101. Carotenoids and Related Compounds

Part 36[1])

Further Syntheses of Zeaxanthin and Rhodoxanthin

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Dedicated to Prof. *Conrad Hans Eugster* on the occasion of his 60th birthday

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Summary

A modification of a previously reported synthesis of zeaxanthin (**1**), and routes to both zeaxanthin and rhodoxanthin (**2**) from α-ionone, are described.

Though one of the most widely distributed xanthophylls in nature, zeaxanthin (**1**) occurs in only small amounts [2]. The studies now reported were aimed at developing shorter and more convenient methods for its synthesis than those hitherto described [2]. A preliminary account of some of these results has been given in a review by *Weedon* [3].

In the $C_{15}+C_{10}+C_{15}\rightarrow C_{40}$ route described in [4], the acetylenic triol intermediate **3** was converted in seven steps into the 'C_{15}-*Wittig* salt' **4** which was condensed with the C_{10}-trienedial **7** to give zeaxanthin (**1**). We found that treatment of the acetylenic triol **3** with lithium aluminium hydride gives the allenic diol **5** in good yield. Reaction of the latter with triphenylphosphonium bromide was apparently accompanied by a rearrangement of the allene to a conjugated diene under the acidic conditions used. The resulting phosphonium salt was formulated as **6** since reaction with the C_{14}-pentaenedial **8** [5] gave 10′-apo-zeaxanthinal **10**. With an excess of the *Wittig* reagent the aldehyde **10** was converted into zeaxanthin. The product, like those from all routes that have been fully described, consists of a mixture of the racemic- and *meso*-forms. It is now known that the natural carotenoid consists of the (3*R*,3′*R*)-enantiomer [6], and the synthesis of this isomer from optically active intermediates (*e.g.* **11**) was recently reported [7].

We next turned our attention to the readily available starting material, α-ionone (**12**), which has not previously been exploited for the preparation of carotenoids

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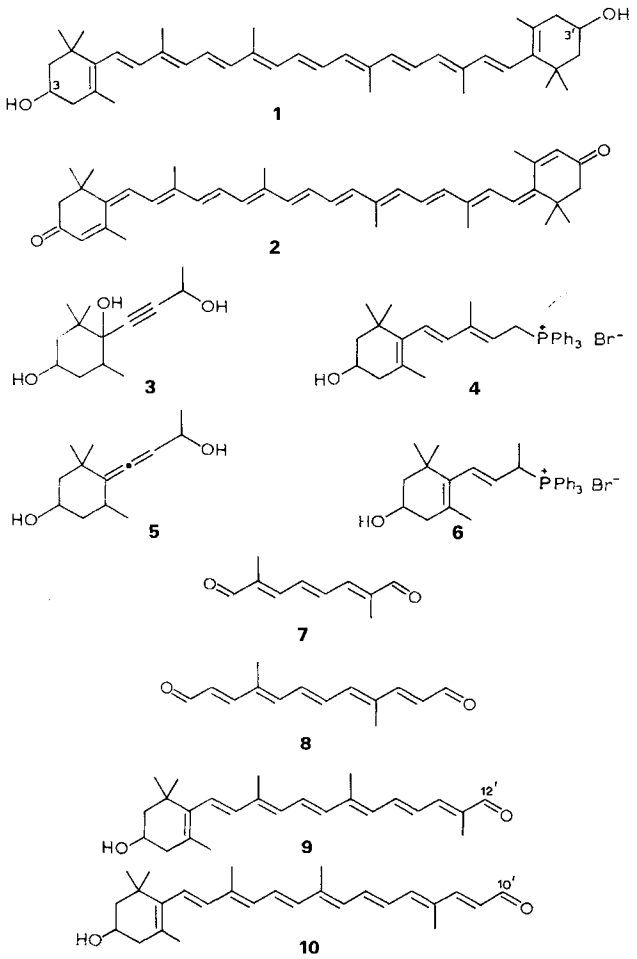
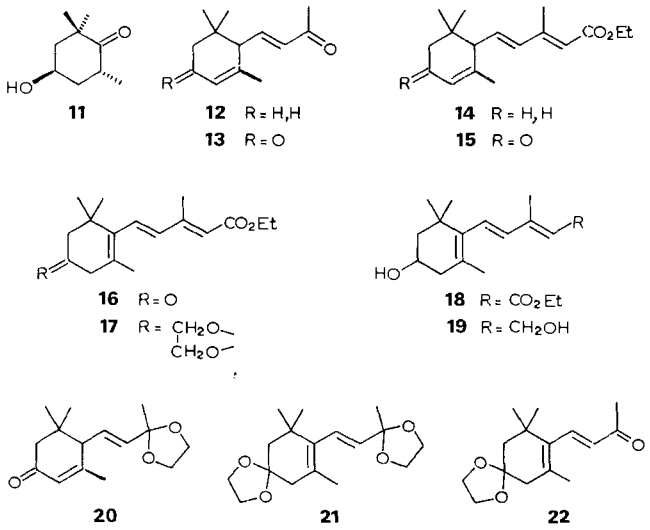


