"Nonbiomimetic" Oxidations of Dihydropyridines

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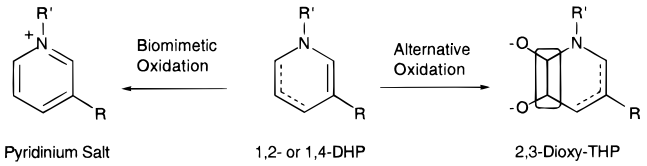
Continuing our research in the development of new transformations of dihydropyridines,[1] we have recently described some "nonbiomimetic" oxidations of these compounds, in which the normal production of the corresponding pyridinium salt is avoided.[2,3] Here we report the studies toward the dioxygenation of the enaminic moiety present in these substrates (Scheme 1).

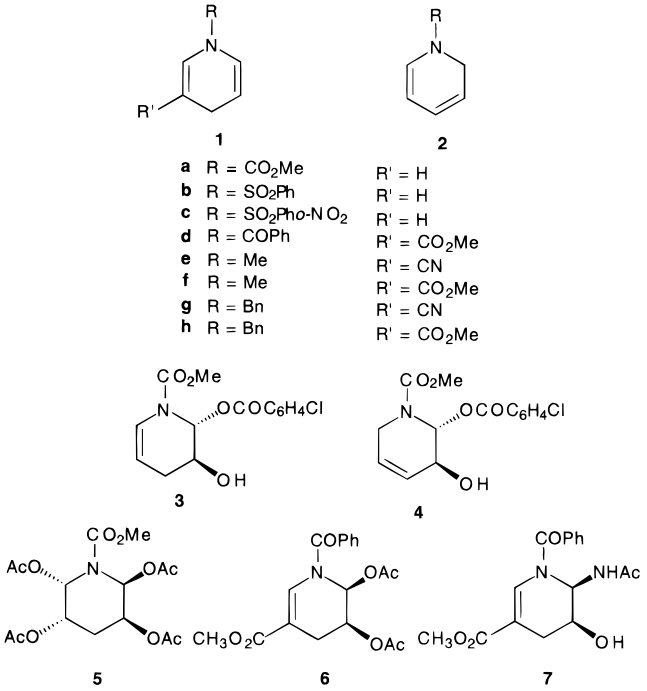
Very little is known about this type of reactions[4,5] and it was decided to study the process with a broad selection of diversely substituted 1,4- and 1,2-dihydropyridines, **1** and **2** respectively. The *N*-methoxycarbonyl derivatives **1a** and **2a** were prepared according to Fowler's method.[6] Phenylsulfonyldihydropyridines **1b** and **1c**[7] were formed using Knaus' procedure.[8] Benzoyl derivative **1d** and the *N*-alkyl-1,4-dihydropyridines **1e**−**h** were prepared through reduction of the corresponding pyridinium salts with sodium cyanoborohydride[9] and sodium dithionite[10] respectively (Scheme 2).

The interaction of dihydropyridines with *m*-CPBA to promote a formal epoxidation was tested first of all.[11] On exposure of **1a** to 1 equiv of *m*-CPBA in CH_2Cl_2 solution

Scheme 1



Scheme 2



at −40 °C, the addition compound **3** was formed (65%).[12,13] The process probably involves an initial oxygen transfer from the peroxy acid to form an unstable aminoepoxide, which is in situ regio- and stereoselectively trapped by the *m*-chlorobenzoic acid present in the solution. In a similar way, **2a** reacted to afford tetrahydropyridinol **4** (66%). The rest of the dihydropyridines underwent extensive decomposition and, in some cases, trace amounts of the corresponding 2-acyloxytetrahydropyridin-3-ol derivatives could be detected (NMR from crude reaction mixtures), together with the biomimetic oxidation products (the *N*-alkylpyridinium salts from **1e**−**h**). No useful double epoxidations were achieved, either by direct treatment of **1a** or **2a** with 2 equiv of *m*-CPBA or by subsequent oxidation of **3** or **4**.

The osmylation of dihydropyridines was explored next, and substrate **1a** was treated with osmium tetroxide solution[14] (catalytic) using 4-methylmorpholine *N*-oxide as stoichiometric reoxidant, to afford, after the usual acetylation, the piperidine derivative **5** as a single

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(1) For reviews on the chemistry of dihydropyridines, see: (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (c) Sausins, A.; Duburs, G. *Khim. Geterotsikl. Soedin.* **1993**, 579. (d) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 291. (e) Kutney, J. P. *Heterocycles* **1977**, *7*, 593. (f) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199.

(2) For a preliminary report of a part of this work, see: Lavilla, R.; Gullón, F.; Barón, X.; Bosch, J. *Chem. Commun.* **1997**, 213.

(3) (a) Lavilla, R.; Coll, O.; Kumar, R.; Bosch, J. *J. Org. Chem.* **1998**, *63*, 2728. (b) Lavilla, R.; Kumar, R.; Coll, O.; Masdeu, C.; Bosch, J., Molins, E.; Espinosa, E. Unpublished results.

(4) Some reports dealing with vicinal dioxygenation of *N*-alkyl-1,4-dihydropyridines with K_2MoO_4, and O_2 in the presence of $CuSO_4$ were not successfully reproduced in our hands: (a) Negievich, L. A.; Grishin, O. M.; Yasnikov, A. A. *Ukr. Khim. Zh.* **1968**, *34*, 684 (*Chem. Abstr.* **1969**, *70*, 11513) (b) Negievich, L. A.; Grishin, O. M.; Yasnikov, A. A. *Ukr. Khim. Zh.* **1968**, *34*, 802 (*Chem. Abstr.* **1969**, *70*, 28776).

