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Density Functional Theory Guided Design of Exo-Selective Dehydroalanine Dienophiles for Application Toward the Synthesis of Palau'amine

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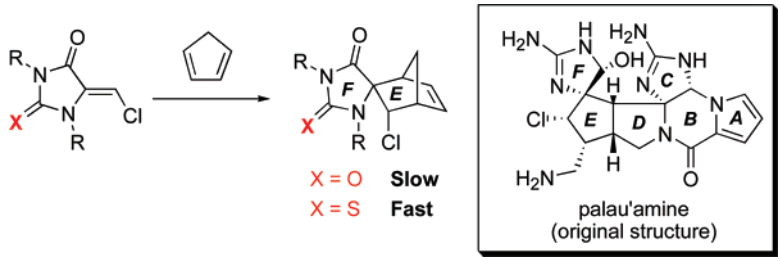


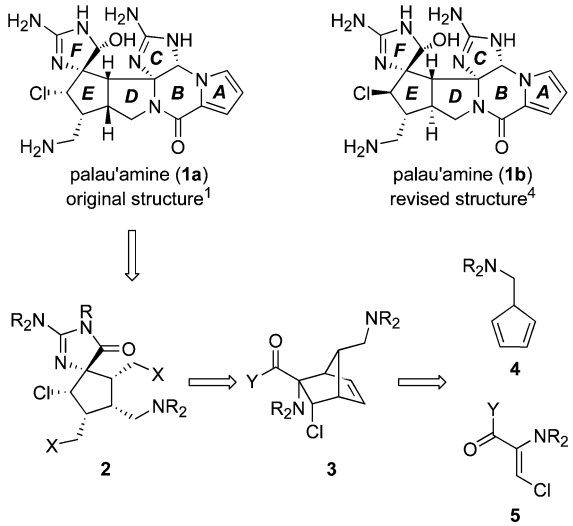
Diels−Alder cycloadditions of dehydroalanine derivatives with cyclopentadiene, applicable to the synthesis of palau'amine, were investigated experimentally and using DFT computations at the B3LYP/6-31G* level of theory. Oxazolone and thiohydantoin dienophiles were found to be significantly more reactive than hydantoins or dehydroalanine methyl esters. The increased reactivity of the thiohydantoins relative to hydantoins is attributed to increased conjugation of nitrogen lone pairs into the thiocarbonyl group. β-Substitution greatly decelerates the cycloadditions due to steric interactions in the transition states outweighing any electronic activation by chlorine. Hydantoins and thiohydantoins were found to be exo-selective, while the corresponding oxazolones and dehydroalanines were unselective.

Introduction

Palau'amine (**1**) is a marine natural product originally isolated in 1993 from the sponge *Stylotella aurantium*.[1] It has been reported to be a potent immunosuppressive agent as well as possessing moderate anticancer and antifungal activity. The natural product, a member of the class of oroidin dimers, is a hexacyclic alkaloid that contains two guanidine units, a pyrrole carboxylic acid, and a densely functionalized E-ring. This challenging structure combined with intriguing biological activity has engendered significant interest from the total synthesis community.[2,3]

The stereochemistry about the E-ring in the natural product is a matter of controversy. The initial proposal by Kinnel et al. (**1a**, Scheme 1) had rings D and E cis-fused and a chloride on the α-face of the molecule. This particular structure is quite a challenging target for synthesis, as the E-ring possesses an α-substituent at each position of the cyclopentane ring. Very recently, three groups proposed a revision of the stereochemistry

SCHEME 1. Palau'amine: Structure and Retrosynthesis



(1) (a) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376. (b) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281. (c) Al-Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237. (d) For, konbu'acidin A, a close relative of palau'amine, see: Kobayashi, J.; Suzuki, M.; Tsuda, M. *Tetrahedron* **1997**, *53*, 15681.

(2) For reviews of synthetic studies toward palau'amine and its relatives, see: (a) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551. (b) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753. (c) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464.

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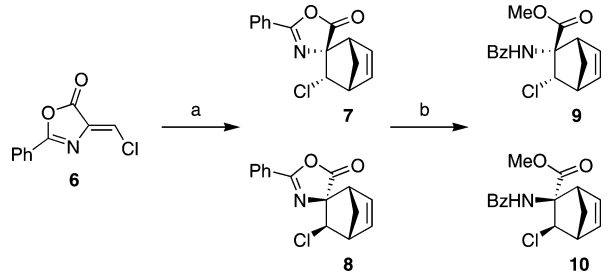
based upon computational studies, correlation with other oroidin dimers, and reisolation and characterization of palau'amine itself. The reassignment is based chiefly upon interpretation of NOE intensities. In the proposed revised structure (**1b**), the D−E fusion is trans and the chloride is on the β-face.[4] In the absence of X-ray crystallographic data, confirmation of the correct structure will hinge upon eventual total synthesis of the natural product. Thus, stereocontrolled syntheses of either E-ring stereopentad are of obvious interest.

Despite significant synthetic interest, no route has yet been reported that fully addresses the originally reported stereochemistry of the E-ring of palau'amine.[5] In particular, installation of the chloride on the α-face has been a significant challenge. As a potential solution to this problem, we envisaged a route involving an exo-selective Diels−Alder cycloaddition of a 5-substituted cyclopentadiene (**4**) with a β-chlorodehydroalanine (**5**). The resulting norbornene (**3**) could then be cleaved to reveal a fully substituted E-ring (**2**) with the desired stereochemistry.

The retrosynthetic plan was predicated on two important factors. First, the Diels−Alder reaction must be exo-selective in order to set the correct stereochemistry of the chloride and spiro-center. While simple dehydroalanines are often exo-selective dienophiles,[6] there was very little information on Diels−Alder reactions of β-chlorodehydroalanines.[7] Second, the strategy hinges upon being able to use a 5-substituted cyclopentadiene. It is well-documented that these types of dienes are prone to 1,5-sigmatropic hydrogen shifts, and thus Diels−Alder reactions at or below room temperature are required for their successful employment.[8]

In this paper, we describe a study of Diels−Alder reactions of β-chlorodehydroalanine derivatives for use in the synthesis of the palau'amine core. In this study, cyclopentadiene was used as a simple model to gauge reactivity and exo/endo-selectivity of a variety of dienophiles. The experimental work was guided by density functional theory (DFT) modeling to predict, a priori, dienophiles that would possess a desirable reactivity and selectivity profile and, ultimately, to predict a surprising accelerating effect of sulfur for oxygen substitution in heterocyclic dienophiles.

SCHEME 2. Cycloaddition of Oxazolone 6[a]



[a] Reagents and conditions: (a) cyclopentadiene (3 equiv), toluene, 23 °C, 12 h; (b) cat. TsOH, MeOH, reflux, 3 h, 95% for two steps, **9**:**10** = 1:1.

