Intramolecular Diels−Alder Reactions of 3-(Tetrahydropyridinyl)indoles: Stereoselective Synthesis of Novel Pentacyclic Ring Systems

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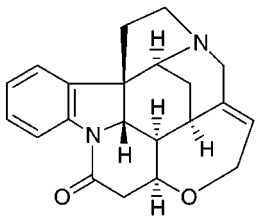
Intramolecular Diels−Alder cycloaddition reactions of 1-(4-pentenoyl)-3-(tetrahydropyridinyl)indoles **7** followed by acid-catalyzed double-bond migration result in the stereoselective formation of novel pentaheterocyclic ring systems related to those of certain *Strychnos* alkaloids. The assignment of the stereochemistry of the cycloadducts was based on the analysis of 1D and 2D DQF−COSY and ROESY ^{1}H NMR spectra. 1-(4-Pentynoyl)-3-(tetrahydropyridinyl)indoles underwent an analogous cyclization to give the corresponding pentacyclic carbazoles in high yields.

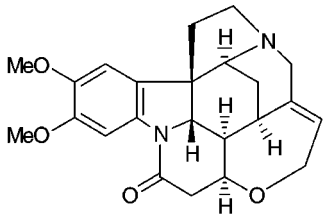
Introduction

A number of indole alkaloids such as strychnine (**1**), brucine (**2**), aspidospermine (**3**), and some derivatives, e.g., the nicotinic receptor antagonist, alcuronium, have been found to possess allosteric binding properties at the five muscarinic acetylcholine receptor subtypes (m1−m5).[1−5] Brucine, for example, is the first known allosteric agent to increase the affinity and function of the neurotransmitter molecule, acetylcholine, selectively at muscarinic m1 receptors.[2] More potent compounds with similar actions on muscarinic receptors may have a potential clinical application in the alleviation of the cognitive symptoms associated with the cholinergic deficit found in the early stages of Alzheimer's disease.[2]

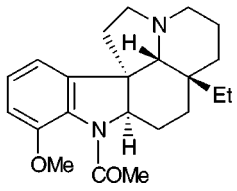
Allosteric interactions with muscarinic receptors have also been observed with other fused multicyclic indole constructs[5−7] (e.g., **4**[6,7]). However, they are structurally complex and have relatively low affinities. Therefore, we have been investigating structurally related indole ring systems which are more amenable to synthesis and to structure−activity correlation analyses. The lead agents have in common a number of structural features which are believed to be important for their activity. These include a partially reduced carbazole ring system, an amide carbonyl group, and a basic nitrogen atom. On the basis of these characteristics and molecular modeling studies, we have designed the novel pentacyclic scaffold **5** that incorporates these features within the ring system and, in addition, offers the potential for locating the basic nitrogen atom in a variety of endo- or exocyclic positions.



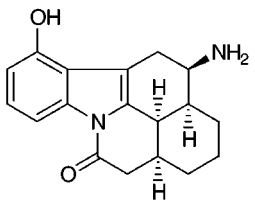
Strychnine **1**



Brucine **2**



Aspidospermine **3**



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Among a variety of potential synthetic approaches, a promising option appeared to be the construction of the pentacycle **5** by means of an intramolecular Diels−Alder reaction (Scheme 1). From FMO considerations, the desired stereochemical outcome would thus be a consequence of the intramolecular [4 + 2] π cycloaddition reaction of the intermediate 1-(4-pentenoyl)-3-(tetrahydropyridinyl)indole (**7**). 3-(Tetrahydropyridinyl)indoles (3-THPIs) **8** are cyclic homologues of 3-vinylindoles. The latter are known to function as dienes and have been used in the inter-[8,9] and intramolecular[10−12] construction of several heterocyclic ring systems. Furthermore, recent MO calculations[13] suggest that 3-THPIs also contain an electron-rich butadiene unit and should participate in similar HOMO (diene)−LUMO (dieneophile)-controlled Diels−Alder processes.

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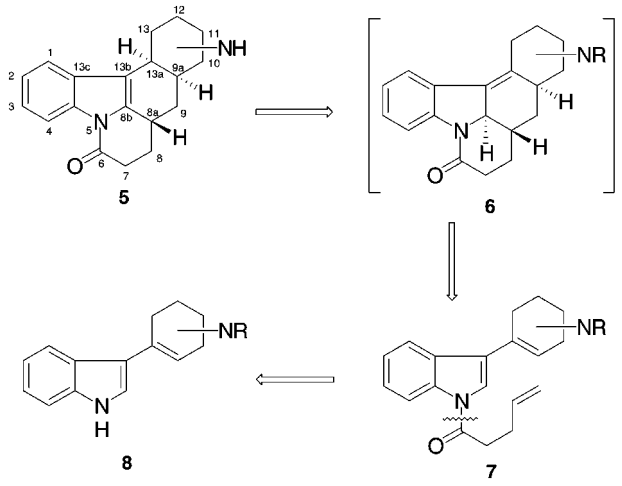
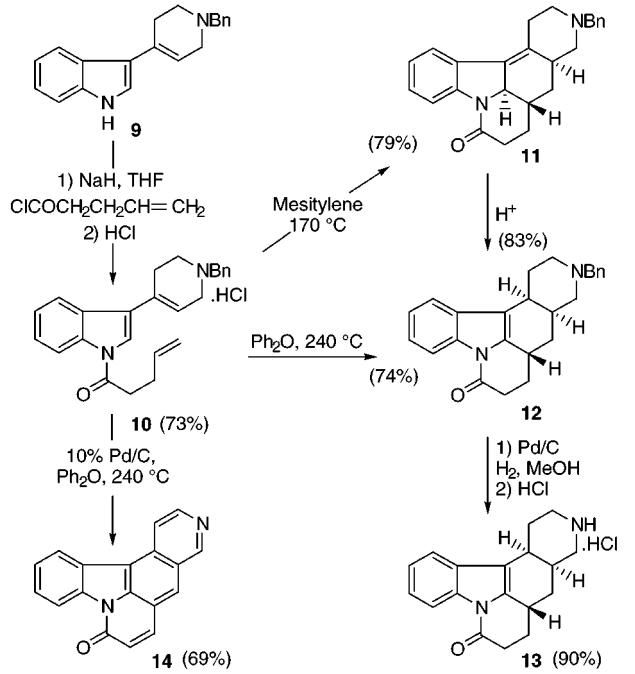
Scheme 1



Scheme 2



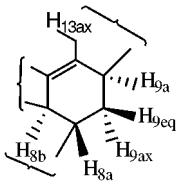
However, previous intermolecular Diels–Alder reactions of analogues of **8** with a limited number of dieneophiles has either led to uncharacterizable products or furnished the desired cycloadducts in poor yields.[13–15] To date, no intramolecular reactions of 3-THPIs have been reported. Nevertheless, this strategy presented us with a relatively short synthetic route to gain entry to the desired molecules.

