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Enantioselective Synthesis of Cadinanes Starting from R-(-)- or S-(+)-Carvone

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Abstract: A new enantioselective synthesis of cadinanes, using the Mukaiyama-Michael reaction, was developed starting from R-(-)- or S-(+)-carvone. This approach gives an easy and direct access to the cadinane skeleton and the scope proved to be complementary to a formylation-annelation sequence. The applicability of the method was demonstrated by the enantioselective synthesis of 1,9-cadinadien-3-one and 4-methoxy-1,9-cadinadien-3-one.

Introduction

Both enantiomers of carvone have been widely used as starting material in enantioselective syntheses of natural products[1]. In our laboratory the conversion of S-(+)-carvone into drimanes[2], (+)-α-cyperone[3], (-)-1,1,4a-trimethyl-2-decalol[4] and (+)-geosmin[4] has been investigated. A conjugate addition-annelation procedure has been developed[5] that opens up alternative approaches towards the synthesis of drimanes[6] and (-)-ambrox[7] and recently the synthesis of eremophilanes has been realised in this way[8].

Although it seems obvious that also cadinane type sesquiterpenes could be made starting from carvone, not many examples have been reported[9]. Recently an access to cadinanes starting from carvone has been described by Beauhaire *et al*[10] which employs a formylation-Robinson annelation sequence for the construction of a *nor* cadinane skeleton. We have investigated this approach also and have obtained similar results although the method appeared to be of limited scope in our hands. Therefore an approach, using the Mukaiyama-Michael reaction, was developed which proved to be limited in scope as well, but complementary to the formylation-annelation sequence. The method gives an easy and direct access to the cadinane skeleton[11].

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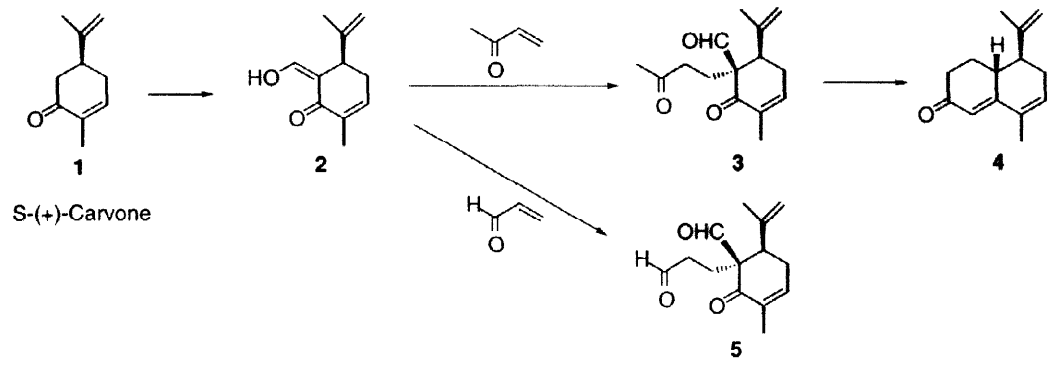
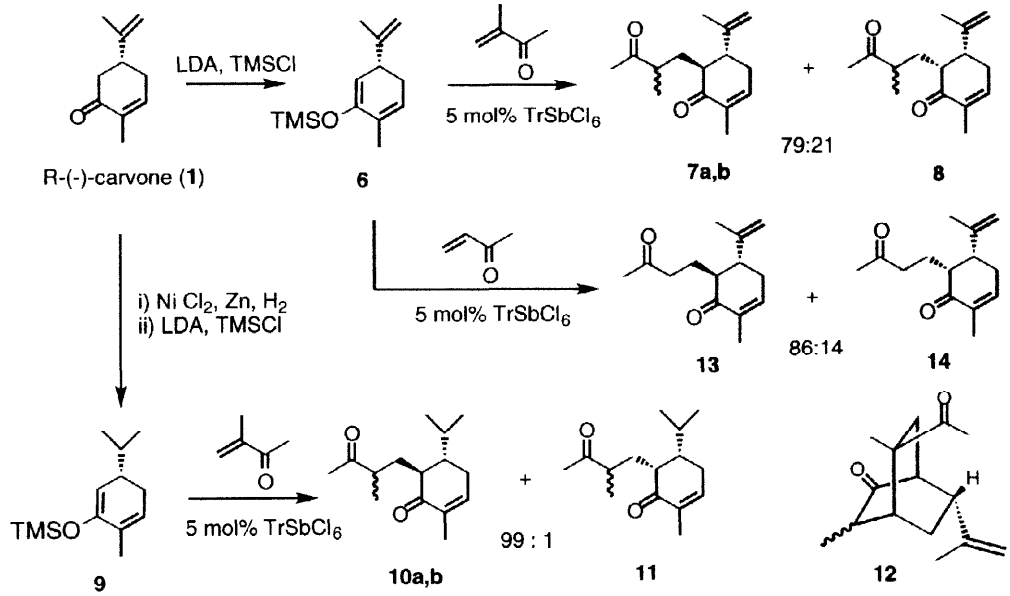
Results and discussion

The formylation of carvone followed by Michael addition to methyl vinyl ketone or acrolein proceeds without difficulties and in a good yield. Further cyclisation of adduct **3** to the *nor* cadinane skeleton **4** could be achieved in 71% yield. In contrast, isopropenyl methyl ketone and acrylonitrile did not react with hydroxymethylene carvone (**2**) in our hands (see scheme 1).



scheme 1

Therefore an alternative approach, using a Mukaiyama-Michael reaction of the kinetic silyl enol ether of carvone **6**, was investigated and this method gave results that were complementary to the formylation-annelation sequence. The Mukaiyama-Michael reaction of silyl enol ether **6** gave good results with isopropenyl methyl ketone but in its turn this reaction proved to be unsuitable for the coupling of **6** with methyl vinyl ketone or acrolein. The reaction shows good stereoselectivity when the silyl enol ether **6** of carvone itself is used and the reaction is practically completely stereoselective with silyl enol ether **9**, where the side chain is reduced to the isopropyl group (see scheme 2).



