Highly Regioselective Nitration Reactions Provide a Versatile Method of Functionalizing Benzocycloheptapyridine Tricyclic Ring Systems: Application toward Preparation of Nanomolar Inhibitors of Farnesyl Protein Transferase

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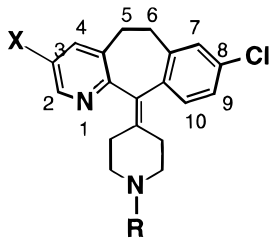
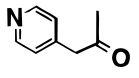
A comprehensive study of nitration reaction of azatricyclic systems has been carried out. Whereas classical nitrations using $KNO_3-H_2SO_4$ at low temperatures gave nitrated products mainly at the 9-position, use of tetrabutylammonium nitrate−trifluoroacetic anhydride (TBAN−TFAA) resulted in exclusive nitration of the 3-position in the case carbamates **1**, and **4**−**6** and the tricyclic ketone **7**. These 3-nitro tricyclic derivatives have been valuable intermediates for the preparation of the very potent farnesyl protein transferase inhibitors such as the tricyclic pyridyl acetamide **32** and other new analogues.

The benzocycloheptapyridine system has emerged as an important pharmacophore in such therapeutic areas as allergy,[1] platelet activating factor (PAF),[2] and cancer.[3] For example, the tricyclic carbamate **1**, commonly known as loratadine, is currently the best selling nonsedating H_1-antihistamine.[4] The tricyclic acetamide **2** has been reported as a dual antagonist of PAF and histamine.[5] We recently reported that functionalization of the 3-pyridyl position with a methyl group resulted in tricyclic compound **3** that had greatly enhanced potency in farnesyl protein transferase (FPT) inhibition.[3a] This discovery prompted us to look for a convenient method to functionalize this and other positions of the tricyclic ring system. Our objective was to determine which functionalities and at what positions on the tricyclic ring system would enhance potency as FPT inhibitors. One reaction that proved very successful toward this end was the regioselective nitration using either $H_2SO_4-KNO_3$ or tetrabutylammonium nitrate−trifluoroacetic anhydride (TBAN−TFAA).



1: X = H, R = COOEt **2: X = H, R = $COCH_3$**

3: X = CH_3, R = 

The fact that the benzocycloheptapyridine tricyclic ring system contains a pyridine and phenyl ring separated from each other by a cycloheptyl ring system presents itself as an interesting molecule for chemical modification. One possible way to functionalize the tricyclic system at various positions has been previously described by Piwinski and co-workers.[2c] In their work, the required functionalities were introduced prior to building the tricyclic ring systems by total synthesis. We have sought a more efficient and convenient way of effecting the desired functionalization of the tricyclic ring system, starting from the readily available carbamate **1**.

Simple halogenation reactions with reagents such as Br_2,[6] Br_2−iron filings,[7] and $Br_2-Al_2O_3$[8] were unsuccessful.

(1) Villani, F. J.; Magatti, C. V.; Vashi, D. B.; Wong, J. K.; Popper, T. L. *Arzneim-Forsch. Drug Res.* **1986**, *36*, 1311.

(2) (a) Piwinski, J. J.; Wong, J. K.; Green, M. J.; Ganguly, A. K.; Billah, M. M.; West, R. E., Jr.; Kreutner, W. *J. Med. Chem.* **1991**, *34*, 457. (b) Billah, M. M.; Egan, R. W.; Ganguly, A. K.; Green, M. J.; Kreutner, W.; Piwinski, J. J.; Siegel, M. I.; Villani, F. G.; Wong, J. K. *Lipids* **1991**, *26*, 1172. (c) Wong, J. K.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Anthes, J. C.; Billah, M. M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1073.

(3) (a) Njoroge, F. G.; Doll, R. J.; Vibulbhan, B.; Alvarez, C. S.; Bishop, W. R.; Petrin, J.; Kirschmeier, P.; Carruthers, N. I.; Wong, J. K.; Albanese, M. A.; Piwinski, J. J.; Catino, J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem.* **1997**, *5*, 101. (b) Njoroge, F. G.; Vibulbhan, B.; Alvarez, C. S.; Bishop, W. R.; Petrin, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2977. (c) Mallams, A. K.; Njoroge, F. G.; Doll, R. J.; Snow, M. E.; Kaminiski, J. J.; Rossman, R. R.; Vibulbhan, B.; Bishop, W. R.; Kirschmeier, P.; Liu, M.; Bryant, M. S.; Alvarez, C. S.; Carr, D.; James L.; King, I.; Li, Z.; Lin, C.-C.; Petrin, J.; Remiszewski S. R.; Taveras, A, G.; Wang, S.; Wong, J. K.; Catino, J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem.* **1997**, *5*, 93. (d) Bishop, W. R.; Bond, R.; Petrin, J.; Wang, L.; Patton, R.; Doll, R. J.; Njoroge, F. G.; Catino, J.; Schwartz, J.; Windisor, W.; Syto, R.; Carr, D.; James, L.; Kirschmeier, P.; Carr, D. *J. Biol. Chem.* **1995**, *270*, 30611.

(4) Kreutner, W.; Chapman, R. W.; Gulbenkian, A.; Siegel, M. I.; *Allergy (Copenhagen)* **1987**, 42, 57. (b) Barnett, A.; Iorio, L. L.; Kreutner, W.; Tozzi, S.; Ahn, H. S.; Gulbenkian, A. *Agents Actions* **1984**, *14*, 590.

(5) (a) Billah, M. M.; Chapman, R.; Egan, R. W.; Gilchrest, H.; Piwinski, J. J.; Sherwood, J.; Siegel, M. I.; West, R. E.; Kreutner, W. *Pharmacol. Exp. Ther.* **1990**, *252*, 1090. (b) Billah, M. M.; Chapman, R.; Watnick, A. S.; Egan, R. W.; Siegel, M. I.; Kreutner, W. *New Drugs Asthma Therapy* **1991**, 313.

