Further Understandings of Regio- and Stereoselectivity in the Diels-Alder Reaction: Diels-Alder Reaction of Allenic Ester with 4-(Bulky)alkyl-substituted 3-siloxy-1,3-butadiene

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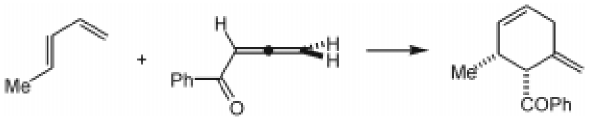
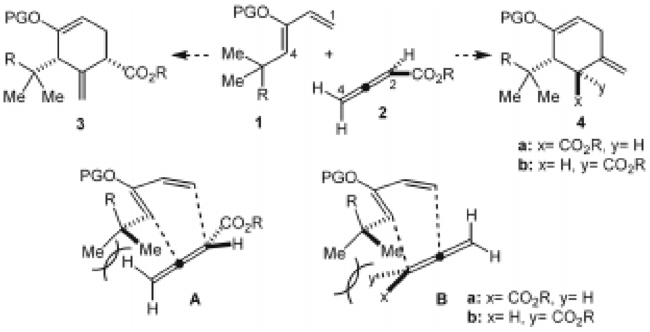
Electron-poor allenes undergo high regio- and stereoselective Diels-Alder reactions with alkyl-substituted dienes as shown in equation 1.[1,2] Observed regioselectivity and stereoselectivity agree well with predictions based upon the frontier molecular orbital (FMO) theory.[3] In connection with development of new synthetic methods using Diels-Alder reaction, we became interested in the regio- and stereochemical problems of the (4+2) cyclization of an electron-poor allenes with bulky alkyl-substituted alkoxydienes such as **1**. Thus, we planned to study the regio- and stereochemistry of the Diels-Alder reaction between diene **1** and allenic ester **2**. At the outset, we envisaged that the regiochemical outcome of this cycloaddition might be opposite to predictions based on the FMO theory, considering the structural nature of **2** (Scheme 1). We reasoned that transition state **A**, preferred one based on the HOMO-LUMO interaction, leading to "*para* product" **3** would invoke the severe steric interaction between the C-4 hydrogen of **2** and the bulky substituent at C-4 of the diene **1** but there would be no such steric congestion in the transition state **B** leading to the "*meta* product" **4**. Additionally, we envisioned that if the regiochemistry of this cyclization is controlled by the steric factor rather than the electronic factor, the stereochemistry might also be controlled by the steric factor, *i.e.* the *exo* adduct **4a** *via* transition state $\mathbf{B_a}$ would be preferred to the *endo* adduct **4b** *via* transition state $\mathbf{B_b}$. If this is the case, this regio- and stereochemical outcome would constitute a rare example that both the regio- and stereochemistry are controlled by steric factors rather than electronic factors based on the HOMO-LUMO interaction.



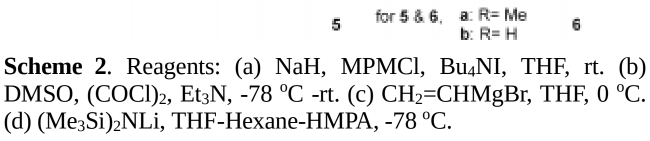
(1)

To test these notions, diene **6a** was first synthesized, in five steps from 3,3-dimethyl-1,5-pentanediol (Scheme 2). The diol was monoprotected as its MPM ether and subsequent Swern oxidation yielded the corresponding aldehyde. The Grignard addition of vinylmagnesium bromide to the aldehyde, followed by Swern oxidation afforded the vinyl ketone **5a** (42%, 4 steps). When **5a** was treated with *t*-butyldimethylsilyl chloride (TBSCl) and lithium bis(trimethylsilyl)amide in tetrahydrofuran (THF)-hexane containing hexamethylphosphoramide (HMPA) at 78 ^{o}C,[4] the desired diene **6a** was obtained exclusively in 82% yield.



