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S-(+)-Carvone as Starting Material in Synthesis (Part 4)[1]. Conjugate Addition of Cyanide and Grignard Nucleophiles Followed by Annulation to Functionalized Decalones.

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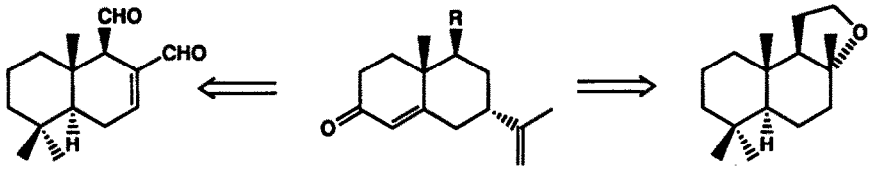
Abstract: Two conjugate addition/annulation methodologies for S-(+)-carvone are reported. The conjugate addition of Grignard reagents, followed by the Lewis acid catalyzed Michael reaction of the intermediate silyl enol ethers with MVK and cyclization of the diketones, gave decalones **2a-d** stereoselectively and in good yield. The conjugate addition of cyanide anion followed by base catalyzed Robinson annulation with MVK and dehydration gave decalone **2e** stereoselectively in very high yield.

S-(+)-Carvone (**1**) is an excellent, commercially available, chiral starting material in the synthesis of natural occurring compounds[2]. In earlier work we reported about the synthesis of chiral decalones from R-(-) and S-(+)-carvone starting with a Robinson annulation[1a,c] or with a Diels-Alder reaction[1b]. In this paper we report on the synthesis of more functionalized decalones **2** via two different conjugate addition-annulation methodologies. Dependent on the choice of the substituent R, the decalones **2** are potentially useful chirons for the synthesis of drimane sesquiterpenes like the insect antifeedant (-)-polygodial **3** and of the olfactive compound (-)-Ambrox® **4** (Scheme 1).

Scheme 1



3
(-)-polygodial

2

4
(-)-Ambrox®

The first approach to the decalones **2** was the conjugate addition of a few alkyl Grignard reagents to S-(+)-carvone (**1**), trapping of the intermediate enolates as their silyl enol ethers, followed by the Lewis acid catalyzed silyl enol ether variation of the Robinson annulation.

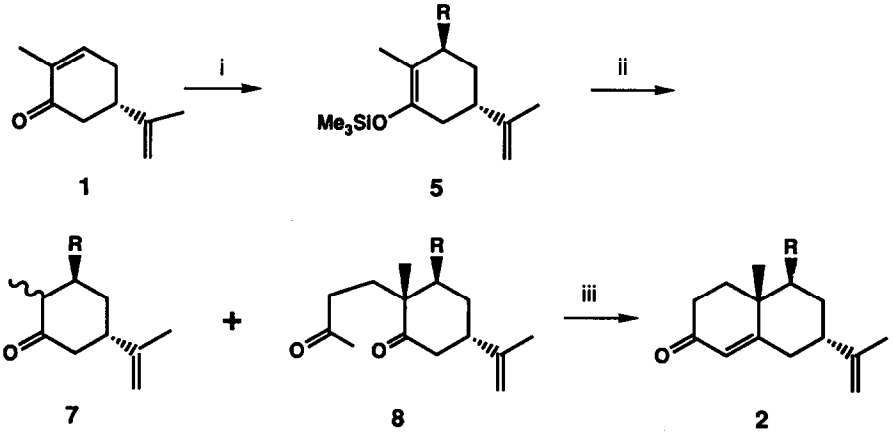
The second method was based on the 1,4-addition of nucleophiles like thiophenolate, alcoholate and

cyanide to S-(+)-carvone, followed by the base catalyzed Robinson annulation of these carvone derivatives.

From the literature it is known that the Robinson annulation of sterically hindered cyclohexanones, like 2,3-dialkylated cyclohexanones proceeds in low yield and with poor stereoselectivity under the normal basic conditions[3]. The acid-catalyzed Michael addition of methyl vinyl ketone, followed by cyclization of the intermediate diketones sometimes gives a considerable improvement of the Robinson annulation in yield and in stereoselectivity[4]. Although one step procedures for conjugate addition-*alkylation* are often successful[5], only a few examples of the tandem conjugate addition-*Michael reactions* are known[6], probably because the intermediate organocopper enolate requires a not commercially available α-trimethylsilyl ketone[7] as Michael acceptor, to avoid multiple addition and polymerization. Trapping of the intermediate enolates as their silyl enol ethers usually proceeds quite well[8] and therefore the Lewis acid catalyzed silyl enol ether variation of the Robinson annulation[9] seems to be the best option for the synthesis of decalones **2** from S-(+)-carvone **1** with alkyl groups as substituents.