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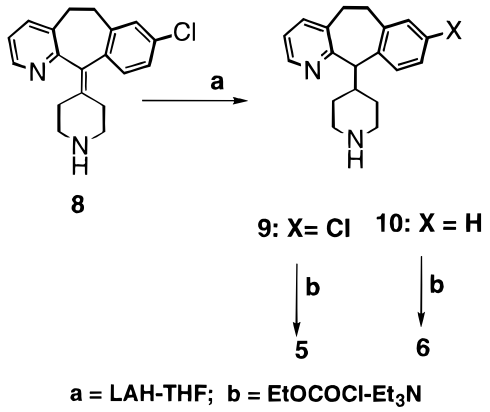
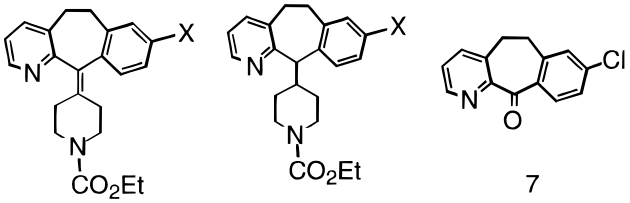
Scheme 1



Very early in this endeavor, we realized that the pyridine and the phenyl rings of the tricyclic ring system responded differently toward chemical reactions: thus chemistry that is known to work well for isolated pyridine and phenyl ring systems did not work in a similar manner on the tricyclic ring systems. While in search for methods of functionalizing the tricyclic ring systems, we found out that classic nitration using $KNO_3-H_2SO_4$[11] at low temperature effected nitration of the benzocycloheptapyridine tricyclic ring systems exclusively on the phenyl ring. However, use of tetrabutylammonium nitrate−trifluoroacetic anhydride (TBAN−TFAA) resulted in exclusive nitration at the 3-position of the pyridine ring.

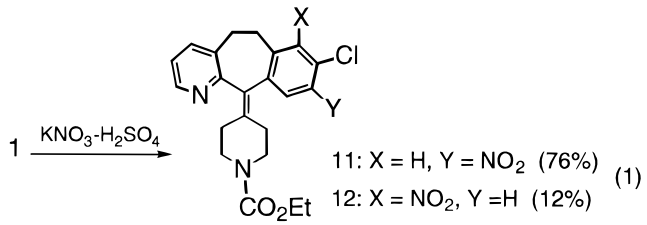
The following panel of five tricyclic carbamates and a ketone were evaluated in the two nitration protocols.



Results and Discussions

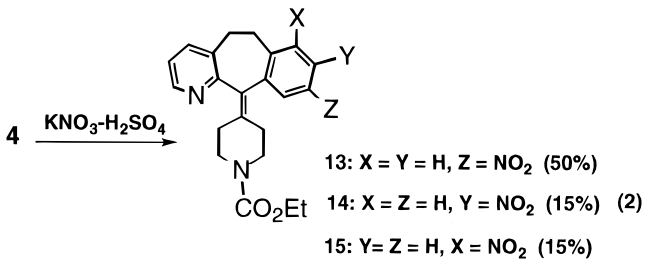
Preparation of the starting materials **1**,[9] **4**,[1] and **7**[10] has been previously reported. Compound **5** and **6** were prepared as outlined in Scheme 1. Reduction of the C-11 double-bond amine **8**[2c] with lithium aluminum hydride (LAH) at refluxing THF temperatures afforded the 8-chloro amine **9** and 8-des-chloro amine **10**. Amines **9** and **10** were acylated using ethyl chloroformate to give the desired carbamates **5** and **6**, respectively.

Efforts to nitrate tricyclic carbamate **1** using classic nitration procedure, i.e., heating **1** in the presence of concentrated sulfuric acid and nitric acid, were unsuccessful. However, when $KNO_3-H_2SO_4$[11] was used as the nitrating reagent and the reaction conducted at temperatures between −5 and −10 °C, tricyclic carbamate **1** was exclusively nitrated on the phenyl ring at positions 9 and 7 to give the nitro carbamates **11** and **12** in 76 and 12% yields, respectively (eq 1).



^{1}H NMR of the carbamate **11** had two characteristic singlets at δ 7.40 and 7.80 corresponding to H-7 and H-10, respectively, whereas the nitro carbamate **12** exhibited two conspicuous doublets at δ 7.25 and 7.35 arising from H-9 and H-10, respectively. Using these reaction conditions no multiple nitrations were observed. This was probably due to the fact that introduction of the first nitro group might have deactivated the phenyl ring such that any further electrophilic nitration was difficult.

In the nitration of **1** using the conditions stipulated above, it was possible that the nitro group was directed either to the 7- or the 9-position by the ortho-directing effect of chlorine group at C-8. To investigate this possibility, the 8-des-chloro carbamate compound **4** was subjected to $KNO_3-H_2SO_4$ nitration conditions as described above. Similar results to those obtained from nitration of compound **1** were achieved. As shown in eq 2, nitration of the des-chloro carbamate **4** afforded the 9-nitro carbamate **13** in 50% yield, and the 7- and 8-nitro carbamates **14** and **15** were isolated in equal amounts of 15% each. This result clearly suggested that the chloro group did not play a major role in directing the position of attack of the nitro group on the phenyl ring system.



To determine whether the double bond at C-11 had any influence on the incoming nitro group, the C-11 single-bond bond compound **5** was nitrated under conditions similar to those described above (eq 3) to give the 9-nitro compound **16** in 65% yield and the 7-nitro carbamate **17** in 17% yield. In this reaction, formation of ~1% 7,9-dinitro carbamate **18** was observed. Results obtained in this experiment indicated that the major player in directing the position of the nitration was most likely the C-6 of the ethano bridge.

When the 8-des-chloro tricyclic carbamate **6** was nitrated using $KNO_3-H_2SO_4$ (eq 4), the major compound

(6) (a) Finar, I. L.; Miller, D. B. *J. Chem. Soc.* **1961**, 2769. (b) Drewry, D. T.; Scrowston, R. M. *J. Chem. Soc.* **1969**, *C*, 2750. (c) Newman, M. S.; Dhawan, B.; Tuncay, A. *J. Org. Chem.* **1976**, *41*, 3924.

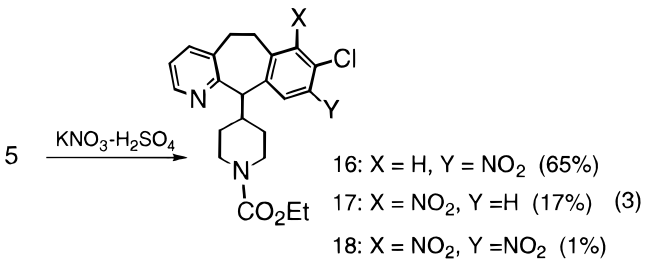
(7) (a) Wisansky, W. A.; Ansbacher, S. *Organic Syntheses;* Wiley: New York, 1955; Collect. Vol. III, p 138. (b) Basu, B.; Mukherjee, D. *Tetrahedron Lett.* **1984**, *25*, 4445. (c) Chatterjee, A.; Banerjee, D. *J. Chem Soc.* **1971**, 1859. (d) Hall D. M. *J. Chem. Soc.* **1951**, 1375.

(8) Ranu, B. C.; Sarkar, D. C.; Charkraborty, R. *Synth. Commun.* **1992**, 22, 1095.