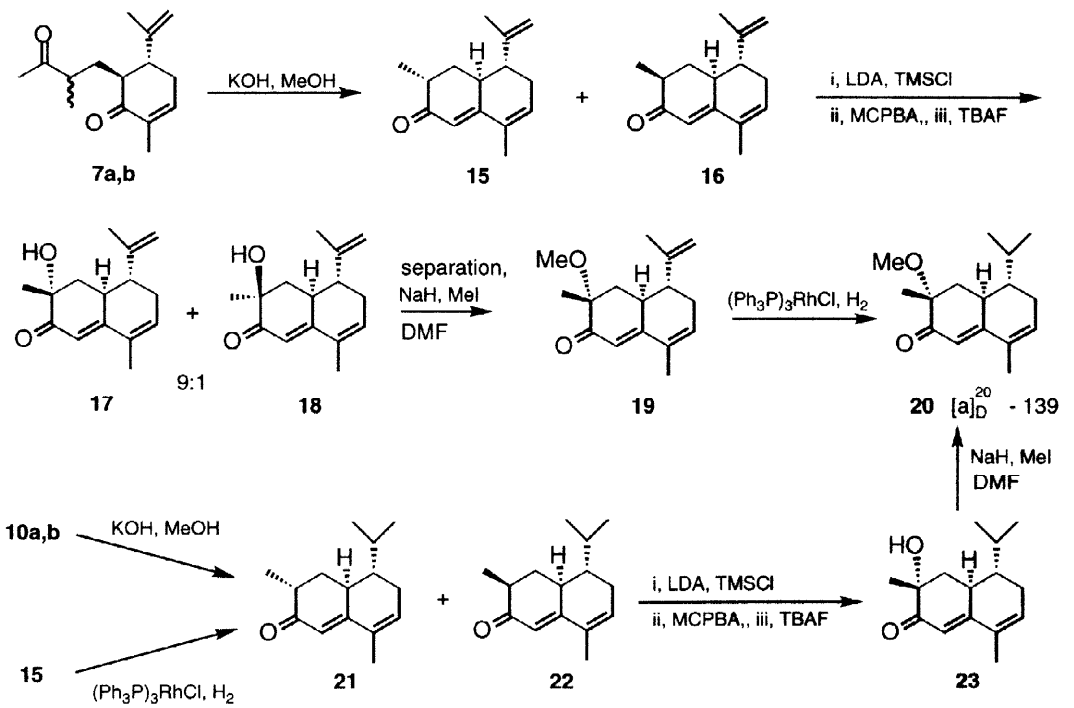
scheme 2

The reaction has to be quenched quickly because longer reaction times give rise to further intramolecular reactions of the intermediate silyl enol ether to bicyclic products **12** and after 4 h these bicyclic compounds are the only reaction products observed[12, 13].

Quenching after 5 minutes proved to be most effective and the reaction mixture then contains starting material, *mono*-adduct and bicyclic product in a ratio 5:85:9. The Mukaiyama-Michael reaction of silyl enol ether **6** with methyl vinyl ketone does not give satisfactory results; even quenching after 1 minute results in the formation of 30% of bicyclic products next to starting material and only a 28% yield was obtained of a mixture of *trans*- and *cis* mono-adducts **13** and **14** in an 84:16 ratio respectively.

To illustrate the utility of this approach for the synthesis of cadinanes, some further transformations of the adducts **7**, **10** and **25** leading to the natural products 1,9-cadinadien-3-one (**26**)[14] and 4-methoxy-1,9-cadinadien-3-one (**29**)[15] were performed (see schemes 3 and 4).

The cyclisation of the diketones **7** with KOH in methanol for 1 h at room temperature gave the unsaturated bicyclic ketones **15** and **16** in 70% yield based on carvone, the ratio of the epimers depends on the reaction conditions. The kinetic ketone **15** can be obtained as the only product when a large excess of base was used for a short reaction period (3-5 min). Kinetic protonation of the enolate of ketone **16** or its silyl enol ether failed to give **15** in our hands and only ketone **16** could be recovered[16]. The double bond in the isopropenyl group of compound **15** can be hydrogenated selectively with Wilkinson's catalyst to give compound **21**, no reduction of the endocyclic conjugated double bonds was observed after 24 h.

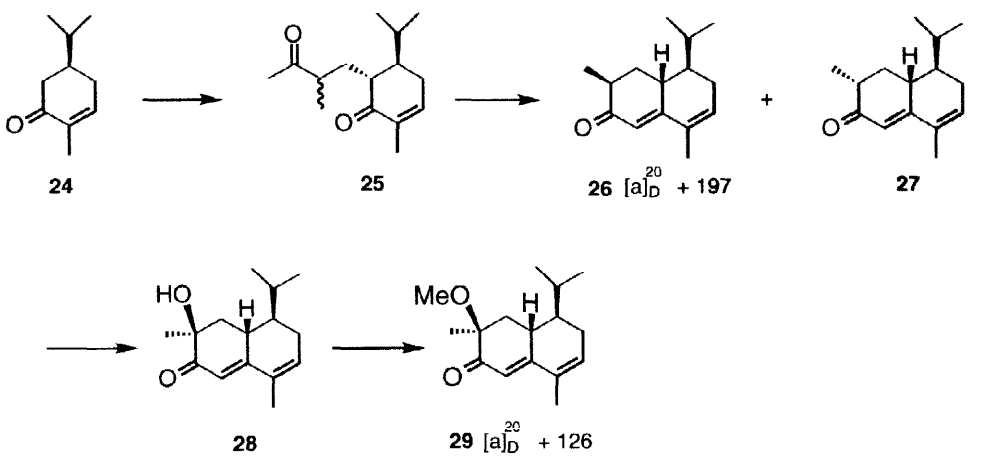


scheme 3

The transformation of ketones **15** and **16** into 4-methoxy-1,9-cadinadien-3-one (**20**) was realised via epoxidation of the corresponding TMS-enol ether. The cleavage of the intermediate epoxide occurred already during reaction and could be completed by treatment of the crude reaction mixture with tetrabutylammonium

