JOC*Article*

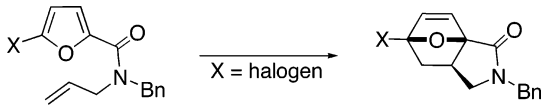
Halo Substituent Effects on Intramolecular Cycloadditions Involving Furanyl Amides

Albert Padwa,* Kenneth R. Crawford, and Christopher S. Straub
Department of Chemistry, Emory University, Atlanta, Georgia 30322

Susan N. Pieniazek and K. N. Houk*
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

houk@chem.ucla.edu

Received February 5, 2006



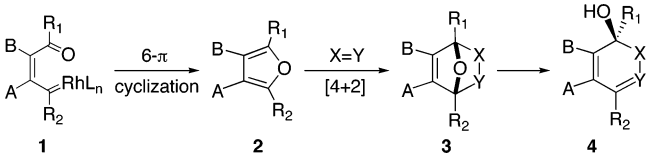
Intramolecular Diels−Alder reactions involving a series of *N*-alkenyl-substituted furanyl amides were investigated. Stable functionalized oxanorbornenes were formed in high yield upon heating at 80−110 °C. The cycloaddition reactions include several bromo-substituted furanyl amides, and these systems were found to proceed at a much faster rate and in higher yield than without substitution. This effect was observed by incorporating a halogen in the 3- or 5-position of the furan ring and appears to be general. The origin of increased cycloaddition rates for halo-substituted furans has been investigated with quantum mechanical calculations. The success of these reactions is attributed to increases in reaction exothermicities; this both decreases activation enthalpies and increases barriers to retrocycloadditions. Halogen substitution on furan increases reactant energy and stabilizes the product, which is attributed to the preference of electronegative halogens to be attached to a more highly alkylated and therefore more electropositive framework.

Introduction

Diels−Alder reactions involving furan as a diene form oxanorbornenes that have been used in the syntheses of numerous complex targets.[1] Rh(II)-catalyzed cyclizations[2] represent useful methods for preparing furan substrates (Scheme 1).[3] We have relied on this and other methods for the strategic incorporation of various functional groups into the furan moiety that allow for facile subsequent transformations.[4]

The preparation of *N*-alkenyl-substituted furanyl amides for intramolecular Diels−Alder reactions has also been achieved.[5] Certain systems of this type, however, gave low yields of [4+2]-cycloadducts. A survey of the literature reveals similar examples of seemingly well-designed substrates for intramolecular cycloaddition that fail, usually due to substrate inertness[6] or the tendency of the products to undergo retrocycloadditions.[7,8]

SCHEME 1



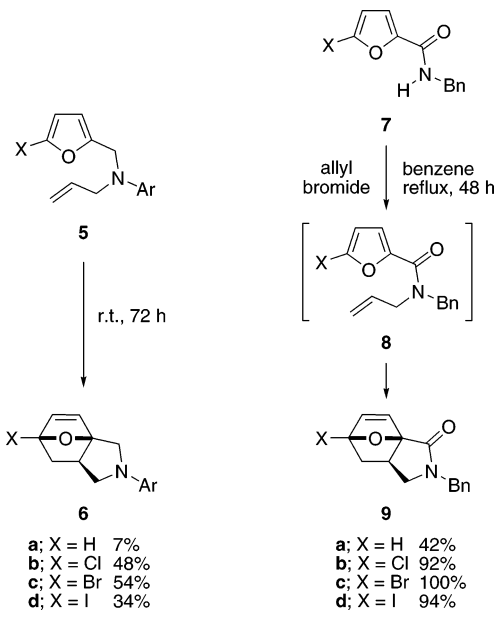
The yields of intramolecular Diels−Alder reactions involving furan are highly sensitive to both diene and dienophile substitu-

(1) (a) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521−13642. (b) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179−14233. (c) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795−819. (d) Ashton, P. R.; Brown, G. R.; Isaacs, N. S.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Slawin, A. M. Z.; Smith, D. R.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 6330−6353. (e) Löffler, M.; Schlüter, A.-D.; Gessler, K.; Saenger, W.; Toussaint, J.-M.; Brédas, J.-L. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2209−2212. (f) Valdés, C.; Spitz, U. P.; Kubik, S. W.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1885−1887.

(2) (a) Padwa, A.; Krumpe, K. E.; Gareau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523−2530. (b) Padwa, A.; Xu, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5881−5882. (c) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6971−6972. (d) Baird, M. S.; Buxton, S. R.; Whitley, J. S. *Tetrahedron Lett.* **1984**, *25*, 1509−1512. (e) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Org. Chem.* **1988**, *53*, 2875−2877. (f) Padwa, A.; Krumpe, K. E.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 2633−2636. (g) Padwa, A.; Chiacchio, U.; Garreau, Y.; Kassir, J. M.; Krumpe, K. E.; Schoffstall, A. M. *J. Org. Chem.* **1990**, *55*, 414−416. (h) Padwa, A.; Austin, J. A.; Xu, S. L. *J. Org. Chem.* **1992**, *57*, 1330−1331. (i) Padwa, A.; Krumpe, K. E.; Kassir, J. M. *J. Org. Chem.* **1992**, *57*, 4940−4948. (j) Padwa, A.; Austin, D. J.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 4103−4106. (k) Padwa, A.; Chiacchio, U.; Fairfax, D. J.; Kassir, J. M.; Litrico, A.; Semones, M. A.; Xu, S. L. *J. Org. Chem.* **1993**, *58*, 6429−6437. (l) Padwa, A.; Kassir, J. M.; Semones, M. A.; Weingarten, M. D. *J. Org. Chem.* **1995**, *60*, 53−62. (m) Padwa, A.; Austin, D. J.; Chiacchio, U.; Kassir, J. M.; Rescifina, A.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 5923−5926. (n) For a mini review, see: Padwa, A. *J. Organomet. Chem.* **2001**, *617*, 3−16.

10.1021/jo0602322 CCC: $33.50
Published on Web 06/28/2006

tion, as well as to the nature and length of the tether.[1b] In particular, substitution on furan greatly affects the chemical reactivity of these reactions. The group of Jakopcic found that chlorine, bromine, or iodine substituents on furan increase cycloaddition yields and cycloadduct stability (see yields for conversion of **5** to **6**).[9] Our group also reported increased rates and yields of reactions with halogen substitution (see conversion of **7** to **9**).[5] The possibility that simple halogen substitution might turn previous failures into successes led us to explore the origins of this halogen effect.[10]



In this study, we report the generality of the furan halogen effect by experimental and computational studies. Reactions yielding intramolecular cycloadducts substituted on different positions of furan have been explored experimentally. The origin of the increased rates and yields for halo-substituted intramolecular Diels−Alder reactions has been investigated with quantum mechanical calculations. Synthetic versatility provided by halogen substitution, which allows for several derivatizations of the oxanorbornene cycloadducts, is also described herein.

