161. General Synthesis of Ketones from Carboxylic Esters and Carboxamides by Use of Mixed Organolithium-Magnesium Reagents: Syntheses of Artemisia Ketone[1])

by **Charles Fehr*, José Galindo,** and **Roland Perret**

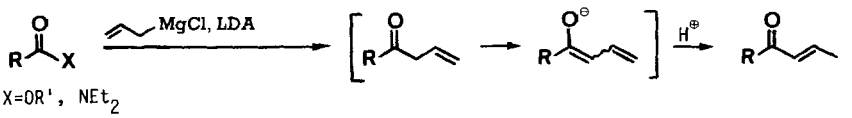
Firmenich SA, Research Laboratories, CH-1211 Geneva 8

(4.VIII.87)

The novel reagents formed by combination of *Grignard* reagents (RMgX) with lithium diisopropylamide (LDA) convert non-enolizable or slowly enolizable carboxylic esters or carboxamides into ketones which are protected from further reaction by their *in situ* conversion into enolates. These enolates can be trapped with electrophiles such as Me_3SiCl and allyl bromide. The scope of this *Grignard* mono-addition is illustrated by two direct syntheses of artemisia ketone (**14**).

Recently, we published a procedure for converting non-enolizable or slowly enolizable carboxylic esters or amides into ketones, using [allyl-MgCl, LDA] as reagent (LDA = lithium diisopropylamide) [1]. This transformation proceeds *via* rapid deprotonation of the initially formed ketones by their *in situ* conversion into enolates *(Scheme 1)* and was applied to efficient syntheses of α-damascone, β-damascone, and β-damascenone.

Scheme 1

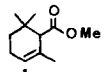
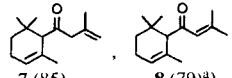
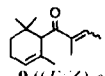
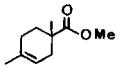
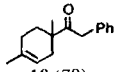
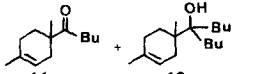
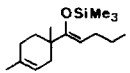
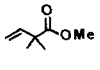
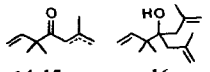


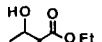
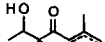
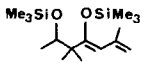
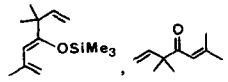
The general preparative value of this transformation which is the synthetic equivalent of a *Grignard* mono-addition [2] has prompted us to extend it to other allylic and non allylic *Grignard* reagents *(Table)*. [Methallyl-MgCl, LDA] exhibits a reactivity which is very similar to that of [allyl-MgCl, LDA]: thus, methyl α-cyclogeranate [3] (**1**; *Entry 1*) is converted into ketone **7** in excellent yield and high selectivity (ketone *vs.* tertiary alcohol 98:2), whereas normal *Grignard* reaction in the absence of LDA mainly leads to the diallylic alcohol (selectivity ketone *vs.* tertiary alcohol 21:79). [Crotyl-MgCl, LDA] *(Entry 2)* undergoes reaction essentially (9:1) with allylic transposition. Isomerization with Al_2O_3 [4] affords a mixture of propenyl ketones **9** (57%).

The selectivity for ketone formation strongly depends on the ease of deprotonation of the intermediate ketones. Thus, [$PhCH_2MgCl$, LDA] reacts with cyclohexenyl ester **2** [5] *(Entry 3)* to afford benzyl ketone **10** with high selectivity (97:3), whereas the reaction of ester **2** with [BuLi, LDA] *(Entry 4)* mainly leads to the tertiary alcohol **12**. However,

[1]) Part of this work was presented at the Swiss Chemical Society Meeting in Berne, October 10, 1986.

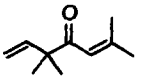
Table. *Reaction of Carboxylic Esters and* in situ *Generated Carboxamides Yielding Ketones*

Entry	Substrate	Reagents (equiv.)	Products (yield [%] from ester)	Ketone/alcohol selectivity with LDA	(without LDA)
1	 **1**	MgCl (1.7), LDA (1.05)	 7 (85), **8** (79)[a]	98:2	(21:79)
2	**1**	MgCl (1.7), LDA (1.05)	 (57)[a][b] **9** (*(E:Z) ca.* 1:1)	99:1	(79:21)
3	 **2**	$PhCH_2MgCl$ (1.1), LDA (1.05)	 **10** (79)	97:3	(39:61)
4	**2**	BuLi (1.5), LDA (2.0)	 **11** + **12** [c]	25:75	(14:86)
5	**2**	1) $LiNEt_2$ (1.15)[d] 2) BuLi (1.3), LDA (1.3) 3) Me_3SiCl (3.0)	 **13** (80)[e]	97:3	(90:10)
6	 **3**	MgCl (1.15), LDA (1.15)	 **14,15** **16** [c]	12:88	(1:99)

