Introduction of Heteroatom-Based Substituents into 1,4-Dihydropyridines by Means of a Halogen-Mediated, Oxidative Protocol: Diamination, Sulfonylation, Sulfinylation, Bis-Sulfanylation, and Halo-Phosphonylation Processes

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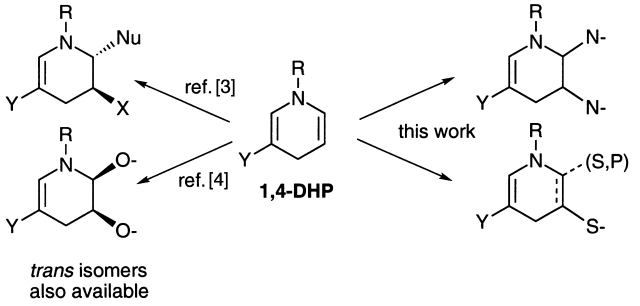
Abstract: The natural tendency of 1,4-dihydropyridines to undergo "biomimetic" oxidation to afford pyridinium salts can be switched off and, through the use of reagents that interact electrophilically with the enamine moiety present in the heterocyclic system, it is possible to promote alternative oxidations. In this way, efficient regio- and stereocontrolled synthetic methods have been developed that lead to diversely substituted di- and tetrahydropyridines. These include iodoazidation, diamination, bis-sulfonamidation, sulfonylation, sulfinylation, thiocyanation, sulfanylation, bis-sulfanylation, and halo-phosphonylation processes.

Keywords: amination · dihydropyridines · heterocycles · oxidations · synthetic methods

Introduction

The rich synthetic chemistry of 1,4-dihydropyridines (1,4-DHPs)[1] suffers from a serious drawback that severely hampers their use in preparative processes: they readily undergo oxidation (spontaneously in many cases) to the corresponding pyridinium salts. Nature extensively implements this reactivity (as well as the reverse reaction) in many NADH-dependent metabolic steps. On the other hand, it would be highly desirable to profit from the nucleophilic character of the enamine moiety present in the molecule for synthetic purposes. In this context, the most classical reactivity of 1,4-dihydropyridines towards protonation or carbon-centered electrophiles has emerged as a powerful tool for the total synthesis of indole alkaloids.[2] More recently we have opened the door to the possibility of carrying out some "nonbiomimetic" oxidations of 1,4-dihydropyridines in which the normal production of the corresponding pyridinium salt is avoided. For instance, the oxidative addition of halonium ions (*N*-halosuccinimide or related alkoxyhalogenations) has proven to be a successful method for the preparation of 2-substituted 3-halo-1,2,3,4-tetrahydropyridines, which, in turn, may be considered as valuable synthetic intermediates.[3] Additionally, vicinal dihydroxylation and formal epoxidation of dihydropyridines have been achieved in our laboratories, and the resulting 2,3-dioxytetrahydropyridines have been elaborated into a variety of 2-substituted-3-hydroxytetrahydropyridines.[4]

The introduction of nitrogen-, sulfur-, and phosphorous-based functionalities into the dihydropyridine ring system through the above-mentioned oxidative methodology would represent a highlight in this field, taking into account the potential impact of the resulting heterocyclic systems in natural product synthesis and in medicinal chemistry, where the preparation of diversely substituted (and functionalized) piperidines constitutes a highly pursued goal (Scheme 1).



Scheme 1. Nonbiomimetic oxidation of 1,4-dihydropyridines.

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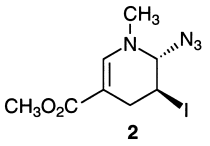
Results and Discussion

First of all, we envisaged a co-halogenation process,[5] in which the nucleophilic partner would be a nitrogen species of low basicity. After much experimentation, we found that the interaction of dihydropyridine **1a** (Scheme 2) with bis(collidine)iodonium tetrafluoroborate[6] in the presence of trimethylsilyl azide[7] stereoselectively afforded the somewhat unstable *trans* iodoazide **2** in acceptable yield (66%).[8] However, the introduction of acetamido, trifluoroacetamido, and phenylsulfonamido substituents from a variety of halonium sources was less successful.[9] Although cyanamide, cyanate, and acetonitrile have also been used as the nucleophilic partners in alkene additions promoted by halogen sources,[10] in our case only sluggish reactions resulted under these conditions and, apart from by-products previously described,[11] no addition compounds were detected. The low nucleophilicity of the iminium-attacking species may be the factor most responsible for the failure of the above experiments.



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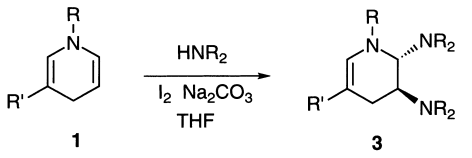
The use of amines as nucleophiles in the electrophilic oxidative addition to carbon–carbon double bonds is normally avoided[12] because of the facile oxidation of the nitrogen atom or its coordination with the electrophile. We felt, however, that this process could be dramatically reduced because of the high reactivity of the enamine moiety present in the dihydropyridine system, which may rapidly trap the electrophilic halogen to form a 3-halo-3,4-dihydropyridinium ion. In good agreement with our expectations, the treatment of dihydropyridine **1a** in THF solution with iodine (3.5 equiv) in the presence of excess pyrrolidine gave the 2,3-diaminotetrahydropyridine **3a** stereoselectively in 87% yield (Scheme 2).[13] The stereochemistry of the addition was ascertained by NMR methods (including homo- and heterocorrelation techniques). The small H2–H3 coupling constant observed suggests a *trans* relationship between the two pyrrolidine groups and a major conformation in which these substituents are axial (it should be noted that in a tetrahydropyridine ring such a substitution pattern displays no substantial 1,3-diaxial interactions). This stereochemical assignment was further confirmed by means of X-ray analysis of a single crystal of tetrahydropyridine **3g** (see below), although in the solid state the preferred conformation shows equatorial piperazine substituents (Figure 1).

Abstract in Spanish: *La tendencia natural de las 1,4-dihidropiridinas a sufrir oxidaciones "biomiméticas" para proporcionar sales de piridinio se puede interrumpir y, mediante el uso de reactivos que interaccionan de modo electrófilo con la porción enamínica presente en el sistema heterocíclico, es posible promover oxidaciones alternativas. De esta forma se han desarrollado métodos sintéticos eficaces, regio- y estereocontrolados, que conducen a di- y tetrahidropiridinas diversamente sustituidas mediante procesos de iodoazidación, diaminación, bis-sulfonamidación, sulfonilación, sulfinilación, tiocianación, sulfanilación, bis-sulfanilación, y halofosfonilación.*



1 **3**

a	R = Me	R' = CO_2Me	**a**	R = Me	R' = CO_2Me	R^2N = pyrrolidinyl
b	R = Me	R' = CN	**b**	R = Me	R' = CO_2Me	R^2N = piperidino
c	R = Bn	R' = CN	**c**	R = Me	R' = CN	R^2N = pyrrolidinyl
			d	R = Me	R' = CN	R^2N = piperidino
			e	R = Me	R' = CN	R^2N = morpholino
			f	R = Bn	R' = CN	R^2N = pyrrolidinyl
			g	R = Bn	R' = CN	R^2N = 4-methyl-1-piperazinyl
			h	R = Me	R' = CO_2Me	R^2N = butylamino

Scheme 2. Vicinal diamination of dihydropyridines.

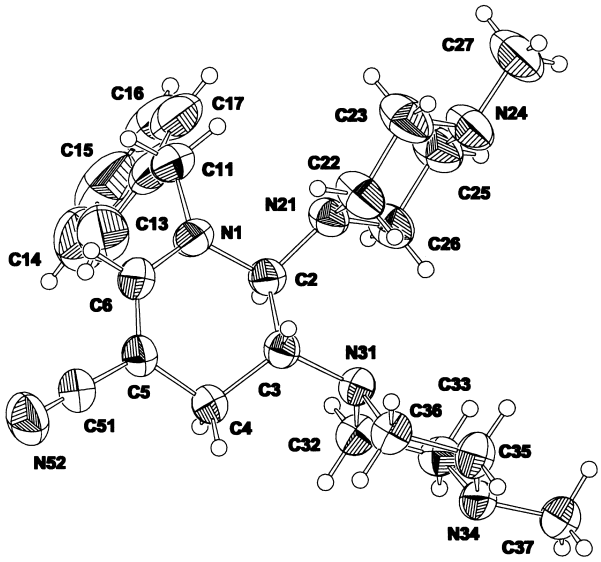


Figure 1. X-ray structure of compound **3g**.

The formation of **3a** can be rationalized by considering the initial formation of a *trans*-2-amino-3-iodotetrahydropyridine, which would undergo an internal SN reaction followed by a stereoselective ring opening of the resulting aziridinium ion promoted by a second equivalent of the secondary amine.[14]

The reaction seems to be quite general, and works well with different alkyl groups (methyl and benzyl) attached to the dihydropyridine nitrogen, and different electron-withdrawing groups at the 3-position (methoxycarbonyl and cyano). Several cyclic secondary amines were tested, including pyrrolidine, piperidine, morpholine, and *N*-methylpiperazine, and the corresponding *trans* vicinal diamines **3a–g** were isolated in good yields in all cases (Table 1).[15] It should be noted that the diamination of olefins usually involves multistep sequences and/or the use of expensive organometallic reagents.[16] The yields were slightly improved by the addition of solid Na_2CO_3 to the reaction mixture; however, efforts to reduce the amount of iodine and/or secondary amine to stochiometric amounts resulted in decreased yields, even after longer reaction times. The reaction can also be conducted with catalytic amounts (10% mol) of KI in a two-phase system (Et_2O/H_2O) with household bleach (NaClO) as the stochiometric oxidant; in this way **3e** (25%) was obtained after 48 h.[17] The mechanism probably involves the oxidation of iodide to iodine, which is then transferred to the organic phase

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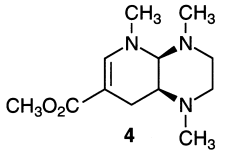
Table 1. Vicinal diamination reactions from dihydropyridines **1**.

