examined. The fragment at *m/e* 98 amounted to 14.4% of the total ionization, and we may safely assume that it is best represented by the ion radical of cyclohexanone enol (Scheme 3). This is in accord with the fact that on irradiation in cyclohexane **7** is converted (> 60% yield) to a new tricyclic alcohol **8** (m.p. 64°) for which the analytical and spectral data are in agreement with the structure assigned.

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189. Synthetic Studies on Damascenones

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Dedicated to Dr. *Roger Firmenich* on the occasion of his 65th birthday

(12. VII. 71)

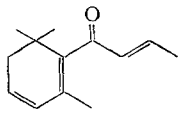
Summary. The odor principle β-damascenone and its isomer α-damascenone have been prepared by treatment of the corresponding ethyl safranates with excess allyl lithium followed by alkoxide catalyzed isomerization of the resulting products with β,γ-unsaturated ketonic side-chains. Addition of allyltriphenylphosphorane (preferably prepared from allyltriphenylphosphonium chloride) rather than the propenyl isomer to ethyl α-isopropylidene-acetoacetate produced ethyl α-safranate. This represents a new, potentially general method for the synthesis of functionalized cyclohexadienes.

Damascenone (**1**)[1], a trace constituent of Bulgarian rose oil (*Rosa damascena Mill.*) has an exceptionally powerful, as well as pleasing, odor and promises to become a key

[1] Doricenone (trade mark applied for by *Firmenich & Co.*, Geneva).

substance in the creation of modern fragrances. Its chemical structure, elucidated in the research laboratories of *Firmenich & Co.* [1], is characterized by the presence of a trimethylcyclohexadienyl ring previously discovered in the structure of vitamin A_2 but rare among natural products. In the original synthesis of damascenone (**1**) the disubstituted cyclic double bond was introduced in the final stages by bromination-dehydrobromination of a cyclohexene, a procedure employed earlier in the synthesis of vitamin A_2 [2].

We have explored a new route to damascenone (**1**) which begins with the construction of the trimethylcyclohexadiene ring and terminates with the elaboration of the side chain.



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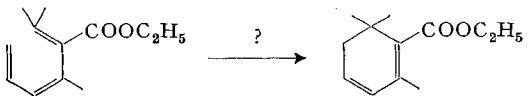
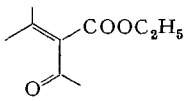
An attractive approach to a useful cyclohexadiene would be the cyclization of the triene ester **2** to ethyl β-safranate (**3**) by an electrocyclic reaction and an attempt to



2 **3**

realise this was made by an effort to prepare the triene ester **2** for which ethyl α-isopropylideneacetoacetate (**4**) served as starting material. A known procedure by condensation of acetone with ethyl acetoacetate in hot acetic anhydride containing zinc chloride was disappointing [3]; we obtained ketoester **4** only in low yield, and always contaminated with ethyl diacetylacetate (**7**). Fortunately the latter substance and unreacted ethyl acetoacetate can be removed from the desired **4** by extraction with aqueous sodium carbonate and aqueous sodium hydroxide, respectively. A more efficient synthesis has now been developed. Addition of two equivalents of methylmagnesium bromide to an ether solution of ethyl diacetylacetate (**7**) [4], followed by work-up with acetic anhydride and distillation, afforded the conjugated ketoester **4** (63%) contaminated by only 3% of the non-conjugated isomer **5** and usually less than 5% of the enol acetate **6**. Parenthetically, aqueous work-up after the Grignard reaction yielded mostly ethyl acetoacetate, undoubtedly resulting from retro-aldol cleavage of



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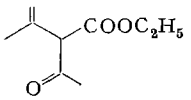

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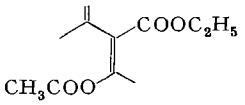

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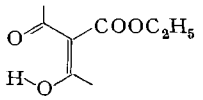

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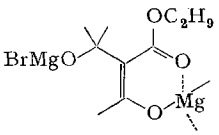

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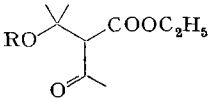
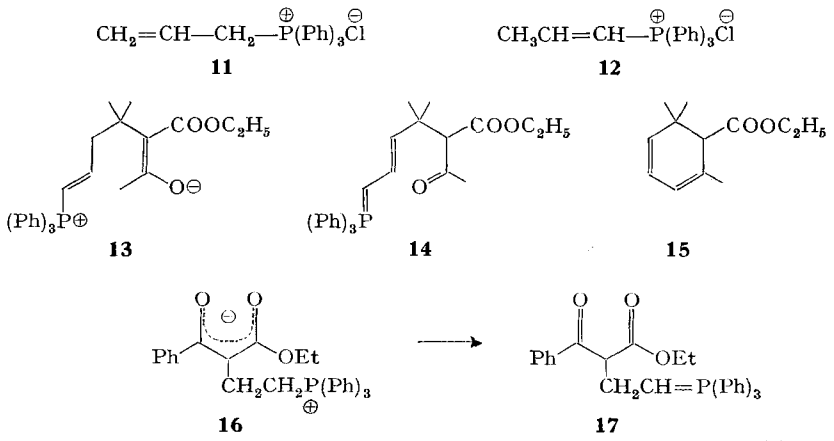


9 R=H
10 R=$COCH_3$

the intermediate hydroxyketone **9**. In agreement with this hypothesis the corresponding acetate **10**, produced by acylation of the magnesium chelate **8**, does not undergo this cleavage but loses acetic acid on work-up.

