BENZO[*H*]-1,6-NAPHTHYRIDINE SYNTHESIS VIA INTRAMOLECULAR DIELS-ALDER REACTIONS OF ARYL OXAZOLES: SYNTHETIC APPROACH TO 2-BROMOLEPTOCLINIDINONE[1]

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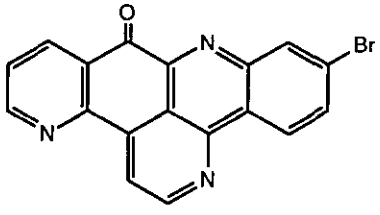
Abstract - A new route for the synthesis of benzo[*h*]-1,6-naphthyridines is described. The method involves the intramolecular Diels-Alder cycloaddition of aryl oxazoles with substituted acrylamides to give pyridines and was developed as a route to the antileukemic aromatic alkaloid 2-bromoleptoclinidinone.

In 1987 Bloor and Schmitz published the structure of a novel brominated pentacyclic aromatic alkaloid 2-bromoleptoclinidinone (**1**).[3] This compound, isolated from an ascidian, showed good cytotoxicity vs. PS (ED_{50} 0.4 μg/ml). Because of its unusual structure and good biological activity, we began a program in 1988 aimed at the total synthesis of **1** and its analogues. However, in 1988, Kobayashi and coworkers isolated a closely related antileukemic alkaloid, ascididemnin, from a marine tunicate and determined its structure to be **2**.[4] The appearance of this new report prompted Schmitz to reexamine the structural assignment and in 1989, a structural revision was published indicating **3** as the correct structure for 2-bromoleptoclinidinone.[5] We wish to report here the full details of our approach to the synthesis of the original structure of 2-bromoleptoclinidinone (**1**), a route which involves the intramolecular Diels-Alder cycloaddition of aryl oxazoles to give benzo[*h*]-1,6-naphthyridines.



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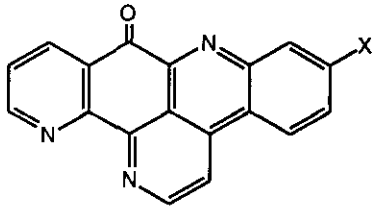
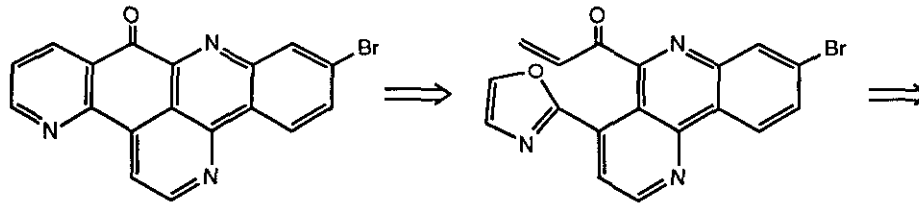


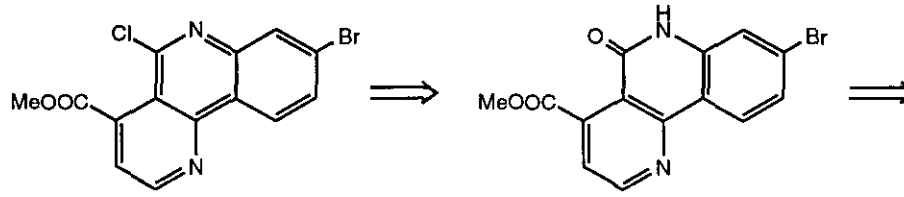
2 X = H
3 X = Br

A retrosynthetic analysis applied to **1** indicates that the required pentacyclic aromatic system could be easily assembled from the simple aromatic **8** by two successive intramolecular Diels-Alder reactions of oxazoles with

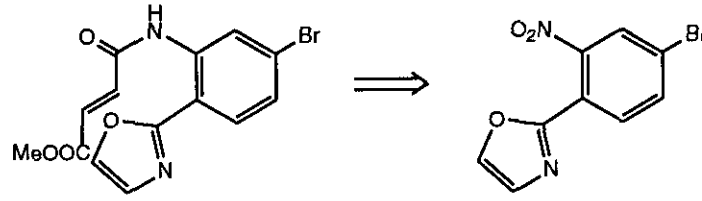
activated alkenes. Thus conversion of **8** into the β-carbomethoxyacrylamide (**7**) followed by cycloaddition would afford the tricyclic aromatic benzo[*h*]-1,6-naphthyridine (**6**). Conversion of the amide to the chloroimine (**5**) and then to the oxazole enone (**4**) would set the stage for a final intramolecular Diels-Alder reaction to produce 2-bromoleptoclinidinone (**1**). Diels-Alder reactions of oxazoles and activated alkenes to give pyridines are well-known,[6] having first been studied in the 1950s by Kondrat'eva.[7] The yields in intermolecular cycloadditions are not always high.[8] The intramolecular version of this process has been used recently by Weinreb and Levin as the key high-yielding step in a synthesis of eupolauramine.[9] Thus it seemed reasonable that the two related intramolecular Diels-Alder reactions of aryl oxazoles with activated alkenes, e.g., **7** → **6** and **4** → **1**, would allow us to efficiently prepare **1**.