Entry	Dihydropyridine	Secondary amine	Product	Yield [%]
1	**1a**	pyrrolidine	**3a**	87
2	**1a**	piperidine	**3b**	90
3	**1b**	pyrrolidine	**3c**	94
4	**1b**	piperidine	**3d**	89
5	**1b**	morpholine	**3e**	84
6	**1c**	pyrrolidine	**3f**	79
7	**1c**	1-methylpiperazine	**3g**	86
8	**1a**	butylamine	**3h**	33
9	**1a**	MeNH-$(CH_2)_2$-NHMe	**4**	80

where the reaction takes place and the iodide ions are regenerated. Although the yield is not as high as in the previous conditions, it clearly shows the feasibility of the use of more economical oxidants.

This remarkable process is also suitable for the formation of cyclic diamino adducts. Thus, when dihydropyridine **1a** was allowed to react with iodine in the presence of *N*,*N*′-dimethylethylenediamine, the bicyclic adduct **4** was obtained in 80% yield as a slightly unstable oil. The stereochemistry of the ring fusion was determined to be *cis*, as the coupling constant between the ring fusion hydrogens is small ($J < 1$ Hz; a *trans*-decalin-type fusion would result in a much larger coupling constant). This was confirmed by NOE and NOESY experiments. The difference with respect to the previous acyclic systems (where only *trans* products **3** were obtained) may reflect that, in the present case, the intramolecular nucleophilic attack on the initially formed *trans*-2-amino-3-iodotetrahydropyridine takes place faster at the remaining secondary amino group to give a *cis*-fused six-membered ring. Alternatively, an aziridinium intermediate could undergo ring-opening to give a 3-amino-3,4-dihydropyridinium cation, which could be intramolecularly trapped by the remaining secondary amino group.



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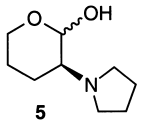
In contrast to the above results, the use of simple primary amines (methylamine, ethylenediamine) or NH_3 resulted in complex reaction mixtures, from which the desired compounds, as well as the corresponding aziridines, were detected (MS) in trace amounts. However, butylamine did react with **1a** under the usual reaction conditions (I_2, Na_2CO_3) to afford the corresponding diaminotetrahydropyridine **3h**, although in a lower yield (33%).

The extension of this methodology to enol ethers was tested next: when 3,4-dihydro-2*H*-pyran was treated with iodine and pyrrolidine, an unstable compound was obtained (presumably the corresponding 2,3-diaminotetrahydropyran; MS and NMR evidence), which decomposed during column chromatography to furnish the hemiacetal **5** (27%, nonoptimized yield) as an anomeric mixture.[18] It is worth mentioning that cyclohexene failed to yield significant amounts of the corresponding addition product[19] on treatment with iodine and pyrrolidine under the above reaction conditions. This suggests that only electron-rich olefins are good substrates for this kind of oxidative addition.



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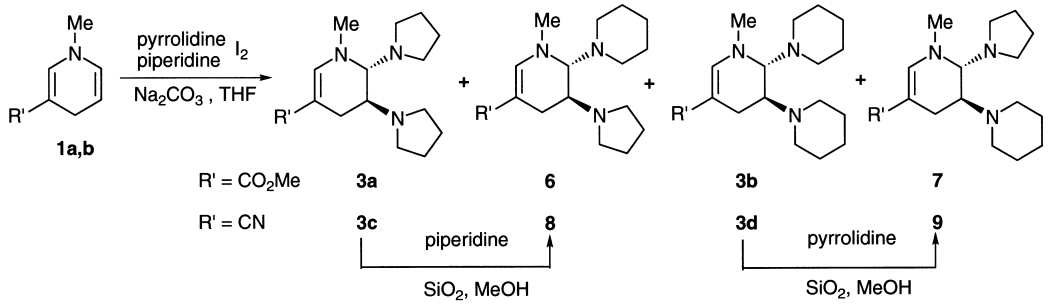
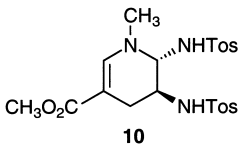
In order to broaden the scope of the reaction, we performed some experiments aimed at the simultaneous incorporation of two different amines. As expected, the use of an equimolecular mixture of pyrrolidine and piperidine as co-reactants in the iodine-promoted oxidation of dihydropyridines **1a** and **1b** resulted in the formation of mixtures of the four possible diamination compounds (Scheme 3, see the Supporting Information for details).[20] To improve the access to the "heterodiamines" formed in the process, a selective synthesis of **8** and **9** was undertaken and, after some experimentation, it was found that the "homodiamines" **3** undergo a selective transaminalization[21] in MeOH in the presence of SiO_2. Under these conditions, **3c** reacts with excess piperidine to yield selectively **8** (41%). In an analogous transformation, **3d** was converted to **9** on treatment with pyrrolidine (22%; nonoptimized yields). A rationale for these results may invoke a similar mechanism to that proposed for the diamination reaction, in which the acid catalysis promotes the departure of the 2-amino substituent (probably with anchimeric assistance of the neighboring 3-amino group) to form an iminium ion, which is stereoselectively trapped by the amine (in excess) to yield the new *trans*-aminal. These regiodiverse compounds could be conveniently purified and characterized.

Next, the aziridination of dihydropyridines **1** was investigated.[22] In recent times, very efficient methods for this process have been developed for alkenes and enol ethers.[23] We were particularly attracted to the protocols published by Sharpless et al.[23a] and Komatsu et al.,[23b] because of their mechanistic similarities to the diamination reaction described



Scheme 3. Preparation of regiodiverse diamines **6**–**9**.



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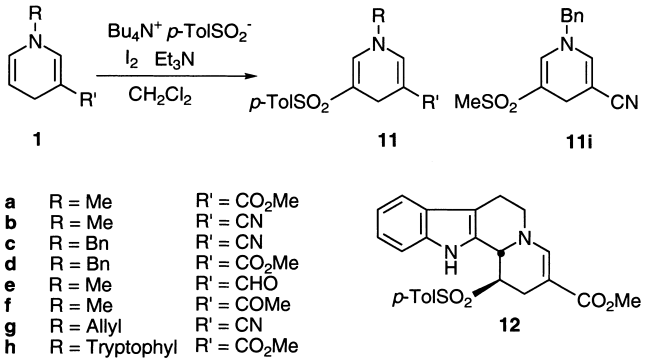
above. In this way, when dihydropyridine **1a** was treated with I_2, chloramine T trihydrate and tetrabutylammonium iodide in a two-phase system (CH_2Cl_2/H_2O), disulfonamide **10** was produced in 33% yield. Trace amounts of the corresponding *cis* isomer were also isolated. Modifications of the nature or the stoichiometry of the reagents, solvent, or reaction conditions did not improve the yield; only the addition of the potassium salt of *p*-toluenesulfonamide slightly increased the yield to 40%. A reasonable explanation would involve the initial formation of an aziridine, which being highly strained would stereoselectively react with a second equivalent of chloramine to yield the *trans*-disulfonamide.

The introduction of a sulfone moiety into the dihydropyridine ring was studied next.[24] In fact, we had initially planned to carry out a halosulfonylation[25] of the enamine moiety in the *N*-alkyl-1,4-dihydropyridines **1**. However, when **1a** was treated with iodine in the presence of sodium *p*-toluenesulfinate in MeOH, 3-sulfonyldihydropyridine **11a** was obtained in 30% yield (Scheme 4). The structure proposed for this



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Scheme 4. Sulfonylation of dihydropyridines **1**.

compound is consistent with the spectroscopic data (^1H and ^{13}C NMR, IR, UV, MS) and was later confirmed by a NOESY experiment, which showed correlations between the benzylic protons and the hydrogens at positions 2 and 6 in **11d**, thus ruling out a regioisomeric α-sulfonyldihydropyridine (which might be the result of the initial β-attack of the iodine, followed by a sulfinate addition upon the resulting iminium ion and subsequent dehydroiodination). After some experimentation (for instance, dihydropyridine treatment with *p*-toluenesulfonyl chloride in the presence of a tertiary amine was ineffective), we found an efficient method to carry out this transformation, which involves the use of iodine and Et_3N (a base to facilitate the deprotonation) and the sulfinates are supplied as the tetrabutyl ammonium salts.[26] This allows the reactions to be performed in nonpolar solvents, such as CH_2Cl_2. In this way, a general procedure (different β-electron-withdrawing and *N*-alkyl groups are tolerated) typically affords the corresponding sulfones **11a–f** in 65–88% yield (Scheme 4, Table 2), thus showing the synthetic usefulness of the protocol. The mechanistic scenario probably involves the

Table 2. Sulfonylation reactions from dihydropyridines **1**.

