

Unexpected Regioselectivity in the Synthesis of Pyranonaphthoquinone via the Diels–Alder Reaction

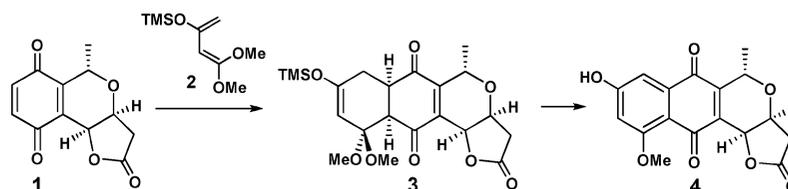
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ABSTRACT



The unusual regioselectivity in the Diels–Alder reactions of pyranoquinone 1 with (4,4-dimethoxybuta-1,3-dien-2-yloxy)trimethylsilane 2 are explored by both computations and experiments. The regioselectivity is controlled by the electrostatic interaction of the lactone ring-oxygen and the vicinal quinone oxygen on the transition structure, which can be tuned by the terminal methyl group of the butadienes.

The Diels–Alder (DA) reaction of substituted butadiene with pyranoquinone is the key step in the synthesis of the core structure of the pyranonaphthoquinone family, a series of biologically important natural products such as kalafungin, frenolicin B, and crisamicin A (Figure 1).¹

A decade ago, Kraus and co-workers synthesized pyranonaphthoquinone 8 via a Diels–Alder reaction with high regioselectivity.² Based on the model, Kraus suggested that the

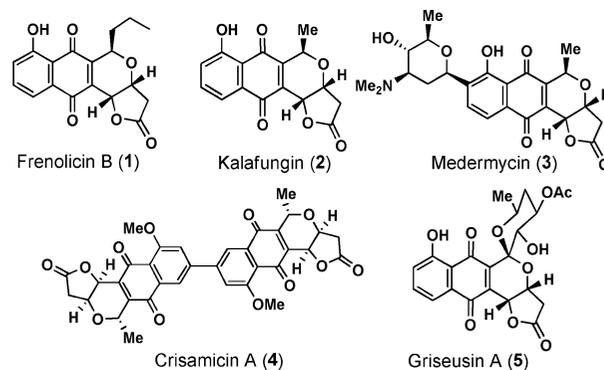


Figure 1. Naturally occurring pyranonaphthoquinones.

regioselectivity was dictated by the molecular geometry and the unequal charge distribution of the dienophile induced by the lactone ring oxygen (Scheme 1, eq 1).

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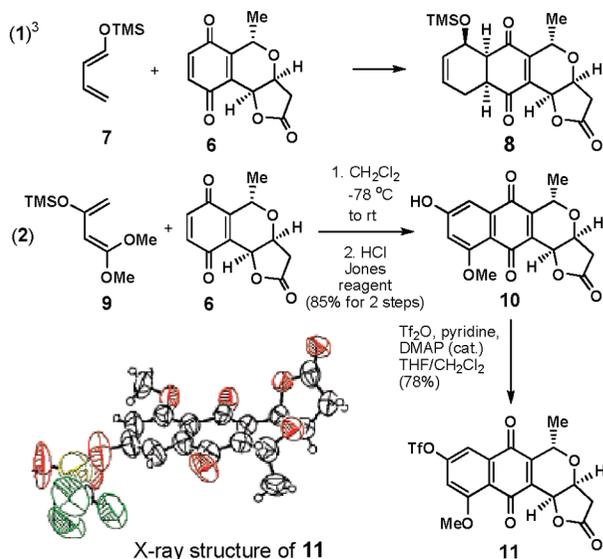
[‡] Jinan University.

(1) (a) Fang, X.-P.; Anderson, J. E.; Chang, C.-J.; Fanwick, P. E.; McLaughlin, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1655. (b) Bergy, M. E. *J. Antibiot.* **1968**, *21*, 454. (c) Hoeksema, H.; Krueger, W. C. *J. Antibiot.* **1976**, *29*, 704. (d) Tsukamoto, M.; Muriika, K.; Hirayama, M.; Hirano, K.; Yoshida, S.; Kojiri, K.; Suda, H. *J. Antibiot.* **2000**, *53*, 26. (e) Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T.; Nakata, M. *J. Antibiot.* **1991**, *44*, 901.

