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Exo-Selective Diels−Alder Reactions of Vinylazepines. Origin of Divergent Stereoselectivity in Diels−Alder Reactions of Vinylazepines, Vinylpiperideines, and Vinylcycloalkenes

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Diels−Alder reactions of vinylazepines with *N*-phenylmaleimide afforded exclusively the exo cycloadduct, while high endo stereoselectivity was observed, as previously reported, in analogous reactions of vinylpiperideines. This curious contrast was confirmed by X-ray analysis of cycloadducts not susceptible to epimerization. The stereoselectivity of Diels−Alder reactions of vinylazepines, vinylpiperideines, and vinylcycloalkenes exhibits surprising divergence depending on the detailed diene structure, and DFT calculations (Becke3LYP) were undertaken to shed light on these observations. The model calculations correctly predict the major stereoisomers in these reactions, though they tend to significantly underestimate the stereoselectivity. The results suggest some general considerations in predicting or controlling the stereochemistry of this class of Diels−Alder reactions.

Introduction

Diels−Alder reactions employing vinylcycloalkenes and related dienes provide a rapid entry into polycyclic structures. However, to fully take advantage of the power of these reactions, the synthetic chemist must be able to predict or control their stereoselectivity. In connection with synthetic studies relating to the synthesis of stenine, we have observed surprising examples of exo selectivity as well as reversals of endo/exo stereoselectivity with changes in diene structures. This has led to a broader study of endo/exo stereoselectivity with vinylcycloalkenes of this type. The combined experimental/theoretical investigation here provides insight into these results as well as observations of exo selectivity in related Diels−Alder reactions.

Stenine (**1**), a polycyclic alkaloid, was isolated from extracts of the roots of *Stemona tuberosa*.[1] A unique structural feature of this alkaloid is the central azepinoindole core structure (BCD ring system **2**) (Figure 1). The complex polycyclic architecture of stenine has attracted synthetic efforts by several research groups. Hart and Chen reported a racemic total synthesis of stenine in 1990. Enantioselective syntheses of (−)-stenine were later independently described by Wipf and Morimoto.[2] In all three syntheses, the order of ring formation was BD → BDC, where the azepine ring was introduced last. We were attracted to the possibility of using a Diels−Alder reaction employing an azepine-derived 2-(*N*-acylamino)-1,3-diene (**3**) to construct the azepinoindole ring system in a unique order (i.e., BC → BDC).[3]

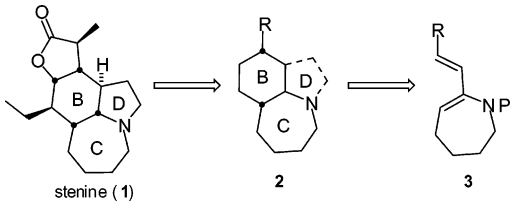

FIGURE 1. Retrosynthetic analysis of stenine (**1**).

Only recently have reports describing Diels−Alder reactions of cyclic 2-(*N*-acylamino)-1,3-dienes appeared in the literature. Cha studied piperideine-derived enecarbamates and found these dienes react with ethyl acrylate with unusual meta regioselectivity and no endo/exo stereoselectivity.[4] However, *N*-phenylmaleimide was found to afford exclusively the endo cycloadduct, a result later corroborated by Occhiato.[5] Reactions of pyrollidine-derived 2-(*N*-acylamino)-1,3-dienes with *N*-phenylmale-

(1) (a) Gotz, M.; Edwards, O. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. IX, pp 545−551. (b) Gotz, M.; Strunz, G. M. In *Alkaloids: MTP International Review of Sciences*; Wiesner, K., Ed.; Butterworth: London, 1973; Series One, Vol. IX, pp 143−160.

(2) (a) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236−6240. (b) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840−3849. (c) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106−11112. (d) Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 904−906. (e) Morimoto, Y.; Iwahashi, M.; Kinoshita, T.; Nishida, K. *Chem.−Eur. J.* **2001**, *7*, 4107−4116.

(3) During the preparation of this manuscript two syntheses of stenine have appeared that use a Diels−Alder reaction as a key step: (a) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515−1517. (b) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316−4318.

(4) Du Ha, J.; Kang, C. H.; Belmore, K. A.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 3810−3811.

(5) Occhiato, E. G.; Trabocchi, A.; Guama, A. *Org. Lett.* **2000**, *2*, 1241−1242.

