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146. Regiospecific Acylation, Alkylation, and Aldol Condensation Using Magnesium Enolates Resulting from the Conjugate Addition of *Grignard* Reagents to α,β-Unsaturated Ketones

by **Ferdinand Näf** and **René Decorzant**

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(15. V. 74)

Summary. The magnesium 3,3-dimethylcyclohex-1-enolate **11**, formed in the copper catalyzed addition of methylmagnesium iodide to 3-methylcyclohex-2-enone, has been subjected to regiospecific electrophilic reactions such as acylation, alkylation, and aldol condensation in order to find a new access to the damascones, ionones and carotenoids. By way of illustration a new synthesis of γ-damascone is described.

Introduction. – Regioselective substitution of non-symmetrical ketones at the α-position is a frequent problem in organic synthesis, and several sophisticated methods have been developed for those cases where the usual substitution leads to the wrong isomer or to an isomeric mixture[1]).

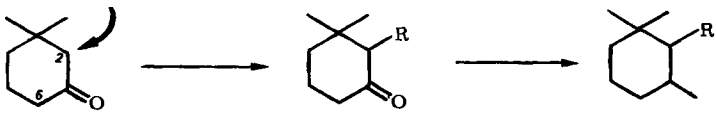
This problem can readily be solved by generating the desired enolate anion and then trapping it with an electrophile under non-equilibrating, kinetically controlled conditions.

Stork was the first to alkylate enolate anions which had been specifically generated from α,β-unsaturated ketones with lithium in liquid ammonia [2]. Since then, specific alkylation experiments have been reported in which enolate anions were generated either by reduction of

[1]) See *e.g.* [1], pp. 492 and 734.

α-halo ketones [3] [4], α-acyloxy ketones [4], or by cleavage of enol acetates [5] [6] and enol silyl ethers [6] [7] with an organolithium reagent. It has recently been shown that *Grignard* reagents as well as dialkylcopperlithium compounds, on conjugate addition to α,β-unsaturated carbonyl compounds, produce enolate anions which are valuable intermediates for further transformations. Under non-equilibrating conditions they have been alkylated regiospecifically with electrophiles such as allyl bromide [8], methyl iodide [8b–d] [9], 3,5-dimethyl-4-chloro-methylisoxazole [10], methyl vinyl ketone [12], and methyl α-trimethylsilylvinyl ketone [13].

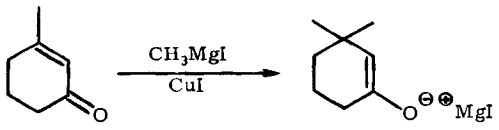
The present publication describes our efforts towards the regioselective substitution of 3,3-dimethylcyclohexanone (**1**) at its hindered C(2) position in order to find a novel, general access to compounds such as damascones, ionones, and carotenoids all possessing the structural element **A**:



1 **A**

By way of illustration a new synthesis of γ-damascone [14] is described and a synthesis of vitamin A, based on this approach, is under investigation in our laboratory at present.

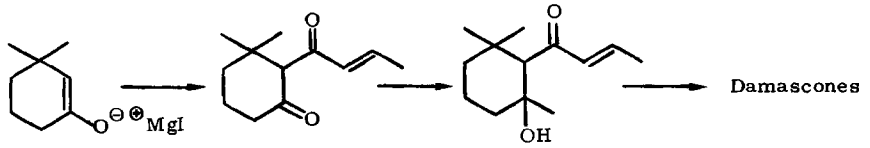
Results and Discussion. – The magnesium enolate **1i** seemed a useful intermediate not only for its possible regiospecific acylation or alkylation but also in view of its facile accessibility. It was generated from 3-methyl-2-cyclohexenone (**2**)[2]) [15]



2 **1i**

using the known [16] copper (I)-catalyzed conjugate addition of methylmagnesium iodide in ether at 0° and was allowed to react with acyl halides, alkyl halides, and aldehydes[3]).

Acylation of magnesium enolate 1i (Table 1). – First, enolate **1i** was trapped with acetyl chloride (**3**) at 0°. In ether a 33% yield of the desired C-acylation product **4**

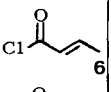
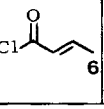


1i **27** **28**

[2]) *Aldrich Chemical Co.*, Milwaukee, Wis. 53210.

[3]) The *Michael* addition of **1i** to methyl vinyl ketone and methyl α-trimethylsilylvinyl ketone was also attempted but proved unsatisfactory from a synthetic point of view; however, see [12] [13].

