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RAPID, REGIOSPECIFIC SYNTHESES OF DEUTERIUM SUBSTITUTED 6-[^{18}F]FLUORODOPAMINE (α,α-D_2; β,β-D_2 and $\alpha,\alpha,\beta,\beta$-$D_4$) FOR MECHANISTIC STUDIES WITH POSITRON EMISSION TOMOGRAPHY

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SUMMARY

Doubly labeled (^{18}F and deuterium) 6-fluorodopamine (6-FDA) isotopomers were prepared to probe the contribution of metabolism by monoamine oxidase (MAO) and dopamine β-hydroxylase (DBH) on the kinetics of 6-[^{18}F]FDA in baboon heart. Specifically deuterated 6-[^{18}F]FDA-α,α-D_2 and 6-[^{18}F]FDA-β,β-D_2 were prepared by a six-step synthesis starting from nucleophilic aromatic substitution with NCA [^{18}F]fluoride on 6-nitropiperonal or 6-nitropiperonal-D in a decay corrected radiochemical yield of 3-10% (EOB). 6-[^{18}F]FDA-$\alpha,\alpha,\beta,\beta$-$D_4$ was prepared in 4 steps in a radiochemical yield of 16-20% (EOB) and specific activity 2-5 Ci/μmol (EOB). The regiospecificity of deuterium substitution in the synthesis of 6-[^{18}F]FDA-$\alpha,\alpha,\beta,\beta$-$D_4$ was verified using piperonal as a substrate.

Key words: 6-fluorodopamine, 6-fluoronorepinephrine, fluorine-18, deuterium isotope effect, PET, heart, MAO, DBH.

INTRODUCTION

We have developed the first route to no-carrier-added F-18 labeled catecholamines and have initiated mechanistic studies with a view to using these labeled compounds to assess neuronal activity in the heart with PET (positron emission tomography). Specific activities of 2-5 Ci/μmole were obtained making it possible to use these radiotracers in baboons and humans with no hemodynamic effects [1, 2, 3]. Comparative PET studies have provided the first evidence for stereoselective retention of 6-[^{18}F]fluoronorepinephrine (6-[^{18}F]FNE) demonstrating its similarity to norepinephrine [4]. 6-[^{18}F]Fluorodopamine (6-[^{18}F]FDA) has also been proposed as a PET radiotracer for studies of the neuronal activity in the heart based on

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the rationale that, like (-)-NE, it would be transported into the cardiac sympathetic neuron and converted into (-)-6-[^{18}F]FNE within the vesicle by dopamine β-hydroxylase (DBH) [5]. However, 6-[^{18}F]FDA clears more rapidly from heart than (-)-6-[^{18}F]FNE. This observation has stimulated an examination of the biochemical processes responsible for the clearance of 6-[^{18}F]FDA.

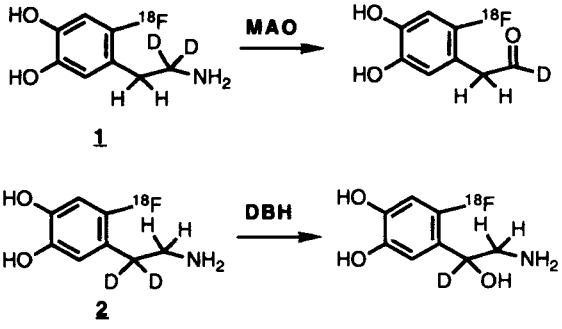
Deuterium isotope effects have been used for many years to assess the contribution of the cleavage of a specific C-H bond on the rate of a chemical or biochemical process [6, 7]. This mechanistic approach has also been applied in PET studies examining the role of monoamine oxidase B (MAO B) in the retention of [^{11}C]L-deprenyl in the living brain. This novel application of kinetic isotope effects demonstrated that the chemical transformation contributing to a PET image could be identified without tissue sampling and without pharmacological intervention [8]. The application of this approach in PET requires the development of synthetic methods which are amenable to the regiospecific introduction of deuterium and to rapid incorporation of a short-lived positron emitting nuclide in the same synthetic scheme.

