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REGIOSELECTIVE DEUTERIUM LABELING OF 1,4-DISUBSTITUTED-1,2,3,6-TETRAHYDROPYRIDINES

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SUMMARY

Reactions leading to the regioselective deuterium labeling of the 1,4-disubstituted-1,2,3,6-tetrahydropyridine system are presented. Three synthetic approaches were explored: Base catalyzed proton-deuteron exchange, reductive deuteration, and ring synthesis using deuterated agents. The methods were applied to various pyridinium salts, pyridones, and piperidones. The syntheses of several new labeled compounds are described and a brief review of the relevant literature is included.

Keywords: tetrahydropyridine, MPTP, deuterium, isotope, regioselective

INTRODUCTION

In addition to their agonist and antagonist properties on various receptors,[1-6] 1,4-disubstituted 1,2,3,6-tetrahydropyridines are proving to be useful probes to investigate the catalytic pathway of the flavin (FAD) containing enzymes monoamine oxidases A and B (MAO-A and MAO-B).[7-9] Interest in this area was initiated by the discovery that the parkinsonian inducing properties of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, **1**) are dependent on its MAO-B catalyzed oxidation to give the dihydropyridinium species $MPDP^+$ (**2**)[10,11] which undergoes further oxidation to the 1-methyl-4-phenylpyridinium MPP^+ species (**3**) (Scheme 1), the ultimate neurotoxin.[10]

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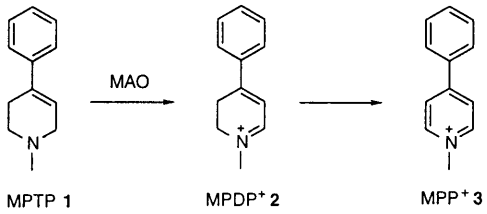
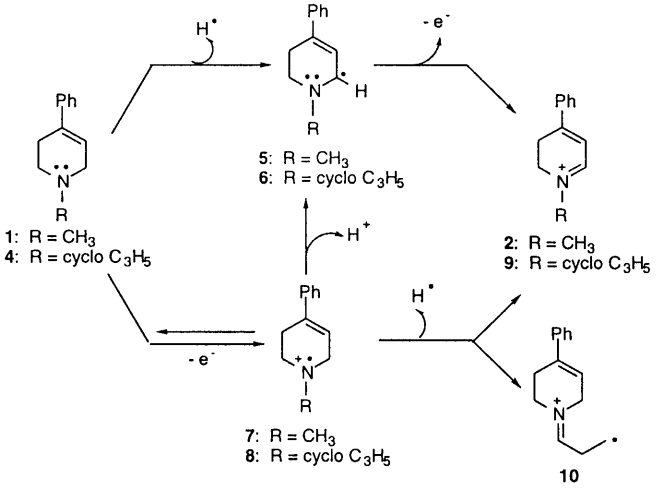
Scheme 1. MAO-B catalyzed oxidation of MPTP (**1**)



Based on earlier results, two principal pathways may be considered to account for the MAO catalyzed oxidation of MPTP (Scheme 2). The first involves hydrogen atom transfer (HAT) to generate the allylic radical **5** which subsequently undergoes electron transfer to yield the product **2**.[11] The second pathway, which is based on the mechanism based inactivation properties of cyclopropylamines, involves an initial single electron transfer (SET) leading to the aminyl radical cation **7** followed by deprotonation and a second electron transfer to yield **2**.[12] The inactivating properties of cyclopropylamines are thought to be mediated by the primary carbon centered radical **10** generated by spontaneous ring opening of the cyclopropylaminyl radical cation **8** which then reacts with a thiol group or the flavin moiety in the active site of the enzyme.[13,14]

Scheme 2. Proposed pathways leading to tetrahydropyridine derived dihydropyridinium metabolites and the mechanism based inactivation properties of N-cyclopropyl analogs



Definitive experimental evidence to distinguish between the proposed pathways is lacking. The availability of MPTP and related analogs bearing deuterium at specific positions of the tetrahydropyridine moiety offers opportunities to investigate isotope effects and other mechanistic

aspects of these enzyme catalyzed reactions. A large isotope effect ($^{D}k_{cat}/K_M$ = 7) has been observed for the MAO-B catalyzed oxidation of MPTP-*6,6-d*$_2$ to MPDP$^+$-*6-d*$_1$.[15] Interest in extending these types of studies to a variety of 1-methyl and 1-cyclopropyl-4-substituted-1,2,3,6-tetrahydropyridine derivatives has prompted us to develop more general methods for the regioselective incorporation of deuterium into this system. In this paper we describe synthetic methods for the regioselective deuteration of the various positions of the tetrahydropyridinyl moiety of MPTP by reaction pathways that may be applicable for a variety of MPTP analogs and related classes of compounds.

