Diastereofacial Selectivity of *O*-Protected α-Hydroxy Aldehydes: Temperature and Solvent Effect

Gianfranco Cainelli,*[a] Daria Giacomini,*[a] Paola Galletti,[a] Paolo Orioli,[a] and Francesca Paradisi[a]

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Temperature dependence measurements allow the evaluation of stereoselectivity in terms of differential enthalpy and entropy of activation. An analysis of diastereoselectivity in the addition reaction of *n*BuLi to *O*-protected α-hydroxy aldehydes revealed the great importance of the entropic contribution in directing the facial diastereoselectivity. In many cases, the resulting Eyring plots show an inversion temperature (T_{inv}). The existence of the T_{inv} as well as the enthalpic and entropic dominance of one diastereoisomer greatly depend on the reaction solvent.

Introduction

The stereochemical control of a process has become the primary focus of activity for many researchers in both the academic and the industrial world. Many efforts are devoted to achieving high levels of stereoselectivity in order to obtain enantiomerically and diastereomerically pure intermediates.[1] In these studies, it is important to take into account the fact that selectivity is a kinetic phenomenon. When a kinetically controlled reaction generates two stereoisomers by two parallel reaction pathways, and with overall rate constants k and k', the stereoselectivity is expressed as the ratio (Equation 1):

$$S = k/k' \quad (1)$$

Temperature and solvent directly influence rate constants, and so they are easily accessible parameters for modifying stereoselectivity.[2]

The effect of temperature on S can be analyzed according to the Eyring equation[3] which shows a linear relationship between the logarithmic value of the stereoselectivity and the inverse temperature $1/T$.

$$\ln S = ln(k/k') = -\Delta\Delta G^{\ddagger}/RT = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R \quad (2)$$

Equation 2 shows that both the differential activation enthalpy ($\Delta\Delta H^{\ddagger}$) and the differential activation entropy ($\Delta\Delta S^{\ddagger}$) contribute to the stereoselectivity. It is important to underline that, in stereoselective processes, the $\Delta\Delta H^{\ddagger}$ value is generally quite small; thus, the temperature values in the accessible experimental range render the $\Delta\Delta S^{\ddagger}$ term a determining contribution to S, even at low T. The recognition of the importance of $\Delta\Delta S^{\ddagger}$ on diastereo- and enantioselectivity reveals a new aspect in the control and in the design of asymmetric reactions.

[a] Dipartimento di Chimica "G. Ciamician",
University of Bologna
Via Selmi 2, 40126, Bologna, Italy
Fax: (internat.) + 39-051/209-9456
E-mail: cainelli@ciam.unibo.it, giacomin@ciam.unibo.it

For many different reactions there exist experimental data showing a non-linear relationship between S and $1/T$. In these cases, the corresponding Eyring plots generally consist of two straight lines, intersecting at a point defining a temperature called the inversion temperature (T_{inv}).[4] This break point leads to two sets of activation parameters, one for $T < T_{inv}$ and the other for $T > T_{inv}$.

In previous papers we have demonstrated that the presence of a T_{inv} accounts for a particular effect of the reaction solvent on the stereoselectivity.[5] In the addition reaction of *n*BuLi to 2-phenylpropanal in a series of linear hydrocarbons, we reported that the experimental values of T_{inv} are directly linked to the length of the carbon atom chain of the reaction solvent.[6] Furthermore, we found a good linear correlation between T_{inv} and the melting points of the solvents used. Very recently, in addition reactions of organolithium and Grignard reagents to (2*S*)-*O*-*tert*-butyldimethylsilyllactal and (2*S*)-*O*-*tert*-butyldimethylsilylmandelic aldehyde, we observed that T_{inv} is little dependent on the nucleophiles, but mainly on the aldehyde-solvent couple.[7] Moreover, variable temperature ^{13}C NMR experiments on those aldehydes in the same reaction solvent showed a break in the linear dependence of the C=O chemical shift vs. temperature. We named this break temperature T_{NMR}. T_{NMR} proved quite similar to the T_{inv} obtained in diastereoselective reactions of the same aldehyde in the same solvent. These results prove that the solvation brings about the presence and tunes the value of the inversion temperature. Therefore, we formulated a new interpretation of the inversion temperature. *An Eyring plot showing a T_{inv} derives from a superposition of two linear trends produced by two different solvation clusters. These two solute-solvent clusters behave like two different supermolecules with different thermodynamic properties, and therefore different stereoselectivities. At a temperature lower than T_{inv}, one cluster is present in solution: at a temperature higher than T_{inv}, the other cluster is present. The T_{inv} represents the interconversion temperature between these two supermolecules* (Figure 1). This interpretation does not imply any change at the T_{inv} either in the

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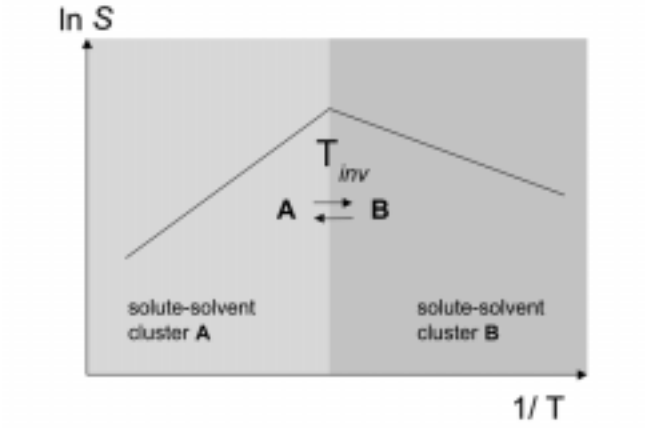
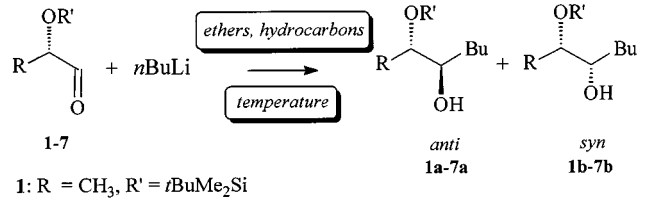


Figure 1. The T_{inv} in an Eyring plot as the interconversion temperature between two supramolecules A and B

rate-determining step or in the reaction mechanism, as stated in earlier interpretations.[8]

Our investigation into facial diastereoselectivity of α-hydroxy aldehydes[9] in reactions with nucleophiles continues, and in the present paper we focus on the influence of the reaction solvent in a series of *O*-silyloxy- and α-alkoxy aldehydes, differing in the side chain, and in the *O*-protecting group (Scheme 1).