Results and Discussion

A series of intramolecular cycloaddition reactions leading to the syntheses of oxanorbornenes were undertaken, and these results are summarized in Table 1. Cycloadduct **9c** was prepared by one-pot N-allylation and intramolecular cycloaddition of secondary amide **7c** under phase-transfer conditions. Alternatively, heating a sample of *N*-allyl furanylamide **8c** at 110 °C for 90 min provided the stable oxatricycle **9c** as a single diastereomer. The stereochemistry of **9c** is consistent with the preferred exo orientation of the tether in the Diels−Alder cycloaddition reaction and is analogous to that reported for related furanyl systems possessing short tethers.[11] In contrast, the unsubstituted furan amide **8a** (X = H) was heated for one week at 110 °C to complete its transformation into **9a**. Conducting the N-allylation at reflux temperatures, furans **7a** and **7c** allowed the direct conversion into cycloadducts **9a** and **9c**. After 48 h, bromofuran **7c** was completely transformed to cycloadduct **9c**, whereas the unsubstituted variant **7a** gave a mixture of **8a** (40%) and cycloadduct **9a** (48%) at 110 °C. Incorporation of a halogen at the 5-position of furan provides a significant rate enhancement. This effect appears to be general,[9] and when the analogous 5-chloro- and 5-iodofurans, **7b** and **7d**, were subjected to the allylation conditions in benzene at reflux, cycloadducts **9b** and **9d** were isolated in 92% and 94% yield, respectively.

Cycloadditions involving dihalogenated furans were also investigated. The substrates 3-bromo-, **10**, and 4,5-dibromo-, **12**, substituted furanyl amides yielded the expected intramolecular Diels−Alder cycloadducts **11** (92%) and **13** (74%) under allylation conditions for 48 h.

Bromine substitution also dramatically influenced the rate of cycloadditions involving substituted dienophiles (systems **15** and **17**). For example, although the cycloaddition of **14a** was only 40% complete after 6 days of constant heating at 80 °C, bromofuran **14b** was completely converted to **15b** after only 36 h.[12] A rate enhancement over the unsubstituted furan was observed for the more highly activated bromo furanyl amides obtained by N-alkylation of **7c** with **16a** and **16b**, which afforded **17a** (85%) and **17b** (70%) upon refluxing in benzene for 90 min.

Theoretical Calculations. Our experimental studies demonstrate that halogen substitution can increase rates and yields of intramolecular Diels−Alder cycloaddition reactions (Table 1). In a recent communication,[10] we computationally explored the origin of this halogen effect with the high-accuracy CBS-QB3 method. Halogen substitution (fluorine, chlorine, and bromine) on furan increases exothermicities by 4−9 kcal/mol, which causes smaller decreases in activation barriers (2−3 kcal/mol), and creates larger barriers to retrocycloadditions. This indicates that the stabilizing effect of halogens increases as bond forming between diene and dienophile proceeds. Several other representative substituents and hydrocarbon dienes were investigated for comparison. The origin of these substituent effects is the

(3) (a) Kinder, F. R.; Padwa, A. *Tetrahedron Lett.* **1990**, *31*, 6835−6838. (b) Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21−28. (c) Padwa, A.; Straub, C. S. *Org. Lett.* **2000**, *2*, 2093−2095.

(4) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412−3424.

(5) Crawford, K. R.; Bur, S. K.; Straub, C. S.; Padwa, A. *Org. Lett.* **2003**, *5*, 3337−3340.

(6) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188−7194.

(7) (a) Kwart, H.; King, K. *Chem. Rev.* **1968**, *68*, 415−447. (b) Gschwend, H. W.; Hillman, M. J.; Kisis, B. *J. Org. Chem.* **1976**, *41*, 104−110. (c) Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1985**, *26*, 591−594. (d) Cauwbergs, S.; De Clercq, P. J.; Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1988**, *29*, 2493−2496. (e) McNelis, B. J.; Sternbach, D. D.; MacPhail, A. T. *Tetrahedron* **1994**, *50*, 6767−6782. (f) Hudlicky, T.; Butora, G.; Fearnley, S. P.; Gum, A. G.; Persichini, P. J., III; Stabile, M. R.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2393−2398. (g) Heiner, T.; Kozhushkov, S. I.; Noltemeyer, M.; Haumann, T.; Boese, R.; de Meijere, A. *Tetrahedron* **1996**, *52*, 12185−12196. (h) Prajapati, D.; Laskar, D. D.; Sandhu, J. S. *Tetrahedron Lett.* **2000**, *41*, 8639−8643.

(8) Jung, M. E.; Min, S.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10834−10835.

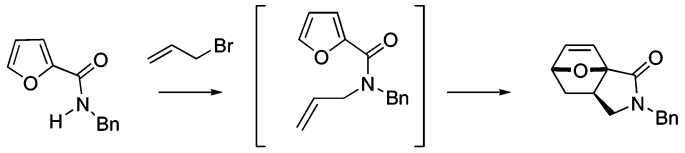
(9) Klepo, Z.; Jakopcic, K. *J. Heterocycl. Chem.* **1987**, 1787−1791.

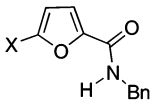
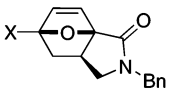
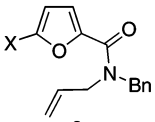
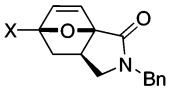
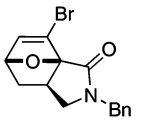
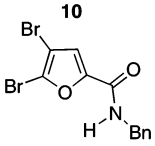
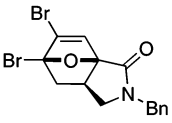
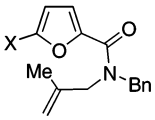
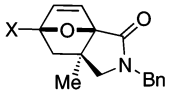
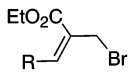
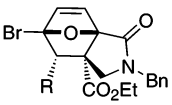
(10) Pieniazek, S. N.; Houk, K. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1442−1445.