The following three basic synthetic approaches have been explored: (1) base catalyzed proton-deuteron exchange of pyridinium systems, 2-pyridones, 4-pyridones, and 4-piperidones; (2) reductive deuterations of pyridinium systems and the corresponding 2-pyridones and dihydro-2-pyridones; and (3) ring syntheses with deuterated reagents.

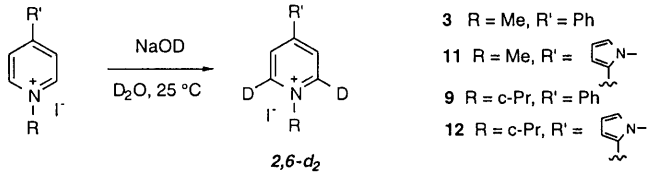
RESULTS AND DISCUSSION

1- Base catalyzed proton-deuteron exchange reactions

Pyridinium Salts

The based-catalyzed deprotonation of pyridinium salts and pyridones leads to the incorporation of deuterium using D_2O as solvent (Scheme 3).[16] With 4-substituted pyridinium salts, the exchange takes place exclusively in positions 2 and 6. The method has been successfully applied to various 1,4-disubstituted pyridinium salts (**3**,[18] **9**, **11**,[17] and **12**) to yield deuterated products with 99% deuterium incorporation after two exchange reactions. The deuterated pyridinium products can be conveniently recovered by lyophilisation of the reaction mixture.

Scheme 3. Alkaline proton-deuterium exchange of pyridinium salts

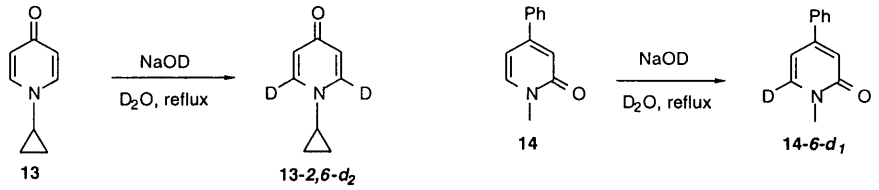


Pyridone Derivatives

The proton-deuterium exchange in 2- and 4-pyridones takes place at a slower rate and requires a higher reaction temperature (Scheme 4).[19] We obtained high deuterium incorporations

(> 98%) and high yields with N-cyclopropyl-4-pyridone (**13**) and N-methyl-4-phenyl-2-pyridone (**14**)[36].

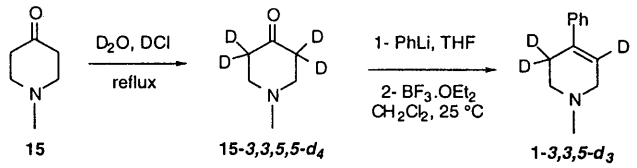
Scheme 4. Base-catalyzed proton-deuterium exchange of 2- and 4-pyridones



Piperidone Derivatives

Incorporation of deuterium to prepare tetradeuterated haloperidol, a piperidinol antipsychotic agent, was achieved by reaction of 1-protected-4-piperidone with D_2O and acetone-d_6 in DCl.[20] The method was readily adapted to the preparation of MPTP-*3,3,5-d*$_3$ (Scheme 5). Four deuterium atoms were incorporated in positions α to the carbonyl group of 1-methyl-4-piperidone (**15**). Subsequent phenyllithium addition to the carbonyl group afforded an intermediate piperidinol (**16**)[21] which, when dehydrated in aprotic medium in the presence of $BF_3.OEt_2$ as catalyst, yielded MPTP-*3,3,5-d*$_3$. As expected, classical dehydration under protic conditions (HCl/AcOH) resulted in deuterium-hydrogen exchange. Similarly, a pentadeuterated phenyl ring was simply introduced by addition of the corresponding Grignard or lithium derivative to 4-piperidone **15**.[18]