1-7 *anti* **1a-7a** *syn* **1b-7b**

1: R = CH_3, R' = *t*$BuMe_2Si$
2: R = CH_3, R' = *i*Pr_3Si
3: R = CH_3, R' = *t*Bu
4: R = Ph, R' = *t*$BuMe_2Si$
5: R = C_2H_5, R' = *t*$BuMe_2Si$
6: R = C_6H_{13}, R' = *t*$BuMe_2Si$
7: R = $C_{11}H_{23}$, R' = *t*$BuMe_2Si$

Scheme 1

Results and Discussion

Reaction of *n*BuLi with α-*O*-protected aldehydes **1**−**7** proceeded smoothly to give *anti* **1a**−**7a** and *syn* **1b**−**7b** 1,2-monoprotected diols. In all experiments the addition reaction was performed by introducing a stoichiometric amount of *n*BuLi (2.5 M *n*-hexane solution) into solutions of aldehydes in different dry solvents at constant temperature (Scheme 1). *T* was varied over a range of about 130 °C. The diastereomeric *anti*/*syn* ratio was determined in each experiment by GC analysis of the crude reaction mixture. Data were analyzed according to the modified Eyring Equation 3 where *anti*/*syn* is the ratio of the corresponding chromatographic areas. The data have been treated by the least-squares method in order to obtain linear relationships.

$$\ln S = \ln(anti/syn) = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R \quad (3)$$

Diastereofacial Selectivity in the Addition of *n*BuLi to *O*-Protected-Lactal and Homologues

Plots in Figure 2 refer to *n*BuLi addition to *O*-TBDMS-lactal **1** in THF, *t*BuOMe, *n*-hexane, *n*-decane, and propane. In Table 1. At low temperature, ethers exhibited the best diastereoselectivity in favor of the *anti* isomer. Hydrocarbons gave lower values.

It is interesting to note that in *n*-hexane the best stereoselectivity was obtained at high temperature. This result is sharply in contrast with the common idea that a better stereoselectivity could be obtained by lowering the reaction temperature. In the case of (2*S*)-lactal **1**, the *anti*/*syn* ratio declines with the shortening of the solvent alkyl chain from *n*-hexane to propane. While a continuous linear correlation was observed in *t*BuOMe, propane, and *n*-decane, inversion temperatures were found in THF and *n*-hexane (T_{inv} = −12.7 °C and T_{inv} = −83 °C, respectively). According to our interpretation, in these solvents two solvation clusters are in equilibrium at the T_{inv}.

By application of Equation 3, measurements of temperature dependence give insight into the interplay of enthalpy and entropy in determining the stereoselectivity.[10] The activation differential enthalpy ($\Delta\Delta H^{\ddagger}$) gains in importance in ethers, with their high and similar slopes (Table 2). In con-

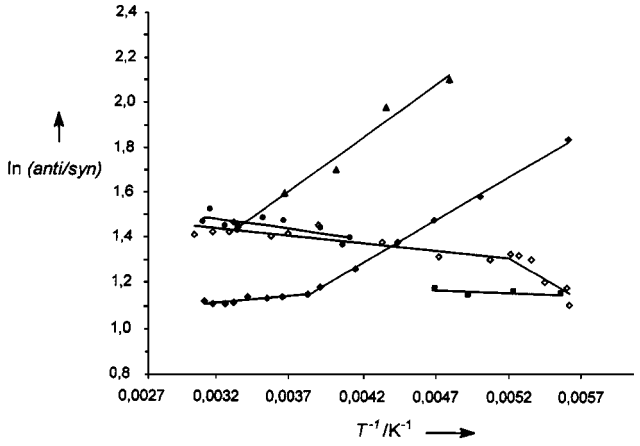


Figure 2. Eyring plots of *n*BuLi addition to **1** in THF (◆), *t*BuOMe (▲), propane (■), *n*-hexane (◇), and *n*-decane (●)

Table 1. *anti*/*syn* Ratio in *n*BuLi addition to **1** at selected temperatures in ethers and hydrocarbons

T/ °C	Solvent	*anti*/*syn*
42	THF	75.2:24.8
43	*n*-hexane	80.6:19.4
44.5	*n*-decane	82.1:17.9
29.5	THF	75.3:24.7
27	*t*BuOMe	81.1:18.9
30	*n*-hexane	80.6:19.4
27	*n*-decane	80.7:19.3
−59	THF	81.5:18.5
−63	*t*BuOMe	89.5:10.5
−60	propane	76.5:23.5
−61	*n*-hexane	78.9:21.1
−94	THF	86.3:13.7
−93	propane	76.1:23.9
−94	*n*-hexane	76.6:23.4

Table 2. Differential activation parameters and inversion temperatures for *n*BuLi addition to aldehydes **1**–**7**