Entry	Dihydropyridine	Product	Yield [%]
1	**1a**	**11a**	80
2	**1b**	**11b**	77
3	**1c**	**11c**	74
4	**1d**	**11d**	88
5	**1e**	**11e**	65
6	**1f**	**11f**	74
7	**1g**	**11g**	80
8	**1h**	**11h**[a]	40
9	**1c**	**11i**[b]	57

[a] In this experiment pentacycle **12** (20%) was also obtained. [b] Prepared through reaction with preformed $MeSO_2I$.

intermediacy of an iminium ion formed by the interaction of the enamine moiety with the sulfonyl iodide which is generated in situ, although a radical process can not be completely excluded from these experiments (see intramolecular processes below). Preformation of tosyl iodide did not result in higher yields. However, because of the difficulties found in the formation of the tetrabutylammonium methanesulfinate, and the low solubility of the corresponding sodium salt, we prepared methanesulfonyl iodide,[25c] which reacted with dihydropyridine **1c** to produce mesyldihydropyridine **11i** (57%, Table 2, entry 9), to widen the preparative scope of the reaction.

At this point we explored the possibility of trapping the intermediate of these sulfonylation processes with a suitable substituent attached to the dihydropyridine nitrogen, to form a new carbon–carbon bond. For this reason, we prepared dihydropyridines **1g** and **1h**, which bear an *N*-allyl and an *N*-tryptophyl group, respectively. However, under the standard reaction conditions, **1g** afforded the "normal" β-sulfonyldihydropyridine **11g** (80%); no cyclization products were detected.[27] More satisfactorily, *N*-(tryptophyl)dihydropyridine **1h** gave the expected indoloquinolizidine **12**, although in moderate yield (20%); sulfonyldihydropyridine **11h** was the major product (40%). According to the NMR experiments (COSY, HETCOR, NOESY), the stereochemistry of **12** is *trans*, with a major conformation in solution which displays the indole and sulfonyl substituents axially in the flattened tetrahydropyridine ring. In this case, the addition of a sulfonyl moiety to the enamine double bond furnishes an iminium ion, which undergoes either deprotonation to afford **11h** or electrophilic cyclization of the indole ring to stereoselectively give **12**. Interestingly, **11h** does not cyclize to **12** under acidic conditions (MeOH/HCl or trifluoroacetic acid (TFA), 20 °C to 90 °C).

On account of the versatility of vinylsulfones in organic synthesis,[28] we decided to investigate some conjugate additions upon the push–pull olefinic systems present in dihydropyridines **11**. The addition of KCN under vigorous conditions to sulfonyldihydropyridine **11c** afforded the symmetric 3,5-dicyano-1,4-dihydropyridine **13** in 75% yield (Scheme 5). This surprising result may be explained in terms of a conjugate nucleophilic addition followed by in situ elimination of *p*-toluenesulfinate to yield an α,β-unsaturated

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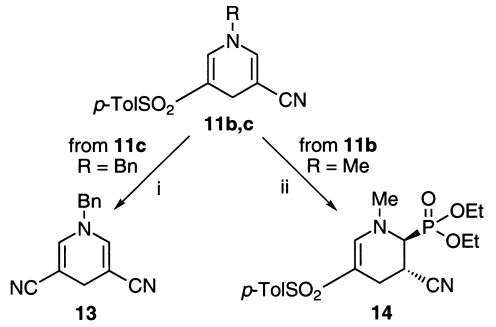
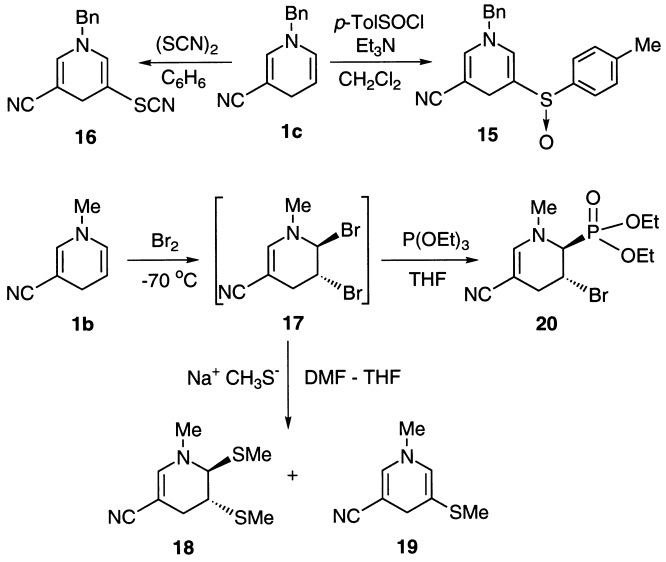


Scheme 5. Conjugate additions to sulfonyldihydropyridines **11**. Reaction conditions: i) KCN, [18]crown-6, *t*BuOH, reflux (75%); ii) $NaPO(OEt)_2$, EtOH, reflux (30%).

nitrile (a 2,5-dicyano-1,4-dihydropyridine),[29] which, in turn, would be the substrate for a new 1,4-addition–elimination process and would ultimately lead to the relatively stable dihydropyridine **13**.[30] On the other hand, treatment of **11b** with sodium diethylphosphite resulted in the formation of *trans*-phosphonate **14** (30%) (Scheme 5), thus indicating a selective conjugate addition to the enaminonitrile moiety. The synthetic potential of this chemistry was not explored further.

β-Sulfinyl-1,4-dihydropyridines have attracted considerable attention recently because of their use as NADH analogues and their efficiency in enantioselective reductions.[31] However, their synthesis involves multistep procedures that start with substituted pyridine derivatives. In connection with our previous experience, a direct sulfinylation of dihydropyridines **1** seemed to be a reasonable way to prepare such compounds. When *p*-toluenesulfinyl chloride[32] was added to a solution of dihydropyridine **1c** in the presence of Et_3N, the expected racemic sulfoxide **15** was obtained in 45% (nonoptimized) yield (Scheme 6). Although enantioselective synthesis was not



Scheme 6. Sulfinylation, thiocyanation, bromination, sulfanylation and bromophosphonylation of dihydropyridines **1**.

possible by the use of chiral *N*-sulfinyloxazolidinones,[33] the separation of the enantiomers was conveniently achieved through chiral HPLC. In an analogous manner, thiocyanation[34] was achieved through interaction with thiocyanogen; this procedure allowed a clean conversion of dihydropyridine **1c** into **16** (91%).[35] The structural assignment was secured with a NOESY experiment, which showed a correlation between the benzylic protons and the olefinic hydrogens of the heterocycle.

On the other hand, bis-sulfanylation of dihydropyridines[36] was planned through the nucleophilic displacement of the bromine atoms present in the unstable intermediate **17**,[37] which could be conveniently prepared by addition of bromine to a solution of dihydropyridine **1b** in THF at $-78\,^{\circ}C$. Unfortunately, compound **17** proved to be very reactive and underwent extensive decomposition at room temperature.[38] However, the ^1H NMR, ^{13}C NMR, and COSY spectra at $-28\,^{\circ}C$ in solutions of $CDCl_3$ gave clean spectroscopic data which supported the above-mentioned structure. Although the reaction proceeds in high yield (<95%), a small amount of a white precipitate is formed, which was identified as 3-cyano-1-methylpyridinium bromide (NMR analysis). This suggests a kinetic competition between the halogenation process and the biomimetic oxidation.[39] Interestingly, when a solution of dibromide **17** in THF was treated with sodium methanethiolate (DMF added as a co-solvent), *trans*-2,3-bis-(methylsulfanyl)tetrahydropyridine **18** was formed in 55% yield, together with minor amounts of 3-methylsulfanyldihydropyridine **19** (11%). In contrast, when the reaction was carried out in CH_2Cl_2, a nearly equimolecular mixture of **18** and the corresponding *cis* isomer was obtained.[40]

Finally, after several unsuccessful attempts to introduce a phosphorus substituent onto the dihydropyridine ring (interaction of 1,4-dihydropyridines **1** with halophosphates, halophosphites, $POCl_3$, PCl_3, phosphites in the presence of oxidants, etc. under various conditions), phosphonate **20** (65%) was prepared by the addition of triethylphosphite to the dibromide **17**.[41] The *trans* stereochemistry observed suggests the departure of the α-bromide in **17** to furnish an iminium ion which would undergo phosphite addition at the less-hindered face (*anti* with respect to the β-bromide) to stereoselectively afford **20**.[42]

Conclusions

A dramatic change in the natural tendency of *N*-alkyl-1,4-dihydropyridines to undergo oxidation to give the corresponding pyridinium salts is the result of the electrophilic interaction of the enamine moiety of these heterocyclic systems with suitable reagents. In this way, convenient procedures for the preparation of highly substituted di- and tetrahydropyridines with good levels of regio- and stereocontrol have been developed, to allow access to iodoazides, diamino derivatives (including primary and secondary cyclic amines, ethylene diamine, and sulfonamides), sulfones, sulfoxides, thiocyanates, thioethers, and halophosphonates in facile synthetic protocols. These protocols may prove useful in the broadening of the molecular diversity of piperidine-based compounds.

