

# Inverse Temperature Dependence in the Diastereoselective Addition of Grignard Reagents to a Tetrahydrofurfural

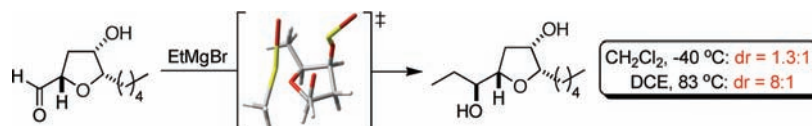
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## ABSTRACT



A remarkable example of inverse-temperature-dependent diastereoselectivity was uncovered while investigating the addition of Grignard reagents to a 3-hydroxytetrahydrofurfural. The free hydroxyl group in the tetrahydrofurfural was found to play a key role in these processes, a result corroborated through a series of DFT calculations that also highlighted an entropic preference for the formation of one diastereomer.

A number of biologically active compounds possess the 2-(1-hydroxyethyl)-tetrahydrofuran subunit, and synthetic approaches to these substances often involve the diastereoselective addition of organometallic reagents to tetrahydrofurfurals. For example, annonaceous acetogenins,<sup>1</sup> many natural<sup>2</sup> and unnatural<sup>3</sup> carbohydrates, and the structurally related marine oxylipids **2**<sup>4</sup> and **4**<sup>5</sup> (Figure 1) have all been accessed via synthetic routes that incorporate this strategic coupling reaction. The diastereochemical outcome of these addition reactions are often rationalized by cyclic chelate models (e.g., **6**) similar to

that originally proposed by Wolfrom and Hanessian<sup>6</sup> for the addition of methyl magnesium iodide to the protected dialdose **5**. In this case, it was reasoned<sup>6</sup> that coordination between the Grignard reagent and both the carbonyl and tetrahydrofuran ring oxygen directs nucleophilic attack to the less hindered *si* face of the aldehyde to provide **7** selectively. However, there are a number of exceptions to this model, and as a result, a thorough screen of both solvents<sup>2c,e</sup> and organometallic reagents<sup>7</sup> is often required to optimize the diastereoselectivity of these processes.<sup>3c</sup> The addition of organometallic reagents to oxygenated tetrahydrofurfurals (e.g., **5**) is further complicated by additional coordination sites, and consequently both the relative configuration<sup>2d</sup> and choice of protecting group<sup>1b</sup> for the oxygen substituents on the tetrahydrofuran ring play key roles in determining the degree and direction of stereoselection. Previously, we reported the development of a general synthetic strategy that provides access to all configurational isomers of the 3-hydroxytetrahydrofuran scaffold from a

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(1) (a) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3622. (b) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739. (c) Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 723.

(2) (a) Yamashita, A.; Norton, E.; Petersen, P. J.; Rasmussen, B. A.; Singh, G.; Yang, Y.; Mansour, T. S.; Ho, D. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3345. (b) Suzuki, T.; Chida, N. *Chem. Lett.* **2003**, *32*, 190. (c) Takahashi, S.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 607. (d) Giuliano, R. M.; Villani, F. J. *J. Org. Chem.* **1995**, *60*, 202. (e) Takahashi, S.; Kuzuhara, H. *Chem. Lett.* **1992**, 21.

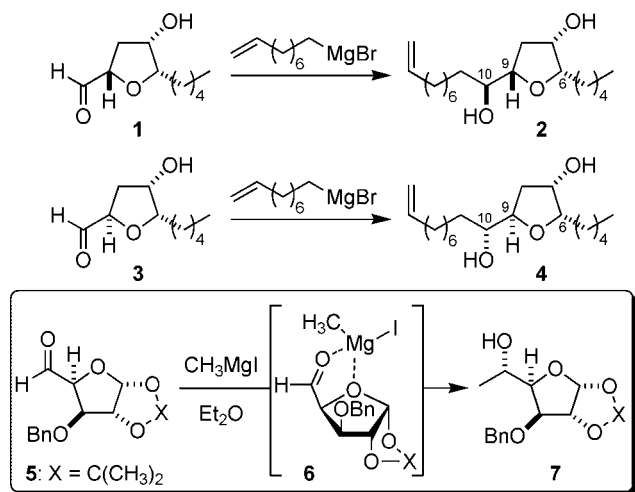
(3) (a) Kim, K. S.; Ahn, Y. H.; Park, S. B.; Cho, I. H.; Joo, Y. H.; Youn, B. H. *J. Carbohydr. Chem.* **1991**, *10*, 911. (b) Amouroux, R.; Ejjiyar, S.; Chastrette, M. *Tetrahedron Lett.* **1986**, *27*, 1035. (c) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809. (d) Yoshimura, J.; Ohgo, Y.; Ajisaka, K.; Konda, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 916. (e) Horton, D.; Hughes, J.; Thomson, J. J. *Org. Chem.* **1968**, *33*, 728.

