Heterocyclization of Functionalized Vinylic Derivatives of Imidazo[1,2-*a*]pyridines

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Heterocyclization of functionalized vinylic derivatives of imidazo[1,2-*a*]pyridines was explored experimentally and theoretically using semiempirical AM1 and ab initio methods. A range of functionalized vinylic derivatives (azido, amino, and carbodiimide groups) were prepared for conversion into pyrroloazaindoles **19**−**22**, imidazo[1,*x*]-, (*x* = 5, 6, 7, 8), [2,6]-, and [2,7]naphthyridines **28**−**30**, **35**−**38** by thermal reaction. In the case of vinylic groups in the 5 position, peri annulation also was observed. The experimental and theoretical data are compared and discussed.

Introduction

The azaindole systems are used as important building blocks in natural or synthetic bioactive compounds through their isosterism with indole. Recently, the diazasugar kifunensine **1** was isolated from *Tasatosporia kifunense* and reported as a new immunomodulator (Figure 1).[1] In the wye ring system **2a**,**b**, the Y base was isolated and identified as a component of $tRNA^{phe\ 2}$ with an antiviral activity.[3] Variation of the basic imidazo[1,2-*a*]pyridine (IP) ring structure affords a new series **3a**−**c** that shows antiproliferative activity[4b,c] or azino-fused benzimidazolium salts that are intercalating agents **4a**,**b**.[4a,d,e] Recently, new nitrogen bridgehead systems such as compounds **5a**,**b** were shown to be highly potent and selective glycine antagonists, which have been used for the prevention of ischemia, Alzheimer's disease,[5] and neurodegenerative disorders caused by viral infections such as AIDS.[6b] Also, we observed that the pyrroloindole

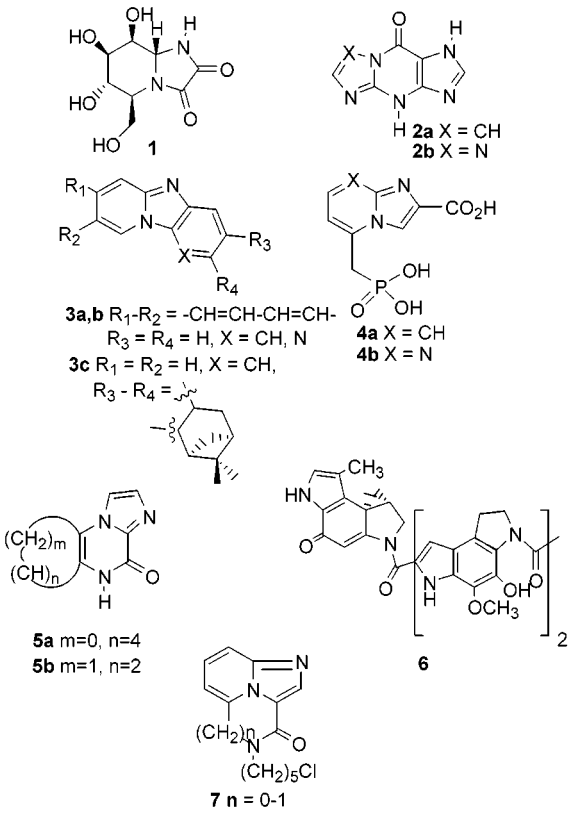

Figure 1.

(PI) moiety was found in compounds **6** derived from the antibiotic (+)-CC-1065.[6a] The promising pharmacological activities of the imidazo[1,2-*a*]pyridine (IP), [1,2-*a*]pyrimidine (IPM), [1,2-*a*]quinoxaline (IQ), or [2,1-*a*]isoquinoline (IIQ) nucleus[7] have prompted chemists to develop many synthetic methods. Extensive application of heterocyclization from the imidazole moiety,[8] using synthetically attractive methods recently developed by Moody[9] and Molina,[10] such as thermal treatment of azidovinyl

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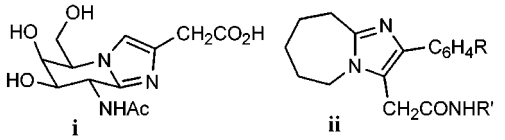

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or carbodiimide synthons, are representative examples.[11] In contrast, the synthetic potential of the pyridinic moiety has long remained unexplored.[12a,c,d] Recently, tricyclic structures, such as **7** and isosteres in which the C(3) and C(5) of IP are bridged, were obtained by peri annulation.[12c,f−h]

We have been studying the reactivity of the nitrogen bridgehead systems, and especially the bioactive imidazo[1,2-*a*]pyridine moiety, for several years. We report here a new synthetic route for pyrroloazaindoles and naphthyridinoimidazoles by regioselective cyclization of vinyl azide-, amine-, or heterocumulene-substituted imidazo[1,2-*a*]pyridines. The products form a potentially useful class of agents for neurodegenerative disorders,[5] could be envisaged as a composite template of potent dual ACE/NEP inhibitors,[7u,13] and are also of interest as possible inhibitors of HIV-l replication.[14]

Results and Discussion

To access pyrrolo, pyridino, pyrimidino, and diazepino moieties, three new models of IPs substituted by (A) an aminovinylic group, (B) an azirine fragment derived from an azidovinylic group,[15] and (C) a heterocumulene were

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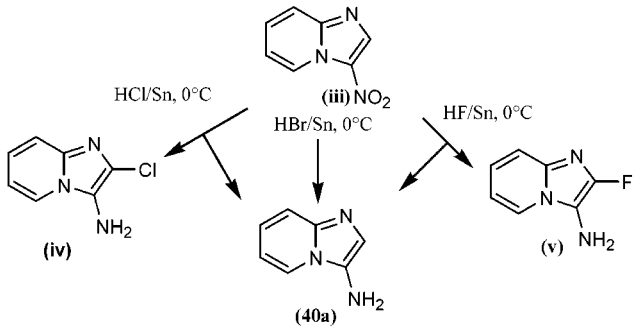

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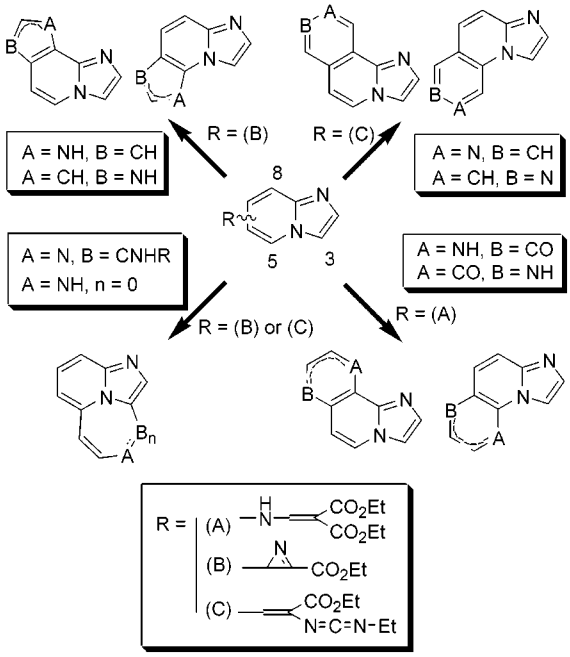
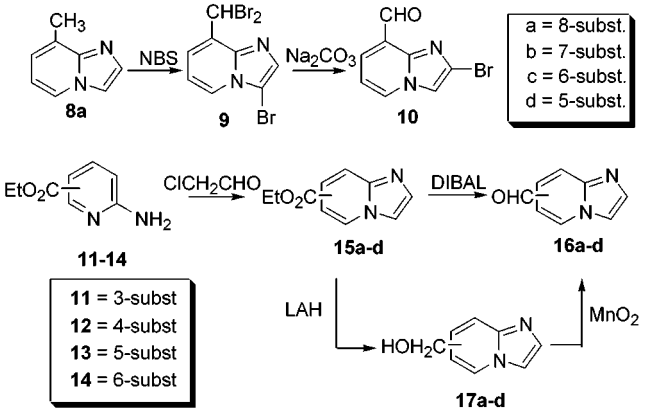


Figure 2.

