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GRIGNARD AND HYDRIDE ADDITION TO A KETENE INTERMEDIATE: A NOVEL ACCESS TO α-DAMASCONE AND α-CYCLOCITRAL ⁂

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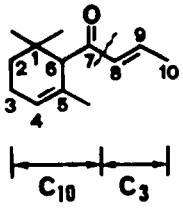
Abstract - α-Damascone (1), a rose fragrance chemical, was synthesized by an allylmagnesium chloride addition to ketene 7 as key step. When the same ketene 7 was reduced by two different aluminium hydride reagents, α-cyclocitral was obtained. The presumed intermediates, enolates II and III, were first trapped as silyl enol ethers and then hydrolyzed with D_2O to give the expected α-monodeuterated carbonyl compounds. Mixed aluminium hydride reduction of ketenes is recommended as a facile entry into the chemistry of aldehyde enolates.

α-Damascone (1), a carotenoid metabolite, is one of the most important representative of the so-called rose ketones,[1,2,3,4] and was found in tea oil.[3] α-Damascone (1) exhibits a strong odour of roses with a pronounced green, fruity undertone reminiscent of green apples, and has become a much appreciated and widely utilized fragrance chemical.[4] In view of its commercial importance, several syntheses have been reported, all of which, however, possess certain drawbacks.



1

α-damascone [a]

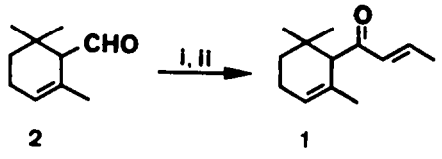
One of the synthetic strategies consists in assembling a C_{10} unit with a C_3 chain as exemplified by the first synthesis of α-damascone (1) by Demole *et al.*:[1] 1-propenylmagnesium bromide was allowed to react with α-cyclocitral (2),[b] and this was followed by chromium trioxide oxidation of the allylic alcohol intermediate (scheme 1).

⁂ Dedicated to Professor R.A. Raphael on the occasion of his 65th birthday.

[a] Throughout the publication, the carotenoid numbering shown is used.

[b] α-Cyclocitral[5a] is obtained in moderate yields by either acid-catalyzed cyclization of citral-anil[5b,c,d], citral-pyrrolidine enamine,[5e] or ozonolysis of α-ionone.[5f] For a detailed discussion of the cyclocitral problem, *cf.* [5g]

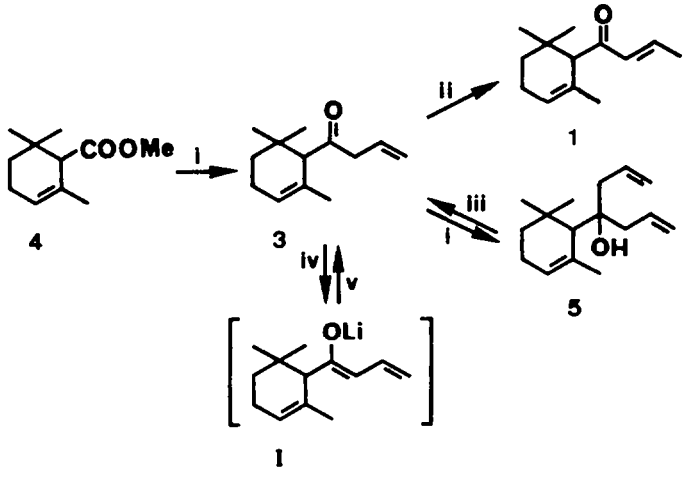
Scheme 1



Reagents: I) ~Br/Mg; II) CrO_3/py

Since α-cyclocitral (2) is not commercially available and the chromium trioxide oxidation possesses serious technico-economical drawbacks, direct Grignard reaction between methyl α-cyclogeraniate (4) and allylmagnesium chloride was reported in the patent literature.[6] A major disadvantage of this approach resides in a double addition of the allylic Grignard reagent leading, *via* 3, to the carbinol 5[6,7] (scheme 2).