In this paper, we report the details of our investigation that culminated in the successful stereoselective synthesis of a series of novel pentacyclic tetrahydrocarbazolones which possess similar binding properties to the initial lead compounds. An abstract reporting some of the results has been published.[16]

Results and Discussion

The requisite 3-THPI **9** was prepared from the condensation of indole and *N*-benzylpiperidone under basic conditions according to our previously published procedure.[17] Acylation of the indole nitrogen with 4-pentenoyl chloride under anhydrous conditions afforded the Diels–Alder precursor **10** in 73% yield (Scheme 2). We anticipated that the intramolecular Diels–Alder reaction would occur at temperatures higher than or comparable to those reported for analogous intramolecular cyclization of 3-vinylindoles[18] (>160 °C), as there are no electron-withdrawing substituents on the dieneophile. Indeed, no reaction was detected in refluxing toluene or xylene for 48 h. However, we were able to effect cycloaddition by conducting the reaction in boiling mesitylene for 120 h to give **11** as a stable crystalline solid in 79% yield. The latter underwent an acid-catalyzed [1,3]-hydrogen shift in a stereospecific manner, furnishing **12** as the sole product. Moreover, we were able to drastically reduce the cyclization time to about 2 h by heating **10** in diphenyl ether at 240 °C under argon gas flow and accomplish cyclization and double-bond migration in one step in 74% yield. Finally, debenzylation of the rearranged adduct using H_2–Pd/C gave the target secondary amine **13** in 90% yield.

Table 1. Coupling Constants for Diagnostic Protons of Diels–Alder Adducts 11 and 25



	coupling constants (Hz)	
	11	**25**
$J_{9a,8b}$	3.2	1.8
$J_{9a,9ax}$	~0	1.8
$J_{9a,9eq}$	8.0	6.6
$J_{9ax,9eq}$	−13.2	~−13[a]
$J_{8a,9ax}$	13.0	~10[a]
$J_{8a,9eq}$	3.0	small[a]
$J_{8a,8b}$	9.6	10.0
$J_{8b,13ax}$	3.2	4.5

[a] Some uncertainty as to the precise magnitude due to partial overlap of H9ax and H9eq resonances.

Full analyses of the 1D and 2D COSY ^{1}H NMR spectra of **11** and **13** were entirely consistent with their expected stereochemistries. For example, in the spectra of **11**, the coupling constant of 9.6 Hz between H_{8a} and H_{8b} at 1.78 and 4.10 ppm, respectively, was compatible with their trans diaxial configuration. The long-range homoallylic coupling constant of 3.2 Hz between H_{8b} and H_{9a} confirms their diaxial relationship[19] as does the magnitude of the coupling constants of H_{9a} and H_{8a} to the axial and equatorial H_9 protons (Table 1). The relative stereoconfiguration of the two hydrogens H_{9a} and H_{13a} in the rearranged adduct **13** was assigned as gauche on the basis of their small coupling constant ($J_{9a,13a}$ = 4.5 Hz).

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Scheme 3

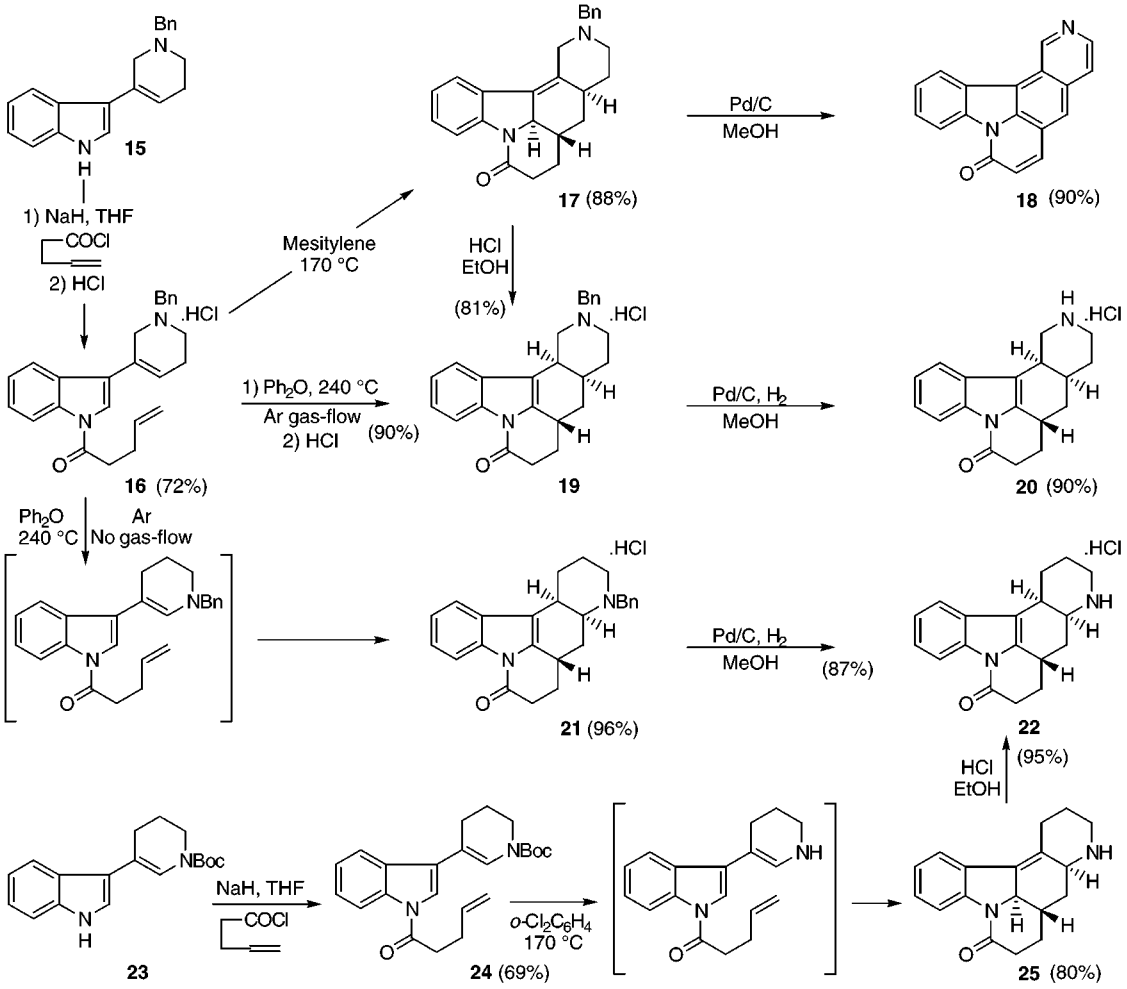
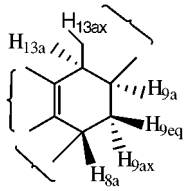