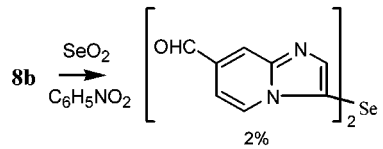
obtained by a rapid and efficient synthetic route from aldehyde or amino groups. The different sequences of annulations are shown in Figure 2.

Access to the Wye-Like Structures. The first step in our synthesis of wye isosteres required aldehydes **16a**−**d** (Scheme 1). According to the reactivity of methyl azaindolizines with the NBS procedure[17] reported in the literature, dibromomethyl compound **9** can be obtained by treating **8a**[18] with NBS. Treatment of **9** with aqueous sodium carbonate solution afforded the aldehyde **10** (55% yield), which is the result of a thermal Dimroth rearrangement[19] of the 2-bromoimidazole moiety. Attempts to extend this method to **8b**−**d**[18] were unsuccessful and

Scheme 1



produced only intractable byproducts. Bromination of the methyl group occurs only at the C(8) position of the imidazo[1,2-*a*]pyridine, due to the "pyridinic" atom N-1. An alternative approach using the DDQ method[20] on compounds **8a**−**d** failed, although the oxidation reaction of the methyl group in azaindenes has been well described, notably by Paudler.[19c] The aldehyde was first obtained (but with a 3-selenation) in very low yield (<2%) by oxidation of **8b** with selenium dioxide[21,22] at 210 °C in nitrobenzene, but this failed with **8a**,**c**,**d**. Since the direct oxidation of the methyl group seems difficult, we tried the reduction of the ester group of compounds **15a**−**d** (80−93%) according to the modified protocol of Yamanaka.[23] Condensation of **11**,[23d] **12**,[24a] **13**,[25] and **14**[24b,c] with chloracetaldehyde according to Hand's procedure[26]



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(15) It is clear that bond reorganization of the vinyl azides give azirines at least in the primary stage of their decomposition.[16a−g] In a preliminary work, we reported that azirine can be observed as intermediate from vinyl azide/nitrene group.[16g] So, we explore the promotion of thermolysis of azides. On the other hand, in principe the azine (or nitrene) has two sites for attack at N(1) or C(7) for 8-substituted IP. But endeavours to encourage reaction at N(1) of IP failed excepted when the C-ortho position is blocked. This could be due to the potential reversibility of the $N(1)^{+}-N^{-}$ bond to the nitrene. By exemple, IP[1,8] having heterocumulene moiety on the position 2 gives zwitterionic compounds by N-annulation under thermal conditions.[8q]

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(20) Canoira, L.; Rodriguez, J. G.; Subirats, J. B.; Escario, J. A.; Jimenez, I.; Martinez-Fernandez, A. *Eur. J. Med. Chem.* **1989**, *24*, 39.

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(22) (a) Preliminary experiments with selenium dioxide conducted by Paudler on the expected oxidation of the methyl group to the aldehyde failed with formation of the diarylselenide: Hand, E. S.; Paudler, W. W. *J. Org. Chem.* **1976**, *41*, 3549. (b) Under more vigorous conditions, we have conducted an experiment that shows that oxidation with SeO_2 should be possible. NMR ^1H ($CDCl_3$) δ 7.02 (d, 2 H, $J = 7$ Hz), 7.60 (s, 2 H), 8.31 (s, 2 H), 9.39 (d, 2 H, $J = 7$ Hz), 9.93 (s, 2 H); NMR ^{13}C ($CDCl_3$) δ 103.90, 116.61, 117.97, 120.9, 129.32, 142.05, 147.22, 177.55.

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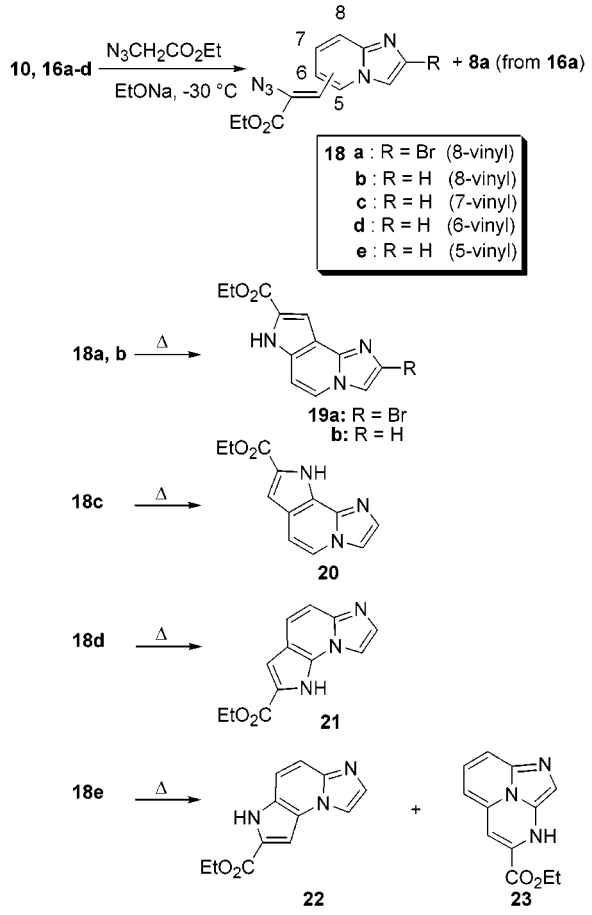
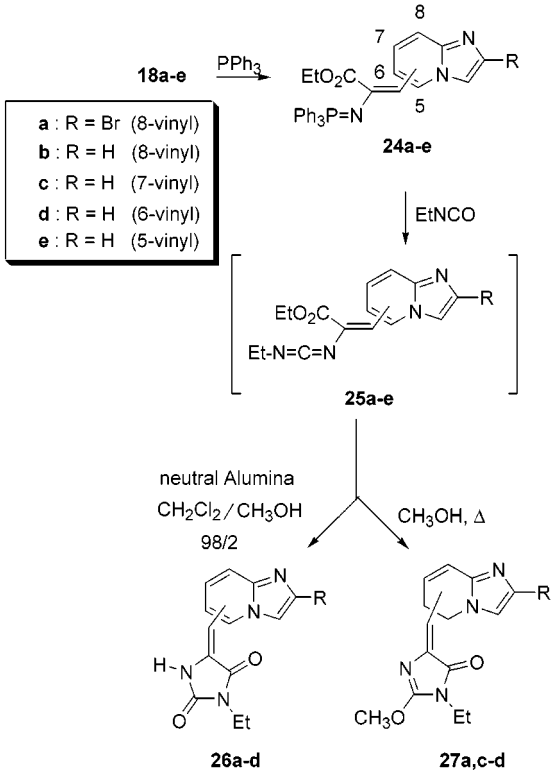
Scheme 2



gave imidazopyridine compounds **15a**−**d,** which were directly reduced with DIBALH at −70 °C to produce aldehydes **16a**−**d** with an overall yield of 17−79%. TLC showed that the reduction was an incomplete and low-yielding alternative even under forcing conditions (i.e., excess of DIBALH, temperature, solvent), with the presence of alcohols **17a**−**d** and starting esters with wide-ranging nonreproducible yields. However, since extending this procedure to vinyl azides would have required multigram quantities of aldehydes, we continued to work on optimization. The final optimized sequence was a two-step protocol beginning with reduction of esters **15a**−**d** with $LiAlH_4$ followed by MnO_2 oxidation without purification of alcohols **17a**−**d** to afford aldehydes **16a**−**d** in reproducible overall yields of 83, 72, 60, and 83%, respectively.

