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A convenient synthesis of deuterium labeled tertiary aliphatic nitro ketones and nitriles – starting materials for preparation of deuterated cyclic nitrones, isomeric hydroxylamines, and corresponding *C*-nitroso compounds

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ABSTRACT

Tertiary aliphatic β- and γ-nitro nitriles and ketones deuterated in (several) selected positions had been synthesized. The deuterated nitro compounds served as a starting material for the corresponding deuterium labeled nitrones or hydroxylamines (reducing with aluminum amalgam). Further oxidation of the last two groups of compounds with sodium periodate or *m*-CPBA afforded the relevant deuterated tertiary *C*-nitroso compounds.

1. Introduction

In the electron impact ionization mass spectra (EIMS) of some tertiary α-, β-, and γ-nitroso carbonyl compounds $(CH_3)_2C(NO)(CH_2)_nCOR$ (n=0,1,2; R=CH_3, OCH_3), the unexpected presence of the abundant MH^+ ions and the absence of $M^{+\bullet}$ ions has been observed.[1,2] Similar phenomena, although not so strongly marked, have been observed in the EI mass spectra of tertiary α-, β-, γ-, and δ-nitroso nitriles $(CH_3)_2C(NO)(CH_2)_nC{\equiv}N$ (n=0,1,2,3).[3] However, the molecular ions were also present in some mass spectra.

To examine the phenomenon of MH^+ ion formation and to assign the origin of hydrogen in the cationized molecules, the mass spectra of β- and γ-nitroso nitriles were compared with the spectra of their isotopologues,[4] deuterium labeled at specific carbon atoms **3a**,**c**–**g**.[3] In order to investigate EIMS of those deuterated compounds, their synthesis was necessary. Since procedures for the introduction of a deuterium atom into the investigated compounds were either unknown or difficult to achieve, we needed quick and efficient methods for the introduction of deuterium atoms into selected positions of the investigated molecules. Although the syntheses of the α–δ-nitroso nitriles as well as the intermediate nitro nitriles, nitrones, and hydroxylamines have been described in previous papers,[3,5,6] the synthetic details for the deuterated compounds preparation have never been published.

In this paper we report new methods for the insertion of deuterium atoms into simple aliphatic compounds bearing nitro, nitroso, and hydroxylamine groups and the nitrone moiety. The compounds of interest are presented in Schemes 1 and 2.

For MS studies deuterium labeling should be applied in various sites in the molecule. First, effective methods for the synthesis of specifically deuterated starting materials (tertiary β- and γ-nitro nitriles **1a**,**c**–**f**, Scheme 1) were developed. Then, the intermediate deuterium labeled aminonitrones or hydroxylamines **2a**,**c**–**f**, and finally the corresponding β- and γ-nitroso nitriles **3a**,**c**–**f** were synthesized. Moreover, the method of synthesis of the pentadeuterated γ-nitroso ketone $(CH_3)_2C(NO)CH_2CD_2–CO–CD_3$ (**3b**) was developed, in addition to the already developed[2] preparation of its monodeuterated isotopologue $(CH_3)_2C(NO)CH_2CHD–CO–CH_3$ (**3h**), via the corresponding deuterated γ-nitro ketones **1b** and **1h** (Scheme 2).