Scheme 2



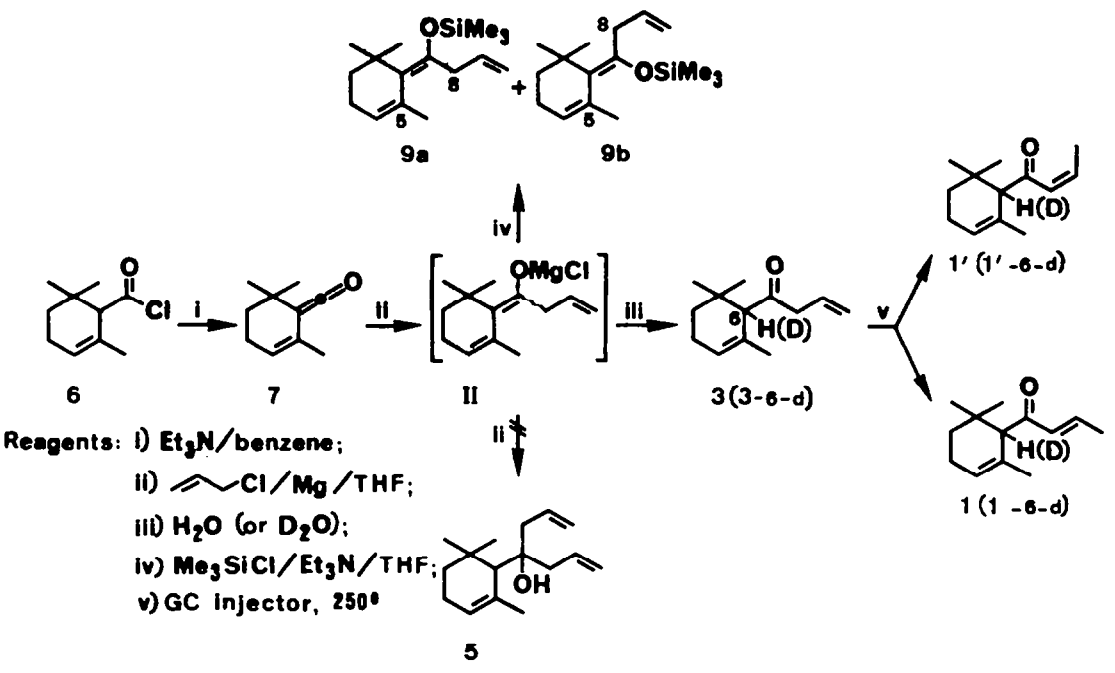
Reagents: I) ~Cl/Mg/ether; II) p-TsOH;
III) KH/HMPA; IV) LDA/ether; V) NH_4Cl/H_2O

Originally puzzled by the formation of the undesired waste product 5, Snowden and Schulte-Elte[7] developed a general method to cleave by base a homoallylic alcohol into a ketone and an alkene allowing 5 to be transformed into the α-damascone precursor 3; the value of this fragmentation has been further shown in a total synthesis of (±)-trichodiene [10], also *cf.*[8,9]

A more elegant approach to α-damascone (1) by Fehr *et al.*[11] starts with methyl α-cyclogeraniate (4) and uses a Grignard addition of allylmagnesium halide in the presence of a strong base, such as lithium diisopropylamide. The primary addition product, ketone 3, is rapidly deprotonated to give enolate I which protects the molecule from a second attack by allylmagnesium chloride.[11] Hydrolysis of enolate I followed by acid-catalyzed isomerization gives α-damascone (1) (scheme 2).

We now present a simple alternative access to α-damascone (1) and α-cyclocitral (2) using cheap reagents and starting materials in conjunction with straightforward classical chemistry (scheme 3). The key step consists in a Grignard addition to the stable ketene 7[12] which is readily

Scheme 3



accessible in four steps from commercial citral.[c] When ketene 7 was allowed to react with a solution of allylmagnesium chloride in THF at room temperature (3 h) and the resulting mixture was hydrolyzed with aqueous ammonium chloride, mostly monoaddition products were obtained, consisting (by GC) of 3,[6,7] 1,[1] and 5[6,7] (80:11:9 ratio, 70% yield of 3 and 1). Acid-catalyzed isomerization[6,7] of this mixture using a trace of *p*-toluenesulphonic acid gave pure α-damascone (1) (35% yield based on 7).

Analogously, lithium aluminium hydride reduction of ketene 7 followed by hydrolysis furnished α-cyclocitral (2) (35% yield) (scheme 4). Use of sodium bis(2-methoxyethoxy)aluminium hydride in toluene[d] increased the yield of α-cyclocitral to 53%. Catalytic hydrogenation of 7 (5% Pd/C, cyclohexane, atmospheric pressure) was not successful, the starting material being recovered.