Condensation of the aldehydes **10** and **16a**−**d** with ethyl azidoacetate in ethanolic sodium ethoxide at −30 °C gave the azidovinylic compounds **18a**−**e** (10−68%) (Scheme 2). From **16a**, an appreciable amount of **8a** was formed along with **18b**. Precautions were taken to ensure that the solution containing the light-sensitive unstable azidovinylic **18e** was kept below 0 °C. These structures were confirmed by IR (ν_{azido} 2050−2100 cm^{-1}) and ^1H and ^{13}C NMR analysis. The long-range $^{13}C-^1H$ coupling constant between the olefin proton and the carbonyl carbon in the coupled ^{13}C NMR spectrum proved the (*Z*) configuration of the vinylic fragment.[27] Thermal rearrangement of the azides **18a**−**e** was performed under neutral conditions at 130 °C in dilute chlorobenzene

Scheme 3



solution (Scheme 2). Theoretically, there could be many possible isomers for thermolysis of these azido compounds. However, the ^1H NMR spectra of **19**−**21** (obtained respectively from **18a**−**d**) is quite simple and corresponds to a single isomer. Thus, the azide **18a** was converted into the expected tricyclic ester **19a** in 98% yield by cyclization onto the C(8)−C(7) bond. Similarly, angular annulation products were found from azidovinylics **18b**−**d**, which gave, after chromatographic purification over neutral alumina, compounds **19b**, **20**, and **21** in 84, 30, and 36% yields, respectively. These structures were unambiguously secured by ^1H and ^{13}C NMR analysis. These results showed that during intramolecular cyclization of vinyl azide synthons on the pyridine sites the regiospecificity was an angular annulation.

In agreement with theoretical calculations, the thermal cyclization of **18e** gave a tricyclic structure **23** (2%) (*m*/*z* = 229) in low yield but also an ortho annulation product **22** (35%). Structure **23** was secured by ^1H and ^{13}C NMR spectra with in particular the absence of the signal H−C(3).

Iminophosphoranes **24a**−**e** were prepared from **18a**−**e** by a standard Staudinger reaction in 51−95% yields (Scheme 3). The conversion of **24a**−**e** to carbodiimides **25a**−**e** involves initial aza-Wittig reaction between **24a**−**e** and ethyl isocyanate. When the crude products **25a**−**d** were chromatographed, an alumina-supported reaction led to aza analogues of the chromophore moieties of wild-type GFP-Y66W[11,27b] (or aplysinopsins) like **26a**−**d** via intermediate isoureas (see Scheme 3 and the Experimental Section). When these carbodiimides **25a**−**d** were heated in methanol solution, they gave compounds

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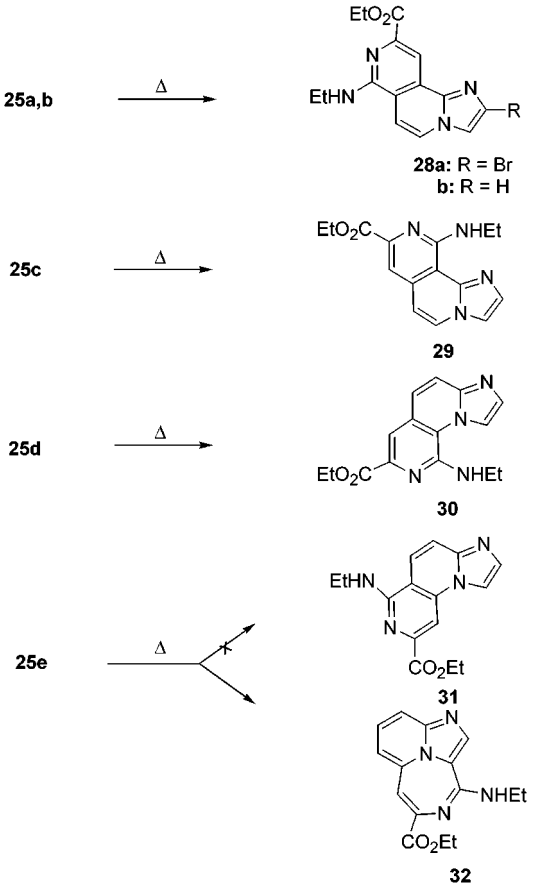
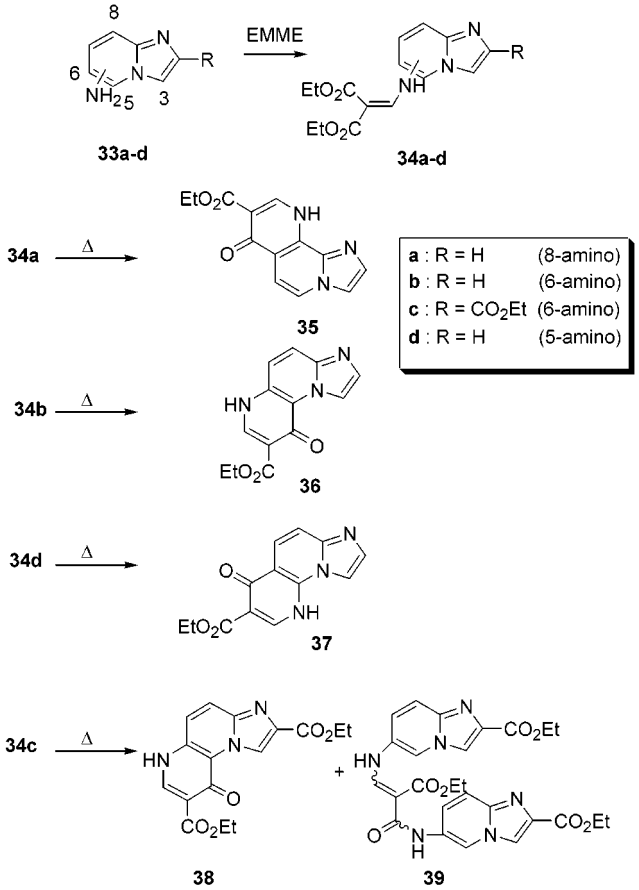
Scheme 4



Scheme 5



27a,**c**,**d** in 51, 45, and 40% overall yields. We assigned a *Z* configuration consistent with our findings[11] and those of Vögeli.[27a] Interestingly, treatment of **24e** with ethyl isocyanate under similar reaction conditions resulted in a spontaneous thermo-induced regioselective conversion of the carbodiimide **25e** to a (c−d) fused IP derivative **32** (42%) containing the [1,4]diazepine moiety (Scheme 4). No competing cyclization at position 6 of imidazopyridine was observed.

We turned our attention to the construction of the imidazonaphthyridine skeletons. Crude carbodiimides **25a**−**d** were used without further purification. Heating carbodiimides **25a**−**d** in boiling chlorobenzene caused an angular cyclization to give the fused pyridines **28**−**30** with 38−52% yields. These cyclizations proceeded regioselectively; i.e., experimentally, we observed an angular cyclization when carbodiimides were at positions 7 and 6, rather than a linear annulation. No evidence of N(1) annulation was observed with 8-substituted derivatives.