Entry	Aldehyde	Solvent	T_{inv} [°C]	$T>T_{inv}$ $\Delta\Delta H^{\ddagger}$ [kcal/mol]	$\Delta\Delta S^{\ddagger}$ [cal/mol K]	$T<T_{inv}$ $\Delta\Delta H^{\ddagger}$ [kcal/mol]	$\Delta\Delta S^{\ddagger}$ [cal/mol K]
1	1	THF	−12.7	−0.11±0.03	1.86±0.1	−0.77±0.01	−0.66±0.05
2	1	*t*BuOMe	−	−0.9±0.1	−0.3±0.4		
3	1	propane	−	0.03±0.04	2.5±0.2		
4	1	*n*-hexane	−83.0	0.12±0.02	3.2±0.1	1.1±0.2	8.4±1.1
5	1	*n*-decane	−	0.17±0.06	3.5±0.2		
6	2	THF	−44.8	−0.58±0.05	−0.4±0.2	−1.20±0.07	− 3.0±0.3
7	3	THF	−19.8	−0.20±0.07	1.8±0.3	0.6±0.1	5.0±0.4
8	4	THF	−63.1	0.61±0.05	2.7±0.2	1.2±0.1	5.5±0.7
9	4	*t*BuOMe	−55.9	0.21±0.03	1.4±0.1	−0.69±0.03	−2.7±0.1
10	4	propane	−76.9	−0.18±0.06	−1.3±0.3	−1.41±0.01	−7.5±0.8
11	4	*n*-butane	−62.7	−0.08±0.06	−0.7±0.2	−0.56±0.06	−3.0±0.4
12	4	*n*-pentane	−40.2	0.51±0.05	1.8±0.2	−0.45±0.04	−2.3±0.2
13	4	*n*-hexane	−15.0[a]	0.90±0.03	3.4±0.1	0.28±0.05	1.0±0.2
14			−58.4[b]	0.28±0.05	1.0±0.2	−0.7±0.1	−3.6±0.4
15	4	*n*-heptane	−8.9[a]	1.06±0.06	3.9±0.2	0.21±0.02	0.7±0.1
16			−60.8[b]	0.21±0.02	0.7±0.1	−0.70±0.02	−3.6±0.1
17	4	*n*-octane	−30.4	1.1±0.1	4.2±0.5	−0.34±0.2	−1.8±0.7
18	4	*n*-nonane	5.5	1.5±0.1	5.1±0.3	0.38±0.07	1.3±0.3
19	4	*n*-decane	−0.2	0.8±0.1	2.8±0.3	−0.06±0.07	−0.3±0.3
20	4	*n*-undecane	−	0.76±0.04	2.8±0.1		
21	4	*n*-dodecane	26.7	1.6±0.2	5.5±0.7	0.27±0.15	1.1±0.5
22	4	cyclohexane	25.4	0.9±0.1	3.2±0.4	2.5±0.2	8.6±0.9
23	5	THF	−30.7	0.4±0.1	3.0±0.4	−0.76±0.06	−1.7±0.3
24	5	*n*-hexane	−59.3	−0.49±0.04	0.2±0.1	−0.16±0.02	1.8±0.1
25	6	THF	−45.8	−0.19±0.04	0.4±0.2	−0.75±0.04	−2.1±0.2
26	6	*n*-hexane	−	−0.39±0.02	0.46±0.06		
27	7	THF	−44.1	−0.4±0.1	−0.4±0.3	−0.91±0.03	−2.7±0.2
28	7	*n*-hexane	−	−0.49±0.03	0.0±0.1		

[a] T_{inv}1. − [b] T_{inv}2.

trast, hydrocarbons gave more flattened curves, because of a small $\Delta\Delta H^{\ddagger}$ contribution. In this case, entropy differences ($\Delta\Delta S^{\ddagger}$) mainly act in determining the diastereofacial selectivity. Under these conditions, any prediction of stereoselectivity based on classical models,[11] such as Cram's chelated model or Felkin-Ahn's, based only on enthalpic differences, fails because of the neglecting of the entropy effect.[12]

Modulation of stereoselectivity by solvent polarity is not surprising. However, our results clearly indicate that stereoselectivity can be modulated by solvents with similar polarities, and even in the presence of dispersive and unspecific interactions as exist in hydrocarbons. We indeed observed for the first time that the length of the solvent alkyl chain influences the diastereomeric ratio.

As mentioned above, classical models for asymmetric induction are mainly based on steric and stereoelectronic features of the α-chiral carbonyl compound. With the aim of determining the influence of steric factors, we varied the natures of substituents R and R′ (Scheme 1), studying a series of aldehyde homologues of (2*S*)-lactal in their reaction with *n*BuLi. Figure 3 gives the corresponding Eyring plots obtained from *anti*/*syn* data at different temperatures in THF and *n*-hexane.

In THF, each aldehyde exhibited two linear regions and a characteristic T_{inv}. Homologous aldehydes **5**, **6**, and **7** differ from *O*-TBDMS-lactal **1** in all temperature ranges, both in THF and in *n*-hexane. However, the difference in diastereofacial selectivity diminished until it vanished between **6** and **7**, while in *n*-hexane all of them exhibited the highest stereoselectivity at low *T*, in contrast with **1**. Interestingly, in *n*-hexane at low temperature all hydroxy aldehydes reached an isoselective point at around −90 °C.

In classical conformational models, the diastereofacial selectivity is ascribed to the steric hindrance of the carbonyl side chain with respect to the incoming nucleophile. This interaction should be more pronounced at low temperature, where less conformational freedom is expected. But we observed exactly the opposite: in *n*-hexane at low *T* the diastereoselectivity of these substrates is less affected by the side chain steric hindrance of the carbonyl compound.

The use of protecting groups as a means of controlling π-facial selectivity has already attracted considerable attention. In the case of α-hydroxy carbonyl compounds, the advantages offered by chelation with a metal cation have been a topic of extensive studies.[13] In particular, many attempts have been addressed at manipulating the stereoselectivity by means of chelating or non-chelating *O*-protection.

For this purpose, we compared *O*-*tert*-butyldimethylsilyl lactal **1** with *O*-triisopropylsilyl and *O*-*tert*-butyl derivatives **2** and **3** in addition reactions with *n*BuLi in THF. Data are reported in Figure 4. All three plots show inversion temperatures (see Table 2). The *O*-protecting group exerted its influence on the diastereomeric ratio mainly at low *T*. Below T_{inv}, compounds **1** and **2** present negative enthalpic contributions (Table 2, entry 1 and 6). It is interesting to note that aldehydes **1** and **3** exhibited an opposite $\Delta\Delta H^{\ddagger}$ at low *T*, so that there is an enthalpic switching from the *anti* to the *syn* isomer on changing the protecting group. If the $\Delta\Delta H^{\ddagger}$ were the sole contribution to the selectivity, the same switching would be expected in the experimental data. On