The conjugate addition of methyl magnesium bromide and vinyl magnesium bromide to S-(+)-carvone **1** in the presence of a catalytic amount of cuprous bromide-dimethyl sulfide complex (CuBr.Me_2S), 2 equivalents of trimethylchlorosilane (TMSCl) and hexamethylphosphoric triamide (HMPA) at -40°C, afforded **5a** en **5b** in 86% and 80% yield respectively, with a diastereomeric excess (*de* = % major diastereomer - % minor diastereomer) for the *trans* isomer of 86% and 94% respectively. Allyl magnesium chloride yielded under the same reaction conditions solely the 1,2-addition product **6**[10] (figure 1). Addition to the carbonyl group was diminished by the use of a stoichiometric amount of the copper complex (CuBr.Me_2S) and by lowering of the temperature to -100 °C. Under these conditions silyl enol ether **5c** was obtained in 73% yield, with a *de* for the *trans* isomer of 88%, together with 7% of the 1,2 addition product **6.** The thermodynamic silyl enol ether **5d** was synthesized by heating a mixture of *trans* and *cis* (-)-dihydrocarvone **7d**, TMSCl, sodium iodide and triethylamine (Et_3N) in acetonitrile at 80 °C to give **5d** in 85% yield accompanied with 6% of the kinetic silyl enol ether.

Scheme 2



Reagents i: RMgX, Me_2S.CuBr, TMSCl, HMPA, THF, low temperature (see text); ii: MVK, $BF_3.Et_2O$, isopropanol, CH_2Cl_2, nitromethane, -65 °C; iii: NaOMe, MeOH.

The conditions of Duhamel[8a] for the formation of diketones from silyl enol ethers and MVK were applied to the silyl enol ethers **5**, but appreciable amounts of desilylated products **7** were obtained together with the diketones **8**. An adaptation of these conditions and a lowering of the temperature to -65 °C instead of -20 °C, improved the yield of the diketones **8** to 65-75% and the formation of the desilylated products **7** was diminished to 15-25% (Table 1, Scheme 2). The stereoselectivity for the alkyl substituted silyl enol ethers **5a-c** was excellent with *de* 's for the major diketones **8** of 92 - 94 %. The *de* for the hydrogen substituted silyl enol ether **5d** was only 40%. The diketones **8a-c** were easily cyclized by stirring the mixture for 20 hours in basic medium (0.2M sodium methoxide in methanol) to afford even better *de* 's for the decalones **2** after purification (Table 1) in agreement with a previous report[8a]. The mixture of diketones **8d** was stirred for a shorter period in basic medium (3 h) to afford hydroxyketone **9** and decalone **10** in 66% and 24% respectively.

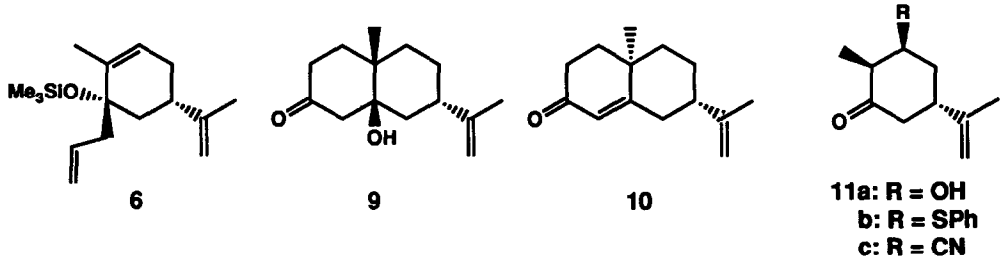
Table 1: Preparation of Decalones 2 from Silyl enol ethers 5

Silyl enol ether	Ketone 7 yield (%)[a]	Diketone 8 yield (%)[a]	*de* (%)	Decalone 2 yield (%)[b]	*de* (%)
5a (R=Me)	25	65	92[c]	87	98[c]
5b (R=vinyl)	23	65	94[c]	89	98[c]
5c (R=allyl)	15	75	92[c]	95	96[c]
5d (R=H)	19	70	40	90	[d]

a: from **5**; b: from **8**; c: besides the major isomer, 2 minor isomers were present in the mixture; d: hydroxyketone **9** and decalone **10** could be separated by column chromatography and were obtained pure (figure 1).