with oxygen substituents in the 3- and 3′-positions. Condensation with ethyl diethylphosphonoacetate gave α-ionylidene acetate (**14**) [8] which, on oxidation with *t*-butyl chromate, yielded the 3-keto-derivative **15** [9]. Reaction of the latter with ethane-1,2-diol, in the presence of *p*-toluenesulfonic acid, gave the acetal **17**; the migration of the ring double bond from the 'α'- to the 'β-position', an essential feature of the synthesis, has many analogies in the steroid field [10]. Mild hydrolysis of the acetal **17** gave the keto-ester **16**, but this isomerized rapidly with loss of the desired chromophore. This difficulty was circumvented by taking advantage of the comparative stability of cyanoborohydride to acid [11]. Hydrolysis of **17**, in the presence of this hydride, resulted in reduction of **16** as it was formed to give the hydroxy-ester **18**. Subsequent reduction with lithium aluminium hydride then furnished the diol **19**.

Reaction of **19** with triphenylphosphonium bromide yielded the known 'C_{15}-*Wittig* salt' **4**, previously prepared from an allylic isomer of **19** [4]. Condensation



of **4** with the C_{10}-triene dial **7** gave 12′-apo-zeaxanthinal **9** and zeaxanthin as described by *Loeber et al.* [4].

Reaction of 3-keto-α-ionone **13**, obtained by *t*-butyl chromate oxidation of α-ionone [12] [13], with ethane-1,2-diol gave two main products, the mono-acetal **20** in the α-series, and the diacetal **21** in the β-series. Treatment of **21** with dilute acid resulted in quantitative selective hydrolysis to form the mono-acetal **22**, a key intermediate in the synthesis of rhodoxanthin **2** by *Surmatis et al.* [14] [15]. This carotenoid is the principal pigment in the ripe berries of the yew tree, *Taxus baccata* [16], and may be converted into zeaxanthin [2].

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Experimental Part

General. Reactions were carried out in an inert atmosphere, and solvents were evaporated under reduced pressure. Thin layer chromatograms (TLC.) were on *Merck* Kieselgel H with F_{254} indicator; the eluent is indicated in parentheses. Light petroleum refers to the fraction b.p. 60–80°, unless the contrary is indicated. UV. spectra were run in ethanol, and ^{1}H-NMR. spectra at 100 MHz in $CDCl_3$ (bands are indicated as follows: *s*, singlet; *d*, doublet; *t*, triplet; *qa*, quadruplet; *m*, multiplet; br., broad). Only selected IR. bands and MS. lines are quoted.

4-(4-Hydroxy-2,2,6-trimethylcyclohexylidene)-3-buten-2-ol (**5**). Lithium aluminium hydride (1.0 g) was added slowly to a solution of *4-(1,4-dihydroxy-2,2,6-trimethylcyclohexyl)-3-butyn-2-ol* **3** [4] (5.0 g in 50 ml of tetrahydrofuran), and the mixture was heated under reflux for 3 h and then cooled. Saturated aq. sodium potassium tartrate solution (5 ml) was added. The crude product was isolated and 15 ml of $CHCl_3$ was added. The solid, consisting of **3** (1.0 g), was filtered off. The filtrate was evaporated to give the allenic diol **5** (3.5 g) as an oil. – IR. (film): 3396 and 1961 cm^{-1}. – ^{1}H-NMR.: 0.96 (*d*, J=6, 3 H); 1.00 (*s*, 6 H); 1.25 (*d*, J=6, 3 H); 1.40–1.94 (*m*, 4 H); 2.60 (*m*, 3 H, 2 H exchangeable on shaking with D_2O); 4.12 (*m*, 1 H); 4.27 (*m*, 1 H) and 5.35 (*m*, 1 H). – MS.: 210 (M^+, 10), 192 ($M-18$, 11), 177 (6), 159 (6), 148 (43), 133 (54), *83* (100).

