Synthesis and Spectroscopic Properties of Isomeric Trideuterio- and Tetradeuterio Pyridines

James W. Pavlik* and Somchoke Laohhasurayotin

Department of Chemistry and Biochemistry
Worcester Polytechnic Institute
Worcester, MA 01609
jwpavlik@wpi.edu

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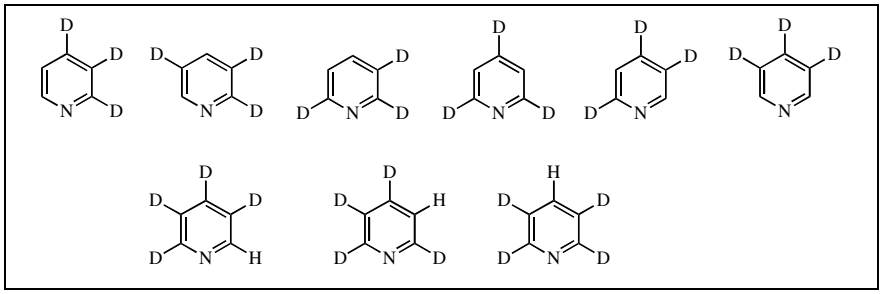

The syntheses of the six possible isomeric trideuteriopyridines and the three possible isomeric tetradeuteriopyridines are described. These deuteriopyridines were characterized by their mass and NMR spectra.

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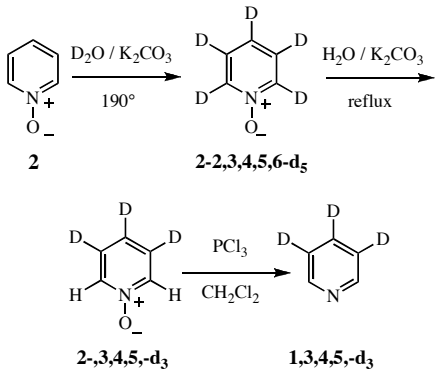
INTRODUCTION

As part of our interest in the vapor phase photochemistry of pyridine, [1,2] we were interested in obtaining pure samples of the six possible isomeric trideuteriopyridines and of the three possible isomeric tetradeuteriopyridines shown in Table 1. To our knowledge, neither the synthesis nor spectroscopic properties of either set of deuterated isomers have been reported.

RESULTS AND DISCUSSION

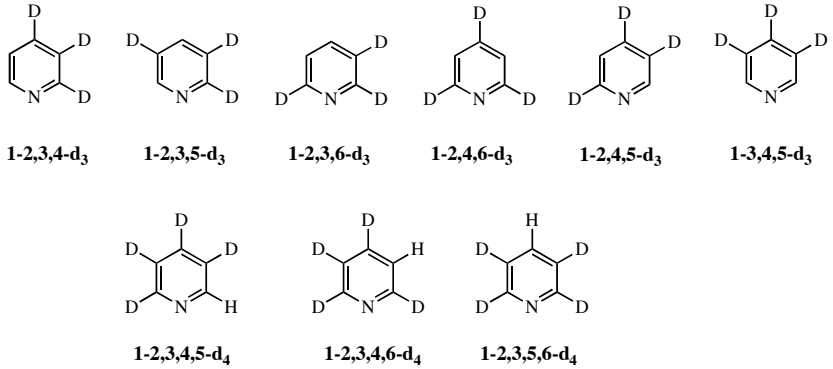
Trideuteriopyridines. 3,4,5-Trideuteriopyridine (**1-3,4,5-d_3**) was synthesized from pyridine N-oxide (**2**) as shown in Scheme 1. Base catalyzed deuterium exchange at 190° [3,4] gave **2-2,3,4,5,6-d_5** which exhibited a molecular ion in the mass spectrum at m/z = 100, consistent with perdeuteration. In addition, the ^{13}C-nmr spectrum exhibited triplets at δ 139.4 (C2,6, J = 28.5 Hz), 126.1 (C4, J = 25.6 Hz), and 125.9 (C3,5, J = 26.3Hz) due to

Scheme 1



2 **2-2,3,4,5,6-d_5** **2-,3,4,5,-d_3** **1,3,4,5,-d_3**

Table 1



1-2,3,4-d_3 **1-2,3,5-d_3** **1-2,3,6-d_3** **1-2,4,6-d_3** **1-2,4,5-d_3** **1-3,4,5-d_3**

1-2,3,4,5-d_4 **1-2,3,4,6-d_4** **1-2,3,5,6-d_4**

^{13}C-D coupling at each ring position. Selective exchange of deuterium for hydrogen at ring positions 2 and 6 in refluxing aqueous potassium carbonate led to **2-3,4,5-d$_3$**. The mass spectrum of the product exhibited a molecular ion at m/z = 98, confirming the exchange of two deuterium atoms for protons while the ^{1}H- and ^{13}C-spectra confirmed that the exchange occurred at ring positions 2 and 6. Thus, the ^{1}H-NMR spectrum exhibited an intense singlet at δ 8.18, where H2 and H6 are known to absorb, while the ^{13}C-NMR spectrum showed a singlet at δ 139.1 for the C2 and C6 ring atoms but triplets at δ 126.1 (C4, J = 25.6 Hz) and δ 125.9 (C3,5, J = 26.3 Hz) confirming that only C2 and C6 were bonded to protons. As shown in Tables 1 and 2, the ^{1}H and ^{13}C-NMR spectra confirmed that reduction of N-oxide **2-3,4,5-d$_3$** to **1-3,4,5-d$_3$** using phosphorous trichloride [5] occurred without change of the labeling pattern.