Annulation Reaction of Aminovinyl Esters. The regioselective fused pyridine annulation was subsequently completed by the synthesis of the azaisosteric bacterial coenzyme methoxatin.[28] The substitution products **34a**−**d** (56−88%) were obtained by refluxing a mixture of amines **33a**,[12e] **33b**,[12a] **33c**,[12e] or **33d**[12e] with diethyl ethoxymethylenemalonate (EMME) in boiling toluene (Scheme 5). Analytical data agree with the proposed structures. In particular, the ^{1}H NMR spectra of products **34a**−**d** showed a NH−CH ^{1}H, ^{1}H coupling constant of 13 Hz.[29] Compounds **34a**−**d** were expected to cyclize to 1,2-dichlorobenzene at 180 °C. The cyclization of **34a** led to regiospecifically angularly annulated [1,7]naphthyridinic **35** in 48% yield. The ^{1}H NMR spectrum confirmed **35** and showed an ^{1}H, ^{1}H coupling constant of 7 Hz that was compatible only with H−C(6) and H−C(5) moieties, respectively, and a singlet at δ = 8.39 identified as the new naphthyridinic proton H−C(9). This result was extended to compounds **34b**, **34d**, regiospecifically cyclized to give the corresponding [1,5] and [1,8]naphthyridinic systems of **36** and **37** in 49 and 92% yield, respectively. The spectral properties of **36** and **37** were similar to those of the isomeric compound **35**. Further data and final confirmation for the structure of **35**−**37** are provided by unambiguous structural assignment from ^{13}C NMR and mass spectroscopies (see the Experimental Section). Under the same conditions, 2-ester derivative **34c** afforded two chromatographically unseparable compounds **38** (*m*/*z* 329) and **39** (*m*/*z* 534) (contaminated by **34c**) in a 1:7 ratio. The tautomeric pyridin-4-one form of **35**−**38** is supported by the ^{15}N NMR literature. The 1-azaindolizine synthon[30] contains two different types of sp^2 hybridization nitrogen atoms basically referred to as "pyridine type" and "pyrrole type" and were used to account for the difference in the resulting nitrogen shieldings.

To rationalize these convenient routes to new azatricyclic synthons, series of molecular orbital calculations were undertaken (Figure 3, sequences 1−4).

(28) (a) MacKenzie, A. R.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1983**, 1372. (b) MacKenzie, A. R.; Moody, C. J.; Rees, C. W. *Tetrahedron* **1986**, *42*, 3259.

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(30) Witanowski, M.; Sicinska, W.; Grabowski, Z.; Webb, G. A. *Org. Magn. Reson.* **1990**, *28*, 988.

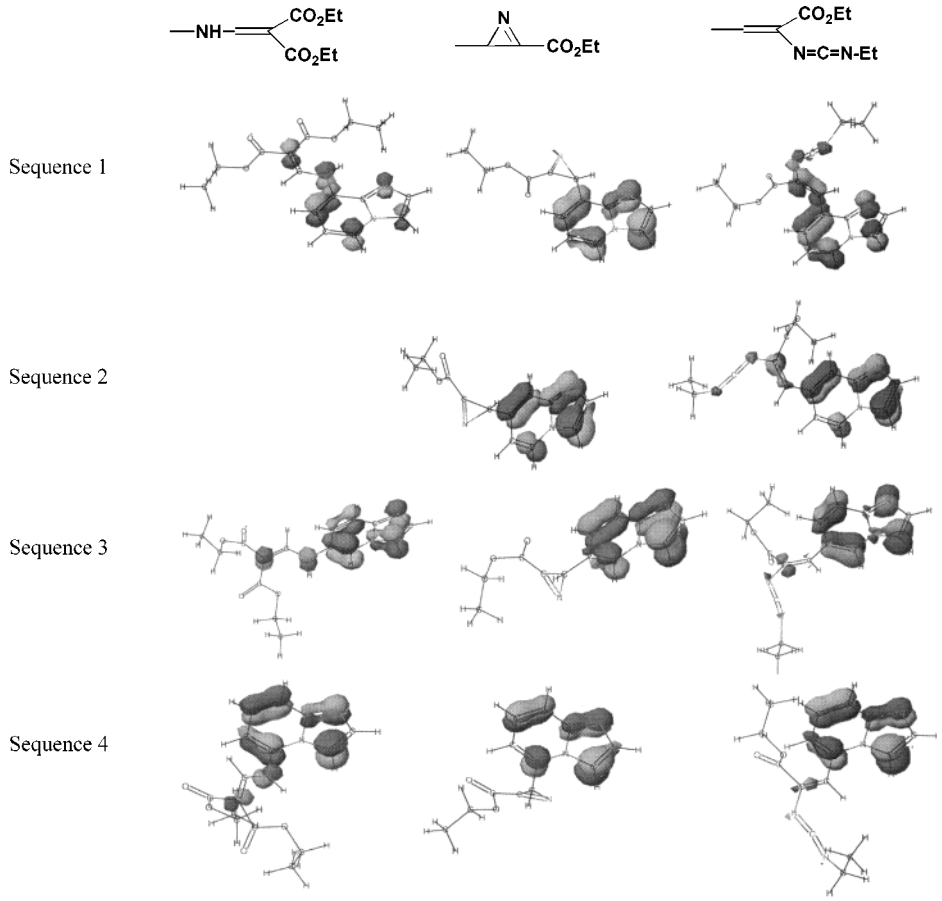

Figure 3. AM1-calculated polarization of the HOMO of imidazopyridines **18b**−**e**, **25b**−**e**, and **34a**,**b**,**d**.

Semiempirical Calculations. Semiempirical molecular orbital calculations employing the AM1[33a] approach as advocated[33b−d] are reported. Starting geometries were generated by molecular mechanistic optimization using the modeling package CAChe 4.02[34a] or MAD[34b,c] installed on an SGI Origin 200 work station. The structural and energy refinements were carried out using the PRECISE option of MOPAC 6.0 with the AM1 quantum chemistry method. The MOPAC reactivities were used to evaluate heats of formation and energies of HOMO orbitals of molecules. Experimental data,[7,8n,11,12f,d,e] and theoretical calculations[12h,18,21,35] confirm that the most reactive site for electrophilic substitution reactions is the C(3); for the C(5) position results for the pyridinic moiety are conflicting.[36] Comparison of the data (bond lengths and angles) from the AM1 optimized structures with those found from X-ray data of the basic IP[21,32b,e] showed close agreement (Figure 3).

The delocalization of the HOMO depicted in Figure 3 shows that the charge density distribution in the highest occupied MO of sequence 1 (C(8), A−C) or 2 (C(7), B, C) is solely localized on the ortho position, to generate angular heterocycles. Compounds of sequence 3 (C(6), A−C) were found to undergo an angular or sometimes linear cyclization. Interestingly, the HOMO of sequence 4 (C(5), A−C) predicts a peri annulation along with a possible angular annulation on C(6) for A, C.