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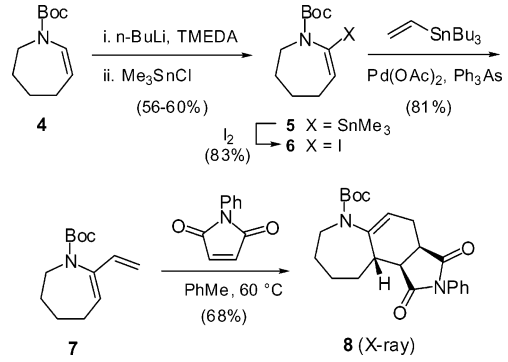
SCHEME 1



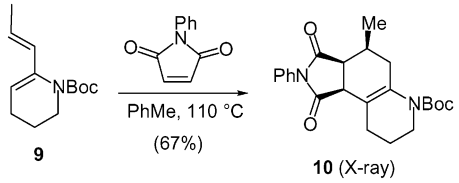
imide also exhibit exclusive endo selectivity.[6] No studies on the seven-membered azepine dienes (cf. **3**) have been reported.

Results and Discussion

Cyclic 2-(*N*-acylamino)-1,3-dienes have been prepared from the Stille and Suzuki cross-coupling of lactam-derived enol triflates or phosphates.[6a,7] The enol triflate derived from caprolactam has been reported in the literature;[7a,e] however, we found this enol triflate to be inconvenient to work with due to its hydrolytic instability. As an alternative, we prepared the corresponding α-iodo enecarbamate (**6**) from readily available enecarbamate **4** (Scheme 1).[8] Treatment of **4** with *n*-BuLi−TMEDA followed by reaction with Me_3SnCl gave stannane **5** in 56−60% yield.[9] Reaction of **5** with iodine in THF then afforded iodo enecarbamate **6** in 83% yield as a white crystalline solid. Next, palladium-mediated cross-coupling of **6** with vinyltributylstannane gave 2-(*N*-acylamino)-1,3-diene **7** in 81% yield. The Diels−Alder cycloaddition between **7** and *N*-phenylmaleimide proceeded in toluene at 60 °C (3 h) to afford **8** as the only observable cycloadduct. By single-crystal X-ray analysis, **8** was found to be the exo product shown.

In light of the opposite literature results with smaller rings, this was very surprising. In earlier studies, the stereochemistry of the cycloadducts derived from the Diels−Alder reaction of *N*-phenylmaleimide and cyclic 2-(*N*-acylamino)-1,3-dienes were assigned on the basis of NMR analysis. To corroborate these structural assignments, the cycloaddition of diene **9** with *N*-phenylmaleimide was studied. This afforded product **10**, resulting from an endo cycloaddition followed by double-bond migration. The structure of **10** was confirmed by X-ray analysis (Scheme 2).

SCHEME 2



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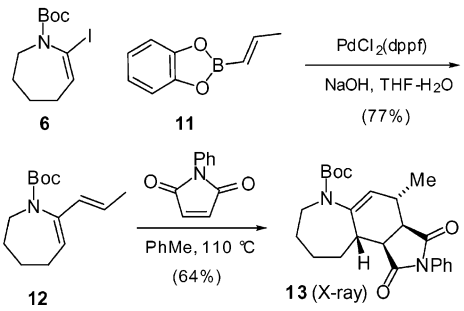
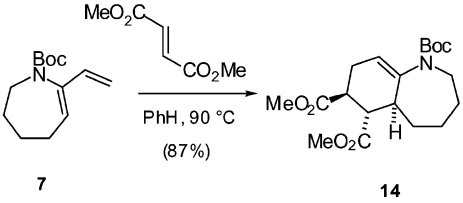


SCHEME 4



Double-bond migration in the product enamides, as observed both in **10** and previously,[4] is presumably catalyzed by adventitious acid. This isomerization raised the concern that **8** might be the result of an initial endo cycloaddition followed by epimerization of the ring fusion carbon. This possibility was explored using diene **12**, readily available from cross-coupling of **6** with catecholboronate **11**. In this case, the Diels−Alder cycloadduct includes an additional stereochemical marker center that is *not* epimerizable. Reaction of **12** with *N*-phenylmaleimide afforded only **13**, established as exo by X-ray analysis, in 64% yield (Scheme 3).