(5) For a 4 + 2 cycloaddition involving *N*-acyl-1,2-dihydropyridines and singlet oxygen, see: (a) Natsume, M.; Sekine, Y.; Ogawa, M.; Soyagimi, H.; Kitagawa, Y. *Tetrahedron Lett.* **1979**, 3473. (b) Utsunomiya, I.; Ogawa, M.; Natsume, M. *Heterocycles* **1992**, *33*, 349. For the osmylation of *N*-acyl-1,2-dihydropyridines, see: (c) Tschamber, T.; Backenstrass, F.; Neuburger, M.; Zehnder, M.; Streith, J. *Tetrahedron* **1994**, *50*, 1135. (d) Tschamber, T.; Rodríguez-Pérez, E.-M.; Wolf, P.; Streith. J. *Heterocycles* **1996**, *42*, 669.

(6) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321.

(7) The *o*-nitrophenylsulfonyl group was selected because of its easy and mild cleavage; see: Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(8) Knaus, E. E.; Redda, K. *Can. J. Chem.* **1977**, *55*, 1788.

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(10) Brewster, M. E.; Simay, A.; Czako, K.; Winwood, D.; Farag, H.; Bodor, N. *J. Org. Chem.* **1989**, *54*, 3721.

(11) For a general review on the oxidation of enamines, see: Pittaco, G.; Valentin, E. V. In *The Chemistry of Enamines;* Rappoport, Z., Ed. (*The Chemistry of Functional Groups,* Patai, S.; Rappoport, Z., Eds.); Wiley: Chichester, 1994; Part 2, Chapter 17.

(12) For a similar reaction taking place upon an *N*-acyl-1,2,3,4-tetrahydropyridine, see: Masamune, T.; Hayashi, H.; Takasugi, M.; Fukuoka, S. *J. Org. Chem.* **1972**, *37*, 2343.

(13) The related interaction of peracids with enol ethers has been reported: (a) Wood, H. B., Jr.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 3234. (b) Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W.; Schreiner, E. P.; Suzuki, T.; Iwabuchi, Y.; Smith, A. L.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7593.

(14) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063.

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stereoisomer (77%). The stereochemical outcome of this double dihydroxylation is in good agreement with the previously reported osmylation of dihydropyridine **2a**,[5c] in which the second oxidation takes place on the less substituted face of the tetrahydropyridine intermediate.[15] Analogously, *N*-benzoyl-3-substituted dihydropyridine **1d** was converted into the corresponding diacetoxy tetrahydropyridine **6** (70%). Attempted dihydroxylations of *N*-sulfonyl- or *N*-alkyldihydropyridines under the same conditions resulted in decomposition or pyridinium salt formation. However, small amounts of 2,3-dihydroxytetrahydropyridines were obtained from the osmylation of **1f** and **1h**[16] when a $(DHQ)_2PHAL - K_2[OsO_2(OH)_4]$ system[17] was used, apparently suggesting that the ligand-accelerated catalysis helps to overcome (although to a small extent) the natural tendency of *N*-alkyl-1,4-dihydropyridines to undergo oxidation to the corresponding pyridinium salts. Also problematic were the aminohydroxylation reactions[18] upon dihydropyridines **1**. Only compounds **1d** and **1f** were converted to the corresponding 2-acetamido-3-hydroxytetrahydropyridines, although in very low yields. For instance, compound **7** was isolated from **1d** in 5% yield, in a process that also formed traces of the corresponding diol, whereas the products obtained from **1f** could not be isolated and were only detected from the crude reaction mixture by NMR.

Looking for a reagent that could efficiently transfer an oxygen atom to the olefin moiety of the highly reactive *N*-alkyl-1,4-dihydropyridines, we became interested in the properties of dimethyldioxirane (DMD).[19] Especially appealing were the reports on the epoxidation of enol ethers[20] and enamines,[21] which are sensitive substrates difficult to oxidize by other methods. On the other hand, it should be mentioned that a chemically related dioxetane was involved in the "normal" (biomimetic) oxidation of a NADH analogue.[22]

Scheme 3

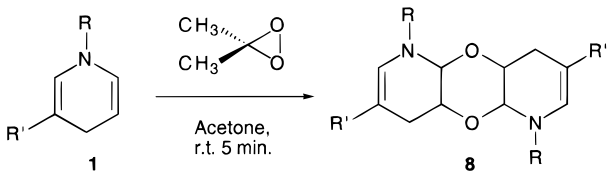


Table 1. DMD Oxidation Reactions from Dihydropyridines 1

entry	dihydropyridine	product	yield (%)
1	**1e**	**8e**	72
2	**1f**	**8f**	75
3	**1g**	**8g**	69
4	**1h**	**8h**	60

