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The Synthesis of Chiral Decalones, (-)-1,1,4a-Trimethyl-2-decalol and (+)-Geosmin from S-(+)-Carvone (part 3)[1]

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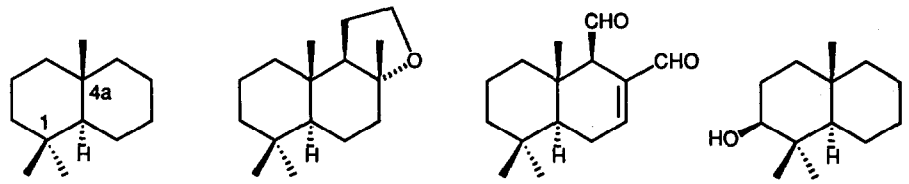
Abstract: *The cholesterol biosynthesis inhibitor (-)-1,1,4a-trimethyl-2-decalol (4), the chiral decalones 6 and 7, and (+)-geosmin (9) were synthesized from S-(+)-carvone. Annelation of S-(-)-dihydrocarvone followed by methylation gave compound 8 which was used as a key intermediate for the synthesis of decalol 4 and ketone 5. A short isomerisation-ozonation sequence was developed for the removal of the isopropenyl group. Ketones 6 and 7 were obtained from decalone 5 through carbonyl transpositions. (+)-geosmin (9) was synthesized using a Criegee rearrangement to remove the isopropenyl group.*

The 1,1,4a-trimethyl-*trans*-decalin nucleus **1** is a common structural element in a large number of naturally occurring compounds[2] with diverse biological activities. Representative examples are (-)-Ambrox® (**2**), a famous molecule in perfumery[3], (-)-polygodial (**3**), an insect antifeedant with a peppery taste to the human tongue[4], and (-)-decalol **4** which shows an inhibitory effect on the cholesterol biosynthesis[5].

Figure 1

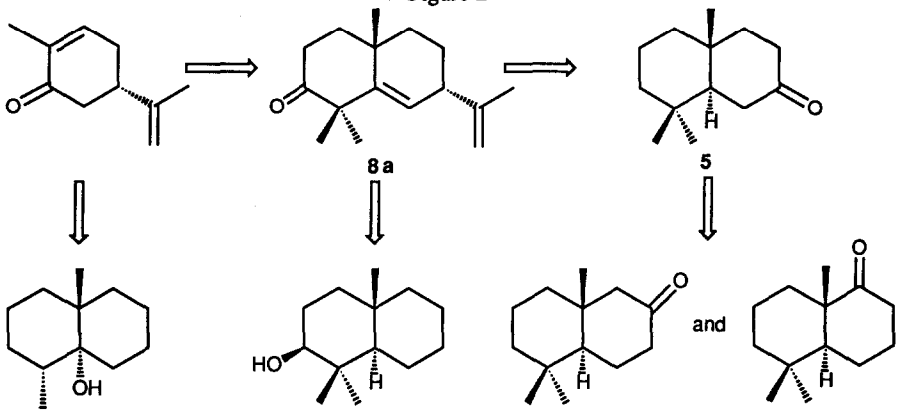


1 **2** **3** **4**

Synthons like the decalones **5**, **6** and **7**, or their precursors, have appeared to be suitable starting materials for the synthesis of these compounds[6]. Here we report on the synthesis of the chiral decalones (-)-**5**, (-)-**6** and (-)-**7**, starting from S-(+)-carvone, the main component of caraway-seed oil. The use of S-(+)-carvone as

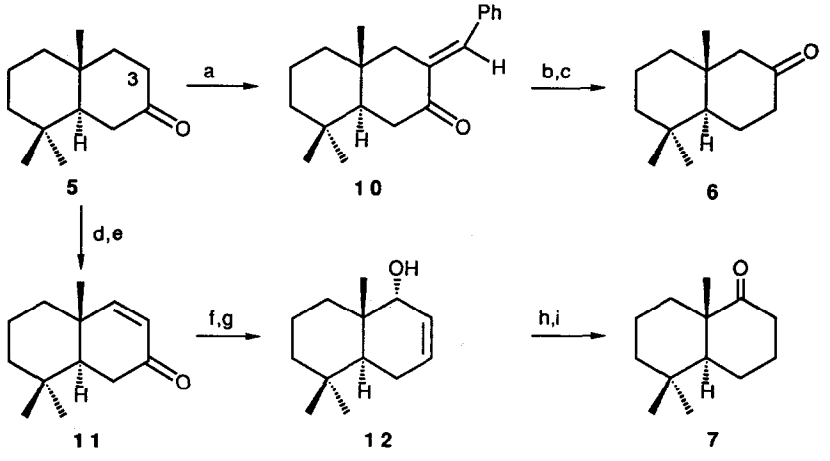
starting material is further demonstrated by the synthesis of (-)-decalol **4** and (+)-geosmin **9**, the enantiomer of naturally occurring (-)-geosmin, an interesting product in olfactive studies[7].