(2) (a) Kraus, G. A.; Li, J. *J. Am. Chem. Soc.* **1993**, *115*, 5859. (b) Kraus, G. A.; Li, J.; Gordon, M. S.; Jensen, J. H. *J. Org. Chem.* **1995**, *60*, 2254.

(3) The pyranoquinone here is the enantiomer of that used in Kraus' experiments, which is for the convenience of discussion and does not influence the conclusion.

Scheme 1. Syntheses of Pyranoquinones **8** and **11**



We recently finished the total synthesis of crisamicin A (**4** in Figure 1),⁴ and one of the key steps is the intermolecular Diels–Alder reaction to construct the tetracyclic core structure in **10** (Scheme 1, eq 2); compound **10** was then converted to its triflate **11**, and its structure was confirmed by X-ray study. Interestingly, the regioselectivity for the formation of **8** and **10** is opposite to each other with regard to the terminal substituents, which inspired us to do further investigation for this important reaction. Herein we report our combined efforts of both computations and experiments for study of this important reaction and found that the substituents on the butadiene could tune the electrostatic interaction between the oxygen of the lactone ring and the oxygen of the vicinal quinone on the transition structure, leading to the unusual regioselectivity observed in our Diels–Alder reaction.

Calculations were carried out with the B3LYP⁵ density functional method as implemented in the Gaussian03 suite of programs.⁶ The 6-31G* basis set⁷ was used for C, O, and H; the LanL2dz basis set was used for Si.⁸ All the stationary points were confirmed by the frequency calculations.

The B3LYP-optimized pyranoquinone **1** had two distinct structures, axial-like and equatorial-like with regard to the conformations of the methyl group on the dihydropyran ring. The axial-like structure was more stable than the equatorial-

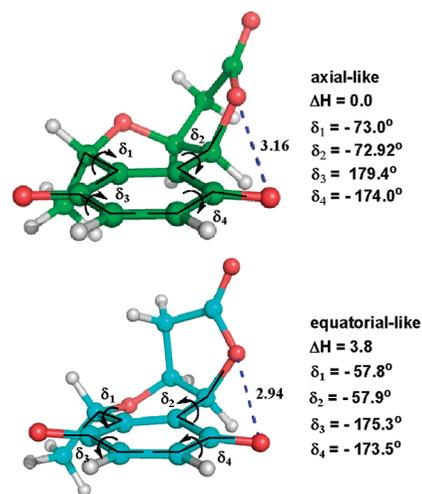
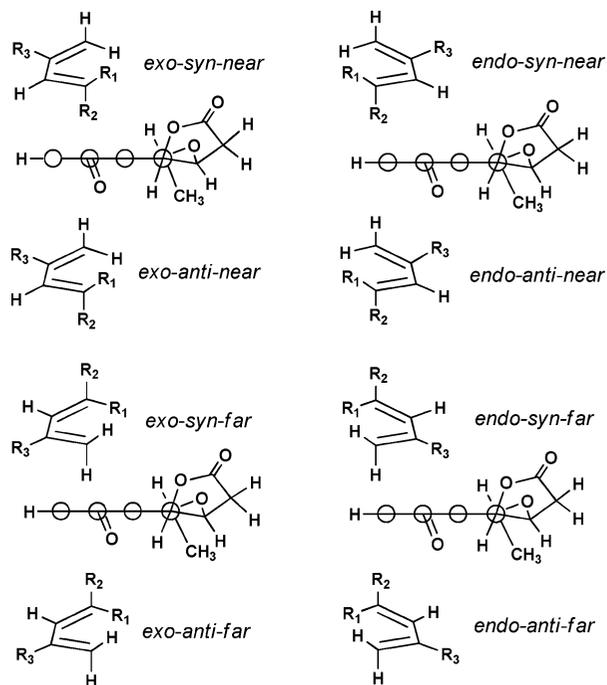


Figure 2. B3LYP-optimized structures of the pyranoquinone. Distances are in angstroms. Dihedral angles are in degrees. Relative enthalpies are in kcal/mol. The axial-like and equatorial-like conformations are defined according to their δ_1 ; $|\delta_1| > 60^\circ$ (axial-like) and $|\delta_1| < 60^\circ$ (equatorial-like). The puckering of quinone is defined according to δ_3 and δ_4 , the deviation from the plane.