1 **4**



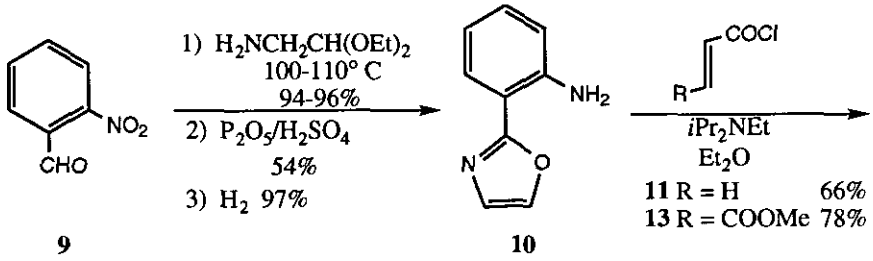
5 **6**



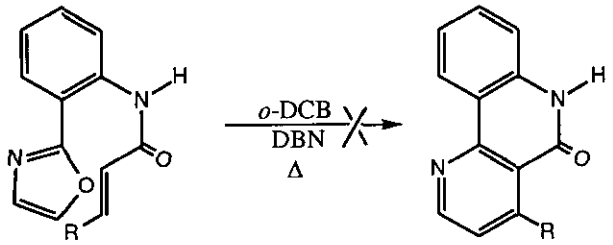
7 **8**

We decided to first examine the synthetic route on the simpler des-bromo system to prepare leptoclinidinone. Therefore the amine (**10**) was prepared from 2-nitrobenzaldehyde (**9**) in three steps[10] and acylated with acryloyl chloride (**11**) to give the amide (**12**) in good yield. The first attempts at cyclization of **12** under standard conditions,[9] e.g., heating for an extended period in *o*-dichlorobenzene (*o*-DCB) in the presence of diazabicyclononene (DBN), were unsuccessful, returning only starting material and the deacylated amine. A more reactive

dienophile was then attached by acylation of the amine (**10**) with the ester acid chloride (**13**)[11] to give the amide (**14**) in high yield. Again thermolysis of **14** in the presence of base did not produce any desired product. It is likely that compounds (**12**) and (**14**) exist predominately in a conformation which allows an internal hydrogen

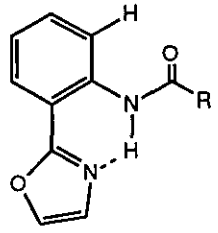


9 **10**

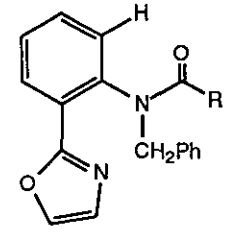


12 R = H
14 R = COOMe

bond between the amide NH and the oxazole nitrogen, which would cause the intramolecular Diels-Alder reaction to be slower than expected. The proton ortho to the amide in **12** and **14** (and in the *N*-benzoyl analogue **15**) resonates at very low field (8.83 to 8.99) compared to the analogous proton in the *N*-benzyl analogues (**16**) and (**17**), which resonates 2 ppm higher (presumably due to a 90° rotation about the aryl-*N* bond). We therefore decided to investigate the use of these *N*-alkylamides in the cycloaddition.



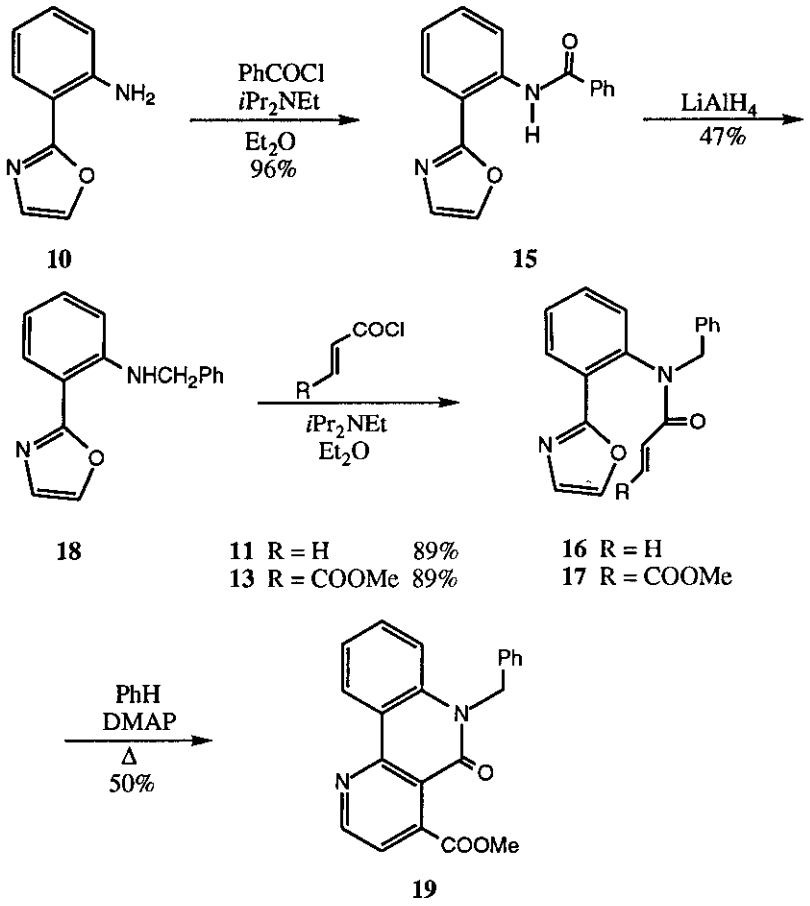
	δ
12 R = $CH=CH_2$	8.86
14 R = (*E*)-CH=CH-COOMe	8.83
15 R = C_6H_5	8.99



