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Insect Growth Regulators. XVI[1] Syntheses of Juvenoids with the 3,3-Dimethylcyclohexane System

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New cyclic juvenoids containing the 3,3-dimethylcyclohexane (esters **16**, **18**, **22**, **26**, and ethers **28 a, b**) or the 5,5-dimethyl-2-cyclohexene system (esters **15**, **17**, **21**, **25**, and ethers **27 a, b**) have been obtained by a several-step synthesis starting from dimedone (**1**). The compounds obtained exhibited morphogenetic activity against larvae of *Dysdercus cingulatus* and they were inactive on pupae of *Tenebrio molitor*.

(Keywords: Claisen rearrangement; gem-Dimethylcyclohexane derivatives; Juvenoids)

Insekten-Wachstumsregulatoren. XVI[1]. Synthesen von Juvenoiden mit dem 3,3-Dimethylcyclohexan-System

Ausgehend von Dimedon (**1**) wurden in mehrstufigen Synthesen neue, cyclische Juvenoide hergestellt, die das 3,3-Dimethylcyclohexan- (Ester **16**, **18**, **22**, **26** und Ether **28 a, b**) oder 5,5-Dimethyl-2-cyclohexen-System (Ester **15**, **17**, **21**, **25** und Ether **27 a, b**) enthalten. Die erhaltenen Verbindungen zeigen morphogenetische Aktivität gegenüber Larven von *Dysdercus cingulatus* und sind inaktiv gegenüber Puppen von *Tenebrio molitor*.

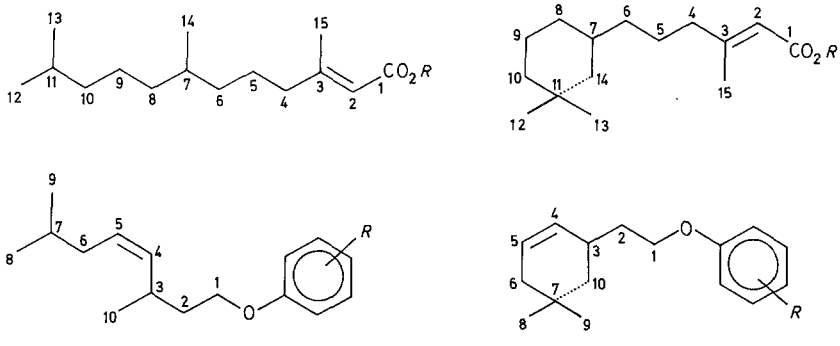
Introduction

One of the most important aims in studies on the effect of structural changes in analogs of insect juvenile hormones on their biological activities is to establish the "biologically active" conformation of juvenoids and thereby to estimate the shape of their biological receptor. It seems that comparative studies of biological activities of aliphatic juvenoids and their cyclic analogs could be very helpful for the solution of this problem. The activities of the latter compounds can be, in fact, ascribed only to

these conformations of aliphatic juvenoids which are forced by the presence of the cyclic system in the isoprenoid chain. Carrying out comparative studies of this type, we have synthesized cyclic juvenoids containing the cyclopentane[2,3] or cyclohexane[4] ring.

In this work we present the syntheses of further juvenoids with the cyclohexane system representing the cyclic analogs of the aliphatic juvenoids described earlier[5,6] or synthesized by us[7]. Comparing the structures of both classes of juvenoids (Scheme 1), one can see that they differ in the structure of the terminal isoprenoid segment and that this segment in the cyclic structure is "rolled" in the cyclohexane or cyclohexene ring by junction of the carbon atoms C-11 and C-14 in esters or C-7 and C-10 in ethers. This junction limits the flexibility of the isoprenoid chain and fixes the geometry of the C_8-C_9, C_9-C_{10}, and C_{10}-C_{11} (in esters) or C_4-C_5, C_5-C_6, and C_6-C_7 bonds (in ethers) as *s-cis*, and the C_7-C_8 (in esters) or C_3-C_4 bonds (in ethers) as *s-trans*.

Scheme 1



Results and Discussion

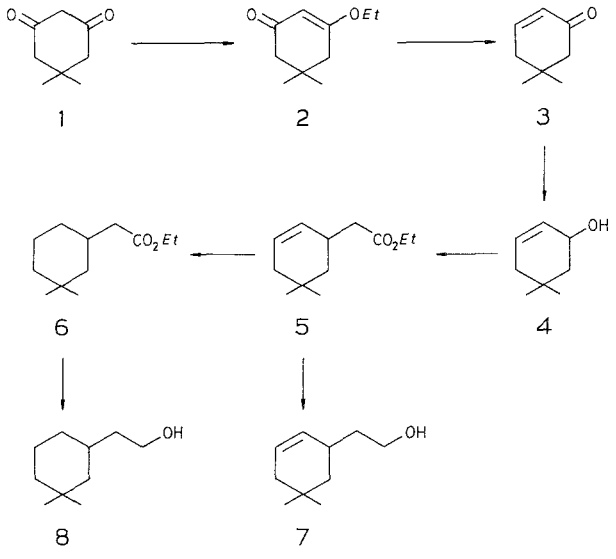
Starting materials for the direct synthesis of the juvenoid alcohols **7** and **8** were obtained from dimedone (**1**), the reaction sequence being shown in Scheme 2.

The α,β-unsaturated ketone **3** was prepared by the method of *Frank* and *Hall*[8]. Dimedone (**1**) was first converted into ethoxyketone **2** which was then reduced with $LiAlH_4$ to give ketone **3** in 91% yield. Ketone **3** was reduced ($LiAlH_4$) to the allylic alcohol **4** which after *Claisen* rearrangement by the orthoacetate method[9] (with ethyl orthoacetate) afforded the γ,δ-unsaturated ester **5**. This compound was hydrogenated over Pd/C yielding the saturated ester **6**. Alcohols **7** and **8** were obtained by the reduction ($LiAlH_4$) of esters **5** and **6**, respectively.