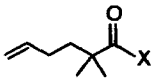
7	 **4**	1) LDA (1.05)[f] 2)  MgCl (1.5), LDA (1.5)	 **20,21** (75)	84:16	(12:88)
8	**4**	1) LDA (1.05)[f] 2) MgCl (1.5), LDA (1.5) **3) NEt_3 (2.0), Me_3SiCl (5.0)**	 **22** (70)[c])		
9	**4**	1) LDA (1.05) 2) $LiNEt_2$ (1.1)[d]) 3) MgCl (2.2), LDA (2.2)	**20,21** (67)	98:2	(66:34)
10	 **5**	1) LDA (1.05) 2) CH_3CHO (1.1)[g]) 3) MgCl (1.5), LDA (1.5)	**20,21** (68)		
11	 **6**	1) MgCl (1.2), LDA (1.1) 2) Me_3SiCl (3.0), NEt_3 (1.2)	 **25** (71)[c]) **14** (71)[a])	94:6	(23:77)

[a]) After treatment with acid or Al_2O_3 (see *Exper. Part*).
[b]) Reaction stops after 80% conversion.
[c]) Not isolated.
[d]) *In-situ* generation of diethyl amide.
[e]) See *Footnote 2*.
[f]) Higher ketone/alcohol selectivity, when generated diisopropylamine is deprotonated with BuLi, but also concomitant formation of butyl ketone.
[g]) *In-situ* generation of **4** (as lithium alkoxide).

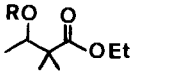
almost exclusive formation of ketone **11** can be achieved, when ester **2** is converted *in situ* into the corresponding diethyl amide prior to the organometallic reaction *(Entry 5)*. Treatment of the resulting ketone enolate with Me_3SiCl directly leads to enol silyl ether **13**[2][3]).



14



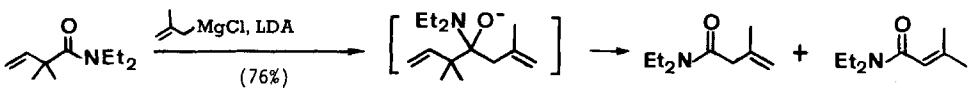
i X = OEt
ii X = NEt_2



iv R = CH_3
v R =

As a synthetic application, the following reactions *(Entries 6–11)* show different approaches towards the synthesis of artemisia ketone (**14**) [7]. Somewhat surprisingly, methyl 2,2-dimethyl-3-butenoate[4]) (**3**, *Entry 6*) mainly underwent double addition of the methallyl *Grignard* reagent. From our earlier work [1], we know that the related ethyl 2,2-dimethyl-5-hexenoate (**i**) also undergoes double *Grignard* addition of the allyl moiety, whereas the corresponding diethylamide **ii** mainly affords the propenyl ketone. Therefore, we submitted amide **17**[5]) to the organometallic reaction *(Scheme 2)*. However, instead of the expected *Grignard* reaction, the initially formed addition product **iii** undergoes C–C bond cleavage to give amides **18** and **19** as the only products! This is an interesting example of the β-cleavage of homoallylic alkoxides [9] in which the prenyl carbanion is a stronger nucleofuge than the diethyl amide group.

Scheme 2



17 **iii** **18** **19**

As non enolizable α- or β-hydroxy esters have already been shown to undergo selective *Grignard* mono-additions of the allyl group [1], we next tested the reactivity of hydroxy ester **4** which is readily available from ethyl isobutyrate (**5**) by aldol condensation with acetaldehyde. Successive treatment of ester **4** *(Entry 7)* with LDA and [methallyl-MgCl, LDA] afforded hydroxy ketones **20**/**21** (*ca.* 1:1) with good selectivity (84:16) and 75% yield[6]). Trapping of the ketone enolate with Me_3SiCl/NEt_3 gave (*Z*)-dienol silyl ether **22**[2]) in 70% yield *(Entry 8)*. By converting ester **4** *in situ* into the diethylamide *(Entry 9)*, the ketone selectivity was improved to 98:2, and the ketones **20**/**21** were isolated in 67% yield.

---

[2]) (*Z*)-Configuration tentatively assigned [6].

[3]) For a discussion about the factors governing the *Grignard* mono-addition, see [1].

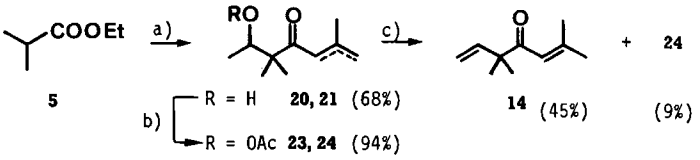
[4]) Prepared from 2,2-dimethyl-3-butenoyl chloride [8] ($MeOH/NEt_3$).

[5]) Prepared from 2,2-dimethyl-3-butenoyl chloride [8] (Et_2NH (1.1 equiv.), NEt_3 (1.1 equiv.), Et_2O, 10°).

