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Origins of Regioselectivity of Diels−Alder Reactions for the Synthesis of Bisanthraquinone Antibiotic BE-43472B

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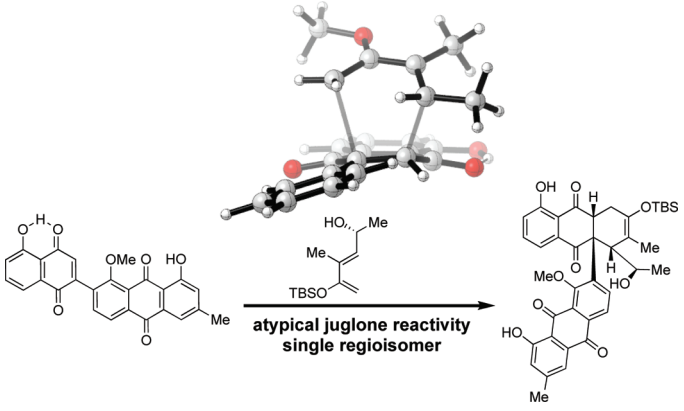

The regioselectivities of several Diels−Alder reactions utilized en route to bisanthraquinone antibiotic BE-43472B are examined using density functional theory calculations. These reactions involve highly substituted dienes and juglone dienophiles, and there is an opposite regiochemical outcome for Diels−Alder reactions with β-aryl substituted juglones when compared to reactions of unsubstituted juglone. In this article, the effect of an aromatic conjugating group bonded to juglone is explored.

Introduction

The bisanthraquinone antibiotic BE-43472B (**1**, Figure 1), which was isolated by Rowley and co-workers from a strain of streptomycete found in green algae,[1] has been shown to have significant bactericidal activity against a variety of pathogens, including some of those that demonstrate resistance to commonly used antibiotics.[2] In addition to antibiotic activity, this compound previously appeared in a Japanese patent, where it was claimed to be an antitumor agent.[3] The development of new antibiotics is currently an area of keen interest as a result of the increasing resistance of bacterial strains to conventional treatments.[4]

Nicolaou et al. recently assigned the absolute configuration and completed the total synthesis of **1** as well as several related compounds.[5] The key to the success of their synthetic pathway was a regioselective Diels−Alder reaction of a highly substituted diene with a juglone-based dienophile. Juglone-based dienophiles have been used in the synthesis of a number of complex organic molecules, several of which

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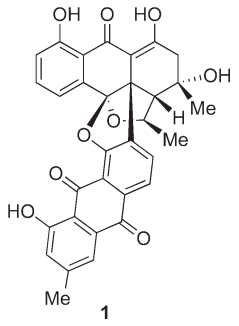
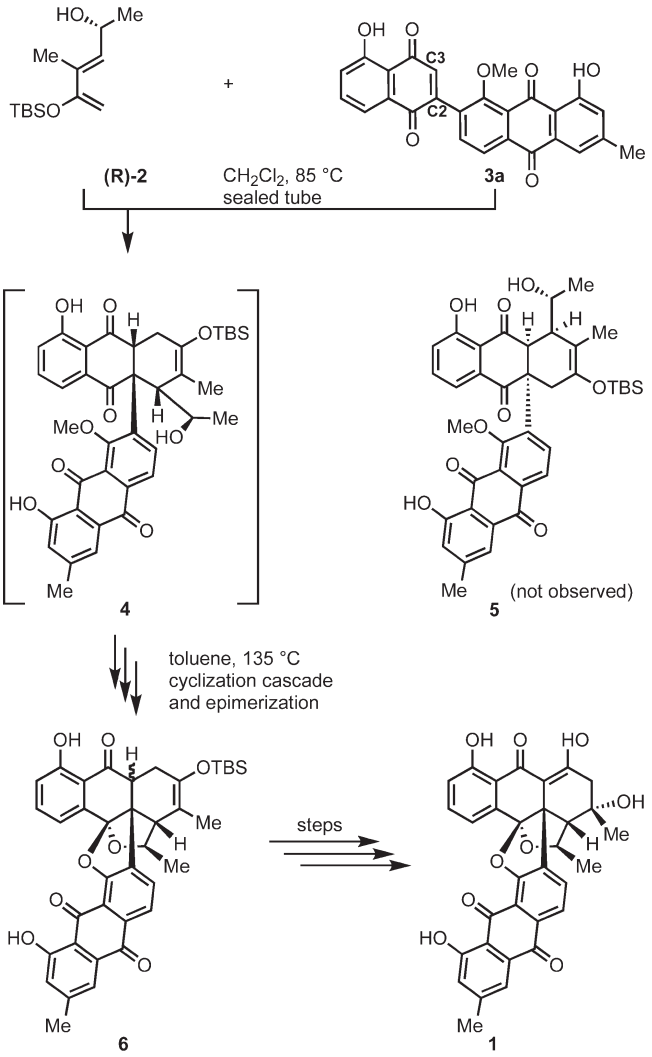