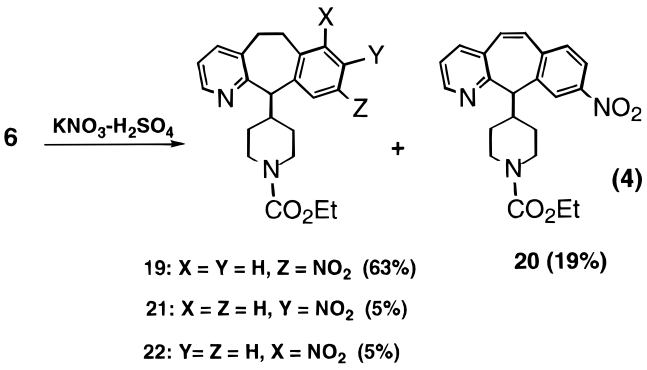
(9) Schumacher, D. P.; Murphy, B. L.; Clark, J. E.; Tahbaz, P.; Mann, T. A. *J. Org. Chem.* **1989**, *54*, 242.

(10) Villani, F. J.; Daniels, P. J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C. *J. Heterocycl. Chem.* **1971**, *8*, 73.

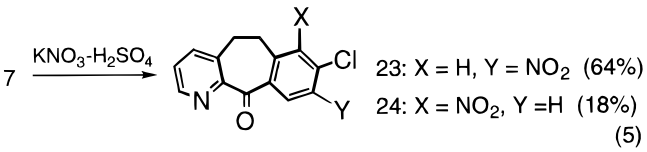
(11) Pendergast W.; Johnson, J. V.; Dickerson, S. H.; Dev. I. K.; Duch, D. S.; Ferone, R.; Hall, W. R.; Humpreys, J.; Kelly, J. M.; Wilson, D. C. *J. Med. Chem.* **1993**, *36*, 2279.



formed was the 9-nitro tricyclic carbamate **19**, obtained in 63% yield. The 8- and 7-nitro tricyclic carbamates **21** and **22** were formed in 10% combined yield in a ratio of 1:1. These two compounds were inseparable; however, ^{1}H NMR, NOE, and COSY experiments were consistent with the two structures. In addition to these nitrated products, the 9-nitro 5,6-didehydro carbamate **20** was formed in 19% yield. Compound **20** could be envisioned to arise from **19** through chemistry similar to that described by Buncel and co-workers.[12] In their study, this group observed that *p*-nitrotoluene in the presence of a base formed some *p*-nitrostyrene type of compounds that were postulated to be formed through an electron transfer mechanism. The electron-withdrawing nitro group para to the bridgehead methylene makes the C-6 hydrogen labile and subsequently amenable to free radical abstraction. We, however, cannot explain why the 5,6-didehydro compounds analogous to **20** were not formed in the previous cases.

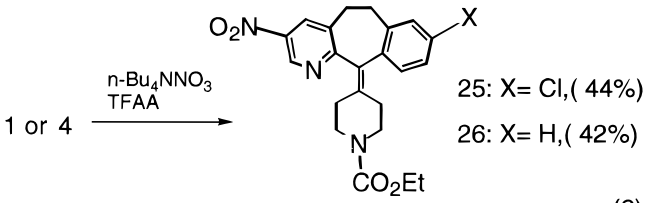


Nitration of aza ketone **7** in H_2SO_4−KNO_3 gave the 9-nitro ketone **23** as the major product in 64% yield and the 7-nitro ketone **24** in 18% yield (eq 5); again there was no multiple nitration observed in this case.



At this point we realized that by using classic nitration conditions we were only going to effect nitration on the phenyl ring but not on the pyridyl ring. The fact that we could specifically nitrate the phenyl ring was a very important finding to us since by manipulating the nitro compounds, a variety of substituents could be introduced at any position in the phenyl ring. The nitro group at either the 7- or 9-position rendered the chloro group at position 8 substantially labile for possible nucleophilic displacement reactions. It was also clear that the presence of a nitro group at positions 9 or 7 made the C-6 methylene hydrogen considerably acidic such that further functionalization of the 6-position of the bridgehead was possible (to be published elsewhere).

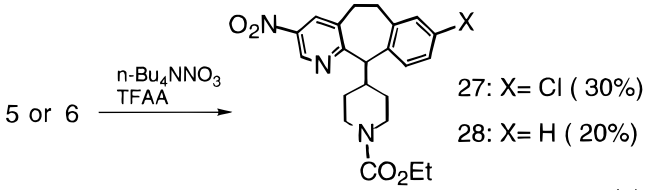
To introduce functionalities at the various positions of the pyridine ring, attempts to use nitrating reagents such as $NaNO_3$−TMSCl−$AlCl_3$,[13] recently reported by Olah's group, or $AgNO_3$−TFAA[14] resulted mainly in recovered starting material. However, treatment of **1** with tetrabutylammonium nitrate−trifuoroacetic anhydride (TBAN−TFAA)nitrating system[15] resulted with exclusively nitration at 3-position of the pyridine ring[16] to give the 3-nitro carbamate **25** in 44% yield (eq 6). This was a very important finding because some of our more potent FPT inhibitors were functionalized at the 3-position of the tricyclic pyridine.



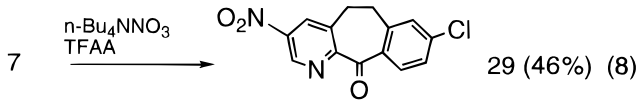
To explore the scope of this nitration reaction, we again took a panel of tricyclic compounds that were of interest to us in the FPT project and investigated whether this reaction was general to the benzocycloheptapyridine tricyclic ring system. One of the intriguing things was that Masci[15] had previously reported that TBAN−TFAA could be used to nitrate benzene, toluene, and mesytylene. It was unusual then that in a tricyclic ring system such as **1** we did not observe any nitration on the phenyl ring using similar conditions. Another important observation was that at about 50% conversion to the nitro compound the reaction did not go to completion even after adding excess nitrating reagent. However, a substantial amount of starting material was recovered after reaction workup and purification.

To evaluate whether the chlorine at the 8-position was deactivating the phenyl group toward TBAN−TFAA reaction, nitration of the 8-des-chloro tricyclic carbamate **4** was carried out (eq 6). Even in the case where the reaction was carried out in the presence of excess nitrating reagent, the major product formed was 3-nitro carbamate **26**. No nitration on the phenyl ring was detected.

Nitration of either the 8-chloro carbamate **5** or the 8-des chloro carbamate **6** in the C-11 single-bond series also gave exclusively the 3-nitro-substituted products **27** and **28**,[17] respectively (eq 7). In neither of these two cases was nitration on the phenyl ring observed.



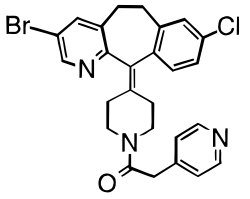
Treatment of **7** with TBAN−TFAA resulted in formation of the 3-nitro ketone **29** in 46% yield (eq 8). As in the previous cases there was no nitration on the phenyl ring.



