1-(Dialkylamino)isobenzofurans: Generation and Use for Annelation of Aromatic Rings

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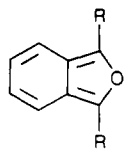
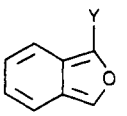
Three methods are reported for the generation of the heretofore unreported 1-(dialkylamino)isobenzofurans. These are (1) metal-catalyzed decomposition of an *o*-(diazomethyl)benzamide (**9** to **3**), (2) fluoride-induced α elimination of an *o*-[bromo(trimethylsilyl)methyl]benzamide (**48** to **3**), and (3) deprotonation of a cyclic imidate salt (**51** to **3**). The first two reactions are consistent with the intermediacy of a carbene. The precursors for all three approaches can be synthesized from tertiary benzamides by ortho-lithiation strategies. Reaction of the transient 1-(dialkylamino)isobenzofurans with dieneophiles in a $\pi^4s + \pi^2s$ cycloaddition is the key step in a one-pot sequence that provides annelation of an aromatic ring by a 2,3-substituted 1-(dialkylamino)-4-hydroxycyclohex-1-ene ring. The sequence of formation of the 1-(dialkylamino)isobenzofuran, regio- and stereospecific cycloaddition, ring opening, and proton transfer, is illustrated by the preparations of **15–23**, **32**, and **33** from *N,N*-diisopropylbenzamides. The ring annelation is extended to naphthalene and pyridine rings to provide **40**, **41**, and **44**, respectively. Transformations of annelated products to higher and lower oxidation states are reported.

Use of the powerful $\pi^4s + \pi^2s$ cycloaddition for annelation of aromatic rings often is achieved by intramolecular reaction of a transient *o*-xylylene with an olefin.[1] Intermolecular uses of this approach suffer from limited availability and high reactivity of the π^4 partner. One strategy for extending this methodology is to generate a reactive but relatively stable derivative of the penultimate aromatic component.

Isobenzofurans (**1**) are well-known derivatives of *o*-xylylenes; indeed, 1,3-diphenylisobenzofuran (**2**) is a stable readily available compound which is nonetheless among the most reactive dienes.[2] Substitution of an electron-



1, R = H
2, R = C_6H_5



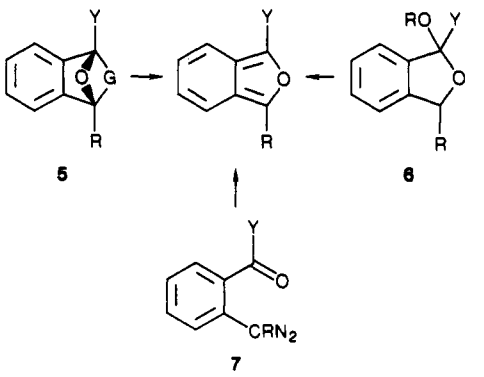
3, Y = NR_2
4, Y = OR

donating heteroatom at the 1-position of isobenzofuran should raise the HOMO and decrease the HOMO–LUMO gap in a "normal demand" Diels–Alder reaction. Under FMO theory nitrogen would be more effective than oxygen and the 1-(dialkylamino)isobenzofurans should be more reactive than the parent system and show higher regio- and stereoselectivity.[3] Moreover, as shown in Scheme II, the cycloadduct of a 1-dialkylamino-substituted isobenzofuran and a dienophile could undergo ring opening and proton transfer, to provide the enamide function in a regio- and stereospecific annelation of the aromatic ring.[3b,c]

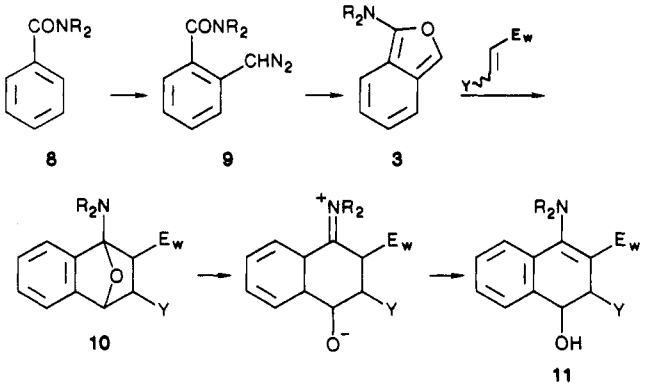
In order to investigate the chemistry of the 1-(dialkylamino)isobenzofurans **3** we have devised routes to these species and undertaken studies of the reactions of **3** as π^4s component with typical Diels–Alder dienophiles.[4] Rickborn and co-workers have recently developed the chemistry of 1-alkoxyisobenzofurans **4** and shown them to be reactive π^4 systems.[5]

Syntheses of isobenzofurans fall into the three general categories shown in Scheme I: fragmentation of **5** in a retro $\pi^4s + \pi^2s$ reaction,[6] acid- or base-induced 1,4-elimination of a cyclic precursor **6**,[7] or intramolecular reaction of a

Scheme I



Scheme II



(1) For examples, see: Oppolzer, W. *Synthesis* **1978**, 793. Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3. Magnus, P.; Gallagher, T. *Tetrahedron* **1981**, *37*, 3889. Clivet, J. E.; Dunach, E.; Volhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6710 and references cited therein.

(2) For reviews of isobenzofurans, see: Haddadin, M. J. *Heterocycles* **1978**, *9*, 865. Friedrischen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135.

(3) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976. (b) Contreras, L.; MacLean, D. B. *Can. J. Chem.* **1980**, *58*, 2573. (c) Warrener, R. N.; Hammer, B. C.; Russel, R. A. *J. Chem. Soc., Chem. Commun.* **1981**, 942.

(4) For a preliminary report see: Beak, P.; Chen, C.-W. *Tetrahedron Lett.* **1983**, 2945.

(5) For a recent report and leading references, see: Mir-Mohamad Sadeghy, B.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 1477.

(6) Fieser, L. F.; Haddadin, M. J. *J. Am. Chem. Soc.* **1964**, *43*, 1599. Fieser, L. F.; Haddadin, M. J. *Can. J. Chem.* **1965**, *43*, 1599. Warrener, R. N. *J. Am. Chem. Soc.* **1971**, *93*, 2346. Wege, D. *Tetrahedron Lett.* **1971**, 2337. Wiersum, U. E.; Mijs, W. J. *J. Chem. Soc., Chem. Commun.* **1972**, 347. For a review of synthetic application, see: Wiersum, U. E. *Aldrichimica Acta* **1981**, *14*, 53.

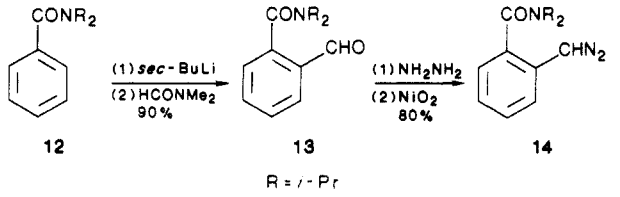
0022-3263/86/1951-3325$01.50/0

diazo group with an adjacent carbonyl group as for 7.[8] In most cases, the isobenzofuran is trapped by a dienophile in situ under conditions of its generation. The fragmentation approach provided the earliest successful syntheses and required vigorous conditions although recent FVP modifications allow isolations of isobenzofurans.[6] The 1,4-elimination reaction has been nicely developed for 1-alkoxyisobenzofurans, and these have been effectively used for ring annelations.[7] The third approach appears to be limited to two examples, one of which provides 1-methoxyisobenzofuran (4, Y = OCH_3) from treatment of methyl α-(diazomethyl)benzoate with a copper salt.[8b] The 1-(dialkylamino)isobenzofurans do not appear to have been reported prior to our work.[4]

Results and Discussion

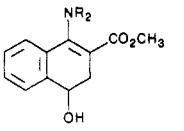
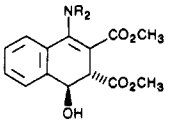
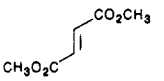
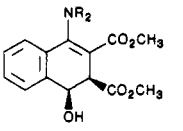
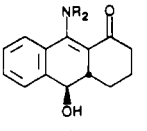
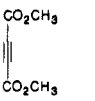
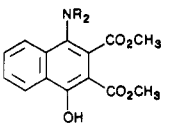
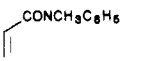
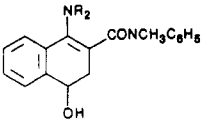
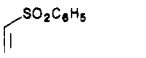
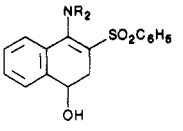
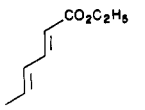
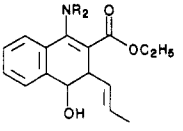
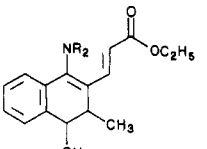
Synthetic Sequence. The principal method we have developed for the generation of 1-(dialkylamino)isobenzofurans 3 is an extension of work by Ibata and Hamaguchi[8b] and by Contreras and MacLean[3b] as outlined in Scheme II. The first step is conversion of an aromatic amide to an *o*-diazomethyl derivative 9, which is the immediate precursor of 3. Regiospecific cycloaddition of 3 and a dienophile provides 10, which undergoes ring opening and proton transfer to give 11. The dihydronaphthalene 11 may be converted to an aromatic or tetralin ring which has nitrogen and oxygen at the benzylic positions with selected substituents at the other two positions. Thus annelation of the aromatic ring by six-membered carbocyclic ring at different oxidation levels and with control of the substituents is possible by this approach.

Strategy based on ortho lithiation of tertiary aromatic amides is used to prepare the *o*-diazomethyl derivatives.[9] Thus, *N,N*-diisopropylbenzamide (12) can be ortho metalated by *sec*-BuLi at −78 °C in THF and treated with *N,N*-dimethylformamide (DMF) to give 2-formyl-*N,N*-diisopropylbenzamide (13) in 90% yield. Further elaboration of 13 by treatment with hydrazine hydrate and a catalytic amount of pyridine in diethyl ether solution affords the crude hydrazone which can be oxidized by nickel peroxide to the diazo benzamide 14 in 80% yield. The presence of the diazo group is established by a strong diazo absorption at 2150 cm^{-1} in the IR spectrum of 14.



Conversions of 14 to annelated products 11, as shown in Scheme II, occurs on exposure to a dienophile in the presence of 5% $Cu(arcac)_2$ or 1% $Rh_2(OAc)_4$. Reactions of 14 which provide the annelated products 15–23 are summarized in Table I.

Table I. Reaction of *N,N*-Diisopropyl-2-(diazomethyl)benzamide (14) with Dienophiles

dienophile	product[a]	yield, %
	 15	52[b]
	 16	75[b]
	 17	43[b,c]
	 18	33,[b] 44[c]
	 19	49,[c] 28[b,e]
	 20	56[b]
	 21	39[c]
	 22	6[c]
	 23	35[c,f]

[a] R = *i*-Pr. [b] $Cu(acac)_2$ is the catalyst. [c] $Rh_2(OAc)_4$ is the catalyst [d] The balance of the product undergoes dehydration. [e] 30 mol % $Cu(acac)_2$ is used. [f] Both cis and trans isomers are isolated and characterized by spectroscopic methods.