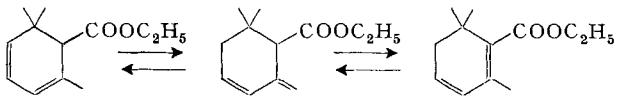
Wittig condensation of the ketoester **4** with the ylide prepared from allyltriphenylphosphonium chloride (**11**) and butyl lithium gave none of the anticipated triene **2** but ethyl α-safranate (**15**)[2]) initially in variable yield. From a series of at least thirty condensations, run under carefully defined conditions, we learned that the nature of the base, the conditions used in the preparation of the ylide and its condensation with the ketone **4** had little effect on the yield, but that the origin of the phosphonium salt was critical. Allyltriphenylphosphonium chloride (**11**) prepared from triphenylphosphine in excess refluxing allyl chloride (b.p. 45°) was far superior to material prepared from equimolar amounts of the components in boiling benzene (b.p. 80°). Analysis of such salts by NMR. spectroscopy revealed the presence of large amounts of propenyltriphenylphosphonium chloride (**12**) when prepared by the latter method. This isomerization was known to be catalyzed by alkoxides [6] but the thermal instability of allyltriphenylphosphonium chloride seems not to have been detected. Allyltriphenylphosphonium bromide, containing a less nucleophilic anion, is however stable in refluxing benzene. The corresponding ylide can also be used successfully in the synthesis of ethyl α-safranate (**15**) provided the *Wittig* condensation is performed under 'salt free' conditions [7]. The cause of the difference in behavior between allyl **11** and propenyl **12** salts is not known with certainty. Proton abstraction yields, of course, the same phosphorane but the propenylphosphonium salt (**12**) might not only lose a proton but might also accept the nucleophilic phosphorane or even butyl lithium and so give products other than ethyl α-safranate (**15**). The mechanism leading to the latter substance deserves comment, because its formation to the exclusion of the β-isomer **3** is in contradiction with the intermediacy of the triene **2**. A more satisfactory sequence starts with bond formation between the γ-, rather than the sterically more crowded α-carbon atom of the ylide and the β-position of the conjugated ketone to give the phosphonium betaine **13**. Proton transfer to the ylide **14** followed by intramolecular *Wittig* condensation would complete the overall change. Although



[2]) For an earlier, different preparation, see [5].

1,4-addition of phosphonium ylides to unsaturated ketones are rare [8] the exceptionally electron deficient double bond in **4** should facilitate such a process. More questionable is the transformation of the phosphonium betaine **13** to the ylide **14** because such an equilibrium was sought, but not found, between the tautomers **16** and **17** [9]. On the other hand, scale molecular models indicate enolate and ester groupings in **13** to be non-planar. The resulting increased basicity of the enolate and the presence of a more acidic vinylphosphonium grouping might account for the difference in behavior between the phosphonium betaines **13** and **16**.

With a short synthesis of ethyl α-safranate accomplished, we turned to isomerization experiments. Exposure of **15** to *p*-toluenesulfonic acid in hot benzene led to a mixture of isomers containing 20% of starting material, 20% of ethyl γ-safranate (**18**)[2] and 60% of ethyl β-safranate (**3**). That equilibrium had indeed been reached was verified by converting isomers **18** and **3** to the same mixture. As anticipated the equilibrium is in favor of the fully conjugated ester **3** but not by much because for steric reasons, the carbonyl group is not coplanar with the cyclohexadiene. This is also reflected in the UV. spectra, ethyl β-safranate (**3**) has maximum absorption at 274 nm[3] whereas the α-isomer **15** absorbs at 270 nm.



15 **18** **3**

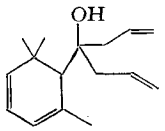
Brief exposure of the α-ester **15** to sodium ethoxide in hot ethanol gave a mixture of starting material (55%) and a new isomer **20** (45%) resulting from rate–controlled protonation of enolate **19** at the sterically least encumbered position. Isomerization of the α-ester **15**, in dimethylsulfoxide in presence of potassium *t*-butoxide, was accompanied by much polymerization and the distribution of isomers found, again does not represent a steady state (see Experimental).

