136. Homologues of *p*-Menthane Derivatives in Roman Camomile

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Dedicated to Professor *George Büchi* on the occasion of his 60th birthday

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Summary

5-Isopropyl-2-propyl-2-cyclohexen-1-one (**1**) and 5-isopropyl-2-(2-methylpropyl)-2-cyclohexen-1-one (**2**), homologues of the *p*-methene ketone carvotanacetone, have been identified in the oil of *Anthemis nobilis*. Their synthesis involved allylation of a cyclohexane-1,3-dione, and the acid-catalyzed cyclization to dihydrofurans of the 2-allylcyclohexane-1,3-diones is described. The stereochemistry of metal hydride reduction of 3-ethoxy-5-isopropyl-2-propyl-2-cyclohexen-1-one (**18**) is mentioned in the course of the synthesis of the natural products. Some biogenetic considerations are discussed.

In the course of an analysis of the oil of Roman camomile *(Anthemis nobilis)*, the two ketones, **1** and **2**, were isolated[1]). Because very small amounts were available from natural sources, we carried out syntheses of the racemates.

In the first synthesis, we prepared 4-isopropyl-2-methoxy-2-cyclohexen-1-one (**3**) by the annelation method of *Wenkert* [2], and found the yields were poor, in accord with other workers [3]. We used the morpholine enamine **4** in place of the more expensive pyrrolidine enamine. The major difficulty of the route was in scale-up; while the removal of methanol from 1,4-dimethoxy-2-butanone (**5**) with *p*-toluenesulfonic acid runs well on the small scale described [2] [3], larger amounts tend to polymerize during the preparation. More rapid distillation results in lower yields, but the resulting mixture of **5** with the vinyl ketone **6** can be used as such in the cyclization to **3**.

Reaction of propylmagnesium bromide in ether on **3** yielded the corresponding tertiary alcohol **7**, mostly in a single configuration which, we feel, must be the isomer having both alkyl substituents on the same side of the ring, based on the 'axial-attack' model for *Grignard* additions [4]. Treatment of the crude mixture of these alcohols with *p*-toluenesulfonic acid in refluxing toluene led to a 7:1

[1]) Full details of the isolation procedure and of accompanying products will be described in a forthcoming paper [1].

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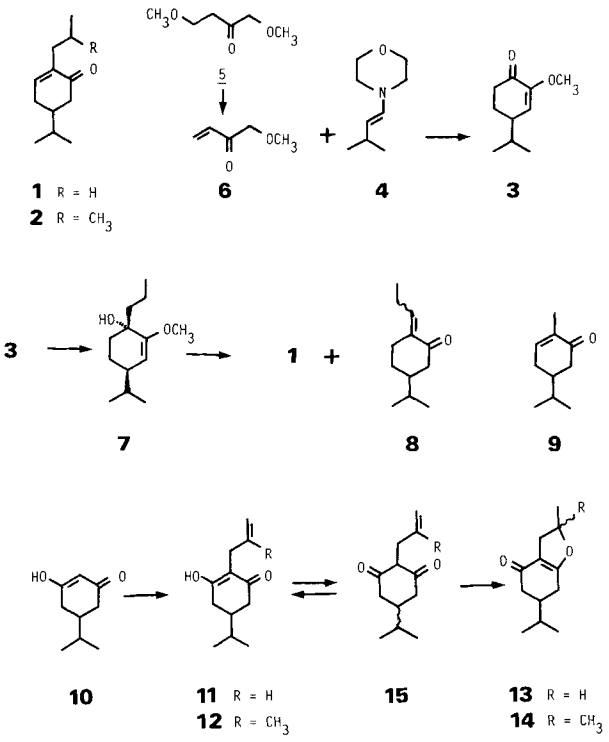
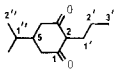


mixture of the desired ketone **1** (spectrally identical with the natural product) and the isomers **8** with an exocyclic double bond.