Table 2. Coupling Constants for Diagnostic Protons of Rearranged Diels–Alder Adducts 13, 20, and 22



	coupling constants (Hz)		
	13	**20**	**22**
$J_{9a,13a}$	4.5	4.2	4.5
$J_{9a,9ax}$	3.9	4.0	3.9
$J_{9a,9eq}$	3.9	4.0	3.9
$J_{9ax,9eq}$	−14.1	∼−14	−14.1
$J_{8a,9ax}$	12.2	11.8	12.2
$J_{8a,9eq}$	5.4	5.4	5.4

The axial orientation of H_{8a} in **13** was indicated first by the large coupling to the H_{9ax} proton (12.2 Hz) due to their antiperiplanar relationship and second by the small coupling of both H_{9a} and H_{8a} to H_{9eq} (Table 2) due to the gauche orientations of these protons. The acid-catalyzed 1,3-rearrangement of the double bond in **11** to **12** proceeded with retention of the basic stereochemistry and no detectable generation of diastereoisomers.

The synthetic scheme also offered the possibility of obtaining the fully aromatic pentacycle **14** via catalytic dehydrogenation. This compound is analogous to the naturally occurring ring structures of the canthine and picrasidine alkaloids which have a wide range of pharmacological actions[20] and to a number of pyridocarbazoles reported recently to have antitumor properties.[21,22] The intramolecular cyclization of **10** and subsequent dehydrogenation of the ring system in diphenyl ether containing Pd/C proceeded efficiently to give the fully unsaturated pentacycle **14** in 69% yield.

With this method in hand for the elaboration of the pentacyclic framework, we wished to expand our SAR studies and increase muscarinic receptor affinity by relocating the secondary amine nitrogen in **13** from the 11-position to the 12-position (i.e., to the adjacent endocyclic position). We envisioned that a synthetic approach analogous to that shown in Scheme 2, but starting with **15**,[17] would yield the desired isomeric pentacycle (Scheme 3). Following the almost identical reaction conditions and procedures for acylation and cyclization, **19** could be obtained directly from **16** in 90% yield. As found for the reactions depicted in Scheme 2, the cyclized intermediate **17** was isolated in 88% yield if the reaction was carried out in boiling mesitylene, and it could be isomerized to **19** under acidic conditions. Debenzylation of **19** gave **20** as the sole product in 90% yield. The fully

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(21) Leon, P.; Garbay-Jaureguiberry, C.; Barsi, M. C.; Le Pecq, J. B.; Roques, B. P. *J. Med. Chem.* **1987**, *30*, 2074–2080.
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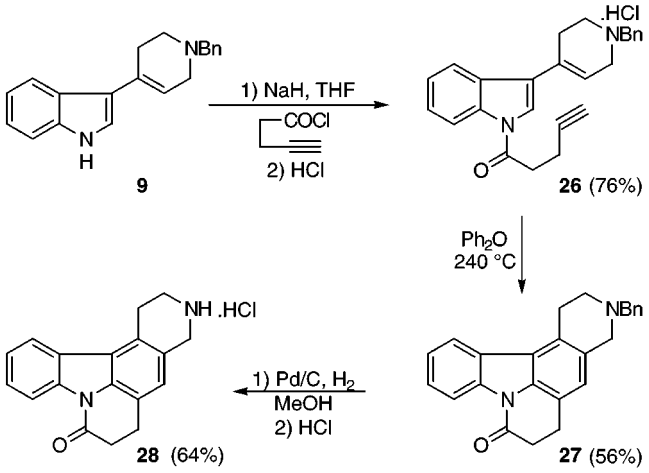
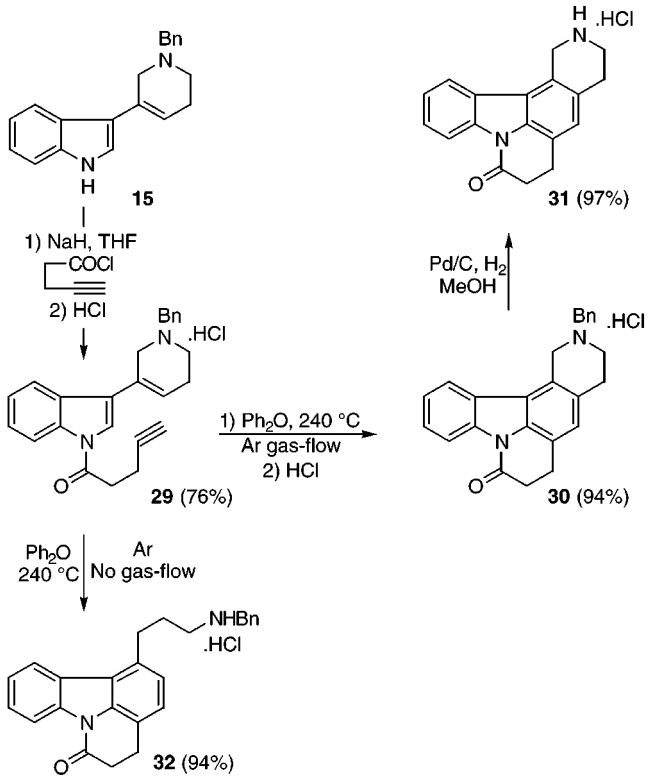
Scheme 4



Scheme 5



aromatized compound **18** was also obtained by catalytic dehydrogenation of **17** with Pd/C in refluxing MeOH in 90% yield.