[6]) The free OH function is essential for high selectivity. The methyl ether **iv** and the THP ether **v**, under the same conditions, lead essentially to products from double *Grignard* addition. Apparently, complexation of the organometallic reagent with the OH function of ester **4** plays an important role in this *Grignard* mono-addition.

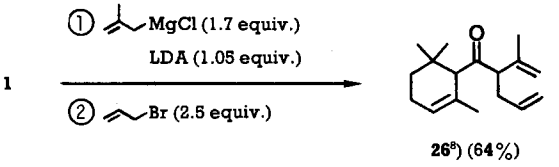
Entry 10 shows that it is not necessary to isolate the aldol product **4**: ethyl isobutyrate (**5**) is successively treated with LDA and acetaldehyde to give the lithium alkoxide of ester **4**. Addition of [methallyl-MgCl, LDA] to the reaction mixture then directly gives the desired ketones **20/21** in 68% overall yield. This sequence allows the formation of two C,C bonds in one operation and the construction of the skeleton of artemisia ketone (**14**) starting from very simple building blocks. The isomeric ketones **20/21** were converted into artemisia ketone (**14**) by pyrolysis of the acetates **23/24** at 445° followed by C=C bond isomerization (Al_2O_3)[7]) *(Scheme 3)*.

Scheme 3



A second direct access to artemisia ketone (**14**) has been achieved from methyl 3,3-dimethylacrylate (**6**; *Table, Entry 11*) by reaction with [prenyl-MgCl, LDA]. In contrast to all previous examples, ketone-enolate formation is forced to occur on the moiety originating from the substrate ester. Indeed, trapping of the enolate by Me_3SiCl afforded (*Z*)-enol silyl ether **25**[2]).

Besides the interest of converting esters into sterically hindered ketones, this method should also prove valuable for the direct and often selective preparation of enolates or enol silyl ethers, whose reactivity towards electrophiles would allow the elaboration of even more complex systems, as exemplified with the tandem *Grignard* alkylation reaction affording ketone **26**[8]).



26[8]) (64%)

Experimental Part

General. TLC: silica gel *F 254* plates *(Merck)*; detection with EtOH/anisaldehyde/H_2SO_4 18:1:1. Column chromatography: silica gel *60* (*Merck*, 0.063–0.2 mm, 70–230 mesh, ASTM). GC: *Varian* instrument, model *3500*; capillary column *DB1 30W* (15 m × 0.319 mm). IR: *Perkin-Elmer-297* spectrometer; band positions in cm^{-1}. ^{1}H-NMR: *Varian EM 360* (60 MHz) or *Bruker WH 360* (360 MHz); chemical shifts δ in ppm rel. to TMS as internal standard. MS: *Finnigan 1020* automated GC/MS instrument, electron energy 70 eV, signals in *m/z* (rel. %).

3-Methyl-1-(2,6,6-trimethyl-2-cyclohexenyl)-2-buten-1-one (**8**; *Table, Entry 1*). A soln. of BuLi in hexane (81.4 ml, 1.42 N, 116 mmol) was added at 0° to a stirred soln. of $(i\text{-}Pr)_2NH$ (11.79 g (16.52 ml), 117 mmol) in THF (110 ml). After complete addition, the clear yellow soln. was allowed to attain 20° and treated with a soln. of

[7]) Alternatively **20/21** were treated with BuLi and $CO(OMe)_2$ (*ca.* 50% conversion) and the products pyrolyzed at 445° under N_2 (80% yield).

[8]) Mixture of diastereoisomers (*ca.* 1:1).

(2-methylallyl)magnesium chloride in THF (86.2 ml, 2.17 N, 187 mmol)[9]). The resulting grey soln. was heated at 30°, and a soln. of methyl α-cyclogeranate [3] (= methyl 2,6,6-trimethyl-2-cyclohexene-1-carboxylate; **1**; 20.0 g, 110 mmol) in THF (20 ml) was added dropwise within 5 min at 35–40°. After 1 h, the pale yellow-green soln. was quenched with aq. NH_4Cl soln./ice and extracted with Et_2O. The org. phase was washed with aq. 5% HCl, aq. sat. $NaHCO_3$, and aq. sat. NaCl soln,, dried (Na_2SO_4), evaporated, and distilled (62–75°/0.1 Torr) to afford *3-methyl-1-(2,6,6-trimethyl-2-cyclohexenyl)-3-buten-1-one* (**7**; 20.2 g (94% pure), 85%). ^{1}H-NMR (60 MHz, only significant signals): 2.82 (br. *s*, 1 H); 3.19 (*s*, 2 H); 4.73 (br. *s*, 1 H); 4.85 (br. *s*, 1 H); 5.51 (br., 1 H).