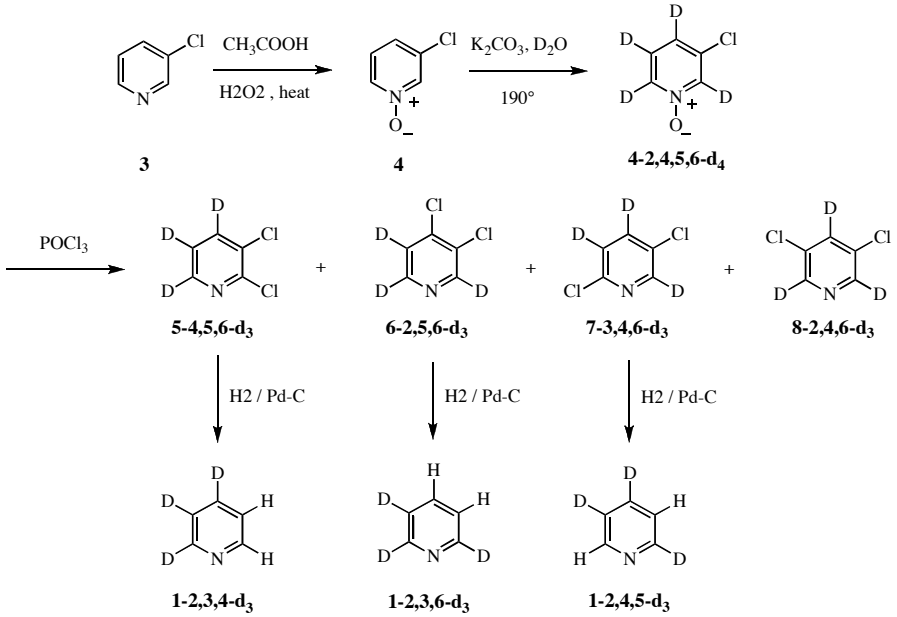
1-2,3,4-d$_3$, **1-2,4,5-d$_3$** and **1-2,3,6-d$_3$** were synthesized from commercially available 3-chloropyridine (**3**) as shown in Scheme 2. N-oxidation [6] followed by perdeuteration [3,4] provided 2,4,5,6-tetradeuterio-3-chloropyridine-N-oxide (**4-2,4,5,6-d$_4$**), confirmed by the mass spectrum which exhibited a molecular ion at m/z = 133 and the ^{13}C-NMR spectrum which showed a singlet for C3 and four triplets for the four non-equivalent ring carbon atoms bonded to deuterium. Reaction of this compound with phosphorous oxychloride [7] provided the four dichlorotrideuteriopyridine isomers **5-4,5,6-d$_3$**, **6-2,5,6-d$_3$**, **7-3,4,6-d$_3$,** and **8-2,4,6-d$_3$** which were separated by flash column chromatography. Hydrogenolysis over palladium on charcoal converted **5-4,5,6-d$_3$**, **6-2,5,6-d$_3$**, and **7-3,4,6-d$_3$** to **1-2,3,4-d$_3$**, **1-2,3,6-d$_3$**, and **1-2,4,5-d$_3$** respectively. Although it was not possible to unambiguously assign the structures of these three dichloropyridine isomers on the basis of their ^{13}C-NMR spectra, the resulting trideuteriopyridines could be unambiguously distinguished by their ^{1}H-NMR spectra.

The ^{1}H-NMR spectrum of **1-2,3,4-d$_3$**, exhibited two doublets with J = 4.8 Hz. The magnitude of this coupling constant confirms that the two adjacent ring protons must be α and β to the ring nitrogen as in the assigned structure [9,10]. Alternatively, the ^{1}H-NMR spectrum of **1-2,3,6-d$_3$** exhibited two doublets with J = 7.6 Hz. This larger coupling constant indicates that neither proton can be α to the ring nitrogen and thus must be β and γ to nitrogen as in the assigned structure [9,10]. Finally, the ^{1}H-NMR spectrum of **1-2,4,5-d$_3$** exhibits two singlets at δ 7.36 and 8.59 where H 3(5) and H 2(6) of pyridine are known to absorb. Unambiguous assignment of these structures thus confirmed that the assigned structures for the dichloropyridines are also correct.

Although **1-2,4,6-d$_3$** could be prepared by hydrogenolysis of **8-2,4,6-d$_3$**, the yield of this dichloro isomer was too low for this approach. Instead, **1-2,4,6-d$_3$** was synthesized from pyridine N-oxide (**2**) as shown in Scheme 3.

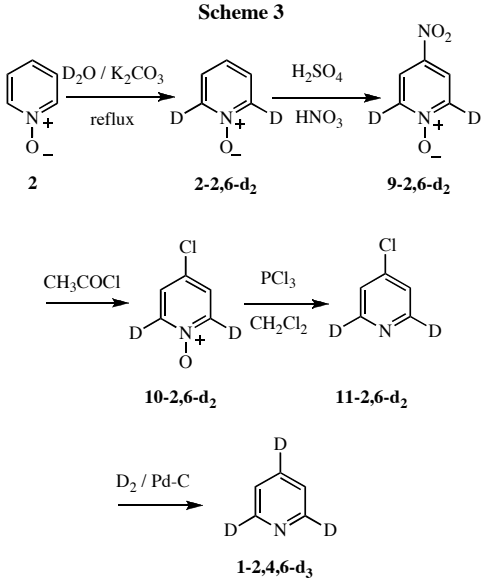
The sequence started with selective deuteration at ring positions 2 and 6 to provide **2-2,6-d$_2$** [3,4]. Nitration with fuming nitric acid [11], replacement of nitro by chloro by reaction with acetyl chloride [11] followed by reduction with PCl_3 in dichloromethane [5] gave 4-chloro-2,6-dideuteriopyridine **11-2,6-d$_2$**. Mass spectral analyses confirmed that each of these intermediate compounds remained dideuterated while the ^{13}C-NMR spectra

Scheme 2



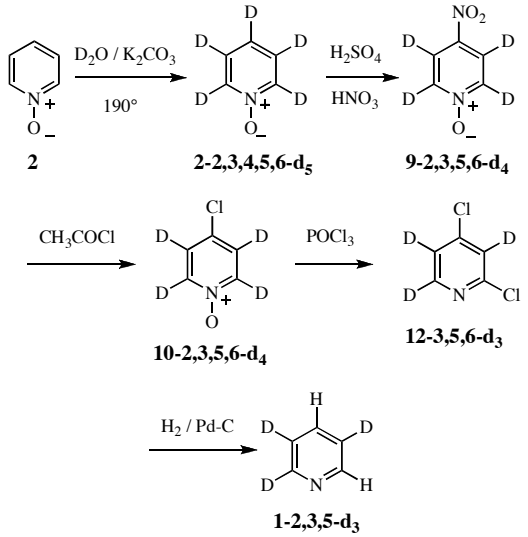
confirmed that the two deuterium atoms were bonded to carbon atoms adjacent to the ring nitrogen. Reduction of **11-2,6-d$_2$** with deuterium and palladium on charcoal [8] gave the desired **1-2,4,6-d$_3$**. As shown in Tables 1 and 2, the ^{1}H-NMR spectrum exhibited a singlet at δ 7.08 where the C3 proton of pyridine is known to absorb while the ^{13}C-NMR spectrum exhibited a singlet at δ 123.9 where the C3 is known to absorb and triplets at δ 136.1 for C4 and at δ 149.8 for C2(6) confirming that deuterium atoms were bonded to C2(6) and C4 of the pyridine ring.

Scheme 3



1-2,3,5-d$_3$ was synthesized by a similar procedure shown in Scheme 4. This involves synthesis of 2,4-dichloropyridine-3,5,6-d$_3$ (**12-3,5,6-d$_3$**) by the sequence of reactions shown. Hydrogenolysis using hydrogen gas and palladium on charcoal [8] gave the desired **1-2,3,5-d$_3$**.

