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THE CONVERSION OF (-)- AND (+)-DIHYDROCARVONE INTO CHIRAL INTERMEDIATES FOR THE SYNTHESIS OF (-)-POLYGODIAL, (-)-WARBURGANAL AND (-)-MUZIGADIAL

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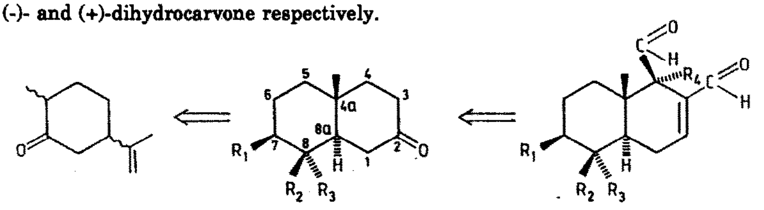
Abstract: (-)-Dihydrocarvone was converted into (-)-(4aR, 8aR)-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethylnaphthalene-2(H)-one (1) via an efficient route in which a Wolff-Kishner reduction, accompanied with a double bond isomerisation brought on a major simplification. Ketone **1** is a suitable intermediate for the syntheses of the insectantifeedants (-)-polygodial and (-)-warburganal. (+)-Dihydrocarvone was converted into (+)-(4aR, 7S, 8aR)-4a,7-dimethyl-8-methylene-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2(1H)-one (2), an intermediate ketone for the synthesis of (-)-muzigadial.

Recently we described the conversion of the racemic decalones **1** and **2** into the racemic insect antifeedants polygodial **3**, warburganal **4** and muzigadial **5**[1]. There is however a strong necessity for the production of nonracemic drimane insectantifeedants because of the possible phytotoxic effects of the unnatural enantiomers[2]. Several syntheses of natural (-)-polygodial and (-)-warburganal starting from natural products[3] or from (S)-2,2-dimethyl-3-hydroxycyclohexanone[4] have been reported but there is still a need for syntheses of these compounds starting from commercially available chiral starting materials. Besides non of the reported routes can be applied easily for the synthesis of natural (-)-muzigadial. Therefore we now report on two routes for the syntheses of the chiral decalones **1** and **2** starting from (-)- and (+)-dihydrocarvone respectively.



(-) or (+)-
dihydrocarvone

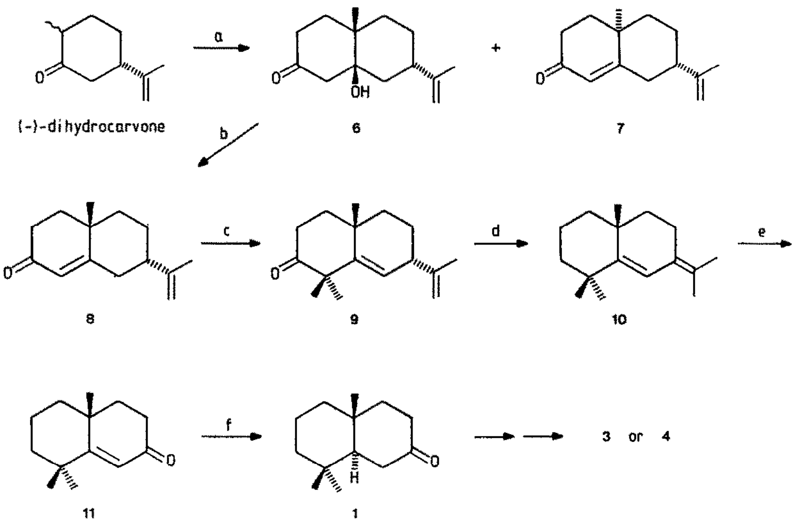
1 . R_1 = H, $R_2 = R_3 = CH_3$
2 . $R_1 = CH_3$; $R_2 = R_3 = CH_2$

3 . $R_1 = R_4$ = H ; $R_2 = R_3 = CH_3$
4 . R_1 = H ; $R_2 = R_3 = CH_3$; R_4=OH
5 . $R_1 = CH_3$; $R_2 = R_3 = CH_2$; R_4=O

Both enantiomers of carvone and dihydrocarvone have been widely used in the enantiospecific synthesis of many sesquiterpenes[5]. In some cases the isopropenyl group of (dihydro)carvone just served as a chiral handle which was removed, or converted into an useful functional group, at a suitable stage in the total synthesis[6]. This strategy was used also in the conversion of (-)- and (+)-dihydrocarvone into the chiral decalones **1** and **2** respectively.