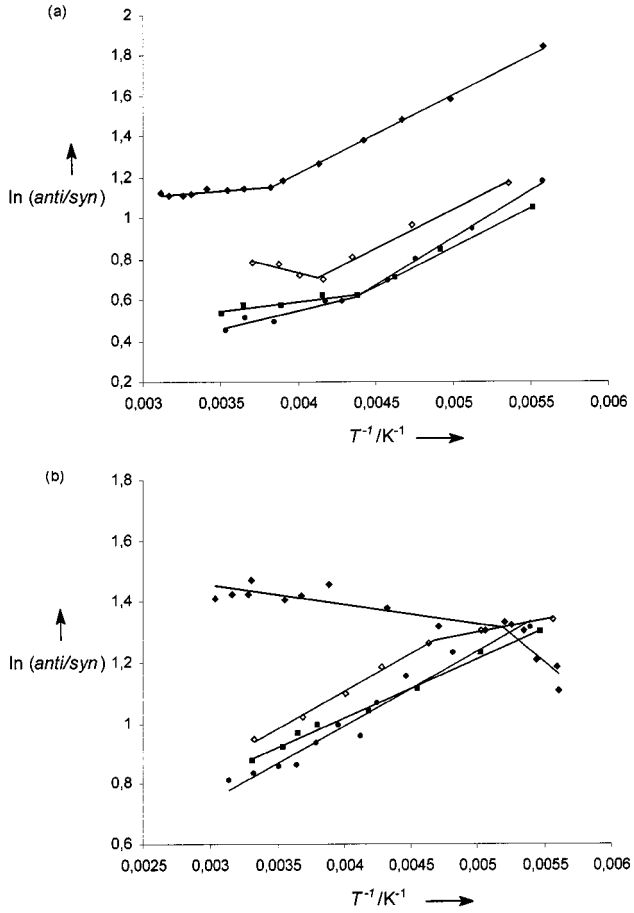


Figure 3. Eyring plots of *n*BuLi addition in THF (a) and n-hexane (b) to aldehydes **1** (◆), **5** (◇), **6** (■), and **7** (●)

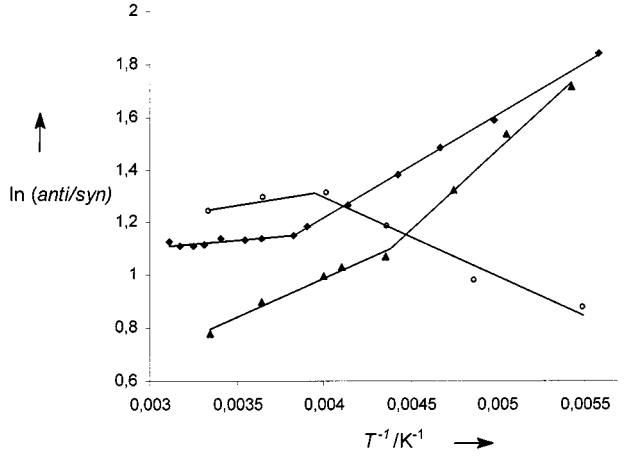


Figure 4. Eyring plots of *n*BuLi addition to **1** (◆), **2** (▲), **3** (○) in THF

the contrary, **3** still gave predominantly the *anti* isomer. This result clearly derives from the $\Delta\Delta S^{\ddagger}$ term, whose relative high value favors the *anti* product (see Table 2, entry 7). Once again, the entropic contribution proves very important and directs the diastereofacial selectivity.

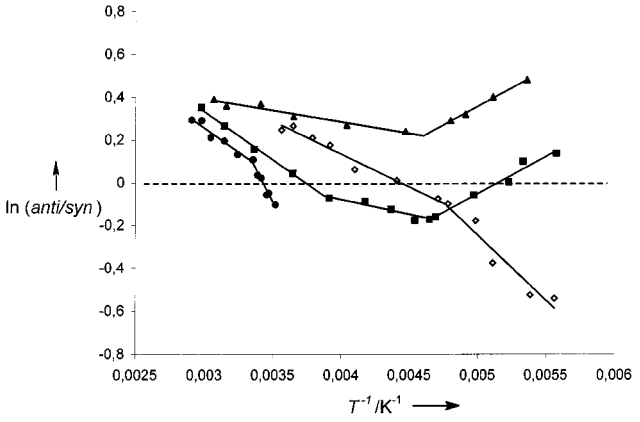


Figure 5. Eyring plots of nBuLi addition to **4** in THF (◇), *t*BuOMe (▲), *n*-hexane (■), and cyclohexane (●)

Diastereofacial Selectivity in the *n*BuLi Addition to Mandelic Aldehyde

The dependence of facial selectivity on reaction solvents becomes more strict in the case of *n*-butyllithium addition to *O*-*tert*-butyldimethylsilyloxy-mandelic aldehyde **4**. Figure 5 gives selectivity data for *n*BuLi addition to **4** in THF, *t*BuOMe, *n*-hexane, and cyclohexane.

Although this aldehyde produced a low diastereomeric ratio, inversion temperatures are easily recognized in all the plots. In THF, *n*-hexane, and cyclohexane, there is an *x* axis crossing. This occurs whenever two diastereoisomers are differentially favored by enthalpy and entropy.[10] In *n*-hexane, this crossing occurred twice: once in the high and once in the low temperature region. Two inversion temperatures exist in this plot, and it is hard to interpret this experimental result as a consequence of a double change in the reaction mechanism, in the style of earlier explanations of the T_{inv}. According to our hypothesis, two inversion temperatures imply the presence of three different solvation clusters.

Very interesting is the different behavior of a cyclic vs. a linear solvent: the former (THF or cyclohexane) shows a convex shape of the plot, the latter (*n*-hexane, *t*BuOMe) a concave shape and this mainly results from a slope change in the low temperature region. The concavity of the plot results from a lowering of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ above and below the T_{inv}. In contrast, the convexity is determined by an increase in $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. At low T in *t*BuOMe the *anti* isomer is preferred, while in THF the *syn* prevails. Therefore, the change in solvent framework from linear to cyclic is able to invert the diastereoselectivity and also to switch in sign the enthalpic and entropic contributions.

