

Total synthesis of (\pm) γ_2 -cadinene

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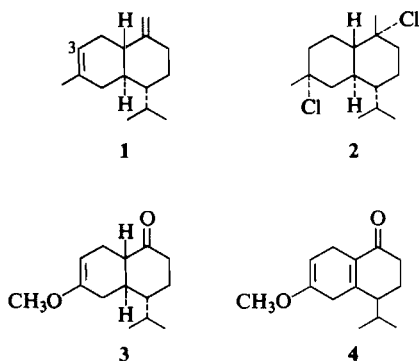
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A total synthesis of (\pm) γ_2 -cadinene is described. The synthetic terpene was characterized by conversion to (\pm)-cadinene dihydrochloride.

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γ_2 -Cadinene (**1**), isolated from Vetiver oil (*Vetiveria zizanioides* Linn.), is a relatively recently discovered member of the cadinane group of sesquiterpenoids. It has been assigned structure **1** (1). In connection with some other work, to be reported later, we took advantage of an opportunity to complete a total synthesis of **1** as a racemate which in turn was converted to (\pm)-cadinene dihydrochloride (**2**) (2). By so doing we were able to ascertain the stereochemical course of our synthetic work.



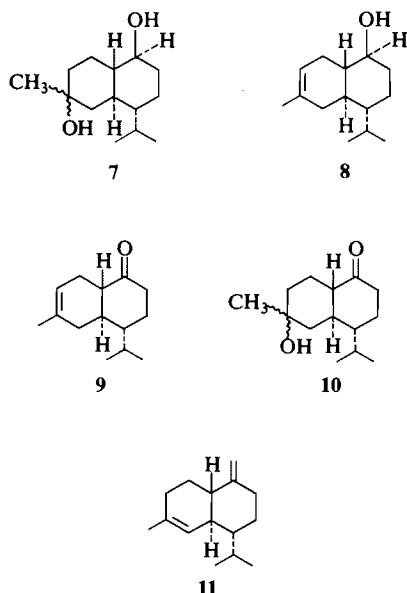
The ketoenol ether (**3**) (2) served as starting material. This was prepared, as previously reported (2), in eight steps from *p*-anisaldehyde and methylisobutyl ketone. It had previously been reported as an oil but we were fortunate in obtaining it as a crystalline compound. The stereochemistry assigned to **3** follows from the fact that it was obtained by reduction of **4** with lithium in liquid ammonia (3) and its eventual conversion to **1** thence to **2**. The absolute stereochemistry of the latter has been firmly established (4). The fact that it was unchanged after submission to equilibrating conditions (see Experimental) is further proof of the assigned *trans* ring fusion in **3**.

Reduction of **3** with lithium aluminum hydride afforded the alcohol **5** in 73% yield. The hydroxyl

group in **5** is assigned the equatorial orientation on the basis of the nuclear magnetic resonance (n.m.r.) spectra of subsequent compounds (vide infra). Treatment of **5** with a dilute methanolic solution of oxalic acid converted it to the keto alcohol (**6**) in 95% yield. The broad signal with a half-width ($w_{1/2}$) of 20 Hz at δ 3.23 in the n.m.r. spectrum is indicative of an axial proton associated with a secondary alcohol (5), hence the assignment of the secondary hydroxyl group in **5**, **6**, **7**, and **8** to the equatorial orientation. In **5** this signal is partially obscured by the signal for the OCH_3 group at δ 3.51.

A Grignard reaction with methylmagnesium bromide converted **6** into a mixture of epimeric diols **7**, one of which was obtained in 40% yield as a crystalline compound. Selective dehydration of **7** under mild conditions afforded the olefin **8** in 80% yield. This olefin was also obtained by dehydration of the material from the mother liquors which had deposited crystalline **7**. The overall yield of **8** from **6** was 75%. Oxidation of **8** with the Sarett reagent (6) gave the enone **9** in 65% yield. The same enone was obtained by dehydration of the keto alcohol **10**, obtained by oxidation of the diol **7** with the Jones reagent (7). This ketone (**9**) was unchanged after submission to equilibrating conditions as in the case of **3** (see Experimental).