Scheme 5. Synthesis of MPTP-*3,3,5-d*$_3$

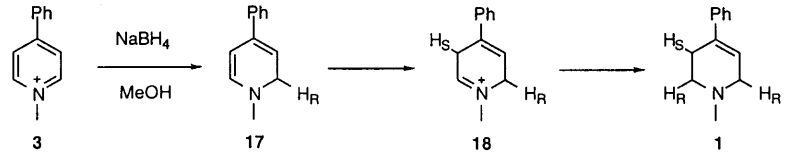


2- Reductive Deuterations

Pyridinium Derivatives

Reduction of pyridinium salts with sodium borohydride in protic solvent is a convenient way to generate 1,4-disubstituted-1,2,3,6-tetrahydropyridines. The mechanism of this reaction has been described by Lyle and proceeds as shown in Scheme 6.[22-25] Initial addition of hydride affords the 1,2-dihydropyridine intermediate **17** which is selectively protonated at C-5 [24,26] to yield the conjugate acid **18**. Hydride reduction of **18** affords the 1,2,3,6-tetrahydropyridine **1**.

Scheme 6. Mechanism of reduction of pyridinium salt **3** to 1,2,3,6-tetrahydropyridine **1**.



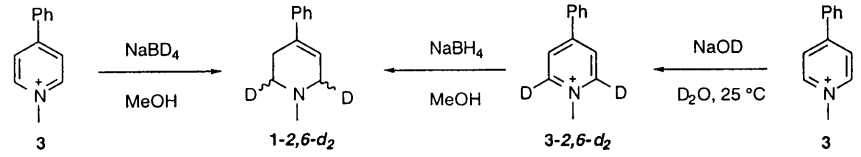
H_R = proton coming from the reducing agent
H_S = proton coming from the solvent

The reaction proceeds smoothly and quantitatively with 1,4-disubstituted pyridinium species, and results in the incorporation of a proton from the solvent at position 3 of the final tetrahydropyridine and two protons from the reducing agent at positions 2 and 6. Combinations in the use of $NaBH_4$ (or $NaBD_4$) with CH_3OH (or H_2O) or CD_3OD (or D_2O) allows specific labelings of the tetrahydropyridine ring. The C_3-monodeuterated N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1-*3-d*$_1$**) and N-cyclopropyl-4-phenyl-1,2,3,6-tetrahydropyridine (**4-*3-d*$_1$**) analogs were easily obtained by reduction of the corresponding pyridinium intermediates with $NaBH_4$ in D_2O or CD_3OD.[22,27]

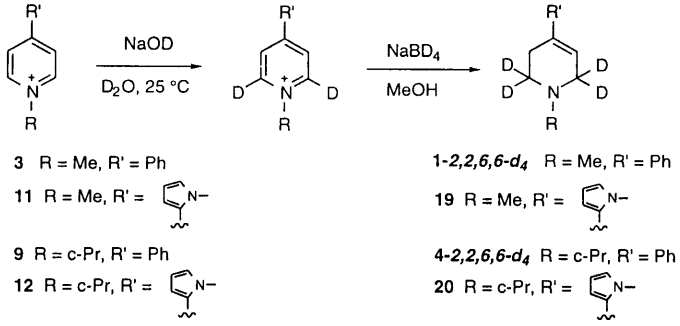
It is apparent (Scheme 6) that reduction of pyridinium salts with $NaBD_4$ affords deuterium incorporation into position 2 and 6.[18] The same final tetrahydropyridine-*2,6-d*$_2$ derivatives could be obtained using base-catalysed proton-deuterium exchange on the pyridinium intermediates followed by reduction with $NaBH_4$. In both cases, the reactions are selective and quantitative (Scheme 7).

Tetrahydropyridines-*2,2,6,6-d*$_4$ are accessible using combinations of alkaline exchange and reduction from the corresponding pyridinium starting materials. These compounds are of particular interest for enzyme studies and several derivatives have been prepared in high yields and with high deuterium incorporation from the corresponding pyridinum salts (Scheme 8).[17,18]

Scheme 7. Dideuterium labeling at position 2 and 6 of the tetrahydropyridine

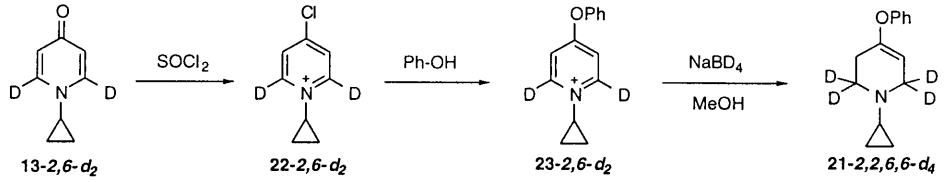


Scheme 8. Synthesis of tetrahydropyridine-2,2,6,6-d_4 derivatives from pyridinium salts