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. TLC and column chromatography were carried out on SiO_2. 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 stated, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference at 200, 300, or 500 MHz (^{1}H); 50.3 or 75 MHz (^{13}C); and 121.4 MHz (^{31}P). Only noteworthy IR absorptions are listed. UV spectra were obtained in MeOH or EtOH. The starting *N*-alkyl-1,4-dihydropyridines **1** were prepared by reduction of the corresponding pyridinium salts with sodium dithionite, following published procedures.[43]

Methyl *trans*-2-azido-3-iodo-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (2): To a solution of dihydropyridine **1a** (200 mg, 1.30 mmol) in anhydrous CH_2Cl_2 (10 mL) kept under an inert atmosphere at 0 °C were added trimethylsilyl azide (1.73 mL, 14.5 mmol) and a solution of bis(collidine)iodonium tetrafluoroborate (670 mg, 1.96 mmol) in anhydrous CH_2Cl_2 (10 mL). The resulting solution was stirred for 2 h at 0 °C. Water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were washed with aqueous $Na_2S_2O_3$ solution (50 mL, 0.5 M) and brine (50 mL), dried, filtered, and evaporated. The residue was chromatographed (silica gel, Et_2O/CH_2Cl_2 9:1) to give the somewhat unstable 2-azidotetrahydropyridine **2** as a foam. Yield: 278 mg (66 %); ^{1}H NMR $\delta = 7.31$ (s, 1H), 4.76 (br s, 1H), 4.43 (m, 1H), 3.71 (s, 3H), 3.17 (s, 3H), 2.86 (m, $J = 18.2$, 1.8, 1.7 Hz, 1H), 2.75 (m, $J = 18.2$, 4.4, 1.8 Hz, 1H); ^{13}C NMR $\delta = 167.7$, 141.9, 96.1, 77.8, 51.1, 42.4, 26.3, 19.6; IR (KBr): $\tilde{\nu} = 2102$, 1689, 1630 cm^{-1}; MS (EI): *m*/*z* (relative intensity): 322 (15) $[M]^+$, 280 (45), 152 (97), 138 (100).

General method for oxidative diamination reactions: A solution of I_2 (3.5 mmol) in THF (50 mL) was added dropwise under N_2 atmosphere to a stirred suspension of dihydropyridine **1** (1 mmol), secondary amine (25 mmol), and Na_2CO_3 (95 mmol) in THF (50 mL) kept at 0 °C. The mixture was stirred at room temperature until no dihydropyridine was detected by TLC (usually 1–3 h). Water (150 mL) was added, and the mixture was extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ solution (100 mL, 0.5 M) and brine (100 mL), and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc) to yield the pure 2,3-diaminotetrahydropyridine **3** (Table 1).

Methyl *trans*-1-methyl-2,3-bis(1-pyrrolidinyl)-1,2,3,4-tetrahydropyridine-5-carboxylate (3a): Obtained as an oil (87 %); ^{1}H NMR: $\delta = 7.39$ (s, 1H), 3.66 (s, 3H), 3.57 (br s, 1H), 3.09 (s, 3H), 2.59 (m, 10H), 2.30 (m, $J = 16.8$, 4.4, 1.4 Hz, 1H), 1.75 (m, 8H); ^{13}C NMR: $\delta = 168.4$, 144.9, 93.1, 78.0, 58.4, 51.8, 50.1, 50.0, 43.2, 22.9, 22.8, 20.5; IR (KBr): $\tilde{\nu} = 1681$, 1630 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 288 nm (4.48); MS (EI) *m*/*z* (%): 293 ([M^+], 6), 223 (15), 221 (23), 166 (100), 152 (15); HRMS (EI): mass calcd for $C_{16}H_{27}N_3O_2$ 293.2103, found 293.2093.

Methyl *trans*-1-methyl-2,3-dipiperidino-1,2,3,4-tetrahydropyridine-5-carboxylate (3b): Obtained as a white solid (90 %); m.p. 105.5–106.5 °C (hexanes/Et_2O); ^{1}H NMR: $\delta = 7.35$ (s, 1H), 3.69 (d, $J = 4.8$ Hz, 1H), 3.65 (s, 3H), 2.93 (s, 3H), 2.90 (m, 1H), 2.70 (m, 2H), 2.50 (m, 8H), 1.51 (m, 12H); ^{13}C NMR: $\delta = 168.7$, 147.0, 92.8, 77.3, 57.7, 50.4, 50.2, 48.4, 39.8, 26.6, 26.4, 24.5, 24.6, 20.1; IR (KBr): $\tilde{\nu} = 1684$, 1629 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 291 nm (4.33); MS (CI) *m*/*z* (%): 322 (11) $[M+H]^+$; MS (EI) *m*/*z* (%): 321 (21) $[M]^+$, 237 (21), 235 (100), 221 (56), 194 (98), 152 (10); HRMS (EI): mass calcd for $C_{18}H_{31}N_3O_2$ 321.2416, found 321.2423; anal. calcd for $C_{18}H_{31}N_3O_2$: C 67.25, H 9.72, N 13.07; found: C 66.96, H 9.98, N 13.06.

***trans*-1-Methyl-2,3-bis(1-pyrrolidinyl)-1,2,3,4-tetrahydropyridine-5-carbonitrile (3c)**: Obtained as a white solid (94 %); m.p. 89–92 °C (hexanes/Et_2O); ^{1}H NMR: $\delta = 6.77$ (s, 1H), 3.48 (s, 1H), 3.04 (s, 3H), 2.60–2.35 (m, 10H), 2.18 (m, $J = 16.6$, 1.8, 1.8 Hz, 1H), 1.76 (m, 8H); ^{13}C NMR: $\delta = 146.5$, 123.4, 78.3, 72.3, 57.8, 52.1, 50.5, 43.5, 23.1, 23.0, 22.9; IR (KBr): $\tilde{\nu} = 2182$, 1633 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 270 nm (4.19); MS (EI) *m*/*z* (%): 260 (1) $[M]^+$, 190 (14), 188 (13), 166 (100), 119 (25); HRMS (EI): mass calcd for $C_{15}H_{24}N_4$ 260.2001, found 260.2002.

***trans*-1-Methyl-2,3-dipiperidino-1,2,3,4-tetrahydropyridine-5-carbonitrile (3d)**: Obtained as a white solid (89 %); m.p. 116–117 °C (hexanes/Et_2O); ^{1}H NMR: $\delta = 6.74$ (s, 1H), 3.66 (d, $J = 5.7$ Hz, 1H), 2.89 (m, $J = 5.7$ Hz, 1H), 2.88 (s, 3H), 2.70 (m, 2H), 2.51–2.35 (m, 7H), 2.24 (m, $J = 15.9$, 5.7 Hz, 1H), 1.50 (m, 12H); ^{13}C NMR: $\delta = 148.2$, 123.3, 76.9, 71.5, 57.3, 50.2, 48.4, 39.6, 26.5, 26.3, 24.9, 24.5, 21.8; IR (KBr): $\tilde{\nu} =$ 2174, 1628 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 275 nm (4.20); MS (EI) *m*/*z* (%): 288 (1) $[M]^+$, 204 (23), 202 (53); 194 (100), 119 (25); anal. calcd for $C_{17}H_{28}N_4$: C 70.83, H 9.72, N 19.44; found: C 70.53, H 9.85, N 19.49.

***trans*-1-Methyl-2,3-dimorpholino-1,2,3,4-tetrahydropyridine-5-carbonitrile (3e)**: Obtained as a white solid (84 %); m.p. 133–134 °C (acetone/Et_2O); ^{1}H NMR: $\delta = 6.77$ (s, 1H), 3.68 (m, 9H), 2.96 (s, 3H), 2.89 (m, $J = 11.0$, 5.8 Hz, 1H), 2.76 (m, 2H), 2.55 (m, 6H), 2.41 (m, $J = 16.2$, 5.9 Hz, 1H), 2.33 (m, $J = 16.2$, 5.8 Hz, 1H); ^{13}C NMR: $\delta = 147.8$, 122.5, 76.4, 72.4, 67.3, 67.1, 56.7, 49.7, 48.2, 40.7, 21.4; IR (KBr): $\tilde{\nu} = 2182$, 1631 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 273 nm (4.34); MS (EI) *m*/*z* (%): 292 (4) $[M]^+$, 206(19), 204 (99), 198 (100), 119 (22), 100 (68); anal. calcd for $C_{15}H_{24}N_4O_2$: C 61.64, H 8.21, N 19.17; found: C 61.45, H 8.37, N 19.08.

***trans*-1-Benzyl-2,3-bis(1-pyrrolidinyl)-1,2,3,4-tetrahydropyridine-5-carbonitrile (3f)**: Obtained as an oil (79 %); ^{1}H NMR: $\delta = 7.30$ (m, 5H), 6.85 (d, $J = 1.1$ Hz, 1H), 4.43 (d, $J = 15.9$ Hz, 1H), 4.36 (d, $J = 15.9$ Hz, 1H), 3.64 (s, 1H), 2.66–2.25 (m, 11H), 1.77 (m, 4H), 1.62 (m, 4H); ^{13}C NMR: $\delta =$ 146.2, 137.2, 128.4, 127.9, 127.7, 123.5, 76.0, 72.6, 59.0, 57.9, 51.5, 50.4, 23.4, 23.3, 23.2; IR (KBr) $\tilde{\nu} = 2179$, 1626 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 276 nm (4.43); MS (EI) *m*/*z* (%): 336 (1) $[M]^+$, 266 (16), 265 (20), 195 (17), 174 (75), 166 (72), 91 (100); HRMS (EI): mass calcd for $C_{21}H_{28}N_4$ 336.2314, found 336.2300.