Results

Initial Cycloadditions. Ample precedent exists for Diels−Alder cycloadditions of dehydroalanine dienophiles.[6] In contrast, only one example of a Diels−Alder reaction of a β-chlorodehydroalanine derivative, 4-(chloromethylene)-2-phenyl-5(4*H*)-oxazolone (**6**), has been reported.[7] While exo/endo-selectivity was not examined in this case, modest exo-selectivity was reported for 4-(acyloxymethylene)-2-phenyl-5(4*H*)-oxazolones.[9]

We found that oxazolone **6**[10] underwent smooth cycloaddition with cyclopentadiene at room temperature in toluene over the course of 12 h (Scheme 2). Analysis of the crude reaction mixture indicated a 1:1 ratio of cycloadducts **7** (exo) and **8** (endo). Separation of the cycloadducts was facilitated by conversion to methyl esters **9** and **10**, each isolated in 47% yield, and stereochemistry was assigned by NOE analysis. Addition of Lewis acid catalysts (e.g., Et_2AlCl, $ZnCl_2$) greatly accelerated the cycloaddition (2 h, 0 °C) but afforded no improvement in diastereoselectivity. Furthermore, diastereoselectivity was essentially unaffected by changes in solvent polarity.[11]

N-Acyldehydroalanines have been examined extensively in Diels−Alder cycloadditions. Moderate to good exo-selectivity has been observed depending on the nature of the *N*-acyl and ester groups.[6] We examined β-chlorodehydroalanine methyl ester **12**, which was conveniently prepared in 54% yield by chlorination of dehydroalanine **11**[12] followed by elimination with DABCO[13] (Scheme 3). We were surprised to find that dienophile **12** failed to undergo cycloaddition under standard thermal conditions (xylenes, 150 °C) or under the influence of Lewis acid catalysts (e.g., Et_2AlCl, $TiCl_4$, $SnCl_4$, BF_3•Et_2O, TMSOTf). This low reactivity stands in sharp contrast to the nonchlorinated analogs, which react readily in refluxing toluene.[6] Ester **12** did eventually react under forcing conditions (i.e., in neat cyclopentadiene at 180 °C in a sealed tube) to afford a 53% yield of a 1.4:1 mixture of cycloadducts, favoring the exo-product.

While these initial studies showed some success in Diels−Alder reactions of β-chlorodehydroalanine derivatives, the low

(3) For recent synthetic studies toward palau'amine and its relatives, see: (a) Tan, X.; Chen, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4345. (b) Nakadai, M.; Harran, P. G. *Tetrahedron Lett.* **2006**, *47*, 3933. (c) Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223. (d) Wang, S.; Dilley, A. S.; Poullenec, K. G.; Romo, D. *Tetrahedron* **2006**, *62*, 7155. (e) Krishnamoorthy, P.; Sivappa, R.; Du, H.; Lovely, C. J. *Tetrahedron* **2006**, *62*, 10555. (f) Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, *7*, 965. (g) Lanman, B. A.; Overman, L. E. *Heterocycles* **2006**, *70*, 557. (h) Gergely, J.; Morgan, J. B.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 9144. (i) O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 4762.

(4) (a) Grube, A.; Kock, M. *Angew. Chem., Int. Ed.* **2007**, *46*. 2320. (b) Buchanan, M. S.; Carroll, A. R.; Addelpalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **2007**, *72*, 2309. (c) Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett.* **2007**, *48*, 2127. (d) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573.

(5) Carreira has developed a route to the corresponding cyclopentane in the axinellimines that would be applicable to the synthesis of the revised structure of palau'amine. See: Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793.

(6) (a) Horikawa, H.; Nishitani, T.; Iwasaki, T.; Mushika, Y.; Inoue, I.; Miyoshi, M. *Tetrahedron Lett.* **1980**, *21*, 4101. (b) Cativiela, C.; Lopez, P.; Mayoral, J. A. *Tetrahedron: Asymmetry* **1990**, *1*, 61.

(7) (a) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **1999**, *64*, 5764. For a Diels−Alder reaction of 3-chloro-2-nitroacrolein, see: Hoffman, J. M.; Phillips, B. T.; Cochran, D. W. *J. Org. Chem.* **1984**, *49*, 193.

(8) Corey, E. J.; Weinshenker, N. M.; Schaff, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

(9) (a) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **2001**, *66*, 4941. (b) Abbiati, G.; Clerici, F.; Gelmi, M. L.; Gambini, A.; Pilati, T. *J. Org. Chem.* **2001**, *66*, 6299.

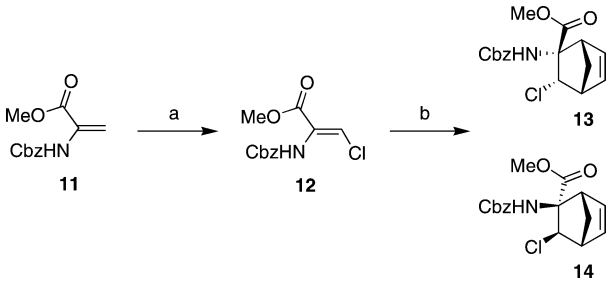
(10) Bland, J. M.; Stammer, C. H.; Varughese, K. I. *J. Org. Chem.* **1984**, *49*, 1634.

(11) Exo/endo-selectivity varied from 0.8 to 1.1:1.0 when using toluene, dichloromethane, chloroform, acetone, acetonitrile, nitromethane, *tert*-butyl alcohol, or water as solvent. No obvious correlation of diastereoselectivity to solvent dielectric constant was observed. For a full table of results, see the Supporting Information.

(12) Torrini, I.; Pagani Zecchini, G.; Paglialunga Paradasi, M. *Synth. Commun.* **1989**, *19*, 695.

(13) Richards, K. D.; Kolar, A. J.; Srinivasan, A.; Stephenson, R. W.; Olsen, R. K. *J. Org. Chem.* **1976**, *41*, 3674.

SCHEME 3. Synthesis and Cycloaddition of Dehydroalanine Methyl Ester 12[a]



[a] Reagents and conditions: (a) Cl_2, CH_2Cl_2, 0 °C, 2 min, then DABCO, MeCN, 0 °C, 15 min, 54%; (b) cyclopentadiene (20 equiv), neat, sealed tube, 180 °C, 100 min, 53%, **13**:**14** = 1.4:1.

diastereoselectivity of **6** and **12**, as well as the low reactivity of **12**, were not optimal for our total synthesis efforts. Thus, we initiated a computational study to identify dienophiles that would be sufficiently reactive to permit use of a 5-substituted cyclopentadiene while at the same time favoring exo-cycloaddition products. Importantly, we focused on a series of heterocyclic dienophiles that might be easily converged on the final spiroimidazolinol found in palau'amine.

Computational Studies. The computational study was begun by studying simplified models of **6** and **12** in Diels−Alder reactions with cyclopentadiene at the B3LYP/6-31G* level of theory using Gaussian 03.[14] Beginning with the oxazolone **15** as a model for **6**, exo- and endo-transition states were located (**TS 15-exo** and **TS 15-endo**, Figure 1).[15] The transition states are moderately polarized, with positive charge buildup on the diene and negative charge on the dienophile.[16] Both transition states are highly asynchronous, with significant bond formation at the β-carbon. Despite this asynchronous nature, an IRC calculation on the exo-transition state indicated that the reaction is concerted: the transition state proceeds directly to cycloadduct in the forward direction. The computed activation enthalpies for the two transition states revealed that the exo-pathway was only slightly favored (0.2 kcal/mol). This small enthalpy difference is consistent with the low observed selectivity in the cycloaddition of **6** (Scheme 2). The cycloaddition overall was predicted to be exothermic by 12.1 kcal/mol, with very little difference in enthalpy between exo- and endo-products.[17] Subsequently, we incorporated the C2-phenyl group present in **6** and found little change in the overall transition state structures or activation energies.

