JOC Article

A Sequential Pummerer−Diels−Alder Route for the Generation and Trapping of Furo[3,4-*c*]pyridines: Synthesis of Heterocyclic Analogues of 1-Arylnaphthalene Lignans

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The Pummerer reaction of an *o*-benzoyl-substituted pyridylmethyl sulfoxide generates an α-thiocarbocation, the interception of which by a neighboring keto functionality produces an α-thio-substituted furo[3,4-*c*]pyridine as transient intermediate; the latter undergoes a Diels−Alder cycloaddition with an added dienophile. Base-induced ring opening of the cycloadduct followed by aromatization gives an isoquinoline derivative that may be looked upon as a heterocyclic analogue of 1-arylnaphthalene lignans. This procedure occurs readily with electron-poor dienophiles and the entire sequence can be run in one pot. The facility of the sequential Pummerer−Diels−Alder reaction hinges on the experimental conditions, the best results being obtained with heptafluorobutyric anhydride as the triggering agent in toluene containing a catalytic amount of *p*-toluenesulfonic acid. In the absence of a dienophile it is possible to isolate and characterize a rather unstable furo[3,4-*c*]pyridine derivative. An intramolecular variant of this protocol is also feasible with use of unactivated alkenyl tethers of variable length; however, the bridged cycloadducts are unisolable in these cases as they undergo spontaneous ring opening and aromatization to yield cycloalka[*h*]isoquinolines. The usefulness of the sequential Pummerer−Diels−Alder reaction is further demonstrated through the synthesis of a heterolignan with a built-in lactone ring via oxidation of the initial [4+2]-cycloadduct followed by extrusion of phenyl sulfinate and elaboration of the resulting hydoxylated isoquinoline derivative.

Introduction

Isobenzofurans have for a long time served as an interesting class of reactive intermediates in organic synthesis. As functional analogues of *o*-xylylenes, they take part in both inter- and intramolecular Diels−Alder reactions leading to a variety of polycyclic ring systems including natural products of biological significance.[1] In contrast, heteroanalogues of isobenzofurans have received much less attention, although this situation is rapidly changing in recent years.[2,3] The heteroaromatic isobenzofurans reported to date include furo[3,4-*b*]furans, thieno[2,3-*c*]furans, furo[3,4-*d*]oxazoles, furo[3,4-*d*]isooxazoles, furo[3,4-*d*]thiazoles, furo[3,4-*b*]benzofurans, benzo[4,5]thieno[2,3-*c*]furans, furo[3,4-*b*]indoles, furo[3,4-*b*]-pyridines, furo[3,4-*c*]pyridines, furo[3,4-*d*]pyridazines, furo[3,4-*d*]quinoxalines, and furo[3,4-*c*]cinnolines.[3] During the course of our studies on heteroisobenzofurans, we have recently reported the synthesis of a remarkably stable furo[3,4-*c*]pyridine intermediate[4] and established the unique advantages of intramolecular Diels−Alder reactions of furo[3,4-*c*]pyridines in the synthesis of conformationally restricted analogues of nicotine and anabasine.[5] The utility of heteroisobenzofurans as potential building blocks for the construction of polycyclic heteroaromatics is critically dependent on their availability as appropriate dienes. The methods so far reported for the generation of furo[3,4-*c*]pyridines include (i) thermal retro-Diels−Alder reactions of 1,4-epoxides,[6] (ii) lithiation and subsequent *o*-silylation of pyridine-phthalides,[7] and (iii) the Hamaguchi−Ibata reaction of *o*-aminodiazocarbonyl precursors.[4,5] As part of our continuing interest in the chemistry of azaisobenzofurans, we were particularly interested in the generation of thio-substituted furo[3,4-*c*]pyridines by a Pummerer-based route and their ap-

* Corresponding author.

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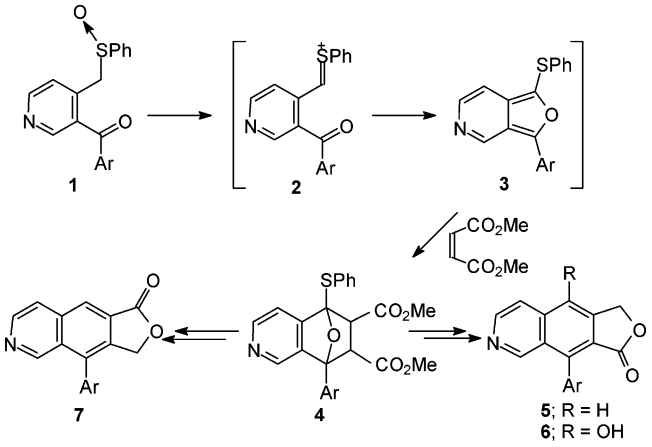
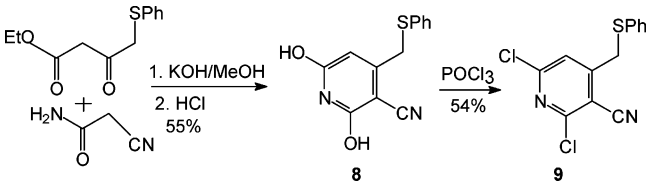
SCHEME 1



SCHEME 2



plications in the synthesis of heterocyclic analogues of 1-arylnaphthalene lignans of biological significance.

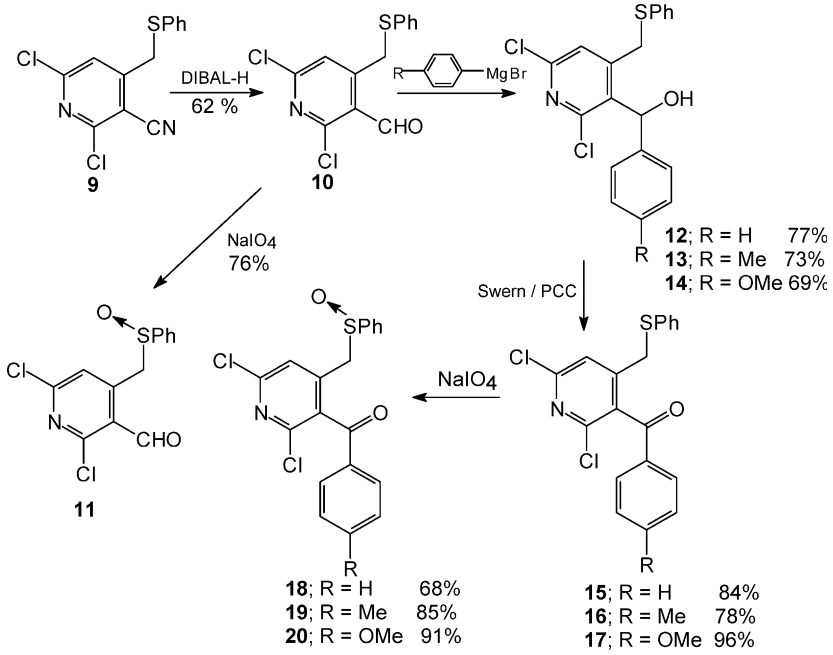
Our strategy toward arylisoquinoline lignans **5**−**7** is based on the pioneering work of Padwa et al. as outlined in Scheme 1.[8] This involves generation of α-thiocarbocation **2** from sulfoxide **1** and its interception by a neighboring carbonyl group to give furo[3,4-*c*]pyridine **3**; the latter should undergo a Diels−Alder reaction with an added dienophile to give **4**, which is readily convertible to heterolignans **5**−**7**. In a preliminary communication,[9] we reported the Pummerer-based generation of furo[3,4-*c*]pyridines using heptafluorobutyric anhydride as a modified triggering agent and their subsequent trapping. In this paper we report the full details of our efforts in this area including inter alia synthesis of some nitrogen-containing heterocyclic analogues of 1-arylnaphthalene lignans.

Results and Discussions

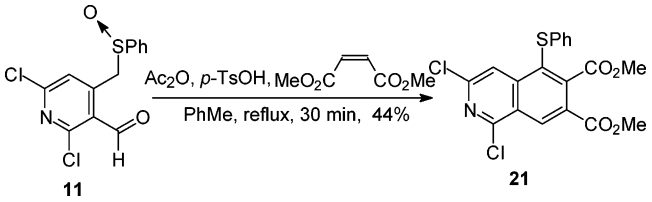
Our studies began with nitrile **9**, which was prepared following a slightly modified method as reported by Bobbitt and Scola for the synthesis of 4-methyl-3-substituted pyridines.[10] Thus, condensation of ethyl 4-(phenylthio)acetoacetate[11] with cyanoacetamide in the presence of potassium hydroxide and acidification of the resulting monopotassium salt gave **8** (Scheme 2). Conversion of **8** to the corresponding nitrile **9** was then accomplished by exposure to phosphorus oxychloride at an elevated temperature.