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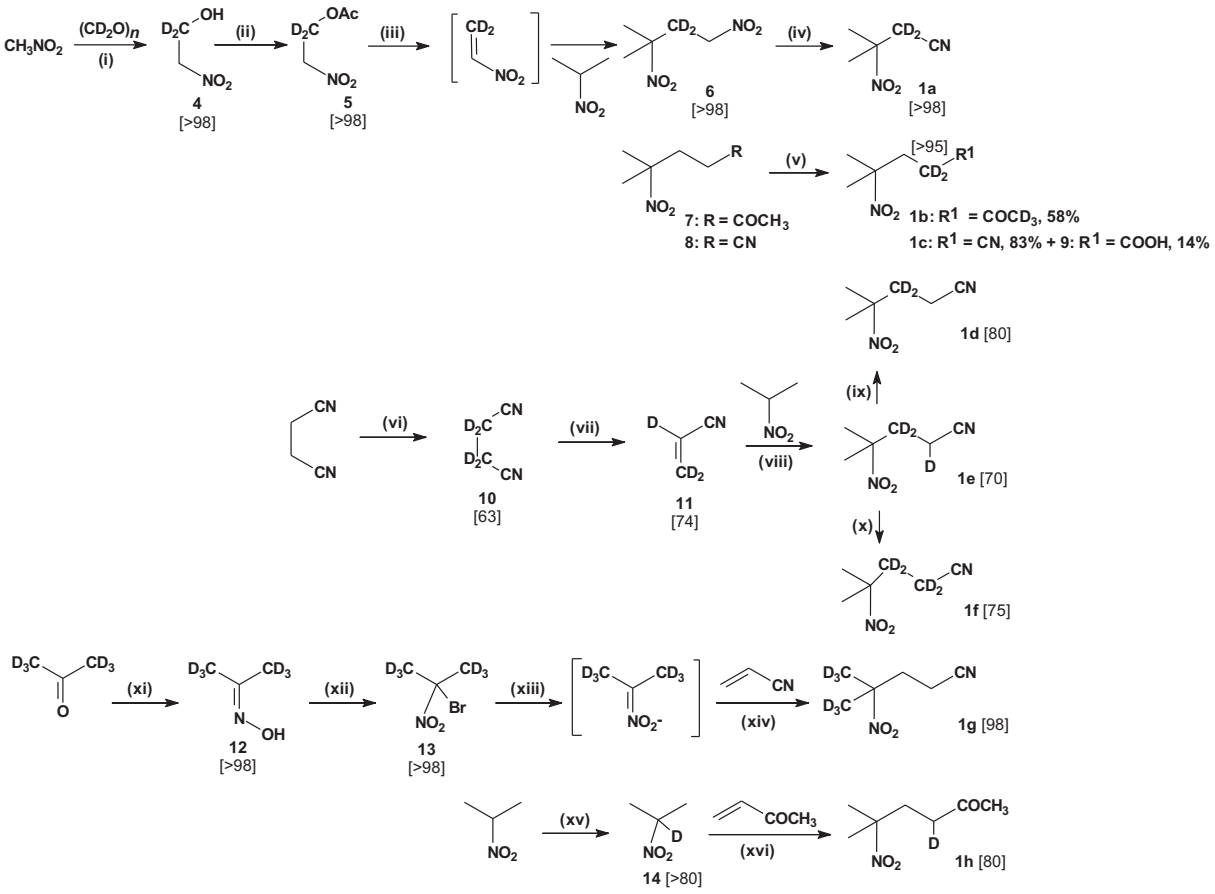


Scheme 1. Syntheses of deuterium labeled nitro nitriles and ketones **1a**–**h**. (i) KOH/MeOH, 2 h at rt, reflux 15 min, the numbers in square brackets give the percentage fraction of deuterium [%D] in marked positions; (ii) AcCl, 0 °C, 1 h, 92%; (iii) 4% aq NaOH, 45 °C, 2 h, 53%; (iv) PCl_3/pyridine, rt, two days, 81%; (v) D_2O/NaOD, Et_2O, $MeOc_3N^+Cl^-$, rt, 12 h, four reaction cycles, 58%; (vi) D_2O/$Ca(OD)_2$, rt, 24 h, five reaction cycles; (vii) 3 Å MS, 550 °C, 2 h, 53%; (viii) $Bu_4N^+OH^-$/dioxane, 12 h at rt, reflux 2 h, 57%; (ix) H_2O/NaOH, Et_2O, $MeOc_3N^+Cl^-$, rt, 12 h, four reaction cycles, 82%; (x) D_2O/NaOD, Et_2O, $MeOc_3N^+Cl^-$, rt, 12 h, four reaction cycles, 73%; (xi) $NH_2OH\cdot HCl$, Na_2CO_3/H_2O, rt, 12 h, 65%; (xii) NBS, Na_2CO_3, dioxane/H_2O, rt, three days, 55%; (xiii) $NaBH_4$, Et_2O/H_2O, 1 h at -10 °C, 1 h at rt; (xiv) rt, 24 h, 31%; (xv) C_2H_5ONa, then D_3PO_4/D_2O, 48%;[2] (xvi) $Bu_4N^+OH^-/Et_2O/D_2O$, reflux 1 h, 64%.[2]

2. Results and discussion

The syntheses of the starting materials—the deuterium labeled nitro compounds **1** are presented in Scheme 1, and the intermediate hydroxylamines **2a**,**h** or nitrones **2b**–**g** as well as the corresponding nitroso compounds **3** in Scheme 2 (the isotopic purities are given in square brackets).