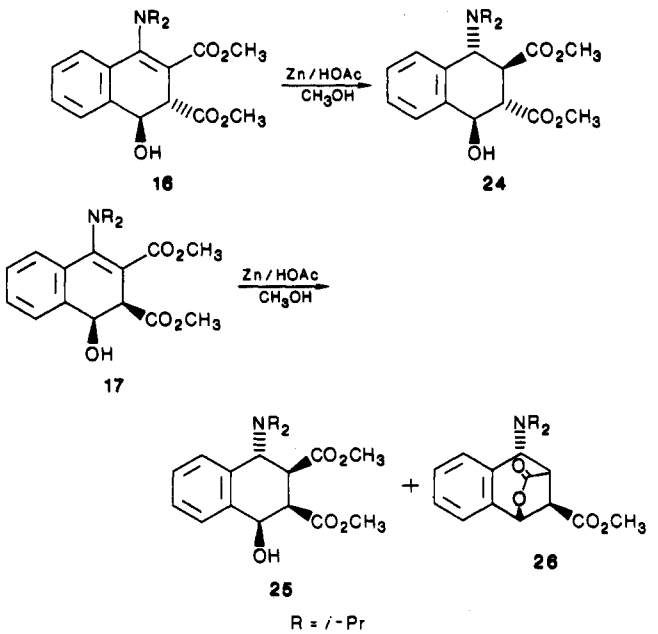
(7) Rickborn, B.; Naito, K. *J. Org. Chem.* **1980**, *45*, 4061. Rickborn, B.; Makhlouf, M. A. *J. Org. Chem.* **1982**, *47*, 34. Rickborn, B.; Moss, R. *J. Org. Chem.* **1982**, *47*, 5391. Rodrigo, R.; Keay, B. A.; Lee, D. K. W. *Tetrahedron Lett.* **1980**, *21*, 3663. Smith, J. G.; Welankiwar, S. S.; Chu, N. G.; Lai, E. H.; Sonheimer, S. J. *J. Org. Chem.* **1981**, *46*, 4658. Smith, J. G.; Chu, N. G. *J. Org. Chem.* **1981**, *46*, 4083. Smith, J. G.; Dibble, P. W. *J. Org. Chem.* **1983**, *48*, 5361. Iwao, M.; Inoue, H.; Kuraishi, T. *Chem. Lett.* **1984**, 1263. Troll, T.; Schmid, K. *Tetrahedron Lett.* **1984**, 2981. Gilchrist, T. L.; Faragher, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 336. Rodrigo, R.; Keay, B. A. *Tetrahedron* **1984**, *40*, 4597. Rodrigo, R.; Keay, B. A.; Rajapaksa, D. *Can. J. Chem.* **1984**, *62*, 1093. Keay, B.; Plavmann, H. P.; Rodrigo, R.; Rajapaksa, D. *Can. J. Chem.* **1983**, *61*, 1987. Rodrigo, R.; Keay, B. A. *J. Am. Chem. Soc.* **1982**, *104*, 4725 and references cited therein.

(8) (a) Tomer, K. B.; Harrit, N.; Rosenthal, I.; Büchardt, O.; Kumler, P. L.; Creed, D. *J. Am. Chem. Soc.* **1973**, *95*, 7402. (b) Ibata, T.; Hamaguchi, M. *Chem. Lett.* **1976**, 287.

(9) For an excellent review for ortho-metalation chemistry, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1. For a summary of tertiary amide directed ortho metalations including annelations, see: Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *47*, 34. For other annelations based on ortho-lithiation strategies, see: Sibi, M. P.; Dankwardt, J. W.; Snieckus, V. *J. Org. Chem.* **1986**, *51*, 271 and references cited therein.

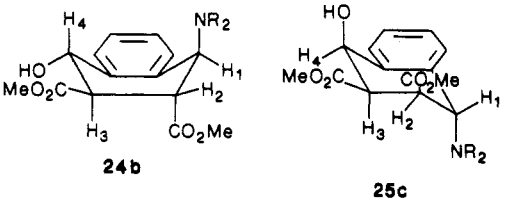
The structural assignments are based on interpretations of the ^1H NMR spectra. For example, the 360-MHz ^1H NMR spectrum of **15** shows a broad absorption at 4.74 ppm, which is assigned as the benzylic hydrogen, and a doublet absorption (J = 5.8 Hz) at 2.81 ppm, which is assigned to the allylic hydrogens. The alternative regioisomer is ruled out because the ^1H NMR spectrum of that compound should display a doublet vinylic hydrogen signal.[10] The geometrically isomeric dienophiles dimethyl maleate and dimethyl fumarate give **16** and **17**. Only one stereoisomer is isolated in each case, and it is estimated that 5% of a minor isomer would have been detected. The coupling constants between the allylic hydrogen and benzylic hydrogens in compound **16** and **17** are 4.7 and 5.6 Hz, respectively, values which are ambiguous for determination of the relative stereochemistries. However, preparation of the dihydro derivatives, **24** and **25** by the reduction of **15** and **16**, respectively, provide compounds that are useful in defining the stereochemistry of the adducts.

Reduction of **16** by zinc–acetic acid in methanol gives only one product, **24**, in 55% yield.[11] Upon similar treatment of **17**, two major products, identified as the tetrahydronaphthalene **25** and the lactone **26** are produced in 31% and 33% yields, respectively.



The 360-MHz ^1H NMR spectrum of **24** shows a singlet at 4.62 ppm, which is assigned as H_1, and a doublet at 5.23 ppm, which is assigned as H_4. With the assistance of a double resonance experiment, a coupling constant of J 9.7 Hz between H_3 and H_4 is assigned. The ^1H NMR spectrum of **17** also shows a singlet at 4.54 ppm assigned as H_1, a multiplet at 3.40–3.34 ppm assigned as H_2 and H_3, and a doublet of doublets at 5.11–5.07 ppm assigned to H_4. With the confirmation by double resonance and D_2O exchange experiments, the coupling between H_3 and H_4 is determined as 4.9 Hz. In order to rationalize the lack of observable spin–spin coupling between H_1 and H_2 for both **24** and **25**, the dihedral angle is considered to be ca. 90°.[12]

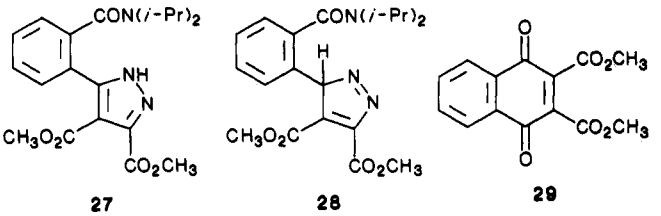
In the conformation which fulfills this stipulation, H_1 and H_2 are in pseudoequatorial positions and the steric interaction between the bulky diisopropyl amino group and its neighbor substituents, the peri hydrogen, and the 2-carboxy group are minimized. The large coupling constant between H_3 and H_4 observed for **24** is consistent with a boat conformation, **24b**, which has both H_3 and H_4 at axial positions. In the case of **25** the coupling constant of 4.9



Hz between H_3 and H_4 suggests a dihedral angle about 60° between these nuclei, in accord with conformation **25c**. The isolation of the lactone **26** as a major product of the reduction of **17** is also in accord with the assigned stereochemistry. Confirmation of the stereochemistry is provided by a 16% NOE of the allylic hydrogen upon irradiation of the slowly exchanging hydroxyl proton of **16**.

In the reaction of **14** and cyclohexenone which provides **18** only one regio and stereoisomer was isolated. The stereochemistry of the benzylic and adjacent tertiary hydrogen is assigned as trans on the basis of the coupling constant of a 13.1-Hz coupling which indicates a dihedral angle close to 180°.[12] Thus the formations of **16**–**18** are consistent with endo specificity in the cycloaddition step.

The reaction of **14** and dimethyl acetylene dicarboxylate in the presence of $Rh_2(OAc)_4$ gives **19**, in 49% yield. This can be rationalized as a result of deprotonation at the carbon bearing the oxygen and in a ring-opened iminum species analogous to that shown in Scheme II. It is interesting that the pyrazole **27** is produced in 82% yield if 5 mol % $Cu(acac)_2$ is used as the catalyst. The formation



of **27** can be rationalized by a 1,3-dipolar addition to give **28**, which then leads to **27** or a protomer. Apparently $Rh_2(OAc)_4$ decomposes the diazo compound to 1-(*N*,*N*-diisopropylamino)isobenzofuran more effectively than the copper catalyst.[13] Oxidation of **19** with silver oxide provides **29** in 55% yield. It is also noted that **23** is obtained with cis and trans dispositions of the methyl and hydroxyl groups.

Extension of this approach to substituted rings is successful in some cases. Thus substitution of a methoxy group at the 3-position in **30** and of chlorine at the 6-position in **31** provide the *o*-diazomethyl intermediate and the expected annelated products **32** and **33** in 31% yields on reaction with dimethyl maleate. Compound **32** is unstable and undergoes dehydration on standing. If a methoxy or trimethylsilyl group is at the 6-position **34** and

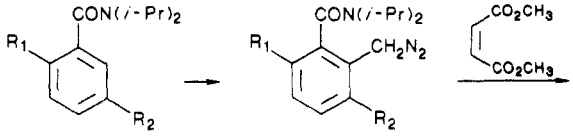
(10) Upon irradiation of the signal at 4.74 ppm the doublet absorption at 2.81 ppm collapses to a singlet. Upon irradiation at 2.81 ppm, however, the singlet absorption at 4.74 remains broad. That this is due to coupling with the hydroxyl product is established by the fact that upon shaking the solution with D_2O; the absorption at 4.74 ppm becomes a triplet.

(11) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972; pp 173–183.

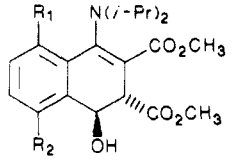
(12) Lambert, J. B.; Shurrell, H. F.; Verbit, L.; Cooks, R. G.; Stout, G. H. *Organic Structural Analysis*; MacMillan: New York, 1976; pp 65–71.

(13) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.*, **1984**, *49*, 1917. Doyle, M. D.; Dorow, R. L.; Griffin, J. H.; Tablyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44. Doyle, M. P.; Griffin, J. H.; Baheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.

35 can be prepared, but the annelated products are not formed in attempts to carry out the next step.

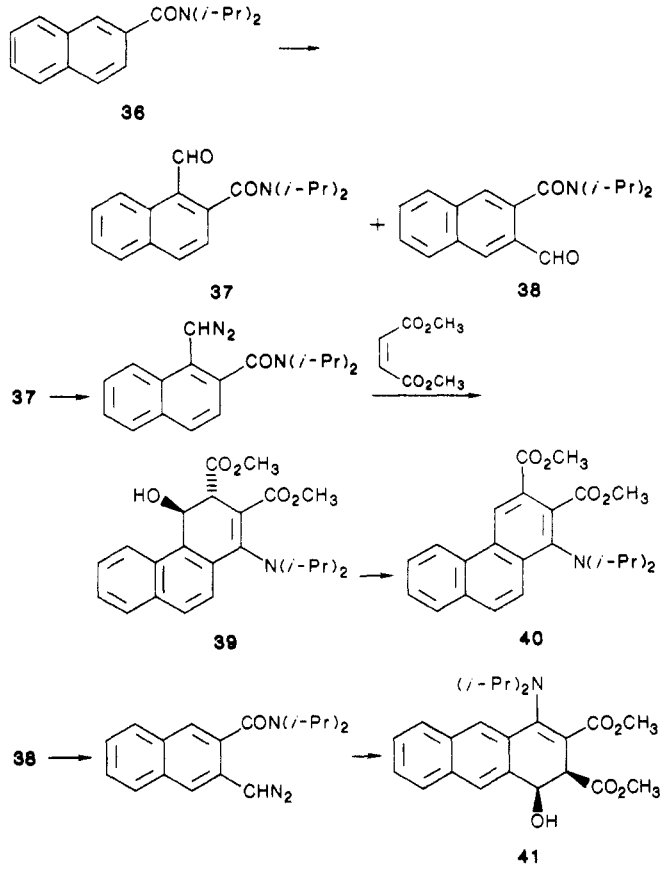


30, R_1 = H, R_2 = OCH_3
31, R_1 = Cl, R_2 = H
34, R_1 = OCH_3, R_2 = H
35, R_1 = $Si(CH_3)_3$, R_2 = H



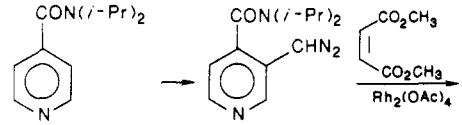
32, R_1 = H, R_2 = OCH_3
33, R_1 = Cl, R_2 = H

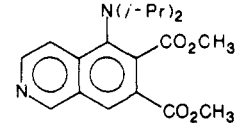
The sequence can be extended to *N,N*-diisopropyl-2-naphthamide (**36**). Lithiation with *sec*-BuLi and treatment with excess of DMF give a mixture of the 1-formyl-2-naphthamide **37** and the 3-formyl-2-naphthamide **38**,[14] in 22% and 10% yields. The aldehydes **37** and **38** were separately converted to 1-(diazomethyl)-2-naphthamide and the 3-(diazomethyl)-2-naphthamide. Treatment of



the diazo compound from **37** with rhodium acetate and dimethyl maleate provided **39** in 49% yield. This compound was characterized by spectral methods but converted readily to the phenanthrene **40** on standing. Reaction of the diazo compound from **38** with copper acetylacetonate and dimethyl fumarate provides **41** in 28% yield. Presumably these reactions involve precedented benzo[*f*]- and benzo[*e*]isobenzofurans.[15] Attempts to carry out the same sequence with *N,N*-diisopropyl-1-naphthamide failed at the cyclization step. Presumably this and the failures with **34** and **35** are due to steric repulsions which inhibit formation of the 1-(dialkylamino)isobenzofuran.