The first and the most numerous group of juvenoids, namely the esters **15–18**, were obtained by the *Wadsworth-Emmons* reaction[10] of ketones **13** or **14** (esters **15** and **17** from **13**, or **16** and **18** from **14**) with appropriate alkyl (diethylphosphono)acetates (s. Scheme 3).

Ketone **13** was obtained from alcohol **7** via tosylate **9** and bromide **11** which was used for alkylation of ethyl acetoacetate. Alkaline hydrolysis

Scheme 2

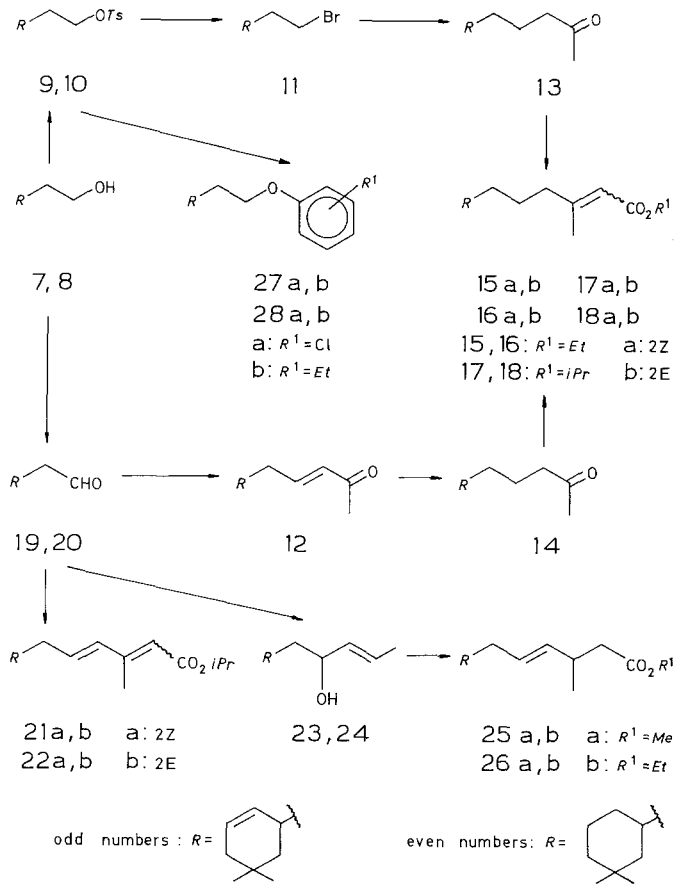


and subsequent decarboxylation of the intermediate keto ester afforded ketone **13** in 77% yield. Ketone **14** was obtained from alcohol **8** by the following reaction sequence: alcohol **8** was oxidized with pyridinium chlorochromate[11] to aldehyde **20** which was subjected to the *Wittig* reaction with $Ph_3P{=}CHCOCH_3$ to give the α,β-unsaturated ketone **12** (92%); the (*E*)-configuration of the double bond formed in **12** was confirmed by the IR (970 cm^{-1}) and ^{1}H-NMR spectra ($J = 16$ Hz for olefinic protons); ketone **12** was hydrogenated over *Raney*-nickel to ketone **14**.

α,β-Unsaturated esters **15–18** were obtained as isomeric (*E,Z*)-mixtures. Pure isomers were isolated by means of column chromatography. The (*Z*)-configuration was assigned to isomers for which the doublet from the methyl group at C-3 was at higher field ($\delta = 2.17$ ppm) in the ^{1}H-NMR spectrum, and the (*E*)-configuration for those at lower field (2.42 ppm, deshielding effect of the ester group *cis*-oriented in relation to

the methyl group). The dienoic esters **21** and **22** [mixtures of isomers (2 *Z*, 4 *E*) and (2 *E*, 4 *E*)] were obtained from the reaction of aldehydes **19** or **20** with isopropyl 4-(diethylphosphono)-3-methyl-2-butenoate [mixture (*Z*) : (*E*) = 48 : 52]. Pure isomers of these esters were isolated by

Scheme 3



means of preparative column chromatography and the corresponding configurations were assigned based on the position of signals from the methyl group at C-3 and the olefinic proton H-4 in the ^{1}H-NMR spectra. The signal of the methyl group for isomers (2 *Z*, 4 *E*) occurred at 2.13 ppm and the multiplet of proton H-4 at 7.84 ppm (deshielding effect of the ester group), whereas for isomers (2 *E*, 4 *E*) the corresponding signals were at 2.52 and 6.22–6.38 ppm.

The γ,δ-unsaturated esters **25 a, b** and **26 a, b** were also obtained from aldehydes **19** and **20** by the *Grignard* reaction with 1-propenylmagnesium

bromide [above 95% of the (*E*)-isomer] and subsequent *Claisen* rearrangement of alcohols **23** or **24** formed with methyl or ethyl orthoacetate.

Compounds **23–26** possess two chiral carbon atoms, each of them should occur as a pair of racemic diastereoisomers. Gas-chromatographic analysis (column 3 m length, 15% Carbowax 1000 on Chromosorb P, 130 °C) of alcohols **23** and **24** showed that these compounds are indeed the equimolar mixtures of diastereoisomers. This fact was also confirmed by the ^{1}H-NMR spectra of **23** and **24** with the use of shift reagent Eu(*TFC*)$_3$ applied for determination of enantiomeric purity. Changes of positions of signals from the *gem*-methyl groups were observed in these spectra. In the case of alcohol **24**, whose "normal" (100 MHz) ^{1}H-NMR spectrum exhibited only one six-proton singlet derived from these groups, the spectrum with Eu(*TFC*)$_3$ (dose ca. 120 mg in 5% solution of **24** in CCl_4, *TMS* as external standard) showed the presence of two pairs of singlets ($J = 15$ Hz) indicating that four enantiomers, forming a pair of diastereoisomeric racemic mixtures, are involved. Alcohol **23**, exhibiting two singlets from the *gem*-methyl groups in the 100 MHz NMR spectrum, showed two groups ($J = 17$ Hz) four singlets each in the spectrum with the use of Eu(*TMC*)$_3$.