[3-(4-Hydroxy-2,6,6-trimethyl-1-cyclohexenyl)-1-methyl-2-propen-1-yl]triphenylphosphonium bromide (**6**). A solution of the allenic diol **5** (1.05 g) and triphenylphosphonium bromide (1.70 g) in 5 ml $CHCl_3$ was stirred at 20° for 18 h. Evaporation, and trituration of the residue with ether, gave the *Wittig* salt **6** as a pale yellow solid (2.21 g) which was used without further purification.

The (*R*)-isomer of **6** has previously been prepared by a different route [7].

10'-Apo-zeaxanthinal (**10**). Aq. KOH-solution (10%, 0.5 ml) was added dropwise to a solution of the preceding *Wittig* salt (60 mg) and 4,9-dimethyl-2,4,6,8,10-dodecapentaenedial (**8**) (11 mg) [5] in 2-propanol (3 ml). The mixture was stirred at 20° for 24 h, and then poured into water. Isolation of the product with ether, and TLC. (acetone/light petroleum 1:4), gave *10'-apo-zeaxanthinal* (**10**) (11 mg). – UV. (EtOH): 444. – UV. (light petroleum): 434. – IR. (KBr disc): 3458, 1659, 1606 and 966. – ^{1}H-NMR.: 1.08 (*s*, 6 H); 1.76 (*s*, 3 H); 1.78 (*m*, 2 H); 1.97 (*s*, 6 H); 2.01 (*s*, 3 H); 3.96 (*m*, 1 H); 6.14–7.08 (11 H); 9.58 (*d*, *J* = 8, 1 H). – MS.: 392 (M^+, 40), 223 (11), 208 (18), 193 (43), *149* (100).

Zeaxanthin (**1**). Aq. KOH-solution (10%, 0.3 ml) was added dropwise to a solution of *10'-apo-zeaxanthinal* (**10**) (10 mg) and the *Wittig* salt **6** (30 mg) in 2-propanol (2 ml). The mixture was stirred at 20° for 3 h, and then poured into water. Isolation of the product with ether and TLC. (25% acetone in light petroleum) gave *zeaxanthin* (**1**) (8.5 mg), identical with the synthetic product previously reported [4]. It did not separate from natural (3*R*,3'*R*)-zeaxanthin on mixed TLC.

Ethyl 5-(2,6,6-trimethyl-2-cyclohexenyl)-3-methyl-2,4-pentadienoate (ethyl α-ionylideneacetate) (**14**). Condensation of α-ionone (**12**) with ethyl diethylphosphonoacetate in the presence of sodium ethoxide, following the procedure of *Manchand et al.* [8] gave **14** (74%), b.p. 170–180°/12 torr. – UV.: 268 (identical with λ_{max} in [8]). – IR. (film): 1708, 1628, 1612 and 980. The product consisted mainly of the (2*E*,4*E*)-isomer. A sample of the latter was isolated by TLC. – ^{1}H-NMR.: 0.83 (*s*, 3 H); 0.92 (*s*, 3 H); 1.28 (*t*, *J* = 7, 3 H); 1.55 (br. *s*, 3 H); *ca.* 1.98 (br., 3 H); 2.26 (*s*, 4 H); 4.14 (*qa*, *J* = 7, 2 H); 5.42 (br. *s*, 1 H); 5.70 (*s*, 1 H); 5.74–6.16 (*m*, 2 H).

Ethyl 5-(4-oxo-2,6,6-trimethyl-2-cyclohexenyl)-3-methyl-2,4-pentadienoate (ethyl 3-keto-α-ionylideneacetate) (**15**). Chromium trioxide (28 g) was added slowly to a well stirred solution of *t*-butylalcohol (41 g) in CCl_4 (175 ml). After the mixture had been stirred for 1 h, the deep red solution was separated from the aq. layer and dried. The solution was filtered, cooled to 0°, and glacial acetic acid (36 ml) and acetic anhydride (4 ml) were added.

