Unusual Oxidative Bond-Forming Reactions upon 1,4-Dihydropyridines: Manganese(III)-Promoted, Single- and Double-Malonate Additions†

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Received September 25, 2000

The relevance of 1,4-dihydropyridines[1] as valuable intermediates in the total synthesis of natural products has been highlighted in several reviews.[2] In the vast majority of the successful synthetic approaches, the key dihydropyridines are formed by reduction or nucleophilic addition to the corresponding pyridinium salts and are immediately transformed into "stable" heterocyclic systems by redox processes or (more commonly) by electrophilic interaction at the enaminic β-position and subsequent cyclization upon an activated aromatic ring (Wenkert procedure). In connection with studies on the synthesis of indole alkaloids, we decided to explore the possibility of promoting radical additions to the enamine moiety present in the dihydropyridine and, in this way, to expand the synthetic exploitation of these versatile compounds (see Scheme 1).

Due to the electron-rich nature of the olefin moiety of the dihydropyridines, we envisaged favorable interactions with electrophilic radicals, which in turn would be easily formed in oxidative processes from β-dicarbonyls.[3] This approach confronts an intrinsic problem, namely the easy oxidation of dihydropyridines (NADH is naturally converted into NAD^+ in the cellular metabolism). In the last years, however, we have reported the capability of diversely substituted dihydropyridines to engage in what we call *nonbiomimetic oxidations*, avoiding the usual oxidation pathway leading to pyridinium salts. These bond-forming processes have allowed the attachment of oxygen, nitrogen, sulfur, phosphorus, and halogen atoms in regio- and stereocontrolled reactions.[4] A rather simple explanation for this reactivity may involve a kinetic preference for the chemically productive oxidation pathway rather than the electron transfer process. Ideally, in our case, the oxidant would selectively interact with a malonate (or a related substrate), yielding the radical, which would undergo β-addition to the dihydropyridine. The resulting α-amino radical would be in situ oxidized to an iminium ion. A final nucleophilic trapping by the aromatic ring (or the solvent) would yield the 2,3-disubstituted tetrahydropyridine. The main synthetic novelty with respect to previous approaches resides in the incorporation of an "electrophilic" malonate residue at the β-position of a pyridine ring system, whereas "nucleophilic" malonates have usually been linked to α-[5] and γ-positions.[2a,b]

Several oxidants such as $Co(OAc)_2$,[6] Ag_2CO_3,[7] CAN,[8] and $Mn(OAc)_3$[9] have been employed for the oxidative generation of electrophilic radicals from β-dicarbonyls, the latter two being the most widely used. *N*-Alkyl-1,4-dihydropyridines **1**, bearing representative substituents at positions 1 and 3, were selected as starting materials for our studies; their preparation was accomplished by $Na_2S_2O_4$ reduction of the corresponding pyridinium salts **2**, which in turn were prepared by quaternization of the commercially available pyridines with the appropriate alkyl halides (methyl iodide, ethyl iodide, benzyl bromide, and tryptophyl bromide).[10]

The first experiments were unsuccessful and only resulted in the *biomimetic* oxidation of the dihydropyridines. Thus, on treatment of **1a**,**b** with $Co(OAc)_2$, Ag_2CO_3/Celite (Fétizon reagent) or CAN in the presence of an excess of dimethyl malonate in MeOH solution, we only detected the formation of the corresponding pyridinium salts **2a**,**b**. Although enol ethers[8b] and enamines[11] do react under the above conditions, in our case the easier

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† This paper is dedicated to Professor Ernest Wenkert on the occasion of his 75th birthday.

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(5) Although less common than γ-addition processes, several reports deal with the addition of malonates to the α-position of pyridinium salts: (a) Wanner, J. M.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1983**, *39*, 3673. (b) Wenkert, E.; Michelotti, E. L.; Pyrek, J. St. *J. Org. Chem.* **1984**, *49*, 1832. (c) Wenkert, E.; Angell, C.; Drexler, J.; Moeller, P. D. R.; Pyrek, J. St.; Shi, Y.-J.; Sultana, M.; Vankar, Y. *J. Org. Chem.* **1986**, *51*, 2995.