19 **20**

For introduction of the remaining three required carbon atoms, the most available α-isomer of ethyl safranate (**15**) was at first used. Exposure of the ester to propenylmagnesium bromide led to recovery of starting material, whereas allylmagnesium bromide produced the diallylcarbinol **21** without a trace of ketone. Experiments with allyl lithium [11] were more encouraging, for with one equivalent of this reagent an approximately 50% mixture of the desired ketone **22** and starting ester was produced, and use of at least two equivalents of allyl lithium raised the yield of **22** to 84%. Clearly, addition of allyl lithium to the initially formed, highly hindered ketone **22** does not compete favorably with proton abstraction giving the enolate **24**, which on aqueous work-up affords the β,γ-unsaturated ketone by irreversible protonation in

[3] *Wendt* [10] reports λ_{max} 291 nm for β-safranic acid, a measurement we have not repeated but consider erroneous.

α to the carbonyl group [12]. In agreement with this hypothesis work-up with deuterium oxide led to incorporation of a single deuterium atom whose location, shown in **23**, followed from the NMR. spectrum. The contrast between the behavior of the two organometallic reagents towards the ester **15** is striking and we have not found analogies, if they exist. The trienone **22** turned out to be highly labile and some of its reactions were examined. Single passage through a gas chromatograph led to quantitative conversion to the tricyclic ketone **26**, by an unusually facile intramolecular



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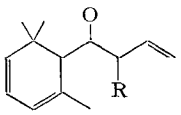
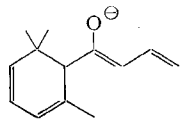


22 R=H
23 R=D



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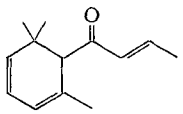

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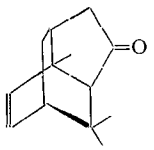

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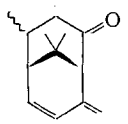

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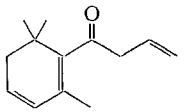
Diels-Alder reaction. Potassium *t*-butoxide, in *t*-butanol at room temperature, caused isomerization to the conjugated isomer **25** which we have named α-damascenone, using the widely accepted ionone nomenclature. The β,γ-unsaturated ketone **22** is also sensitive to acids, *p*-toluenesulfonic acid causing all three double bonds to shift to produce β-damascenone (**1**), but this method is unfortunately of no preparative value because the major products formed are the epimeric bicyclic ketones **27** [13] resulting from a proton catalyzed cyclization of α-damascenone (**25**).

β-Damascenone (**1**) is available in nearly quantitative yield from the condensation of ethyl β-safranate (**3**) with allyl lithium followed by base initiated isomerization of the resulting β,γ-unsaturated ketone **28**. We were unable to synthesize it from the known β-safronitrile (**29**) [14], which with allylmagnesium bromide gave only non-volatile products and with allyl lithium the two isomeric nitriles **30** and **31**. The possibility that a *Cope* rearrangement is involved in the genesis of either nitrile is excluded; both are stable at 250°, conditions used for their gas chromatographic separation, consequently they result from 1,4 and 1,6 addition, respectively, of allyl



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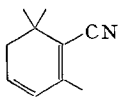

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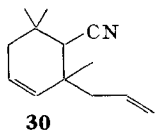

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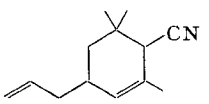

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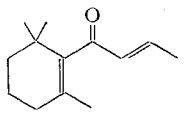

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lithium to **29**. We attribute the difference in behavior of the nitrile **29** and the corresponding ester **3** to a nearly planar arrangement of unsaturated centers in the nitrile (λ_{max} 287 nm) and the lower reactivity of the latter towards organometallic reagents.

When β-damascenone (**1**) was submitted to catalytic hydrogenation using a palladium on carbon catalyst a mixture of reduction products was produced. On the other hand, *Lindlar* catalyst gave β-damascone (**32**)[1]) in nearly quantitative yield.

We are indebted to *Firmenich & Co.*, Geneva, for generous support and to Dr. *G. Ohloff* of this firm for having kept us informed of his independent studies on the synthesis of damascenones.

Experimental Section

Microanalyses were performed at the M.I.T. Microchemical Laboratory. M.p.'s and b.p.'s are uncorrected. The following spectrometers and solvents were used: NMR., *Varian* T-60 (CCl_4, tetramethylsilane as internal standard); IR., *Hitachi Perkin-Elmer* Model 247 ($CHCl_3$); UV., *Cary* Model 14 (EtOH); MS., *Hitachi Perkin-Elmer* RMU-60 (only molecular ion peak and the two most intense peaks listed). GLC. analyses were performed on an F & M720 instrument, using silicon rubber gum SE-30 and Carbowax 20 M columns.

Ethyl α-isopropylidene-acetoacetate (**4**). – A. To a solution of 25.5 g (0.15 mol) of diketo-ester **7** [4] in 400 ml dry ether, was added dropwise 110 ml (0.33 mol) of 3 M CH_3MgBr in ether, while the temperature was maintained at 5–10°. The resulting suspension was stirred for 24 h at room temperature, then 50 ml of acetic anhydride was added with cooling. After 2 h at 20° the mixture was poured into cold water, the organic layer separated, washed with 5% aq. NaOH, then water, dried (Na_2SO_4), and evaporated. Distillation yielded 16.1 g (63%) of ketoester **4**, b.p. 94–96°/8 Torr (lit. [3]: 82–87°/4 Torr). According to GLC. this product was contaminated with 3% of keto-ester **5** and 5% of enol acetate **6**. Pure samples were obtained by chromatography on silica gel with benzene, followed by GLC. collection.