A mechanistic rationale of the two ketene reactions was suggested by literature and corroborated by experiment. Grignard[17] and organolithium reagents[18,19,20] are known to add in a 1,2-fashion to ketenes producing magnesium and lithium enolates prior to hydrolysis. In the damascone case, the expected magnesium enolate II was trapped as the silyl enol ether 9,[e] both geometrical isomers 9a and 9b (9:1 ratio)[f,g] being formed. Enolate II is automatically protected from an undesired, second attack by allylmagnesium chloride, and is hydrolysed - as are similar dienolates - with formal protonation at the α-position[23] leading to the deconjugated ketone 3. As additional proof hydrolysis

[c] Citral is oxidized (by $NaClO_2$[13] or Ag_2O[14]) to (*Z/E*)-geranic acid[13,14,15] which, upon acid-catalyzed cyclization, leads to α-cyclogeranic acid.[14,15] Chlorination (oxalyl chloride[12]) gives α-cyclogeranyl chloride (6)[12,16] which, upon heating with triethylamine at 160°, produces the stable ketene 7.[12]

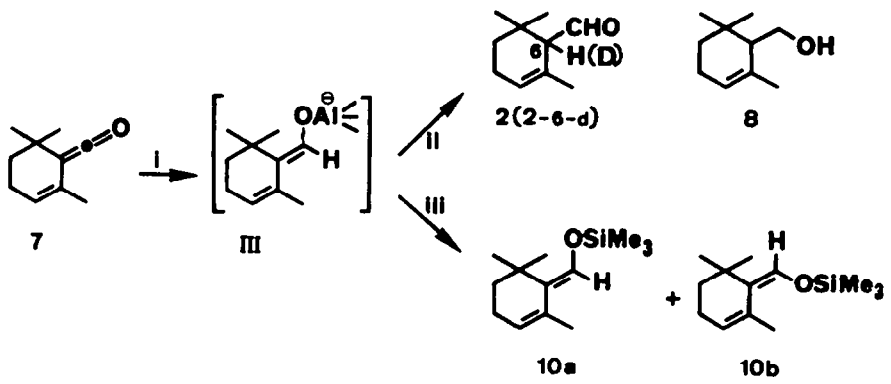
[d] Trade name VITRIDE^R, Hexel Corporation, San Francisco, USA.

[e] For the silylation of enolates, see *e.g.*[19,21,22]

[f] The NMR attribution of the geometric isomers is in accord with the deshielding effect of the silyl ether oxygen upon either the gem dimethyl groups (in 9a) or the methyl group at carbon-5 (in 9b). Shielding of the C-5 methyl group by the C-8 methylene and of the C-8 methylene by the C-5 methyl group in 9a as opposed to 9b was also observed. The observation of a nuclear Overhauser effect (nOe) in 9a, namely signal enhancement of the C-5 methyl group upon irradiation at the C-8 methylene, confirmed the present stereochemical assignment.

[g] We should emphasize, however, that the (*Z/E*)-ratio of the silyl enol ethers is not necessarily an *accurate* measure for the (*Z/E*)-ratio of the initial enolates since this ratio may be influenced by the silylation selectivity and/or (destructive) work-up.

Scheme 4



Reagents: I) $LiAlH_4$ or $(MeOCH_2CH_2O)_2AlH_2Na$; II) HCl/H_2O (or D_2O); III) $CF_3C(OSiMe_3)=N-SiMe_3$

of II with D_2O exclusively furnished the monodeuteroketone 3-6-*d* (for deuteration of organic compounds, *cf.*[24]).

In the cyclocitral case, a similar mechanism, *via* aldehyde aluminium enolate III could be demonstrated. Silylation of III led to the enol silyl ethers 10a and 10b (2:1 ratio).[g,h] Again deuterolysis of III occurred at the α-position producing monodeutero-aldehyde 2-6-*d*.

Nucleophilic attack to ketene 7 is obviously controlled by the adjacent geminal substituents, and shows a pronounced *anti* preference (*i.e.* opposite to the gem methyl groups) in both cases, the complex hydride reduction and the allyl Grignard addition.[i]

It should be emphasized that aldehyde enolates are potentially useful intermediates in the directed aldol condensation. Our hydride reduction of ketenes[j] is an elegant entry into this class of compounds which is not easily accessible by other means. A subsequent publication will report further work concerning aldehyde enolate chemistry.