FIGURE 1. The structure of bisanthraquinone antibiotic BE-43472B (**1**).

SCHEME 1. Diels–Alder Reaction Employed in the Synthesis of Antibiotic 1, Which Is Followed by a Cyclization Cascade and Epimerization and Several Subsequent Synthetic Steps to Afford (+)-BE-43472B (1)



also have antibiotic activity, including the anthrapyran metabolite indomycinone,[6] the anthraquinone kwanzoquinone C,[7] a variety of angucyclines,[8] galtamycinone,[9] and urdamycinone.[10] In the synthesis of antibiotic **1**, upon heating of diene (*R*)-**2** and juglone-type dienophile **3a** in dichloromethane, a single Diels–Alder adduct **4** was formed (Scheme 1). Further heating in toluene, which allows for a cyclization cascade and epimerization to occur, furnished the octacyclic framework **6** of BE-43472B.

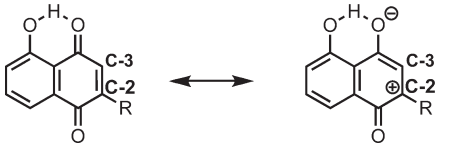


FIGURE 2. Polarization of juglones due to internal hydrogen bonding. Juglone (R = H) typically reacts with C-2 as the most electrophilic position, however, juglone-derivatives (R = anthraquinone) were found react with C-3 as the most electrophilic position.

Fundamental studies of regiocontrol in Diels–Alder cycloadditions between juglone and juglone derivatives with a variety of dienes have been performed, notably by Trost,[11] Kelly,[12] and Boeckmann.[13] The rationale for the observed regioselectivity in cycloadditions of juglones with polar dienes is based on the presence of a strong internal hydrogen bond in juglone between the phenol proton and adjacent carbonyl. This internal Brønsted acid coordination polarizes the π-system of juglones so that the most electrophilic site is the carbon atom β to the hydrogen-bonded carbonyl (C-2 in Figure 2).[14] This regioselectivity is found to be dependent upon diene polarity,[13] with weakly polarized dienes typically giving lower selectivities than more highly polarized dienes, however, Lewis acid catalysts may also be used to influence regiochemical control.[11] In Nicolaou's key Diels–Alder reaction between **2** and **3a** (Scheme 1), the more nucleophilic, unsubstituted diene terminus is found to attack α to the aromatic substituent of the dienophile, at C-3. This regiochemical outcome is intriguing because it is contrary to expectation based on the rationale outlined above, where the carbon atom β to the hydrogen-bonded carbonyl (C-2) is typically more electrophilic due to internal Brønsted activation. The fact that the reaction between **2** and **3a** proceeds with complete regioselectivity also indicates that the aromatic substituent at the β position on the dienophile has a