Conjugated ketoester **4**. IR.: 1730, 1700, 1640, 1615 cm^{-1}. NMR.: 1.3 (3H, *t*, J = 7.5 Hz); 1.9 (3H, *s*); 2.0 (3H, *s*); 2.15 (3H, *s*); 4.2 (2H, *q*, J = 7.5 Hz) ppm. UV.: 227 nm (ε = 7900). MS.: *m/e*: 170 (16), 96 (100), 43 (98). *Unconjugated ketoester* **5**. IR.: 1730, 1710, 1640 cm^{-1}. NMR.: 1.3 (3H, *t*, J = 7 Hz), 1.8 (3H, *s* with fine splitting), 1.9 (1H, *s*), 2.1 (2H, *s*), 3.9 (0.7H, *s*), 4.1 (2H, *q*, J = 7 Hz), 4.7–5.1 (2H), 12.6 (0.3H, *s*), ppm. UV.: 255 nm (ε = 2260); immediately after basification: 284 nm (ε = 9300). MS.: *m/e*: 170 (5), 82 (56), 43 (100).

Enol acetate **6**. IR.: 1755, 1705, 1650, 905 cm^{-1}. NMR.: 1.3 (3H, *t*, J = 7 Hz), 1.9 (3H, *s* with fine splitting), 2.0 (3H, *s*), 2.1 (3H, *s*), 4.1 (2H, *q*, J = 7 Hz), 4.9 (1H, *s* broad), 5.1 (1H, *s* broad) ppm. UV.: 216 nm (ε = 9900). MS.: *m/e*: 212 (1), 170 (18), 96 (68), 43 (100).

B. According to [3]. A mixture of 260 g (2 moles) of ethyl acetoacetate, 174 g (3 moles) of acetone, 256 ml of acetic anhydride and 38 g of fused zinc chloride was heated under reflux for 60 h. Pentane was added, the mixture washed several times with water, and after drying (Na_2SO_4) and evaporation, the product was distilled. The fraction collected between 75–100°/8 Torr (135 g) was dissolved in pentane, extracted with 6 × 100 ml of aq. 10% Na_2CO_3, washed with water, dried (Na_2SO_4), and evaporated. Fractional distillation through a *Vigreux* column afforded 70.5 g (21%) of 95% pure ethyl α-isopropylidene-acetoacetate (**4**), b.p. 92–95°/8 Torr.

The combined Na_2CO_3 extracts were acidified with 2 N H_2SO_4 and extracted with ether, the organic layer washed with water, dried (Na_2SO_4), and evaporated. The remaining oil was distilled to give 27.5 g (8%) of ethyl diacetylacetate (**7**), b.p. 88–91°/8 Torr. For the isolation of keto-ester **4** it was advantageous to wash a pentane solution of the crude distillate with cold 5% NaOH. In addition to diketo-ester **7** traces of ethyl acetoacetate were thus removed, and keto-ester **4** could be obtained in 95% purity without fractional distillation.

Allyltriphenylphosphonium chloride (**11**) was obtained in 81% yield by refluxing a solution of 52.5 g of triphenylphosphine in 300 ml of allyl chloride for 96 h; m.p. 221–227° (lit. [6]: 234–235°). The NMR. spectrum indicated the presence of *ca.* 10% of the propenyl isomer **12**. IR.: 2320, 2450, 1635, 1585, 985, 930 cm^{-1}. NMR. ($CDCl_3$): 4.9 (2H, *d* of *d*, J = 15 and 5 Hz), 5.2–5.9 (3H), 7.7–8.2 (15H) ppm.

3-Propenyltriphenylphosphonium chloride (**12**). A stirred mixture of 52.5 g (0.2 mol) of triphenylphosphine, 23 g (0.3 mol) of freshly distilled allyl chloride and 300 ml of benzene was heated under reflux for 16 h. The precipitate was filtered off, washed with ether, and dried *in vacuo* to give 4.5 g (7%) of **12**, m.p. 224–230° (lit. [6]: 235–236°). IR.: 3320, 2450, 1635, 1610, 1585, 960 cm^{-1}. NMR. ($CDCl_3$): 2.4 (3H, *d* with fine splitting, $J = 7$ Hz), 6.2–8.2 (17H) ppm.