The overall yield of the products **9** and **10** from (-)-dihydrocarvone were in this case 39% and 14%, respectively. So the stereoselectivity and the yield of the Robinson annulation of (-)-dihydrocarvone **7d** was not improved by this Lewis acid catalyzed silyl enol ether variation[11] and the normal basic conditions gave better results in this case[1a]. The high stereoselectivity of the alkylated silyl enol ethers **5a-c** is probably caused by the steric effect of the alkyl substituent.

Figure 1



6 **9** **10** **11a: R = OH**
b: R = SPh
c: R = CN

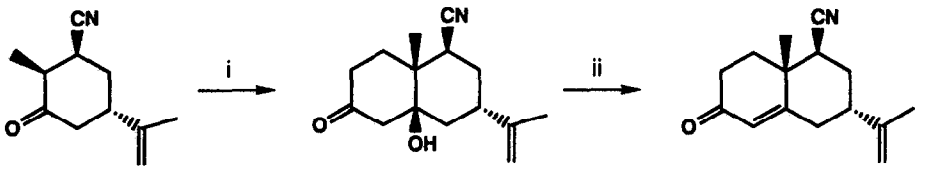
The preparation of decalones **2** with other substituents than alkyl groups can also lead to very useful intermediates. The silyl enol ether variation of the Robinson annulation was not suitable for **11a**[12], **11b**[13] and **11c**[14]. The silyl enol ethers of **11a** and **11b** could not be prepared in our hands and the silyl enol ether of **11c** gave in the Lewis acid catalyzed reaction mainly desilylation.

The base catalyzed Robinson annulation of **11a** and **11b** gave elimination of water and thiophenol, respectively and S-(+)-carvone was the only isolated product in both cases.

The base catalyzed Robinson annulation of 2,3-dialkylated cyclohexanones normally proceeds in a low yield and with poor stereoselectivity. To our surprise, the Robinson annulation of cyano ketone **11c** with MVK under basic conditions gave the Robinson annulation product **12** in high yield (90%) and with excellent stereoselectivity. This result was very encouraging for further research, especially because the adduct **12** crystallized from the reaction mixture and the starting cyano ketone **11c** could be obtained easily also in a crystalline state in 95% yield.

Some special remarks have to be made to enable the production of **11c** and **12** in an easy way and on a scale up to 100g or more. It proved to be important to use crystalline **11c** for the Robinson annulation; this stereoisomer crystallized directly out of the reaction mixture when *potassium* cyanide was used for the conjugate addition. Further purification of the adduct mostly was not necessary but could be done by crystallization from ethanol. The use of *sodium* cyanide for the conjugate addition reaction gave an emulsion and workup of the reaction mixture by extraction yielded an oily mixture which gave unsatisfactory results in the following annulation reaction. When crystalline **11c** was used for the Robinson annulation, the adduct **12** also crystallized from the reaction mixture and could be isolated simply by filtration. Refluxing of this hydroxyketone **12** with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in toluene afforded the cyano decalone **2e** in high yield (91%) (Scheme 3).

Scheme 3



11c **12** **2e**

Reagents i: MVK, NaOMe, MeOH; ii: *p*-TsOH, toluene, reflux.

The Robinson annulation of **11c** with MVK yielded exclusively the annulation product with the nitrile and angular methyl group in a *cis*-relationship. Consequently the nitrile group in **11c** had a strong stimulating and directing effect on the yield and the stereoselectivity in the base catalyzed Robinson annulation.

The multi functionalized cyano decalone **2e** is an excellent starting material for the synthesis of many terpenes and steroids. The conversion of decalones **2c** and **2e** into drimanes and into (-)-Ambrox® will be reported in the next publications.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were determined on a Bruker AC-E-200. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale) and in $CDCl_3$ as the solvent. Mass spectral data and HRMS measurements were obtained on a AEI MS 902 spectrometer. Elemental analyses were carried out using a Carlo Erba Elemental Analyser 1106. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at room temperature in chloroform as the solvent with the concentrations denoted in g/100ml. GLC analyses were carried out on a Fisons MEGA8000 chromatograph provided with a 30 m fused silica capillaire column (DB-5 MS). Organic extracts were dried on $MgSO_4$ prior to filtration and evaporation of the solvent under reduced pressure. Flash chromatography was performed on Merck silica gel (230 - 400 mesh). The petroleum ether (PE) used as eluent had a boiling range of 40-60 °C.

