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Stereoselective conjugate additions of Grignard reagents to cyclopentadienones

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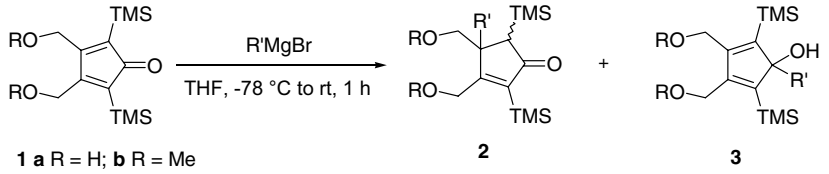
Abstract—Conjugate addition reactions of Grignard reagents with cyclopentadienones having trimethylsilyl groups at the α and α′ positions, and 1-hydroxyethyl substitutents at the β and β′ positions, are reported; excellent stereoselectivity was observed and the relative stereochemistry of three of the products was determined by X-ray methods.

1. Introduction

Cyclopentadienones are promising versatile intermediates for organic synthesis, since they undergo a variety of cycloaddition reactions[1] and are potential double Michael acceptors. In the latter context, we have previously reported[2] studies on reactions of Grignard reagents with cyclopentadienones **1**, which are activated toward conjugate addition by the presence of trimethylsilyl groups at the dienone α,α′-positions.[3] Regiocontrolled 1,4- or 1,2- additions were observed, depending on the nature of the Grignard reagent and the oxymethyl substituents (R = H or Me in the structures). Addition of MeMgBr or vinylMgBr to **1a** afforded only 1,4-adducts **2**, while allylMgBr gave only 1,2-adduct **3**, while for **1b** vinyl- and allyl-Grignard reagents gave only 1,4-addition but MeMgBr gave only 1,2-addition. Since the cyclopentenone products from 1,4-addition are also potential Michael acceptors, and therefore useful as synthetic building blocks, we have investigated this reaction with substrates that have branched, and therefore chiral hydroxyalkyl side chains at the enone β and β′ positions, in an effort to determine whether stereoselectivity can be achieved.



1 a R = H; **b** R = Me

2

3

(1)

2. Results and discussion

The cyclopentadienones used in this study were prepared as described elsewhere.[4] Treatment of **4** with MeMgBr, vinylmagnesium bromide or PhMgBr in THF generated 1,4 adducts **5** as the only isolable products. Interestingly, reaction with MeMgBr in dichloromethane afforded 1,2-adduct **6** as the major product (55% yield; 3:1 mixture of diastereomers), with **5a** being isolated in only 5% yield. In contrast, vinylmagnesium bromide and PhMgBr gave results essentially identical to those in THF. It is likely that these nucleophiles in dichloromethane have modified structures and/or reactivity due to the weak coordinating ability of this solvent with Mg^{2+}, and such modification might result in a change from 1,4- to 1,2-addition, depending on the nature of the Grignard reagent. However, we do not

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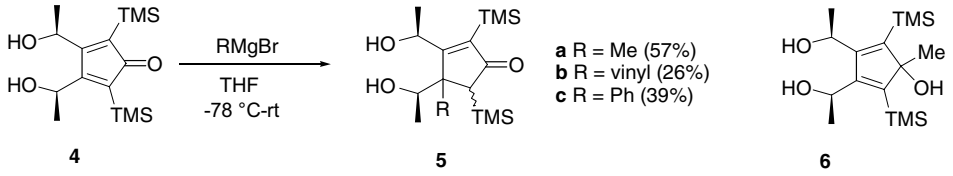
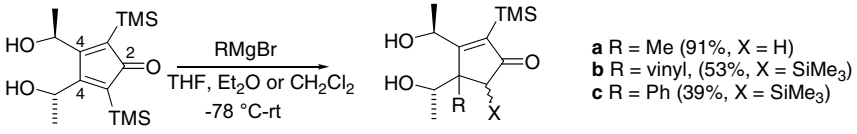
have sufficient understanding of the various solution structures of these reagents to warrant a full explanation of this behavior. We have not yet studied the possible effects of other metal ions in these reactions.