When dihydropyridine **1e** was treated at room temperature with a DMD solution,[23] the dioxane **8e** was obtained in acceptable yield (72%), together with some of the corresponding pyridinium salt, indicating a kinetic competition between the two oxidation pathways. The process can be rationalized by considering the initial epoxidation of the enamine double bond, with subsequent ring-opening of the oxirane ring to give a zwitterionic species that undergoes dimerization.[21a−c] Substrates **1f**, **1g**, and **1h** underwent similar transformations, affording the corresponding dioxanes **8f** − **8h** in yields ranging from 60% to 75% (dihydropyridines **1a**−**d** and **2a** afforded low yields of unstable compounds) (Scheme 3 and Table 1). In contrast, the use of dioxiranes generated in situ from 2-chlorocyclohexanone or 1,1,1-trifluoroacetone in the presence of stoichiometric amounts of Oxone[24] was not satisfactory (only pyridinium salts were produced), thus making evident the incompatibility of dihydropyridines with strong oxidants such as peroxy acids. The stereochemical analysis of **8e** indicated a major isomer with a center of symmetry, showing a cis stereochemistry for the oxygens at C2−C3 and an anti relation between the two tetrahydropyridine moieties.[25] Minor amounts of other isomer were isolated, probably with a syn stereochemistry. The stereochemical assignments were based on the coupling constants in the ^1H NMR spectra and on ^1H-^1H COSY, HMQC, and NOESY experiments. Dioxanes **8e**−**h** were stable enough to be chromatographed (decomposition took place to a reduced extent), spectroscopically characterized, and stored in the freezer under an inert atmosphere for months.

It is well known that α-alkoxyamines can promote the formation of iminium ions in the presence of Lewis acids and, in this way, allow the introduction of substituents at the nitrogen α-position through nucleophilic addition. Accordingly, we envisaged a set of transformations of this type to make the above nonbiomimetic oxidation of dihydropyridines synthetically useful for the preparation

(15) For a discussion about the influence of conformational solvent effects and hydrogen-bonding in the stereocontrol of double dihydroxylations, see: (a) Donohoe, T. J.; Moore, P. R.; Beddoes, R. L. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 43. (b) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.

(16) Methyl *cis*-2,3-dihydroxy-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (6%): ^1H NMR δ_7.27 (s, 1H), 4.60 (m, 1H), 3.88 (m, 1H), 3.68 (s, 3H), 3.21 (d, J = 5 Hz, 1H), 3.06 (s, 3H), 2.65 (dd, J = 18.3 and 4.3 Hz, 1H), 2.47 (d, J = 5 Hz, 1H), 2.31 (dd, J = 18.3 and 9.6 Hz, 1H);^{13}C NMR δ_168.5, 144.8, 93.8, 80.7, 67.0, 51.0, 39.6, 25.0. Methyl *cis*-1-benzyl-2,3-dihydroxy-1,2,3,4-tetrahydropyridine-5-carboxylate (7%): ^1H NMR δ_7.40−723 (m, 6H), 4.60 (m, 1H), 4.53 (d, J = 15 Hz, 1H), 4.37 (d, J = 15 Hz, 1H), 3.88 (m, 1H), 3.69 (s, 3H), 2.69 (dd, J = 18 and 4 Hz, 1H), 2.35 (m, 3H); MS (EI) *m/z* (relative intensity) 263 (M^+, 10), 245 (16), 204 (8), 91 (100).

(17) See, for instance: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(18) Different versions of this transformation were investigated, following the protocols developed by Sharpless: (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. (b) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810. (c) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813. (d) Brucko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483.

(19) (a) Crandall, J. K. In *Encyclopedia of Reagents for Organic Synthesis*. Paquette, L. A., Ed. Wiley: Chichester, **1995**, Vol. 3, p 2061. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (c) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.

(20) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

(21) (a) Adam, W.; Peters, E.-M.; Peters, K.; von Schnering, H.-G.; Voerckel, V. *Chem. Ber.* **1992**, *125*, 1263. (b) Adam, W.; Ahrweiler, M.; Paulini, K.; Reissig, H.-U.; Voerckel, V. *Chem. Ber.* **1992**, *125*, 2719. (c) Adam, W.; Reinhardt, D.; Reissig, H.-U.; Paulini, K. *Tetrahedron* **1995**, *51*, 12257. (d) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255.

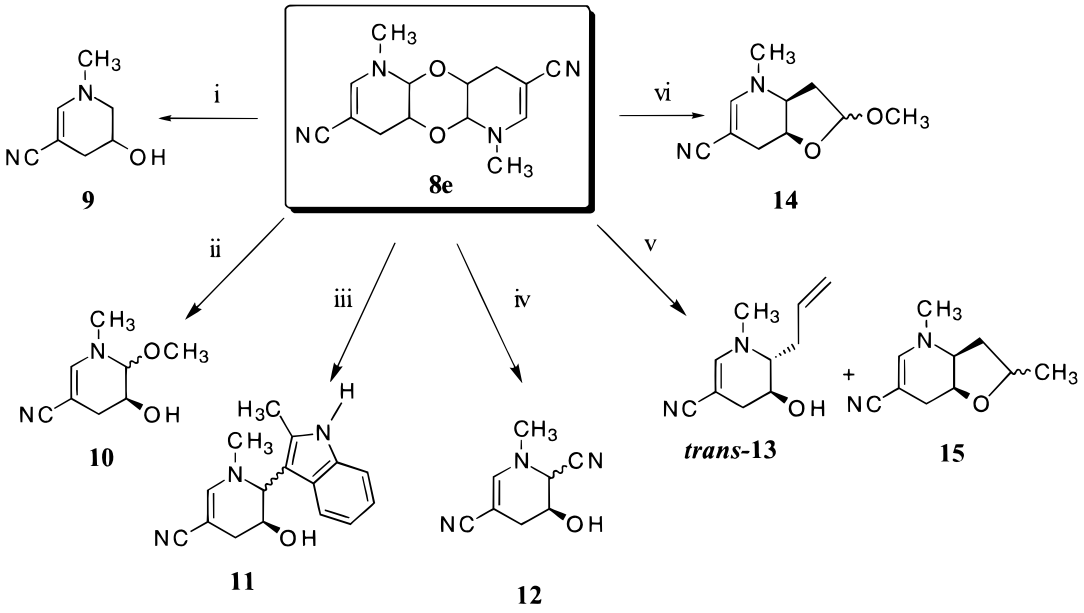
(22) Adam, W.; Heil, M.; Hutterer, R. *J. Org. Chem.* **1992**, *57*, 4491.