Meanwhile, we had developed the more efficient synthesis starting from 3-hydroxy-5-isopropyl-2-cyclohexen-1-one (**10**), readily available from sodium diethyl malonate and 5-methyl-3-hexen-2-one [5], and based on the well known route to carvotanacetone **9** [6]. It has been known from at least 1932 [7] (with much confirmation later [8] [9]) that enolized cyclohexane-1,3-diones lead to *O*-alkylation with saturated alkyl halides (except for methyl) while allyl halides generally yield predominantly C-allylated compounds. Accordingly, the enol **10** was treated with allyl bromide in aqueous alkaline solution [10] [11], when a reasonable yield of the C-allyl compound **11** was obtained. The methallyl compound **12** was similarly obtained using methallyl chloride. These compounds (**11** and **12**) cannot be purified by gas chromatography because they readily undergo cyclization to the dihydrofuran compounds **13** and **14** respectively, on metallic surfaces or in the presence of acid, and their NMR. spectra are not immediately interpretable in terms of the formulae **11** and **12**. Thus the ^{1}H-NMR. spectra vary with the amount of the keto-tautomers **15** present in the mixture; reasonably reproducible spectra can be achieved by addition of trifluoroacetic acid. The ^{13}C-NMR. data obtained at 90.5 MHz are given in the upper part of the *Table*. The conditions for these measurements involve a temperature of about 40° in the sample, and rapid equilibration (between the enols **11** and **12**, and the stereoisomers of the

diketones **15**) occurs so that C(4) is equivalent to C(6); its signal is often so broad that it is difficult to see at all, and C(1) does not give a visible signal. Measured at 22.63 MHz, the ^{13}C-NMR. spectra are taken at *ca.* 25°, and show the signals in the lower part of the *Table.* A broad signal is now visible for C(1), and the surrounding C-atoms have slightly different values, but the molecule still behaves as a rapidly equilibrating mixture. We accordingly placed more faith in the value of the elemental analyses than is at present customary.

Table. *^{13}C-NMR. data of 5-isopropyl-2-propylcyclohexane-1,3-dione*

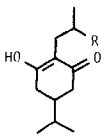


	C(1)	C(2)	C(5)	C(4)	C(1′)	C(2′)	C(3′)	C(1″)	C(2″)	H_3C–C(2′)
Measured at 90.5 MHz and *ca.* 40°										
11	[a])	113.5	39.5	37[b])	26.5	136.4	116.0	31.9	19.5	–
12	[a])	112.7	39.7	36.8[b])	30.1	144.6	110.0	31.9	19.5	22.2
16	[a])	115.5	39.7	37.2[b])	23.8	21.8	14.0	31.9	19.6	–
17[c])	[a])	114.8	39.7	37.2[b])	30.6	27.6	22.5	31.8	19.6	22.5
Measured at 22.63 MHz and *ca.* 25°										
11	188.1[b])	113.2	39.6	36.8	26.1	136.2	114.4	31.8	19.5	–
12	188.2[b])	113.0	39.8	36.8	29.9	144.3	110.0	31.8	19.6	22.6

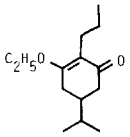
[a]) Signal not visible.
[b]) Broad signal.
[c]) Measured in $CDCl_3 + (CD_3)_2SO$; all others in $CDCl_3$.

Catalytic hydrogenation of the allyl compounds **11** and **12** yielded respectively **16** and **17**. Initially we converted **16** to the enol ether **18** which, in turn, was reduced with lithium aluminium hydride. There were formed approximately equal amounts of the desired unsaturated ketone **1**, *trans*-3-ethoxy-5-isopropyl-2-propyl cyclohexene (**19**), and *cis*-5-isopropyl-2-propyl-2-cyclohexen-1-ol (**20**). Formation of the *cis*-alcohol **20** is not surprising; it is the expected product of hydride reduction of the ketone **1** (*cf.* [12]), but the *trans*-ether **19** is more unusual. The first stage of the reduction must involve reduction of the carbonyl group to a *cis*-hydroxyl group bound to aluminium. In the work-up stage this group might be able to deliver a hydride ion stereospecifically *via* **21**, or an analogous intermediate, to the C-atom in the allyl position (*cf.* [13]).

It was more convenient in small-scale work to reduce the enol-ketones **16** and **17** directly with lithium aluminium hydride. The major products were the alcohols



16 R = H
17 R = CH_3



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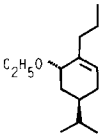

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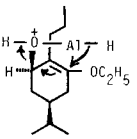

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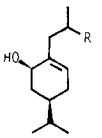
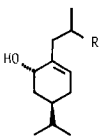


20 R = H
23 R = CH_3



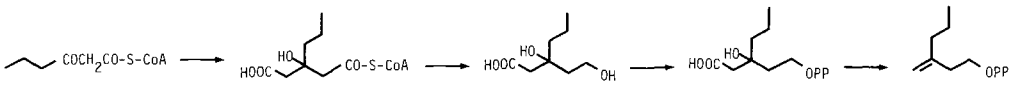
22 R = H
24 R = CH_3

20 and **22** (from **16**) and **23** and **24** (from **17**). The stereoselectivity observed when the enol ether **18** is reduced is no longer observed, and nearly equal amounts of *cis*- and *trans*-isomers were isolated.