***trans*-1-Benzyl-2,3-bis(4-methyl-1-piperazinyl)-1,2,3,4-tetrahydropyridine-5-carbonitrile (3g)**: Obtained as a white solid (86 %); m.p. 154–156 °C (acetone/Et_2O); ^{1}H NMR: $\delta = 7.38–7.22$ (m, 5H), 6.95 (s, 1H), 4.54 (d, $J =$ 14.8 Hz, 1H), 4.16 (d, $J = 14.8$ Hz, 1H), 3.68 (d, $J = 6.5$ Hz, 1H), 2.82 (m, 2H), 2.51–2.34 (m, 17H), 2.30 (s, 3H), 2.24 (s, 3H); ^{13}C NMR: $\delta = 147.6$, 136.7, 128.5, 127.8, 127.6, 122.6, 73.6, 72.5, 57.2, 55.5, 55.2, 55.0, 48.7, 47.1, 46.2, 45.8, 21.1; IR (KBr): $\tilde{\nu} = 2185$, 1619 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 278 nm (4.34); MS (EI) *m*/*z* (%): 394 (1) $[M]^+$, 295 (18), 294 (18), 224 (44), 203 (58), 195 (12), 91 (80), 58 (100); anal. calcd for $C_{23}H_{34}N_6$: C 70.05, H 8.62, N 21.31; found: C 69.97, H 8.80, N 21.23. Single crystals of **3g** suitable for X-ray crystallography were grown by slow evaporation in a saturated acetone/Et_2O solution.

Methyl *trans*-1-methyl-2,3-bis(butylamino)-1,2,3,4-tetrahydropyridine-5-carboxylate (3h): Following the general procedure given above, the reaction of dihydropyridine **1a** and butylamine gave diamine **3h** as a white solid (33 %) after chromatography (silica gel, 98:2 EtOAc/NEt_3). Further purification may be achieved by recrystallization from acetone/Et_2O. White crystals, m.p. 121–123 °C; ^{1}H NMR: $\delta = 7.32$ (s, 1H), 3.75 (d, $J = 2.8$ Hz, 1H), 3.67 (s, 3H), 3.12 (s, 3H), 2.92 (m, 1H), 2.75–2.49 (m, 5H), 2.18 (m, $J = 16.9$, 4.7, and 1.2 Hz, 1H), 1.40 (m, 10H), 0.91 (t, $J = 7.1$ Hz, 3H), 0.89 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 169.1$, 144.3, 91.3, 74.5, 51.8, 50.6, 46.7, 46.0, 42.5, 32.7, 32.6, 32.4, 20.7, 20.3, 13.9; IR (KBr): $\tilde{\nu} = 3300$, 1682, 1620 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 280 nm (3.85); MS (EI) *m*/*z* (%): 297(1) $[M]^+$, 225 (8), 224 (8), 170 (100), 152 (15); anal. calcd for $C_{16}H_{31}N_3O_2$: C 64.65, H 10.43, N 14.13; found: C 64.43, H 10.09, N 14.06.

Methyl 1,4,5-trimethyl-1,2,3,4,4*a*,5,8,8*a*-octahydropyrido[2,3-*b*]pyrazine-7-carboxylate (4): Following the general procedure for the oxidative diamination of dihydropyridines, the reaction of dihydropyridine **1a** and *N*,*N*′-dimethylethylenediamine gave tetrahydropyridine **4** after column chromatography (silica gel, CH_2Cl_2/EtOAc) as a slightly unstable oil (80 %, contaminated by a minor impurity). ^{1}H NMR: $\delta = 7.23$ (s, 1H), 3.61 (s, 3H), 3.13 (br s, 1H), 2.99 (s, 3H), 2.86 (m, 1H), 2.76 (m, 2H), 2.43–2.19 (m, 4H), 2.38 (s, 3H), 2.22 (s, 3H); ^{13}C NMR: $\delta = 168.0$, 144.3, 94.4, 78.6, 56.1, 50.6, 47.3, 42.2, 42.0, 41.9, 24.7; IR (KBr): $\tilde{\nu} = 1686$, 1634 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 287 nm (4.29); MS (CI) *m*/*z* (%): 240 (80) $[M+H]^+$; MS (EI) *m*/*z* (%): 239 (10) $[M^+]$, 208 (12), 152 (39), 112 (100); HRMS (EI): mass calcd for $C_{12}H_{21}N_3O_2$ 239.1634, found 239.1631.

3-(1-Pyrrolidinyl)tetrahydro-2*H*-pyran-2-ol (5): Following the general procedure for the oxidative diamination of dihydropyridines, the reaction of 3,4-dihydro-2*H*-pyran (0.5 mL, 5.46 mmol), pyrrolidine (5 mL, 60.5 mmol), I_2 (4.16 g, 16.4 mmol), and Na_2CO_3 (10 g) afforded an oily residue (605 mg, presumably the diaminopyran). Column chromatography (silica gel, CH_2Cl_2/EtOAc) gave hemiacetal **5** as a white solid (255 mg,

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27%, anomeric mixture). Further purification may be achieved by recrystallization from acetone/Et_2O. White crystals; m.p. 129–131 °C; ^{1}H NMR: δ (data for the major anomer) = 5.16 (d, J = 3.3 Hz, 1H), 3.91 (m, 1H), 3.53 (m, 1H), 2.57 (m, 4H), 2.26 (m, 1H), 1.80–1.60 (m, 9H); ^{13}C NMR: δ (data for the major anomer) = 91.4, 62.9, 58.9, 50.9, 24.1, 23.6, 23.0; IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1}; MS (EI) m/z (%): 171 (5) [M^+], 142 (28); 97 (100); anal. calcd for $C_9H_{17}NO_2$: C 63.16, H 9.94, N 8.18; found: C 63.18, H 10.06, N 8.24.

General procedure for the exchange of the 2-amino group in compounds 3c and 3d: To a solution of homodiamine **3** (1 mmol) in MeOH (20 mL) were added SiO_2 (200 mg) and excess of the secondary amine (piperidine for **3c**, and pyrrolidine for **3d**, 2 mL). The mixture was refluxed under an inert atmosphere (6 d for **3c**, 3 weeks for **3d**). The volatiles were removed under reduced pressure and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc increasing polarity) to yield the pure heterodiamine.

***trans*-1-Methyl-2-piperidino-3-pyrrolidinyl-1,2,3,4-tetrahydropyridine-5-carbonitrile (8)**: Obtained as a white solid (41%); m.p. 105–106 °C (Et_2O/hexanes); ^{1}H NMR: δ = 6.82 (s, 1H), 3.66 (m, 1H), 2.98 (s, 3H), 2.77 (m, 1H), 2.52 (m, 8H), 2.34 (m, 2H), 1.75 (m, 4H), 1.50 (m, 6H); ^{13}C NMR: δ = 147.4, 123.4, 77.9, 70.9, 56.2, 51.0, 49.5, 42.1, 26.6, 24.8, 23.2; IR (KBr): $\tilde{\nu}$ = 2190, 1631 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 272 nm (4.34); MS (EI) m/z (%): 274 (1) [M]$^+$, 190 (8), 188 (10), 180 (100), 119 (20); anal. calcd for $C_{16}H_{26}N_4$: C 70.03, H 9.55, N 20.42; found: C 69.94, H 9.68, N 20.37.

***trans*-1-Methyl-3-piperidino-2-pyrrolidinyl-1,2,3,4-tetrahydropyridine-5-carbonitrile (9)**: Obtained as a white solid (22%); ^{1}H NMR: δ = 6.73 (s, 1H), 3.67 (d, J = 3.5 Hz, 1H), 2.95 (s, 3H), 2.78 (m, 1H), 2.64 (m, 4H), 2.51–2.32 (m, 6H), 1.75 (m, 4H), 1.48 (m, 6H); ^{13}C NMR: δ = 147.3, 123.4, 75.7, 72.6, 57.3, 51.1, 49.1, 42.1, 26.5, 24.6, 23.6, 21.3; IR (KBr): $\tilde{\nu}$ = 2184, 1633 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 273 nm (4.12); MS (EI) m/z (%): 274 (1) [M]$^+$, 204 (21), 202 (80); 180 (100), 119 (51). HRMS (EI): mass calcd for $C_{16}H_{26}N_4$ 274.2157, found 274.2152.

Methyl *trans*-1-methyl-2,3-bis(*p*-tolylsulfonamido)-1,2,3,4-tetrahydropyridine-5-carboxylate (10): To a solution of dihydropyridine **1a** (100 mg, 0.65 mmol) and $Bu_4N^+I^-$ (60 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added an aqueous (5 mL) solution of chloramine T trihydrate (184 mg, 0.65 mmol) and potassium *p*-toluenesulfonamide (547 mg, 2.61 mmol). I_2 (17 mg, 67 μmol) was immediately added, and the resulting mixture was stirred under N_2 atmosphere for 1 h at room temperature. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ (20 mL, 0.5 M) and Na_2CO_3 (100 mL) solutions, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc 6:4) to yield the *cis* isomer of disulfonamide **10** (7 mg, 2%). ^{1}H NMR: δ = 7.82 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.10 (s, 1H), 5.40 (br s, 1H), 4.66 (d, J = 8.9 Hz, 1H), 4.50 (m, 1H), 3.61 (s, 3H), 3.30 (m, 1H), 2.83 (s, 3H), 2.47 (s, 3H), 2.44 (s, 3H), 2.35 (dd, J = 16.5 and 4.4 Hz, 1H), 1.90 (dd, J = 16.5 and 8.9 Hz, 1H); IR (KBr): $\tilde{\nu}$ = 3247, 1676, 1626 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 280 (4.40), 226 nm (4.42); MS (EI) m/z (%): 493 (1) [M]$^+$, 322 (5), 167 (100). Elution with hexanes/EtOAc (1:1) yielded the *trans* bis-sulfonamide **10** (128 mg, 40%). Further purification may be achieved by recrystallization from acetone/Et_2O; white crystals; m.p. 109–111 °C; ^{1}H NMR: δ = 7.75 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.12 (s, 1H), 5.62 (d, J = 8.3 Hz, 1H), 5.00 (d, J = 7.3 Hz, 1H), 4.48 (d, J = 8.3 Hz, 1H), 3.56 (s, 3H), 3.32 (m, 1H), 2.70 (s, 3H), 2.46 (s, 3H), 2.44 (s, 3H), 2.23 (dd, J = 17.1 and 4.4 Hz, 1H), 2.09 (br d, J = 17.1, 1H); ^{13}C NMR: δ = 168.1, 144.6, 143.8, 143.6, 137.6, 136.9, 129.8, 129.7, 127.0, 126.9, 91.5, 67.6, 51.0, 48.5, 40.7, 21.6, 21.1; IR (KBr): $\tilde{\nu}$ = 3258, 1670, 1626 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 283 (4.23), 228 nm (4.27); MS (EI) m/z (%): 493 (1) [M]$^+$, 462 (1), 322 (5), 167 (72), 128 (100); anal. calcd for $C_{16}H_{31}N_3O_2 \cdot \frac{1}{3}H_2O$: C 52.89, H 5.58, N 8.41; found: C 53.00, H 5.93, N 8.08.