(3S,5S)-2,3-Dimethyl-5-isopropenyl-1-trimethylsilyloxy-cyclohex-1-ene (5a)

To a solution of 0.35 g of $CuBr.Me_2S$ (1.7 mmol) and 10 ml of HMPA (57 mmol) in 40 ml of THF was added dropwise, 15 ml of a 3 M methyl magnesium bromide solution in diethyl ether under a nitrogen atmosphere at -40 °C. After 10 min, 4.00 g of S-(+)-carvone (**1**) (26.7 mmol) and 6.68 ml of TMSCl (53 mmol) were added. After stirring for 1h at -40 °C, 5.05 g of Et_3N (50 mmol) was added, followed by 50 ml of water. The mixture was extracted 3 times with ether. The combined organic layers were washed with water, dried and evaporated. The residue was purified by flash chromatography on silica gel with PE as the eluent to give 5.46 g of silyl enol ether **5a** as a colourless oil (22.9 mmol, 86%) as a 93/7 *trans/cis* mixture according to GLC.

^1H NMR: δ 0.15 (s, 9H); 1.02 (d, J = 7.0 Hz, 3H); 1.72 (s, 3H); 1.4 - 2.5 (m, 9 H); 4.70 (bs, 2H). ^{13}C NMR: δ 0.5 (q*3); 14.4 (q); 19.4 (q); 20.5 (q); 33.3 (d); 34.9 (t); 35.5 (t); 36.9 (d); 108.4 (t); 115.7 (s); 142.2 (s); 149.1 (s). HRMS: calcd (M^+) *m/e* 238.1753 ; found *m/e* 238.1750. $[\alpha]_D$ = -72.4 (c = 0.6).

(3R,5S)- 5-Isopropenyl-2-methyl-1-trimethylsilyloxy-3-vinylcyclohex-1-ene (5b)

To a solution of 0.34 g of $CuBr.Me_2S$ (1.7 mmol) and 11.6 ml of HMPA (67 mmol) in 30 ml of THF was added dropwise 50 ml of a 1 M vinyl magnesium bromide solution in THF under a nitrogen atmosphere at -40 °C. After 30 min at -40 °C, a mixture of 5.0 g of S-(+)-carvone (**1**) (33.3 mmol) and 8.45 ml of TMSCl (67 mmol) was added in 25 ml of THF. After 30 min 6.77 g of Et_3N (67 mmol) was added, followed by 50 ml of water. The mixture was extracted 3 times with ether. The combined organic layers were washed with water, dried and evaporated. The residue was purified by flash chromatography on silica gel with PE as the eluent to give 6.70 g of silyl enol ether **5b** as a colourless oil (26.8 mmol, 80%) as a 97/3 *trans-cis* mixture according to GLC.

^1H NMR: δ 0.17 (s, 9H); 1.53 (s, 3H); 1.70 (s, 3H); 1.4 - 1.7 (m, 2H); 1.96 - 2.05 (m, 2H); 2.35 (septet, J = 5.3 Hz, 1H); 2.71 (m, 1H); 4.69 (bs, 2H);4.97 (t, J = 12.3 Hz, 2H); 5.76 (m, 1H). ^{13}C NMR: δ 0.5 (q*3); 14.8 (q); 20.5 (q); 33.1 (t); 35.3 (t); 36.8 (d); 43.3 (d); 108.6 (t); 112.0 (s); 114.4 (t); 140.9 (d); 144.1 (s); 148.9 (s). HRMS: calcd (M^+) *m/e* 250.1753; found *m/e* 250.1753. $[\alpha]_D$ = -186 (c = 0.3).

(3S,5S)-5-Isopropenyl-2-methyl-3-(prop-2'-enyl)-1-trimethylsilyloxy-cyclohex-1-ene (5c)

To a solution of 11.0 g of $CuBr.Me_2S$ (53.5 mmol) in 100 ml of THF was added under an nitrogen atmosphere 25 ml of a 2 M solution of allyl magnesiumchloride in THF at -100 °C. After 15 min at -100 °C a