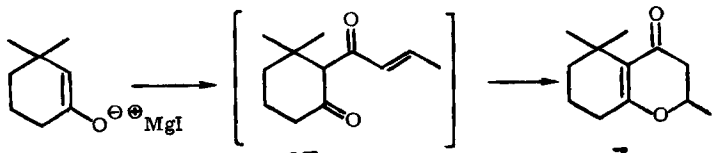
Table 1. *Reaction of magnesium enolate* **1i** *with acid chlorides* **3** *and* **6** *in ether or 1,2-dimethoxyethane* (DME)

Experiment	Reactants	Solvent	Distribution of C(2)- and O-acylation products		Total yield of acylated products
			C(2)-acylation	O-acylation	
1a	**1i** +  **3**	ether	**4** 62%	**5** 38%	39 - 53%
1b	**1i** +  **3**	DME	**4** 0%	**5** 100%	63%
2a	**1i** +  **6**	ether	**7** 86%	**8** 14%	48%
2b	**1i** +  **6**	DME	**7** 5%	**8** 95%	52%

could be isolated, the ratio between C- and O-acylation products being **4**/**5** ~62/38. In 1,2-dimethoxyethane (DME), however, only the O-acylation product **5** was formed.

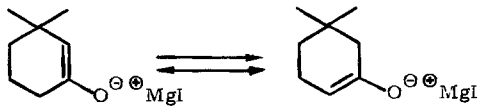
In the hope of realizing a short damascone synthesis (**1i** → **27** → **28** → damascones) enolate **1i** was treated directly with crotonyl chloride (**6**).

In ether the main product was hexahydrochromone **7** (instead of **27**) together with a little **8**; replacement of ether by DME favoured the O-acylation product **8** (**7**/**8** ~4/96). We assume that **7** was formed *via* the C-acylated intermediate **27** which cyclized under the reaction conditions to give **7**.



1i **27** **7**

In all these experiments (Table 1, exp. 1a–2b) the electrophilicity of both acyl chlorides (**3** and **6**) was high enough to trap the enolate **1i** prior to its equilibration (**1i** ⇌ **1ii**). However, there was a clear-cut difference in the C/O acylation ratio between



1i **1ii**

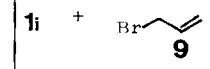
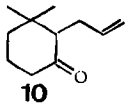
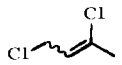
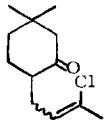
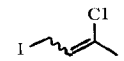
the saturated acyl chloride (**3**) and the unsaturated one (**6**) (compare exp. 1a and 1b with 2a and 2b, Table 1). This may be explicable by the *Pearson-Klopman* principle which states that a hard reagent attacks the hard site of an ambident ion and a soft reagent prefers the soft site [17]. The relatively hard **3** should therefore prefer reaction at the hard oxygen of enolate anion **1i** and favour **5**; the relatively softer **6**, on the

other hand, should have a higher affinity for the soft C(2) and favour **7**. The solvent effect on the C/O acylation ratio was also noteworthy: a reasonable amount of C-acylated product was obtained only in the relatively nonpolar diethyl ether whereas DME gave O-acylated products almost exclusively (compare exp. 1a and 2a with 1b and 2b, Table 1).

These results are in good agreement with a recent, detailed investigation of *House et al.* [18]. Solvent-separated enolate ion pairs, favoured in good solvating solvents, such as DME or DMF rather than ether, and by the presence of metal cations such as lithium or sodium rather than magnesium, tend to be O-acylated. However, contact enolate ion pairs, favoured in non-solvating solvents and by the presence of metal cations such as magnesium, exhibit a preference for C-acylation.

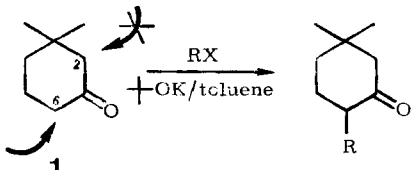
Alkylation of 1i (see Table 2). – Alkylation of enolate **1i** with allyl bromide (**9**), 3-chlorobut-2-enyl chloride (**12**) and 3-chlorobut-2-enyl iodide (**14**) in hexamethylphosphoramide (HMPA)/ether at ~0° was also tried (see Table 2). Allyl bromide (**9**) gave the less stable kinetic alkylation product **10** as main product. However, both chloride **12** and iodide **14** led to the thermodynamically more stable, less hindered alkylation product **13**[4]) (derived from **1ii**). Under our reaction conditions the chloride **12** and the iodide **14** are not electrophilic enough to trap the enolate **1i** prior to its equilibration with **1ii** in contrast to the behaviour of allyl bromide (**9**) and the acid chlorides **3** and **6**.

Table 2. *Reactions of magnesium enolate* **1i** *with allyl halides* **9**, **12** *and* **14** *in ether or ether-hexamethylphosphoramide* (HMPA)

Experiment	Reactants	Solvent	Main product	Yield
3	**1i** +  **9**	ether-HMPA (1 : 1)	 **10**	55%
4	**1i** +  **12**	ether-HMPA (1 : 1)	 **13**	31%
5a	**1i** +  **14**	ether-HMPA (1 : 1)	**13**	54%
5b	**1i** + **14**	ether	no alkylation products formed	

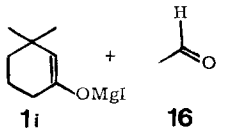
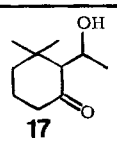
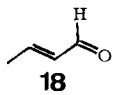
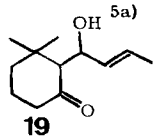
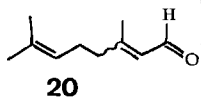
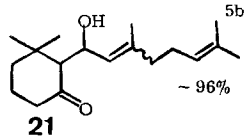
[4]) The minor reaction products (about 20% of the distilled mixture) have not been analysed.