Figure 2



Recently an adapted Robinson annelation of S-(-)-dihydrocarvone, obtained by Li bronze reduction of S-(+)-carvone, was reported as a convenient route towards the synthesis of isopropenyl-trimethylnaphthalenone **8a** and ketone **5**[8]. A key step in this approach was the transformation of the isopropenyl group into a carbonyl group *(vide infra)*.

scheme 1



(a) PhCHO, NaOH; (b) $LiAlH_4$, $AlCl_3$; (c) O_3, thiourea; (d) PBB, HOAc;
(e) LiBr, Li_2CO_3, DMF, 120 °C; (f) H_2O_2, NaOH; (g) H_2NNH_2, HOAc; (h) PDC; (i) H_2,10% Pd/C.

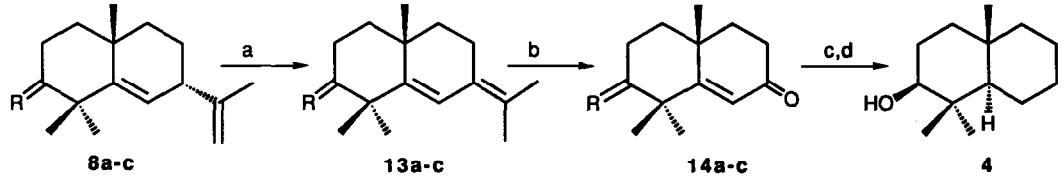
With ketone **5** in hand, the decalones **6** and **7** were synthesised via a 1,2[9]- or a 1,3[10]-carbonyl transposition, respectively (see scheme 1). The 3-position of ketone **5** was functionalized by benzylidation with benzaldehyde under basic conditions. This benzylidene derivative **10** was reduced with a mixture of $LiAlH_4$ and

$AlCl_3$ in ether to afford a mixture of double bond isomers which was submitted to ozonolysis without further purification. The desired ketone **6**[11] was obtained as the only product though in a moderate 17% yield from **5**.

For the 1,3-carbonyl transposition, ketone **5** was brominated with pyridinium bromide perbromide (PBB) in acetic acid to give a crystalline α-bromo ketone in 82% yield[12]. Dehydrobromination in DMF at 120 °C gave the enone **11** in 93% yield[13]. The epoxidation of the olefinic bond in **11** afforded stereoselectively an α-epoxy ketone which was reduced to the α,β-unsaturated alcohol **12** in 94% yield by a Wharton-reduction[14]. Oxidation of **12** followed by catalytic reduction of the double bond finally gave **7** in an overall yield of 45% from **5**.

The synthesis of enantiomerically pure decalol (-)-**4** from S-(+)-carvone was carried out as depicted in scheme 2. In compound **8** an isomerisation of the olefinic bond in the isopropenyl sidechain to the conjugated exocyclic position is a practical approach for the transformation of this former chiral handle into a carbonyl group. It turned out that simply heating with KOH in diethylene glycol (DEG) was sufficient for this purpose. This procedure proved to be compatible with hydroxy and acetal groups, whereas a carbonyl group in the molecule gave rise to incomplete reactions and competing aldol condensations. The resulting dienes **13 a-c** are rather unstable compounds and the selective ozonolyses to the unsaturated ketones should be carried out instantaniously. The ozonolysis of **8a,b** to **14a,b** can also be accomplished directly when the reaction is carried out in methanol whereby the intermediate methoxy hydroperoxides are oxidized by $Cu(OAc)_2$ and $FeSO_4$[15]. The dissolving metal reduction[16] of **14b**, followed by a Wolff- Kishner reduction of the carbonyl group finally gave (-)-decalol **4** in 38% overall yield from **8a**.

scheme 2



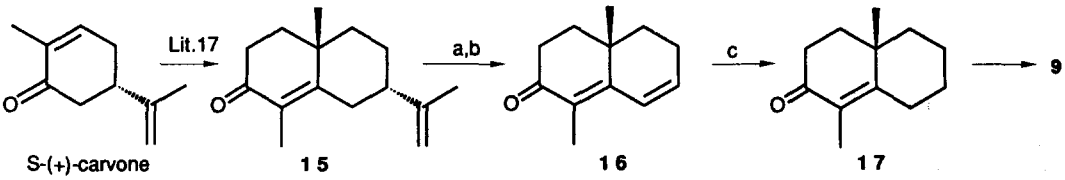
8a-c **13a-c** **14a-c** **4**

a, R=O; b, R=H,β-OH; c, R=O-CH_2-CH_2-O

(a) KOH, DEG, 200°C; (b) O_3, thiourea; (c) Li/NH_3, t-BuOH; (d) H_2NNH_2, KOH, DEG, 200°C

Another way to remove the chiral handle was practised in the synthesis of (+)-geosmin **9** (scheme 3). The isopropenyl group in **15**, which was obtained via a Robinson annelation of S-(-)-dihydrocarvone with ethyl vinyl ketone[17], was submitted to ozonolysis in methanol followed by the addition of acetic anhydride[18]. The resulting δ-acetoxy-α,β-unsaturated ketone was treated with sodium methoxide to give the dienone **16** in 74% yield. Conjugate reduction of **16** with L-selectride[8] in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) gave enone **17** which was converted into (+)-geosmin **9** using the procedure of Gosselin[7g]. (+)-Geosmin was obtained in this way from S-(+)-carvone in 12% overall yield.