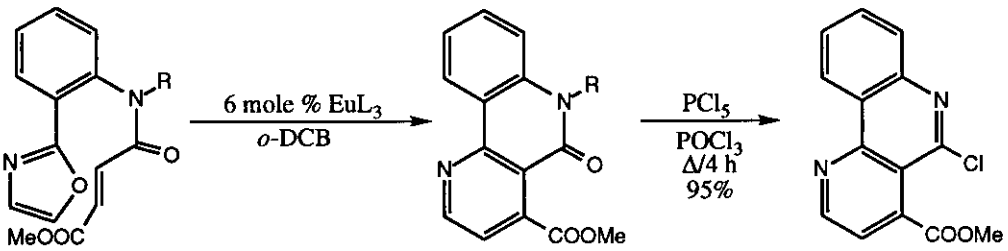
	δ
16 R = $CH=CH_2$	6.87
17 R = (*E*)-CH=CH-COOMe	6.80

Acylation of the amine (**10**) with benzoyl chloride afforded in excellent yield the amide (**15**), which was reduced to the benzylamine (**18**). Acylation with acryloyl chloride gave the *N*-benzylacrylamide (**16**). In like fashion the

ester amide (**17**) was prepared from **18** and **13** in good yield. Although heating the simple acrylamide (**16**) gave very little cycloadduct, warming of the ester amide (**17**) in benzene for 18 h with 0.75 eq. of DMAP afforded the desired tricycle (**19**) in 50% purified yield. Thus this procedure is a useful route to benzo[*h*]-1,6-naphthyridine systems.



At this time Levin published the results of his study of the effects of europium salts on intramolecular oxazole Diels-Alder reactions.[12] We therefore heated the amide (**17**) in *o*-dichlorobenzene at 75°C for 9 h in the presence of 6 mole % $Eu(hfc)_3$ and obtained the desired tricycle (**19**) in 87% yield. These reaction conditions worked equally well on the secondary amide. Thus heating the amide (**14**) in deoxygenated *o*-dichlorobenzene at reflux for 18 h in the presence of 6 mole % $Eu(fod)_3$ afforded the desired benzo[*h*]-1,6-naphthyridine (**20**) in 85% yield as yellow crystals. This unsubstituted lactam was then easily converted into the desired chloroimine (**21**) in 95% yield by refluxing it with $PCl_5/POCl_3$. All that was left to complete the synthesis of leptoclinidinone was to

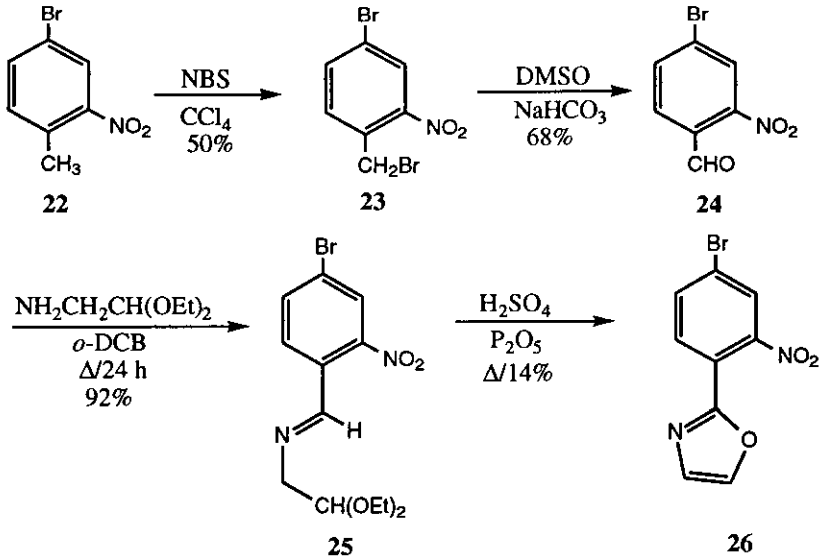


17 R = CH_2Ph L = hfc 75°C/9 h 87% **19** R = CH_2Ph **21**
14 R = H L = fod Δ/18 h 85% **20** R = H

convert the aryl chloride to an enone and the aryl ester to a 2-oxazolyl unit and carry out the final Diels-Alder cycloaddition.