Ethyl α-safranate (**15**). – A. To a suspension of 23.7 g (70 mmol) of allyltriphenylphosphonium chloride (**11**) in 350 ml of dry ether were added, under nitrogen at 5–10°, 48 ml (77 mmol) of 1.6 M butyl lithium in hexane. Stirring was continued for 1 h at the same temperature, then a solution of 9.5 g (56 mmol) of keto-ester **4** in 50 ml of ether was added dropwise. After 1 h at room temperature cold water was added, the organic layer separated, washed with water, dried (Na_2SO_4) and evaporated. The partly crystallized residue was extracted several times with hexane, and the combined extracts filtered through a column containing 50 g of aluminium oxide *Merck*. Evaporation and distillation of the eluate afforded 6.55 g (60%) of ester **15**, b.p. 93°/8 Torr. IR.: 1725, 1660, 1600 cm^{-1}. NMR.: 1.1 (6H, *s*), 1.3 (3H, *t*, $J = 7$ Hz), 1.8 (3H, *s*), 2.7 (1H, *s*), 4.1 (2H, *q*, $J = 7$ Hz), 5.2–5.8 (3H, *m*), ppm. UV.: 270 nm ($\varepsilon = 4220$). MS.: *m/e*: 194 (17), 121 (100), 105 (38).

$C_{12}H_{18}O$ Calc. C 74.19 H 9.34% Found C 74.12 H 9.55%

B. A suspension of 28.7 g (75 mmol) of allyltriphenylphosphonium bromide [15] in 400 ml of hexane was treated with 44 ml (70 mmol) of 1.6 M methyl lithium in ether and the resulting solution stirred for 6 h at room temperature. To this mixture was added, dropwise at 5–10°, 9.5 g (56 mmol) of keto-ester **4** diluted with 30 ml of hexane. After 1 h at room temperature the mixture was filtered, the residue washed with a 2:1 hexane-ether mixture, and the combined filtrates were washed with water, dried, and evaporated. The residue with hexane was filtered through 50 g of aluminium oxide to give 7.51 g (69%) of pure ester **15**, b.p. 95°/8 Torr.

Acid-catalyzed equilibration of ester **15**. A mixture of 2.00 g of ester **15**, 25 ml of benzene and 100 mg of *p*-toluenesulfonic acid was refluxed under nitrogen for 4 h, the solution diluted with pentane, washed with 5% sodium hydrogencarbonate solution, and water, then dried (Na_2SO_4) and evaporated. Distillation of the residue afforded 1.87 g (93%) of a mixture, b.p. 96°/8 Torr. GLC. analysis (6 ft silicon rubber SE-30) indicated a composition of isomeric esters **15**, **18** and **3** in the ratio 20:22:58. Separation was achieved by chromatography on $AgNO_3$-impregnated silicic acid[4]), in hexane containing increasing amounts of benzene. Analytical samples were obtained by GLC. collection.

Ethyl γ-safranate **18**. IR.: 1725, 1640, 1600, 895 cm^{-1}. NMR.: 0.9 (3H, *s*), 1.0 (3H, *s*), 1.2 (3H, *t*, $J = 7$ Hz), 1.7 (1H, *d* of *d*, $J = 18$ and 5 Hz), 2.4 (1H, *d*, $J = 18$ Hz), 2.9 (1H, *s*), 4.1 (2H, *q*, $J = 7$ Hz), 4.9 (2H, *s* broad), 5.5–6.2 (2H, *m*) ppm. UV.: 234 nm ($\varepsilon = 12{,}800$). MS.: *m/e*: 194 (12), 121 (100), 105 (40).

$C_{12}H_{18}O_2$ Calc. C 74.19 H 9.34% Found C 74.34 H 9.60%

Ethyl β-safranate **3**. IR.: 1705, 1650, 1590 cm^{-1}. NMR.: 1.0 (6H, *s*), 1.3 (3H, *t*, $J = 7$ Hz), 1.8 (3H, *s*), 2.1 (2H, *d*, $J = \sim 2$ Hz), 4.2 (2H, *q*, $J = 7$ Hz), 5.8 (2H, *m*) ppm. UV.: 274 nm ($\varepsilon = 5200$). MS.: *m/e*: 194 (22), 121 (81), 107 (100).

$C_{12}H_{18}O_2$ Calc. C 74.19 H 9.34% Found C 74.18 H 9.58%

Pure samples of esters **18** and **3** were equilibrated under the same conditions; ester **18** gave a mixture of isomers **15**, **18** and **3**, ratio 19:22:59, whereas for **3** the ratio was 19:21:60.

Base catalyzed equilibration of ester **15**. – A. To 30 ml of a 0.5 M solution of sodium ethoxide in ethanol was added, under nitrogen, 1.0 g of ester **15**. The mixture was heated under reflux for 60 min, a few drops of acetic acid were added, and after removal of most of the solvant *in vacuo*, water was added and the mixture extracted with pentane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to a residue which, by distillation, gave 0.92 g of a 55:45 mixture of isomers **15** and **20**, b.p. 92°/8 Torr. A pure sample of ester **20** was obtained by GLC. collection: IR.: 1705, 1640 cm^{-1}. NMR.: 1.1 (6H, *s*), 1.3 (3H, *t*, $J = 7$ Hz), 1.7 (3H, *s*) 2.6 (2H, *s*), 4.2 (2H, *q*, $J = 7$ Hz), 5.4 (2, *m*) ppm. UV.: 232 nm ($\varepsilon = 1320$). MS.: *m/e*: 194 (100), 107 (100), 91 (32).