The enone **9** was subjected to a Wittig reaction and the product was purified by chromatography on silica gel impregnated with 20% of silver nitrate. Thereby, (\pm) γ_2 -cadinene (**1**) was obtained in 90% yield. The synthetic terpene gave rise to a single peak on vapor phase chromatog-



raphy (v.p.c.) under conditions whereby a mixture of cadinenes was separated into three components. The v.p.c., thin layer chromatography (t.l.c.) (silica gel—silver nitrate with various solvents), and n.m.r. spectrum all indicated that our synthetic compound (**1**) was uncontaminated.

Unfortunately, we have been unable to obtain a pure sample of naturally occurring γ_2 -cadinene for direct comparison with our synthetic terpene. The infrared (i.r.) spectrum of **1** was similar to that of a published (1) spectrum of $(-)\gamma_2$ -cadinene but there were differences in the detailed pattern of the fingerprint region. However, the i.r. spectrum of **1** was distinctly different from a spectrum of natural γ -cadinene (**11**). The possibility of our synthetic terpene being **11** is also excluded by the nature of the n.m.r. signal due to the vinylic proton at C₃. This signal appeared as a broad multiplet at δ 5.48 whereas the corresponding vinylic proton in **11** should resemble a singlet because the dihedral angle with the vicinal proton is approximately 90°.

Treatment of the synthetic terpene (**1**) with hydrogen chloride gas in ether, with rigorous exclusion of moisture afforded, in 60% yield, (\pm) -cadinene dihydrochloride (**2**). The i.r. spectrum of the dihydrochloride was superimposable on the spectra of samples of cadinene dihydrochloride obtained from natural cadinenes. The conversion to cadinene dihydrochloride excludes the possibility of our compound (**1**)

belonging to the bulgarene or amorphene series¹ (**8**). The remaining possibility, that our synthetic terpene might be " γ_2 -muurolene"² (**1** with *cis* ring fusion) is excluded by the fact that the precursor ketones **3** and **9** have been shown, by equilibration, to possess *trans* ring fusions. The conversion of **1** to (\pm) -cadinene dihydrochloride under conditions whereby muurolene dihydrochloride could be expected in good yield from compounds of the muurolene (*cis* ring fusion) series (**9**, **10**) provides further evidence against this possibility.

The synthetic route described above affords an opportunity to accomplish syntheses, through the various intermediates, of virtually all of the cadinenes. Moreover, since the appropriate optically active diketone corresponding to the starting material **3** has been prepared from cryptone (**11**), total syntheses of naturally occurring enantiomers of the cadinane series should now be possible.³

Experimental

General

The n.m.r. spectra were determined in deuteriochloroform (CDCl₃) solutions with a Varian T-60 instrument. Chemical shifts are expressed in parts per million (δ values) downfield from the tetramethylsilane signal as internal standard. Petroleum ether refers to the fraction with boiling point range 30–60°.

Reaction products were isolated by the following procedure. The product was extracted into the specified solvent and the extract was washed with appropriate aqueous solutions as indicated and finally with saturated brine. The aqueous washings were extracted three times with the solvent and the combined extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated *in vacuo* on a rotary evaporator.

Ketoenol Ether (**3**)

The ketoenol ether (**3**) was prepared from *p*-anisaldehyde and methylisobutyl ketone in eight steps as previously described (2). The crude product was purified by column chromatography on silica gel. The column was rapidly developed with increasing proportions of ether in petroleum ether and the product was eluted with 10% of ether in petroleum ether. In a typical experiment when 13.0 g of crude product was chromatographed on 110 g of silica gel (column diameter 2.40 cm) there was obtained, after crystallization from pentane, 4.50 g of crystalline

¹The isopropyl group is *trans* to the vicinal hydrogen atom at the ring junction in the bulgarene and amorphene series.

²To our knowledge this compound has never been isolated.

³After submission of this work for publication, a synthesis of $(+)\epsilon$ -cadinene along lines similar to those described in this paper was reported (ref. 12).

3, m.p. 47–48°; ν_{\max} (Nujol) 1712 (ketone) and 1675 cm^{-1} (double bond); n.m.r., δ 0.77 and 0.97 (3H each, doublets, $J = 7.0$ Hz, isopropyl group⁴), 3.51 (3H, singlet, OCH_3), 4.63 (1H, multiplet, vinylic H); the overall yield of crystalline compound for the eight steps was ca. 10%.

A sample of 3 was unchanged after refluxing with a mixture (1:1) of ethanol – 10% aqueous sodium hydroxide for 1½ h.

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_2$: C, 75.64; H, 9.97. Found: C, 75.52; H, 10.15.