fluoride (TBAF) to give a mixture of the hydroxyketones **17** and **18** in 74% yield. As expected, the attack of the double bond occurred from the pseudo-axial position leading to the most stable product with an equatorial methyl group, trans to the isopropenyl group. The stereochemistry of compound **17** was confirmed by X-ray analysis[17]. In the hydroxylation of the ketones **15** and **16**, a 10% yield of the minor epimer **18** was obtained, this result again witnesses that the isopropenyl group does not create enough steric hindrance to give complete stereoselectivity in the epoxidation reaction. The synthesis of 4-methoxy-1,9-cadinadien-3-one was completed by methylation of the hydroxy group followed by selective homogeneous hydrogenation of the double bond in the isopropenyl group. The presence of N,N-dimethylformamide (DMF)[18] in the reaction mixture is crucial for a good result in the methylation reaction (85% yield). The spectral data (400 MHz ^{1}H) of synthesised methoxy ketone **20** were in full agreement with those reported in the literature for the natural product, however, the magnitude and sign of the optical rotation of our synthetic product **20** ($[\alpha]_D$ -139.7°) was different from that reported for the natural product ($[\alpha]_D$ +28°). Special spectral decoupling experiments were carried out to confirm our assignment of the configuration of the proton at C-6 in compound **20**, because during the methylation under basic conditions, in theory an epimerisation may occur. It was found that the coupling constant *J* between the protons at C-6 and C-7 was 11 Hz, which confirms their *trans* relationship. Therefore we came to the conclusion that we had synthesised the enantiomer of the natural product and some additional experiments were carried out to definitively confirm the stereochemical assignments.

First the reduced compound **10** was cyclised and the mixture of bicyclic ketones **21** and **22** was hydroxylated and methylated to give the same enantiomer **20**, which had been synthesised before. Similar as in the Mukaiyama-Michael reaction of **9**, it was observed that the epoxidation of the silyl enol ether of **21** and **22** was more selective than that of the silyl enol ether of ketones **15** and **16**, again indicating the greater steric influence of the isopropyl group in comparison to that of the isopropenyl group.



scheme 4

Secondly the enantiomer of **20** and **21** was synthesised starting from S-(+)-carvone. Since the compounds with an isopropyl sidechain gave greater selectivity in their reactions, S-(+)-carvone was first reduced to **24**. This compound was subsequently transformed in an analogous procedure as described above, into (+)-1,9-cadinadien-3-one (**26**) and into (+)-4-methoxy-1,9-cadinadien-3-one (**29**). For **26** the absolute configuration was assumed in the literature to be as indicated, probably in analogy to other cadinanes that were isolated from

the same plant. Its optical rotation ($[\alpha]_D$ + 197) was not determined before. The optical rotation of **29** now had the same sign, but the rotation ($[\alpha]_D$ + 126) was higher than that reported in the literature ($[\alpha]_D$ + 28)[15].

Experimental

General and instumentation. Melting points are uncorrected. Infrared spectra were recorded on a FTIR, Biorad FTS 7 spectrometer and only characteristic absorptions are reported. ^{1}H NMR spectra were measured in deuteriochloroform solutions with residual $CHCL_3$ as internal standard on Bruker AC-E 200 or DPX 400 where specified, operating at 200 and 400 MHz, respectively. ^{13}C NMR spectra were recorded on Bruker AC-E 200 operating at 50 MHz. Chemical shifts are reported in parts per million (δ) and coupling constants are in Hz. MS data were determined at 70 eV on a Hewlett Packard 5890B series Mass Selective Detector, coupled with a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 μm. The ratios m/z and relative intensities (%) are indicated for the significant peaks. Helium was used as the carrier gas. HRMS data were obtained with a Finnigan MAT 95 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 20 °C for chloroform solutions and concentrations are specified in g/100 mL. Gas chromatography was performed on a 5890 Series II Hewlett Packard gas chromatograph using a DB-17 fused silica bonded capillary column (30 m x 0.25 mm i.d.), programmed from 100-250 °C at a rate of 10 °C/min. Column chromatography was performed on Merck silica gel 60 using mixtures of petroleum ether (b.p. 40–60 °C) (PE) and EtOAc (EA) as the solvent system. Solvents were dried and freshly distilled by common practice. All reactions were carried out under a positive pressure of nitrogen. Usual work up refers to washing extracts with brine, drying over anhydrous $MgSO_4$, filtering and evaporating under reduced pressure. Reactions were monitored by TLC silica gel plates (Merk Kieselgel 60 F-254) and visualisation of the compounds was accomplished by u. v. light, and/or spraying with an anisaldehyde acidic solution.

(5R)-5-Isopropyl-2-methyl-2-cyclohexen-1-one and **(5S)-5-Isopropyl-2-methyl-2-cyclohexen-1-one** were prepared[19] in 64% yield from R-(-)-carvone ($[\alpha]_D$ = -54.3) and S-(+)-carvone($[\alpha]_D$ = +40.3), respectively. GC R_t 4.23 min; ^{1}H NMR 0.87 (d, J = 6.8, 6H), 1.53 (m, J = 6.8, 1H), 1.73 (m, 3H,), 1.82-2.37 (m, 4H), 1.49 (ddd, J = 15.6, 3.4, 1.5, 1H), 6.71 (m, 1H).

Isopropenyl methyl ketone was prepared[20] in 40% yield. ^{1}H NMR 1.84 (br s, 3H), 2.30 (s, 3H), 5.78 (br s, 1H), 5.93 (s, 1H); IR (film) 3073, 2970, 1681, 1632, 1364, 1142, 938.

(5R)-6-Hydroxymethylene-5-isopropenyl-2-methyl-2-cyclohexen-1-one (2)

To 4.8 g of a 50% suspension of sodium hydride in mineral oil (100 mmol) in 200 mL of dry ether was added dropwise a mixture of 12.0 g (80 mmol) of S-(+)-carvone and 14.8 g (160 mmol) of ethyl formate in 100 mL of dry ether at room temperature. After stirring overnight the reaction mixture was washed with 3 portions of 100 mL of a 1 M aqueous potassium hydroxide solution. The combined aqueous layers were acidified with hydrochloric acid and extracted with ether. The etheral extracts were washed with brine and dried over $MgSO_4$. Evaporation under reduced pressure gave 13.90 g (97%) of crude hydroxymethylene ketone **2** as a yellow oil which was used without further purification. An analytical sample was obtained by flash column chromatography on silicagel with PE/EA 98:2 as eluent.