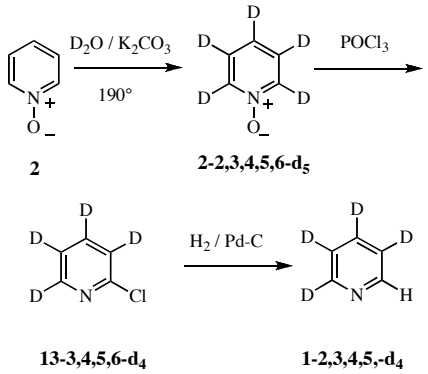
Scheme 4



The mass spectrum of this compound exhibited a molecular ion at m/z = 82, consistent with a trideuterated pyridine. The ^{1}H- and ^{13}C-spectra, summarized in Tables 1 and 2 confirmed that the deuterium atoms were at ring positions 2, 3 and 5. Thus, the ^{1}H-NMR spectrum exhibited singlets at δ 7.75 and 8.60 where protons at ring positions 4 and 2 are known to absorb whereas the ^{13}C-NMR spectrum exhibited triplets at δ 150.2, 124.2, and 123.8 confirming that the carbon atoms at ring positions 6, 3, and 5 are all bonded to deuterium.

Tetradeuteriopyridines. 2,3,4,5-Tetradeuteriopyridine (**1-2,3,4,5-d$_4$**) was prepared from pyridine N-oxide (**2**) as shown in Scheme 5. Treatment of pyridine N-oxide-d$_5$ (**2-2,3,4,5,6-d$_5$**) with phosphorus oxychloride [7] provided a mixture of 4-chloropyridine-d$_4$ and 2-chloropyridine-d$_4$ (**13-3,4,5,6-d$_4$**) from which the latter was obtained in pure form by column chromatography. The ^{13}C-NMR spectrum of this compound exhibited four triples at δ 149.4 (J = 28.1 Hz), 138.2 (J = 25.2 Hz), 124.1 (J = 26.6 Hz), and 121.7 (J = 25.4 Hz) for the C6, C4, C3 and C5 ring carbons respectively and a singlet at δ 151.5 for the C2 carbon, confirming that the chlorine is bonded to this ring position. Reduction with hydrogen over palladium on charcoal [8] gave the desired **1-2,3,4,5-d$_4$**. The ^{1}H-NMR spectrum of this product exhibited one singlet at δ 8.60 where protons at C2 or C6 of pyridine are known to absorb. In addition to triplets in the ^{13}C-NMR spectrum for C3, C4 and C5, the carbons at ring positions 2 and 6 appeared as a sharp singlet at δ 148.6 overlapping with a triplet (J = 27.2 Hz) at δ 148.3 confirming that one of these carbon atoms is bonded to a proton while the other is bonded to deuterium.

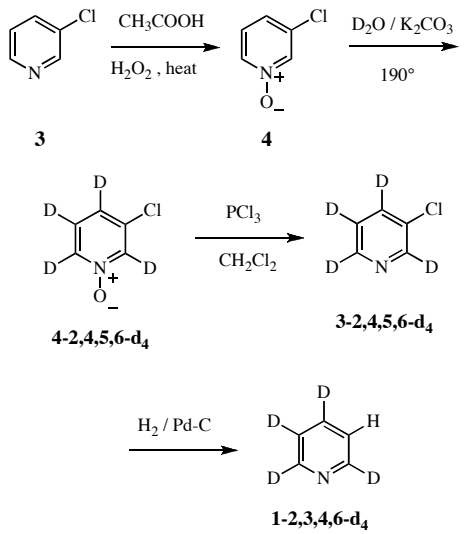
Scheme 5



2,3,4-6-Tetradeuteriopyridine (**1-2,3,4,6-d$_4$**) was synthesized as shown in Scheme 6. 3-Chloropyridine (**3**) was oxidized [12] and perdeuterated as previously shown in Scheme 2 to yield 3-chloropyridine N-oxide-d$_4$ (**4-2,4,5,6-d$_4$**). Reduction with phosphorous trichloride [5] provided 3-chloropyridine-d$_4$ (**3-2,4,5,6-d$_4$**). In contrast to the 2-chloro-isomer, **13-3,4,5,6-d$_4$**, shown in Scheme 5, the ^{13}C-NMR spectrum of the 3-chloro-isomer exhibited

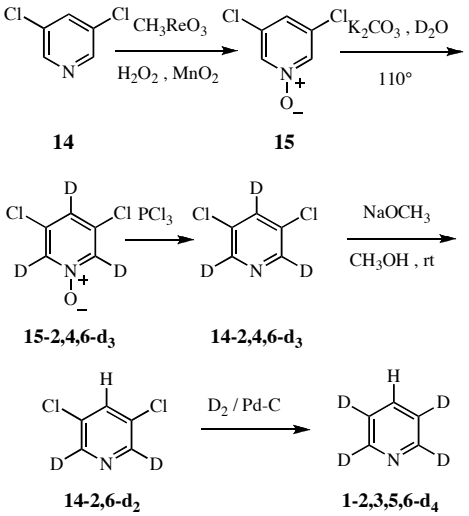
triplets at δ 148.8 (J = 28.0 Hz), 147.7 (J = 28.7 Hz), 136.0 (J = 26.1 Hz) and 124.3 (J = 25.8 Hz) for the C2, C6, C4 and C5 ring atoms respectively and a singlet at δ 132.4 confirming that the C3 ring carbon is bonded to the chlorine atom. Further reduction with hydrogen over palladium on charcoal [8] provided **1-2,3,4,6-d$_4$**. In this case the ^{1}H-NMR spectrum exhibited one singlet at δ 7.36 where the H3 or H5 protons of pyridine are known to absorb while the ^{13}C-NMR exhibited three triplets and a sharp singlet at δ 126.1 confirming that only the C3 ring carbon is bonded to a proton.

Scheme 6



Scheme 7 shows the synthetic route used to prepare 2,3,5-6-tetradeuteriopyridine (**1-2,3,5,6-d$_4$**). 3,5-Dichloropyridine **(14)** was first oxidized with methyltrioxorhenium (VII), [12] then perdeuterated to yield **15-2,4,6-d$_3$**, and reduced with PCl_3 [5] to provide **14-2,4,6-d$_3$**.