The natural products **1** and **2** were obtained from isomer mixtures, respectively of **20** and **22**, and **23** and **24**, by oxidation with excess manganese dioxide, and were identical (retention time on GLC. and TLC., NMR. and MS.) with the natural products.

The question of the biogenesis of these C_{12}- and C_{13}-ketones must remain open. Most of the naturally occurring C_{12}-terpenoids can be derived from sesquiterpenes by the loss of a C_3-unit[2]). It is difficult to formulate such a route to **1** and **2** from any known sesquiterpene skeleton. It is possible to formulate a mevalonate-type of route which branches from the butyryl-coenzyme A of the fatty acid biogenetic pathway. This would lead to 3-propyl-3-butenyl pyrophosphate *(Scheme)* and thus to **1** by combination with dimethylallyl pyrophosphate. It is, however, very difficult to account for the branched chain homologue **2** by a route of this nature. On the other hand, it is perhaps significant that *Anthemis nobilis* is surprisingly poor in monoterpenoids – those we have identified are frequently in an esterified form [1] – but rich in products derived from amino-acids by oxidative degradation [20], such as angelic, isobutyric and methacrylic esters (*cf. e.g.* [21]). It has already been shown that leucine and valine are incorporated into monoterpenoid biogenesis [22], and it is not difficult to postulate a route from valine to **2**, although **1** presents a problem here, because α-aminobutyric acid is not a common natural amino-acid.

Scheme



We thank Mr. *Walter Thommen* for valuable assistance with the NMR.-spectra.

Experimental Part

General remarks. NMR. spectra were recorded in $CDCl_3$ on a *Hitachi-Perkin Elmer* R20B (60 MHz), a *Bruker* HX-90 (90 MHz), or a *Bruker* WH-360 (360 MHz) instrument. Chemical shifts are given in ppm downfield from TMS (=0 ppm), coupling constants (*J*) in Hz; $w_{1/2}$ means the width of a signal (in Hz) at half its height. Mass spectra were measured either on an *Atlas* CH-4 mass spectrometer using an inlet temperature of *ca.* 150°, or a *MAT* 112 instrument coupled with a capillary gas chromatograph, both spectrometers using electrons of 70 eV. Results are quoted in *m/z* (% most important fragment), and generally the values of the ten most important fragments are given. Column chromatography was carried out on *Merck* H (Type 60) silica gel using a *Jobin-Yvon* medium pressure chromatograph, and gas-liquid chromatography (GLC.) on a *Carlo-Erba* type GT chromatograph with He as carrier gas.

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[2]) A recent report of a C_{12}-terpenoid [14] suggested that this is a unique occurrence. Actually many are known, *e.g.* from sandalwood oil [15], geijerone [16], albene [17], some C_{12}-ketones from vetyver oil [18], and one from angelica root oil that is less easily linked with a sesquiterpene [19].

Isolation of 5-isopropyl-2-propyl-2-cyclohexen-1-one (**1**) *and 5-isopropyl-2-(2-methylpropyl)-2-cyclohexen-1-one* (**2**) *from the oil of* Anthemis nobilis. A combination of distillation and column chromatography [1] yielded a fraction which had b.p. 60–65°/0.01 Torr, and polarity on a silica gel column approximately that of phenylethyl isobutyrate (the major constituent of the fraction). GLC. on silicone oil enabled the separation of phenylethyl isobutyrate from **1**, the latter having a longer retention time. The pure compound was obtained by GLC. *(Carbowax).* – ^{1}H-NMR. (360 MHz): 0.88 (*t*, J=7.5, CH_3CH_2); 0.910 and 0.913 (2 *d*, J=7, 9 H); 1.40 (apparently $d\times qa$, J=7.5, 2 H, CH_2CH_3); 1.57 (6 lines, J=7, 1 H, $CH(CH_3)_2$); 1.83 (*m*, 1 H, H–C(5)); 2.05–2.20 (*m*, 4 H); 2.39 ($d\times d\times d$, J=18, 6 and 5, H_{eq}–C(4)); 2.52 ($d\times d\times d$, J=16, 3.5 and 1.5, 1 H, H_{eq}–C(6)); 6.70 (*d*, J=6 and further coupling, 1 H, H–C(3)). – MS.: 180 (60, M^+), 137 (39), 110 (100), 109 (25), 95 (47), 81 (37), 67 (32), 53 (19), 41 (29).