As indicated in the above discussion, nitration using TBAN−TFAA could not be pushed further by addition of an excess amount of nitrating reagent. It is possible that as the reaction progresses, TFAA quarternizes the tricyclic pyridine nitrogen, rendering the molecule unreactive to any further nitration. The observed starting material would therefore come from the decomposed *N*-acyl product from pyridine after workup.

To further understand whether the TBAN−TFAA was going through the classical NO_2^+ or a free radical mechanism, nitration of carbamate **1** was carried out in the presence of excess free radical scavenger TEMPO.[18] Analysis of the reaction mixture after 16 h showed that no appreciable amount of nitration was effected. This implied that the TBAN−TFAA reaction was possibly going through a free radical mechanism similar to that proposed by Evans et al.[18] As shown in Scheme 2 tetrabutylammonium nitrate reacts with trifluoroacetic anhydride to form the nitrotrifuoroacetate adduct **30** that subsequently decomposes to trifluroacetyl and the nitronium free radicals; the latter reacts with the tricyclic substrate to give the 3-nitro products of type **31**.

We have exploited the TBAN−TFAA nitration method in the preparation of tricyclic pyridyl acetamide **32**, a compound that inhibited 50% of farnesyl protein transferase at 60 nM. Work on synthesis of **32** will be reported separately.[19]



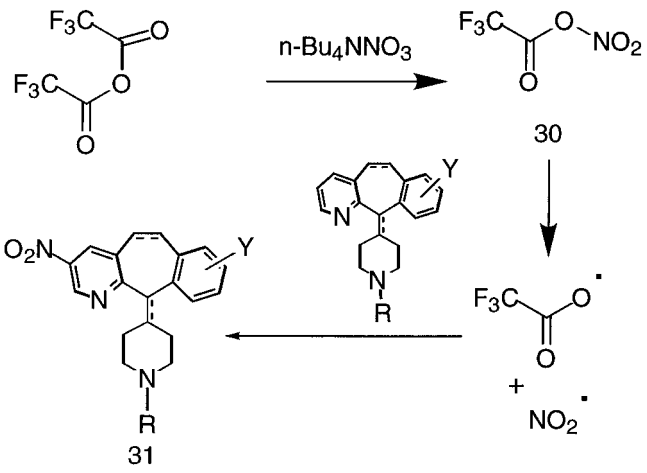
32

FPT IC_{50} = 60 nM

Summary

Two modes of nitration of the benzocycloheptapyridine ring system, one using $KNO_3-H_2SO_4$ and the other one using tetrabutylammonium nitrate−trifluoroacetic acid anhydride, have been explored. Whereas the former reaction was found to give nitrated products mainly in the phenyl group of the tricyclic ring system, TBAN−TFAA reaction mainly effected nitration in the 3-position of the pyridine ring of this system. We have utilized this information to synthesize highly potent FPT inhibitors as potential antitumor drugs.[19]

Scheme 2



Experimental Section

Melting points were determined with an Electrothermal digital melting point apparatus and are uncorrected. Elemental analyses were performed by the Physical-Analytical Chemistry Department, Schering-Plough Research Institute, on either a Leeman CE 440 or a FISONS EA 1108 elemental analyzer. FT-IR spectra were recorded using a BOMEN Michelson 120 spectrometer. Mass spectra were recorded using EXTREL 401 (chemical ionization), JEOL or MAT-90 (FAB), VG ZAB-SE (SIMS), or Finnigan MAT-CH-5 (EI) spectrometers. In general, structures of the compounds were determined by coupling constants, coupling information from the COSY spectra, and 1D NOE experiments. The ^1H and ^{13}C NMR spectra were obtained on Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz, ^1H; 75.5 MHz, ^{13}C), or XL-400 (400 MHz, ^1H; 100 MHz, ^{13}C) and are reported as ppm downfield from Me_4Si with number of protons, multiplicities, and coupling constants in hertz indicated parenthetically. For ^{13}C NMR, a Nalorac Quad nuclei probe was used.

Preparation of Starting Materials. 4-[8-Chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (5) and 4-[6,11-Dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (6). Amine **8**[2c] (66 g, 2.1 mol) was dissolved in 1 L of THF, and lithium aluminum hydride (24.32 g, 6.4 mol) was added. Reaction mixture was refluxed under nitrogen for 4 h. It was cooled to room temperature. Ether (3 L) was added followed by saturated Na_2SO_4 and $MgSO_4$. The mixture was stirred for 0.5 h, filtered, concentrated on a rotary evaporator, and purified by flash chromatography, eluting with 10% methanol (saturated with ammonia)−CH_2Cl_2 to afford 17.7 g of crude product as a mixture of 8-chloro amine **9** and the des-chloro amine **10**. This mixture was subjected to reverse phase HPLC eluting with 37% MeOH−H_2O (with 0.1% TFA) whereby 3.6 g of amine **9** and 1.25 g of amine **10** were obtained. Amine **9** was treated with 8 equiv of ethyl chloroformate and refluxed in toluene for 12 h. Volatiles were removed, and the resulting crude material was purified on silica gel chromatography eluting with 70% EtOAc−hexanes to afford the 8-chloro carbamate **5** in 50% yield: mp 58−60 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 3H), 1.18−1.29 (m, 4H), 2.20−2.40 (br s, 1H), 2.50−2.70 (br m, 2H), 2.80−3.04 (br m, 2H), 3.32−3.58 (br m, 2H), 3.92 (br d, J = 7.5 Hz, 1H), 4.00−4.20 (m, 2H), 4.11 (q, J = 7.5 Hz, 2H), 7.05−7.20 (m, 4H), 7.42 (br d, J = 7.5 Hz, 1H), 8.35 (br d, J = 5.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 15.1, 31.5, 31.7, 32.0, 32.4, 41.6, 44.3, 44.4, 61.6, 63.0, 122.6, 126.5, 130.5, 133.0, 133.8, 134.3, 137.5, 139.4, 139.4, 141.0, 146.3,

