Diels−Alder Reaction of 2-Amino-Substituted Furans as a Method for Preparing Substituted Anilines

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5-Amino-2-furancarboxylic acid methyl ester undergoes a facile Diels−Alder cycloaddition with a variety of dienophiles to afford ring-opened cycloadducts that are readily dehydrated using $BF_3 \cdot OEt_2$ to give polysubstituted anilines. In each case, the cycloaddition proceeds with high regioselectivity, with the electron-withdrawing group being located *ortho* to the amino group. The most favorable FMO interaction is between the HOMO of the furanamine and the LUMO of the dienophile. The atomic coefficient at the ester carbon of the furan is larger than that at the amino center, and this nicely accommodates the observed regioselectivity. The [4 + 2]-cycloaddition of *N*-(5-nitrofuranyl)morpholine with methyl vinyl ketone affords a mixture of three phenols. One of the phenols is derived from a Diels−Alder reaction followed by nitro group ejection and subsequent aromatization. The remaining two phenols are the result of cleavage of the initially formed oxabicyclic intermediate with concomitant migration of the nitro group. The mild reaction conditions with which furan-2-carbamic acid *tert*-butyl ester undergoes Diels−Alder cycloaddition with *N*-phenylmaleimide allow for the ready isolation of the initial oxybridged cycloadduct.

Heterocycles such as furan, thiophene, and pyrrole undergo Diels−Alder reactions despite their stabilized 6π-aromatic electronic configuration.[1−3] By far the most extensively studied five-ring heteroaromatic system for Diels−Alder cycloaddition is furan and its substituted derivatives.[4,5] The resultant 7-oxabicyclo[2.2.1]heptanes are valuable synthetic intermediates that have been further elaborated to substituted arenes, carbohydrate derivatives, and various natural products.[6−13] A crucial synthetic transformation employing these intermediates involves the cleavage of the oxygen bridge to produce functionalized cyclohexene derivatives.[14−19] In many cases, however, this strategy is not feasible because of the low reactivity of furan toward monoactivated dienophiles.[20,21] Lewis acid catalysis,[22] interaction with metals,[23] or use of high pressure[24] helps to overcome the sluggishness of furan toward Diels−Alder cycloaddition. Incorporation of an electron-donating group onto the 2-position of furan has also been employed as a means to enhance the reactivity of the heteroaromatic ring system.[25] MO calculations show that the presence of an amino group in the 2-position of the furan nucleus increases its HOMO energy relative to that of furan.[26] A significant increase in the HOMO coefficient at the C-5 position compared to that at the C-2 position also occurs, consistent with an increase in electron density at that position due to resonance interaction with the amino substituent.

From our recent work dealing with α-amino isobenzofurans,[27] we have become interested in the Diels−Alder reaction of 2-aminofurans as a method for preparing substituted aniline derivatives **4** (Scheme 1) since these compounds are important starting materials for the preparation of various pharmaceuticals.[28−30] Molecules containing derivatized anilines in their structure include antibiotics,[31] analgesics,[32] and β-adrenergic blockers.[33]

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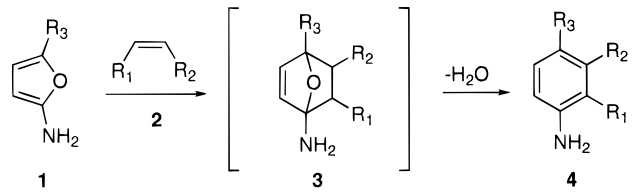
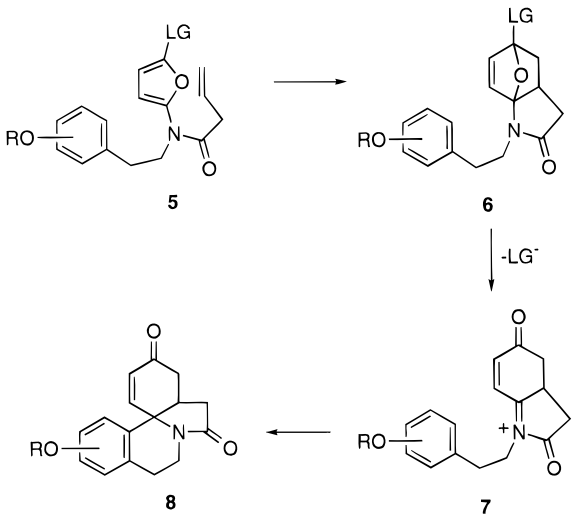
Scheme 1



Scheme 2

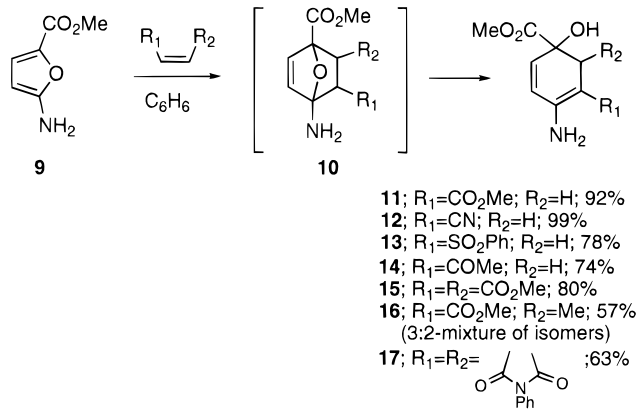


Anilines are also key intermediates in the synthesis of a variety of aromatic compounds *via* diazotization[34] and nucleophilic substitution reactions.[35] Our long-range goal involves using 2-amino-substituted furans such as **5** that contain both a suitable leaving group (LG) and an olefinic tether to allow for an intramolecular Diels−Alder reaction (Scheme 2). The resultant cycloadduct is expected to readily undergo ring opening to generate a vinylogous *C*-acyliminium ion of type **7**. Our intention is to use this sequence of reactions for a rapid entry into the erythrinane family of alkaloids.[36] With this goal in mind, model studies were undertaken to determine the facility with which 2-aminofurans would undergo Diels−Alder cycloadditions.[37] The present paper documents the results of these studies.

Results and Discussion

There are only a few cases in the literature where [4 + 2]-cycloadditions of 2-aminofurans have been investigated.[38] The paucity of examples is undoubtedly due to the inaccessibility and inherent instability of the 2-aminofuran systems.[39] Several groups have attempted to

Scheme 3



synthesize 2-aminofuran itself but have failed to isolate the parent compound due to its lability.[40] Addition of electron-withdrawing groups to the furanamine nucleus is known to enhance its stability.[39] These stable furanamines participate in [4 + 2]-cycloaddition chemistry, but the examples reported to date produce products that do not contain useful substitution patterns.[38] The furanamine ester **9**, first reported by Freure and Johnson,[41] is known to exhibit typical enamine behavior,[42] but there have been no reports dealing with its cycloaddition chemistry. We reasoned that the Diels−Alder reaction of **9** with various dienophiles should afford amino-substituted 7-oxabicyclo[2.2.1]heptenes **10** that would be expected to spontaneously ring-open to furnish substituted anilines. In order to test this possibility, methyl 5-nitrofuroate was synthesized by a slight modification of the literature procedure.[41] Catalytic reduction using palladium on calcium carbonate afforded furanamine **9** in 63% overall yield. Unlike many furan Diels−Alder reactions that require high pressure[24] or Lewis acid catalysts[22] to obtain satisfactory yields of cycloadduct, furanamine **9** reacted smoothly with several monoactivated olefins by simply heating in benzene at 80 °C to give cyclohexadienols **11**−17 (Scheme 3). In each case, the cycloaddition proceeded with complete regioselectivity, with the electron-withdrawing group being located *ortho* to the amino group. The structure assignment was made on the basis of ^{1}H-NMR spectroscopy, which showed the presence of two vinylic protons and a methylene set of hydrogens. The regiochemical results are perfectly consistent with FMO theory.[43] The most favorable FMO interaction is between the HOMO of the furanamine and the LUMO of the dienophile. The atomic coefficient at the ester carbon of the furan is larger than at the amino center, and this nicely accommodates the observed regioselectivity.