7 (Kraus diene): R₁ = H, R₂ = OTMS, R₃ = H
9 (Our diene): R₁ = OMe, R₂ = OMe, R₃ = OTMS

Figure 3. Eight different methods for the cycloaddition of pyranoquinone **6** with substituted dienes **7** and **9**. The *syn* in *exo-syn-near* represents diene approaches to the quinone plane from the same face of lactone oxygen. The *near* in *exo-syn-near* indicates that the terminal substituents are close to the side of the lactone oxygen and away from the site of the methyl group of pyranoquinone. Others are defined in a similar way.

(4) Li, Z.; Gao, Y.; Tang, Y.; Dai, M.; Wang, G.; Wang, Z.; Yang, Z. *Org. Lett.* **2008**, *10*, 3017.

(5) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 1623. (e) Hehre, W. J.; Radom, L.; Schleyer, P. V.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.

(6) Frisch, M. J. *Gaussian 03, D.02*; Gaussian, Inc.; Wallingford, CT, 2004. See the Supporting Information for the full reference.

(7) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *54*, 2257. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

(8) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284.

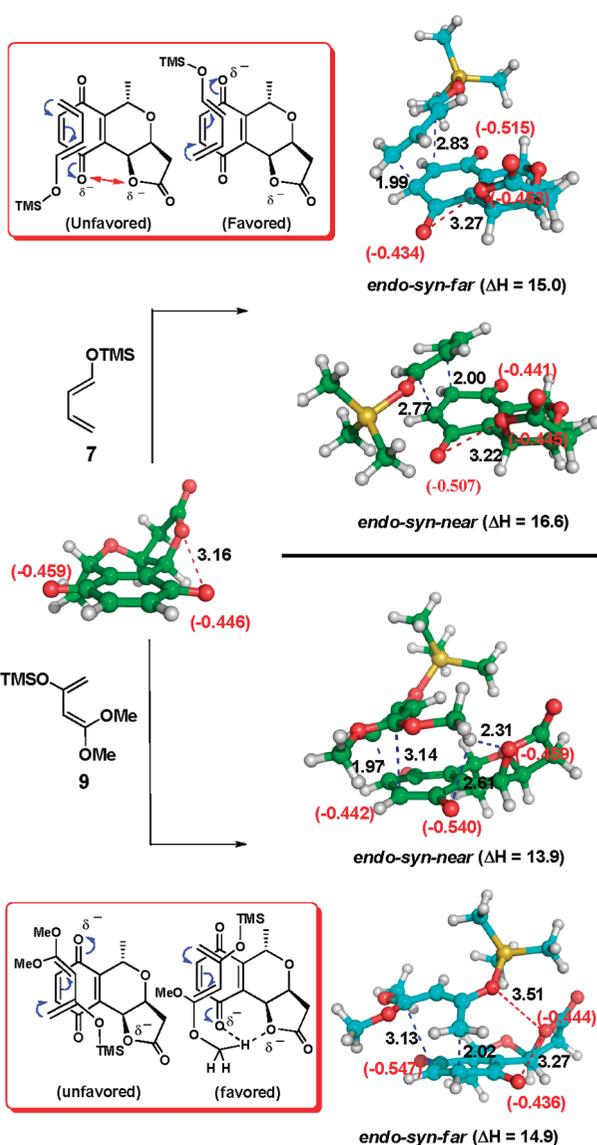


Figure 4. Transition structures for pyranoquinones with substituted butadienes **7** and **9**. Distances are in angstroms. Activation enthalpies are in kcal/mol. The Mulliken charges of quinone and lactone oxygen are shown in parentheses.