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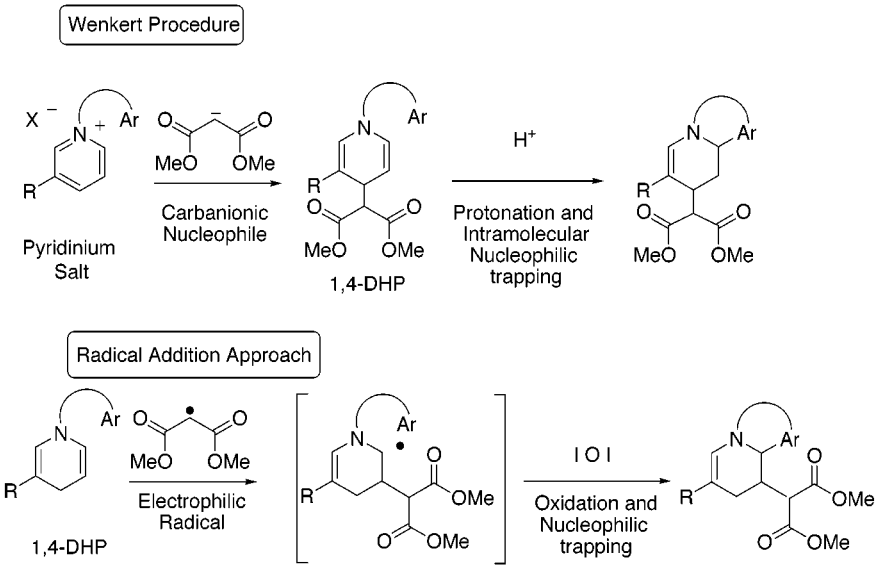
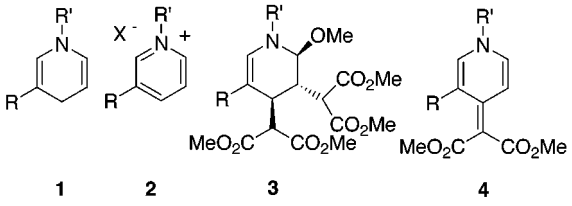
10.1021/jo001407p CCC: $20.00
Published on Web 01/25/2001

Scheme 1



electron-transfer pathway led exclusively to the observed oxidation. In fact, this well-documented process has found some synthetic applications in the oxidation of Hantzsch dihydropyridines.[1a,12] Despite a similar report dealing with $Mn(OAc)_3$,[13] we tried an analogous experiment with this reagent and were pleased to isolate (albeit in low yield, ≈10%) tetrahydropyridine **3a**, together with minor amounts of anhydro base **4a**. The structural assignment of these new compounds was performed with the aid of spectroscopical techniques (IR, UV, MS, ^1H and ^{13}C NMR, as well as bidimensional NMR experiments, including COSY, NOESY, HETCOR, and HMBC) and elemental analysis (Figure 1).



1 **2** **3** **4**

a : R = CN R' = Me
b : R = CN R' = Et
c : R = CN R' = Bn
d : R = CN R' = tryptophyl
e : R = CO_2Me R' = Me
f : R = $CONH_2$ R' = Bn

Anhydro base[14] **4a** shows an unusually high chemical shift for H-5 in the ^1H NMR spectrum (around 2 ppm higher than expected for this kind of enaminic hydrogens). This fact may reflect the anisotropic deshielding of one carbonyl group nearby. In an optimized structure (calculation performed with MMF94 and AM-1 Hamiltonian, using SPARTAN on SGI) the distance between this hydrogen and the oxygen atom of the syn (coplanar) carbonyl group is 1.9 Å, thus justifying the observed effect. Interestingly, the two diastereotopic methoxycarbonyl groups give rise to only one set of signals in the ^1H and ^{13}C NMR spectra, probably because of a fast interconversion on the NMR time scale. With respect to tetrahydropyridine **3a**, the chemical connectivity was secured through the HMBC spectrum, which allowed the unequivocal assignment of the most significant signals. The only isomer detected shows a *trans-trans* stereochemistry, displaying the three contiguous substituents axially in the main conformation (vicinal coupling constants between H_2-H_3 and H_3-H_4 around 1.2 Hz). It should be noted that in a flattened six-membered ring (with three sp^2 atoms) this arrangement does not suffer from serious 1,3-diaxial repulsions, and, on the other hand, it may test the benefits of an anomeric-type effect.