(23) DMD solutions were prepared according to Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377, and the dioxirane content (ca. 0.07 M) was determined by iodometric titration.

(24) For the use of catalytic DMD epoxidations, see: (a) Yang, D.; Wong, M. K.; Yip, Y. C. *J. Org. Chem.* **1995**, *60*, 3887. (b) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (c) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391. (d) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831.

(25) .For related structures, see: (a) Koppenhoefer, B.; Winter, B.; Bayer, E. *Liebigs Ann. Chem.* **1983**, 1986. (b) Adam, W.; Peters, K.; Sauter, M. *Synthesis* **1994**, 111. (c) Agami, C.; Couty, F.; Hamon, L.; Prince, B.; Puchot, C. *Tetrahedron* **1990**, *46*, 7003. Also see refs 12 and 21c.

Scheme 4[a]



[a] Reagents and conditions: i. Et_3SiH, $TiCl_4$, THF, −60 °C, 5 min, (95%). ii. MeOH, TFA, 0 °C, 5 min, (96%, trans:cis 3:1). iii. 2-Methylindole, TFA, 20 °C, 5 min, (84%, trans:cis 2.5:1). iv. TMSCN, $TiCl_4$, CH_2Cl_2, 0 °C, 5 min, (67%; trans:cis 1.5:1). v. AllylTMS, $TiCl_4$, CH_2Cl_2, −78 °C, 5 min, then SiO_2 column chromatography, (*trans*-13 46%, 15 7%). vi. 1-Methoxyethene, $BF_3{\cdot}Et_2O$, THF−CH_2Cl_2, −60 °C, 5 min, (60%, mixture of isomers at the acetalic carbon).

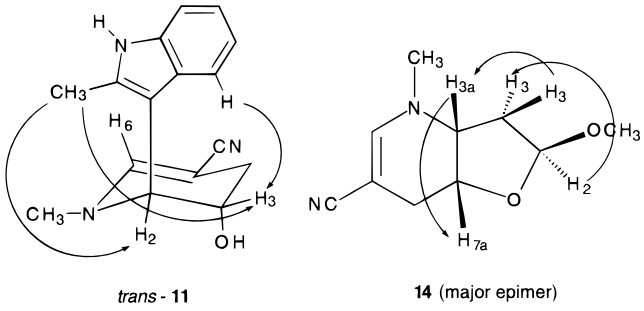


Figure 1.

of 2-substituted 3-hydroxy-1,2,3,4-tetrahydropyridines (see Scheme 4). The reduction of **8e** with Et_3SiH in the presence of $TiCl_4$ afforded the tetrahydropyridinol **9** (95%).[26] TFA-induced addition of MeOH gave the "monomeric" equivalent **10** (96%) as a diastereomeric mixture, the trans isomer being the major compound (3:1 vs the cis isomer).[27] The addition of heteroaromatics was next investigated and, on interaction of dioxane **8e** with 2-methylindole under acid catalysis, adduct **11** (84%) was formed with moderate stereoselectivity (trans:cis 5:2). The stereochemistry of both isomers was assigned with the aid of monodimensional NOE and ROESY experiments, showing the spatial connectivity depicted in Figure 1. On the other hand, α-aminonitrile **12** (67%, trans:cis 3:2) was prepared through $TiCl_4$-mediated TMSCN addition to **8e**. Allylsilane addition to the iminium ion generated from **8e** on $TiCl_4$ treatment[28] gave the expected *trans*-2-allyl-3-hydroxytetrahydropyridine **13** (46%), together with a small amount of a bicyclic furopyridine **15** (7%), which was not present in the crude reaction mixture but eluted after the main compound on column chromatography on silica gel. Probably, its formation is the result of an acid-catalyzed cyclization of the minor cis isomer (*cis*-**13**) produced in the addition step.[29] In fact, this addition − cyclization sequence can be carried out more efficiently, thus gaining practical access to the above-mentioned bicyclic systems. Thus, on $BF_3{\cdot}Et_2O$-promoted methoxyethene addition to dioxane **8e**,[30] partially reduced furopyridine **14** (60%) was obtained as an epimeric mixture at the acetalic carbon. Remarkably, in sharp contrast with the above nucleophilic additions, the stereochemistry at the ring fusion is cis (determined from NOE and ROESY experiments; see Figure 1), thus suggesting that a reversible addition of the enol ether forms a stabilized carbocation, which would undergo intramolecular trapping by the hydroxyl group to close the tetrahydrofuran ring. Only a cis arrangement would favor the cyclization and, probably, the initially formed trans cationic intermediate would equilibrate with the more reactive cis isomer.