This compound (**1**) was followed on the silicone oil GLC. column by 5-isopropyl-2-(2-methylpropyl)-2-cyclohexen-1-one (**2**). – ^{1}H-NMR. (360 MHz): 0.83 and 0.84 (2 *d*, together 6 H); 0.911 and 0.917 (2 *d*, J=7, together 6 H); 1.57 (6 lines, J=7, 1 H); 1.72 (7 lines, 1 H, $CH_2CH(CH_3)_2$); 1.83 (*m*, 1 H, H–C(5)); 2.0–2.2 (*m*, 4 H); 2.39 ($d\times d\times d$, J=18, 6 and 5, 1 H, H_{eq}–C(h)); 2.52 ($d\times d\times d$, J=16, 3.5 and 1.5, 1 H, H_{eq}–C(6)); 6.64 ($d\times d$, J=6 and 2, 1 H, H–C(3)). – MS.: 194 (92, M^+), 151 (48), *124* (100), 112 (37), 95 (55), 82 (47), 81 (77), 53 (37), 43 (48), 41 (57).

Synthesis of 4-isopropyl-2-methoxy-2-cyclohexen-1-one (**3**) (*cf.* [3]). Distillation of 90 g of 1,4-dimethoxy-2-butanone with 0.1 g of *p*-toluenesulfonic acid at 10 Torr [2] yielded 60 g of a mixture of unchanged dimethoxybutanone containing 46% (determined by GLC.) of 1-methoxy-3-buten-2-one (**6**). This mixture was heated under reflux in 800 ml of toluene with 200 g of 4-(3-methyl-1-buten-1-yl)-morpholine (**4**). After 24 h, 110 g of acetic acid was added and refluxing continued for 5 h. Cooling, washing ($NaHCO_3$-solution, H_2O), followed by evaporation and distillation yielded 14 g of **3**, b.p. 60–65°/0.1 Torr. The ^{1}H-NMR. spectrum was somewhat different from that reported [3]. – ^{1}H-NMR. (90 MHz): 0.84 (*d*, J=6, 6 H); 3.63 (*s*, 3 H); 5.78 (*d*, J=2, 1 H).

Synthesis of 4-isopropyl-2-methoxy-1-propyl-2-cyclohexen-1-ol (**7**). *Grignard* reagent made with 0.65 g of magnesium and 3.6 g of propyl bromide was reacted on 4.5 g of the aforementioned ketone **3** to yield **7**. After work-up, GLC. *(OV 17)* showed a ratio of isomers of 9:1 which was used without purification in the next step. The major isomer was collected for spectral analysis. – ^{1}H-NMR. (60 MHz): 0.90 (*m*, 9 H); 3.52 (*s*, 3 H); 4.54 (*d*, J=3, 1 H). – MS.: 212 (2.7, M^+), 169 (54), 151 (43), *137* (100), 109 (60), 95 (38), 71 (59), 69 (48), 43 (51), 41 (41).

Dehydration of 4-isopropyl-2-methoxy-1-propyl-2-cyclohexen-1-ol (**7**). A solution of 4.5 g of the alcohol **7** and 0.1 g of *p*-toluenesulfonic acid in 60 ml of toluene was refluxed for 3.5 h. After washing ($NaHCO_3$-solution, H_2O) and evaporation, the residue was distilled (b.p. 55–60°/0.1 Torr) to give 2.3 g of a mixture of two substances (ratio 7:1 by GLC. on *Carbowax*), separated by liquid chromatography in toluene into the following. The major compound, eluted first was 5-isopropyl-2-propyl-2-cyclohexen-1-one (**1**), spectrally identical (^{1}H-NMR., MS.) with the natural product described above. The second (minor) compound eluted was 5-isopropyl-2-propylidenecyclohexan-1-one (**8**). – ^{1}H-NMR. (90 MHz): 0.93 (*d*, J=6, 6 H); 1.06 (*t*, J=7, 3 H); 6.60 (*t*, J=7, 1 H). – MS.: 180 (100, M^+), 137 (42), *109* (100), 95 (58), 81 (49), 69 (45), 67 (93), 55 (58), 43 (44), 41 (75).