Reduction of **9** with diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 gave aldehyde **10**, which on oxidation with sodium periodate in methanol yielded the corresponding sulfoxide **11** (Scheme 3). In addition, a series of other pyridine-containing sulfoxide precursors **18**−**20** was synthesized from their corresponding keto-sulfides **15**−**17** by oxidation with $NaIO_4$. The main drawback in $NaIO_4$-mediated oxidation of sulfides **15**−**17** is long reaction time, i.e., 15−20 days are required to obtain sulfoxides in acceptable yields. For rapid access to these sulfoxides we subsequently found that 70% conversion of pyridine-containing keto-sulfoxides **18**−**20** could be achieved by treatment of sulfides **15**−**17** with peracetic acid for a brief period (cf. 30 min). The synthesis of the desired keto-sulfides **15**−**17** was accomplished by the treatment of aldehyde **10** with an aryl-Grignard reagent in THF and subsequent oxidation of the resultant alcohols **12**−**14** under Swern/PCC conditions. It should be mentioned here that alcohol **14** did not undergo clean oxidation under Swern oxidation conditions and best results (96% yield) were obtained by treatment with PCC in CH_2Cl_2.

SCHEME 3



SCHEME 4



To test the viability of the proposed sequential Pummerer−Diels−Alder process, we first treated simple sulfoxide **11** with a suitable dienophile under standard Pummerer reaction conditions developed by Padwa et al.[8] Thus, exposure of **11** to a mixture of acetic anhydride, dimethyl maleate, and a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in refluxing toluene for 30 min gave **21** in 44% yield as a white crystalline solid (Scheme 4). In this case, the [4+2]-adduct (cf. **4**) underwent spontaneous ring cleavage followed by dehydration.

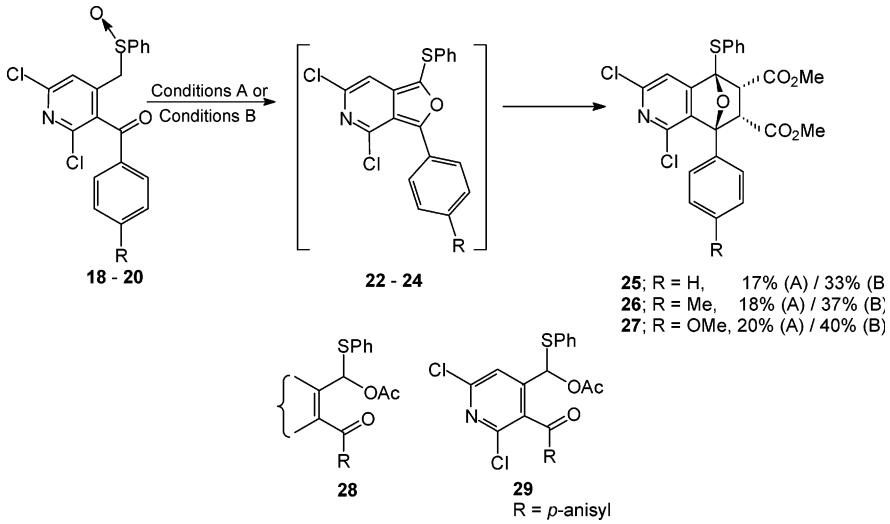
However, when keto-sulfoxide **18** was used, the sequential Pummerer−Diels−Alder reaction proceeded as expected, but here the bridged product **25** was obtained in only 17% yield (Scheme 5). The stereochemistry of **25** is tentatively assigned on the basis of the Alder endo rule. Similarly, keto-sulfoxides **19** and **20** gave **26** and **27** in only 18% and 20% yields, respectively. Here the stereochemistry of **26** was fully supported by an X-ray crystal structure determination.[12] The above route turned out to be less efficient in all cases in view of the formation of major products, e.g. acetoxy sulfides of type **28** and miscellaneous other side products, which were not further characterized (Scheme 5). For example, in the Pummerer reaction of **20** the acetoxy sulfide **29** was isolated as a white crystalline compound. Even using trifluoroacetic anhydride[8] in place of acetic anhydride did not help in improving yields of these products, e.g. **26**. This prompted us to develop a modified triggering protocol to achieve acceptable yields of the desired bridged cycloadducts. After considerable efforts with a variety of Pummerer promoters, we overcame this difficulty simply by replacing acetic anhydride by heptafluorobutyric anhydride. In this modified protocol (conditions B), keto-sulfoxides **18**−**20** smoothly gave the bridged cycloadducts **25**−**27** with improved yields as shown in Scheme 5. This improvement is either due to the poorer nucleophilicity of "counterion" toward Pummerer intermediate (cf. **2**) generated in the reaction medium, thereby preventing the formation of sulfides of type **28**, or due to better leaving group ability of the same "counterion" from **28**.

In the absence of a dienophile the Pummerer reaction of sulfoxide **20** generates the α-thio-substituted furo[3,4-*c*]pyridine **24** as a yellow oil. This intermediate is quite unstable and undergoes aerial decomposition attended with disappearance of color in a few hours. However, we were able to isolate and characterize it by ^{1}H NMR spectroscopy. It may be noted that azaisobenzofuran **24** also undergoes Diels−Alder reaction with less reactive dienophiles. Thus, exposure of sulfoxide **20** to the Pummerer−Diels−Alder reaction protocol in the presence of methyl acrylate as dienophile gave a 4:1 mixture (^{1}H NMR) of cycloadducts, the major of which was identified as **30** on the basis of single-crystal X-ray crystallography;[13] the minor product is tentatively assigned as **31** (Scheme 6).

The regio- and stereoselectivity in the cycloaddition of **24** with methyl acrylate may be rationalized by FMO theory.[14] This is a normal demand $\pi^4_s + \pi^2_s$ process with a HOMO-LUMO gap of 4.8 eV between the HOMO of **24** and LUMO of methyl acrylate. The atomic coefficients of the interacting orbitals, e.g., 0.314 (phenylthio-substituted carbon) and 0.23 (anisyl carbon) of the π^4 system, e.g., **24,** match with 0.63 and 0.464 of the π^2 acrylate system to provide the product **30**, and the secondary orbital interaction, which leads to endo addition, is also favorable.[15]

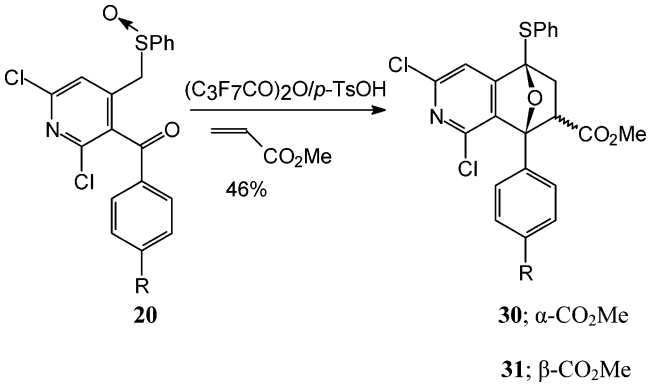
The Pummerer-based route for the generation and trapping of α-thiosubstituted furo[3,4-*c*]pyridines can also be extended to intramolecular cases (Scheme 7). Toward this end tethered sulfoxides **36** and **37** were prepared in a similar fashion as described before simply by changing the aryl Grignard reagent by an alkenyl Grignard reagent and then oxidation of alcohols **32** and **33** with PCC followed by further oxidation of the resulting sulfides **34** and **35** (Scheme 7). Subjection of **36** and **37**

SCHEME 5[a]



[a] Conditions: (A) Ac_2O, *p*-TsOH, dimethyl maleate, PhMe, reflux, 1 h; (B) $(C_3F_7CO)_2O$, *p*-TsOH, dimethyl maleate, PhMe, reflux, 1 h.