In summary, we have described several *nonbiomimetic* oxidation reactions of 1,2- and 1,4-dihydropyridines that allow the vicinal dioxygenation of these substrates, and we have carried out some transformations of the corre-

(26) This transformation represents a two-step sequence for the *anti*-Markownikoff water addition to 1,4-dihydropyridines.

(27) The preferred formation of trans isomers in this type of reactions may reflect the more favorable approach of the nucleophile from the less sterically hindered face of the iminium ion, away from the electron-rich hydroxyl group. See, for instance: Khan, S. D.; Dobbs, K. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 4602. Also see ref 25c.

(28) For related transformations, see: (a) Kozikowski, A. P.; Park, P. *J. Org. Chem.* **1984**, *49*, 1674. (b) Sakagami, H.; Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1433. (c) Hartman, G. D.; Philips, B. T.; Halczenko, W.; Springer, J. P.; Hirshfield, J. *J. Org. Chem.* **1987**, *52*, 1136.

(29) Interestingly, when attempting the reaction at 0 °C the only isolated compound (10%, NMR and MS evidence) was a bicyclic analogue of **15**, bearing a (trimethylsilyl)methyl group at C-2, thus indicating that an intramolecular trapping of the carbocation by the hydroxyl group had taken place instead of the usual elimination to regenerate the double bond. For a related situation, see ref 28c.

(30) For additions or addition-cyclization sequences of enol ethers to iminium ions, see: (a) Natsume, M.; Masashi, O. *Heterocycles* **1980**, *14*, 169. (b) Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753.

sponding 2,3-dioxytetrahydropyridines into 2-substituted 3-hydroxytetrahydropyridines. Although the rationalization of the oxidation processes seems problematic because they are probably influenced by several factors such as the nature of the oxidant, the reaction conditions, and the stability and the substitution pattern of the dihydropyridines, the experimental procedures reported may fulfill the practical needs on this type of reactivity. Considering the synthetic implications of the above methodology, these results may lead to interesting transformations of dihydropyridines, a class of compounds with a relevant role in biochemistry and in natural product synthesis.

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 sodium sulfate. 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.

General Method for *m*-CPBA Oxidations. A solution of *m*-CPBA (3.5 mmol) in anhydrous CH_2Cl_2 (25 mL) was added dropwise under N_2 atmosphere to a stirred solution of dihydropyridine **1a** or **2a** (3 mmol) in CH_2Cl_2 (50 mL) kept at −40 °C, and stirring was continued at this temperature until no dihydropyridine was detected by TLC (usually 1 h). Aqueous NaOH (1 M, 30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2, elution with Et_2O) to yield pure tetrahydropyridinols **3** or **4**.

Methyl *trans*-2-(3-Chlorobenzoyloxy)-3-hydroxy-1,2,3,4-tetrahydropyridine-1-carboxylate (3) (65%). Recrystallization from hexanes − Et_2O gave white crystals, mp 119−121 °C. ^{1}H NMR δ_8.06 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.40 (m, 1H), 6.70 (bs, 1H), 5.92 (bs, 1H), 5.17 (m, 1H), 4.90 (bs, 1H), 3.81 (s, 3H), 2.45 (m, 2H), 1.65 (bs, 1H);^{13}C NMR δ_164.5,_154.0,_134.5, 133.2, 131.4, 129.7, 129.6, 127.9, 122.6, 102.6, 73.6, 70.8, 53.4, 22.1;_IR (KBr) 3400, 1723, 1693, 1625; UV (MeOH) 290 (3.93), 282 (4.06); Anal. Calcd for $C_{14}H_{14}ClNO_5$: C, 53.94; H, 4.52; N, 4.49. Found: C, 53.76; H, 4.55; N, 4.48.

Methyl *trans*-2-(3-Chlorobenzoyloxy)-3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (4) (66%). Recrystallization from hexanes − Et_2O gave white crystals, mp 117−119 °C. ^{1}H NMR δ_8.05 (s, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 7.3 Hz, 1H), 7.39 (m, 1H), 6.16 (d, J = 4.1 Hz, 1H), 5.95 (m, 1H), 5.73 (m, J = 10.3 Hz, 1H), 5.38 (bs, 1H), 4.03 (m, J = 18.4, 6.0 and 2.9 Hz, 1H), 3.68 (s, 3H), 3.65 (m, J = 18.4, 8.3 and 2.4 Hz, 1H), 2.70 (bs, 1H);^{13}C NMR δ_164.5,_155.3,_134.5, 133.3, 131.2, 129.7, 129.6, 127.9, 125.9, 121.6, 72.4, 69.4, 53.1, 40.1;_IR (KBr) 3376, 1721, 1687; UV (MeOH) 280 (4.09); Anal. Calcd for $C_{14}H_{14}ClNO_5$: C, 53.94; H, 4.52; N, 4.49. Found: C, 53.88; H, 4.54; N, 4.44.