As a model for dehydroalanine ester **12**, transition states for methyl carbamate **16** were computed using the same level of theory. Due to greater conformational flexibility, a suite of transition states could be found. Two main exo-transition state conformations, differing in the twist of the carbamate relative to the olefin, were found, and each of these main transition state structures had four substructures differing in *s*-cis and *s*-trans conformations of the enoate and cis/trans isomers of the carbamate. Carbamate twisting in these transition states results from minimization of A-1,3 strain, and while it is also reflected in the ground-state structure, the twisting is more pronounced in the transition state. A single main endo-transition state conformation was located, again with four substructures due to enoate and carbamate rotation. Within all main transition state groups, the *s-cis*-enoate and *trans*-carbamate were favored, and the lowest enthalpy exo- and endo-transition states are shown in Figure 1. As with the oxazolone, the transition states are asynchronous, with bond formation more developed at the β-carbon. The computations predict modest exo-selectivity for **16** (0.7 kcal/mol favoring exo) and, with an activation enthalpy of 23.1 kcal/mol, they also correctly predict that it should be significantly less reactive than the oxazolone.

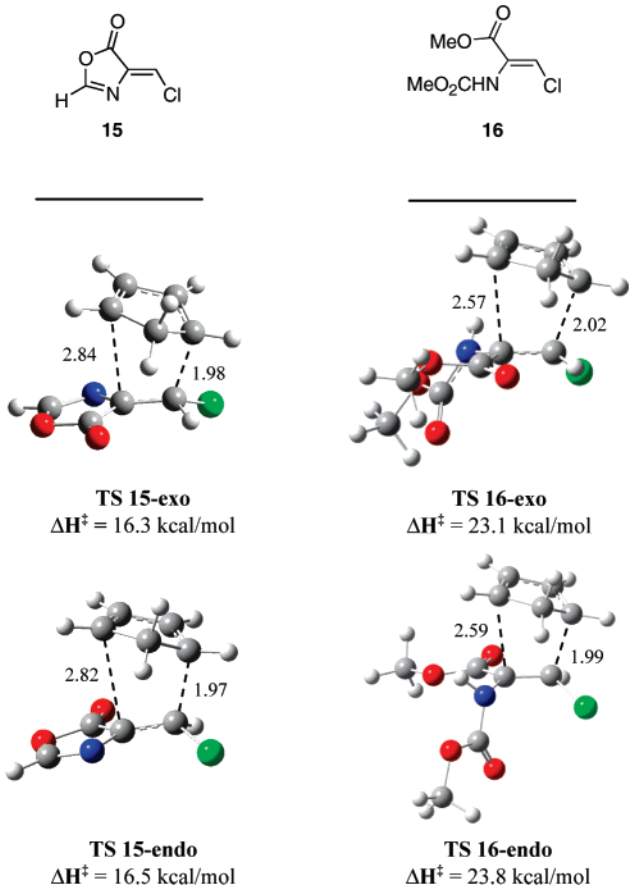


FIGURE 1. B3LYP/6-31G* computed transition states for cycloaddition of oxazolone **15** and dehydroalanine **16**. Bond lengths of the forming bonds are shown in Å.

The DFT modeling correctly predicted the deactivation of the dehydroalanine by the β-chlorine substituent. Exo- and endo-transition states were located for the unchlorinated analogs of **16** (see Supporting Information for transition states). The transition states lacked the twist of the carbamate found in the chlorinated dienophile. Importantly, the computations indicated a transition state activation enthalpy of 18.9 kcal/mol, representing a 4.2 kcal/mol deactivation by the β-chlorine.

Transition states for the above dienophiles were also modeled at the MP2/6-31G* level of theory. The MP2 transition states were also asynchronous, although not to the same extent as for the B3LYP structures. For instance, the DFT transition state bond lengths for **TS** *exo*-**15** were 2.84 and 1.98 Å, while MP2/6-31G* predicted bond lengths of 2.57 and 2.14 Å (see

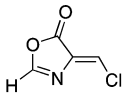
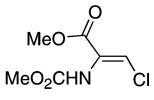
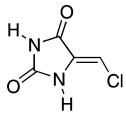
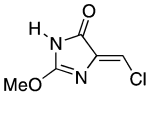
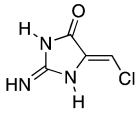
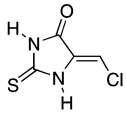
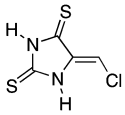
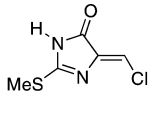
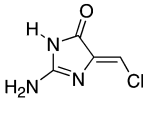
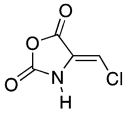
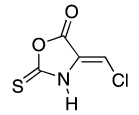
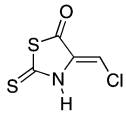
(14) Frisch, M. J.; et al. *Gaussian 03*, revision C.02, Gaussian Inc., Wallingford, CT 2004.

(15) All transition states were characterized by frequency calculations and shown to have a single negative eigenvalue.

(16) Charge analysis, using the CHelpG method (Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361), indicated a charge buildup of +0.31 on the diene.

(17) Control experiments on several Diels−Alder adducts showed no sign of reversibility. In combination with the fact that the reactions are exothermic, the cycloadditions were assumed to be under kinetic control.

CHART 1. B3LYP/6-31G* Diels−Alder Transition State Enthalpies for Reaction of Cyclopentadiene with Heterocyclic Dienophiles[a]

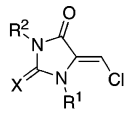
			
	15	**16**	**17**
$\Delta H^{\ddagger}_{exo}$	**16.3**	**23.1**	**20.4**
$\Delta\Delta H^{\ddagger}$	0.2	0.7	2.2
			
	18	**19**	**20**
$\Delta H^{\ddagger}_{exo}$	**19.6**	**21.0**	**18.1**
$\Delta\Delta H^{\ddagger}$	0.7	2.4	2.1
			
	21	**22**	**23**
$\Delta H^{\ddagger}_{exo}$	**15.7**	**18.4**	**19.9**
$\Delta\Delta H^{\ddagger}$	nd[b]	0.6	0.8
			
	24	**25**	**26**
$\Delta H^{\ddagger}_{exo}$	**18.7**	**16.6**	**15.8**
$\Delta\Delta H^{\ddagger}$	2.1	2.0	1.5

[a] $\Delta H^{\ddagger}_{exo}$ = exo transition state enthalpy, relative to ground state, in kcal/mol. $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{endo} - \Delta H^{\ddagger}_{exo}$. [b]For substrate **21**, attempted minimization of the endo transition state leads to cycloaddition across the ene-thione.

Supporting Information for transition states). The MP2 calculations predicted substantially lower activation enthalpies across the board (e.g., 1.1 kcal/mol for oxazolone **15**) and displayed a bias toward endo transition states that was not reflected in experimental results. For instance, oxazolone **15** and ester **16** were predicted to be endo selective by 0.6 and 0.8 kcal/mol, respectively, at MP2−6/31G*. Thus, while it is possible that the DFT calculations overestimate the asynchronous nature of the transition state, all subsequent calculations were completed at the B3LYP/6-31G* level due to the reasonable agreement with experiment and reduced computational cost relative to MP2.

A series of heterocyclic dienophiles was examined using DFT to predict their reactivity and potential exo/endo-selectivity (Chart 1). In particular, the dienophiles chosen for examination were ones with potential to be transformed into the spiroimidazolinol found in palau'amine. First among these was hydantoin **17**. The transition state geometries for cycloaddition of **17** with cyclopentadiene were quite similar to those found with oxazolone **15**. However, while the activation enthalpy for **17** was predicted to be higher (20.4 kcal/mol), the calculations indicated a 2.2 kcal/mol difference between exo- and endo-transition states (favoring exo). The *O*-methyl hydantoin **18** was found to be slightly more reactive than **17**, but the exo-selectivity was predicted to be significantly lower.