4 5 6 (2)

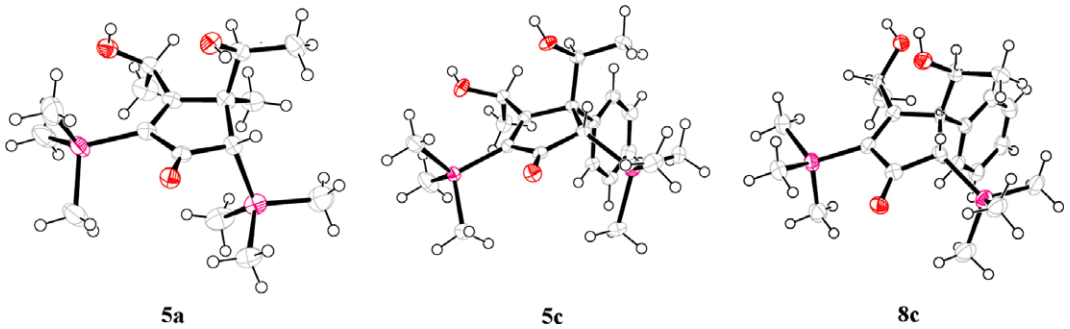
Most reactions in Eq. 2 were incomplete after several hours at room temperature, even when 10 equiv of Grignard reagents were used, possibly a result of steric hindrance from the methyl groups. Consequently, the isolated yields from these reactions were rather poor, but good regioselectivity was observed, and all 1,4 adducts were obtained as single diastereomers. In the case of MeMgBr reaction in THF, 23% of starting material **4** was recovered, while vinylMgBr returned 4% and PhMgBr 27% unreacted cyclopentadienone. The results of conjugate additions to cyclopentadienone **7** are very similar to those for **4**. Most reactions gave 1,4 adducts as the only products. Treatment of **7** with MeMgBr in THF generated the desilylated 1,4 adduct **8a** (X = H) in 91% yield; presumably, the TMS group is removed hydrolytically during work-up. Reaction in dichloromethane was not tested due to its pronounced tendency to favor 1,2-addition. For vinylmagnesium bromide, low yield (8%) of 1,4 adduct was obtained in dichloromethane, while in THF an inseparable mixture of all possible isomers was observed, which was not further characterized. However, satisfactory yield (53%) of **8b** (X = $SiMe_3$) as a single diastereomer was obtained when this reaction was run in Et_2O, together with 28% recovery of starting material. Reaction of **7** with PhMgBr generated 1,4 adduct **8c** in acceptable yields in either solvent. A significant amount of starting material was recovered (34% when using THF), presumably again due to steric hindrance in **7**. Again, the role of solvent in these reactions is complex and poorly understood. The relative stereochemistry for adducts **5a**, **5c**, and **8c** was determined by X-ray crystallography (Fig. 1).



7 8 (3)

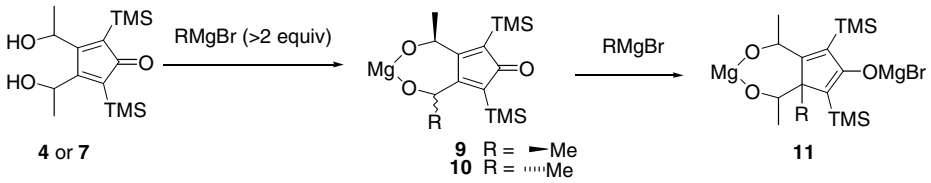
Since adducts **5a** and **5c** have identical stereochemistry, the stereocontrol observed in these reactions is independent of nucleophile, and it is assumed that the 1,4 vinyl adduct **5b** has the same stereo structure as **5a** and **5c**. In an effort to explain the observed stereoselectivity, we speculate that reaction of cyclopentadienone **4** or **7** with excess (>2 equiv) Grignard reagent generates chelate intermediate **9** or **10** prior to nucleophile addition (Scheme 1).

Molecular models of the corresponding bicyclic diastereomers **9** and **10** were constructed and minimized using SPARTAN '04 (Fig. 2). Solvent coordination with the alk-



5a 5c 8c

Figure 1. X-ray structures of **5a**, **5c** and **8c** (both enantiomers were present in each; only one is shown).



Scheme 1.

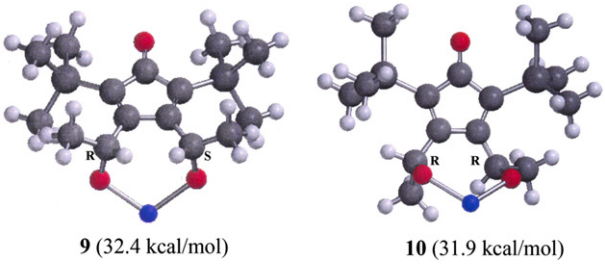


Figure 2. Ball and stick models of **9** and (*ent*-) **10**.

oxymagnesium system has been ignored, so these calculations represent very crude approximations of the actual (unknown) structures. The conformation of **9** with both methyl pseudo axials is much higher energy (35.2 kcal/mol) than the diequatorial structure **9** shown in Figure 2. The trans configuration for **10** dictates an axial/equatorial orientation for the methyl substituents, as shown in the model. The slightly lower energy of **10** compared with **9** is likely a result of the absence of one allylic strain interaction between the equatorial methyl and the TMS group, which is replaced by a 1,3-diaxial methyl-hydrogen interaction. Evidently, the diaxial conformation of **9** is much higher energy because of the much greater 1,3-diaxial interaction between the methyl groups.