Vinyl azepine **12** reacted with ethyl acrylate in toluene at 110 °C overnight to provide a mixture of isomers, presumably consisting of regio- and stereoisomers as reported by Cha when utilizing a piperidine derived diene analogous to **12**.[4] In contrast, the doubly activated dienophile dimethyl fumarate reacted with vinyl azepine **7** to provide a *single* Diels−Alder adduct **14** (Scheme 4). The structure of **14** was assigned by preparation of a crystalline derivative followed by single-crystal X-ray analysis.[10] In this case, the methyl carboxylate group closest to the ring fusion carbon adopts an exo orientation and the second carboxylate group occupies an endo orientation.

The striking reversal of exo/endo stereoselectivity between azepene-derived 2-(*N*-acylamino)-1,3-dienes and their smaller-ring congeners is unusual. Quite a few exo-selective Diels−Alder reactions are known, but they tend to involve recognizable structural motifs. For example, exocyclic s-cis dienophiles of all types tend to be exo-

(6) (a) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131−8140. (b) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803−805.

(7) (a) Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656−2657. (b) Okita, T.; Isobe, M. *Synlett* **1994**, 589−590. (c) Okita, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 3737−3744. (d) Tsushima, K.; Hirade, T.; Hasegawa, H.; Murai, A. *Chem. Lett.* **1995**, 801−802. (e) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459−2465. (f) Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757−1758.

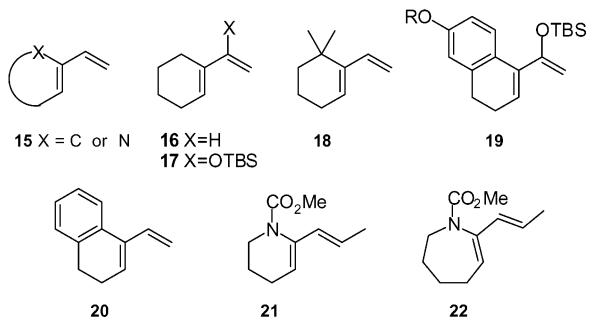
(8) Enecarbamate **4** was prepared from Boc-protected homopiperidine by electrochemical methoxylation followed by acid-catalyzed elimination of methanol. Cf. Nyberg, K. *Synthesis* **1976**, 545−546. For an alternative preparation starting from carporlactam see ref 9b.

(9) (a) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056−9062. (b) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155−158.

(10) Structure determination of **14** is described in the Supporting Information.

selective.[11] Preferential exo cycloaddition is often observed in the reaction of cyclopentadiene with α-substituted dienophiles.[12] The unique sterics of metal carbene dienophiles also result in exo selectivity.[13]

The Diels–Alder reactions of vinylcycloalkenes and cyclic 2-(*N*-acylamino)-1,3-dienes, as in **15**, would appear to compose a motif in which the endo/exo stereoselectivity is highly variable. While 1-vinylcyclohexene (**16**) and the silyloxy derivative **17** afford endo cycloadducts,[14,15] Danishefsky obtained the exo cycloadduct from a reaction of the dimethyl derivative **18**,[16] and Corey observed exo selectivity in a reaction of **19**.[15] Others have reported low endo selectivity of the reaction of diene **20** and congeners.[17] In these examples and those above, seemingly minor changes in the structure of the "spectator" ring lead to reversed stereochemistry.



To gain insight into stereoselectivity with this class of dienes, the model reactions of **16**, **18**, **20**, **21**, and **22** with maleimide were studied in Becke3LYP calculations employing a 6-31G* basis set. Isotope effects have supported the accuracy of transition structure geometries obtained from this level of calculation for simple Diels–Alder reactions.[18] This study was complicated by multiple possible reactive conformations, particularly with **22**. Molecular dynamics/simulated annealing was used to identify candidate conformations, and notably found structures for **22** corresponding to the chair, boat, and twist-chair conformations of cycloheptane.[19] The possible