Figure 6 gives data obtained with **4** and *n*BuLi in a series of linear hydrocarbons with even and odd numbers of carbon atoms. In this case, the T_{inv} increases with lengthening of the solvent alkyl chain. A particularly good correlation has been found between the experimentally determined T_{inv} and the melting points of hydrocarbons, especially when considering the odd and the even series separately (Fig-

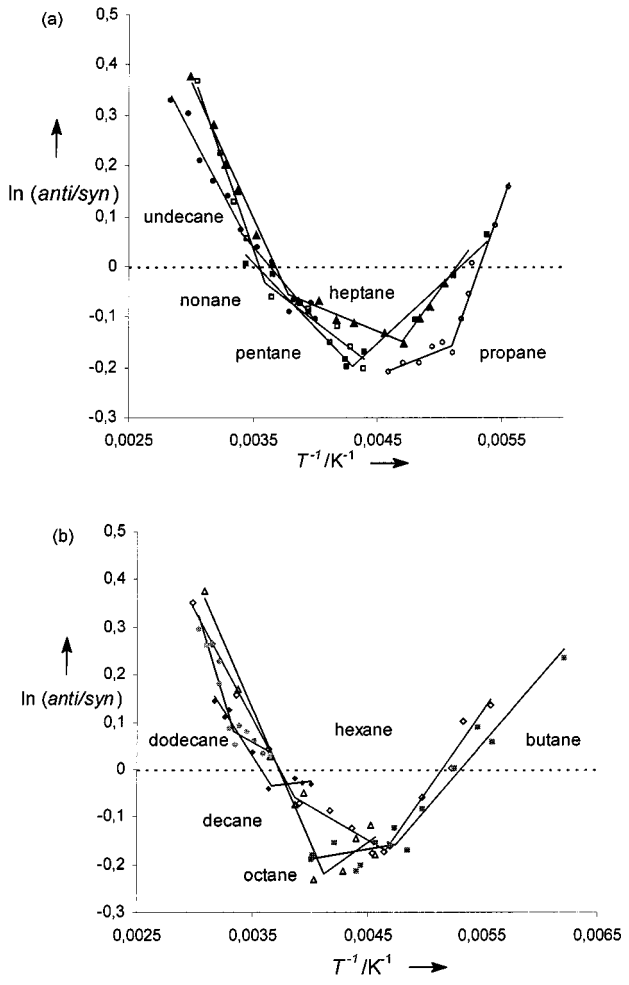


Figure 6. Eyring plots of *n*BuLi addition to **4** in linear odd- (a) and even-numbered (b) hydrocarbons: propane (o), *n*-pentane (■), *n*-heptane (▲), *n*-nonane (□), *n*-undecane (●), *n*-butane (■), *n*-hexane (◇), *n*-octane (△), *n*-decane (◆), and *n*-dodecane (●)

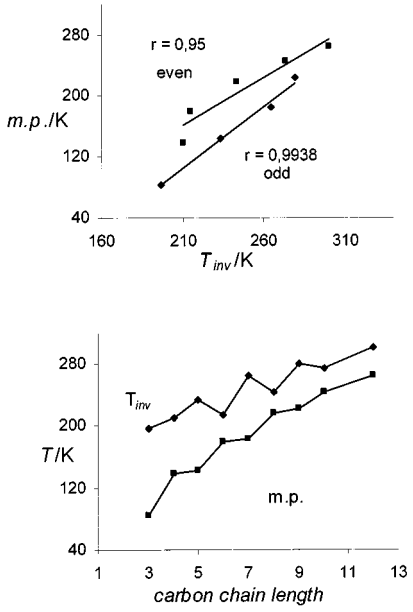


Figure 7. Correlation between hydrocarbon melting points and T_{inv} found for aldehyde **4**

ure 7). It is noteworthy that, the longer the chain length, the smaller are the relative differences in the two linear trends. Plotting the inversion temperatures vs. the number of solvent carbon atoms evidences an alternating character as with the corresponding melting points.

Dependence of melting temperatures on the chain length in *n*-alkanes has been interpreted in terms of molecular level interactions and dynamics.[14] Recently, melting point alternation in even and odd hydrocarbons was interpreted by Boese et al. on the basis of a difference in crystal packing due to the interaction of the terminal methyl groups.[15] The dependence of T_{inv} on the solvent chain length in a manner so similar to the m.p. alternation authoritatively correlates the essential nature of inversion temperatures with a change in the molecular level interactions present in solution between even- and odd-numbered hydrocarbons. This supports our hypothesis that the T_{inv} accounts for a change in the supramolecular structure of solute-solvent clusters, which must have a more ordered structure than generally assumed.

Dependence of T_{inv} on Nucleophiles

The aggregation state of the organometallic species involved as nucleophiles is a particular aspect of the problem, because it is known that the degree of aggregation of *n*BuLi can be solvent and temperature dependent.[16] Recently, we reported that organolithium and Grignard reagents undergoing addition reactions with **1** and **4** in the same solvent produced similar T_{inv}s (Table 3). We have indeed observed that *n*BuLi, *t*BuLi, and *n*BuMgBr, certainly possessing different molecular structures in solution, give differently shaped Eyring plots (Figure 8) but quite close values of the corresponding T_{inv}s. This result clearly accounts for a limitation on the influence of the nature of the organometallic compound on T_{inv}.

Table 3. Inversion temperatures (T_{inv}) in the nucleophilic addition of *n*BuLi, *t*BuLi, and BuMgBr to aldehydes **1** and **4** in *n*-hexane and THF

Aldehyde	Nucleophile	Solvent	T_{inv} [°C]
1	*n*BuLi	THF	−12
1	*t*BuLi	THF	−13
1	*n*BuMgBr	THF	+1
1	*n*BuLi	*n*-hexane	−83
1	*t*BuLi	*n*-hexane	−81
4	*n*BuLi	THF	−63
4	*t*BuLi	THF	−65

All those dynamic processes that contribute equally to the overall rate constants k and k' have no effect on the selectivity, because they cancel out in the ratio (Equation 1). This is the case for aggregation processes of organometallic reagents that take place before the reacting event.

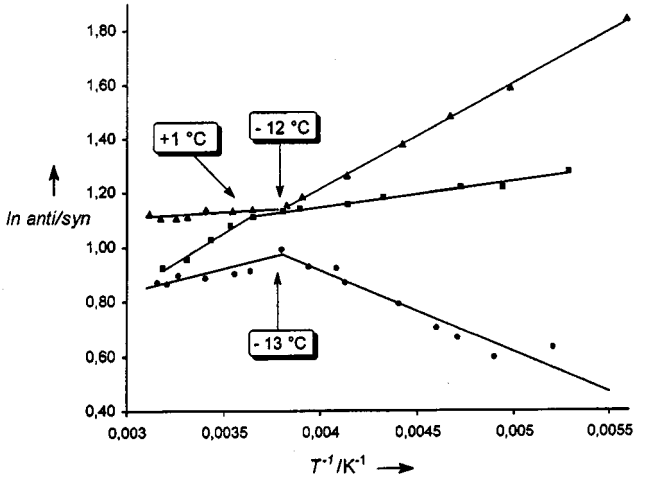


Figure 8. Eyring plots for the nucleophilic addition of *n*-butyllithium (▲), *tert*-butyllithium (●), and *n*-butylmagnesium bromide (■) to **1** at various temperature in THF

Temperature-Dependent ^{13}C NMR Measurements

Nuclear magnetic resonance spectra are affected by intermolecular interactions with the solvent: these have a significant influence on the chemical shift as well as on coupling constants.[17]

Our proposed dependence of T_{inv} on solvation is reinforced by performed ^{13}C NMR experiments recording the evolution of C=O chemical shift with regard to temperature.