(11) (a) Woo, S.; Keay, B. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1411−1414. (b) Rogers, C.; Keay, B. A. *Tetrahedron Lett.* **1991**, *32*, 6477−6480. (c) Rogers, C.; Keay, B. A. *Synlett* **1991**, 353−355. (d) Rogers, C.; Keay, B. A. *Can. J. Chem.* **1992**, *70*, 2929−2947. (e) DeClercq, P. J.; Van Royen, L. A. *Synth. Commun.* **1979**, *9*, 771−780. (f) Van Royen, L. A.; Mijngher, R.; DeClercq, P. J. *Bull. Soc. Chim. Belg.* **1984**, *93*, 1019−1036. (g) Fischer, K.; Hunig, S. *J. Org. Chem.* **1987**, *52*, 564−569. (h) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617−4626.

(12) The slow conversion of furan **14a** to oxabicyclo **15a** (40%) over a 6-day period was followed every 24 h and was shown not to be the result of a retro Diels−Alder equilibrium.

TABLE 1. Experimental Results for Furanyl Amide Intramolecular Cycloadditions



variable	substrate	cycloadduct	R.C.[a]	time	yield	ref
a; X = H **b;** X = Cl **c;** X = Br **d;** X = I	 **7**	 **9**	*(i)* *(ii)* *(ii)* *(ii)*	48 h	48% 92% 100% 94%	*5*
a; X = H **c;** X = Br	 **8**	 **9**	*(iii)* *(iii)*	1 week 1.5 h	98% 99%	*5*
	 **10**	 **11**	*(ii)*	48h	92%	*this work*
	 **12**	 **13**	*(ii)*	48 h	74%	*this work*
a; X = H **b;** X = Br	 **14**	 **15**	*(iv)* *(iv)*	6 days 36h	40% 82%	*5*
a; R = H **b;** R = Ph	**7c** +  **16**	 **17**	*(v)* *(vi)*	1.5 h	85% 70%	*this work*

[a] Reaction Conditions: (*i*) (a) NaOH, K_2CO_3, *n*-Bu_4NHSO_4, toluene, room temperature, (b) allyl bromide, toluene, 110 °C; (*ii*) (a) NaOH, K_2CO_3, *n*-Bu_4NHSO_4, benzene, room temperature, (b) allyl bromide, benzene, 80 °C; (*iii*) toluene, 110 °C; (*iv*) benzene, 80 °C; (*v*) (a) NaOH, K_2CO_3, *n*-Bu_4NHSO_4, benzene, room temperature, (b) **16a**, benzene, 80 °C; (*vi*) (a) NaOH, K_2CO_3, *n*-Bu_4NHSO_4, benzene, room temperature, (b) **16b**, benzene, 80 °C.

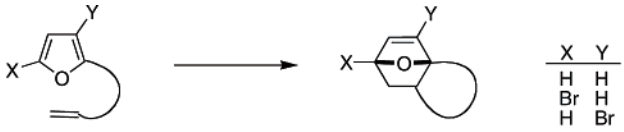
energetic preference for electronegative halogens to be attached to the saturated and more highly alkylated carbon.[10] This is more electropositive than the alkene carbon of furan, and the electronegative halogen forms a stronger bond to the more electropositive carbon. Electropositive groups stabilize both carbocations and carbon centers carrying electronegative substituents by means of hyperconjugative and σ-inductive effects.[13]

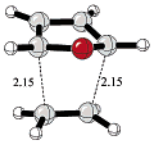
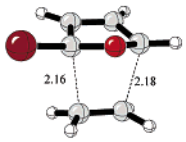
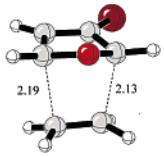
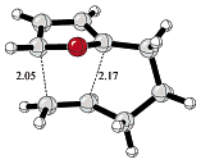
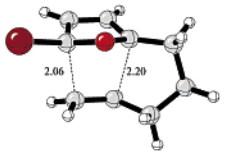
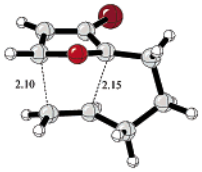
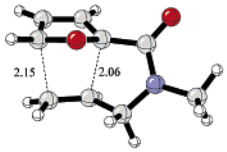
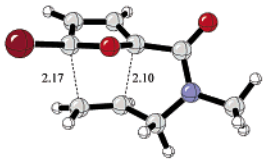
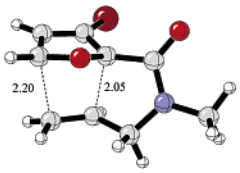
In this work, the initial studies are extended to intramolecular systems. The kinetic and thermodynamic facilitation of intramolecular cycloadditions has been investigated using B3LYP/6-31G(d). The effect of bromination on two different positions of furan has been considered. Furanyl amides **C** (Table 2) have been chosen as computational models for the experimental systems in Table 1. The corresponding parent intermolecular reaction (**A**, Table 2) and an intramolecular system involving a tether with three methylene units (**B**, Table 2) were also explored computationally to test the generality of this halogen effect.

Activation and reaction enthalpies for model reactions **A**−**C** are given in Table 2. In comparison with our previous CBS-QB3 calculations,[10] B3LYP/6-31G(d) performs well in reproducing the effect of bromine substitution on activation and reaction enthalpies. For the intermolecular case (**A**), B3LYP/6-31G(d) enthalpies show an overestimation of reactant stability with respect to the TS and product. However, the relative changes in activation and reaction enthalpies upon bromination

(13) (a) Dill, J. D.; Schleyer, P. v. R.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 1663−1668. (b) Clark, T.; Spitznagel, G. W.; Klose, R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1984**, *106*, 4412−4419. (c) Schleyer, P. v. R. *Pure Appl. Chem.* **1987**, *59*, 1647−1660. (d) Luo, Y.-R.; Benson, S. W. *J. Phys. Chem.* **1988**, *92*, 5255−5257. (e) Dorigo, A. E.; Houk, K. N.; Cohen, T. *J. Am. Chem. Soc.* **1989**, *111*, 8976−8978. (f) Wiberg, K. B. *J. Org. Chem.* **1991**, *56*, 544−550. (g) Harvey, J. N.; Viehe, H. G. *J. Prakt. Chem.* **1995**, *337*, 253−256.