EXPERIMENTAL

Bulb-to-bulb distillation was done on a Büchi apparatus with external temperature reading. Gas chromatography (GC) was done on a Hewlett-Packard 5890 instrument using a Methyl Silicone 530mμ x 5m column (HP n° 190 955) unless otherwise stated. IR spectra were measured in $CHCl_3$ on a Perkin-Elmer 125 spectrometer, and UV spectra in C_2H_5OH on a Kontron Uvikon-880 instrument. NMR spectra were measured in $CDCl_3$ on a Bruker WH-360 instrument (operating at 360 MHz for ^{1}H-NMR spectra, using the Bruker Software Library DISN 85; chemical shifts are in ppm downfield from tetramethylsilane, and coupling constants *J* are in Hz). Mass spectra (MS) were obtained using a Finnegan 1020 quadrupole spectrometer coupled to a gas chromatograph containing a 30m glass capillary column packed with SE 54 stationary phase. Generally the most prominent values of *m/z* are quoted, with the relative abundance in brackets.

Ketene 7.- It was prepared as described earlier[12] in 71% yield from α-cyclogeranic acid chloride 6.[12,16] It could be stored without obvious decomposition at -10° in the refrigerator for several weeks. The spectral data of 7 were identical with those reported. λ_{max} 233nm (ε 9460); ν_{max} 2080, 1705, 1640, 1380, 1360.- ^{1}H-NMR: 1.13 (*s*, 6H); 1.42 (*t*, *J* 7, 2H); 1.74 (*d*, *J* 2, 3H); 2.1 (*m*, 2H);

[h] Configurational assignment by NMR in analogy to 9a/9b.

[i] For a general discussion of the stereoselectivity of nucleophilic attack of unsymmetrical ketenes, *cf.*[18,19,20] and references quoted therein.

[j] A new general access to ketenes has recently been reported by Seebach *et al.*[18] from 2,6-di-*tert*-butyl-4-methylphenyl esters *via* their lithium enolates.

5.14 (broad *t*, *J* ∿5, 1H).- MS: 150 (M^+, 64), 135 (100), 122 (9), 107 (94), 91 (90), 79 (83), 65 (19), 53 (15), 39 (21).

iso-α-Damascone (3) from ketene 7 and allylmagnesium chloride.- Allyl chloride (1.53 g, 20 mmol) in anhydrous THF (20 ml) was added to a stirred suspension of magnesium turnings (0.48 g, 20 mmol) in anhydrous THF (5 ml) at 20-30°. The mixture was stirred at 20-30° for 1 h (acidimetric titration of the whole base: 12 mmol). Ketene 7 (1.5 g, 10 mmol) in anhydrous THF (10 ml) was added dropwise to the Grignard solution at 20-25°. The reaction was slightly exothermic and the yellow colour of the ketene solution disappeared immediately. The mixture was stirred at room temperature for 3 h, concentrated in the vacuum on a Rotovapor (bath temperature 40-50°), hydrolyzed with ice-water and aqueous ammonium chloride, extracted with ether, washed (1N HCl, $NaHCO_3$, H_2O), dried ($MgSO_4$) and concentrated. The crude material (2 g) was bulb-to-bulb distilled (85-95°/0.01 Torr) giving 1.61 g of a mixture of 3,[6,7] 1,[1] and 5[6,7] (80:11:9). Yield of 3 and 1 ∿70% . The compounds obtained were identical in all respects with authentic material.

Acid-catalyzed isomerization of *iso*-α-damascone (3) into α-damascone (1).- *iso*-α-Damascone (mixture from the previous reaction, 0.96 g, ∿5 mmol) and p-toluenesulphonic acid (30 mg) were stirred at 20° for 28 h. The reaction mixture was taken up in ether, washed ($NaHCO_3$, H_2O), dried ($MgSO_4$), and concentrated. The crude material (0.9 g) was bulb-to-bulb distilled (70-80°/0.01 Torr) giving 0.71 g of a mixture containing α-damascone (1) and diallyl carbinol 5 (82:18). The compounds obtained were identical with authentic material.