Calculations for cyclization of azides **18b**−**e** and carbodiimides **25b**−**e** carried out using a semiempirical AM1 calculation are consistent with experimental angular or peri annulation for **19b**, **20**, **21**, **23**, **28b**, **29**, **30,** and **32**. However, AM1 predicts incorrectly the angular cyclization on C(6) of **18e** affording **22** and cannot discriminate between the ortho and peri annulation for **25e**. A series of H−F SCF/MO ab initio calculations using the 6-31G* basis set optimized at the B3LYP 6-31G*[33c] was per-

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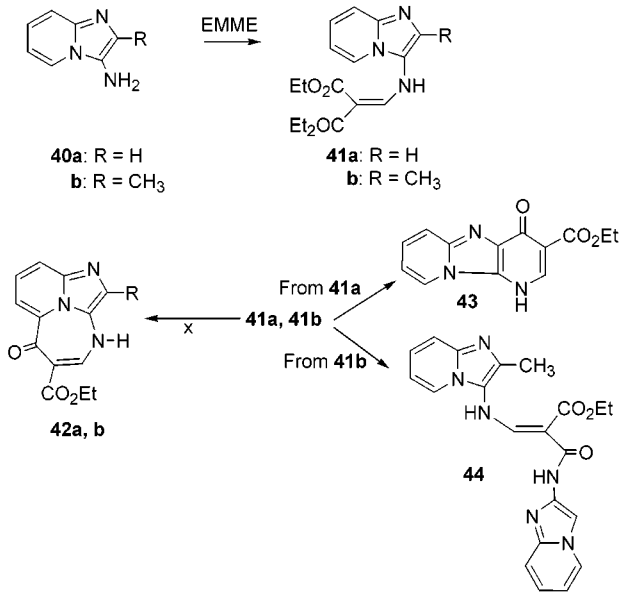
(34) (a) CaChe 4.02 Oxford Molecular group, Magdalen Centre, Oxford Science, Park, Sandford-on-Thames, Oxford, 0X4 4GA, England. (b) MAD, proquantum and prosimulate softwares, Oxford Molecular group, Magdalen Centre, Oxford Science, Park, Sandford-on-Thames, Oxford, 0X4 4GA, England. Hartree−Fock and B3LYP ab initio calculations were performed using Gaussian 94 package (6.31G(d,p)).[34c] (c) Frisch, M. J.; Schlegel, H. B.; Gill, P. M.; Johnson, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, J. A. M.; Raghavachari, K.; Al-Laham, V. G. Z.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, R. G.; Martin, R. L.; Fox, D. J.; Binkley, D. J. D.; Baker, J.; Stewart, J. P.; Head-Gordon, C. G.; Pople, J. A. Gaussian 94, Inc., Pittsburgh, PA, 1995.

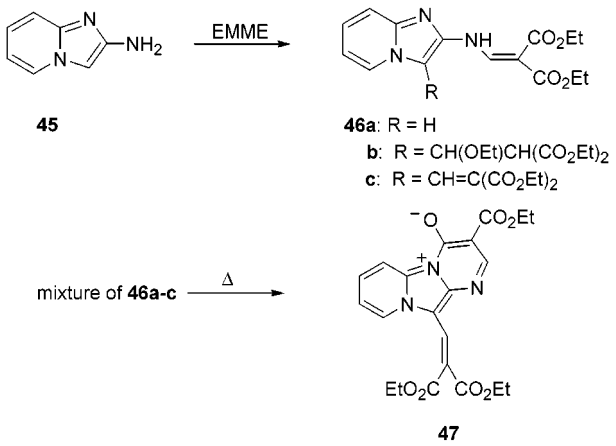
(35) Paudler, W. W.; Blewitt, H. L. *Tetrahedron* **1965**, *21*, 353.

(36) (a) Some years ago, the synthesis of 1,4-diazacycl[3,2,2]azine was accomplished by Paudler and co-workers.[33b] These compounds are subject to facile acid-catalysed hydrolysis affording carboxaldehyde derivatives. (b) Paudler, W. W.; VanDahm, R. A.; Park, Y. N. *J. Heterocycl. Chem.* **1972**, *9*, 81. (c) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522.

Scheme 6



Scheme 7



formed for **25e**.[37] For compound **25e**, the optimized geometry of the vinylheterocumulene atoms places them inside the IP molecular plane. The topology of the HOMO centered on the C-3 imidazole ring and the Mulliken charge analysis (C-3: 0.176; C-6: −0.01) discriminate between the ortho and peri annulation.

Extension to the Imidazolic Moieties. To complete our previous work, we wished to extend this method to 3-amino derivatives (Scheme 6). From these compounds, three alternative annulations are possible: C(3) → C(5), C(2) → C(3), or C(2) → N(1) after a Dimroth rearrangement. Treatment of amino compounds **40a**,**b**[12b] with EMME afforded the corresponding vinylamines **41a**[8c] and **41b** in 53 and 52% yield, respectively. Under thermal conditions, **41a** led to the known dipyridoimidazole **43**,[8c] whereas vinylamine **41b** gave a "dimeric" structure **44** in moderate yield. No trace of diazepine compounds was detected. For compound **43** ($CDCl_3$, 0.15 equiv of chromium(III)acetylacetonate), the resonances obtained at δ 128 (N(10)), 166 (N(5)), and 189 (N(1)) confirm the pyridinone form[31] also favored by the ester group.[32] The complete structural analysis of **43** was established by INEPT experiments, in which the long-range interactions of H(2) with carbons C(3) (106.8), C(4) (161.0), CO_2Et (170.3), and C(10a) (145.2) were identified.

We explored the reactivity of the 2-amino-IP **45**[38] and the possibility of promoting C(2) → N(1) or C(2) → C(3) annulation (Scheme 7). Treatment of **45** with EMME under the same conditions produced an unseparable mixture of **46a**−**c** in a ratio of 1:10:9 in a combined yield of 47%. On heating in 1,2-dichlorobenzene for 10 h, this mixture underwent N-annulation to give the zwitterionic structure **47** in a low yield of (12%).

In conclusion, we describe a simple synthetic route for the synthesis of pyrroloazaindoles **19**−**22**, imidazo[1,*x*]-, (*x* = 5, 6, 7, 8), [2,6]-, and [2,7]naphthyridines **28**−**30**, **35**−**38** from vinylic derivatives. This method also generates derivatives on pyridinic sites of IP such as **15a**−**d**, **16a**−**d**, and **17a**−**d**. In general, the experimental data and theoretical calculations agreed, but we observed a specific reactivity of the 5-position giving the corresponding tetrahydroimidazobenzodiazepinone (TIBO) isosteres[14a,39] by peri annulation.

Experimental Section

Instrumentation. Melting points were determined on a Kofler apparatus and are not corrected. NMR (400 MHz for ^{1}H or 100 MHz for ^{13}C) were recorded on a Bruker AC 400 spectrophotometer using $CDCl_3$, CD_3OD, CD_2Cl_2, or DMSO-d_6 as solvent. Infrared spectra were recorded on a Beckman Acculab 2 spectrophotometer. Mass spectral analyses were performed on a Hewlett-Packard 5985B or 5989A instrument. The purity of compounds not submitted for combustion Analysis was assessed from their proton or carbon NMR spectra. Toluene was dried over Na. Other dry solvents were stored over molecular sieves.

Preparation of Ethyl Imidazopyridine Propenoate 18a−**e.** Ethylazidoacetate (10.38 g, 80.0 mmol) was added dropwise at −30 °C to a stirred solution containing sodium (0.80 g, 35.0 mmol) in dry ethanol (25 mL). To this solution was added dropwise a mixture of aldehyde **10**, **16a**−**d** (8.00 mmol) in dry ethanol (10 mL). The reaction mixture was returned back room temperature and stirred for 3 h. The solution was poured into aqueous saturated ammonium chloride solution (100 mL) and then extracted with ether. The organic layers were dried over anhydrous sodium sulfate and removed in vacuo. The crude product was chromatographed on alumina column eluting with methylene chloride to afford the azide derivatives **18a**−**e**.