$C_{12}H_{18}O_2$ Calc. C 74.19 H 9.34% Found C 74.20 H 9.66%

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[4]) Silicic acid *Mallinckrodt* (80 g) was added to a solution of 20 g of $AgNO_3$ in 120 ml of water and the resulting slurry was dried at 110°.

B. A mixture of 729 mg of ester **15**, 8 ml of dry dimethylsulfoxide and 30 mg of potassium *t*-butoxide was allowed to stand under nitrogen for 7 h at room temperature; then diluted with water, extracted with ether, washed with water, dried (Na_2SO_4) and evaporated. Distillation of the residue gave 513 mg (70%) of a mixture of isomers, b.p. ~100°/8 Torr, GLC., showing 3 peaks. Collection gave esters **15**, **18** and a mixture of **3** and **20**. NMR. analysis of the latter, and GLC. analysis of the whole showed the ratio of esters **15**, **18**, **3** and **20** to be 14:23:50:13.

Diallyl carbinol **21**. The *Grignard* reagent prepared from 1.45 g (12 mmol) of allyl bromide and 600 mg (25 mmol) of 40 mesh magnesium powder in 15 ml of ether was added at −60° to a solution of 1.94 g (10 mmol) of ester **15** in 25 ml of ether. After 1 h at room temperature cold sat. NH_4Cl solution was added, the mixture extracted with pentane, the organic layer washed with water, dried (Na_2SO_4) and evaporated to give 2.56 g of an oil. This product was chromatographed on 60 g of $AgNO_3$-impregnated silicic acid[4]). Benzene eluted 960 mg of unreacted ester **15**, b.p. 85°/6 Torr. Ether eluted 754 mg of alcohol **21**, b.p. 71°/0.1 Torr. IR.: 3590, 1840, 1640, 1595, 995, 915 cm^{-1}. NMR.: 1.0 (3H, *s*), 1.3 (3H, *s*), 1.4 (1H, *s*, disappears on exchange with D_2O), 1.9 (3H, *s*), 1.9 (1H, *s*), 2.3 (4H, *d* with fine splitting, J = 6Hz), 4.7–6.3 (9H, *m*) ppm. UV.: 272 nm (ε = 4380). MS.: *m/e*: 191 (2), 69 (100), 41 (84).

Ketone **22**. The method of *Eisch* was used [11]. A suspension of 2.4 g (0.35 mol) of finely cut lithium wire in 40 ml of tetrahydrofuran (distilled from LAH) under nitrogen was cooled to 0°. A few crystals of biphenyl were added, followed by *ca.* 2 ml of a solution of 9.4 g (70 mmol) of allyl phenyl ether in 10 ml of ether and after the reaction had started (indicated by the appearance of a greenish color) the remainder of the solution was added dropwise at −15°. The cooling bath was removed, stirring continued for 30 min, and the resulting solution of allyl lithium was removed from excess lithium by means of a syringe and added slowly to a stirred solution of 3.88 g (20 mmol) of ester **15** in 40 ml of ether at −60°, under nitrogen. After warming to room temperature, the mixture was poured into cold water and extracted twice with pentane. The combined extracts were washed with water, dried (Na_2SO_4), evaporated and distilled to give 3.19 g (84%) of ketone **22**, b.p. 41–43°/0.05 Torr. For analysis, a sample was obtained by chromatography on silicic acid, using hexane + 2% ethyl acetate as eluent. IR.: 1695, 1650, 1590, 990, 915 cm^{-1}. NMR.: 1.0 (3H, *s*), 1.1 (3H, *s*), 1.7 (3H, *s*), 2.6 (1H, *s*), 3.2 (2H, *d* with fine splitting, J = 7Hz), 4.7–6.1 (6H, *m*) ppm. UV.: 267 nm (ε = 3900). MS.: *m/e*: 190 (7), 121 (100), 105 (44).

$C_{13}H_{18}O$ Calc. C 82.06 H 9.54% Found C 81.90 H 9.85%

A small sample of the above reaction mixture was worked up as before but with D_2O replacing H_2O. The NMR. spectrum of the resulting product was identical with that of the previous product, except for the 2H doublet at 3.2 ppm which became a broad 1H signal.

α-Damascenone (**25**). To a solution of 140 mg of potassium in 40 ml of dry *t*-butanol under nitrogen was added 2.46 g of ketone **22** in 5 ml of *t*-butanol. After 5 min at room temperature, a few drops of acetic acid were added, the mixture concentrated *in vacuo*, water added and the mixture extracted with pentane. The organic layer was washed with water, dried (Na_2SO_4), evaporated and distilled to yield 1.76 g (72%) of α-damascenone (**25**), b.p. 39°/0.04 Torr. IR.: 1680, 1650, 1620, 1590, 965 cm^{-1}. NMR.: 0.95 (3H, *s*), 1.0 (3H, *s*), 1.7 (3H, *s*) 1.8 (3H, *d* of *d*, J = ~1 and 7Hz), 2.6 (1H, *s*), 5.2–7.0 (5H, *m*) ppm. UV.: 235 nm (ε = 10,500); 266 nm (ε = 4650). MS.: *m/e*: 190 (8), 121 (71), 69 (100).