(12) Buncel, E.; Mennon, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 3499.
(13) Olah, G. A.; Ramaiah, P.; Sandford, G.; Orlinkov, A.; Prakash, G. K. S. *Synthesis* **1994**, 468.
(14) Gokhale, U. B.; Joshi, A. A. *Indian. J. Chem.* **1993**, *32B* 1073.
(15) Masci, B. *J. Org. Chem.* **1985**, *50*, 0, 4081.
(16) Nitration of the 3-position of the pyridine ring has been previously achieved in very low yields, i.e., 1−3% using either $HNO_3-H_2SO_4$ or $KNO_3-H_2SO_4$ and conducting the reaction at very high temperatures (330 °C): Ege, S. *Organic Chemistry*; Health: Lexington, 1984, 1827. Kirpalt, A.; Reiter, E. *Ber. Dtsch. Chem. Ges.* **1925**, *58*, 699. More recently, Bakke and co-workers have successfully nitrated pyridine to give 3-nitropyridine in moderate yields: Bakke, J. M.; Rane, E. *Synthesis* **1997**, 281.
(17) In the course of this nitration we observed formation of 4-[3-nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-nitropiperidine.
(18) Evans, P. A.; Longmire, J. M. *Tetrahedron Lett.* **1994**, *35*, 8345.
(19) Njoroge, F. G.; Vibulbhan, B.; Rane, D. F.; Bishop, W. R.; Petrin, J.; Patton, R.; Bryant, M. S.; Chen, K.-J.; Nomeir, A. A.; Lin, C, C-.; Liu, M.; King, I.; Chen, J.; Lee, S.; Yaremko, B.; Dell, J.; Lipari, P.; Malkowski, M.; Li, Z.; Catino, J.; Doll, R. J.; Girijavallabhan, V.; and Ganguly, A. K. *J. Med. Chem.* **1997**, *40*, 4290.

156.0; IR (film) ν_{max} 1106, 1439, 1483, 1576, 1692, 2980, 3442 cm^{-1}; MS *m/z* (rel intensity) 229.1 (13.12), 351.3 (18.94), 385.2 (100, MH^+). Anal. Calcd for $C_{22}H_{25}N_2O_2Cl$: C, 68.65; H, 6.55; N, 7.28. Found: C, 68.50; H, 6.62; N, 7.19.

In a similar manner, amine **10** was converted to carbamate **6** in 80% yield: ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (t, J = 7.5 Hz, 3H), 1.06−1.40 (m, 4H), 2.20−2.45 (br s, 1H), 2.51−2.72 (m, 2H), 2.81−3.08 (br m, 2H), 3.20−3.64 (m, 2H), 4.10 (q, J = 7.5 Hz, 2H), 3.87−4.20 (m, 3H), 7.03−7.22 (m, 5H), 7.41 (d, J = 7.5 Hz, 1H), 8.35 (br d, J = 5.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1, 31.5, 31.8, 32.4, 32.5, 41.5, 44.3, 44.4, 61.5, 63.2, 122.4, 126.5, 127.6, 130.6, 132.80, 132.9, 135.0, 139.0, 139.5, 146.0, 148.0, 159.0; IR (film) ν_{max} 1102, 1437, 1688, 1922, 2908, 2976 cm^{-1}; MS *m/z* (rel intensity) 305 (10), 351 (100, MH^+). Anal. Calcd for $C_{22}H_{26}N_2O_2$ 0.2 H_2O: C, 74.66; H, 7.58; N, 7.91. Found: C, 74.66; H, 7.50; N, 7.94.

Nitrations. General Procedures for Nitrating with KNO_3−H_2SO_4 Reaction Conditions (Method A). Typical Example: Preparation of 4-[8-Chloro-9-nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (11) and 4-[8-Chloro-7-nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (12). Tricyclic compound **1** (20 g, 50.25 mmol) was stirred in 400 mL of concentrated H_2SO_4 at room temperature until all the solid dissolved. The resulting solution was cooled between −10 and − 5 °C (ice−MeOH bath). KNO_3 (5.1 g, 50.25 mmol, 1 equiv) was added portionwise, making sure that the temperature did not go above −5 °C. The reaction mixture was stirred at this temperature for 16 h. It was then poured into ice, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. Combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and concentrated. Purification on silica gel eluting with 30% EtOAC−hexanes gave compound **11** (the less polar) in 76% yield: ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7.5 Hz, 3H), 2.22−2.60 (m, 4H), 2.72−2.99 (m, 2H), 3.08−3.28 (m, 2H), 3.32−3.55 (m, 2H), 3.71−3.98 (m, 2H), 4.15 (q, J = 7.5 Hz, 2H), 7.15 (dd, J = 7.5 Hz, 5.0 Hz, 1H), 7.40 (s, 1H), 7.45 (dd, J = 7.5 Hz, 2.5 Hz, 1H); 7.80 (s, 1H), 8.45 (dd, J = 7.5 Hz, 2.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 30.6, 30.8, 30.9, 31.7, 44.6, 61.4, 122.8, 125.7, 126.5, 132.1, 132.4, 132.9, 137.7, 138.8, 139.8, 144.4, 145.4, 147.1, 155.4, 155.99; IR (film) ν_{max} 1114, 1226, 1519, 1698, 2865, 3447 cm^{-1}; MS *m/z* (rel intensity) 428.2 (100, MH^+). Anal. Calcd for $C_{22}H_{22}N_3O_4Cl$ 0.3 H_2O: C, 60.98; H, 5.22; N, 9.70. Found: C, 61.03; H, 5.37; N, 9.68.

The more polar 7-nitro compound **12** was obtained in 12% yield: ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J = 7.5 Hz, 3H), 2.25−2.62 (m, 4H), 2.70−3.50 (m, 2H), 3.10−3.47 (m, 4H), 3.76−3.94 (m, 2H), 4.17 (q, J = 7.5 Hz, 2H), 7.15 (m, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H) 7.48 (dd, J = 7.5 Hz, 2.5 Hz, 1H), 8.44 (dd, J = 5.0 Hz, 2.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 26.3, 26.4, 30.5, 30.9, 44.1, 61.5, 123.7, 123.7, 128.6, 128.7, 128.7, 128.8, 130.5, 130.5, 131.8, 149.5, 155.3; IR (film) ν_{max} 1112, 1436, 1535, 1696, 2980, 3445 cm^{-1}; MS *m/z* (rel intensity) 246.1 (6.01), 382.1 (6.94), 428.2 (100, MH^+), 429.2 (35.97), 430.2 (40.56). Anal. Calcd for $C_{22}H_{22}N_3O_4Cl$: C, 61.76; H, 5.18; N, 9.82. Found: C, 61.79; H, 5.64; N, 9.72.