mixture of 5.0 g of S-(+)-carvone (**1**) (33.3 mmol) and 8.45 ml of TMSCl (67 mmol) in 25 ml of THF was added dropwise in 30 min. After 1.5 h 5.97 g of HMPA (33.3 mmol) and 6.73 g (67 mmol) of Et_3N were added. Water was added and the mixture was extracted 3 times with PE. The combined organic layers were washed with water, dried and evaporated. The residue was purified by flash chromatography on silica gel with PE as the eluent to give first 0.59 g of the 1,2-addition product **6** (2.2 mmol, 7%) as a colourless oil, followed by 6.42 g of the 1,4 addition product **5c** as a 94/6 *trans/cis* mixture according to GLC (24.3 mmol, 73%).
5c: ^{1}H NMR: δ 0.18 (s, 9H); 1.58 (s, 3H); 1.70 (s, 3H); 1.2 - 1.4 (m, 1H); 1.5 - 2.5 (m, 7H); 4.69 (bs, 2H); 4.95 (s, 1H); 5.01 (d, J = 9 Hz, 1H); 5.65 - 5.90 (m, 1H). ^{13}C NMR: δ 0.5 (q*3); 14.6 (q); 20.6 (q); 30.6 (t); 35.2 (t); 36.7 (d); 37.2 (t); 38.6 (d); 108.4 (t); 114.3 (s); 115.5 (t); 137.9(d); 143.2 (s); 149.0 (s). HRMS: calcd (M^+) *m/e* 264.1909 ; found *m/e* 264.1909. $[\alpha]_D$ = -43.5 (c = 0.5).
6: ^{1}H NMR: δ 0.08 (s, 9H); 1.67 (s, 3H); 1.69 (s, 3H); 1.46 - 2.47 (m, 7H); 4.67 - 4.69 (m, 2H); 4.95 - 5.06 (m, 2H); 5.36 - 5.39 (m, 1H); 5.75 - 5.96 (m, 1H). ^{13}C NMR: δ 1.9 (q*3); 17.2 (q); 20.4 (q); 30.7 (t); 39.3 (d); 40.4 (t); 44.5 (t); 108.4 (t); 116.5 (t); 122.3 (d); 135.1 (d); 139.2 (s); 148.9 (s). HRMS: calcd (M^+-15) *m/e* 249.1674; found *m/e* 249.1673. $[\alpha]_D$ = + 63.3 (c = 1.0).

(5S)-5-Isopropenyl-2-methyl-1-trimethylsilyloxy-cyclohex-1-ene (5d)
To 1.70 g of a mixture of isomers of (-)-dihydrocarvone (11.2 mmol) in 50 ml of acetonitrile was added 2.02 g of triethylamine (20 mmol), 2.16 g of trimethyl silyl chloride (20 mmol) and 3.00 g of sodium iodide (20 mmol). The mixture was heated to 80 °C and stirred for 4 h. Water was added and the reaction mixture was extracted 3 times with PE and the combined organic layers were washed with water, dried and evaporated. Flash chromatography with PE as the eluent gave 2.12 g (9.5 mmol, 85%) of silylenolethers **5d** as a 94/6 *thermodynamic/kinetic* mixture as a colourless oil.
^{1}H NMR: δ 0.15 (s, 9H); 1.54 (s, 3H); 1.70 (s, 3H); 1.2 - 2.3 (m, 7H); 4.70 (bs, 2H). ^{13}C NMR: δ 0.5 (q*3); 15.9 (q); 20.5 (q); 27.7 (t); 29.8 (t); 35.3 (t); 42.2 (d); 108.4 (t); 111.1 (s); 142.0 (s); 149.1 (s). HRMS: calcd (M^+) *m/e* 224.1596 ; found *m/e* 224.1595. $[\alpha]_D$ = -73.4 (c = 0.4).

General procedure for the synthesis of the diketones 8.
Silyl enol ether **5** was dissolved in CH_2Cl_2 (1mmol/ml) with 2 equivalents of nitromethane under a nitrogen atmosphere. The solution was cooled to -78 °C and 2 equivalents of MVK and isopropanol were added. After 30 minutes 1 equivalent of $BF_3.Et_2O$ was added dropwise. The temperature was raised to -65 °C and the mixture was stirred for 2 h. A saturated $NaHCO_3$ solution was added and the aqueous layer was extracted 3 times with CH_2Cl_2. The organic layers were washed with water, dried and evaporated. Flash chromatography of the residue with EtOAc/PE = 1/10 as the eluent gave first an epimeric mixture of desilylated products **7**, followed by the diketones **8**.

(2R,3S,5S) and (2S,3S,5S)-2,3-Dimethyl-5-isopropenylcyclohexanone as a mixture of C2-epimers (7a)
^{1}H NMR: major signals of the major epimer: δ 0.79 (d, J = 7.3 Hz, 3H); 1.70 (s, 3H); 4.70 (s, 1H); 4.73 (s, 1H). ^{1}H NMR: major signals of the minor epimer: δ 0.95 (d, J = 6.8 Hz, 3H); 1.70 (s, 3H); 4.68 (s, 1H); 4.79 (s, 1H). HRMS: calcd (M^+) *m/e* 166.1358 ; found *m/e* 166.1354.