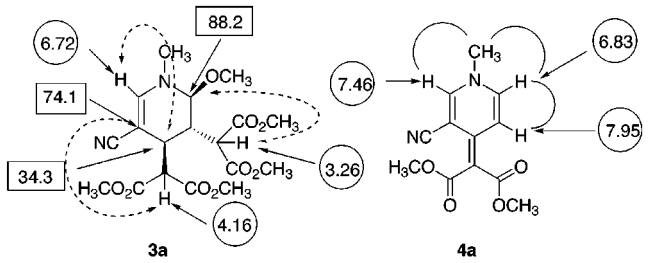
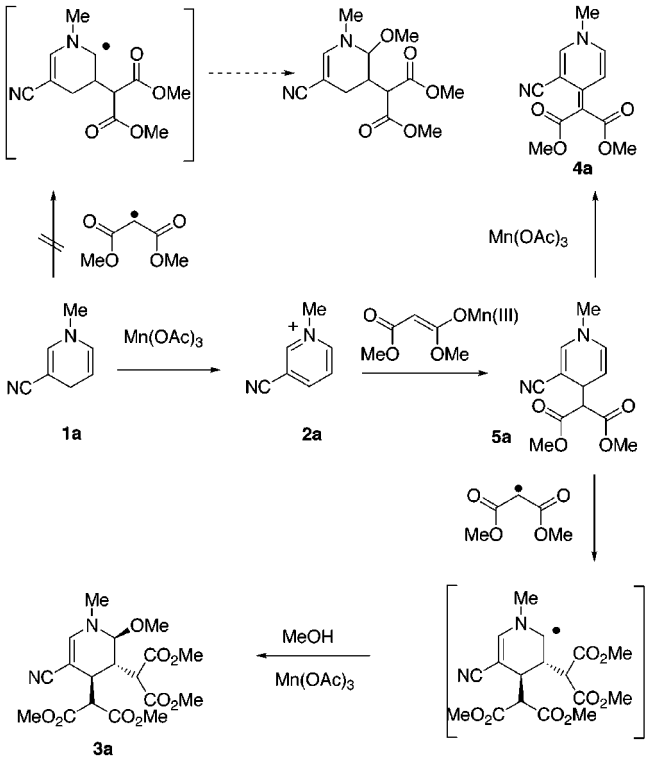


Figure 1. Structural assignment [Diagnostic data. Rounded boxes (^1H NMR chemical shifts), squared boxes (^{13}C NMR chemical shifts), plain curves (NOESY correlations), dashed curves (HMBC correlations)] for compounds **3a** and **4a**.

Several questions were raised at this moment. The mechanistic rationale behind this reaction was the first to be looked at. This rare process may be tentatively explained by considering again a kinetic competition between the biomimetic and nonbiomimetic oxidation pathways. In this case (see Scheme 2) the dihydropyridine **1a** would be oxidized to the corresponding salt **2a** (this step would bias the initially planned radical addition) to subsequently suffer the nucleophilic attack of the malonate [in an almost neutral medium, probably through the Mn(III) enolate]. The resulting 1,4-dihydropyridine **5a** would then undergo a further oxidation by $Mn(OAc)_3$ to give anhydro base **4a** and would interact competitively with the electrophilic malonyl radical [generated from the

(12) Pfister, J. R. *Synthesis* **1990**, 689.
(13) For the $Mn(OAc)_3$-promoted oxidation of Hantzsch dihydropyridines, see: Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 21.
(14) (a) Rodig, O. R. In *Pyridine and its Derivatives* (*The Chemistry of Heterocyclic Compounds* Vol. 14); Abramovitch, R. A., Ed.; Wiley: New York, 1974; Part 1, pp 351−353.

Scheme 2



corresponding Mn(III) enolate] to afford an α-amino radical. Oxidation followed by nucleophilic trapping by the solvent (MeOH) would account for the formation of the final bis(malonyl)tetrahydropyridine **3a**. The stereochemical outcome of the whole sequence is in agreement with the favored trans stereochemistry of radical additions on substituted cyclohexenes[15] and the stereocontrolled trapping of iminium ions.[16]