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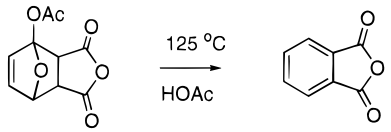
Cyclohexadienols **11**−**17** are derived by formation of an initial 1:1-cycloadduct (*i.e.*, **10**) from the dienic system of the furan ring and the dienophile. The initial cycloadducts were not isolated, as they undergo ready ring opening, assisted by the lone pair of electrons on the adjacent nitrogen atom. The influence of both the amino and ester groups is evident by the extremely facile cleavage of the oxybridge intermediates under the thermal conditions used in the reaction. This behavior stands in contrast to the related oxabicyclic system **18**, which was reported to undergo ring cleavage only when treated with acetic acid at elevated temperatures (125 °C).[44]



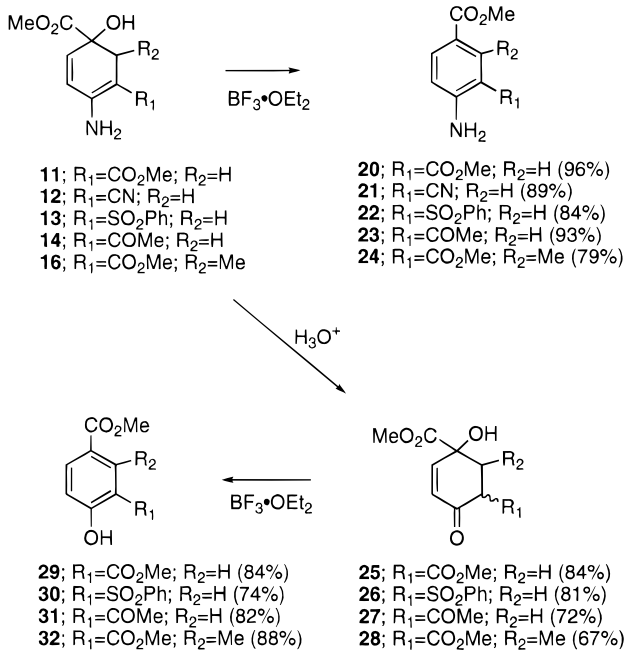
18 **19**

Reaction of the less reactive methyl crotonate with furanamine **9** required heating in a sealed tube at 145 °C in order for the reaction to proceed. The cycloaddition afforded a 3:2-diastereomeric mixture of cyclohexadienols **16**. As expected from Alder's *endo* rule, the reaction of furans with ethylenic dienophiles generally results in the initial formation of *endo*-cycloadducts that are converted to the thermodynamically more stable *exo*-isomers on further heating (*vide infra*). Molecular mechanics calculations indicate that the *exo*-cycloadduct derived from methyl crotonate is several kcal (*ca.* 3.5 kcal/mol) lower in energy than the *endo*-adduct. Ring opening of the transient oxabicyclic intermediate to the observed diastereomeric mixture reflects this thermodynamic difference.

A number of reaction conditions were explored to convert the resultant dienes to the corresponding aniline derivatives. We eventually found that subjection of the initially formed cycloadducts to 1 equiv of $BF_3{\cdot}OEt_2$ in benzene at 80 °C for 1 h resulted in smooth dehydration to give the polysubstituted aniline systems **20**−**24** in excellent yield. When the initially formed cycloadducts were exposed to an aqueous THF solution containing 1 equiv of *p*-TSOH at 25 °C for 30 min, they were smoothly converted to the corresponding cyclohexenones (*i.e.*, **25**−**28**). Further treatment with $BF_3{\cdot}OEt_2$ afforded the related phenols **29**−**32** in *ca.* 80% yield (Scheme 4). Thus, a wide range of aromatic amines and phenols are readily available from furanamine **9** and an appropriate dienophile.

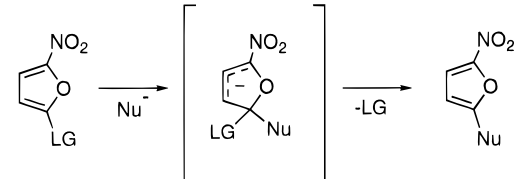
Having established the suitability of furanamine **9** to participate in Diels−Alder cycloadditions, we next examined the effect of incorporating an electron-withdrawing substituent on the furan ring that is also capable of acting as a leaving group. We reasoned that a "*push*−*pull*" stabilized heteroaromatic system such as a 2-amino-5-nitro-substituted furan would be an ideal compound to study. 2,5-Dinitrofuran (**33b**) is readily available from 2-nitrofuran by treatment with concentrated nitric acid.[45] A survey of the literature revealed that only a few examples exist involving nucleophilic substitution of this diactivated furan. The majority of these cases utilize thiolates as substrates, but there are a few examples where amine and alkoxide nucleophiles have also been

Scheme 4



employed.[46] These substitutions proceed by an addition−elimination mechanism *via* the Meisenheimer intermediate **34** shown in Scheme 5. Indeed, reaction of 2,5-dinitrofuran (**33b**) with a typical secondary amine such as morpholine in ether at 35 °C afforded the morphilino-substituted nitrofuran **36** in 97% yield. In contrast to the cycloaddition reaction of furanamine **9**, the reaction of furan **36** with methyl vinyl ketone (120 °C, 5 h) gave only a 20% yield of the expected phenol **37** derived from a [4 + 2]-cycloaddition followed by nitro group ejection and subsequent aromatization. Interestingly, two additional phenolic products (**38** and **39**) were also isolated from the reaction mixture in 20% and 10% yield, respectively. These nitro-substituted phenols are the result of

Scheme 5



cleavage of the initially formed oxabicyclic intermediate **40** with concomitant migration of the nitro group. A reasonable mechanism for their formation is outlined in Scheme 6. Following opening of the oxabridge, a 1,2-migration of the nitro group to the adjacent double bond of iminium ion **41** results in the formation of phenol **38**, after proton loss and oxidation to the aromatic system. The formation of **39** may be rationalized by invoking a competitive sequence involving 1,3-cyclohexadiene **42** as a transient intermediate that undergoes a suprafacial 1,5-hydrogen shift followed by nitro group migration to

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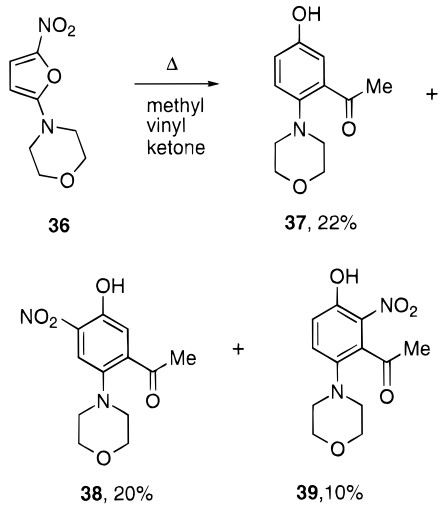
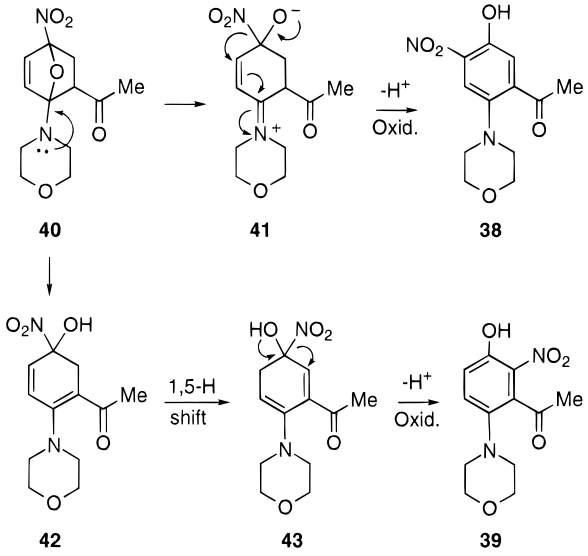
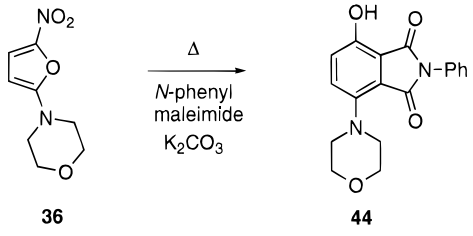