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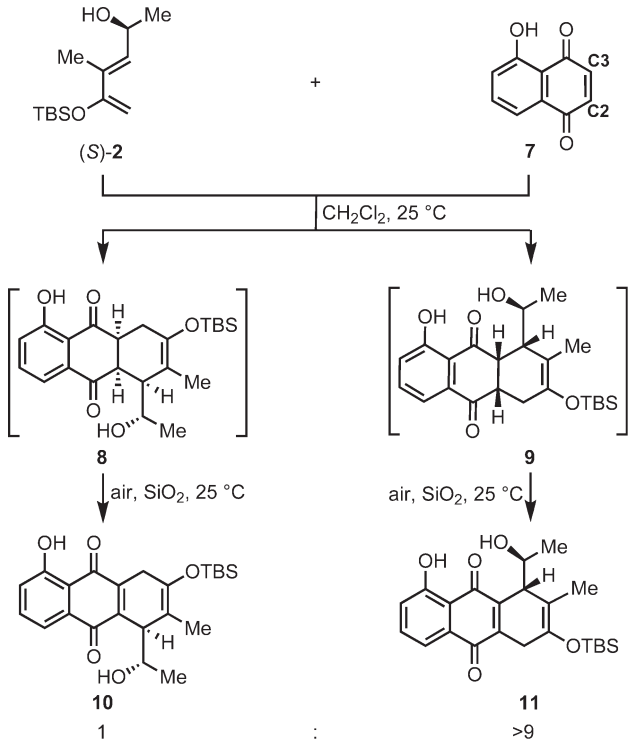
SCHEME 2. After Subsequent Oxidation, the Diels–Alder Reaction of (*S*)-2 with Juglone (7) Provides Regioisomeric Adducts 10 and 11 in a 1 to Greater Than 9 Ratio

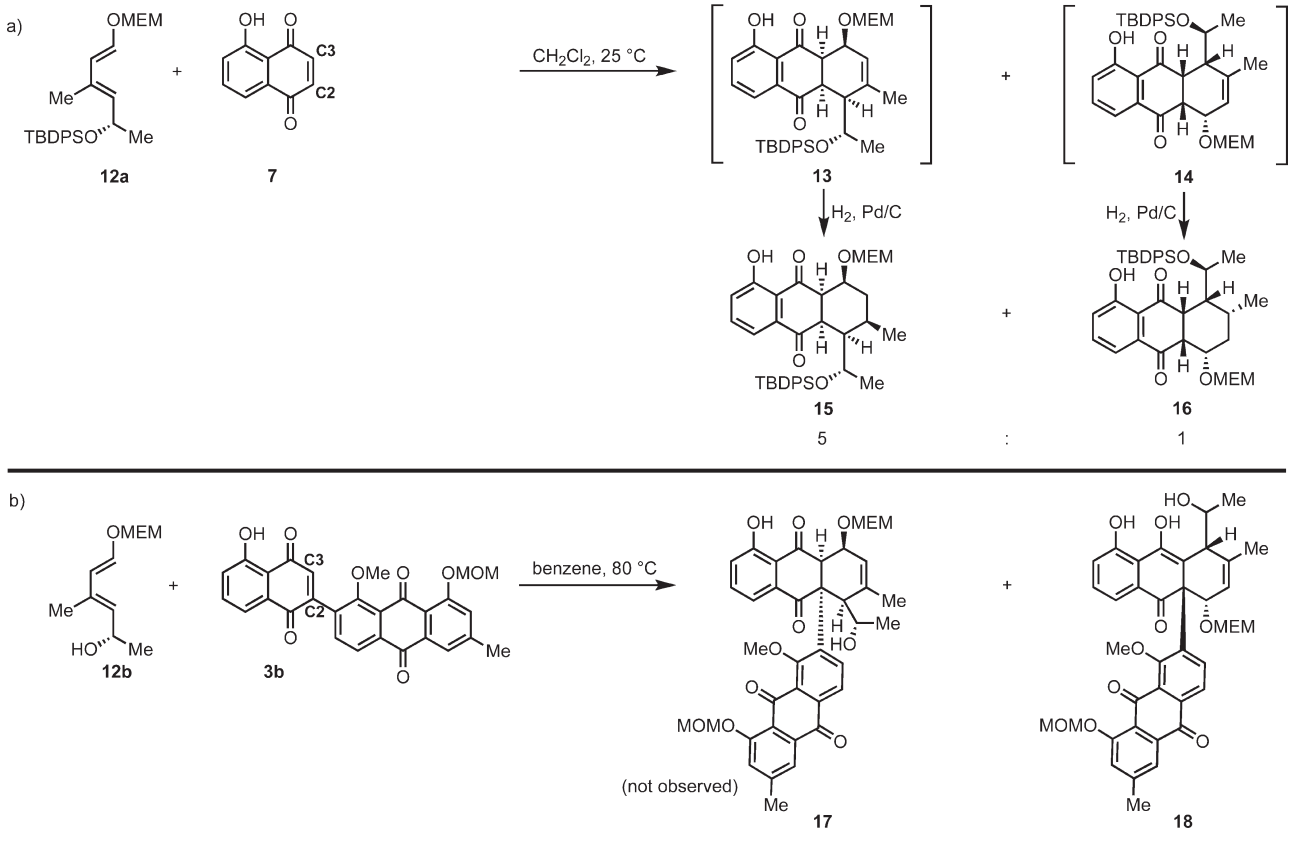


significant, and crucial, effect on the regiochemical outcome of this Diels–Alder reaction.