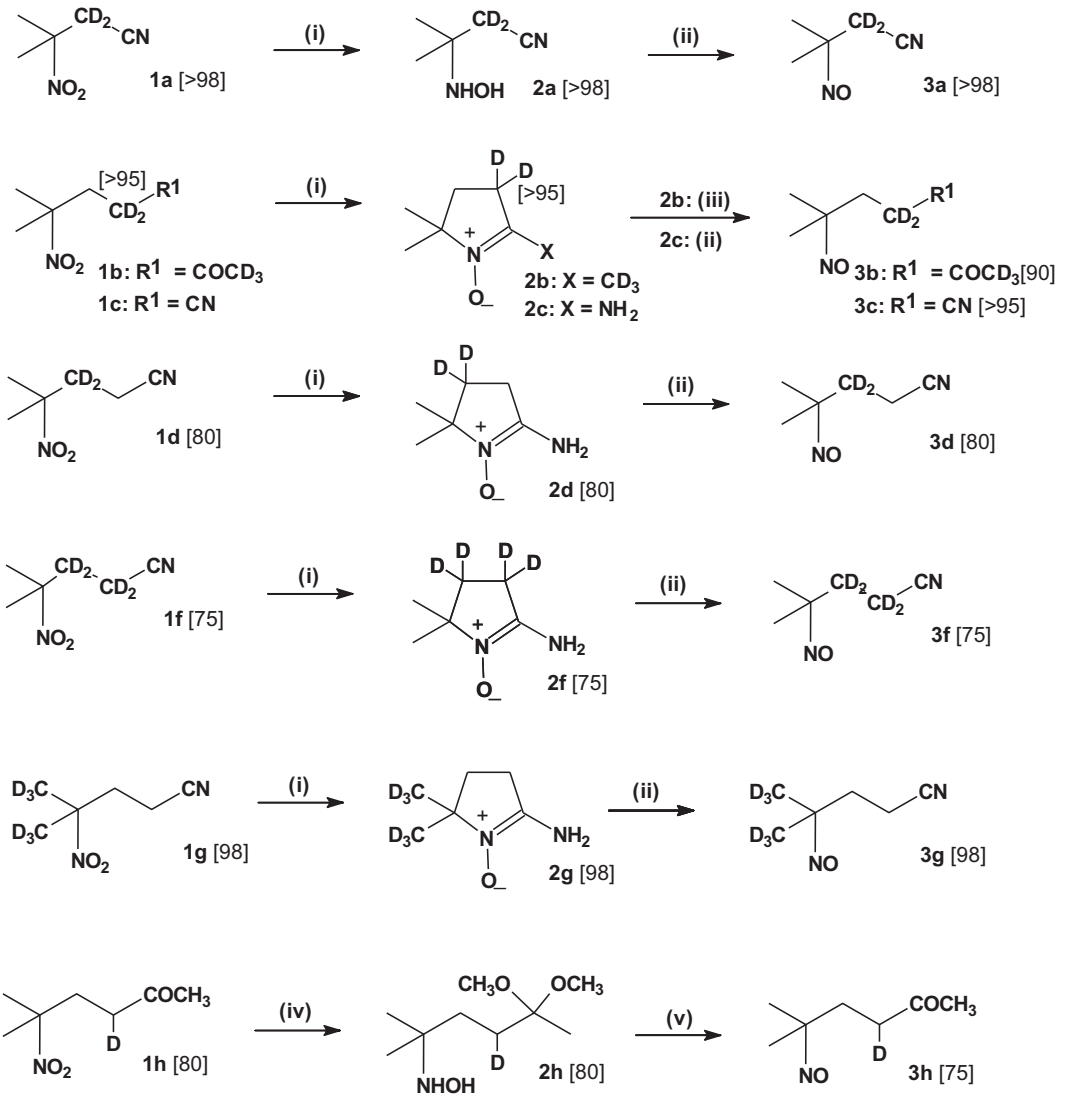
2.1. Syntheses of the deuterated starting materials

Some selected deuterated isotopologues **1a**,**c**–**f** of two aliphatic tertiary β- and γ-nitro nitriles: 3-methyl-3-nitrobutanenitrile (**15**)[6] and 4-methyl-4-nitropentanenitrile (**8**), and of an aliphatic tertiary γ-nitro ketone, 5-methyl-5-nitrohexan-2-one (**7**) (isotopologues **1b** and **1h**) were synthesized as starting materials (Scheme 1).