Alcohol 5

A solution of 6.50 g of the ketoenol ether (3) in 160 ml of ether was added, over a period of 75 min, to a refluxing mixture of 1.50 g of lithium aluminum hydride in 160 ml of ether. After addition was completed the mixture was refluxed for 4 h, cooled, treated with 1.5 ml of concentrated brine and stirred for 18 h. Sodium sulfate was added to the mixture and the solids were removed by filtration and washed with ether. The combined filtrate and washes were evaporated *in vacuo*. The residue, on crystallization from methylcyclohexane, afforded 5.06 g (73%) of crystalline 5, m.p. 103°; ν_{\max} (Nujol) 3350 (OH) and 1675 cm^{-1} (double bond); n.m.r. δ 3.51 (3H, singlet, OCH_3), 4.65 (1H, broad multiplet, vinylic H), 3.25 (1H, very broad multiplet, $\text{H}-\text{C}-\text{OH}$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_2$: C, 74.95; H, 10.78. Found: C, 75.12; H, 11.05.

Keto Alcohol (6)

A solution of 5.0 g of 5, 33 ml of methanol and 7.5 ml of 0.6 *M* aqueous oxalic acid was left at room temperature for 75 min. The solvent was evaporated *in vacuo* and the residue dissolved in 50 ml of ether. The ethereal solution was worked up in the usual manner by washing with bicarbonate solution and brine. The residue, on crystallization from ether – petroleum ether afforded 4.47 g (95%) of crystalline 6, m.p. 61–63°; ν_{\max} (Nujol) 3290 (OH) and 1712 cm^{-1} (ketone); n.m.r., δ 3.23 (1H, broad multiplet, $w_{1/2} = 20$ Hz, $\text{H}-\text{C}-\text{OH}$).

Anal. Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 74.25; H, 10.54. Found: C, 74.39; H, 10.67.

Diol 7

To a stirred solution of 100 ml of a 1 *M* ethereal solution of methylmagnesium bromide (freshly prepared) at –40 °C was added over a period of 45 min, a solution of 5.25 g of keto alcohol 6 in 150 ml of ether. After addition of the keto alcohol the reaction mixture was allowed to come to room temperature over a period of 1 h then stirred for a further 24 h. The solution was then treated with 52 ml of 2 *N* hydrochloric acid, washed with bicarbonate solution and thiosulfate solution, and worked up in the usual manner. The residue was crystallized from ethyl acetate – petroleum ether whereby 2.17 g (38%) of 7 was obtained as a crystalline compound, m.p. 149°; ν_{\max} (Nujol) 3350 cm^{-1} (OH); n.m.r., δ 1.23 (3H, singlet, CH_3), 3.17 (1H, broad multiplet, $w_{1/2} = 20$ Hz, $\text{H}-\text{C}-\text{OH}$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{26}\text{O}_2$: C, 74.29; H, 11.58. Found: C, 74.19; H, 11.44.

⁴This pair of doublets appears in the n.m.r. spectra of all succeeding compounds.

Enol 8

A solution of 2.40 g of the diol 7 and 2.4 g of *p*-toluene sulfonic acid in 2400 ml of benzene was stirred at 52° for 2 h. The benzene solution was cooled, washed with bicarbonate solution and worked up in the usual manner. The residue, on crystallization from pentane, afforded 1.92 g (80%) of crystalline 8, m.p. 79–80°; ν_{\max} (Nujol) 3250 cm^{-1} (OH); n.m.r., δ 1.65 (3H, singlet, CH_3), 3.17 (1H, broad multiplet, $w_{1/2} = 20$ Hz, $\text{H}-\text{C}-\text{OH}$), 5.40 (1H, broad multiplet, vinylic H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}$: C, 80.71; H, 11.61. Found: C, 80.43; H, 11.68.

This enol (8) was also obtained by dehydration of the material from the mother liquors from which the diol 7 had crystallized. Dehydration of 596 mg of such material afforded 428 mg (78%) of 8 identical with the compound described above. The overall yield of 8 from the keto alcohol 6 was 75%.

