

Profound Preference for the CO-Eclipsed Conformation in 1,5-Dienyl-3,4-diols: The Origin of π -Facial Selectivity

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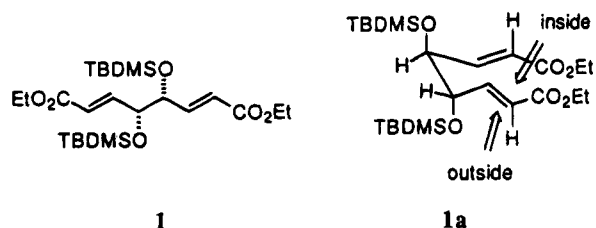
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A variable-temperature NMR study shows that the derivatives of 1,5-dienyl-3,4-diols do not have rigid conformation at room temperature as suggested previously. These compounds favor the CO-eclipsed conformer to a greater degree than their mono-allylic counterparts. The influence of the substituents on conformation in these compounds follows the same trends observed for monochiral-centered allylic ethers. The silyl ethers prefer the CO-eclipsed form while the methyl and benzyl ethers favor the CH-eclipsed conformation. The MOM ether group mimics the methyl ether and promotes the CH-eclipsed form.

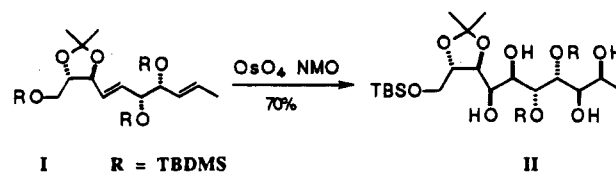
Introduction

A subject of continued interest in current organic chemistry involves the understanding and controlling of diastereofacial additions to unsaturated molecules.^{1,2} The ground state conformations of chiral substrates have been found to play an important role in the outcome of π -facial selectivity.^{3–7} Recently unusually high diastereofacial selectivity in a number of reactions was reported for the bis-silylated allylic compound **1** by Saito and co-workers.^{8,9} A rigid ground state conformation was suggested for **1** to account for the observed stereospecificity.⁹ It is proposed that the bulk of the TBDMSO groups force this diene to adopt conformation **1a**. The inside faces of the two double bonds are mutually shielded from attack by chemical reagents. Therefore, reactions occur only from the outside faces, leading to virtually complete π -facial selectivity. All stereochemical results of various reactions are consistent with this proposal.^{8–10}

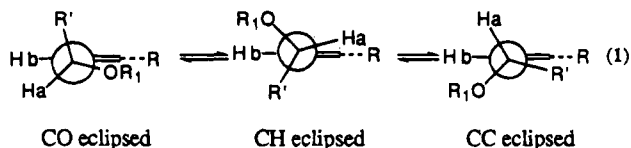


Some of us have employed this method for the stereoselective synthesis of polyols.¹⁰ For example, hydroxy-

lation of the bis-TBDMS ether **I** afforded the tetrol **II** as a single isomer. We are intrigued by the extremely high



π -facial selectivity displayed by compound **1**. However, the rationale provided by Saito concerning the origin of the selectivity was unsatisfactory to us. Particularly, the high rotational barriers suggested for **1** were surprising.⁹ We recently reported studies of the rotational isomerism around a $C_{sp^3}-C_{sp^2}$ bond in chiral alkenes.¹¹ It was found that rapid equilibrium occurs even at -80°C among the three isomers, eq 1. Since compound **1** is closely related to these chiral alkenes, we decided to examine the conformational behavior of **1** and certain analogues of interest as synthetic intermediates. We have found, by



variable-temperature (VT) NMR, that (1) consistent with conformation **1a**, suggested by Saito, the bis-allylic compounds have a profound preference for the CO-eclipsed form and (2) compound **1** and several of its derivatives are not conformationally rigid at room temperature. Alternative conformations, represented by **B–F**, cannot be ruled out by the VT NMR data. These conformers can be generated by rotation of the central $C_{sp^3}-C_{sp^3}$ and the adjacent $C_{sp^3}-C_{sp^2}$ bonds. Thus, the forms **A**, **B**, and **C** correspond to CO-eclipsed conformers and the forms **D**, **E**, and **F** to CH-eclipsed conformers in eq 1.