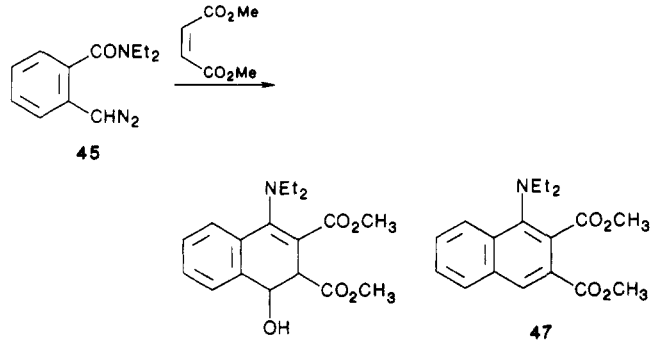
This approach can be used with a heteroaromatic ring. Thus metalation of *N,N*-diisopropylisonicotinamide (**4**) by *sec*-BuLi[16] and the reaction with dimethyl formamide, hydrazine, and nickel peroxide oxidation give the diazo compound **43** in 34% yield. Decomposition of **43** by





$Rh_2(OAc)_4$ in the presence of dimethyl maleate gives the isoquinoline derivative **44** in 35% yield. If copper acetylacetonate is used as the catalyst only a trace of **44** is obtained. The product **44** is characterized by high-resolution ^1H NMR and mass spectral data and is considered to be formed via a 1-amino-6-azaisobenzofuran.[17]

When this methodology is applied to *N,N*-diethyl-*o*-(diazomethyl)benzamide (**45**), which is prepared by the same sequence as used heretofore, the ring-annelated products are obtained only in low yield. Reaction of **45** with dimethyl maleate with $Cu(acac)_2$ as the catalyst gives **46** in 16% yield and the naphthalene **47** in 5% yield. With rhodium acetate as catalyst, **47** is formed in 21% yield. In this and other cases of low yields, substantial amounts of the 2-formylbenzamides are obtained.



Frontier Orbitals. The key to the regio- and stereospecificity of the annelation sequence in Scheme II is the reaction of a 1-(dialkylamino)isobenzofuran with a dienophile. This is a "normal demand" $\pi^4_s + \pi^2_s$ process with a HOMO–LUMO gap of 0.58β between the HOMO of 1-aminoisobenzofuran and LUMO of methyl acrylate.[3,18]

(14) Snieckus, V.; Watanabe, M. *J. Am. Chem. Soc.* **1980**, *102*, 1457.

(15) For other examples of benzo[*f*]isobenzofurans, see: Rickborn, B.; Mir-Mohamad-Sadeghy, B. *J. Org. Chem.* **1983**, *48*, 2237. Rickborn, B.; Ghodso, S.; Johnson, R.; Woodling, R. *J. Org. Chem.* **1983**, *48*, 3869. Wege, D.; Stringer, M. B. *Tetrahedron Lett.* **1980**, 3831.

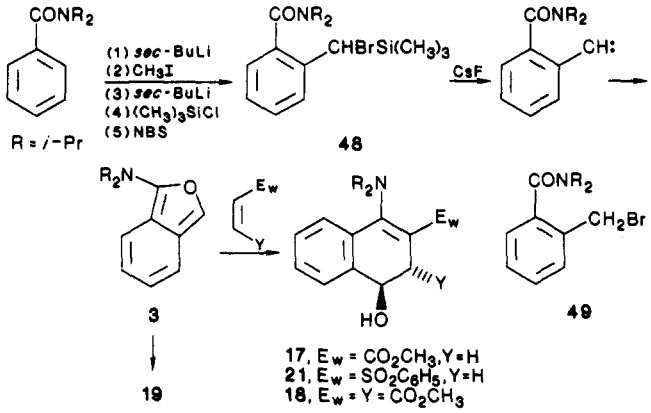
(16) Epsztajn, J.; Berski, Z.; Brzezinski, J. Z.; Jozwrak, A. *Tetrahedron Lett.* **1980**, 4739.

(17) Wiersum, V. E.; Eldred, C. D.; Vrijhof, P.; Van der Plas, H. C. *Tetrahedron Lett.* **1972**, 174.

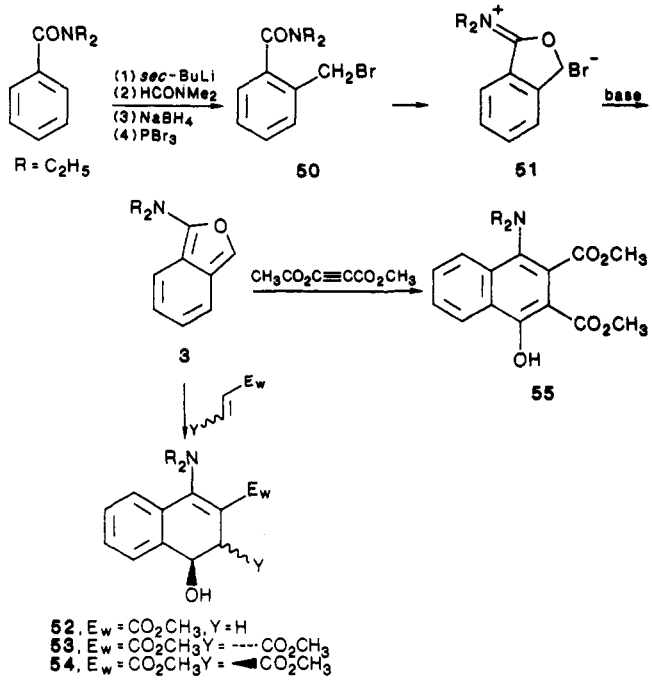
(18) The "inverse demand" reaction has a HOMO–LUMO gap of 1.493. The energy levels and coefficients of the interacting orbitals are available in the supplementary material.

The analogous HOMO–LUMO gaps for 1-alkoxyisobenzofuran and isobenzofuran are 0.63β and 0.67β, respectively. The regiospecificity and stereospecificity also may be rationalized by FMO theory. Thus the terminal coefficients of the interacting orbitals as 0.40 and −0.61 of the π^4 system match with 0.29 and −0.66 of the π^2 acrylate system to provide **10** and the secondary orbital interaction which leads to "endo" addition is also favorable.[3,19]

Alternative Routes to 1-(Dialkylamino)isobenzofurans. The conversion of **14** to 1-(*N*,*N*-diisopropylamino)isobenzofuran (**3**, R = *i*-Pr) could involve an intermediate carbene, a metal carbene complex, or metal-assisted loss of nitrogen concerted with formation of an oxygen carbon bond.[13,19] In order to determine if the possible carbene intermediate could behave in the required manner, alternative generation of that species was effected by an α elimination. The carbene precursor *o*-[bromo(trimethylsilyl)methyl]benzamide **48** was prepared via lithiation strategies. Desilylation of **48** by treatment with cesium fluoride in the presence of methyl acrylate, phenyl vinyl sulfone, and dimethyl maleate gave **16** (44%), **21** (46%), and **15** (51%). Reaction in the presence of dimethyl acetylenedicarboxylate gave **19** (57%). Use of cyclohexenone as a dienophile provided the (bromomethyl)benzamide **49**, apparently because the desilylation is followed by proton removal from the ketone. This observation may be taken to rule out an alternative mechanism of displacement by the carbonyl oxygen prior to desilylation. The regio- and stereochemistry of the annelated products strongly implicates the 1-(dialkylamino)isobenzofuran as an intermediate.



An experiment in which a 1-(dialkylamino)isobenzofuran was generated from a precursor which has the intact heterocyclic skeleton was also carried out.[7] The salt **51** was formed when the oil *N*,*N*-diethyl-*o*-(bromomethyl)benzamide (**50**) was allowed to stand at ambient temperature. This solid was insoluble in ether and the structure assigned on the basis of ^1H and ^{13}C NMR and IR spectroscopy. When **51** was treated with 2,2,6,6-tetramethylpiperidine in the presence of methyl acrylate, **52** was obtained in 44% yield. Reaction of **51** and base with dimethyl maleate, and dimethyl fumarate provided mixtures of **53** and **54**. The different ratios of the **53** and **54** formed from the maleate and fumarate are attributed to isomerization of the dienophile or of the products under the reaction conditions. Treatment of **51** with dimethyl acetylenedicarboxylate and



the base provided **55** in 71% yield.

Confirmation of a 1-(dialkylamino)isobenzofuran as a common intermediate in these reactions is further supported by an investigation of the relative reactivities of different dienophiles. The ratios of products from reactions of **14** with 20 equiv of 1:1 ratios of dimethyl maleate/methyl acrylate and phenyl vinyl sulfone/methyl acrylate are 3.5 and 1.8 (±0.2) independent of whether rhodium acetate or copper acetylacetonate was the catalyst. The ratio of products from the reaction of **48** with cesium fluoride in the presence of methyl acrylate and phenyl vinyl sulfide is 1.8 (±0.2). In carrying out this study we found dimethyl fumarate to be much more reactive than other dienophiles.[20] The yield in Table I for this dienophile is low apparently because **17** undergoes dehydration under the reaction conditions to give 1-(*N*,*N*-diisopropylamino)-2-carbomethoxynaphthalene.

Conclusions

Synthetically the approach shown in Scheme II is useful for the regiospecific annelation of aromatic amides. By the use of a 1,2-disubstituted dienophiles stereospecificity can be achieved at two of the carbon centers in the new ring. The annelated products that are available with a variety substitution patterns may be readily converted by oxidation or reduction to other useful compounds. Although the yields are modest the reaction is a convenient one-pot procedure.

The present work appears to provide the first report of a 1-(dialkylamino)isobenzofuran. The generation of this species by two different carbene routes is consistent with precedents from the work of Büchardt and Ibata.[8] Further use of this approach for novel and useful reactive species is under investigation.

Experimental Section

General. All NMR spectra were recorded of solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ (ppm) downfield from an internal tetramethylsilane standard. Mass spectra were recorded by Carter Cook and associates on Varian CH-5 and 731 mass spectrometers. Elemental analyses were performed by J. Nemeth and associates.

(19) Cunico, R. F.; Chou, B. B. *J. Organomet. Chem.* **1978**, *154*, C45–C48. Cunico, R. F.; Han, Y.-K. *J. Organomet. Chem.* **1978**, *162*, 1–16. Stang, P. J.; Fox, D. P. *J. Org. Chem.* **1979**, *42*, 1667. Stang, P. J.; Fox, D. P.; Bjork, J. A. *J. Org. Chem.* **1983**, *48*, 3994. Examples of selectivity differences between carbene complexes or carbenoids and the corresponding free carbene can be found in: Moss, R. A.; Pilkiewicz, F. G. *J. Am. Chem. Soc.* **1974**, *96*, 5632. Moss, R. A.; Joyce, M. A.; Pilkiewicz, F. G. *Tetrahedron Lett.* **1975**, 2425.

(20) Huisgen, R.; Li, X. *Tetrahedron Lett.* **1983**, *4181*, 4185.

Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Gas–liquid phase chromatographic (glpc) analyses were performed with a Hewlett-Packard 5790 GC using either a 75 m × 0.25 mm SE 52/54 FSOT capillary column or a $^3/_{16}$ in. × 6 ft OV-17 packed column. Medium-pressure liquid chromatography (MPLC) separations were performed on a 12 in. × 1 in. column packed with Ventron 43–64 mesh silica gel and hexane/ethyl acetate as eluants.