CHART 2. Activation Enthalpies for *N*-Substituted Hydantoins and Thiohydantoins[a]



X = O	**17a**	**17b**	**17c**	**17d**	**17e**
R^1	H	Me	Ac	H	Ac
R^2	H	Me	H	Ac	Ac
$\Delta H^{\ddagger}_{exo}$	**20.4**	**22.6**	**18.2**	**19.4**	**17.6**
$\Delta\Delta H^{\ddagger}$	2.2	2.2	2.1	2.1	1.9

X = S	**20a**	**20b**	**20c**	**20d**	**20e**
R^1	H	Me	Ac	H	Ac
R^2	H	Me	H	Ac	Ac
$\Delta H^{\ddagger}_{exo}$	**18.1**	**20.0**	**16.4**	**17.3**	**15.6**
$\Delta\Delta H^{\ddagger}$	2.1	2.2	2.3	2.0	1.5

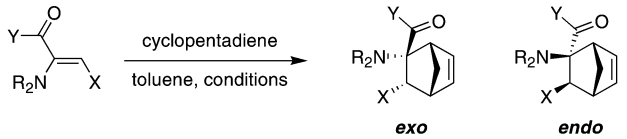
[a] $\Delta H^{\ddagger}_{exo}$ = exo transition state enthalpy, relative to ground state, in kcal/mol. $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{endo} - \Delta H^{\ddagger}_{exo}$.

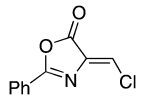
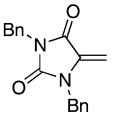
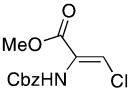
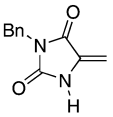
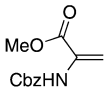
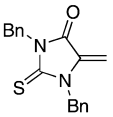
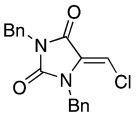
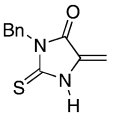
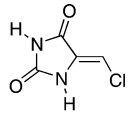
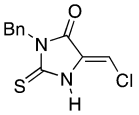
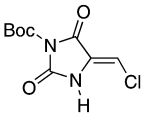
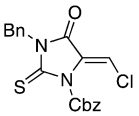
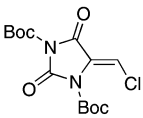
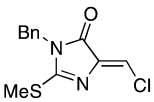
Exploring hydantoin-like structures further, it was found that the nature of the heteroatom attached to C2 had a profound effect on reactivity. While replacing the oxo group in hydantoin with an imino group (e.g., **19**) resulted in an increase in activation enthalpy, replacing the C2 oxo group with a thiono group significantly lowered the activation enthalpy. Thiohydantoin **20** was predicted to have an activation enthalpy of 18.1 kcal/mol (2.3 kcal/mol lower than hydantoin **17**) while still maintaining a high exo-selectivity. Replacing the remaining oxo group in the thiohydantoin with a thione (e.g., **21**) further lowered the activation barrier for the exo-cycloadduct (16.1 kcal/mol). However, attempts to locate an endo-transition state only located a lower enthalpy structure where cyclopentadiene acts as a 2π component adding across the enethione.[18] A series of cyclic anhydrides were also examined. *N*-Carboxyanhydride **24** was predicted to be exo-selective, but less reactive than the thiohydantoin, while incorporation of sulfur as in **25** and **26** further reduced the activation enthalpy with only a slight loss of exo-selectivity.

Finally, we explored the incorporation of additional electron-withdrawing groups in the hydantoin and thiohydantoin series. As shown in Chart 2, electron-withdrawing groups at either N1 or N3 lowered the predicted activation enthalpy (e.g **17c,d** versus **17a** and **20c,d** versus **20a**). In contrast, incorporation of a methyl

(18) α,β-unsaturated thiocarbonyls are known to be excellent dienes. See: Boger, D. L. *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon: Oxford 1991; Vol. 5, pp 451−512.

TABLE 1. Experimental Diels–Alder Cycloaddition Results[a]



entry	dienophile		T (°C)	t (h)	conversion[b] (yield)[c]	*exo*/*endo*[d]	entry	dienophile		T (°C)	t (h)	conversion[b] (yield)[c]	*exo*/*endo*[d]
1		**6**	23	12	100 (95)[e]	50:50	8		**27a**	110	16	53	87:13
2[f]		**12**	150	16	0 (0)	---	9		**27b**	23	16	27	79:21
3		**11**	110	16	50 (54)	67:33	10		**28a**	23	12	33 (27)	93:7
4[f]		**17f**	150	16	0 (0)	---	11		**28b**	23	8	100 (100)	87:13
5		**17a**	110	16	6 (6)	85:15	12[g]		**20f**	40	16	76 (73)	87:13
6		**17g**	90	16	57	89:11	13[g]		**20g**	40	16	40	80:20
7		**17h**	90	16	53	76:24	14[g]		**22**	40	16	45 (34)	59:41

[a] All reactions were conducted with cyclopentadiene (3.0 equiv) in toluene (0.1 M), except as noted. [b] ^{1}H NMR conversion (%). [c] Isolated yield (%). [d] Determined by ^{1}H NMR of the crude reaction mixture. [e] Two-step yield following methanolysis. [f] Reaction run in xylenes. [g] Reaction run in dichloromethane.

group at N1 increased the activation enthalpy by approximately 2 kcal/mol.

Evaluation of Hydantoin and Thiohydantoin Dienophiles. On the basis of the computational results, we explored Diels–Alder reactions of chloromethylene hydantoins and thiohydantoins. These were chosen over the *N*-carboxy anhydride derivatives based on their synthetic accessibility as well as their closer semblance to the palau'amine F-ring. The necessary hydantoin dienophiles were prepared by condensation of ureas with chloropyruvic acid followed by *N*-acylation, if desired. The thiohydantoins were prepared by condensation of the dianion of *N*-carbamoyl-protected β-chlorodehydroalanine benzylamide with thiophosgene. In addition to the chloromethylene dienophiles, simple *exo*-methylene hydantoins and thiohydantoins were prepared for purposes of comparison. Full details of the syntheses of all dienophiles have been reported elsewhere.[19]

To evaluate the reactivity and selectivity across a range of dienophiles, a standard set of conditions was adopted (0.1 M concentration of dienophile, 3.0 equiv of cyclopentadiene). Reactions were generally conducted for 16 h, and their conversion from starting material to products was estimated by ^{1}H NMR.[20] The results of this study are shown in Table 1.

As expected, hydantoins were generally more reactive than dehydroalanine **12** and displayed higher exo-selectivity than either **6** or **12**. Although dibenzylhydantoin **17f** failed to react under the standard conditions, even at reflux in xylenes, simple hydantoin **17a** did give a small amount of product at 110 °C in toluene, and *N*-Boc-protected hydantoins **17g** and **17h** afforded reasonable conversions at 90 °C.[21] In all cases, the reactions showed at least 3:1 selectivity favoring the exo-product, with selectivities as high as 9:1. As with the dehydroalanines, we

(19) Cernak, T. A.; Gleason, J. L. *Heterocycles* **2007**, *71*, 117. See Supporting Information for synthesis of **22**.

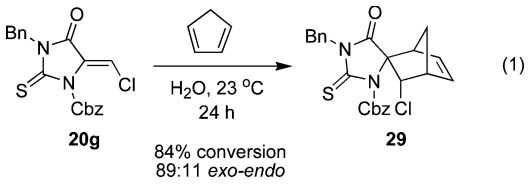
(20) Cycloadditions were generally devoid of side products. Isolated yields were difficult to obtain for hydantoin and thiohydantoin dienophiles due to consistent comigration of unreacted dienophile and cycloadduct upon silica gel chromatography. Pure cycloadducts were obtained either by exhaustive cycloaddition in the presence of an excess of cyclopentadiene or by accepting losses on chromatography. See Supporting Information for details on individual compounds.