The *t*-butyl chromate reagent was added dropwise to a stirred solution of **14** (15 g) in CCl_4 (75 ml) at 50° and the mixture was kept at this temperature for 6 days. The resulting dark green mixture was cooled and stirred vigorously at 0–10° with saturated aq. oxalic-acid solution, and then with finely powdered oxalic acid, to remove all trace of red colour. The organic layer was separated, washed with water, then with saturated aq. $NaHCO_3$-solution, dried and evaporated. Chromatography of the residual oil (13 g) on a column of silica gel (10% deactivated, 700 g), using gradient elution (benzene, benzene/acetone 99.5:0.5), gave the ethyl (2*E*,4*E*)-3-keto-α-ionylideneacetate (**15**) (5.1 g) as an oil. – UV.: 267 (269, for the corresponding methyl ester [9]). – IR. (film): 1714, 1670, 1628, 1612 and 980. – ^{1}H-NMR.: 0.97 (*s*, 3 H); 1.05 (*s*, 3 H); 1.27 (*t*, *J* = 7, 3 H); 1.88 (*s*, 3 H); 2.08 (*d*, *J* = 16, 1 H); 2.26 (*s*, 3 H); 2.37 (*d*, *J* = 16, 1 H); 2.66 (*d*, *J* = 9, 1 H); 4.15 (*qa*, *J* = 7, 2 H); 5.76 (*s*, 1 H); 5.90 (*s*, 1 H); 5.94 (*d* × *d*, J_1 = 9, J_2 = 16, 1 H); 6.22 (*d*, *J* = 16, 1 H). – MS.: 276 (M^+, 16), 231 (12), 220 (5), 180 (7), 174 (47), 147 (32), 146 (60), *139* (100), 91 (37).

A sample of the (2*Z*,4*E*)-isomer of **15** was also isolated from the chromatogram. – ^{1}H-NMR.: 1.00 (*s*, 3 H); 1.08 (*s*, 3 H); 1.29 (*t*, *J* = 7, 3 H); 1.94 (*s*, 3 H); 2.01 (*s*, 3 H); 2.10 (*d*, *J* = 16, 1 H); 2.40 (*d*, *J* = 16, 1 H); 2.74 (*d*, *J* = 10, 1 H); 4.16 (*qa*, *J* = 7, 2 H); 5.69 (*s*, 1 H); 5.92 (*s*, 1 H); 5.93 (*d* × *d*, J_1 = 10, J_2 = 16, 1 H); 7.72 (*d*, *J* = 16, 1 H).

Ethyl 5-(4,4-ethylenedioxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienoate (**17**). A mixture of ethyl 3-keto-α-ionylideneacetate (**15**) (mixture of (2*Z*,4*E*)- and (2*E*,4*E*)-isomers; 200 mg), ethane-1,2-diol (80 mg), benzene (25 ml) and *p*-toluenesulfonic acid monohydrate (5 mg) was heated under reflux, the water liberated during the reaction being removed (*Soxhlet* extractor containing calcium hydride). After 16 h more acid (8 mg) was added. The mixture was heated under reflux for a further 24 h, then cooled and diluted with ether. The ethereal solution was washed with dilute aq. $NaHCO_3$-solution, then with water, dried and evaporated. Preparative TLC. (light petroleum/acetone 87:13) of the residual oil (214 mg) gave:

a) The (2*E*,4*E*)-isomer (61 mg). – UV.: 260 and 294 (258 and 295 in [15]). – IR. (film): 1710, 1615, 990 and 893. – ^{1}H-NMR.: 1.11 (*s*, 6 H); 1.28 (*t*, *J* = 7, 3 H); 1.72 (*s*, 5 H); 2.32 (*s*, 5 H); 3.93 (*s*, 4 H); 4.15 (*qa*, *J* = 7, 2 H); 5.72 (*s*, 1 H); 6.10 (*d*, *J* = 16 Hz, 1 H); 6.52 (br. *d*, *J* = 16, 1 H). – MS.: 320 (M^+, 50),

280 (18), 275 (12), 265 (14), *234* (100), 219 (28), 205 (90), 188 (60), 181 (21), 173 (25), 167 (30), 161 (47), 153 (93), 134 (49), 87 (100).

b) The (2*Z*,4*E*)-isomer (53 mg). – UV.: 264 and 307. – IR. (film): 1710, 1615, 990 and 960. – ^{1}H-NMR.: 1.14 (*s*, 6 H); 1.26 (*t*, *J* = 7, 3 H); 1.70 (*s*, 2 H); 1.80 (*s*, 3 H); 2.02 (*s*, 3 H); 2.32 (*s*, 2 H); 3.92 (*s*, 4 H); 4.13 (*qa*, *J* = 7, 2 H); 5.62 (*s*, 1 H); 6.51 (br. *d*, *J* = 16, 1 H); 7.64 (*d*, *J* = 16, 1 H). – MS.: 320 (M^+, 74), 275 (16), 264 (20), 234 (100), 219 (15), 205 (88), 188 (66), 173 (21), 161 (43), *139* (100), 134 (44), 99 (55), 87 (85).