Some features of this mechanistic proposal deserve comment. The initial oxidation of dihydropyridine **1a**, although documented, was demonstrated by running the process starting from the corresponding salt **2a**. In this way, tetrahydropyridine **3a** and anhydro base **4a** were positively identified from the resulting reaction mixture. Also 1,4-dihydropyridine **5a** was produced at a lower temperature (40 °C) with reduced amounts of $Mn(OAc)_3$, both from **1a** and **2a**. It is noteworthy that this compound could be isolated and characterized by spectroscopic methods, which is unusual for this type of labile 1,4-dihydropyridine intermediates. Further treatment of this dihydropyridine **5a** with $Mn(OAc)_3$ in MeOH afforded a mixture of **3a** and **4a**, although under similar conditions **4a** is not converted into tetrahydropyridine **3a**, in agreement with the mechanistic sequence depicted in Scheme 2. It should be remarked that in the Wenkert procedure, the key dihydropyridines are produced in a highly basic nonpolar medium, and some degradation and/or the reversibility of the process causes the yield to be usually low (typically around 15%).[17] In our case, dihydropyridine **5a** was isolated simply by removing the volatiles (including the excess of dimethyl malonate) from the organic phase after an extraction (EtOAc) from an aqueous mixture ($MeOH-H_2O$), and the yield was higher (25% from **1a**, 68% from **2a**). This may lead to a practical improvement of the original procedure.

The possibility of using metal salts to promote this type of conjugate addition was explored, but $FeCl_3$ failed to catalyze the dimethyl malonate (or other β-dicarbonyl compounds) addition to pyridinium salt **2a** under several experimental conditions.[18] With respect to the optimization of the process, carrying out the reaction in MeOH at reflux temperature from salt **2a** resulted in the almost exclusive formation of the anhydro base **4a** in an increased yield (52%), whereas careful control of the conditions [usual reaction time 8h (TLC control), reflux temperature, 5 equiv of $Mn(OAc)_3$, and 10 equiv of dimethyl malonate] allowed the preparation of **3a** in 42% yield starting from **1a**; the use of an excess of dimethyl malonate (25 equiv) did not increase the yield. AcOH, which is the usual solvent for Mn(III)-promoted reactions, was avoided because of the unstability of dihydropyridines in acids, and MeOH was used instead. The addition of $Cu(OAc)_2$[19] or the use of ultrasound activation[20] did not improve the yield.[21]

The scope of the reaction was studied next, and we examined the effect of different alkyl substituents on the heterocyclic nitrogen. Dihydropyridines **1b**, **1c**, and **1d** (with ethyl, benzyl, and tryptophyl groups, respectively) were used. Following the previously developed method, the corresponding tetrahydropyridines **3b** (33%) and **3c** (25%) were obtained, whereas **3d** was isolated only in minute amounts,[22] the main products being the corresponding anhydro base **4d** (12%) and indoloquinolizidine **6d** (10%), the latter coming from the acid-promoted cyclization of the intermediate dihydropyridine **5d**. When the reaction was carried out at a lower temperature with reduced amounts of oxidant, and the crude **5d** exposed to a dry HCl saturated Et_2O solution, the yield of **6d** improved to 30% (Scheme 3).

We have also modified the electron-withdrawing group at the β-position of dihydropyridines **1**. No bis-malonate products were obtained from substrates **1e** and **1f**, the corresponding anhydro bases being obtained instead. In

(15) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996; pp 139−143.

(16) See for instance: Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1007−1046.

(17) (a) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 5370. (b) Also see ref 2. (c) For a higher yield, see: Jokela, R.; Taipale, T.; Ala-Kaila, K.; Lounasmaa, M. *Heterocycles* **1986**, *24*, 2265.

(18) For recent examples, see: (a) Christoffers, J.; Oertling, H.; Leitner, M. *Synlett* **2000**, 349. (b) Christoffers, J.; Oertling, H. *Tetrahedron* **2000**, *56*, 1339.