Ethyl α-azido-*β*-(imidazo[1,2-*a*]pyridin-8-yl)propenoate (18b): yield 10%; mp 105−152 °C; IR (KBr) 2100, 1700, 1600, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3 H, J = 7 Hz), 4.39 (q, 2 H, J = 7 Hz), 6.83 (t, 1 H, J = 7 Hz), 7.57 (d, 1 H, J = 1 Hz), 7.61 (d, 1 H, J = 1 Hz), 7.76 (s, 1 H), 8.06 (dd, 1 H, J = 7, 1 Hz), 8.17 (dd, 1 H, J = 7, 1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.25 62.5, 112.4, 113.2, 117.1, 122.2, 125.3, 125.5, 125.8, 128.2, 133.1, 144.6, 162.3. Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.28; N, 27.24. Found: C, 56.12; H, 4.32; N, 27.27. Further elution gave the 8-methyl compound **8a** (yield 10%).

Thermolysis of Azide Compounds. A solution of azide **18a**−**e** (0.29 mmol) in chlorobenzene (10 mL) was stirred at reflux temperature for 10 min. After cooling, the solution was concentrated in vacuo to dryness. The residual material was chromatographed on neutral alumina eluting with methylene chloride to give the cyclized compounds **19**−**23**.

Ethyl imidazo[1,2-*a*]pyrrolo[3,2-*c*]pyridine-8-carboxylate (19b): yield 84%; mp 154−156 °C; ^{1}H NMR ($CDCl_3$) δ

(37) Total energies (au) of **25e**: HF/6-31G*: −944.852340; B3LYP/6-31G*: −950.684420.

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1.36 (t, 3 H, $J = 7$ Hz), 4.44 (q, 2 H, $J = 7$ Hz), 6.94 (d, 1 H, $J = 7$ Hz), 7.49 (m, 2 H), 7.63 (s, 1 H), 7.86 (d, 1 H, $J = 7$ Hz), 10.05 (brs, 1 H). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.80; N, 18.34. Found: C, 62.78; H, 4.477; N, 18.32.

Ethyl imidazo[1,2-*a*]pyrrolo[2,3-*c*]pyridin-8-carboxylate (20): yield 30%; mp 153−155 °C; IR (KBr) 1685, 1375, 1200, 1185, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, 3 H, $J = 7$ Hz), 4.39 (q, 2 H, $J = 7$ Hz), 7.06 (d, 1 H, $J = 7$ Hz), 7.25 (s, 1 H), 7.59 (s, 1 H), 7.69 (s, 1 H), 7.80 (d, 1 H, $J = 7$ Hz), 12.00 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5, 60.9, 108.5, 110.2, 113.8, 119.9, 121.7, 125.4, 127.4, 131.7, 137.4, 161.4; MS *m/z* 229 (M^+, 100), 183 (98), 155 (50), 129 (37). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.80; N, 18.34. Found: C, 62.63; H, 4.80; N, 18.27.

Ethyl imidazo[1,2-*a*]pyrrolo[3,2-*e*]pyridin-7-carboxylate (21): yield 36%; mp 155−157 °C; IR (KBr) 1705, 1255, 1195, 720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (t, 3 H, $J = 7$ Hz), 4.40 (q, 2 H, $J = 7$ Hz), 7.29 (m, 2 H), 7.58 (d, 1 H, $J = 9.5$ Hz), 7.62 (s, 1 H), 8.40 (s, 1 H), 13.30 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4, 60.4, 110.4, 121.4, 122.4, 128.7, 131.4, 131.5, 132.2, 160.9, 167.0; MS *m/z* 229 (M^+, 26), 183 (100), 155 (38), 128 (26), 71 (46), 69 (93), 57 (95), 55 (85). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.80; N, 18.34. Found: C, 62.63; H, 4.78; N, 18.27.

Ethyl imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyridin-7-carboxylate (22): yield 35%; ^1H NMR (DMSO-d_6) δ 1.36 (t, 3 H, $J = 7$ Hz), 4.35 (q, 2 H, $J = 7$ Hz), 7.44 (s, 2 H), 7.56 (m, 2 H), 8.31 (s, 1 H), 11.02 (brs, 1 H); ^{13}C NMR (DMSO-d_6) δ 14.3, 60.6, 100.5, 112.2, 114.0, 114.2, 124.0, 124.1, 125.0, 131.9, 144.4, 160.7; MS *m/z* 229 (M^+, 47), 183 (100), 155 (51), 128 (62). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.80; N, 18.34. Found: C, 62.72; H, 4.79; N, 18.30. Further elution gave **4-ethoxycarbonyl-2a,3-dihydro-1,3,8b-triazacenaphthylene (23)**: yield 2%; ^1H NMR (DMSO-d_6) δ 1.35 (t, 3 H, $J = 7$ Hz), 4.43 (q, 2 H, $J = 7$ Hz), 6.25 (d, 1 H, $J = 7$ Hz), 6.63 (t, 1 H, $J = 7$ Hz), 7.42 (s, 1 H), 7.81 (d, 1 H, $J = 7$ Hz), 7.84 (s, 1 H), 11.56 (s, 1 H); MS *m/z* 229 (M^+, 56), 183 (27), 129 (52), 73 (100), 60 (98).

General Procedure for the Preparation of Iminophosphoranes 24a−e. To a solution of vinyl azides **18a−e** (6.00 mmol) in dry methylene chloride (20 mL) was added dropwise, at 0 °C, a solution of triphenylphosphine (1.57 g, 5.99 mmol) in the same solvent (20 mL). The reaction mixture was stirred at room temperature for 12 h and the solvent was removed in vacuo. The crude product was purified by chromatography on alumina column, eluting with methylene chloride to give the iminophosphoranes **24a−e**.

(*Z*)-Ethyl α-[(triphenylphosphoranylideneamino)-*β*-(imidazo[1,2-*a*]pyridin-8-yl)]propenoate (24b): yield 95%; mp 135−136 °C; IR (KBr) 1690, 1560, 1420, 1305, 1210 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H, $J = 7$ Hz), 3.88 (q, 2 H, $J = 7$ Hz), 6.66 (t, 1 H, $J = 7$ Hz), 7.40 (m, 9 H), 7.45 (s, 1 H), 7.56 (s, 1 H), 7.58 (d, 1 H, $J = 7.5$ Hz), 7.72 (m, 6 H), 7.82 (d, 1 H, $J = 7$ Hz), 8.95 (d, 1 H, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 60.7, 107.4 (d, $^3J_{P-C} = 20$ Hz), 112.4, 112.5, 122.0, 122.1, 127.3, 128.0 (d, $^3J_{P-C} = 12$ Hz), 130.8, 131.7, 132.0 (d, $^2J_{P-C} = 10$ Hz), 132.3 (d, $^3J_{P-C} = 103$ Hz), 139.4 (d, $^2J_{P-C} = 7$ Hz), 144.8, 167.2 (d, $J = 8$ Hz); MS (*m/z*) 491 (M^+, 29), 462 (100), 262 (50), 183 (45), 108 (23). Anal. Calcd for $C_{30}H_{26}N_3O_2P$: C, 73.32; H, 5.30; N, 8.55. Found: C, 73.38; H, 5.31; N, 8.57.