Our recent study shows that the CO-eclipsed forms are favored if the vinyl substituent **R** is an electron-withdrawing group (EWG), and the CH-eclipsed forms

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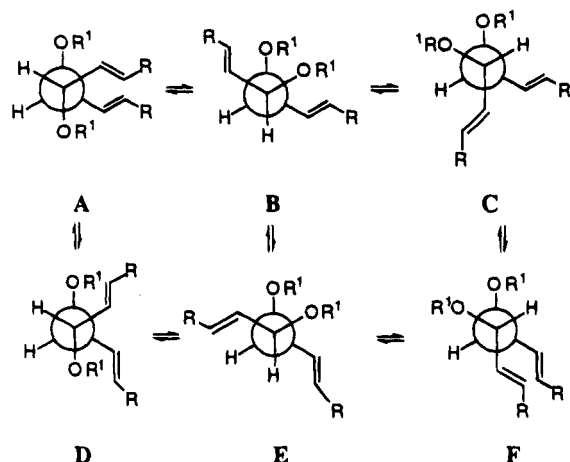
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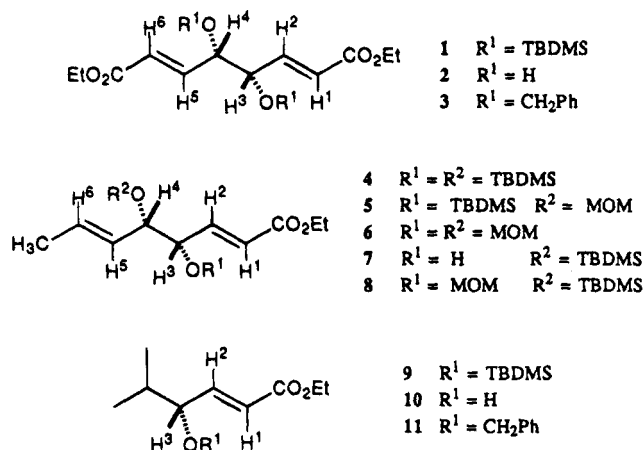
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are favored if R is an electron-donating group (EDG). We have also shown that the ether substituent R^1 plays a part in the conformational preference as well.¹¹ Allyl silyl ethers ($R^1 = \text{SiR}_3$) were found to prefer the CO-eclipsed form while methyl ethers ($R^1 = \text{Me}$) favor the CH-eclipsed form. Therefore, compound **1**, with $R = \text{CO}_2\text{Et}$ and $R^1 = \text{TBDMS}$, possesses all the substituents for a preferred CO-eclipsed conformation. To study the effect of the ether substituent on the conformational preferences of **1**, we have chosen to examine compounds **1–3** and **4–8**. Compounds **4–8** represent synthetic intermediates with both electron-withdrawing and electron-donating double bond substituents.



Results and Discussion

The variable-temperature ^1H NMR data for **1–8** are compiled in a table in the supplementary material and plotted graphically in Figures 1–8. Compounds **1–3** have a C_2 symmetry axis and show a preference for the CO-eclipsed form. The coupling constants, $^3J_{23}$, become smaller as the temperature decreases, indicating that the CO-eclipsed form becomes more populated at lower temperatures. For comparison, we have plotted the VT ^1H NMR data for the bis-allylic compounds **1–3** along with their corresponding mono-allylic counterparts, i.e., the derivatives of ethyl 4-hydroxy-5-methyl-2-hexenoate **9–11** in Figures 1–3.¹¹ Compounds **9–11** were chosen because they are the most structurally similar to the bis-allylic compounds **1–3**.

A. 1,5-Dienyl-3,4-diol Derivatives Prefer the CO-Eclipsed Form to a Greater Extent Than Their Mono-Allylic Counterparts. At a given temperature, the bis-allylic compounds **1–3** display considerably smaller

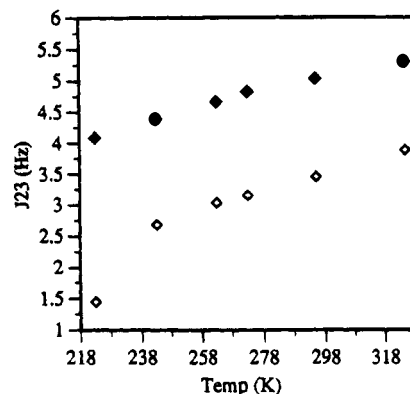


Figure 1. Spin–spin coupling constants ($^3J_{23}$, Hz) as a function of temperature for compounds **1** (\diamond) and **9** (\blacklozenge).

