Transformation of Carotol into the Hydroindane-Derived Musk Odorant

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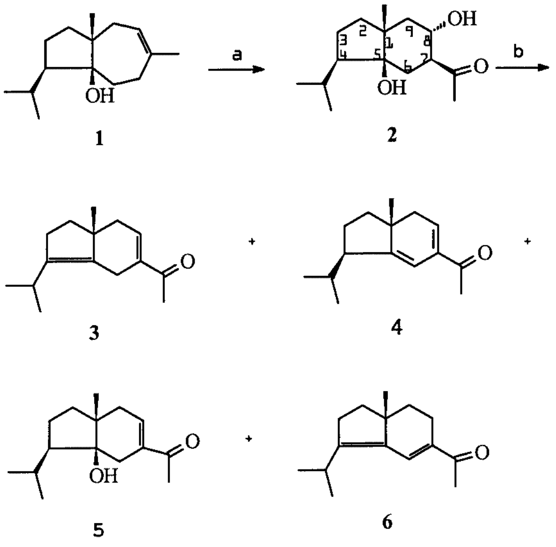
Ozonolysis of carotol (**1**) gives dihydroxy ketone **2** (63% yield), the absolute configuration of which was established by X-ray crystallography. An acidic dehydration of **2** delivers a mixture of isomeric ketones **3** and **4** (3:1) that, catalysed by Pd/C in cyclohexene, yields a 1:1 thermodynamic mixture of **3** and **6**. Ketone **6** exhibits an intensive musk odour.

Introduction

The imitation of natural fragrances is a matter of art in which both perfumers and chemists are deeply involved; the latter by trying to produce the natural fragrances by structural and molecular modification. The musk odour belongs to the most appreciated scents in perfumery, which is why many papers deal with its structure-odour relationship and with the manufacture of compounds that produce such an odour.[1,2] Limited sources of natural musks of macrocyclic structure and their synthetic analogues have caused the development of syntheses of many polycyclic non-nitro molecules with aromatic (benzene) ring, possessing also a musky odour. This type of compounds has began to replace the nitro-musks and became the industry standard for economic, stable and easy to use musk scents.[3] In this paper we want to describe the synthesis of a new, accidentally discovered musk odorant of polycyclic structure (indane derivative) but without an aromatic ring.



Scheme 1. (a) O_3, Zn/AcOH, 63%; (b) TsOH/toluene, 70%

Results and Discussion

Starting from carotol,[4−6] the main sesquiterpene component of carrot seed essential oil,[7,8] we accomplished the synthesis of a few compounds with a hydroindane carbon skeleton (Scheme 1).

Ozonolysis of carotol (**1**) in acetic acid followed by a Zn/AcOH reduction according to a modified method[9,10] delivered dihydroxy ketone **2** in 63% yield, as a result of spontaneous intramolecular condensation of the intermediate oxo aldehyde.[11,12] Structure **2** was established earlier[4,11] but the stereochemistry of its new stereogenic centres was unknown. The compound was then purified by crystallisation from toluene to give large, white crystals and the absolute configuration of its chiral atoms as $R_{C1},R_{C4},S_{C5},S_{C7},S_{C8}$ was determined by X-ray crystallography. A view with the atom numbering scheme of the basic molecule is presented in Figure 1.

Tables of bond lengths, bond angles and torsional angles for the non-hydrogen atoms, as well as the hydrogen-bond-

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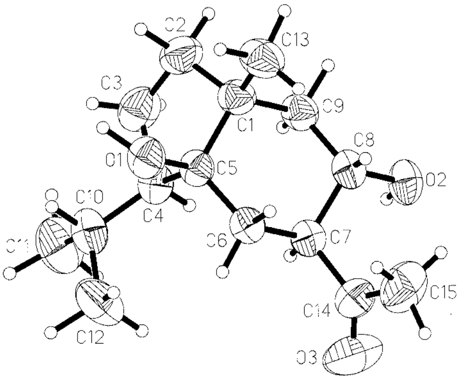

Figure 1. View of a molecule of dihydroxy ketone **2** with atom numbering scheme; ellipsoids are shown with 50% probability

ing geometry, asymmetry parameters for the five- and six-membered rings and the angles formed by some least-squares planes are available as Supporting Information for this paper (see footnote on the first page of this paper). The crystal of ketone **2** belongs to the host-guest type with the ketone as the host and toluene as the guest (Figure 2).