(21) Higher temperatures resulted in thermal Boc deprotection.

did observe that the β-chloride had a deleterious effect on the cycloaddition. Simple exomethylene hydantoins **27a** and **27b** were much more reactive than the corresponding chlorinated substrates (**17f** and **17a**).

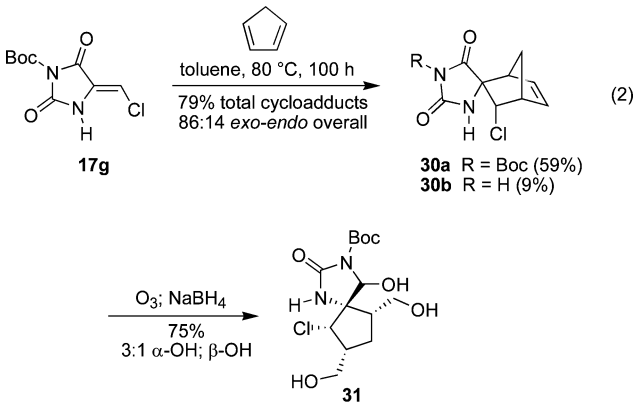
Gratifyingly, as predicted by the DFT computations, it was found that thiohydantoins were significantly more reactive than the corresponding hydantoins. For example, whereas reaction of hydantoin **27b** proceeded to only 27% conversion after 16 h at room temperature, corresponding thiohydantoin **28b** reacted to completion in only 8 h. As with other dienophiles, incorporation of a β-chloride in the thiohydantoins slowed the cycloaddition. However, cycloaddition of both thiohydantoin **20f** and *N*-CBz acylated thiohydantoin **20g** proceeded smoothly at 40 °C in dichloromethane. In all cases, the exo/endo-ratio of the cycloadducts was of synthetically useful levels. If, however, the thiohydantoin is *S*-methylated (e.g., **22**), the selectivity drops sharply. In the case of **20f**, the product was highly crystalline and X-ray crystallographic analysis confirmed our stereochemical assignment of the exo-product (see Supporting Information for details).

Although unacylated thiohydantoin **20f** was found to be slightly more reactive in dichloromethane, an unexpected result given the DFT predictions (Chart 2), it was observed that the acylated form (**20g**) was more reactive in water.[22] When the reaction was conducted in a water emulsion, **20g** was sufficiently reactive to undergo cycloaddition at room temperature (eq 1).[23] In this instance, an 84% conversion could be realized while the high exo-selectivity of the reaction was maintained.



(1)

Finally, to show the viability of this route to produce highly substituted spirocyclopentanes, the cycloaddition in entry 6 (Table 1) was repeated for a longer period of time to increase conversion, resulting in a 59% isolated yield of pure exo-cycloadduct **30a**, along with a small amount of product **30b** where the Boc group had been cleaved (eq 2). The cycloadduct



(2)

was subjected to ozonolysis in methanol followed by reductive workup with $NaBH_4$ to afford spirocyclopentane **31** in 75% yield. The isolated product proved to be an inseparable 3:1 mixture of hemiacetal stereoisomers resulting from reduction at C4 of the hydantoin. Although lacking the fifth cis-substituent, the remainder of this product possesses the correct stereochemistry for the originally reported structure of palau'amine.

Discussion

The Diels−Alder cycloaddition is a tremendously powerful transformation in organic synthesis. Yet, after more than 75 years since its discovery,[24] there is still much to be learned about this important reaction. In the present context, it was necessary to optimize both reactivity and selectivity of the dienophiles for potential application to palau'amine synthesis. Specifically, we observed a significant deactivating effect of chlorine at the β-position of the dienophile, an activating effect in changing from a carbonyl to a thiocarbonyl, and a marked difference in diastereoselectivity between oxazolones and hydantoins or thiohydantoins.

The deactivation of dienophiles by chlorine has been previously observed.[25] In our studies, we observed a drastic decrease in reactivity upon β-chlorination of dehydroalanines, hydantoins, and thiohydantoins. Upon examining orbital energies computed by DFT for chlorinated versus unchlorinated dienophiles (see Supporting Information), it was evident that the chlorine group has the LUMO lowering effect expected of an electron-withdrawing group. This would normally be expected to accelerate the cycloaddition. A likely explanation to this dichotomy is that an increase in steric interactions is overriding the favorable electronic influence of the chlorine substituent. Due to the asynchronous nature of the transition states, the diene is tilted toward the β-position of the dienophile, resulting in nonbonding interactions between β-substituents and the C−H on the reacting end of the diene. In **TS 15-exo**, the distance between the chloride and the diene carbon is 2.98 Å, well within the sum of the van der Waals radii of the two atoms (3.66 Å).

The increased reactivity of the thiohydantoins versus hydantoins is an intriguing observation. Considering simple electronegativity, it would be expected that the hydantoin would possess more effective electron-withdrawing groups. However, the DFT calculations clearly showed that the thiohydantoin has a lower LUMO than the hydantoin. The origin of this difference presumably resides in the greater delocalization of the nitrogen lone pairs into the thiocarbonyl, making the nitrogen a weaker donor into the dienophilic portion of the molecule. Greater conjugation of nitrogen lone pairs with the thiocarbonyl of thioamides and thioureas is well precedented and results in C−N bonds that are shorter and have greater barriers to rotation when compared to the corresponding ureas.[26] Comparing crystallographic data for hydantoins to that of thiohydantoins reveals slightly shorter C−N bonds in thiohydantoins, and these observations were echoed in our computational results.[27] A natural bond order (NBO) analysis of our dienophiles indicated

(22) Incorporation of solvent (CH_2Cl_2, H_2O) in the DFT calculations using the standard PCM method did not alter significantly either relative reactivity between dienophiles nor exo/endo selectivity.

(23) (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Eng.* **2005**, *44*, 3275. (b) Breslow, R.; Rideout, D. C. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

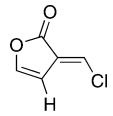
(24) (a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1669.

(25) (a) Williard, P. G.; de Laszlo, S. E. *J. Org. Chem.* **1985**, *50*, 3738. (b) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (c) Cayzer, T. N.; Paddon-Row, M. N.; Moran, D.; Payne, A. D.; Sherburn, M. S.; Turner, P. *J. Org. Chem.* **2005**, *70*, 5561.

(26) (a) Haushalter, K. A.; Lau, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1996**, *118*, 8891. (b) Glendening, E. D.; Hrabal, II, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 12940.

that $n_N \rightarrow \pi^*_{C=S}$ overlap in the thiohydantoins is stronger than $n_N \rightarrow \pi^*_{C=O}$ in the corresponding hydantoins.[28,29] This results in a reduction of electron donation into the dienophilic portion of the molecule and hence an increase in dienophile reactivity.[30]

Finally, we were intrigued by the difference in exo-selectivity between oxazolone **6** and the hydantoins and thiohydantoins. Cycloadditions of α-substituted dienophiles are known, particularly with cyclopentadiene, to afford higher than usual amounts of exo-cycloadducts. A significant contributor to this exo-selectivity is steric repulsion between the α-substituent and the CH_2 group of cyclopentadiene.[31] In the present context, there is very little steric difference between oxazolone **6** and hydantoin **17** or thiohydantoin **20** (or their unchlorinated analogs), yet the latter are moderately to highly exo-selective, and the former is not. The only steric difference between **6** and **17**/**20** in the vicinity of the approaching diene is a hydrogen. However, selectivity in the hydantoins and thiohydantoins only varied a small amount across a variety of N1-substitution patterns. Furthermore, computations on butenolide **32**, which should be



32

isosteric with **17**/**20** in the vicinity of the approaching diene, indicated that it too should show low diastereoselectivity. From the sum of these observations, it can be concluded that sterics are not the major factor in the difference in selectivity between oxazolone **6** and the hydantoins or thiohydantoins. In addition, it was possible to discount secondary orbital effects as a source of the difference in exo/endo-selectivity, as there is not a significant difference in relative sizes of orbital coefficients on the carbonyl carbon between the oxazolones and the hydantoins/thiohydantoins.