Unfortunately, in the case of esters **25 a, b** and **26 a, b**, neither gas chromatography nor application of Eu(*TFC*)$_3$ for measurement of the ^{1}H-NMR spectra (100 MHz) afforded any data about the composition of mixtures of diastereoisomers. However, since starting compounds for the *Claisen* reaction, alcohols **23** and **24**, are the mixtures of diastereoisomers, the products of this rearrangement are most certainly also such mixtures[12, 13].

The last group of juvenoids, the alkyl aryl ethers **27 a, b** and **28 a, b**, were obtained by alkylation of potassium *p*-chloro- or *p*-ethylphenolates with tosylates **9** or **10**.

The biological activity of the juvenoids obtained was tested on larvae of *Dysdercus cingulatus* and pupae of *Tenebrio molitor*. The results of tests showed that these compounds are moderately active on *Dysdercus c.* and inactive on *Tenebrio m.* Comparison of doses of aliphatic juvenoids and their cyclic analogs at which metamorphosis of insects is disturbed, indicates that the former compounds are about ten times more active than the latter ones.

More detailed results of biological investigations and conclusions therefrom will be the subject of a separate paper.

Experimental

The course of all reactions and the purity of products were controlled by means of thin-layer (TLC) and gas-liquid (GLC) chromatography. TLC was carried out on silica gel G (Merck). Chromatograms were developed with mixtures

of petroleum ether, ethyl ether and acetone in various ratios and detected with 20% ethanolic H_2SO_4. Preparative column chromatography was carried out on silica gel (100–200 mesh, Marchery-Nagel), the eluent being a petroleum ether-ethyl ether-acetone mixture (various ratios). GLC was performed on a Chromatron GCHF-18.3.4 apparatus using columns with 2 and 3 m length coated with 10% XE-60 on Chromosorb G.

The ^{1}H-NMR spectra were recorded for 10% CCl_4 solutions on a 100 MHz Tesla BS-497 apparatus with *HMDS* as external standard. The IR spectra were taken for the same solutions on a Perkin-Elmer 621 spectrophotometer.

The starting material was commercial dimedone (**1**, 5,5-dimethyl-1,3-cyclohexanedione) from POCh, m.p. 147–148 °C.

The experimental C, H values agree with the molecular formulas given.

3-Ethoxy-5,5-dimethyl-2-cyclohexen-1-one (**2**)

A mixture of dimedone (**1**, 50 g, 0.36 mol), absolute ethanol (68 ml, 1.16 mol), and *p*-toluenesulfonic acid (1.3 g) in benzene (400 ml) was heated with azeotropic removal of water until **1** reacted completely. A residue after evaporation of benzene was distilled *in vacuo* to afford **2** (49.5 g, 82.5%), b.p. 86 °C ($1.33 \cdot 10^2$ Pa) Lit.[8]: b.p. 98 °C ($1.33 \cdot 10^2$ Pa), m.p. 57–58 °C; ^{1}H-NMR (δ, ppm): 1.34 [s, 6 H, —$(CH_3)_2$C—], 1.65 (t, J = 6.5 Hz, 3 H, —OCH_2CH_3), 2.34, 2.49 [2 s, 4 H, —CH_2—$C(CH_3)_2$—CH_2—], 4.18 (q, J = 6.5 Hz, 2 H, —OCH_2CH_3), 5.46 (s, 1 H, C=CH—); IR (cm^{-1}): 1 660 (s), 1 610 (s).

5,5-Dimethyl-2-cyclohexen-1-one (**3**)

Ethoxyketone **2** (49.5 g, 0.295 mol) was reduced with $LiAlH_4$ (3.6 g, 0.095 mol). 10% H_2SO_4 solution was used for hydrolysis. After normal working up and distillation, ketone **3** (33.3 g, 91%), b.p. 70 °C/$16 \cdot 10^2$ Pa, n_D^{20} = 1.4733 (Lit.[8]: b.p. 75 °C/$20 \cdot 10^2$ Pa, n_D^{20} = 1.4710), was obtained. ^{1}H-NMR (δ, ppm): 1.32 [s, 6 H, —$(CH_3)_2$C—], 2.44–2.58 (m, 4 H, —CH_2—CO—, —CH=CH—CH_2—), 6.18 (d, J = 10 Hz, split in t, J = 2 Hz, 1 H, —CH=CH—CO—), 7.04 (d, J = 10 Hz, split in t, J = 4 Hz, 1 H, —CH=CH—CO—); IR (cm^{-1}): 3 050 (m), 1 685 (s), 1 610 (s).

5,5-Dimethyl-2-cyclohexen-1-ol (**4**)

Ketone **3** (12.4 g, 0.1 mol) was reduced with $LiAlH_4$ (1.9 g, 0.05 mol) in a standard manner. Alcohol **4** (11.5 g, 91%), b.p. 93 °C/$26.67 \cdot 10^2$ Pa, n_D^{20} = 1.4745, was obtained. ^{1}H-NMR (δ, ppm): 1.21, 1.28 [2 s, 6 H, —$(CH_3)_2$C—], 4.38 [s, 1 H, —CH(OH)—], 4.44 [m, 1 H, —CH(OH)], 4.91 (m, 2 H, —CH=CH—); IR (cm^{-1}): 3 330 (s, b), 3 040 (m), 1 650 (m), 1 280 (s), 1 050 (s). $C_8H_{14}O$ (126.19).