TABLE 2. Activation and Reaction Enthalpies (kcal/mol) for Cycloadditions Involving Furan or Bromofurans[a]



	unsubstituted	substituted	
A. *no tether*			
	TS1	**TS2**	**TS3**
$\Delta H^{\ddagger}$	25.9	24.4	24.0
ΔH	–5.3	–9.6	–8.6
B. *methylene tether*			
	TS4	**TS5**	**TS6**
$\Delta H^{\ddagger}$	29.1	27.1	27.3
ΔH	4.0	–0.6	0.9
C. *amide tether*			
	TS7	**TS8**	**TS9**
$\Delta H^{\ddagger}$	28.0	26.6	25.1
ΔH	0.9	–3.0	–3.0

[a] Bond lengths are given in Å.

are very close to the CBS-QB3 numbers. In general, bromine substitution on furan decreases activation enthalpies ($\Delta\Delta H^{\ddagger} =$ 1.4−2.0 kcal/mol) and increases exothermicities ($\Delta\Delta H = 3.1-$ 4.6 kcal/mol). This trend is common for both intermolecular, **A**, and intramolecular reactions, **B** and **C**. In comparison with the more than 3 kcal/mol absolute increases in reaction exothermicities, reaction enthalpy differences of 2- vs 3-bromo (intermolecular) and 5- vs 3-bromofurans (intramolecular) are less than 1.5 kcal/mol. The position of the halogen on the ring has only minor consequences.

The type of tether influences the absolute activation and reaction enthalpies, the amide linker showing slightly lower activation enthalpies and higher exothermicities than the alkyl tether. However, the relative energies of brominated vs unsubstituted systems are conserved for all reactions **A**−**C**. **TS9**, the 3-bromo furanyl amide, is the only case that deviates from the general trend. The effect of bromine substitution on activation and reaction enthalpies is ∼1.5 kcal/mol larger than those expected from this trend. In this case, the observed deviation can be explained by an additional stereoelectronic effect introduced by substitution at position 3 of furan. Repulsion between the amide carbonyl oxygen and the bromine substituent causes a deviation of 22° in the dihedral angle around the C−C bond connecting the furan ring and the amide group (Figure 1). This deviation from coplanarity between the two moieties is ∼10° larger than that observed in the unsubstituted (**TS7**) and 5-bromo-substituted (**TS8**) cases. The decrease in conjugation causes a destabilization of the reactant with respect to the

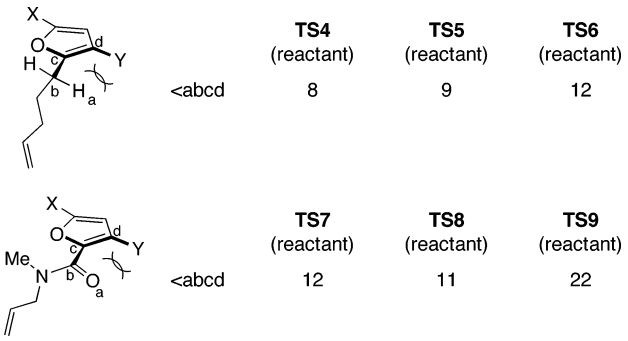
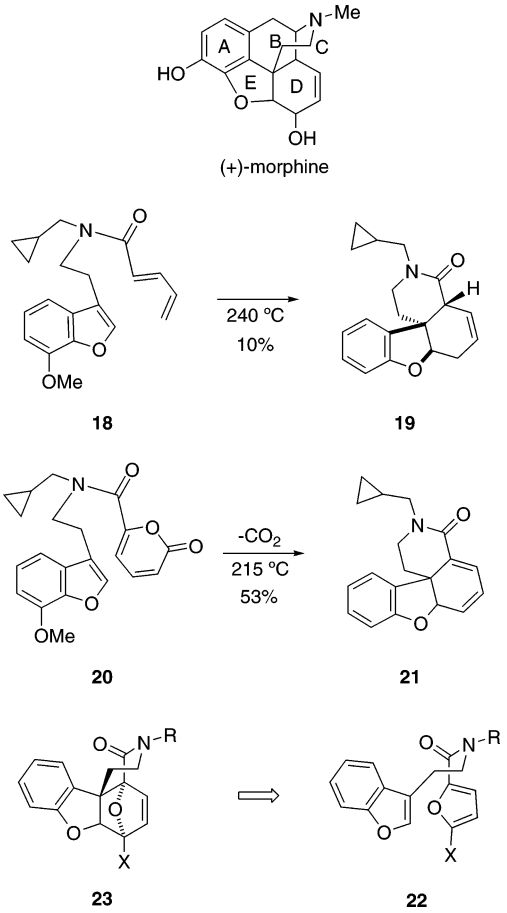


FIGURE 1. Tether conformations relative to the furan ring.

SCHEME 2. Approaches to the ACDE Core of Morphine

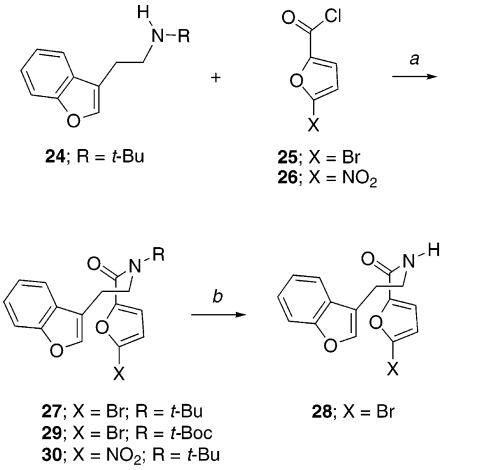


TS and product, providing both a further decrease in activation enthalpy and an additional increase in reaction exothermicity. Similar steric effects caused by bulky substituents at the vicinal position with respect to the tether have been reported by Klein.[14] Since bromine is not a bulky substituent, this steric effect is only significant for the amide tether type due to the coplanarity requirement. As shown in Figure 1, bromine has a minor effect in the conformation of the alkyl linker. This agrees with **TS6** fitting in the general trends expected for halogen substitution on furan.

Finally, it was originally suggested that rate acceleration with brominated systems may result from transition state stabilization due to the polarizability of the substituent.[5] If the electronic structure of a transition state is altered due to this substituent effect, changes in forming bond distances and/or synchronicity would be expected. However, all transition structures located in Table 2 involving furan and nonactivated alkenes are concerted and rather synchronous. Intramolecular reactions are slightly more asynchronous than intermolecular ones (cf. **TS4**−**TS9** with **TS1**−**TS3**), and halogen substitution has a minimal effect on the synchronicity. These results support the rationale of the origin of the halogen effect, as do the parallel effects on activation barriers and reaction enthalpies.[10]

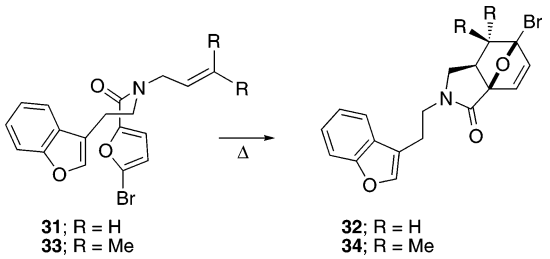
Morphine. The remarkable rate enhancements in the cycloadditions involving bromofurans, combined with our recent success with cycloadditions across heteroaromatic π-systems,[15]

SCHEME 3



Reagents: (a) Et_3N, CH_2Cl_2, 0 °C; (b) Δ, μW or Lewis acid.