Scheme 7



The mass spectrum of this compound exhibited a molecular ion at m/z = 152, consistent with a tri-deuterated-dichloropyridine. In addition, the ^{13}C-NMR spectrum exhibited triplets at δ 146.7 (J = 29.1 Hz) for the equivalent C2,6 carbon atoms, a triplet at δ 135.8 (J = 26.5 Hz) for the C4 carbon atom, and a singlet at δ 132.4 for the equivalent C3,5 carbons bonded to chlorine. Treatment of this compound with sodium methoxide in methanol at room temperature then allowed selective exchange of the C4 deuterium with hydrogen to provide **14-2,6-d$_2$** [13]. The mass spectrum of this compound exhibited a molecular ion at m/z = 151 confirming the exchange of one deuterium for hydrogen while the triplet at δ 135.8 for the C4 carbon in the ^{13}C-NMR spectrum of the reactant, **14-2,4,6-d$_3$**, was replaced with a singlet at δ 136.0 for the C4 carbon in the ^{13}C-NMR spectrum of the product, **14-2,6-d$_3$**. This confirms that the exchange took place selectively at the C4 ring position. Treatment of this compound with deuterium over palladium on charcoal [8] provided the final desired product, **1-2,3,5,6-d$_4$**. As required, the ^{1}H-NMR spectrum exhibited one singlet at δ 7.75 where the proton at ring position 4 is known to absorb while the ^{13}C-NMR spectrum exhibited triplets at δ 150.3 and 124.2 for C2,6 and C,3,5 respectively, and a singlet at δ 136.5 for the C4 ring carbon atom.

Table 1

^{1}H-NMR Chemical Shifts (δ ppm) of Deuterated Pyridines *

Compound	Ring Position				
	2	3	4	5	6
1-2,3,4-d$_3$	-----	-----	-----	7.34, d J = 4.8 Hz	7.34, d J = 4.8 Hz
1-2,3,5-d$_3$	-----	-----	7.75, s	-----	8.60, s
1-2,3,6-d$_3$	-----	-----	7.76, d J = 7.6 Hz	7.34, d J = 7.6 Hz	-----
1-2,4,6-d$_3$**	-----	7.08, s	-----	7.08, s	-----
1-2,4,5-d$_3$	-----	7.36, s	-----	-----	8.59, s
1-3,4,5-d$_3$	8.44, s	-----	-----	-----	8.44, s
1-2,3,4,5-d$_4$	-----	-----	-----	-----	8.60, s
1-2,3,4,6-d$_4$**	-----	-----	-----	7.36, s	-----
1-2,3,5,6d$_4$	-----	-----	7.75, s	-----	-----

* Spectra recorded in acetone-d$_6$ unless otherwise noted. ** Spectra recorded in deuteriochloroform

EXPERIMENTAL

Synthesis of 3,4,5-Trideuteriopyridine (1-3,4,5-d$_3$).

Pyridine N-oxide-d$_5$ (2-2,3,4,5,6-d$_5$). A solution of pyridine N-oxide (**2**) (2.0 g, 21 mmol) and potassium carbonate (2.0 g) dissolved in deuterium oxide (20 mL) was heated in an autoclave at 190°C for 5 hours. The resulting solution was concentrated by rotary evaporation and the liquid residue was dissolved in deuterium oxide (10 mL) and heated again in an

Table 2

^{13}C-NMR Chemical Shifts (δ ppm) of Deuterated Pyridines *

Compound	Ring Position				
	2	3	4	5	6
1-2,3,4-d_3	150.2, t J = 26.8 Hz	124.0, s J = 25.4 Hz	136.2, t J = 25.3 Hz	124.4, s	150.6, s
1-2,3,5-d_3	150.2, t J = 27.6 Hz	124.2, t J = 24.6 Hz	136.3, s	123.8, t J = 24.9 Hz	150.5, s
1-2,3,6-d_3	150.3, t J = 27.8 Hz	124.1, t J = 25.6 Hz	136.4, s	123.5, s	150.3, t J = 27.8 Hz
1-2,4,6-d_3**	149.8, t J = 27.1 Hz	123.9,s	136.1,t J = 25.1 Hz	123.9, s	149.8, t J = 27.8 Hz
1-2,4,5-d_3	150.3, t J = 26.9 Hz	124.3,s	136.2,t J = 25.3 Hz	124.1,t J = 25.0 Hz	150.6,s
1-3,4,5-d_3	151.7, s	125.3,t J = 25.3 Hz	137.2,t J = 24.9 Hz	125.3,t J = 25.3 Hz	151.7,s
1-2,3,4,5-d_4	148.3,t J = 27.2 Hz	122.1,t J = 25.2 Hz	134.1,t J = 24.6 Hz	122.0,t J = 25.5 Hz	148.6,s
1-2,3,4,6-d_4**	152.1,t J = 30.4 Hz	125.8,t J = 25.8 Hz	138.0,t J = 24.9 Hz	126.1,s	152.1,t J =30.4 Hz
1-2,3,5,6d_4	150.3,t J = 27.9 Hz	124.2,t J = 25.5 Hz	136.5,s	124.2,t J = 25.5 Hz	150.3,t J =27.9 Hz

* Spectra recorded in acetone-d_6 unless otherwise noted. ** Spectra recorded in deuteriochloroform

autoclave at 190˚C for an additional 5 hours. The resulting solution was extracted with chloroform (6 x 20 mL). The organic extract was dried (sodium sulfate) and concentrated to dryness to give **2-2,3,4,5,6-d_5** as a highly hygroscopic white solid: yield 2.0 g (20 mmol, 95%) mp 50˚C, ^{13}C-NMR (deuteriochloroform) δ 139.4 (t, C2,6, J = 28.5Hz), 126.1 (t, C4, J = 25.6Hz), 125.9 (t, C3,5, J = 26.3 Hz); MS m/z (%) 100 (100), 84 (81).

Pyridine N-oxide-3,4,5-d_3 (2-3,4,5-d_3). Pyridine N-oxide-d_5 (**2-2,3,4,5,6-d_5**) (0.96g, 9.6 mmol) was dissolved in 10% aqueous sodium carbonate (120 mL) and heated at reflux for 12 hours. The resulting solution was extracted with dichloromethane (5 x 10 mL). The organic extract was dried (sodium sulfate) and concentrated to dryness to give **2-3,4,5-d_3** as a liquid which solidified upon standing in a desiccator to provide a white solid: yield 0.48 g (4.9 mmol, 51%); ^{13}CNMR (deuterium oxide) δ 139.2 (s, C2,6), 132.5 (t, C4, J = 26.0 Hz), 127.3 (t, C3,5, J = 25.9 Hz).