scheme 3



S-(+)-carvone **15** **16** **17**

(a) O_3, MeOH, Ac_2O, Et_3N, DMAP; (b) $NaOCH_3$; (c) L-selectride, DMPU

EXPERIMENTAL PART

^{1}H NMR spectra were recorded on a Bruker CPX-300 spectrometer. Chemical shifts are reported in ppm downfield relative to TMS (δ-scale) and in $CDCl_3$ as solvent. Mass spectral data and HRMS measurements were recorded on a AEI MS 902 spectrometer. Elemental analysis were obtained from a Carlo Erba Elemental Analyser 1106. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points are uncorrected. For reactions under dry conditions the glass-ware was dried at 150°C for one night, and was flushed with dry nitrogen while cooling down. Usually the reaction mixture was diluted with water and extracted with ether. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Flash chromatography was performed on silica gel (230-400 mesh) and mixtures of petroleum ether (boiling range 40-60°C) and ethyl acetate were used as eluens.

(+)-(4aR,8aS)-3(E)-Benzylidene-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one (10)

To a solution of 0.73 g (3.76 mmol) of **5**[8] in 25 mL of absolute ethanol was added 1.0 g (9.4 mmol) of benzaldehyde and a solution of 0.15 g (2.7 mmol) of potassium hydroxide in 15 mL of absolute ethanol. The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, water and CH_2Cl_2 were added. The aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (petroleum ether-ethyl acetate, 97:3) to yield 0.70 g (66%) of **10** as pale yellow crystals which were recrystallized from ethanol.

mp: 94-100°C; $[\alpha]_D$=+180° (c=0.65, $CHCl_3$); ^{1}H NMR: 0.87(s,9H); 1.1-1.7(m,7H); 2.2-2.8(m,4H); 7.37(m,5H); 7.54(dd, J=1,3Hz,1H); MS, *m/e* (rel intensity): 282(M^+,100), 159(22), 123(32), 117(21), 116(48), 115(35), 91(17), 41(30); HRMS, calcd for $C_{20}H_{26}O$ (M^+): 282.1983; Found: 282.1982; Anal. Calcd for $C_{20}H_{26}O$: C, 85.05; H, 9.28; Found: C, 84.78; H, 9.24.

(-)-(4aS,8aR)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-naphthalen-2(1H)-one (6)

A mixture of 0.66 g (4.9 mmol) of $AlCl_3$ and 0.19 g (4.9 mmol) of $LiAlH_4$ in 25 mL of dry ether was stirred for 15 min at room temperature. A solution of 0.70 g (2.48 mmol) of **10** and 0.33 g (2.48 mmol) of $AlCl_3$ in 25 mL of dry ether was added dropwise. The reaction mixture was stirred for 15 min and then refluxed for an additional 30 min. After cooling the excess of $LiAlH_4$ was destroyed with 1 mL of water and 1 mL of 4 M NaOH and $MgSO_4$ was added. The solvent was filtered and evaporated in vacuo and the residue was filtered over silicagel using petroleum ether as eluens. The solvent was evaporated in vacuo and the residue was dissolved in 30 mL of methanol and 10 mL of CH_2Cl_2. The solution was cooled to -80°C and ozonized. When the reaction was finished, 0.20 g (2.6 mmol) of thiourea was added and the mixture was allowed to come to room temperature and stirred for an additional hour. The solvents were evaporated under reduced pressure and the residu was dissolved in CH_2Cl_2 and washed with water and brine. The solvent was dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 98:2) to yield 121 mg (25%) of **6** as white crystals. mp: 89-91°C; (Lit[11b]: 88-90°C).

$[\alpha]_D$=-81.0° (c=0.37, $CHCl_3$); (Lit[11b]: $[\alpha]_D$=-86.1°); ^{1}H NMR: 0.83(s,3H); 0.87(s,3H); 0.94(s,3H); 1.2-1.7(m,7H); 1.9-2.5(m,6H); HRMS, calcd for $C_{13}H_{22}O$ (M^+): 194.1670; Found: 194.1674.

(+)-(4aS,8aS)-4a,5,6,7,8,8a-Hexahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one (11)

To a stirred solution of 2.12 g (10.9 mmol) of 5[8] in 40 mL of acetic acid at room temperature was added 3.8 g (11.9 mmol) of pyridinium bromide perbromide. The orange reaction mixture was stirred for 3 h and then water was added. After the usual work up the residue was purified by flash chromatography (petroleum ether-ethyl acetate, 95:5) to give 2.45 g (82%) of a white solid which was recrystallized from ethanol to give white needles of **(-)-(3S,4aR,8aS)-3-bromo-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one.**

mp: 145-148°C; $[\alpha]_D$=-19.9° (c=0.52, $CHCl_3$); ^1H NMR: 0.81(s,3H); 0.83(s,3H); 1.16(s,3H); 1.0-1.9(m,8H); 2.1-2.4(m,2H); 2.66(dd,J=3,14Hz,1H); 4.74(dd,J=6,13Hz,1H); MS, *m/e* (rel intensity): 274(M^+,18), 272(18), 193(33), 164(79), 162(78), 109(45), 95(37), 81(66), 70(46), 69(82), 67(50), 55(94), 41(100); HRMS, calcd for $C_{13}H_{21}BrO$ (M^+): 272.0776; Found: 272.0779; Anal. Calcd for $C_{13}H_{21}BrO$: C, 57.14; H, 7.74; Found: C, 56.86; H, 7.70.