(4) (a) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046.

(5) (a) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731. (b) Wang, Z.-M.; Shen, M. *J. Org. Chem.* **1998**, *63*, 1414. (c) Chikashita, H.; Nakamura, Y.; Uemura, H.; Itoh, K. *Chem. Lett.* **1993**, 477. (d) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641. (e) Hatakeyama, S.; Sakurai, K.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 1333.

(6) Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800.

(7) For the optimization of diastereoselectivity through screening of organometallic reagents and additives see refs 1b, 2c, 2d, and 2e.

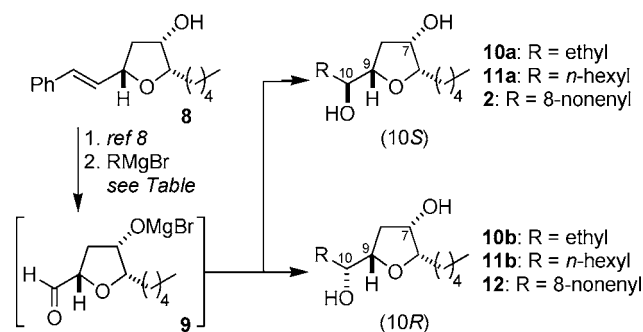


**Figure 1.** Marine oxylipids **2** and **4** and the chelation model **6** for diastereoselective Grignard additions to tetrahydrofurfural **5**.

common intermediate (DOI 10.1021/ol802711s). As an extension of this work, we demonstrated these methods in short syntheses of the diastereomeric marine natural products **2** and **4**. The final step in both syntheses involved the addition of 8-nonenyl magnesium bromide to an unprotected 3-hydroxytetrahydrofurfural (e.g., **1** and **3**). During the optimization of these syntheses we uncovered a remarkable, inverse-temperature-dependent diastereoselective Grignard addition reaction. The discovery of this reaction as well as mechanistic insight based on Kohn–Sham hybrid B3LYP calculations are described below.

While the chelation model (e.g., **6**) predicts that addition of 8-nonenyl magnesium bromide to **1** would provide the desired 10*S* diastereomer **2**, we were aware that a similar reaction carried out on a protected analogue (i.e., **1**, OH = OBn) in THF affords a 4:1 mixture of diastereomeric alcohols favoring the undesired *R* configuration at C10.<sup>4</sup> Bearing this in mind, we set out to explore this process on the readily available and unprotected tetrahydrofurfural **1**<sup>8</sup> and focused our initial efforts on addition reactions involving EtMgBr.<sup>9</sup> As summarized in Table 1, we observed a pronounced relationship between solvent and diastereoselectivity for this reaction. For example, while the addition was nonselective in THF, the production of one diastereomer was favored in noncoordinating solvents (entries 1–3).<sup>10</sup> Each of the reactions described in entries 1–3 were sluggish at –78 °C and were consequently allowed to gradually warm to room temperature to ensure complete consumption of the aldehyde **1**. The diastereomeric alcohols **10a** and **10b** proved to be separable by chromatography, and the major product from the reaction carried out in CH<sub>2</sub>Cl<sub>2</sub> (entry 3) was converted to