General procedure for the sulfonylation reactions: To a solution of dihydropyridine **1** (1 mmol), tetrabutylammonium *p*-toluenesulfinate (1.5 mmol), and Et_3N (2 mmol) in anhydrous CH_2Cl_2 (40 mL) was added a CH_2Cl_2 (5 mL) solution of I_2 (1.3 mmol), and the resulting mixture was stirred under N_2 atmosphere for 1 h at room temperature. An aqueous $Na_2S_2O_3$ solution (20 mL, 0.5 M) was added, and the organic phase was separated and evaporated. The residue was dissolved in EtOAc (30 mL), washed with brine (6 × 100 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2). Elution with hexanes/EtOAc yielded sulfone **11** (Table 2).

Methyl 1-methyl-5-tosyl-1,4-dihydropyridine-3-carboxylate (11a): Obtained from dihydropyridine **1a** as a yellow solid (80%); m.p. 175–177 °C (acetone/Et_2O); ^{1}H NMR: δ = 7.71 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 6.97 (s, 1H), 6.87 (s, 1H), 3.67 (s, 3H), 3.10 (s, 3H), 3. 09 (s, 2H), 2.42 (s, 3H); ^{13}C NMR: δ = 166.9, 143.9, 139.3, 137.6, 135.8, 129.6, 127.7, 113.0, 103.2, 51.4, 41.0, 21.5, 20.7; IR (KBr): $\tilde{\nu}$ = 1694, 1590 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 363 (3.67), 262 (3.89), 228 nm (4.14); MS (EI) m/z (%): 307 (11) [M]$^+$, 292 (20), 151 (100); anal. calcd for $C_{15}H_{17}NO_4S$: C 58.62, H 5.57, N 4.56; found: C 58.37, H 5.82, N 4.38.

1-Methyl-5-tosyl-1,4-dihydropyridine-3-carbonitrile (11b): Obtained from dihydropyridine **1b** as a yellow oil (77%); ^{1}H NMR: δ = 7.69 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 6.94 (s, 1H), 6.41 (s, 1H), 3.09 (s, 5H), 2.49 (s, 3H); ^{13}C NMR: δ = 144.4, 141.8, 137.1, 135.3, 129.8, 127.7, 118.8, 111.1, 83.8, 41.2, 22.0, 21.5; IR (KBr): $\tilde{\nu}$ = 2205, 1591 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 363 (3.76), 261 (3.88), 228 nm (4.18); MS (EI) m/z (%) 274 (12) [M]$^+$, 209 (13), 118 (100); HRMS (EI): mass calcd for $C_{14}H_{14}N_2O_2S$ 274.0776, found 274.0768.

1-Benzyl-5-tosyl-1,4-dihydropyridine-3-carbonitrile (11c): Obtained from dihydropyridine **1c** as a yellow solid (74%); m.p. 131–134 °C (CH_2Cl_2); ^{1}H NMR: δ = 7.71 (d, J = 8.3 Hz, 2H), 7.31–7.26 (m, 7H), 7.06 (s, 1H), 6.44 (s, 1H), 4.41 (s, 3H), 3.13 (s, 2H), 2.46 (s, 3H); ^{13}C NMR: δ = 144.5, 140.9, 136.5, 135.2, 134.6, 129.9, 129.3, 128.8, 127.8, 127.3, 118.8, 111.8, 84.8, 58.0, 22.5, 21.7; IR (KBr): $\tilde{\nu}$ = 2206, 1674, 1592 cm^{-1}; UV (EtOH): λ_{max} (log ε) = 363 (3.78), 229 nm (4.16); MS (EI) m/z (%): 350 (3) [M]$^+$, 194 (12), 91 (100).

Methyl 1-benzyl-5-tosyl-1,4-dihydropyridine-3-carboxylate (11d): Obtained from dihydropyridine **1d** as a yellow solid (88%); m.p. 138–140 °C (CH_2Cl_2/Et_2O); ^{1}H NMR: δ = 7.72 (d, J = 8.4 Hz, 2H), 7.38–7.15 (m, 7H), 7.05 (s, 1H), 6.94 (s, 1H), 4.41 (s, 2H), 3.63 (s, 3H), 3.12 (s, 2H), 2.42 (s, 3H); ^{13}C NMR: δ = 166.8, 143.9, 138.6, 137.1, 135.7, 135.6, 129.7, 129.1, 128.4, 127.8, 127.1, 113.6, 103.9, 57.8, 51.5, 21.6, 21.2; IR (KBr): $\tilde{\nu}$ = 1693, 1593 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 368 (3.65), 230 nm (4.09); MS (EI) m/z (%): 383 (3) [M]$^+$, 368 (2), 227 (19), 91 (100); anal. calcd for $C_{21}H_{21}NO_4S$: C 65.78, H 5.52, N 3.65; found: C 65.43, H 5.61, N 3.59.

1-Methyl-5-tosyl-1,4-dihydropyridine-3-carbaldehyde (11e): Obtained from dihydropyridine **1e** as an oil (65%). ^{1}H NMR: δ = 9.18 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 6.60 (s, 1H), 3.22 (s, 3H), 3.05 (s, 2H), 2.43 (s, 3H); ^{13}C NMR: δ = 188.3, 147.9, 144.3, 136.9, 135.2, 129.8, 127.9, 116.2, 115.8, 41.5, 21.7, 19.0; IR (KBr): $\tilde{\nu}$ = 1676, 1652, 1583 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 378 nm (4.06); MS (EI) m/z (%): 277 (18) [M]$^+$, 212 (4), 121 (100); anal. calcd for $C_{14}H_{15}NO_3S \cdot \frac{1}{2}H_2O$: C 58.72, H 5.63, N 4.89; found: C 58.80, H 5.95, N 4.84.

Methyl 1-methyl-5-tosyl-1,4-dihydro-3-pyridyl ketone (11f): Obtained from dihydropyridine **1f** as a yellow solid (74%); m.p. 157–160 °C (acetone/Et_2O); ^{1}H NMR: δ = 7.73 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.00 (s, 1H), 6.80 (s, 1H), 3.18 (s, 3H), 3.05 (s, 2H), 2.43 (s, 3H), 2.18 (s, 3H); ^{13}C NMR: δ = 194.5, 144.0, 140.6, 136.8, 135.6, 129.7, 127.9, 114.9, 113.9, 41.5, 24.6, 21.6, 20.3; IR (KBr): $\tilde{\nu}$ = 1678, 1626, 1583 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 382 (4.03), 265 (3.97), 230 nm (4.34); MS (EI) m/z (%): 291 (41) [M]$^+$, 290 (30), 135 (100); anal. calcd for $C_{15}H_{17}NO_3S \cdot \frac{1}{3}H_2O$: C 60.59, H 5.99, N 4.71; found: C 60.39, H 5.79, N 4.50.

Methyl 1-allyl-5-tosyl-1,4-dihydropyridine-3-carboxylate (11g): Obtained from dihydropyridine **1g** as a yellow solid (80%); m.p. 93–95 °C (acetone/Et_2O); ^{1}H NMR: δ = 7.72 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.00 (s, 1H), 6.89 (s, 1H), 5.80 (m, 1H), 5.30 (m, 2H), 3.85 (d, J = 4.8 Hz, 2H), 3.67 (s, 3H), 3.12 (s, 2H), 2.43 (s, 3H); ^{13}C NMR: δ = 166.9, 143.9, 138.4, 136.8, 135.7, 132.1, 129.6, 127.8, 119.2, 113.3, 103.5, 56.5, 51.5, 21.6, 21.2; IR (KBr): $\tilde{\nu}$ = 1698, 1590 cm^{-1}; UV (MeOH): λ_{max} (log ε) = 365 (3.64), 231 nm (4.02); MS (EI) m/z (%): 333 (10) [M]$^+$, 318 (13), 177 (100), 91 (100); anal. calcd for $C_{17}H_{19}NO_4S \cdot \frac{1}{3}H_2O$: C 60.16, H 5.84, N 4.13; found: C 60.18, H 6.08, N 3.98.