Synthesis of 2-allyl-3-hydroxy-5-isopropyl-2-cyclohexen-1-one (**11**) (*cf.* [10] [11]). About 125 g of crude 3-hydroxy-5-isopropyl-2-cyclohexen-1-one (**10**, 343 g of the paste obtained following [8], and containing *ca.* 60% water) and 50.4 g of KOH in 176 ml of H_2O were stirred at 0–5° while 122 g of allyl bromide were added dropwise over 1 h. The temperature was allowed to rise to 20° and stirring was continued for 15 h. Since the pH had now become neutral, 10 ml of 50% KOH-solution was added and stirring continued, raising the temperature to 55°. After 2 h, another 25 ml of 40% KOH-solution was added and stirring continued for 1 h. The mixture was cooled to RT. and extracted with ether (5 × 100 ml). The ether was washed once with water and allowed to stand. The crystals which formed were removed by filtration and the ether evaporated to half its volume, when more crystals formed. The total weight of crystals thus obtained was 98.6 g. For analysis, the product was recrystallized from ether/pentane, m.p. 141–143°. – ^{1}H-NMR. (360 MHz, CF_3COOH added): 0.95 (*d*, J=7, 6 H, $CH(CH_3)_2$); 1.61 ($d\times qa$, J=7 and 7, 1 H, $CHCH(CH_3)_2$); 1.93 (*m*, 1 H, H–C(5)); 2.29 ($d\times d$, J=12 and 17, 2 H, H–C(4) and H_{ax}–C(6)); 2.59 ($d\times d$, J=4 and 17, 2 H, H–C(4) and H_{eq}–C(6)); 3.08 (*d*, J=6, 2 H, C=CCH_2CH=); 5.17, 5.21 and 5.84 (*ABX* system, J=7, 10 and 17, each 1 H, CH=CH_2). Without added CF_3COOH, some signals were less sharp; the following were characteristic: 0.95 and 0.96 (2 *d*, J=6.5) (the major CH_3 signals were unchanged from the measure-

ment in acid solution); 1.58 (*m*); *ca.* 1.70 (*m*, weak); 2.19 (br. *t*); 2.48 (*d*×*d*, *J*=5 and 17); 3.14 (*d*, *J*=6); 3.45 (*t*, *J*=6, H–C(2) in a keto form); 5.13, 5.19 and 5.85 (CH=CH_2). – MS.: 194 (77, M^+), 179 (63), 124 (81), 97 (58), *96* (100), 81 (44), 69 (38), 55 (44), 41 (74), 39 (38).

$C_{12}H_{18}O_2$ (194.26) Calc. C 74.19 H 9.34% Found C 74.18 H 9.27%

If the crude mixture was chromatographed on silica gel in $CHCl_3$, a lower yield of the pure product **11** was obtained, preceded by elution of 2,2-diallyl-5-isopropylcyclohexane-2,5-dione, recognizable by the spectra. – ^{1}H-NMR. (60 MHz): 0.92 (*d*, *J*=6, 6 H); 2.52 (*m*, 4 H); 4.8–6.0 (*m*, 6 H). – MS.: 234 (16, M^+), 193 (30), *97* (100), 80 (21), 79 (24), 55 (24), 41 (93), 39 (21), 27 (21).

Synthesis of 3-hydroxy-5-isopropyl-2-(2-methyl-2-propenyl)-2-cyclohexen-1-one (**12**). The reaction of 20 g of 3-hydroxy-5-isopropyl-2-cyclohexen-1-one (**10**) with 14.5 g of methallyl chloride yielded **12** which was then purified for analysis by chromatography in $CHCl_3$ over silica gel. The first substance eluted was 2,2-bis(2-methyl-2-propenyl)-5-isopropylcyclohexane-1,3-dione. – ^{1}H-NMR. (60 MHz): 0.94 (*d*, *J*=6, 6 H); 1.61 (*d*, *J*=2, 6 H); 2.55 (*d*, *J*=6, 4 H); 4.58 (2 H) and 4.82 (2 H) (*m*, C=CH_2). – MS.: 262 (47, M^+), 193 (68), 164 (53), 149 (45), 108 (80), 97 (83), 55 (69), 43 (57), *41* (100). The title product **12** was eluted shortly after; m.p. 135–136°. – ^{1}H-NMR. (360 MHz): 0.93 (*d*, *J*=6.5, 6 H); 1.59 (*d*×*qa*, *J*=7 and 7, 1 H, C*H*(CH_3)$_2$); 1.70 (*s*, 3 H); 1.85 (*m*, 1 H, H–C(5)); 3.12 and 3.18 (2 *d*, *J*≈15, each 1 H, more clearly visible after addition of D_2O, C=CCH_2C=); 4.90 and 4.92 (2 *s*, each 1 H, C=CH_2). – MS.: 208 (84, M^+), *193* (100), 147 (69), 110 (53), 97 (40), 96 (44), 95 (53), 55 (42), 43 (41), 41 (59). The similarity of this MS. with that of the corresponding benzofuran (**14**) (given below) suggests that some transformation to **14** occurred in the inlet system.