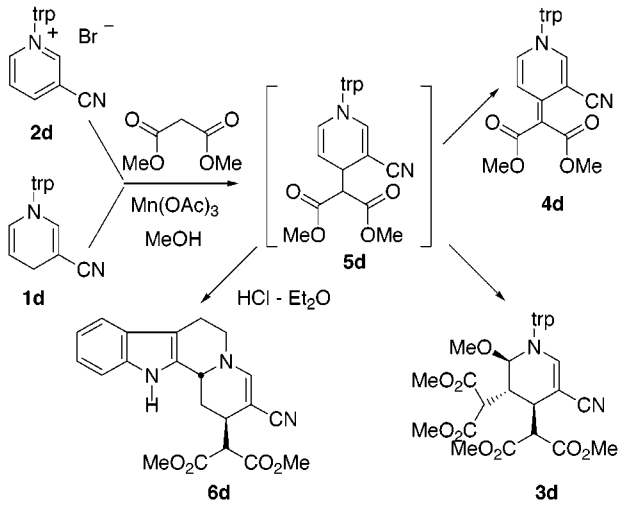
(19) For recent examples, see: (a) Cossy, J.; Bouzide, A. *Tetrahedron* **1999**, *55*, 6483. (b) Ishibashi, H.; Toyao, A.; Takeda, Y. *Synlett* **1999**, 1468. Also see ref 9.

(20) (a) Peters, D. In *Transition Metals for Organic Synthesis. Building Blocks and Fine Chemicals*, Beller, M.; Bolm, C., Eds. Wiley − VCH: Weinheim, 1998; Vol 2, pp 428−430. (b) For a recent result, see: Linker, T.; Linker, U. *Angew. Chem., Int. Ed.* **2000**, *39*, 902.

(21) In an attempt to carry out this transformation without the need of an oxidant, we tested the atom transfer additions of bromomalonates [see: Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140] to dihydropyridines **1** (toluene, AIBN, or Me_6Sn_2). No productive processes were observed, and the dihydropyridines remained unreacted, even after long reaction times or decomposition took place and the corresponding pyridinium salts were detected. A plausible explanation may be the abstraction of an allylic hydrogen atom from the dihydropyridine by the malonate radical. For a similar situation, see: Truksa, S. V.; Nibler, A.; Schatz, B. S.; Krosley, K. W.; Gleicher, G. J. *J. Org. Chem.* **1992**, *57*, 2967.

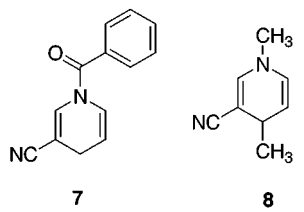
(22) Tryptophyltetrahydropyridine **3d**: ^1H NMR δ 8.15 (br s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.23−7.10 (m, 2H), 7.03 (d, J = 1.5 Hz, 1H), 6.45 (s, 1H), 4.36 (br s, 1H), 4.23 (d, J = 12.0 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.80−3.70 (m, 2H), 3.66 (s, 3H), 3.36 (s, 3H), 3.18 (d, J = 10.2 Hz, 1H), 3.00 (m, 3H), 2.85 (d, J = 12.0 Hz, 1H).

Scheme 3



these cases, the corresponding pyridinium salts **2** underwent the malonate addition to yield dihydropyridines **5** to a comparable extent. Also, similar additions with 3-formyl- or 3-acetyl-1,4-dihydropyridines resulted in failure. The apparent exclusivity of the cyano group in allowing the transformation may be related with the lower rate of (biomimetic) oxidation measured in 3-cyano-1,4-dihydropyridines as compared with dihydropyridines bearing other substituents at the β-position.[10] This would allow the intermediate dihydropyridines **5a**−**c** to undergo a kinetically competitive radical addition at a rate comparable with the rate of oxidation to the anhydro base, whereas in the remaining cases the latter process would overshadow the former.

To test the reactivity of dihydropyridines less prone to undergo the biomimetic oxidation, we prepared the *N*-benzoyldihydropyridine **7**[23] but, after the interaction with $Mn(OAc)_3$ and dimethyl malonate under the usual conditions, only complex mixtures were produced, and the expected products were not detected.



Finally, we examined the influence of the substitution at the γ-position of the dihydropyridine ring.[24] As it was clear that the unsubstituted substrates **1** are first oxidized and converted to γ-malonyldihydropyridines **5**, which *then* suffer the radical addition, it is tempting to suggest that a γ-substituent may slow the rate of the oxidation step and consequently favor the addition process. However, unfortunately, reactions from 4-methyldihydropyridine **8**[25] were not productive, and the expected product was only detected in trace amounts (NMR and MS evidence).