By analogy with the parent neurotransmitter dopamine, 6-fluorodopamine would be expected to be metabolized by MAO and by DBH after uptake by the cardiac sympathetic neuron. MAO catalyzes the cleavage of the C-H bond alpha to the amino group [9] and DBH cleaves the benzylic C-H bond catalyzing the formation of (-)-norepinephrine [10, 11]. Since these two enzymes cleave different C-H bonds, the use of specific deuterium substituted tracers offers the potential for probing their contribution in the observed clearance of F-18 from the heart after the injection of 6-[^{18}F]FDA. We report here the preparation of 6-[^{18}F]FDA-α,α-D_2 **1** and 6-[^{18}F]FDA-β,β-D_2 **2**, for mechanistic PET studies via a six-step synthesis starting from nucleophilic aromatic substitution with NCA [^{18}F]fluoride. We have also synthesized 6-[^{18}F]FDA-α,α,β,β,-D_4 (**3**) in a 4-step synthesis for comparison with **1** and **2**. The regiospecificity of deuterium substitution in the synthesis of **3** was confirmed by carrying out the synthetic sequences using piperonal as a substrate.

RESULTS AND DISCUSSION

We have reported a four-step synthesis for the preparation of high specific activity 6-[^{18}F]FDA [2]. After the nucleophilic aromatic substitution with NCA [^{18}F]fluoride, the side chain was constructed by the condensation of aldehyde with nitromethane. This strategy has been used to prepare various doubly labeled (^{18}F, deuterium) 6-FDA radiotracers to assess the contribution of MAO and DBH to the behavior of 6-[18F]FDA in the heart. For example, our model studies with piperonal shown in Scheme **4** suggest that 6-[^{18}F]FDA with α,β-D_2, α-D_1 or α,α,β-D_3 can be prepared when 6-nitropiperonal is used as precursor. Similarly, α,β,β-D_3, β-D_1, α,α,β,β-D_4-6-[^{18}F]FDA can also be obtained if deuterated 6-nitropiperonal **8** is used as precursor. However, since there are two important enzymes (MAO and DBH) involved in metabolism of 6-FDA, deuterium atoms at both α and β positions would complicate the interpretation of kinetic differences arising from deuterium substitution.

Scheme 1. Specifically deuterated 6-[^{18}F]FDA derivatives for probing the contribution of MAO and DBH to the kinetic patterns in the heart.



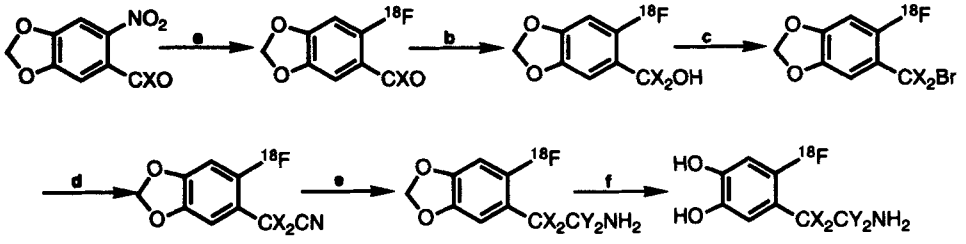
1

2

Moreover, it has been shown that both MAO and DBH stereoselectively remove only the pro-R hydrogen [12, 13, 14, 15]. Thus, two deuterium atoms at one carbon are essential since the preparation of only the R-deuterium isotopomer by an enzymatic method [15] is not practical for multiple-step synthesis with a short lived nuclide such as ^{18}F. Specifically deuterated 6-[^{18}F]FDA-α,α-D_2 (1) and 6-[^{18}F]FDA-β,β-D_2 (2) are therefore the most appropriate candidates for unambiguously assessing the contribution of metabolism by MAO and DBH on the kinetics of 6-[^{18}F]FDA.

The synthetic paths for 6-[^{18}F]FDA-α,α-D_2 (1) and 6-[^{18}F]FDA-β,β-D_2 (2) are summarized in Scheme 2. The six-step sequences are the same for both compounds except for the reversal of the order for the two reductions with lithium aluminum hydride ($LiAlH_4$) and lithium alumium deuteride ($LiAlD_4$). The synthesis of 2 utilized deuterated 6-nitropiperonal (8) as starting material, which was prepared by the route shown in Scheme 5.