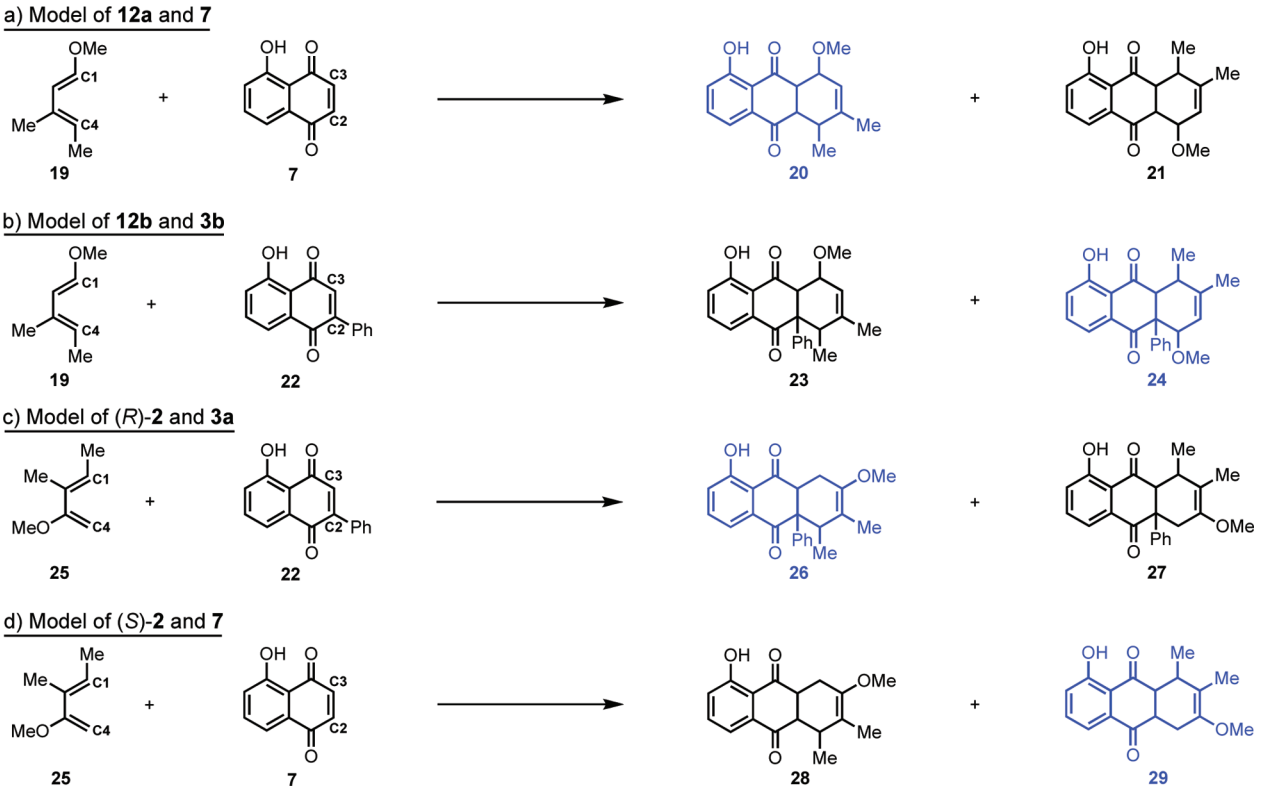
Other Diels–Alder reactions performed en route to antibiotic **1** also provide an interesting basis for a regioselectivity study. Upon reaction of diene (*S*)-**2** (the enantiomer of the diene in Scheme 1) with unsubstituted juglone (**7**), the preferred regioisomer results from the reaction of the nucleophilic terminus of the diene with the carbon β to the hydrogen-bonded carbonyl (C-2), as anticipated based on electronic considerations (Scheme 2). Adducts **8** and **9** were not isolated but were oxidized upon exposure to air and silica gel. Oxidized adducts **11** and **10** were obtained in a greater than 9 to 1 ratio. Thus, the regioselectivity is reversed when unsubstituted juglone is used, further indicating that the anthraquinone substituent on **3a** plays a crucial role in determining the regioselectivity of the reaction.