3,4,5-Trideuteriopyridine (1-3,4,5-d_3).A solution of pyridine N-oxide-3,4,5-d_3 (**2-3,4,5-d_3**) (0.48g, 4.9 mmol) in dichloromethane (40 mL) was added dropwise to phosphorous trichloride (1.0 mL) at 0˚C. The resulting solution was heated at reflux for 1 hour, poured onto ice (20 g), and made basic with 10N aqueous sodium hydroxide. The aqueous phase was extracted with dichloromethane (3 x 10 mL). The organic extract was dried (sodium sulfate) and concentrated. The residual oil was purified by distillation (Kugelrohr, 95˚C, water aspirator) to give 3,4,5-trideuteriopyridine (**1-3,4,5-d_3**) as a colorless liquid: yield 0.18g (2.2 mmol, 45%); MS m/z (%) 82 (100), 55 (90). The ^{1}H and ^{13}C-NMR data are given in Tables 1 and 2.

Synthesis of 2,3,4-Trideuteriopyridine (1-2,3,4-d_3), 2,3,6-Trideuteriopyridine (1-2,3,6-d_3) and 2,4,5-Trideuteriopyridine (1-2,4,5-d_3).

3-Chloropyridine N-oxide (4). 3-Chloropyridine (**3**) (2.0 g, 17.6 mmol), glacial acetic acid (10.8 mL) and hydrogen peroxide (3.6 mL, 30%) were heated at 80˚C for 10 hours. The resulting solution was concentrated and the liquid residue was made basic with solid potassium carbonate and then shaken with chloroform (50 mL). The solid material was removed by filtration and the filtrate was dried (sodium sulfate) and concentrated to give **4** as a light yellow solid: yield 1.69g (13.0 mmol, 74%); mp; 54-55˚C; ^{1}H-NMR (deutriochloroform) δ (DEPT-135) 139.2(+), 138.2 (+), 133.8(0), 126.9(+), 126.3(+); MS m/z (%) 131 (27), 129 (100), 115 (33), 113 (95).

3-Chloropyridine N-oxide-2,4,5,6-d_4 (4-2,4,5,6-d_4). A solution of 3-chloropyridine N-oxide (**4**), (1.69 g, 13.0 mmol) and potassium carbonate (1.0 g) dissolved in deuterium oxide (10 mL) was heated in an autoclave at 190˚C for 5 hours. The resulting solution was concentrated, re-dissolved in deuterium oxide (10 ml) and heated again in an autoclave for an additional 5 hours. The resulting solution was extracted with dichloromethane (5 x 20 mL). The organic extract was dried (sodium sulfate) and concentrated to give **4-2,4,5,6-d_4** as a yellow solid: yield 0.8 g (6.0 mmol, 46%); mp 52-54˚C; ^{13}C-NMR (deuteriochloroform) δ 138.9 (t, C2, J = 30.2 Hz), 137.9 (t, C6, J = 28.9 Hz), 133.6 (s, C3), 126.1 (t, C5, J = 26.9 Hz), 125,8 (t, C4, 25.8 Hz); MS m/z(%) 135(33), 133 (100), 119 (19), 117 (61).

2,3-Dichloropyridine-4,5,6-d_3(5-4,5,6-d_3), 3,4-dichloropyridine-2,5,6-d_3 (6-2,5,6-d_3), 2,5-dichloropyridine-3,4,6-d_3 (7-3,4,6-d_3), and 3,5-dichloropyridine-2,4,6-d_3 (8-2,4,6-d_3). A mixture of 3-chloropyridine N-oxide-2,4,5,6-d_4 (**4-2,4,5,6-d_4**) (2.20g, 16.5 mmol) and phosphorus oxychloride (16.5 mL) was heated at 120˚ C for 2 hours. The resulting solution was concentrated by distillation to give a brown liquid which was mixed with ice (10 g) and made basic with saturated aqueous potassium carbonate and extracted with dichloromethane (10 x 20 mL). The organic extract was dried (sodium sulfate) and concentrated. The resulting brown liquid residue (1.90 g) was subjected to column chromatography (silica gel). Elution with hexane (10%) – dichloromethane (90%) gave four fractions.

Fraction one gave 2,5-dichloropyridine – 3,4,6-d_3 (**7-3,4,6-d_3**) as a white solid: yield 0.34 g (2.3 mmol, 13.7%); ^{13}C-NMR (deuteriochloroform) δ 149.7 (s, C2), 148.5 (t, C6, J = 28.8 Hz), 138.5 (t, C4, J = 26.1 Hz), 131.1 (s, C5), 125.2 (t, C3, J = 26.4

Hz); MS m/z (%) 154(10), 152 (54), 150 (100), 117 (25), 115 (79).

Fraction two gave 2,3-dichloropyridine – 4,5,6-d_3 (**5-4,5,6-d_3**) as a white solid: yield 0.62 g (4.1 mmol, 25%); ^{13}C-NMR (deuteriochloroform) δ 149.6 (s, C2), 147.3 (t, C6, J = 28.1 Hz), 138.8 (t, C4, J = 25.9 Hz), 131.0 (s, C3), 123.1 (t, C5, J = 25.5 Hz); MS m/z (%) 154 (11), 152 (59), 150 (96), 117 (31), 115 (100).

Fraction three gave 3,5-dichloropyridine-2,4,6-d_3 (**8-2,4,6-d_3**) as a white solid: yield 0.07g (0.5 mmol, 2.8 %); ^{13}C-NMR (deuteriochloroform) δ 146.8 (t, C2, 6, J = 29.2Hz), 135.7 (t, C4, J = 26.3 Hz), 132.4 (s, C3, 5); MS m/z (%) 154 (10), 152 (66), 150 (100), 117 (19), 115 (61).

Fraction four gave 3,4-dichloropyridine-2,5,6-d_2 (**6-2,5,6-d_3**) as a yellow liquid: yield 0.20 g (1.3 mmol, 8%; ^{13}C-NMR (deuteriocloroform) δ 150.4 (t, C2, J = 29.2 Hz), 148.2 (t, C6, J = 28.0 Hz), 142.3 (s, C4), 131.3 (s, C3), 125.2 (t, C5, J = 26.5 Hz); MS m/z (%) 150 (10), 152 (64), 150 (100), 117 (20), 115 (67).

2,3,4-Trideuteriopyridine (1-2,3,4-d_3). 2,3-Dichloropyridine – 4,5,6-d_3 (**5-4,5,6-d_3**) (0.37 g, 2.5 mmol), Pd-C (10%, 0.2 g), potassium carbonate (0.6 g), and methanol (15 ml) were sealed with a septum in a Büchner flask equipped with a magnetic stirring bar and a balloon secured on the sidearm. The flask was purged with nitrogen and charged with sufficient hydrogen gas to inflate the balloon. After stirring at room temperature for 4 hours the flask was unsealed and the catalyst was removed by filtration. The filtrate was acidified with conc hydrochloric acid and then concentrated to give a wet solid. This was made alkaline with saturated aqueous potassium carbonate, extracted with dichloromethane (5 x 20 ml), and the organic extract dried (sodium sulfate). The solvent was removed by fractional distillation (Vigreux column) and the residue purified by distillation (Kugelrohr) to give 2,3,4-trideuteriopyridine (**1-2,3,4-d_3**) as a colorless liquid; yield 0.11g (1.3 mmol, 52%); MS m/z (%) 82 (100), 55 (45), 54 (59). The ^{1}H and ^{13}C-NMR data are given in Tables 1 and 2.