The H/D exchange is usually easy when the exchanged protons are labile, i.e., in positions α- to the electron withdrawing groups C=O or CN, for instance employing the phase transfer catalysis (PTC) isotopic exchange with D_2O in diethyl ether in presence of catalytic amounts of sodium deuteroxide and a quaternary ammonium salt.[7] However, the attempts to obtain 3-methyl-3-nitro[2,2-D_2]butanenitrile (**1a**), an α-deuterated β-nitro nitrile in direct H/D exchange of the labile α- hydrogen atoms at carbon C-2 failed. The treatment of 3-methyl-3-nitrobutanenitrile (**15**)[6] with D_2O/NaOD in conditions as described below for compounds **7** and **8** afforded only minor amounts of partially deuterated products and the recovered starting material. The main reaction product (yield 56%) was senecionitrile $(CH_3)_2C{=}CH{-}C{\equiv}N$, obtained after nitrous acid molecule elimination resulting in a conjugated multiple bond system formation.

Finally, a similar reaction pattern as for 3-methyl-3-nitrobutanenitrile (**15**)[6] was chosen to obtain its [2,2-D_2] isotopologue **1a**, starting from commercial [D_2]paraformaldehyde $(CD_2O)_n$. In the first step, the aldolisation of commercial nitromethane (in great excess to avoid further aldolization products formation) with [D_2]paraformaldehyde was carried out according to Noland,[8] affording almost quantitatively 2-nitro[1,1-D_2]ethanol (**4**). The crude nitroalcohol **4** was then directly transformed into 2-nitro[1,1-D_2]ethyl acetate (**5**) using the excess of acetyl chloride, in 92% yield (calculated on deuterated paraformaldehyde).[9] The nitro acetate **8** was treated with 2-nitropropane (**9**) in diluted aqueous sodium hydroxide solution.[9] After acetic acid elimination, the in situ formed 1-nitro[2,2-D_2]ethene was transformed into 3-methyl-1,3-dinitro[2,2-D_2]butane (**6**), the Michael adduct, in 53% yield. The primary nitro group $-CH_2NO_2$ of the dinitro compound **6** was then selectively reduced to the cyano group using phosphorus trichloride in pyridine,[10] affording 3-methyl-3-nitro[2,2-D_2]butanenitrile (**1a**) in 81% yield and with the excellent isotopic purity >98% (Scheme 1).

5-Methyl-5-nitro[1,1,1,3,3-D_5]hexan-2-one (**1b**) was obtained from 5-methyl-5-nitrohexan-2-one (**7**) employing the phase transfer catalysis (PTC) isotopic exchange with D_2O in diethyl ether in presence of catalytic amounts of sodium deuteroxide and methyltrioctylammonium chloride (Aliquat 336™). In the same manner, 4-methyl-4-nitro[2,2-D_2]pentanenitrile (**1c**) was obtained from the corresponding γ-nitro nitrile **8**. 4-Methyl-4-nitro[2,2-



Scheme 2. Syntheses of deuterium labeled nitroso nitriles and ketones **3a**–**h**. (i) Al(Hg), Et_2O/D_2O, rt, 2 h, 72–81%; (ii) $NaIO_3/NaHCO_3$, H_2O, rt, 0.5 h, 15–46%; (iii) *m*-CPBA, $CHCl_3$, 0 °C, 2 h, 76%; (iv) 1. MeOH/Amberlite IR 120/3 Å MS, rt, 24 h, 52%, 2. Al(Hg), Et_2O/D_2O, rt, 2 h, 57%; (v) NaOBr aq −10 °C, 15 min, 89%.

D_2]pentanoic acid (**9**), the hydrolysis product of the nitrile **1c**, was isolated as a side product, as well. The isotopic purities of deuterated compounds **1b** and **1c** were both greater than 95% (Scheme 1).