(-)-Dihydrocarvone was converted into (-)-ketone **1** starting with a conventional Robinson annelation[7] (scheme 1). The ketol **6** could be isolated easily using a procedure in which dehydration of this intermediate was prevented. This could be accomplished by performing the reaction with KOH as catalyst at 0° in ether/ethanol as solvent, using a relatively short reaction time of one to two hours. After work up the residu was subjected to Kugelrohr distillation which gave a 25% recovery of (-)-dihydrocarvone and a 72% yield of a mixture of ketol **6** and enone **7**. The ketol **6** could be isolated from this mixture in a total yield of 55% via crystallisation from hexane followed by column chromatography of the mother liquor. The ketol **6** could be separated easily by chromatography from the enone **7** which was eluted first in 17% yield. Longer reaction times and higher reaction temperatures resulted in dehydration of ketol **6** to enone **8** which could be separated from enone **7** with difficulty.

scheme 1



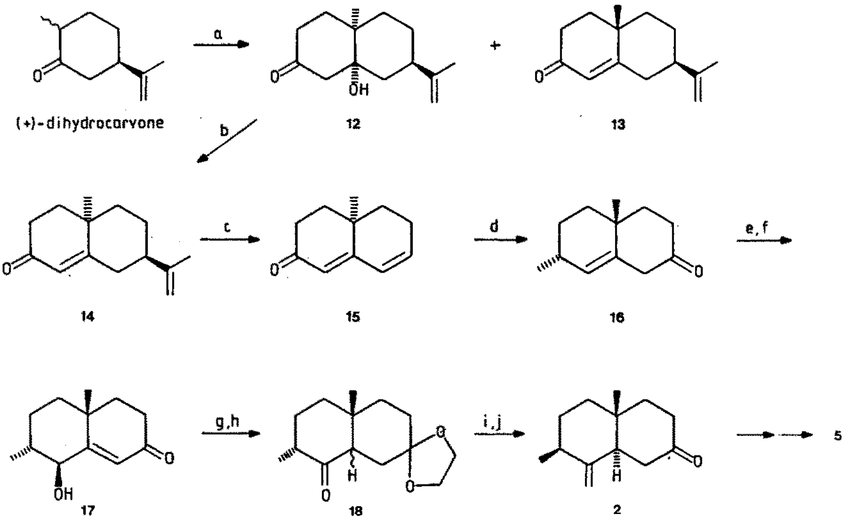
a. MVK, KOH, 0°C ; b. KOH, CH_3OH, Δ ; c. CH_3I, KOtBu ; d. $H_2N—NH_2$, KOH, 200 °C ; e. O_3 ; f. Li, NH_3.

Ketol **6** could be dehydrated[7] and methylated[8] following standard procedures to give **9**. When this ketone **9** was submitted to a Wolff-Kishner reduction, a complete isomerisation of the olefinic bond from the isopropenyl sidechain to the conjugated exocyclic position was observed as an accompanying reaction. Since selective ozonolysis of this exocyclic double bond proved possible in good yield, this sequence thus provided a short route for the conversion of the former chiral handle into the desired carbonyl group at C-2. Lithium-ammonia reduction of the double bond then gave the (-)-ketone **1** which can be converted into (-)-polygodial or (-)-warburganal as described[1].

(+)-Ketone **2**, the starting material for the synthesis of (-)-muzigadial[1], was obtained as depicted in scheme 2. In order to obtain the desired R-configuration at C-4a in this ketone **2**, the ketol **12** had to have the R-configuration at C-4a which required the use of (+)-dihydrocarvone as starting material for the Robinson annelation.

Enone **14** was obtained from (+)-dihydrocarvone as described for its enantiomer **8**. The isopropenyl group in **14** was removed by ozonolysis in methanol followed by decomposition of the ozonide with Cu^{++} and Fe^{++} salts[9] to give the dienone **15**. Conjugate addition of $(CH_3)_2CuLi$ gave the deconjugated enone **16** with the methyl groups in the transposition, the C-7 epimer was formed in trace amounts. Enone **16** was converted into its dienol acetate which was oxidized with oxone ^{R} to the known unsaturated ketol **17**[10]. The isomerisation and selective protection of **17** to **18** followed by epimerisation, Wittig reaction and hydrolysis then gave (+)-ketone **2** as described[10], thus providing the chiral starting material for the synthesis of (-)-muzigadial[1].