SCHEME 4



prompted us to examine possible synthetic applications of these reactions.[16] Ciganek had previously reported the intramolecular Diels−Alder reaction of **18** to provide the ACDE core of morphine **19**, albeit in only 10% yield (Scheme 2).[17] α-Pyrone derivative **20**, on the other hand, produced **21** in 53% yield.[17] Inspired by this report, we envisioned an alternative approach involving intramolecular Diels−Alder reaction of furanyl amide **22** to furnish the cycloadduct **23**.

Acylation of *tert*-butylamine **24** with acyl chloride **25**, derived from commercially available 5-bromo-2-furoic acid, gave the desired tertiary amide **27** in good yield (Scheme 3). Unfortunately, all of our attempts to effect the cycloaddition of **27** only resulted in the removal of the labile *tert*-butyl group to give **28**. Thermal conditions (heating at 180 °C in xylene), microwave assistance, and the addition of several Lewis acids (i.e., $SnCl_4$, $TiCl_4$, $ZnCl_2$·OEt_2, BF_3·OEt, TMSOTf) failed to promote the desired cycloaddition. Similarly, our attempts to add across the benzofuran ring using the related *t*-Boc furanyl amide **29** also failed to produce a cycloadduct. Extended heating of **29** furnished the unsubstituted amide **28** in 92% yield.

The *N*-allyl-substituted furanyl amide **31** readily reacted at 80 °C, furnishing cycloadduct **32** in 89% yield. The more encumbered *N*-prenyl-substituted amide **33** also underwent the

(14) Klein, L. L. *J. Org. Chem.* **1985**, *50*, 1770−1773.

(15) (a) Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643−4645. (b) Meija-Oneto, J. M.; Padwa, A. *Org. Lett.* **2004**, *6*, 3241−3244.

(16) (a) Szántay, C.; Dörnyel, G.; Blaskó, G. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Brossi, A., Eds.; Academic Press: London, 1994; Vol. 45, pp 127−232. (b) Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, 1995; pp 357−369. (c) Hudlicky, T.; Butora, G.; Fearnley, S. P.; Gum, A. G.; Stabile, M. R. In *Studies in Natural Products Chemistry*; Rahman, A.-U., Ed.; Elsevier: Amsterdam, 1996; Vol. 18, pp 43−154. (d) Novak, B. H.; Hudlicky, T.; Reed, J. W.; Mulzer, J.; Trauner, D. *Curr. Org. Chem.* **2000**, *4*, 343−362. (e) Bentley, K. W. *Nat. Prod. Rep.* **2000**, *17*, 247−268. (f) Blakemore, P. R.; White, J. D. *Chem. Commun.* **2002**, 1159−1168.

(17) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261−6262.

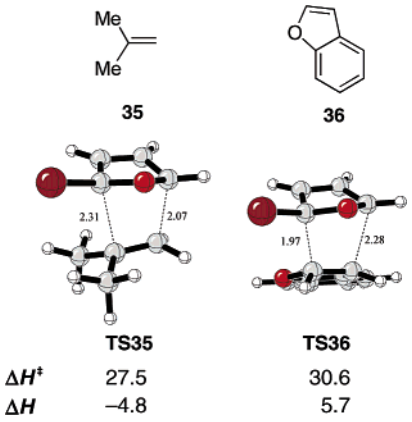


FIGURE 2. Activation and reaction enthalpies (kcal/mol) of Diels−Alder reactions involving isobutene (**35**) and benzofuran (**36**) with 2-bromofuran.

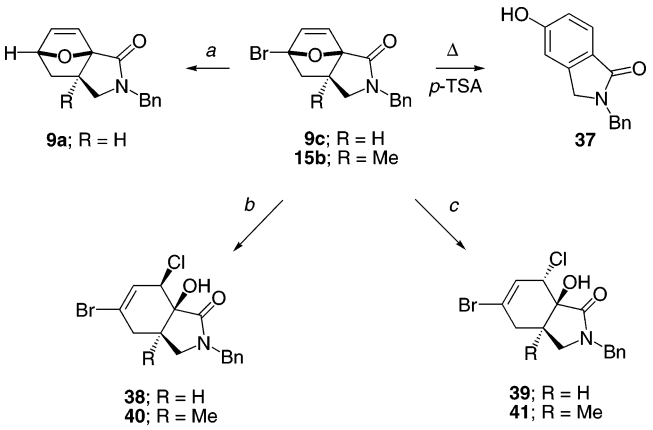
cycloaddition, although heating at 180 °C (24 h) was required for the cycloaddition to proceed (Scheme 4). As in the case of amides **27**, **29**, and **30**, amides **31** and **33** failed to undergo cycloaddition across the π-bond of benzofuran. In the latter two compounds, cycloaddition takes place with the competing alkene dienophile (Scheme 4).

Model Diels−Alder reactions (Figure 2) involving 2-bromofuran with isobutene (**35**) or benzofuran (**36**) have been calculated at the B3LYP/6-31G(d) level of theory. The activation enthalpy of **TS36** is higher ($\Delta\Delta H^{\ddagger} \sim 3$ kcal/mol) and the reaction enthalpy is significantly more endothermic ($\Delta\Delta H \sim 11$ kcal/mol) than those of the same reaction involving isobutene (**TS35**). These examples reveal the limitations of the halogen activation of furan. This activation is not strong enough to allow the cycloaddition with the highly unreactive and aromatic dienophile, benzofuran.

Versatility of Halo-Furanyl Amide Cycloadducts. Oxanorbornenes are known to be valuable synthetic intermediates used to construct substituted arenes, carbohydrate derivatives, and various natural products.[18] An important synthetic transformation employing these intermediates involves cleavage of the oxygen bridge to produce functionalized cyclohexene derivatives.[19] We have examined possible cleavage reactions of bromo-oxatricyclonorbornenes **9c** and **15b**. These transformations open the possibility for the syntheses of various highly functionalized nitrogen heterocycles.