Syntheses of 4-methyl-4-nitro[3,3-D_2]pentanenitrile (**1d**) and 4-methyl-4-nitro[2,2,3,3-D_4]pentanenitrile (**1f**) were much more complicated (Scheme 1). Succinonitrile was used as a starting material, and the H/D exchange with D_2O containing $Ca(OD)_2$[11] gave 77% of [D_4(D_3)]succinonitrile (**10**) (63% of [D_4] and 37% of [D_3]compound) and minor amounts of the corresponding amide. The deuterated compound **10** was heated to 550 °C over molecular sieves 3 Å in a quartz tube.[11] After DCN or HCN elimination, [D_3(D_2)]acrylonitrile (**11**) was obtained in 53% yield. The crude compound **11** contained 74% of [D_3]acrylonitrile and 26% of its isotopologue [D_2], thus the isotopic purity was increasing without isotopologue separation. The Michael addition of 2-nitropropane to the deuterated acrylonitrile (**11**) in standard conditions yielded 57% of 4-methyl-4-nitro[2,3,3-D_3]pentanenitrile (**1e**) with about 70% isotopic purity.

The D/H exchange of the labile deuterium atom in position 2 of the compound (**1e**) (with H_2O/NaOH) resulted in 4-methyl-4-nitro[3,3-D_2]pentanenitrile (**1d**) formation in 82% yield (isotopic purity 80%), whereas H/D exchange of the hydrogen atom in the same position 2 (with D_2O/NaOD) yielded 73% of 4-methyl-4-nitro[2,2,3,3-D_4]pentanenitrile (**1f**) with isotopic purity 75%.

The synthesis of 4-[D_3]methyl-4-nitro[5,5,5-D_3]pentanenitrile (**1g**) was performed in four steps, starting from [D_6]acetone, which was transformed into [D_6]acetone oxime (**12**) using hydroxylamine hydrochloride in aqueous sodium carbonate in 65% yield.[12] The oxime **12** was treated with *N*-bromosuccinimide (NBS) in 50% aqueous dioxane[13] affording 2-bromo-2-nitro[D_6]propane (**13**) in 55% yield. The bromo nitro compound **13** was treated with sodium borohydride in aqueous ethanol,[14] and the resulting 2-nitro[1,1,1,3,3,3-D_6]propane (in anion form) was not isolated, but the Michael addition to acrylonitrile was carried out, directly affording 4-[D_3]methyl-4-nitro[5,5,5-D_3]pentanenitrile (**1g**) in 31% yield. The isotopic purities of the compound **1g** and all intermediates were excellent (98–99% D).

The synthesis of 5-methyl-5-nitro[3-D]hexan-2-one (**1h**) was performed in three steps.[2] 2-Nitropropane was treated with sodium in boiling anhydrous ethanol, resulting the 2-nitropropane sodium salt in 91% yield. The dry salt was acidified with hot D_3PO_4 (obtained in situ from phosphorus pentoxide and D_2O), affording after double distillation 2-nitro[2-D]propane (**14**) in 48% yield and isotopic purity 80%. The Michael addition to methyl vinyl ketone in

boiling ether/D_2O/tetrabutyl ammonium hydroxide resulted 5-methyl-5-nitro[3-D]hexan-2-one (**1h**) in 64% yield and isotopic purity 80%.

2.2. Aluminum amalgam reduction of deuterium labeled β- and γ-nitro nitriles or ketones

As has been previously noted for tertiary γ-nitro ketones with the keto group protected as a dimethyl ketal,[2] the modified procedure[6] of aluminum amalgam reduction of nitro compounds **1a**–**g** in moist diethyl ether[15] afforded appropriate deuterium labeled hydroxylamine **2a** or nitrones **2b**–**g** in good to high yields (Scheme 2). To decrease the possibility of the isotope back-exchange (deuterium by hydrogen) the 'moisture' of the ethyl ether was realized by addition of some D_2O to anhydrous ethyl ether.

The monodeuterated γ-nitro ketone **1h** was processed in a different way.[2] The keto group was protected as a dimethyl ketal with anhydrous methanol in the presence of cationite Amberlite IR 120 and dry 3 Å molecular sieves at room temperature, affording 2,2-dimethoxy-5-methyl-5-nitro[3-D]hexane (**15**) in 52% yield. The dimethyl ketal **15** was subsequently treated with aluminum amalgam[15] affording the appropriately protected hydroxylamine **2h** in 57% yield (Scheme 2). Isotopic purity: 80%.