SCHEME 6

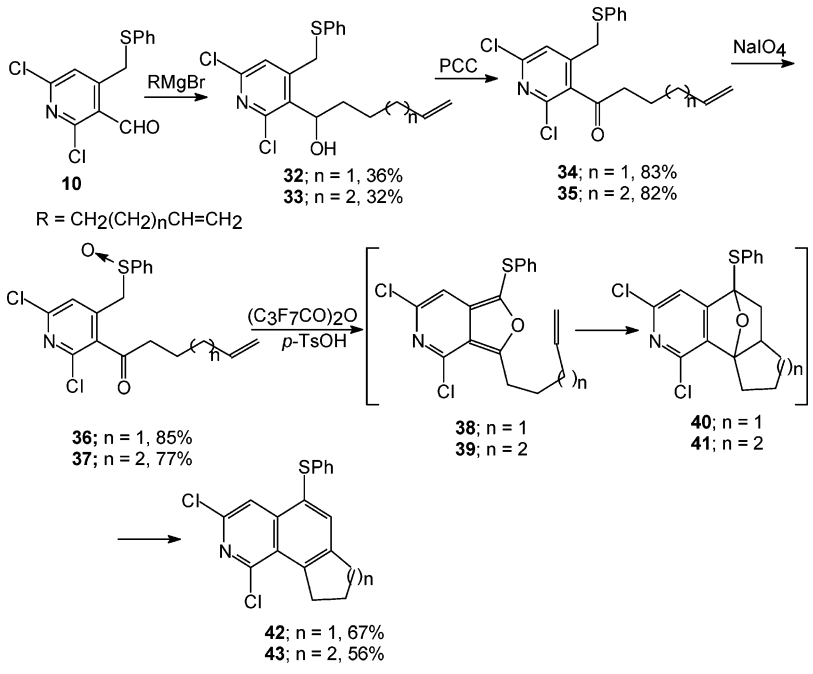


to the modified Pummerer conditions (heptafluorobutyric anhydride/*p*-TsOH) led to polycyclic ring systems **42** and **43** in one pot with good yields. The need for our new triggering agent for initiating the Pummerer reaction is best exemplified in these intramolecular series. For example, when keto-sulfoxide **36** was subjected to the other Pummerer conditions[8] (Ac_2O/*p*-TsOH in refluxing toluene) only the acetoxy product (cf. **28**) was obtained; no trace of product resulting from an intramolecular Diels−Alder reaction could be detected in the crude reaction mixture by TLC. The high-yielding intramolecular [4+2]-cycloaddition reaction of **38** and **39** is obviously related to entropic factors which place the tethered double bond in close proximity to the diene system.

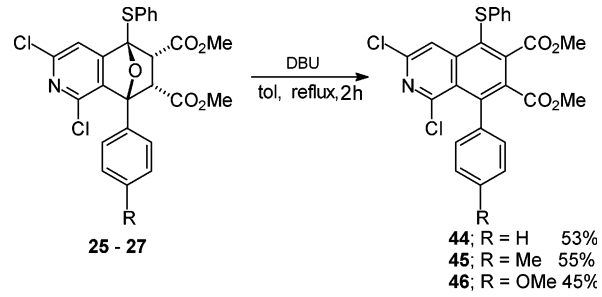
Since thiol groups can be released from appropriately substituted precursors at tumors, namely by bioreduction[16] or by antibody-directed enzyme catalysis,[17] azaisobenzofuran Diels−Alder adducts, e.g. **25**−**27**, with bridgehead sulfide groups may be looked upon as potential antitumor prodrugs where cleavage of a sulfide linkage can lead to aromatization of the oxanorbornyl ring system.[18] Chemically, we have been able to accomplish aromatization of **25**−**27** with DBU in refluxing toluene to give **44**−**46** in 45−55% yields (Scheme 8).The structure of one of these products, **44**, was fully established by X-ray crystallography.[19] Incidentally, initial attempts for the ring opening of **25**−**27** with a variety of other reagents, e.g. MeOH/HCl, *p*-TsOH in refluxing toluene, and CF_3COOH, were unsuccessful. The synthesis of these compounds, e.g. **46**, also can be conducted in one pot by exposing keto-sulfoxide **20** to the Pummerer conditions (conditions B) and then adding DBU to the reaction mixture. Compounds **44**−**46** may be looked upon as heterocyclic analogues of potentially bioactive 1-arylnaphthalene lignans.[20] The usefulness of the sequential Pummerer−Diels−Alder reaction was also demonstrated through the synthesis of a heterolignan[20] with a built-in lactone ring via oxidation of the initial [4+2]-cycloadduct followed by extrusion of phenyl sulfinate and elaboration of the resulting hydoxylated isoquinoline derivative. Thus, the phenylsulfanyl group present in **26** was oxidized [21] by using $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ to give sulfone **47**. Ring opening followed by extrusion of phenylsulfinate was done by exposure of **47** to DBU in refluxing toluene to give the hydroxy isoquinoline derivative **48** (Scheme 9). Selective reduction of the ester group proximal to the phenolic hydroxy group in **48** with $NaBH_4$ as reported in the analogous naphthalene series,[22] however, failed. We overcame this problem by prior methylation of the hydroxy group and DIBAL-H reduction of the resulting methyl ether **49** to give heterolignan **50** directly. The position of the lactone carbonyl in **50** was determined by NOE experiment, which showed significant enhancement of the OMe signal upon irradiation of the adjacent CH_2 singlet. The selectivity in the ester reduction stems from the fact that the tolyl group that is orthogonal to the plane of the isoquinoline ring effectively shields the adjacent carbomethoxy group.

In conclusion, we have demonstrated that the sequential Pummerer−Diels−Alder reaction sequence is suited

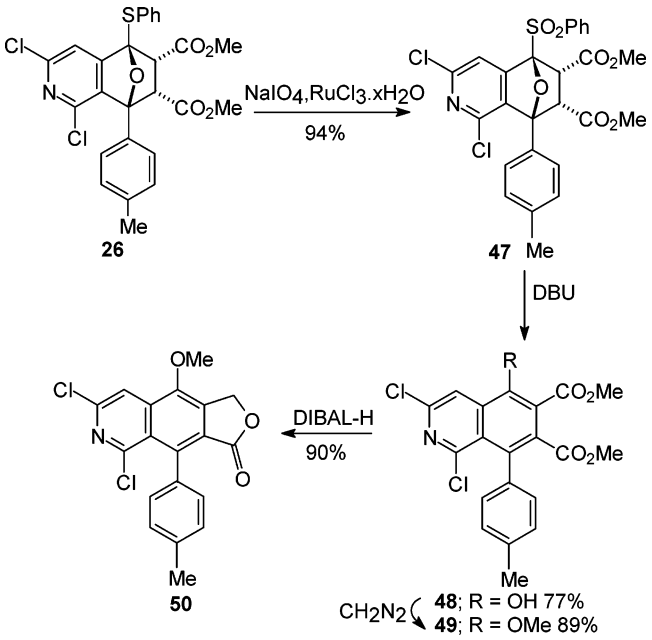
SCHEME 7



SCHEME 8



SCHEME 9



to efficient synthesis of a variety of heterocyclic ring systems including the potentially bioactive heterolignans. The key intermediates in this cascade process are α-thio-substituted furo[3,4-*c*]pyridines, which in some cases can be isolated and independently reacted with a suitable dienophile to give [4+2]-cycloadducts. However, we found it to be most convenient to carry out these reactions in an all tandem fashion. Our results clearly indicate that this methodology provides rapid entry into heteroaromatic *o*-quinodimethanes.

Experimental Section

All melting points are uncorrected. Unless otherwise noted, all reactions were carried out under inert atmosphere in flame-dried flasks. Solvents and reagents were dried and purified by distillation before use as follows: Tetrahydrofuran and toluene from sodium benzophenone ketyl, dichloromethane and acetonitrile from P_2O_5, DMSO from CaH_2, Et_3N and pyridine from solid KOH, and methanol from Mg. After drying, organic extracts were evaporated under reduced pressure and the residue was flash chromatographed on silica gel (Acme's, particle size 230−400 mesh), using an ethyl acetate−petroleum ether (60−80 °C) mixture as eluent unless specified otherwise.

2,6-Dichloro-4-[(phenylthio)methyl]nicotinonitrile (9). A mixture containing cyanoacetamide (5.06 g, 60.21 mol) and ethyl 4-(phenylthio)acetoacetate[11] (14.33 g, 60.21 mol) in 50 mL of methanol was warmed to attain solution and potassium hydroxide (4.14 g, 73.82 mol) dissolved in 20 mL of methanol was added dropwise with stirring. The mixture was heated at reflux; after 2 h a brown precipitate formed and heating was continued for an additional 5 h. Then the reaction mixture was cooled and 2,6-dihydroxy-4-[(phenylthio)methyl]nicotinonitrile monopotassium salt so formed was separated by filtration, dissolved in warm water, cooled, and acidified with concentrated hydrochloric acid. The product was separated by filtration, washed with cold methanol, dried in air, and finally further dried at 120−130 °C in vacuo for 5 h to give 8.4 g (55%) of 2,6-dihydroxy-4-[(phenylthio)methyl]nicotinonitrile (**8**) as an off-white solid: chars at 268 °C, mp 275−278 °C; IR (KBr) 3100, 2221 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:DMSO-d_6) δ 3.98 (s, 2H), 5.68 (s, 2H), 7.10−7.43 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$, DMSO-d_6) δ 36.1 (t), 89.2 (s), 92.1 (d), 116.0 (s), 126.7 (d), 128.8 (d), 129.7 (d), 134.1 (s), 159.0 (s), 161.3 (s), 161.8 (s).