HRMS found M^+ 178.0992. $C_{11}H_{14}O_2$ requires 178.0994; $[\alpha]_D$ + 7.6 (c 6.6); ^{1}H NMR 1.68 (s, 3H), 1.81 (s, 3H), 2.37 (m, 2H), 3.23 (t, J = 7 Hz), 4.75 (s, 1H), 4.81 (s, 1H), 6.46 (m, 1H), 7.40 (d, J = 9 Hz, 1H), 14.50, (d, J = 9 Hz, 1H); ^{13}C NMR 15.2 (q), 19.4 (q), 28.8 (t), 41.5 (d), 109.4 (s), 113.4 (t), 134.3 (s), 140.9 (d), 145.4 (s), 168.8 (d), 189.2 (s); MS 178 (M^+, 38), 109 (100), 91 (44), 41 (36).39 (59).

(5R)-5-Isopropenyl-8-methyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (4)

To a solution of 5.5 g (30.9 mmol) **2**, 5 mL of triethylamine and one pellet of KOH in 100 mL of ethyl acetate was added methyl vinyl ketone at 0 °C. After stirring at 0 °C for 2.5 h the reaction mixture was acidified with 2 M aqueous HCl solution and extracted with ethyl acetate and after evaporation of the solvent the residue was dissolved in 100 mL of methanol. Aqueous KOH solution was added to the methanol solution at 0 °C. After 1 h methanol was evaporated and the product was extracted with ethyl acetate followed by usual work up. Recrystallization of the residu from diisopropylether afforded 3.4 g (71%) **4** as slightly yellow crystals with m.p. 71-72 °C.

^{1}H NMR 1.69 (s, 3H), 1.84 (s, 3H), 4.82 (bs, 2H), 5.94 (bs, 1H), 6.12, (m 1H); ^{13}C NMR 18.2 (q), 19.4 (q), 27.7 (t), 31.8 (t), 37.9 (t), 38.1 (d), 48.7 (d), 113.6 (t), 122.1 (d), 131.8 (d), 136.8 (s), 145.9 (s), 159.2 (s), 200.8 (s).

(1R,6R)-1-(3'-oxopropyl)-6-isopropenyl-3-methyl-2-oxo-3-cyclohexene-1-carboxaldehyde (5)

A solution of 13.1 g (73.6 mmol) of **2** in 200 mL of ethyl acetate was treated with 8.7 g (85.9 mmol) of triethylamine and a pellet of potassium hydroxide and cooled to 0 °C. A solution of 4.8 g (85.9 mmol) of freshly distilled acrolein was added dropwise with stirring. After 1 h the reaction mixture was diluted with ether and washed with diluted hydrochloric acid. After drying over $MgSO_4$ the solution was concentrated under reduced pressure and purified by flash chromatography to give 15.9 g (92%) of **5** as a viscous colourless oil.

HRMS found 234.1254. $C_{14}H_{18}O_3$ requires M^+ 234.1256; ^{1}H NMR 1.61 (s, 3H), 1.74 (s, 3H), 2.0-2.8 (m, 7H), 4.62 (s, 1H); 4.77 (s, 1H), 6.67 (m, 1H), 9.62 (s, 1H), 9.78 (s, 1H); ^{13}C NMR 15.6 (q), 22.0 (q), 23.6 (t), 28.5 (t), 38.4 (t), 49.0 (d), 60.6 (s), 115.4 (t), 134.7 (s), 143.2 (d), 143.4 (s), 197.5 (s), 200.5 (d), 201.7 (d); MS 234 (M^+, 5), 121 (100), 82 (82), 41 (71), 39 (88).

General procedure for the preparation of the TMS enol ethers of carvone and dihydrocarvone.

A solution of ketone (4 mmol) in THF (10 mL) was added to a stirred solution of LDA (4.32 mmol) in THF (10 mL) at -78 °C in the presence of a catalytic amount of phenanthroline. After 20 min TMSCl (0.6 mL, 4.75 mmol) was added and the reaction mixture was allowed to warm to room temperature for 1 h until the red color of the phenanthroline anion had faded. The solution was then poured into a cold saturated solution of $NaHCO_3$ and brine (1:1). The water phase was extracted with PE followed by the usual work up. The crude TMS enol ethers were used without further purification.

General procedure for the Mukaiyama reaction of the dienol silyl ethers .

Trityl antimonium hexachloride (786 mg, 1.36 mmol) was added in one portion to a stirred solution of the dienol silyl ether (25 mmol) and the unsaturated ketone (27 mmol) at -78 °C. The reaction was quenched with pyridine (4 mL) after 5 min (after 1 min for methyl vinyl ketone). The mixture was warmed to room temperature, 2 M HCl (40 mL) in THF (50 mL) was added and stirring was continued for 1 h. Then the water phase was extracted with PE, washed subsequently with 1 M solution of HCl, a saturated solution of $NaHCO_3$ followed by usual work up and flash chromatography with (PE/EA 92:8) as eluent.

Diketones **7a, 7b and 8** were isolated in 70% yield in a ratio of 64:21:15 respectively.

(2S,2'R,3R)-3-Isopropenyl-6-methyl-2-(2'-methyl-3'-oxo-butyl)-5-cyclohexen-1-one (7a)

Compound **7a** was isolated as an oil, partly separated from its 2R isomer **8**. GC R_t 9.30 min (R_t of 2R-isomer **8** 9.51 min); IR (film) 3073, 2970, 2925, 1712, 1667, 1433, 1364, 893; ^{1}H NMR 1.08 (d, *J* = 7.4, 3H), 1.36 (ddd, *J* = 13.7, 10, 4, 1H), 1.73 (br s, 6H), 1.78 (ddd, *J* = 13.7, 10, 3, 1H), 2.11 (s, 3H), 2.98 (dqd, *J* = 10, 7.4, 4, 1H), 4.77 (br d, *J* = 15, 2H), 6.59 (m, 1H); ^{13}C NMR 16.0, 18.2, 18.7, 28.7, 30.5, 31.7, 45.2, 47.2, 49.0, 113.4, 134.8, 142.9, 145.8, 202.3, 213.4; MS 234 (M^+, 1), 219 (2), 201 (7), 191 (10), 173 (5), 162 (28), 150 (100).