A suspension of 1.0 g (11.5 mmol) of lithium bromide and 1.42 g (19.2 mmol) of lithium carbonate in 25 mL of dry dimethylformamide was heated to 120°C. To this mixture was added 2.1 g (7.7 mmol) of the bromide. The temperature was kept at 120°C for 2 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and dried over $MgSO_4$, filtered and evaporated in vacuo. The yellow residue was submitted to flash chromatography (petroleum ether-ethyl acetate, 95:5) to give 1.37 g (93%) of **11** as a colourless oil.

$[\alpha]_D$=+9.2° (c=1.2, $CHCl_3$); ^1H NMR: 0.85(s,3H); 0.88(s,3H); 1.06(s,3H); 1.1-1.8(m,7H); 2.3-2.4(m,2H); 5.72(d,J=10Hz,1H); 6.60(d,J=10Hz,1H); MS, *m/e* (rel intensity): 192(M^+,27), 150(90), 135(44), 109(40), 95(47), 79(51), 69(87), 67(47), 55(44), 41(100), 39(50); HRMS, calcd for $C_{13}H_{20}O$ (M^+): 192.1514; Found: 192.1511.

(-)-(1S,4aS,8aS)-1,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-naphthalen-1-ol (12)

To a solution of 1.0 g (5.2 mmol) of **11** in 25 mL of methanol was added 1.36 mL (1.66 g; 16 mmol) of 35% H_2O_2 and 0.45 mL (2.7 mmol) of a 6 M NaOH solution in water. The reaction mixture was stirred at room temperature for 1.5 h. After the usual work up a yellow oil was obtained which was purified by flash chromatography (petroleum ether-ethyl acetate, 95:5) to give 0.82 g (76%) of **(-)-(3S,4S,4aS,8aS)-3,4-epoxy-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one** as a colourless oil, which solidified on standing.

mp: 74-75°C; $[\alpha]_D$=-122° (c=0.85, $CHCl_3$); ^1H NMR: 0.80(s,6H); 0.92(s,3H); 1.1-1.7(m,6H); 1.8-2.1(m,2H); 2.36(dd,J=5,18Hz,1H); 3.03(d,J=4Hz,1H); 3.22(d,J=4Hz,1H); MS, *m/e* (rel intensity): 208(M^+,1), 147(32), 123(33), 109(43), 107(25), 95(44), 93(25), 81(41), 79(26), 69(57), 67(41), 55(43), 43(33), 41(100), 39(40); HRMS, calcd for $C_{13}H_{20}O_2$ (M^+): 208.1463; Found: 208.1456; Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.67; Found: C, 74.78; H, 9.84.

A solution of 0.80 g (3.84 mmol) of the epoxide in 25 mL of methanol was cooled to 0°C. To this solution 0.55 mL (11.5mmol) of hydrazine hydrate was added dropwise. After stirring for 20 min 50 mL of acetic acid was added and stirring was continued for 1 h. Water was added and the mixture was extracted with ether. The combined ethereal layers were washed with water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 93:7) to give 0.70 g (94%) of **12** as a white solid.

mp: 82-87°C; $[\alpha]_D$=-168° (c=0.65, $CHCl_3$); ^1H NMR: 0.79(s,3H); 0.86(s,3H); 0.88(s,3H); 1.1-2.1(m,10H); 3.24(d,J=5Hz,1H); 5.7-5.9(m,2H); MS, *m/e* (rel intensity): 194(M^+,8), 124(36), 109(100), 81(21), 70(74), 55(25), 41(39); HRMS, calcd for $C_{13}H_{22}O$ (M^+): 194.1671; Found: 194.1677; Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41; Found: C, 79.97; H, 11.49.

(-)-(4aS,8aS)-3,4,4a,5,6,7,,8,8a-Octahydro-5,5,8a-trimethyl-naphthalen-1(2H)-one (7)

To a stirred solution of 445 mg (2.29 mmol) of **12** in 25 mL of methylene chloride was added 1.30 g (3.44 mmol) of pyridinium dichromate. The orange reaction mixture was stirred overnight at room temperature. The mixture was diluted with methylene chloride and filtered over anhydrous $MgSO_4$ and silicagel. Evaporation of the solvent in vacuo yielded 410 mg (92%) of the desired **(-)-(4aS,8aS)-4a,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-naphthalen-1(4H)-one** as a colourless oil, which solidified on standing.

mp: 30-34°C; $[\alpha]_D$=-49.9° (c=0.88, $CHCl_3$); ^1H NMR: 0.86(s,3H); 0.93(s,3H); 1.01(s,3H); 1.0-1.6(m,6H); 1.7-1.9(m,1H); 2.1-2.4(m,2H); 5.80(ddd,J=1.5,2.5,10Hz,1H); 6.84(m,1H); MS, *m/e* (rel intensity): 192(M^+,28), 177(29), 109(100), 91(24), 81(25), 79(36), 68(36), 55(39), 41(72), 39(51); HRMS, calcd for $C_{13}H_{20}O$ (M^+): 192.1514; Found: 192.1515; Anal. Calcd for $C_{13}H_{20}O$: C, 81.19; H, 10.48; Found: C, 81.04; H, 10.68.