All compounds obtained from commercial sources were used without further purification unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium/benzophenone under an atmosphere of dry nitrogen. Dimethoxyethane (DME), tetramethylethylenediamine (TMEDA), diisopropylamine, hexamethylphosphoric triamide (HMPA), benzene, pyridine, *N,N*-dimethylformamide (DMF), and dimethyl sulfoxide (Me_2SO) were distilled from CaH_2 under N_2 and stored over 4-Å molecular sieves under an atmosphere of dry N_2. Thionyl chloride and oxalyl chloride were distilled before use. *n*-Butyllithium and *sec*-butyllithium were titrated prior to use according to the procedure of either Watson and Eastham[21] or Shapiro et al.[22]

Preparation of Amides. Amides generally were prepared by addition of a CH_2Cl_2 solution of the acid chloride to excess amine in a cold (0 °C), vigorously stirred CH_2Cl_2 solution. After the addition was complete, the reaction mixture was allowed to warm to ambient temperature for at least 3 h. Extractive workup afforded the crude amide, which was purified by distillation, recrystallization, or chromatography. The criteria for purity of the known amides were thin-layer chromatography (TLC) and ^1H NMR spectra that are consistent with the structural assignments.

The acid chlorides were either obtained commercially or prepared from the acid by reaction with excess $SOCl_2$ at reflux, followed by removal of excess $SOCl_2$ by distillation. In the latter case, the crude acid chloride was used without further purification.

Metalations of Amides. In general, lithiations with *sec*-butyllithium/TMEDA were performed according to procedure A and metalations with *s*-butyllithium according to procedure B. If both procedure A and B failed, the lithium–bromine exchange method of procedure C was used. The typical procedures presented below represent reactions on a scale of 1–2 mmol of amide. Variations of these procedures, the amounts of reagents used, and purification methods are given with spectroscopic and analytical data of the individual products.

Procedure A. To a stirred solution of TMEDA in 30 mL of THF under a N_2 atmosphere which was cooled in a −78 °C bath was added 1.1 equiv of *s*-butyllithium, followed by a solution of the amide in 5–10 mL of THF. After being allowed to stir for the indicated time at −78 °C, the solution was treated with excess electrophile in 5–10 mL of THF. After the addition was complete, the mixture was allowed to warm to ambient temperature gradually prior to the addition of ca. 30 mL of H_2O. Removal of most of THF in vacuo at room temperature was followed by extraction with 30–40 mL of either ether or dichloromethane. The organic portion was dried over $MgSO_4$ and concentrated in vacuo to give the crude product.

Procedure B. To a stirred solution of the amide in 20–30 mL of THF cooled to −78 °C was added *sec*-butyllithium dropwise. The resulting solution was kept at −78 °C for the indicated time. Procedure A was subsequently followed.

Procedure C. To a stirred solution of the bromo amide in 20–30 mL of THF cooled in −78 °C bath was added *n*-butyllithium. The resulting solution was stirred for the indicated time. Then the electrophile was added, and the solution was allowed to warm to ambient temperature prior to quenching with saturated NH_4Cl. Procedure A was subsequently followed.

(21) Watson, S. C.; Eastham, J. F. *J. Organmet. Chem.* **1967**, *9*, 165–168.
(22) Lipton, M. F.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155–158.
(23) Krauss, G. A.; Nemenschwander, K. *Synth. Commun.* **1980**, 9. Rapport, H.; Snyder, C. D. *J. Am. Chem. Soc.* **1972**, *94*, 227.
(24) Bellassoued, M.; Habbachi, F.; Gaudemar, M. *Synthesis* **1983**, 745.

***N,N*-Diisopropyl-2-formylbenzamide (13).** Procedure B: 2.750 g (13.4 mmol) of *N,N*-diisopropylbenzamide (**12**), 13.4 mL (14.7 mmol) of *sec*-BuLi −78 °C, 1 h. A 5-mL sample of neat *N,N*-dimethylformamide (DMF) was added. Workup gave a crude solid which on recrystallization from pentane gave 2.811 g (90%) of the 2-formylbenzamide **13** as a light yellow solid: mp 95–96 °C; ^1H NMR δ 1.08 (d, J = 7 Hz, 6 H, NCHCH_3), 1.55 (9 d, J = 7 Hz, 6 H, NCHCH_3), 3.53 (m, 2 H, NCHCH$_3$), 7.95–7.15 (m, 4 H, Ar H), 1.01 (s, 1 H, CHO); IR (KBr) 2754, 1701, 1615 cm^{-1}; MS, m/e 233 (M^+). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.09. Found: C, 72.13; H, 8.32; N, 6.20.

***N,N*-Diisopropyl-*o*-formylisonicotinamide.** Procedure A: 2.821 g (13.7 mmol) of isonicotinamide (**42**), 13.7 mL (15.1 mmol) of *sec*-BuLi, −78 °C, 1 h. A 5-mL sample of DMF at −78 °C was added. Workup gave a crude oil. The compound was purified by MPLC on silica gel with various ratio of EtOAc/hexane as eluant to give 1.218 g of *o*-formylisonicotinamide in 38% yield as a white solid: mp 93–94 °C; ^1H NMR δ 1.19–1.11 (d, J = 7 Hz, 6 H, NCHCH_3), 1.66–1.58 (d, J = 7 Hz, 6 H, NCHCH_3), 3.70–3.29 (m, 2 H, NCHCH$_3$), 7.19 (m, 2 H, Ar H), 8.89 (d, J = 5 Hz, 1 H, Ar H), 9.06 (9 s, 1 H, Ar H), 10.13 (s, 1 H, ArCHO). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.37; H, 7.90; N, 11.65.

***N,N*-Diisopropyl-1-formyl-2-naphthamide (37) and *N,N*-Diisopropyl-3-formyl-2-naphthamide (38). Procedure B:** 3.257 g (12.8 mmol) of 2-napthoic amide **36**, 12.2 mL (14.1 mmol) of *sec*-BuLi, −78 °C, 1 h. A 5-mL sample of DMF was added. Workup as usual gave a crude oil. Separation by MPLC on silica gel with various ratios of EtOAc/hexane afforded 0.8 g of 1-formyl-2-naphthamide **37** in 22% yield and 0.358 g of 3-formyl-2-naphthamide **38** in 10% yield, respectively. **37** was a white solid: mp 127–128 °C; ^1H NMR δ 1.13–1.11 (d, J = 6.7 Hz, 6 H, CH$_3$), 1.65–1.63 (d, J = 6.7 H, 6 H, CH$_3$), 3.65–3.57 (m, 2 H, NCHCH$_3$), 7.29–7.36 (m, 4 H, Ar H), 8.12–8.10 (d, J = 9.7 Hz, 1 H, Ar H), 9.23–9.21 (d, J = 8.7 Hz, 1 H, Ar H), 10.60 (s, 1 H, Ar CHO). Decoupling: irradiation at 8.11 ppm simplified the region at 7.29–7.36 ppm; irradiation at 9.22 ppm simplified only the region 7.29–7.36 ppm. MS (70 eV), m/e 283 (M^+); IR (KBr) 2741, 1694, 1613 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.85; H, 7.37; N, 4.75.

38 was a white solid: mp 166–167 °C; ^1H NMR δ 1.67–1.10 (m, 12 H, NCHCH_3), 3.67–3.57 (m, 2 H, NCHCH$_3$), 7.69–7.61 (m, 2 H, Ar H), 7.71 (s, 1 H, Ar H), 7.71 (s, 1 H, Ar H), 7.90–7.88 (d, J = 8.1 Hz, 1 H, Ar H), 8.03–8.00 (d, J = 8.0 Hz, 1 H, Ar H), 8.43 (s, 1 H, Ar H), 10.19 (s, 1 H, ArCHO). Decoupling: irradiation at 7.99 ppm simplified the region of 7.69–7.61 ppm; irradiation at 8.01 ppm simplified the region 7.69–7.61 ppm. MS (70 eV), m/e 283 (M^+); IR (KBr) 2694, 2734, 1695, 1630 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.45; H, 7.30; N, 4.77.

***N,N*-Diethyl-2-formylbenzamide.** Procedure A: 6.302 g (35.6 mmol) of diethylbenzamide, 40 mmol of *sec*-BuLi, 6 mL of TMEDA, 150 mL of THF; −78 °C, 30 min. A 10-mL sample of ethyl formate was added. Workup as usual gave a crude oil. Purification by flash column chromatography on silica gel with various ratio of EtOAc/hexane mixtures gave 2.038 g of the 2-formylbenzamide in 28% yield. Procedure C: 2.319 g (13.1 mmol) of *N,N*-diethyl-2-bromobenzamide, 14.4 mmol of *n*-BuLi, 100 mL of ether; −78 °C, 30 min. A 10-mL portion of ethyl formate was added. Workup as usual gave a crude oil, which was purified by flash column chromatography on silica gel with a 1:1 ratio of EtOAc/hexane mixture was eluant to afford 600 mg of 2-formylbenzamide as an oil in 30% yield: ^1H NMR δ 1.04–1.06 (t, J = 6.2 Hz, 3 H, NCH$_2$CH_3) 1.30–1.34 (t, J = 6.4 Hz, 3 H, NCH$_2$CH_3), 3.09–3.13 (q, J = 7.1 Hz, 2 H, NCH_2CH$_3$), 3.60–3.66 (q, J = 7.0 Hz, 2 H, NCH_2CH$_3$), 7.35–7.96 (m, 4 H, Ar H), 10.06 (s, 1 H, ArCHO). This material was used in the next step without further purification.

***N,N*-Diisopropyl-2-formyl-3-methoxybenzamide.** Procedure B: 1.144 g (4.9 mmol) of 3-methoxybenzamide, 5.4 mmol of *sec*-BuLi; −78 °C, 1 h. A 5-mL portion of DMF was added. Workup as usual gave the crude product. This material was recrystallized from pentane to give the product, 1.139 g (89%), as a white solid: mp 161–163 °C; ^1H NMR δ 10.49 (s, 1 H, ArCHO), 7.57–7.49 (dd, J = 7.5 and 7.5 Hz, 1 H, Ar H), 6.96 (d, J = 7.5 Hz, 1 H, Ar H), 6.78 (d, J = 7.5 Hz, 1 H, Ar H), 3.94 (s,

3 H, OCH_3), 3.55–3.43 (m, 2 H, $NCHCH_3$), 1.60 (br s, 6 H, $NCHCH_3$), 1.08 (d, J = 6.6 Hz, 6 H, $NCHCH_3$). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.38; H, 8.15; N, 5.27.

***N,N*-Diisopropyl-2-formyl-6-chlorobenzamide.** Procedure B: 993 mg (4.1 mmol) of 2-chlorobenzamide, 4.6 mmol of *s*-BuLi in THF; –78 °C, 1 h. A 5-mL portion of DMF was added. Workup as usual gave 1.081 g of crude product. The crude product was recrystallized from ether to afford the product, 1.081 g, as a white solid in 97% yield; mp 139–141 °C; ^{1}H NMR δ 10.40 (s, 1 H, ArCHO), 7.86–7.40 (m, 2 H, Ar H), 3.62–3.48 (m, 2 H, $NCHCH_3$), 1.66–1.57 (m, 6 H, $NCHCH_3$), 1.24 (d, J = 6.7 Hz, 3 H, $NCHCH_3$), 1.06 (d, J = 6.7 Hz, 3 H, $NCHCH_3$). Anal. Calcd for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; N, 5.23; Cl, 13.24. Found: C, 62.89; H, 6.81; N, 5.18; Cl, 13.10.

***N,N*-Diisopropyl-2-methylbenzamide.** Procedure B: 3.151 g (15.4 mmol) of diisopropylbenzamide, 17 mmol of *sec*-BuLi; –78 °C, 1 h. A 3-mL sample of methyl iodide was added. Workup as usual gave the crude material, which was recrystallized from hexane to give 2.877 g of product in 86% yield as a white solid: mp 99–101 °C; ^{1}H NMR δ 7.23–7.20 (m, 4 H, Ar H), 3.69–2.47 (m, 2 H, $NCHCH_3$), 2.31 (s, 3 H, $ArCH_3$), 1.57 (d, J = 7.0 Hz, 6 H, $NCHCH_3$), 1.10–0.92 (m, 6 H, $NCHCH_3$); MS, m/e 219 (M^+), 204 ($M^+ - CH_3$), 119 ($M^+ - NC_6H_{14}$). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.94; H, 9.76; N, 6.35.