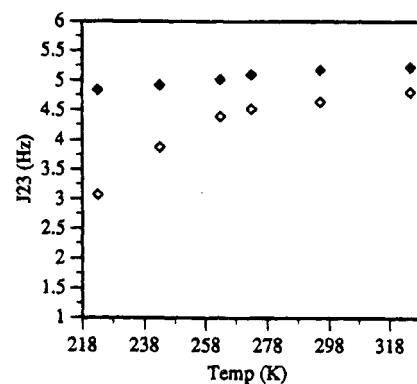


Figure 2. Spin–spin coupling constants ($^3J_{23}$, Hz) as a function of temperature for bis-allylic diol **2** (\diamond) and allylic alcohol **10** (\blacklozenge).

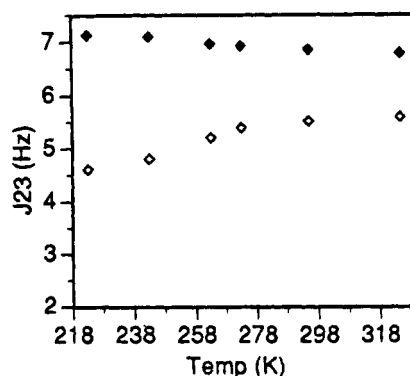


Figure 3. Spin–spin coupling constants ($^3J_{23}$, Hz) as a function of temperature for bis-allylic benzyl ether **3** (\diamond) and the mono-allylic benzyl ether **11** (\blacklozenge). The monochiral-centered benzyl ether prefers the CH-eclipsed form, and the bis-allylic benzyl ether favors the CO-eclipsed form.

three-bond coupling, $^3J_{23}$, than the corresponding mono-allylic ethers **9–11**. The TBDMS ether **1** exhibits coupling from 1.45–3.87 Hz (Table 1, supplementary material) while **9** falls in the range 4.09–5.29. The same coupling in diol **2** varies from 3.07–4.81 Hz while that of the corresponding mono-allylic alcohol **10** ranges from 4.84–5.23 Hz. The most dramatic contrast is seen in the benzyl ether **3** and its mono-allylic counterpart **11**. The bis-allylic benzyl ether shows a preference for the CO-eclipsed form while the mono-allylic compound **11** favors the CH-eclipsed form (see Figure 3). These observations support Saito's conformational assignment to silyl ether **1a**, although in chloroform there is rapid rotation around

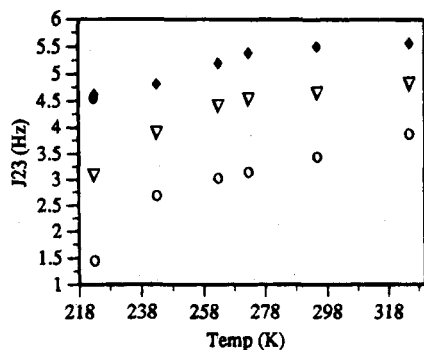


Figure 4. Spin-spin coupling constants ($^3J_{23}$, Hz) as a function of temperature for bis-allylic silyl ether **1** (O), diol **2** (∇), and the benzyl ether **3** (\blacklozenge). Protective group effect: the silyl ether **1** enhances the CO-eclipsed form and the benzyl ether **3** counterbalances the vinyl electron-withdrawing group effect.

the $C_{sp^3}-C_{sp^2}$ bond in the temperature range of -30 to 50 °C. This is evidenced by the changing coupling constants $^3J_{23}$ and the sharp peaks in the 1H NMR spectra observed in this temperature range. Below -50 °C there is a broadening of the H3 and H2 proton peaks, indicating a slowing of rotation.