Scheme 2: Synthesis of 6-[^{18}F]FDA-α,α-D_2 (1) and 6-[^{18}F]6FDA-β,β-D_2 (2).

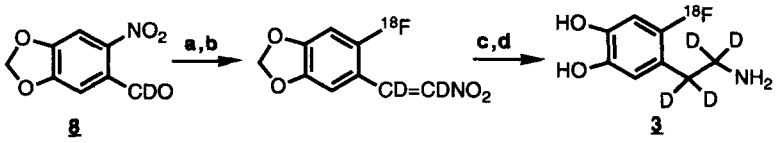


1 X=H, Y=D
2 X=D, Y=H

For 1: (a). $^{18}F^-$; (b). $LiAlH_4$; (c). $SOBr_2$; (d). CN^-; (e). $LiAlD_4$; (f). HI
For 2: (a). $^{18}F^-$; (b). $LiAlD_4$; (c). $SOBr_2$; (d). CN^-; (e). $LiAlH_4$; (f). HI

In our hands, the crucial step of this six-step synthetic pathway was the displacement of bromide with cyanide (Scheme 2). The progress of the reaction was monitored by radio-TLC (silica, 5:16 ethyl acetate:hexane; 6-[^{18}F]fluoropiperonyl bromide R_F=0.78, 6-[^{18}F]fluoropiperonyl acetonitrile R_F=0.52). Many trials with

Scheme 3: Synthesis of 6-[^{18}F]FDA-α,α,β,β-D_4 (3).