We recorded ^{13}C NMR spectra of aldehydes **1**, **2**, and **4** in [D_8]THF or [D_{14}]*n*-hexane, warming from −90 to +40 °C (Figure 9). In all cases we noted a lowering in δ on warming.

This can be interpreted as an increasing of the shielding of the carbonyl group on raising the temperature. On going from THF to *n*-hexane there is a solvent effect on δ, with a difference of about 4 ppm in the C=O chemical shift of **1**: the ethereal solvent enhances the shielding, thanks to a higher electron density on carbonyl than the hydrocarbon. Moreover, by closer inspection, it could be recognized that both plots are composed of two linear segments, intersecting at a temperature we named T_{NMR}. For aldehyde **1** in *n*-hexane it is easier to recognize the break at −68 °C, while in THF we determined a T_{NMR} by applying the least median squares (LMS) method in order to define objectively the segments of the straight line given by experimental data.[18] In this case the T_{NMR} was found at 0 °C.

Similar behavior was observed for aldehydes **2** and **4** in THF, which showed T_{NMR} at −47 °C and −42 °C. All these T_{NMR}s, within experimental error, lay quite near to the corresponding T_{inv}s evident in the Eyring plot of the same aldehyde reacting with different nucleophiles in the same solvent. Therefore, it appears clear that T_{NMR} and T_{inv} are linked as two independent experimental observations of the same phenomenon. These results reinforce our hypothesis concerning the solvation-dependent natures of T_{inv} and T_{NMR}.

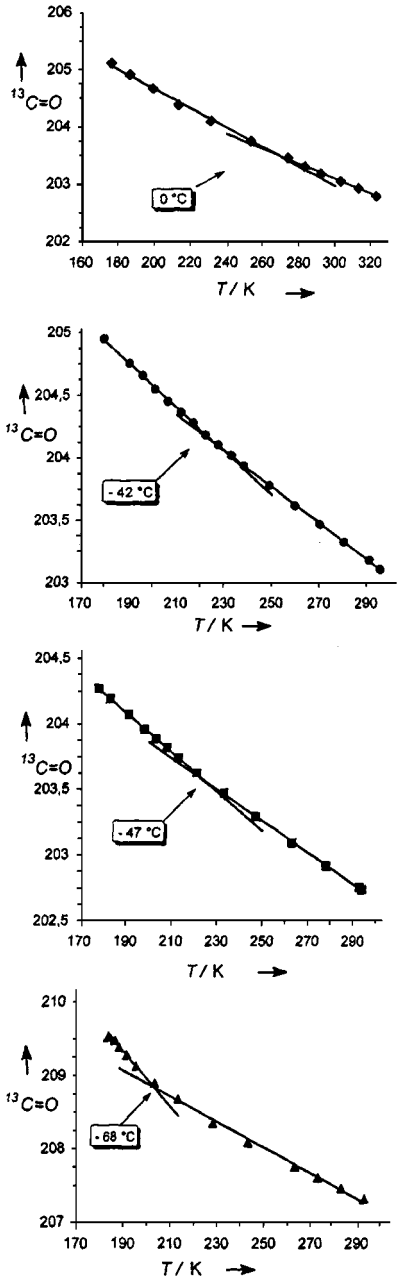


Figure 9. ^{13}C=O Chemical shifts vs. temperature in [D_8]THF for **1** (◆), **2** (●), **4** (■), and in [D_{14}]-*n*-hexane for **1** (▲)

Conclusion

We have demonstrated that, in nucleophilic addition of organometallic reagents to *O*-protected-α-hydroxy aldehydes, the diastereofacial selectivity is deeply dependent on temperature and on solvent. Solute-solvent interactions modulate the free activation energies acting on the enthalpic and entropic terms. We found that the $\Delta\Delta S^{\ddagger}$ value often exerts a determining influence on the diastereofacial selectivity, even at low temperature. In many cases, plots of ln *S* vs. $1/T$ showed inversion temperatures. From ^{13}C NMR analysis of $\delta_{C=O}$ for some aldehyde-solvent pairs, we obtained a T_{NMR} quite close to the value of the T_{inv} for the

same pair. These results demonstrate that the T_{inv} represents the interconversion temperature of two different solvation clusters which act as two different supramolecules with different stereoselectivities.

Experimental Section

General Remarks: All reactions were performed in flame-dried glassware under an atmosphere of argon. − ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 300 instrument operating at 75.5 MHz, using a 5 mm probe. All chemical shifts have been quoted relative to deuterated solvent impurity signals, δ in ppm, *J* in Hz. The temperature was controlled by a VT unit, using the flow of temperature-regulated nitrogen gas. The temperature was calibrated using chemical shift differences in a methanol sample.[19] − FT-IR: Nicolet 205 FT measured as films between NaCl plates and reported in cm^{-1}. − GC-MS: HP5980, HP-1, or HP-5 capillary column connected to HP5970 (70 eV). − GC: FISONS G8000, column: HP-5 M.S. crosslinked 5% PhMeSilicone, 30 m × 0.25 mm × 0.25μm, chiral column OV 1701 H. − TLC: Merck 60F$_{254}$. − Column chromatography: Merck silica gel 200−300 mesh. To set and maintain temperature in a range of ±1 °C during reactions, liquid N_2/acetone baths in Dewar containers or oil baths with water cooling were used. Temperature referred to the interior of the reaction apparatus.