α-Cyclocitral (2) by lithium aluminium hydride reduction of ketene 7.- A solution of ketene 7 (1.5 g, 10 mmol) in anhydrous ether (10 ml) was added at 20-30° to a slurry of lithium aluminium hydride (0.19 g, 5 mmol) in anhydrous ether (10 ml). The mixture was stirred at 25° for 2 h, then water (5 ml) followed by 10% hydrochloric acid (20 ml) was added, and the mixture was extracted with ether, washed ($NaHCO_3$, H_2O), dried ($MgSO_4$), and concentrated. The crude material (1.4 g) was bulb-to-bulb distilled (90-100°/0.01 Torr) giving 0.73 g of volatile material, containing 73% of α-cyclocitral (2)[5] (35% yield based on 7). The compound obtained was identical in all respects with an authentic sample prepared according to ref.[5c] ^{1}H-NMR: 0.91 (*s*, 3H); 0.99 (*s*, 3H); 1.31-1.39 (*m*, 1H); 1.59 (broad *s*, 3H); 2.36 (*d*, *J* 5, 1H); 5.73 (broad *s*, 1H); 9.47 (*d*, *J* 5, 1H).- MS: 152 (M^+, 5), 137 (4), 134 (3), 123 (59), 107 (20), 94 (43), 81 (100), 67 (34), 55 (21), 41 (30).

α-Cyclocitral (2) by sodium bis(2-methoxyethoxy)aluminium hydride reduction of ketene 7.- A 70% solution of $(CH_3OCH_2CH_2O)_2AlH_2Na$ in toluene[d] (1 ml, ∿3.5 mmol) was added to a solution of ketene 7 (0.75 g, 5 mmol) in cyclohexane (5 ml) at 10-20° (exothermic reaction, external cooling). The originally yellow ketene solution became colourless after the addition. The mixture was stirred at 20° for 2 h, poured into a mixture of crushed ice and 10% aqueous HCl, extracted twice with ether, washed (1N HCl, saturated $NaHCO_3$, H_2O), dried ($MgSO_4$), and concentrated. The crude material (0.7 g) was bulb-to-bulb distilled (90-100°/10 Torr) to give 0.48 g of volatile material, containing 75% of α-cyclocitral (2) without the corresponding alcohol 8 (53% yield of 2 based on ketene 7).

Silyl enol ethers 9a and 9b.- Ketene 7 (0.37 g, 2.5 mmol) in anhydrous THF (5 ml) was added at 20° to a Grignard solution made from magnesium (0.24 g, 10 mmol), allyl chloride (0.76 g, 10 mmol) in THF (12 ml) as described previously. After 1 h at room temperature, the solution, which is assumed to contain enolate II, was treated dropwise with a solution of trimethylchlorosilane (1.08 g, 10 mmol) in anhydrous THF (5 ml) followed by triethylamine (1.01 g, 10 mmol) at room temperature. After stirring at 20° for 3 h the mixture was poured onto ice-cold NH_4Cl solution, extracted (pentane, 2x), washed with ice-cooling (1N HCl, saturated $NaHCO_3$, H_2O, aqueous NaCl), dried (SO_4Mg), and concentrated (25°). Bulb-to-bulb distillation (70-80°/0.01 Torr) gave 0.58 g of an oil which, by NMR analysis, contained 9a and 9b (9:1) as main products. GC analysis gave the same ratio. For analysis the compounds were captured by GC (10% silicone on Chromosorb W, 0.4 x 250 cm).- 9a. ^{1}H-NMR: 0.13 (*s*, 9H); 1.12 (*s*, 6H); 1.31 (*m*, 2H); 1.81 (broad *s*, 3H, C(5)-CH_3); 1.89 (*m*, 2H); 2.95 (*d*, *J* 5, 2H, C(8)H_2); 5.0 (*m*, 2H); 5.51 (*t*, 1H); 5.74 (*d* of *d* of *t*, 1H). NOe experiment: irradiation at 2.95 (C(8)H_2) gave increase (10%) at 1.81 (C(5)CH_3) exclusively.- MS: 264 (M^+, 10), 249 (5), 233 (14), 208 (3), 193 (4), 181 (2), 167 (2), 159 (7), 150 (4), 143 (2), 135 (12), 117 (7), 107 (12), 91 (14), 73 (100), 59 (5), 45 (15).- 9b. ^{1}H-NMR: 0.05 (*s*, 9H); 1.08 (*s*, 6H); 1.31 (*m*, 2H); 1.83 (broad *s*, 3H, C(5)-CH_3); 1.89 (*m*, 2H); 3.04 (*d*, *J* 5, 1H); 5.0 (*m*, 2H); 5.42 (*t*, 1H); 5.74 (*d* of *d* of *t*, 1H).- MS: 264 (M^+, 11), 249 (5), 235 (1), 223 (13), 208 (4), 193 (5), 181 (2), 169 (1), 159 (8), 150 (6), 135 (13), 117 (7), 107 (12), 91 (16), 73 (100), 59 (5), 45 (15).