2,4,5-Trideuteriopyridine (1-2,4,5-d_3). 2,5-Dichloropyridine-3,4,6-d_3 (**7-3,4,6-d_3**) (0.41 g, 2.7 mmol) was treated as above to give 2,4,5-trideuteriopyridine (**1-2,4,5-d_3**) as a colorless liquid: yield 0.12g (1.5 mmol, 55.5%); MS m/z (%) 82 (100), 55 (43), 54 (59). The ^{1}H and ^{13}C-NMR data are given in Tables 1 and 2.

2,3,6-Trideuteriopyridine (1-2,3,6-d_3). 3,4-Dichloropyridine -2,5,6-d_3 (**6-2,5,6-d_3**) (0.27 g, 1.8 mmol) was treated as above to give 2,3,6-trideuteriopyridine (**1-2,3,6-d_3**) as a colorless liquid: yield 0.08 g (1.0 mmol, 54.2 %); MS m/z (%) 82 (100), 55 (33), 54 (70). The ^{1}H and ^{13}C-NMR data are given in Tables 1 and 2.

Synthesis of 2,3,5-Trideuteriopyridine (1-2, 3, 5-d_3).

4-Nitropyridine N-oxide-2,3,5,6-d_4 (9-2,3,5,6-d_4). A mixture of pyridine N-oxide-d_5 (**2-2,3,4,5,6-d_5**) (2.74 g, 27.4 mmol), conc sulfuric acid (10.0 mL), and fuming nitric acid (5.0 mL) was heated at 130° C for 5 hours. The resulting mixture was poured onto ice (100 g) and made basic with saturated aqueous sodium carbonate solution. The precipitate was removed by filtration and the filtrate was extracted with dichloromethane (8 x 20 mL). The extract was dried (sodium sulfate) and evaporated to give 4-nitropyridine N-oxide-2,3,5,6-d_4 (**9-2,3,5,6-d_4**) as a yellow solid that was recrystallized from acetone to yield a yellow crystalline solid: yield 2.47 g (17.1 mmol, 62.4%); ^{13}C-NMR (deuteriochloroform) δ 142.7 (s, C4), 140.5 (t, C2, 6, J = 29.8 Hz), 121.2 (t, C3, 5, J = 26.7 Hz); MS m/z (%) 144 (53), 128 (40), 114 (43).

4-Chloropyridine N-oxide-2,3,5,6-d_4 (10-2,3,5,6-d_4). Acetyl chloride (11.0 mL) was added to 4-nitropyridine N-oxide-2,3,5,6-d_4 (**10-2,3,5,6-d_4**) (2.12 g, 14.7 mmol) which was warmed to 50°C in a water bath. The resulting mixture was refluxed for approximately 30 minutes until a white solid formed. The excess acetyl chloride was removed under reduced pressure and the white solid residue was mixed with crushed ice (50 g), made basic with saturated aqueous sodium carbonate, and extracted with dichloromethane (8 x 20 mL). The extract was dried (sodium sulfate) and concentrated to give **10-2,3,5-6-d_4** as a white solid which was recrystallized from acetone to yield white crystals: yield 1.84 g (13.7 mmol, 93.2%); ^{13}C-NMR (acetone-d_6) δ 1.40.1 (t, C2,6, J = 28.8 Hz), 132.0 (s, C4), 126.7 (t, C3,5, J = 26.2 Hz); MS m/z (%) 135 (30), 133 (100), 117 (64), 82 (59).

2,4-Dichloropyridine-3,5,6-d_3 (12-3,5,6-d_3). A mixture of 4-chloropyridine N-oxide-d_4 (**10-2,3,5,6-d_4**) (1.7g, 12.7 mmol) and phosphorous oxychloride (13 mL) was heated at 110° for 2 hours. The excess phosphorous oxychloride was removed under reduced pressure and the yellow residue was mixed with crushed ice (3 g), made basic with saturated aqueous sodium carbonate, and extracted with dichloromethane (8 x 20 ml). The extract was dried (sodium sulfate) and concentrated to give a red liquid which was subjected to preparative layer chromatography (silica gel), 9:1 dichloromethane-hexane to give **12-3,5,6-d_3** as a colorless liquid: yield 0.90 g (6.0 mmol, 47.2%); ^{13}C-NMR (deuteriochloroform) δ 152.6 (s, C6), 150.2 (t, C2, J = 28.2 Hz), 146.1 (s, C4), 124.6 (t, C3, J = 26.8 Hz), 123.0 (t, C5, J = 26.2 Hz); MS m/z (%) 154 (8), 152 (59), 150 (59), 150 (91), 117 (33), 115 (100), 78 (41).

2,3,5-Trideuteriopyridine (1-2,3,5-d_3). 2,4-Dichloropyridine-3,5,6-d_3, (**12-3,5,6-d_3**), (0.40 g, 2.6 mmol) was subjected to catalytic hydrogenolysis as described for 2,3-dichloropyridine-4,5,6-d_3 (**5-4,5,6-d_3**) to give 2,3,5-trideuteriopyridine (**1-2,3,5-d_3**) as a colorless liquid: yield 0.16 g (2.1 mmol, 77%); MS m/z (%) 82 (100), 55 (48), 54 (66). The ^{1}H and ^{13}C-NMR data are given in Tables 1 and 2.

Synthesis of 2,4,6-Trideuteriopyridine (1-2,4,6-d_3).

Pyridine N-oxide-2,6-d_2 (2-2,6-d_2). A solution of pyridine N-oxide **(2)** (2.0 g, 21 mmol) in deuterium oxide (20 ml) containing sodium carbonate (3.0 g) was heated at reflux for 12 hours, cooled to room temperature, and extracted with dichloromethane (10 x 20 mL). The extract was dried (sodium sulfate) and concentrated and the white solid was dried in a vacuum desiccator to yield **2-2,6-d_2**) as a white solid: 1.65 g (17 mol, 81.0%); ^{1}H-NMR (deuterium oxide) δ 7.41 (m, 1H), 7.22 (m, 2H); ^{13}C-NMR (deuterium oxide) (DEPT-135) δ135.9 (0) (t, C2, 6, J = 28.3), 132.9 (+) (s, C4), 127.5 (+) (s, C3, 5); MS m/z (%) 98 (64), 97 (100), 82 (73), 81 (100).