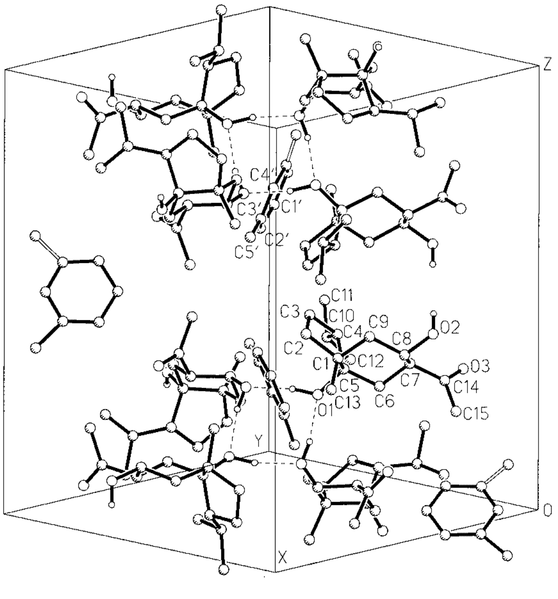

Figure 2. Crystal packing diagram of dihydroxy ketone **2**; open-line bonds mark methyl groups of disordered toluene molecules in the second position

In the next step, dihydroxy ketone **2** was treated with *p*-toluenesulfonic acid in boiling toluene to give a set of compounds in 70% yield (distilled product). Two of them, **3** and **4** in a ratio 3:1, respectively, composed ca. 88% of the mixture (GC). The other two compounds **5** and **6** represented 7% of the mixture, and the remaining 5% of components were not identified at this stage of study. The odour of the mixture was rather unattractive, but a very weak musk scent could be recognized.

Inspired by this odour sensation, 50−200-mg samples of the mixture were subjected to flash chromatography, under variable conditions, to isolate a component responsible for the musk scent. Unfortunately, all attempts to isolate the desired compound failed, thereby frustrating this potential method. Ketone **3**, as the main component was obtained in 98% pure state (GC) and appeared to be odourless. Its structure was confirmed by NMR spectroscopy. Examination of the ^{1}H NMR (^{1}H-^{1}H COSY) and ^{13}C NMR (DEPT) data revealed two salient features which allowed the unambiguous differentiation between **3** and the other anticipated ketones. Firstly, one allylic proton at C(6) (δ = 3.15 ppm, d, J^2 = 20 Hz) is coupled with the other geminal proton (δ = 2.74 ppm, m, 1 H) and with protons at C(8) and C(9) with small coupling constants. Secondly, in the ^{13}C NMR spectrum there are three olefinic carbon singlets and one doublet clearly locating the C−C double bonds in the molecule. The isomeric ketone **4**, however, could be isolated only in ca. 85% purity and its structure was deduced based on major signals of its ^{13}C NMR spectrum as containing two single substituted olefinic carbon atoms (δ = 134.55 and 110.96 ppm) and two quaternary olefinic carbon atoms (δ = 155.1 and 137.38 ppm). The fraction exhibited a strong, but non-musk odour. The product of partial dehydration, hydroxy ketone **5**, was also isolated and its structure was confirmed in a similar way. Again, two coupled doublets at δ = 3.08 (J^2 = 17.5 Hz) and 1.93 (J^2 = 17.5 Hz) ppm in the ^{1}H NMR spectrum of **5** indicated the persistence of the isolated allylic methylene group.

Independently of the above, the hydroxy ketone **5** was also obtained quantitatively from diol **2** by its alkaline and regiospecific dehydration using sodium hydroxide in ethanol.

Finally, a ca. 3:1 mixture of ketones **3** and **4**, was subjected to a series of isomerisation experiments including acidic (H_2SO_4, TsOH), basic (EtONa) and Pd-catalytic conditions. The experiments were carried out by refluxing the substrate material (10 mg) in different solvents (10 mL) (toluene, ethanol, ethanol/water, cyclohexane and cyclohexene) for 4 h and the results were "monitored" by smelling the crude reaction product. To our surprise, the only condition tried under which an intensive musk odour emanated was Pd/C in cyclohexene. The resulted product consisted of **3** (55%), **6** (32%) and **4** (6%). Refluxing of the above mixture for another 3 h resulted in the formation of a ca. 1:1 thermodynamic mixture of **3** and **6**, and a further 7 h of reaction did not bring about a successive increase of ketone **6**. Similar outcomes could be observed when Pd/Al_2O_3 in cyclohexene was used, however, the corresponding isomerisation times had to be doubled. Both isomers were readily separated by column chromatography and identified by NMR. Integration at δ = 7.30 ppm, corresponding to one vinylic proton, in combination with the presence of four olefinic carbon atoms, including the tertiary one, proves the proposed structure **6**. It is worth to note that the NMR spectroscopic data of ketone **6** are in good agreement with those reported in the literature[13] for an analogue where the acetyl group was replaced by COOMe.