Ketone 9

To a mixture of 1.8 g of chromic anhydride in 20 ml of pyridine was added 832 mg of enol 8 in 20 ml of pyridine. The mixture was stirred at room temperature for 8 h. The solvent was removed *in vacuo* at room temperature and 150 ml of cold water was added to the residue. The aqueous mixture was worked up in the usual manner with ether. The crude product was chromatographed on a column (diameter 3.0 cm) of 35 g of silica gel impregnated with 20% of silver nitrate. Elution of the column with pentane–benzene (3:1) afforded 727 mg (87%) of crystalline 9, m.p. 35°; ν_{\max} (film) 1715 cm^{-1} (ketone); n.m.r., δ 1.67 (3H, singlet, CH_3), 5.47 (1H, multiplet, vinylic H).

A sample of this compound was unchanged after refluxing with a (50%) mixture of ethanol – 10% aqueous sodium hydroxide for 1½ h.

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C, 81.49; H, 10.74. Found: C, 81.27; H, 10.52.

This compound was also obtained by dehydration of the keto alcohol 10 as follows. A solution of 330 mg of 10 and 16 mg of *p*-toluenesulfonic acid in 50 ml of benzene was refluxed for 5 h. Water was removed by means of a Dean–Stark trap. After cooling, the reaction solution was washed with 5% sodium carbonate solution and worked up in the usual manner. Distillation of the resulting oil *in vacuo* at 64° onto a cold finger afforded 304 mg of 9 identical with the enone obtained by oxidation of 8 (*vide supra*).

Keto Alcohol 10

A stirred solution of 258 mg of the diol 7 in 30 ml of acetone was cooled on an ice-bath and treated with 0.4 ml of 8 *N* Jones reagent (7). After 5 min, 6 ml of methanol was added and stirring was continued for 5 min then 18 ml of 5% sodium carbonate was added and the product was worked up with ether in the usual manner. Crystallization of the residue from ether – petroleum ether afforded 190 mg (67%) of 10, m.p. 110°; ν_{\max} (Nujol) 3400 cm^{-1} (OH); n.m.r., δ 1.23 (3H, singlet, CH_3).

Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_2$: C, 74.95; H, 10.78. Found: C, 74.51; H, 10.88.

(±)γ₂-Cadinene (1)

The Wittig reaction was carried out in an atmosphere

of dry oxygen-free nitrogen as follows. To a suspension of 1.35 g of methyltriphenylphosphonium bromide in 25 ml of ether was added 1.9 ml of a 2.3 *M* ethereal solution of *n*-butyllithium. The mixture was stirred at room temperature for 2 h. The resulting yellow suspension was treated with a solution of 250 mg of the enone 9 in 38 ml of tetrahydrofuran and stirring was continued at room temperature for 1 h. Ether was removed by distillation until the temperature reached 65° and the solution was refluxed at this temperature for 3 h. Water (2.5 ml) was added to the reaction solution and the organic solvent was removed *in vacuo*. The product was dissolved in 150 ml of pentane and the solution was washed with water. The residue obtained by evaporation of the extracts *in vacuo* was chromatographed on a column (diameter 2.0 cm) of 14.5 g of silica gel impregnated with 20% silver nitrate. After developing with 5% of benzene in cyclohexane the terpene was eluted with 10–25% benzene in cyclohexane. Thereby 226 mg (91%), of (\pm) γ_2 -cadinene was obtained as a clear oil; n.m.r., δ 0.73 and 0.93 (3H each, doublets, $J = 7.0$ Hz, isopropyl group), 1.68 (3H, singlet, CH₃), 4.60 and 4.72 (1H each, broad overlapping singlets, exocyclic CH₂), 5.48 (1H, broad multiplet resembling a poorly developed triplet, vinylic H). The v.p.c. on a column (10' \times 3/8") of 3% XE60 on Chromosorb W with the column temperature at 150° gave rise to a single peak with retention time of 4 min 10 s.

Anal. Calcd. for C₁₅H₂₄: C, 88.16; H, 11.89. Found: C, 87.91; H, 11.99.

Conversion of (\pm) γ_2 -Cadinene to (\pm)-Cadinene Dihydrochloride (2)

The following manipulations were carried out with exclusion of moisture. A solution of 80 mg of synthetic (\pm) γ_2 -cadinene in 5 ml of dry ether was saturated at –20° with dry hydrogen chloride gas. The solution was left at 5° for 18 h then the solvent was evaporated under a stream of dry nitrogen. The residue, after several crystallizations from petroleum ether, afforded 64 mg

(60%) of crystalline 2, m.p. 105° (lit. (2) m.p. 105–106°). The i.r. spectrum of the synthetic dihydrochloride was superimposable on the spectra of samples of optically active dihydrochloride obtained from natural cadinenes.

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