4-Nitropyridine N-oxide-2,6-d_2 (9-2,6-d_2). A mixture of pyridine N-oxide-2,6-d_2 (**2-2,6-d_2**) (1.80 g, 18 mmol), conc sulfuric acid (4 mL), and fuming nitric acid (2 mL) was heated at 130°C for 5 hours. The resulting mixture was poured onto ice (20 g), made basic with saturated aqueous sodium carbonate solution, and extracted with dichloromethane (5 x 20 mL). The extract was dried (sodium sulfate) and evaporated to give 4-nitropyridine N-oxide- 2,6-d_2 (**9-2,6-d_2**) which was recrystallized from acetone to give lustrous yellow crystals: yield 1.58 g (11 mmol, 61.1 %); ^{1}H-NMR (deuteriochloroform) δ 8.41 (S, 2H); ^{13}C-NMR (deuteriochloroform) (DEPT-135) δ 142.2 (0)) (s,

C4), 139.9 (0) (t, C2,6, J = 29.0 Hz), 120.8 (+) (s, C3,5); MS m/z (%) 142 (34), 126 (78).

4-Chloropyridine N-oxide-2,6-d_2 (10-2,6-d_2). Acetyl chloride (5.0 mL) was added to 4-nitropyridine N-oxide-2,6-d_2 (**9-2,6-d_2**) (1.0 g, 7.0 mmol) which was warmed to 50°C in a water bath. The resulting mixture was refluxed for approximately 30 minutes until a yellow solid appeared. The resulting solid was cooled in an ice bath and mixed with cold water. After the vigorous reaction stopped, the solution was made basic with saturated aqueous sodium bicarbonate and extracted with dichloromethane (7 x 20 mL). The extract was dried (sodium sulfate) and concentrated to give **10-2,6-d_2** as a white solid: yield 0.75 g (5.7 mmol, 81%) ^{1}H-NMR (deuteriochloroform) δ 7.21 (s, 2H; ^{13}C-NMR (deuteriochloroform) (DEPT 135) δ 140.2 (0) (t, C2, 6, J = 28, 5 Hz), 132.3 (0) (s, C4), 126.7 (+) (s, C3, 5); MS m/z (%) 131 (26), 115 (100).

2,4,6-Trideuteriopyridine (1-2,4,6-d_3). 4-Chloropyridine-2,6-d_2 (**10-2,6-d_2**) (0.12 g, 1.1 mmol) dissolved in ether (20 mL), Pd-C (10%, 0.07 g), potassium carbonate (0.3 g) and a magnetic stirring bar were sealed with a septum in a 50 mL Büchner flask fitted with a balloon secured on the sidearm. The flask was purged with nitrogen and charged with sufficient deuterium gas to inflate the balloon. After stirring at room temperature for 4 hours the flask was unsealed and the catalyst was removed by filtration. The filtrate was concentrated and the residue was purified by distillation (Kugelrohr, 100°C, waster aspirator) to give 2, 4, 6-trideuteriopyridine (**1-2,4,6-d_3**) as a colorless liquid: yield 0.042 g (0.51 mmol, 46.8%), MS m/z (%) 82 (100), 54 (56). The ^{1}H and ^{13}C-NMR data are given in Tables 1 and 2.

Synthesis of 2,3,4,5-Tetradeuteriopyridine (1-2,3,4,5-d_4).

2-Chloropyridine-3,4,5,6-d_4 (13-3,4,5,6,-d_4). A mixture of pyridine N-oxide-d_5 (**2-2,3,4,5,6-d_5**) (1.33 g, 13.0 mmol) and phosphorous oxychloride (11.0 mL) was heated at 120° for 3 hours. The resulting solution was concentrated by distillation. The viscous residue was dissolved in ice water, made strongly alkaline with aqueous ammonia and the resulting red solution extracted with dichloromethane (5 x 20 mL). The organic extract was dried (sodium sulfate) and concentrated. The resulting red liquid was subjected to column chromatography (silica gel). Elution with dichloromethane gave **13-3,4,5,6-d_4** as a colorless liquid: yield 0.44 g (3.7 mmol, 28%); ^{13}C-NMR (deuteriochloroform) δ 151.5 (s, C2), 149.4 (t, C6, J = 28.1 Hz), 138.2 (t, C4, J = 25.2 Hz), 124.1 (t, C3, J = 26.6 Hz), 121.7 (t, C5, J = 25.4 Hz); MS m/z (%) 119 (25), 117 (79), 116 (7), 82 (100).

2,3,4,5-Tetradeuteriopyridine (1-2,3,4,5-d_4). 2-Chloropyridine (**13-3,4,5,6-d_4**) (0.44 g, 3.7 mmol), Pd-C (10%, 0.1 g), potassium carbonate (0.6 g) and methanol (10 mL) were sealed with a septum in a Büchner flask equipped with a magnetic stirring bar and a balloon secured in the sidearm. The flask was purged with nitrogen and charged with sufficient hydrogen gas to inflate the balloon. After stirring at room temperature for 4 hours it was unsealed and the catalyst removed by filtration. The filtrate was acidified with concentrated hydrochloric acid and the solvent was removed by rotary evaporation. The residue was made basic with aqueous potassium carbonate and extracted with dichloromethane (3 x 10 mL). The organic extract was dried (sodium sulfate) and the solvent removed by distillation. The residue was distilled (Kugelrohr) at reduced pressure (water aspirator) to give **1-2,3,4,5-d_4** as a colorless liquid; yield 0.10 g (1.2 mmol, 32.4%); MS m/z (%) 83 (100), 82 (11), 55 (57). The ^{1}H and ^{13}C-NMR data are given in Tables 1 and 2.

Synthesis of 2,3,4,6-Tetradeuteriopyridine (1-2,3,4,6-d_4).

3-Chloropyridine-2,4,5,6-d_4 (14-2,4,5,6-d_4). A solution of 3-chloropyridine N-oxide-2,4,5,6-d_4 (**4-2,4,5,6-d_4**) (0.76 g. 5.7 mmol) in dichloromethane (30 mL) was added dropwise to phosphorous trichloride (0.82 mL) at 0°C. The resulting solution was heated at reflux for 2 hours, poured onto ice (20 g), and made basic with saturated aqueous potassium carbonate. The aqueous phase was extracted with dichloromethane (3 x 10 mL). The organic extract was dried (sodium sulfate) and evaporated to give **14-2,4,5,6-d_4** as a pale yellow liquid: yield 0.60 g (5.1 mmol, 89.5%); ^{13}C-NMR (deuteriochloroform) δ 148.8 (t, C2, J = 28.0 Hz), 147.7 (t, C6, J = 28.7 Hz), 136.0 (t, C4, J = 26.1 Hz), 132.4 (s, C3), 124.3 (t, C5, J = 26.8 Hz); MS m/z (%) 117 (100), 82 (66.3).