$C_{13}H_{20}O_2$ (208.29) Calc. C 74.96 H 9.68% Found C 74.68 H 9.67%

Synthesis of cis- *and* trans-*6-isopropyl-2-methyl-2,3,4,5,6,7-hexahydrobenzo [b]furan-4-ones* (**13**). A solution of 5 g of 2-allyl-3-hydroxy-5-isopropyl-2-cyclohexen-1-one **11** and 0.1 g of *p*-toluenesulfonic acid in 100 ml of toluene was heated under reflux for 16 h, then washed with $NaHCO_3$-solution and water and evaporated. Distillation yielded 3.5 g of *cis*- and *trans*-**13**, b.p. 66°/0.1 Torr, which was purified by GLC. (*OV 17* column) for analysis. – UV. (EtOH): 273 (14,700). – IR. (neat): 1635. – ^{1}H-NMR. (360 MHz): 0.94 (*d*, *J*=6.5, 6 H, the *d* for the two isomers were just resolved with 1 Hz separation); 1.39 and 1.43 (2 *d*, *J*=6.5, together 3 H, C*H*$_3$CH, two isomers); 1.63 (*m*, 1 H, C*H*(CH_3)$_2$); 1.97 (*m*, 1 H, H–C(6)); 2.93 (*m*, 1 H); 4.95 (*m*, 1 H, OC*H*CH_3). – ^{13}C-NMR.: 19.6, 19.8 and 22.0 (3 *qa*, 3 CH_3); 27.7 and 27.8 (*t*, C(7)); 32.0 (*d*, C(1′)); 33.0 and 33.1 (*t*, C(3)); 40.8 (*t*, C(5)); 41.2 and 41.3 (*d*, C(6)); 82.4 and 82.6 (*d*, C(2)); 112.4 and 112.7 (*s*, C(3a)); 177.2 and 177.3 (*s*, C(7a)); 195.2 (*s*, C(4)). – MS.: 194 (45, M^+), 179 (13), 151 (21), *124* (100), 98 (22), 96 (58), 69 (18), 43 (17), 41 (30).

$C_{12}H_{18}O_2$ (194.26) Calc. C 74.19 H 9.34% Found C 74.32 H 9.28%

Synthesis of 6-isopropyl-2,2-dimethyl-2,3,4,5,6,7-hexahydrobenzo [b]furan-4-one (**14**). This was prepared in the same way from 3-hydroxy-5-isopropyl-2-(2-methyl-2-propenyl)-2-cyclohexen-1-one (**12**) in 84% yield, and had b.p. 71°/0.1 Torr. – ^{1}H-NMR. (360 MHz): 0.94 (*d*, *J*=6.5, 6 H); 1.41 and 1.45 (2 *s*, each 3 H); 1.62 (*d*×*qa*, *J*=7 and 7, 1 H); 1.97 (*m*, 1 H); 2.12 and 2.16 (2 *t*, *J*=15, each 1 H, H–C(5) and H_{ax}–C(7)); 2.41 (*m*, 2 H, H–C(5) and H_{eq}–C(7)); 2.61 (*s*, 2 H, H_2C(3)). – ^{13}C-NMR.: 19.6, 19.8, 28.3, 28.4 (4 *qa*, **4** CH_3); 28.0 (*t*, C(7)); 32.1 (*t*, C(1′)); 38.9 (*t*, C(3)); 40.8 (*t*, C(5)); 41.2 (*d*, C(6)); 90.7 (*s*, C(2)); 112.3 (*s*, C(3a)); 176.2 (*s*, C(7a)); 195.4 (*s*, C(4)). – MS.: 208 (72, M^+), *193* (100), 147 (68), 138 (36), 123 (30), 112 (26), 96 (38), 95 (29), 43 (30), 41 (39).

$C_{13}H_{20}O_2$ (208.29) Calc. C 74.96 H 9.68% Found C 74.86 H 9.49%

Synthesis of 3-hydroxy-5-isopropyl-2-propyl-2-cyclohexen-1-one (**16**). A solution of 20 g of 2-allyl-3-hydroxy-5-isopropyl-2-cyclohexen-1-one (**11**) in 100 ml of ethanol was shaken in H_2 with 0.1 g of 10% Pt/C. In ½ h 2,200 ml of H_2 were absorbed (calc. 2,309 ml). The catalyst was filtered off and the solvent evaporated to leave a quantitative yield of **16**, m.p. 174.5–175.5°. – ^{1}H-NMR. (360 MHz): 0.90 (*t*, *J*=7, C*H*$_3$$CH_2$) and 0.94 (*d*, *J*=7) (9 H together); 1.39 (*d*×*qa*, *J*=7 and 7, 2 H); 1.58 (*m*, 1 H); *ca.* 1.8 (*m*, 2 H); 2.22 (*m*, 2 H); 2.48 (*m*, 2 H); the presence of the diketo form gave rise to further signals, notably at 3.30. – MS.: 196 (31, M^+), 167 (30), 112 (34), *97* (100), 84 (31), 69 (40), 55 (64), 43 (54), 41 (64), 27 (35).