Concurrent with this work, the preparation of the required bromo compound was under way. The known 4-bromo-2-nitrotoluene[13] (**22**) was brominated to give the bromomethyl compound (**23**) in 50% yield along with 36% recovered starting material. Oxidation to the aldehyde (**24**) was effected with DMSO and mild base. Condensation of the aldehyde (**24**) with aminoacetaldehyde diethyl acetal gave the imine (**25**) in 92% yield. Final oxidative cyclization of **25** by heating with sulfuric acid and P_2O_5 gave the desired oxazole (**26**) in an up optimized yield of 14%. At this point, the structural revision of 2-bromoleptoclinidinone (**3**)[5] appeared and all further work on the incorrect structure (**1**) was terminated.

We have shown the utility of intramolecular Diels-Alder reactions of aryloxazoles with carbomethoxyacrylamides as a method for the high-yielding preparation of benzo[*h*]-1,6-naphthyridine systems.



22 **23** **24**

25 **26**

EXPERIMENTAL

^{1}H Nmr were recorded on a Bruker AF-200 spectrometer, operating at 200.132 MHz, a Bruker AM-360 spectrometer, operating at 360.134 MHz or a AM-500 spectrometer, operating at 500.132 MHz, and are so noted. ^{13}C Nmr spectra were also recorded on the AF-200, AM-360 and AM-500, operating at 50.323, 90.556 and 125.760 MHz, respectively, and are so noted. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer or a Perkin-Elmer series 1500 FTIR. Melting points were obtained on a Fischer-Johns melting point apparatus and are uncorrected. High and low resolution mass spectra were recorded on a double focusing instrument (AEI model MS-902). Gas chromatography analysis were performed using a Hewlett-Packard 5790A series gas chromatograph with a SE-30 crosslinked methyl silicone gum column (12 m x 0.2 mm x 0.33 mm film thickness). Microanalyses were conducted by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. ^{1}H Nmr and ^{13}C nmr data are reported in ppm (δ) downfield from tetramethylsilane. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Second order spectra in which couplings cannot be obtained by inspection are reported as multiplets and the line spacings are given in Hertz (Hz). Ir data are reported in wave numbers (cm^{-1}). The following abbreviations are used to indicate qualitative *intensities: vs = very strong, s = strong, m = medium, w = weak, br = broad. All significant bands are reported.* Thin layer chromatography was performed using Merck silica gel 60 F_{254} 0.2 mm plates. Visualization was accomplished using ultraviolet light or ceric sulfate (1.5 g) and ammonium molybdate (1.0 g) in 10% aqueous sulfuric acid (100 ml). Flash chromatography was carried out according to the method of Still, *et al.*[14] Solvent systems are reported as either volume:volume mixtures or volume percent mixture. Concentration *in vacuo* or at reduced pressure refers to removal of solvent by use of a Büchi rotary evaporator with a heated water bath under water aspirator pressure, except for *o*-dichlorobenzene which was removed under vacuum pump pressure. All inorganic solutions are aqueous and concentrations are indicated in percent weight, except brine (saturated sodium chloride) and saturated ammonium chloride. The following solvents and reagents were distilled from the indicated agent under dry nitrogen: tetrahydrofuran (THF) and ether from sodium benzophenone ketyl; methylene chloride, hexamethylphosphoramide (HMPA) and diisopropylethylamine from calcium hydride, methanol and ethanol from magnesium turnings. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under reduced pressure and dried over 4Å molecular sieves. All other reagents were purified by literature procedures.

2-[2-(*N*-Acryloylamino)phenyl]oxazole (12). To a solution of the amine[10] (**10**) (170 mg, 1.06 mmol) in ether (10 ml) at -78° C was added diisopropylethylamine (155 mg, 1.2 mol). After 15 min, acryloyl chloride

(**11**) (100 mg, 1.1 mmol) was added dropwise. After stirring 1.5 h at -78° C, the solution was warmed to room temperature. A white precipitate formed and after 2 h the reaction mixture was filtered through Celite. A pale yellow solid was obtained upon evaporation of the solvent. Purification of crude **12** by flash chromatography using 25% ether in hexanes as the eluent afforded 141 mg (62%) of **12** as white needles, mp 101-103° C. 360 MHz ^{1}H Nmr ($CDCl_3$) δ: 8.86 (1H, dd, *J* = 0.8, 8.4 Hz), 7.97 (1H, dd, *J* = 1.5, 7.9 Hz), 7.69 (1H, d, *J* = 1.0 Hz), 7.43 (1H, m), 7.26 (1H, d, *J* = 1.0 Hz), 7.12 (1H, m), 6.47 (2H, m), 5.79 (1H, dd, *J* = 1.6, 9.8 Hz). 90 MHz ^{13}C Nmr ($CDCl_3$) δ: 164.18, 160.69, 137.63, 137.50, 132.50, 131.40, 127.07, 126.88, 126.85, 122.88, 120.17, 113.33. Ir ($CDCl_3$): 3235 (m), 3110 (m), 3000 (m), 1675 (s), 1590 (vs), 1430 (s) cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70. Found: C, 67.09; H, 4.61.