(2S,2'S,3R)-3-Isopropenyl-6-methyl-2-(2'-methyl-3'-oxo-butyl)-5-cyclohexen-1-one (7b)

Compound **7b** was isolated as an oil. GC R_t 9.81 min; IR (film) 3072, 2968, 1710, 1668, 1369, 896; ^{1}H NMR 1.00 (d, *J* = 7.1, 3H), 1.24 (ddd, *J* = 14, 9, 2.5, 1H), 1.69 (s, 3H), 1.73 (m, 3H), 1.96 (ddd, *J* = 14, 9.5, 4.4, 1H), 2.15 (s, 3H), 2.81 (dqd, *J* = 9.5, 7.1, 2.5, 1H), 4.73 (br d, *J* = 10, 2H), 6.58 (m, 1H); ^{13}C NMR 15.6, 16.0, 18.8, 28.1, 30.8, 31.2, 45.4, 46.9, 49.0, 113.9, 134.8, 143.0, 145.1, 202.0, 212.8; MS 234 (M^+, 1), 219 (2), 201 (5), 191 (13), 173 (5), 162 (28), 150 (100).

Diketones **10a** and **10b** were isolated in 68% yield in a ratio of 78:22 respectively.

(2S,2'R,3S)-3-Isopropyl-6-methyl-2-(2'-methyl-3'-oxo-butyl)-5-cyclohexen-1-one (10a)

Compound **10a** was isolated as an oil. GC R_t 9.04 min; IR (film) 2960, 2925, 1712, 1665, 1459, 1365; ^{1}H NMR 0.82 (d, *J* = 6.4, 3H), 0.83 (d, *J* = 6.4, 3H), 1.04 (d, *J* = 7.2, 3H), 1.37 (ddd, *J* = 13.8, 9.4, 5, 1H), 1.65 (m, 1H), 1.68 (m, 1H), 1.87 (ddd, *J* = 13.8, 9.4, 5, 1H), 2.15 (s, 3H), 2.63 (dqd, *J* = 9.4, 7.2, 5, 1H), 6.53 (br t, *J* = 3.4, 1H); ^{13}C NMR 15.9, 17.7, 19.4, 20.8, 29.0, 32.7, 134.2, 142.7, 202.7, 212.8; MS 236 (M^+, 1), 193 (8), 175 (3), 152 (8), 121 (38), 109 (100).

(2S,2'S,3S)-3-Isopropyl-6-methyl-2-(2'-methyl-3'-oxo-butyl)-5-cyclohexen-1-one (10b)

Compound **10b** was isolated as an oil. GC R_t 9.41 min; IR (film) 2962, 1713, 1666, 1449; ^{1}H NMR 0.78 (d, *J* = 6.4, 3H), 0.80 (d, *J* = 6.4, 3H), 1.03 (d, *J* = 7.2, 3H), 1.40 (ddd, *J* = 13.8, 7.6, 3.9, 1H), 1.63 (m, 1H), 1.65 (m, 1H), 2.01 (ddd, *J* = 13.8, 10, 5.8, 1H), 2.09 (s, 3H), 2.65 (m, 1H), 6.51 (m, 1H); ^{13}C NMR 15.9, 16.6, 18.9, 20.7, 25.1, 28.2, 28.6, 32.3, 45.0, 45.7, 47.8, 134.3, 142.6, 202.6, 212.4; MS 236 (M^+, 1), 193 (8), 175 (3), 152 (8), 121 (38), 109 (100).

Diketones **13** and **14** were isolated in 28% yield in a ratio of 84:16 respectively.

(2S,3R)-3-Isopropenyl-6-methyl-2-(3'-oxo-butyl)-5-cyclohexen-1-one (13)

Compound **13** was isolated as an oil, partly separated from its 2R-isomer **14**. GC R_t 9.51 min (R_t of 2R-isomer 9.66 min); IR (film) 3092, 1714, 1668, 1435, 1366, 897; ^{1}H NMR 1.50 (m, 1H), 1.60 (m, 3H), 1.80 (m, 1H), 1.97 (s, 3H), 4.65 (m, 2H), 6.50 (m, 1H); ^{13}C NMR 16.3, 16.3, 18.8, 21.9, 30.2, 31.3, 41.2, 48.4, 114.0, 135.3, 143.6, 145.7, 201.7, 209.3; MS 220 (M^+, 3), 205 (8), 187 (17), 177 (12), 162 (43), 149 (87), 121 (87), 82 (100).

General procedure for the Robinson annelation.

Mixtures of epimeric ketones (25 mmol) were dissolved in a 1 M solution of KOH in methanol (100 mL). The resulting solution was stirred at room temperature for 1 h and then poured into a 2 M solution of HCl (60 mL). The water layer was extracted with PE, followed by the usual work up and flash chromatography (PE/EA 92:8).

Decalones **15** and **16** were isolated in 66 % yield in a ratio of 38:62 respectively.

(3R,4aS,5R)-3,8-Dimethyl-5-isopropenyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (15)

Compound **15** was isolated as an oil, b.p. 130 °C/0.04 mm (kugelrohr); HRMS found M^+ 216.1510. $C_{15}H_{20}O$ requires M^+ 216.1514; $[\alpha]_D$ +28.7 (*c* 1.37); GC R_t 10.86 min; IR (film) 3060, 1664, 1633, 1580, 894; ^1H NMR 1.13 (d, *J* = 7.3, 3H),1.68 (s, 3H), 1.73 (m, 1H), 1.83 (m, 3H), 2.50 (m, 2H), 4.79 (s, 2H), 5.86 (d, *J* = 1.5, 1H), 6.12 (m, 1H);^{13}C NMR 16.3 (q), 18.3 (q), 19.6 (q), 32.2 (t), 33.2 (d), 34.3 (t), 40.3 (d), 48.9 (d), 113.9 (t), 121.1 (d), 132.1 (s), 136.8 (d), 146.1 (s), 158.4 (s), 204.4 (s); MS 216 (M^+, 12), 188 (1), 174 (47), 159 (33), 146 (75), 131 (100).