A mixture containing **8** (4 g, 15.5 mmol) and $POCl_3$ (5.8 mL, 62.0 mmol) was heated in a sealed tube at 150 °C for 9 h. It was then cooled to room temperature and transferred into 100 mL of ice cold water. The mixture was filtered with repeated washings with water. The residue was dissolved in hot methanol, heated for 10 min with activated charcoal, filtered, and concentrated. The resulting brown oil was purified by chromatography (EtOAc:petroleum ether 1:99) to give 2.45 g (54%) of **9** as a yellow solid. An analytical sample was obtained by recrystallization from petroleum ether to give colorless needles: mp 118−119 °C; IR (KBr) 2231, 1567, 1530, 1336 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.12 (s, 2H), 7.13 (s, 1H), 7.32 (br s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) 37.5 (t), 109.2 (s), 112.6 (s), 123.1 (d), 128.6 (d), 129.3 (d), 131.9 (s), 132.5 (d), 152.5 (s), 153.6 (s), 156.3 (s). FAB MS *m*/*z* (rel intensity) 295 ($[M+H]^+$, 46), 242 (4), 186 ($[M - SC_6H_5]H^+$, 4), 165 (8); HRMS (FAB) calcd for $C_{13}H_9Cl_2N_2S$ $(M+H)^+$ *m*/*z* 294.9863, found 294.9856. Anal. Calcd for $C_{13}H_8Cl_2N_2S$: C, 52.89; H, 2.72; N, 9.48. Found: C, 52.68; H, 2.81; N, 9.39.

2,6-Dichloro-4-[(phenylthio)methyl]nicotinaldehyde (10). To a stirred solution of **9** (4 g, 13.56 mmol) in 60 mL of CH_2Cl_2 cooled to −78 °C was added 15 mL of DIBAL-H (1.0 M solution in toluene) dropwise over a period of 1 h. The resulting mixture was allowed to attain room temperature. After 2 h of stirring at room temperature the solution was quenched with saturated aqueous NH_4Cl at 0 °C, stirred for another 1 h at that temperature, and then acidified with 3 N

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HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by chromatography (EtOAc:petroleum ether 1:99) to give 2.5 g (62%) of aldehyde **10** as a white crystalline solid: mp 61−62 °C; IR (KBr) 1688, 1565, 1526, 1317 cm^{-1}; ^1H NMR (200 MHz $CDCl_3$:CCl_4 7:3) δ 4.36 (s, 2H), 7.00 (s, 1H), 7.28 (br s, 5H), 10.42 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.2 (t), 124.9 (s), 125.0 (d), 128.0 (d), 129.1 (d), 132.2 (d), 133.3 (s), 153.4 (s), 154.2 (s), 154.4 (s), 190.2 (d). Anal. Calcd for $C_{13}H_9Cl_2NOS$: C, 52.36; H, 3.03; N, 4.69. Found: C, 52.23; H, 3.19; N, 4.68.

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**(4-methylphenyl)methanol (13).** To a stirred solution of aldehyde **10** (1 g, 3.5 mmol) in 20 mL of dry THF was added dropwise a tolylmagnesium bromide solution (16.8 mL, 0.4 M) [prepared from *p*-bromotoluene (1.23 mL, 10 mmol) and Mg (480 mg, 20 mmol) in 24 mL of THF] over a period of 10 min at −78 °C. During addition a blood red color was formed. After 1 h of stirring the mixture was slowly warmed to 0 °C and then quenched with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by chromatography (EtOAc:petroleum ether 10:90) giving 950 mg (73%) of **13** as a white crystalline solid: mp 129−131 °C; IR (KBr) 3371, 1575, 1524, 1104 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.36 (s, 3H), 3.46 (s, 1H), 3.84 (d, 1H, J_{AB} = 15.3 Hz), 4.26 (d, 1H, J_{AB} = 15.3 Hz), 6.57 (br s, 1H), 6.82−7.41 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.1 (q), 35.4 (t), 70.9 (d), 125.0 (d), 125.2 (d), 127.0 (d), 129.0 (d), 129.3 (d), 130.1 (d), 134.3 (s), 134.4 (s), 137.2 (s), 137.6 (s), 149.5 (s), 149.8 (s), 152.9 (s). FAB MS *m*/*z* (rel intensity) 390 ($[M + H]^+$, 100), 372 ($[M - H_2O]H^+$, 26), 279 (31), 264 (42), 227 (10), 219 (5), 188 (4), 120 (10); HRMS (FAB) calcd for $C_{20}H_{18}Cl_2NOS$ $(M+H)^+$ *m*/*z* 390.0486, found 390.0486. Anal. Calcd for $C_{20}H_{17}Cl_2NOS$: C, 61.56; H, 4.38; N, 3.58. Found: C, 61.34; H, 4.19; N, 3.85.

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**(phenyl)methanol (12)** was prepared by a similar method starting from aldehyde **10** (820 mg, 2.75 mmol) and bromobenzene in 77% yield as a white crystalline solid: mp 146−148 °C; IR (KBr) 3506, 1605, 1571, 1326, 1066 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.2 (br s, 1H), 3.80 (d, 1H, J_{AB} = 15.2 Hz), 4.23 (d, 1H, J_{AB} = 15.2 Hz), 6.62 (s, 1H), 6.98−7.45 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.5 (t), 70.9 (d), 125.0 (d), 125.1 (d), 127.1 (d), 127.5 (d), 128.5 (d), 129.0 (d), 130.3 (d), 133.9 (s), 134.0 (s), 140.4 (s), 149.5 (s), 149.9 (s), 152.6 (s). Anal. Calcd for $C_{19}H_{15}Cl_2NOS$: C, 60.66, H, 4.01; N, 3.72. Found: C, 60.61; H, 3.91; N, 3.85.

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**(4-methoxyphenyl)methanol (14)** was prepared by a similar method starting from aldehyde **10** (450 mg, 1.51 mmol) and *p*-bromoanisol in 69% yield as a white crystalline solid: mp 116−118 °C; IR (KBr) 3351, 1569, 1525, 1098 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.50 (br s, 1H), 3.78 (s, 3H), 3.86 (d, 1H, J_{AB} = 15.3 Hz), 4.27 (d, 1H, J_{AB} = 15.2 Hz), 6.56 (br s, 1H), 6.72−7.35 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 35.5 (t), 55.3 (q), 70.8 (d), 114.1 (d), 125.1 (d), 126.6 (d), 127.2 (d), 129.1 (d), 130.3 (d), 132.6 (s), 134.3 (s), 149.5 (s), 149.8 (s), 152.9 (s), 159.1 (s). Anal. Calcd for $C_{20}H_{17}Cl_2NO_2S$: C, 59.13; H, 4.21; N, 3.44. Found: C, 59.41; H, 4.31; N, 3.19.

1-{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**-hex-5-en-1-ol (32)** was prepared by a similar method starting from aldehyde **10 (**400 mg, 1.34 mmol) and 5-bromo-1-pentene in 36% yield: ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.31−2.18 (m, 6H), 2.88 (br s, 1H), 4.25 (d, 1H, J_{AB} = 13.3 Hz), 4.43 (d, 1H, J_{AB} = 13.3 Hz), 4.89−5.08 (m, 2H), 5.27−5.37 (m, 1H), 5.62−5.91 (m, 1H), 7.01 (s, 1H), 7.19−7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 70:30) δ 25.4 (t), 33.3 (t), 35.8 (t), 36.4 (t), 71.1 (d), 115.1 (t),125.4 (d), 127.7 (d), 129.2 (d), 131.7 (d), 134.4 (s), 134.5 (s), 138.0 (d), 148.3 (s), 148.9 (s), 151.7 (s). Anal. Calcd for $C_{18}H_{19}Cl_2NOS$: C, 58.71; H, 5.19; N, 3.80. Found: C, 58.93; H, 5.31; N, 3.49.

1-{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**-hept-6-en-1-ol (33)** was prepared by a similar method starting from aldehyde **10** (440 mg, 1.47 mmol) and 6-bromo-1-hexene in 32% yield as a yellow oil: IR ($CHCl_3$) 3308, 1568, 1533, 1307 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 70:30) δ 1.28−2.15 (m, 8H), 2.47 (br s, 1H), 4.27 (d, 1H, J_{AB} = 13.4 Hz), 4.44 (d, 1H, J_{AB} = 13.4 Hz), 4.90−5.05 (m, 2H), 5.21−5.45 (m, 1H), 5.65−5.85 (m, 1H), 7.04 (s, 1H), 7.27−7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 25.5 (t), 28.4 (t), 33.5 (t), 36.1 (t), 36.4 (t), 71.1 (d), 114.5 (t), 125.3 (d), 127.7 (d), 128.9 (d), 131.6 (d), 134.4 (s), 134.6 (s), 138.5 (d), 148.2 (s), 148.9 (s), 151.7 (s).