$C_{13}H_{18}O$ Calc. C 82.06 H 9.54% Found C 82.03 H 9.57%

Isomerization of ketone **22**. A mixture of 289 mg of **22**, 25 mg of *p*-toluenesulfonic acid and 4 ml of benzene was heated under reflux for 2 h. The mixture was diluted with pentane, washed with 5% sodium hydrogencarbonate solution and water, dried (Na_2SO_4), and evaporated. Distillation of the remaining oil at ~80° (bath temp.)/0.1 Torr gave 201 mg of a mixture of compounds **25** (5%), **1** (30%) and **27** (62%). Pure samples were obtained by GLC. collection from a silicon rubber column. Identity of ketones **25** and **1** was confirmed by comparison of retention times and spectra with authentic samples. A mixture of bicyclic ketones **27**, which showed 2 peaks on a carbowax 20M column, had the following spectra: IR.: 1800, 1705, 1630, 1595, 895 cm^{-1}. NMR.: 0.9–1.1 (9H, 6 lines), 1.5–3.0 (5H, *m*), 5.0 (2H, *s*), 5.7–6.1 (1H, *m*), 6.3 (1H, *d* with fine splitting, J = 10Hz) ppm. UV.: 234 nm. MS.: *m/e*: 190 (33), 106 (81), 91 (100). The individual epimers separated on the same column had identical UV. spectra and very similar IR. spectra.

Thermolysis of ketone **22**. Ketone **22** was prepared as described from 1.75 g (0.25 mol) of lithium, 8.3 g (62 mmol) of allyl phenyl ether and 3.1 g (16 mmol) of ethyl α-safranate (**15**). After work-up the crude reaction mixture was dissolved in 25 ml of xylene, the solution heated under reflux for 1 h, the solvent evaporated, and the remaining oil purified by chromatography on silica gel. Benzene eluted 2.13 g (70%, based on ester **15**) of pure tricyclic ketone **26**, b.p. 45°/0.05 Torr. IR.: 1730 cm^{-1}. NMR.: 0.9 (3H, *s*), 0.95 (3H, *s*), 1.2 (3H, *s*), 1.3 (1H, *s* broad), 2.0 (1H, *s*), 1.4–2.6 (5H, *m*), 5.9 (1H, *d* with fine splitting, $J = 8$ Hz), 6.5 (1H, *d* of *d*, $J = 7$ and 8 Hz) ppm. MS.: *m/e*: 190 (4), 121 (83), 98 (100).

β-Damascenone (**1**). Allyl lithium, prepared as before from 1.2 g (0.17 mol) of lithium and 4.7 g (35 mmol) of allyl phenyl ether, was added to a solution of 2.02 g (10.4 mmol) of ester **3** in 20 ml of ether at −60°. Work-up gave 1.96 g of product, b.p. 44–46°/0.05 Torr. The NMR. spectrum showed it to be a *ca.* 2:1 mixture of ketones **28** and **1**. Isomerization of the product was carried out as before with a solution of 20 mg of potassium in 30 ml of *t*-butanol to yield 1.70 g (86%, based on ester **3**) of β-damascenone, b.p. 51°/0.08 Torr (lit. [1]: 57°/0.001 Torr). IR.: 1665, 1630, 1610 cm^{-1}. NMR.: 1.0 (6H, *s*), 1.6 (3H, *s*), 1.9 (3H, *d* of *d*, $J = \sim 1$ and 7 Hz), 2.1 (2H, *d*, $J = \sim 2$ Hz), 5.7–7.1 (4H, *m*) ppm. UV.: 228 nm ($\varepsilon = 12{,}000$); 255 nm ($\varepsilon = 500$); 310 nm ($\varepsilon = 2000$). MS.: *m/e*: 190 (19), 121 (100), 69 (62).

$C_{13}H_{18}O$ Calc. C 82.06 H 9.54% Found C 81.89 H 9.87%

β-Damascone (**32**). A solution of 380 mg (2 mmol) of β-damascenone (**1**) in 10 ml of ethyl acetate was hydrogenate in the presence of 50 mg of *Lindlar* catalyst [16], hydrogen uptake, after 90 min at 20°/760 Torr, being 46 ml (0.96 eq). The mixture was filtered, evaporated and distilled to yield 328 mg of ~90% pure (GLC.) β-damascone (**32**). A pure sample, obtained by chromatography, on silicic acid, in hexane+1% ethyl acetate, had b.p. ~60° (bath)/0.08 Torr ([1]: 55°/0.001 Torr). IR.: 1670, 1640, 1625, 1610 cm^{-1}. NMR.: 1.0 (6H, *s*), 1.5 (3H, *s*), 1.9 (3H, *d* of *d*, $J = 7$ and ~1 Hz), 1.3–2.2 (6H, *m*), 5.9–6.9 (2H, *m*) ppm. UV.: 226 nm ($\varepsilon = 12{,}300$), 271 ($\varepsilon = 2840$). MS.: *m/e*: 192 (42), 177 (100), 69 (48).