Ketone **6** exhibits a typical musk scent oscillating between the macrocyclic and polycyclic ones and may be considered as a powerful odorant. However, a subtle sandalwood undertone can also be recognized.

Having at our disposal the ketone **6**, its presence in an amount of 2% (GC) in the dehydration product of dihydroxy ketone **2**, could be confirmed by GC/MS. Interestingly, only ca. 3% of a dihydro compound (based on GC/MS data), derived from the **3/4** mixture, could be detected as a result of an intraphase hydrogen transfer catalysed by Pd/C during 7 h of reflux of the mixture in cyclohexene.

To the best of our knowledge, the optically active ketone **6** is the first example published of polycyclic musk with indane carbon skeleton but not containing an aromatic ring, and in this respect it can be considered as a unique one.

Experimental Section

General: Carotol was obtained by a laboratory fractional distillation of the essential oil of *Daucus carota* L. ssp. *sativus* (Koral variety cultivated in Poland) and was employed for ozonolysis as a 94% fraction, b.p. 106−110 °C/0.7 Torr. For analytical purposes, a 99.49% carotol sample was isolated by column chromatography from the fraction, $[\alpha]_D^{29} = +27.7$ (c = 0.04, $CHCl_3$). Pd catalyst: 10% palladium on activated charcoal (Fluka). Flash chromatography: silica gel for TLC (Merck Kieselgel 60 G, Art.7731), hexane and hexane/ethyl acetate (1.5−5%). GC was performed with a Carlo Erba Vega 6000 gas chromatograph equipped with capillary columns: CP SIL 5CB (30 m), temperature program 60−280 °C (4°/min); Rtx-1 (30 m), 60−200 °C (6°/min), nitrogen as carrier gas (60 kPa). GC/MS data were obtained with a Carlo Erba GC 8000 coupled to an MD 800 Fisons Instrument using the above columns. ^1H NMR (250 MHz) and ^{13}C NMR (62.90 MHz) were recorded with a Bruker apparatus using $CDCl_3$ solutions with TMS as internal standard. Optical rotations were measured with an Autopol IV polarimeter. Crystal and molecular structure of dihydroxy ketone **2** ($C_{15}H_{26}O_3 \cdot 1/2C_7H_8$) was determined using data collected at room temperature with a CAD4 diffractometer with graphite-monochromatized Cu-K_α radiation. Crystal data and experimental details of the X-ray analysis are shown in Table 1.[14]

(1*R*,4*R*,5*S*,7*S*,8*S*)-7-Acetyl-5,8-dihydroxy-4-isopropyl-1-methylbicyclo[4.3.0]nonane (2): A solution of a carotol fraction (6.2 g) in acetic acid (35 mL) was ozonized according to the described procedure[9] and the crude product was extracted with ethyl acetate (4 × 80 mL), washed with water (3 × 30 mL) and dried with Na_2SO_4. After solvent evaporation under vacuum, the residue was refrigerated for 3 d, then filtered to deliver 5.7 g of a crystalline material. The solid was recrystallised from toluene to give 4.2 g (63%) of dihydroxy ketone **2**, m.p.85−88 °C, $[\alpha]_D^{20} = +17.9$ (c = 0.02, $CHCl_3$). ^1H NMR: δ =0.97 (d, J = 6.7 Hz, 3 H), 1.02 (s, 3 H), 1.10 (d, J = 6.5 Hz, 3 H), 1.65−1.42 (7 H), 1.75 (m, 1 H), 2.19 (s, 3 H), 2.0 (m, 1 H), 2.27 (dd, J = 13.5, 3.7 Hz, 1 H), 2.59 (ddd, J = 13.6, 10.0, 3.7 Hz, 1 H), 4.04 (ddd, J = 11.6, 10.0, 5.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 19.9 (q), 22.6 (q), 23.1 (q), 25.6 (t), 29.1 (q), 29.7(d), 33.3 (t), 36.8 (t), 43.4 (t), 47.4 (s), 48.8 (d), 55.6 (d), 67.2 (d), 82.1 (s), 211.8 (s) ppm. IR (microscope): $\tilde{\nu}$ = 3249, 3224, 1706, 1285, 1135, 1032 cm^{-1}. GC/MS (70 eV): m/z (%) = 254 (12) [M^+], 43 (100), 109 (48), 41 (39), 55 (37), 140 (35), 170 (33), 69 (30), 97 (28), 95 (26), 127 (23). $C_{15}H_{26}O_3$ (254.36): calcd. C 70.82, H 10.30; found C 73.11, H 10.05.