$C_{12}H_{20}O_2$ (196.28) Calc. C 73.43 H 10.27% Found C 73.46 H 10.20%

3-Hydroxy-5-isopropyl-2-(2-methylpropyl)-2-cyclohexen-1-one (**17**) was prepared in the same way from 13 g of 3-hydroxy-5-isopropyl-2-(2-methyl-2-propenyl)-2-cyclohexen-1-one (**12**). – ^{1}H-NMR. (360 MHz): 0.88 and 0.93 (2 *d*, $J=7$, each 6 H); 1.58 (*d*×*qa*, $J=7$ and 7, 1 H, $CH(CH_3)_2$); 1.74 (*m*, 3 H); 1.85 (*m*, 1 H, H–C(5)); 2.13 (*d*, 2 H); 2.48 (*m*, 2 H). – MS.: 210 (27, M^+), 195 (27), 167 (55), *155* (100), 112 (30), 97 (94), 84 (31), 69 (41), 55 (58), 43 (38), 41 (57).

$C_{13}H_{22}O_2$ (210.31) Calc. C 74.24 H 10.54% Found C 74.26 H 10.48%

Synthesis of 3-ethoxy-5-isopropyl-2-propyl-2-cyclohexen-1-one (**18**). A mixture of 50 g of 3-hydroxy-5-isopropyl-2-propyl-2-cyclohexen-1-one (**16**), 65 g of ethyl orthoformate and 0.1 g of boron trifluoride etherate in 75 ml of ethanol was heated under reflux for 3 days. Excess solid K_2CO_3 was added, and after stirring for 1 h, the mixture was filtered and evaporated. The residue was distilled to yield 14 g of pure **18**, b.p. 83°/0.1 Torr. For analysis, this was purified by GLC. *(Carbowax)*. – ^{1}H-NMR. (60 MHz): 0.85–1.00 (9 H); 1.32 (*t*, $J=7$, 3 H); 4.01 (*qa*, $J=7$, 2 H).

$C_{14}H_{24}O_2$ (224.33) Calc. C 74.95 H 10.78% Found C 74.86 H 10.82%

Reduction of 3-ethoxy-5-isopropyl-2-propyl-2-cyclohexen-1-one (**18**) *with lithium aluminium hydride.* A mixture of 1.4 g of lithium aluminium hydride in 60 ml of dry ether was stirred under N_2 while 13.0 g of 3-ethoxy-5-isopropyl-2-propyl-2-cyclohexen-1-one (**18**) in 50 ml of dry ether was added dropwise. After stirring for 7 h, wet ether, followed by a few drops of water, was added, and the precipitate was filtered off and washed with CH_2Cl_2. The combined organic phases were washed with 50 ml of H_2O, 4×50 ml aq. HCl-, $NaHCO_3$-solution and H_2O. Drying and evaporating gave 9 g of residue which was distilled, yielding 6 g of volatile material, b.p. 49°/0.1 Torr. For analysis GLC. *(Carbowax)* enabled the following substances to be identified (in order of elution, yields are given in % of the distillate, determined by GLC.).

trans-*3-Ethoxy-5-isopropyl-2-propylcyclohexene* (**19**, 32%). – ^{1}H-NMR. (360 MHz): 0.88 and 0.90 (*d*, $J=7$), 0.89 (*t*, $J=7$, together 9 H); 1.21 (*t*, $J=7$, CH_3CH_2O); 1.10 (*m*, 1 H); 1.96–2.10 (*m*, 4 H); *ABX* system, A 3.41 (*d*×*qa*, $J=7$ and 10, 1 H); B 3.65 (the B branch is superimposed on a further 1 H having $w_{1/2}$ max 8 Hz (H_{eq}–C(3)); 5.56 (*d*, $J=4.5$, 1 H, H–C(1) with an HO_{ax}–C(3), *cf.* corresponding alcohols **21** and **22** below). A signal at 5.49 of *ca.* 10% of the intensity of the signal at 5.56 could correspond to the presence of the *cis*-isomer. – MS.: 210 (43, M^+), 181 (26), *167* (100), 139 (39), 121 (24), 111 (16), 79 (26), 55 (21), 43 (48), 41 (30).