Methyl (2*RS*, 3*RS*, 5*RS*, 6*RS*)-2,3,5,6-Tetraacetoxypiperidine-1-carboxylate (5). To a stirred solution of dihydropyridine **1a** (255 mg, 1.8 mmol) and 4-methylmorpholine *N*-oxide (535 mg, 3.9 mmol) in a mixture of acetone (2 mL) and water (1.2 mL) was added a solution of osmium tetroxide in *t*-BuOH prepared according to ref 14 (1 mL), and the resulting mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, the residue was taken up in Ac_2O (4 mL) and Et_3N (8 mL), and the mixture was stirred at room temperature for 15 h. Et_2O was added (100 mL), and the reaction mixture was successively washed with aqueous Na_2SO_3 (10%, 100 mL) and $NaHCO_3$ (10%, 100 mL) solutions and brine (100 mL). The organic phase was dried (Na_2SO_4) and evaporated, and the residue was chromatographed (silica gel, Et_2O) to yield piperidine **5** (528 mg, 77%). Recrystallization from hexanes− Et_2O gave white crystals, mp 154−156 °C. ^{1}H NMR δ_6.80_(d, J = 2.7 Hz, 2H), 5.34 (m, J = 8.9 and 2.7 Hz, 2H), 3.73 (s, 3H), 2.13 (m, J = 8.9 Hz, 2H), 2.06 (s, 6H), 2.00 (s, 6H);^{13}C NMR δ_169.9,_169.1,_153.6,_73.9,_65.1,_53.8,_25.1,_20.8,_20.5;_IR (KBr) 1748, 1735, 1732; Anal. Calcd for $C_{15}H_{21}NO_{10}$: C, 47.98; H, 5.64; N, 3.73. Found: C, 47.86; H, 5.70; N, 3.79.

Methyl *cis*-2,3-Diacetoxy-1-benzoyl-1,2,3,4-tetrahydropyridine-5-carboxylate (6). Following the above experimental procedure, diacetate **6** (70%) was obtained from dihydropyridine **1d**. Recrystallization from hexanes − Et_2O gave white crystals, mp 164−166 °C. ^{1}H NMR δ_7.94_(s, 1H), 7.54 (m, 5H), 6.74 (d, J = 3.1 Hz, 1H), 5.31 (m, 1H), 3.73 (s, 3H), 2.74 (d, J = 19.5 Hz, 1H), 2.54 (m, J = 19.5, 4.3 and 2.2 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H);^{13}C NMR δ_170.3,_169.5,_168.1,_167.4,_134.1,_132.4,_131.9,_128.7,_128.4,_106.8,_73.6,_63.7,_51.7,_21.1,_20.9,_20.7;_IR (KBr) 1756, 1742, 1702, 1689, 1636; UV (MeOH) 264 (4.16); Anal. Calcd for $C_{18}H_{19}NO_7$: C, 59.83; H, 5.26; N, 3.87. Found: C, 59.99; H, 5.30; N, 3.78.

General Method for DMD Oxidations. A 1.1-fold excess of DMD solution (0.07 M) in acetone[23] was added to a solution of the dihydropyridine **1e**−**h** (1 mmol) in acetone (20 mL) at 0 °C. The progress of the reaction was monitored by TLC. When all the starting material was consumed (ca. 5 min), the solvent was removed under reduced pressure and the residue was chromatographed (neutral alumina, CH_2Cl_2 − MeOH) to give the corresponding dioxane **8e**−**h**.

Dioxane 8e (72%). Major isomer: ^{1}H NMR (CD_3OD) δ 2.18 (ddd, J = 16.3, 2.7 and 1.5 Hz, 2H), 2.60 (ddd, J = 16.3, 3.7 and 1.9 Hz, 2H), 3.15 (s, 6H), 3.83 (m, 2H), 4.51 (dd, J = 2.6 and 1.5 Hz, 2H), 6.98 (dd, J = 1.9 and 0.8 Hz, 2H); ^{13}C NMR (CD_3OD) δ: 24.4, 39.3, 63.9, 70.3, 80.4, 122.7, 146.0; IR (NaCl) 2189, 1630; MS (EI) m/z (relative intensity) 272 (M^+, 8), 136 (51), 119 (100); UV (MeOH) 266 (4.7); HRMS (EI) mass calcd for $C_{14}H_{16}N_4O_2$ 272.1273, found 272.1272. Minor isomer: ^{1}H NMR (CD_3OD) δ 2.25−2.45 (m, 4H), 2.89 (s, 6H), 3.87 (m, 2H), 4.65 (d, J = 2.6 Hz, 2H), 6.89 (s, 2H); ^{13}C NMR (CD_3OD) δ 26.9, 41.2, 68.5, 73.7, 88.7, 123.2, 148.4; MS (EI) m/z (relative intensity) 272 (M^+, 7), 136 (39), 119 (100).

3-Hydroxy-1-methyl-1,2,3,4-tetrahydropyridine-5-carbonitrile (9). To a stirred solution of dioxane **8e** (50 mg, 0.18 mmol) in dry CH_2Cl_2 (15 mL) kept at −60 °C were added $TiCl_4$ (0.35 mL, 3.17 mmol) and Et_3SiH (0.3 mL, 3.5 mmol), and stirring was continued for 5 min at this temperature. Saturated aqueous NH_4Cl (50 mL) and saturated aqueous Na_2CO_3 (100 mL) were added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried and evaporated under reduced pressure to give a residue that was purified by column chromatography (silica gel, CH_2Cl_2) to furnish tetrahydropyridine **9** (47 mg, 95%). ^{1}H NMR δ 2.20 (m, 2H), 2.49 (m, J = 15.9 Hz, 1H), 2.95 (s, 3H), 3.01 (m, J = 12.6, 5.6, 2.5 and 0.9 Hz, 1H), 3.17 (m, J = 12.6, 2.6 and 1.1 Hz, 1H), 4.19 (bs, 1H), 6.79 (d, J = 0.9 Hz, 1H); ^{13}C NMR δ 30.0, 42.9, 52.9, 61.9, 69.5, 123.0, 147.5; IR (NaCl) 3400, 2181, 1627; MS (EI) m/z (relative intensity) 138 (M^+, 46), 95 (100); UV (MeOH) 275 (4.3).