In conclusion, a very unusual chemically productive oxidation of *N*-alkyl-1,4-dihydropyridines is described. Although the scope of the reaction seems to be limited (only cyano groups are tolerated at the β-position of the dihydropyridine ring), the process deserves interest as it involves a triple action mode for the $Mn(OAc)_3$ (oxidant, enhancer for the nucleophilicity of the dimethyl malonate and promoter of the formation of the electrophilic malonate radical) in a stereoselective cascade reaction.

Experimental Section

General. All solvents were purified and dried by standard methods. All reagents were of commercial quality from freshly opened containers. Organic extracts were dried with anhydrous Na_2SO_4. Melting points were determined in a capillary tube and are uncorrected. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference at 200, 300, or 500 MHz (^{1}H) and 50.3 or 75 MHz (^{13}C). Only noteworthy IR absortions are listed (cm^{-1}). UV spectra were obtained in MeOH solution.

Tetrahydropyridine 3a. A solution of dihydropyridine **1a** (120 mg, 1 mmol), dimethyl malonate (1.32 g, 1.14 mL, 10 mmol), and $Mn(OAc)_3$ dihydrate (1.34 g, 5 mmol) in MeOH (10 mL) was stirred at reflux temperature under N_2 atmosphere until no dihydropyridine was detected by TLC (8 h). EtOAc (50 mL) was added, and the mixture was successively washed with aqueous Na_2CO_3 (10%, 100 mL) and $Na_2S_2O_3$ (0.5 M, 100 mL) solutions and brine (100 mL). The organic phase was dried and evaporated, and the residue was chromatographed (silica gel pretreated with Et_3N, elution with hexanes/CH_2Cl_2) to yield **3a** (173 mg, 42%) as a waxy solid. ^{1}H NMR δ 6.72 (s, 1H), 4.25 (m, J = 1.2 Hz, 1H), 4.16 (d, J = 11.1 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.38 (s, 3H), 3.26 (d, J = 9.0 Hz, 1H), 3.03 (s, 3H), 3.01 (m, 1H), 2.90 (m, J = 11.1, 1.2, and 1.2 Hz, 1H);^{13}C NMR δ 168.2, 167.9, 167.6, 167.5, 146.4, 120.6, 88.2, 74.1, 56.5, 54.3, 53.0, 52.8, 52.6, 52.5, 52.4, 42.7, 35.1, 34.3; IR (KBr) 2195, 1726, 1635; UV (MeOH) 266 (4.10); EI MS (*m*/*z*, %) 249 (100); CI MS (NH_3, *m*/*z*, %) 430 (M + NH_4^+, 100), 413 (M + H^+, 1). Anal. Calcd for $C_{18}H_{24}N_2O_9$: C, 52.43; H, 5.83; N, 6.80. Found: C, 52.59; H, 5.89; N, 6.83. Further elution with CH_2Cl_2/MeOH afforded anhydro base **4a** (20 mg, 8%).

Tetrahydropyridine (3b). Operating as above, from dihydropyridine **1b**, the ethyl derivative **3b** (33%) was obtained as a foam. ^{1}H NMR δ 6.78 (s, 1H), 4.27 (br s, 1H), 4.19 (d, J = 11.5 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.35 (s, 3H), 3.22 (m, 1H), 3.17 (m, 1H), 3.08 (d, J = 9.4 Hz, 1H), 2.97 (br d, J = 9.4 Hz, 1H), 2.85 (br d, J = 11.5 Hz,1H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 168.2, 167.9, 167.7, 167.4, 145.1, 120.8, 86.9, 74.2, 56.0, 54.3, 53.1, 52.8 (2C), 52.5, 52.3, 48.8, 34.7, 34.3, 14.6; IR (KBr) 2195, 1735, 1635; UV (MeOH) 264 (4.31); EI MS (*m*/*z*, %) 426 (M^+, 15), 295 (15), 263 (100). CI MS (NH_3, *m*/*z*, %) 444 (M + NH_4^+, 100); HRMS (EI) mass calcd for $C_{19}H_{26}N_2O_9$ 426.1638, found 426.1639.