Scheme 1

With **6a** in hand, the Diels-Alder reaction with the allenic ester **7**[5] was examined (Scheme 3). When **6a** was heated with **7** at ~110 ^{o}C for 24 h, the cyclization took place to produce a chromatographically homogeneous mixture of two cycloadducts in which one isomer predominates (> 10 : 1) in 55% yield. As it was difficult to assign the regio- and stereochemistry of these adducts from their ^{1}H NMR data, the mixture was hydrolyzed (HF-pyridine, THF) to give rise to a mixture of products. The regiochemistry of the predominant hydrolysis product (52%) was assigned as shown in **10a** based on the ^{1}H NMR coupling data ($J_{4,5}$ = ~0 Hz) and its H,H-COSY spectrum. To further establish the stereochemistry of the major cycloadduct, **10a** was reduced with $NaBH_4$ to give an exclusive product. The structure of this product was assigned as shown in **11** based on the ^{1}H NMR coupling data, which further allowed us to assign the major cycloadduct as **9a**, a cycloadduct via the *exo* transition state. The C-4 hydrogen (δ 2.15 ppm) in **11** appears as a



Scheme 2. Reagents: (a) NaH, MPMCl, Bu_4NI, THF, rt. (b) DMSO, $(COCl)_2$, Et_3N, -78 ^{o}C -rt. (c) CH_2=CHMgBr, THF, 0 ^{o}C. (d) $(Me_3Si)_2NLi$, THF-Hexane-HMPA, -78 ^{o}C.

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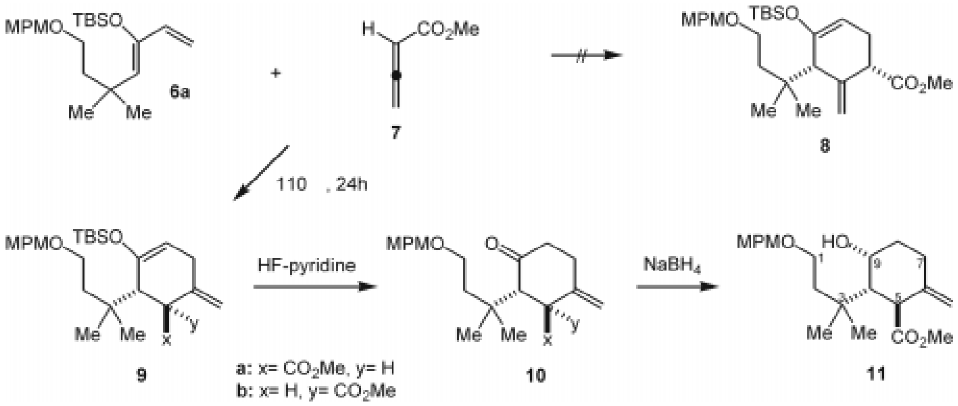
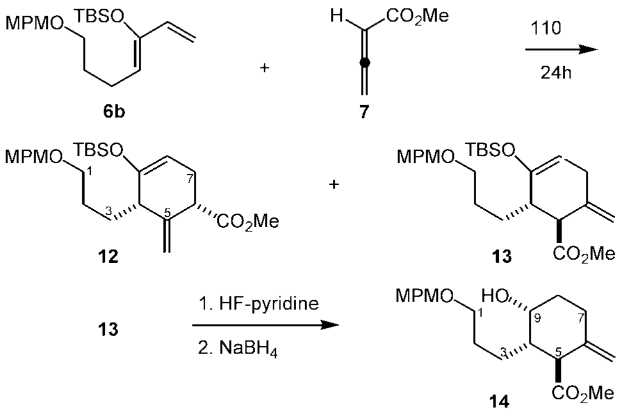


