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Stereochemistry of Grignard Additions to α-Keto Esters

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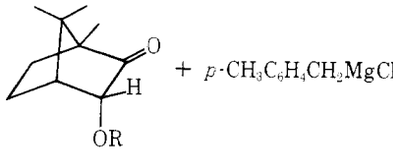
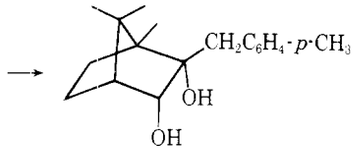
We have previously reported[1] unexpected stereospecificity in Grignard additions to α-keto esters in the bornane series and now wish to describe unexpected results obtained with a series of α-keto esters in the 2,2,5,5-tetramethyltetrahydrofuran series. In the earlier work, *cis*-2,3-dihydroxy-2- (or 3-) (*p*-methylbenzyl)bornanes were obtained from the four possible α-ketol *p*-chlorobenzoates even when this required the unusual exo attack of *p*-methylbenzylmagnesium chloride on the bornane system. For example, reaction of the *p*-chlorobenzoate **1a** of 3-*endo*-hydroxy-2-bornanone (**1b**) with the reagent afforded only 2,3-*cis*,*endo*-dihydroxy-2-*exo*-(*p*-methylbenzyl)bornane (**2**) and bis(*p*-methylbenzyl)-*p*-chlorophenylcarbinol (**3**).