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**(4-methylphenyl)methanone (16).** To a stirred solution of **13** (2 g, 5.12 mmol) in 20 mL of dry CH_2Cl_2 was added PCC (1.7 g, 7.7 mmol) at room temperature. After 1.5 h of stirring the solution was filtered over a short Celite pad. The yellow solution was then concentrated under reduced pressure and purified by chromatography (EtOAc:petroleum ether 5:95) to give 1.55 g (78%) of **16** as a white solid: mp 105−107 °C; IR (KBr) 1658, 1602, 1565, 1325 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.42 (s, 3H), 3.90 (s, 2H), 7.05−7.35 (m, 8H), 7.64 (d, 2H, J = 8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.9 (q), 35.6 (t), 123.6 (d), 127.5 (d), 129.1 (d), 129.7 (d), 129.8 (d), 130.8 (d), 133.0 (s), 133.4 (s), 133.6 (s), 145.7 (s), 146.7 (s), 150.6 (s), 150.9 (s), 192.0 (s). Anal. Calcd for $C_{20}H_{15}Cl_2NOS$: C, 61.87; H, 3.89; N, 3.60. Found: C, 62.09; H, 3.97; N, 3.83.

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**-(phenyl)methanone (15).** To a stirred solution of oxalyl chloride (0.278 mL, 3.13 mmol) in 10 mL of CH_2Cl_2 cooled at −60 °C was added DMSO (0.453 mL, 6.39 mmol) in 5 mL of CH_2Cl_2 dropwise via dropping funnel in 15 min under argon atmosphere. The mixture was stirred for 30 min followed by addition of **12** (800 mg, 2.13 mmol) in 10 mL of CH_2Cl_2 over a period of 10 min. After 30 min of stirring Et_3N (1.5 mL, 10.65 mmol) was added and the reaction mixture was allowed to attain room temperature and stirred for 1 h. Then 100 mL of cold H_2O was added to the mixture. The organic layer was separated and washed with 1% HCl and brine. Finally the organic fraction was concentrated in vacuo and purified by chromatography (EtOAc:petroleum ether 5:95) to give 670 mg of **15** in 84% yield: IR (KBr) 1666, 1602, 1555, 1332 cm^{-1}; ^1H NMR (200 MHz $CDCl_3$:CCl_4 7:3) δ 3.90 (s, 2H), 7.00−7.85 (m, 11H); ^{13}C NMR (50 MHz $CDCl_3$:CCl_4 7:3) δ 35.7 (t), 123.7 (d), 127.6 (d), 128.9 (d), 129.2 (d), 129.6 (d), 130.9 (d), 132.7 (s), 133.5 (s), 134.5 (d), 135.8 (s), 146.7 (s), 150.8 (s), 151.1 (s), 192.5 (s).

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**(4-methoxyphenyl)methanone (17)** was obtained by the PCC oxidation of alcohol **14** (400 mg, 0.98 mmol) in 96% yield as a yellow oil. IR (KBr) 1660, 1595, 1564, 1343 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.88 (s, 3H), 3.90 (s, 2H), 6.90 (d, 2H, J = 9.1 Hz), 7.12−7.28 (m, 6H), 7.70 (d, 2H, J = 8.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 35.6 (t), 55.4 (q), 114.2 (d), 123.4 (d), 127.5 (d), 128.9 (s), 129.1 (d), 130.8 (d), 132.0 (d), 133.0 (s), 133.7 (s), 146.7 (s), 150.5 (s), 150.7 (s), 164.6 (s), 190.7 (s). Anal. Calcd for $C_{20}H_{15}Cl_2NO_2S$: C, 59.41; H, 3.74; N, 3.46. Found: C, 59.22; H, 3.63; N, 3.59.

1-{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**-hex-5-en-1-one (34)** was obtained by the PCC oxidation of **32** (170 mg, 0.462 mmol) in 83% yield as a yellow oil. IR ($CHCl_3$) 1707, 1565, 1530, 1325 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.68−1.97 (m, 2H), 2.08−2.19 (m, 2H), 2.87 (t, 2H, J = 7.3 Hz), 3.88 (s, 2H), 4.97−5.12 (m, 2H), 5.67−5.91 (m, 1H), 6.99 (s, 1H), 7.13−7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 22.3 (t), 32.8 (t), 36.1 (t), 43.4 (t), 115.6 (t), 123.9 (d), 128.2 (d), 129.4 (d), 131.9 (d), 133.3 (s), 134.8 (s), 137.5 (d), 145.7 (s), 149.7 (s), 150.3 (s), 202.7 (s). DCI-MS *m*/*z* (rel intensity) 366 ($[M + H]^+$, 100), 383 ($[M + NH_4]^+$, 82);

HRMS (FAB) calcd for $C_{18}H_{18}Cl_2NOS$ $(M + H)^+$ *m/z* 366.0486, found 366.0500.

1-{2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl}-hept-6-en-1-one (35) was obtained by PCC oxidation of **33** (110 mg, 0.29 mmol) in 82% yield as a yellow oil: IR ($CHCl_3$) 1702, 1567, 1532, 1329 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.38−1.61 (m, 2H), 1.65−1.85 (m, 2H), 1.92−2.21 (m, 2H), 2.86 (t, 2H, J = 7.2 Hz), 3.87 (s, 2H), 4.92−5.13 (m, 2H), 5.72−5.91 (m, 1H), 6.99 (s, 1H), 7.16−7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 22.7 (t), 28.2 (t), 33.5 (t), 36.1 (t), 43.9 (t), 115.0 (t), 124.0 (d), 128.2 (d), 129.4 (d), 131.9 (d), 133.3 (s), 134.9 (s), 138.1 (d), 145.6 (s), 149.7 (s), 150.3 (s), 202.8 (s).

{2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl}-(4-methylphenyl)methanone (19). To a slurry of **16** (430 mg, 1.10 mmol) in a 1:1 mixture of CH_3OH and H_2O (6 mL) was added $NaIO_4$ (246 mg, 1.15 mmol) at 0 °C; then the mixture was warmed to room temperature. After 15−20 days 5 mL of CH_2Cl_2 was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified over chromatography (EtOAc:petroleum ether 20:80) to give 380 mg (85%) of sulfoxide **19** as a white solid: mp 162−164 °C; IR (KBr) 1668, 1603, 1570, 1532, 1327, 1085, 1045 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.45 (s, 3H), 3.79 (d, 1H, J = 12.8 Hz), 3.92 (d, 1H, J = 12.8), 7.15−7.85 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.8 (q), 60.4 (t), 123.7 (d), 125.2 (d), 129.3 (d), 129.7 (d), 129.9 (d), 131.7 (d), 133.4 (s), 133.5 (s), 142.5 (s), 143.5 (s), 145.9 (s), 147.0 (s), 150.7 (s), 191.9 (s). DCI-MS *m/z* (rel intensity) 404 ($[M + H]^+$, 100), 421 ($[M + NH_4]^+$, 84); HRMS (FAB) calcd. for $C_{20}H_{16}Cl_2NO_2S$ $(M + H)^+$ *m/z* 404.0279, found 404.0262. Anal. Calcd for $C_{20}H_{15}Cl_2NO_2S$: C, 59.43; H, 3.73; N, 3.46. Found: C, 59.29; H, 3.78; N, 3.52.

{2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl}-(phenyl)methanone (18) was obtained by similar oxidation of sulfide **15** (640 mg, 1.71 mmol) in 68% yield as a yellow oil: IR (KBr) 1665, 1605, 1577, 1532, 1333, 1085, 1045 cm^{-1}; ^1H NMR (200 MHz $CDCl_3$:CCl_4 7:3) δ 3.74 (d, 1H, J = 12.9 Hz), 3.90 (d, 1H, J = 12.9 Hz), 7.18 (s, 1H), 7.22−7.92 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 60.1 (t), 123.7 (d), 125.3 (d), 129.0 (d), 129.3 (d), 129.7 (d), 131.8 (d), 133.3 (s), 134.8 (d), 135.8 (s), 142.5 (s), 143.7 (s), 147.0 (s), 150.9 (s), 192.4 (s). Anal. Calcd for $C_{19}H_{13}Cl_2NO_2S$: C, 58.48; H, 3.35; N, 3.58. Found: C, 58.19; H, 3.13; N, 3.68.

{2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl}-(4-methoxyphenyl)methanone (20) was obtained by the oxidation of keto sulfide **17** (390 mg, 0.96 mmol) in 91% yield as a white crystalline solid: mp 142−143 °C; IR (KBr) 1687, 1595, 1324, 1153, 1041 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.73 (d, 1H, J = 12.9 Hz), 3.84 (s, 3H), 3.87 (d, 1H, J = 12.9 Hz), 6.90 (d, 2H, J = 8.9 Hz), 7.14 (s, 1H), 7.24−7.58 (m, 5H), 7.72 (d, 2H, J = 8.69); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 55.5 (q), 60.4 (t), 114.3 (d), 123.7 (d), 125.1 (d), 128.9 (s), 129.3 (d), 131.6 (d), 132.2 (d), 133.7 (s), 142.7 (s), 143.5 (s), 146.9 (s), 150.5 (s), 164.8 (s), 190.5 (s).