A soln. of the distillate and TsOH (400 mg) in toluene (90 ml) was stirred at 70° for 15 h, poured into aq. sat. $NaHCO_3$ soln., and the product was extracted (Et_2O). Distillation (60–73°/0.1 Torr) afforded **8** (17.9 g, 79% from **1**). IR ($CDCl_3$): 2910, 1670, 1610, 1440. ^{1}H-NMR (60 MHz): 0.88 (*s*, 3 H); 0.94 (*s*, 3 H); 1.00–1.30 (*m*, 1 H); 1.60 (br. *s*, 3 H); *ca.* 1.70–2.20 (*m*, 3 H); 1.90 (*d*, *J* = 2, 3 H); 2.13 (*d*, *J* = 2, 3 H); 2.66 (br. *s*, 1 H) 5.53 (*m*, 1 H); 6.13 (*m*, 1 H). MS: 206 (2, M^+), 83 (100), 55 (9).

(E/Z)-2-Methyl-1-(2,6,6-trimethyl-2-cyclohexenyl)-2-buten-1-one (**9**; *Table, Entry 2*). It was proceeded as described for **7** with BuLi/hexane (18.2 ml, 1.59 N, 28.8 mmol), $(i\text{-}Pr)_2NH$ (2.96 g (4.15 ml), 29.4 mmol), (2-butenyl)magnesium chloride in THF [9]) (20.2 ml, 2.32 N, 46.7 mmol), **1** (5.0 g, 27.5 mmol) [3], and THF (80 ml). Workup and bulb-to-bulb distillation (60–75°/0.1 Torr) afforded an oil (4.54 g) consisting of **9**, the isomeric β,γ-unsaturated ketones (mixture of diastereoisomers), and **1** (16%)[10]). The oil was dissolved in Et_2O (300 ml), treated with neutral Al_2O_3 (*Fluka*, act. 1, 100–125 mesh; 22.5 g) and stirred at 20° for 6 h [4]. Filtration *(Celite)* and chromatography (silica gel) with CH_2Cl_2 afforded **9** (*E*/*Z*) *ca.* 1:1, 3.23 g, 57%). IR ($CDCl_3$): 2930, 1655, 1635, 1440, 1230. ^{1}H-NMR (60 MHz): signals of (*E*)-**9**: 0.80 (*s*, 3 H); 0.96 (*s*, 3 H); *ca.* 0.95–1.40 (*m*, 2 H); 1.56 (br. *s*, 3 H); 1.83 (*s*, 3 H); 1.95 (br. *d*, *J* = 7, 3 H); *ca.* 1.80–2.40 (*m*, 2 H); 3.54 (br. *s*, 1 H); 5.62 (*m*, 1 H), 6.82 (*q*, *J* = 7, 1 H); characteristic signals of (*Z*)-**9**: 0.95 (*s*, 6 H); 1.90 (br. *d*, *J* = 8, 3 H); 2.04 (*q*, *J ca.* 1.5, 3 H); 3.35 (br. *s*, 1 H); 5.82 (*q*, *J* = 8, 1 H). MS ((*E*)-**9**): 206 (4, M^+), 123 (7), 83 (100), 55 (31).

1-(1,4-Dimethyl-3-cyclohexenyl)-2-phenyl-1-ethanone (**10**; *Table, Entry 3*). A soln. of **2** [5] (2.0 g, 12.0 mmol) in THF (10 ml) was treated at 20° with a mixture of LDA (12.6 mmol) and benzylmagnesium chloride[9]) (7.33 ml, 1.80 N, 13.2 mmol) in THF/hexane (60 ml) as described above. Workup and bulb-to-bulb distillation (70–85°/0.1 Torr) gave **10** (2.29 g (95% pure), 79%). IR (neat): 2920, 1710, 1450. ^{1}H-NMR (60 MHz): 1.16 (*s*, 3 H); 1.67 (br. *s*, 3 H); *ca.* 1.80–2.15 (*m*, 5 H); 2.50 (br. *d*, *J* = 17, 1 H); 3.81 (*s*, 2 H); 5.34 (*m*, 1 H); 7.24 (br. *s*, 5 H). MS: 228 (2, M^+), 137 (24), 109 (100), 91 (22), 67 (27).