As a rule, an allylic OTBDMS group was found to stabilize the CO-eclipsed form whereas a OMe group favored the CH-eclipsed form.¹¹ The effect of the oxygen substituents on the conformational preferences of **1-8** are consistent with our previous report. The benzyl ether and the methoxymethyl (MOM) ether appear to mimic the methyl ether. As shown by the plots in Figure 4 the bis-silyl ether **1** exhibits the smallest $^3J_{23}$ coupling constants indicating the highest preference for the CO-eclipsed form. The bis-benzyl ether **3** shows the largest $^3J_{23}$ of the three bis-allylic compounds, indicating the lowest preference for the CO-eclipsed form. However, unlike its mono-allylic counterpart, the bis-benzylic ether still retains its preference for the CO-eclipsed form. This finding is unexpected and reflects the characteristics of the bis-allylic compounds.

B. 1,5-Dienyl-3,4-diol Derivatives Exhibit Non-linear Temperature Dependence of Conformational Population. The most interesting aspect of the rotational profile displayed by the C_2 symmetric compounds **1-3** is the nonlinearity of population vs temperature. Our recent studies of mono-allylic alcohol derivatives showed excellent linearity in the temperature range of -80 to 100 °C.¹¹ The bis-allylic compounds, as shown in Figures 1-4, exhibit a sharp drop in coupling constants $^3J_{23}$ ($^3J_{45}$) at temperatures below -40 °C. This indicates a sudden increase in preference for conformation **A** and/or **B**. This observation can be rationalized by a coupling of rotations, i.e., the central $C_{sp^3}-C_{sp^3}$ bond rotation is coupled to rotations of the $C_{sp^3}-C_{sp^2}$ bonds. As the temperature drops, the less stable conformers (presumably **B** and **C**) shift toward the most stable conformation (presumably **A**). This population decrease in **B** and **C** (not proven), in turn, would lead to a shift of the high-energy conformers **E** and **F** (proven by the VT NMR data) toward **B** and **C**. As a result, the shift in populations of $C \rightarrow B \rightarrow A$ also accelerates the shift from **D**, **E**, and **F** to **A**, **B**, and **C**. The coupled rotation appears to magnify the temperature effect on the population of rotational isomers.

C. A MOM Ether Can Reverse a Vinyl EWG Effect and Promote the CH-Eclipsed Form. Unlike

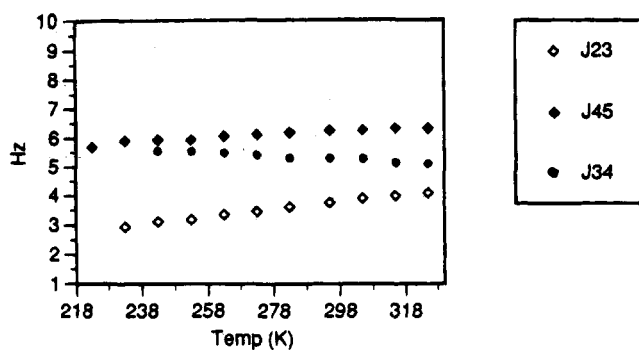


Figure 5. Spin-spin coupling constants ($^3J_{23}$, $^3J_{34}$, $^3J_{45}$, Hz) as a function of temperature for bis-allylic compound **4**.

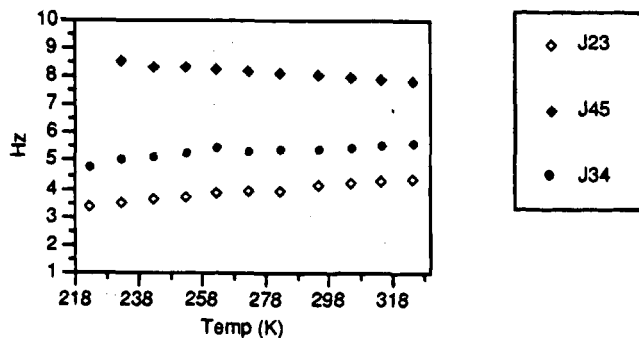


Figure 6. Spin-spin coupling constants ($^3J_{23}$, $^3J_{34}$, $^3J_{45}$, Hz) as a function of temperature for bis-allylic compound **5**.