2.3. Oxidation of deuterated nitrones and hydroxylamines to β- and γ-nitroso nitriles or ketones

All deuterium labeled nitrones and hydroxylamines **2a**–**h** were subsequently smoothly transformed (Scheme 2):

- Into deuterium labeled β- and γ-nitroso nitriles **3a**, **c**, **d**, **f**, **g** using sodium iodate in water[16] in 15–66% yield, isotopic purity 75–98%,
- Into the corresponding pentadeuterated γ-nitroso ketone **3b** using *m*-chloroperbenzoic acid (*m*-CPBA) in chloroform[17] in 66% yield, 90% isotopic purity, and
- Into monodeuterated γ-nitroso ketone **3h** by sodium hypobromite oxidation and simultaneous deprotection of **2h** at −20 °C[15] in 87% yield, 75% isotopic purity.[2]

3. Conclusions

The deuterated tertiary aliphatic β- and γ-nitro nitriles and ketones, the corresponding aluminum amalgam reduction products: nitrones and hydroxylamines, as well as their oxidation products—deuterium labeled tertiary aliphatic β- and γ-nitroso nitriles and ketones were synthesized. The deuterium atoms were smoothly introduced in various sites of the starting materials, nitro nitriles and ketones, using methods specific for every compound with good to excellent isotopic purity. The deuterated nitro compounds were then transformed into corresponding deuterium labeled nitrones, hydroxylamines, and nitroso compounds without significant loss of the isotopic purity.

4. Experimental

4.1. General

^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini-200 spectrometer at 200 MHz in $CDCl_3$, unless otherwise stated. Chemical shifts values are given in δ [ppm] units relative to TMS. The Fourier-transform infrared (FTIR) spectra were recorded on a Perkin-Elmer FTIR 1640 spectrophotometer; ν_{max} in cm^{-1}. The electron ionization mass spectra (EIMS) were recorded on an AMD-604 spectrometer at 70 eV.

Deuterium oxide, [D_6]acetone, and deuterated paraformaldehyde were purchased from Aldrich. Other commercial grade chemicals were used without further purification, unless stated otherwise. Commercial aluminum foil, thickness 13 μm was used. Flash chromatography was performed using a 230–400 mesh silica gel (Merck). The solvents were purified and/or distilled before use and stored under dry argon, where necessary.

The known nitro compounds **7**[18] and **8**[19] were prepared according to the literature.

4.2. Synthesis of the deuterated starting materials

*4.2.1. 2-Nitro[1,1-D_2]ethanol (**4**).* [D_2]paraformaldehyde (98.6% D, 0.5 g, 15.6 mmol) was suspended in nitromethane (84.5 g, 75 mL, 1.38 mol, about ninetyfold mole excess). To this suspension, 3 M methanolic solution of potassium hydroxide (0.15 mL) was added and the reaction mixture was stirred for 2 h at room temperature, and then heated to reflux for 15 min (at 100 °C). The excess of nitromethane was removed under vacuum and the resultant red oil of the deuterated nitroethanol **4** (1.5 g, yield practically quantitative) was used in the next step (procedure 4.2.2) without further purification. FTIR (film): 3376 (O–H), 2970 (C–H), 2236, 2112 (C–D), 1554 (NO_2); MS, *m*/*z* (int.%): 75 (1, $[M-H_2O]^{+\bullet}$), 88 (2), 61 (97, $[M-CD_2O]^{+\bullet}$), 46 (100, NO_2^+). Isotopic purity (MS): >98% D.

*4.2.2. 2-Nitro[1,1-D_2]ethyl acetate (**5**) (according to[9]).* The crude 2-nitro[1,1-D_2]ethanol (**4**) (1.5 g, 15.6 mmol) (obtained in the previous step) was stirred with acetyl chloride (2.32 g, 2.1 mL, 29.5 mmol) for 1 h at 0 °C and then 2 h at room temperature. The excess of acetyl chloride was removed under vacuum, and the residue was distilled at 52–54 °C/0.4 Torr, affording the deuterated nitro acetate **5** as a colorless oil (1.95 g, 14.4 mmol) in 92% yield (from [D_2]paraformaldehyde). FTIR (film): 2975 (C–H), 2180, 2130 (C–D), 1752 (C=O), 1566 (NO_2), 1264 (C–O); ^{1}H NMR: 2.03 (s, 3H, CH_3CO), 4.57 (s, 2H, CH_2NO_2); isotopic purity (NMR): >98% D; MS, *m*/*z* (int.%): 118 (0.3), 89 (5, $[M-NO_2]^+$), 88 (4), 60 (3), 43 (100, $CH_3C{\equiv}O^+$).