(2R,3S,5S)-2,3-Dimethyl-5-isopropenyl-2-(3-oxobutyl)-cyclohexanone (8a)
^{1}H NMR: δ 0.85 (d, J = 7.1 Hz, 3H); 0.91 (s, 3H); 1.68 (s, 3H); 2.08 (s, 3H); 1.4 - 2.7 (m, 10H); 4.65 (s, 1H); 4.75 (s, 1H). ^{13}C NMR: δ 15.9 (q); 18.5 (q); 20.8 (q); 29.8 (q); 30.3 (t); 32.3 (t); 36.5 (d); 38.2 (t); 40.2 (d); 42.5 (t); 50.8 (s); 110.3 (t); 147.1 (s); 208.0(s); 215.3 (s) . HRMS: calcd (M^+) *m/e* 236.1776 ; found *m/e* 236.1776 $[\alpha]_D = -38.3$ (c = 0.3).

(2R,3R,5S) and (2S,3R,5S)-5-Isopropenyl-2-methyl-3-vinylcyclohexanone as a mixture of C2-epimers (7b)
^{1}H NMR: major signals of the major epimer: δ 0.91 (d, J = 6.7 Hz, 3H); 1.68 (s, 3H); 4.68 (s, 1H); 4.73 (s, 1H); 4.94 - 5.07 (m, 2H); 5.46 - 5.64 (m, 1H). ^{1}H NMR: major signals of the minor epimer: δ 0.99 (d, J = 6.2 Hz, 3H); 1.68 (s, 3H); 4.64 (s, 1H); 4.81 (s, 1H); 4.94 - 5.07 (m, 2H); 5.46 - 5.64 (m, 1H). HRMS: calcd (M^+) *m/e* 178.1358; found *m/e* 178.1355.

(2R,3R,5S)-5-Isopropenyl-2-methyl-2-(3-oxobutyl)-3-vinylcyclohexanone (8b)
^{1}H NMR: δ 0.90 (s, 3H); 1.67 (s, 3H); 2.07 (s, 3H); 1.6 - 2.7 (m, 10H); 4.64 (s, 1H); 4.77 (s, 1H); 4.96 (m, 1H); 5.02 (s, 1H); 5.57 - 5.75 (m, 1H). ^{13}C NMR: δ 19.5 (q); 20.8 (q); 29.7 (q); 30.3 (t); 31.0 (t);38.0 (t); 40.4 (d); 42.3 (t); 47.3(d); 49.8 (s); 110.6 (t); 116.4 (t); 137.5 (d); 146.8 (s); 207.8 (s); 214.6 (s). HRMS: calcd (M^+) *m/e* 248.1776 ; found *m/e* 248.1779. $[\alpha]_D = -38.1$ (c = 0.4).

(2R,3S,5S) and (2S,3S,5S)-5-Isopropenyl-2-methyl-3-(prop-2'-enyl)cyclohexanone as a mixture of C2-epimers (7c)
^{1}H NMR: major signals of the major epimer: δ 0.99 (d, J = 6.8 Hz, 3H); 1.69 (s, 3H); 4.68 (s, 1H); 4.73 (s, 1H); 4.95 - 5.06 (m, 2H); 5.54 - 5.80 (m, 1H). ^{1}H NMR: major signals of the minor epimer: δ 1.09 (d, J = 6.7 Hz, 3H); 1.69 (s, 3H); 4.65 (s, 1H); 4.78 (s, 1H); 4.95 - 5.06 (m, 2H); 5.54 - 5.80 (m, 1H). HRMS: calcd (M^+) *m/e* 192.1514; found *m/e* 192.1514.

(2R,3S,5S)-5-Isopropenyl-2-methyl-2-(3-oxobutyl)-3-(prop-2'-enyl)cyclohexanone (8c)
^{1}H NMR: δ 0.96 (s, 3H); 1.68 (s, 3H); 2.10 (s, 3H); 1.6 - 2.7 (m, 12H); 4.64 (s, 1H); 4.77 (s, 1H); 4.95 (m, 1H); 5.02 (s, 1H); 5.65 - 5.70 (m, 1H). ^{13}C NMR: δ 18.8 (q); 20.9 (q); 27.6 (t); 29.8 (q); 29.9 (t); 33.2 (t); 38.1 (t); 39.6 (d); 40.6 (d); 42.3 (t); 50.9 (s); 110.5 (t); 116.2 (t); 136.6 (d); 147.0 (s); 208.3 (s); 215.3 (s). HRMS: calcd (M^+) *m/e* 262.1932 ; found *m/e* 262.1932. $[\alpha]_D = -62.2$ (c = 0.2).

(2R,5S) and (2S,5S)-5-Isopropenyl-2-methyl-2-(3-oxobutyl)cyclohexanone as a mixture of C2-epimers (8d)
^{1}H NMR: major signals of the major epimer: δ 0.96 (s, 3H); 1.69 (s, 3H); 2.08 (s, 3H); 4.67 (s, 1H); 4.72 (s, 1H). ^{1}H NMR: major signals of the minor epimer: δ 1.09 (s, 3H); 1.69 (s, 3H); 2.11 (s, 3H); 4.67 (s, 1H); 4.72 (s, 1H).