***N,N*-Diisopropyl-2-(trimethylsilylmethyl)benzamide.** Procedure A: 542 mg (2.5 mmol) of *o*-methylbenzamide, 2.14 mL (2.7 mmol) of *sec*-BuLi, 0.5 mL (2.7 mmol) of TMEDA; 5 min, –78 °C. A 10-mL portion of trimethylsilylchloride was added. Workup as usual gave the crude oil. The crude oil was separated by MPLC on silica gel with various ratios of EtOAc/hexane mixture as eluants to give 632 mg of product in 88% yield as a colorless oil: ^{1}H NMR δ 7.18–7.01 (m, 4 H, Ar H), 3.64–3.45 (m, 2 H, $NCHCH_3$), 2.05 (s, 2 H, $ArCH_2SiMe_3$), 1.56 (d, J = 7 Hz, 6 H, $NCHCH_3$), 1.12 (d, J = 6.7 Hz, 3 H, $NCHCH_3$), 1.04 (d, J = 6.7 Hz, 3 H, $NCHCH_3$); IR (neat) 2963, 1632 cm^{-1}; MS, (70 eV) m/e 291 (M^+), 248 ($M^+ - C_3H_7$), 191 ($M^+ - NC_6H_{14}$). Anal. Calcd for $C_{17}H_{29}NOSi$: C, 72.07; H, 10.51; N, 4.20. Found: C, 72.08; H, 10.62; N, 4.21.

General Procedure for the Preparation of Hydrazones. The *o*-formylbenzamide was dissolved in a small amount of ether and added to a tenfold excess of hydrazine hydrate and a catalytic amount of pyridine in 25 mL of ether. The reaction mixture was stirred vigorous at ambient temperature overnight. If the hydrazone was a solid, the material was collected by filtration and washed with copious amounts of water. If the hydrazone was an oil, the organic layer was extracted with ether and washed with saturated NaCl solution. The organic portion was dried over $MgSO_4$ (anhydrous) and concentrated in vacuo to give the crude hydrazone, which was used for the next step without further purification unless otherwise specified.

***N,N*-Diisopropyl-*o*-(hydrazonomethyl)benazmide.** From 1.501 g (6.4 mmol) of the 2-formylbenzamide **13** and 64 mmol of hydrazine hydrate was obtained 1.211 g (77%) of a white solid: mp 135–138 °C; ^{1}H NMR δ 7.8–7.1 (m, 4 H, Ar H), 5.5 (br, 2 H, NNH_2), 3.56 (m, 2 H, $NCHCH_3$), 1.05 (d, J = 6 Hz, 12 H, $NCHCH_3$); MS (70 eV) m/e 247 (M^+).

***N,N*-Diisopropyl-*o*-(hydrazonomethyl)isonicotinamide.** From 1.2 g (5.1 mmol) of the 2-formylisonicotinic amide and 51 mmol of hydrazine hydrate (without addition of pyridine as catalyst) was obtained 0.436 g (34%) of the crude hydrazone as a yellow solid: ^{1}H NMR δ 8.92 (s, 1 H, Ar H), 8.49 (d, J = 5 Hz, 1 H, Ar H), 7.67 (s, 1 H, $ArCHNNH_2$), 7.04 (d, J = 5 Hz, 1 H, Ar H), 5.73 (br s, 2 H, NNH_2), 3.70–3.33 (m, 2 H, $NCHCH_3$), 1.64–1.56 (d, J = 7 Hz, 6 H, $NCHCH_3$), 1.14–1.06 (d, J = 7 Hz, 6 H, $NCHCH_3$).

***N,N*-Diisopropyl-1-(hydrazonomethyl)-2-naphthamide.** From 901 mg (3.2 mmol) of the 1-formyl-2-naphthoamide **37** and 32 mmol of hydrazine hydrate was obtained 917 mg (97%) of the hydrazone as a yellow solid: mp 75–77 °C; ^{1}H NMR δ 8.73 (d, J = 8.2 Hz, 1 H, Ar H), 8.29 (s, 1 H, $ArCHNNH_2$), 7.86–7.24 (m, 5 H, Ar H), 5.71 (br s, 2 H, $ArCHNNH_2$) 3.72–3.50 (m, 2 H, $NCHCH_3$), 1.72–1.60 (m, 6 H, $NCHCH_3$), 1.21–1.05 (m, 6 H, $NCHCH_3$).

***N,N*-Diisopropyl-3-(hydrazonomethyl)-2-naphthamide.** From the 3-formyl-2-naphthoamide **38** and a tenfold excess of hydrazine hydrate was obtained a colorless oil in 67% yield: ^{1}H NMR δ 1.01–1.22 (m, 6 H, $NCHCH_3$), 1.52–1.57 (d, J = 6 Hz, 6 H, $NCHCH_3$), 3.62 (m, 2 H, $NCHCH_3$), 4.80 (br s, 2 H, $ArCHNNH_2$), 7.36–7.88 (m, 5 H, Ar H), 3.07 (s, 1 H, Ar H), 8.76 (s, 1 H, $ArCHNNH_2$).

***N,N*-Diethyl-2-(hydrazonomethyl)benzamide.** From the 2-formylbenzamide and a tenfold excess of hydrazine hydrate was obtained an oil in 64g yield: ^{1}H NMR δ 7.78–7.19 (m, 4 H, Ar H), 7.72 (s, 1 H, $ArCHNNH_2$), 5.62 (br s, 1 H, $ArCHNNH_2$), 4.51 (br s, 1 H, $ArCHNNH_2$), 3.62–3.52 (q, J = 7.0 Hz, 2 H, NCH_2CH_3), 3.26–3.05 (m, 2 H, NCH_2CH_3), 1.26 (t, J = 7.0 Hz, 3 H, NCH_2CH_3), 1.10–0.97 (m, 3 H, NCH_2CH_3).

***N,N*-Diisopropyl-3-methoxy-2-(hydrazonomethyl)benzamide.** From *N,N*-diisopropyl-3-methyl-2-formylbenzamide and a tenfold excess of hydrazine hydrate was obtained the product as a white solid in 93% yield: mp >250 °C; ^{1}H NMR δ 8.06 (s, 1 H, $ArCHNNH_2$), 7.28–6.72 (m, 3 H, Ar H), 5.49 (br s, 2 H, $ArCHNNH_2$), 3.85 (a, 3 H, $ArOCH_3$), 3.82–3.46 (m, 2 H, $NCHCH_3$), 1.55 (d, J = 6.7 Hz, 6 H, $NCHCH_3$), 1.12 (d, J = 6.7 Hz, 3 H, $NCHCH_3$), 1.03 (d, J = 6.7 Hz, $NCHCH_3$).

***N,N*-Diisopropyl-2-(hydrazonomethyl)-6-chlorobenzamide.** From 732 mg (2.6 mmol) of *N,N*-diisopropyl-6-chloro-2-formylbenzamide and 26 mmol of hydrazine hydrate was obtained 607 mg (75%) of the hydrazine as a white solid: mp 150–153 °C; ^{1}H NMR δ 7.35–7.26 (m, 4 H, $ArCHNNH_2$, Ar H), 4.64–4.20 (m, 2 H, $ArCHNNH_2$), 3.62–3.52 (m, 2 H, $NCHCH_3$), 1.62–1.57 (m, 6 H, $NCHCH_3$), 1.28 (d, J = 6.4 Hz, 3 H, $NCHCH_3$), 1.07 (d, J = 6.6 Hz, 3 H, $NCHCH_3$).

General Procedure for the Conversion of *o*-(α-Diazomethyl)benzamides 9 to Ring-Annelated Products. To a CH_2Cl_2 solution containing 1 mmol of hydrazone was added a fourfold excess nickel peroxide, and the solution was stirred for 2 h until no more gas was evolved. The black particles were removed by filtration with Celite and the filtrant concentrated under reduced pressure at room temperature to give the *o*-(diazomethyl)benzamide which was characterized by an IR absorption near 2150 cm^{-1} and used directly for the next step without further purification.

To a benzene solution (40 mL) containing 10 mg of $Cu(acac)_2$ or 2 mg of $Rh_2(OAc)_4$ and a twofold excess of the dienophile at 80 °C the diazobenzamide in 10 mL of benzene was added via a syringe pump over a 2-h period. After the addition was complete, the solution was allowed to reflux 10 min. The mixture was then filtered through a pad of silica gel and concentrated in vacuo to give a crude oil, which was separated by MPLC on silica gel with various ratios of EtOAc/hexane as eluant. Repeated MPLC separation or recrystallization was used to provide analytically pure products. The yields are calculated from the crude hydrazones and were not optimized.

***trans*-*N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-4-hydroxy-3,4-dihydronaphthalene (16).** The reaction was carried out with 463 mg (1.8 mmol) of **14**, 39 mmol of dimethyl maleate, and $Cu(acac)_2$. MPLC afforded 513 mg of **16** in 75% yield as a yellow oil: ^{1}H NMR δ 7.37–7.27 (m, 4 H, Ar H), 5.0 (br s, 1 H, ArCHOH), 4.07 (d, J = 4.7 Hz, 1 H, $CHOHCHCO_2CH_3$), 3.77 (s, 3 H, CO_2CH_3), 3.59 (9 s, 3 H, CO_2CH_3), 3.65–3.61 (m, 2 H, $NCHCH_3$), 2.18 (br s, 1 H, OH), 1.10–1.09 (m, 12 H, $NCHCH_3$). Decoupling: upon irradiation at 5.0 ppm the absorption at 4.07 ppm became singlet. ^{13}C NMR δ 171.4, 168.3, 150.2, 136.6, 129.5, 128.5, 127.1, 120.7, 69.0, 52.1, 51.6, 51.0, 23.5, 22.8, 20.7; MS, m/e 361 (M^+), 346 ($M^+ - C_3H_7$); exact mass calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1886; IR (neat) 3450, 1731 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.14; H, 7.71; N, 3.84.

***cis*-*N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-4-hydroxy-3,4-dihydronaphthalene (17).** The reaction was carried out with 527 mg (2.1 mmol) of **14**, 4.2 mmol of dimethyl fumarate, and 20 mg of $Cu(acac)_2$. MPLC afforded 333 mg of **17** in 43% yield as a yellow solid: mp 107–108 °C; ^{1}H NMR δ 7.69–7.24 (m, 4 H, Ar H), 5.10–5.06 (dd, J = 5.6 and 10.7 Hz, 1 H, ArCHOH), 3.94 (d, J = 5.6 Hz, 1 H, $CHOHCHCO_2CH_3$), 3.86 (d, J = 10.7 Hz, 1 H, CHOH), 3.80 (s, 3 H, CO_2CH_3), 3.57 (m, 2 H, $NCHCH_3$), 3.52 (s, 3 H, CO_2CH_3), 1.64–1.03 (m, 12 H, $NCHCH_3$). Decoupling: upon irradiation at 5.08 ppm, the absorption at 3.94 ppm and 3.86 ppm became a singlet; upon irradiation at 3.94 ppm, the absorption at 5.08 became a doublet, and

the absorption at 3.86 ppm remained unchanged; upon irradiation at 3.86 ppm, the absorption at 5.08 ppm became a doublet, and the absorption at 3.94 ppm remained unchanged. MS, *m/e* 361 (M^+), 346 ($M^+ - CH_3$), 330 ($M^+ - OCH_3$); IR (KBr) 3555, 1719, 3555, 1719, 3555, 1719 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 173.3, 167.7, 151.9, 140.3, 136.3, 130.0, 128.4, 127.2, 120.3, 69.6, 52.0, 51.7, 51.5, 51.2, 51.0, 47.8, 23.8, 22.8, 22.0. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.56; H, 7.42; N, 3.91.

***N,N*-Diisopropyl-1-amino-2-(methoxycarbonyl)-4-hydroxy-3,4-dihydronaphthalene (15).** The reaction was carried out with 567 mg (2.3 mmol) of hydrazone **14**, a large excess (47 mmol) of methyl acrylate, and $Cu(acac)_2$. MPLC afforded 367 mg of **15** in 53% yield as a yellow solid: mp 85–86 °C; ^1H NMR δ 7.75–7.26 (m, 4 H, Ar H), 4.74 (br s, 1 H, ArC*H*OH), 3.78 (s, 3 H, CO_2CH_3), 3.56–3.52 (m, 2 H, NC*H*CH_3), 2.81 (d, *J* = 5.8 Hz, 2 H, ArCHOHC*H*$_2$), 1.11–1.07 (m, 12 H, NCHC*H*$_3$); MS, *m/e* 303 (M^+), 272 ($M^+ - OCH_3$); IR (KBr) 3470, 1760 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.12; H, 8.42; N, 4.39.