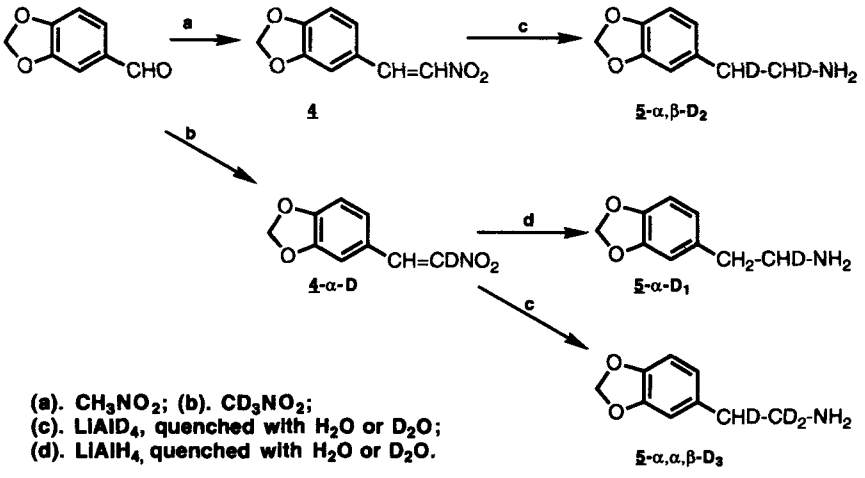


8 3

(a). $^{18}F^-$; (b). CD_3NO_2; (c). $LiAlD_4$; (d). HI

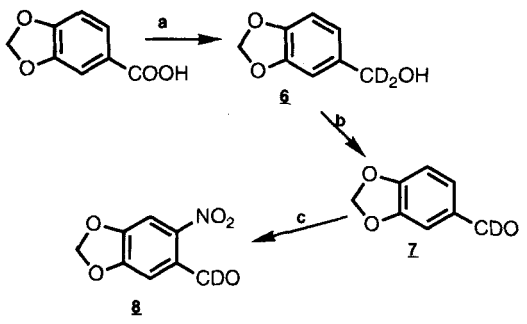
potassium cyanide in different solvent systems such as DMSO, DMF and CH_3CN gave variable and irreproducible yields. The main problems appeared to the poor solubility of the cyanide reagent and competing product decomposition when heating. KCN was more soluble in DMSO then in either DMF or CH_3CN, though still not homogeneous after heating to 90°C for 10 min. However, product decomposition was more rapid in DMSO upon heating for 20 min at 75°C, as compared to that in CH_3CN and DMF. The presence of the phase transfer reagent Kryptofix 222 did not facilitate product formation. An attempt to convert the alcohol to the nitrile in one step [16] by treatment with NaCN/Me_3SiCl and a catalytic amount of NaI in DMF/CH_3CN (1:1) was not successful. However, we found lithium cyanide to be an effective reagent for the conversion of benzylic bromides to the corresponding nitriles. Lithium cyanide is soluble in many organic solvents [17]. The use of lithium cyanide in DMF (0.5 M, commercially available) gave 30-35% yields for the displacement of bromide with cyanide with slow decomposition after prolonged heating. However, a freshly prepared solution of lithium cyanide in anhydrous THF (0.5M) gave a much cleaner reaction (70% yield in a reaction time of 12 min at 60°C according to radio-TLC) and no significant decomposition occurred while heating. The rest of the synthesis (the two reductions, bromination and hydrolysis) usually gave quantitative yields and the first

Scheme 4: Chemical verification of deuterium substitution.



(a). CH_3NO_2; (b). CD_3NO_2;
(c). $LiAlD_4$, quenched with H_2O or D_2O;
(d). $LiAlH_4$, quenched with H_2O or D_2O.

Scheme 5: Synthesis of deuterated 6-nitropiperonal



(a). $LiAlD_4$; (b). PDC; (c). HNO_3

step (fluorination) gave 60%-70% yields. The C_{18} sep-pak purification after cyanation which removed excess LiCN and the use of a silica sep-pak after the second reduction to remove any unreacted intermediates that were not amines, were required in order to obtain a pure product. The overall radiochemical yield was 3-10% (EOB) in a total synthesis time 150 min and the specific activity was 2 Ci/μmol (EOB).

The preparation of 6-[^{18}F]FDA-α,α,β,β-D_4 **3** followed a procedure similar to that described for 6-[^{18}F]FDA [2] except for the substitution of deuterated 6-nitropiperonal **8** as precursor, and the use of CD_3NO_2 and $LiAlD_4$ as reagents (Scheme 3). The chemical verifications of deuterium substitution under the reaction conditions were supported by the model reactions described in Scheme 4. The reaction of the nitroethylenes (**4** or **4-a-D**) with $LiAlD_4$ resulted in deuterium substitution on both α and β carbons upon quenching the reaction with either H_2O or D_2O. The radiochemical yield for the four-step radiosynthesis was 16-20% (EOB) in a total synthesis time of 110 min and the specific activity of **3** was 2-5 Ci/μmol (EOB). The higher radiochemical yield and relatively shorter synthesis time make **3** a more promising candidate as compared to **2**, if metabolism by MAO plays a key role in the rapid clearance of 6-[^{18}F]FDA, and if the isotope effect from the deuterium substitution at the β position is negligible.

We are currently using PET to study the behavior of these deuterium substituted tracers in baboon heart as a means of probing clearance mechanisms for 6-[^{18}F]FDA. In addition to providing mechanistic information, deuterium substitution will be examined as a means of changing radiotracer specificity by controlling the rate of metabolism in vivo. The results of these studies will be reported elsewhere.

EXPERIMENTAL

6-Nitropiperonal, piperonylic acid, $LiAlH_4$, $LiAlD_4$ (98 atom % D), thionyl bromide, and HI were obtained from Aldrich Chemical Co.. Lithium cyanide was purchased from Alfa. [^{18}F]Fluoride ion was made by 17.4 Mev proton irridiation of [^{18}O]H_2O in a silver target. ^{1}H NMR spectra were obtained in $CDCl_3$ on a Bruker 300

MHz NMR spectrometer and are reported in parts per million downfield from tetramethylsilane. Mass spectra were recorded with a Finnegan-Mat GC-MS 5100 mass spectrometer using electron impact ionization at 70 eV. HPLC analyses were carried out with a Perkin-Elmer liquid chromatograph equipped with a radioactivity monitor and detector.