General Procedures for Nitrating with TBAN−TFAA Reaction Conditions (Method B). Typical Example: Preparation of 4-[8-Chloro-3-nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (25). Tricyclic carbamate **1** (5.69 g, 14.9 mmol) was dissolved in 35 mL of CH_2Cl_2 under an N_2 atmosphere, and the solution was stirred at ∼0 °C. To this solution was added a mixture of Bu_4NNO_3 (4.98 g, 16.3 mmol) and trifluoroacetic anhydride (3.12 g, 2.1 mL, 14.9 mmol) dissolved in 20 mL of CH_2Cl_2, and the solution was cooled to 0 °C. The reaction mixture was stirred at 0 °C for 2 h and stirred at room temperature overnight. It was basified with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated. Purification by flash chromatography eluting first with 10% EtOAc−hexanes and then 20% EtOAc−hexanes afforded the nitro carbamate **25** in 44% yield: ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7.5 Hz, 3H), 2.19−2.60 (m, 4H), 2.79−2.96 (m, 1H), 2.98−3.10 (m, 1H), 3.14−3.32 (m, 2H), 3.36−3.57 (m, 2H), 3.68−3.92 (m, 2H), 4.17 (q, J = 7.5 Hz, 2H), 7.06−7.25 (m, 3H), 8.26 (d, J = 2.5 Hz, 1H), 9.22 (d, J = 2.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 30.9, 31.6, 44.5, 44.6, 61.4, 126.6, 129.0, 130.6, 132.3, 132.7, 133.6, 134.5, 136.3, 138.8, 140.2, 141.9, 142.8, 155.3, 162.6; IR (film) ν_{max} 1114, 1230, 1436, 1516, 1896, 2980, 3461 cm^{-1}; MS *m/z* (rel intensity) 231.8 (16.56), 382.3 (10.90), 427.0 (14.55), 428.0 (100, MH^+), 429.0 (34.36). Anal. Calcd for $C_{22}H_{22}N_3O_4Cl$: C, 61.75; H, 5.18; N, 9.82. Found: C, 61.33; H, 5.40; N, 9.55.

Attempted Nitration of Carbamate 1 in the Presence of Free Radical Scavenger TEMPO (2,2,6,6-Tetramethyl-1-piperidinyloxy Free Radical). Reaction was carried out essentially in the same way as described in method B above, in this case 4 equivof TEMPO was added. Analysis of the reaction mixture by TLC and NMR showed that there was no appreciable amount of nitration effected.

4-[9-Nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin−11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (13), 4-[8-Nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (14), and 4-[7-Nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (15). Nitration of carbamate **4** using conditions similar to those described in method A above followed by purification on silica gel eluting with 50−60% EtOAc−hexanes gave the 9-nitro carbamate **13** as the less polar compound in 50% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.5 Hz, 3H), 2.23−2.61 (m, 4H), 2.80−3.00 (m, 2H), 3.12−3.24 (m, 2H), 3.34−3.56 (m, 2H), 3.75−3.89 (m, 2H), 4.11 (q, J = 7.5 Hz, 2H), 7.09−7.18 (m, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 8.02 (dd, J = 7.5 Hz, 3.8 Hz, 1H), 8.09 (d, J = 3.8 Hz, 1H), 8.43 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 30.5, 30.7, 31.1, 31.9, 44.6, 61.3, 61.4, 122.3, 122.6, 124.2, 130.0, 133.0, 137.7, 139.1, 140.5, 145.5, 146.1, 146.9, 155.4, 156.0; MS *m/z* (rel intensity) 394.2 (100, MH^+). Anal. Calcd for $C_{22}H_{23}N_3O_4$ 0.3 H_2O: C, 66.25; H, 5.96; N, 10.54. Found: C, 66.33; H, 6.18; N, 10.56.

The more polar 7- and 8-nitro carbamates coeluted during this separation but were subsequently separated on a normal phase HPLC (silica gel), eluting with 50% EtOAc−hexanes. The faster moving 8-nitro carbamate **14** had a retention time of 25.4 min and was obtained in 15% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3H), 2.21−2.42 (m, 3H), 2.46−2.58 (m, 1H), 2.84−3.00 (m, 2H), 3.11−3.22 (m, 2H), 3.35−3.58 (m, 2H), 3.74−3.91 (m, 2H), 4.11 (q, J = 7.5 Hz, 2H), 7.12−7.19 (m, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.99−8.09 (m, 2H), 8.42 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 30.5, 30.8, 31.2, 31.6, 44.6, 61.3, 121.3, 122.7, 123.0, 124.0, 130.1, 133.2, 138.0, 139.2, 139.4, 146.2, 146.7, 147.0, 155.3, 156.0; MS *m/z* (rel intensity) 394.1 (100, MH^+). Anal. Calcd for $C_{22}H_{23}N_3O_4$ 0.3 H_2O: C, 66.25; H, 5.96; N, 10.54. Found: C, 66.55; H, 6.15; N, 10.39.

The slower moving 7-nitro carbamate **15** had a retention time of 35.6 min and was also obtained in 15% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.5 Hz, 3H), 2.15−2.64 (m, 4H), 3.08−3.46 (m, 6H), 3.82−3.92 (m, 2H), 4.13 (q, J = 7.5 Hz, 2H), 7.09−7.16 (m, 1H), 7.24−7.32 (m, 2H), 7.39−7.48 (m, 1H), 7.71 (d, J = 7.5 Hz, 1H), 8.38−8.42 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 26.4, 30.4, 31.0, 44.5, 44.6, 44.7, 61.3, 122.5, 123.0, 126.9, 132.1, 132.6, 133.1, 139.0, 139.4, 144.1, 146.2, 146.3, 150.0, 154.0, 155.4; MS *m/z* (rel intensity) 246.2 (12.32), 348.1 (5.51), 394.2 (100, MH^+). Anal. Calcd for $C_{22}H_{23}N_3O_4$ 0.3 H_2O: C, 66.25; H, 5.96; N, 10.54. Found: C, 66.38; H, 6.27; N, 10.39.

4-[8-Chloro-9-nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (16), 4-[8-Chloro-5,6-dihydro-7-nitro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (17), and 4-[8-Chloro-5,6-dihydro-7,9-dinitro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (18). Nitration of carbamate **5** using conditions similar to

those described in method A above followed by purification on normal phase HPLC (silica gel based) eluting with 45% EtOAc−hexane afforded the 9-nitro carbamate **16** (retention time 12.7 min) in 65% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18−1.54 (m, 2H), 1.26 (t, J = 7.5 Hz, 3H), 2.24−2.44 (m, 1H), 2.53−2.75 (m, 2H), 2.88−3.13 (m, 2H), 3.32−3.62 (m, 2H), 3.95−4.24 (m, 3H), 4.11 (q, J = 7.5 Hz, 2H), 7.08−7.18 (m, 2H), 7.34 (s, 1H), 7.45 (br d, J = 7.5 Hz, 1H), 7.75 (s, 1H), 8.33−8.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 30.5, 31.0, 31.2, 41.1, 43.7, 43.9, 61.3, 122.5, 125.4, 127.7, 128.7, 133.1, 133.5, 138.6, 138.7, 145.3, 146.8, 146.9, 146.9, 155.4, 157.3; IR (film) ν_{max} 1122, 1439, 1528, 1692, 2981, 3452 cm^{-1}; MS *m*/*z* (rel intensity) 430.1 (100, MH^+). Anal. Calcd for $C_{22}H_{24}N_3O_4Cl$ 0.6 H_2O: C, 61.46; H, 5.63; N, 9.77. Found: C, 60.98; H, 5.92; N, 9.63.