***N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-4-hydroxynaphthalene (19).** The reaction was carried out with 4.4 mg (1.7 mmol) of hydrazone **14**, 2 mmol of dimethyl acetylenedicarboxylate (DMAD), and $Rh_2(OAc)_4$. After filtration through a pad of silica gel, the solution was condensed in vacuo, the excess of DMAD was removed by Kugelrohr distillation, and the residue was separated by MPLC to give 294 mg of **19** in 49% yield as a colorless oil: ^1H NMR δ 12.14 (s, 1 H, Ar OH), 8.45–7.64 (m, 4 H, Ar H), 3.95 (s, 3 H, CO_2CH_3), 3.90 (s, 3 H, CO_2CH_3), 3.85–3.70 (m, 2 H, NC*H*CH_3), 1.2–0.95 (m, 12 H, NCHC*H*$_3$); MS, *m/e* 359 (M^+), 344 ($M^+ - CH_3$), 328 ($M^+ - OCH_3$); IR (neat) 3550 (br), 2971, 1740, 1664 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 66.83; H, 7.01; N, 4.00. Found: C, 66.70; H, 7.04; N, 3.72.

***N,N*-Diisopropyl-1-amino-2-(*N*-phenyl-*N*-methylcarbamoyl)-4-hydroxy-3,4-dihydronaphthalene (20).** The reaction was carried out with 204 mg (0.8 mmol) of hydrazone **14**, 1.6 mmol of *N*-methyl-*N*-phenylacrylamide, and $Rh_2(OAc)_4$. MPLC afforded 173 mg of **20** in 56% yield as a white solid: mp 154–156 °C; ^1H NMR (90 MHz) δ 7.61–7.00 (m, 9 H, Ar H, $NCH_3C_6H_5$), 4.64 (br, 1 H, ArC*H*OH), 3.68–3.40 (m, 2 H, NC*H*CH_3), 3.44 (s, 3 H, NCH_3), 2.52 (br, 2 H, ArCHOHC*H*$_2$), 2.0 (br, 1 H, OH), 1.01 (m, 12 H, NCHC*H*$_3$); IR (KBr) 3423, 2965, 161 3 cm^{-1}; MS, *m/e* 378 (M^+), 363 ($M^+ - CH_3$). Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.80. Found: C, 75.75; H, 8.06; N, 7.29.

***N,N*-Diisopropyl-1-amino-2-(phenylsulfonyl)-4-hydroxy-3,4-dihydronaphthalene (21).** The reaction was carried out with 266 mg (1.1 mmol) of **14**, 2.2 mmol of phenyl vinyl sulfone, and $Rh_2(OAc)_4$. MPLC afforded 226 mg, which was further purified by MPLC to give 162 mg (39%) of **21** as a yellow oil: ^1H NMR δ 8.0–7.76 (m, 9 H, Ar H, $SO_2C_6H_5$), 4.65 (m, 1 H, ArC*H*OHCH$_2$), 3.75–3.71 (m, 2 H, NC*H*CH_3), 3.02–2.79 (m, 2 H, CHOHC*H*$_2$), 1.60–1.06 (m, 12 H, NC*H*CH_3). Decoupling: upon irradiation of the absorption at 4.65 ppm, the absorption at 3.0 ppm became an AB quartet (*J* = 15.8 Hz). MS, *m/e* 244 ($M^+ - SO_2Ph$). Anal. Calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63; S, 8.32. Found: C, 68.36; H, 7.15; N, 3.17; S, 8.40.

***N,N*-Diisopropyl-10-amino-1-oxo-5-hydroxy-3,4,4a,5-tetrahydroanthracene (18).** The reaction was carried out with 284 mg (1.1 mmol) of **14**, 2.0 mmol of cyclohexen-1-one, and $Cu(acac)_2$. MPLC afforded crude products which were purified again by MPLC to give 117 mg of **18** in 33% yield as a red oil: ^1H NMR δ 7.86–7.27 (m, 4 H, Ar H), 4.53 (d, *J* = 13.1 Hz, 1 H, ArC*H*OH), 3.46–1.41 (m, 6 H, C*H*$_2$), 1.16 (d, *J* = 6.3 Hz, 6 H, NCHC*H*$_3$). Decoupling: upon irradiation of the absorption at 4.53 ppm, the absorption pattern at 2.75 ppm simplified; upon irradiation of the absorption at 2.75 ppm, the absorption at 4.53 ppm became a singlet and the absorption at 2.49–1.35 ppm also simplified. IR (neat) 3360, 1680, 1660 cm^{-1}; MS, *m/e* 313 (M^+), 298 ($M^+ - CH_3$); exact mass calcd for $C_{20}H_{27}NO_2$ 313.2042, found 313.2026. Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.20; H, 8.67; N, 4.39.

***N,N*-Diisopropyl-8-amino-5-hydroxy-6,7-bis(carboxymethyl)-5,6-dihydrophenanthrene (39).** The reaction was carried out with 260 mg (0.9 mmol) of amide, 1.8 mmol of dimethyl maleate, and $Cu(acac)_2$. MPLC afforded 185 mg of **39** in 52% yield as a yellow oil: ^1H NMR δ 8.26–7.35 (m, 6 H, Ar H), 5.74 (br s, 1 H, ArC*H*OH), 4.27 (d, *J* = 2.9 Hz, 1 H, ArCHOHC*H*), 3.74 (s, 3 H, CO_2CH_3), 3.70–360 (m, 2 H, NC*H*CH_3), 3.40 (s, 3 H, CO_2CH_3), 2.10 (br s, 1 H, OH), 1.28–1.08 (m, 12 H, NCHC*H*$_3$). Decoupling: upon irradiation of the absorption at 5.74 ppm, the absorption at 4.27 ppm became a singlet. MS, *m/e* 411 (M^+), 396 ($M^+ - CH_3$), 380 ($M^+ - OCH_3$). This compound is unstable and upon standing at room temperature is converted to the dehydrated product *N,N*-diisopropyl-8-amino-6,7-bis(methoxycarbonyl)-phenanthrene (**40**). MPLC gives a yellow solid: mp 99–100.5 °C; ^1H NMR δ 9.31 (s, 1 H, Ar H), 8.77 (d, *J* = 8.2 Hz, 1 H, Ar H), 8.07 (d, *J* = 8.2 Hz, Ar H), 7.95–7.68 (m, 4 H, Ar H), 4.00 (s, 3 H, CO_2CH_3), 3.98 (s, 3 H, CO_2CH_3), 3.84–3.78 (m, 2 H, NC*H*CH_3), 1.14 (d, *J* = 6.1 Hz, 6 H, NCHC*H*$_3$), 1.02–0.99 (d, *J* = 6.1 Hz, 6 H, $NCHCH_3$); MS, *m/e* 393 (M^+). Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.20; H, 6.97; N, 3.52.

***N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-4-hydroxy-3,4-dihydroanthracene (41).** The reaction was carried out with 295 mg (1.0 mmol) of hydrazone, 2.0 mmol of dimethyl fumarate, and $Rh_2(OAc)_4$. MPLC afforded 93 mg of **41** in 23% yield as a yellow oil: ^1H NMR δ 8.18 (s, 1 H, Ar H), 7.98 (s, 1 H, Ar H), 7.88–7.43 (m, 4 H, Ar H), 5.21–5.18 (m, 1 H, ArC*H*OH), 4.07–4.04 (m, 2 H, OH, ArCHOHC*H*), 3.82 (s, 3 H, CO_2CH_3), 3.80–3.62 (m, 2 H, NC*H*CH_3), 3.47 (s, 3 H, CO_2CH_3), 1.28–1.02 (m, 12 H, NCHC*H*$_3$); MS, *m/e* 411 (M^+), 396 ($M^+ - CH_3$), 380 ($M^+ - OCH_3$); exact mass calcd for $C_{24}H_{29}NO_5$ (4.11.2046, found 4.11.2046. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.01; H, 7.29; N, 3.39.

***N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-6-azanaphthalene (44).** The reaction was carried out with 260 mg (1.0 mmol) of amide, 2.0 mmol of dimethyl maleate, and $Rh_2(OAc)_4$. MPLC afforded 128 mg of **44** in 35% yield as a colorless oil: ^1H NMR δ 9.3 (s, 1 H, Ar H), 8.66–8.44 (m, 2 H, Ar H), 7.95–7.88 (d, *J* = 6.1 Hz, 1 H, Ar H), 2.0 (s, 6 H, CO_2CH_3), 3.92–3.61 (m, 2 H, NC*H*CH_3), 1.16–0.93 (m, 12 H, $NCHCH_3$); MS, *m/e* 344 (M^+), 329 ($M^+ - CH_3$), 313 ($M^+ - OCH_3$).

***N,N*-Diisopropyl-1-amino-2-(ethoxycarbonyl)-3-(1-propenyl)-4-hydroxy-3,4-dihydronaphthalene (22) and *N,N*-Diisopropyl-1-amino-2-[2-(ethoxycarbonyl)ethenyl]-3-methyl-4-hydroxy-3,4-dihydronaphthalene (23).** The reaction was carried out with 486 mg (2.0 mmol) of **14**, 4.0 mmol of ethyl sorbate, and $Rh_2(OAc)_4$. MPLC afforded **22**, *cis*-**23**, and *trans*-**23**.

22: 4.1 mg (6%); yellow oil; ^1H NMR δ 7.65–7.26 (m, 4 H, Ar H), 5.79–5.59 (m, 1 H, CH=CH), 5.12–4.92 (m, 2 H, CH=C*H*, ArC*H*OH), 4.25–4.19 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 3.53–3.49 (m, 2 H, NC*H*CH_3). 3.31–3.27 (m, 1 H, ArCHOHC*H*), 1.82–1.79 (d, *J* = 10.7 Hz, ArCHO*H*), 1.63–1.61 (dd, *J* = 6.5 and 1.4 Hz, CH=CHO*H*$_3$), 1.33–1.02 (m, 15 H, NCHC*H*$_3$, $CO_2CH_2CH_3$); IR (neat) 3461, 2977, 1701 cm^{-1}.

cis-**23**: 150 mg (21%); yellow oil; ^1H NMR δ 8.18–8.14 (d, *J* = 16.1 Hz, 1 H, *H*C=CH), 7.55–7.20 (m, 4 H, Ar H), 6.07–6.02 (d, *J* = 161 Hz, 1 H, HC=C*H*), 4.39 (s, 1 H, ArC*H*OH), 4.26–4.22 (m, 2 H, $CO_3CH_2CH_3$), 3.84 (br, 1 H, NC*H*CH_3), 3.63 (br, 1 H, NC*H*CH_3), 3.04–3.02 (q, *J* = 7.3 Hz, 1 H, C*H*CH_3), 1.35–0.96 (m, 15 H, NCHC*H*$_3$, $CO_2CH_2CH_3$), 0.94–0.92 (d, *J* = 7.3 Hz, 3 H, CHC*H*$_3$); MS, *m/e* 357 (M^+), 314 ($M^+ - C_3H_7$), 312 ($M^+ - OC_2H_5$); IR (neat) 3440, 1880, 1703, 1610 cm^{-1}.

trans-**23**: 92 mg (13%), yellow oil; ^1H NMR δ 8.14–8.09 (d, *J* = 16.1 Hz, 1 H, *H*C=CH), 7.53–7.27 (m, 4 H, Ar H), 5.98–5.93 (d, *J* = 16.1 Hz, 1 H, HC=CH), 5.08 (br s, 1 H, ArC*H*OH), 4.27–4.22 (m, 2 H, $CO_2CH_2CH_3$), 3.76 (br, 1 H, NC*H*CH_3), 3.61 (br, 1 H, NC*H*CH_3), 2.84–2.81 (m, 1 H, ArCHOHC*H*CH_3), 2.1 (br, 1 H, OH), 1.55–0.93 (m, 15 H, NCHC*H*$_3$, $CO_2CH_2CH_3$), 0.89–0.87 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$). MS, *m/e* 357 (M^+), 314 ($M^+ - C_3H_7$), 312 ($M^+ - OC_2H_5$).

