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The reaction of 4-methoxybenzylmagnesium chloride with aldehydes. The formation of 4-exomethylenecyclohexenones

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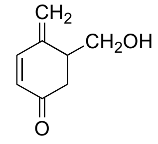
Abstract—The reaction of 4-methoxybenzylmagnesium chloride with aldehydes provides good yields of 4-exomethylenecyclohexenones.

In the course of a synthesis of malibatol A, we required the alcohol **1**.[1] Since 4-methoxybenzylmagnesium chloride (**2**) was commercially available, we reacted it with aldehyde **3** in THF at 0 °C followed by mild aqueous acid workup. Unexpectedly, the product in 93% yield was not the desired alcohol **1** but the 'dearomatized' adduct **4**. Alcohol **4** was unstable and was oxidized to the diketone **5**. The structures of **4** and **5** were supported by NMR[2] and mass spectrometry.

The production of alcohol **4** could be rationalized by the cyclic six-atom transition state shown below. Hydrolysis of the enol ether during workup would provide ketone **4**.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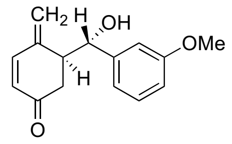
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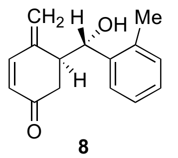
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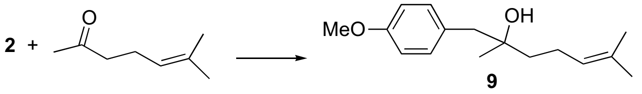
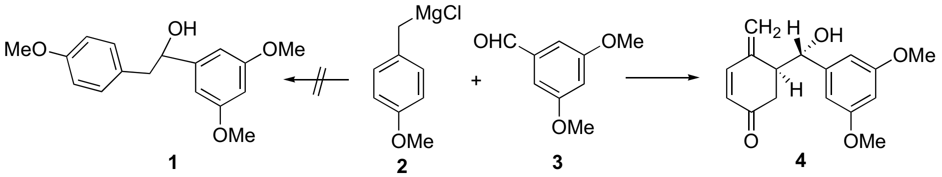
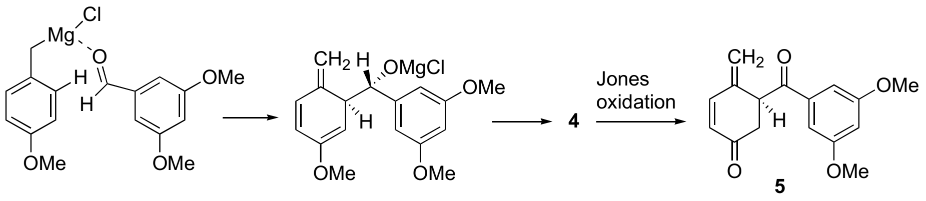


The reaction of Grignard **2** with gaseous formaldehyde, *m*-methoxybenzaldehyde and *o*-tolualdehyde afforded alcohols **6**, **7** and **8** in 65%, 59% and 38% yields, respectively. Interestingly, the reaction of **2** with 6-methyl-5-hepten-2-one produced alcohol **9**, possibly due to steric





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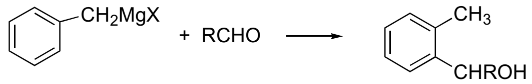
destabilization of the cyclic six-atom transition state relative to the direct addition.

Reports of the formation of abnormal products such as **10** with benzylic Grignard reagents date back to 1932.[3–8] These products have been reported by several researchers with the generalization that aldehydes are more prone to the formation of abnormal products than ketones. In all of the cases that we could find, the initially formed adduct aromatized to the *ortho*-substituted toluene.



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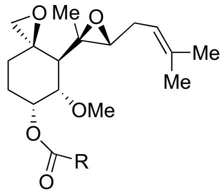
The production of compounds such as **4**, **6**, **7** and **8** is intriguing and generates a class of compounds for which there are few synthetic pathways.[9–11] The products generated by this chemistry may be useful in organic synthesis; for example, in the production of novel analogs of fumagillin (**11**), a natural product whose analogs are of interest to researchers in angiogenesis.[12]



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References and notes

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2. Representative experimental: To a solution of 4-methoxybenzylmagnesium chloride (50 mL of a 0.25 M solution in THF) was slowly added a solution of 3,5-dimethoxy benzaldehyde (2.00 g, 12.0 mmol) in 20 mL of THF at 0 °C. The reaction was stirred at 0 °C for 15 min and then quenched with 10% HCl. The solvent was evaporated in vacuo and the residue extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated. The residue was purified by silica gel flash chromatography using 3:1 hexane/ethyl acetate. The product, a light yellow oil, was obtained in 93% yield.
   ^{1}H NMR of **5**: 2.62 (dd, $J = 6$, 18 Hz, 1H), 2.82 (dt, $J = 3$, 18 Hz, 1H), 3.77 (s, 6H), 4.74 (t, $J = 6$ Hz, 1H), 5.33 (s, 1H), 5.41 (s, 1H), 5.97 (d, $J = 10$ Hz, 1H), 6.61 (s, 1H), 6.92 (d, $J = 10$ Hz, 1H), 7.03 (s, 1H). ^{13}C NMR: 39.2, 47.3, 55.8, 105.8, 106.9, 123.2, 128.6, 137.3, 138.9, 145.0, 161.2, 196.9, 198.0. ^{1}H NMR of **7**: (300 MHz, CDCl$_3$) δ 7.09–7.29 (4H, m), 5.96 (1H, d, $J = 12$ Hz), 5.52 (1H, s). 5.45 (1H, s), 4.52 (1H, d, $J = 12$ Hz), 3.85 (3H, s), 2.98 (1H, t, $J = 6.6$ Hz), 2.52 (1H, dd, $J = 16.8$ Hz, $J = 6.6$ Hz), 2.28 (1H, dd, $J = 16.8$ Hz, $J = 6.6$ Hz); ^{13}C NMR δ 198.5, 148.7, 141.6, 138.1, 135.1, 131.2, 128.8, 126.3, 126.1, 123.6, 110.1, 71.3, 58.3, 46.5, 42.1. ^{1}H NMR of **8**: (300 MHz, CDCl$_3$) δ 7.30 (1H, d, $J = 8$ Hz), 7.09–7.19 (3H, m), 5.96 (1H, d, $J = 12$ Hz), 5.49 (1H, s), 5.35 (1H, s), 4.81 (1H, d, $J = 12$ Hz), 3.08 (1H, t, $J = 6.6$ Hz), 2.50 (1H, dd, $J = 16.8$ Hz, $J = 6.6$ Hz), 2.22 (3H, s), 2.18 (1H, dd, $J = 16.8$ Hz, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.5, 146.6, 140.8, 139.4, 135.9, 130.8, 128.1, 126.7, 126.5, 123.6, 114.1, 71.3, 47.7, 40.1, 19.6.
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