(Z)-1-(1,4-Dimethyl-3-cyclohexenyl)-1-(trimethylsiloxy)-1-pentene (**13**; *Table, Entry 5*). Ester **2** [5] (2.0 g, 12.0 mmol) in THF (8 ml) was added at 0° to a soln. of $LiNEt_2$ (13.8 mmol), prepared from Et_2NH (1.02 g (1.45 ml), 14.0 mmol) in THF (30 ml) and BuLi in hexane (8.70 ml, 1.58 N, 13.8 mmol) at 0°. After 10 min, a mixture of LDA (15.6 mmol) in THF (35 ml) and BuLi in hexane (15.6 mmol) was added at 20°. After 30 min, the soln. was cooled at 0° and treated with Me_3SiCl (4.00 g (4.67 ml), 36.8 mmol). The cooling bath was removed and stirring continued at 20° for 1 h. Evaporation, filtration (*Celite*, pentane) and bulb-to-bulb distillation (100–110°/0.05 Torr) afforded **13** (2.70 g (95% pure), 80%). IR (neat): 2950, 1650, 1245, 1075. ^{1}H-NMR (360 MHz): 0.22 (*s*, 9 H); 0.88 (*t*, *J* = 7, 3 H); 1.00 (*s*, 3 H); 1.20–1.50 (*m*, 4 H); 1.63 (br. *s*, 3 H); 1.78 (br. *d*, *J* = 17, 1 H); 1.80–2.00 (*m*, 4 H); 2.15 (br. *d*, *J* = 17, 1 H); 4.49 (*t*, *J* = 7, 1 H); 5.30 (br., 1 H). MS: 266 (2, M^+), 209 (15), 169 (12), 119 (11), 105 (9), 75 (22), 73 (100).

N,N-*Diethyl-3-methyl-3-butenamide* (**18**) *and* N,N-*Diethyl-3-methyl-2-butenamide* (**19**; *Scheme 2*). A soln. of **17**[5]) (1.0 g, 5.92 mmol) in THF (20 ml) was treated at 0° with a mixture of LDA (6.22 mmol) and (2-methylallyl)magnesium chloride (6.50 mmol) in THF/hexane (20 ml). The cooling bath was removed and stirring continued at 20° for 1 h. Workup and bulb-to-bulb distillation (80–90°/4 Torr) afforded **18**/**19** (3:1; 701 mg, 76%). IR ($CDCl_3$): 2960, 2920, 1620, 1440. ^{1}H-NMR (60 MHz): **18**: 1.17 (*t*, *J* = 7, 6 H); 1.83 (*s*, 3 H); 3.07 (*s*, 2 H); 3.30 (*q*, *J* = 7, 4 H); 4.75 (*s*, 1 H); 4.88 (*s*, 1 H); **19**: 1.13 (*t*, *J* = 7, 6 H); 1.86 (br. *s*, 3 H); 1.93 (*s*, 3 H); 3.38 (*q*, *J* = 7, 4 H); 5.80 (br. *s*, 1 H). MS (**18**): 155 (24, M^+), 140 (13), 100 (83), 72 (100), 58 (23). MS (**19**): 155 (12, M^+), 140 (28), 83 (100), 55 (24).

Ethyl 2,2-Dimethyl-3-hydroxybutanoate (**4**). A soln. of ethyl isobutyrate (**5**) (30.0 g, 259 mmol) in THF (50 ml) was added within 30 min to a soln. of LDA (278 mmol) in THF/hexane (400 ml) at −75°. The soln. was stirred for 30 min and treated with acetaldehyde (12.58 g (16.1 ml), 286 mmol). The mixture (−45° after addition) was

---

[9]) Prepared by addition of 2-methylallyl chloride (1.0 equiv.) in THF to a suspension of Mg (1.2 equiv.) in THF (350 ml of THF/mole of 2-methylallyl chloride) at 5° (initiation of the reaction at 25°); estimated yield *ca.* 90%. Same procedure for 2-butenyl, benzyl, and 3-methyl-2-butenyl (= prenyl) *Grignard* reagents.

[10]) Moreover, 3% of isomeric ketones, presumably derived from the reaction with the primary center of (2-butenyl)magnesium chloride, were detected.

allowed to attain 10° (30 min). Workup and distillation (78–79°/4 Torr) gave **4** (34.27 g, 86%). IR (neat): 3500, 2970, 1715, 1260. ^{1}H-NMR (60 MHz): 1.13 (*d*, *J* = 7, 3 H); 1.16 (*s*, 6 H); 1.28 (*t*, *J* = 6.5, 3 H); 2.80 (*s*, 1 H); 3.88 (*q*, *J* = 6.5, 1 H); 4.17 (*q*, *J* = 7, 2 H). MS: 116 (78), 115 (13), 99 (11), 88 (100), 87 (44), 73 (72), 70 (58), 57 (13).

6-Hydroxy-2,5,5-trimethyl-1-hepten-4-one (**20**) *and 6-Hydroxy-2,5,5-trimethyl-2-hepten-4-one* (**21**; *Table, Entry 7*). Ester **4** (2.0 g, 12.5 mmol) in THF (20 ml) was treated at − 75° with LDA (13.2 mmol) in THF/hexane (20 ml). The soln. was allowed to attain 10° and was added with a syringe to a soln. of LDA (18.7 mmol) and (2-methylallyl)magnesium chloride (18.7 mmol) in THF/hexane (50 ml) at 25°. The mixture was stirred at 40° for 20 min and poured into a vigourously stirred ice-cold aq. sat. NH_4Cl soln. Extractive isolation and bulb-to-bulb distillation (100–110°/4 Torr) afforded **20/21** (*ca.* 1:1; 1.60 g, 75%). IR (neat): 3420, 2910, 1680, 1610, 1440, 1370. ^{1}H-NMR (60 MHz): 1.10–1.20 (2 *s*, 1 *d*, 9 H); 1.76 (*s*, 3 H, **20**); 1.94 (*s*, 3 H, **21**); 2.14 (*s*, 3 H, **21**); 2.80 (*s*, 1 H); 3.27 (*s*, 2 H, **20**); 3.95 (*q*, *J* = 6, 1 H); 4.73 (br., 1 H, **20**); 4.95 (br., 1 H, **20**); 6.30 (br. *s*, 1 H; **21**). MS (**20**): 126 (2), 115 (31), 87 (100), 70 (71), 69 (55), 55 (25). MS (**21**): 126 (3), 101 (7), 83 (100), 70 (67), 55 (31).