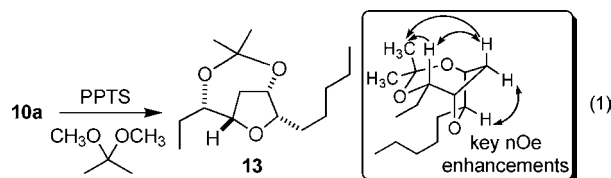
**Table 1.** Addition of Grignard Reagents to Aldehyde **1**



entry	R <sup>9,17</sup>	solvent	temp (°C)	products (ratio) <sup>a</sup>	% yield <sup>b</sup>
1	ethyl	THF	–78 to 20	<b>10a:10b</b> (1:1)	57
2	ethyl	PhCH <sub>3</sub>	–78 to 20	<b>10a:10b</b> (2:1)	62
3	ethyl	CH <sub>2</sub> Cl <sub>2</sub>	–78 to 20	<b>10a:10b</b> (3.3:1)	67
4	ethyl	CH <sub>2</sub> Cl <sub>2</sub>	–40	<b>10a:10b</b> (1.3:1)	nd <sup>c</sup>
5	ethyl	CH <sub>2</sub> Cl <sub>2</sub>	–35	<b>10a:10b</b> (2:1)	42 <sup>d</sup>
6	ethyl	CH <sub>2</sub> Cl <sub>2</sub>	20	<b>10a:10b</b> (5:1)	52
7	ethyl	DCE	20	<b>10a:10b</b> (5:1)	52
8	ethyl	DCE	20 <sup>e</sup>	<b>10a:10b</b> (1:1)	nd <sup>f</sup>
9	ethyl	DCE	20 <sup>g</sup>	<b>10a:10b</b> (5:1)	nd <sup>f</sup>
10	ethyl	DCE	40	<b>10a:10b</b> (5.1:1)	nd <sup>f</sup>
11	ethyl	DCE	60	<b>10a:10b</b> (5.8:1)	nd <sup>f</sup>
12	ethyl	DCE	83	<b>10a:10b</b> (8:1)	70
13	<i>n</i> -hexyl	DCE	40	<b>11a:11b</b> (3.6:1)	nd <sup>f</sup>
14	<i>n</i> -hexyl	DCE	83	<b>11a:11b</b> (8:1)	73
15	8-nonenyl	DCE	83	<b>2:12</b> (5.5:1)	65

<sup>a</sup> Ratio determined from analysis of <sup>1</sup>H NMR spectra of crude reaction mixtures. <sup>b</sup> Combined isolated yield of both diastereomers over two steps from **8**. <sup>c</sup> After 20 h the reaction had reached 60% conversion. <sup>d</sup> After 17 h the reaction had reached 55% conversion. <sup>e</sup> 10 equiv of 15-crown-5 was added. <sup>f</sup> Yield not determined. <sup>g</sup> 10 equiv of MgBr<sub>2</sub> was added.

the corresponding acetonide **13** (eq 1). As indicated (see inset), a series of 1D NOESY experiments carried out on this conformationally rigid acetonide permitted unambiguous assignment of the relative configuration of the newly formed carbinol chirality center as 10*S*.<sup>11</sup> Consequently, the major diastereomer produced from the addition of EtMgBr to the aldehyde **1** in CH<sub>2</sub>Cl<sub>2</sub> (entry 3) was confidently assigned as the 10*S* diastereomer **10a**.



Surprisingly, repetition of the reaction described in entry 3 (Table 1) at –40 or –35 °C led to an erosion in diastereoselectivity, while at room temperature in either CH<sub>2</sub>Cl<sub>2</sub> or dichloroethane (DCE) the stereoselectivity was restored (entries 4–7). Addition of 15-crown-5 caused a significant decrease in the diastereomeric ratio, but MgBr<sub>2</sub> had little effect (entries 8

(8) The tetrahydrofurfural **1** was prepared by ozonolysis of **8** followed by reductive workup with polymer-supported triphenylphosphine (PS-PPh<sub>3</sub>). As the tetrahydrofurfural **1** decomposes on silica gel, following the removal of the PS-PPh<sub>3</sub> by filtration and concentration, the resulting aldehyde was used without further purification. A full account of the synthesis of compound **1** is described in the preceding manuscript.

(9) Ethyl magnesium bromide was purchased from Aldrich as a 3.0 M solution in Et<sub>2</sub>O.