Methyl (*E*)-4-[(2-[2-oxazolyl]phenyl)amino]-4-oxo-2-butenoate (14). To the oxazole (**10**) (1.41 g, 8.81 mmol) in ether (100 ml) at room temperature was added diisopropylethylamine (2.27 g, 17.6 mmol). The solution was cooled to -78° C and acid chloride[11] **13** (1.45 g, 9.69 mmol) was added dropwise. The reaction was warmed to room temperature after 30 min and stirred for 18 h. Water (100 ml) was added, the organic layer was separated and the aqueous phase was extracted with methylene chloride (3 x 75 ml). The combined organic layers were dried over $MgSO_4$, filtered and absorbed onto silica gel (9 g). Flash chromatography using 25% ether in hexanes as the eluent afforded 1.88 g (78%) of compound (**14**) as a pale yellow solid, mp 152-153° C. 200 MHz ^{1}H Nmr ($CDCl_3$) δ: 12.25 (1H, br, NH), 8.83 (1H, dd, *J* = 0.9, 8.6 Hz), 8.00 (1H, dd, *J* = 1.5, 7.9 Hz), 7.73 (1H, s), 7.46 (1H, ddd, *J* = 1.5, 7.7, 8.6 Hz), 7.32 (1H, s), 7.19 (1H, d, *J* = 15.3 Hz), 7.18 (1H, ddd, *J* = 0.9, 7.7, 7.9 Hz), 6.98 (1H, d, *J* = 15.3 Hz), 3.85 (3H, s). 50 MHz ^{13}C Nmr ($CDCl_3$) δ: 166.02, 162.16, 160.68, 138.01, 137.90, 137.12, 131.62, 130.44, 127.35, 127.05, 123.73, 120.50, 113.75, 52.25. Ir ($CDCl_3$): 1720 (s), 1680 (s), 1610 (s), 1595 (s), 1310 (vs) cm^{-1}. HRms (*m/z*): 272.0775, calcd for $C_{14}H_{12}N_2O_4$ 272.0798.

2-[2-(*N*-Benzoylamino)phenyl]oxazole (15). To the oxazole (**10**) (1.17 g, 7.3 mmol) in THF (20 ml) at room temperature was added diisopropylethylamine (2.23 g, 17.2 mmol). The solution was cooled to -78° C and benzoyl chloride (1.13 g, 8.0 mmol) was added slowly. The reaction was warmed to room temperature after 20 min and stirred for 18 h. Water (100 ml) was added, the reaction mixture was extracted with ethyl acetate (3 x 25 ml) and the organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded 1.85 g (96%) of the amide (**15**) as fine yellow crystals. The amide was used without further purification in subsequent transformations. A small portion was purified for high resolution mass spectroscopy by flash chromatography using 30% ether in hexanes as the eluent to give a white solid, mp 150-152°C. 200 MHz ^{1}H

Nmr ($CDCl_3$) δ: 12.53 (1H, br, NH), 8.99 (1H, d, J = 8.5 Hz), 8.16 (1H, dd, J = 1.8, 5.3 Hz), 8.14 (1H, s), 8.04 (1H, m), 7.70 (1H, s), 7.53 (5H, m), 7.16 (1H, m). 50 MHz ^{13}C Nmr ($CDCl_3$) δ: 166.06, 161.04, 138.01, 137.83, 135.20, 131.79, 131.67, 128.68, 127.73, 127.29, 127.17, 123.00, 120.42, 113.76. Ir ($CDCl_3$): 1678 (w), 1619 (m), 1592 (s), 1542 (s), 1500 (m), 1314 (s) cm^{-1}. HRms (*m/z*): 264.0880, calcd for $C_{16}H_{12}N_2O_2$ 264.0900.

2-[2-(*N*-Benzylamino)phenyl]oxazole (18). The amide (**15**) (1.72 g, 6.5 mmol) in THF (100 ml) was added dropwise to a mixture of lithium aluminum hydride (990 mg, 26 mmol) in THF (100 ml) at room temperature. After stirring for 5 h, the reaction mixture was quenched by the addition of water (1 ml), then 15% aqueous sodium hydroxide (1 ml), followed by water (3 ml). The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in *vacuo*. Purification of crude **18** by flash chromatography using 20% ether in hexanes as the eluent afforded 758 mg (47%) of the amine as a colorless oil. 200 MHz ^1H Nmr ($CDCl_3$) δ: 8.55 (1H, br, NH), 7.90 (1H, m), 7.61 (1H, s), 7.46-7.17 (7H, m), 6.83 (2H, m), 4.53 (2H, d, J = 5.7 Hz). 50 MHz ^{13}C Nmr ($CDCl_3$) δ: 162.02, 146.78, 139.30, 136.57, 131.50, 128.55, 127.68, 127.05, 126.96, 126.91, 115.34, 111.26, 109.32, 47.07. Ir ($CDCl_3$): 3300 (s), 3000 (m), 1605 (s), 1585 (s), 1325 (m) cm^{-1}. HRms (*m/z*): 250.1099, calcd for $C_{16}H_{14}N_2O$ 250.1107.