Reactivity of Carbodiimides 25a−e. To a solution of iminophosphoranes **24a−e** (2.4 mmol) in dry toluene (35 mL) was added dropwise at 0 °C ethyl isocyanate (2.4 mmol). The solution was stirred at 0 °C for 30 min and then at room temperature for 19 h. The solvent was removed off under reduced pressure to give heterocumulene **25a−e**, which were used in the next reaction without further purification.

Method A. The crude carbodiimides were poured onto an alumina column. Elution with methylene chloride then with methylene chloride/methanol (98/2, v/v) afforded compounds **26a−d**.

Method B. A solution of the appropriate carbodiimide (0.46 mmol) was refluxed for 2 h in methanol (40 mL) After evaporation of the solvent, the residue was chromatographed on an alumina column with methylene chloride as eluent to give the hydantoins **27a**,**c**,**d**.

Method C. A solution of the carbodiimides **25a−e** (0.52 mmol) in 1,2-dichlorobenzene (100 mL) was stirred at reflux temperature for 19 h (10 min for **25e**). After cooling, the solution was concentrated in vacuo to dryness and the residual material was chromatographed on neutral alumina eluting with methylene chloride to afford tricyclic derivatives **28−32**.

(*Z*)-5-[(Imidazo[1,2-*a*]pyridin-8-yl)methylidene]-1*H*-3-ethylimidazolidin-2,4-dione (26b): yield 35%; mp 251−253 °C; IR (KBr) 1760, 1700, 1660, 1400 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.18 (t, 3 H, $J = 7$ Hz), 3.54 (q, 2 H, $J = 7$ Hz), 6.58 (s, 1 H), 7.01 (t, 1 H, $J = 7$ Hz), 7.57 (d, 1 H, $J = 7$ Hz), 7.73 (d, 1 H, $J = 1$ Hz,), 8.09 (d, 1 H, $J = 1$ Hz), 8.60 (d, 1 H, $J = 7$ Hz), 10.27 (brs, 1 H); ^{13}C NMR (DMSO-d_6) δ 13.4, 33.0, 105.0, 112.8, 113.1, 122.9, 128.5, 129.5, 130.9, 141.9, 145.7, 152.9, 163.5; MS *m/z* 256 (M^+, 95), 184 (45), 157 (100).

(*Z*)-5-(Imidazo[1,2-*a*]pyridin-7-yl]methylidene)-3-ethylimidazolin-2-methoxy-4-one (27c): yield 45%; mp 153−155 °C; IR (KBr) 1735, 1680, 1600, 1490, 1375, 1285, 1160, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, 3 H, $J = 7$ Hz), 3.59 (q, 2 H, $J = 7$ Hz), 4.19 (s, 3 H), 6.85 (s, 1 H), 7.56 (s, 1 H), 7.66 (m, 2 H), 8.05 (d, 1 H, $J = 7$ Hz), 8.22 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 34.5, 56.7, 113.0, 114.3, 119.2, 120.5, 125.0, 131.2, 135.0, 139.4, 145.5, 163.7, 168.8; MS *m/z* 270 (M^+, 100), 184 (23), 156 (48), 86 (21), 58 (41). Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.22; H, 5.19; N, 20.74. Found: C, 61.97; H, 5.21; N, 20.66.

9-Ethoxycarbonyl-7-(*N*-ethylamino)imidazo[2,1-*a*][2,6]-naphthyridine (28b): yield 49%; mp 189−191 °C; IR (KBr) 3420, 1700, 1555, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3 H, $J = 7$ Hz), 1.44 (t, 3 H, $J = 7$ Hz), 3.73 (m, 2 H), 4.44 (q, 2 H, $J = 7$ Hz), 5.55 (m, 1 H), 7.13 (d, 1 H, $J = 7$ Hz), 7.64 (s, 1 H), 7.70 (s, 1 H), 8.03 (d, 1 H, $J = 7$ Hz), 8.53 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.8, 36.7, 61.4, 106.3, 108.4, 113.5, 114.8, 124.5, 129.1, 132.9, 141.8, 144.1, 154.5, 165.8; MS *m/z* 284 (M^+, 100), 256 (35), 195 (24), 184 (39). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.38; H, 5.63; N, 19.72. Found: C, 63.13; H, 5.66; N, 19.64.

8-Ethoxycarbonyl-10-(*N*-ethylamino)imidazo[2,1-*a*][2,7]-naphthyridine (29): yield 43%; mp 141−143 °C; IR (KBr) 1725, 1600, 1255, 1240, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (m, 6 H), 3.94 (m, 2 H), 4.54 (q, 2 H, $J = 7$ Hz), 7.10 (d, 1 H, $J = 7$ Hz), 7.70 (s, 1 H), 7.72 (d, 1 H, $J = 1.5$ Hz), 7.75 (d, 1 H, $J = 1.5$ Hz), 8.16 (d, 1 H, $J = 7$ Hz), 9.30 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4, 15.0, 36.1, 61.5, 106.6, 110.1, 112.5, 114.1, 126.7, 131.5, 135.8, 141.8, 144.5, 155.3, 166.2; MS *m/z* 284 (M^+, 37), 255 (23), 210 (90), 195 (41), 182 (37), 149 (32), 69 (76), 57 (100). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.38; H, 5.63; N, 19.72. Found: C, 63.13; H, 5.66; N, 19.64.

9-Ethoxycarbonyl-3-(*N*-ethylamino)imidazo[1,2-*a*][1,7]-naphthyridine (30): yield 38%; IR (KBr) 1735, 1540, 1280, 1245, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (m, 6 H), 3.67 (m, 2 H), 4.46 (q, 2 H, $J = 7$ Hz), 4.95 (m, 1 H), 7.41 (d, 1 H, $J = 9.5$ Hz), 7.72 (s, 1 H), 7.73 (d, 1 H, $J = 9.5$ Hz), 7.83 (s, 1 H), 8.54 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.8, 37.8, 61.5, 114.8, 115.1, 120.2, 121.5, 125.0, 129.9, 133.3, 140.4, 145.6, 149.4, 165.3; MS *m/z* 284 (M^+, 53), 210 (100), 195 (25), 169 (15), 128 (14). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.38; H, 5.63; N, 19.72. Found: C, 63.13; H, 5.66; N, 19.84.

5-Ethoxycarbonyl-3-(*N*-ethylamino)pyrido[6,1,2-*cd*]-2,3a,7-triazaazulene (32): yield 42%; mp 139−141 °C; IR (KBr) 1715, 1600, 1555, 1295, 1265, 1235, 795, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (m, 6 H), 3.51 (q, 2 H, $J = 7$ Hz), 4.30 (q, 2 H, $J = 7$ Hz), 6.62 (d, 1 H, $J = 7$ Hz), 7.14 (dd, 1 H, $J = 9$, 7 Hz), 7.48 (s, 1 H), 7.53 (d, 1 H, $J = 9$ Hz), 7.69 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 15.5, 62.7, 109.5, 111.5, 115.3, 124.6, 133.6; MS *m/z* 284 (M^+, 100), 209 (19), 195 (46), 169 (84), 156 (23). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.38; H, 5.63; N, 19.72. Found: C, 63.52; H, 5.65; N, 19.80.

General Procedure for the Preparation of Diethyl 3-*N*-Imidazo[1,2-*a*]pyridinylaminomethylene Malonates. Diethyl ethoxymethylenemalonate (7.00 g, 32.0 mmol) was added to a stirred solution of the corresponding amine **33a−d**,[12a,12e] **40a**,**b**,[12b] and **45**[38] (20.0 mmol) in toluene. The mixture was refluxed for 10 h and then cooled to room temperature. After removal solvent, the residue was purified by chromatography (alumina/CH_2Cl_2) to provide the pyridinic malonates **34a−d** and imidazolic malonates **41a**,[8c] **41b,** and **46a−c**.