(10) For examples of Grignard reactions in CH<sub>2</sub>Cl<sub>2</sub>, see: (a) Brown, D. S.; Charreau, P.; Ley, S. V. *Synlett* **1990**, 749. (b) Franck, X.; Hocquemiller, R.; Figadère, B. *Chem. Commun.* **2002**, 160.

and 9),<sup>12</sup> highlighting the importance of chelation in directing the Grignard addition to the *si* face of the aldehyde. Remarkably, further increases to the reaction temperature resulted in *increased selectivity for the desired 10S diastereomer 10a* (entries 10–12). In fact, in DCE at reflux (83 °C), **10a** was produced<sup>13,14</sup> as the major component of an 8:1 mixture of diastereomers.<sup>15,16</sup> A similar trend was observed using *n*-hexyl magnesium bromide<sup>17</sup> in DCE (entries 13 and 14). Employing these optimized conditions, 8-nonenyl magnesium bromide was added to **1** (entry 15) in DCE at reflux to provide the natural product **2** as the major component of a 5.5:1 mixture of diastereomers.

On the basis of the results summarized in Table 1, it is clear that the formation of the 10*S* diastereomers **10a**, **11a**, and **2** are favored in polar, noncoordinating solvents, consistent with a chelation-controlled addition.<sup>18,19</sup> Unfortunately, a series of <sup>1</sup>H NMR spectra recorded on a mixture of EtMgBr and **1** in CD<sub>2</sub>Cl<sub>2</sub> at various temperatures (–50 °C to rt) failed to offer any additional insight into this unusual process.<sup>20,21</sup> However, it is worth considering the nature of the Grignard reagent and the structure and solvation of the intermediate magnesium alkoxide **9** generated by deprotonation of the alcohol function in the tetrahydrofurfural **1**. More specifically, as the reaction temperature is decreased, a shift in the Schlenk equilibrium<sup>22</sup> that favors a more reactive<sup>23</sup> Et<sub>2</sub>Mg species may account for the poor diastereocontrol.<sup>24</sup> Alternatively, temperature-dependent changes in the solvation and/or aggregation of the magnesium alkoxide **9** may account for the associated changes in diastereoselectivity. Interestingly, the stereoselective addition of EtMgBr or *n*-HexMgBr to the C9-epimeric *trans*-aldehyde **3** (Figure 1) showed little dependence on solvent or temperature,<sup>25</sup> suggesting the *cis*-relationship between the aldehyde and hydroxyl group in **1** is key to the temperature-dependent diastereoselectivity.

(11) In the <sup>1</sup>H NMR spectra of **10a** and **10b** (CDCl<sub>3</sub>) the protons at C10 resonate at δ 3.40 and δ 3.76 ppm, respectively. These chemical shift values are consistent with those reported for *threo* and *erythro* diastereomers of α-substituted 2-tetrahydrofuranmethanols. For the use of this mnemonic in the configurational assignment of α-substituted 2-tetrahydrofuranmethanols, see: (a) Harmange, J.-C.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1992**, 33, 5749. (b) Gale, J. B.; Yu, J.-G.; Hu, X. E.; Khare, A.; Ho, D. K.; Cassidy, J. M. *Tetrahedron Lett.* **1993**, 34, 5847.

(12) When the reactions described by entries 9–11 were repeated with the addition of MgBr<sub>2</sub> (10 equiv), a considerable number of byproducts were formed and the observed ratio of **10a:10b** differed only slightly from those reported in entries 9–11.

(13) For selected crude <sup>1</sup>H NMR spectra, see Supporting Information.

(14) For temperature and solvent effects in the diastereoselective addition of nucleophiles to carbonyl compounds, see: (a) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Eur. J. Org. Chem.* **2003**, 2268. (b) Cainelli, G.; Giacomini, D.; Galletti, P.; Orioli, P. *Eur. J. Org. Chem.* **2001**, 4509. (c) Cainelli, G.; Giacomini, D.; Galletti, P. *Chem. Commun.* **1999**, 567.

(15) When a solution of **10a** and **10b** (8:1 mixture) in DCE was treated with EtMgBr and heated at reflux for 1 h, there was no change in the ratio of these substances. This result indicates that the diastereoselectivities summarized in Table 1 are not the result of a selective decomposition of **10b** under the reaction conditions.