Ethyl (5,5-dimethyl-2-cyclohexen-1-yl)acetate (**5**)

A mixture of alcohol **4** (10.3 g, 0.08 mol), ethyl orthoacetate (65.0 g, 0.4 mol), and propionic acid (0.1 ml) was heated at 138 °C with simultaneous distilling off ethanol for 36 h. Pure ester **5** (13.2 g, 81%), b.p. 76 °C/$1.33 \cdot 10^2$ Pa, n_D^{20} = 1.4578, was obtained. ^{1}H-NMR (δ, ppm): 1.18, 1.21 [2 s, 6 H, —$(CH_3)_2$C—], 1.50 (t, J = 7 Hz, 3 H, —OCH_2CH_3), 4.33 (q, J = 7 Hz, 2 H, —OCH_2CH_3), 5.70–5.88 (m, 2 H, —CH=CH—); IR (cm^{-1}): 3 040 (w), 1 730 (s), 1 650 (m), 710 (s). $C_{12}H_{20}O_2$ (196.28).

Ethyl (3,3-dimethylcyclohexyl)acetate (**6**)

Ester **5** (9.8 g, 0.05 mol) in absolute ethanol (100 ml) was hydrogenated over 10% Pd/C (2.0 g). Ester **6** (9.3 g, 95%), b.p. 102.5 °C/13.33 · 10^2 Pa, n_D^{20} = 1.4479, was obtained. ^{1}H-NMR (δ, ppm): 1.22, 1.24 [2 s, 6 H, —$(CH_3)_2$C—], 1.54 (t, J = 7 Hz, 3 H, —OCH_2CH_3), 4.36 (q, J = 7 Hz, 2 H, —OCH_2CH_3); IR (cm^{-1}): 1 730 (s). $C_{12}H_{22}O_2$ (198.30).

2-(5,5-Dimethyl-2-cyclohexen-1-yl)-ethanol (**7**)
2-(3,3-dimethylcyclohexyl)-ethanol (**8**)

Alcohols **7** and **8** were quantitatively obtained by reduction of esters **5** and **6**, respectively, with $LiAlH_4$.

7: b.p. 90 °C/8 · 10^2 Pa, n_D^{20} = 1.4674. ^{1}H-NMR (δ, ppm): 1.17, 1.22 [2 s, 6 H, —$(CH_3)_2$C—], 3.88 (t, J = 7 Hz, 2 H, —CH_2—OH), 4.72–4.85 (m, 2 H, —CH=CH—); IR (cm^{-1}): 3 350 (s), 1 650 (m), 1 370 (s), 1 050 (s), 690 (s). $C_{10}H_{18}O$ (154.24).

8: b.p. 99.5 °C/13.33 · 10^2 Pa, n_D^{20} = 1.4651. ^{1}H-NMR (δ, ppm): 1.20 [s, 6 H, —$(CH_3)_2$C—], 3.76 (s, 1 H, —CH_2—OH), 3.82 (t, J = 7 Hz, 2 H, —CH_2—OH); IR (cm^{-1}): 3 350 (s), 1 365 (s), 1 050 (s). $C_{10}H_{20}O$ (156.26).

Tosylate of 2-(5,5-dimethyl-2-cyclohexen-1-yl)-ethanol (**9**)
Tosylate of 2-(3,3-dimethylcyclohexyl)-ethanol (**10**)

Tosyl chloride (4.3 g, 0.022 mol) was added to a cooled (ice and water) solution of alcohol **7** (2.8 g, 0.018 mol) in anhydrous pyridine (30 ml) and the mixture was stirred until **7** reacted completely (TLC). Then the mixture was pured into ice with the calculated amount of concentrated hydrochloric acid. The product was extracted with ethyl ether and the extracts were washed with water and dried over $MgSO_4$. A residue after evaporation of the solvent was purified by column chromatography (petroleum ether—acetone 19 : 1). Pure tosylate **9** (4 g, 74%), n_D^{20} = 1.5094, was obtained. ^{1}H-NMR (δ, ppm): 1.12, 1.18 [2 s, 6 H, —$(CH_3)_2$C—], 2.74 (s, 3 H, —C_6H_4—CH_3), 4.31 (t, J = 7 Hz, 2 H, —CH_2O—), 5.56–5.86 (m, 2 H, —CH=CH—), 7.58, 8.0 (m, 4 H, AA′BB′, —C_6H_4—); IR (cm^{-1}): 3 040 (w), 1 650 (w), 1 600 (m), 1 500 (w), 1 470 (s), 690 (s). $C_{17}H_{24}O_3S$ (308.42).

Tosylate **10** was obtained analogously from alcohol **8** in 81% yield; n_D^{20} = 1.5159. ^{1}H-NMR (δ, ppm): 1.14 [s, 6 H, —$(CH_3)_2$C—], 2.73 (s, 3 H, —C_6H_4—CH_3), 4.25 (t, J = 7 Hz, 2 H, —CH_2O—), 7.55, 7.98 (m, 4 H, AA′BB′, —C_6H_4—); IR (cm^{-1}): 1 600 (m), 1 500 (w). $C_{17}H_{26}O_3S$ (310.44).

1-Bromo-2-(5,5-dimethyl-2-cyclohexen-1-yl)-ethane (**11**)

Tosylate **9** (2.8 g, 0.09 mol) was added to lithium bromide (2.35 g, 0.027 mol) in anhydrous acetone (30 ml) and the mixture was refluxed for 1 h and then stirred at room temp. for 24 h. When the tosylate has reacted completely (TLC), the mixture was diluted with water and the product was extracted with ethyl ether. The extracts were washed with water and dried over anhydrous $CaCl_2$. After evaporation of the solvent the crude product was subjected to column chromatography (petroleum etherethyl ether 19 : 1) and then distilled. Pure bromide **11** (1.65 g, 86%), b.p. 90–91 °C/30.67 · 10^2 Pa, n_D^{20} = 1.4945, was obtained. ^{1}H-NMR (δ, ppm): 1.20, 1.26 [2 s, 6 H, —$(CH_3)_2$C—], 3.7 (t, J = 7 Hz, 2 H, —CH_2—Br), 5.64–5.9 (m, 2 H, —CH=CH—); IR (cm^{-1}): 3 040 (w), 1 650 (m), 680 (s), 650 (s). $C_{10}H_{17}Br$ (217.15).