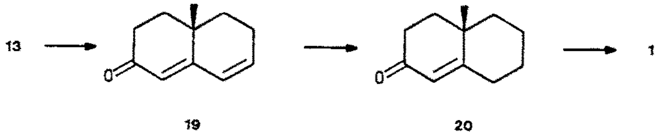
scheme 2



a. MVK, KOH, 0°C ; b. KOH, CH_3OH, Δ ; c. O_3, Cu^{++}, Fe^{++} ; d. $(CH_3)_2CuLi$; e. Ac_2O, TsOH ; f. oxone ; g. HBr, $(C_2H_5)_2O$; h. $H^{\oplus}$, $(HOCH_2)_2$; i. Φ_3PCH_2 ; j. $H^{\oplus}$, H_2O.

The enone **13**, obtained as a byproduct in the Robinson annelation of (+)-dihydrocarvone, could be converted into the dienone **19** by ozonolysis as described for its epimer **14** (scheme 3). Selective 1,6 reduction with Li-selectride gave the enone **20** in 86% yield. The conversion of **20** into ketone **1** is standard chemistry.

scheme 3



The number of steps and the overall yields in the syntheses of the chiral ketones **1** and **2** from (-)- and (+)-dihydrocarvone are comparable with those of the syntheses of racemic **1** and **2** starting from 2-methylcyclohexanone or 2,5-dimethylcyclohexanone respectively.

EXPERIMENTAL PART

Boiling points and melting points are uncorrected. Routine ^1H NMR spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale). $CDCl_3$ was used as solvent unless stated otherwise. Mass spectral data and high resolution mass measurements were obtained using an AEI-MS-902 spectrometer. Elemental analyses were carried out using a Carlo Erba Elemental Analyser 1106. Optical rotations were measured on a Bellingham and Stanley polarimeter.

Aqueous solutions were usually extracted three times with ether. The combined ethereal extracts were dried on magnesium sulfate prior to filtration and evaporation of the solvent under reduced pressure. Flash chromatography was performed on silica gel (230-400 mesh). The petroleum ether used as eluens had a boiling range of 40-60°C.

(-)-(4aS, 7S, 8aS)-8a-Hydroxy-7-isopropenyl-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2(1H)-one (6)

Methyl vinyl ketone (8.12 g, 116 mmol) in 100 ml of ether was added over a period of 1h to a mixture of (-)-dihydrocarvone (15.2 g, 100 mmol) in 150 ml of ether and KOH (2.24 g, 40 mmol) in 10 ml of ethanol at 0°C. After the addition was complete, stirring was continued for 1h. The reaction mixture was washed with water and with brine and the ethereal solution was dried. The ether was evaporated and the residu was submitted to Kugelrohr distillation which gave 3.8 g (25%) of recovered (-)-dihydrocarvone and 15.6 g of a mixture of **6** and enone **7**. The mixture of **6** and **7** solidified and was recrystallized from hexane to yield 7.7 g (35%) of pure **6**. Flash chromatography (petroleum ether-ether, 1:1) of the mother liquor first yielded 3.5 g (17%) of enone **7** as a yellow oil. Further elution with petroleum ether-ether 1:3 gave another crop of 4.4 g (20%) of ketol **6** as a white crystalline solid, mp 109°C, $[\alpha]_D$ -51.9 (c=1.0 in $CHCl_3$).

The enantiomer **12** was prepared following the same procedure, starting from (+)-dihydrocarvone. It was obtained in 55% yield as a white crystalline solid, mp 109°C, $[\alpha]_D$ + 55.3 (c=1.7 in $CHCl_3$).

(-)-(4aR, 7S)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methylnaphthalene-2(3H)-one (7)

This enone **7** was obtained as described above as a yellow oil in 17% yield, $[\alpha]_D$ -79 (c=1.2 in $CHCl_3$).

The enantiomer **13** was prepared following the same procedure, starting from (+)-dihydrocarvone. It was obtained in 15% yield as a yellow oil, $[\alpha]_D$ + 80.6 (c=1.8 in $CHCl_3$).