In addition to the Diels–Alder reactions of the enantiomers of **2** with both substituted and unsubstituted juglones, the reaction of diene **12a**, bearing a β-methoxyethoxymethyl ether (OMEM) group at its C-1 terminus, with juglone (**7**) was also undertaken and similar results were obtained—reaction of the nucleophilic C-4 terminus of the diene with the carbon β to the hydrogen-bonded carbonyl on the dienophile **7** (C-2) is preferred (Scheme 3a). Adducts **13** and **14** were not isolated but were reduced subsequently to give **15** and **16** in a 5:1 ratio. Diene **12b**, which is the deprotected analogue of **12a**, was reacted with substituted juglone **3b**, which differs from **3a** (Scheme 1) only by protection of the phenolic alcohol of the anthraquinone with

SCHEME 3. (a) Reaction of Substituted Diene 12a with Juglone Gives 15 and 16 in a 5 to 1 Ratio; (b) Adduct 18 Is the Preferred Diastereomer When Diene 12b Reacts with Substituted Juglone 3b



SCHEME 4. Model Systems Used in the Computational Study of Diels–Alder Reactions with Juglone Dienophiles: Products that are Predicted to be Preferred Based on Experimental Results with the Nonsimplified Reactants Are Shown in Blue



a methoxymethyl (MOM) protecting group (Scheme 3b). As for the previous case, the regioselectivity of the reaction is switched upon the incorporation of an aromatic substituent β to the intramolecular hydrogen-bond of juglone, giving only a single regioisomer where C-3 acts as the most electrophilic position. To understand how the anthraquinone substituent on juglone alters the regioselectivity of the reaction, a computational study using density functional theory (DFT) calculations was undertaken.

Computational Methods

All calculations were performed with Gaussian 09[15] using the density functional B3LYP with the 6-31G(d) basis set. Vibrational frequencies were computed for all optimized structures in order to verify that they were either minima or transition states, and the unscaled zero-point energies are included in all thermodynamic quantities. Calculations with a conductor-like polarizable continuum solvation model (CPCM)[16] of dichloromethane were performed to evaluate the effects of the experimentally used solvent. The solute surface was defined with UAKS radii in each case. To validate the results obtained at the chosen basis set, single point energy calculations were carried out on all optimized structures with a larger basis set at the B3LYP/6-311G(d,p) level. For each of the reactions studied, the same regiochemical trend is predicted regardless of the basis set used, both giving almost identical quantitative predictions (see Supporting Information).

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Results and Discussion

To predict the regioselectivity of several Diels–Alder reactions involving juglone-based dienophiles, the reactions of interest were simplified to the model systems shown in Scheme 4.

The reaction of **12a** and juglone (**7**) has been explored using 1-methoxy-3,4-dimethyl-1,3-butadiene (**19**) as a model for **12a**. Because of the intramolecular hydrogen-bonding of juglone, the carbon β to this hydrogen-bonded carbonyl (C-2) is the more electrophilic position of the dienophile. The substitution of the diene renders the 4-position the most nucleophilic, primarily as a result of the electron-donating methoxy group at C-1. Therefore, it would be expected that diene **19** and **7** would preferentially give regioisomer **20**, which is what is predicted computationally (see Table 1). The transition states for both regioisomers have similar geometries—both are asynchronous with similar forming bond lengths (Figure 3). However, the preferred **TS-20** ($\Delta H^{\ddagger}$ = 14.9 kcal/mol) is slightly more asynchronous and is electronically favored, resulting in a lower activation energy than for **TS-21** ($\Delta H^{\ddagger}$ = 16.1 kcal/mol).