5-(5,5-Dimethyl-2-cyclohexen-1-yl)-2-pentanone (**13**)

Bromide **11** (1.6 g, 0.0073 mol) in *DMF* (10 ml) was added to the sodium derivative of ethyl acetoacetate formed from ester (1.45 g, 0.011 mol) and NaH (0.26 g, 0.011 mol) in *DMF* (20 ml). The mixture was heated on a water bath for 16 h, then it was poured into water and the intermediate keto ester was extracted with petroleum ether. To a residue after evaporation of the solvent, 5% NaOH solution (30 ml) was added and the mixture was heated on a water bath for 24 h. The cooled mixture was diluted with water and extracted with petroleum ether. The combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). The crude product after evaporation of the solvent was distilled *in vacuo* to afford ketone **13** (1.1 g, 77%), b.p. 96 °C/5.33 · 10^2 Pa, n_D^{20} = 1.4668. ^{1}H-NMR (δ, ppm): 1.16, 1.22 [2 s, 6 H, —$(CH_3)_2$C—], 2.32 (s, 3 H, —CO—CH_3), 5.70–5.86 (m, 2 H, —CH=CH—); IR (cm^{-1}): 3 040 (w), 1 725 (s). $C_{13}H_{22}O$ (194.31).

(5,5-Dimethyl-2-cyclohexen-1-yl)-acetaldehyde (**19**)
(3,3-Dimethylcyclohexyl)-acetaldehyde (**20**)

Alcohol **8** (4.0 g, 0.026 mol) was added in one portion to a slurry of pyridinium chlorochromate (11.2 g, 0.052 mol) and anhydrous sodium acetate (0.7 g, 0.008 mol) in anhydrous methylene chloride (100 ml) and the mixture was stirred for 2 h. Then CH_2Cl_2 was distilled off and the residue was extracted with petroleum ether. The ethereal solution was filtered through "Florisil" and evaporated. The crude product was chromatographed on a column (petroleum ether—ethyl ether 19 : 1) and distilled *in vacuo*. Pure aldehyde **20** (3.0 g, 76%) was obtained. Pure aldehyde **19** (yield 51%) was obtained analogously from alcohol **7**.

19: b.p. 97–98 °C/29.67 · 10^2 Pa, n_D^{20} = 1.4762. ^{1}H-NMR (δ, ppm): 1.21, 1.23 [2 s, 6 H, —$(CH_3)_2$C—], 5.65–5.9 (m, 2 H, —CH=CH—), 10.0 (t, J = 2 Hz, 1 H, —CHO); IR (cm^{-1}): 3 030 (m), 2 720 (m), 1 725 (s), 1 650 (w). $C_{10}H_{16}O$ (152.23).

20: b.p. 93–93.5 °C/24 · 10^2 Pa, n_D^{20} = 1.4592. ^{1}H-NMR (δ, ppm): 1.20, 1.22 [2 s, 6 H, —$(CH_3)_2$C—], 9.92 (t, J = 2 Hz, 1 H, —CHO); IR (cm^{-1}): 2 720 (s), 1 720 (s). $C_{10}H_{18}O$ (154.24).

5-(3,3-Dimethylcyclohexyl)-3-penten-2-one (**12**)

A mixture of aldehyde **20** (1.0 g, 0.0065 mol) and Ph_3P=$CHCOCH_3$ (4.1 g, 0.013 mol) in anhydrous CH_2Cl_2 (40 ml) was refluxed for 6 h. After the whole aldehyde had reacted, the solvent was distilled off and petroleum ether was added to the residue. Triphenylphosphine oxide was filtered off and the filtrate was evaporated. The crude product was purified by means of column chromatography (petroleum ether—ethyl ether 19 : 1). Pure ketone **12** (1.15 g, 92%), b.p. 72–72.5 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4783, was obtained. ^{1}H-NMR (δ, ppm): 1.2 [s, 6 H, —$(CH_3)_2$C—], 2.42 (s, 3 H, —CO—CH_3), 6.22 (d, J = 16 Hz, 1 H, —CH=CH—CO—), 6.94 (d, J = 16 Hz split in t, J = 7 Hz, 1 H, —CH=CH—CO—); IR (cm^{-1}): 3 050 (w), 1 675 (s), 1 630 (s), 970 (s). $C_{13}H_{22}O$ (194.31).

5-(3,3-Dimethylcyclohexyl)-2-pentanone (**14**)

Ketone **14** was obtained in 94% yield by hydrogenation of ketone **12** over *Raney*-nickel; b.p. 112–113 °C/5.33 · 10^2 Pa, n_D^{20} = 1.4590. ^{1}H-NMR (δ, ppm): 1.20 [s, 6 H, —$(CH_3)_2$C—], 2.34 (s, 3 H, —CO—CH_3), 2.6 (t, J = 7 Hz, 2 H, —CH_2—CO—); IR (cm^{-1}): 1 720 (s). $C_{13}H_{24}O$ (196.32).

Ethyl (2Z)- and (2E)-6-(5,5-dimethyl-2-cyclohexen-1-yl)-3-methyl-2-hexenoate (**15a** *and* **15b**)

Ketone **13** (0.5 g, 0.0025 mol) in anhydrous *DMF* (5 ml) was added to the sodium derivative formed from ethyl (diethylphosphono)-acetate (0.65 g, 0.0029 mol) and NaH (0.14 g of 50% reagent, 0.0029 mol). The mixture was stirred for 12 h at room temp. and then was heated on a water bath for further 8 h. The cooled mixture was diluted with water and extracted with petroleum ether. The extracts were washed with saturated NaCl solution and dried over $MgSO_4$. A mixture of esters **15** [0.4 g, 60%, 75% of (2*E*)- and 25% of (2*Z*)-isomer] was obtained.

Analogously, the mixture of esters **17a** (24%) and **17b** (76%) was obtained in 56% yield by the reaction of ketone **13** with isopropyl (diethylphosphono)acetate. Ketone **14** was reacted with ethyl (diethylphosphono)acetate to give in 68% yield a mixture of esters **16a** (25%) and **16b** (75%) and with isopropyl (diethylphosphono)acetateesters **18a** (24%) and **18b** (76%) (yield 71%).