1a, R = *p*-ClC$_6$H$_4$CO
b, R = H

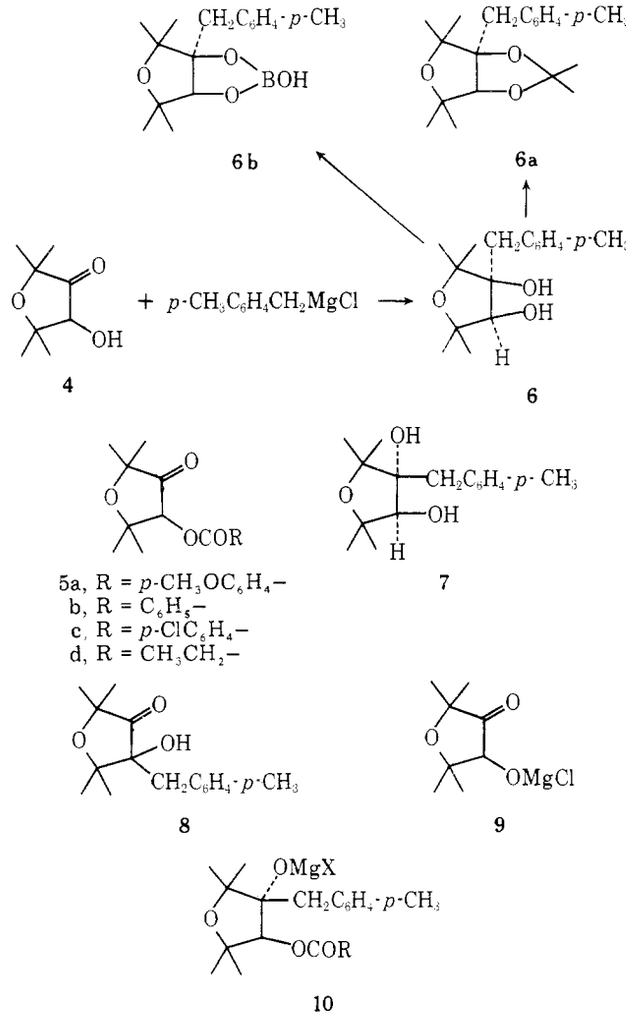


2

+ (*p*-CH$_3$C$_6$H$_4$CH$_2$)$_2$CC$_6$H$_4$-*p*-Cl

3

In the course of an investigation of photochemical reactions of the unusual α-diketone, 2,2,5,5-tetramethyltetrahydrofuran-3,4-dione,[2] with aldehydes, the corresponding α-ketol **4** and a number of its esters (**5a–d**) became available. In view of the earlier results, it appeared of interest to investigate their reactions with the Grignard reagent. Reaction of **4** with *p*-methylbenzylmagnesium chloride afforded the *cis*-diol **6** in nearly quantitative yield. The cis configuration was assigned on the basis of rapid cleavage with sodium periodate and formation of an acetonide (**6a**) and a borate ester (**6b**), both of which regenerated **6** upon hydrolysis. The *trans*-diol **7** was obtained together with **6** and **6b** upon sodium borohydride reduction of 3-hydroxy-3-(*p*-methylbenzyl)-2,2,5,5-tetramethyltetrahydrofuran-4-one[2] (**8**) or together with **6** from Grignard reactions of the esters **5a–d**. Pure **7** was isolated from its mixture with **6** by reaction of the mixture with acetone and anhydrous cupric sulfate, followed by chromatographic separation of **7** from **6a**. In addition to this failure to form an acetonide, the trans configuration of **7** was confirmed by its complete failure to form a borate ester or to react with sodium periodate under conditions comparable to those used successfully with **6**. Both **6** and **7** were oxidized to **8** under mild conditions.



Gas chromatographic retention times of **6** and **7** differed markedly. It was thus readily possible to establish the stereochemistry of reaction of the esters **5a–d** with *p*-methylbenzylmagnesium chloride and to compare the results with the complete specificity observed in the bornane series and with **4**. Results of a series of experiments using a 3.5-fold excess of Grignard reagent are summarized in Table I. It is interesting

Table I. Reactions of Esters of 3-Hydroxy-2,2,5,5-tetramethyltetrahydrofuran-4-one (4) with *p*-Methylbenzylmagnesium Chloride[a]

Ester	Registry no.	*cis*-Diol **6**,[b] %	*trans*-Diol **7**,[b] %
p-Methoxybenzoate **5a**	64314-66-5	20	80
Benzoate **5b**	64314-67-6	25	75
p-Chlorobenzoate **5c**	64314-68-7	50	50
Propionate **5d**	64314-69-8	68	32

[a] Addition of ca. 0.08 M ester in ether to a 3.5-fold excess of ca. 0.34 M Grignard reagent in ether. [b] Determined by gas chromatographic analysis.

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to note the considerable variation in product composition; the least stabilized ester group, the propionate **5d**, afforded 68% of *cis*-diol **6** while the most stabilized ester, the *p*-methoxybenzoate **5a**, yielded only 20% of **6**. The only other compounds present in significant amounts were the appropriate tertiary alcohol and 1,2-bis(*p*-tolyl)ethane.[3]

These surprising results appear to reflect a competition between initial attack of Grignard reagent at the ester or at the ketone carbonyl groups,[4] in contrast to α-keto esters in the bornane series where it was shown that the initial attack occurred at the ester group to give an α-ketol (e.g., **1b**). In the case of initial attack at the ester group, which would be most preferred with **5d** and least so with **5a**, the initial product would be the same solvated magnesium salt **9** which is formed by reaction of **4** with the reagent. This species is attacked from the side of the molecule trans to the original ester or hydroxyl group either because of the considerable steric bulk of the solvated OMgCl group or due to stabilization of the transition state for *cis*-diol formation by coordination with magnesium or due to a combination of both factors.[5,6]

It then follows that the initial attack of reagent at the keto group of the intact keto ester involves considerable stereoselectivity in the opposite sense, with attack occurring preferentially from the same side as the ester group. The resulting intermediate, **10**, would then react further at the ester function to give *trans*-diol **7**. The factors responsible for this selectivity are unclear; possibly coordination of Grignard reagent with the ester carbonyl group plays a role. It might be noted that both benzoin and its methyl ether reacted stereospecifically with Grignard reagents;[7] both reactions followed the same stereochemical course.