Tetrahydropyridine (3c). Operating as above, from dihydropyridine **1c**, the benzyl derivative **3c** (25%) was obtained as a foam. ^{1}H NMR δ 7.35 (m, 3H), 7.19 (m, 2H), 6.88 (br s, 1H), 4.35 (d, J = 14.3 Hz, 1H), 4.29 (d, J = 14.3 Hz, 1H), 4.23 (d, J = 11.1 Hz, 1H), 4.16 (br s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.47 (s, 3H), 3.28 (s, 3H), 3.06 (d, J = 10.5 Hz, 1H), 2.96 (br d, J = 10.5 Hz, 1H), 2.87 (br d, J = 11.1 Hz, 1H); ^{13}C NMR δ 167.8, 167.7, 167.6, 167.3, 145.7, 135.1, 129.0 (2C), 128.4, 120.6, 85.7, 74.8, 57.3, 56.2, 54.3, 53.1, 52.8, 52.7, 52.6, 51.9, 34.5, 34.2; IR (NaCl) 2196, 1732, 1630; UV (MeOH) 266 (4.18); EI MS (*m*/*z*, %) 488 (M^+, 5), 357 (6), 325 (100). HRMS (EI) mass calcd for $C_{24}H_{28}N_2O_9$ 488.1794, found 488.1786.

Anhydro Base (4a). A solution of pyridinium salt **2a** (246 mg, 1 mmol), dimethyl malonate (1.32 g, 1.14 mL, 10 mmol), and $Mn(OAc)_3$ dihydrate (1.34 g, 5 mmol) in MeOH (10 mL) was

(23) For the method, see: Obika, S.; Nishiyama, T.; Tatematsu, S.; Nishimoto, M.; Miyashita, K.; Imanishi, T. *Heterocycles* **1997**, *44*, 537.

(24) For an intramolecular reductive radical addition to γ-substituted-1,4-dihydropyridines, see: Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349.

(25) (a) Dihydropyridine **8** was prepared from 3-cyano-4-methylpyridine[25b,c] by methylation followed by dithionite reduction. (b) Lounasmaa, M.; Johansson, C.-J. *Tetrahedron* **1977**, *33*, 113. (c) Bobbitt, J. M.; Scola, D. A. *J. Org. Chem.* **1960**, *25*, 560.

stirred at reflux temperature under N_2 atmosphere for 8 h. EtOAc (50 mL) was added, and the mixture was successively washed with aqueous Na_2CO_3 (10%, 100 mL) and $Na_2S_2O_3$ (0.5 M, 100 mL) solutions and brine (100 mL). The organic phase was dried and evaporated, and the residue was chromatographed (silica gel pretreated with Et_3N). On elution with hexanes/CH_2Cl_2, tetrahydropyridine **3a** (39 mg, 10%) was obtained. Further elution with CH_2Cl_2/MeOH yielded anhydro base **4a** (129 mg, 52%) as a yellow solid. Further purification may be achieved by recrystallization from acetone−Et_2O, mp 181−183 °C. ^{1}H NMR δ 7.95 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 6.83 (dd, J = 8.1 and 1.8 Hz, 1H), 3.66 (br s, 6H), 3.51 (s, 3H); ^{13}C NMR δ 167.9, 146.8, 143.9, 135.7, 115.8, 115.4, 98.2, 94.3, 50.8, 43.0; IR (KBr) 2220, 1722, 1705, 1680, 1640; UV (MeOH) 353 (4.41); EI MS (*m*/*z*, %) 248 (M^+, 100), 217 (100), 159 (48), 148 (54), 132 (70). Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.84; N, 11.29. Found: C, 57.92; H, 4.73; N, 11.23.

Anhydro Base (4d). Obtained as a yellow solid foam in 12% yield by oxidation of dihydropyridine **1d** under the above conditions. Further purification may be achieved by recrystallization from acetone−Et_2O, mp 112−114 °C. ^{1}H NMR δ 8.40 (br s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.22−7.15 (m, 2H), 7.00 (d, J = 1.8 Hz, 1H), 6.81 (d, J = 1.3 Hz, 1H), 6.59 (dd, J = 8.0 and 1.3 Hz, 1H), 3.96 (t, J = 7.2 Hz, 2H), 3.75 (br s, 6H), 3.10 (t, J = 7.2 Hz, 2H); ^{13}C NMR δ 167.0, 145.4, 142.2, 136.3, 134.0, 125.9, 123.3, 122.5, 119.9, 117.6, 115.9, 115.0, 111.8, 108.9, 99.5, 93.6, 56.9, 51.3, 26.7; IR (NaCl) 3400, 2220, 1705, 1680, 1636; UV (MeOH) 356 (4.12), 271 (3.72); EI MS (*m*/*z*, %) 377 (M^+, 20), 345 (15), 216 (25), 144 (100). Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.84; H, 5.04; N, 11.14. Found: C, 66.62; H, 5.38; N, 10.87.