To a stirred solution of 380 mg (1.98 mmol) of the above obtained enone in 25 mL of methanol was added 25 mg of 10% Pd/C, and the solution was purged with hydrogen and stirred for 1 h. The reaction mixture was filtered through hyflo and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 96:4) to give 355 mg (92%) of **7** as a colourless oil.

$[\alpha]_D$=-40.0° (c=1.1, $CHCl_3$); (Lit[19]: $[\alpha]_D$=-39.1°, Lit[20]: $[\alpha]_D$=-42.3°); ^1H NMR: 0.85(s,3H); 0.88(s,3H); 1.12(s,3H); 1.3-1.8(m,7H); 2.0-2.2(m,4H); 2.55(m,2H); MS, *m/e* (rel intensity): 194(M^+,51), 179(37), 161(60), 123(76), 111(48), 109(50), 95(64), 81(55), 69(57), 67(80), 55(80), 41(100); HRMS, calcd for $C_{13}H_{22}O$ (M^+): 194.1670; Found: 194.1672.

(-)-(2S,4aS,7S)-7-Isopropenyl-1,2,3,4,4a,5,6,7-octahydro-1,1,4a-trimethyl-naphthalen-2-ol (8b)

To a stirred suspension of 0.27 g (7,0 mmol) of $LiAlH_4$ in dry ether was added dropwise a solution of 2.0 g (13.4 mmol) of **8a**[8] in 50 mL of dry ether. The mixture was stirred for 1 h, then 0.45 mL of water and 0.45 mL of 4 M NaOH were added. This mixture was stirred for 15 min and another 0.45 mL of water was added and stirring was continued for an additional 30 min. The solvent was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 90:10) to give 1.82 gram (90%) of **8b** as a white solid.

mp: 90-92°C; $[\alpha]_D$=-125° (c=0.85, $CHCl_3$); ^1H NMR: 1.03(s,3H); 1.13(s,3H); 1.14(s,3H); 1.73(s,3H); 0.8-1.9(m,9H); 2.63(m,1H); 3.24(dd,J=5,11Hz,1H); 4.54(br.s,1H); 4.76(br.s,1H); 5.42(d,J=6Hz,1H); MS, *m/e* (rel intensity): 234(M^+,24), 216(95), 201(100), 148(41), 135(79), 133(41), 121(38), 108(48), 93(38); HRMS, calcd for $C_{16}H_{26}O$ (M^+): 234.1983; Found: 234.1992. Anal. Calcd. for $C_{16}H_{26}O$: C,81.99; H, 11.18; Found: C, 82.01; H, 11.10.

(-)-(4aS,7S)-2,2-(Ethylenedioxy)-7-isopropenyl-1,2,3,4,4a,5,6,7--octahydro-1,1,4a-trimethyl-naphthalene (8c)

A mixture of 2.0 g (8.6 mmol) of **8a**[8] and 100 mg of p-toluenesulfonic acid and 4.9 mL (86 mmol) of ethylene glycol in 150 mL of benzene was refluxed for 21 h using a Dean-Stark apparatus. The reaction mixture was washed with saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. The solvent was filtered and evaporated and the residue was purified by flash chromatography (petroleum ether-ether, 98:2) to give 1.90 g (80%) of **8c** as a colourless oil.

$[\alpha]_D$=-139° (c=3.7, $CHCl_3$); ^1H NMR: 1.04(s,3H); 1.20(s,6H); 1.76(s,3H); 1.0-2.3(m,8H); 2.5-2.8(m,1H); 3.91(s,4H); 4.68(br.s,1H); 4.79(br.s,1H); 5.37(d,J=5Hz,1H); MS, *m/e* (rel intensity): 276(M^+,5), 261(0.3), 135(1), 119(12), 105(8), 99(100), 91(5); HRMS, calcd for $C_{18}H_{28}O_2$ (M^+): 276.2089; Found: 276.2086.

(-)-(4aS)-7-Isopropylidene-3,4,4a,5,6,7-hexahydro-1,1,4a-trimethyl-naphthalene-2(1H)-one (13a)

A solution of 1.81 g (7.8 mmol) of ketone **8a**[8] and 0.68 g (12 mmol) of KOH in 30 mL of DEG was heated under N_2 at 200°C. After 15 min the reaction mixture was poured into 200 mL of water and worked up as usual. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 96:4) to afford 1.13 g (55%) of a colourless oil.

$[\alpha]_D$=-55.7° (c=1.0, $CHCl_3$); 1.03(s,3H); 1.27(s,6H); 1.73(s,3H); 1.80(s,3H); 0.8-2.7(m,8H); 6.38(s,1H); MS, *m/e* (rel intensity): 232(M+,100), 217(70), 189(78), 161(35), 146(38), 133(45), 119(38), 105(33), 91(32), 55(28), 41(44); HRMS, calcd for $C_{16}H_{24}O$ (M^+): 232.1827; Found: 232.1831.

(-)-(2S,4aS)-7-Isopropylidene-1,2,3,4,4a,5,6,7-octahydro-1,1,4a-trimethyl-naphthalen-2-ol (13b)

To a solution of 4.74 g (20.2 mmol) of **8b** in 150 mL of diethylene glycol was added 3.42 g (61 mmol) of KOH. The reaction mixture was heated under nitrogen at 200°C for 2.5 h. The mixture was allowed to cool and 75 mL of water was added. The reaction mixture was neutralized with 4 M HCl and the solution was extracted with ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 90:10) to give 4.65 g (98%) of **13b** as a yellow oil.