The structural assignment of compounds **10**, **11** and **13**, was based, apart from spectral arguments, on the result of direct alkylation of 3,3-dimethylcyclohexanone (**1**) with allyl chloride (**15**) and 3-chloro-2-butenyl chloride (**12**) using potassium *t*-butoxide/toluene at 80°. In both cases the predominant isomers were assumed to be formed by attack on the less hindered C(6) position and therefore to have structures **11** and **13**, respectively.



Aldol condensation *via* magnesium enolate 1i (Table 3). – The classic aldol condensation, which usually leads to a mixture, has recently been improved by condensing a preformed magnesium or zinc enolate with an aldehyde. By this method only the desired aldol is formed, even if it is thermodynamically unstable [19]. Therefore we were tempted to investigate regiospecific aldol condensation by making use of magnesium enolates which originate from conjugate addition of *Grignard* reagents to α,β-unsaturated ketones. The results so far obtained with **1i** (see Table 3) convincingly demonstrate the usefulness of this sequence: the desired, sterically hindered aldols **17**[5a]), **19**[5a]), and **21**[5b]) were obtained in 75–96% yield without detectable amounts of the other possible aldol products.

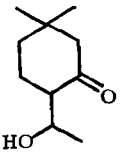
Table 3. *Aldol condensation via magnesium enolate* **1i**

Experiment	Starting materials	Reaction product and yield
8	 **1i** **16**	 5a) **17** 75%
9	**1i** +  **18**	 5a) **19** ~ 90%
10	**1i** +  **20**	 5b) **21** ~ 96%

[5a]) According to the NMR. spectrum only one diastereomer of unknown relative configuration was formed.

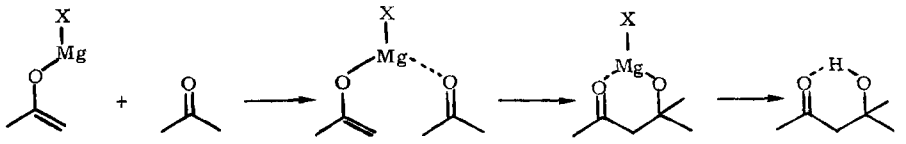
[5b]) Mixture of diastereomers.

The structure of **17** has been rigorously proved by NMR. spectroscopy using the $Eu(fod)_3$ shift agent and double irradiation technique. The C(2) proton which is superimposed on the C(6) methylene in the uncomplexed 90-MHz spectrum was shifted downfield to a much greater extent than the C(6) methylene protons. The C(2) proton showed a clean doublet (J = 6 Hz) which collapsed to become a singlet when the neighbouring O–C–*H* was irradiated. On these grounds the alternative, thermodynamically more stable structure **17a** can be excluded. Structures of **19** and **21** have been attributed by analogy.



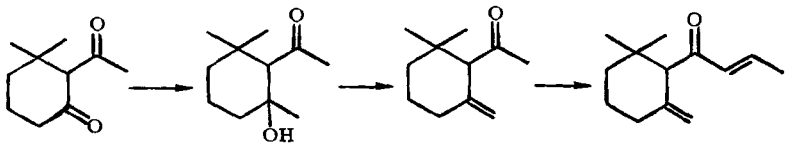
17a

The mechanism of this aldol condensation is best interpreted following *House et al.* [18] (see Scheme).

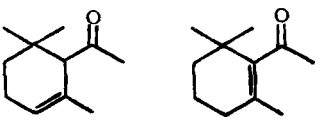


Interaction of the acidic magnesium of enolate **1i** with the basic aldehyde oxygen might form a loose complex which then reacts in a 6-membered transition state to give a keto alkoxide as a stable magnesium chelate. The stability of such magnesium chelates in nonpolar solvents is high enough to prevent further, undesired transformations, such as retroaldol cleavage, formation of α,β-unsaturated carbonyl compounds etc., which often diminish the preparative value of the classic aldol condensation. On treatment with aqueous ammonium chloride, however, the intermediate magnesium enolates are readily decomposed to give the free aldols.

γ-Damascone from 4. – Transformation of acetylcyclohexanone **4** into γ-damascone (**26**) was readily accomplished by the following three classical steps. *Grignard*



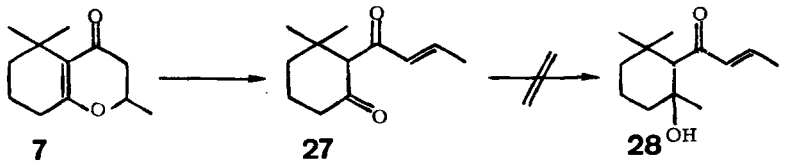
4 **22** **23** **26**



24 **25**

addition to **4** gave alcohol **22**, m.p. 87–88°, which was dehydrated by thionyl chloride/pyridine to a mixture of **23** (66%), **24** (18%), and **25** (16%). From this mixture the γ-isomer **23** was separated by either fractional distillation or column chromatography. The last step, condensation of **23** with acetaldehyde using bromomagnesium N-methylanilide as a base[6]) yielded pure γ-damascone (**26**) in 87%.