Scheme 3



Scheme 4

doublet of doublets with coupling constants of $J_{4,5}$ = 8.8 Hz and $J_{4,9}$ = 2.0 Hz, establishing the *trans* and *cis* arrangements of hydrogens at C-5 and C-9, respectively, relative to the axial C-4 hydrogen. The minor hydrolysis product (8%) was assigned the structure **10b**, based upon its decoupling studies, which accordingly originates from the cycloadduct **9b**, a cycloadduct via the *endo* transition state. None of the other regioisomers including compound **8** were obtained. Thus, the regio- and stereochemical outcomes of cyclization between **6a** and **7** were opposite to predictions based on the FMO theory. This result constitutes a rare example that both the regio- and stereochemistry are controlled by steric factors rather than electronic factors based on the HOMO-LUMO interaction.

To examine the degree that the presence of dimethyl group at C-5 of diene **6a** has affect on the regio- and stereochemical outcomes of cycloaddition with **7**, a diene **6b** was also prepared and cycloadded to **7** (Scheme 4). The synthesis of diene **6b** was carried out in a similar manner to the synthesis of diene **6a,** starting from 1,5-pentanediol (Scheme 2). Interestingly enough, when **5b** was treated with TBSCl and lithium bis(trimethylsilyl)amide in THF-hexane-HMPA at 78 °C, the desired diene **6b** was also obtained exclusively in 78% yield. Cyclization between the diene **6b** and **7** proceeded smoothly in refluxing toluene to provide a mixture of two predominant cycloadducts with a selectivity of 4 : 1, along with small amounts of other cycloadducts. From an analysis of ^{1}H NMR spectroscopic data and an application of the Alder *endo* rule, the major cycloadduct was assigned as shown in structure **12**. ^{1}H decoupling data supported the regiochemical assignment of **12**. The observed coupling constants ($J_{6,7}$ = 9.8 Hz and 5.9 Hz) and the Alder *endo* rule strongly suggested the assigned stereochemistry in structure **12**. The minor product was assigned as shown in structure **13** by correlation with **9a** and correlation of **14** with **11**. ^{1}H coupling pattern of **13** is similar to those of **9a**. And ^{1}H coupling data ($J_{4,5}$ = 8.6 Hz and $J_{4,9}$ = ~2.0 Hz) of **14**, obtained *via* two-step sequence of hydrolysis (HF-pyridine) and NaBH$_4$ reduction, were closely related to those of **11**. Thus, in the cyclization between **6b** and **7**, the regio- and stereochemical outcomes are in agreement with predictions based on the FMO theory. However, the production of **13** in the significant ratio indicates that the structural feature of allenic ester **7** has influence on the mode of cycloaddition to some degree. In the (4+2) cycloaddition of **6a** and **7**, this structural feature of **7**, in combination with the presence of dimethyl groups at C-5 of **6a**, is magnified to direct the cycloaddtion in opposite regio- and stereochemical senses to predictions based on the HOMO-LUMO interaction by the FMO theory.

In conclusion, the present result provides a rare example that both the regio- and stereochemistry in the Diels-Alder reaction are controlled by steric factors rather than electronic factors based on the HOMO-LUMO interaction.

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References and Notes

1. For a review on cycloadditions of allenes, see: Pasto, D. L. *Tetrahedron* **1984**, *40*, 2805.
2. Gras, J.-L. *J. Chem. Res*. **1982**, 300.
3. (a) For a good review on the FMO theory, see: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: London, U.K., 1976. (b) For a discussion of the application of FMO theory to dipolarophiles, see: Houk, K. N.; Watts, C. R.; Luskus, J. L. *J. Am. Chem. Soc*. **1973**, *95*, 7301.
4. Jung, S. H.; Yeo, M. S.; Kim, S. O.; Cheong, C. H. *Bull. Korean Chem. Soc.* **1997**, *18*, 344.
5. (a) Lang, R. W.; Hansen, H.-J. *Helv. Chim. Acta* **1980**, *63*, 438. (b) For the use of this allene as a Diels-Alder dienophile, see: Fink, M.; Gerlach, H. *Helv. Chim. Acta* **1982**, *65*, 2563.