3-Hydroxy-2-methoxy-1-methyl-1,2,3,4-tetrahydropyridine-5-carbonitrile (10). To a stirred solution of dioxane **8e** (70 mg, 0.25 mmol) in dry CH_2Cl_2 (15 mL) kept at 0 °C were added MeOH (0.5 mL) and TFA (0.25 mL), and stirring was continued for 5 min at this temperature. Saturated aqueous Na_2CO_3 (100 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried and evaporated under reduced pressure to give a residue that was purified by column chromatography (silica gel, CH_2Cl_2−hexanes) to furnish tetrahydropyridine **10** (81 mg, 96%) as a mixture of epimers (trans:cis 3:1). ^{1}H NMR δ_(trans isomer) 2.12 (m, J = 16.6, 2.2 and 1.3 Hz, 1H), 2.40 (m, J = 16.6, 3.8 and 1.9 Hz, 1H), 3.09 (s, 3H), 3.38 (s, 3H), 3.93 (m, 1H), 4.07 (dd, J = 3.2 and 1.2 Hz, 1H), 6.77 (dd, 1H, J = 2.0 and 1.0 Hz, 1H); ^{13}C NMR δ_(trans isomer) 25.6, 42.6, 56.4, 61.8, 73.1, 89.4, 122.1, 145.2; IR (NaCl) 3420, 2190, 1632; MS (EI) m/z (relative intensity) 168 (M^+, 100), 137 (95), 95 (90). UV (MeOH) 267 (4.2); HRMS (EI) mass calcd for $C_8H_{12}N_2O_2$ 168.0899, found 168.0902.

3-Hydroxy-1-methyl-2-(2-methyl-3-indolyl)-1,2,3,4-tetrahydropyridine-5-carbonitrile (11). To a stirred solution of

dioxane **8e** (23 mg, 0.08 mmol) in a 1:1 mixture of AcOEt − dioxane (10 mL) at room temperature were added 2-methylindole (27 mg, 0.21 mmol) and TFA (5 drops), and stirring was continued for 5 min at this temperature. Saturated aqueous Na_2CO_3 (100 mL) was added, and the resulting mixture was extracted with AcOEt (3 × 30 mL). The combined organic layers were dried and evaporated under reduced pressure to give a residue that was purified by column chromatography (silica gel, AcOEt−hexanes) to furnish *trans*-**11** (26 mg, 60%). ^{1}H NMR δ 2.33 (dd, J = 15.6 and 6.7 Hz, 1H), 2.43 (s, 3H), 2.50 (dd, J = 15.6 and 4.0 Hz, 1H), 2.81 (s, 3H), 4.20 (m, J = 6.7, 5.4 and 4.0 Hz, 1H), 4.30 (d, J = 5.4 Hz, 1H), 7.02 (s, 1H), 7.07−7.20 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 8.10 (bs, 1H); ^{13}C NMR δ 11.8, 28.3, 40.9, 60.6, 66.4, 69.2, 108.0, 110.6, 117.8, 119.8, 120.0, 121.6, 122.2, 134.5, 136.1, 148.5; IR (NaCl) 3400, 2185, 1627; MS (EI) *m*/*z* (relative intensity) 267 (M^+, 34), 173 (100), 144 (67); UV (MeOH) 274 (4.5); HRMS (EI) mass calcd for $C_{16}H_{17}N_3O$ 267.1372, found 267.1381. On elution with AcOEt, *cis* -**11** (10 mg, 24%) was obtained. ^{1}H NMR δ 2.17 (dd, J = 15.3 and 8.9 Hz, 1H), 2.44 (s, 3H), 2.50 (dd, J = 15.3 and 5.0 Hz, 1H), 2.83 (s, 3H), 4.19 (m, 1H), 4.57 (bs, 1H), 7.00 (s, 1H), 7.06−7.18 (m, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 8.11 (bs, 1H); ^{13}C NMR δ 12.2, 29.1, 41.2, 58.5, 67.3, 69.7, 104.9, 110.5, 118.7, 119.9, 120.2, 121.5, 123.5, 135.1, 135.2, 148.7; IR (NaCl) 3400, 2183, 1625; MS (EI) *m*/*z* (relative intensity) 267 (M^+, 34), 173 (100), 144 (66).

3-Hydroxy-1-methyl-1,2,3,4-tetrahydropyridine-2,5-dicarbonitrile (12). To a stirred solution of dioxane **8e** (50 mg, 0.18 mmol) in dry CH_2Cl_2 (30 mL) kept at 0 °C were added $TiCl_4$ (0.35 mL, 3.17 mmol) and TMSCN (0.6 mL, 4.3 mmol), and stirring was continued for 5 min at this temperature. Saturated aqueous NH_4Cl (50 mL) and saturated aqueous Na_2CO_3 (100 mL) were added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried and evaporated under reduced pressure to give a residue that was purified by column chromatography (silica gel, CH_2Cl_2) to furnish dinitrile **12** (40 mg, 67%) as a mixture of epimers (trans: cis 3:2). ^{1}H NMR δ_(trans isomer) 2.30 (m, J = 16.8, 2.6 and 2.3 Hz, 1H), 2.75 (m, J = 16.8, 3.6 and 2.0 Hz, 1H), 3.08 (s, 3H), 3.98 (dd, J = 2.6 and 2.3 Hz, 1H), 4.39 (m, 1H), 6.77 (d, 1H, J = 2.0 Hz, 1H); ^{13}C NMR δ_(trans isomer) 27.2, 41.3, 52.7, 63.2, 76.3, 115.4, 120.7, 145.5; IR (NaCl) 3500, 2196, 1629; MS (EI) *m*/*z* (relative intensity) 163 (M^+, 85), 134 (100), 107 (59); UV (MeOH) 265 (4.8); HRMS (EI) mass calcd for $C_8H_9N_3O$ 163.0746, found 163.0746.