Experimental Section

Melting points are uncorrected. Infrared spectra were determined in potassium bromide pellets and NMR spectra in deuteriochloroform solution at 60 MHz using tetramethylsilane as the internal standard.

Gas Chromatographic Analysis. A 10 ft × ⅛ in. glass column packed with 1% XE-60 on 100–120 mesh Gaschrom Q was used at 160 °C and 30 mL of N_2/min. Retention times were 1,2-bis(*p*-tolyl)ethane, 1.7; acetonide **6a**, 2.5; *cis*-diol **6**, 6.0; *trans*-diol **7**, 10.0; and tertiary alcohol **3**, 14.5 min.

***cis*-3-(*p*-Methylbenzyl)-2,2,5,5-tetramethyltetrahydrofuran-3,4-diol (6).** The Grignard reagent prepared from freshly distilled *p*-methylbenzyl chloride (0.56 g) and magnesium (0.12 g) in ether (5 mL) was treated with a solution of hydroxy ketone **4** (0.16 g) in ether (5 mL). After stirring at room temperature for 1.5 h, 1 drop of water was added, and the solution was poured into cold, dilute sulfuric acid. The layers were separated, the aqueous layer was washed twice with ether, and the combined ether extracts were washed with sodium bicarbonate solution, dried over sodium sulfate, and concentrated. The crude product was crystallized twice from hexane to give analytically pure **6** (0.25 g, 94%): mp 132.5–133 °C; IR max 3460, 3200 cm^{-1}; IR (CH_2Cl_2) 3560 cm^{-1}; NMR δ 1.16 (6 H), 1.33 (6 H), 1.66 (d, J = 7 Hz, 1 H) superimposed on a broad absorption centered at about 1.7 (1 H, both 1.66 and 1.7 disappeared on addition of deuterium oxide), 2.35 (3 H), 2.83 (2 H), 4.10 (d, J = 7 Hz, 1 H; converted to a singlet upon addition of deuterium oxide), 7.23 (4 H). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.79; H, 9.20.

A sample (5 mg) of **6** in a few drops of acetone was treated with a few drops of 8 N chromic acid solution, followed after 1 min by a few drops of methanol. Extraction with ethyl acetate, drying, and concentration to a small volume was followed by GC analysis. A peak identical in retention time with that of 3-(*p*-methylbenzyl)-3-hydroxy-2,2,5,5-tetramethyltetrahydrofuran-4-one[2] (**8**) was observed.

A solution of **6** (11 mg) in methanol (2 mL) was treated with an aqueous solution (0.75 mL) of sodium metaperiodate (0.5 g/3 mL). After 20 min at room temperature, crystals of sodium iodate began to separate; GC analysis after 10 h showed that all **6** had been consumed.

A solution of **6** (17 mg) in methanol (2 mL) was treated with an aqueous solution (7 mL) of boric acid (110 mg/20 mL). White crystals began to separate after 0.5 h. After 3 h at room temperature, the crystals of the borate ester **6b** were filtered: mp 184–187 °C; identical by comparison of the IR spectra with **6b** obtained from reduction of **8** with sodium borohydride.

Separation of Cis and Trans Diols. The mixture (1.05 g) of diols **6** and **7** from the reaction of **5c** with *p*-methylbenzylmagnesium chloride was dissolved in dry acetone (10 mL) and anhydrous cupric sulfate (1.0 g) added. The resulting slurry was stirred magnetically at room temperature and portions (1.0 g) of cupric sulfate were added after 24 and 48 h. Progress of the reaction was followed by GC. After 7 days, the peak for *cis*-diol **6** had almost completely disappeared with concomitant formation of the peak corresponding to acetonide **6a**; the peak for the trans-isomer **7** was unchanged. The solution was filtered, the cupric sulfate was washed with acetone, and the combined acetone solutions were evaporated under reduced pressure to give a colorless oil (1.04 g) which was chromatographed on Florisil (14 g). Elution with hexane afforded **6a** (0.27 g). A sample was evaporatively distilled at 150 °C (0.05 mm pressure) to give **6a** as a colorless oil: IR max (film) 1380, 1080 cm^{-1}; NMR δ 0.6 (3 H), 1.30 (9 H), 1.38 (3 H), 1.45 (3 H), 2.28 (3 H), 2.98 (2 H), 4.24 (1 H), 7.10 (4 H). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.46; H, 9.08.