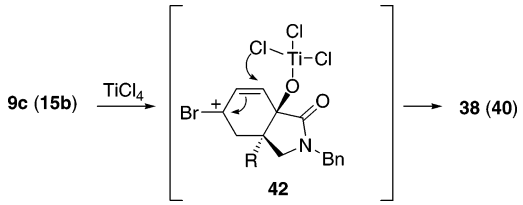
Our initial efforts focused on the bridgehead oxabicyclic radical derived from **9c** because very little is known about such intermediates. Exposure of **9c** to *n*-Bu_3SnH under standard radical initiation conditions failed to give any products derived from oxabicyclic ring opening and instead gave largely the simple reduction product **9a** in 60% yield (Scheme 5). Heatinga sample of **9c** in the presence of *p*-TsOH in xylene afforded the phenol **37** in 95% yield. The Lewis acid $TiCl_4$ was used to promote ring opening at temperatures as low as 0 °C to α-hydroxylactam **38** in 98% yield as a single diastereomer. Changing the Lewis acid to Me_2AlCl allowed for the synthesis of the epimer hydroxylactam **39** in 95% yield. Similarly, cycloadduct **15b** afforded the corresponding hydroxylactams **40** and **41** with $TiCl_4$ and Me_2AlCl, respectively. The stereochemical assignments of compounds **40** and **41** were unequivocally established on the basis of X-ray crystallography.

SCHEME 5



Reagents: (a) *n*-Bu_3SnH, AIBN, heat; (b) $TiCl_4$; (c) Me_2AlCl

SCHEME 6



In the case of $TiCl_4$, cycloadduct **9c** (or **15b**) may undergo an eventual ring opening to give intermediate **42**, which then delivers a chloride from the same face as the neighboring oxygen to furnish **38** (or **40**), where the chloro and hydroxy groups are cis disposed (Scheme 6).

The preferred chloride attack, when Me_2AlCl is used as the Lewis acid, occurs on the side opposite to the hydroxy functionality, which corresponds to the less-congested face of the π-bond.

(18) (a) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173−185. (b) Reymond, J. L.; Pinkerton, A. A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128−2135. (c) Renaud, P.; Vionnet, J. P. *J. Org. Chem.* **1993**, *58*, 5895−5896. (d) Eggette, T. A.; de Koning, H.; Huisman, H. O. *J. Chem. Soc., Perkin Trans. 1* **1978**, 980−989. (e) Ogawa, A.; Iwasawa, Y.; Nose, T.; Suami, T.; Ohba, S.; Ito, M.; Saito, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 903−906. (f) Just, G.; Kim, S. *Tetrahedron Lett.* **1976**, 1063−1066. (g) Murai, A.; Takahashi, K.; Taketsuru, H.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1981**, 221−222. (h) Kotsuki, H.; Nishizawa, H. *Heterocycles* **1981**, *16*, 1287−1290. (i) Cox, P. J.; Simpkins, N. S. *Synlett* **1991**, 321−323. (j) Van Royen, L. A.; Mijngheer, R.; De Clerq, P. J. *Tetrahedron Lett.* **1983**, *24*, 3145. (k) Smith, A. B.; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. *J. Org. Chem.* **1985**, *50*, 3239−3241. (l) Smith, A. B.; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. *J. Am. Chem. Soc.* **1986**, *108*, 3040−3048. (m) Best, W. M.; Wege, D. *Tetrahedron Lett.* **1981**, *22*, 4877−4880.

(19) (a) Le Drian, C.; Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1989**, *72*, 338−347. (b) Takahashi, T.; Iyobe, A.; Arai, Y.; Koizumi, T. *Synthesis* **1989**, 189−191. (c) Guilford, A. J.; Turner, R. W. *J. Chem. Soc., Chem. Commun.* **1983**, 466−467. (d) Yang, W.; Koreeda, M. *J. Org. Chem.* **1992**, *57*, 3836−3839. (e) Suami, T. *Pure Appl. Chem.* **1987**, *59*, 1509−1520. (f) Harwood, L. M.; Jackson, B.; Prout, K.; Witt, F. J. *Tetrahedron Lett.* **1990**, *31*, 1885−1888. (g) Koreeda, M.; Jung, K.-Y.; Hirota, M. *J. Am. Chem. Soc.* **1990**, *112*, 7413−7414. (h) Reynard, E.; Reymond, J.-L.; Vogel, P. *Synlett* **1991**, 469−471. (i) Ogawa, S.; Yoshikawa, M.; Taki, T. *J. Chem. Soc., Chem. Commun.* **1992**, 406−408. (j) Ogawa, S.; Tsunoda, H. *Liebigs Ann. Chem.* **1992**, 637−641. (k) Jung, M. E.; Street, L. *J. Am. Chem. Soc.* **1984**, *106*, 8327−8329. (l) Mirsadeghi, S.; Rickborn, B. *J. Org. Chem.* **1985**, *50*, 4340−5919. (m) Grieco, P. A.; Lis, R.; Zelle, R. E.; Finn, J. *J. Am. Chem. Soc.* **1986**, *108*, 5908−5919. (n) Takayama, H.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1986**, *27*, 5509−5512. (o) Hanessian, S.; Beaulieu, P.; Dube, D. *Tetrahedron Lett.* **1986**, *27*, 5071−5074. (p) Arjona, O.; Dios, A.; Pradilla, R. F.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906−3916.

Conclusion

The generality of halogen substitution on furan increasing reaction rates and yields of Diels−Alder reactions has been explored. This effect is beneficial because several reactions involving poor tethers or dienophiles have been known to fail or be low yielding. This effect is general for inter- and intramolecular cycloadditions, regardless of halogen position or tether type. These substituent effects are a manifestation of the energetic preference for electronegative halogens to be attached to a more highly alkylated and therefore more electropositive carbon. Halo substitution on furan is not enough to allow cycloadditions with aromatic benzofuran, a limitation to this method. We have further demonstrated the importance of the halo-substituted furanyl amide cycloadducts by using simple reagents to produce synthetically interesting polycycles.

Computational Methods

All structures were fully optimized at B3LYP/6-31G(d)[20] in Gaussian 03.[21] The nature of stationary points was confirmed by frequency analysis, with the minima and TS having zero and one imaginary frequency, respectively. We have shown that B3LYP/6-31G(d) calculations are accurate for many hydrocarbon pericyclic reactions.[22] This method gives a trend similar to the high-accuracy (mean absolute error ∼ 1 kcal/mol) CBS-QB3 level of theory[23] when comparing the energetics of brominated to unsubstituted Diels−Alder reactions involving furan.