The N-cyclopropyl-4-phenoxy-1,2,3,6-tetrahydropyridine-2,2,6,6-d_4 (**21-2,2,6,6-d_4**) was prepared from the dideuterated N-cyclopropyl-4-pyridone (**13-2,6-d_2**,) which was converted to the 4-chloro-1-cyclopropyl-2,6-d_2-pyridinium chloride salt (**22-d_2**). Nucleophilic substitution of the chloro group with the phenoxy group followed by reduction with $NaBD_4$ afforded **21-2,2,6,6-d_4** (Scheme 9).[28]

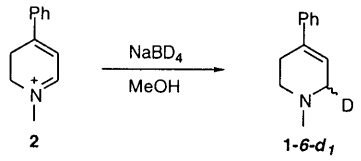
Scheme 9. Preparation of N-cyclopropyl-4-phenoxy-1,2,3,6-tetrahydropyridine-2,2,6,6-d_4 (**21-2,2,6,6-d_4**)



Dihydropyridinium Derivatives

Deuteration at position 6 of the tetrahydropyridine is achieved by reduction of the dihydropyridinium species with $NaBD_4$ in methanol (Scheme 10).[29,30] The dihydropyridinium intermediates are generated from the corresponding N-oxides by treatment with trifluoroacetic anhydride.[31] The reduction proceeds smoothly, with the only limitation being the availability of the dihydropyridinium species. The reaction, illustrated with the 1-methyl-4-phenyl-2,3-dihydropyridinium species **2**, was performed with different substituents at the C_4 position and with N-cyclopropyldihydropyridinium derivatives.[28,32]

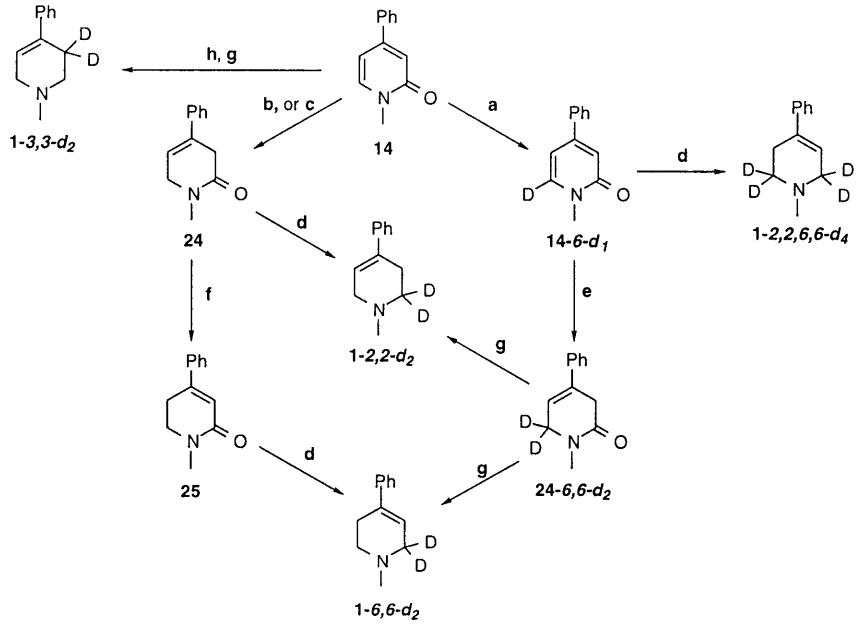
Scheme 10. Reduction of dihydropyridinium to tetrahydropyridine-*6-d*$_1$.



Pyridone Derivatives

Reductions of 2-pyridones with $LiAlH_4$ to yield the 1,2,3,6-tetrahydropyridine system have been studied by Ferles and Holik.[33,34] More recently we undertook the selective reduction of 1-methyl-4-phenyl-2-pyridone (**14**).[35] This 2-pyridone was reduced quantitatively with L-Selectride in THF and in 70% yield with $LiAlH_4$ in THF to the corresponding 3,6-dihydro-2-pyridone **24** which could be isomerized to the conjugated 5,6-dihydro-2-pyridone **25** (Scheme 11). Reduction of 1-methyl-4-phenyl-5,6-dihydro-2-pyridone (**25**) with $LiAlD_4$ in refluxing Et_2O afforded the corresponding *6,6*-dideuterated tetrahydropyridine **1-*6,6-d*$_2$** in good yield (81%).[15,36] This

Scheme 11. Regioselective synthesis of deuterated analogs of MPTP starting from 2-pyridone **14**.