(Z)-4,6-Bis(trimethylsiloxy)-2,5,5-trimethyl-1,3-heptadiene (**22**; *Table, Entry 8*). Ester **4** (4.0 g, 25.0 mmol) in THF (40 ml) was treated at − 78° with LDA (26.0 mmol) in THF/hexane (50 ml). The soln. was warmed to 10° and added with a syringe to a soln. of LDA (37.5 mmol) and (2-methylallyl)magnesium chloride (37.5 mmol) in THF/hexane (110 ml) at 25°. The mixture was stirred at 40° for 20 min, cooled to − 20°, and treated successively with NEt_3 (5.05 g (6.9 ml), 50.0 mmol) and Me_3SiCl (13.6 g (15.8 ml), 125 mmol). The cooling bath was removed and stirring continued at 20° for 15 h. The mixture was poured into pentane/aq. sat. $NaHCO_3$ soln./ice. The org. phase was washed with aq. 5% HCl soln./ice, aq. sat. $NaHCO_3$ soln./ice, and aq. sat. NaCl soln./ice, dried (Na_2SO_4), evaporated, and bulb-to-bulb distilled (100–120°/0.1 Torr) to afford **22** (5.50 g, 70%). IR (neat): 2950, 1630, 1240. ^{1}H-NMR (360 MHz): 0.06 (*s*, 9 H); 0.14 (*s*, 9 H); 0.89 (*s*, 3 H); 0.99 (*s*, 3 H); 0.99 (*d*, *J* = 6, 3 H); 1.72 (*s*, 3 H); 3.86 (*q*, *J* = 6, 1 H); 4.90 (br. *s*, 1 H); 4.92 (br. *s*, 1 H); 4.94 (*s*, 1 H). MS: 147 (5), 117 (100), 73 (91).

6-Hydroxy-2,5,5-trimethyl-1-hepten-4-one (**20**) *and 6-Hydroxy-2,5,5-trimethyl-2-hepten-4-one* (**21**; *Table, Entry 9*). Ester **4** (2.0 g, 12.5 mmol) in THF (5 ml) was added at − 70° to a soln. of LDA (13.2 mmol) in THF/hexane (15 ml). The soln. was warmed at 10° (20 min) and treated with $LiNEt_2$ (14.0 mmol) in THF/hexane (15 ml). After 30 min, the soln. was added with a syringe to a soln. of LDA (27.5 mmol) and (2-methylallyl)magnesium chloride (27.5 mmol) in THF/hexane (80 ml) at 25°. The mixture was stirred at 38° for 20 min. Workup and bulb-to-bulb distillation (100–110°/4 Torr) afforded **20/21** (*ca.* 1:1; 1.42 g, 67%).

Ketones **20/21** *from Ethyl Isobutyrate* (**5**; *Table, Entry 10*). Ethyl isobutyrate (**5**; 5.0 g, 43.1 mmol) was treated with LDA (45.3 mmol) and acetaldehyde (2.10 g (2.70 ml), 47.7 mmol) as described above (preparation of **4**). The soln. was transferred at 10° *via* syringe to a soln. of LDA (64.6 mmol) and (2-methylallyl)magnesium chloride (64.6 mmol) in THF/hexane (180 ml), and stirred at 40° for 20 min as described above (*Table, Entry 7*). Yield of **20/21** (*ca.* 1:1): 4.98 g (68%).