$[\alpha]_D$=-96° (c=1.3, $CHCl_3$); ^1H NMR: 1.03(s,3H); 1.12(s,3H); 1.20(s,3H); 1.70(s,3H); 1.78(s,3H); 0.7-2.5(m,9H); 3.20(dd,J=5,11Hz,1H); 6.40(s,1H); MS, *m/e* (rel intensity): 234(M^+,100), 219(21), 201(60), 177(55), 148(51), 85(57), 83(83); HRMS, calcd for $C_{16}H_{26}O$ (M^+): 234.1983; Found: 234.1982.

(-)-(4aS)-2,2-(Ethylenedioxy)-7-isopropylidene-1,2,3,4,4a,5,6,7-octahydro-1,1,4a-trimethyl-naphthalene (13c)

A solution of 0.98 g (3.6 mmol) of **8c** and 0.68 g (12 mmol) of KOH in 30 mL of diethylene glycol was heated at 200°C under a nitrogen atmosphere for 15 min. The mixture was poured into 100 mL of water and neutralized with 4 M HCl. The mixture was extracted with ether. The combined etheral layers were washed with water and brine and dried over $CaCl_2$, filtered and evaporated in vacuo. The crude oil was submitted to flash chromatography (petroleum ether-ether, 98:2) to give 0.88 g (90%) of **13c** as a colourless oil.

$[\alpha]_D$=-105° (c=4.0, $CHCl_3$); ^1H NMR: 1.12(s,3H); 1.20(s,3H); 1.23(s,3H); 1.72(s,3H); 1.79(s,3H); 0.9-2.5(m,8H); 3.93(s,4H); 6.38(s,1H); MS, *m/e* (rel intensity): 276(M^+,6); 261(7), 177(1), 162(3), 99(100), 91(100); HRMS, calcd for $C_{18}H_{28}O_2$ (M^+): 276.2089; Found: 276.2084.

(-)-(4aS)-3,4,4a,5-Tetrahydro-1,1,4a-trimethyl-naphthalen-2(1H),7(6H)-dione (14a)

A solution of 1.16 g (5.0 mmol) of **13a** in 50 mL of methanol was ozonozed at -80°C untill a pale blue colour appeared. The excess of ozone was expelled by a stream of nitrogen and 0.21 g (2.8 mmol) of thiourea was added. After being stirred for 3 h at room temperature the reaction mixture was concentrated in vacuo and dissolved in water and worked up ats usual to give after flash chromatography (petroleum ether-ether, 70:30) 0.67 g (65%) of the dienone **14a** as an oil.

$[\alpha]_D$=-23° (c=0.45, $CHCl_3$); ^1H NMR: 1.20(s,3H); 1.32(s,6H); 1.4-3.0(m,8H); 5.97(s,1H); MS, *m/e* (rel intensity): 206(M^+,100), 191(18), 178(23), 163(19), 152(44), 151(41), 135(26), 123(49), 107(26), 70(60); HRMS, calcd for $C_{13}H_{18}O_2$ (M^+): 206.1307; Found: 206.1303.

A solution of 710 mg (3.0 mmol) of **8a**[8] in 50 mL of methanol was cooled to -80°C and ozonized untill a pale blue colour appeared and the solution was purged with nitrogen to remove the excess of ozone. To this mixture was added 1.2 g (6.0 mmol) of $Cu(OAc)_2.H_2O$ and 850 mg (3 mmol) of $FeSO_4.7H_2O$. The reaction mixture was allowed to come to room temperature and was stirred for an additional 2 h. The solvent was evaporated in vacuo and water and 1 M HCl were added. The aqueous layer was worked up as usual. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 85:15) to give 163 mg (26%) of **14a** as an oil, which solidified on standing, with all data corresponding to the above mentioned.

(-)-(4aR,7S)-7-Hydroxy-4,4a,5,6,7,8-hexahydro-4a,8,8-trimethyl-naphthalen-2(3H)-one (14b)

A stirred solution of 1.95 g (8.3 mmol) of **13b** in 50 mL of methanol was cooled to -80°C and ozonized untill a pale blue colour appeared. The excess of ozone was removed by flushing with nitrogen and 0.80 g (10.5 mmol) of thiourea was added. The reaction mixture was stirred for 3 h at room temperature. The methanol was partly evaporated in vacuo and water was added followed by the usual work up procedure. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 75:25) to give 1.10 g (63%) of **14b** as a colourless oil.

$[\alpha]_D$=-76.6° (c=3.0, $CHCl_3$); ^1H NMR: 1.02(s,3H); 1.12(s,3H); 1.23(s,3H); 0.9-2.6(m,8H); 2.81(br.s,1H); 3.32(dd,J=5,11Hz,1H); 5.90(s,1H); MS, *m/e* (rel intensity): 208(M^+,41), 193(50), 152(100), 123(48), 109(41), 43(39); HRMS, calcd for $C_{13}H_{20}O_2$(M^+): 208.1462; Found: 208.1461.