A shorter alternative, based on the direct, regioselective introduction of the crotonyl side chain into 3,3-dimethylcyclohexanone (**1**) as mentioned earlier (see p. 1318), proved unsuccessful. Although hexahydrochromone **7** could be opened by potassium *t*-butoxide in refluxing benzene to give the crotonylcyclohexanone **27** in good yield, **27** could not be alkylated selectively at the ring carbonyl to give **28**.



7 **27** **28**

We are indebted to Drs. *G. Ohloff* and *K.-H. Schulte-Elte* for encouragement and helpful discussions.

Experimental Section[7])

1. *Preparation and reaction of magnesium enolate* **11** *with acetyl chloride* (**3**) *to give* **1**, **5**, *and* **4**. – a) *In ether.* Methylmagnesium iodide, prepared from Mg (1.44 g; 60 mmol) and methyl iodide (8.52 g; 60 mmol) in abs. ether (40 ml), was treated with finely powdered Cu I (~200 mg) at –5°. After the mixture had been stirred 5 min at –5° 3-methyl-2-cyclohexenone [15] (5.5 g; 50 mmol) in abs. ether (20 ml) was added and stirring continued an additional 30 min at –5°. A solution of acetyl chloride (3.92 g; 50 mmol) in abs. ether (10 ml) was added with efficient stirring at –15° to –5°. The reaction mixture was stirred 30 min at 0° and 30 min at 25°, and then poured onto a mixture of iced 2N aqueous HCl (25 ml). The product was extracted with ether, washed (brine), dried ($MgSO_4$) and distilled: 5.1 g, b.p. 33–55°/0.01 mm. Analysis by GLPC.[8]) showed the presence of 3,3-dimethylcyclohexanone (**1**) (~35%), 3,3-dimethyl-1-cyclohexenyl acetate (**5**) (~25%) and 3,3-dimethyl-2-acetyl-1-cyclohexanone (**4**) (~40%). For preparative purposes a larger operation (~0.5 mol) was run, and after fractionation, using a *Fischer* column (type MS 300; ~40 plates), a 33% yield of pure **4** was obtained.

b) *In 1,2-dimethoxyethane* (DME). If the ether of the methyl *Grignard* reagent was replaced by DME (by adding DME and distilling off the ether) and for the following operations DME was used as solvent, only 3,3-dimethyl-1-cyclohexenyl acetate (**5**) (~63% yield), b.p. 38–40°/0.01 mm, was obtained.

Spectral data of **4**. 60 MHz NMR.: 0.98 (3 H, *s*); 1.03 (3 H, *s*); 2.1 (3 H, *s*); 3.48 (1 H, *s*). – IR. (CCl_4): 1720, 1695. – MS.: 168 (M^+, 23), 153 (12), 125 (9), 111 (100), 100 (14), 85 (21), 69 (20), 55 (31), 43 (84), 41 (24), 39 (14), 27 (12).

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[6]) This is analogous to *Cookson*'s synthesis of damascenone [19].

[7]) NMR. spectra: *Varian* A 60 and *Hitachi Perkin-Elmer* R-20B, in CCl_4 solution, and *Bruker* HF×90, in $DCCl_3$ solution, δ-scale (ppm); abbreviations: *s* = singlet, *d* = doublet, *t* = triplet *q* = quartet, *m* = multiplet, *J* = spin-spin coupling constant (Hz). IR. spectra: *Perkin Elmer* 125, max. in cm^{-1}. Mass spectra: *Atlas* CH_4, inlet temperature *ca.* 150°; electron energy *ca.* 70 eV; intensity of molecular ions (M^+) and fragment ions are given as *m/e* in % of the most abundant ion (100%). UV. spectra: *Optica* CF–4. Gas liquid phase chromatography (GLPC.): *Carlo Erba* GT with 5 mm×2 m metal columns; carrier gaz 40 ml He/min; column support Chromosorb W/50–80 mesh; peaks are given in the order of increasing retention time.

[8]) 5 mm×2 m column; 5% Silicon, 150°.

Spectral data of **1**. 60 MHz NMR.: 0.96 (3 H and 3 H, *s* and *s*). – IR. (neat): 1700. – MS.: 126 (M^+, 26), 111 (15), 93 (<1), 83 (100), 69 (22), 55 (64), 41 (36), 27 (14).

Spectral data of **5**. 60 MHz NMR.: 1.0 (3 H and 3 H, *s* and *s*); 2.0 (3 H, *s*); 5.03 (1 H, *s'*). – IR. (CCl_4): 3010, 1750, 1685, 1210. – MS.: 168 (M^+, 1), 153 (<1), 126 (10), 111 (100), 93 (1), 83 (3), 69 (1), 55 (10), 43 (26), 41 (4), 27 (2).