Synthesis of 6-[^{18}F]FDA-α,α-D_2 1 (*or 6-[^{18}F]FDA-β,β-D_2 2*)

Excepting those portions indicated specifically for compound **2** (in bold italic), the procedures for preparation of compound **1** and **2** are the same.

To an azeotropically dried residue of NCA [^{18}F]fluoride ion, K_2CO_3 (4 mg) and Krytofix 222 (20mg) was added a solution of 6-nitropiperonal (***or deuterated 6-nitropiperonal 8***) (12 mg) in DMSO (0.3 mL). The mixture was heated at 120-125° for 10 min in a 10 cc silicone-coated tube (Vacutainer). The reaction mixture was cooled to room temperature, treated with anhydrous ether (0.2 mL) and $LiAlH_4$ (1M in ether, 0.5 mL) and then stirred at room temperature for 5 min. (***or treated with anhydrous ether (0.7 mL), $LiAlD_4$ (21 mg) and then stirred at room temperature for 3 min and refluxed at 60 °C for 3 min***). The resulting mixture was quenched with H_2O (0.4 mL) and extracted with ether (2 x 4 mL). The ethereal extracts were dried by passing through K_2CO_3 drying tubes and collected in a test tube. To the residue, after concentration to 1 mL in a warm water bath with a N_2 stream, was added pyridine (50 μL), thionyl bromide (60 μL) and then stirred at room temperature for 5 min. The mixture was diluted with H_2O (4 mL) and extracted with CH_2Cl_2 (2 x 4 mL). The CH_2Cl_2 extracts were dried (K_2CO_3) and collected in a test tube. After concentration, the residue was taken up in a solution of LiCN (17 mg) in THF(0.9 mL) (prepared by vortexing for 5 min) and refluxed at 60°C for 12 min. The resulting mixture was diluted with H_2O (2 x 5 mL) and passed through a C_{18} sep-pak. C_{18} sep-pak was rinsed with pentane (4 mL) and CH_2Cl_2 (4 mL). The rinse solutions were dried (K_2CO_3) and collected in a test tube. After evaporation of the solvent , the residue was treated with anhydrous ether (0.7 mL), $LiAlD_4$(21 mg) at 0°C (***or anhydrous ether (0.2 mL) and $LiAlH_4$(1 M in ether, 0.5 mL)***) and then refluxed at 60°C for 10 min. The reaction mixture was quenched with H_2O (0.4 mL) at 0°C and extracted with ether (2 x 4mL). The ethereal extracts were passed through a silica sep-pak, and the sep-pak was washed with a mixture of CH_3CN/H_2O/HOAc (5/4/1). The mixture was evaporated at 140°C. The residue was treated with HI (1 mL), H_3PO_2(3 drops) and then refluxed at 170°C for 7 min. The crude final product which was evaporated to dryness was taken up in 1.4 mL of HPLC solvent and injected onto a semipreparative HPLC column for purification. Conditions: Phenomenex ODS1, 5 μ, 25 x 1.0 cm column; mobile phase 20% methanol in 27.5 mM citric acid, pH 2.9, 2.0 mL/min. Deuterated 6-[^{18}F]FDA eluted at 14-16 min. After removal of the solvent by rotary evaporation, the final product **1** (or **2**) was formulated in saline containing 4 drops of 4.2% $NaHCO_3$ for intravascular injection. The specific activity (2 Ci/μmol at EOB) and radiochemical purity (99%) were indicated by analytical radio-HPLC (Phenomenex ODS1, 5 μ, 25 x 0.46 cm, UV 254 nm) using the same

solvent as described above. Deuterated 6-[^{18}F]FDA eluted at 8 min at the flow of 1.0 mL/min.