Experimental Section

5-Bromofuran-2-carboxylic Acid Benzylamide (7c). To a solution of 5-bromo-2-furoic acid (10 g, 52 mmol) in CH_2Cl_2 (65 mL) at 0 °C was added $(COCl)_2$ (6.8 mL, 79 mmol) and DMF (50 μL). The flask was fitted with a drying tube containing $CaSO_4$, and the resulting solution was warmed to room temperature for 1.5 h. Concentration under reduced pressure afforded the crude acid chloride as a yellow solid that was used directly in the next step without further purification. A solution of this acid chloride in THF (20 mL) was added slowly to a solution of benzylamine (6.2 mL, 57 mmol) and Et_3N (15 mL, 100 mmol) in THF (20 mL) at 0 °C. The solution was warmed to room temperature over 1 h, and then H_2O was added. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The yellow oil obtained was subjected to silica gel flash chromatography to give furanyl amide **7c** (15 g, 100%) as a white solid. All of its spectroscopic properties were identical to those reported previously.[24]

5-Bromofuran-2-carboxylic Acid Allyl-benzylamide (8c). A mixture of furan **7c** (1.0 g, 3.6 mmol), powdered NaOH (0.6 g, 14 mmol), K_2CO_3 (0.5 g, 3.6 mmol), and *n*-Bu_4NHSO_4 (0.01 g, 0.01 mmol) in benzene (20 mL) was stirred for 1 h at room temperature. Allyl bromide (0.6 mL, 7.2 mmol) was added, and the reaction mixture was stirred at room temperature for 22 h. The mixture was diluted with water, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude oil was subjected to silica gel flash chromatography to give 1.1 g (99%) of **8c** as a colorless oil: IR (neat) 1711, 1624, 1572, 1478, 1414, 1261, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.08 (brs, 2H), 4.59−4.88 (m, 2H), 5.08−5.35 (m, 2H), 5.79−5.95 (m, 1H), 6.39 (brs, 1H), 6.83−7.10 (m, 1H), and 7.16−7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.8, 49.7, 113.2, 117.8, 118.7, 124.5, 127.5, 128.6, 132.9 (br), 134.2, 136.7, 149.2, 159.1; HRMS calcd for $C_{15}H_{14}BrNO_2$ 319.0208, found 319.0208.

3-Benzyl-10-oxa-3-aza-tricyclo[5.2.1.0]dec-8-en-2-one (9a). A 0.16 g sample of **8a** (0.66 mmol) in toluene (7 mL) was heated at 125 °C for 7 days. The mixture was concentrated under reduced pressure, and the residue was subjected to silica gel flash chromatography to give 0.16 g (98%) of **9a** as a white solid: mp 140−141 °C; IR (film) 1690, 1446, 1282, 1158, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (dd, 1H, J = 11.7 and 7.5 Hz), 1.75−1.90 (m, 1H), 2.21 (ddd, 1H, J = 16.1, 8.1, and 3.0 Hz), 3.11 (dd, 1H, J = 9.5 and 8.5 Hz), 3.40 (dd, 1H, J = 9.5 and 8.5 Hz), 4.48 (s, 2H), 5.10−5.20 (m, 1H), 6.37−6.45 (m, 1H), 6.54−6.62 (m, 1H), 7.16−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.0, 38.7, 46.7, 51.4, 81.4, 91.8, 127.4, 127.8, 128.6, 133.0, 135.8, 137.1, 168.1. Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.51; H, 6.11; N, 5.74.

5-Bromofuran-2-carboxylic Acid (2-Benzofuran-3-yl-ethyl)-*tert*-butylamide (27). To a solution of 2-benzofuran-3-yl-ethanol[25] (6.2 g, 38 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added Et_3N (8.0 mL, 57 mmol) and TsCl (8.4 g, 44 mmol). The resulting solution was allowed to warm slowly to room temperature and was then stirred for 12 h. At the end of this time, the reaction mixture was washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to afford the crude tosylate (10.1 g, 84%) that was immediately carried forward in the next step. The crude tosylate (10.1 g) was dissolved in MeCN (160 mL) and was treated sequentially with $NaHCO_3$ (8.1 g, 96 mmol) and *tert*-butylamine (8.4 mL, 80 mmol). The resulting suspension was warmed to 50−55 °C for 2 h. The mixture was cooled to room temperature and was treated with additional $NaHCO_3$ (8.1 g, 96 mmol) and *tert*-butylamine (8.4 mL, 80 mmol). After heating for an additional 8 h at 50−55 °C, the suspension was cooled to room temperature, filtered through a pad of Celite, and concentrated under reduced pressure to give a tan oil. The crude (2-benzofuran-3-yl-ethyl)-*tert*-butylamine (**24**) solidified upon standing in the freezer (5.0 g, 72%) and was used directly in the next step without further purification.

To a solution of **24** (0.44 g, 2.0 mmol) and Et_3N (0.5 mL, 3.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added a cooled solution of 5-bromo-2-furoyl chloride (**25**) (0.4 g, 2.0 mmol) in CH_2Cl_2 (5 mL) dropwise. After warming to room temperature over 1 h, the reaction mixture was subjected to normal aqueous workup. The crude product was purified by silica gel flash chromatography to give **27** (0.84 g, 73%) as a pale yellow oil: IR (neat) 1639, 1476, 1452,

(20) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(22) (a) Guner, V. A.; Khuong, K. S.; Houk, K. N.; Chuma, A.; Pulay, P. *J. Phys. Chem. A* **2004**, *108*, 2959−2965. (b) Guner, V.; Khuong, K. S.; Leach, A. G.; Lee, P. S.; Bartberger, M. D.; Houk, K. N. *J. Phys. Chem. A* **2003**, *107*, 11445−11459.

(23) (a) Nyden, M. R.; Petersson, G. A. *J. Chem. Phys.* **1981**, *75*, 1843−1862. (b) Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081−6090. (c) Petersson, G. A.; Tensfeldt, T.; Montgomery, J. A. *J. Chem. Phys.* **1991**, *94*, 6091−6101. (d) Montgomery, J. A.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1994**, *101*, 5900−5909.

(24) Rai, U. K.; Shanker, B.; Singh, S.; Rao, R. B. *Indian J. Chem., Sect. B* **1988**, *27*, 674−675.

(25) Albanez-Walker, J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 4917−4920.

1012, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 9H), 3.07 (t, 2H, $J = 8.1$ Hz), 3.83 (t, 2H, $J = 8.1$ Hz), 6.32 (d, 1H, $J = 3.4$ Hz), 6.86 (d, 1H, $J = 3.4$ Hz), 7.17−7.34 (m, 2H), 7.40 (d, 1H, $J = 8.1$ Hz), 7.46 (d, 1H, $J = 7.5$ Hz), 7.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 28.7, 45.7, 58.2, 111.5, 113.2, 116.8, 118.0, 119.2, 122.4, 123.0, 124.3, 127.6, 141.8, 151.7, 155.2, 160.7; HRMS calcd for $C_{19}H_{20}BrNO_3$ 389.0627, found 389.0625.