$C_{13}H_{20}O$ Calc. C 81.20 H 10.48% Found C 81.02 H 10.73%

Nitriles **30** *and* **31**. Allyllithium, prepared as described above from 0.84 g (120 mmol) of lithium and 1.64 g (12 mmol) of allyl phenyl ether, was added, under nitrogen at −60°, to a solution of 1.76 g (12 mmol) of β-safranonitrile (**29**) [14] in 25 ml of ether. After 2 h stirring at room temperature the dark colored reaction mixture was poured into water, the organic layer separated, washed with 2N HCl, water, 5% sodium hydrogencarbonate solution, dried (Na_2SO_4), and evaporated. Distillation of the residue gave 0.74 g (33%) of a *ca.* 2:3 mixture of nitriles **30** and **31**, b.p. 40–48°/0.05 Torr. Separation was achieved by GLC. – *Nitrile* **30**: IR.: 2230, 1850, 1660, 1640, 1000, 920 cm^{-1}. NMR.: 1.1 (3H, *s*), 1.15 (3H, *s*), 1.25 (3H, *s*), 1.8 (2H, *d*, $J = 3$ Hz), 2.1 (2H, *d*, $J = 7$ Hz), 2.5 (1H, *s*), 4.8–6.0 (5H, *m*) ppm. MS.: *m/e*: 189 (2), 148 (100), 106 (50). – *Nitrile* **31**: IR.: 2230, 1840, 1640, 995, 915 cm^{-1}. NMR.: 1.0 (3H, *s*), 1.1 (3H, *s*), 1.9 (3H, *s* with fine splitting), 0.8–2.2 (5H, *m*), 2.9 (1H, *s* broad), 5.8–6.0 (4H, *m*) ppm. MS.: *m/e*: 189 (3), 148 (100), 106 (40).

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190. Die Stereochemie der Irone

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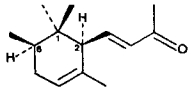
Herrn Dr. *Roger Firmenich* zum 65. Geburtstag gewidmet

(29. VI. 71)

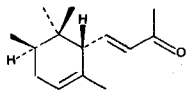
Summary. The 6*R* configuration of (+)-*cis*-γ-irone [(+)-**4**] was established by chemical correlation with (−)-camphor. (+)-*cis*-γ-irone [(+)-**4**] was converted into (+)-*cis*-α-irone [(+)-**1**], (−)-*trans*-α-irone [(−)-**2**], and (+)-β-irone [(+)-**3**], which therefore also have the 6*R* configuration. The 2*S* configurations of (+)-*cis*-α-irone [(+)-**1**] and (+)-*trans*-α-irone [(+)-**2**] were determined by comparison of their circular dichroism with that of *R*-α-ionone [(+)-**5**]. The 2*S* configuration of (+)-*cis*-γ-irone [(+)-**4**] was established by chemical correlation with (+)-*cis*-α-irone [(+)-**1**].

Der Strukturbeweis für α- und β-Iron durch Synthese [1] [2] gelang erst mehr als 75 Jahre nach ihrer Entdeckung [3] im ätherischen Öl einer Schwertlilienart [4]. Bis heute ist die Aufklärung der Stereochemie dieser Serie von Veilchenriechstoffen über Ansätze nicht hinausgegangen. So versuchte man z.B. die relativen Konfigurationen über die *Auwers-Skita*'sche Regel zuzuordnen [5]. Ob diese Regel hier in ihrer ursprünglichen oder revidierten [6] Form angewendet werden kann, ist allerdings fraglich[1]). Ebenso reichen die bisher vorliegenden Fakten für die Festlegung der Chiralitätszentren nicht aus [7].

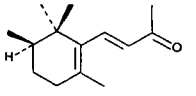
In der vorliegenden Arbeit werden nun Versuche beschrieben, die zur Aufklärung der absoluten Konfiguration der Irone **1**–**4** führten.



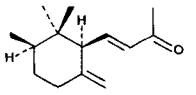
(+)-1
(+)-(2*S*:6*R*)-*cis*-α-Iron
$[\alpha]_D^{20}$: +109°



(−)-2
(−)-(2*R*:6*R*)-*trans*-α-Iron
−420°



(+)-3
(+)-(6*R*)-β-Iron
$[\alpha]_D^{20}$: +59°



(+)-4
(+)-(2*S*:6*R*)-*cis*-γ-Iron
+2°

[1]) Vgl. die ausführliche Diskussion darüber bei *Storni* [7].