(+)-(4aS, 7S)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methylnaphthalene-2(3H)-one (8)

A solution of 18.3 g (82 mmol) of **6** and 8 g of KOH in 100 ml of ethanol was stirred overnight at room temperature. The mixture was diluted with water and extracted with ether (5x100 ml). The combined extracts were washed with water and brine, dried and evaporated. The residu was purified by Kugelrohr distillation at 0.4 torr. The 110-120°C-fraction was collected to give 14.5 g (87%) of **8** which solidified upon standing, mp 37-39°C.
^{1}H NMR δ 1.25 (s, 3H); 1.70 (s, 3H); 1.0-2.80 (m, 11H); 4.75 (s, 1H); 4.86 (s, 1H); 5.80 (s, 1H).
HRMS: Calcd (M^+) m/e 204.1514, found m/e 204.1519
$[\alpha]_D$ + 180.1 (c=1.2 in $CHCl_3$).

(-)-(4aS, 7S)-3,4,4a,5,6,7-Hexahydro-7-isopropenyl-1,1,4a-trimethylnaphthalene-2(1H)-one (9)

To a solution of 16.4 g (146 mmol) of potassium *tert*-butoxide in 270 ml of *tert*-butylalcohol was added a solution of 13.5 g (66 mmol) of enone **8** in 100 ml of *tert*-butyl alcohol at room temperature under nitrogen. The reaction mixture was stirred for 30 min and then iodomethane (12.4 ml, 200 mmol) was added. The reaction mixture was stirred for 3 h at room temperature and then poured into water. The water solution was extracted with ether (5 x 200 ml) and the combined ethereal extracts were washed with brine and dried. The solvents were evaporated and the residu was distilled in a Kugelrohr at 0.6 torr. The fraction from 110-120°C was collected to yield 14.4 g (93%) of **9** as a colourless oil[6a].
^{1}H NMR δ 0.97 (s, 3H); 1.23 (s, 3H); 1.26 (s, 3H); 1.0-2.8 (m, 12H), 4.63 (br s, 1H); 4.84 (br s. 1H), 5.50 (d, J = 4.5 Hz, 1H).
HRMS: Calcd (M^+) m/e 232.1827, found m/e 232.1830
$[\alpha]_D$ -65.5 (c=1.0 in $CHCl_3$).

(-)-(4aR)-2-Isopropylidene-2,3,4,4a,5,6,7,8-octahydro-4a,8,8-trimethylnaphthalene (10).

To a solution of 5.2 g (104 mmol) of hydrazine hydrate and 5.2 g (92 mmol) of KOH in 50 ml of diethylene glycol was added 6.7 g (29 mmol) of ketone **9**. The reaction mixture was heated for 3 h at 120°C and then the excess of hydrazine hydrate and water was removed by distillation. The reaction temperature was raised to 210°C and heated for 2 h. After cooling the reaction mixture was poured into water and extracted with ether (3 x 100 ml). The ethereal solution was washed with brine and dried on $CaCl_2$. The ether was evaporated and the residu was purified by flash chromatography (petroleum ether). A yield of 4.3 g (70%) of diene **10** was obtained as a colourless oil.
^{1}H NMR δ 1.17 (br s, 9H); 1.73 (s, 3H); 1.82 (s, 3H); 1.2-1.7 (m, 7H); 2.1-2.5 (m, 3H); 6.33 (s, 1H).
HRMS: Calcd (M^+) m/e 218.2034, found m/e 218.2033
$[\alpha]_D$ -70.6 (c=1.0 in $CHCl_3$).

(-)-(4aR)-4,4a,5,6,7,8-Hexahydro-4a,8,8-trimethylnaphthalene-2(3H)-one (11).

A solution of 5.0 g (23 mmol) of **10** in 200 ml of methanol was ozonolyzed at -80°C and the reaction was monitored using gas chromatography. The ozonolysis was continued untill all the starting material was consumed. The ozonides were reduced by introducing 2 g of dimethylsulfide at -80°C. The reactionmixture was stirred for 3 h and the temperature was raised to room temperature. Then the volatile products were evaporated and the residu was purified by flash chromatography (petroleum ether-ether 85:15). A yield of 3.44 g (78%) of **11**, was obtained as a yellow oil.
^{1}H NMR δ 1.13 (s, 3H); 1.20 (s, 3H); 1.33 (0,3H); 1.4-2.0 (m, 8H); 2.3-2.7 (m, 2H); 5.97 (s, 1H).
HRMS: Calcd (M^+) m/e 192.1514, found m/e 192.1517.
$[\alpha]_D$ -105° (c=1.0 in $CHCl_3$).