5-Isopropyl-2-propyl-2-cyclohexen-1-one (**1**, 26%) was found identical (NMR., MS., and retention time on *Carbowax* and *OV17*) with the natural product.

cis-*5-Isopropyl-2-propyl-2-cyclohexen-1-ol* (**20**, 26%). – ^{1}H-NMR. (360 MHz): 0.88 and 0.90 (*d*, $J=7$), 0.91 (*t*, $J=7$, together 9 H); 1.17 (*m*, 1 H); 4.22 ($w_{1/2}=20$, 1 H, H_{ax}–C(3)); 5.47 (*d*, $J=5$, 1 H, H–C(1) with an HO_{ax}–C(3)). – MS.: 182 (45, M^+), 153 (62), *139* (100), 97 (27), 83 (34), 79 (39), 69 (31), 55 (38), 43 (65), 41 (41).

$C_{12}H_{22}O$ (182.29) Calc. C 79.06 H 12.16% Found C 79.03 H 12.13%

cis- *and* trans-*5-Isopropyl-2-propyl-2-cyclohexen-1-ol* (*cis*-(**20**) and *trans*-(**22**)). To a suspension of lithium aluminium hydride (1 g, 0.025 mol) in 150 ml of dry ether at 0° was added in small portions 10 g of 3-hydroxy-5-isopropyl-2-propyl-2-cyclohexen-1-one (**16**). The mixture was stirred for 0.5 h at 0°, then allowed to cool to RT. (1.5 h). A few drops of H_2O were added, and the solution was filtered and the residue washed with $CHCl_3$. The combined organic filtrates were evaporated, leaving 2.3 g of residue consisting largely of a 1:1 mixture of the **20** and **22**. For analysis, these were separated by GLC. *(Carbowax)* and characterized by the spectra. The *trans*-isomer (**22**) was eluted first. – ^{1}H-NMR. (360 MHz): 0.89–0.90 (*m*, 9 H); 4.06 ($w_{1/2}=8$, 1 H, H_{eq}–C(3)); 5.56 (*d*, $J=6$, 1 H, H–C(1), HO_{ax}–C(3)). – The MS. was nearly identical with that of the *cis*-isomer (**20**) described above. The *cis*-isomer (**20**) was eluted second, and was identical (NMR., MS.) with the compound described in the foregoing experiment.

cis- *and* trans-*5-Isopropyl-2-(2-methylpropyl)-2-cyclohexen-1-ol* (cis-**23** and *trans*-**24**) were prepared from 3-hydroxy-5-isopropyl-2-(2-methylpropyl)-2-cyclohexen-1-one (**17**) as in the foregoing experiment. The isomers were separated by GLC. *(Carbowax)*. The *trans*-isomer **24** was eluted first. – ^{1}H-NMR. (360 MHz): 0.90 and 0.91 (2 *d*, $J=7$, 12 H together); 4.04 ($w_{1/2}=8$, 1 H, H_{eq}–C(3)); 5.54 (*d*, $J=4.5$, 1 H, H–C(1)). The *cis*-isomer **23**, eluted second, had ^{1}H-NMR. (360 MHz): 0.82 and 0.88 (2 *d*, $J=7$, each 3 H); 0.90 and 0.93 (*d*, $J=7$, each 3 H); 1.16 (*m*, 1 H); 4.19 ($w_{1/2}=20$, 1 H, H_{ax}=C(3)); 5.47

(*d*, J=4.5, 1H, H–C(1)). – MS.: 196 (30, M^+), *153* (100), 139 (78), 93 (24), 83 (27), 69 (34), 57 (27), 55 (33), 43 (54), 41 (40) (practically identical with that of the *trans*-isomer).

$C_{13}H_{24}O$ (196.32) Calc. C 79.52 H 12.32% Found C 79.53 H 12.16%

5-Isopropyl-2-propyl-2-cyclohexen-1-one (**1**). To a stirred suspension of 48 g of MnO_2 (*Merck*, activated for 1 h at 120°) in 500 ml of petroleum ether (b.p. 50–70°) was added over 30 min 4.8 g of a mixture of the isomers of 5-isopropyl-2-propyl-2-cyclohexen-1-ol (**20** and **22**). After 4.5 h the reaction was complete; the MnO_2 was allowed to settle (overnight), and the mixture was filtered and evaporated. The residue was chromatographed in $CHCl_3$ over silica gel. For analysis, the material was purified by GLC. *(Carbowax)* and was identical (GLC., ^{1}H-NMR. and MS.) with the natural product.

5-Isopropyl-2-(2-methylpropyl)-2-cyclohexen-1-one (**2**) was prepared similarly from the isomers of 5-isopropyl-2-(2-methylpropyl)-2-cyclohexen-1-ol (**23** and **24**) and showed identical properties (GLC., NMR. and MS.) with the natural product.

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