Ethyl *N*-(imidazo[1,2-*a*]pyridin-8-yl)aminomethylenemalonate (34a): yield 88%; mp 136−138 °C; IR (KBr) 3210, 1710, 1640, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7 Hz), 1.33 (t, 3 H, J = 7 Hz), 4.22 (q, 2 H, J = 7 Hz), 4.31 (q, 2 H, J = 7 Hz), 6.72 (t, 1 H, J = 7 Hz), 6.84 (d, 1 H, J = 7 Hz), 7.57 (s, 1 H), 7.59 (s, 1 H), 7.88 (d, 1 H, J = 7 Hz), 8.83 (d, 1 H, J = 13 Hz), 11.54 (d, 1 H, J = 13 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.1, 60.2, 60.5, 95.7, 104.9, 112.0, 113.8, 121.0, 128.5, 133.0, 138.7, 150.1, 165.60, 167.9; MS m/z 303 (M^+, 45), 257 (100), 184 (30), 157 (50). Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.41; H, 5.61; N, 13.86. Found: C, 59.33; H, 5.59; N, 13.91.

General Procedure for the Preparation of Imidazonaphthyridinic (35−38), Dipyridoimidazolic (43, 47) and Diimidazopyridinic (39, 44) Compounds. A malonate derivative **(**1.00 g) was added to 1,2-dichlorobenzene (50 mL), and the solution was heated at 180 °C for 4 h. After cooling, the solvent was removed in vacuo and the residue was washed with methylene chloride.

From malonate derivative **34a** was obtained **8-ethoxycarbonyl-7,10-dihydro-7-oxo-imidazo[1,2-*h*][1,7]naphthyridine** (**35**): yield 48%; mp > 260 °C; IR (KBr) 3180, 1750, 1700, 1650, 1360, 1210 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.32 (t, 3 H, J = 7 Hz), 4.20 (q, 2 H, J = 7 Hz), 7.47 (d, 1 H, J = 7 Hz), 7.78 (s, 1 H), 8.21 (s, 1 H), 8.39 (s, 1 H), 8.44 (d, 1 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 14.1, 59.8, 107.5, 113.6, 116.4, 121.4, 123.1, 129.7, 133.4, 136.5, 143.2, 164.2, 171.8; MS m/z 257 (M^+, 77), 230 (21), 211 (100), 185 (35), 158 (15). Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.28; N, 16.34. Found: C, 60.82; H, 4.28; N, 16.37.

From malonate derivative **34b** was obtained **8-ethoxycarbonyl-6,9-dihydro-9-oxo-imidazo[1,2-*a*][1,5]naphthyridine** (**36**): yield 49%; mp >260 °C; IR (KBr) 3200, 1710, 1580, 1420, 1305 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.35 (t, 3 H, J = 7 Hz), 4.30 (q, 2 H, J = 7 Hz), 7.63 (d, 1 H, J = 9 Hz), 7.81 (s, 1 H), 8.04 (d, 1 H, J = 9 Hz), 8.62 (s, 1 H), 9.64 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 14.9, 60.5, 114.4, 115.0, 117.9, 122.9, 124.4, 132.3, 137.3, 142.0, 147.5, 164.7, 166.5; m/z (FAB) 258 (MH^+, 53). Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.28; N, 16.34. Found: C, 60.56; H, 4.27; N, 16.28.

From malonate derivative **34d** was obtained **7-ethoxycarbonyl-6,9-dihydro-6-oxoimidazo[1,2-*a*][1,8]naphthyridine** (**37**): yield 92%; mp 247−249 °C; IR (KBr) 1720, 1640, 1480, 1240, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (t, 3 H, J = 7 Hz), 4.54 (q, 2 H, J = 7 Hz), 7.59 (d, 1 H, J = 9 Hz), 7.68 (s, 1 H), 7.75 (d, 1 H, J = 9 Hz), 8.41 (s, 1 H), 9.01 (s, 1 H); ^{13}C NMR (CD_3OD)_δ_17.1, 65.9, 111.6, 112.9, 117.3, 125.1, 134.3, 148.2, 153.1, 168.7; MS m/z 257 (M^+, 25), 211 (100), 155 (34), 69 (40), 57 (43). Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.28; N, 16.34. Found: C, 60.88; H, 4.30; N, 16.38.

From malonate derivative **34c** (alumina, CH_2Cl_2/EtOH 99/1, v/v) was obtained the starting material **34c** (yield 11%) and a mixture of cyclized compound **38** and diimidazopyridinic derivative **39** in a ratio of 1/7. **Ethyl 8-ethoxycarbonyl-6,9-dihydro-9-oxoimidazo[1,2-*a*][1,5]naphthyridine-2-carboxylate** (**38**)**:** ^1H NMR ($CDCl_3$) δ 1.47 (m, 6 H), 4.43 (m, 4 H), 7.93 (AB system, 2 H, J = 9.5 Hz), 8.84 (s, 1 H), 8.90 (s, 1 H), 9.40 (s, 1 H); m/z (FAB) 330 (MH^+, 62). Compound **39**: ^1H NMR ($CDCl_3$) δ 1.42 (m, 9 H), 2.45 (s, 3 H), 4.74 (m, 6 H), 7.08 (d, 1 H, J = 9.5 Hz), 7.27 (d, 1 H, J = 9.5 Hz), 7.61 (d, 1 H, J = 9.5 Hz), 7.77 (d, 1 H, J = 9.5 Hz), 8.18 (s, 1 H), 8.23 (s, 1 H), 8.28 (s, 1 H), 8.44 (d, 1 H, J = 12.5 Hz), 9.2 (s, 1 H), 11.08 (brs, 1 H), 12.25 (d, 1 H, J = 12.5 Hz); MS m/z 534 (M^+, 1), 231 (52), 185 (75), 159 (100), 133 (89), 93 (38).

From a mixture of malonates **46a**−**c**, chromatographic workup afforded the zwitterionic compound **47**: yield 12%; mp 215−217 °C; IR (KBr) 1725, 1510, 1250 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 1.28 (t, 3 H, J = 7 Hz), 1.36 (m, 6 H), 4.31 (m, 6 H), 7.63 (t, 1 H, J = 7 Hz), 7.87 (m, 1 H), 7.90 (s, 1 H), 8.58 (d, 1 H, J = 7 Hz), 8.82 (s, 1 H), 9.22 (d, 1 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.4, 14.7, 60.5, 62.0, 62.2, 100.8, 106.8, 116.6, 102.6, 123.4, 124.5, 124.8, 131.1, 133.6, 145.0, 156.2, 160.4, 165.1, 165.5, 165.7; MS m/z 427 (M^+, 100), 382 (45), 355 (38), 283 (32), 78 (21). Anal. Calcd for $C_{22}H_{21}N_3O_7$: C, 60.13; H, 4.82; N, 9.56. Found: C, 60.16; H, 4.80; N, 9.52.

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Supporting Information Available: ^1H NMR, ^{13}C NMR, MS, and CHN analysis for compounds **9**, **10**, **15a**−**d**, **16a**−**d**, **17a**−**d**, **18a**,**c**−**e**, **19a**, **24a**,**c**−**e**, **26a**,**c**,**d**, **27a**,**d**, **28a**, **34b**−**d**, **41a**,**b**, **43**, **44**, and **46a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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