Pure isomers of these esters were isolated by means of column chromatography (petroleum ether—ethyl ether 485 : 15).

15a: b.p. 109–110 °C/0.67 · 10^2 Pa, n_D^{20} = 1.4838. ^{1}H-NMR (δ, ppm): 1.18, 1.22 [2 s, 6 H, —$(CH_3)_2$C—], 1.54 (t, J = 7 Hz, 3 H, —OCH_2CH_3), 2.17 [d, J = 1.5 Hz, 3 H, —(CH_3)C=CH—], 4.36 (q, J = 7 Hz, 2 H, —OCH_2CH_3), 5.7–5.88 [m, 3 H, —CH=CH—, —(CH_3)C=CH—]; IR (cm^{-1}: 3040 (m), 1720 (s), 1650 (s). $C_{17}H_{28}O_2$ (264.39).

15b: b.p. 116–117 °C/0.67 · 10^2 Pa, n_D^{20} = 1.4865. ^{1}H-NMR (δ, ppm): 2.42 [d, J = 1.5 Hz, 3 H, —(CH_3)C=CH—], 5.72–5.88 [m, 3 H, —CH=CH—, —(CH_3)C=CH—]; IR (cm^{-1}): 3030 (m), 1715 (s), 1650 (s). $C_{17}H_{28}O_2$ (264.39).

17a: b.p. 110–111 °C/0.67 · 10^2 Pa, n_D^{20} = 1.4801. ^{1}H-NMR (δ, ppm): 1.19, 1.25 [2 s, 6 H, —$(CH_3)_2$C—], 1.53 [d, J = 7 Hz, 6 H, —$OCH(CH_3)_2$], 2.17 [d, J = 1.5 Hz, 3 H, —(CH_3)C=CH—], 5.23 [sep, J = 7 Hz, 1 H, —$OCH(CH_3)_2$], 5.73–5.85 [m, 3 H, —CH=CH—, —(CH_3)C=CH—]; IR (cm^{-1}): 3040 (m), 1720 (s), 1650 (s). $C_{18}H_{30}O_2$ (278.42).

17b: b.p. 118–119 °C/0.67 · 10^2 Pa, n_D^{20} = 1.4821. ^{1}H-NMR (δ, ppm): 2.42 [d, J = 1.5 Hz, 3 H, —(CH_3)C=CH—], 5.73–5.85 [m, 3 H, —CH=CH—, —(CH_3)C=CH—]; IR (cm^{-1}): 3030 (m), 1715 (s), 1650 (s). $C_{18}H_{30}O_2$ (278.42).

16a: b.p. 111–112 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4758. ^{1}H-NMR (δ, ppm): 1.2 [s, 6 H, —$(CH_3)_2$C—], 1.55 (t, J = 7 Hz, 3 H, —OCH_2CH_3), 2.17 [d, J = 1.5 Hz, 3 H, —(CH_3)C=CH—], 4.37 (q, J = 7 Hz, 2 H, —OCH_2CH_3), 5.82 [m, 1 H, —(CH_3)C=CH—]; IR (cm^{-1}): 1715 (s), 1645 (s). $C_{17}H_{30}O_2$ (266.41).

16b: b.p. 115–116 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4786. ^{1}H-NMR (δ, ppm): 2.42 [d, J = 1.5 Hz, 3 H, —(CH_3)C=CH—], 5.83 [m, 1 H, —(CH_3)C=CH—]; IR (cm^{-1}): 1715 (s), 1650 (s). $C_{17}H_{30}O_2$ (266.41).

18a: b.p. 120–121 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4720. ^{1}H-NMR (δ, ppm): 1.2 [s, 6 H, —$(CH_3)_2$C—], 1.52 [d, J = 7 Hz, 6 H, —$OCH(CH_3)_2$], 2.17 [d, J = 1.5 Hz, 3 H, —(CH_3)C=CH—], 5.22 [sep, J = 7 Hz, 1 H, —$OCH(CH_3)_2$], 5.8 [m, 1 H, —(CH_3)C=CH—]; IR (cm^{-1}): 1710 (s), 1645 (s). $C_{18}H_{32}O_2$ (280.44).

18b: b.p. 123–124 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4751. ^{1}H-NMR (δ, ppm): 2.42 [d, J = 1.5 Hz, 3 H, —(CH_3)C=CH—], 5.82 [m, 1 H, —(CH_3)C=CH—]; IR (cm^{-1}): 1710 (s), 1645 (s). $C_{18}H_{32}O_2$ (280.44).

Isopropyl (2Z,4E)- and (2E,4E)-6-(5,5-dimethyl-2-cyclohexen-1-yl)-3-methyl-2,4-hexadienoate (**21a** *and* **21b**)

Aldehyde **19** (0.75 g, 0.005 mol) was added to the sodium derivative formed

from isopropyl 4-(diethylphosphono)-3-methyl-2-butenoate [1.65 g, 0.00625 mol, mixture of isomers (*E*) : (*Z*) = 52 : 48] and NaH (0.15 g, 0.00625 mol) in anhydrous *THF* (30 ml) with a mixture of *DMF* (1 ml). After stirring for 6 h at room temp. water was added and product was extracted with ethyl ether. The extracts were washed with water and dried ($MgSO_4$). After evaporation of ether the mixture of esters **21** [0.8 g, 62%, 57% of the (2 *Z*, 4 *E*)- and 43% of the (2 *E*, 4 *E*)-isomer] was obtained.

Analogously, the mixture of esters **22 a** (58.6%) and **22 b** (41.4%) was obtained from aldehyde **20** in 77.5% yield.

Pure isomers were isolated by means of column chromatography (petroleum ether—ethyl ether 24 : 1).