*4.2.3. 3-Methyl-1,3-nitro[2,2-D_2]butane (**6**) (according to[9]).* A solution of 2-nitro[1,1-D_2]ethyl acetate (**5**) (1.71 g, 12.66 mmol) in methanol (2 mL) was added at room temperature with stirring to a solution of 2-nitropropane (1.24 g, 1.25 mL, 13.96 mmol) in 4% aqueous sodium hydroxide (13 mL). The reaction mixture was stirred for 2 h at 45 °C, cooled down to room temperature, and washed with methylene chloride (4×10 mL). The combined separated organic layers were washed with water (2×5 mL), dried over magnesium sulfate and filtered. The filtrate concentrated under vacuum, affording a red oil. After distillation using a diffusion pump at 62–63 °C/0.005 Torr, the deuterated dinitro compound **6** was obtained as a colorless oil (1.1 g, 6.71 mmol) in 53% yield. FTIR (film): 2996 (C–H), 2210 (C–D), 1548 (NO_2), 856 (C–N); ^{1}H NMR: 1.63 (s, 6H, $2CH_3$), 4.44 (s, 2H, CH_2); MS, *m*/*z* (int.%): 118 (1, $[M-NO_2]^+$), 88 (11), 72 (6), 70 (100), 60 (14), 58 (16). Isotopic purity (MS): >98% D.

*4.2.4. 3-Methyl-3-nitro[2,2-D_2]butanenitrile (**1a**) (according to[10] with some modifications).* Phosphorus trichloride (1.97 g, 1.25 mL, 14.38 mmol) was slowly added with stirring at rt to a solution of 3-methyl-1,3-nitro[2,2-D_2]butane (**6**) (1.0 g, 6.09 mmol) in dry pyridine (20 mL) under argon. The red-brown reaction mixture was stirred under argon for two days at room temperature, then cooled to 0 °C and diluted hydrochloric acid (3 M, 120 mL) was carefully added. The reaction mixture was washed with ethyl ether (10 mL×5). The combined separated organic layers were washed with diluted hydrochloric acid (3 M, 10 mL×2) and dried over magnesium sulfate. The solution was concentrated under vacuum, affording a yellow oil. The vacuum distillation (60 °C/0.3 Torr) afforded a colorless oil (that solidified on standing) of the

deuterated nitro nitrile **1a** (0.63 g, 4.9 mmol) in 81% yield. FTIR (film): 2996 (C–H), 2260 (C≡N), 2200 (C–D) 1546 (NO_2), 862 (C–N); ^{1}H NMR: 1.77 (s, 6H, $2CH_3$); isotopic purity (NMR): >98% D; MS, *m/z* (int.%): 84 (100, $[M-NO_2]^+$), 82 (7, $[M-HNO_2]^{+\bullet}$), 57 (80, $C_4H_5D_2^+$), 41 (30).

4.2.5. 40% solution of sodium deuteroxide in deuterium oxide. Sodium (5 g, 0.215 mol) was carefully added in several portions to deuterium oxide (99+% D, 14 g) under a fume hood to prevent autoignition. After sodium is dissolved, the viscous liquid is transferred to a plastic bottle and tightly closed.

*4.2.6. 5-Methyl-5-nitro[1,1,1,3,3-D$_5$]hexan-2-one (**1b**).* 5-Methyl-5-nitrohexan-2-one (**7**)[18] (2 g, 12.5 mmol) was dissolved in the mixture of dry ethyl ether (10 mL), deuterium oxide (99+% D, 10.7 g, 10 mL, 0.536 mol), 40% solution of sodium deuteroxide (NaOD) in deuterium oxide (0.25 mL) and a catalytic amount of trioctylmethylammonium chloride (Aliquat 336™, 0.05 mL, i.e., one drop). The two-phase mixture stirred intensively for 12 h at room temperature, the organic layer was separated, and a new portion of NaOD, D_2O, and the ammonium salt was added and stirred again for next 12 h (cycle two). After four reaction cycles, the organic layer was washed with deuterium oxide (2.5 mL), dried over magnesium sulfate, filtered, and the solvent was removed. After vacuum distillation at 52 °C/0.2 Torr, the deuterated nitro ketone **1a** (colorless oil, 1.2 g) was isolated in 58% yield. FTIR (film): 2945 (C–H), 1735 (C=O), 1545 (NO_2), 857 (C–N); ^{1}H NMR: 1.56 (s, 6H, $2CH_3$), 2.14 (s, 2H, CH_2); isotopic purity (NMR): >95% D; MS, *m/z* (int.%): 118 (6, $[M-NO_2]^+$), 117 (1, $[M-HNO_2]^{+\bullet}$), 95 (5), 55 (5), 46 (100, NO_2^+).