Starting Materials: Gaseous propane and *n*-butane from steel cylinders were dried with two $CaCl_2$ traps and condensed into the reaction vessel; all other hydrocarbons were dried by distillation from sodium, THF and *t*BuOMe from sodium-benzophenone, and stored on 4 Å molecular sieves. BuLi (commercial 2.5 M solution in hexane) was titrated shortly before use. Aldehydes **1−7** were prepared starting from the corresponding *O*-protected-α-hydroxy-esters[20] by DIBAl-H reduction.[21]

In a typical experiment, the aldehyde (**1−7**) (1 mmol) was dissolved in anhydrous solvent (20 mL) under inert atmosphere, and the solution was cooled or warmed to the desired temperature; then *n*-butyllithium, *tert*-butyllithium, or *n*-butylmagnesium bromide (1.2 mmol) was added. After the starting aldehyde had disappeared (GC-monitoring), the reaction was quenched with a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (3 × 50 mL), and dried with Na_2SO_4. Chromatography of the residue on a silica gel column gave the mixtures of alcohols **1a-7a** and **1b-7b**, so that the chemical yields could be calculated; these ranged from 80 to 90%. From GC analysis of the crude products or of the corresponding *O*-trimethylsilyl-derivatives or *O*-trifluoroacetates, the *anti*/*syn* ratios and the %*de* values were obtained. The average standard deviation for the %*de* measurements was less than 1%. After removal of the *O*-protecting group, the 1,2-diol configurations were determined by comparison with reported data.[22]

(2*S*,3*R*)-2-*tert*-Butyldimethylsilyloxy-3-heptanol, *anti* Isomer (1a): IR (neat): $\tilde{\nu}$ = 3350 cm^{-1}, 1250, 1100. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.90 (m, 12 H), 1.08 (d, 3 H, *J* = 6.2 Hz), 1.36 (m, 6 H), 1.95 (br. s, 1 H), 3.53 (m, 1 H), 3.77 (dq, 1 H, *J* = 3.7 Hz, *J* = 6.2 Hz). − ^{13}C NMR (300 MHz, $CDCl_3$): −5.0, −4.6, 13.9, 16.6, 19.6, 22.7, 25.7, 28.2, 31.6, 71.2, 75.1. − MS (70 eV): *m*/*z* (%) = 231 (1) [M$^+$ − CH_3], 189 (33) [M$^+$ − *t*Bu], 159 (45), 119 (43), 75 (100).

(2*S*,3*S*)-2-*tert*-Butyldimethylsilyloxy-3-heptanol, *syn* Isomer (1b): IR (neat): $\tilde{\nu}$ = 3350 cm^{-1}, 1250, 1100. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.90 (m, 12 H), 1.15 (d, 3 H, *J* = 6.2 Hz), 1.36 (m, 6 H), 1.95 (br. s, 1 H), 3.35 (m, 1 H), 3.64 (m, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): −4.9, −4.4, 13.9, 17.9, 20.1, 22.7, 25.7, 27.9, 33.1, 71.6, 75.6. − MS (70 eV): *m*/*z* (%) = 231 (1) [M$^+$ − CH_3], 189 (33) [M$^+$ − *t*Bu], 159 (45), 119 (43), 75 (100).

(2*S*,3*R*)-2-Triisopropylsilyloxy-3-heptanol, *anti* Isomer (2a): IR (neat): $\tilde{\nu}$ = 3480 cm^{-1}, 1350, 1100. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.0 Hz); 1.08 (m, 21 H), 1.11 (d, 3 H, *J* = 6.2 Hz), 1.2−1.6 (m, 6 H), 2.2 (br. s, 1 H), 3.66 (m, 1 H), 3.90 (dq, 1 H, *J* = 3.1 Hz, *J* = 6.2). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = 12.3, 13.9, 16.1, 18.0, 22.8, 28.3, 31.7, 71.2, 75. − MS (70 eV): *m*/*z* (%) = 245 (68) [M$^+$ − *i*Pr], 201 (21), 157 (17), 131 (100) [M$^+$ − Si(*i*Pr)$_3$], 103 (41), 75 (49).

(2*S*,3*S*)-2-Triisopropylsilyloxy-3-heptanol, *syn* Isomer (2b): IR (neat): $\tilde{\nu}$ = 3480 cm^{-1}, 1350, 1100. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.0 Hz), 1.08 (m, 21 H), 1.20 (d, 3 H, *J* = 6.2 Hz), 1.2−1.6 (m, 6 H), 2.3 (br. s, 1 H), 3.31 (m, 1 H), 3.80 (quintet, 1 H, *J* = 5.7 Hz). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = 12.5, 12.6, 13.9, 18.1, 20.2, 22.8, 28.0, 32.7, 72.2, 76.2. − MS (70 eV): *m*/*z* (%) = 245 (68) [M$^+$ − *i*Pr], 201 (21), 157 (17), 131 (100) [M$^+$ − Si(*i*Pr)$_3$], 103 (41), 75 (49).

(2*S*,3*R*)-2-*tert*-Butyloxy-3-heptanol, *anti* Isomer (3a): IR (neat): $\tilde{\nu}$ = 3450 cm^{-1}, 1250, 1100. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, *J* = 6.7 Hz), 1.05 (d, 3 H, *J* = 5.9 Hz), 1.20 (s, 9 H), 1.35 (m, 6 H), 1.98 (br. s, 1 H), 3.57 (m, 2 H). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.0, 15.6, 22.8, 28.9, 28.3, 32.1, 69.4, 74.1, 75.0. − MS (70 eV): *m*/*z* (%) = 131 (6) [M$^+$ − *t*Bu], 101 (68), 87 (22), 69 (70), 57 (100).

(2*S*,3*S*)-2-*tert*-Butyloxy-3-heptanol, *syn* Isomer (3b): IR (neat): $\tilde{\nu}$ = 3450 cm^{-1}, 1250, 1100. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, *J* = 6.7 Hz), 1.13 (d, 3 H, *J* = 5.9 Hz), 1.23 (s, 9 H); 1.35 (m, 6 H), 1.98 (br. s, 1 H); 3.20 (m, 1 H), 3.4 (m, 1 H). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.0, 19.7, 22.8, 28.1, 28.9, 32.7, 71.0, 73.8, 75.2. − MS (70 eV): *m*/*z* (%) = 131 (6) [M$^+$ − *t*Bu], 101 (68), 87 (22), 69 (70), 57 (100).