It is more complicated to intuitively postulate the preferred regioisomer when the juglone is substituted with an aromatic group such as a phenyl group in the model system. Will the withdrawing effect of the hydrogen-bonded carbonyl or the conjugating effect of the aromatic ring control the regioselectivity? It was observed experimentally that the regioselectivity is indeed switched upon this substitution. The nucleophilic termini of the dienes (C-4) react at the carbon α to the hydrogen-bonded carbonyl (C-3) in the β-anthraquinone-substituted juglones. Diene **19** was also

TABLE 1. Computational Results for Juglone Diels–Alder Reactions (kcal/mol, B3LYP/6-31G(d))

reagents		ΔH	ΔG		ΔH	ΔG	predicted ratio[a] (based on ΔG)	experimental ratio[b]
19 + **7**	**20**-TS	14.9	29.8	**21**-TS	16.1	31.1	**20**:**21** = 1.7:1	**20**:**21** = 5:1
	20	−18.7	−2.6	**21**	−17.5	−1.6		
19 + **22**	**23**-TS	22.8	38.3	**24**-TS	17.2	32.6	**23**:**24** = 1:>99	**18** (single diastereomer)
	23	−7.7	9.1	**24**	−6.4	10.1		
25 + **22**	**25**-TS	16.2	31.6	**27**-TS	25.0	40.3	**26**:**27** = >99:1	**4** (single diastereomer)
	25	−10.5	5.3	**27**	−9.5	6.3		
25 + **7**	**28**-TS	16.7	31.4	**29**-TS	14.9	29.6	**28**:**29** = 1:21	10:11 = 1:>9
	28	−21.1	−6.0	**29**	−22.2	−7.2		

[a]Predicted ratio of the simplified model systems. [b]Experimentally observed ratio of the corresponding products.

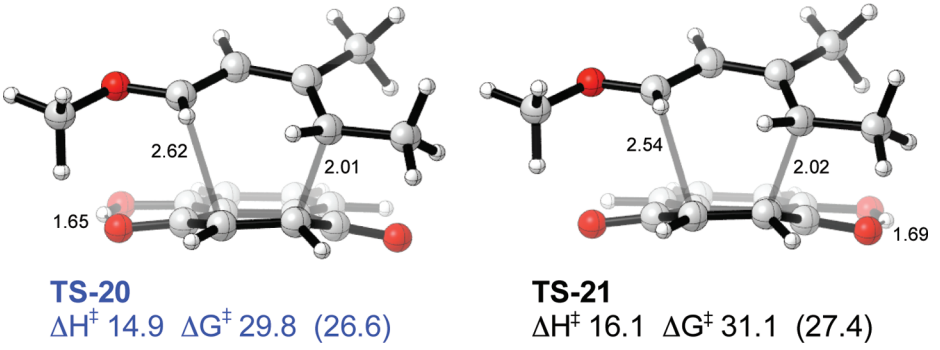

FIGURE 3. Transition structures for the model reaction of diene **19** with juglone (**7**). B3LYP/6-31G(d) energies in kcal/mol, with dichloromethane value in parentheses. The favored TS is labeled in blue. Selected distances in Å.

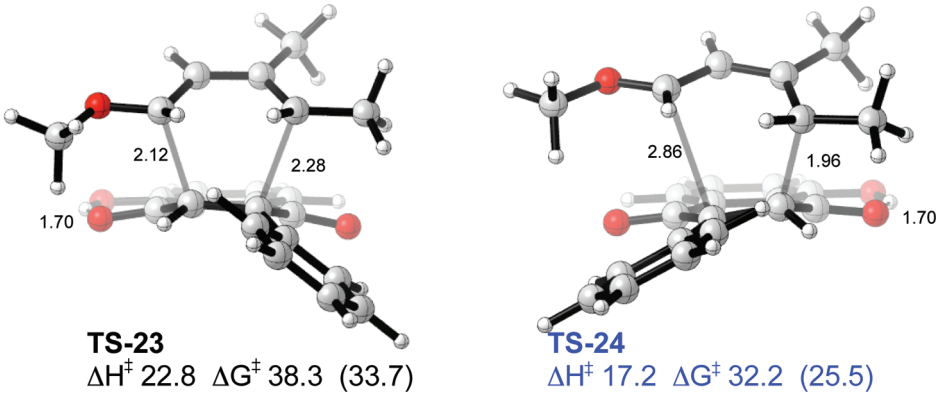

FIGURE 4. Transition structures for the model reaction of diene **19** with juglone **22**. B3LYP/6-31G(d) energies in kcal/mol, with dichloromethane value in parentheses. The favored TS is labeled in blue. Selected distances in Å.