A solution of 234 mg (1.0 mmol) of **8b** in 25 mL of methanol was cooled to -80°C and ozonized untill a pale blue colour appeared and the solution was purged with nitrogen to remove the excess of ozone. To this mixture was added 400 mg (2.0 mmol) of $Cu(OAc)_2.H_2O$ and 330 mg (1.2 mmol) of $FeSO_4.7H_2O$. The reaction mixture was allowed to come to room temperature and was stirred for an additional 2 h. The solvent was evaporated in vacuo and water and 1 M HCl were added. The aqueous layer was worked up as usual. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 75:25) to give 97 mg (47%) of **14b** as a colourless oil, with all data corresponding to the above mentioned.

(-)-(4aS)-7,7-(Ethylenedioxy)-4,4a,5,6,7,8-hexahydro-4a,8,8-trimethyl-naphthalen-2(3H)-one (14c)

A solution of 2.32 g (10.0 mmol) of **13c** in 50 mL of methanol was ozonized at -80°C untill a light blue colour appeared. The excess of ozone was expelled by a stream of nitrogen and 0.42 g (5.6 mmol) of thiourea was added. After being stirred for 3 h at room temperature the reaction mixture was concentrated in vacuo. The residue was dissolved in water and worked up as usual to give after flash chromatography (petroleum ether-ethyl acetate, 50:50) 1.34 g (65%) of the enone **14c** as a colourless oil. $[\alpha]_D$=-90° (c=2.3, $CHCl_3$).

^{1}H NMR: 1.10(s,3H); 1.27(s,3H); 1.38(s,3H); 1.4-2.8(m,8H); 3.96(br.s,4H); 5.95(s,1H); MS, *m/e* (rel intensity): 250(M^+,2), 235(4), 99(100); HRMS, calcd for $C_{15}H_{22}O_3$ (M^+): 250.1569; Found: 250.1571.

(-)-(2S,4aS,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-1,1,4a-trimethyl-naphthalen-2-ol (4)

To a solution of 10 mg of lithium in 4 mL of ammoniak was added 10 mL of dry ether. A solution of 208 mg (1.0 mmol) of **14b** in 5 mL of dry ether was added dropwise. After 15 min solid NH_4Cl was added and the ammonia was allowed to evaporate. Water was added and the mixture was worked up as usual. The crude product was purified by flash chromatography (petroleum ether-ethyl acetate, 85:15) to give 170 mg (81%) of **(-)-(4aR,7S,8aS)-7-hydroxy-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one** as a white solid.

mp: 88-90°C; (Lit[6c]: 91.6-92°C); $[\alpha]_D$=-4.9° (c=0.81, $CHCl_3$); (Lit[6c]: $[\alpha]_D$=-5.2°); ^{1}H NMR: 0.78(s,3H); 0.91(s,3H); 1.10(s,3H); 1.0-1.8(m,7H); 2.1-2.5(m,5H); 3.22(dd,J=7,9Hz,1H); MS, *m/e* (rel intensity): 210(M^+,100), 167(44), 111(35), 97(48), 69(36); HRMS, calcd for $C_{13}H_{22}O_2$ (M^+): 210.1620; Found: 210.1618.

A solution of 140 mg (0.66 mmol) of the above mentioned hydroxy ketone in 12 mL of diethylene glycol and 0.6 mL of hydrazine hydrate was heated at 150°C under a nitrogen atmosphere for 1.5 h, after which 0.75 g (13.4 mmol) of KOH was added. The excess hydrazine was removed by distillation and the reaction was heated at 210°C for 2 h. The solution was cooled, poured into ice water and extracted three times with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 1 M HCl, water, $NaHCO_3$ and brine. The solvent was dried over $MgSO_4$, filtered and evaporated in vacuo to give 105 mg (81%) of **4** as a white solid.

mp: 85-87°C; (Lit[6c]: 86.5-87.4°C); $[\alpha]_D$=-9.4° (c=0.32, $CHCl_3$); (Lit[6c]: $[\alpha]_D$=-11.3°); ^{1}H NMR: 0.70(s,3H); 0.86(s,3H); 0.90(s,3H); 0.7-1.8(m,14H); 3.17(dd,J=7,9Hz,1H); HRMS, calcd for $C_{13}H_{24}O$ (M^+): 196.1827; Found: 196.1828.

(+)-(4aS)-4,4a,5,6-Tetrahydro-1,4a-dimethyl-naphthalen-2(3H)-one (16)

A stirred solution of 12.2 g (55.9 mmol) of **15**[17] in a mixture of 170 mL of CH_2Cl_2 and MeOH (5:1) was cooled to -80°C and ozonized untill a pale blue colour appeared. The mixture was treated with 75 mL (795 mmol) of acetic anhydride, 75 mL (536 mmol) of Et_3N and 0.3 g of DMAP. The reaction mixture was allowed to come to 0°C and stirred for an additional 2 h. The solution was poured into 1 M HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and saturated aqueous $NaHCO_3$. The solvent was dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was dissolved in 50 mL of methanol, and 150 mL of 1 M $NaOCH_3$ was added. After stirring for 15 min the methanol was partly evaporated under reduced pressure, followed by the usual work-up procedure. The crude oil was purified by flash chromatography (petroleum ether-ethyl acetate, 96:4) to give 7.31 g (74%) of **16** as a colourless oil.