Dihydropyridine (5a). A solution of dihydropyridine **1a** (246 mg, 1 mmol), dimethyl malonate (660 mg, 0.57 mL, 5 mmol), and $Mn(OAc)_3$ dihydrate (536 mg, 2 mmol) in MeOH (10 mL) was stirred at 40 °C under N_2 atmosphere for 1 h. EtOAc (50 mL) was added, and the mixture was successively washed with aqueous Na_2CO_3 (10%, 100 mL) and $Na_2S_2O_3$ (0.5 M, 100 mL) solutions and brine (100 mL). The organic phase was dried and evaporated, and the excess malonate was removed by heating under high vacuum (0.01 Torr, 60 °C) to yield labile dihydropyridine **5a** (63 mg, 25%) slightly impurified. Starting from pyridinium salt **2a** and operating as above, dihydropyridine **5a** was obtained in 68% yield. ^{1}H NMR δ 6.61 (d, J = 1.2 Hz, 1H), 5.84 (dd, J = 7.9 and 1.2 Hz, 1H), 4.84 (dd, J = 7.9 and 5.0 Hz, 1H), 3.97 (dd, J = 6.4 and 5.0 Hz, 1H), 3.76 (s, 6H), 3.52 (d, J = 6.4 Hz, 1H), 3.01 (s, 3H); ^{13}C NMR δ 167.2, 144.6, 130.3, 120.1, 101.7, 77.6, 58.3, 52.5, 40.9, 34.1; IR (NaCl) 2194, 1730, 1678; EI MS (*m*/*z*, %) 250 (M^+, 16), 249 (16), 191 (28), 159 (50), 119 (60), 83 (100).

Indoloquinolizidine 6d. Operating as above, from dihydropyridine **1d** (250 mg, 1 mmol), crude dihydropyridine **5d** was obtained and then dissolved in anhydrous THF (50 mL). The resulting solution was kept at 0 °C, and enough of a HCl-saturated Et_2O solution was added to reach pH 2−3. The solution was stirred at room temperature for 2 h and then poured into aqueous saturated Na_2CO_3 solution (125 mL) and extracted with EtOAc. The organic phase was dried and evaporated, and the residue was chromatographed (silica gel, elution with CH_2Cl_2/MeOH) to yield indoloquinolizidine **6d** (115 mg, 30%) as a foam. ^{1}H NMR δ 8.27 (br s, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.21−7.08 (m, 2H), 7.00 (s, 1H), 4.48 (br d, J = 11.4 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.70 (m, 1H), 3.58 (d, J = 9.6 Hz, 1H), 3.54 (m, 1H), 3.3 (m, J = 9.6, 5.1, and 2.1 Hz, 1H), 2.90 (m, 1H), 2.78 (m, 1H), 2.46 (m, J = 16.2, 2.1, and 1.8 Hz, 1H), 1.88 (m, J = 16.2, 11.4, and 5.1 Hz, 1H); ^{13}C NMR δ 168.1, 167.8, 148.9, 136.2, 131.1, 126.5, 122.2, 121.9, 119.7, 117.9, 111.1, 107.9, 72.7, 56.9, 53.0, 52.8, 50.9, 47.8, 32.1, 30.7, 21.7; IR (NaCl) 3300, 2187, 1750, 1730, 1627; UV (MeOH) 275 (4.64); EI MS (*m*/*z*, %) 379 (M^+, 25), 246 (100). HRMS (EI) mass calcd for $C_{21}H_{21}N_3O_4$ 379.1532, found 379.1533.

Acknowledgment. This work was supported by the DGICYT, Spain (project PB94-0214). Thanks are also due to the Comissionat per Universitats i Recerca (Generalitat de Catalunya) for Grant SGR99-00079. A. S thanks Università "La Sapienza" (Roma) for a fellowship. Professors A. Vallribera and R. Pleixats (Universitat Autonoma de Barcelona) are thanked for helpful discussions.

Supporting Information Available: Experimental procedures for compounds **7** and **8**. ^{1}H and ^{13}C NMR spectra of compounds **3b**, **3c**, **5a**, and **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001407P