21 a: b.p. 111.5–112 °C/1.33 · 10^2 Pa, n_D^{20} = 1.5070. ^{1}H-NMR (δ, ppm): 1.20, 1.26 [2 s, 6 H, —$(CH_3)_2$C—], 1.52 [d, J = 6.5 Hz, 6 H, —OCH$(CH_3)_2$], 2.13 [m, 3 H, —(CH_3)C=CH—], 5.24 [sep, J = 6.5 Hz, 1 H, —OC**H**$(CH_3)_2$], 5.7–5.96 [m, 3 H, —**CH**=**CH**—, —(CH_3)C=**CH**—], 6.26 [d, J = 16 Hz split in t, J = 6.5 Hz, 1 H, —**CH**=CH—(CH_3)C=CH—], 7.84 [d, J = 16 Hz, 1 H, —CH=**CH**—(CH_3)C=CH—]; IR (cm^{-1}): 3 030 (w), 1 695 (s), 1 635 (s), 970 (s). $C_{18}H_{28}O_2$ (276.40).

21 b: b.p. 118–119 °C/1.33 · 10^2 Pa, n_D^{20} = 1.5103. ^{1}H-NMR (δ, ppm): 2.52 [m, 3 H, —(CH_3)C=CH—], 5.73–5.94 [m, 3 H, —**CH**=**CH**—, —CH=CH—(CH_3)C=**CH**—], 6.22–6.38 [m, 2 H, —**CH**=**CH**—(CH_3)C=CH—]; IR (cm^{-1}): 3 030 (w), 1 705 (s), 1 635 (m), 970 (s). $C_{18}H_{28}O_2$ (276.40).

22 a: b.p. 128–129 °C/1.33 · 10^2 Pa, n_D^{20} = 1.5032. ^{1}H-NMR (δ, ppm): 1.20 [s, 6 H, —$(CH_3)_2$C—], 1.52 [d, J = 6.5 Hz, 6 H, —OCH$(CH_3)_2$], 2.13 [d, J = 1.5 Hz, 3 H, —(CH_3)C=CH—], 5.22 [sep, J = 6.5 Hz, 1 H, —OC**H**$(CH_3)_2$], 5.74 [m, 1 H, —(CH_3)C=**CH**—], 6.26 [d, J = 16 Hz split in t, J = 6.5 Hz, 1 H, —**CH**=CH—C(CH_3)=CH—], 7.82 [d, J = 16 Hz, 1 H, —CH=**CH**—C(CH_3)=CH—]; IR (cm^{-1}): 3 060 (w), 1 700 (s), 1 635 (s), 970 (s). $C_{18}H_{30}O_2$ (278.42).

22 b: b.p. 125–126 °C/0.67 · 10^2 Pa, n_D^{20} = 1.5064. ^{1}H-NMR (δ, ppm): 2.52 [m, 3 H, —(CH_3)C=CH—], 5.82 [m, 1 H, —(CH_3)C=**CH**—], 6.22–6.36 [m, 2 H, —**CH**=**CH**—C(CH_3)=CH—]; IR (cm^{-1}): 3 040 (w), 1 705 (s), 1 635 (m), 1 610 (s), 970 (s). $C_{18}H_{30}O_2$ (278.42).

5-(5,5-Dimethyl-2-cyclohexen-1-yl)-2-penten-3-ol (**23**)*
5-(3,3-Dimethylcyclohexyl)-2-penten-3-ol (**24**)*

Aldehyde **19** (0.6 g, 0.004 mol) was added to 1-propenylmagnesium bromide formed from 1-propenyl bromide (0.75 g, 0.006 mol) and magnesium (0.15 g, 0.006 g-at.) in anhydrous *THF* (30 ml) and the mixture was stirred for 6 h. Then saturated NH_4Cl solution was added and the product was extracted with ethyl ether. The ethereal solution was washed with saturated NaCl solution and dried over $MgSO_4$. The crude product was purified by means of column chromatography (petroleum ether—acetone 9 : 1) and distilled *in vacuo*. Pure alcohol **23** (0.5 g, 65.8%), b.p. 109–110 °C/5.33 · 10^2 Pa, n_D^{20} = 1.4880, was obtained. ^{1}H-NMR (δ, ppm): 1.20, 1.22 [two broad s, 6 H, —$(CH_3)_2$C—], 1.99 (m, 3 H, —CH=CH—**CH**$_3$), 2.41 [s, 1 H, —CH(**OH**)], 4.7–4.9 [m, 1 H, —**CH**(OH)—], 5.6–5.86 (m, 4 H, —**CH**=**CH**—); IR (cm^{-1}): 3 620 (m), 3 350 (m, b), 3 030 (m), 1 650 (w), 1 360 (s), 1 050 (s), 960 (s). $C_{13}H_{22}O$ (194.31).

* Note: These numbers denote a mixture of a pair of diastereomeric racemates: (*RR*), (*SS*), (*RS*), (*SR*).

Alcohol **24** was obtained similarly (yield 64.5%) from aldehyde **20**; b.p. 84 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4783. ^{1}H-NMR (δ, ppm): 1.23 [s, 6 H, —$(CH_3)_2$C—], 1.98 (d, J = 6.5 Hz, 3 H, —CH=CH—CH_3), 2.4 [s, 1 H, —CH(OH)—], 4.15–4.35 [m, 1 H, —CH(OH)—], 5.63–5.80 (m, 2 H, —CH=CH—); IR (cm^{-1}): 3 360 (s), 1 630 (w), 1 350 (s), 1 090 (s), 960 (s). $C_{13}H_{24}O$ (196.32).

Ethyl (4 E)-6-(5,5-dimethyl-2-cyclohexen-1-yl)-3-methyl-4-hexenoate (**25 b**)*

A mixture of alcohol **23** (0.3 g, 0.0015 mol), ethyl orthoacetate (1.65 g, 0.011 mol) and propionic acid (0.001 ml) was heated at 138 °C for 1 h. The residue after distilling off an excess of orthoacetate was distilled *in vacuo* to afford pure (GLC) ester **25 b** (0.35 g, 86%).