the activated enone π-bond. Proton loss and oxidation results in the formation of the isomeric nitrophenol **39**. After some experimentation, we eventually found a set of conditions that suppressed nitro group migration. The best conditions for minimizing formation of nitrophenols **38** and **39** consisted of performing the cycloaddition in refluxing ethanol in the presence of potassium carbonate.

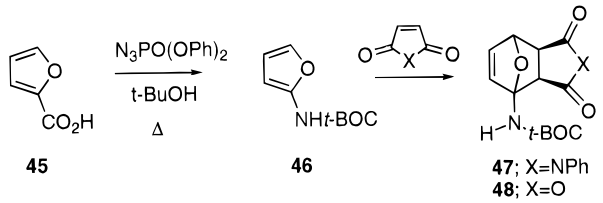
Scheme 6



These conditions resulted in the isolation of cycloadduct **37** in 83% yield. A similar set of conditions using *N*-phenylmaleimide as the dienophile furnished phenol **44** in 69% yield with no signs of any competitive nitro group migration products.



An additional system we chose to investigate was carbamate **46** as this compound is devoid of an electron-withdrawing substituent in the 5-position of the furan ring. Not only would this system provide some insight into the effect that electron-deficient groups have on the ring cleavage reaction, but it would also allow us to evaluate the reactivity of a simpler 2-aminofuran toward [4 + 2]-cycloaddition. A convenient method for transforming carboxylic acids to the corresponding carbamate derivatives involves the use of diphenyl phosphorazidate.[47] This reagent is known to generate a transient acyl azide that undergoes a subsequent Curtius rearrangement. Indeed, we found that the treatment of 2-furoic acid (**45**) with diphenyl phosphorylazidate in 2-methyl-2-propanol at 80 °C afforded *tert*-butyl carbamate **46** in 73% yield. Whereas the reaction of furanamine **9** with *N*-phenylmaleimide required refluxing in benzene for 12 h, carbamate **46** reacted at 25 °C (8 h) to give the *exo*-cycloadduct **47** in 77% yield. A similar cycloaddition occurred with maleic anhydride, furnishing the related *exo*-cycloadduct **48** in 79% yield.



The cycloadducts obtained from the above reactions were shown to possess *exo*-stereochemistry on the basis of the absence of a vicinal ^{1}H-coupling between the bridgehead hydrogen and the hydrogen atom located at the ring fusion. The *exo*-adduct possesses a dihedral angle of 83° between these two hydrogens, while the *endo*-adduct exhibits a dihedral angle of only 37° between these atoms.[48] There is good literature precedent for the preferred formation of the *exo*-isomer when furans are allowed to react with various dienophiles under thermodynamic control.[49] The crystalline product derived from the Diels−Alder reaction of furan with maleic anhydride was originally formulated as the *endo*-adduct,[50] but Woodward and Bauer subsequently showed that the adduct actually has the *exo*-configuration.[51] A further examination of the reaction at a later point in time by NMR spectroscopy revealed that the *endo*-isomer is the primary cycloadduct formed, although it was completely converted to the *exo*-isomer as the reaction progressed.[49] Since the formation of both adducts is reversible, and since the *exo*-isomer is 1.9 kcal/mol more stable than the *endo*-adduct, the *exo*-isomer is eventually the final product isolated. We assume a similar rationale in order to explain the exclusive formation of *exo*-adduct **47** (or **48**) from the reaction of **46** with *N*-phenylmaleimide or maleic anhydride.

It is noteworthy that the mild reaction conditions with which carbamate **46** undergoes [4 + 2]-cycloaddition allows for the ready isolation of the oxabridged compounds **47** and **48**. The robust nature of these cycloadducts suggests that the presence of an electron-withdrawing group at the bridgehead position plays a role in facilitating the oxybridge cleavage reaction. For example,

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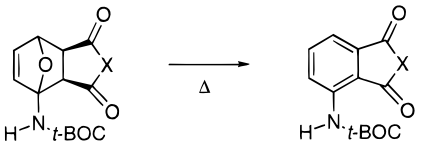
(48) The *exo*-stereochemical assignment of compounds **47** and **48** is supported with ^{1}H-NMR data from the literature that are consistent with the observed vicinal coupling constants; see: Mulzer, J.; Kappert, M.; Huttner, G.; Jibril, I. *Tetrahedron Lett.* **1985**, *26*, 1631. Parella, T.; Casas, R.; Ortuno, R. M. *Magn. Reson. Chem.* **1992**, *30*, 1084.

(49) Lee, M. W.; Herndon, W. C. *J. Org. Chem.* **1978**, *43*, 518.

(50) Diels, O.; Alder, K. *Chem. Ber.* **1929**, *62*, 557.

(51) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948**, *70*, 1161.

heating cycloadduct **47** at 80 °C in chloroform or benzene for 10 h resulted in its complete recovery. Only when the cycloadduct was heated at 110 °C in toluene was it possible to isolate **49**, which is derived from the ring-opening sequence. Similar conditions were also required in order to induce the maleic anhydride cycloadduct **48** to dehydrate so as to form **50** in 60% yield.

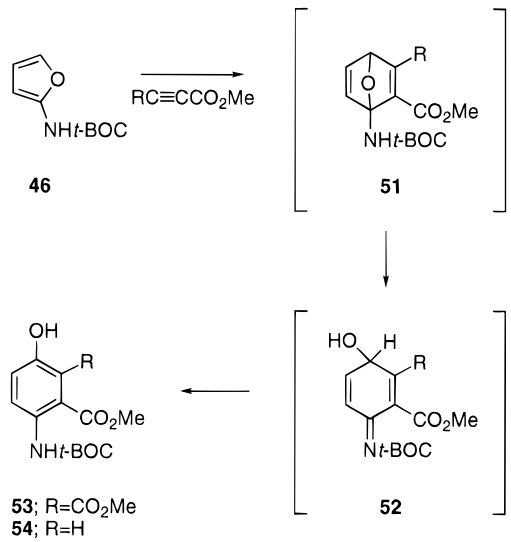


47; X=NPh
48; X=O

49; X=NPh
50; X=O

The facility with which carbamate **46** undergoes the Diels–Alder reaction with *N*-phenylmaleimide is not surprising when the calculated HOMO energy levels of the various substituted furans examined are compared.[26] The FMO calculations indicate that carbamate **46** possesses the highest lying HOMO and therefore is expected to have the smallest HOMO–LUMO gap (Figure 1). Competitive studies clearly demonstrated the difference in reaction rates. Thus, a 1:1 mixture of furanamine **9** and carbamate **46**, when treated with *N*-phenylmaleimide in refluxing benzene, afforded cycloadduct **47** as the exclusive product. Similarly, the reaction of the morphilino-substituted nitrofuran **36** and carbamate **46** with *N*-phenylmaleimide furnished only cycloadduct **47** derived from carbamate **46**. However, a 1:1 mixture of cycloadducts **17** and **44** was obtained from the reaction of *N*-phenylmaleimide with furans **9** and **36** (1:1 mixture).

