a layer of celite, and washed with ethyl acetate. Finally, the solvent was evaporated and the residue purified by TLC as mentioned above.

Yield: 0.021 g (68.7%) of **7**; $C_{17}H_{26}O$ (246.39); IR (NaCl; liquid film) $\nu = 3327$, 3084, 1727, 1644, 1605, 1440, 1376, 1007, 886, 826 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.37$–1.45 (m, 3H), 1.64 (s, 3H), 1.72 (s, 6H), 1.99–2.31 (m, 5H), 4.05 (s, 2H, 11-H), 4.64–4.68 (m, 3H, 15-H, 15′-H, 17-H), 4.92 (s, 1H, 17′-H), 5.24 (t, 1H, 9-H), 5.47 (m, 1H, 3-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 147.9$ (C-1), 145.9 (C-14), 131.3 (C-2), 128.6 (C-9), 124.9 (C-3), 110.2/109.6 (C-15, C-17), 91.9 (C-10), 61.7 (C-11), 44.3/43.8) (C-5, C-6), 34.0 (C-4), 27.4/25.1 (C-7, C-8), 21.3/19.8 (3×CH_3, C-12, C-13, C-16) cm^{-1}; MS: *m/z* (r.I.) = 246 (M^+, 6), 231 (1), 228 (1), 215 (1), 213 (2), 204 (2), 200 (1), 188 (5), 187 (10), 145 (36), 133 (100), 119 (36), 105 (60), 91 (63), 41 (68).

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