(a) NaOD, D_2O, reflux; (b) L-Selectride, THF, -35 °C; (c) $LiAlH_4$, THF, 10 °C; (d) $LiAlD_4$, Et_2O, reflux; (e) $LiAlD_4$, THF, 10 °C; (f) *t*-BuOK, *t*-BuOH, 25 °C; (g) $LiAlH_4$, Et_2O, reflux; (h) $LiAlH_4$, THF, -5 °C and then D_2O.

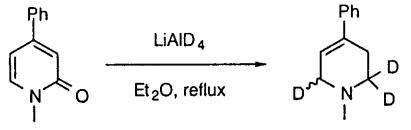
compound is also accessible via the reduction of 1-methyl-4-phenyl-2-pyridone-*6-d1*, (**14-*6-d1***) with $LiAlD_4$ in THF and controled conditions of time and temperature followed by reduction with $LiAlH_4$ in refluxing Et_2O. The *2,2-d2* analog (**1-*2,2-d2***) was obtained from the 2-pyridone **14** by reduction with L-Selectride in THF followed by reduction of the dihydropyridone **24** with $LiAlD_4$ in refluxing Et_2O. Complete reduction of the 2-pyridone **14-*6-d1*** with $LiAlD_4$ led to the tetradeuterated analog **1-*2,2,6,6-d4***.[35]

According to a previously reported mechanistic study of the reduction of 2-pyridones with $LiAlH_4$, two deuterium atoms are incorporated at once at the C_3 position when the hydrolysis of the reaction is performed in deuterated water.[35]

The complete reduction of 2-pyridone **14** with $LiAlD_4$ affords the trideuterated tetrahydropyridine with two deuterium atoms at position 2, replacing the carbonyl group, and one deuterium atom at position 6 (Scheme 12). These compounds are also accessible via the dihydropyridinium intermediates obtained from the corresponding tetrahydropyridine-*2,2,6,6-d4* species, by reduction with $NaBH_4$.

The isomeric tetrahydropyridine **1-*2,6,6-d3*** might be prepared from **14-*6-d1*** by reduction with L-Selectride followed by isomerization of the double bond and subsequent reduction of the carbonyl group with $LiAlD_4$. All of these reactions proceed in yields over 95%.

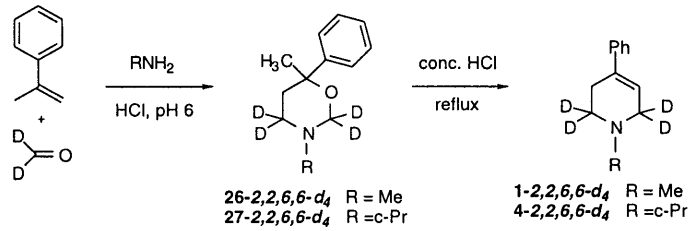
Scheme 12. Preparation of tetrahydropyridine-*2,2,6-d3*



3- Ring Syntheses

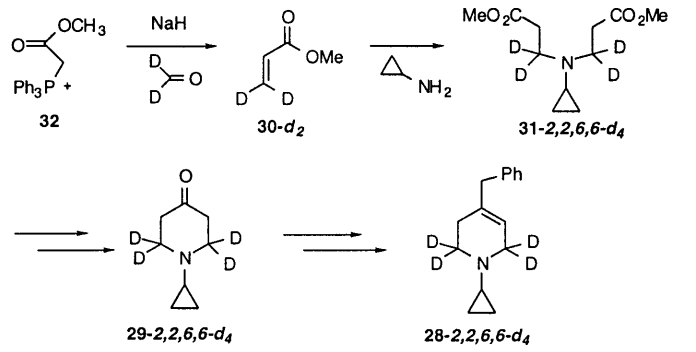
MPTP (**1**) was prepared in 1956 by condensation of styrene, formaldehyde, and methylamine hydrochloride in refluxing aqueous HCl.[37] The reaction proceeds via the intermediate oxazine **26** that rearranges to the 1,2,3,6-tetrahydropyridine (Scheme 13). This reaction is particularly interesting because of the availability of both deuterium and ^{13}C labeled styrene and formaldehyde. The tetradeuterated MPTP analog **1-*2,2,6,6-d4*** and its N-cyclopropyl analog (**4-*2,2,6,6-d4***) were synthesized from deuterated formaldehyde and methylamine hydrochloride and cyclopropylamine.[15,38]