The reaction of carbamate **46** with dimethyl acetylenedicarboxylate did not give the expected cycloadduct **51** but instead afforded the ring-opened product **53** (63%). The cycloaddition of **46** with methyl propiolate furnished the phenolic carbamate **54** (68%) in accordance with calculated FMO orbital coefficients. The regiochemistry of **54** was determined by coupled ^{13}C-NMR experiments. A signal at 152 ppm, consisting of a doublet further split into triplets, is indicative of a phenolic aromatic carbon with hydrogen atoms at the α- and α′-positions, as in **54**. A triplet centered at 132 ppm, typical of aromatic carbamates, is also consistent with the regiochemical assignment.

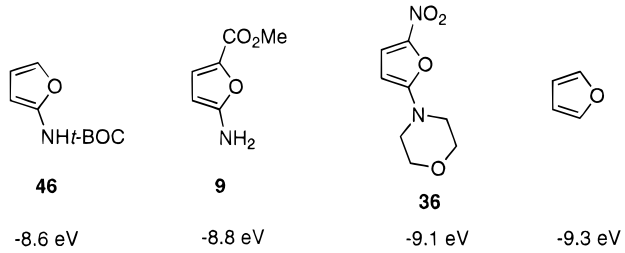


46

51

53; R=CO_2Me
54; R=H

52



46 **9** **36**

-8.6 eV -8.8 eV -9.1 eV -9.3 eV

Figure 1. HOMO energy levels of various furans.

In conclusion, the Diels–Alder reaction of 2-amino-substituted furans proceeds with various dienophiles to furnish [4 + 2]-cycloadducts that are readily converted to polysubstituted anilines. Further application of the method to intramolecular cycloadditions and its utilization for the synthesis of the erythrinane alkaloid family are in progress and will be reported in due course.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed under an atmosphere of dry argon in flame-dried glassware. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate–hexane mixture as the eluent unless specified otherwise.

5-Amino-2-furancarboxylic Acid Methyl Ester (9). To 400 mL of acetic anhydride at −5 °C was added 168 mL (3.5 mol) of fuming nitric acid. To this solution was added 85 mL (0.8 mol) of methyl furoate in 140 mL of acetic anhydride at −5 °C over 2 h. The reaction was stirred at −5 °C for 2 h and then quenched with ice–water. The aqueous layer was extracted with ether, and the combined ethereal layers were washed with a saturated $NaHCO_3$ solution and water, and dried over Na_2SO_4. After removal of the solvent, the resulting yellow solid (168 g, 92%) was used in the next step without further purification.

To a solution containing 168 g (0.7 mol) of the above solid in 700 mL of CH_2Cl_2 at −5 °C was added 127 mL (0.7 mol) of *N*,*N*-diisopropylethylamine. After the addition, the mixture was allowed to warm to rt, stirred for 15 h, and then poured over 70 mL of concd HCl and 500 g of ice. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with a saturated $NaHCO_3$ solution and water and dried over Na_2SO_4. Removal of the solvent under reduced pressure left a crude solid that was dissolved in CH_2Cl_2 and filtered through a pad of silica gel. After removal of the solvent, the resulting residue was recrystallized from methanol to give 113 g (91%) of 5-nitro-2-furancarboxylic acid methyl ester as a pale yellow solid: mp 80–81 °C (lit.[41] mp 81–82 °C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.98 (s, 3H), 7.30 (d, 1H, J = 3.8 Hz), 7.35 (d, 1H, J = 3.8 Hz).

To a solution containing 20 g (11.6 mol) of 5-nitro-2-furancarboxylic acid methyl ester in 200 mL of methanol was added 1 g of 5% Pd/$CaCO_3$. The mixture was hydrogenated at 40 psi for 20 h, filtered through a bed of Celite, and concentrated under reduced pressure. The resulting black solid was dissolved in 25% EtOAc/CH_2Cl_2 and filtered through a pad of silica gel. After removal of the solvent, the resulting pale yellow solid was recrystallized from acetonitrile to give 10.3 g (63%) of methyl 5-aminofuroate (**9**) as a pale yellow solid: mp 133–134 °C (lit.[52] mp 133–134 °C); IR (KBr) 3226, 1683, 1627, 1530 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.83 (s, 3H), 4.32 (brs, 2H), 5.29 (d, 1H, J = 3.6 Hz), 7.11 (d, 1H, J = 3.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 51.4, 87.1, 122.6, 135.1, 158.5, 159.0.

4-Amino-1-hydroxycyclohexa-3,5-diene-1,3-dicarboxylic Acid Dimethyl Ester (11). A mixture containing 0.19 g

(52) Krkoska, P.; Jurasek, A. *Chem. Zvesti* **1969**, *23*, 139.

(1.3 mmol) of furan **9** and 5 mL of methyl acrylate in 10 mL of benzene was heated at reflux for 48 h. The solvent was removed under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.28 g (92%) of **11** as a yellow solid: mp 102−103 °C; IR (KBr) 3445, 3335, 1736, 1671 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.87 (d, 1H, J = 17.1 Hz), 2.93 (d, 1H, J = 17.1 Hz), 3.20 (s, 1H), 3.71 (s, 3H), 3.82 (s, 3H), 6.02 (d, 1H, J = 9.6 Hz), 5.60−6.40 (brs, 2H), 6.17 (d, 1H, J = 9.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 32.8, 50.6, 53.1, 71.7, 85.6, 127.2, 133.7, 149.2, 169.7, 175.1. Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.97; H, 5.80; N, 6.06.

4-Amino-5-cyano-1-hydroxycyclohexa-2,4-dienecarboxylic Acid Methyl Ester (12). A mixture containing 0.24 g (1.7 mmol) of furan **9** and 4 mL of acrylonitrile in 10 mL of benzene was heated at reflux for 18 h. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.33 g (99%) of **12** as a pale yellow solid: mp 93−94 °C; IR (KBr) 3241, 2181, 1735, 1659 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.61 (d, 1H, J = 16.8 Hz), 2.90 (d, 1H, J = 16.8 Hz), 3.71 (s, 1H), 3.83 (s, 3H), 4.72 (brs, 2H), 6.07 (d, 1H, J = 9.8 Hz), 6.17 (d, 1H, J = 9.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 33.3, 53.4, 67.7, 70.6, 120.0, 125.0, 133.4, 149.7, 174.3. Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N,14.43. Found: C, 55.55; H, 5.18; N, 14.36.

4-Amino-5-(benzenesulfonyl)-1-hydroxycyclohexa-2,4-dienecarboxylic Acid Methyl Ester (13). A mixture containing 0.15 g (1.1 mmol) of furan **9** and 0.27 g (1.6 mmol) of phenyl vinyl sulfone in 10 mL of benzene was heated at reflux for 4 days. The solvent was removed under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.26 g (78%) of **13** as a pale yellow solid: mp 124−125 °C; IR (KBr) 3511, 3237, 1728, 1659, 1566 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.65 (d, 1H, J = 16.5 Hz), 2.79 (d, 1H, J = 16.5 Hz), 3.07 (s, 1H), 3.67 (s, 3H), 5.66 (brs, 2H), 5.94 (d, 1H, J = 9.6 Hz), 6.09 (d, 1H, J = 9.6 Hz), 7.48−7.59 (m, 3H), 7.86−7.90 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 33.3, 53.3, 71.7, 91.4, 126.4, 127.3, 128.9, 132.6, 134.3, 142.1, 145.0, 174.3. Anal. Calcd for $C_{14}H_{15}NO_5S$: C, 54.36; H, 4.89; N, 4.53. Found: C, 54.43; H, 4.92; N, 4.49.