Heating a sample of **6a** (8 mg) in 1 mL of 50% aqueous acetic acid for 4 h resulted in complete conversion to **6** as shown by GC monitoring of the reaction.

Further elution of the column with 50–80% benzene–hexane afforded crystalline *trans*-diol **7** (0.48 g), mp 108–115 °C. Crystallization from hexane gave the analytical sample of **7**: mp 120–120.5 °C; IR max 3560, 3345 cm^{-1}; IR (CH_2Cl_2) 3620, 3570 cm^{-1}; NMR δ 1.20 (3 H), 1.28 (6 H), 1.37 (3 H), 1.60 (br, 1 H, disappeared upon addition of deuterium oxide), 2.25 (d, J = 4 Hz, 1 H, converted to a singlet upon addition of deuterium oxide), 7.10 (d, J = 8 Hz, 2 H), 7.21 (d, J = 8 Hz, 2 H). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.67; H, 9.14.

7 was recovered unchanged after 24 h of treatment with sodium periodate or boric acid under conditions described above for **6**.

Reduction of 3-(*p*-Methylbenzyl)-3-hydroxy-2,2,5,5-tetramethyltetrahydrofuran-4-one (8) with Sodium Borohydride. A solution of **8**[2] (1.00 g) and sodium borohydride (0.60 g) in methanol (20 mL) was allowed to stand overnight at room temperature. Water (10 mL) and acetic acid (5 mL) were added and, after 10 min, the solution was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated salt solution, dried, and concentrated to give a clear oil (1.18 g) which was shown by GC analysis to contain **6** and **7** in a ratio of about 1:4.

The mixture was chromatographed on silica gel (35 g). Elution with 20% benzene–hexane afforded the borate ester **6b** (0.50 g). A sample was recrystallized from aqueous methanol to give **6b** as white crystals: mp 183–185 °C; IR max 3450 cm^{-1} (br). Elution with 10–40% ethyl acetate–benzene gave a mixture (0.74 g) of **6** and **7**.

The crude product from another reduction of **8** (0.25 g) was refluxed for 3 h in a solution prepared from sodium hydroxide (2 g), methanol (8 mL), and water (3 mL). After the usual workup the crude product (0.22 g) was shown by GC analysis to contain 43% of **6** and 57% of **7**.

Reactions of Keto Esters 5a–d with *p*-Methylbenzylmagnesium Chloride. Solutions of esters in anhydrous ether (1 g of ester/50 mL of ether) were added to a 3.5-fold excess of Grignard reagent prepared from magnesium and *p*-methylbenzyl chloride in ether (1 g of chloride/25 mL of ether). Reaction times and workup were as described above for the reaction of **4**. The crude reaction products were analyzed by gas chromatography. No significant peaks were observed except those due to 1,2-bis(*p*-tolyl)ethane, **6**, **7**, and the tertiary alcohol derived from the ester.

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Registry No.—**4**, 14744-19-5; **6**, 64314-70-1; **6a**, 64314-71-2; **6b**, 64314-72-3; **7**, 64314-73-4; **8**, 64314-74-5; *p*-methylbenzylmagnesium chloride, 29875-07-8.

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(3) Preparation of the Grignard reagent from *p*-methylbenzyl chloride is invariably accompanied by 5–10% of the coupling product, 1,2-bis(*p*-tolyl)ethane.
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