2,6-Dichloro-4-[(phenylsulfinyl)methyl]nicotinaldehyde (11) was obtained by similar oxidation of sulfide **10** (90 mg, 0.3 mmol) by $NaIO_4$ in 76% yield as a white solid: mp 150−152 °C; IR (KBr) 1705, 1564, 1527, 1327, 1035 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 4.08 (d, 1H, J = 11.8), 4.75 (d, 1H, J = 11.9 Hz), 7.05 (s, 1H), 7.50 (br s, 5H), 10.26 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 59.1 (t), 124.0 (d), 125.6 (s), 127.1 (d), 129.1 (d), 131.5 (d), 142.4 (s), 145.0 (s), 153.6 (s), 154.0 (s), 190.1 (d). FAB MS *m/z* (rel intensity) 626 ($2M^+$, 9), 314 ($[M + H]^+$, 100), 273 (6), 188 ($[M - C_6H_5SO]^+$, 28), 165 (6); HRMS (FAB) calcd for $C_{13}H_{10}Cl_2NO_2S$ $(M+H)^+$ *m/z* 313.9809, found 313.9819. Anal. Calcd for $C_{13}H_9Cl_2NO_2S$: C, 49.70; H, 2.88; N, 4.45. Found: C, 49.81; H, 2.93; N, 4.29.

1-{2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl}hex-5-en-1-one (36) was obtained by similar oxidation of keto sulfide **34** (90 mg, 0.246 mmol) by $NaIO_4$ in 85% yield as a yellow oil: IR ($CDCl_3$) 1702, 1530, 1328, 1123, 1085 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.78−1.95 (m, 2H), 2.12−2.27 (m, 2H), 2.96−3.02 (m, 2H), 3.71 (d, 1H, J = 12.8 Hz), 4.12 (d, 1H, J = 12.9 Hz), 4.99−5.11 (m, 2H), 5.71−5.88 (m, 1H), 6.83 (s, 1H), 7.42−7.58 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 22.6 (t), 32.7 (t), 43.6 (t), 59.0 (t), 115.5 (t), 123.9 (d), 125.3 (d), 129.5 (d), 132.0 (d), 136.0 (s), 137.6 (d), 141.7 (s), 142.0 (s), 146.0 (s), 150.3 (s), 203.4 (s). Anal. Calcd for $C_{18}H_{17}Cl_2NO_2S$: C, 56.56; H, 4.47; N, 3.66. Found: C, 56.69; H, 4.53; N, 3.51.

1-{2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl}hept-6-en-1-one (37) was obtained by similar oxidation of keto sulfide **35** (100 mg, 0.263 mmol) by NaIO4 in 77% yield as yellow oil: IR ($CHCl_3$) 1702, 1633, 1563, 1392, 1094, 1048 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.38−2.19 (m, 6H), 2.81−3.09 (m, 2H), 3.72 (d, 1H, J = 12.9 Hz), 4.11 (d, 1H, J = 12.9 Hz), 4.89−5.16 (m, 2H), 5.69−5.91 (m, 1H), 6.85 (s, 1H), 7.41−7.82 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 22.9 (t), 28.2 (t), 33.6 (t), 43.7 (t), 57.7 (t), 114.9 (t), 126.2 (d), 128.4 (d), 129.7 (d), 134.7 (d), 136.5 (s), 138.2 (s), 138.3 (d), 139.2 (s), 146.5 (s), 150.6 (s), 203.3 (s). Anal. Calcd for $C_{19}H_{19}Cl_2NO_2S$; C, 57.57; H, 4.82; N, 3.53. Found: C, 57.80; H, 5.01; N, 3.51.

General Procedure for Pummerer−Diels−Alder Reaction. Conditions A: A mixture containing acetic anhydride (10 mmol), appropriate dienophile (4 mmol), and a catalytic amount of *p*-toluenesulfonic acid in dry toluene (10 mL) was heated at reflux under argon. To this mixture was added a toluene solution of keto-sulfoxide (1 mmol) dropwise over a period of 10 min. After addition was complete the yellow mixture was heated at reflux for an additional 1 h. The reddish yellow solution was cooled and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was concentrated and purified by preparative layer chromatography.

Conditions B: A mixture containing heptafluorobutyric anhydride (10 mmol), appropriate dienophile (4 mmol), and a catalytic amount of *p*-toluenesulfonic acid was heated at reflux under argon. To this mixture was added keto-sulfoxde (1 mmol) in dry toluene dropwise over a period of 10 min. After complete addition, the yellow mixture was heated at reflux for an additional 1 h. The reddish yellow solution was cooled and washed with saturated $NaHCO_3$ solution. The organic layer was concentrated and purified by preparative layer chromatography.

Dimethyl 1,3-Dichloro-5-(phenylthio)isoquinoline-6,7-dicarboxylate (21) was prepared following conditions A from sulfoxide **11** (100 mg, 0.32 mmol) in the presence of dimethyl maleate (0.15 mL, 1.27 mmol) in 44% yield as a white crystalline solid: mp 109−111 °C; IR (KBr) 1706, 1569, 1530, 1327 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.98 (s, 3H), 4.01 (s, 3H), 7.30−7.07 (m, 5H), 8.21 (d, 1H, J = 0.9 Hz), 9.10 (d, 1H, J = 0.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.0 (q), 53.2 (q), 118.9 (d), 125.5 (s), 127.0 (d), 127.2 (s), 128.5 (d), 128.9 (s), 129.4 (d), 131.9 (d), 134.9 (s), 142.8 (s), 144.5 (s), 147.8 (s), 152.9 (s), 164.0 (s), 167.0 (s). Anal. Calcd for $C_{19}H_{13}Cl_2NO_4S$: C, 54.03; H, 3.09; N, 3.31. Found: C, 53.89; H, 3.25; N, 3.42.

Dimethyl 3,5-Dichloro-1-(4-methylphenyl)-8-(phenylthio)-11-oxa-4-azatricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene-9,-10-dicarboxylate (26) was prepared by the treatment of keto-sulfoxide **19** (100 mg, 0.247 mmol) with dimethyl maleate (0.124 mL, 1 mmol) under conditions B in 37% yield as a yellowish white solid: mp 199−200 °C; IR (KBr) 1742, 1633, 1595, 1336 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.41 (s, 3H), 3.56 (s, 6H), 3.58 (d, 1H, J = 11 Hz), 4.14 (d, 1H, J = 11 Hz), 7.19−7.69 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.4 (q), 52.0 (q), 52.4 (q), 52.6 (d), 53.6 (d), 90.0 (s), 93.7 (s), 118.0 (d), 128.1 (d), 129.2 (d), 129.6 (d), 131.1 (s), 135.5 (d), 137.8 (s), 139.4 (s), 143.8 (s), 148.8 (s), 157.5 (s), 167.7 (s), 169.0 (s). FAB MS *m/z* (rel intensity) 530 ($[M + H]^+$, 11), 386 (3), 273 (3), 235 (6), 165 (4); HRMS (FAB) calcd for $C_{26}H_{22}Cl_2NO_5S$

$(M+H)^+$ *m*/*z* 530.0596, found 530.0589. Anal. Calcd for $C_{26}H_{21}Cl_2NO_5S$: C, 58.88; H, 3.98; N, 2.64. Found: C, 58.65; H, 3.94; N, 2.87.

Dimethyl 3,5-Dichloro-1-phenyl-8-(phenylthio)-11-oxa-4-azatricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene-9,10-dicarboxylate (25) was prepared in a similar manner (conditions B) from keto sulfoxide **18** (100 mg, 0.26 mmol) in 33% yield as a yellowish white solid: mp 174−175 °C; ^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.57 (s, 6H), 3.61 (d, 1H, J = 11.2 Hz), 4.16 (d, 1H, J = 11.2 Hz), 7.25−7.70 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 51.9 (q), 52.3 (q), 52.5 (d), 53.5 (d), 89.8 (s), 93.7 (s), 117.9 (d), 127.7 (s), 127.9 (s), 128.0 (d), 128.4 (d), 129.1 (d), 129.4 (d), 129.5 (d), 133.9 (s), 135.3 (d), 137.7 (s), 148.7 (s), 157.2 (s), 167.6 (s), 168.9 (s). Anal. Calcd for $C_{25}H_{19}Cl_2NO_5S$: C, 58.15; H, 3.70; N, 2.71. Found: C, 58.45; H, 3.38; N, 2.91.