5-Acetyl-4-amino-1-hydroxycyclohexa-2,4-dienecarboxylic Acid Methyl Ester (14). A mixture containing 0.21 g (1.5 mmol) of furan **9** and 5 mL of methyl vinyl ketone in 10 mL of benzene was heated at reflux for 1 h. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.24 g (74%) of **14** as a yellow solid: mp 128−129 °C; IR (KBr) 3369, 1736, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 2.86 (d, 1H, J = 16.2 Hz), 3.01 (d, 1H, J = 16.2 Hz), 3.25 (brs, 1H), 3.84 (s, 3H), 6.03 (d, 1H, J = 9.6 Hz), 6.21 (d, 1H, J = 9.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 27.5, 34.7, 53.1, 72.1, 95.2, 127.3, 135.4, 150.5, 174.7, 197.0. Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N 6.63. Found: C, 56.84; H, 6.25; N, 6.55.

4-Amino-1-hydroxy-cyclohexa-3,5-diene-1,2,3-tricarboxylic Acid Trimethyl Ester (15). A mixture containing 0.16 g (1.1 mmol) of furan **9** and 0.28 mL (2.2 mmol) of dimethyl maleate in 4 mL of toluene was heated in a sealed tube at 150 °C for 17 h. The mixture was taken up in CH_2Cl_2 and was filtered through a pad of silica gel. Removal of the solvent under reduced pressure followed by subjection of the residue to flash silica gel chromatography gave 0.26 g of a 1:3 mixture of two diastereomers of **15** in 80% yield. The minor diastereomer (yellow solid, mp 167−168 °C) exhibited the following spectral properties: IR (KBr) 3324, 1734, 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 6H), 3.77 (s, 3H), 4.11 (s, 1H), 4.15 (s, 1H), 5.95 (d, 1H, J = 9.9 Hz), 6.06 (d, 1H, J = 9.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 46.9, 50.9, 52.2, 53.5, 74.8, 76.3, 126.7, 136.6, 151.0, 169.1, 172.3, 172.4. Anal. Calcd for $C_{12}H_{15}NO_7$: C, 50.53; H, 5.30; N 4.91. Found: C, 50.66; H, 5.41; N, 4.82.

The major diastereomer (yellow solid, mp 93−94 °C) exhibited the following spectral properties: IR (KBr) 3438, 3331, 1738, 1674 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.57 (s, 4H), 3.65 (s, 3H), 3.78 (s, 3H), 4.07 (s, 1H), 6.06 (d, 1H, J = 9.9 Hz), 6.38 (d, 1H, J = 9.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 49.9, 50.9, 52.2, 53.1, 72.6, 84.7, 127.4, 133.3, 150.9, 169.3, 171.3, 172.8. Anal. Calcd for $C_{12}H_{15}NO_7 \cdot H_2O$: C, 47.53; H, 5.65; N 4.62. Found: C, 47.70; H, 5.65; N, 4.62.

4-Amino-1-hydroxy-2-methylcyclohexa-3,5-diene-1,3-dicarboxylic Acid Dimethyl Ester (16). A mixture containing 0.20 g (1.4 mmol) of furan **9** and 4 mL of methyl crotonate was heated in a sealed tube at 140−145 °C for 18 h. The mixture was diluted with CH_2Cl_2 and filtered through a pad of silica gel. After removal of the solvent under reduced pressure, the resulting residue was subjected to flash silica gel chromatography to give 0.20 g (57%) of **16** as a 3:2 mixture of diastereomers. The minor diastereomer (0.08 g, 24%) exhibited the following spectral properties: yellow solid; mp 155−156 °C; IR (KBr) 3321, 3218, 1732, 1660, 1614, 1533 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.10 (d, 3H, J = 6.9 Hz), 3.06 (s, 1H), 3.07 (dq, 1H, J = 6.9 and 1.1 Hz), 3.70 (s, 3H), 3.72 (s, 3H), 5.88 (dd, 1H, J = 9.8 and 1.1 Hz), 5.93 (d, 1H, J = 9.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.3, 36.3, 50.6, 53.2, 77.6, 93.3, 126.8, 136.3, 149.5, 169.8, 174.9. Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N 5.81. Found: C, 54.66; H, 6.26; N, 5.79.

The major diastereomer (0.12 g, 33%) exhibited the following spectral properties: orange solid; mp 145−146 °C; IR (KBr) 3328, 1741, 1667, 1595, 1005 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, 3H, J = 6.8 Hz), 2.88 (s, 1H), 3.13 (dq, 1H, J = 6.8, 0.9 Hz), 3.72 (s, 3H), 3.83 (s, 3H), 6.02 (d, 1H, J = 9.8 Hz), 6.44 (dd, 1H, J = 9.8, 0.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.6, 38.2, 50.7, 52.6, 75.4, 92.1, 126.7, 133.0, 148.7, 169.8, 173.6. Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.74; H, 6.26; N, 5.79.

7-Amino-1,3-dioxo-2-phenyl-2,3-dihydro-1*H*-isoindole-4-carboxylic Acid Methyl Ester (17). A mixture containing 0.2 g (1.5 mmol) of furan **9** and 0.3 g (1.6 mmol) of *N*-phenylmaleimide in 15 mL of benzene was heated at reflux for 12 h. The solvent was removed under reduced pressure. The crude solid was recrystallized from a 1:1 mixture of CH_2Cl_2 and EtOAc to give 0.26 g (63%) of **17** as a yellow solid: mp 215−216 °C; IR (KBr) 3180, 1761, 1700, 1633 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.95 (s, 3H), 5.72 (brs, 2H), 6.91 (d, 1H, J = 8.7 Hz), 7.37−7.52 (m, 5H), 7.88 (d, 1H, J = 8.7 Hz); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 52.0, 109.5, 116.1, 120.4, 127.5, 127.9, 128.7, 130.8, 131.9, 135.7, 148.7, 164.6, 165.6, 167.7. Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08. Found: C, 64.80; H, 4.12.

4-Aminoisophthalic Acid Dimethyl Ester (20). To a solution containing 0.25 g (1.1 mmol) of 4-amino-1-hydroxycyclohexa-3,5-diene-1,3-dicarboxylic acid dimethyl ester (**11**) in 10 mL of benzene was added 0.20 mL (1.6 mmol) of $BF_3 \cdot OEt_2$. The mixture was heated at reflux for 2 min, quenched with a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 0.22 g (96%) of **20** as a white solid: mp 127−128 °C; IR (KBr) 3452, 3345, 1690, 1621 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 3H), 3.88 (s, 3H), 6.30 (brs, 2H), 6.65 (d, 1H, J = 8.7 Hz), 7.89 (dd, 1H, J = 8.7, 2.1 Hz), 8.57 (d, 1H, J = 2.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 51.6, 109.6, 116.0, 117.6, 134.1, 134.8, 153.7, 166.5, 168.0. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30. Found: C, 57.34; H, 5.29.

4-Amino-3-cyanobenzoic Acid Methyl Ester (21). To a solution containing 0.18 g (0.93 mmol) of 4-amino-5-cyano-1-hydroxycyclohexa-2,4-dienecarboxylic acid methyl ester (**12**) in 10 mL of benzene was added 0.20 mL (1.6 mmol) of $BF_3 \cdot OEt_2$. The mixture was heated at reflux for 10 min, quenched with a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After removal of the solvent, the residue was subjected to flash silica gel chromatography to give 0.16 g (89%) of **21** as a white solid: mp 156−157 °C; IR (KBr) 3463, 2222, 1726, 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3H), 4.85 (brs, 2H), 6.75 (d, 1H, J = 8.7 Hz), 7.98 (dd, 1H, J = 8.7, 2.1 Hz), 8.12 (d, 1H, J = 2.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 52.0, 95.4, 114.4, 116.6, 119.8, 134.9, 135.2, 152.6, 165.4. Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.23; H, 4.53; N, 15.92.

