dieser Arbeit wurde bislang nicht zwischen diesen sehr ähnlichen und leicht ineinander umwandelbaren Diastereomeren unterschieden.

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199. Regiospecific Intramolecular Aldol Condensation Induced by Conjugate Addition of Lithium Dimethylcuprate to ζ-Oxo-α,β-enones

Preliminary Communication [1][1]

by **Ferdinand Näf, René Decorzant** and **Walter Thommen**

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(12. VIII. 75)

Summary. ζ-Oxo-α,β-enones react with lithium dimethylcuprate to give cyclic aldols such as hydroxydecalone **1** and hydroxyspiro[4.5]decanone **2** in a regio- and stereospecific manner. This new reaction, a combination of conjugate methyl addition to α,β-enones with directed intramolecular aldolisation, is suggested to proceed *via* either enoate anions, such as **8** and **11**, or radical anions, such as **9** ⇀ **10** and **12** ⇀ **13**, as intermediates.

Recently we [2] and others [3–6] have shown that metal enolates resulting from the conjugate addition of metal alkyls to α,β-unsaturated ketones are valuable intermediates for *intermolecular* aldol condensations (*Scheme 1*).

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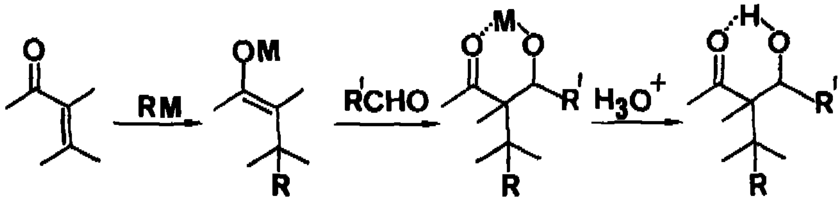
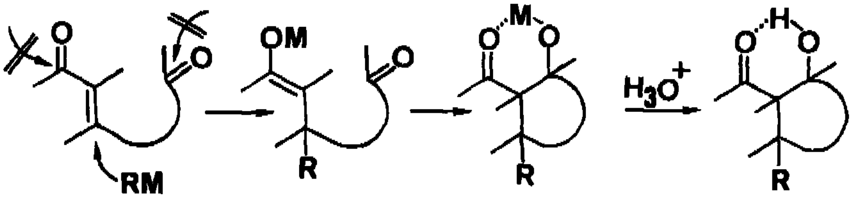
[1] Part of this work was presented at the Swiss Chemical Society Autumn Meeting, Neuchâtel, October 11, 1974.

Scheme 1

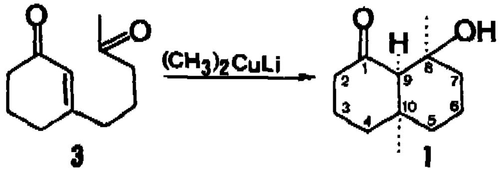


In this context we have examined a formal *intramolecular* variant of this aldol condensation to try to construct cyclic β-hydroxy ketones in a regio- and stereoselective manner (*Scheme 2*).

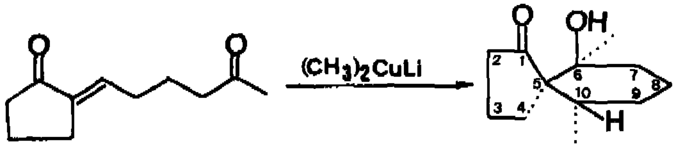
Scheme 2



We have now found that lithium dimethylcuprate [7] – but not methylmagnesium bromide with catalytic amounts of a Cu(I) salt – undergoes a clean reaction[2] with the ζ-oxo-α,β-enones **3** and **4** to give, after work up, the bicyclic hydroxy ketones **1**[3]



3 **1**



4 **2**

and **2**[3][4]. In the case of the ε-formyl-α,β-enone **6**, even at –60°, the reaction gave consideral amounts of the carbonyl addition product **5**.