(3S,4aS,5R)-3,8-Dimethyl-5-isopropenyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (16)

Compound **16**[15] was isolated as a white solid, m.p. 73-74 °C (hexane, -70 °C), b.p. 110 °C/0.02 mm (kugelrohr); HRMS found M^+ 216.1513. $C_{15}H_{20}O$ requires M^+ 216.1514; $[\alpha]_D$ -91.5 (*c* 1.06); GC R_t 10.81 min; IR ($CHCl_3$) 3060, 1656, 1631, 1585, 898; ^1H NMR 1.12 (d, *J* = 6.6, 3H), 1.23 (td, *J* = 13.5, 11.6, 1H), 1.70 (br s, 3H), 1.83 (br s, 3H), 1.96 (dt, *J* = 13.5, 4, 1H), 2.30 (m, 1H), 2.48 (tdd, *J* = 11.6, 4, 2.2, 1H), 4.82 (m, 2H), 5.92 (d, *J* = 2.2, 1H), 6.10 (m, 1H); ^{13}C NMR 15.1 (q), 18.2 (q), 19.3 (q), 31.8 (t), 36.3 (t), 38.5 (d), 41.6 (d), 48.7 (d), 113.5 (t), 121.8 (d), 136.1 (d), 136.6 (s), 145.8 (s) 158.3 (s), 202.8 (s); MS 216 (M^+, 17), 188 (5), 174 (45), 159 (35), 146 (82), 131 (100).

Decalones **21** and **22** were isolated in 73% yield in a ratio of 46:54 respectively.

(3R,4aS,5S)-3,8-Dimethyl-5-isopropyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (21)

Compound **21** was isolated as a white solid; m.p. 57-58 °C (hexane); HRMS found M^+ 218.1672. $C_{15}H_{22}O$ requires M^+ 218.1671; $[\alpha]_D$ -226.4 (*c* 1.05); Spectra and chromatographic data are identical to those of **26**.

(3S,4aS,5S)-3,8-Dimethyl-5-isopropyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone(22)

Compound **22** was isolated as a white solid; m.p. 58-59 °C (hexane, -70 °C); HRMS found M^+ 218.1667. $C_{15}H_{22}O$ requires M^+ 218.1671; $[\alpha]_D$ -286.7 (*c* 1.41); Spectra and chromatographic data are identical to **27.**

The decalones **26** and **27** were isolated in 52 % yield in a ratio of 35:65 respectively.

(3S,4aR,5R)-3,8-Dimethyl-5-isopropyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (26)

Compound **26** was isolated as a white solid; m.p. 50-51 °C (hexane, -70 °C); HRMS found M^+ 218.1668, $C_{15}H_{22}O$ requires M^+ 218.1671. $[\alpha]_D$ +197.1 (*c* 0.99); GC R_t 11.18 min; IR (film) 1666, 1634, 1581, 881; ^1H NMR 0.79 (d, *J* = 7, 3H), 0.89 (d, *J* = 7, 3H), 1.13 (d, *J* = 7.8, 3H), 1.45 (tdd, *J* = 11.7, 4.9, 3.9, 1H), 1.70 (m, 1H), 1.78 (m, 3H), 2.00 (m, 3H), 2.16 (ddd, *J* = 18.6, 5.9, 4.4, 1H), 2.40 (tdd, *J* = 12.2, 4.4, 2.4, 1H), 2.51 (m, 1H), 5.81 (d, *J* = 1.9, 1H), 6.12 (br d, *J* = 5.9, 1H); ^{13}C NMR 14.3 (q), 16.1 (q), 19.3 (q), 20.7 (q), 24.9 (t), 26.1 (d), 32.8 (t), 33.1 (d), 39.8 (d), 43.6 (d), 120.1 (d), 131.5 (s), 137.2 (d), 159.0 (s), 203.9 (s); MS 216 (M^+, 17), 190 (2), 176 (7), 147 (3), 133 (100).

(3R,4aR,5R)-3,8-Dimethyl-5-isopropyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (27)

Compound **27** was isolated as a white solid; m.p. 52-54°C (hexane); HRMS found M^+ 218.1680. $C_{15}H_{22}O$ requires M^+ 218.1671; $[\alpha]_D$ +238.7 (*c* 0.59); GC R_t 11.07 min; IR (film) 1668, 1634, 1586, 872; ^1H NMR 0.82 (d, *J* = 6.8, 3H), 0.92 (d, *J* = 6.8, 3H), 1.14 (d, *J* = 6.4, 3H), 1.32 (td, *J* = 14.6, 11.5, 1H), 1.44 (tdd, *J* = 12, 4.7, 3.4, 1H), 1.80 (m, 3H), 2.40 (tdd, *J* = 12.1, 4, 2.4, 1H), 5.90 (d, *J* = 2, 1H), 6.12 (m, 1H); ^{13}C NMR 14.6 (q), 15.2 (q), 19.4 (q), 20.9 (q), 24.8 (t), 26.2 (d), 35.3 (t), 38.9 (d), 41.2 (d), 44.0 (d), 121.4 (d), 131.4 (s), 136.8 (d), 159.4 (s), 202.6 (s); MS 218 (M^+, 17), 190 (2), 176 (7), 147 (5), 133 (100).

General procedure for the hydroxylation reaction.

The decalones were converted into the silyl enol ethers by adding a solution of the decalone (4 mmol) in THF (10 mL) to a stirred solution of LDA (4.32 mmol) in THF (10 mL) at -78 °C in the presence of a catalytic amount of phenanthroline. After 20 min TMSCl (0.6 mL, 4.75 mmol) was added and the reaction mixture was allowed to warm to room temperature for 1 h until the red color of the phenanthroline anion had faded. After work up as described in the general procedure for the TMS enol ethers of carvone and dihydrocarvone a slurry of MCPBA (4.4 mmol) in hexane (20 mL) was added to the stirred mixture of the crude TMS enol ether (4 mmol) and $NaHCO_3$ (4 mmol) at -50 °C. Then temperature was raised to -10 °C and the mixture was stirred for 20 min. When the hydroxy ketone began to crystallize, the mixture was warmed to ambient temperature and stirred for another 20 min. A solution of $NaHCO_3$ and $Na_2S_2O_3$ (1:1) was added and the water phase was extracted with EA, washed with a saturated solution of $NaHCO_3$ and followed by usual work up. The obtained crystalline material was dissolved in THF (10 mL) and a 1.1 M solution of TBAF in THF (1 mL) was added. The solution was stirred for 20 min at room temperature and a saturated solution of $NaHCO_3$ was added followed by EA (50 mL). The water layer was washed with a 1 M solution of HCl and with a saturated solution of $NaHCO_3$, followed by usual work up. The obtained material was purified by crystallization from hexane-ether; an additional yield was obtained after chromatography of the mother liquor with PE/EA 85:15 as eluent.