used as a model for **12b**, and β-anthraquinone-substituted juglone **3b** was modeled with β-phenyl-substituted juglone (**22**) in order to reduce the computational cost and also to obtain a more generalized model useful for the prediction of regioselectivity in similar Diels–Alder reactions. Juglones **3b** and **22** were found to be very similar electronically: computed electrostatic potential surfaces, lowest unoccupied molecular orbital coefficients, and Mulliken atomic charges were all similar (see Supporting Information), so a phenyl substituent is a good model for the larger bisanthraquinone used in experiment. In this system, the transition structure for the preferred regioisomer (**TS-24**, $\Delta H^{\ddagger}$ = 17.2 kcal/mol) is significantly more asynchronous than **TS-23** ($\Delta H^{\ddagger}$ = 22.8 kcal/mol, Figure 4). The forming bond length is shorter between the C-3 carbon adjacent to the phenyl group on the juglone and the nucleophilic terminus of the diene. Computational predictions fully agree with the experimental results—the conjugating effect of the aromatic moiety is more electronically dominant than the electron-withdrawing effect of the hydrogen-bonded carbonyl.

To obtain the necessary adduct of a β-anthraquinone-substituted juglone, diene (*R*)-**2** was used in the synthesis of antibiotic BE-43472B instead of diene **12b**. Both enantiomers of diene **2** were modeled with 3-methoxy-1,2-dimethyl-1,3-butadiene (**25**) and the same juglone-type dienophiles as used in the preceding computations (**7** and **22**) were employed. The transition states for the reaction of diene **25** with juglone **22** are similar to those of this dienophile with diene **19**—the lower energy transition structure (**TS-26**, $\Delta H^{\ddagger}$ = 16.2 kcal/mol, for **TS-27**: $\Delta H^{\ddagger}$ = 25.0 kcal/mol) is the one in which the carbon adjacent to the phenyl group on the juglone (C-2) combines with the nucleophilic terminus of the diene (C-4) (Figure 5a). This preferred transition state is again more asynchronous than the transition structure of the other possible regioisomer. The higher energy of the transition structure leading to the disfavored adduct suggests that steric