Scheme 13. Synthesis of **1-*2,2,6,6-d*$_4$** and its N-cyclopropyl analog **4-*2,2,6,6-d*$_4$** from deuterated formaldehyde



The tetradeuterated 4-benzyl-1-cyclopropyl-1,2,3,6-tetrahydropyridine derivative **28-*2,2,6,6-d*$_4$** was recently synthesized by addition of the Grignard reagent of benzylbromide to the tetradeuterated N-cyclopropylpiperidone **29-*2,2,6,6-d*$_4$** and subsequent dehydration of the intermediate piperidinol.[39] The tetradeuterated piperidone **29-*2,2,6,6-d*$_4$** was prepared by condensation of cyclopropylamine and deuterated methyl acrylate (**30-*d*$_2$**) followed by ring closure in alkaline medium and decarboxylation under acidic conditions (Scheme 14).[40] Methyl acrylate-d_2 (**30-*d*$_2$**) was prepared according the literature from deuterated formaldehyde and methoxycarbonylmethyltriphenylphosphonium bromide **32**.[41]

Scheme 14. Synthesis of 4-benzyl-1-cyclopropyl-1,2,3,6-tetrahydropyridine-2,2,6,6-d_4 **28-*2,2,6,6-d*$_4$**



CONCLUSION

Alkaline exchange coupled with sodium borohydride (deuteride) reduction in methanol is a selective and quantitative method that can be employed with a variety of substituents to generate various tetrahydropyridines labeled in the 2 and 6 positions. The 2- or 4-pyridones affords a larger

panel of regioselectivities but the accessibility of the starting pyridone might be critical for some compounds. Only a few examples of regioselective deuterations of the tetrahydropyridine ring are described here, but several other multideuterations are accessible using combinations of the reported methods. The availability of various regioselectively labeled tetrahydropyridines also renders possible the synthesis of regioselectively labeled piperidines by simple catalytic hydrogenation of the double bond.

EXPERIMENTAL PART

General section. Reagents and starting materials were obtained from commercial suppliers and were used without further purification. THF and Et_2O were distilled from sodium/benzophenone ketyl. All reactions were conducted using flame dried glassware under an atmosphere of dry N_2. Chromatography refers to flash column chromatography on silica gel unless otherwise noted. Melting points were performed on a Thomas-Hoover melting point apparatus and are uncorrected. Proton spectra were recorded on Bruker WP 270-MHz and Varian 400-MHz spectrometers. Exponential function (LB = 0.1-0.2) was applied to the FID to obtain integrals and gaussian function (LB = -1, GB = 0.25) to record coupling constants. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane (δ = 0 ppm). Spin multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet) or m (multiplet). Coupling constants (J) are given in hertz (Hz). Gas chromatography-electron ionization mass spectrometry (GC-EIMS) was performed on a Hewlett Packard 5890 GC fitted with an HP-1 capillary column which was coupled to a Hewlett Packard 5870 mass-selective detector. Data were acquired using an HP 5970 Chemstation. Normalized peak heights are reported as a percentage of the base peak.

Alkaline exchanges

The pyridinium salt was dissolved in D_2O (8 mL for 1 mmole of compound) and 5 N NaOD in D_2O (0.2 eq.) was added. The reaction was monitored by ^1H NMR by following the disappearance of the signal of the protons in position α to the nitrogen atom. The reaction took one or two days depending of the compound. After completion of the reaction, the water was removed by lyophilisation and the pyridinium could be recrystallized from methanol/ether.

1-Methyl-4-(1-methylpyrrol-2-yl)pyridinium-*2,6-d*$_2$ Iodide (11). The product was obtained as a yellow solid, mp 175-177 °C (lit.[42] mp d_0 analog 178-180 °C); ^1H NMR (CD_3OD,

270 MHz) δ 7.49 (2H, s), 6.75 (1H, dd, *J* = 1.6 Hz, *J* = 2.6 Hz), 6.59 (1H, dd, *J* = 1.6 Hz, *J* = 4.0 Hz), 5.95 (1H, dd, *J* = 2.6 Hz, *J* = 4.0 Hz), 3.82 (3H, s), 3.49 (3H, s).