General procedure for the cyclisation of the diketones 8 to the decalones 2
The diketones **8** were dissolved into a 0.2 M solution of NaOMe in methanol and the mixture was stirred for 20 h at room temperature. Water was added and the mixture was extracted 3 times with ether. The combined

organic layers were washed with water, dried and evaporated. The residue was flash chromatographed with EtOAC/PE =1/10 as the eluent to give the cyclisation products **2** as colourless oils.

(4aR,5S,7S)-4a,5-Dimethyl-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-naphthalene-2(3H)-one (2a)
^{1}H NMR: δ 0.82 (d, J = 6.6 Hz, 3H); 1.08 (s, 3H); 1.66 (s, 3H); 1.4 - 2.7 (m, 10H); 4.70 (s, 1H); 4.80 (s, 1H); 5.76 (s, 1H). ^{13}C NMR: δ 14.8 (q); 15.7 (q); 22.5 (q); 32.0 (t); 33.8 (t); 35.1 (d); 35.2 (t); 36.0 (t); 38.6 (s); 39.5 (d); 111.9 (t); 125.2 (d); 146.8 (s); 170.8 (s); 199.0 (s). HRMS: calcd (M^+) *m/e* 218.1671 ; found *m/e* 218.1677. $[\alpha]_D$ = +155 (c = 0.4).

(4aR,5R,7S)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methyl-5-vinylnaphthalene-2(3H)-one (2b)
^{1}H NMR: δ 1.14 (s, 3H); 1.68 (s, 3H); 1.6 - 2.8 (m, 10H); 4.74 (s, 1H); 4.85 (s, 1H); 4.99 (dd, J = 10.7 Hz, J = 2.0 Hz, 1H); 5.07 (d, J = 1.8 Hz, 1H); 5.64 - 5.82 (m, 1H); 5.79 (s, 1H). ^{13}C NMR: δ 16.9 (q); 22.4 (q); 29.2 (t); 33.7 (t); 35.5 (t); 35.6 (t); 38.3 (s); 39.1 (d); 46.4 (d); 112.3 (t); 116.5 (t); 125.6 (d); 137.4 (d); 146.4 (s); 169.7 (s); 198.9 (s). HRMS: calcd (M^+) *m/e* 230.1668 ; found *m/e* 230.1668. $[\alpha]_D$ = +54.7 (c = 0.3).

(4aR,5S,7S)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methyl-5-(prop-2'-enyl)-naphthalene-2(3H)-one (2c)
^{1}H NMR: δ 1.11 (s, 3H); 1.65 (s, 3H); 1.2 - 2.7 (m, 12H); 4.69 (s, 1H); 4.81 (s, 1H); 4.96 (m, 1H); 5.03 (s, 1H); 5.69 (m, 1H); 5.80 (s, 1H). ^{13}C NMR: δ 16.5 (q); 22.3 (q); 28.2 (t); 33.3 (t); 33.7 (t); 35.0 (t); 36.0 (t); 38.7 (s); 39.3 (d); 41.3 (d); 112.1 (t); 116.2 (t); 125.6 (d); 137.2 (d); 146.3 (s); 170.4 (s); 199.0 (s). HRMS: calcd (M^+) *m/e* 244.1827; found *m/e* 244.1830 $[\alpha]_D$ = +74.0 (c = 0.3).

(4aS,7S,8aS)-8a-Hydroxy-7-isopropenyl-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2(1H)-one (9)
^{1}H NMR: δ 1.16 (s, 3H); 1.64 (s, 3H); 1.3 - 2.9 (m, 14H); 4.63 (d, J = 5.4 Hz, 2H). ^{13}C NMR: δ 20.7 (q); 21.4 (q); 25.7 (t); 31.4 (t); 34.5 (t); 36.4 (s); 37.3 (t); 39.5 (t); 39.6 (d); 53.1 (t); 75.2 (s); 108.7 (t); 148.7 (s);209.3 (s). mp=109-110 °C. $[\alpha]_D$ = -51.9 (c = 1.0).

(4aR,7S)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methylnaphthalene-2(3H)-one (10)
^{1}H NMR: δ 1.19 (s, 3H); 1.70 (s, 3H); 1.3 - 2.6 (m, 11H); 4.70 (s, 2H); 5.69 (s, 1H). ^{13}C NMR: δ 20.4 (q); 21.9 (q); 26.9 (t); 33.7 (t); 35.3 (s); 37.5 (t); 37.6 (t); 41.0 (t); 45.9 (d); 109.1 (t); 124.3 (d); 148.3 (s); 169.5 (s); 199.3 (s). $[\alpha]_D$ = -79 (c = 1.2).