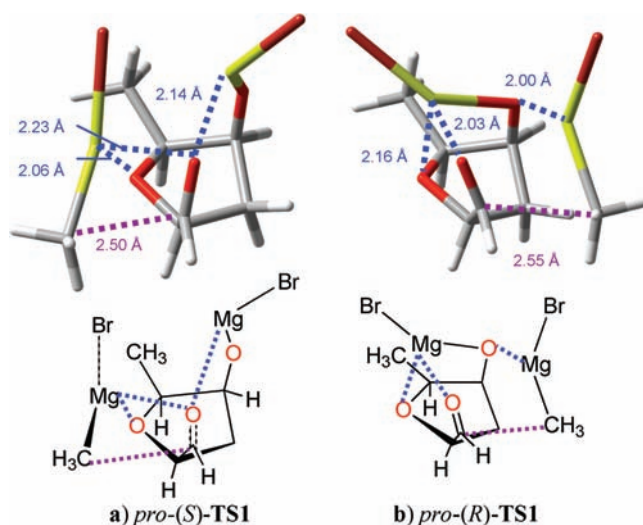
(16) For examples of inverse temperature dependence in Grignard additions to aldehydes see ref 3a and Markó, I. E.; Chesney, A.; Hollinshead, D. M. *Tetrahedron: Asymmetry* **1994**, 5, 569.

(17) *n*-Hexyl magnesium bromide was purchased from Aldrich as a 2.0 M solution in Et<sub>2</sub>O.

(18) For a detailed description of chelation controlled Grignard additions, see: Eliel, E. L.; Frye, S. V.; Hortelano, E. R.; Chen, X.; Bai, X. *Pure Appl. Chem.* **1991**, 63, 1591.

(19) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, 99, 1191.

Considering the diversity of factors<sup>20,21</sup> that may contribute to the results summarized in Table 1 and our incomplete understanding of the addition of organometallic reagents to oxygenated tetrahydrofurfurals (*vide supra*), we were intrigued as to whether or not DFT calculations would provide insight into the role played by the 3-hydroxy group in these reactions.<sup>25</sup> Accordingly, the low energy first-order saddle points *pro*-(*S*)-**TS1** (ΔΔ*G* = 0 kcal/mol) and *pro*-(*R*)-**TS1** (ΔΔ*G* = 1.41 kcal/mol) that correspond to stereofacial additions of CH<sub>3</sub>MgBr to the magnesium alkoxide derived from a *cis*-3-hydroxytetrahydrofurfural were computed at the B3LYP/6-21G(d) level using the Gaussian 03 suite of programs (Figure 2).<sup>26</sup> As indicated in Figure 2, an intricate



**Figure 2.** Lowest energy transition structures corresponding to (a) *pro*-(*S*) and (b) *pro*-(*R*) additions of CH<sub>3</sub>MgBr to the magnesium alkoxide of a *cis*-3-hydroxytetrahydrofurfural.

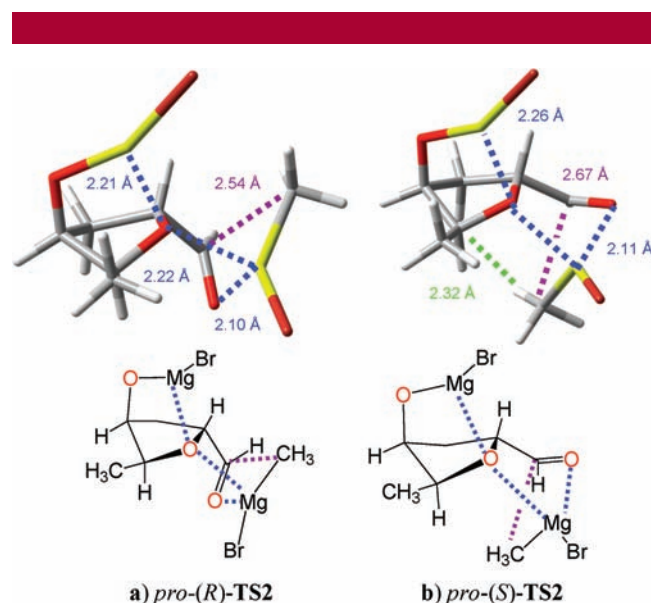
network of chelation modes was found in both transition structures that involved a γ-chelate between the magnesium alkoxide and the aldehyde oxygen measured at 2.14 Å in *pro*-(*S*)-**TS1** and 2.03 Å in *pro*-(*R*)-**TS1**. This chelation mode effectively locks the aldehyde and tetrahydrofuran oxygens