1-Cyclopropyl-4-chloropyridinium-*2,6-d*$_2$ Chloride (22-*2,6-d*$_2$·Cl). The compound was obtained as a white solid, mp 215-217 °C (lit.[28] mp d_0 analog 218-220 °C); ^{1}H NMR (DMSO-d_6, 270 MHz) δ 8.29 (2H, s), 4.39 (1H, m), 1.40 (2H, m), 1.24 (2H, m). [28]

1-Cyclopropyl-4-phenylpyridinium-*2,6-d*$_2$ Chloride (9-*2,6-d*$_2$·Cl). The product was obtained as a white solid, mp 192-194 °C. ^{1}H NMR (CD_3OD, 270 MHz) δ 9.02 (2H, s), 8.00 (2H, m), 7.65 (3H, m), 4.45 (1H, m), 1.42 (4H, m). Anal. Calcd. for 9-d_0 $C_{14}H_{14}ClN$: C, 72.57; H, 6.09; N, 6.04. Found: C, 72.35; H, 6.42; N, 5.87.

1-Cyclopropyl-4-pyridone-*2,6-d*$_2$ (13-*2,6-d*$_2$). To a solution (or suspension) of 4-pyridone (**13**)[28] in D_2O (2 mL for 1 mmole of compound) and CD_3OD (0.5 mL for 1 mmole of compound) was added 5 N NaOD in D_2O (0.7 eq) The resulting reaction mixture was heated under reflux for 36 h. After cooling to room temperature, the pyridone was extracted with CH_2Cl_2, the organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. ^{1}H NMR at this stage revealed typically about 90% deuterium incorporation. The exact same procedure was repeated to afford the deuterated pyridone **13-*2,6-d*$_2$** (incorporation > 99%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.32 (2H, s), 3.41 (1H, m), 1.02 (4H, m). MS (rel int) 137 (54, $M^{\cdot+}$), 108 (100), 81 (30), 68 (17).

1-Methyl-4-piperidone-*3,3,5,5-d*$_4$ (15-*3,3,5,5-d*$_4$). In anhydrous conditions, a solution of the commercial piperidone **15** (3.7 g, 32.7 mmol) in D_2O (5 mL) and CD_3OD (1 mL) containing DCl (1.5 mL, 37% v/v in D_2O) was heated under reflux for 24 h. After lyophilisation, the orange solid (4.1 g) obtained displayed an ^{1}H NMR spectrum indicating 75% deuterium incorporation. The reaction was repeated to give **15-*3,3,5,5-d*$_4$** (97%) as an orange solid: ^{1}H NMR (CD_3OD, 270 MHz) δ 2.71 (2H, s), 2.41 (5H, bs). MS (rel int) 117 (100, $M^{\cdot+}$), 73 (24), 72 (89).

Reduction of pyridinium salts with $NaBD_4$.

The pyridinium salt in methanol at 0 °C was treated with $NaBD_4$ (2 eq) portionwise over a 10 min period and then the reaction mixture was allowed to warm to room temperature. By 30 min, the reduction was complete (TLC analysis). The reaction mixture was evaporated under reduced pressure and the solid residue was partitioned between CH_2Cl_2 and H_2O. The organic phase was dried over $MgSO_4$ and evaporated to give the deuterium labeled tetrahydropyridine as its free base which was purified by crystallization of its oxalate salt.

Oxalate salt of 1-methyl-4-(1-methyl-pyrrol-2-yl)-1,2,3,6-tetrahydropyridine-*2,2,6,6-d4* (19-*2,2,6,6-d4*.$H_2C_2O_4$). The compound was crystallized from CH_3CN and obtained as a white solid, mp 119-120 °C (lit.[42] mp of **19-*d0*·$H_2C_2O_4$** 120-121 °C); ^1H NMR (CD_3OD, 270 MHz) δ 6.52 (1H, t, *J* = 1.8 Hz), 5.98 (1H, m), 5.87 (1H, m), 5.56 (1H, s), 3.52 (3H, s), 2.81 (3H, s), 2.60 (2H, s). MS (rel int) 180 (65, M·+), 179 (24), 165 (10), 149 (58), 135 (47), 121 (52), 98 (95).