compounds **1-3**, the bis-allylic compounds **4-8** do not have a C_2 symmetry axis. There is an EWG (CO_2Et) on the right half and an EDG (CH_3) on the left half of these molecules. The rule that an EDG favors the CH-eclipsed and an EWG favors the CO-eclipsed form still holds in these structures. Therefore, in general, the left half of compounds **4-8** prefers the CH-eclipsed form ($^3J_{45}$ (\blacklozenge) $\sim 6-9$ Hz) while the right half prefers the CO-eclipsed form ($^3J_{23}$ (\diamond) $\sim 2-5$ Hz, see Figures 5-9). These substituent-dependent trends are either reinforced or offset by the protective groups. For example, the $^3J_{45}$ of **4** gradually decreases at lower temperatures (Figure 5), indicating a favored CO-eclipsed form, which suggests that the combined effect of the TBDMS protective group and the bis-allylic structure can overcome the effect of the vinyl substituent. On the other hand, the protective group ($R^2 = MOM$) of **5** reinforces the CH-eclipsed form, and $^3J_{45}$ increases at lower temperatures. Thus, the MOM ether, like methyl or benzyl, prefers the CH-eclipsed form. This is most obvious for compound **6**, which shows slightly increased $^3J_{23}$ at lower temperatures, indicating that the MOM group reverses the electron-withdrawing (CO_2Et) vinyl substituent effect and the CH-eclipsed form becomes slightly favored.

The protons H_4 and H_3 of compounds **4-8** are non-equivalent and give rise to coupling constant $^3J_{34}$, from which the conformation of the central $C_{sp^3}-C_{sp^3}$ bond can be studied. Due to the lack of C_2 symmetry, the conformations **G-M** need to be considered for **4-8** in addition to **A-F**. Please note that conformers **G-J** are CO-eclipsed at the rear half and CH-eclipsed at the front half of the Newman projections, while conformers **K-M** are just the reverse. Rapid equilibrium occurs among the rotamers (**A-M**) for compounds **4-8** in the temperature range of -50 to 50 °C. This is evidenced by the gradual change in the coupling constants of $^3J_{34}$ and by the sharp

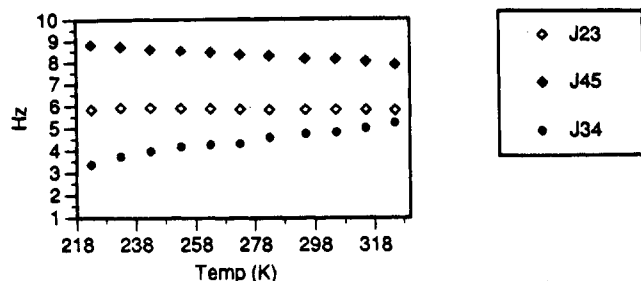


Figure 7. Spin-spin coupling constants (${}^3J_{23}$, ${}^3J_{34}$, ${}^3J_{45}$, Hz) as a function of temperature for bis-allylic compound **6**.

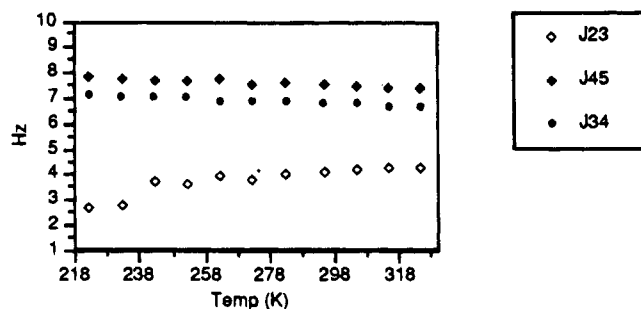


Figure 8. Spin-spin coupling constants (${}^3J_{23}$, ${}^3J_{34}$, ${}^3J_{45}$, Hz) as a function of temperature for bis-allylic compound **7**.