$[\alpha]_D$=+442° (c=3.1, $CHCl_3$); ^1H NMR: 1.03(s,3H); 1.73(s,3H); 1.4-1.9(m,2H); 2.1-2.7(m,6H); 6.15(m,1H); 6.39(m,1H); MS, *m/e* (rel intensity): 176(M^+,100), 161(65), 148(44), 134(53), 133(87), 119(63), 105(91), 91(69), 77(43), 41(42), 39(47); HRMS, calcd for $C_{12}H_{16}O$ (M^+): 176.1201; Found: 176.1204.

(+)-(4aS)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-naphthalen-2(3H)-one (17)

A solution of 2.5 g (14.1 mmol) of **16** in 15 mL of dry THF was added dropwise to a stirred solution of 16.5 mL (16.5 mmol) of L-selectride and 9.8 mL (77 mmol) of DMPU in 85 mL of dry THF at 0°C. After 5 h the temperature was raised to room temperature and stirring was continued for 2 h. Water was added and the reaction mixture was worked up as usual. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 98:2) to give 1.96 g (77%) of **17** as a colourless oil.

$[\alpha]_D$=+197° (c=2.2, $CHCl_3$); ^1H NMR: 1.10(s,3H); 1.64(s,3H); 1.1-2.1(m,9H); 2.2-2.7(m,3H); MS, *m/e* (rel intensity): 178(M^+,100), 163(77), 136(88), 135(55), 121(88), 107(57), 93(76), 91(49), 79(67), 77(46), 67(32), 55(35), 53(35), 41(73), 39(60); HRMS, calcd for $C_{12}H_{18}O$ (M^+): 178.1357; Found: 178.1356.

(+)-geosmin (9)

To a solution of 1.4 g (7.8 mmol) of **17** in 75 mL of CH_2Cl_2 was added 2.05 g (9.4 mmol) of m-CPBA. The reaction mixture was stirred overnight and water was added. After the usual work up procedure the residue was purified by flash chromatography (petroleum ether-ethyl acetate, 98:2) to give 1.17 g (76%) of **(-)-(1S,1R,4aS,8aR)-1,8a-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4a-dimethyl-naphthalen-2(3H)-one** as a colourless oil.

$[\alpha]_D$=-52° (c=2.1, $CHCl_3$); ^1H NMR: 0.97(s,3H); 1.30(s,3H); 1.05-1.25(m,1H); 1.3-2.5(m,11H); MS, *m/e* (rel intensity): 194(M^+,1), 176(22), 133(22), 109(93), 81(33), 67(60), 55(34), 43(100), 41(51), 39(37); HRMS, calcd for $C_{12}H_{18}O_2$ (M^+): 194.1307; Found: 194.1299.

A solution of 0.95 g (4.9 mmol) of the above obtained oil in 10 mL of methanol was added dropwise to a solution of 175 mg (4.6 mmol) of $NaBH_4$ in 20 mL of methanol. The reaction mixture was stirred at room temperature for 3 h, 0.5 ml of water was added. The methanol was partly evaporated in vacuo and water was added followed by the usual work-up procedure. The residue was purified by flash chromatography (petroleum ether-ethyl acetate, 80:20) to afford 0.85 g (88%) of a stereoisomeric mixture of **1,8a-epoxy-1,2,3,4,4a,5,6,7,8,8a-decahydro-1,4a-dimethyl-naphthalen-2-ol** as a colourless oil.

^1H NMR: 1.01(s,3H); 1.35(s,3H); 0.7-1.0(m,1H); 1.3-1.9(m,11H); 2.45(d,J=11Hz,1H); 3.71(dd,J=5,10Hz,1H); MS, *m/e* (rel intensity): 196(M^+,0.1), 112(100), 84(31), 67(28), 55(26), 43(70), 41(36); HRMS, calcd for $C_{12}H_{20}O_2$ (M^+): 196.1463; Found: 196.1465.

To an ice cold solution of 0.80 g (4.1 mmol) of the mixture of alcohols in 25 mL of chloroform was added 1.3 mL (16 mmol) of pyridine and 1.2 g (6.0 mmol) of p-toluenesulfonyl chloride. The reaction mixture was stirred overnight, and poured into water followed by the usual work up procedure. The crude oil was dissolved in 35 mL of dry THF and was added dropwise to a suspension of 0.26 g (6.8 mmol) of $LiAlH_4$ in 25 mL of dry THF. The reaction mixture was refluxed for 1.5 h, and after cooling to room temperature 0.45 mL of water and 0.45 mL of 4 M NaOH were added and stirring was continued for 30 min, followed by the usual work up. The residue was purified by flash chromatography (ether-pentane, 2:98) to give 0.37 g (60%) of **9** as a yellow oil.

$[\alpha]_D$=+15.5° (c=1.2, $CHCl_3$); Lit[7a]: $[\alpha]_D$=-16.5° ((-)-geosmin); .^{1}H NMR: 0.74(d,J=7Hz,3H); 0.99(s,3H); 1.16(s,1H); 0.9-1.8(m,15H); *m/e* (rel intensity): 182(M^+,4), 112(100), 69(22), 55(50), 43(58), 41(75), 39(33); HRMS, calcd for $C_{12}H_{22}O$ (M^+): 182.1670; Found: 182.1662.

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