Monodeutero-ketone 3-6-*d*.- The enolate solution, prepared as described above (2 ml), was added at 25° to D_2O (0.2 ml). The solution was filtered, concentrated (<30°), and analyzed by GC: one major peak was detected. NMR analysis of this crude material showed 3-6-*d* as main product. However attempts to trap 3-6-*d* by injecting the crude material on a filled column (10% silicone on Chromosorb W, 0.4 x 250 cm) generated a mixture of 3-6-*d* (20%), 1'-6-*d* (55%), and 1-6-*d* (25%), the latter two compounds are therefore not the result of deuterolysis but were formed in the injector of the gas chromatograph.- 3-6-*d*. ^{1}H-NMR: 0.91 (*s*, 3H); 0.94 (*s*, 3H); 1.58 (*s*, 3H); 2.8 (*s*, 1H ∿90% absent, C(6)-D(H)); ABX system with A 3.21 (*d* of *d*, J_{AB} 17, J_{AX} 7, 1H), B 3.32 (*d* of *d*, J_{BA} 17, J_{BX} 7, 1H); 5.12 (*d*, *J* 17, 1H); 5.19 (*d*, *J* 10, 1H); 5.6 (*s*, 1H); 5.94 (*d* of *d* of *t*, *J* 7, 10, and 17) .- 1a-6-*d*. ^{1}H-NMR: 0.87 (*s*, 3H); 0.96 (*s*, 3H); 1.57 (broad *s*, 3H); 1.9 (*d* of *d*, *J* 2 and 7, 3H); 2.90 (*s*, 1H ∿90% absent, C(6)-D(H)); 5.62 (broad *s*, 1H); 6.32 (*d*, *J* 14, 1H); 6.89 (*d* of *q*, *J* 7 and 14).- 1b-6-*d*. 0.89 (*s*, 3H); 0.94 (*s*, 3H); 1.59 (*s*, 3H); 2.1 (*d*, *J* 7, 3H); 2.7 (*s* absent, C(6)-D); 5.6 (broad *s*, 1H); 6.16 (*d* of *q*, *J* 11 and 7, 1H); 6.32 (*d*, *J* 11, 1H).

Silyl enol ethers 10a and 10b.- Ketene 7 (0.3 g, 2 mmol) in cyclohexane (5 ml) was treated dropwise with a solution (0.6 ml, ∿2 mmol) of Vitride (70%) in toluene[d] at 10-20°. After stirring for 2 h at 25°. *N,O*-bis(trimethylsilyl)trifluoroacetamide was added at 25°. The solution was stirred for 3 h

at 25°, poured onto ice, extracted with pentane, washed (ice-cold NH_4Cl, ice-cold $NaHCO_3$, H_2O), dried ($MgSO_4$), and concentrated (20°). The crude material (0.74 g) was bulb-to bulb distilled (90-100°/10 Torr) to give 0.31 g of 10a and 10b (2:1). For analysis the compounds were captured by GC (10% silicone on Chromosorb W, 0.4 x 250 cm).- 10a. ^{1}H-NMR: 0.21 (*s*, 9H); 1.21 (*s*, 6H); 1.75 (*s*, 3H); 5.4 (*t*, 1H); 6.33 (*s*, 1H).- MS: 224 (M^+, 22), 209 (36), 193 (1), 181 (3), 165 (2), 151 (1), 134 (7), 119 (55), 103 (9), 91 (15), 73 (100), 59 (6), 45 (20).- 10b. ^{1}H-NMR: 0.19 (*s*, 3H); 1.02 (*s*, 6H); 2.03 (*s*, 3H); 5.33 (*t*, 1H); 6.21 (*s*, 1H).- MS: 224 (M^+, 28), 209 (52), 193 (2), 181 (4), 165 (2), 151 (2), 134 (9), 119 (67), 103 (9), 91 (23), 73 (100), 59 (6), 45 (19).

Monodeutero-α-cyclocitral (2-6-*d*).- The enolate solution (2 ml), prepared as described in the previous experiment, was added at 25° to D_2O (0.2 ml). The solution was filtered (cotton wool), concentrated (<30°) and analyzed by NMR and GC (one major peak). ^{1}H-NMR: 0.90 (*s*, 3H); 0.99 (*s*, 3H); 1.59 ("*s*", 3H); 5.72 ("*s*", 1H); 9.46 (*s*, 1H).

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