Dipole effects have been used in several instances to explain diastereoselectivity in Diels−Alder reactions.[32] In our case, we did not see a direct correlation between selectivity and dipole moments of the reactants. For instance, aligning the dipole moments of oxazolone and cyclopentadiene in opposite directions would lead to a prediction of an exo-selective reaction. Further, the dipole of both the hydantoin and thiohydantoin are at right angles to that of cyclopentadiene in either the exo- or endo-approach. One correlation that did exist was found in the computed dipole moment of the transition states. The difference between dipole moments of exo- and endo-transition states was negligible in both hydantoin and thiohydantoin transition states, but was significantly larger for the oxazolone exo-transition state relative to the endo-transition state. Thus, one source of the selectivity difference could be a destabilization of the exo-transition state for the oxazolones. Unfortunately, no correlation between solvent polarity (ϵ) and exo/endo-selectivity was observed in the oxazolone experiments to support this possibility.

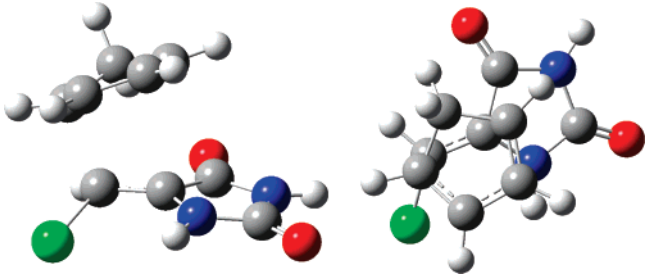


FIGURE 2. Two views of **TS-17-exo** transition state showing proximity of hydantoin nitrogen and diene for potential n→π* donation.

If one considers canonical forms, a correlation does exist between exo-selectivity and the directionality of the lone pair on the α-nitrogen of the dienophile. Houk has previously proposed stabilizing interactions of nitrogen lone pairs in ene additions to imines and complimentary destabilizing interactions in Diels−Alder cycloadditions of imines.[33,34] More recently, in the predicted cycloaddition of 1*H*-azirine with cyclopentadiene, interaction of the nitrogen lone pair with the developing C2−C3 π-bond has been cited as a stabilizing factor in the endo-transition state.[35] In our case, oxazolone **6**, with the lone pair in the plane of the alkene (orthogonal to the π-system), displays low stereoselectivity. In contrast, the nitrogen on the exo-selective hydantoin and thiohydantoin has a lone pair that points toward the incoming diene in the transition state (Figure 2). The lone pairs in the hydantoins and thiohydantions are conjugated to the adjacent carbonyl or thiocarbonyl groups but are presumably more available than the electrons of the C=N π-system in the oxazolone and may have a stabilizing interaction with the positive charge on the diene in the transition state. In support of this, NBO calculations[28] on the exo-transition states of hydantoins and thiohydantoins showed a small (~1 kcal/mol) but consistent interaction between the nitrogen lone pair and the incoming diene. No corresponding interactions are observed in either the hydantoin or thiohydantoin endo-transition states or any of the oxazolone transition states. This interaction may amplify the general trend toward exo-selectivity normally observed with α-substituted dienophiles.[36]

(27) (a) Chowdhry, M. M.; Mingos, D. M. P.; White, A. J. P.; Williams, D. J. *J. Chem. Soc. Perkin Trans.* **2000**, *1*, 3495. (b) Roszak, A. W.; Weaver, D. F. *Acta Crystallogr.* **1998**, *C54*, 1168. (c) Camerman, A.; Camerman, N. *Acta Crystallogr.* **1971**, *B27*, 2205.

(28) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. NBO, version 3.1.

(29) Second-order perturbation energies: $n_{N1} \rightarrow \pi^*_{C=X}$ 95.0 kcal/mol (thiohydantoin), 75.7 kcal/mol (hydantoin); $n_{N1} \rightarrow \pi^*_{C=C}$ 48.1 kcal/mol (thiohydantoin), 50.4 kcal/mol (hydantoin); $n_{N3} \rightarrow \pi^*_{C=X}$ 84.8 kcal/mol (thiohydantoin), 67.7 kcal/mol (hydantoin); $n_{N3} \rightarrow \pi^*_{C=O}$ 71.2 kcal/mol (thiohydantoin), 74.8 kcal/mol (hydantoin).

(30) Evans has noted the increased dienophilicity of thiazolidine thionyl acrylates compared to oxazolidinyl acrylates in copper-catalyzed Diels−Alder reactions, although in that case the difference in rates was attributed to the greater affinity of sulfur-based dienophiles for Cu^{II} Lewis acids. See ref 25b.

(31) (a) Mellor, J. M.; Webb, C. F. *J. Chem. Soc.: Perkin Trans. 2* **1974**, 17. (b) Fotiadu, F.; Michel, F.; Buono, G. *Tetrahedron Lett.* **1990**, *31*, 4863. (c) Mark, V. *J. Org. Chem.* **1974**, *39*, 3181. (d) Houk, K. N.; Luskus, L. J. *J. Am. Chem. Soc.* **1971**, *93*, 4606.

(32) (a) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297. (b) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380.

(33) Thomas, B. E., IV; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 790.

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(36) A referee noted the possibility for a C−H···O interaction between the methylene of cyclopentadiene and carbonyl oxygens in the exo-transition states. Weak C−H···O interactions were observed in NBO calculations on *exo*-**15**, *exo*-**17**, and *exo*-**20** transition states. However, the interaction was no stronger in the hydantoin and thiohydantoin transition states than for the oxazolone. Thus, while it may lead to some overall stabilization of the exo-transition states, it does not account for the higher selectivity observed with hydantoins and thiohydantoins.

Conclusion

In this study, we have used DFT modeling not only to probe mechanistic questions that arose from synthetic studies but more importantly it was also used as a tool to guide the exploration of Diels−Alder dienophiles appropriate for use in total synthesis. The modeling predicted a surprising accelerating effect of thiohydantoin dienophiles over the corresponding hydantoins that was borne out in several cycloaddition experiments. This acceleration results from increased delocalization of nitrogen lone pairs into the thiocarbonyl, thus reducing its electron-donating properties. Hydantoins and thiohydantoins were also found to be significantly more exo-selective than the corresponding oxazolones and dehydroalanines, the source of which is preliminarily attributed to directionality of the nitrogen lone pair.

Dehydroalanines and alkylidine oxazolones have been used extensively in the synthesis of carbocyclic α-amino acids.[6,7,9,37] The higher diastereoselectivity observed with the thiohydantoins as well as the high reactivity gives them the potential to be highly useful in the synthesis of these complex structures. In the context of palau'amine and related oroidin alkaloids, the high exo-selectivity and high reactivity of alkylidene thiohydantoins should enable their use with 5-substituted cyclopentadienes to access the original stereochemistry of the hexasubstituted cyclopentane core of these natural products.[38] This work will be reported in due course.