Interestingly, though unexpectedly, the intramolecular Diels–Alder reaction of **16** in diphenyl ether conducted in an *enclosed vessel under argon* furnished **21**, an isomer of **19** (which had been prepared at the same temperature but in an *open vessel under a steady argon gas flow*). The structure of **21** was established by the analysis of the ^{1}H COSY and ROESY spectra of **22**, the debenzylation product of **21**. The relative orientations of the methine protons in **22** were similar to those found in **13** and **20** (Table 2). The coupling constants between the six resolved 11-, 12-, and 13-CH_2 protons show that the tetrahydropyridine ring is in the chair conformation. The ROESY cross-peaks between the H_1 proton on the indole ring and the H_{13a} and both the 13-protons in **22** confirm their proximity to this proton: no other NOEs were observed between the indole ring protons and any other protons under the experimental conditions used. NOEs between (H_{7ax} and H_{8a}), (H_{8ax} and H_{9ax}), (H_{9ax} and H_{13a}), and (H_{9a}, H_{13ax}, and H_{11ax}) confirm the 1,3-diaxial orientations of the methine protons and the chair conformation of the tetrahydropyridine ring. The lack of NOEs between the 12-protons and any noncoupled protons is also in agreement with the proposed structure.

A mechanistic explanation for the formation of **21**, isomeric to **19**, is that HCl, released in situ in the enclosed vessel from the salt, catalyzes the migration of the double bond in the allylamine isomer **16** to the thermodynamically more stable enamine isomer, resulting in the formation of the cycloadduct **21** (Scheme 3). In an open vessel, HCl will be lost to the atmosphere, the rearrangement will not occur, and **17** is the sole product.

A direct synthesis of **22** from the enamide **23**, following the same intramolecular approach (Scheme 3), was also accomplished. The starting enamide was synthesized readily from the condensation of indole and *N*-(*tert*-butoxycarbonyl)-3-piperidone under base-catalyzed conditions[17] and acylated to give the Diels–Alder precursor **24**. The butadiene-1,4-diamine unit in **24** would be anticipated to have a greatly reduced eneophilicity because of the strong electron-withdrawing property of the carbamate function. However, as the Boc protecting group is thermally unstable,[24] cleavage to a secondary amine at cyclization temperatures (>170 °C) was anticipated to regenerate the electron-rich diene system in situ which was expected to cyclize readily.

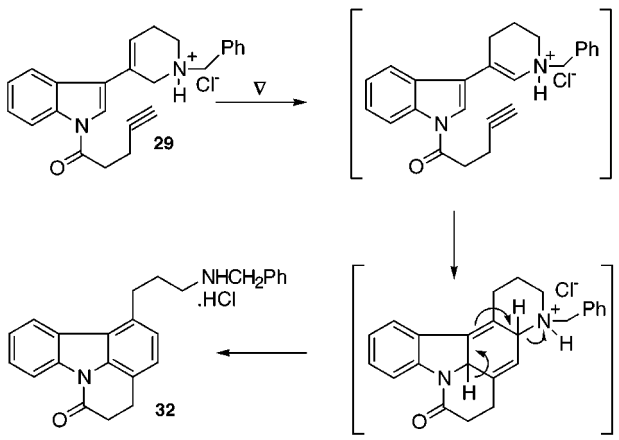
As predicted, the thermal cyclization of **24** in boiling *o*-dichlorobenzene for 44 h afforded **25** as a single product in 80% yield. The CHN analysis and MS and ^{1}H NMR spectra of **25**, including the coupling constants (Table 2) and comparison with the spectra of **22**, were in agreement with the expected structure. The structure of **25** has also been confirmed by X-ray crystallography.[23] Treatment of **25** with ethanolic HCl at 90 °C led to the exclusive formation of **22**. The ^{1}H NMR spectrum of this product was identical to that obtained from debenzylation of **21**.

To investigate further the scope of this intramolecular reaction, we extended our studies to include the alkyne equivalent as the dieneophile (Scheme 4). Thus, acylation of **9** with 4-pentynoyl chloride furnished **26** which readily cyclized to produce pyrido-annelated carbazole **27** as a single product in 56% yield. Debenzylation by catalytic hydrogenation proceeded cleanly and efficiently to yield the secondary amine **28**. In exactly the same manner, acylation of 3-(tetrahydropyridin-3-yl)indole **15** followed by subsequent cyclization and debenzylation gave the pyrido-annelated carbazole **31** in 69% overall yield (Scheme 5).

Interestingly, when this cycloaddition was conducted in an enclosed vessel, we isolated a different product in 94% yield which was characterized by ^{1}H NMR, CHN analysis, and MS as **32**. A possible mechanism for the formation of the tetracyclic structure is shown in Scheme 6. The presence of HCl in the reaction vessel at elevated temperatures catalyzes the migration of the double bond toward the thermodynamically more stable enamine intermediate as observed earlier in the **16** to **24** trans-

(23) Furukawa, Y. Personal communication.
(24) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141–6142.

Scheme 6



formation (Scheme 3). Cycloaddition is then followed by aromatization of the carbazole ring through cleavage of the carbon−nitrogen bond rather than by elimination of hydrogen (Scheme 6).

In conclusion, the intramolecular Diels−Alder reactions of 3-(tetrahydropyridinyl)indoles with alkene and alkyne moieties as dieneophiles provide a simple and flexible synthetic entry to a number of novel saturated and unsaturated pentacyclic carbazoles, which are structurally related to a number of biologically active natural products. With an alkene as dienophile, the reaction proceeds stereoselectively, affording a single cycloadduct which can isomerize stereospecifically under acid conditions. With an alkyne as dienophile, cycloaddition is followed by a loss of hydrogen, furnishing pentacyclic carbazoles as the sole products in the reaction. In addition, at elevated temperatures, the Diels−Alder precursors **16** and **29** undergo an acid-catalyzed 1,3-double bond rearrangement to generate enamines in situ which readily cyclize to yield novel heterocycles. The allosteric actions of the compounds described here together with a number of their analogues have been evaluated in binding and functional assays at muscarinic receptor subtypes.[16,25]

Experimental Section

4-Pentenoic acid and 4-pentynoic acid were purchased from Aldrich Chemical Co. and converted to their corresponding acid chlorides by the usual methods. Anhydrous THF and MeOH were prepared according to the procedures described by Perrin and Armarego.[26] All reactions were carried out under a slow stream of argon unless otherwise stated. Melting points (mp) were carried out in open capillaries and are uncorrected. The ^{1}H NMR spectra were recorded on Bruker AM 400 WB and AM 500 and Varian Unity 600 spectrometers using the facilities at the MRC Biomedical NMR Centre, National Institute for Medical Research, Mill Hill. NMR experiments were performed at 25−30 °C and included DQF−COSY[27] and ROESY[28] (mixing time 500 ms) experiments. Chemical shifts are reported in ppm downfield of internal tetramethylsilane (TMS) unless otherwise indicated. Mass spectra were run by fast atom bombardment on a VG Analytical ZAB-SE double-focusing magnetic sector mass spectrometer. Elemental analyses were performed by the microanalytical section of the Chemistry Department, University College London. Column chromatography was carried out on Merck silica gel 60 (70−230 mesh ASTM).