The 7-nitro carbamate **17** eluted at 23.15 min and was obtained in 17% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11−1.53 (m, 2H), 1.25 (t, J = 7.5 Hz, 3H), 2.21−2.42 (m, 1H), 2.53−2.72 (m, 2H), 2.78−3.08 (m, 2H), 3.29−3.50 (m, 2H), 3.99−4.22 (m, 3H), 4.12 (q, J = 7.5 Hz, 2H), 7.10−7.34 (m, 3H), 7.45 (br d, J = 7.5 Hz, 1H), 8.34−8.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 26.3, 26.4, 31.1, 41.1, 41.2, 43.9, 61.3, 122.6, 122.7, 123.4, 127.8, 134.06, 134.10, 134.12, 134.2, 138.7, 139.9, 140.0, 146.8, 155.5, 157.2; IR (film) ν_{max} 1252, 1537, 1693, 2979, 3443 cm^{-1}; MS *m*/*z* (rel intensity) 430 (100, MH^+). Anal. Calcd for $C_{22}H_{24}N_3O_4Cl$ 0.2 H_2O: C, 60.95; H, 5.67; N, 9.69. Found: C, 60.89; H, 6.08; N, 9.57.

The 7,9-dinitro carbamate **18** eluted at 12.1 min and was obtained in 1% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.16−1.42 (m, 2H), 1.25 (t, J = 7.5 Hz, 3H), 2.24−2.43 (m, 1H), 2.55−2.76 (m, 2H), 2.82−3.11 (m, 2H), 4.04−4.28 (m, 3H), 4.12 (q, J = 7.5 Hz, 2H), 7.12−7.22 (m, 1H), 7.41−7.51 (m, 1H), 7.89 (s, 1H), 8.36−8.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 26.7, 26.8, 31.7, 41.1, 40.8, 43.4, 61.3, 123.0, 123.1, 129.1, 132.4, 132.4, 136.2, 136.2, 138.7, 138.8, 141.0, 141.1, 147.1, 155.3, 155.6; IR (film) ν_{max} 1252, 1441, 1545, 1693, 2979, 3474, 3535 cm^{-1}; MS *m*/*z* (rel intensity) 475 (100, MH^+). Anal. Calcd for $C_{22}H_{23}N_4O_6Cl$: C, 55.63; H, 4.88; N, 11.80. Found: C, 55.44; H, 5.39; N, 11.38.

4-[9-Nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (19), 4-[9-Nitro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (20), 4-[8-Nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (21), and 4-[7-Nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (22). Nitration of carbamate **6** using conditions similar to those described in method A above followed by purification on silica gel eluting with 50% EtOAc−hexanes gave two fractions, each of which was found to be a mixture of two products. The less polar fraction was further purified on normal-phase HPLC (silica gel); elution with 30% EtOAc−hexane afforded the 9-nitro carbamate **19** (retention time 42.66 min) in 63% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15−1.30 (m, 2H) 1.24 (t, J = 7.5 Hz, 3H), 2.28−2.77 (m, 4H), 2.88−3.19 (m, 2H), 3.32−3.70 (m, 2H), 3.94−4.26 (m, 4H), 4.10 (q, J = 7.5 Hz, 2H), 7.10−7.19 (m, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.44 (br, d, J = 7.9 Hz, 1H), 8.01 (dd, J = 8.3 Hz, 2.4 Hz, 1H), 8.04 (s, 1H), 8.36 (dd, J = 5.0 Hz, 1.5 Hz, 1H); IR (film) ν_{max} 1252, 1522, 1694, 2852, 2981, 3064, 3452 cm^{-1}; MS *m*/*z* (rel intensity) 240.3 (15.12), 349.3 (14.24), 396.3 (100, MH^+). Anal. Calcd for $C_{22}H_{25}N_3O_4$ 0.3 H_2O: C, 65.92; H, 6.44; N, 10.48. Found: C, 65.91; H, 6.56; N, 10.09.

The faster moving eluant, compound **20** (retention time 39.49 min), 19% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15−1.30 (m, 2H), 1.24 (t, J = 7.5 Hz, 3H), 2.28−2.77 (m, 4H), 3.94−4.26 (m, 4H), 4.10 (q, J = 7.5 Hz, 2H), 6.99 (d, J = 17.5 Hz, 1H), 7.07 (d, J = 17.5 Hz, 1H), 7.24−7.29 (m, 1H), 7.49 (d, J = 8.5 Hz, 1H), 8.11 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 8.56 (dd, J = 5.0 Hz, 1.0 Hz, 1H); MS *m*/*z* (rel intensity) 318 (7), 364 (78), 394 (100, MH^+), 422 (16); FAB HRMS calcd for $C_{22}H_{24}N_3O_4$ 394.1767, found 394.1765

The more polar material from flash chromatography was found to contain the 8-nitro carbamate **21** and the 7-nitro carbamate **22** in a combined yield of 10% and existing in a ratio of 1:1. Signal arising from the two compounds were clearly identified from a combination of ^{1}H NMR, NOE, and COSY experiments. Extracted ^{1}H NMR signals: for **21** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 3H), 1.30−1.52 (m, 2H), 1.55−1.70 (br s, 1H), 2.30−2.43 (br s, 1H), 2.54−2.70 (br s, 2H), 2.95−3.68 (m, 4H), 4.02−4.22 (m, 4H), 4.12 (q, J = 7.5 Hz, 2H), 7.08−7.16 (m, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.41−7.47 (m, 1H), 7.98 (dd, J = 8.0 Hz, 2.5 Hz, 1H), 8.02−8.08 (m, 1H); for **22** ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 3H), 1.30−1.52 (m, 2H), 1.55−1.70 (br s, 2H), 2.95−3.68 (m, 4H), 4.02−4.22 (m, 4H), 4.12 (q, J = 7.5 Hz, 2H), 7.08−7.16 (m, 1H), 7.25−7.27 (m, 1H), 7.38 (br d, J = 7.3 Hz, 1H), 7.41−7.47 (m, 1H), 7.56 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 8.32−8.39 (m, 1H); MS *m*/*z* (rel intensity) 240.3 (11.38), 350.3 (3.92), 396.3 (100, MH^+).