(1S,2S, 5S)-5-Isopropenyl-2-methyl-3-oxo-cyclohexane-1-carbonitrile (11c)
To a solution of 25.0 g (0.167 mol) of S-(+)-carvone (**1**) in 75 ml of ethanol (96%) at 0 °C was added slowly a solution of 15 g (0.23 mol) of KCN in 35 ml of H_2O to give a brown mixture. To this mixture was added 11 ml (0.17 mol) of glacial acetic acid in 2 h. After some time the product started to crystallize. Stirring was continued overnight at 0 °C. The reaction mixture was filtered, and the precipitate was washed with water / ethanol (1/2) and recrystallized from ethanol to give 28.1g (0.159 mmol, 95%) of **11c** as white crystals, mp 95 - 96 °C.
^{1}H NMR: δ 1.30 (d, J = 6.5 Hz, 3H); 1.75 (s, 3H); 1.8 - 2.9 (m, 6H); 3.35 (m, 1H); 4.77 (s, 1H); 4.87 (s, 1H).

HRMS: calcd (M^+) *m/e* 177.1153; found *m/e* 177.1154. $[\alpha]_D$ = +10.2 (c = 0.2).

(1S,3S,4aS,8aR)-Decahydro-4a-hydroxy-3-isopropenyl-8a-methyl-6-oxo-1-naphthalenecarbonitrile (12)
To a solution of 50.0 g (282 mmol) of cyanocarvone **11c** and 75 ml (0.9 mol) of MVK in 600 ml of MeOH was added dropwise 150 ml of a 1 M $NaOCH_3$ solution in MeOH at 0 °C. After stirring overnight the product crystallized from the reaction mixture. Water (1000 ml) was added and the mixture was allowed to stand at 0 °C overnight. The mixture was filtered and washed with water. The resulting crystals **12** (62.7 g, 254 mmol, 90%) were dried under vacuum over P_2O_5 and were used without further purification, mp 191 - 192 °C.
^1H NMR: δ 1.52 (s, 3H); 1.70 (s, 3H); 1.4 - 2.1 (m, 5H); 2.2 - 2.4 (m, 3H); 2.5 (dd, J = 6.9 Hz, 14.2 Hz, 1H); 2.6 - 2.9 (m, 3H); 4.70 (s, 1H); 4.77 (s, 1H). ^{13}C NMR: δ 19.5 (q); 20.8 (q); 28.7(t); 31.5 (t); 35.7 (d); 36.5 (d); 36.8 (t); 38.6 (s); 39.1 (t); 53.0 (s); 74.7 (t); 110.0 (t); 121.3 (s); 146.7 (s); 207.3 (s). HRMS: calcd. (M^+) *m/e* 247.1576; found *m/e* 247.1572. Anal: calcd for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.55; N, 5.66; found: C, 72.71; H, 8.50; N, 5.68. $[\alpha]_D$ = -41.3 (c = 0.3).

(1S,3S,8aR)-3-Isopropenyl-8a-methyl-1,2,3,4,6,8,8a-octahydro-6-oxo-1-naphthalenecarbonitrile (2e)
To a solution of 134 g (0.54 mol) of alcohol **12** in 1000 ml of toluene was added at reflux temperature 0.9 g of *p*-TsOH. The solution was refluxed for 1 h in a Dean-Stark apparatus.The organic layer was washed with a saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. After evaporation of the solvent and recrystallization from ethanol 112 g (0.49 mol, 91%) of **2e** was obtained as pale yellow crystals, mp 106 - 107 °C.
^1H NMR: δ 1.39 (s, 3H); 1.69 (s, 3H); 1.74 - 1.90 (m, 1H); 2.11 - 2.21 (m, 3H); 2.41 - 2.71 (m, 6H); 4.73 (s, 1H); 4.91 (s, 1H); 5.82 (s, 1H). ^{13}C NMR: δ 18.3 (q); 22.3 (q); 27.1 (t); 33.4 (t); 34.5 (t); 35.7 (t); 35.9 (d); 37.3 (s); 38.1 (d); 113.8 (t); 119.6 (s); 126.9 (d); 144.7 (s); 164.0 (s); 197.3 (s). HRMS: calc. (M^+) *m/e* 229.1467; found *m/e* 229.1472. Anal: calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.10.; found: C, 78.43; H, 8.47; N, 6.03. $[\alpha]_D$ = +202 (c = 0.4).

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