(20) For discussions regarding temperature-dependent effects in stereoselective synthesis, see: (a) Sivaguru, J.; Solomon, M. R.; Poon, T.; Jockusch, S.; Bosio, S.; Adam, W.; Turro, N. J. *Acc. Chem. Res.* **2008**, 41, 387. (b) Pracejus, H. *Liebigs Ann. Chem.* **1960**, 634, 9. (c) Hamuda, T.; Fukuda, T.; Imanishi, F. H.; Katsuki, T. *Tetrahedron* **1996**, 52, 515. (d) Meyer-Stork, M. A.; Haag, D.; Scharf, H.-D. *J. Chem. Soc., Perkin Trans. 2* **1997**, 593. (e) Muzart, J.; Hénil, F.; Aboulhoda, S. *J. Tetrahedron: Asymmetry* **1997**, 8, 381. (f) Enders, D.; Gielen, H.; Breuer, K. *Tetrahedron: Asymmetry* **1997**, 8, 3571. (g) Li, B.; Wang, Y.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2007**, 72, 990. (h) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Eur. J. Org. Chem.* **2003**, 2268. (i) Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 523. (j) Cainelli, G.; Giacomini, D.; Galletti, P.; Orioli, P. *Eur. J. Org. Chem.* **2001**, 4509. (k) Lombardo, M.; Fabbri, S.; Trombini, C. *J. Org. Chem.* **2001**, 66, 1264. (l) Inoue, Y.; Ikeda, H.; Kaneda, M.; Sumimura, T.; Everitt, S. R. L.; Wada, T. *J. Am. Chem. Soc.* **2000**, 122, 406. (m) Göbel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 1329. (n) Hei, X.-M.; Song, Q.-H.; Li, X.-B.; Tang, W.-J.; Wang, H.-B.; Guo, Q.-X. *J. Org. Chem.* **2005**, 70, 2522. (o) Adam, W.; Stegmann, V. R. *J. Am. Chem. Soc.* **2002**, 124, 3600. (p) Abe, M.; Kawakami, T.; Ohata, S.; Nozaki, K.; Nojima, M. *J. Am. Chem. Soc.* **2004**, 126, 2838.



in a *synclinal* orientation in *pro*-(*S*)-**TS1** ( $-54.0^\circ$ ) and a *synperiplanar* orientation in *pro*-(*R*)-**TS1** ( $-15.1^\circ$ ). Beyond the similarity of this  $\gamma$ -chelate, however, the two first-order saddle points were decidedly different. For example, a cyclic chelation mode consistent with **6**<sup>6</sup> (Figure 1) was found in *pro*-(*S*)-**TS1**, whereas *pro*-(*R*)-**TS1** contained a hybrid-type  $\alpha/\gamma$ -chelate involving the aldehyde and tetrahydrofuran oxygens and the magnesium alkoxide, as well as an interaction between the magnesium alkoxide oxygen and the second equivalent of  $\text{CH}_3\text{MgBr}$ . Interestingly, the calculated preference for *pro*-(*S*)-**TS1** is related to a favorable entropy for this transition structure ( $\Delta\Delta S^\ddagger = 1.54$  kcal/mol), as the  $\Delta\Delta H$  term ( $-0.13$  kcal/mol) actually favors *pro*-(*R*)-**TS1**. Importantly, the calculated energetics correctly predict preferential formation of the 10*S* diastereomer (theoretical dr = 7.3:1, experimental dr = 8:1) and highlight the key role played by the magnesium alkoxide function in the low energy transition structure *pro*-(*S*)-**TS1**.