2. *Preparation and reaction of magnesium enolate* **1i** *with crotonyl chloride* (**6**) *to give* **8** *and* **7**. a) *In ether.* Methylmagnesium iodide, prepared from Mg (1.29 g; 54 mmol), and methyl iodide (7.67 g; 54 mmol) in abs. ether (40 ml), was treated with finely powdered CuI (200 mg) at ~2°. After a solution of 3-methyl-2-cyclohexenone (**2**) (4.95 g; 45 mmol) in abs. ether (10 ml) had been added dropwise at –5° to 0° during 30 min crotonyl chloride (4.7 g; 45 mmol) in abs. ether (10 ml) was added (exothermic reaction) during ~30 min with efficient stirring at ~0°. The resulting mixture was stirred 30 min at 0° to 3°, 30 min at 25°, and then poured onto iced aqueous HCl. Extraction with ether and distillation (at 70–90°/0.01 mm) gave ~4.2 g of an oil which contained ~14% of **8** and ~86% of **7** according to GLPC.[9]).

b) *In 1,2-dimethoxyethane* (DME). If the ether of the methyl *Grignard* reagent was replaced by DME (by adding DME and distilling off the ether) and for the following operations DME was used as solvent, distillation at 50–56°/0.01 mm gave ~5.1 g of an oil which consisted of ~95% **8** and 5% **7**.

Spectral data of **7**: 60 MHz NMR.: 1.16 (3 H, *s*); 1.23 (3 H, *s*); 1.35 (3 H, *d*, J = 6 Hz); 2.0–2.5 (2 H and 2 H); 4.3 (1 H, *m*). – IR. (CCl_4): 1660, 1587. – MS.: 194 (M^+, 15), 179 (58), 165 (<1), 151 (2), 137 (100), 123 (<1), 111 (6), 96 (<1), 81 (4), 69 (4), 55 (25), 44 (7), 41 (12), 39 (5), 27 (3). – UV. (EtOH): λ_{max} = 237.5 mm ($\varepsilon \sim 12000$).

Spectral data of **8**: 60 MHz NMR.: 1.0 (3 H and 3 H, *s* and *s*); 1.86 (3 H, $d \times d$, J_1 = 7 Hz, J_2 = ~2 Hz); 5.06 (1 H, *s'*); 5.77 (1 H, $d \times q$, J_1 = 15 Hz, J_2 = 2 Hz); 6.92 (1 H, $d \times q$, J_1 = 15 Hz, J_2 = 7 Hz). – IR. (CCl_4): 3050, 1730, 1685, 1655, 965. – MS.: 194 (M^+, <1), 179 (<1), 166 (<1), 126 (2), 111 (13), 93 (<1), 82 (<1), 69 (100), 55 (3), 41 (15), 39 (6), 27 (2).

3. *Reaction of magnesium enolate* **1i** *with allyl bromide* **9** *to give* **10**. Methylmagnesium iodide, prepared from Mg (1.44 g; 60 mmol) and methyl iodide (8.52 g; 60 mmol) in abs. ether (30 ml), was treated with finely powdered CuI (~ 200 mg) at –5°. After the mixture had been stirred 5 min at –5° 3-methylcyclohexenone (5.5 g; 50 mmol) in abs. ether (10 ml) was added. The reaction mixture was treated with 40 ml of anhydrous hexamethylphosphortriamide (HMPA) to yield a white precipice (exothermic process!). Allyl bromide (8.05 g; 67 mmol) in HMPA (10 ml) was added at –5° and the reaction mixture became doughy. After stirring overnight the mixture was poured onto iced 2N HCl (~25 ml), extracted with ether, washed ($NaHCO_3$ and water), dried ($MgSO_4$) and distilled (*Vigreux* apparatus). ~6.59 g of a colourless distillate, b.p. 83–96°/10 mm, was obtained, containing ~70% of **10** (~55% yield) as determined by GLPC.[10]).

Spectral data of **10**: 60 MHz NMR.: 0.85 (3 H, *s*); 1.03 (3 H, *s*); 1.4–2.7 (9 H); 4.7–5.2 (2 H, *m*); 5.2–6 (1 H, *m*). – IR. (liq.): 3080, 1710, 1635, 990, 910. – MS.: 166 (M^+, 54), 151 (32), 133 (7), 123 (29), 109 (58), 96 (80), 95 (86), 81 (51), 69 (92), 55 (88), 41 (100), 27 (34).

4. *Reaction of magnesium enolate* **1i** *with 3-chloro-2-butenyl chloride* **12** *to give* **13**. A solution of magnesium enolate **1i** (~50 mmol) in 80 ml of HMPA/ether 1:1 was prepared as described in experiment 3. 3-Chloro-2-butenyl chloride (8.12 g; 65 mmol) in HMPA was added at –5° and the reaction mixture allowed to react at room temperature overnight. Work up and distillation in a *Vigreux* apparatus gave two fractions: 1) 3.63 g boiling at 83–95°/0.01 mm, and 2) 2.88 g b.p. 120–135°/0.01 mm. Fraction one contained ~89% of **13** (~31% yield) as determined by GLPC.[11]). Fraction two contains probably dialkylated products.