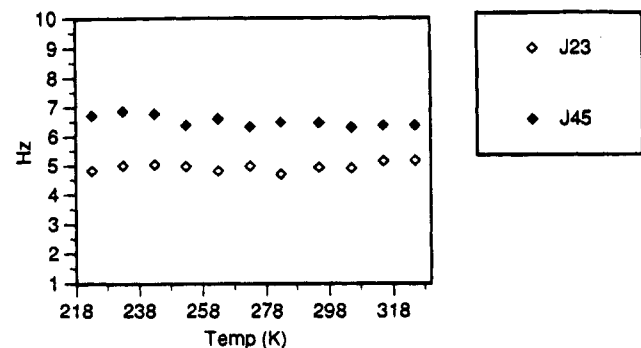
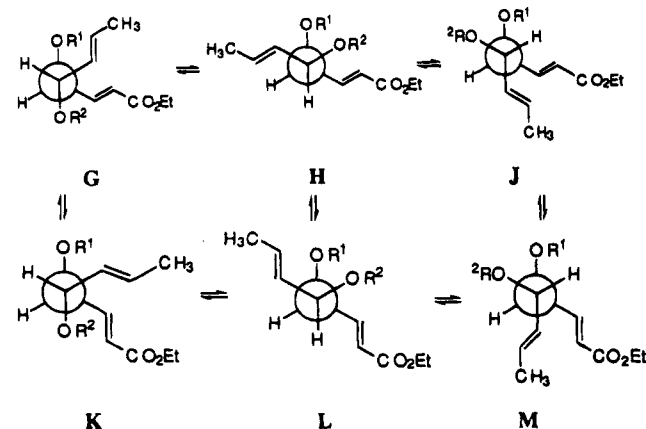


Figure 9. Spin-spin coupling constants (${}^3J_{23}$, ${}^3J_{34}$, ${}^3J_{45}$, Hz) as a function of temperature for bis-allylic compound **8**.

signals observed in their ${}^1\text{H}$ NMR spectra. It is clear from Figures 7 and 8 that compound **6** prefers the H-gauche forms (**A**, **B**, **D**, **E**, and **G**, **H**, **K**, **L**; smaller and



decreasing ${}^3J_{34}$ at low temperatures) while **7** favors the H-anti forms (**C**, **F**, and **J**, **M**; larger and increasing ${}^3J_{34}$ at low temperatures). Compounds **4** and **5** appear to have little preference for either the H-gauche or the

H-anti forms as evidenced by the very slight change in ${}^3J_{34}$ (5.1–5.6 Hz at 243–325 K for **4** and 5.6–4.7 Hz at 223–325 K for **5**). The order of preference for the H-gauche form is as follows: **6** > **5** > **4** > **7**. Unfortunately, the ${}^3J_{34}$ of **8** cannot be read precisely due to the overlap of H3 and H4. Intramolecular hydrogen bonding may explain the preference of **7** for the H-anti form.

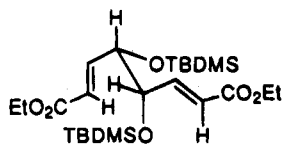
With a knowledge of the central dihedral angle (from ${}^3J_{34}$) and the two $\text{C}_{\text{sp}^2}\text{--C}_{\text{sp}^3}$ orientations (from ${}^3J_{23}$ and ${}^3J_{45}$), one can locate the most stable conformation among the 12 rotamers. For example, compound **5** shows decreasing ${}^3J_{23}$ and ${}^3J_{34}$ and increasing ${}^3J_{45}$ (Figure 6), which indicate a preferred CO-eclipsed form on the right half of the molecule, a CH-eclipsed form on the left half, and the H-gauche arrangement of the central $\text{C}_{\text{sp}^3}\text{--C}_{\text{sp}^3}$ bond, suggestive of conformations **G** or **H**. Compound **7**, on the other hand, shows a decreasing ${}^3J_{23}$ (Figure 8) and increasing ${}^3J_{34}$ and ${}^3J_{45}$, which suggest that conformation **J** is the most stable form. By the same reasoning, compound **4** favors conformation **A** and/or **B**, and **6** prefers **D**, **E**, and **G**, **H**. (This conclusion was drawn because the 4,5-coupling suggests a CH-eclipsed conformation while 2,3-coupling is essentially unchanged and thus favors neither a CO- nor a CH-eclipsed conformation. Therefore, a compromise of conformations **D**, **E**, **G**, and **H** appear to be reasonable.) Molecular mechanics calculations give different results when different force fields are employed. We have performed calculations using MM2, MM3, and the cff91 force fields.¹² None of these methods gives useful information. The inability of the molecular mechanics in predicting stable conformations of **1** lies in their failure to identify the CO-eclipsed conformation as the more stable isomer. A detailed investigation on this matter will be discussed in a future publication.