Sulfonylation of tryptophyl dihydropyridine (1h):[43b] Following the above general reaction procedure (THF as the solvent instead of CH_2Cl_2), column chromatography (elution with hexanes/EtOAc, 1:1) gave methyl 5-tosyl-1-tryptophyl-1,4-dihydropyridine-3-carboxylate (**11h**) as an oil. Yield: 40%; ^{1}H NMR: δ = 9.20 (br s, 1H), 7.57 (m, 3H), 7.41 (d, J = 7.3 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.20 (m, 1H), 7.09 (m, 2H), 6.88 (s, 2H), 3.63 (s, 3H), 3.61

(t, $J = 7.0$ Hz, 2H), 3.07 (t, $J = 7.0$ Hz, 2H), 3.04 (s, 2H), 2.44 (s, 3H); ^{13}C NMR: d = 166.5, 144.0, 138.6, 137.0, 136.2, 135.4, 129.6, 127.8, 126.1, 122.6, 122.3, 119.7, 118.2, 112.5, 111.4, 111.0, 103.2, 55.1, 51.5, 26.3, 21.7, 21.0; IR (KBr): $\tilde{\nu} = 3200$, 1678, 1591 cm^{-1}; UV (EtOH): λ_{max} ($\log\varepsilon$) = 370 (3.70), 273 (3.98), 222 nm (4.49); MS (EI) *m*/*z* (%): 436 (5) $[M]^+$, 280 (19), 144 (99), 130 (100); HRMS (EI): mass calcd for $C_{24}H_{24}N_2O_4S$ 436.1457, found 436.1457. Elution with hexanes/EtOAc (3:7) afforded methyl *trans*-1-tosyl-3,4-dehydroindolo[2,3-*a*]quinolizidine-3-carboxylate (**12**). Yield: 20%; m.p. 119–120 °C; ^{1}H NMR: $\delta = 9.54$ (br s, 1H), 7.80 (d, $J = 8.5$ Hz, 2H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 8.5$ Hz, 1H), 7.31 (d, $J = 8.5$ Hz, 2H), 7.22 (s, 1H), 7.16 (m, $J = 8.5$ Hz, 1H), 7.09 (m, $J = 8.0$ Hz, 1H), 5.27 (m, 1H), 3.85 (dd, $J = 12.5$ and 5.5 Hz, 1H), 3.67 (dd, $J = 14.0$ and 5.0 Hz, 1H), 3.57 (s, 3H), 3.51 (m, 1H), 2.90 (m, 1H), 2.76 (m, 1H), 2.60 (dd, $J = 16.5$ and 7.5 Hz, 1H), 2.45 (dd, $J = 16.5$ and 6.0 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR: δ = 167.8, 146.0, 145.9, 136.0, 133.9, 130.0, 129.7, 129.2, 126.1, 122.4, 119.6, 118.1, 111.5, 109.7, 94.6, 62.5, 52.4, 51.0, 50.8, 22.0, 21.6, 19.9; IR (KBr): $\tilde{\nu} = 3200$, 1668, 1627 cm^{-1}; UV (MeOH): λ_{max} ($\log\varepsilon$) = 283 (4.52), 224 nm (4.72); MS (EI) *m*/*z* (%): 436 (3) $[M]^+$, 279 (100), 265 (58); anal. calcd for $C_{24}H_{24}N_2O_4S$: C 66.04, H 5.54, N 6.42; found: C 65.87, H 5.24, N 6.28.

1-Benzyl-5-mesyl-1,4-dihydropyridine-3-carbonitrile (11i): To a solution of dihydropyridine **1c** (100 mg, 0.51 mmol) and Et_3N (0.15 mL, 1.1 mmol) in anhydrous CH_2Cl_2 (20 mL) was added a solution of methanesulfonyl iodide[25c] (143 mg, 0.70 mmol) in CH_2Cl_2 (5 mL), and the resulting mixture was stirred under N_2 atmosphere for 2 h at room temperature. An aqueous $Na_2S_2O_3$ solution (20 mL, 0.5 M) was added, and the organic phase was separated and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (SiO_2, Et_2O/acetone/DEA 90:8:2) to yield sulfone **11i** (oil, 80 mg, 57%). ^{1}H NMR: δ = 7.40–7.27 (m, 5H), 6.92 (s, 1H), 6.53 (s, 1H), 4.40 (s, 2H), 3.40 (s, 2H), 2.89 (s, 3H); ^{13}C NMR: δ = 141.2, 137.8, 130.2, 129.4, 128.9, 127.4, 118.1, 111.2, 86.0, 58.0, 40.2, 22.9; IR (KBr): $\tilde{\nu} = 2205$, 1676, 1595 cm^{-1}; UV (EtOH): λ_{max} ($\log\varepsilon$) = 336 (3.40), 248 nm (3.63); MS (EI) *m*/*z* (%): 274 (1) $[M]^+$, 194 (8), 91(100); HRMS (EI): mass calcd for $C_{14}H_{14}N_2O_2S$ 274.0776, found 274.0776.

1-Benzyl-1,4-dihydropyridine-3,5-dicarbonitrile (13): A mixture of dihydropyridine **11c** (170 mg, 0.48 mmol), KCN (312 mg, 4.8 mmol), and [18]crown-6 (12.7 mg, 4.8 μmol) in *tert*-butyl alcohol (2 mL) was refluxed under an inert atmosphere for 48 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (50 mL.). The organic solution was washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, hexanes/EtOAc 8:2) to give dihydropyridine **13** (solid, 80 mg, 75%). M.p. 185–186 °C (decomp); ^{1}H NMR: δ = 7.40 (m, 3H), 7.19 (m, 2H), 6.50 (s, 2H), 4.35 (s, 2H), 3.24 (s, 2H); ^{13}C NMR: δ = 141.1, 134.3, 129.4, 128.9, 127.4, 118.6, 83.7, 58.0, 24.1; IR (KBr): $\tilde{\nu}$ = 2199, 1589 cm^{-1}; UV (EtOH): λ_{max} ($\log\varepsilon$) = 354 (3.65), 212 nm (4.30); MS (EI) *m*/*z* (%): 221(6) $[M]^+$, 91 (100); anal. calcd for $C_{14}H_{11}N_3 \cdot 1/2\,H_2O$: C 73.02, H 5.25, N 18.25; found: C 73.19, H 5.13, N 18.02.

Diethyl *trans*-3-cyano-1-methyl-5-tosyl-1,2,3,4-tetrahydropyridine-2-phosphonate (14): NaH (112 mg, 60% w/w, 2.82 mmol) was added to a solution of diethyl phosphite (394 mg, 2.82 mmol) in absolute EtOH (5 mL). After the mixture had been stirred for 15 min at room temperature, sulfonyldihydropyridine **11b** (130 mg, 0.37 mmol) was added, and the resulting solution was stirred at reflux temperature for 24 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (50 mL). The organic solution was washed with water (3 × 20 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, hexanes/EtOAc 8:2) to give tetrahydropyridine **14** (oil, 46 mg, 30%). ^{1}H NMR: $\delta = 7.70$ (d, J = 8.0 Hz, 2H), 7.40 (s, 1H), 7.27 (d, $J = 8.0$ Hz, 2H), 4.06 (m, 4H), 3.67 (m, J = 14.4, 1.8, and 1.8 Hz, 1H), 3.49 (m, $J = 5.5$, 5.5, 1.8, and1.8 Hz, 1H), 3.24 (s, 3H), 2.63 (m, $J = 17.0$ and 5.5 Hz, 1H), 2.41 (br d, $J = 17.0$ Hz, 1H), 2.39 (s, 3H), 1.26 (t, $J = 6.9$ Hz, 6H); ^{13}C NMR: δ = 143.1, 142.4, 138.1, 129.6, 127.0, 118.3 (d, ^3J(C,P) = 23.4 Hz), 100.4, 63.9 (d, ^2J(C,P) = 7.1 Hz), 63.2 (d, ^2J(C,P) = 7.6 Hz), 56.3 (d, ^1J(C,P) = 162.6 Hz), 44.0, 23.3 (d, ^2J(C,P) = 4.6 Hz), 21.5, 21.4, 16.5 (d, ^3J(C,P) = 8.6 Hz); ^{31}P NMR: $\delta = 16.9$; IR (KBr): $\tilde{\nu} = 2190$, 1625 cm^{-1}; UV (MeOH): λ_{max} ($\log\varepsilon$) = 281 (4.24), 223 nm (4.15); MS (EI) *m*/*z* (%): 412 (15) $[M]^+$, 275 (33), 248 (25), 119(100); HRMS (EI): mass calcd for $C_{18}H_{25}N_2O_5PS$ 412.1221, found 412.1204.

1-Benzyl-5-(*p*-tolyl)sulfinyl-1,4-dihydropyridine-3-carbonitrile (15): A solution of *p*-toluenesulfinyl chloride[32] (174 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of dihydropyridine **1c** (200 mg, 1.02 mmol) and Et_3N (0.30 mL, 2.2 mmol) in anhydrous CH_2Cl_2 (20 mL) kept at 0 °C under an inert atmosphere, and the resulting mixture stirred for 1 h at 0 °C. A saturated aqueous Na_2CO_3 solution (60 mL) was added, and the organic phase was separated and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica, hexanes/EtOAc 8:2) to yield sulfoxide **15** (oil, 153 mg, 45%). ^{1}H NMR: δ = 7.50–7.18 (m, 9H), 6.69 (s, 1H), 6.48 (s, 1H), 4.40 (s, 2H), 3.17 (d, $J = 17.0$ Hz, 1H), 2.61 (d, $J = 17.0$ Hz, 1H), 2.43 (s, 3H); ^{13}C NMR: δ = 141.6, 137.0, 135.0, 133.7, 129.9, 129.2, 128.7, 127.3, 124.8, 119.4, 116.4, 83.0, 57.7, 21.4, 19.2 (one quaternary carbon not seen); IR (KBr): $\tilde{\nu} = 2203$, 1672, 1593 cm^{-1}; UV (MeOH): λ_{max} ($\log\varepsilon$) = 352 (3.23), 225 nm (3.88); MS (EI) *m*/*z* (%): 334 (16) $[M]^+$, 319 (19), 227 (35), 55 (100); HRMS (EI): mass calcd for $C_{20}H_{18}N_2OS$ 334.1140, found 334.1140. Chiral HPLC data for (±)-**15**: Daicel Chiralcell OD, hexane/2-propanol 9:1 (0.2% Et_2NH), flow rate 1.3 mL min^{-1}; first eluting enantiomer: retention time 54.4 min; second eluting enantiomer: retention time 60.7 min.