1,2,2,5-Tetramethyl-3-oxo-5-hexenyl Acetate (**23**) *and 1,2,2,5-Tetramethyl-3-oxo-4-hexenyl Acetate* (**24**). Ac_2O (13.0 g (12.0 ml), 127 mmol) was added at 20° to a soln. of **20/21** (20.0 g, 117 mmol), 4-(dimethylamino)pyridine (4.0 g, 32.8 mmol), and pyridine (40 ml). After 1 h, the mixture was poured into H_2O/ice and extracted with Et_2O. The org. phase was washed with aq. 5% HCl, aq. sat. $NaHCO_3$, and aq. sat. NaCl soln., dried (Na_2SO_4), evaporated, and distilled to give **23/24** (*ca.* 1:1; 23.3 g, 94%). B.p. 60°/0.1 Torr. IR ($CDCl_3$): 2960, 1710, 1610, 1440, 1360, 1240. ^{1}H-NMR (60 MHz): 1.10–1.28 (3 *s*, 1 *d*, 9 H); 1.73 (br. *s*, 3 H, **23**); 1.92 (br. *s*, 3 H, **24**); 2.00 (*s*, 3 H); 2.08 (br. *s*, 3 H, **24**); 3.22 (*s*, 2 H, **23**); 4.72 (br., 1 H, **23**); 4.90 (br., 1 H, **23**); 5.19 (*q*, *J* = 6, 1 H); 6.26 (br., 1 H, **24**). MS (**23**): 157 (12), 129 (14), 87 (100), 70 (33), 69 (29), 55 (23), 43 (51). MS (**24**): 83 (100), 70 (39), 55 (23).

Artemisia Ketone (= *3,3,6-Trimethyl-1,5-heptadien-4-one;* **14**). A soln. of **23/24** (*ca.* 1:1; 5.0 g, 23.6 mmol) in cyclohexane (100 ml) was slowly (2 h) introduced with a long needle (30 cm) into a quartz tube (5 m) at 445° under N_2 (100 ml/min). The product mixture was collected in a dry-ice trap. Evaporation and bulb-to-bulb distillation (oven temp. 60–100°/0.1 Torr) afforded 3.05 g of **14/15** (*ca.* 72%), unreacted **23/24** (*ca.* 10%), and unidentified products (*ca.* 18%). ^{1}H-NMR (60 MHz): significant signals of *2,5,5-trimethyl-1,6-heptadien-4-one* (**15**): 1.73 (br. *s*, 3 H); 3.20 (*s*, 2 H); 4.70 (br., 1 H); 4.90 (br., 1 H).

The product mixture was dissolved in Et_2O (200 ml), treated with neutral Al_2O_3 (*Fluka*, 1, 100–125 mesh; 15.2 g) and stirred at 20° for 1 h. Filtration (*Celite*) and chromatography (silica gel) with cyclohexane/AcOEt 98:2 afforded recovered **24** (450 mg, 9%) and **14** [7] (1.62 g, 45%)[7]). IR (neat): 2910, 1675, 1605, 1440. ^{1}H-NMR (60 MHz): 1.21 (*s*, 6 H); 1.92 (*s*, 3 H); 2.16 (*s*, 3 H); 5.13 (*d*, *J* = 18, 1 H); 5.16 (*d*, *J* = 10, 1 H); 5.94 (*dd*, *J* = 10, 18, 1 H); 6.23 (br., 1 H). MS: 152 (1, $M^{+\cdot}$), 83 (100), 69 (3), 55 (21).

Artemisia Ketone (**14**) *from Methyl 3-Methyl-2-butenoate* (**6**; *Table, Entry 11*). A soln. of **6** (8.0 g, 70.2 mmol) in THF (20 ml) was added at 38° to a soln. of LDA (77.2 mmol) and (3-methyl-2-butenyl)magnesium chloride (84.2

mmol) in THF/hexane (200 ml). After 10 min, the soln. was cooled to $-40°$ and treated with NEt_3 (8.51 g (11.7 ml), 84.2 mmol) and Me_3SiCl (22.8 g (26.7 ml), 210 mmol). The temp. was allowed to attain 20° (30 min). Workup (*cf.* **22**) and bulb-to-bulb distillation (90–100°/4 Torr) afforded *2,5,5-trimethyl-4-(trimethylsiloxy)-1,3,6-heptatriene* (**25**; 12.4 g, 90% pure[11]), 71%). ^{1}H-NMR (360 MHz): 0.17 (*s*, 9 H); 1.17 (*s*, 6 H); 1.78 (*s*, 3 H); 4.84 (br. *s*, 1 H); 4.97–5.07 (*m*, 4 H); 5.90 (*dd*, J = 10.5, 18, 1 H).

A soln. of **25** in THF (300 ml) and 5% aq. HCl soln. (30 ml) was stirred at 0° for 2 h. Workup (Et_2O/$NaHCO_3$) and bulb-to-bulb distillation (70°/4 Torr) gave **14** (7.55 g, 71%).