D. The Origin of the Diastereofacial Selectivity of 1,5-Dienyl-3,4-diol Derivatives. On the basis of the VT NMR data of **1–3** (Figures 1–4), the three CO-eclipsed conformations, **A**, **B**, and **C**, are clearly more stable than the CH-eclipsed forms **D**, **E**, or **F**. The ${}^1\text{H}$ VT NMR data of **4–8** shows that rapid rotation still occurs around the central $\text{C}_{\text{sp}^3}\text{--C}_{\text{sp}^3}$ bond. Except for compound **7**, which has an unprotected OH group and favors the H-anti conformation **C** (**J**), the current results are consistent with the H-gauche conformations **A** and/or **B** being more stable, but the data cannot distinguish the two. Other rotamers, such as **C**, **D**, **E**, and **F**, are undoubtedly present. Therefore, according to the Curtin-Hammett principle, the virtually complete π -facial selectivity requires that **A** and/or **B** also lead to the lowest energy transition state arrangement.¹³ The osmylation results of Saito suggest that structural elements in the bis-allylic silyl ether **1** which render the CO-eclipsed conformation more stable also stabilize the transition state. Houk has studied electrophilic additions to unsymmetrically substituted alkenes and concluded that an "inside alkoxy" arrangement of the allylic substituents is energetically favored.¹⁴ Conformations **A**, **B**, and **C** all have an "inside alkoxy" arrangement. As shown in the perspective drawing below, conformation **B** of silyl

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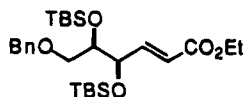
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Conformation **1b**

ether **1** exhibits the same π -face shielding as **A** except that it is the silyloxy groups which provide the shield, whereas in **A** the double bonds protect each other from "inside" attack. The arrangement depicted in **1b** also explains why both double bonds of **1** give >99:1 diastereofacial selectivity in stepwise reactions.⁸ Therefore, the profound preference for the CO-eclipsed form, which is favored in both ground and transition states, could explain the high degree of facial selectivity of additions to one or both double bonds. The central $C_{sp^3}-C_{sp^3}$ bond orientation has no effect on the outcome of the π -facial selectivity since both conformation **A** and **B** expose only one side of the double bond to attack. Conformation **C** is probably considerably higher in energy and of negligible importance.

It is interesting to note that the bis-benzyl ether **3** gives lower π -facial selectivity than the bis-silyl ether **1** (8:1 to 13:1 for **3**¹⁵ and >99:1 for **1**) upon hydroxylation with OsO_4 and NMO. The level of selectivity displayed by **3** is comparable to the mono-allylic compound **12** (selectiv-

**12**

ity in hydroxylation, 9:1),⁸ i.e., "normal" level of selectivity. If one compares the coupling constants of the bis-benzyl ether **3** ($^3J_{23} = 5.5$ Hz) with the mono-allylic silyl

ether **9** ($^3J_{23} = 5.0$ Hz; compound **12** should have comparable coupling constants), similar values of $^3J_{23}$ are observed. The observed preference for the CO-eclipsed form in **9** (\blacklozenge in Figure 1) and **3** (\blacklozenge in Figure 3) and the similar selectivity displayed in their reactions suggests a relationship between the ground state conformational preference and diastereofacial selectivity of hydroxylation reactions. Consequently, the bis-allylic structure is not the only criteria for high π -facial selectivity. Both the TBDMS ether and the CO_2Et group contribute to the preferred ground state and transition state conformation.

Conclusion

1,5-Dienyl-3,4-diols prefer the CO-eclipsed conformation. The rule that silyl ethers promote the CO-eclipsed form and alkyl ethers promote the CH-eclipsed form still holds in bis-allylic compounds. An allylic MOM ether promotes the CH-eclipsed form. The conformation of the bis-allylic compounds is not rigid. The same structural features that enhance the ground state conformational preferences should also operate in the transition state. Currently, it is not clear why the bis-allylic compounds prefer the CO-eclipsed form to a greater degree than their monochiral-centered counterparts. Studies along these lines are currently underway in our laboratories.

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Supplementary Material Available: Table of coupling constants and chemical shifts for compounds **1-11** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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