like structure by ~ 3.8 kcal/mol. This result is consistent with the results of Kraus' modeling.^{2b} The equatorial-like structure was less stable due to the stronger electrostatic repulsion between the oxygen of lactone ring and its vicinal oxygen of quinone and the steric effect of the axial position of the larger lactone ring (Figure 2). On the other hand, the puckering of the quinone ring was not obvious, which indicates that puckering of the quinone ring at the reactant might not contribute much to the regioselectivity.^{2b}

The cycloaddition could occur via eight different methods with regard to regiochemistry and stereochemistry, and the detailed definitions of the different methods are also found in Figure 3.

For the diene **7**, the *endo* transition structures (TSs) were more preferred than the corresponding *exo* TSs ($H_{exo-endo}$ about 4.7 to 5.6 kcal/mol). The *syn* TSs are more stable than

Table 1. B3LYP Enthalpies (kcal/mol) for the *Endo-Syn-near* and *Endo-Syn-Far* TSs of Different Substituents on the Butadienes

entry	butadiene	dienophile	$\Delta H_{near-far}$
1			-1.0 kcal
2		6	-1.3 kcal
3 ^a		6	-0.2 kcal
4		6	0.4 kcal
5		6	1.5 kcal

^a The terminal R group of entry 4 is H. The definitions for *endo-syn-near* and *endo-syn-far* are similar to those of other R groups.

the corresponding *anti* TSs by about 2 kcal/mol. The *syn* preference is because that the quinone ring puckering induced by the *anti* attacking causes larger repulsion with the oxygen of lactone ring. The *near* TSs are ~ 0.7 – 1.6 kcal/mol less stable than the *far* TSs (Table S1, Supporting Information). The most stable two transition states are *endo-syn-near* and *endo-syn-far*, and their activation enthalpies are 16.6 and 15.0 kcal/mol, respectively (Figure 4). This result is in agreement with Kraus' experimental observations in which the *far* product is dominant. The preference of the *far* TS is the result of electron redistribution in TS that led to larger electrostatic repulsion in the *near* TS; the repulsion between oxygen of OTMS and the lactone oxygen might also have some contributions.

For diene **9**, the *syn* TSs were generally more preferred than the *anti* TSs; in those *syn* TSs, the *endo* TSs were more favorable than the *exo* TSs. The most stable two transition states are *endo-syn-near* and *endo-syn-far*, the activation enthalpies of them were 13.9 and 14.9 kcal/mol, respectively (Figure 4). This result is in consistent with our observations in the total synthesis of crisamicin A in which the *near* product is dominant.

The regioselectivity for this multisubstituted diene-based Diels–Alder reaction could be interpreted by the existence of hydrogen bonding between the hydrogen of the methoxy group in diene **9** and the oxygen of the lactone in **6**, which significantly reduces the activation energy of the *near* TS, leading to the unusual regioselectivity of a Diels–Alder

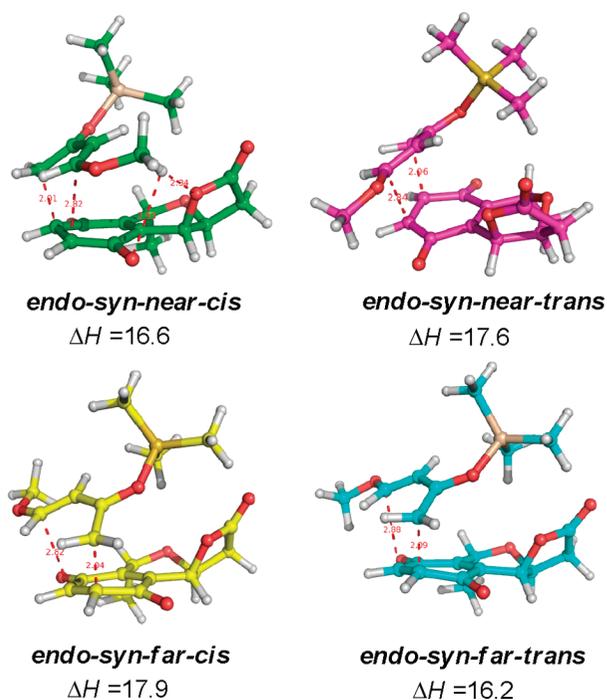


Figure 5. Transition structures for pyranone **6** with substituted butadiene **14**.