4-Amino-3-(benzenesulfonyl)benzoic Acid Methyl Ester (22). To a solution containing 0.080 g (0.25 mmol) of 4-amino-5-(benzenesulfonyl)-1-hydroxycyclohexa-2,4-dienecarboxylic acid methyl ester (**13**) in 5 mL of benzene was added 0.05 mL (0.4 mmol) of $BF_3{\cdot}OEt_2$. The mixture was heated at reflux for 1.5 h, quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 64 mg (84%) of **22** as a white solid: mp 169−170 °C; IR (KBr) 3229, 1711, 1630, 1608 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3H), 5.59 (brs, 2H), 6.66 (d, 1H, J = 8.4 Hz), 7.48−7.59 (m, 3H), 7.92−7.96 (m, 3H), 8.54 (d, 1H, J = 2.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 52.0, 117.2, 119.6, 121.3, 126.9, 129.2, 132.7, 133.4, 135.9, 141.3, 149.5, 165.7. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50. Found: C, 57.55; H, 4.49.

3-Acetyl-4-aminobenzoic Acid Methyl Ester (23). To a solution containing 0.095 g (0.45 mmol) of 5-acetyl-4-amino-1-hydroxycyclohexa-2,4-dienecarboxylic acid methyl ester (**14**) in 5 mL of benzene was added 0.09 mL (0.7 mmol) of $BF_3{\cdot}OEt_2$. The mixture was heated at reflux for 30 min, quenched with a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography of the residue afforded 0.081 g (93%) of **23** as a white solid: mp 128−129 °C; IR (KBr) 3332, 1694, 1618 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.63 (s, 3H), 3.88 (s, 3H), 6.64 (d, 1H, J = 9.0 Hz), 6.90 (brs, 2H), 7.88 (dd, 1H, J = 9.0, 2.0 Hz), 8.46 (d, 1H, J = 2.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 27.7, 51.7, 116.6, 117.0, 117.1, 134.9, 135.0, 153.5, 166.4, 200.6. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N 7.25. Found: C, 62.06; H, 5.77; N, 7.17.

4-Amino-2-methylisophthalic Acid Dimethyl Ester (24). To a solution containing 0.07 g (0.27 mmol) of either diastereomer of 4-amino-1-hydroxy-2-methylcyclohexa-3,5-diene-1,3-dicarboxylic acid dimethyl ester (**16**) in 5 mL of benzene was added 0.04 mL (0.32 mmol) of $BF_3{\cdot}OEt_2$. The mixture was heated at reflux for 11 h, quenched with a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 0.05 g (79%) of **24** as a white solid: mp 90−91 °C; IR (KBr) 3266, 1719, 1703, 1655, 1593 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.58 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 4.92 (brs, 2H), 6.52 (d, 1H, J = 8.7 Hz), 7.77 (d, 1H, J = 8.7 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 19.6, 51.6, 51.9, 113.1, 117.4, 119.9, 134.2, 142.2, 149.6, 167.6, 169.5. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N 6.27. Found: C, 59.17; H, 5.87; N, 6.26.

4-Hydroxyisophthalic Acid Dimethyl Ester (29). To a solution containing 0.3 g (1.5 mmol) of 4-amino-1-hydroxycyclohexa-3,5-diene-1,3-dicarboxylic acid dimethyl ester (**11**) in 10 mL of water was added 0.3 g (1.6 mmol) of *p*-toluenesulfonic acid monohydrate. After being stirred at rt for 30 min, the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.28 g (84%) of 3-hydroxy-6-oxocyclo-4-ene-1,3-dicarboxylic acid dimethyl ester (**25**) as a pale yellow oil that was used in the next step without further purification.

To a solution containing 0.15 g (0.66 mmol) of ester **25** in 10 mL of benzene was added 0.18 mL (1.4 mmol) of $BF_3{\cdot}OEt_2$. The mixture was stirred at rt for 5 min, quenched with a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.12 g (84%) of **29** as a white solid: mp 94−95 °C; IR (KBr) 3196, 1734, 1688, 1581 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.90 (s, 3H), 3.98 (s, 3H), 6.99 (d, 1H, J = 8.7 Hz), 8.08 (dd, 1H, J = 8.7, 2.1 Hz), 8.52 (d, 1H, J = 2.1 Hz), 11.18 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 51.9, 52.5, 112.0, 117.6, 121.3, 132.3, 136.4, 164.9, 165.8, 169.9. Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.03; H, 4.85.

3-(Benzenesulfonyl)-4-hydroxybenzoic Acid Methyl Ester (30). To a solution containing 0.21 g (0.68 mmol) of 4-amino-5-(benzenesulfonyl)-1-hydroxycyclohexa-2,4-dienecarboxylic acid methyl ester (**13**) in 10 mL of water was added 0.15 g (0.79 mmol) of *p*-toluenesulfonic acid monohydrate. After the solution was allowed to stir at rt for 10 min, the mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.17 g (81%) of 5-(benzenesulfonyl)-1-hydroxy-4-oxocyclohex-2-enecarboxylic acid methyl ester (**26**) as an inseparable 1:1 diastereomeric mixture.

To a solution containing 0.17 g (0.54 mmol) of the above mixture in 8 mL of CH_2Cl_2 was added 0.14 mL (1.1 mmol) of $BF_3{\cdot}OEt_2$. The solution was stirred at rt for 40 h, quenched with a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.12 g (74%) of 3-(benzenesulfonyl)-4-hydroxybenzoic acid methyl ester (**30**) as a white solid: mp 124−125 °C; IR (KBr) 3089, 1720, 1708, 1607, 1275 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3H), 7.04 (d, 1H, J = 8.8 Hz), 7.53−7.66 (m, 3H), 7.95−7.99 (m, 2H), 8.10 (dd, 1H, J = 8.8, 2.1 Hz), 8.37 (d, 1H, J = 2.1 Hz), 9.69 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 52.3, 119.3, 123.1, 123.7, 126.9, 131.6, 134.1, 137.0, 141.0, 159.3, 165.0. Anal. Calcd for $C_{14}H_{12}O_5S$: C, 57.53; H, 4.14. Found: C, 57.25; H, 4.23.

3-Acetyl-4-hydroxybenzoic Acid Methyl Ester (31). To a solution containing 0.11 g (0.52 mmol) of 5-acetyl-4-amino-1-hydroxycyclohexa-2,4-dienecarboxylic acid methyl ester (**14**) in 5 mL of water was added 0.11 g (0.58 mmol) of *p*-toluenesulfonic acid monohydrate. After being stirred at rt for 7 h, the mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4. The solution was filtered through a pad of silica gel to give 0.080 g (72%) of 5-acetyl-1,4-dihydroxycyclohexa-2,4-dienecarboxylic acid methyl ester (**27**) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 2.85 (d, 1H, J = 15.9 Hz), and 3.01 (d, 1H, J = 15.9 Hz), 3.65 (s, 1H), 3.83 (s, 3H), 6.22 (d, 1H, J = 9.9 Hz), and 6.43 (d, 1H, J = 9.9 Hz), 15.55 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.4, 34.0, 53.5, 71.8, 101.4, 129.1, 140.4, 174.4, 178.1, 189.6; HRMS calcd for $C_{10}H_{12}O_5$ 212.0685, found 212.0685.