General Procedure for Acylation of 3-(Tetrahydropyridinyl)indoles. A suspension of sodium hydride (60% w/v dispersion in mineral oil, 32 mmol) in THF (30 mL) was added to a cold solution of the appropriate 3-(tetrahydropyridinyl)indole[17] (30 mmol) in THF (300 mL). The mixture was stirred at room temperature for 1 h and then cooled to 0−5 °C. A solution of the appropriate acid chloride (32 mmol) in THF (70 mL) was then added dropwise, and the resulting mixture was stirred for a further 2 h. The mixture was acidified with 2 N hydrochloric acid, and the resulting white precipitate was collected by filtration, washed successively with THF, H_2O, and ether, and dried in vacuo.

1-(4-Pentenoyl)-3-(1-benzyl-1,2,5,6-tetrahydropyridin-4-yl)indole Hydrochloride (10). The product was obtained as a white crystalline solid in 73% yield: mp 263−265 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 2.45 (m, 2H), 2.55 (br s, 2H), 2.94 (t, J = 7.4 Hz, 2H), 3.70 (br s, 2H), 3.90 (s, 2H), 4.18−4.35 (m, 2H), 4.94 (dd, J = 1.2 and 10.2 Hz, 1H), 5.03 (dd, J = 1.6 and 17.1 Hz, 1H), 5.77−5.86 (m, 1H), 6.08 (m, 1H), 7.19 (t, J = 8 Hz, 1H), 7.22−7.29 (m, 1H), 7.32−7.38 (m, 2H), 7.48 (s, 1H), 7.51 (m, 2H), 7.61 (d, J = 8 Hz, 1H), 8.36 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{25}H_{26}N_2O$·HCl: C, 73.79; H, 6.69; N, 6.88. Found: C, 73.55; H, 6.60; N, 6.69.

1-(4-Pentenoyl)-3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)indole Hydrochloride (16). The product was obtained as a white crystalline solid in 72% yield: mp 190−191 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 2.59 (m, 2H), 2.71 (br s, 2H), 3.07 (t, J = 7.3 Hz, 2H), 3.23 (br s, 2H), 3.93 (br s, 2H), 4.28 (br s, 2H), 5.08 (dd, J = 1.3 and 10.2 Hz, 1H), 5.17 (dd, J = 1.7 and 17.1 Hz, 1H), 5.95 (m, 1H), 6.43 (m, 1H), 7.31 (t, J = 8 Hz, 1H), 7.39 (t, J = 8 Hz, 1H), 7.47 (m, 3H), 7.60 (m, 3H), 7.72 (d, J = 8 Hz, 1H), 8.48 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{25}H_{26}N_2O$·HCl: C, 73.79; H, 6.69; N, 6.88. Found: C, 74.18; H, 6.66; N, 6.87.

1-(4-Pentenoyl)-3-(1-(*tert*-butoxycarbonyl)-1,4,5,6-tetrahydropyridin-3-yl)indole (24). Following the general procedure for acylation of **23** with 4-pentenoyl chloride, the reaction mixture was concentrated to half its original volume, and after addition of aqueous acetic acid (0.1 M), it was extracted with ether. Ether was removed under reduced pressure, and the resulting residue was stirred in a small volume of *n*-hexane/EtOAc (4:1), filtered, and washed with hexane. **24** was obtained as a white solid (69% yield): mp 146−147 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 2.01 (br s, 2H), 2.46 (br s, 2H), 2.60 (dt, J = 6.9 and 7.0 Hz, 2H), 3.10 (t, J = 7.0 Hz, 2H), 3.67 (m, 2H), 5.06 (dd, J = 10.1 and 1.3 Hz, 1H), 5.15 (dd, J = 17.1 and 1.3 Hz, 1H), 5.95 (m, 1H), 7.26 and 7.39 (m, 3H), 7.50 and 7.65 (two singlets, rotameric mixture, 1H), 7.77−7.87 (two doublets, J = 8 Hz, rotameric mixture, 1H), 8.53 (m, 1H). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.35; H, 7.27; N, 7.21.

1-(4-Pentynoyl)-3-(1-benzyl-1,2,5,6-tetrahydropyridin-4-yl)indole Hydrochloride (26). Acylation of **9** with 4-pentynoyl chloride according to the general procedure afforded **26** as a white solid (76% yield): mp 263−265 °C; ^{1}H NMR (DMSO-d_6/D_2O) δ 2.61 (td, J = 6.8 and 2.4 Hz, 2H), 2.72 (t, J = 2.4 Hz, 1H), 2.87 (br s, 2H), 3.29 (t, J = 6.8 Hz, 2H), 3.45 (br s, 2H), 3.84 (s, 2H), 4.39 (s, 2H), 6.35 (br s, 1H), 7.37 (t, J = 8 Hz, 1H), 7.43 (t, J = 8 Hz, 1H), 7.51−7.57 (m, 5H), 7.91 (d, J = 8 Hz, 1H), 7.96 (s, 1H), 8.44 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{25}H_{24}N_2O$·HCl: C, 74.15; H, 6.22; N, 6.92. Found: C, 74.13; H, 6.21; N, 6.72.

1-(4-Pentynoyl)-3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)indole Hydrochloride (29). The product was obtained as a white crystalline solid in 76% yield: mp 226−227 °C; ^{1}H NMR (DMSO-d_6/D_2O) δ 2.60−2.65 (m, 4H), 2.69 (t, J = 2.5 Hz, 1H), 3.26 (t, J = 6.7 Hz, 2H), 3.30 (m, 2H), 4.15 (s, 2H), 4.42 (s, 2H), 6.53 (m, 1H), 7.39 (t, J = 8 Hz, 1H), 7.45 (t, J = 8 Hz, 1H), 7.50−7.57 (m, 5H), 7.87 (d, J = 8 Hz, 1H), 7.88 (s,

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1H), 8.43 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{25}H_{24}N_2O$·HCl·0.5H_2O: C, 72.54; H, 6.33; N, 6.77. Found: C, 72.62; H, 6.16; N, 6.59.

Intramolecular Diels−Alder Reactions in Mesitylene. The Diels−Alder precursor (0.01 mol) was suspended in mesitylene (250 mL) and heated to 170 °C for 5 days. The solvent was removed under reduced pressure, and the resulting residue was purified as described.