Dimethyl 3,5-Dichloro-1-(4-methoxyphenyl)-8-(phenylthio)-11-oxa-4-azatricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene-9,10-dicarboxylate (27) was prepared in a similar manner (conditions B) from keto sulfoxide **20** (110 mg, 0.26 mmol) in 40% yield as a white solid: mp 164−166 °C; IR (KBr) 1743, 1596, 1339, 1246 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.55 (s, 3H), 3.56 (s, 3H), 3.57 (d, 1H, J = 10.9 Hz), 3.89 (s, 3H), 4.13 (d, 1H, J = 10.9 Hz), 6.89−7.62 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 51.9 (q), 52.3 (q), 52.5 (d), 53.5 (d), 55.0 (q), 89.7 (s), 93.4 (s), 113.8 (d), 117.9 (d), 125.8 (s), 128.0 (s), 129.1 (d), 129.4 (d), 129.5 (d), 135.4 (d), 137.6 (s), 143.7 (s), 148.7 (s), 157.3 (s), 160.4 (s), 167.5 (s), 168.9 (s). Anal. Calcd for $C_{26}H_{21}Cl_2NO_6S$: C, 57.15; H, 3.87; N, 2.56. Found: C, 56.98; H, 3.97; N, 2.43.

[2,6-Dichloro-3-(4-methoxybenzoyl)pyridin-4-yl](phenylthio)methyl acetate (29) was obtained along with **27** via a Pummerer reaction of keto-sulfoxide **20** under conditions A as a white crystalline solid: mp 123−124 °C; IR (KBr) 1763, 1573, 1661, 1569, 1318 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.98 (s, 3H), 3.88 (s, 3H), 6.75−7.91 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 20.6 (q), 55.5 (q), 77.4 (d), 114.2 (d), 120.6 (d), 128.8 (s), 129.2 (d), 129.5 (d), 129.9 (s), 130.7 (s), 132.3 (d), 134.6 (d), 147.2 (s), 149.7 (s), 150.7 (s), 164.8 (s), 168.3 (s), 189.9 (s). FAB MS *m*/*z* (rel intensity) 461 (M^+, 1), 446 ($[M - CH_3]^+$; 12), 434 ($[M - CO]H^+$, 10), 386 (12), 364 (4), 336 (2), 273 (2), 235 (3), 165 (3). Anal. Calcd for $C_{22}H_{17}Cl_2NO_4S$: C, 57.15; H, 3.70; N, 3.02. Found: C, 57.29; H, 3.58; N, 2.97.

Methyl 3,5-Dichloro-1-(4-methoxyphenyl)-8-(phenylthio)-11-oxa-4-azatricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene-10-carboxylate (30). To a mixture of heptafluorobutyric anhydride (0.47 mL, 1.9 mmol) and a catalytic amount of *p*-toluenesulfonic acid in 5 mL of toluene heated at reflux was added a toluene solution of keto-sulfoxide **20** (80 mg, 0.19 mmol) over a period of 10 min under argon atmosphere. The bright yellow mixture was allowed to reflux for an additional 1 h, concentrated under reduced pressure, and purified by chromatography (EtOAc: petroleum ether 5:95) quickly. The intermediate 4,6-dichloro-3-(4-methoxyphenyl)-1-(phenylthio)furo[3,4-*c*]pyridine (**24**) (40 mg, 52% yield) was obtained as a yellow oil: IR ($CDCl_3$) 1604, 1508, 1259 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.01 (d, 2H, J = 8.8 Hz), 7.11−7.35 (m, 5H), 7.75 (d, 2H, J = 8.8 Hz). To a well-stirred toluene (5 mL) solution of **24** (40 mg, 0.099 mmol) was added methyl acrylate (0.068 mL, 0.76 mmol) and the mixture was heated at reflux for 1 h under argon. The resulting yellow solution was triturated with 5 mL of ether, washed with H_2O, and concentrated under reduced pressure. Purification of the crude product by preparative layer chromatography yielded a mixture of two isomers (23 mg, 46% yield) which on crystallization gave **30** as the major isomer (mp 117−119 °C): IR (KBr) 1736, 1575, 1320, 1220 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.12 (dd, 1H, J_1 = 12.2 Hz, J_2 = 4.2 Hz), 2.58 (dd, 1H, J_1 = 12.2 Hz, J_2 = 10.2 Hz), 3.57 (s, 3H), 3.86 (s, 3H), 3.91 (dd, 1H, J_1 = 10.2 Hz, J_2 = 4.2 Hz), 6.91−7.10 (m, 2H), 7.16 (s, 1H), 7.25−7.39 (m, 3H), 7.51−7.68 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.8 (t), 47.7 (d), 52.4 (q), 55.3 (q), 90.4 (s), 92.8 (s), 113.8 (d), 114.9 (d), 125.9 (s), 129.0 (d), 129.1 (d), 129.3 (s), 130.0 (d), 134.2 (d), 136.7 (s), 143.7 (s), 149.6 (s), 160.0 (s), 160.4 (s), 170.9 (s).

When the reaction was conducted in one pot (cf. conditions B), the overall yield of products **30** and **31** was higher (46%).

1,3-Dichloro-5-(phenylthio)-8,9-dihydro-7*H*-cyclopenta[*h*]isoquinoline (42) was prepared in a similar manner (conditions B) from keto-sulfoxide **36** (50 mg, 0.13 mmol) in 67% yield as a white crystalline solid: mp 109−110 °C; IR (KBr) 1577, 1538, 1278, 1177 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20 (quint, 2H, J = 7.6 Hz), 3.03 (t, 2H, J = 7.7 Hz), 3.74 (t, 2H, J = 7.5 Hz), 7.01−7.45 (m, 5H), 7.78 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.3 (t), 33.3 (t), 36.4 (t), 118.4 (d), 124.9 (s), 126.8(d), 128.1 (s), 129.2 (d), 129.3 (d), 134.3 (s), 135.5 (d), 140.3 (s), 141.5 (s), 142.7 (s), 146.0 (s), 149.9 (s). Anal. Calcd for $C_{18}H_{13}Cl_2NS$: C, 62.42; H, 3.78; N, 4.04. Found: C, 62.24; H, 3.55; N, 4.29.

1,3-Dichloro-5-(phenylthio)-7,8,9,10-tetrahydrobenzo[*h*]isoquinoline (43) was prepared from keto sulfoxide **37** (40 mg, 0.1 mmol) by similar methodology in 56% yield: IR (KBr) 1574, 1539, 1333, 1112, 1025 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$: CCl_4 7:3) δ 1.78−1.98 (m, 4H), 2.79−3.05 (m, 2H), 3.45−3.63 (m, 2H), 7.01−7.41 (m, 5H), 7.60 (s, 1H), 8.17 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.7 (t), 23.2 (t), 31.1 (t), 31.2 (t), 118.3 (d), 126.8 (d), 127.3 (s), 127.9 (s), 129.0 (d), 129.4 (d), 135.7 (s), 136.1 (s), 138.5 (s), 140.8 (d), 141.0 (s), 142.8 (s) 149.0 (s). FAB MS *m*/*z* (rel intensity) 360 ($[M + H]^+$, 21), 273 (3), 235 (6), 165 (5); HRMS (FAB) calcd for $C_{19}H_{16}Cl_2NS$ $(M+H)^+$ *m*/*z* 360.0380, found 360.0381. Anal. Calcd for $C_{19}H_{15}Cl_2NS$: C, 63.34; H, 4.19; N, 3.88. Found: C, 62.98; H, 4.35; N, 4.29.

Dimethyl 1,3-Dichloro-8-(4-methylphenyl)-5-(phenylthio)isoquinoline-6,7-dicarboxylate (45). To a stirred solution of oxa-bridged diester **26** (80 mg, 0.15 mmol) in 5 mL of toluene was added DBU (0.22 mL, 1.5 mmol) dropwise at room temperature. The mixture was heated at reflux for 1.5 h giving a reddish yellow solution, cooled, washed with 10% HCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (EtOAc:petroleum ether 10:90) gave 42 mg (55%) of **45** as a yellow crystalline solid: mp 160−161 °C; IR (KBr) 1735, 1585, 1363, 1333, 1062 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.44 (s, 3H), 3.47 (s, 3H), 3.87 (s, 3H), 7.08−7.40 (m, 9H), 8.36 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.5 (q), 52.5 (q), 53.0 (q), 118.9 (d), 125.0 (s), 127.1 (d), 127.8 (s), 128.6 (d), 128.7 (d), 129.5 (d), 133.5 (s), 134.3 (s), 135.2 (s), 138.5 (s), 141.4 (s), 141.6 (s), 142.8 (s), 146.0 (s), 151.8 (s), 166.6 (s), 166.9 (s). FAB MS *m*/*z* (rel intensity) 512 ($[M + H]^+$, 21), 480 ($[M - OCH_3]^+$, 9), 412 (2), 273 (3), 235 (6), 165 (5). Anal. Calcd for $C_{26}H_{19}Cl_2NO_4S$: C, 60.95; H, 3.73; N, 2.73. Found: C, 60.92; H, 3.85; N, 2.89.