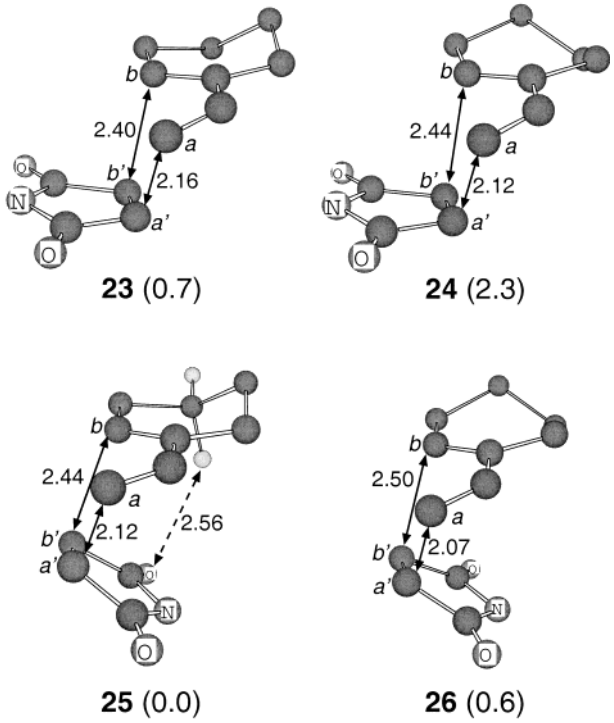


FIGURE 2. Transition structures for the reaction of **16** with maleimide. Energies are relative to isomeric transition structures, in kcal/mol. Most hydrogens have been removed for clarity.

reaction pathways were then explored systematically. This process led to a total of 36 transition structures for the five reactions.

Figures 2 and 3 show selected low-energy transition structures for these reactions, along with relative free-energy barriers at 25 °C (the free energy was estimated as $\Delta E - T\Delta S$ by including zero-point energies and entropies based on the unscaled vibrational frequencies). Complete structures are given in the Supporting Information. In each case, the calculations correctly predict the experimentally observed major isomer.[20] However, they underpredict the degree of selectivity compared to the experimental examples.

Recent work by Paddon-Row and Sherburn suggested the use of MP2 single-point energies on the Becke3LYP structures to more accurately predict endo stereoselectivity in Diels–Alder reactions.[21] When this procedure is applied to the reactions **16**, **18**, and **20**, the MP2/6-31G*//B3LYP/6-31G* free energies correctly predict the endo stereoselectivity with **16** (by 1.2 kcal/mol), but they

(11) (a) Fotiadu, F.; Pardigon, O.; Buono, G.; Le Corre, M.; Hercouet, A. *Tetrahedron Lett.* **1999**, *40*, 867–870. (b) Barluenga, J.; Canteli, R.-M.; Florez, J.; Garcia-Granda, S.; Gutierrez-Rodriguez, A.; Martin, E. *J. Am. Chem. Soc.* **1998**, *120*, 2514. (c) Roush, W. R.; Koyama, K. *Tetrahedron Lett.* **1992**, *33*, 6227. (d) Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708. (d) Pyne, S. G.; Dikic, B.; Gordon, P. A.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1992**, *46*, 73–81.

(12) (a) Kobuke, Y.; Fueno, T.; Furukawa, J. *J. Am. Chem. Soc.* **1970**, *92*, 6548–6553. (b) Essers, M.; Wibbeling, B.; Haufe, G. *Tetrahedron Lett.* **2001**, *42*, 5429–5433. (c) Maruoka, K.; Imoto, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 12115–12116.

(13) (a) Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D.; Waltermire, B. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 6438–6439. (b) Weyershausen, B.; Nieger, M.; Doetz, K. H. *J. Org. Chem.* **1999**, *64*, 4206. (c) Sabat, M.; Reynolds, K. A.; Finn, M. G. *Organometallics* **1994**, *13*, 2084–2087.

(14) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537–562.

(15) Ge, M.; Stoltz, B. M.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1927–1929.

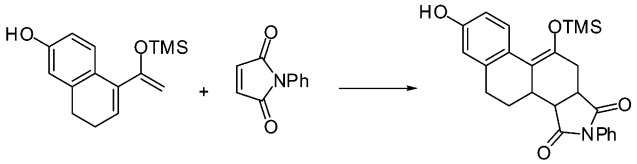
(16) Yoon, T.; Danishefsky, S. J.; de Gala, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 853–855.

(17) (a) Rosillo, M.; Casarrubios, L.; Dominguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2001**, *42*, 7029–7031. (b) Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.* **2000**, *65*, 1697–1701. (c) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Bruno, G.; Caruso, F.; Giannetto, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2901–2908.

(18) Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984–9985.

(19) Hendrickson, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 7036–7043.