Hydroxyketones **17** and **18** were isolated in 74% yield in a ratio of 90:10 respectively.

(3R,4aS,5R)-3,8-Dimethyl-5-isopropenyl-3-hydroxy-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (17).

Compound **17** was isolated as a white solid; m.p. 147-148 °C (hexane-ether); HRMS found M^+ 232.1470. $C_{15}H_{20}O_2$ requires M^+ 232.1463; $[\alpha]_D$ +68.2 (*c* 1.33); GC R_t 11.86 min; IR (KBr): 3363, 3068, 1651, 1621, 1578, 893; ^{1}H NMR 1.35 (s, 3H), 1.51 (dd, *J* = 14.2, 10.2, 1H), 1.72 (br s, 3H), 1.85 (d, *J* = 1.5, 3H), 2.10 (dd, *J* = 14.2, 4.4, 1H), 2.78 (tdd, *J* = 10.2, 4.4, 2, 1H), 4.84 (m, 2H), 5.93 (d, *J* = 2, 1H), 6.16 (m, 1H); ^{13}C NMR 18.0 (q), 19.2 (q), 24.7 (q), 31.9 (t), 33.9 (d), 40.5 (t), 48.3 (d), 71.2 (s), 113.7 (t), 119.4 (d), 131.6 (s), 137.1 (d), 145.8 (s), 159.7 (s), 199.3 (s); MS 232 (M^+, 8), 214 (5), 204 (15), 189 (33), 174 (58), 159 (40), 146 (50), 131 (100).

(3S,4aS,5R)-3,8-Dimethyl-5-isopropenyl-3-hydroxy-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (18).

Compound **18** was isolated as a white solid; m.p. 139-141 °C (hexane-ether); HRMS found M^+ 232.1463. $C_{15}H_{20}O_2$ requires M^+ 232.1463; $[\alpha]_D$ -18.0 (*c* 0.91); GC R_t 12.02 min; IR (KBr) 3403, 3068, 1651, 1621, 1578, 893; ^{1}H NMR 1.38 (s, 3H), 1.57 (br s, 3H), 1.85 (br s, 3H), 3.08 (m, 1H), 4.66 (br d, *J* = 12, 2H), 5.93 (d, *J* = 2.2, 1H), 6.06 (br d, *J* = 6, 1H); ^{13}C NMR 19.0 (q), 22.4 (q), 24.4 (q), 31.5 (t), 33.8 (d), 40.4 (t), 43.7 (d), 71.7 (s), 113.5 (t), 119.1 (d), 132.1 (s), 135.1 (d), 146.1 (s), 158.7 (s), 199.0 (s); MS 232 (M^+, 8), 214 (10), 204 (5), 189 (18), 174 (50), 159 (40), 146 (58), 131 (100).

(3R,4aS,5S)-3,8-Dimethyl-5-isopropyl-3-hydroxy-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone(23).

Compound **23** was isolated as a white solid in 69% yield; m.p. 145-146 °C (hexane-ether); HRMS found M^+ 234.1633. $C_{15}H_{22}O_2$ requires M^+ 234.1620; $[\alpha]_D$ -177.9 (*c* 1.64); Spectroscopic and chromatographic data are identical to **28.**

(3S,4aR,5R)-3,8-Dimethyl-5-isopropyl-3-hydroxy-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (28).

Compound **28** was isolated as a white solid in 68% yield; m.p. 146-147 °C (hexane-ether); HRMS found M^+ 234.1626. $C_{15}H_{22}O_2$ requires M^+ 234.1620; $[\alpha]_D$ +155.0 (*c* 1.22); GC R_t 12.06 min; IR (KBr) 3376, 1653, 1625, 1577, 901; ^{1}H NMR 0.81 (d, *J* = 6.8, 3H), 0.89 (d, *J* = 6.8, 3H), 1.32 (s, 3H), 1.45 (m, 1H), 1.49 (dd, *J* = 14, 10.5, 1H), 1.79 (br s, 3H), 2.28 (dd, *J* = 14, 4.2, 1H), 2.61 (dddd, *J* = 13, 10.5, 4.2, 2.2, 1H), 5.85 (d, *J* = 2.2, 1H), 6.14 (br d, *J* = 5.2, 1H); ^{13}C NMR 14.5 (q), 19.3 (q), 20.9 (q), 24.8 (q), 25.0 (t), 26.3 (d), 34.4 (d), 39.6 (t), 43.6 (d), 71.0 (s), 119.0 (d), 131.5 (s), 137.9 (d), 160.8 (s), 199.1 (s); MS 234 (M^+, 3), 191 (10), 176 (10), 148 (8), 133 (100).

General procedure for the methylation reaction.

Sodium hydride (2.5 mmol) was added to a solution of the hydroxy ketone (1.25 mmol), methyl iodide (2.5 mL), and DMF (2.5 mL) in THF (25 mL). The resulting mixture was refluxed for 1 h, cooled and poured into a cold saturated aqueous solution of NH_4Cl. The water layer was extracted with PE followed by the usual work up and flash chromatography with PE/EA 92:8 as eluent.

(3R,4aS,5R)-3,8-Dimethyl-5-isopropenyl-3-methoxy-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (19).

Compound **19** was isolated as an oil in 80% yield; HRMS found M^+ 246.1610. $C_{16}H_{22}O_2$ requires M^+ 246.1620; $[\alpha]_D$ +104.0 (*c* 1.39); GC R_t 11.31min; IR (film) 3068, 1667, 1633, 1586, 1087, 880; ^{1}H NMR 1.24 (s, 3H), 1.45 (dd, *J* = 14.3, 10.5, 1H), 1.69 (m, 3H), 1.83 (br s, 3H), 2.13 (dd, *J* = 14.3, 4, 1H), 2.35 (m, 1H), 2.85 (tdd, *J* = 10.5, 4, 2.2, 1H), 3.13 (s, 3H), 4.81 (m, 2H), 5.86 (d, *J* = 2.2, 1H), 6.11 (m, 1H); ^{13}C NMR 18.0 (q), 18.1 (q), 19.2 (q), 31.8 (t). 33.8 (d), 41.2 (t), 48.4 (d), 51.3 (q), 75.3 (s), 113.5 (t), 119.6 (d), 131.5 (s), 136.6 (d), 145.8 (s), 159.2 (s), 197.4 (s); MS 246 (M^+, 1), 216 (33), 203 (27), 187 (30), 174 (67), 159 (45), 145 (35), 131 (100).