Intramolecular Diels−Alder Reactions in Diphenyl ether. The Diels−Alder precursor (0.01 mol) was suspended in diphenyl ether (400 mL) at 230−240 °C for about 2 h or until the starting material was fully consumed under a slow stream of argon gas unless otherwise stated. The solution was cooled, and a saturated solution of hydrogen chloride in ether was added until a slight excess of the acid was present. Ether was then added until no more precipitation occurred. The resulting precipitate was collected by filtration, washed exhaustively with ether, and dried in vacuo.

11-Benzyl-7,8,8a,8b,9,9a,10,11,12,13-decahydro-6*H*-dipyrido[3,4-*c*:1′,2′,3′-*lm*]carbazol-6-one (11). The product was obtained as a white crystalline solid in 79% yield: mp 173−174 °C; ^{1}H NMR ($CDCl_3$) δ 1.45−1.58 (m, 2H), 1.63−1.81 (m, 2H), 1.92−2.04 (m, 3H), 2.39 (m, 1H), 2.59 (m, 1H), 2.68−2.74 (m, 2H), 2.88 (m, 1H), 2.97 (m, 1H), 3.03 (m, 2H), 3.49 (d, 1H), 3.55 (d, 1H), 4.10 (m, 1H), 7.05 (t, J = 8 Hz, 1H), 7.21 (t, J = 8 Hz, 1H), 7.25−7.34 (m, 5H), 7.48 (d, J = 8 Hz, 1H), 8.17 (d, J = 8 Hz, 1H); MS *m*/*e* 371 (MH^+, 100), 279 (10). Anal. Calcd for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found: C, 80.88; H, 6.96; N, 7.42.

11-Benzyl-7,8,8a,9,9a,10,11,12,13,13a-decahydro-6*H*-dipyrido[3,4-*c*:1′,2′,3′-*lm*]carbazol-6-one (12). Method 1. A solution of **11** (0.5 g, 1.4 mmol) in mesitylene containing 15% concentrated HCl in EtOH (1 mL) was heated to 150 °C for 1 h under a very slow stream of argon and for a further 30 min under a fast stream of argon. The solvent was removed under reduced pressure, and the resulting free base was recrystallized from 2-propanol to give **12** as a light green crystalline solid (0.45 g, 83%).

Method 2. The resulting crude free base (obtained after the removal of solvent in vacuo), following the general cyclization procedure in diphenyl ether, was chromatographed on silica eluting with EtOAc. The product was recrystallized from EtOAc as light green needles in 74% yield: mp 193−194 °C; ^{1}H NMR (DMSO-d_6/D_2O, 375 K) δ 1.45−1.65 (m, 2H), 1.70−1.81 (m, 1H), 1.95−2.11 (m, 3H), 2.21−2.33 (m, 2H), 2.43−2.52 (m, 2H), 2.56 (m, 1H), 2.63−2.73 (m, 2H), 2.81−3.0 (m, 2H), 3.40 (s, 2H), 7.18−7.33 (m, 7H), 7.60 (d, J = 8 Hz, 1H), 8.30 (d, J = 8 Hz, 1H); MS *m*/*e* 371 (M^+ + 1, 100), 279 (8). Anal. Calcd for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found: C, 80.75; H, 7.08; N, 7.46.

Dipyrido[3,4-*c*:1′,2′,3′-*lm*]carbazol-6-one (14). A suspension of **10** (3.03 g) in diphenyl ether (300 mL) was heated at 240 °C for 2 h under a slow stream of argon. The solution was cooled to room temperature, and 10% Pd/C (1.0 g) was then added. The mixture was reheated to 240 °C for a further 18 h, cooled to about 100 °C, and filtered. The filtrate was cooled to room temperature, and the resulting precipitate was collected by filtration, washed with ether, and dried in vacuo to give a yellow powder (1.39 g, 69%): mp 290−291 °C; ^{1}H NMR (DMSO-d_6) δ 6.94 (d, J = 9.5 Hz, 1H), 7.66−7.75 (m, 2H), 8.37 (d, J = 9.5 Hz, 1H), 8.71−8.80 (m, 5H), 9.63 (s, 1H); HRMS calcd for $C_{18}H_{11}N_2O$ 271.0872, found 271.0720.

12-Benzyl-7,8,8a,8b,9,9a,10,11,12,13-decahydro-6*H*-dipyrido[4,3-*c*:1′,2′,3′-*lm*]carbazol-6-one (17). Recrystallized from 2-propanol as colorless flakes (88% yield): mp 188−190 °C; ^{1}H NMR ($CDCl_3$) δ 1.49−2.02 (m, 7H), 2.31−2.75 (m, 5H), 3.00 (m, 1H), 3.50 (d, J = 13.0 Hz, 1H), 3.13 (d, J = 13.0 Hz, 1H), 4.11 (m, 2H), 6.90 (t, J = 8 Hz, 1H), 7.06 (d, J = 8 Hz, 1H), 7.19 (t, J = 8 Hz, 1H), 7.25 (m, 5H), 8.18 (d, J = 8 Hz, 1H); MS *m*/*e* 371 (MH^+, 57), 279 (5). Anal. Calcd for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found: C, 81.45; H, 7.13; N, 7.46.

12-Benzyl-7,8,8a,9,9a,10,11,12,13,13a-decahydro-6*H*-dipyrido[4,3-*c*:1′,2′,3′-*lm*]carbazol-6-one Hydrochloride (19). The product was obtained by either acid-catalyzed double-bond migration of **17** as described for **12** or by following the general cyclization procedure in diphenyl ether. Recrystallized from a mixture of 2-propanol and ether (yields from each reaction: 81% and 90% respectively): mp 279−281 °C; ^{1}H NMR (500 MHz, CD_3OD, 300 K) δ 1.72 (m, 2H), 1.92 (m, 1H), 2.16 (m, 3H), 2.50 (m, 1H), 2.80−2.96 (m, 3H), 3.08 (m, 1H), 3.27 (m, 1H), 3.38 (m, 1H), 3.54 (m, 2H), 4.20 (d, J = 13.0 Hz, 1H), 4.44 (d, J = 13.0 Hz, 1H), 7.01 (m, 1H), 7.25 (t, J = 8 Hz, 1H), 7.46−7.52 (m, 5H), 7.60 (t, J = 8 Hz, 1H), 8.36 (d, J = 8 Hz, 1H); MS *m*/*e* 371 (MH^+, 100), 279 (2). Anal. Calcd for $C_{25}H_{26}N_2O$·HCl·0.5H_2O: C, 72.19; H, 6.79; N, 6.74. Found: C, 72.45; H, 6.84; N, 6.37.