Spectral data of **13**: 60 MHz NMR.: 0.83 (3 H, *s*); 1.03 (3 H, *s*); 2.06 (3 H, *s*, with fine splitting); 5.5 (1 H, *t*, with fine splitting). – IR. (CCl_4): 1710, 1660, 1635, 990, 910. – MS.: 214 (M^+, 10), 179 (100), 163 (13), 145 (3), 135 (5), 123 (28), 109 (25), 95 (33), 81 (28), 69 (20), 55 (30), 41 (37), 27 (17).

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[9]) 5% Silicon, 180°.

[10]) 5% Carbowax, 175°.

[11]) 5% Carbowax, 200°.

5. *Reaction of magnesium enolate* **1i** *with 3-chloro-2-butenyl iodide* **14**. – a) *In ether HMPA 1:1.* Iodide **14** (lacrimatory!) was prepared from chloride **12** and Na I in acetone by heating the reaction mixture 24 h under reflux. Under the same reaction conditions and with the same molar amounts as described in experiment 3 a distillate (6.85 g) boiling at 77–90°/0.01 mm was obtained. Its main component (~86% of the distillate) again proved identical with **13** (yield ~54%).

b) *In ether.* Under the same reaction conditions as described in experiment 3 but with ether as solvent, only starting material was isolated.

6. *Alkylation of 3,3-dimethylcyclohexanone* (**1**) *with allyl chloride* (**15**) *using potassium* t*-butoxide/toluene.* Potassium *t*-butoxide (5.6 g; 50 mmol) was finely powdered and suspended in toluene (50 ml). 3.3-Dimethylcyclohexanone (6.3 g; 50 mmol) followed by allyl chloride (3.8 g; 50 mmol) was added at 10–20° during ~5 min. After the resulting mixture had been stirred at 80° for 4 h it was poured onto iced water and extracted with ether. The ether extract was washed (water), dried ($MgSO_4$), concentrated and distilled to give ~5.8 g distillate, b.p. 68–115°/10 mm. The distillate contained, according to GLPC. analysis[8]), starting material **1** (20%), **11** (54%), **10** (~2%), and probably dialkylated products (24%).

Spectral data of **11**: 60 MHz NMR.: 0.87 (3 H, *s*); 1.05 (3 H, *s*); 4.7–5.2 (2 H, *m*); 5.2–6 (1 H, *m*). – IR. (CCl_4): 3070, 1710, 1635, 990, 910. – MS.: 166 (M^+, 34), 151 (26), 137 (15), 121 (71), 109 (64), 95 (64), 83 (85), 67 (65), 55 (75), 41 (100), 27 (33).

7. *Alkylation of 3,3-dimethylcyclohexanone* (**1**) *with 3-chlorobut-2-enyl chloride* (**12**) *using potassium* t*-butoxide/toluene.* Under the conditions described in experiment 6, a product boiling at 130–145°/11 mm was obtained, containing a major peak[11]) (68%), which was assumed to have structure **13**.

8. *Preparation and reaction of magnesium enolate* **1i** *with acetaldehyde to give* **17**. Methylmagnesium iodide, prepared from Mg (1.44 g; 60 mmol) and methyliodide (8.52 g; 60 mmol) in abs. ether (40 ml), was treated with finely powdered CuI (~200 mg) at –5°. After the mixture had been stirred 5 min at –5° 3-methyl-2-cyclohexenone (**2**) (5.5 g; 50 mmol) in abs. ether (20 ml) was added and stirring continued an additional 30 min at –5°. A solution of acetaldehyde (2.2 g; 50 mmol) in abs. ether (10 ml) was added with efficient stirring at –15° to –10°. The reaction mixture was stirred 30 min at 0° and 30 min at 25° and then poured into a mixture of iced 2N aqueous HCl (25 ml). The product was extracted with ether, washed (brine), dried ($MgSO_4$) and distilled: 6.34 g of **17**, b.p. 69–73°/0.01 mm, yield 75%. Analysis by GLPC. showed a decomposition.

Spectral data of **17**[6]): 90 MHz NMR.: 1.05 (3 H, *s*); 1.12 (3 H, *s*); 1.3 (3 H, *d*, $J = 7$ Hz); 2.00–2.5 (2 H and 1 H); 3.5 (1 H, *s*, OH); 4.10 (1 H, $d \times q$, $J_1 = 6$ Hz, $J_2 = 7$ Hz). After $Eu(fod)_3$ had been added ($C_{Eu/prod.} \sim 0.2$) the C(2) methine proton appeared at ~4.75 ppm as a doublet ($J = 6$ Hz). This doublet collapsed to become a singlet under irradiation of the neighbouring –C*H*–O. – IR. ($CHCl_3$): 3400, 1685. – MS.: 170 (M^+, 3), 152 (9), 137 (9), 126 (23), 111 (100), 95 (7), 83 (95), 69 (32), 55 (62), 43 (36), 41 (42), 39 (20), 29 (32).