2-[2-(Phenylmethyl[acryloyl]amino)phenyl]oxazole (16). To a solution of the amine (**18**) (34 mg, 0.13 mmol) and diisopropylethylamine (42 mg, 0.32 mmol) in ether (5 ml) at -78° C was added acryloyl chloride (**11**) (15 mg, 0.16 mmol) dropwise. After stirring for one hour at -78° C the reaction mixture was stirred for 18 h at room temperature. The reaction was quenched by the addition of water. The organic layer was separated and the aqueous phase extracted with methylene chloride (3 x 15 ml). The combined organic layers were washed with brine (3 x 15 ml), dried over $MgSO_4$ and concentrated in *vacuo*. Purification of the crude residue by flash chromatography using 50% ether in hexanes afforded 35 mg (89%) of **16** as a colorless viscous oil. 200 MHz ^1H Nmr ($CDCl_3$) δ: 8.13 (1H, dd, J = 1.8, 7.7 Hz), 7.70 (1H, s), 7.46 (1H, ddd, J = 1.3, 7.7, 9.0 Hz), 7.35 (1H, ddd, J = 1.8, 7.8, 9.0 Hz), 7.24 (1H, s), 7.20 (5H, m), 6.87 (1H, dd, J = 1.3, 7.8 Hz), 6.37 (1H, dd, J = 2.0, 16.7 Hz), 5.93 (1H, dd, J = 10.2, 16.7 Hz), 5.63 (1H, d, J = 14.4 Hz), 5.45 (1H, dd, J = 2.0, 10.2 Hz), 4.12 (1H, d, J = 14.4 Hz). 90 MHz ^{13}C Nmr ($CDCl_3$) δ: 165.60, 159.12, 139.21, 138.88, 136.90, 131.31, 130.84, 129.98, 129.13, 128.63, 128.56, 128.28, 128.15, 127.82, 127.26, 125.79, 52.64. Ir ($CDCl_3$): 2980 (s), 1640 (s), 1600 (s), 1410 (s), 1250 (br), 1200 (br) cm^{-1}. HRms (*m/z*): 304.1201, calcd for $C_{19}H_{16}N_2O_2$

304.1213.

Methyl (*E*)-4-[phenylmethyl-(2-[2-oxazolyl]phenyl)amino]-4-oxo-2-butenoate (17). To a solution of the oxazole (**18**) (800 mg, 3.2 mmol) in ether (50 ml) at room temperature was added triethylamine (810 mg, 8.0 mmol). The solution was cooled to -78° C and acid chloride **13** (522 mg, 3.52 mmol) was added dropwise. The solution was warmed to room temperature after 30 min and stirred for 18 h. Water (75 ml) was added, the organic layer separated and the aqueous phase extracted with methylene chloride (3 x 50 ml). The combined organic layers were dried over $MgSO_4$, filtered and absorbed onto silica gel (4 g). Flash chromatography using 50% ether in hexanes afforded 1.06 g (89%) of **17** as a poorly melting white solid. 200 MHz ^{1}H Nmr ($CDCl_3$) δ: 8.05 (1H, dd, J = 1.6, 7.8 Hz), 7.62 (1H, d, J = 0.6 Hz), 7.41 (1H , m), 7.28 (1H, m), 7.11 (6H, m), 6.81 (1H, d, J = 15.3 Hz), 6.80 (1H, m), 6 65 (1H, d, J = 15.3 Hz), 5.45 (1H, d, J = 14.2 Hz), 4.12 (1H, d, J = 14.2 Hz), 3 58 (3H, s). 90 MHz ^{13}C Nmr ($CDCl_3$/acetone-d_6) δ: 164.67, 163.00, 157.80, 144.63, 143.24, 141.72, 139.64, 136.48, 136.21, 135.45, 135.00, 134.32, 134.22, 1333.88, 133.30, 132.52, 130.83, 51.95, 50.77. Ir ($CDCl_3$): 3000 (m), 1725 (s), 1650 (vs), 1625 (m), 1165 (br) cm^{-1}. HRms (*m/z*): 362.1297, calcd for $C_{21}H_{18}N_2O_4$ 362.1267.