10-Benzyl-7,8,8a,9,9a,10,11,12,13,13a-decahydro-6*H*-dipyrido[2,3-*c*:1′,2′,3′-*lm*]carbazol-6-one Hydrochloride (21). A suspension of **16** (1.0 g) in diphenyl ether (100 mL) was heated at 240 °C for 3 h under an atmosphere of Ar in an enclosed vessel (no Ar gas flow). The reaction mixture was cooled and diluted with ether. The resulting precipitate was collected by filtration, washed with ether, and dried in vacuo. The product was obtained as a light green powder (0.96 g, 96%): mp 188−191 °C; ^{1}H NMR (CD_3OD) δ 1.54−1.65 (m, 1H), 1.77−1.88 (m, 2H), 1.93−2.05 (m, 2H), 2.09−2.24 (m, 1H), 2.31−2.38 (m, 1H), 2.74−2.93 (m, 2H), 2.96−3.23 (m, 3H), 3.34−3.43 (m, 1H), 3.67−3.71 (m, 1H), 3.86 (br s, 1H), 4.57 (d, J = 13.4 Hz, 1H), 4.66 (d, J = 13.4 Hz, 1H), 7.25−7.33 (m, 2H), 7.47−7.52 (m, 3H), 7.59−7.63 (m, 2H), 7.67 (d, J = 8 Hz, 1H), 8.40 (dd, J = 8 and 1.4 Hz, 1H); MS *m*/*e* 371 (M^+ + 1, 100), 279 (7). Anal. Calcd for $C_{25}H_{26}N_2O$·HCl·0.25H_2O: C, 72.98; H, 6.74; N, 6.81. Found: C, 72.86; H, 6.93; N, 6.62.

7,8,8a,8b,9,9a,10,11,12,13-Decahydro-6*H*-dipyrido[2,3-*c*:1′,2′,3′-*lm*]carbazol-6-one (25). A solution of **24** (0.5 g) in *o*-dichlorobenzene (75 mL) was heated at 170 °C for 44 h. After removal of the solvent, the residue was recrystallized from a mixture of EtOAc, MeOH, and *n*-hexane to give **25** as colorless cubic crystals (0.29 g, 80%): mp 189−191 °C; ^{1}H NMR ($CDCl_3$) δ 1.49−1.98 (m, 7H), 2.17 (m, 1H), 2.62−2.90 (m, 2H), 2.94 (m, 1H), 3.22 (m, 2H), 3.43 (d, J = 5.6 Hz, 1H), 4.05 (m, 1H), 7.10 (t, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 8.17 (d, J = 8 Hz, 1H); MS *m*/*e* 372 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.26; H, 7.17; N, 10.09.

11-Benzyl-7,8,10,11,12,13-hexahydro-6*H*-dipyrido[3,4-*c*:1′,2′,3′-*lm*]carbazol-6-one (27). The resulting crude free base (obtained after the removal of solvent in vacuo), following the general cyclization procedure in diphenyl ether, was chromatographed on silica, eluting with EtOAc/toluene (1:1) to give **27** as a white crystalline solid in 56% yield: mp 126−127 °C; ^{1}H NMR ($CDCl_3$) δ 2.93 (t, J = 5.9 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 3.20 (t, J = 7.5 Hz, 2H), 3.36 (t, J = 5.9 Hz, 2H), 3.76 (s, 4H), 6.93 (s, 1H), 7.25−7.45 (m, 6H), 7.50 (t, J = 8 Hz, 1H), 7.98 (d, J = 8 Hz, 1H), 8.54 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.64. Found: C, 81.59; H, 5.90; N, 7.50.

12-Benzyl-7,8,10,11,12,13-hexahydro-6*H*-dipyrido[4,3-*c*:1′,2′,3′-*lm*]carbazol-6-one Hydrochloride (30). The product was obtained as a pale yellow powder in 94% yield: mp 291−292 °C; ^{1}H NMR (DMSO-d_6/D_2O) δ 3.03 (t, J = 7.4 Hz, 2H), 3.20−3.30 (m, 4H), 3.53 (br s, 2H), 4.56 (s, 2H), 4.81 (s, 2H), 7.28 (s, 1H), 7.51 (t, J = 8 Hz, 1H), 7.56−7.65 (m, 6H), 7.84 (d, J = 8 Hz, 1H), 8.45 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{25}H_{22}N_2O$·HCl·0.25H_2O: C, 73.70; H, 5.81; N, 6.88. Found: C, 73.90; H, 6.05; N, 6.78.

1-(3-Benzylaminopropyl)-4,5-dihydropyrido[3,2,1-*jk*]carbazole-6-one Hydrochloride (32). The product was prepared by the same procedure described for **21**. The product was obtained as a light green powder in 94% yield: mp 99 °C (dec); ^{1}H NMR (DMSO-d_6/D_2O) δ 1.90−2.30 (m, 2H), 2.90−3.40 (m, 6H), 3.80 (br s, 2H), 4.11 (t, J = 7.0 Hz, 2H), 6.9−7.7 (m, 11H), 8.14 (d, J = 9.0 Hz, 1H), 8.43 (d, J = 9.0 Hz, 1H), 9.51 (br s, 2H)); MS *m*/*e* 369 (M^+ + 1, 100). Anal. Calcd for $C_{25}H_{24}N_2O$·HCl: C, 74.15; H, 6.22; N, 6.92. Found: C, 73.91; H, 6.08; N, 6.59.

Debenzylation Reactions. A suspension of the Diels−Alder adduct (1.0 g) and 5% Pd/C (0.5 g) in MeOH (75 mL) was stirred initially under argon (10 min) and then hydrogen

at atmospheric pressure at 40 °C for 2 h or until the reaction was complete. The reaction mixture was filtered, and ether containing hydrogen chloride was added until there was a slight presence of the acid. The filtrate was taken to dryness, and the resulting residue was purified as described.

7,8,8a,9,9a,10,11,12,13,13a-Decahydro-6*H*-dipyrido[3,4-*c*:1′,2′,3′-*lm*]carbazol-6-one Hydrochloride (13). The product, after recrystallization from 2-propanol, was obtained as colorless needles in 90% yield: mp 333−336 °C; ^{1}H NMR {D_2O, 3-(trimethylsilyl)propionic-*2,2,3,3-d*$_4$ acid, sodium salt)} δ 1.37 (m, 1H), 1.51 (m, 1H), 2.05 (m, 2H), 2.21 (m, 1H), 2.55−2.85 (m, 6H), 3.07 (t, 1H), 3.22 (br s, 1H), 3.35 (m, 2H), 7.25 (m, 2H), 7.55 (d, J = 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H); MS *m/e* 281 (MH^+, 100). Anal. Calcd for $C_{18}H_{20}N_2O$·HCl: C, 68.24; H, 6.68; N, 8.84. Found: C, 68.17; H, 6.81; N, 8.66.