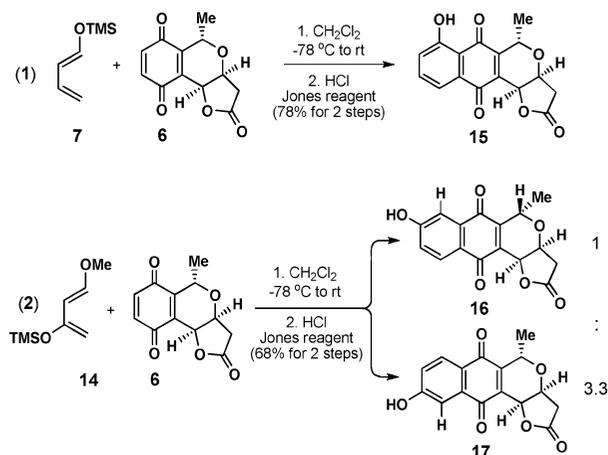
reaction. Roles of such nontraditional hydrogen bonding as $O\cdots H(C)$ interactions have been also discussed in other systems.⁹

To dissect the contributions of the substituents of butadiene on the reaction, further calculations on butadienes with different substituents were performed. Table 1 shows the relative enthalpies of the *endo-syn-near* and *endo-syn-far* TSs. Entries 1–3 indicate that 4,4-dimethoxy groups make major a contribution to the preference of the *near* TS and the 2-OTMS has just minor role. Unexpectedly, entry 4 with a monomethoxy group favors the *far* TS. The main reason is because the terminal methyl group prefers *trans* orientation rather than *cis* orientation in the TS, but the methyl group on the *trans* orientation cannot form $O\cdots H(C)$ interactions and stabilize the *near* TS (Figure 5). It is noted that the *cis* orientation of the terminal methyl group is more stable in the isolated diene.

To further verify our calculations, we have synthesized two additional dienes **7** and **14** and carried out the Diels–Alder reactions under the conditions for the synthesis with quinone

6 to form their corresponding products **15**–**17**, respectively. Accordingly, the diene **7** under our reaction condition gave results identical to those of Kraus and co-workers with the dominant *far* product. However, when diene **14** was applied to the Diels–Alder reaction, two regioisomers **16** and **17** formed, and compound **17** was the major isomer (Scheme 2), which is in good agreement with the calculations. The structures of **16** and **17** were confirmed by HMBC experiments of their NMR study, in which the correlation between the protons and their corresponding carbonyl were observed (Scheme 2).

Scheme 2. Syntheses of Pyranonaphthoquinones **15**–**17**



In summary, B3LYP calculations elucidate the origin of the regioselectivity in intermolecular Diels–Alder reactions of substituted butadienes with pyranone, which is controlled by the electrostatic repulsion between the lactone ring-oxygen and the vicinal quinone oxygen on the transition structure. Shielding of this repulsion by the substituents on the dienes can switch the regioselectivity of Diels–Alder reactions.

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Supporting Information Available: B3LYP Cartesian coordinates and electronic energies of all the stationary points. Full citation for ref 6. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) (a) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441. (b) Corey, E. J.; Rohde, J. J.; Fisher, A.; Azimioara, M. D. *Tetrahedron Lett.* **1997**, *38*, 33. (c) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37. (d) Acevedo, O.; Evanscek, J. D. *Org. Lett.* **2003**, *5*, 649. (e) Bakalova, S. M.; Santos, A. G. *J. Org. Chem.* **2004**, *69*, 8475. (f) Gordillo, R.; Dudding, T.; Anderson, C. D.; Houk, K. N. *Org. Lett.* **2007**, *9*, 501.