1-Benzyl-5-thiocyanato-1,4-dihydropyridine-3-carbonitrile (16): A solution of thiocyanogen[34a] (0.2 M, 5 mL) in benzene was added to a solution of dihydropyridine **1c** (151 mg, 0.77 mmol) in anhydrous benzene (20 mL) under an inert atmosphere, and the resulting mixture stirred for 1 h at room temperature. An aqueous $Na_2S_2O_3$ solution (0.5 M, 30 mL) was added, and the organic phase was separated, washed with brine (30 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield essentially pure thiocyanate **16** as a yellow solid (177 mg, 91%). M.p. 102–104 °C; ^{1}H NMR: δ = 7.40–7.15 (m, 5H), 6.55 (s, 1H), 6.32 (s, 1H), 4.34 (s, 2H), 3.38 (s, 2H), 2.43 (s, 3H); ^{13}C NMR: δ = 141.2, 136.2, 134.8, 129.3, 128.7, 127.3, 119.0, 108.9, 94.8, 81.6, 57.6, 28.7; IR (KBr): $\tilde{\nu}$ = 2203, 2154, 1667 cm^{-1}, 1589; UV (EtOH): λ_{max} ($\log\varepsilon$) = 353 nm (3.73); MS (EI) *m*/*z* (%): 253 (6) $[M]^+$, 226 (1), 91 (100); HRMS (EI): mass calcd for $C_{14}H_{11}N_3S$ 253.0674, found 253.0681.

Bromination of dihydropyridine 1b: Bromine (454 mg, 145 μL, 2.84 mmol) was added to a solution of dihydropyridine **1b** (359 mg, 2.99 mmol) in anhydrous THF (25 mL) kept under inert atmosphere at −78 °C. The resulting precipitate was removed by decantation of the solution, which was used immediately in subsequent reactions. In an experiment carried out in an NMR tube with $CDCl_3$ as the solvent, the dibromoderivative **17** (95%, determined by evaporation of the solvent) was generated as above, and the low-temperature NMR experiments (−28 °C) were performed after filtration of the precipitate. ^{1}H NMR: $\delta = 6.50$ (m, $J = 1.9$ and 0.9 Hz, 1H), 5.86 (m, 1H), 4.73 (m, 1H), 3.58 (m, $J = 17.5$, 4.5, and 1.9 Hz, 1H), 3.01 (s, 3H), 2.70 (m, $J = 17.5$, 2.1, and 2.1 Hz, 1H); ^{13}C NMR: $\delta = 142.4$, 119.9, 80.2, 73.4, 42.8, 41.8, 28.3; MS (EI) *m*/*z* (%, taken from a frozen sample): 282, 280, and 278 (1, 2, 1) $[M]^+$, 200 and 198 (40, 41), 199 and 197 (100, 94). The precipitate (5%, consisting of impure 3-cyano-1-methylpyridinium bromide) was dissolved in [D_6]DMSO and positively identified by comparison with an authentic sample.

Sulfanylation of dihydropyridine 1b: A solution of sodium thiomethoxide (194 mg, 2.77 mmol) in anhydrous DMF (2 mL) was added to a solution of dibromide **17** (prepared as above from dihydropyridine **1b** (222 mg, 1.85 mmol)) in THF kept at −78 °C. The resulting mixture was stirred for 30 min at this temperature, and the cooling bath was removed. Stirring was continued for 12 h. Water (25 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The organic extracts were washed with an aqueous $Na_2S_2O_3$ solution (0.5 M, 30 mL) and brine (30 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield an oil which was purified by column chromatography over silica gel. Elution with hexanes/EtOAc (9:1) afforded *trans*-2,3-bis(methylthio)-1,2,3,4-tetrahydropyridine-5-carbonitrile (**18**) as an oil (163 mg, 55%). ^{1}H NMR: δ = 6.60 (d, $J = 2.1$ Hz, 1H), 4.14 (m, $J = 1.8$ Hz, 1H), 3.16 (m, 1H), 3.08 (s, 3H), 2.96 (m, $J = 16.6$, 5.1, and 2.1 Hz, 1H), 2.30 (m, $J = 16.6$, 1.8, and 1.8 Hz, 1H), 2.20 (s, 3H), 2.19 (s, 3H); ^{13}C NMR: δ = 144.9, 122.0, 73.1, 67.2, 43.4, 42.1, 24.0, 14.9, 14.7; IR (KBr): $\tilde{\nu} = 2186$, 1626 cm^{-1}; UV (EtOH): λ_{max} ($\log\varepsilon$) = 278 nm (3.91); MS (EI) *m*/*z* (%): 214 (11) $[M]^+$, 167 (80), 119 (100); HRMS (EI): mass calcd for $C_9H_{14}N_2S_2$ 214.0598, found 214.0592. Further elution with hexanes/EtOAc (8:2) afforded 5-methylthio-1,4-dihydropyridine-3-carbonitrile (**19**): Foam; yield: 24 mg (11%); ^{1}H NMR: $\delta = 6.45$ (m, 1H), 5.83 (m, 1H), 3.21 (br s, 2H), 2.98 (s, 3H), 2.17 (s, 3H); ^{13}C NMR: δ = 142.2, 127.2, 121.0, 108.9, 76.3, 40.8, 27.6, 14.3; IR (KBr): $\tilde{\nu}$ = 2190, 1624, 1589 cm^{-1}; UV (EtOH): λ_{max} ($\log\varepsilon$) = 348 (3.56), 236 nm (3.83); MS (EI) *m*/*z* (%): 166 (30) $[M]^+$, 165 (60), 103 (100); MS (CI, CH_4) *m*/*z*

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(%): 167 (100) $[M+H]^+$, 195 (30). When the reaction was carried out with a solution of dibromide **17** in CH_2Cl_2, a nearly equimolecular mixture of **18** and the corresponding *cis* isomer was obtained (49%), together with some dihydropyridine **19** (9%). *cis* Isomer (data taken from a mixture with **18**): ^{1}H NMR: $\delta = 6.61$ (m, 1H), 4.22 (br m, 1H), 3.02 (s, 3H), 2.55 (m, 1H), 2.18 (s, 3H), 2.16 (s, 3H), 2.02 (m, 2H); ^{13}C NMR: $\delta = 145.9$, 122.8, 75.3, 64.0, 42.2, 41.5, 26.5, 18.2, 15.0.

Diethyl *trans*-3-bromo-5-cyano-1-methyl-1,2,3,4-tetrahydropyridine-2-phosphonate (20): Triethylphosphite (344 mg, 2.07 mmol) was added to a solution of dibromide **17** in THF [prepared as above from dihydropyridine **1b** (100 mg, 0.83 mmol)] kept at $-78\,^\circ$C. The resulting mixture was stirred for 30 min at this temperature and the cooling bath was removed. Stirring was continued for 12 h. Water (25 mL) was added and the mixture was extracted with EtOAc (3×30 mL). The organic extracts were washed with an aqueous $Na_2S_2O_3$ solution (0.5 M, 30 mL) and brine (30 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield an oil, which was purified by column chromatography (silica gel, hexanes/EtOAc 7:3) to afford phosphonate **20** (oil, 182 mg, 65%). ^{1}H NMR: $\delta = 6.84$ (d, $J =$ 1.5 Hz, 1H), 4.73 (m, 1H), 4.18 (m, 4H), 3.68 (m, $J = 16.5$, 2.1, and 2.1 Hz, 1H), 3.17 (s, 3H), 3.04 (m, $J = 17.1$, 4.2, 4.2, and 1.5 Hz, 1H), 2.49 (m, $J =$ 17.1, 3.6, and 2.1 Hz, 1H); ^{13}C NMR: $\delta = 144.7$, 121.3, 71.3, 63.2 (d, ^2J(C,P) = 7.3 Hz), 62.4 (d, ^2J(C,P) = 7.4 Hz), 61.4 (d, ^1J(C,P) = 152.0 Hz), 43.6, 37.8 (d, ^2J(C,P) = 8.6 Hz), 29.2, 16.0 (d, ^3J(C,P) = 5.0 Hz), 15.9 (d, ^3J(C,P) = 5.0 Hz); ^{31}P NMR: $\delta = 16.5$; IR (KBr): $\tilde{\nu} = 2190$, 1628 cm^{-1}; UV (EtOH): λ_{max} ($\log\varepsilon$) = 279 nm (4.01); MS (EI) *m*/*z* (%): 338 and 336 (2) $[M]^+$, 201, 199 (6), 119(100); HRMS (EI): mass calcd for $C_{11}H_{18}BrN_2O_3P$ 336.0238, found 336.0233.

X-ray crystal structure analysis: Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-127021. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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