Synthesis of 6-[^{18}F]FDA-$\alpha,\alpha,\beta,\beta$-$D_4$ 3

The procedure of the nucleophilic aromatic substitution with $^{18}F^-$ was identical to that described for 1. After heating at 120-125°C for 10 min, the resulting mixture was diluted with H_2O (3 mL) and extracted with CH_2Cl_2 (2 x 4 mL). The extracts were dried (K_2CO_3) and collected in a test tube containing ammonium acetate (13 mg). After removal of the solvent, the residue was treated with CD_3NO_2 (0.6 mL), HOAc (0.1 mL) and then refluxed at 100°C for 7 min. The excess CD_3NO_2 was removed *in vacuo* and the residue was diluted with H_2O (4 mL) and extracted with CH_2Cl_2 (2 x 4 mL). The extracts were dried (K_2CO_3) and collected in a test tube. After evaporation of the solvent, ether (0.2 mL) and $LiAlH_4$ (1 M in ether, 0.5 mL) were added at 0°C and the mixture was stirred at room temperature for 5 min, and then refluxed at 60°C for another 5 min. The resulting mixture was quenched with H_2O (0.4 mL) and extracted with ether (2 x 4 mL). The extracts which were concentrated were treated with HI (1 mL), H_3PO_2 (3 drops) and then refluxed at 170°C for 7 min. The purification, product formulation, and assays for specific activity and radiochemical purity were identical to that described for 1.

Reaction of piperonal and nitromethane (or nitromethane-D_3)

A solution of piperonal (456 mg, 3.04 mmol) and ammonium acetate (500 mg) in nitromethane (20 mL) [18] was gently refluxed at 100°C for 5 h. Water was added and the solution was extracted three times with ether. After drying ($MgSO_4$), solvent was removed to give the nitroethylene 4 (440 mg, 75%), crystallized from aqueous ethanol. The preparation of 4-α-D was identical to that described for 4 except for the substitution of nitromethane-D_3 for nitromethane. ^{1}H NMR ($CDCl_3$) of 4: 6.07 (s, 2H), 6.88 (d, J=7.46 Hz, 1H), 7.0 (s, 1H), 7.09 (d, J=7.6 Hz, 1H), 7.48 (d, J=13.5 Hz, 1H), 7.93 (d, J=13.5 Hz, 1H); MS, m/e (rel. intensity): 193 (M^+, 62), 146 (63), 133 (11), 117 (20), 105 (9), 89 (100), 63 (59), 51 (19), 40 (8). ^{1}H NMR ($CDCl_3$) of 4-α-D: 6.07 (s, 2H), 6.88 (d, J=8.0 Hz, 1H), 7.0 (d, J=1.7 Hz, 1H), 7.09 (dd, J=8.0, 1.7 Hz), 1H), 7.92 (br. t, 1H); MS, m/e (rel intensity): 194 (M^+, 62), 147 (92), 134 (12), 118 (17), 106 (11), 90 (100), 63 (66), 51 (23), 40 (16).

Reaction of 4 and lithium aluminum deuteride ($LiAlD_4$)

The solution of 4 (12 mg) in anhydrous ether (0.2 mL) was treated with a suspension of $LiAlD_4$ (21 mg) in ether (1 mL). After refluxing at 55°C for 1 h, the mixture was cooled in ice and the excess $LiAlD_4$ was decomposed with either H_2O or D_2O (0.4 mL). The resulting mixture was stirred for 2 min and extracted with ether (2 x 4 mL). The extracts were dried ($MgSO_4$) and evaporated to yield 6 mg of a yellow oil. The structures of the compounds obtained by quenching with either H_2O or D_2O was verified by ^{1}H NMR and mass spectrometry to be identical, both having deuterium at α and β positions (5-α,β-D_2). ^{1}H NMR ($CDCl_3$): 6.9-6.6 (aromatic H's), 5.95 (s, 2H),

2.85 (d, J=6.2 Hz, 1H), 2.62 (d, J=6.2 Hz, 1H), 1.90 (br. 2H); MS, m/e (rel. intensity): 167 (M^+, 14), 149 (1.1), 121 (1), 137 (100), 106 (10), 78 (33), 63 (4), 52 (22), 40 (6).