Experimental Section

Methyl 2-(Benzoylamino)-3-chlorobicyclo[2.2.1]hept-5-ene-2-carboxylate (9/10). Oxazolone **6**[10] (104 mg, 0.500 mmol, 1.0 equiv, purity determined by ^{1}H NMR and TLC) was stirred at room temperature in toluene (5.0 mL) in the presence of cyclopentadiene (125 μL, 1.50 mmol, 3.0 equiv) for 12 h and then concentrated in vacuo and the diastereomeric ratio obtained by ^{1}H NMR (exo/endo-cycloadducts were assigned by chemical shift and coupling constant differences in the chloromethine protons and by similarity to related cycloadducts). The oxazolone cycloadducts were unstable to silica gel exposure and were therefore subjected to methanolysis prior to isolation. The crude mixture of cycloadducts was taken up in 15 mL of methanol. *p*-Toluenesulfonic acid monohydrate (5 mg, 0.03 mmol, 0.05 equiv) was added and the solution refluxed under argon for 3 h. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel (hexanes → 20/80 ethyl acetate-hexanes) to obtain the exo-isomer as a white solid (72 mg, 47% yield) and the endo-isomer as a white solid (72 mg, 47% yield). Exo-isomer: IR (KBr) 3349, 2996, 1723, 1655, 730; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (dt, J = 0.8, 4.2 Hz, 1H), 1.92 (d, J = 4.0 Hz, 1H), 3.25 (m, 1H), 3.76 (m, 1H), 3.77 (s, 3H), 4.90 (d, J = 1.4 Hz, 1H), 6.29 (dd, J = 1.3, 2.3 Hz, 1H), 6.39 (dd, J = 1.2, 2.0 Hz, 1H), 6.65 (bs, 1H), 7.41−7.51 (m, 5H), 7.73−7.75 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 45.3, 49.7, 50.3, 53.4, 65.1, 66.5, 127.2, 128.8, 132.0, 133.8, 136.1, 138.0, 166.8, 172.5; mp 176−177 °C; HRMS found 306.0904 ± 0.0009 (MH^+ calcd 306.0897). Endo-isomer: IR (KBr) 3374, 2950, 1723, 1660, 713; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85 (dq, J = 1.9, 9.6 Hz, 1H), 2.09 (d, J = 9.4 Hz, 1H), 3.07 (m, 1H), 3.38 (m, 1H), 3.70 (s, 3H), 4.53 (d, J = 2.4 Hz, 1H), 6.22 (dd, J = 3.0, 5.6 Hz, 1H), 6.29 (dd, J = 3.1, 5.6, 1H), 6.97 (bs, 1H), 7.40−7.56 (m, 5H), 7.79−7.84 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 45.9, 50.9, 52.3, 52.7, 64.6, 65.5, 127.0, 128.5, 131.8, 133.5, 135.5, 136.9, 166.6, 170.8; mp 159−160 °C; HRMS found 306.0892 ± 0.0009 (MH^+ calcd 306.0897).

Methyl (2*Z*)-2-{[(Benzyloxy)carbonyl]amino}-3-chloroacrylate (12). Methyl 2-{[(benzyloxy)-carbonyl]amino}acrylate **11**[12] (1.50 g, 6.4 mmol, 1.0 equiv, purity determined by ^{1}H NMR and TLC) was dissolved in dichloromethane (25 mL) and cooled to 0 °C. Dried chlorine gas was bubbled through the solution with an outlet to a trap containing dilute sodium hydroxide (Figure S2, Supporting Information) over 2 min, at which point the inlet gas was switched to argon and the solution purged until most of the yellow color was gone. The solution was then concentrated in vacuo to afford a clear, colorless oil. The residue was reconstituted in acetonitrile (50 mL) and cooled to 0 °C, and 1,4-diazabicyclo[2.2.2]-octane (787 mg, 7.0 mmol, 1.1 equiv) was added dropwise as a solution in acetonitrile (10 mL), during which time a white precipitate formed. Stirring, open to air at 0 °C, was continued for 15 min, and the solution was diluted with ethyl acetate, washed twice with saturated ammonium chloride and once with brine, dried on anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (10/90 ethyl acetate−hexanes) to a afford a clear, pale yellow oil (932 mg, 54%): IR (KBr) 3293, 2893, 1742, 1705, 1625, 757; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 5.15 (s, 2H), 6.58 (bs, 1H), 6.90 (s, 1H), 7.34−7.39 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 52.7, 67.7, 122.6, 128.1, 128.2, 128.3, 129.2, 135.3, 152.8, 162.5; mp 54−57 °C; HRMS found 269.0459 ± 0.0008 (calcd 269.0455).

Benzyl 2-(Methoxycarbonyl)-3-chlorobicyclo[2.2.1]hept-5-en-2-ylcarbamate (13/14). To dehydroalanine **12** (83 mg, 0.308 mmol, 1.0 equiv) was added cyclopentadiene (500 μL, 6.02 mmol, 20 equiv) in a sealed tube and the mixture stirred at 180 °C for 100 min and cooled to room temperature. The bulk of the dicyclopentadiene was removed by partitioning between hexanes and methanol (with one drop of water added). The methanol layer was concentrated in vacuo and the residue purified by flash column chromatography on silica gel (10/90 ethyl acetate−hexanes) to afford a mixture of exo- and endo-cycloadducts (55 mg, 53% yield). An analytical sample of the exo-isomer was obtained by iterative flash column chromatography on silica gel (hexanes → 10/90 ethyl acetate−hexanes). Exo-isomer: IR (thin film) 3361, 2953, 1738, 1734, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (d, J = 5.0 Hz, 1H), 1.79 (d, J = 5.0 Hz, 1H), 3.21 (s, 1H), 3.49 (s, 1H), 3.76 (s, 3H), 4.99 (d, J = 1.6 Hz, 1H), 5.06 (t, J = 5.6 Hz, 2H), 5.17 (bs, 1H), 6.24 (dd, J = 1.5, 2.9 Hz, 1H), 6.37 (dd, J = 1.4, 2.6 Hz, 1H), 7.30−7.37 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 44.5, 49.5, 50.5, 53.0, 65.0, 65.8, 67.0, 128.2, 128.5, 135.0, 136.2, 138.6, 155.5, 172.4; HRMS found 336.0997 ± 0.0019 (MH^+ calcd 336.0997). Endo-isomer (only clearly resolved peaks are reported for the minor isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (dd, J = 1.5, 10.0 Hz, 9H), 2.02 (d, J = 8.5 Hz, 1H), 3.01 (s, 1H), 3.16 (s, 1H), 3.76 (s, 3H), 4.54 (s, 1H), 5.15 (s, 2H), 5.51 (bs, 1H), 6.21 (dd, J = 2.5, 5.3 Hz, 1H), 6.31 (s, 1H), 7.26−7.41 (m, 5H).

General Procedure for the Diels−Alder Reaction. The dienophile was taken up in toluene or dichloromethane (0.1 M) in a round-bottomed flask fitted with a reflux condenser and a rubber septum. To minimize evaporation of solvent/cyclopentadiene in elevated-temperature reactions, the joint between the reflux condenser and the reaction flask was lightly greased and securely wrapped with Teflon tape and then Parafilm. Freshly cracked cyclopentadiene (3.0 molar equiv) was added, the reaction was run for the allotted time at the allotted temperature (see Table 1), and the mixture was then concentrated in vacuo. An ^{1}H NMR spectrum (relaxation delay = 3 s) of the crude reaction mixture was obtained to determine diastereoselectivity and NMR conversion as reported in Table 1. The products were generally isolated by flash column chromatography on silica gel.