(2-Benzofuran-3-yl-ethyl)-(5-bromofuran-2-carbonyl)carbamic Acid *tert*-Butyl Ester (29). To a solution of amide **28** (0.75 g, 2.2 mmol) in MeCN (5 mL) was added DMAP (0.014 g, 0.11 mmol) and $(Boc)_2O$ (0.64 g, 2.9 mmol), and the resulting solution was allowed to stir for 12 h. The reaction mixture was partitioned between Et_2O and H_2O, and the ether layer was separated. The aqueous layer was washed with Et_2O, and the combined Et_2O layer was dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography to give compound **29** (0.94 g, 97%) as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 3.00−3.12 (m, 2H), 3.95−4.07 (m, 2H), 6.44 (d, 1H, $J = 3.6$ Hz), 7.01 (d, 1H, $J = 3.6$ Hz), 7.19−7.33 (m, 2H), 7.39−7.51 (m, 2H), 7.65−7.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 27.5, 45.5, 83.4, 111.3, 116.7, 118.7, 119.7, 122.4, 124.2, 125.0, 127.9, 142.0, 150.3, 152.5, 155.2, 161.0.

2-Benzyl-5-hydroxy-2,3-dihydroisoindol-1-one (37). A solution of 0.1 g (0.3 mmol) of 3-benzyl-7-bromo-10-oxa-3-aza-tricyclo-[5.2.1.0]dec-8-en-2-one (**9c**), 5 mg of *p*-TsOH, and 5 mL of xylene was heated at 150 °C for 5 h. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 0.07 g (95%) of **37** as a beige solid: mp 222−224 °C; IR (film) 1636, 1592, 1453, 1420, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.54 (brs, 1H), 4.20 (s, 2H), 4.75 (s, 2H), 6.82 (d, 1H, $J = 2.0$ Hz), 6.91 (dd, 1H, $J = 8.4$ and 2.0 Hz), 7.27−7.36 (m, 5H), 7.69 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.4, 49.5, 109.5, 115.9, 123.6, 125.2, 127.8, 128.7, 128.9, 136.9, 143.9, 160.9, 169.5. Anal. calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 73.51; H, 5.44; N, 5.60.

2-Benzyl-5-bromo-7-chloro-7a-hydroxy-2,3,3a,4,7,7a-hexahydroisoindol-1-one (38). To a solution of 0.15 g (0.5 mmol) of 3-benzyl-7-bromo-10-oxa-3-aza-tricyclo[5.2.1.0]dec-8-en-2-one (**9c**) in 8 mL of CH_2Cl_2 cooled in an ice bath was added 0.18 g (0.9 mmol) of $TiCl_4$ dropwise. The reaction mixture was stirred at 0 °C for 2 h, poured into 10 mL of ice water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.15 g (98%) of **38** as a white solid: mp 159−161 °C; IR (film) 1673, 1432, 1426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26−2.34 (m, 1H), 2.40−2.45 (m, 1H), 2.79−2.88 (m, 1H), 3.13 (dd, 1H, $J = 9.2$ and 7.2 Hz), 3.27 (d, 1H, $J = 2.0$ Hz), 3.31 (t, 1H, $J = 9.2$ Hz), 4.45 (d, 1H, $J = 16.0$ Hz), 4.49 (d, 1H, $J = 16$ Hz), 4.83−4.85 (m, 1H), 5.94−5.95 (m, 1H), 7.21−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2, 41.2, 46.6, 47.3, 59.5, 71.4, 124.7, 128.0, 128.2, 128.2, 129.0, 136.0, 171.7. Anal. calcd for $C_{15}H_{15}BrClNO_2$: C, 50.70; H, 4.26; N, 3.94. Found: C, 50.58; H, 4.15; N, 3.97.

2-Benzyl-5-bromo-7-chloro-7a-hydroxy-2,3,3a,4,7,7a-hexahydroisoindol-1-one (39). To a solution of 0.15 g (0.5 mmol) of 3-benzyl-7-bromo-10-oxa-3-aza-tricyclo[5.2.1.0]dec-8-en-2-one (**9c**) in 8 mL of CH_2Cl_2 cooled in an ice bath was slowly added dropwise a 1.0 M solution of Me_2AlCl in hexane (0.6 mmol). The reaction mixture was stirred at 0 °C for 2 h, poured into 10 mL of ice water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.14 g (95%) of **39** as a white solid: mp 187−189 °C; IR (film) 1674, 1446, 1425 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (dd, 1H, $J = 15.2$ and 3.6 Hz), 2.81−2.92 (m, 2H), 3.23 (dd, 1H, $J = 9.2$ and 6.8 Hz), 3.30 (t, 1H, $J = 9.2$ Hz), 4.50 (s, 2H), 4.72 (d, 1H, $J = 5.2$ Hz), 5.74 (d, 1H, $J = 1.6$ Hz), 6.11 (dd, 1H, $J = 5.2$ and 1.6 Hz), 7.20−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 35.2, 46.8, 48.2, 54.2, 75.5, 126.8, 127.2, 127.8, 128.0, 129.1, 135.6, 173.0. Anal. calcd for $C_{15}H_{15}BrClNO_2$: C, 50.70; H, 4.26; N, 3.94. Found: C, 50.81; H, 4.23; N, 3.68.

Acknowledgment. We appreciate the financial support provided by the National Science Foundation (Grant No. CHE-0132651 and CHE-0450779), the National Institutes of Health (GM 059384-24), and the Partnerships for Advanced Computational Infrastructure (PACI). We thank our colleague, Dr. Kenneth Hardcastle, for his assistance with the X-ray crystallographic studies and the University Research Committee of Emory University for funds to acquire a microwave reactor. The computations were performed on the National Science Foundation Terascale Computing System at the Pittsburgh Supercomputing Center (PSC) and on the UCLA Academic Technology Services (ATS) Hoffman Beowulf cluster.

Supporting Information Available: Information concerning the preparation and characterization of compounds using general procedures, ^1H or ^{13}C NMR spectra for new compounds lacking elemental analyses, CIF files with crystallographic data (and ORTEP drawings) for compounds **40** and **41**, and Cartesian coordinates of all of the computed structures together with their total energies. The authors have deposited atomic coordinates for the structures of **40** and **41** with the Cambridge Crystallographic Data Centre. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0602322