9. *Preparation and reaction of magnesium enolate* **1i** *with crotonaldehyde to give* **19**. Methylmagnesium iodide, prepared from Mg (1.44 g; 60 mmol) and methyliodide (8.52 g; 60 mmol) in abs. ether (40 ml), was treated with finely powdered CuI (~200 mg) at –5°. After the mixture had been stirred 5 min at –5° 3-methyl-2-cyclohexenone (**2**) (5.5 g; 50 mmol) in abs. ether 20 ml was added and stirring continued an additional 30 min at –5°. A solution of crotonaldehyde (3.5 g; 50 mmol) in abs. ether (10 ml) was added with efficient stirring at –15° to –10°. The reaction mixture was stirred for 1 h at 20°, then treated with 2N aqueous HCl (25 ml) at 0°. The product was extracted with ether, washed (brine), dried ($MgSO_4$) and the solvent was removed giving 10.0 g of crude alcohol **19** (~90% pure by NMR.-analysis). Subsequent distillation at 93–96°/0.01 mm was not possible without partial retroaldol cleavage and gave only 5.54 g (57%) of **19** and 5.2 g of retroaldol compounds.

Spectral data of **19**: 60 MHz NMR.: 0.98 (3 H, *s*); 1.03 (3 H, *s*); 2.5 (1 H, *d*, $J =$ Hz); 2.93 (1 H, *s*, OH); 4.32 (1 H, $d \times d$ with fine splitting, $J_1 = 6$ Hz, $J_2 = 7$ Hz); 5.5–5.8 (2 H, *m*). – IR. (liq.): 3450, 1690. – MS.: Retroaldol during the vaporisation.

10. *Preparation and reaction of magnesium enolate* **1i** *with citral* **20** *to give* **21**. Methylmagnesium iodide, prepared from Mg (1.44 g; 60 mmol) and methyliodide (8.52 g; 60 mmol) in abs. ether (40 ml), was treated with finely powdered CuI (~200 mg) at –5°. After the mixture had been

stirred 5 min at −5° 3-methyl-2-cyclohexenone (**2**) (5.5 g; 50 mmol) in abs. ether (20 ml) was added and stirring continued an additional 30 min at −5°. A solution of citral (64% *trans*, 36% *cis*) (7.6 g; 50 mmol) in abs. ether (10 ml) was added at −15° to −10°. The reaction mixture was stirred an additional hour at 20°, then treated with 2N aqueous HCl (25 ml) at 0°. The product was extracted with ether, washed (brine), dried ($MgSO_4$). The solvent was removed giving 13.4 g of crude alcohol **21**, yield 96%. Decomposition by distillation and by GLPC.

Spectral data of **21** (mixture of diastereomers): 60 MHz NMR.: 1.0 (3 H, *s*); 1.1 (3 H, *s*); 1.6 (3 H, broad *s*); 1.65 (6 H, broad *s*); 3.18 (1 H, *s*, OH); 4.6 (1 H, *m*); 4.9–5.63 (1 H and 1 H, *m*). – IR. (liq.): 3460, 1695. – MS.: Retroaldol during the vaporisation.

11. *Reaction of acetylketone* **4** *with methylmagnesium iodide to give* **1** *and* **22**. Methylmagnesium iodide, prepared from Mg (6.63 g; 0.276 mol) and methyliodide (40 g; 0.28 mol) in dry ether (250 ml) was treated at 0° to 5° during 30 min with acetylketone **4** (21 g; 0.125 mol) in dry ether (50 ml). The mixture was heated at reflux during 1 h, then cooled to 25°, poured onto a mixture of 10% aqueous HCl and ice, and extracted with ether. The etheral phase was washed (successively with $NaHCO_3$ and brine), dried and concentrated: 23 g crude semicrystalline product which contained according to GLPC.-analysis[10]) ~35% **1**, ~58% **22** and 7% starting material **4**. Crystallization of the crude product from ethanol-water gave ~10 g (44%) of **22**, m.p. 87–88°.

Spectral data of **22**: 60 MHz NMR.: 0.96 (3 H, *s*); 1.03 (3 H, *s*); 1.05 (3 H, *s*); 2.22 (3 H, *s*); 2.4 (1 H, *s*); 3.55 (1 H, *s*, –O*H*). – IR. (CCl_4): 3500, 1693. – MS.: 184 (M^+, 1), 169 (9), 151 (5), 141 (1), 123 (7), 109 (14), 99 (100), 85 (11), 69 (13), 55 (11), 43 (85), 41 (16), 29 (5).

12. *Dehydration of alcohol* **22** *to give* **23**, **24** *and* **25**. Alcohol **22** (11.5 g; 62.5 mmol) dissolved in anh. pyridine (200 ml) was treated dorpwise at −10° during 30 min with thionyl chloride (28 ml). Stirring was continued first 30 min at 0° and then 2 h at 25°. The reaction product was poured onto a mixture of 10% HCl and ice and extracted with ether. The ether extract was washed (successively with $NaHCO_3$ and brine), dried ($MgSO_4$), and concentrated. The crude product (~11 g) showed on GLPC.[8]) 66% of **23**, 18% of **24**, and 16% of **25**. Separation by column chromatography on silica gel (*Merck*) 0.05–0.2 mm with hexane/ether 98:2 gave ~7.25 g (70%) of pure **23**. It was also possible to separate the reaction mixture (11 g) using a *Fischer* column (type MS 300; ~40 plates) which gave ~5.2 g (50%) of pure **23** besides mixed fractions.