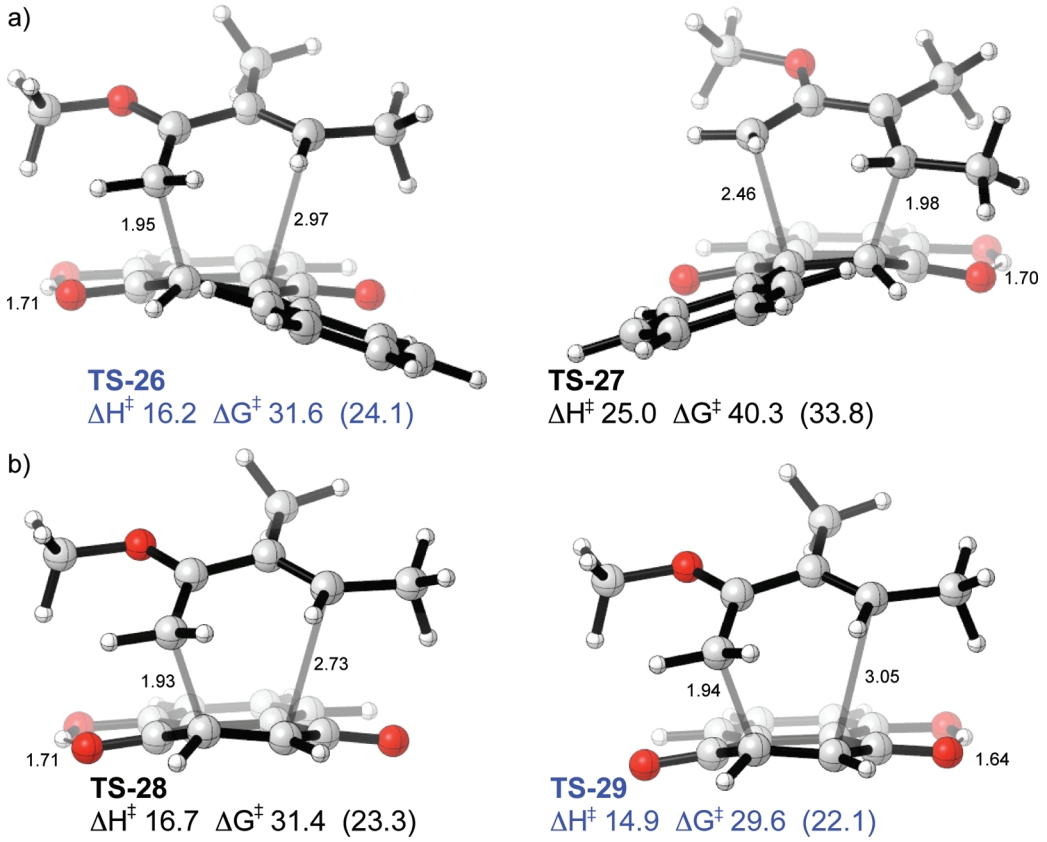

FIGURE 5. Transition structures for the model reactions of diene **19** with juglones (a) **22** and (b) **7**. B3LYP/6-31G(d) energies in kcal/mol, with dichloromethane value in parentheses. Favored TSs labeled in blue. Selected distances in Å.

hindrance to attach at the unsubstituted carbon as well as the conjugating affect of the aromatic group control the regioselectivity. In addition, when diene **25** is modeled with unsubstituted juglone, the electronically expected product **29** is favored (for **TS-28**: $\Delta H^{\ddagger}$ = 16.7 kcal/mol, for **TS-29**: $\Delta H^{\ddagger}$ = 14.9 kcal/mol, Figure 5b). Table 1 summarizes all computational results.

The computed energy differences between competing Diels−Alder transition structures demonstrate that the effect of an aryl substituent on juglone is more potent than the internal hydrogen bond in imparting regiocontrol. For the dienes studied, there is an energetic preference for the more nucleophilic terminus to attack at C-2 of juglone ($\Delta\Delta G^{\ddagger}$ 1.3−1.8 kcal/mol). With a phenyl substituent at C-2, however, this regiochemical preference is overturned, and the nucleophilic terminus of the diene prefers to attack at C-3 ($\Delta\Delta G^{\ddagger}$ 5.7−8.7 kcal/mol). Inspection of the transition structures suggests that synchronicity of bond formation is important in determining regioselectivity. In reactions with juglone **7**, bond formation in the transition structure is always more advanced at the more nucleophilic C-4 terminus of the diene. Transition structures for 2-phenyl juglone **22** show similar asynchronous bond formation when the diene C-4 terminus attacks the dienophile at C-3. However, for the regioisomeric attack of **22**, bond formation is more advanced between the less nucleophilic C-1 terminus of the diene and C-3 of the dienophile. The aryl group strongly activates attack at C-3, overwhelming activation by the hydroxyl group. The phenyl group stabilizes the reactant through conjugation but does not stabilize transition states involving substantial bond formation at C-2, the phenyl-substituted carbon. Consequently, transition states in which the most nucleophilic terminus of the diene attacks C-3 are strongly favored.

Conclusions

The regioselectivities of several Diels−Alder reactions involving juglone-based dienophiles were studied computationally. In unsubstituted juglone, the phenolic proton hydrogen bonds to the neighboring carbonyl group, rendering the carbon β to this hydrogen-bonded carbonyl (C-2) the more electrophilic position of the dienophiles; this position reacts with the more nucleophilic terminus of the diene. However, the effect of an aromatic group β to this intramolecular hydrogen-bond was found to be dominant, as the nucleophilic termini of several dienes are predicted to react at the carbon α to the hydrogen-bonded carbonyl (C-3). Therefore, there is an opposite regiochemical outcome for Diels−Alder reactions with β-aromatic-substituted juglones when compared to reactions of unsubstituted juglone.

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Supporting Information Available: Absolute energies and Cartesian coordinates of stationary points. Complete ref 15. This material is available free of charge via the Internet at http://pubs.acs.org.