Reaction of 4-α-D with $LiAlH_4$ or $LiAlD_4$

The reduction of **4-α-D** with either $LiAlH_4$ or $LiAlD_4$ followed a procedure similar to that described above. The structure of the compound after reduction of **4-α-D** with $LiAlH_4$ was identified to be the phenethylamine with deuterium at the α position (**5-α-D**); and the product was **5-α,α,β-D_3** when $LiAlD_4$ was used. In both cases, there was only one isolated product regardless of whether the reaction was quenched with either H_2O or D_2O. ^1H NMR ($CDCl_3$) of **5-α-D**: 6.8-6.6 (aromatic H's),5.92 (s, 2H), 2.89 (t, J=6.1 Hz, 1H), 2.65 (d, J=6.6 Hz, 1H), 1.5 (br. 2H); MS, m/e (rel. intensity): 166 (M^+, 12), 148 (1.6), 136 (100), 121 (1), 105 (10), 77 (39), 63 (7), 51 (37), 40 (3). ^1H NMR ($CDCl_3$) of **5-α,α,β-D_3**: 6.8-6.6 (aromatic H's), 5.92 (s, 2H), 2.63 (s 1H), 1.5 (br. 2H); MS, m/e (rel. intensity): 168 (M^+, 13), 150 (1), 137 (100), 121 (1), 106 (8), 78 (30), 63 (4), 52 (21), 40 (6).

Synthesis of deuterated piperonyl alcohol 6

Piperonic acid (2.1 g, 12.6 mmol) was added in portions to a suspension of $LiAlD_4$ (1 g, 26.3 mmol) in 200 mL of anhydrous ether at 0°C. The mixture was stirred at room temperature overnight, cooled in ice and the excess $LiAlD_4$ was decomposed by the addition of 1 mL of H_2O, followed by 1mL of 15% NaOH, and 3 mL of H_2O. The suspension of salts in ether was stirred for 15 min and filtered, and the salts were washed several times with ether. The ether solution was dried ($MgSO_4$) and evaporated to give **6** (colorless crystals, 1.823 g, 94%). As the product was analytically pure, the next step was performed without further purification. ^1H NMR ($CDCl_3$): 6.9-6.7 (aromatic H's), 5.96 (s, 2H). There was no detectable peak for CH_2OH. MS, m/e (rel. intensity): 154 (M^+, 100), 137 (61), 135 (0.5), 124 (55), 107(10), 94 (44), 79 (31), 66 (40), 53 (25), 40 (29). The ratio for the relative intensities of mass peaks 135 and 137 (M^+-OH) was 0.5/61, suggesting that the protio piperonyl alcohol impurity was less than 0.8%.

Synthesis of deuterated piperonal 7

The suspension of **6** (1.7 g, 11.0 mmol) and pyridinium dichromate (PDC) (6.66 g, 17.7 mmol) [19] in CH_2Cl_2 (18 mL) was stirred at room temperature for 24 h. The resulting mixture was diluted with ether, filtered and evaporated. The crude product was purified by silica gel column chromatography to afford **7** (colorless crystals, 1.4 g, 85%). ^1H NMR ($CDCl_3$): 7.42 (d, J=7.9 Hz, 1H), 7.35 (s, 1H), 6.94 (d, J=7.9 Hz, 1H), 6.09 (s, 2H). There was no detectable peak for CHO. MS, m/e (rel. intensity): 151 (M^+, 100), 121 (29), 91 (16), 78 (3), 63 (50), 40 (8).

Synthesis of deuterated 6-nitropiperonal 8

Deuterated piperonal **7** (1.1 g, 7.2 mmol) was added in portions over 5 min. to a stirring solution of 60% nitric acid (13 mL) at 0°C [20]. The resulting mixture was

stirred at 30-35°C for 2 h and then cooled in an ice-bath and diluted with 20 mL of ice-water. After extraction with ethyl acetate, the extracts were washed with ice-water, dried ($MgSO_4$) and evaporated to afford the crude product. Purification by silica gel column chromatography yielded deuterated 6-nitropiperonal **8** (yellow solid, 1.2 g, 85%). ^{1}H NMR ($CDCl_3$): 7.55 (s, 1H), 7.36 (sd, 1H), 6.23 (s, 2H); MS, m/e (rel. intensity): 196 (M^+, 27), 166 (72), 148 (26), 120 (68), 108 (84), 80 (100), 64 (96), 53 (58), 40 (18).

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