Methyl 5-oxo-6-phenylmethylbenzo[*h*]-1,6-naphthyridine-4-carboxylate (19). *The oxazole* (**17**) (40 mg, 0.11 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were heated to reflux in benzene (11 ml) for 3 days. Benzene was removed under reduced pressure. Purification of the crude residue by flash chromatography using 50% ether in hexanes afforded 17 mg (50%) of Diels-Alder adduct (**19**) as white needles, mp 160° C. 360 MHz ^{1}H Nmr ($CDCl_3$) δ: 9.04 (1H, d, J = 4.6 Hz), 8.91 (1H, dd, J = 1.5, 8.0 Hz), 7.50 (1H, m), 7.43 (1H, d, J = 4.6 Hz), 7.35 (1H, m), 7.25 (6H, m), 5.61 (2H, s), 4.03 (3H, s). 90 MHz ^{13}C Nmr ($CDCl_3$) δ: 168.82, 160.25, 153.69, 151.00, 143.15, 138.30, 135.69, 131.69, 128.71, 127.23, 122.34, 125.51, 122.99, 120.45, 120.17, 116.61, 115.38, 53.10, 46.24. Ir ($CDCl_3$): 1730 (m), 1650 (s), 1260 (s) cm^{-1}. HRms (*m/z*): 344.1137, calcd for $C_{21}H_{16}N_2O_3$ 344.1162. Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68. Found: C, 73.03; H, 4.79.

Methyl (6*H*)-5-oxobenzo[*h*]-1,6-naphthyridine-4-carboxylate (20). The oxazole (**14**) (1.02 g, 3.74 mmol) was heated to reflux in *o*-dichlorobenzene (125 ml) with $Eu(fod)_3$ (233 mg, 0.22 mmol) for 18 h. The solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography using 50% ether in hexanes afforded 682 mg (85%) of Diels Alder adduct (**20**) as yellow crystals, mp 217-220° C. 200 MHz ^{1}H Nmr ($CDCl_3$) δ: 11.44 (1H, br), 8.65 (1H, d, J = 4.7 Hz), 8.22 (1H, dd, J = 1.2, 7.9 Hz), 7.15 (1H,

m), 7.12 (1H, d, J = 4.7 Hz), 7.00 (1H, m), 6.86 (1H, m), 3.45 (3H, s). 90 MHz ^{13}C Nmr (methanol-d_4/DMSO-d_6) δ: 169.77, 161.32, 155.48, 153.11, 144.13, 139.27, 132.97, 125.96, 124.07, 121.75, 120.18, 118.39, 117.24, 53.67. Ir ($CDCl_3$): 1730 (m), 1670 (vs), 1280 (m) cm^{-1}. HRms (*m/z*): 254.0689, calcd for $C_{14}H_{10}N_2O_3$ 254.0692. Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96. Found: C, 65.85; H, 3.97.

Methyl 5-chlorobenzo[*h*]-1,6-naphthyridine-4-carboxylate (21). The lactam (**20**) (51 mg, 0.20 mmol) and phosphorous pentachloride (58 mg, 0.28 mmol) were heated to reflux in phosphorous oxychloride (0.35 ml, 3.75 mmol) for 4 h. Excess phosphorous oxychloride was removed under reduced pressure and then the reaction was quenched by the careful addition of 10% aqueous ammonium hydroxide. The reaction mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in *vacuo*. Purification of the crude residue by flash chromatography using 20% ethyl acetate in methylene chloride afforded 52 mg (95%) of chloro imidate (**21**) as a white powder, mp 134° C. 200 MHz ^{1}H Nmr ($CDCl_3$) δ: 9.18 (1H, d, J = 4.5 Hz), 9.05 (1H, dd, J = 1.5, 8.0 Hz), 8.07 (1H, dd, J = 1.1, 8.2 Hz), 7.85 (1H, m), 7.75 (1H, m), 7.60 (1H, d, J = 4.5 Hz), 4.07 (3H, s). 50 MHz ^{13}C Nmr ($CDCl_3$) δ: 168.13, 153.09, 150.74, 146.75, 144.88, 140.33, 131.53, 128.38, 128.27, 124.60, 124.50, 121.71, 116.06, 53.56. Ir ($CDCl_3$): 2950 (m), 1730 (vs), 1575 (vs), 1290 (vs), 1165 (s) cm^{-1}. HRms (*m/z*): 272.0358, calcd for $C_{14}H_9{}^{35}ClN_2O_2$ 272.0354. Anal. Calcd for $C_{14}H_9N_2O_2Cl$: C, 61.66; H, 3.33. Found: C, 61.77; H, 3.39.