1-Methyl-4-phenyl-4-piperidinol-*3,3,5,5-d4* (16). The crude mixture of **15-*3,3,5,5-d4*** was treated quickly with a saturated solution of potassium carbonate in D_2O and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to give the piperidone **15-*3,3,5,5-d4*** as a free base. The piperidone (1 eq) was dissolved in anhydrous THF (10 mL per eq) and phenyllithium (1.3 eq) was slowly added at -78 °C. After 1 h at -78 °C, CD_3OD (1 mL) was added and the reaction mixture was allowed to warm to 25 °C. The reaction mixture was partitioned between D_2O and AcOEt. The crude mixture was purified by silica gel chromatography (CH_2Cl_2, then CH_2Cl_2/MeOH) to give the tetradeuterated piperidinol **16** (81% yield) as a yellow pale oil that crystallized, mp = 109-110 °C (lit. mp of **15-*d0***[21] 114-115 °C). ^1H NMR ($CDCl_3$, 270 MHz) δ 7.49 (2H, m), 7.35 (2H, tt, *J* = 7.0 Hz, *J* = 1.6 Hz), 7.26 (1H, t, *J* = 4.0 Hz), 2.72 (2H, d, *J* = 11.8 Hz), 2.42 (2H, d, *J* = 11.8 Hz), 2.33 (3H, s). MS (rel int) 195 (49, M·+), 194 (27), 177 (47), 146 (6), 105 (26), 100 (36), 78 (40), 72 (100), 57 (58).

Oxalate salt of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-*3,3,5-d3* (1-*3,3,5-d3*). Under anhydrous conditions, the piperidinol **16** (390 mg, 2 mmol) in CH_2Cl_2 was treated with $BF_3.OEt_2$ (1M in Et_2O, 40 mmoles) at 25 °C. After 3 h the dehydration was complete and the reaction mixture was treated with NaOD (10% in D_2O, 3 mL). The reaction mixture was extracted with D_2O and CH_2Cl_2. The combined phases were dried over $MgSO_4$ and evaporated under reduced pressure to give the tetrahydropyridine (342 mg, 1.95 mmol, 98% yield). The oxalate salt was formed by addition of an etheral solution of oxalic acid (1.15 eq) to a solution of tetrahydropyridine in ether and the salt was recrystallized from methanol to give **1-*3,3,5-d3*** as a white solid, mp = 163-164 °C (lit.[37] mp of **1-*d0*.*HCl*** 249-251 °C). ^1H NMR (DMSO-d_6, 270 MHz) δ 7.42 (2H, m), 7.33 (2H, m), 7.21 (1H, m), 3.33 (3H, s), 3.01 (2H, s), 2.56 (2H, s). MS (rel int) 176 (100, M·+), 175 (60), 145 (29), 132 (40), 116 (25), 99 (67).

1-Cyclopropyl-4-phenoxy-1,2,3,6-tetrahydropyridine-*2,2,6,6-d4* (21). To a solution of **22** (191 mg, 1 mmol) in CH_3CN (15 mL) was added a solution of phenol (118 mg, 1.2 mmol) in NEt_3 (1 mL) at 25 °C and the reaction mixture was stirred for 14 h. The CH_3CN was evaporated

under reduced pressure and 15 mL of MeOH were added. $NaBD_4$ (6 mmol) was added portionwise at 25 °C. The reaction mixture was stirred for 45 min and then the solvent was evaporated. The residue in CH_2Cl_2 was washed with aqueous K_2CO_3 and water and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in CH_3CN and an etheral solution of oxalic acid was added to give the oxalate salt of **21**. The salt was recrystallized from methanol to give a white solid (195 mg, 0.6 mmol, 60% yield), mp = 149-151 °C (lit.[28] mp of **21-*d*$_0$** 150-152 °C). ^1H NMR ($CDCl_3$, 270 MHz) δ 7.36 (2H, t like, *J* = 7.7 Hz), 7.11 (1H, t, *J* = 7.4 Hz), 7.01 (2H, d, *J* = 7.7 Hz), 4.79 (1H, s), 2.38 (2H, bs), 2.24 (1H, m), 0.68 (2H, m), 0.62 (2H, m). MS (rel int) 219 (38, $M^{\cdot+}$), 203 (100), 142 (7), 126 (15), 109 (16), 94 (25), 77 (34), 70 (26).

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