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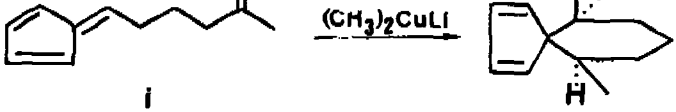
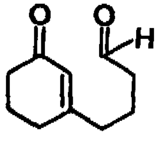
[2] Lithium dimethylcuprate is known to undergo extremely fast conjugate addition to α,β-unsaturated carbonyl compounds, but to react very slowly in a 1,2-fashion with carbonyl compounds (see *e.g.* [8–10]).

[3] The structures shown were firmly established by ^{1}H-NMR. spectroscopy with the aid of Eu(fod)$_3$ shift agent and by ^{13}C-NMR. spectroscopy (for details see [11]).

[4] The spiroannelation **i** to **ii** related to the change **4** → **2** was discovered by *Büchi et al.* [11].



i **ii**



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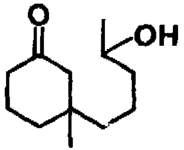

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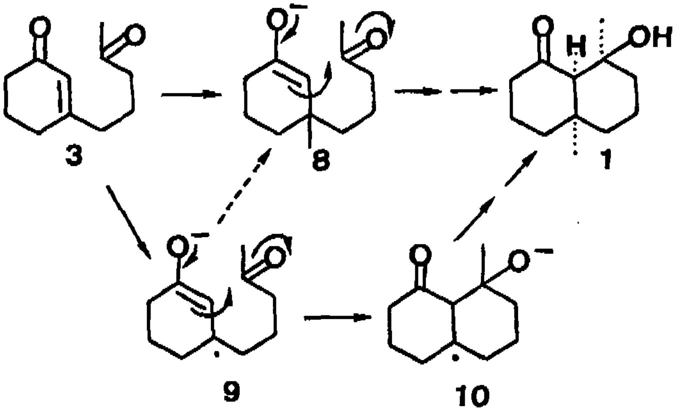
In a typical experiment ethereal lithium dimethylcuprate (prepared from 5.3 ml = 4.5 mmol ethereal methyllithium and 475 mg = 2.4 mmol powdered CuI in 10 ml ether at –10° [7]) was cooled to –60° and then treated with a solution of oxo-enone **3** (360 mg = 2 mmol) in ether (5 ml). The solution was stirred at –60° for 90 min then at 0° for 60 min, when it was poured into ice-cold aqueous 1 N hydrochloric acid and extracted with ether. Washing ($NaHCO_3$ and water), drying ($MgSO_4$) and concentration yielded 0.38 g of material which, after chromatography in hexane/ethyl acetate 7:3 on silica gel, gave only the hydroxydecalone **1**[5]) (250 mg; 63% yield).

Both aldols, **1** and **2**, are products from a kinetically controlled reaction, since they are no longer found if the reaction mixture is equilibrated (24 h at 22°). Likewise, equilibration of **1** and **2** with EtONa/EtOH (22 h at 0°) yields qualitatively the same equilibrium mixture[6]) no longer containing **1** or **2**.

We should like to discuss two of the possible mechanisms for the formation of **1**.

a) Conjugate addition of a methyl group to the enone function of compound **3** may form the enolate intermediate **8**[7]) which could be intercepted by the intramolecular keto group to yield, after hydrolysis, the hydroxydecalone **1**.



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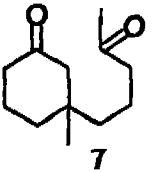
[5] This compound is unstable on distillation or gas chromatography, undergoing a retro aldol cleavage to give the monocyclic compound **7**.



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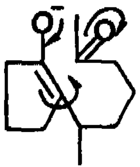
[6] See full paper [1].

[7] Attempts to intercept **8** by protonation to form the monocyclic ketone **7** were negative; addition of water before the reaction was complete yielded only starting material **3** together with the known reaction product **1**.

b) Alternatively, the radical anion **9**, which is likely to be formed from **3** by a one-electron transfer[8]), could be trapped by the intramolecular keto function to give the bicyclic radical intermediate **10**, subsequent combination of **10** with a methyl radical giving **1**.