Ethyl 5-(4-oxo-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienoate (**16**) (ethyl 3-keto-β-ionylidene acetate). One drop of a solution of 2 N HCl (0.6 ml) in methanol (9.5 ml) was added to a solution of the preceding (2*E*,4*E*)-dienoate (**17**) (14 mg) in water/methanol 2:98 (2 ml). After the mixture had been kept at 20° for 12 h the product was isolated with ether. Preparative TLC. (light petroleum/acetone 89:11) gave recovered starting material (least polar), ethyl 3-keto-α-ionylidene acetate (most polar) and an unstable product (5 mg) regarded as the required ethyl 3-keto-β-ionylidene-acetate (**16**). – ^{1}H-NMR.: 1.08 (*s*, 6 H); 1.28 (*t*, *J* = 7, 3 H); 1.74 (*s*, 3 H); 2.33 (*s*, 3 H); 2.39 (*s*, 2 H); 2.87 (br. *s*, 2 H); 4.16 (*qa*, *J* = 7, 2 H); 5.76 (*s*, 1 H); 6.08 (*qa*, *J* = 16, 1 H); 6.48 (*d*, *J* = 16, 1 H).

Ethyl (2*E*,4*Z*)*-5-(4-hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienoate* (**18**). Aq. 2 N HCl was added dropwise to a stirred solution of the (2*E*,4*E*)-acetal **17** (125 mg) and sodium cyanoborohydride (450 mg) in methanol (12 ml). The reaction was monitored by TLC., and when judged to be complete the mixture was diluted with ether. The ethereal layer was separated, washed with water, dried and evaporated. Preparative TLC. (light petroleum/acetone 4:1) gave **18** as a viscous oil (62 mg). – UV.: 264 and 292. – IR. (film): 3480, 1710, 1615, 981. – ^{1}H-NMR.: 1.06 (*s*, 6 H); 1.28 (*t*, *J* = 7, 3 H); 1.70 (*s*, 4 H, 1 H exchangeable with D_2O); 2.31 (*s*, 3 H); 4.15 (*qa*, *J* = 7, 2 H); 5.72 (*s*, 1 H); 6.04 (*d*, *J* = 16, 1 H); 6.48 (*d*, *J* = 16, 1 H). – MS.: 278 (M^+, 19), 263 (2), 260 (4), 245 (7), 234 (5), 219 (5), 217 (11), 199 (15), 187 (14), 157 (18), 119 (24), 105 (31), 91 (33), *86* (100).

(2*E*,4*Z*)*-5-(4-Hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadien-1-ol* (**19**). The preceding hydroxy-ester **18** (62 mg) in ether (5 ml) was added slowly to a stirred suspension of $LiAlH_4$ (100 mg) in ether (20 ml). After the mixture had been stirred for 30 min. saturated aq. sodium-potassium-tartrate solution was added. Isolation of the product with ether gave the diol **19** as a viscous gum (54 mg). – UV.: 242 and 270. – IR. (film): 3390, 1625, 980. – ^{1}H-NMR.: 1.05 (*s*, 6 H); 1.70 (*s*, 3 H); 1.83 (*s*, 3 H); 4.27 (*d*, *J* = 7, 2 H); 5.60 (*t*, *J* = 7, 1 H); 6.02 (*s*, 2 H). – MS.: 236 (M^+, 32), 212 (15), 210 (21), 208 (15), 196 (26), 194 (26), 180 (30), 159 (32), 148 (56), 125 (70), 114 (87), 111 (100), *109* (100).

[5-(4-Hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadien-1-yl]triphenylphosphonium bromide (**4**). A solution of the preceding diol (**19**) (44 mg) and triphenylphosphonium bromide (64 mg) in methanol (3 ml) was kept at 20° for 16 h and then evaporated. Trituration of the residue with ether gave the 'C_{15}-*Wittig* salt' (97 mg), m.p. 93–110° (*Loeber et al.* [4] give m.p. 97–108°).

Condensation of the *Wittig* salt with 2,7-dimethyl-2,4,6-octatrienedial **8** to give 12'-apo-zeaxanthinal (**9**) and zeaxanthin (**1**), proceeded as described by *Loeber et al.* [4].