2-(1-Methylethenyl)-1-(2,6,6-trimethyl-2-cyclohexenyl)-4-penten-1-one (**26**). A soln. of **1** (2.0 g, 11.0 mmol) in THF (5 ml) was added at 35–40° to a soln. of LDA (11.5 mmol) and (2-methylallyl)magnesium chloride (19.8 mmol) in THF/hexane (50 ml). After 1 h, the soln. was cooled to $-78°$ and treated with allyl bromide (3.57 g (2.5 ml), 27.5 mmol). The mixture was allowed to attain 20° (1 h) and stirred at 20° for 1 h. Workup and chromatography (silica gel) with cyclohexane/AcOEt 99:1 gave **26** (1.73 g, 64%) as a partly separated mixture of diastereoisomers. IR (neat): 2910, 1700, 1635, 1435. ^{1}H-NMR (360 MHz): less polar diastereoisomer: 0.85 (*s*, 6 H); 1.05–1.15 (*m*, 1 H); 1.55–1.70 (*m*, 1 H); 1.67 (*s*, 3 H); 1.68 (*s*, 3 H); 1.94–2.50 (*m*, 4 H); 2.98 (*s*, 1 H); 3.42 (*dd*, J = 6, 9, 1 H); 4.95–5.11 (*m*, 4 H); 5.54 (br. *s*, 1 H); 5.66 (*m*, 1 H); more polar diastereoisomer: 0.94 (*s*, 3 H); 0.97 (*s*, 3 H); 1.05–1.15 (*m*, 1 H); 1.45 (*s*, 3 H); 1.61 (*s*, 3 H); 1.55–1.70 (*m*, 1 H); 1.92–2.50 (*m*, 4 H); 3.10 (*s*, 1 H); 3.46 (*dd*, J = 6.5, 10, 1 H); 4.95–5.09 (*m*, 4 H); 5.57 (br. *s*, 1 H); 5.66 (*m*, 1 H). MS (identical for both diastereoisomers): 151 (3), 123 (100), 95 (77), 81 (47), 67 (25), 55 (11), 41 (10).

REFERENCES

[1] C. Fehr, J. Galindo, *Helv. Chim. Acta* **1986**, *69*, 228; C. Fehr, to *Firmenich SA*, Eur. Pat. A1 00 93 840 (prior. 20.4.1982) (*CA:* **1984**, *100*, 102816w).

[2] Recent examples: M.P. Cooke, Jr., *J. Org. Chem.* **1986**, *51*, 951; J.P. Foulon, M. Bourgain-Commerçon, J.F. Normant, *Tetrahedron* **1986**, *42*, 1399; A. Santiago, I. Montes de Lopez-Cepero, G.L. Larson, *Synth. Commun.* **1986**, *16*, 697; T. Hirao, D. Misu, K. Yao, T. Agawa, *Tetrahedron Lett.* **1986**, *27*, 929.

[3] F. Tiemann, E. Semmler, *Chem. Ber.* **1900**, *33*, 3708; L. Ruzicka, H. Schinz, *Helv. Chim. Acta* **1941**, *23*, 959.

[4] M.T. Reetz, B. Wenderoth, R. Urz, *Chem. Ber.* **1985**, *118*, 348.

[5] A.F. Thomas, F. Näf, to *Firmenich SA*, Jpn. Kokai, Tokkyo Koho 8270,831 (1.5.1982) (*CA:* **1982**, *97*, 162450b); A.F. Thomas, M. Lander-Schouwey, *Helv. Chim. Acta* **1984**, *67*, 191; W. Kreiser, P. Below, L. Ernst, *Liebigs Ann. Chem.* **1985**, 194.

[6] C.H. Heathcock, C.T. Buse, W.A. Kleschick, M.C. Pirrung, J.E. Sohn, J. Lampe, *J. Org. Chem.* **1980**, *45*, 1066; G.W. Spears, C.E. Canfield, W.C. Still, *ibid.* **1987**, *52*, 1226.

[7] Recent syntheses: J.E. Dubois, C. Lion, A. Arouisse, *Bull. Soc. Chim. Belg.* **1984**, *93*, 1083; L. Stella, A. Amrollah-Madjdabadi, *Synth. Commun.* **1984**, 1083; J.B. Hendrickson, G.J. Boudreaux, P.S. Palumbo, *J. Am. Chem. Soc.* **1986**, *108*, 2358.

[8] R.A. Russell, *Aust. J. Chem.* **1975**, 2535.

[9] R.L. Snowden, K.H. Schulte-Elte, *Helv. Chim. Acta* **1981**, *64*, 2193; R.L. Snowden, B.L. Muller, K.H. Schulte-Elte, *Tetrahedron Lett.* **1982**, *23*, 335; R.L. Snowden, *Helv. Chim. Acta* **1983**, *66*, 1031; R.L. Snowden, P. Sonnay, *J. Org. Chem.* **1984**, *49*, 1464; U. Burger, D. Erne-Zellweger, C. Mayerl, *Helv. Chim. Acta* **1987**, *70*, 587; for reversible allyl-type *Grignard* reactions, see: R.A. Benkeser, M.P. Siklosi, E.C. Mozdzen, *J. Am. Chem. Soc.* **1978**, *100*, 2134; S.R. Wilson, D.T. Mao, *Tetrahedron Lett.* **1977**, 2559; F. Barbot, P. Miginiac, *Bull. Soc. Chim. Fr.* **1977**, 113.

[11]) Contains small amounts of **14** (*ca.* 5%) and other volatile products (*ca.* 5%).