To the solution containing 0.075 g (0.35 mmol) of ester **27** in 10 mL of benzene was added 0.09 mL (0.7 mmol) of $BF_3{\cdot}OEt_2$. The mixture was stirred at rt for 10 min, quenched with a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude residue was subjected to flash silica gel chromatography to give 0.06 g (82%) of **31** as a white solid: mp 92−93 °C; IR (KBr) 3409, 1720, 1643 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.71 (s, 3H), 3.93 (s, 3H), 7.01 (d, 1H, J = 8.7 Hz), 8.13 (dd, 1H, J = 8.7, 2.0 Hz), 8.49 (d, 1H, J = 2.0 Hz), 12.68 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 26.7, 52.1, 118.6, 119.1, 121.0, 133.2, 137.1, 165.8, 165.9, 204.5. Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.67; H, 5.28.

4-Hydroxy-2-methylisophthalic Acid Dimethyl Ester (32). To a solution containing 0.05 g (0.19 mmol) of 4-amino-1-hydroxy-2-methylcyclohexa-3,5-diene-1,3-dicarboxylic acid dimethyl ester (**16**) in 5 mL of water and 3 mL of THF was added 0.04 g (0.20 mmol) of *p*-toluenesulfonic acid monohydrate. After the mixture was allowed to stir at rt for 12 h, the solution was extracted with CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.03 g (67%) of 3-hydroxy-2-methyl-6-oxocyclohex-4-ene-1,3-dicarboxylic acid dimethyl ester (**28**) as a pale yellow solid: mp 94−95 °C; IR (KBr) 3395, 1741, 1676, 1267 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, 3H, J = 6.6 Hz), 2.94 (m, 1H), 3.54 (s, 1H), 3.60 (d, 1H, J = 12.3 Hz), 3.80 (s, 3H), 3.89 (s, 3H), 6.14 (d, 1H, J = 10.2 Hz), and 6.70 (d, 1H, J = 10.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 13.3, 38.3, 52.3, 54.0, 56.7, 72.7, 129.2, 145.0, 169.7, 174.6, 193.7. Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.59; H, 5.80.

To a solution containing 51 mg (0.21 mmol) of ester **28** in 5 mL of dry CH_2Cl_2 was added 0.05 mL (0.41 mmol) of $BF_3 \cdot OEt_2$. The mixture was stirred at rt for 12 h, quenched with a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.042 g (88%) of 4-hydroxy-2-methylisophthalic acid dimethyl ester (**32**) as a white solid: mp 98−99 °C; IR (KBr) 3367, 1723, 1692, 1596 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.72 (s, 3H), 3.87 (s, 3H), 4.00 (s, 3H), 6.86 (d, 1H, J = 8.9 Hz), 7.85 (d, 1H, J = 8.9 Hz), 11.09 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.0, 52.0, 52.5, 114.5, 115.2, 123.9, 135.9, 143.6, 163.9, 167.9, 171.63. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.96; H, 5.38.

2,5-Dinitrofuran (33b). A modification of the procedure of Freure and Johnson was used to prepare 2-nitrofuran.[41] To 50 mL (0.5 mol) of acetic anhydride at −30 °C was added 22 mL (0.5 mol) of fuming nitric acid while the temperature was maintained below −10 °C. The acetyl nitrate solution was cooled to −30 °C, and a solution containing 40 mL (0.3 mol) of furan in 20 mL of acetic anhydride was slowly added, maintaining the temperature below −30 °C. When the addition was complete, the reaction was allowed to stir for an additional 15 min, poured into ice−water, and neutralized to pH 6 by the slow addition of a 50% NaOH solution while the temperature was maintained at 0 °C. The mixture was extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The red liquid was taken up in 20 mL of dry THF, and the mixture was slowly added to a solution of 40 mL of pyridine in 20 mL of THF. The rate of addition was controlled so as to maintain a temperature of 50 °C. Once the addition was complete, the reaction mixture was cooled to rt and concentrated by distillation under aspirator vacuum. The resulting residue was passed through a silica gel plug, eluting with CH_2Cl_2. The yellow filtrate was concentrated under reduced pressure, and the resulting oil was sublimed at 30 °C (2 mm) to give 16.5 g (53%) of 2-nitrofuran as bright yellow crystals: mp 27−28 °C (lit.[41] mp 28−29 °C).

A modification of the procedure of Hill and White was used in the subsequent nitration step.[45] A solution containing 3.0 g (26 mmol) of 2-nitrofuran in 50 mL of 70% nitric acid was heated at 60 °C for 4 h. After being cooled to rt, the solution was poured into ice−water, neutralized by the careful addition of sodium carbonate, and extracted with CH_2Cl_2. The combined organic extracts were washed with water, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Recrystallization of the residue from ethanol afforded 2.1 g (51%) of 2,5-dinitrofuran (**33b**) as a pale yellow solid: mp 99−101 °C (lit.[45] mp 100−101 °C).

4-(5-Nitrofuran-2-yl)morpholine (36). To a solution of 0.33 g (2.1 mmol) of dinitrofuran **33b** in 25 mL of ether was added 0.28 g (4.5 mmol) of morpholine. The solution was heated at reflux for 2.5 h, cooled to rt, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography to give 0.40 g (97%) of furan **36** as a labile orange solid: mp 114−115 °C; IR ($CHCl_3$) 3119, 2913, 1610, 1517, 1391 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.46 (m, 4H), 3.81 (m, 4H), 5.38 (d, 1H, J = 4.2 Hz), 7.47 (d, 1H, J = 4.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 45.8, 65.8, 87.8, 120.0, 139.6, 159.7; HRMS calcd for $C_8H_{10}N_2O_4$ 198.0640, found 198.0641.

1-(5-Hydroxy-2-morpholin-4-yl-4-nitrophenyl)ethanone (38). A stirred solution containing 300 mg (1.5 mmol) of **36** and 140 mg (2.0 mmol) of methyl vinyl ketone in 50 mL of toluene was heated at reflux for 12 h. The reaction mixture was cooled to rt, concentrated under reduced pressure, and subjected to silica gel chromatography. The first fraction to elute from the column contained 80 mg (20%) of acetophenone **38** as a bright orange solid: mp 159−160 °C; IR ($CHCl_3$) 3272, 2914, 1696, 1618 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.65 (s, 3H), 2.94 (m, 4H), 3.85 (m, 4H), 7.11 (s, 1H), 7.78 (s, 1H), 10.32 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 29.8, 53.4, 66.8, 119.6, 114.9, 133.9, 142.8, 146.0, 151.3, 202.4. Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.88; H, 5.29; N, 10.34.

The second product eluted from the column (45 mg, 10%) was identified as 1-(5-hydroxy-2-morpholin-4-yl-6-nitrophenyl)-ethanone (**39**) as an orange solid: mp 156−157 °C; IR ($CHCl_3$) 3285, 2960, 1709, 1612 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.61 (s, 3H), 2.85 (m, 4H), 3.76 (m, 4H), 7.18 (d, 1H, J = 8.7 Hz), 7.55 (d, 1H, J = 9.0 Hz), 10.43 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 30.9, 53.5, 67.2, 120.9, 130.3, 132.2, 138.5, 142.0, 152.8, 199.6. Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.12; H, 5.27; N, 10.45.

The third product eluted from the column (90 mg, 22%) was identified as 1-(5-hydroxy-2-morpholin-4-ylphenyl)ethanone (**37**) and was isolated as a yellow solid: mp 122−123 °C; IR ($CHCl_3$) 2829, 1684, 1598 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.71 (s, 3H), 2.91 (m, 4H), 3.84 (m, 4H), 6.97 (m, 2H), 7.04 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 30.1, 53.9, 67.2, 115.4, 119.2, 121.2, 137.1, 144.3, 152.5, 205.3. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.01; H, 6.82; N, 6.27.