Formation of the spiro ketone **2** may also occur *via* either metal enolate **11** or radical anions **12** → **13**.



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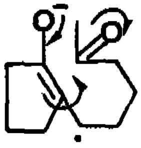

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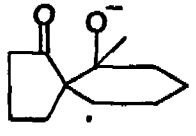

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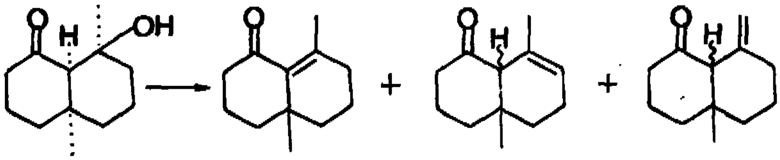
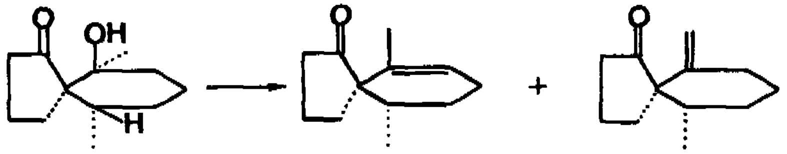
Since the mechanism of these cyclizations remains unclear, it is premature to comment on the high stereoselectivity of the two reactions.

Both aldols, **1** and **2**, were readily dehydrated. Treatment of hydroxydecalone **1** with $SOCl_2$/DMF (5 min at –10°, 1 h at 0°) gave a mixture[9]) of **14b**, **14a** and **14c** (ratio 40:55:5)[10]) in 64% yield.



1 **14a** **14b** **14c**

Hydroxyspiro[4.5]decanone **2** ($SOCl_2$/DMF, 5 min at 0°, 2 h at 23°) yielded 58% of a mixture[9]) of **15b** and **15a** (ratio 1:1)[10]).



2 **15a** **15b**

The oxo-enones **3** and **4** were prepared by methods based on known procedures. Reaction [13] of 3-ethoxy-2-cyclohexenone (**16**) [14] with *Grignard* reagent **17** [15] followed by treatment with 0.5 N aqueous hydrochloric acid 2 h at 40–50° gave **3**[10]).

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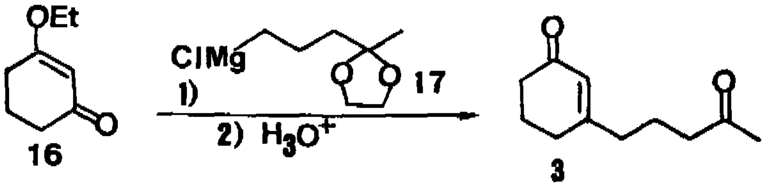
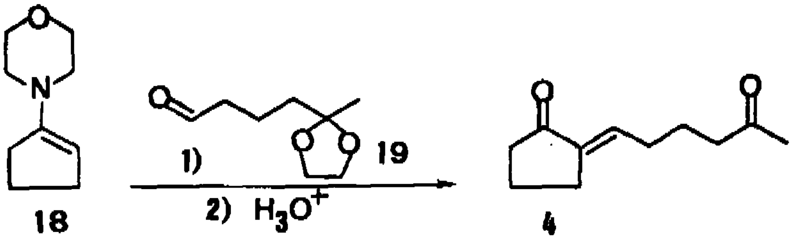
[8]) There is evidence for the formation of radical anions during dialkylcuprate reactions with α,β-enones; for some recent references see *e.g.* [12].

[9]) Separated by gas chromatography on a 20% Carbowax column at 175°; compounds are given in order of increasing retention time.

[10]) NMR., IR., and MS. data (see [1]) are consistent with the assigned structure(s).

Cyclopentanone **4**10) was prepared by condensation of 1-morpholino-cyclopentene (**18**) [16] with aldehyde **19** [17] followed by hydrolysis with 5% aqueous hydrochloric acid at 23°.





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