***N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-5-methoxy-3,4-dihydronaphthalene (39).** The reaction was carried out with 286 mg (1.0 mmol) of hydrazone, 1.5 mmol of dimethyl maleate, and $Rh_2(OAc)_4$. MPLC afforded 184 mg of **39** in 46% yield as a yellow oil: ^1H NMR δ 7.47–7.45 (d, *J* = 7.8 Hz, 1 H, Ar H), 7.33–7.29 (m, 2 H, Ar H), 6.91–6.89 (d, *J* = 8.2 Hz, 1 H, Ar H), 5.47–5.45 (m, 1 H, ArC*H*OH), 4.15 (d, *J* = 2.0 Hz, 1 H, ArCHOHC*H*), 3.77 (s, 3 H, CO_2CH_3), 3.87 (s, 3 H, CO_2CH_3), 3.56 (s, 3 H, $ArOCH_3$), 3.62 (m, 2 H, NC*H*CH_3), 1.98–1.96 (d, *J* = 6.5 Hz, 1 H, ArCHO*H*), 1.18–1.05 (m, 12 H, NCHC*H*$_3$); MS, *m/e* 391 (M^+), 376 ($M^+ - CH_3$), 348 ($M^+ - C_3H_7$). This compound is unstable upon standing at room temperature for a few days

and converts to *N,N*-diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-5-methoxynaphthalene (**40**) a yellow solid, mp 111.5–112 °C. Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.38; H, 744; N, 374.

***N,N*-Diisopropyl-1-amino-2,3-bis(carboxymethyl)-4-hydroxy-8-chloro-3,4-dihydronaphthalene (33).** The reaction was carried out with 278 mg (1.0 mmol) of hydrazone, 1.5 mmol of dimethylmaleate, and $Cu(acac)_2$. MPLC afforded 122 mg of **33** in 31% yield as a yellow oil: ^1H NMR δ 7.32–7.17 (m, 3 H, Ar H), 4.91–4.89 (dd, J = 6.2 and 8.2 Hz, 1 H, ArC*H*OH), 3.85–3.83 (d, J = 6.2 Hz, 1 H, ArCHOHC*H*), 3.75 (s, 3 H, CO_2CH_3), 360 (s, 3 H, CO_2CH_3), 3.59 (m, 2 H, NC*H*CH_3), 3.25 (d, J = 8.2 Hz, 1 H, ArCHO*H*), 1.18 (d, J = 6.5 Hz, 9 H, NCHCH_3), 1.11 (d, J = 6.31 Hz, 3 H, NCHCH_3); MS, 395 (M^+), 397 ($M^+ + 2$). Anal. Calcd for $C_{20}H_{26}ClNO_5$: C, 60.68; H, 6.61; N, 3.54. Found: C, 60.70; H, 6.85; N, 3.57.

Formation of Pyrazole Derivative 27. To a benzene solution containing 3 equiv (0.36 mL) of DMAD and 10 mg of $Cu(acac)_2$ was added the α-diazobenzamide in a small amount of benzene at reflux over 30 min. After the addition was complete, the reaction mixture was filtered through a pad of silica gel. Removal of solvent in vacuo gave a residue, which was separated by MPLC on silica gel with EtOAc/hexane to give 303 mg of pyrazole **27** in 82% yield as a light yellow solid: mp 145 °C; ^1H NMR δ 7.31–7.14 (m, 4 H, Ar H), 3.92 (s, 3 H, CO_2CH_3), 3.72 (s, 3 H, CO_2CH_3), 3.48 (m, 1 H, NC*H*CH_3), 3.31 (m, 1 H, NC*H*CH_3), 1.50 (d, J = 6.7 Hz, 3 H, NCHCH_3), 1.30 (d, J = 6.7 Hz, 3 H, NCHCH_3), 0.93 (d, J = 6.7 Hz, 3 H, NCHCH_3), 0.64 (d, J = 6.7 Hz, 3 H, NCHCH_3); ^{13}C NMR δ 169.51, 163.56, 162.17, 142.67, 142.53, 136.88, 130.45, 129.34, 128.12, 125.33, 112.44, 113.46, 52.17, 51.79, 50.82, 46.07, 20.42, 20.34, 19.82, 19.74. Anal. Calcd for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 61.80; H, 6.55; N, 10.95.

Reduction of *N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-4-hydroxy-3,4-dihydronaphthalene (15). To a CH_3OH (20 mL) solution containing 287 mg (0.8 mmol) of **15** and 8 mL of HOAc was added excess zinc dust in one portion. The reaction mixture was stirred at ambient temperature for 2 h until the yellow color was discharged. The zinc was removed by filtration, and the filtrate was diluted with 20 mL of ether and washed with 10% NaOH solution. The aqueous layer was extracted with ether, and the organic portions were combined and washed with saturated NaCl solution. The organic portions were dried ($MgSO_4$) and evaporated to give an oily residue, which was separated by preparative-scale TLC on silica gel with a 1:1 ratio of EtOAc/hexane as eluant to afford **24** as a white solid. The white solid was recrystallized from hexane to give 142 mg of **24** in 51% yield: mp 105–107 °C; ^1H NMR δ 7.63–7.19 (m, 4 H, Ar H), 5.23 (d, J = 9.7 Hz, 1 H, ArC*H*OH), 4.62 (s, 1 H, ArC*H*NCH), 3.87 (s, 2 H, CO_2CH_3), 3.59 (s, 3 H, CO_2CH_3), 3.53 (d, J = 4.2 Hz, 1 H, NCHC*H* CO_2CH_3), 3.11–3.07 (dd, J = 4.2 and 9.7 Hz, 1 H, CHOHC*H*CO_2CH_3), 3.14 (br s, 2 H, NC*H*CH_3), 1.15 (br s, 12 H, NCHCH_3). Decoupling: upon irradiation at 3.53 ppm, the peaks at 3.11–3.07 ppm became a doublet (J = 9.7 Hz) and the peaks at 5.23 ppm remained unchanged; upon irradiation at 3.11–3.07 ppm, both absorptions at 5.23 and 3.53 ppm became singlets. IR (KBr) 3543, 3440, 2970, 2730 cm^{-1}; MS; 363 (M^+), 348 ($M^+ - CH_3$), 332 ($M^+ - OCH_3$). Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.12; H, 7.99; N, 3.80. Found: C, 65.71; H, 7.76; N, 3.75. Exact mass calcd for $C_{20}H_{29}NO_5$ 363.2045, found 363.2052.

Reduction of *N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-4-hydroxy-3,4-dihydronaphthalene (16). According to the procedure above, excess zinc dust was added to a CH_3OH solution containing 192 mg (0.5 mmol) of **16** and 8 mL of HOAc. Workup in the same manner gave an organic residue, which was separated MPLC on silica gel by using 3:17 ratio of EtOAc/hexane as eluant to give **25** and **26**.

***N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)-4-hydroxy-1,2,3,4-tetrahydronaphthalene (25)**: 59 mg (30.7%) of a white solid; mp 100–102 °C; ^1H NMR δ 7.50–7.23 (m, 4 H, Ar H), 5.11–5.07 (dd, J = 4.9 and 9.2 Hz, ArC*H*OH), 4.76 (d, 1 H, J = 9.2 Hz, ArCHO*H*), 4.54 (s, 1 H, ArC*H*NCH), 3.83 (s, 3 H, CO_2CH_3) 3.69 (s, 3 H, CO_2CH_3), 3.40–3.34 (m, 2 H, C*H*CO_2CH_3, C*H*CO_2CH_3), 2.95 (br s, 2 H, ArCHNC*H*CH_3), 1.26–0.99 (br, 12 H, NCHCH_3). Decoupling: upon irradiation at 5.09 ppm, the peaks at 4.76 ppm become a singlet and the absorption patterns simplify for the absorption at 3.40–3.34 ppm; upon irradiation at 4.76 ppm, only the absorption at 5.09 ppm becomes a doublet (J = 4.9 Hz); upon irradiation at 3.37 ppm, the absorption at 5.11–5.07 ppm becomes a doublet (J = 9.2 Hz). IR (KBr) 3439 (br), 2960, 1740, 1720 cm^{-1}; MS, m/e 363 (M^+), 348 ($M^+ - CH_3$), 332 ($M^+ - OCH_3$). Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.12; H, 7.99; N, 380. Found: C, 66.34; H, 8.12; N, 3.87.

Lactone 26. Recrystallization from pentane gave 62 mg (35.3%) of **26** as a white solid: mp 132–133 °C; ^1H NMR δ 7.55–7.22 (m, 4 H, Ar H), 5.23 (s, 1 H, ArC*H*OCO), 4.49 (s, 1 H, ArC*H*NCH), 3.82 (s, 3 H, CO_2CH_3), 3.44 (s, 1 H), 3.42 (s, 1 H), 3.11 (br, 2 H, NC*H*CH_3), 1.21 (br, 6 H, NCHCH_3), 1.10 (br, 6 H, NCHCH_3); IR (KBr) 2963, 1783, 1740 cm^{-1}; MS, m/e 345 (M^+), 330 ($M^+ - CH_3$), 302 ($M^+ - C_3H_7$). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.20; H, 7.32; N, 4.32.

Oxidation of *N,N*-Diisopropyl-1-amino-2,3-bis(methoxycarbonyl)naphthalene (19) with Silver(II) Oxide. Nitric acid was added dropwise to a THF solution (30 mL) containing 30 mg (0.1 mmol) of **19** and 200 mg (0.4 mmol) of Ag(II)O over a period of 5 min. After being stirred for 30 min, the reaction was diluted with $CHCl_3$ and H_2O, and the aqueous portion was extracted with $CHCl_3$. The organic layers were combined, washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to dryness. The residue was separated by MPLC to give 13 mg of **29** in 55% yield as a yellow solid: mp 100–101 °C; ^1H NMR δ 8.16–8.10 (m, 2 H, Ar H), 7.85–7.81 (m, 2 H, Ar H), 3.95 (s, 6 H, CO_2CH_3). Anal. Calcd for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68. Found: C, 61.08; H, 3.84.

Preparation of *N,N*-Diisopropyl-2-[bromo(trimethylsilyl)methyl]benzamide (48). To a carbon tetrachloride solution (200 mL) containing 1.414 g (3.9 mmol) of *N,N*-diisopropyl-2-methylbenzamide were added 1.01 g (5.0 mmol) of NBS and 10 mg of benzoyl peroxide. The reaction mixture was heated at reflux and irradiated under UV sun lamp for 90 min. The mixture was cooled to room temperature and suspended succimide was removed by filtration through Celite. The filtrate was concentrated under reduced pressure to give a crude oil, which was separated by MPLC on silica gel. The white solid obtained after recrystallization from pentane was 1.142 g (65%) of **48**: mp 89–90 °C; ^1H NMR ($CHCl_3$ was used as internal standard) δ 7.48 (d, J = 8 Hz, 1 H, Ar H) 7.34–7.12 (m, 2 H, Ar H), 7.05–7.07 (d, J = 7.4 Hz, 1 H, Ar H), 4.32 (s, 1 H, ArC*H*BrSiMe$_3$), 3.71–350 (m, 2 H, NC*H*CH_3), 1.56 (d, J = 6.8 Hz, 6 H, NCHCH_3), 1.23 (d, J = 6.7 Hz, 3 H, NCHCH_3), 1.07 (d, J = 6.7 Hz, NCHCH_3), 0.173 (s, 9 H, $SiCH_3$); IR (KBr) 2810, 1621 cm^{-1}; MS, m/e 269 (M^+), 271 ($M^+ + 2$). Anal. Calcd for $C_{17}H_{28}BrNOSi$: C, 55.12; H, 7.62; N, 3.78; Br, 21.57. Found: C, 55.22; H, 7.70; N, 3.79; Br, 21.41.

General Procedure for Annelations of *N,N*-Diisopropyl-2-[bromo(trimethylsilyl)methyl]benzamide (48) Induced by Cesium Fluoride. To a dimethoxyethane (DME) solution containing 1.5 equiv CsF and 1.5 equiv of the dienophile was added 1 mmol of bromo trimethylsilyl benzamide **48** in small amount of DME at reflux. After about 90 min, the reaction was judged complete (TLC) and the reaction was filtered through a pad of silica gel. Removal of the solvent under reduced pressure gave an oily residue, which was separated by MPLC, and the products were further purified by repeated MPLC on silica gel and/or recrystallization.