4-Bromo-1-bromomethyl-2-nitrobenzene (23). To a solution of 4-bromo-2-nitrotoluene[13] (**22**) (3.91 g, 18.11 mmol) in carbon tetrachloride (280 ml) was added *N*-bromosuccinimide (3.22 g, 18.11 mmol). The reaction was initiated by an ultraviolet sunlamp. After stirring 48 h, the reaction mixture was filtered and concentrated in *vacuo*. The crude reaction mixture was purified by chromatography using 10% methylene chloride in hexanes as the eluent. This afforded 2.70 g (50%) of **23** as pale yellow crystals, mp 76° C, and 1.41 g (36%) of recovered starting material (**22**). Compound (**23**): 200 MHz ^{1}H Nmr ($CDCl_3$) δ: 8.31 (1H, d, J = 2.0 Hz), 7.85 (1H, dd, J = 2.0, 8.3 Hz), 7.57 (1H, d, J = 8.3 Hz), 4.90 (2H, s). Ir (neat): 3091(w), 1534 (vs), 1345 (s) cm^{-1}. HRms (*m/z*): 292.8693, calcd for $C_7H_5NO_2{}^{79}Br$ 292.8686.

4-Bromo-2-nitrobenzaldehyde (24). To a solution of **23** (296 mg, 1.00 mmol) in dry DMSO (50 ml) was added anhydrous sodium bicarbonate (504 mg, 6.00 mmol). The reaction mixture was heated at 80° C for 12 h. Water (100 ml) was added to the reaction and the mixture was extracted with methylene chloride (3 x 75 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography using 25% methylene chloride in hexanes as the eluent afforded 145 mg (68%) of aldehyde (**24**) as a pale yellow solid, mp

96-98° C. 200 MHz ^{1}H Nmr ($CDCl_3$) δ: 10.51 (1H, s), 8.39 (1H, d, *J* = 1.5 Hz), 8.04 (1H, dd, *J* = 1.5, 8.2 Hz), 7.97 (1H, d, *J* = 8.2 Hz). Ir (neat): 3104 (w), 1716 (s), 1534 (vs), 1347(s) cm^{-1}. HRms (*m/z*): 230.9631, calcd for $C_7H_4NO_3{}^{81}Br$ 230.9354.

***(4-Bromo-2-nitrobenzalamino)acetaldehyde diethyl acetal* (25).** 4-Bromo-2-nitrobenzaldehyde (**24**) (80 mg, 0.37 mmol) and aminoacetaldehyde diethyl acetal (50 mg, 0.37 mmol) were heated to 110-120° C in *o*-dichlorobenzene (2 ml) in the presence of 4 Å molecular sieves for 24 h. Evaporation of *o*-dichlorobenzene afforded the benzalaminoacetaldehyde (**25**) in a 92% yield as a dark yellow oil. 200 MHz ^{1}H Nmr ($CDCl_3$) δ: 8.64 (1H, br s), 8.15 (1H, d, *J* = 1.9 Hz), 7.96 (1H, d, *J* = 8.4 Hz), 7.78 (1H, dd, *J* = 1.9, 8.4 Hz), 4.83 (1H, dd, *J* = 2.3, 5.3 Hz), 3.84 (2H, dd, *J* = 1.0, 5.3 Hz), 3.70 (2H, dq, *J* = 2.3, 7.0 Hz), 3.60 (2H, dq, *J* = 2.3, 7.0 Hz), 1.22 (6H, t, *J* = 7.0 Hz). 50 MHz ^{13}C Nmr ($CDCl_3$) δ: 158.11, 149.09, 136.41, 131.05, 129.81, 127.17, 124.36, 101.40, 64.14, 62.28, 15.29. Ir (neat): 2965 (m), 1639 (w), 1535 (vs), 1349 (s), 1128 (s), 1093 (s), 1064 (s) cm^{-1}. HRms (*m/z*): 299.0051, calcd for $C_{11}H_{11}N_2O_3{}^{79}Br$ (M^+ - OCH_2CH_3) 299.0032.

2-(4-Bromo-2-nitrophenyl)oxazole (26). Sulfuric acid (4.8 ml) in a 3-neck flask fitted with a mechanical stirrer and a thermometer was cooled in an ice-salt bath. To this was added the benzalaminoacetaldehyde (**25**) (958 mg, 2.75 mmol) at such a rate that the reaction temperature did not exceed 5° C. After stirring 5 min, the cold acid solution was added to phosphorous pentoxide (1.46 g, 10.31 mmol) and sulfuric acid (0.5 ml) at 180° C. The hot molten mixture was stirred vigorously with a mechanical stirrer for 20 min then poured into crushed ice (100 ml). The aqueous solution was extracted with ethyl acetate (2 x 100 ml) and then methylene chloride (1 x 100 ml). The combined organic layers were dried, filtered and concentrated in *vacuo*. Purification by flash chromatography using 50% ether in hexanes afforded 105 mg (14%) of the oxazole (**26**). 200 MHz ^{1}H Nmr ($CDCl_3$) δ: 7.89 (2H, m), 7.78 (1H, m), 7.75 (1H, s), 7.29 (1H, s). Ir (neat): 3125 (w), 1550 (vs), 1375 (s), 925 (m), 844 (m), 769 (m) cm^{-1}. HRms (*m/z*): 269.9455, calcd for $C_9H_5N_2O_3{}^{81}Br$ 269.9463.

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