7,8,8a,9,9a,10,11,12,13,13a-Decahydro-6*H*-dipyrido[4,3-*c*:1′,2′,3′-*lm*]carbazol-6-one Hydrochloride (20). The product, after recrystallization from small quantities of MeOH, was obtained as a white solid in 90% yield: mp 298−301 °C; ^{1}H NMR (DMSO-d_6/D_2O) δ 1.59−1.71 (m, 2H), 1.81−1.95 (m, 2H), 2.15 (m, 2H), 2.45 (m, 1H), 2.79−3.12 (m, 4H), 3.30 (m, 1H), 3.40 (m, 1H), 3.49 (m, 1H), 4.22 (m, 1H), 7.50 (m, 2H), 7.72 (d, J = 8 Hz, 1H), 8.36 (d, J = 8 Hz, 1H); MS *m/e* 281 (MH^+, 100). Anal. Calcd for $C_{18}H_{20}N_2O$·HCl·0.5H_2O: C, 66.35; H, 6.81; N, 8.60. Found: C, 66.39; H, 6.51; N, 8.25.

7,8,8a,9,9a,10,11,12,13,13a-Decahydro-6*H*-dipyrido[2,3-*c*:1′,2′,3′-*lm*]carbazol-6-one Hydrochloride (22). Method 1. Following the procedure described for debenzylation, the crude product, after recrystallization from small quantities of MeOH, was obtained as colorless needless in 87% yield.

Method 2. A solution of **25** (0.10 g) in *o*-dichlorobenzene (15 mL) containing 25% concentrated HCl in EtOH (0.33 mL) was heated at 90 °C for 0.5 h, cooled, and diluted with ether. The resulting precipitate was collected by filtration washed with ether and recrystallized from a mixture of EtOAc, MeOH, and *n*-hexane to give the product as light green needles (0.11 g before recrystallization, 95%): mp 328−331 °C; ^{1}H NMR (CD_3OD) δ 1.54 (m, 1H), 1.72−1.88 (m, 2H), 1.93 (m, 1H), 2.13 (m, 1H), 2.21 (m, 1H), 2.45 (m, 1H), 2.84−2.96 (m, 3H), 3.07−3.20 (m, 2H), 3.30 (m, 1H), 3.55 (m, 1H), 3.89 (m, 1H), 7.27−7.33 (m, 2H), 7.69 (m, 1H), 8.40 (m, 1H); MS *m/e* 281 ($M^+ + 1$, 100). Anal. Calcd for $C_{18}H_{20}N_2O$·HCl: C, 68.24; H, 6.68; N, 8.84. Found: C, 68.61; H, 6.94; N, 8.76.

7,8,10,11,12,13-Hexahydro-6*H*-dipyrido[3,4-*c*:1′,2′,3′-*lm*]-carbazol-6-one Hydrochloride (28). The product, after recrystallization from small quantities of MeOH, was obtained as colorless needles in 64% yield: mp 287−290 °C; ^{1}H NMR (DMSO-d_6/D_2O) δ 2.99 (t, J = 7.5 Hz, 2H), 3.22 (t, J = 7.5 Hz, 2H), 3.47 (t, J = 6.1 Hz, 2H), 3.61 (t, J = 6.1 Hz, 2H), 4.44 (s, 2H), 7.21 (s, 1H), 7.49 (t, J = 8 Hz, 1H), 7.57 (t, J = 8 Hz, 1H), 8.03 (d, J = 8 Hz, 1H), 8.34 (d, J = 8 Hz, 1H); MS *m/e* 277 (MH^+, 100). Anal. Calcd for $C_{18}H_{16}N_2O$·HCl: C, 69.12; H, 5.48; N, 8.96. Found: C, 68.78; H, 5.43; N, 8.73.

7,8,10,11,12,13-Hexahydro-6*H*-dipyrido[4,3-*c*:1′,2′,3′-*lm*]-carbazol-6-one Hydrochloride (31). The product, after recrystallization from MeOH/H_2O (9:1), was obtained as colorless needles (97% yield before recrystallization): mp 295−298 °C; ^{1}H NMR (DMSO-d_6/D_2O) δ 3.02 (t, J = 7.4 Hz, 2H), 3.21 (t, J = 6.0 Hz, 2H), 3.26 (t, J = 7.4 Hz, 2H), 3.53 (t, J = 6.0 Hz, 2H), 4.77 (s, 2H), 7.28 (s, 1H), 7.52 (t, J = 8 Hz, 1H), 7.61 (t, J = 8 Hz, 1H), 7.93 (t, J = 8 Hz, 1H), 8.40 (t, J = 8 Hz, 1H); MS *m/e* 277 (MH^+, 100). Anal. Calcd for $C_{18}H_{16}N_2O$·HCl: C, 69.12; H, 5.48; N, 8.96. Found: C, 69.02; H, 5.50; N, 8.73.

Dipyrido[4,3-*c*:1′,2′,3′-*lm*]carbazol-6-one (18). A suspension of **17** (0.8 g) and 10% Pd/C (0.8 g) in diphenyl ether (80 mL) was heated at 240 °C under a slow stream of argon gas for 24 h. Diphenyl ether was removed in vacuo, and the resulting residue was stirred in small quantities of MeOH. The yellow precipitate was collected by filtration, washed with cold MeOH, and dried in vacuo (0.62 g, 90%): mp 261−262 °C; ^{1}H NMR (CD_3OD) δ 6.95 (d, J = 9.6 Hz, 1H), 7.64−7.74 (m, 2H), 8.08 (d, J = 5.8 Hz, 1H), 8.13 (d, J = 9.6 Hz, 1H), 8.31 (s, 1H), 8.58 (m, 1H), 8.62 (d, J = 5.8 Hz, 1H), 8.80 (m, 1H), 10.14 (s, 1H); HRMS calcd for $C_{18}H_{11}N_2O$ 271.0872, found 271.0690.

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Supporting Information Available: Experimental details for the X-ray crystal structure determination of **25**, ORTEP representation and crystal data tables of positional and anisotropic or isotropic thermal parameters and interatomic distances and angles for **25**, and ^{1}H NMR spectra of compounds (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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