4-Hydroxy-7-morpholin-4-yl-2-phenylisoindole-1,3-dione (44). To a stirred solution containing 125 mg (0.6 mmol) furan **36** in 25 mL of chloroform was added 330 mg (1.9 mmol) *N*-phenylmaleimide and 90 mg (0.7 mmol) of potassium carbonate. The mixture was heated at reflux for 12 h and cooled to rt, and 10 mL of a saturated ammonium chloride solution was added. The mixture was extracted with CH_2Cl_2, and the extracts were dried over Na_2SO_4, concentrated under reduced pressure, and subjected to silica gel chromatography to give 140 mg (69%) of 4-hydroxy-7-morpholin-4-yl-2-phenylisoindole-1,3-dione (**44**) as a yellow solid: mp 200−201 °C; IR ($CHCl_3$) 3319, 1754, 1696, 1498 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.29 (m, 4H), 3.91 (m, 4H), 7.19 (s, 2H), 7.42 (m, 3H), 7.51 (t, 2H, J = 7.8 Hz), 7.94 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 51.7, 67.1, 114.9, 116.4, 125.7, 126.6, 126.8, 128.5, 129.4, 131.5, 144.9 150.3, 166.0, 169.7. Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.70; H, 5.02; N, 8.61.

Furan-2-ylcarbamic Acid *tert*-Butyl Ester (46). A solution containing 2.0 g (18 mmol) of 2-furoic acid (**45**), 5.0 mL (35 mmol) of triethylamine, and 8.0 mL (35 mmol) of diphenyl phosphor azidate in 40 mL of *tert*-butyl alcohol was heated to reflux and maintained at this temperature for 10 h. The solvent was removed by distillation, and the residue was purified by silica gel chromatography to give 2.4 g (73%) of carbamate **46** as a white solid: mp 98−99 °C; IR (KBr) 3267, 2980, 1700, 1546 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 9H), 6.04 (brs, 1H), 6.34 (m, 1H), 6.63 (brs, 1H), 7.06 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.2, 81.3, 95.1, 111.2, 136.0, 145.4, 151.9. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.64. Found: C, 59.09; H, 7.13; N, 7.67.

(2*R,6*S**)-(3,5-Dioxo-4-phenyl-10-oxa-4-azatricyclo-[5.2.1.0^{2,6}]dec-8-en-1-yl)carbamic Acid *tert*-Butyl Ester (47).** A solution containing 1.0 g (5.5 mmol) of carbamate **46** and 0.9 g (5.5 mmol) of *N*-phenylmaleimide in 20 mL of toluene was stirred at rt for 8 h. The resultant white precipitate was washed with cold ether and dried *in vacuo* to give 1.5 g (77%) of **47** as a white solid: mp 147−148 °C; IR (KBr) 3426, 3120, 2968, 1717, 1705, 1506 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 3.05 (d, 1H, J = 6.5 Hz), 3.14 (d, 1H, J = 6.5 Hz), 5.28 (d, 1H, J = 1.9 Hz), 6.55 (m, 2H), 6.73 (m, 1H), 7.31 (m, 2H), 7.49 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.1, 79.9, 81.2, 95.0, 125.4, 127.0, 129.1, 130.0, 132.3, 134.9, 138.1, 149.0, 154.2, 175.0, 175.2. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.08; H, 5.73; N, 7.76.

(2*R,6*S**)-(3,5-Dioxo-4,10-dioxatricyclo[5.2.1.0^{2,6}]dec-8-en-1-yl)carbamic Acid *tert*-Butyl Ester (48).** A solution containing 1.5 g (8.0 mmol) of carbamate **46** and 0.80 g (8.0 mmol) of maleic anhydride in 20 mL of ether was heated to reflux for 4 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 1.8 g (79%) of **48** as a white solid: mp 135−136 °C; IR (KBr) 3407, 2980, 1735, 1704, 1574 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 9H), 3.24 (d, 1H, J = 6.8 Hz), 3.31 (d, 1H, J = 6.8 Hz), 5.31 (d, 1H, J = 1.9 Hz), 6.27 (brs, 1H), 6.55 (m, 1H), 6.72 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.1, 49.2, 50.6, 79.2, 81.1, 95.0, 134.9, 137.1, 153.0, 167.9, 169.1. Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.45; H, 5.33; N, 4.96.

(1,3-Dioxo-2-phenyl-2,3-dihydro-1*H*-isoindol-4-yl)-carbamic Acid *tert*-Butyl Ester (49). A solution containing 0.25 g (0.6 mmol) of cycloadduct **47** in 15 mL of toluene was

heated at reflux for 6 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.13 g (61%) of **49** as a white solid: mp 138−139 °C; IR (KBr) 3367, 3055, 2985, 1723, 1704, 1522 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 9H), 7.51 (m, 6H), 7.71 (m, 1H), 8.58 (d, 1H, J = 8.6 Hz), 8.91 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.1, 81.7, 114.5, 117.1, 123.5, 126.3, 128.1, 129.0 (2C), 131.3, 136.0, 138.5, 152.2, 166.7, 168.9. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.27. Found: C, 67.55; H, 5.41; N, 8.26.

(1,3-Dioxo-1,3-dihydroisobenzofuran-4-yl)carbamic Acid *tert*-Butyl Ester (50). A solution containing 0.31 g (1.1 mmol) of cycloadduct **48** in 20 mL of toluene was heated at reflux for 7 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.17 g (60%) of **50** as a white solid: mp 123−124 °C; IR (KBr) 3361, 3050, 2985, 1718, 1704 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.51 (s, 9H), 7.49 (m, 1H), 7.62 (m, 1H), 8.51 (d, 1H, J = 8.5 Hz), 8.85 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.1, 81.1, 123.5, 123.9, 124.2, 131.3, 135.8, 135.9, 154.4, 166.6, 168.5. Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.39; H, 5.08; N, 5.44.

3-[(*tert*-Butylcarbonyl)amino]-6-hydroxyphthalic Acid Dimethyl Ester (53). A solution containing 1.3 g (7.0 mmol) of carbamate **46** and 1.7 mL (14 mmol) of dimethyl acetylenedicarboxylate in 20 mL of benzene was heated to 45 °C for 4 h. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography to give 2.0 g (89%) of **53** as a yellow solid: mp 98−99 °C; IR (KBr) 3428, 3133, 2980, 1725, 1689, 1524 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 9H), 3.80 (s, 3H), 3.85 (s, 3H), 7.07 (d, 1H, J = 6.5 Hz), 7.25 (brs, 1H), 8.09 (brd, 1H, J = 6.5 Hz), 10.15 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.2, 52.7, 53.0, 80.9, 110.2, 120.5, 120.6, 128.9, 129.7, 153.1, 156.9, 168.0, 169.1. Anal. Calcd for $C_{15}H_{19}NO_7$: C, 55.38; H, 5.89; N, 4.30. Found: C, 55.39; H, 5.87; N, 4.34.

2-[(*tert*-Butylcarbonyl)amino]-5-hydroxybenzoic Acid Methyl Ester (54). A solution containing 2.1 g (11 mmol) of carbamate **46** and 2.0 mL (23 mmol) of methyl propiolate in 20 mL of benzene was heated at reflux for 5 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 1.9 g (63%) of **54** as a white solid: mp 165−166 °C; IR (KBr) 3414, 3309, 2973, 1714, 1679, 1540 cm^{-1}; ^{1}H-NMR (CD_3OD, 300 MHz) δ 1.50 (s, 9H), 3.88 (s, 3H), 6.98 (dd, 1H, J = 9.1, 3.0 Hz), 7.37 (d, 1H, J = 3.0 Hz), 8.04 (d, 1H, J = 9.1 Hz); ^{13}C-NMR (CD_3OD, 75 MHz) δ 27.9, 52.0, 80.5, 116.6, 121.2, 121.8, 134.4, 152.3, 153.9, 168.7. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.40; H, 6.39; N, 5.27.

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Supporting Information Available: ^{1}H-NMR and ^{13}C-NMR spectra for new compounds lacking analyses (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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