(20) A reviewer was concerned that the difference between experimental reaction with **19** and the calculational model **20** was too great. We have carried out calculations on the much more closely analogous reaction shown below (see the Supporting Information). As with the simpler model, the exo transition structure is correctly favored, in this case by 0.75 kcal/mol.



(21) Jones, G. A.; Paddon-Row, M. N.; Sherburn, M. S.; Turner, C. I. *Org. Lett.* **2002**, *4*, 3789–3792.

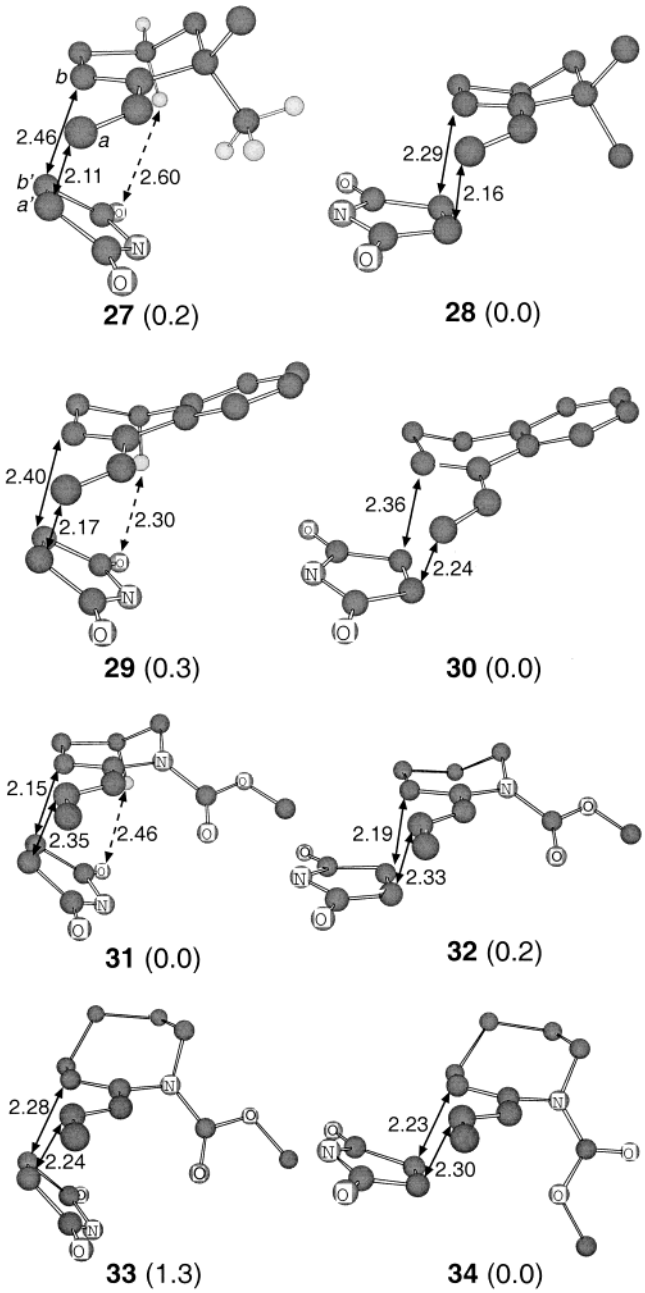


FIGURE 3. Select low energy transition structures for reaction of **18** (**27** and **28**), **20** (**29** and **30**), **21** (**31** and **32**), and **22** (**33** and **34**) with maleimide. Energies are relative to isomeric transition structures, in kcal/mol. Most hydrogens have been removed for clarity.

also predict endo stereoselectivity for **18** and **20** by 0.3 and 1.2 kcal/mol, in contrast to experimental observations with **18** and **19** and in contrast to the B3LYP/6-31G*// B3LYP/6-31G* results in Figures 2 and 3. It is best to keep in mind that any feasible theoretical calculation of relative energies for systems this large will have associated with it some "uncertainty." Considering this uncertainty, along with the structural differences between the experimental and theoretical examples, the agreement of experiment and the B3LYP predictions is quite reasonable. The calculations provide a model that may be examined to analyze the factors affecting the stereoselectivity, and the agreement of predicted major product with experiment suggests that this model adequately represents the major stereochemistry-determining factors.