(-)-(4aR, 8aR)-3,4,4a,5,6,7,8,8a-Octahydro-4a,8,8-trimethylnaphthalene-2(1H)-one (1).

A solution of 1.88 g (9.8 mmol) of **11** and 7.8 g (105 mmol) of *tert* butyl alcohol in 25 ml of dry ether was added to a solution of 0.31 g (45 mmol) of lithium in 100 ml of liquid ammonia. The excess of lithium was destroyed with solid ammonium chloride and the ammonia was evaporated. The residu was dissolved in a water-ether mixture and the water solution was extracted three times with ether. The combined ethereal extracts were washed with brine and dried. The ether was evaporated and the residu was purified by flash chromatography (petroleum ether-ether 85:15). A yield of 1.72 g (90%) of **1** was obtained as white crystals, mp 39°C.
^{1}H NMR δ 0.87 (s, 6H); 1.13 (s, 3H); 1.20-1.80 (m, 9H); 2.10-2.60 (m, 4H).
HRMS: Calcd (M^+) m/e 194.1671, found m/e 194.1670.
$[\alpha]_D$ -12.8 (c=1.0 in $CHCl_3$).

(-)(4aR, 7R)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methylnaphthalene-2(3H)-one (14).

A solution of 2.22 g (10 mmol) of **12** in 25 ml of ethanol was treated at refluxtemperature with 10 ml of a 1.4 molar KOH solution in ethanol. After 1 h the reaction mixture was poured into 100 ml of water and extracted with 5 portions of ether. The combined ethereal extracts were washed with brine and dried. The solvent was evaporated and the residu was purified by column chromatography (petroleum ether-ether 90:10). This afforded 1.85 g (91%) of **14** as a light yellow oil.

^{1}H NMR δ 1.30 (s, 3H); 1.73 (s, 3H); 1.30-2.00 (m, 6H); 2.30-2.60 (m, 5H); 4.77 (s, 1H); 4.87 (s, 1H); 5.82 (s, 1H).
HRMS Calcd (M^+) m/e 204.1514, found m/e 204.1515.
$[\alpha]_D$ -177 (c=2.1 in $CHCl_3$).

(-)-(4aR)-4a-Methyl-4,4a,5,6-tetrahydronaphthalene-2(3H)-one (15).

A solution of 6.12 g (30 mmol) of **14** in 150 ml of methanol was cooled to -80°C. Ozone was introduced till the colour of the solution was very light blue. The excess of ozone was expelled by N_2 and then 12.0 g (60 mmol) of copper(II) acetate monohydrate and 8.34 g (30 mmol) of iron(II) sulfate heptahydrate were added. The resulting mixture was stirred overnight at room temperature and the methanol was evaporated. The residu was dissolved in 50 ml of water and 10 ml of 4 molar hydrochloric acid and this mixture was extracted with 5 portions of 100 ml of ether. The combined extracts were washed with brine and dried. The ether was evaporated and the residu was purified by flash chromatography (petroleum ether-ether 70:30). A yield of 3.42 g (67%) of **15** was obtained as a light yellow oil.
^{1}H NMR δ 1.16 (s, 3H); 1.50-2.00 (m, 4H); 2.30-2.65 (m, 4H); 5.66 (s, 1H); 6.16 (br s, 2H)
HRMS: Calcd (M^+) m/e 162.1045, found m/e 162.1043
$[\alpha]_D$ -476 (c=1.0 in $CHCl_3$).
^{13}C NMR δ 21.2 (q); 23.5 (t); 33.2 (s); 34.1 (t); 35.9 (t); 36.9 (t); 123.5 (d); 127.7 (d); 137.7 (d); 161.9 (s); 199.7 (s).

(+)-(4aR, 7R)-4a,7-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalene-2(1H)-one (16).