(*E*)*-4-(4-Oxo-2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one (3-keto-α-ionone)* (**13**). Oxidation of α-ionone (**12**) with *t*-butyl chromate, as described by *Rodriguez et al.* [13] gave **13** which, after chromatography on a column of silica gel (gradient elution, light petroleum/acetone 98:2 → 92:8), crystallized from a mixture of ether and light petroleum as needles, m.p. 74–76° (*Prelog & Osgan* [12] give m.p. 66–67°). – UV.: 239. – IR. (film): 1673, 1625, 990. – ^{1}H-NMR.: 1.00 (*s*, 3 H); 1.06 (*s*, 3 H); 1.89 (*d*, *J* = 1.5, 3 H); 2.12 (*d*, *J* = 16.5, 1 H); 2.24 (*s*, 3 H); 2.38 (*d*, *J* = 16.5, 1 H); 2.70 (*d*, *J* = 9, 1 H); 5.96 (br. *s*, 1 H); 6.15 (*d*, *J* = 16, 1 H); 6.67 (*d* × *d*, J_1 = 9, J_2 = 16, 1 H). – MS.: 206 (M^+, 15), 191 (2.5), 186 (8), 150 (33), *108* (100), 79 (9), 78 (9), 77 (11.5).

(*E*)*-4-(4-Oxo-2,6,6-trimethyl-2-cyclohexen-1-yl)-2,2-ethylenedioxy-3-butene* (**20**) and (*E*)*-4-(4,4-ethylenedioxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,2-ethylenedioxy-3-butene* (**21**). A solution of 3-keto-α-ionone (**13**) (100 mg), ethane-1,2-diol (70 mg) and *p*-toluenesulfonic acid (trace) in benzene (20 ml) was boiled under reflux for 36 h, the water formed being removed (*Soxhlet* extractor containing calcium hydride). Isolation of the product with ether gave an oil (142 mg). Preparative TLC. (light petroleum/acetone 95:5 → 82:18) gave two main products: a) The *mono-acetal* **20**, as an oil (31 mg). – UV.: 237. – IR. (film): 1667, 1630, 990, 960, 880. – ^{1}H-NMR.: 0.96 (*s*, 3 H); 1.04 (*s*, 3 H); 1.46 (*s*, 3 H); 1.87 (*s*, 3 H); 2.06 (*d*, *J* = 16, 1 H); 2.34 (*d*, *J* = 16, 1 H); 2.54 (*d*, *J* = 8, 1 H); 3.75–4.05 (*m*, 4 H); 5.51 (*d*, *J* = 15, 1 H); 5.73 (*d* × *d*, J_1 = 8, J_2 = 15, 1 H); 5.88 (*s*, 1 H). b) The *diacetal* **21** as an oil (55 mg) which crystallized when kept below 0°. – UV.: 229. – ^{1}H-NMR.: 1.09 (*s*, 6 H); 1.52 (*s*, 3 H); 1.70 (*s*, 5 H); 2.29 (*s*, 2 H);

3.93 (*s*, 8 H); 5.41 (*d*, $J = 16$, 1 H); 6.20 (*d*, $J = 16$, 1 H). – MS.: 294 (M^+, 27), 279 (10), 207 (12), 193 (73), 121 (29), 87 (100).

(E)-4-(4,4-Ethylenedioxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (**22**). One drop of a mixture of 2N aq. HCl (0.5 ml) and methanol (9.5 ml) was added to a solution of the preceding diacetal **21** (51 mg) in methanol/water 2:98 (4 ml), and the reaction was monitored by TLC. After 4 h the reaction mixture was diluted with ether, and the ethereal solution was washed with dilute aq. $NaHCO_3$-solution, then with water, dried and evaporated giving the acetal (44 mg), m.p. 37–39° (*Surmatis et al.* [14] give m.p. 38–39°). – UV.: 290. – IR.: 1690, 1670, 1608, 990. – ^{1}H-NMR.: 1.16 (*s*, 6 H); 1.72 (*s*, 2 H); 1.78 (*s*, 3 H); 2.28 (*s*, 3 H); 2.36 (*s*, 2 H); 3.93 (*s*, 4 H); 6.12 (*d*, $J = 16$, 1 H); 7.22 (*d*, $J = 16$, 1 H). – MS.: 250 (M^+, 23), 235 (33), 207 (18), 149 (43), 121 (68), 105 (13), 91 (13), 87 (73), *86* (100).

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