The low energy transition structures *pro*-(*R*)-**TS2** ( $\Delta\Delta G = 0$  kcal/mol) and *pro*-(*S*)-**TS2** ( $\Delta\Delta G = 0.96$  kcal/mol) (Figure 3), corresponding to  $\text{CH}_3\text{MgBr}$  addition to a *trans*-3-hydro-



**Figure 3.** Lowest energy transition structures corresponding to (a) *pro*-(*R*) and (b) *pro*-(*S*) additions of  $\text{CH}_3\text{MgBr}$  to the magnesium alkoxide of a *trans*-3-hydroxytetrahydrofurfural.

xytetrahydrofurfural, were also calculated. As a result of the positioning of the magnesium alkoxide and aldehyde functions on opposite faces of the tetrahydrofuran ring, these transition structures differed significantly from those discussed above (Figure 2). Notably, both *pro*-(*R*)-**TS2** and *pro*-(*S*)-**TS2** share nearly identical geometries, and both first-order saddle points

(21) For discussions regarding inverse-temperature-dependent effects and the “isoinversion principle”, see: (a) Heller, D.; Buschmann, H.; Neumann, H. *J. Chem. Soc., Perkin Trans 2* **1999**, 175. (b) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Plath, M. W.; Runsink, J. *J. Am. Chem. Soc.* **1989**, *111*, 5367. (c) For a review, see: Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477. (d) Hale, K. J.; Ridd, J. H. *J. Chem. Soc., Chem. Commun.* **1995**, 357.

(22) Paris, G. E.; Ashby, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 1206.

possessed a chelate between the magnesium alkoxide and tetrahydrofuran oxygen and a cyclic five-membered ring coordination motif consistent with that proposed by Wolfrom and Hanessian (Figure 1).<sup>6</sup> Indeed, aside from the obvious facial selectivity of the Grignard reagent, the only major difference between these structures was the presence of a single van der Waals contact (2.32 Å) in *pro*-(*S*)-**TS2** associated with approach of  $\text{CH}_3\text{MgBr}$  from underneath the tetrahydrofuran ring. Again, these calculations correctly predict the preferential formation of the 10*R* diastereomer (theoretical dr = 3.9:1, experimental dr = 2.3:1), which is consistent with the sense and relative magnitude of diastereoselectivity observed in the addition of Grignard reagents to the *trans*-tetrahydrofurfural **3**.<sup>25</sup>

In summary, a remarkable example of inverse-temperature-dependent diastereoselectivity was uncovered while investigating the addition of Grignard reagents to a 3-hydroxytetrahydrofurfural. Notably, the optimized conditions for this process involve the addition of Grignard reagent to a solution of the tetrahydrofurfural **1** in DCE at reflux. While a temperature-dependent shift in the Schlenk equilibrium or change in solvation of the intermediate magnesium alkoxide may play an important role in this unusual process, it is clear that the *cis*-relationship between the alcohol and aldehyde functions on the tetrahydrofuran ring is paramount. Furthermore, on the basis of DFT calculations, a  $\gamma$ -chelate between the magnesium alkoxide and the aldehyde oxygen and an entropic preference for the *pro*-(*S*)-transition structure serve as the key factors responsible for the observed diastereoselectivity. Importantly, these results highlight the effect of additional coordination sites in the diastereoselective addition of organometallic reagents to oxygenated tetrahydrofurals and pave the way for a concise, protecting-group-free synthesis of the marine oxylipid **2**. Efforts to improve our understanding of the relationship between temperature and diastereoselectivity in these reactions using computational methods are currently underway in one of our laboratories, and the results from these studies will be reported in due course.

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**Supporting Information Available:** Detailed experimental procedures and characterization data for each new compound. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(23) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545.

(24) Addition of  $\text{Bu}_2\text{Mg}$  (1 M solution in heptane) to a solution of **1** in DCE at room temperature provided (in low yield) a 1.3:1 mixture of diastereomeric alcohols favoring the 10*S* diastereomer, along with a number of byproducts.

(25) The addition of *n*-hexyl magnesium bromide to **3** was investigated in a variety of solvents at room temperature with the following results (ratio of 10*R*:10*S* diastereomers in brackets): THF (1.5:1),  $\text{CH}_2\text{Cl}_2$  (2.1:1),  $\text{Et}_2\text{O}$  (1.8:1). In DCE, the ratio of 10*R*:10*S* diastereomers (2.3:1) was unchanged when the addition was carried out at temperatures ranging from room temperature to 83 °C.

(26) See Supporting Information for theoretical references as well as a comprehensive explanation of methods used to locate the transition states.