A solution of dimethylcopperlithium was prepared in dry ether by adding 15 ml of a 1.6 molar solution of methyllithium (24 mmol) in ether to a suspension of 2.29 g (12 mmol) of copper(I) iodide in ether at 0°C. After 15 min a solution of 1.84 g (12 mmol) of **15** in ether was added and the reaction mixture was stirred for 30 min. A saturated aqueous ammonium chloride solution was added and stirring was continued for 15 min. The reaction mixture was extracted with ether (3x100 ml) and dried. The ether was evaporated and the residu was purified by flash chromatography (petroleum ether-ether 90:10). A yield of 1.86 g (87%) of **16** was obtained as a yellow oil.
^{1}H NMR δ 0.92 (d, J=6Hz, 3H); 1.20 (s, 3H); 1.45-1.90 (m, 6H); 2.00-2.70 (m, 3H); 2.78 (dd, J=16, 2Hz, 1H); 3.22 (dt, J=16, 2 Hz, 1H); 5.26 (dd, J=3, 2 Hz, 1H)
HRMS: Calcd (M^+) m/e 178.1358, found m/e 178.1354.
^{13}C NMR δ 21.0 (q); 24.0 (q); 26.6 (t); 29.7 (d); 34.2 (s); 35.2 (t); 37.9 (t); 38.1 (t); 48.5 (t); 129.5 (d); 137.1 (s); 209.3 (s).
$[\alpha]_D$ + 42 (c=2.4 in $CHCl_3$).

(+)-(4aR, 7R, 8S)-4a,7-Dimethyl-4,4a,5,6,7,8-hexahydro-8-hydroxynaphthalene-2(3H)-one (17)

To a solution of 1.32 g (7.4 mmol) of **18** in 10 ml of acetic anhydride, a catalytic amount of p. toluenesulfonic acid was added. After 16 h the acetic anhydride was evaporated in vacuo and the residu was dissolved in ether. The ethereal solution was washed with sodium hydrogen carbonate and with brine and dried. The residu was purified by chromatography (petroleum ether-ether 9:1) to give 1.47 g (90%) of the dienol acetate, $[\alpha]_D$ + 261 (c=5.8 in $CHCl_3$). The spectral data were in agreement with the literature[10].

The dienol acetate was dissolved in methanol. Then 1.76 g (21 mmol) of solid sodium hydrogen carbonate was added. At 0°C 5.6 g (8.4 mmol) of oxone R was added. After stirring for 16 h the methanol was evaporated and the residu was dissolved in water and extracted with ether. The ether was evaporated and the residu was purified to afford 0.87 g (81%) of **17**.
^{1}H NMR δ 0.87 (d, J=6Hz, 3H); 1.42 (s, 3H); 1.10-2.85 (m, 10H); 3.30 (br. s, 1H); 3.97 (d, J=2Hz, 1H); 5.78 (s, 1H).
HRMS: Calcd (M^+) m/e 194.1307, found m/e 194.1311.

(+)-(4aR, 7S)-4a,7-Dimethyl-8-methylene-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2(1H)-one (2).

Ketone **2** was prepared from **17** in four steps using standard procedures[10]. Since mixtures of compounds were involved no optical rotations were measured for the intermediate compounds.
Ketone **2** was obtained in 65% overall yield from **17**, mp 65-66°C.
^{1}H NMR δ 0.92 (s, 3H); 1.10 (d, J=6Hz, 3H); 1.20-1.90 (m, 8H); 2.10-2.70 (m, 6H); 4.50 (br.s, 1H); 4.81 (br.s, 1H).
$[\alpha]_D$ + 72 (c=0.25 in $CHCl_3$) .

(+)-(4aS)-4a-Methyl-4,4a,5,6-tetrahydronaphthalene-2(3H)-one (19)

This dienone **19** was prepared from enone **13** as described for its enantiomer **15**. Dienone **19** was obtained in 55% yield as a light yellow oil, $[\alpha]_D$ + 187 (c=6.03 in $CHCl_3$).

(+)-(4aS)-4,4a,5,6,7,8-Hexahydro-4a-methylnaphthalene-2(3H)-one (20)

To a solution of 8.8 mmol of Li-selectride in 40 ml of THF and 8 ml of HMPA was added a solution of 1.30 g (8 mmol) of dienone **19** in 5 ml of THF at 0°C. The reaction mixture was stirred for 1 h at 0°C and then water was added. The layers were separated and the water solution was extracted with ether. The combined ethereal extracts were washed with brine and dried. The solvents were evaporated and the residu was purified by flash chromatography (petroleum ether-ether 3:1) to give 1.12 g (86%) of **20** as a yellow oil.
$[\alpha]_D$ + 202 (c=1.0 in $CHCl_3$).

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