Table 1. Crystal data and experimental details

Empirical formula	$C_{15}H_{26}O_3 \cdot 1/2C_7H_8$
Formula mass	300.42
Crystallographic system	orthorhombic
Space group	$P4_12_12$
a [Å]	14.495(2)
b [Å]	14.495(2)
c [Å]	17.365(3)
V [Å^3]	3648.5(10)
Z	8
D_c [g/cm^3]	1.094
μ [cm^{-1}]	5.69
Crystal dimensions (mm)	0.5 × 0.4 × 0.3
Maximum 2θ [°]	150
Radiation, λ [Å]	Cu-K_α, 1.54184
Scan mode	ω/2θ
Scan width [°]	0.75+0.14tanθ
hkl ranges	h = 0−18, k = 0−18, l = 0−21
No. of reflections: unique	3758
with $I > 0\sigma(I)$	3610
observed with $I > 2\sigma(I)$	3319
No. of parameters refined	276
Largest diff. peak [eÅ^{-3}]	0.186
Largest diff. hole [eÅ^{-3}]	−0.197
Shift/esd max	−0.012
R_{obs}	0.0466
WR_{obs}	0.1433
S_{obs}	1.073
Weighting coeff.[a] m, n	0.1137, 0.0889
Flack χ	0.03(26)
Absolute structure	R_{C1},R_{C4},S_{C5},S_{C7},S_{C8}
R_{int}	0.0278
$T_{meas.}$ [K]	293(2)
F(000)	1320

[a] Weighting scheme $w = [\sigma^2(F_o^2) + (mP)^2 + nP]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$.

(*R*)-7-Acetyl-4-isopropyl-1-methylbicyclo[4.3.0]nona-4,7-diene (3): A mixture of dihydroxy ketone **2** (3.5 g, 13.8 mmol), *p*-toluenesulfonic acid (0.14 g) and toluene (40 mL) was refluxed for 7 h until ca 0.5 mL of water was collected in a Dean−Stark trap. The mixture was then washed with Na_2CO_3 solution and water and the solvent was removed under reduced pressure. The residue was fractionally distilled to give 2.1 g (70%) of a yellowish liquid, b.p. 110−116 °C/0.5 Torr. This material (184 mg) was flash-chromatographed (hexane/EtOAc, 50:1) to deliver (in elution order): **Ketone 3:** 90 mg, $[\alpha]_D^{24} = -58.6$ (c = 0.02, $CHCl_3$). ^1H NMR: δ = 0.94 (d, J = 7.0 Hz, 3 H), 0.95 (s, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 2.32 (s, 3 H), 2.70 (h, J = 6.7 Hz, 1 H), 2.74 (m, 1 H), 3.15 (d, J = 20.0 Hz, 1 H), 6.89 (m, 1 H) ppm. ^{13}C NMR: δ = 20.91 (q), 20.88 (q), 22.2 (t), 24.6 (q), 25.1 (q), 26.5 (d), 28.1 (t), 37.4 (t), 41.5 (t), 44.9 (s), 133.0 (s), 137.6 (s), 138.8 (s), 140.7 (d), 198.6 (s) ppm. IR (neat): $\tilde{\nu}$ = 1670, 1635, 1250, 1060 cm^{-1}. MS (70 eV): m/z (%) = 218 (36) [M^+], 121 (100), 116 (88), 161 (62), 128 (52), 159 (47), 159 (45), 134 (46), 77 (42), 43 (39), 107 (33). $C_{15}H_{22}O$ (218.33): calcd. C 82.51, H 10.16; found C 82.12, H 10.16. **Ketone 4:** 42 mg, 85% purity. ^1H NMR: δ = 2.29 (s, 3 H), 6.20 (d, J = 1.5 Hz, 1 H), 6.67 (dd, J = 6.5, 3.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 17.9 (q), 21.0 (q), 21.3 (q), 24.0 (t), 25.1 (q), 29.9 (d), 38.8 (t), 39.7 (t), 40.1 (s), 49.2 (d), 111.0 (d), 134.5 (d), 137.4 (s), 155.1 (s), 196.6 (s) ppm. MS (70 eV): m/z (%) = 218 (44) [M^+], 116 (100), 115 (86), 43 (69), 160 (65), 91 (52), 131 (50), 77 (41), 105 (37), 141 (23), 161 (19).