As a starting point for understanding these reactions, exo transition structures strongly favor "axial attack" on the six-membered ring dienes (Figure 2). By axial attack, we mean that the incipient b−b′ bond in structures **23**, **25**, and **27**−**32** would initially be in an axial position on a chair conformation of the bystander ring. An example is the 1.6 kcal/mol advantage for **23** over **24**. Similar preferences of 1.6−2.0 kcal/mol are seen with the exo transition structures derived from **18**, **20**, and **21**. This appears analogous to the well-known predilection axial alkylation of cyclohexanone enolates. One generally expects axial attack to be more hindered, but when steric effects are small, axial attack has the advantage of resulting in an initial chair conformation for the bystander ring.[22]

The endo transition structures derived from **16**, **18**, **20**, and **21** also favor an axial attack, but the preference is decreased compared to the exo. For example, **25** is favored over **26** by 0.6 kcal/mol. For the endo pathways, axial attack is sterically hindered by an incipient 1,3-diaxial interactions (cf. **25**). The equatorial attack remains disfavored in the calculations here for all of the six-membered ring dienes. However, the predicted energy difference is small (0.1−0.6 kcal/mol) and within the likely uncertainty in the calculations. Equatorial attack might be expected to be favored for more sterically demanding dienophiles.

Exo axial attack also faces an incipient 1,3-diaxial interaction but it has the advantage of placing the imide ring away from the sterics of the spectator ring. When the sterics are increased, as with **18**, the endo axial approach is hindered and the exo axial attack unsurprisingly becomes favored (compare **27** versus **28**). A more surprising example is the reaction of **20**. In the endo axial transition structure **29**, the cyclohexadiene-like ring is very nonplanar and the axial hydrogen shown has a stronger steric interaction with the dienophile than in any of the analogous structures resulting in a favored exo approach (**30**).

In the transition structures derived from **21**, the piperideine ring and its carbomethoxy substituent have relatively little steric influence on the approaching dienophile, allowing a normal endo stereoselectivity. A surprising observation is that the plane of the carbamate nitrogen in **31** is twisted by 38° relative to the plane of the diene. It might have been expected that the carbamate would try to align the nitrogen lone pair with the diene π orbitals in order to maximize donation to the diene. In the predicted conformation, the nitrogen will have a negligible activating effect. This is consistent with the moderate reactivity of the dienes and explains the meta regioselectivity observed by Cha for these reactions.[4]

The best structures derived from **22**, such as **33** and **34**, all involve a decidedly nonplanar chairlike conformation of the azapine ring with the carbomethoxy group twisted well away from the plane of diene. For the seven-

(22) House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935−942. House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 1000−1003.

membered ring, there is apparently no longer a stereoelectronic effect favoring "axial" attack on the pseudochair; in fact, the structures analogous to **25**, **27**, **29**, and **31** suffer from a severe steric interaction with the seven-membered ring and are 4 kcal/mol higher in energy. Endo attack on the other face of the diene, as in **33**, is better but is still hindered by interaction with the carbomethoxy group. As with the piperideine analogues, the plane of the carbamate nitrogen in **33** is twisted relative to the plane of the diene, but now by 56°. This positions the carbomethoxy group to block one face of the diene. With the highly nonplanar seven-membered ring blocking the other, the exo pathway becomes favored by a substantial margin.

Conclusions

Diels–Alder reactions of vinylazepines and vinylpiperideines fit in with the reactions of vinylcycloalkenes in that the group, as a whole, exhibits highly variable stereoselectivity. This stereoselectivity depends on the detailed structure of the diene and will likely depend on the dienophile as well, so that generalizations regarding the selectivity of these reactions are not yet apparent. Nonetheless, the results here suggest some general considerations in predicting or controlling the stereochemistry of this class of Diels–Alder reactions. To counteract the normal endo preference with simple dienes built from five- and six-membered rings, substituents that maximize a 1,3-diaxial interaction with the incoming dienophile should most readily result in exo selectivity. In analogy with the 6,6-dimethyl derivative **18**, we would predict that axial substituents in the 4-position of vinylcyclohexene would result in exo product formation. Axial substituents in the 3 or 5 positions would likely exert less effect. The greater nonplanarity with seven-membered can readily lead to steric prohibition of the endo pathway. This presents interesting opportunities for control of stereoselectivity in the synthesis of stenine and related molecules, which we are pursuing.

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Supporting Information Available: Experimental procedures, structure determination of **14**, characterization data for all new compounds, X-ray models of **8**, **10**, and **13**, and all theoretical structures and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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