8-Chloro-7-nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-one (23) and 8-Chloro-9-nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (24). Nitration of tricyclic ketone **7** using conditions similar to those described in method A above followed by purification on silica gel eluting with 70% EtOAc−hexanes gave the 9-nitro tricyclic ketone **23** as the more polar compound in 64% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20−3.33 (m, 4H), 7.40−7.44 (m, 1H), 7.48 (s, 1H), 7.67 (dd, J = 7.78 Hz, 1.15 Hz, 1H), 8.62 (s, 1H), 8.72 (dd, J = 4.5 Hz, 1.40 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 34.3, 76.7, 126.6, 128.8, 130.8, 133.2, 136.5, 136.71, 137.7, 146.6, 149.1, 153.1, 190.6; IR (film) ν_{max} 816, 1595, 1662, 2950, 3049, 3095 cm^{-1}; MS (*m*/*z*) (rel intensity) 200.8 (13.66), 245.9 (24.53), 257.0 (13.0), 289.1 (100, MH^+, 291.1 (34.69), 307.2 (6.27). Anal. Calcd for $C_{14}H_9N_2O_3Cl$: C, 58.25; H, 3.15; N, 9.70. Found: C, 58.44; H, 3.06; N, 9.43.

The less polar 7-nitro tricyclic ketone **24** was obtained in 18% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13−3.26 (m, 4H), 7.39−7.43 (m, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.64 (dd, J = 7.8 Hz, 1.5 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 8.70 (dd, J = 4.5 Hz, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 31.3, 76.7, 126.5, 129.0, 129.2, 132.8, 133.6, 136.0, 137.7, 138.0, 149.1, 153.3, 192.4; IR (film) ν_{max} 806, 1535, 1581, 1674, 3072, 3320 cm^{-1}; MS *m*/*z* (rel intensity) 164.8 (6.11), 241.9 (8.75), 289.1 (100, MH^+). Anal. Calcd for $C_{14}H_9N_2O_3Cl$: C, 58.25; H, 3.15; N, 9.70. Found: C, 57.91; H, 3.15; N, 9.41.

4-[3-Nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (26). Nitration of carbamate **4** using conditions similar to those described in method B, followed by purification on silica gel eluting with 30% EtOAc−hexanes, gave the 3-nitro carbamate **26** in 42% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.5 Hz, 3H), 2.22−2.57 (m, 4H), 2.81−3.08 (m, 2H), 3.16−3.28 (m, 2H), 3.41−3.54 (m, 2H), 3.70−3.87 (m, 2H), 4.15 (q, J = 7.5 Hz, 2H), 7.14−7.26 (m, 4H), 8.24 (d, J = 2.5 Hz, 1H), 9.21 (d, J = 2.5 Hz, 1H); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 14.7, 30.7, 30.9, 31.1, 32.0, 44.7, 44.8, 61.4, 126.6, 128.1, 129.1, 129.4, 132.5, 133.9, 135.0, 137.1, 138.0, 139.5, 141.78, 142.8, 155.5, 163.1; IR (film) ν_{max} 753, 1560, 1690, 2907, 2984, 3061, 3441 cm^{-1}; MS *m*/*z* (rel intensity) 364.3 (100), 392.4 (19), 394.3 (98), 395.3 (24). Anal. Calcd for $C_{22}H_{24}N_3O_4$ 0.8 H_2O: C, 64.63; H, 6.31; N, 10.28. Found: C, 64.65; H, 5.72; N, 10.66.

4-[8-Chloro-3-nitro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (27). Nitration of carbamate **5** using conditions similar to those described in method B, followed by purification on silica gel eluting with 30% EtOAc−hexanes, gave the 3-nitro carbamate **27** in 30% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15−1.37 (m, 4H), 1.25 (t, J = 7.5 Hz, 3H), 2.22−2.42 (m, 1H), 2.52−2.74 (m, 2H), 2.85−3.21 (m, 2H), 3.38−3.60 (m, 2H), 4.01−4.22 (m, 3H), 4.12 (q, J = 7.5 Hz, 2H), 7.06−7.22 (m, 3H), 8.23 (br s, 1H), 9.16 (d, J = 2.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1, 31.5, 32.0, 32.1, 41.8, 44.1, 44.3, 61.7, 62.9, 126.9, 130.6, 133.6, 135.8, 136.80, 140.2, 141.7, 143.3, 155.8, 165.8; IR (film) ν_{max} 1115, 1694, 2852, 2939 cm^{-1}; MS *m*/*z* (rel intensity) 232.1 (13.97), 274.1 (20.55), 384.2 (13.17), 430.3 (100, MH^+), 431.3 (34.98). Anal. Calcd for $C_{22}H_{24}N_3O_4Cl$ 0.3 H_2O: C, 60.70; H, 5.70; N, 9.65. Found: C, 60.65; H, 5.77; N, 9.54.

4-[3-Nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperidinecarboxylic Acid Ethyl Ester (28). Nitration of carbamate **6** using conditions similar to those described in method B above followed by purification on silica gel eluting with 10% EtOAc−hexanes gave the 3-nitro carbamate **28** in 20% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, J = 7.5 Hz, 3H), 1.10−1.40 (m, 4H), 2.51−2.78 (br s, 3H), 2.90−3.28 (br s, 2H), 3.39−3.68 (br s, 2H), 4.14 (q, J = 7.5 Hz, 2H), 4.00−4.21 (m, 3H), 7.02−7.23 (m, 4H), 8.21 (br s, 1H), 9.15 (d, J = 2.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1, 31.6, 32.0, 32.1, 32.4, 41.5, 44.2, 44.4, 61.7, 63.5, 127.0, 128.1, 130.8, 130.8, 132.9, 133.6, 135.8, 138.3, 141.6, 143.3, 156.0, 166.0; IR (film) ν_{max} 761, 1521, 1695, 2859, 2940 cm^{-1}; MS m/z (rel intensity) 91 (13), 156 (11), 209 (11), 320 (10), 364 (9), 396 (100, MH^+). Anal. Calcd for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.60; H, 6.43; N, 10.46.

8-Chloro-3-nitro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*β*]pyridin-11-one (29). Nitration of tricyclic ketone **7** using conditions similar to those described in method B followed by purification on silica gel eluting with 30% EtOAc−hexanes gave the 3-nitro tricyclic ketone **29** in 46% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.31 (s, 4H), 7.29 (d, J = 3.75 Hz, 1H), 7.39 (dd, J = 7.5 Hz, 2.5 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 8.45 (d, J = 2.5 Hz, 1H), 9.43 (d, J = 2.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.1, 34.6, 128.2, 130.6, 132.5, 133.5, 134.9, 137.2, 140.4, 143.2, 144.0, 145.0, 156.0, 162.4; IR (film) ν_{max} 1095, 1641, 2935, 3026, 3432 cm^{-1}; MS m/z (rel intensity) 259.1 (80), 260.1 (17), 261.1 (27), 287.2 (14), 289.1 (100, MH^+), 290.1 (19). Anal. Calcd for $C_{14}H_9N_2O_3Cl$: C, 58.25; H, 3.14; N, 9.70. Found: C, 57.91; H, 3.11; N, 9.48.

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