***trans*-2-Allyl-3-hydroxy-1-methyl-1,2,3,4-tetrahydropyridine-5-carbonitrile (13).** To a stirred solution of dioxane **8e** (264 mg, 0.97 mmol) in dry CH_2Cl_2 (30 mL) kept at −78 °C were added $TiCl_4$ (0.4 mL, 3.16 mmol) and allyltrimethylsilane (0.18 mL, 1.5 mmol), and stirring was continued for 5 min at this temperature. Saturated aqueous NH_4Cl (50 mL) and saturated aqueous Na_2CO_3 (100 mL) were added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried and evaporated under reduced pressure to give a residue that was purified by column chromatography (silica gel, CH_2Cl_2) to furnish tetrahydropyridine **13** (160 mg, 46%) as an oil. ^{1}H NMR δ 1.60 (bs, 1H), 1.95 (m, 2H), 2.30 (m, 3H), 3.00 (s, 3H), 3.95 (bs, 1H), 5.10 (m, 1H), 5.12 (m, 1H), 5.70 (m, 1H), 6.79 (s, 1H); ^{13}C NMR δ 26.3, 35.8, 42.5, 61.8, 63.1, 76.8, 114.4, 118.8, 132.9, 146.0; IR (NaCl) 3400, 2182, 1627; MS (EI) *m*/*z* (relative intensity) 178 (M^+, 4), 137 (19), 69 (100). UV (MeOH) 272 (4.5); Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.41; H, 7.86; N, 15.73. Found: C, 67.32; H, 8.07; N, 15.42. On further elution with CH_2Cl_2 - MeOH (99:1). **(3*a RS, 7a RS*)-2,4-Dimethyl-2,3,3*a*,4,7,7*a*-hexahydrofuro[3,2-*b*]pyridine-6-carbonitrile** (**15**, 25 mg, 7%) was obtained as an epimeric mixture at C-2. ^{1}H NMR δ_(major isomer) 1.26 (d, J = 6.2 Hz, 3H), 1.78 (m, J = 13.2, 7.7 and 5.7 Hz, 1H), 2.20−2.40 (m, 3H), 2.91 (s, 3H), 3.56 (dd, J = 9.3 and 4.9 Hz, 1H), 4.23−4.35 (m, 2H), 6.72 (s, 1H);^{13}C NMR δ_(major isomer) 21.8, 24.8, 37.7, 40.2, 58.5, 72.6, 73.4, 79.8, 123.0, 147.3; IR (NaCl) 2183, 1631; MS (EI) *m*/*z* (relative intensity) 178 (M^+, 79), 135 (100), 119 (60).

2-Methoxy-4-methyl-2,3,3*a*,4,7,7*a*-hexahydrofuro[3,2-*b*]-pyridine-6-carbonitrile (14). To a stirred solution of dioxane **8e** (70 mg, 0.25 mmol) in dry CH_2Cl_2 (30 mL) kept at −60 °C were added $BF_3{\cdot}Et_2O$ (0.1 mL, 0.56 mmol) and methoxyethene (0.15 mL, 1.1 mmol) dissolved in THF (5 mL) precooled to −78 °C, and stirring was continued at −60 °C until no starting material was detected by TLC (5 min). Saturated aqueous K_2CO_3 (100 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried and evaporated under reduced pressure to give a residue that was purified by column chromatography (neutral alumina, CH_2Cl_2−hexanes) to furnish bicycle **14** (60 mg, 60%) as a mixture of epimers at the acetalic carbon. ^{1}H NMR δ_(major epimer, 2*RS*, 3a*SR*, 7a*SR*) 1.97 (m, J = 13.7, 7.5 and 2.9 Hz, 1H), 2.40 (m, 1H), 2.47 (m, 2H), 2.92 (s, 3H), 3.35 (s, 3H), 3.55 (m, 1H), 4.25 (m, 1H), 5.02 (dd, J = 5.9 and 2.9 Hz, 1H), 6.72 (s, 1H);^{13}C NMR δ_(major epimer, 2*RS*, 3a*SR*, 7a*SR*) 25.5, 36.6, 40.8, 55.4, 57.1, 73.5, 79.9, 104.0, 123.1, 147.1; IR (NaCl) 2185, 1632; MS (EI) *m*/*z* (relative intensity) 194 (M^+, 22), 119 (100); UV (MeOH) 271 (4.3); HRMS (EI) mass calcd for $C_{10}H_{14}N_2O_2$ 194.1055, found 194.1060.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1d, 7, 8f**−**h**; copies of the ^{1}H and ^{13}C NMR spectra of compounds **8e**−**h**, **9**, **10**, **11**, **12**, **14**, **15** (24 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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