Annelation of 48 with Dimethyl Maleate. From 245 mg (0.7 mmol) of **48** and 1 mmol of dimethyl maleate was obtained 123 mg (51%) of **18** as a yellow oil. The ^1H NMR spectrum of the product is identical with that of previously prepared material.

Annelation of 48 with Methyl Acrylate. From 239 mg (0.6 mmol) of **48** and 6 mmol of methyl acrylate were obtained 85 mg of **17** (55%) and 75 mg of **50** (39%) as colorless oils. The ^1H NMR spectrum of **17** is completely identical with that of previously prepared material.

50: a colorless oil; ^1H NMR δ 7.49–7.11 (m, 4 H, Ar H), 4.81 (d, J = 10 Hz, 1 H, ArCH_2Br), 3.93 (d, J = 10 Hz, 1 H, ArCH_2Br), 3.74 (m, 1 H, NC*H*CH_3), 3.53 (m, 1 H, NC*H*CH_3), 1.50 (t, J = 7.0 Hz, 6 H, NCHCH_3), 1.23 (d, J = 70. Hz, 3 H, NCHCH_3), 1.14 (d, J = 7.0 Hz, 3 H, NCHCH_3); MS, m/e 297 (M^+), 299 ($M^+ + 2$).

Annelation of 48 with Phenyl Vinyl Sulfone. From 303 mg (0.8 mmol) of **48** and 1.2 mmol of phenyl vinyl sulfone was obtained 146 mg of **21** (46%) as a yellow oil. The ^1H NMR spectrum of **21** is identical with that of previously prepared material.

Annelation of 48 with Dimethyl Acetylenedicarboxylate. From 187 mg (0.5 mmol) of **48** and 0.6 mmol of DMAD was obtained 104 mg of **19** (57%) as a colorless oil. The ^1H NMR spectrum is completely identical with that of previously prepared material.

***N,N*-Diethyl-2-(hydroxymethyl)benzamide (56).** To an ether solution (50 mL) containing 271 mg (4.2 mmol) of **13** was added excess $NaBH_4$ at room temperature. After being stirred at room temperature for 3 h, the organic solution was washed with 10% NaOH solution, the aqueous portion was extracted with ether, and the organic portions were combined, washed with saturated NaCl solution, and dried ($MgSO_4$). Removal of solvent in vacuo gave 635 mg of **56** as a colorless oil: ^1H NMR δ 7.44–7.25 (m, 4 H, Ar H), 4.52 (d, J = 4.4 Hz, 2 H, $ArCH_2OH$), 3.64–3.53 (q, J = 7.0 Hz, 2 H, NCH_2CH_3), 3.30–3.19 (q, J = 7.3 Hz, 2 H, NCH_2CH_3), 1.30 (t, J = 7.3 Hz, 3 H, NCH_2CH_3). 1.10 (t, J = 7.0 Hz, 3 H, NCH_2CH_3); IR (neat) 3364, 2974, 1612 cm^{-1}. This compound was used in the next step without further purification.

Bromination of *N,N*-Diethyl-2-(hydroxymethyl)benzamide (56) with Phosphorous Tribromide. To a CH_2Cl_2 (30 mL) solution containing 653 mg (3.2 mmol) of **56** was added an excess of phosphorous tribromide at 0 °C and the reaction temperature kept at 0 °C for 2 h. After aqueous workup, the organic portion was dried over $MgSO_4$, and solvents were evaporated to dryness in vacuo to give 463 mg of an oil, characterized as *N,N*-diethyl-2-(bromomethyl)benzamide (**50**): ^1H NMR ($CDCl_3/D_2O$) δ 7.48–7.19 (m, 4 H, Ar H), 4.60 (br s, 2 H, $ArCH_2Br$), 3.55 (br, 2 H, NCH_2CH_3), 3.17 (q, 2 H, NCH_2CH_3), 1.29 (t, 3 H, NCH_2CH_3), 1.12 (t, 3 H, NCH_2CH_3). Upon standing at room temperature for a few days, a portion of the oil was converted to 0.463 mg (59% yield) of the imidate salt **51**: ^1H NMR δ 8.29–8.25 (d, J = 8.3 Hz, 1 H, Ar H), 7.83–7.28 (m, 3 H, Ar H), 6.18 (s, 2 H, $ArCH_2O$), 4.40–4.29 (q, J = 7.3 Hz, 2 H, NCH_2CH_3), 4.09–3.98 (q, J = 7.3 Hz, 2 H, NCH_2CH_3). 1.67–1.59 (t, J = 7.3 Hz, 3 H, NCH_2CH_3), 1.55–1.47 (t, J = 7.3 Hz, 3 H, NCH_2CH_3); IR (KBr) 2870, 1670 cm^{-1} (C=N); MS, m/e 269 (M^+), 271 ($M^+ + 2$). Anal. Calcd for $C_{12}H_{16}NBrO$: C, 53.35; H, 5.97; N, 5.19. Found: C, 52.96; H, 6.11; N, 4.97; ^{13}C NMR ($CDCl_3$) δ 171.61, 148.26, 136.58, 130.82, 127.50, 123.82, 122.13, 78.99, 49.09, 47.29, 13.31, 12.69.

General Procedure for Base-Induced Annelation of a Cyclic Imidate Salt 51. To a THF solution (30 mL) containing 1.2 equiv of 2,2,6,6-tetramethylpiperidine (TMP) and 1.2 equiv of dienophile was added a portion of imidate salt **51** dissolved in 5 mL of CH_2Cl_2 at reflux. The reaction was stirred at reflux for 15 min prior to filtration through a pad of silica gel. Condensation under reduced pressure gave an oil residue, which was separated by MPLC.

***N,N*-Diethyl-1-amino-2-(methoxycarbonyl)-4-hydroxy-3,4-dihydronaphthalene (52).** The reaction was carried out with 144 mg (0.5 mmol) of **51**, 5 mmol of methyl acrylate, and 0.6 mmol of TMP. MPLC afforded a light yellow solid, and recrystallization from pentane gave 72 mg of **52** in 49% yield as a light yellow solid: mp 78–80 °C; ^1H NMR δ 7.63–7.31 (m, 4 H, Ar H), 4.73 (q, 1 H, $ArCHOH$), 3.78 (s, 3 H, CO_2CH_3), 3.21–3.10 (q, J = 7 Hz, 4 H, NCH_2CH_3), 2.79–2.74 (m, 2 H, $ArCHCH_2$), 2.04 (d, 1 H, $ArCHOH$), 1.12–1.05 (t, J = 7 Hz, NCH_2CH_3); IR (KBr) 3338, 2873, 1714, 1695 cm^{-1}; MS, m/e 275 (M^+), 274 ($M^+ - 1$), 260 ($M^+ - CH_3$), 244 ($M^+ - OCH_3$), 216 ($M^+ - CO_2CH_3$). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.59; H, 7.69; N, 4.93.

Annelation of 51 with Dimethyl Fumarate. The reaction was carried out with 165 mg (0.6 mmol) of **51**, 0.7 mmol of dimethyl fumarate, and 0.6 mmol of TMP. MPLC afforded three products **53**, **54**, and the *N,N*-diethyl-2,3-bis(methoxycarbonyl)naphthalene (**56**).

53: 55 mg (26.9%) as a yellow oil; ^1H NMR δ 7.61–7.31 (m, 4 H, Ar H), 4.92 (d, J = 4.7 Hz, 1 H, $ArCHOH$), 4.03 (d, J = 4.7 Hz, $ArCHOHCHCO_2CH_3$), 3.75 (s, 3 H, CO_2CH_3), 3.56 (s, 3 H, CO_2CH_3), 3.30–3.18 (m, 4 H, NCH_2CH_3) 2.20 (br s, 1 H, $ArCHOH$), 1.13, (t, J = 7.0 Hz, 6 H, NCH_2CH_3); MS, m/e 333 (M^+), 332 ($M^+ - 1$), 328 ($M^+ - CH_3$), 302 ($M^+ - OCH_3$), 274 ($M^+ - CO_2CH_3$). This material dehydrated to **56** upon standing a few days at room temperature.

54: 81 mg (39.7%) as a yellow oil; ^1H NMR δ 7.65–7.21 (m, 4 H, Ar H), 5.13–5.09 (dd, J = 5.5 and 10.7 Hz, 1 H, $ArCHOH$), 3.97 (d, J = 10.7 Hz, 1 H, $ArCHOH$), 3.89 (d, J = 5.5 Hz, 1 H, $ArCHOHCHCO_2CH_3$), 3.78 (s, 3 H, CO_2CH_3), 3.50 (s, 3 H, CO_2CH_3), 3.37–3.13 (m, 4 H, NCH_2CH_3), 1.31–1.04 (m, 6 H, NCH_2CH_3); MS, m/e 333 (M^+), 332 ($M^+ - 1$), 318 ($M^+ - CH_3$), 302 ($M^+ - OCH_3$), 274 ($M^+ - CO_2CH_3$). This material dehydrated to **56** upon standing at ambient temperature for a few days.

56: 32 mg (16.7%) as a white solid; ^1H NMR δ 8.43 (s, 1 H, Ar H), 8.14 (d, J = 8.3 Hz, 1 H, Ar H), 7.94 (d, J = 8.0 Hz, 1 H, Ar H), 7.60–7.55 (m, 2 H, Ar H), 3.97 (s, 3 H, CO_2CH_3), 3.93 (s, 3 H, CO_2CH_3), 3.29 (br s, 4 H, NCH_2CH_3), 1.08–1.04 (t, 6 H, NCH_2CH_3); IR (KBr) 2964, 1639, 1718 cm^{-1}; MS, m/e 315 (M^+), 300 ($M^+ - CH_3$), 284 ($M^+ - OCH_3$). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.34; H, 6.83; N, 4.42.

Annelation of 51 with Dimethyl Maleate. The reaction was carried out with 157 mg (0.6 mmol) of **51**, 0.7 mmol of dimethyl maleate, and 0.7 mmol of TMP. MPLC afforded 76 mg of **53** in 37% yield and 40 mg of **54** in 19% yield, respectively. The ^1H NMR spectra of **53** and **54** are identical with those previously obtained.

***N,N*-Diethyl-1-amino-2,3-bis(methoxycarbonyl)-4-hydroxynaphthalene (55).** The reaction was carried out with 130 mg (0.5 mmol) of **51** and 0.6 mmol of DMAD. MPLC afforded 113 mg of **55** in 71% as a colorless oil: ^1H NMR δ 12.38 (s, 1 H, Ar O*H*), 8.47 (d, J = 8 Hz, 1 H, Ar H). 7.98 (d, J = 8 Hz, 1 H, Ar H), 7.69–7.51 (m, 2 H, Ar H), 3.95 (s, 3 H, CO_2CH_3), 3.91 (s, 3 H, CO_2CH_3), 3.38–3.11 (m, 4 H, NCH_2CH_3), 1.03 (t, J = 7.3 Hz, 6 H, NCH_2CH_3); MS, m/e 331 (M^+), 316 ($M^+ - CH_3$), 300 ($M^+ - OCH_3$), 268 ($M^+ - CO_2CH_3$). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.41; H, 6.53; N, 4.36.

General Procedure for the Comparison of Dienophiles toward 1-(Dialkylamino)isobenzofuran. To a benzene solution (40 mL) containing 10 mg of $Cu(acac)_2$ or 2 mg of $Rh_2(OAc)_4$ and tenfold excess of each dienophile was added 1 equiv of the diazobenzamide in 10 mL of benzene via a syringe pump over a 2-h period. After addition was complete, the solution was allowed to reflux 10 min, and the mixture was then filtrated through a pad of silica gel and concentrated in vacuo to give an oil. The oil was dissolved with ether and extracted with 30 mL of 10% HCl solution. The aqueous layer was neutralized with saturated Na_2CO_3 solution and extracted with 30 mL of ether. The organic portion was dried over $MgSO_4$, and the solvent was evaporated to dryness to give a yellow oily residue. The relative rates of reaction of the dienophiles toward isobenzofuran was determined from comparison of the relative ratio of the benzylic hydrogens absorption which appear between 4.0–5.0 ppm in the ^1H NMR spectra.

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Supplementary Material Available: Table of HOMO and LUMO energies (1 page). Ordering information is given on any current masthead page.