(3R,4aS,5S)-3,8-Dimethyl-5-isopropyl-3-methoxy-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (20).

Compound **20** was isolated as a white solid in 85% yield; m.p. 66-67 °C (hexane, -70 °C); HRMS found M^+ 248.1770. $C_{16}H_{24}O_2$ requires M^+ 248.1776; $[\alpha]_D$ -139.7 (*c* 1.22); Spectroscopic and chromatographic data are identical to **29**.

(3S,4aR,5R)-3,8-Dimethyl-5-isopropyl-3-methoxy-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (29).

Compound **29** was isolated as an oil in 82% yield; HRMS found M^+= 248.1776. $C_{16}H_{24}O_2$ requires M^+ 248.1776; $[\alpha]_D$ +126.0 (*c* 2.16); GC R_t 11.58 min; IR (film) 2958, 1667, 1633, 1587, 1084, 879; ^{1}H NMR (400 MHz) 0.86 (d, *J* = 7, 3H), 0.94 (d, *J* = 7, 3H), 1.28 (s, 3H), 1.46 (tt, *J* =12, 4, 1H), 1.52 (dd, *J* = 14, 10.5, 1H), 1.82 (br s, 3H), 2.18 (m, 1H), 2.38 (dd, *J* = 14, 4, 1H), 2.71 (dddd, *J* = 12, 10.5, 4, 2.3, 1H), 3.15 (s, 3H), 5.85 (d, *J* = 2.3, 1H), 6.15 (br d, *J* = 5.8, 1H); ^{13}C NMR 14.5 (q), 18.2 (q), 19.3 (q), 20.8 (q), 24.9 (t), 26.1 (d), 34.2 (d), 40.2 (t), 43.7 (d), 51.3 (q), 75.1 (s), 119.1 (d), 131.4 (s), 137.3 (d), 160.4 (s), 197.5 (s); MS: 248 (M^+, 1), 218 (10), 205 (5), 189 (7), 176 (12), 133 (100).

General procedure for the homogeneous catalytic hydrogenation.

Methoxy ketone **19** (103 mg, 0.42 mmol) was dissolved in degassed benzene and tris-triphenylphosphine rhodium (I) chloride [freshly prepared from $RhCl_3.3H_2O$ (20 mg) and triphenylphosphine (120 mg)] was added. The vessel was evacuated, filled with hydrogen and the solution was stirred for 24 h at room temperature. Then the solution was filtered through a dry column of silica gel. The column was washed with ether (100 mL) and the combined solvent fractions were concentrated to give methoxyketone **20** (96 mg, 92%).

Following the above procedure ketone **21** was prepared in 90% yield starting from ketone **15**.

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References and Notes

1. Ho, T-L. In *Enantioselective Synthesis, Natural Products from Chiral Terpenes*, John Wiley & Sons Inc.: New York, 1992; pp. 123-184.
2. Jansen, B. J. M.; Kreuger, J. A.; de Groot, Ae. *Tetrahedron* **1989**, *45*, 1447.
3. Haaksma, A. A.; Jansen, B. J. M.; de Groot, Ae. *Tetrahedron* **1992**, *48*, 3121.
4. Swarts, H. J.; Haaksma, A. A.; Jansen, B. J. M.; de Groot, Ae. *Tetrahedron* **1992**, *48*, 5497.
5. Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, Ae. *Tetrahedron* **1994**, *50*, 10037.
6. Swarts, H. J.; Verstegen-Haaksma, A. A.; Jansen, B. J. M.; de Groot, Ae. *Tetrahedron* **1994**, *50*, 10083.
7. Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, Ae. *Tetrahedron* **1994**, *50*, 10095.
8. Jenniskens, L. H. D.; de Groot, Ae. *Tetrahedron Lett.* **1997**, *38*, 7463.
9. (a) Takaki, K.; Ohsugi, M.; Okada, M.; Yasumura, M.; Negoro, K. *J. Chem. Soc. Perkin Trans. I* **1984**, 741. (b) Gallagher, M. J.; Sutherland, M. D. *Aust. J. Chem.* **1965**, *18*, 1111.
10. Beauhaire, J.; Ducrot, P.H.; Simon, I. *Synthetic Commun.* **1995**, *25*, 3015.
11. The numbering system of cadinanes as given in Connolly, J. D.; Hill, R. A. Dictionary of Terpenoids; Chapman & Hall: London, 1991; Vol. 1, Mono- and Sesquiterpenoids; pp. xxiii.
12. Asoaka, M.; Ishibashi, K.; Takahashi, W.; Takei, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2259.
13. Hagiwara, H.; Okano, A.; Uda, H. *J. Chem. Soc. Perkin Trans. I* **1990**, 2109.
14. Jakupovic, J.; Zdero, C.; Grenz, M.; Tsichritzis, F.; Lehmann, L.; Hashemi-Nejad, S. M.; Bohlmann, F. *Phytochemistry* **1989**, *28*, 1119.
15. Mericli, A. H.; Mericli, F.; Jakupovic, J.; Bohlmann, F.; Dominguez, X. A.; Vega, H. S. *Phytochemistry* **1989**, *28*, 1149.
16. The enantiomer of this product was synthesised earlier by Gallagher, M. J. and Sutherland, M. D. *Aust. J. Chem.* **1965**, *18*, 1111.
17. The X-ray crystal structure determination was performed by Dr. S. Menzer and Dr. A.L. Spek, Dept. of Crystal & Structural Chemistry, Utrecht University. Crystallographic data will be published soon in *Acta. Cryst.*, **C**.

18. Stoochnoff, B. A.; Benoiton, N. L. *Tetrahedron Lett.* **1973**, 21.
19. Petrier, C.;Luche, J.-L. *Tetrahedron Lett.* **1987**, *28*, 2351.
20. Landau, E. F.; Irany, E. P. *J. Org. Chem.* **1947**, *12*, 422.