(1*S*,1*R*)-1-*tert*-Butyldimethylsilyloxy-1-phenyl-2-hexanol, *anti* Isomer (4a): IR (neat) $\tilde{\nu}$ = 3400 cm^{-1}, 1250, 1100. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.90 (m, 12 H), 1.26 (m, 6 H), 2.50 (br. s, 1 H), 3.68 (m, 1 H), 4.56 (d, 1 H, *J* = 5.0 Hz), 7.3 (m, 5 H). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = −4.6, −5.1, 13.9, 18.0, 22.5, 25.7, 27.9 31.5, 75.8, 78.9, 127.0, 127.6, 128.0, 141.2. − MS (70 eV): *m*/*z* (%) = 293 (1) [M$^+$ − CH_3], 251 (30) [M$^+$ − *t*Bu], 222 (54), 221 (100), 117 (20), 75 (58), 73 (72).

(1*S*,1*S*)-1-*tert*-Butyldimethylsilyloxy-1-phenyl-2-hexanol, *syn* Isomer (4b): IR (neat) $\tilde{\nu}$ = 3400 cm^{-1}, 1250, 1100. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.90 (m, 12 H), 1.26 (m, 6 H), 2.8 (br. s, 1 H), 3.56 (m, 1 H), 4.36 (d, 1 H, *J* = 7.1 Hz), 7.3 (m, 5 H). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = −4.5, −5.1, 13.9, 18.0, 22.5, 25.7, 27.9, 31.7, 76.2, 79.4, 127.0, 127.6, 128.0, 141.6. − MS (70 eV): *m*/*z* (%) = 293 (1) [M$^+$ − CH_3], 251 (30) [M$^+$ − *t*Bu], 222 (54), 221 (100), 117 (20), 75 (58), 73 (72).

(3*SR*,4*RS*)-3-*tert*-Butyldimethylsilyloxy-4-octanol, *anti* Isomer (5a): IR (neat): $\tilde{\nu}$ = 3400 cm^{-1}, 1250, 1100. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.09 (s, 6 H), 0.89−0.95 (m, 15 H), 1.18−1.68 (m, 8 H), 2.1 (br. s, 1 H), 3.48−3.75 (m, 2 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = −4.7, −4.9, 10.2, 14.0, 18.1, 22.8, 25.8, 25.9, 28.3, 31.5, 74.4, 76.6. − MS (70 eV): *m*/*z* (%) = 245 (1) [M$^+$ − CH_3], 203 (24) [M$^+$ − *t*Bu], 173 (53), 133 (32), 75 (100), 73 (63), 69 (35).

(3*SR*,4*SR*)-3-*tert*-Butyldimethylsilyloxy-4-octanol, *syn* Isomer (5b): IR (neat): $\tilde{\nu}$ = 3400 cm^{-1}, 1250, 1100. − ^{1}H NMR (200 MHz,

$CDCl_3$): δ = 0.09 (s, 6 H), 0.89−0.95 (m, 15 H), 1.18−1.68 (m, 8 H), 2.1 (br. s, 1 H), 3.48−3.75 (m, 2 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = −4.7, −4.9, 9.3, 14.0, 18.0, 23.5, 25.8, 26.5, 28.1, 33.7, 72.2, 76.3. − MS (70 eV): *m*/*z* (%) = 245 (1) [$M^+ - CH_3$], 203 (24) [$M^+ - t$Bu], 173 (53), 133 (32), 75 (100), 73 (63), 69 (35).

(5*SR*,6*RS*)-6-*tert*-Butyldimethylsilyloxy-5-dodecanol, *anti* Isomer (6a): IR (neat): $\tilde{\nu}$ = 3450 cm^{-1}, 1250, 1100. − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.10 (s, 6 H), 0.95 (m, 15 H), 1.35 (m, 16 H), 2.1 (br. s, 1 H), 3.4−3.6 (m, 2 H). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = −4.4, 14.0, 18.1, 22.6, 25.7, 29.5, 30.5, 31.8, 74.7, 75.3. − MS (70 eV): *m*/*z* (%) = 301 (1) [$M^+ - CH_3$], 259 (40) [$M^+ - t$Bu], 229 (98), 173 (15), 161 (10), 105 (33), 83 (15), 75 (100), 55 (23).

(5*SR*, 6*SR*)-6-*tert*-Butyldimethylsilyloxy-5-dodecanol, *syn* Isomer (6b): IR (neat): $\tilde{\nu}$ = 3450 cm^{-1}, 1250, 1100. − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.10 (s, 6 H), 0.95 (m, 15 H), 1.35 (m, 16 H), 2.1 (br. s, 1 H), 3.4−3.6 (m, 2 H). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = −4.4, 14.0, 18.1, 22.7, 25.7, 28.3, 31.4, 33.9, 72.6, 75.1. − MS (70 eV): *m*/*z* (%) = 301 (1) [$M^+ - CH_3$], 259 (40) [$M^+ - t$Bu], 229 (98), 173 (15), 161 (10), 105 (33), 83 (15), 75 (100), 55 (23).

(5*SR*,6*RS*)-6-*tert*-Butyldimethylsilyloxy-5-heptadecanol, *anti* Isomer (7a): IR (neat): $\tilde{\nu}$ = 3400 cm^{-1}, 1250, 1080. − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.9 (m, 15 H), 1.0−1.6 (m, 26 H), 2.1 (br. s, 1 H), 3.4−3.6 (m, 2 H). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = −4.5, −4.6, 13.9, 14.0, 18.0, 22.6−31.8, 74.5, 75.4. − MS (70 eV): *m*/*z* (%) = 329 (45) [$M^+ - t$Bu], 299 (100), 97 (28), 75 (74), 73 (59).

(5*SR*,6*SR*)-6-*tert*-Butyldimethylsilyloxy-5-heptadecanol, *syn* Isomer (7b): IR (neat): $\tilde{\nu}$ = 3400 cm^{-1}, 1250, 1080. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.9 (m, 15 H), 1.0−1.6 (m, 26 H), 2.1 (br. s, 1 H), 3.4−3.6 (m, 2 H); ^{13}C NMR (200 MHz, $CDCl_3$): δ = −4.5, −4.6, 13.9, 14.0, 18.0, 22.6−31.8, 72.6, 75.1. MS (70 eV): *m*/*z* (%) = 329 (45) [$M^+ - t$Bu], 299 (100), 97 (28), 75 (74), 73 (59).

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