Dimethyl 1,3-Dichloro-8-phenyl-5-(phenylthio)-isoquinoline-6,7-dicarboxylate (44) was prepared similarly by treatment of **25** (150 mg, 0.29 mmol) with DBU in 53% yield: mp 178−179 °C; IR (KBr) 1737, 1584, 1375, 1316, 1062 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3. 43 (s, 3H), 3.88 (s, 3H), 7.15−7.32 (m, 6H), 7.35−7.48 (m, 4H), 8.37 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 52.5 (q), 53.0 (q), 119.0 (d), 124.8 (s), 127.2 (d), 127.9 (d), 128.0 (s), 128.6 (d), 128.8 (d), 129.5 (d), 129.6 (d), 133.4 (s), 135.0 (s), 137.3 (s), 141.1 (s), 141.6 (s), 142.7 (s), 146.2 (s), 151.7 (s), 166.6 (s), 166.9 (s).

Dimethyl 1,3-Dichloro-8-(4-methoxyphenyl)-5-(phenylthio)isoquinoline-6,7-dicarboxylate (46) was prepared by similar treatment of **27** (60 mg, 0.11 mmol) with DBU in 45% yield as a white crystalline solid: mp 190−192 °C; IR (KBr) 1740, 1554, 1365, 1332, 1062 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.51 (s, 3H), 3.87 (s, 6H), 6.91−7.01 (m, 2H), 7.12−7.34 (m, 7H), 8.38 (s, 1H). Anal. Calcd for $C_{26}H_{19}Cl_2NO_5S$: C, 59.10; H, 3.62; N, 2.65. Found: C, 59.32; H, 3.59; N, 2.55.

Dimethyl 3,5-Dichloro-1-(4-methylphenyl)-8-(phenylsulfonyl)-11-oxa-4-azatricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene-9,10-dicarboxylate (47). To a mixture of oxa-bridged diester **26** (140 mg, 0.264 mmol) and $NaIO_4$ (240 mg, 1.12 mmol) in a 10 mL mixture of CH_3CN, CCl_4, H_2O (1:1:3) was added a

catalytic amount of $RuCl_3 \cdot xH_2O$. The solution was stirred at room temperature for 2 h and then diluted with 5 mL of CH_2Cl_2. The resulting two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude black residue was diluted with 20 mL of diethyl ether and filtered through a short column of silica gel, which on concentration gives 140 mg (94%) of **47** as a white crystalline solid: mp 202−203 °C; IR (KBr) 1750, 1591, 1333, 1164 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.58 (s, 3H), 3.66 (s, 3H), 4.21 (d, 1H, J = 11.2 Hz), 4.29 (d, 1H, J =11.2 Hz), 7.12 (s, 4H), 7.51−7.99 (m, 5H), 7.93 (s, 1H);^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3 (q), 50.8 (d), 52.6 (q), 53.0 (d), 91.8 (s), 98.0 (s), 118.3 (d), 127.8 (d), 129.2 (d), 129.3 (d), 129.8 (s), 130.2 (d), 134.7 (s), 135.1 (d), 137.6 (s), 140.0 (s), 144.5 (s), 149.2 (s), 152.8 (s), 167.2 (s), 168.4 (s). DCI-MS *m/z* (rel intensity) 562 ($[M + H]^+$, 100), 579 ($[M + NH_4]^+$, 14); HRMS (FAB) calcd for $C_{26}H_{22}Cl_2NO_7S$ $(M + H)^+$ *m/z* 562.0494, found 562.0507.

Dimethyl 1,3-Dichloro-5-hydroxy-8-(4-methylphenyl)-isoquinoline-6,7-dicarboxylate (48). To a stirred solution of sulfone **47** (140 mg, 0.25 mmol) in 10 mL of toluene was added DBU (0.075 mL, 0.5 mmol) at room temperature and the mixture was then heated to reflux for 1 h under argon. The reddish yellow solution was washed with 10% HCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue on chromatographic purification (EtOAc: petroleum ether 30:70) gave 80 mg (77%) of **48** as a white crystalline solid: mp 209 °C; IR (KBr) 3441, 3018, 1732, 1612, 1558, 1199 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.47 (s, 3H), 3.97 (s, 3H), 7.08 (d, 2H, J = 8.1 Hz), 7.17 (d, 2H, J = 8.0 Hz), 8.31 (s, 1H), 12.42 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (q), 51.9 (q), 53.6 (q), 106.0 (s), 116.2 (d), 126.4 (s), 128.2 (d), 128.7 (s), 130.8 (d), 133.4 (s), 134.3 (s), 137.9 (s), 143.7 (s), 144.4 (s), 150.4 (s), 167.7 (s), 169.3 (s). DCI-MS *m/z* (rel intensity) 420 ($[M + H]^+$, 100), 437 ($[M + NH_4]^+$, 7); HRMS (FAB) calcd for $C_{20}H_{16}Cl_2NO_5$ $(M + H)^+$ *m/z* 420.0406, found 420.0410.

Dimethyl 1,3-Dichloro-5-methoxy-8-(4-methylphenyl)-isoquinoline-6,7-dicarboxylate (49). Diazomethane generated from *N*-nitroso *N*-methyl urea (236 mg, 2.29 mmol) and 40% aqueous KOH in diethyl ether was added to 120 mg (0.28 mmol) of **48** at 0 °C. After vigorous hand stirring the ice bath was removed and the reaction mixture was left at room temperature overnight. Ether was removed under reduced pressure and the residue on chromatographic purification (EtOAc: petroleum ether 20:80) gave 110 mg (89%) of **49** as a white solid: mp 135−137 °C; IR (KBr) 1740, 1560, 1338, 1208 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.41 (s, 3H), 3.44 (s, 3H), 3.93 (s, 3H), 4.07 (s, 3H), 7.09 (d, 2H J = 8.0 Hz), 7.17 (d, 2H, J = 8.0 Hz), 8.03 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$: CCl_4 7:3) δ 21.4 (q), 52.2 (q), 53.0 (q), 63.7 (q), 115.0 (d), 124.1 (s), 125.4 (s), 128.3 (d), 130.0 (d), 134.1 (s), 134.4 (s), 134.6 (s), 136.5 (s), 137.9 (s), 144.9 (s), 151.3 (s), 153.0 (s), 165.4 (s), 167.0 (s). Anal. Calcd for $C_{21}H_{17}Cl_2NO_5$: C, 58.09; H, 3.94; N, 3.22. Found: C, 58.19; H, 3.89; N, 3.41.

5,7-Dichloro-9-methoxy-4-(4-methylphenyl)furo[3,4-*g*]-isoquinolin-3(1*H*)-one (50). To a stirred solution of **49** (50 mg, 0.11 mmol) in 10 mL of CH_2Cl_2 cooled to −78 °C was added 0.25 mL of DIBAL-H (1.0 M solution in toluene) dropwise under argon. The resulting mixture was stirred for 30 min at the same temperature and then allowed to warm to 0 °C. The reaction mixture was quenched with 2 mL of saturated aqueous NH_4Cl solution and stirred for 30 min, then it was acidified with 20% HCl and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduce pressure and on preparative layer chromatographic purification gave 40 mg (90%) of **50** as a white crystalline solid: mp 252−254 °C; IR (KBr) 1779, 1573, 1460, 1333 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3H), 4.19 (s, 3H), 5.59 (s, 2H), 7.01−7.35 (m, 4H), 8.14 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5 (q), 59.9 (q), 65.8 (t), 114.8 (d), 124.5 (s), 125.7 (s), 128.5 (d), 129.0 (s), 129.3 (d), 131.7 (s), 137.0 (s), 137.7 (s), 138.2 (s), 145.3 (s), 147.8 (s), 152.5 (s), 167.3 (s). FAB MS *m/z* (rel intensity) 374 ($[M + H]^+$, 8), 329 ($[M - CO_2]^+$, 3) 273 (6), 242 (5), 165 (6); HRMS (FAB) calcd for $C_{19}H_{14}Cl_2NO_3$ $(M+H)^+$ *m/z* 374.0351, found 374.0351. Anal. Calcd for $C_{19}H_{13}Cl_2NO_3$: C, 60.98; H, 3.49; N, 3.74. Found: C, 60.71; H, 3.32; N, 3.85.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **8**, **9**, **16**, **19**, **26**, **30**, **32**, **34**, **42**, **45**, **47**, **49**, and **50**. This material is available free of charge via the Internet at http://pubs.acs.org.

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