Alcohol **24** yielded in an analogical reaction ester **26 b** in 88% yield. Alcohols **23** and **24** refluxed with methyl orthoacetate in the presence of catalytic amounts of propionic acid gave esters **25 a** (77%) and **26 a** (72%), respectively.

Physical and spectral constants of esters **25 a***, **b*** and **26 a***, **b*** are as follows.

25 a*: b.p. 87–88 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4681. ^{1}H-NMR (δ, ppm): 1.16, 1.23 [2 s, 6 H, —$(CH_3)_2$C—], 1.32 [d, J = 7 Hz, 3 H, —(CH_3)CH—], 3.87 (s, 3 H, —OCH_3), 5.6–5.87 (m, 4 H, —CH=CH—); IR (cm^{-1}): 3 030 (w), 1 735 (s), 970 (s). $C_{16}H_{26}O_2$ (250.37).

25 b*: b.p. 91–92 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4673. ^{1}H-NMR (δ, ppm): 1.17, 1.24 [2 s, 6 H, —$(CH_3)_2$C—], 1.33 [d, J = 7 Hz, 3 H, —(CH_3)CH—], 1.52 (t, J = 7 Hz, 3 H, —OCH_2CH_3), 4.34 (q, J = 7 Hz, 2 H, —OCH_2CH_3), 5.6–5.86 (m, 4 H, —CH=CH—); IR (cm^{-1}): 3 030 (w), 1 735 (s), 970 (s). $C_{17}H_{28}O_2$ (264.39).

26 a*: b.p. 94–95 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4671. ^{1}H-NMR (δ, ppm): 1.23 [s, 6 H, —$(CH_3)_2$C—], 1.34 [d, J = 7 Hz, 3 H, —(CH_3)CH—], 3.94 (s, 3 H, —OCH_3), 5.52–5.75 (m, 2 H, —CH=CH—); IR (cm^{-1}): 1 735 (s), 970 (s). $C_{16}H_{28}O_2$ (252.38).

26 b*: b.p. 99–100 °C/1.33 · 10^2 Pa, n_D^{20} = 1.4662. ^{1}H-NMR (δ, ppm): 1.25 [s, 6 H, —$(CH_3)_2$C—], 1.34 [d, J = 7 Hz, 3 H, —(CH_3)CH—], 1.57 (t, J = 7 Hz, 3 H, —OCH_2CH_3), 4.37 (q, J = 7 Hz, 2 H, —OCH_2CH_3), 5.5–5.72 (m, 2 H, —CH=CH—); IR (cm^{-1}): 1 735 (s), 970 (s). $C_{17}H_{30}O_2$ (266.41).

Alkyl aryl ethers (**27 a, b** *and* **28 a, b**)

Tosylate **9** or **10** (0.005 mol) in *DMF* (5 ml) was added to the appropriate potassium phenolate (from 0.006 mol of phenol and 0.006 mol of powdered KOH) in *DMF* (20 ml). The mixture was stirred until all tosylate reacted (TLC). Then the mixture was diluted with water and the product was extracted with petroleum ether. Extracts were washed with 5% KOH solution, then with water, and dried over $MgSO_4$. The crude products were purified by means of column chromatography (petroleum ether—acetone 49 : 1) and distillation.

27 a: yield 76.9%, b.p. 153–154 °C/1.33 · 10^2 Pa, n_D^{20} = 1.5283. ^{1}H-NMR (δ, ppm): 1.18, 1.24 [2 s, 6 H, —$(CH_3)_2$C—], 4.22 (t, J = 7 Hz, 2 H, —CH_2O—), 5.77–5.9 (m, —CH=CH—), 7.0, 7.42 (m, 4 H, AA′BB′, —C_6H_4—); IR (cm^{-1}): 3 040 (m), 1 600 (s), 1 585 (m), 1 500 (s), 1 475 (s). $C_{16}H_{21}OCl$ (264.79).

27 b: yield 79.3%, b.p. 152–153 °C/1.33 · 10^2 Pa, n_D^{20} = 1.5172. ^{1}H-NMR (δ, ppm): 1.19, 1.24 [2 s, 6 H, —$(CH_3)_2$C—], 1.48 (t, J = 7 Hz, 3 H, —C_6H_4—CH_2CH_3), 2.84 (q, J = 7 Hz, 2 H, —C_6H_4—CH_2CH_3), 4.22 (t, J = 7 Hz, 2 H, —CH_2O—), 5.78–5.88 (m, 2 H, —CH=CH—), 6.96, 7.24 (m, 4 H, AA′BB′, —C_6H_4—); IR (cm^{-1}): 3 040 (w), 1 610 (s), 1 585 (m), 1 510 (s), 1 480 (s). $C_{18}H_{26}O$ (258.39).

28 a: yield 77.2%, b.p. 122–123 °C/0.67 · 10^2 Pa, n_D^{20} = 1.5241. ^{1}H-NMR (δ, ppm): 1.2 [s, 6 H, —$(CH_3)_2$C—], 4.08–4.28 (m, 2 H, —CH_2O—), 7.0, 7.4 (m, 4 H,

AA'BB', —C_6H_4—); IR (cm^{-1}): 1600 (m), 1580 (m), 1490 (s), 1470 (s). $C_{16}H_{23}OCl$ (266.80).

28b: yield 79.7%, b.p. 124–125 °C/0.67 · 10^2 Pa, n_D^{20} = 1.5122. ^{1}H-NMR (δ, ppm): 1.2 [s, 6H, —$(CH_3)_2C$—], 1.48 (t, J = 7 Hz, 3H, —C_6H_4—CH_2CH_3), 2.82 (q, J = 7 Hz, 2H, —C_6H_4—CH_2CH_3), 4.08–4.26 (m, 2H, —CH_2O—), 6.96, 7.24 (m, 4H, AA'BB', —C_6H_4—); IR (cm^{-1}): 3040 (w), 1610 (m), 1580 (w), 1510 (s), 1470 (s). $C_{18}H_{28}O$ (260.41).

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