Spectral data of **23**: 60 MHz NMR.: 0.86 (3 H, *s*); 0.93 (3 H, *s*); 2.06 (3 H, *s*); 3.04 (1 H, *s*); 4.7 (1 H, '*s*'); 4.82 (1 H, '*s*'). – IR. (CCl_4): 3070, 1715, 1640. – MS.: 166 (M^+, 20), 151 (16), 133 (<1), 123 (73), 109 (39), 93 (18), 81 (49), 69 (21), 55 (18), 43 (100), 41 (33), 39 (18), 27 (13).

Spectral data of **24**: 60 MHz NMR.: 0.9 (3 H, *s*); 0.92 (3 H, *s*); ~1.6 (3 H, *m*); 2.11 (3 H, *s*); 2.7 (1 H, '*s*'); 5.6 (1 H, *m*). – MS.: 166 (M^+, 25), 151 (6), 133 (<1), 123 (100), 109 (17), 95 (17), 81 (76), 67 (17), 55 (16), 43 (77), 41 (25), 39 (16), 27 (11).

Spectral data of **25**: 60 MHz NMR.: 1.05 (3 H and 3 H, *s* and *s*); 1.58 (3 H, *s*); 2.2 (3 H, *s*). – MS.: 166 (M^+, 20), 151 (52), 133 (<1), 123 (72), 109 (20), 91 (7), 81 (38), 67 (12), 55 (10), 43 (100), 39 (16), 27 (7).

13. *γ-Damascone* (**26**) *from* **23**. N-methylaniline (161 mg; 1.5 mmol) in dry benzene (1 ml) was added at 0° to a *Grignard* solution prepared from Mg (36 mg; 1.5 mmol) and ethyl bromide (116 µl, 1.5 mmol) in abs. ether (2 ml). Methyl ketone **23** (166 mg, 1 mmol) in benzene (1 ml) was then added under ice cooling. The mixture was stirred 30 min at room temperature, cooled again (ice-bath), and treated with acetaldehyde (88 mg; 2 mmol) in benzene (1 ml) during 20 min. After stirring for additional 30 min the mixture was poured onto ice/2N HCl, and extracted with pentane. The pentane extract was washed (successively with $NaHCO_3$ and brine), dried ($MgSO_4$), and concentrated. The crude material (~200 mg) was dissolved in benzene (5 ml), treated with *p*-toluene sulfonic acid (20 mg), and heated under reflux for 3 h. Then the brown solution was washed ($NaHCO_3$ and brine), dried ($MgSO_4$), and distilled (bulb distillation) at 65–85° (bath temp.)/0.05 mm to give ~170 mg (87%) of γ-damascone (**26**) [14].

Spectral data of **26**: 90 MHz NMR.: 0.91 (3 H, *s*); 0.95 (3 H, *s*); 1.88 (3 H, $d \times d$, $J_1 = 7$ Hz, $J_2 = \sim 2$ Hz); 3.22 (1 H, *s*); 4.7 (1 H, '*s*'); 4.86 (1 H, '*s*'); 6.18 (1 H, $d \times q$, $J_1 = 15$ Hz, $J_2 = \sim 2$ Hz); 6.85 (1 H, $d \times q$, $J_1 = 15$ Hz, $J_2 = 7$ Hz). – MS.: 192 (M^+, 7), 177 (2), 159 (<1), 149 (2), 136 (2), 123 (5), 109 (4), 93 (1), 81 (9), 69 (100), 55 (3), 41 (20), 27 (4).

14. *Crotonyl ketone* **27** *from hexahydrochromone* **7**. Hexahydrochromone **7** (19.4 g; 0.1 mol) and potassium *t*-butoxide (13.5 g; 0.12 mol) in abs. benzene (100 ml) were heated under reflux for 3 h in an argon atmosphere. The reaction mixture was poured onto ice, neutralized with acetic acid, and extracted with ether. The ether extract was washed (brine), dried ($MgSO_4$), and concentrated: 18.6 g crude **27**. Distillation at 80–85°/0.1 mm gave ~14.5 g (75%) pure **27**.

Spectral data of **27**: 60 MHz NMR.: 0.95 (3 H, *s*); 0.99 (3 H, *s*); 1.87 (3 H, $d \times d$, $J_1 = 7$ Hz, $J_2 = \sim 1.5$ Hz); 3.55 (1 H, '*s*'); 6.05 (1 H, $d \times q$, $J_1 = 16$ Hz, $J_2 = \sim 1.5$ Hz); 6.83 (1 H, $d \times q$, $J_1 = 16$ Hz, $J_2 = 7$ Hz). – IR. (CCl_4): 3040, 1710, 1680, 1663, 1625, 965. – MS.: 194 (M^+, 6), 179 (13), 166 (<1), 151 (2), 137 (8), 126 (5), 111 (21), 95 (3), 83 (<1), 69 (100), 55 (10), 41 (26), 27 (3).

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