(1*R*,4*R*,5*S*)-7-Acetyl-5-hydroxy-4-isopropyl-1-methylbicyclo[4.3.0.]-non-7-ene (5): A mixture of dihydroxy ketone **2** (1 g) and 10% ethanolic solution of NaOH (15 mL) was refluxed for 2 h and then the mixture was concentrated under vacuum at room temperature. The residue was dilute with water (6 mL) and the product was extracted with ether (3 × 20 mL). The solution was next washed neutral with water, dried with anhydrous $MgSO_4$ and the solvent was removed under vacuum to give 0.9 g of pure hydroxy ketone **5** (> 99%, GC, TLC): $[\alpha]_D^{21} = -55.0$ ($c = 0.07$, $CHCl_3$). ^1H NMR: δ = 0.84 (d, J = 6.6 Hz, 3 H), 0.86 (s, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 1.93 (d, J = 17.5 Hz, 1 H), 2.23 (s, 3 H), 3.02 (d, J = 17.5 Hz, 1 H), 6.68 (m, 1 H) ppm. ^{13}C NMR: δ = 19.3, 21.7, 22.7, 24.68, 24.73, 28.9 (d), 30.2, 34.7, 39.1, 44.1, 49.2 (d), 80.5, 136.6 (s), 138.5 (d), 198.5 (s) ppm. IR (neat): $\tilde{\nu}$ = 3500, 1670, 1250, 1080, 760 cm^{-1}. MS (70 eV): m/z (%) = 236 (10) [M^+], 140 (100), 43 (88), 97 (76), 137 (56), 41 (51), 55 (31), 69 (22), 79 (21), 123 (17), 151 (15). $C_{15}H_{24}O_2$ (236.34): calcd. C 76.22, H 10.24; found C 75.79, H 10.26.

(*R*)-7-Acetyl-5-isopropyl-1-methylbicyclo[4.3.0]nona-4,6-diene (6): A 3:1 mixture of ketones **3** and **4** (120 mg) was refluxed in cyclohexene (15 mL) in the presence of 10% Pd/C (15 mg) for 7 h and the product was filtered and concentrated under reduced pressure. The residue was flash-chromatographed (hexane/EtOAc, 50:1.2) to yield ketone **3** (30 mg) and **6** (25 mg) and the rest (50 mg) as a **3**/**6** mixture. **Ketone 6:** $[\alpha]_D^{24} = +108$ ($c = 0.01$, $CHCl_3$). ^1H NMR: δ = 0.90 (s, 3 H), 1.05 (d, J = 6.8 Hz, 3 H), 1.08 (d, J = 7.0 Hz, 3 H), 2.36 (s, 3 H), 2.94 (h, J = 7.0 Hz, 1 H), 7.30 (d, J = 2.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.9 (q), 21.0 (q), 21.6 (q, 2C), 21.8 (t), 26.9 (d), 29.3 (t), 35.0 (t), 38.7 (t), 44.4 (s), 129.2 (d), 135.2 (s), 136.4 (s), 152.3 (s), 199.3 (s) ppm. IR (neat): $\tilde{\nu}$ = 1660, 1630, 1580, 1250, 1050 cm^{-1}. MS (70 eV): m/z (%) = 218 (60) [M^+], 216 (100), 203 (66), 43 (65), 159 (54), 175 (50), 128 (49), 131 (47), 115 (44), 91 (37), 77 (28). $C_{15}H_{22}O$ (218.33): calcd. C 82.51, H 10.24; found C 82.07, H 10.25.

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[14] CCDC-179908 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc. cam. ac. uk].

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