2,3,4,6-Tetradeuteriopyridine (1-2,3,4,6-d_4). 3-Chloropyridine-2,4,5,6-d_4 (**14-2,4,5,6-d_4**) (0.30 g, 2.6 mmol), Pd-C (10 %, 0.08 g), potassium carbonate (0.6 g), and methanol (10 mL) were sealed with a septum in a Büchner flask equipped with a magnetic stirring bar and a balloon secured on the sidearm. The flask was purged with nitrogen and then charged with sufficient hydrogen gas to inflate the balloon. After stirring at room temperature for 4 hours the flask was unsealed and the catalyst removed by filtration. The filtrate was acidified with concentrated hydrochloric acid (2 mL) and the methanol was removed by rotary evaporation. The residue was made basic saturated aqueous potassium carbonate and extracted with dichloromethane (3 x 15 mL). The organic extract was dried (sodium sulfate) and concentrated by distillation through a Vigreux column. The residue was distilled (Kugelrohr, 100° C) at reduced pressure (water aspirator) to give **1-2,3,4,6-d_4** as a colorless liquid: yield 0.068g (0.82 mmol, 32%); MS m/z (%) 83 (100), 55 (67). The ^{1}H and ^{13}C NMR data are given in Tables 1 and 2.

Synthesis of 2,3,5,6-Tetradeuteriopyridine (1-2,3,5,6-d_4).

3,5-Dichloropyridine N-oxide (15). Hydrogen peroxide (30%, 17.0 mL) was added to a mixture of 3,5-dichlorpyridine (14) (14.8 g, 100 mmol) and methyltrioxorhenium (VII) (0.050 g, 0.2 mmol) in dichloromethane (40 mL) and allowed to stir for 17 hours. Manganese dioxide (0.025 g) was added to the resulting biphasic mixture and stirring was continued until oxygen evolution stopped (~ 1 hour). The aqueous phase was separated and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (sodium sulfate) and concentrated to give a white solid which was subjected to column chromatography (silica gel). Elution with ethylacetate: dichloromethane (1:1) gave **15** as a white solid, mp 109.110.5° C (lit. [12], 111° C: yield 11.5 g (70 mmol, 70%); ^{1}H-NMR (deuteriochloroform) δ 8.15 (s, 2H), 7.27 (s, 1H); ^{13}C-NMR (deuteriochloroform) δ 137.8 (C2, 6), 133.7 (C3,5), 126.5 (C4); MS m/z % 165 (67), 163 (100), 147 (54).

3,5-Dichloropyridine N-oxide-2,4,6-d_3 (15-2,4,6-d_3). A solution of 3,5-dichloropyridine N-oxide (15) (1.0 g, 6.1 mmol) and potassium carbonate (1.0 g) in deuterium oxide (10 mL) was heated at 100° C for 8 hours. Cooling of the resulting solution gave **15-2,4,6-d_3** as white needles that were collected by filtration. The filtrate was extracted with dichloromethane (3 x 10 mL). The organic extract was dried (sodium sulfate) and concentrated to additional **15-2, 4, 6, d_3** as white crystals. The total yield, 0.84 g (5.0 mmol, 82%); ^{13}C-NMR (deuteriochloroform) δ 137.6 (t, C26, J = 29.6 Hz), 133.5 (s, C3,5), 126.4

(t, C4, J = 27.2 Hz); MS m/z (%) 168 (47), 166 (74), 152 (68), 150 (100), 115 (62).

3,5-Dichloropyridine-2,4,6-d_3 (14-2,4,6-d_3). A solution of 3,5-dichloropyridine N-oxide-2,4,6-d_3 (**15-2,4,6-d_3**) (0.83 g, 5.0 mmol) in dichloromethane (30 mL) was added dropwise to phosphorous trichloride (0.64 mL) at 0° C. The resulting solution was heated at reflux for one hour, poured onto ice (15 g), and made basic with saturated aqueous potassium carbonate and extracted with dichloromethane (3 x 10 mL). The organic extract was dried (sodium sulfate) and concentrated to give **14-2,4,6-d_3** as a white solid: yield 0.69 g (4.6 mmol, 92%); ^{13}C-NMR (deuteriochloroform) δ 146.7 (t, C2,6, J = 29.1 Hz), 135.8 (t, C4, J = 26.5 Hz), 132.4 (s, C3,5); MS m/z (%) 152 (64), 150 (100), 117 (17), 115 (53).

3,5-Dichloropyridine-2,6-d_2 (14-2,6-d_2). A solution of 3,5-dichloropyridine-2,4,6-d_3 (**14-2,4,6-d_3**) (0.59 g, 3.9 mmol) in methanol (17 mL) containing sodium methoxide (1.5 *M*) was stirred for 24 hours in a water bath maintained at room temperature. The resulting solution was concentrated, mixed with water (10 mL), and extracted with dichloromethane (5 x 10 mL). The organic extract was dried (sodium sulfate) and the solvent removed to give **14-2,6-d_2** as a white solid: yield 0.33 g (2.2 mmol, 56%); ^{1}H-NMR (deuteriochloroform) δ 7.71 (s); ^{13}C-NMR 146.8 (t, C2,6 J = 29.3 Hz); 136.0 (s, C4), 132.5 (s, C3,5); MS m/z (%) 151 (63), 149 (100), 114 (58).

2,3,5,6-Tetradeuteriopyridine (1-2,3,5,6-d_4). 3,5-Dichloro-pyridine-2,6,-d_2 (**14-2,6-d_2**) (0.30 g, 2.0 mmol). Pd-C (10%, 0.3 g), potassium carbonate (0.6 g), and methanol-d (10 mL) were sealed with a septum in a Büchner flask equipped with a magnetic stirrer and a balloon secured on the sidearm. The flask was purged with nitrogen and charged with sufficient deuterium gas to inflate the balloon. After stirring at room temperature for 4 hours the flask was unsealed and the catalyst removed by filtration. The filtrate was acidified with concentrated hydro chloric acid (2.0 mL) concentrated, and made basic with saturated aqueous potassium carbonate. The aqueous solution was extracted with dichloromethane (5 x 20 mL), the organic extract was dried (sodium sulfate), and concentrated by fractional distillation (Vigreux column). The liquid residue was distilled (Kugelrohr, 100° C, water aspirator) to give **1-2,3,5-6** as a olorless liquid: yield 0.079 g (1.0 mmol, 50%). The ^{1}H and ^{13}C-NMR data are given in Tables 1 and 2.

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