Nucleophile addition is expected to proceed along the least hindered approach trajectory. Addition of a nucleophile to **9** or **10** forms enolate **11** (Scheme 1), so the energies of all possible enolates from each diastereomeric cyclopentadienone (**4** and **7**) may give some clues concerning the stereoselectivity (Fig. 3; solvent is omitted). In the structure of **9**, there are only two possible approaches for the nucleophile due to its *meso* character, from the bottom or top face (**12** and **13**). The nucleophile prefers attacking at the under side of **9** to give enolate **12** with lower energy (assuming the transition state is product-like).

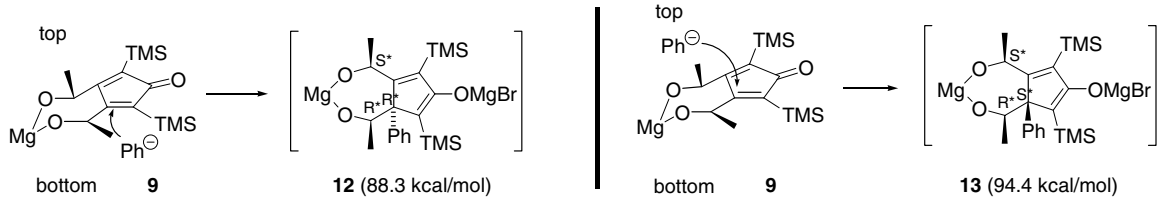


Figure 3. MM2 energies of enolate intermediates from conjugate addition to intermediate **9**.

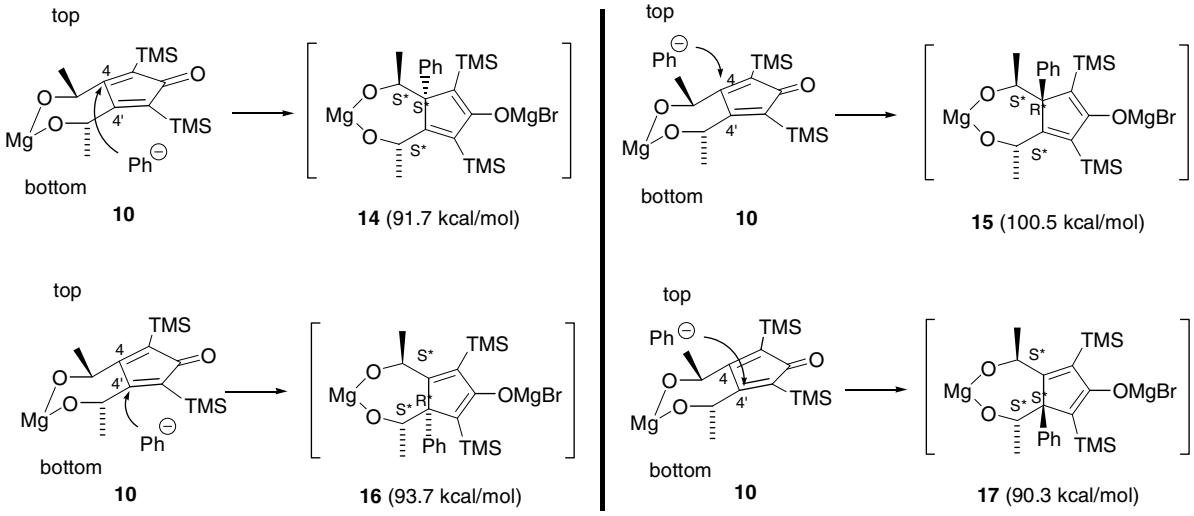


Figure 4. MM2 energies of enolate intermediates from conjugate addition to intermediate **10**.

The stereochemistry of **12** corresponds with that in the X-ray structure of **5c**. Note that this approach trajectory is remote from the oxygens of the chelated intermediate, suggesting that coordination between them and the magnesium of the incoming Grignard reagent is not a controlling factor in this reaction. When the same speculation is employed for **10** (Fig. 4), four enolate structures (**14**–**17**) are possible (the identical stereoisomers are different conformers). The calculated energies indicate that the nucleophile prefers attacking on the upper face of **10**, at the carbon adjacent to the axial methyl but from the direction *anti* to that methyl, to give **17** with the correct stereochemistry compared to the X-ray structure of **8c**.

Acknowledgments

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Supplementary data

Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 628574–628576. Copies of this data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.125.

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