1′-Benzyl-3-chloro-2′-thioxo-5′-oxo-1′*H*-spiro(bicyclo[2.2.1]-hept-5-ene-2,4′-imidazolidine) (Table 1, entry 12). Thiohydantoin **20f**[19] (82 mg, 0.323 mmol, 1.0 equiv, purity determined by ^{1}H NMR and TLC) was gently refluxed in deoxygenated dichloromethane

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(38) DFT calculations predict similar selectivity and reactivity for *E*-β-chloromethylene hydantoin and thiohydandtoin dienophiles, suggesting that our approach might be extended to access the chloride stereochemistry of **1b** and the axinellamines.

(3.2 mL) in the presence of cyclopentadiene (80 μL, 0.969 mmol, 3.0 equiv) for 16 h. The system was cooled and concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (toluene) to afford the pure exo-product (71 mg, 69% yield) as white foam and a sample containing a mixture of unreacted starting material and the endo-cycloadduct, which was repurified by preparative thin layer chromatography (10/90 ethyl acetate−hexanes, developed twice) to afford the clean endo-cycloadduct (4.0 mg, 4% yield) as a white oil. Crystals of the exo-cycloadduct suitable for X-ray studies were grown from dichloromethane−hexanes using the isopiestic method. Exo-isomer: IR (thin film) 3187, 2954, 1742, 1495, 1337, 1211, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (d, J = 10.0 Hz, 1H), 2.30 (d, J = 10.0 Hz, 1H), 3.07 (s, 1H), 3.29 (s, 1H), 4.60 (d, J = 3.2 Hz, 1H), 4.98 (AB, J = 14.8 Hz, 1H), 5.04 (AB, J = 15.2 Hz, 1H), 6.38 (dd, J = 3.1, 4.9 Hz, 1H), 6.54 (dd, J = 3.0, 5.0 Hz, 1H), 6.96 (bs, 1H), 7.27−7.34 (m, 5H), 7.40 (d, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.5, 44.7, 49.2, 52.2, 65.6, 69.2, 127.9, 128.3, 128.6, 135.2, 135.5, 140.0, 175.4, 182.7; mp 116.0−117.5 °C; ESI-HRMS found 319.0666 ± 0.0007 (MH^+ calcd 319.0666). Endo-isomer: IR (thin film) 3205, 2984, 1744, 1496, 1344, 1209, 731; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94 (AB, J = 10.0 Hz, 1H), 1.97 (AB, J = 8.5 Hz, 1H), 2.92 (s, 1H), 3.15 (s, 1H), 4.02 (s, 1H), 4.98 (s, 2H), 6.25 (m, 1H), 6.32 (m, 1H), 7.26−7.40 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.9, 46.8, 52.8, 53.0, 64.3, 68.6, 127.9, 128.4, 128.6, 134.6, 136.6, 162.7, 182.3; ESI-HRMS found 341.0486 ± 0.0000 (MNa^+ calcd 341.00486).

***tert*-Butyl 3-Chloro-2′,5′-dioxo-1′*H*-spiro[bicyclo[2.2.1]hept-5-ene-2,4′-imidazolidine]-1′-carboxylate (30).** Hydantoin **17g**[19] (165 mg, 0.669 mmol, 1.0 equiv) was heated at 80 °C in toluene (1.3 mL) in the presence of cyclopentadiene (555 mL, 6.69 mmol, 10.0 equiv) for 100 h. The system was cooled, poured onto silica gel, and then purified by gradient elution (1/99 CMA−dichloromethane → 5/95 CMA−dichloromethane; CMA = 80/18/2 chloroform−methanol−ammonium hydroxide). Exo-isomer: IR (KBr) 3342, 2944, 1825, 1767, 1721, 1608, 763; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.65 (dd, J = 1.1, 6.5 Hz, 1H), 2.27 (d, J = 6.8 Hz, 1H), 3.12 (m, 1H), 3.25 (m, 1H), 4.60 (d, J = 3.0 Hz, 1H), 6.25 (bs, 1H), 6.35 (dd, J = 2.9, 3.6 Hz, 1H), 6.47 (m, 1H), 8.69 (bs, 1H); 13C NMR (300 MHz, $CDCl_3$) δ 28.2, 43.8, 49.4, 52.6, 66.2, 67.1, 86.1, 135.5, 139.9, 146.0, 151.6, 172.3; mp 119−121 °C (dec); HRMS found 313.0962 ± 0.0009 (calcd for MH+ 313.0955). Endo-isomer: IR (thin film) 3210, 2988, 1813, 1782, 1717, 771; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (s, 9H), 1.90 (m, 2H), 2.92 (s, 1H), 3.13 (s, 1H), 4.07 (d, J = 2.0 Hz, 1H), 5.81 (bs, 1H), 6.30 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 27.9, 46.8, 52.7, 53.8, 64.7, 66.2, 86.0, 134.9, 136.0, 145.6, 151.0, 170.3; HRMS found 313.0962 ± 0.0009 (MH^+ calcd 313.0955).

Diol 31. Alkene **30a** (110 mg, 0.352 mmol, 1 equiv) was dissolved in dichloromethane (2.0 mL) and methanol (2.0 mL) and cooled to −78 °C. Ozone was passed through the solution over the course of 1 h, at which point the reaction temperature was −10 °C. Extra dichloromethane was added in ∼1 mL aliquots to maintain a constant volume. Sodium borohydride (67 mg, 1.76 mmol, 5.0 equiv) was added and the solution was allowed to warm rapidly to 23 °C. After 50 min at this temperature, the reaction was quenched by addition of a saturated solution of ammonium chloride and extracted with dichloromethane and then ethyl acetate. The combined organic fractions were dried on anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a white solid (108 mg). Purification by flash column chromatography on silica gel afforded a 3:1 mixture of aminals, as evidenced by ^{1}H NMR, as a white solid (93 mg, 75% yield). α-OH-isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 1.52 (m, 1H), 1.53 (s, 9H), 2.07 (ddd, J = 8.8, 8.8, 13.2 Hz, 1H), 2.41 (m, 1H), 2.72 (dddd, J = 8.4, 8.4, 8.4, 8.4 Hz, 1H), 3.77−3.53 (m, 4H), 4.44 (d, J = 8.0 Hz, 1H), 5.31 (s, 1H); ^{13}C NMR (400 MHz, CD_3OD) δ 28.3, 28.5, 41.2, 42.8, 61.7, 62.8, 69.6, 70.4, 83.8, 85.2, 151.4, 156.5; ESI-HRMS found 373.1137 ± 0.0002 (MNa^+ calcd 373.1137). β-OH-isomer (only clearly resolved peaks are reported for the minor isomer)**:** ^{1}H NMR (400 MHz, CD_3OD) δ 2.21 (dddd, J = 7.9, 7.9, 7.9, 7.9 Hz, 1H), 4.83 (d, J = 5.6 Hz, 1H), 5.43 (s, 1H); ^{13}C NMR (400 MHz, CD_3OD) δ 29.5, 44.2, 47.6, 62.8, 64.4, 66.8, 70.2, 86.7, 151.6.

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Supporting Information Available: Complete citation for ref 14, solvent polarity screening results, stereochemical assignments of Diels−Alder cycloadducts, full experimental and characterization details, and selected spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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