*4.2.7. 4-Methyl-4-nitro[2,2-D$_2$]pentanenitrile (**1c**).* 4-Methyl-4-nitropentanenitrile (**8**)[19] (1.42 g, 10 mmol) was dissolved in the mixture of dry ethyl ether (10 mL), deuterium oxide (99+% D, 4 g, 3.6 mL, 0.2 mol), 40% solution of sodium deuteroxide (NaOD) in deuterium oxide (0.25 mL) and a catalytic amount of Aliquat 336™ (one drop). The two-phase mixture stirred intensively for 12 h at room temperature, the organic layer was separated, and the new portion of NaOD, D_2O, and the ammonium salt was added and stirred again for next 12 h (cycle two). After four reaction cycles, the organic layer was washed with deuterium oxide (2.5 mL), dried over magnesium sulfate, filtered, and the solvent was removed. After vacuum distillation at 55–56 °C/0.05 Torr, the deuterated nitro nitrile **1c** (colorless oil, 1.2 g) was isolated in 83% yield. FTIR (film): 2985 (C–H), 2250 (C≡N), 1540 (NO_2), 855 (C–N); ^{1}H NMR: 1.65 (s, 6H, $2CH_3$), 2.31 (s, 2H, CH_2); isotopic purity (NMR): >95% D; MS, *m/z* (int.%): 98 (100, $[M-NO_2]^+$), 97 (13, $[M-HNO_2]^{+\bullet}$), 69 (57), 55 (95), 53 (10).

*4.2.8. [D$_4$(D$_3$)]Succinonitrile (**10**) (according to[11]).* Succinonitrile (20 g, 0.25 mol) was dissolved in deuterium oxide (99+% D, 22.4 g, 20 mL, 1.12 mol) and calcium oxide (0.3 g) was added with stirring. The reaction mixture was stirred intensively for 24 h at room temperature. The deuterium oxide was removed under vacuum at 80 °C, to the residue a new portions of deuterium oxide (20 mL) and calcium oxide (0.3 g) were added and stirred for next 24 h (cycle two). After five reaction cycles, the deuterium oxide was removed under vacuum at 80–85 °C as above. The residual was washed with hot (50 °C) chloroform (15 mL×4), dried over magnesium sulfate, filtered, and the solvent was removed under vacuum. The resulting pale yellow waxy solid (18.33 g) contained 89% of [D_4] and [D_3] deuterated succinonitrile **10** (63:37), as well as 11% of deuterated partial hydrolysis product—3-cyano[D_4(D_3)]propionamide. The yield of [D_4(D_3)]succinonitrile (**10**): 77%, the crude product was processed in the next step (procedure 4.2.9) without further purification. FTIR (film): 2256 (C≡N), 2188 (C–D), 1680 ($CONH_2$); MS, *m/z* (int.%): 84 (22, $M^{+\bullet}$), 82 (11), 56 (100), 52 (13), 42 (57); isotopic purity (MS): 63% [D_4]succinonitrile and 37% [D_3]succinonitrile.

*4.2.9. [D$_3$(D$_2$)]Acrylonitrile (**11**) (according to[11]).* A quartz tube of the pyrolysis apparatus filled with 3 Å molecular sieves (size 1/6″, 19.2 g) was pre-heated under argon at 500 °C for 2 h. The crude deuterated succinonitrile **10** (10 g, 0.1 mol) was loaded into a dropping funnel with a pressure equalizing arm, equipped with a heating tape and heated to 60 °C in order to melt the waxy starting material. The molten deuterated succinonitrile **10** was then dropped (one drop every 5 s) onto the bed of molecular sieves heated to 550 °C in the pyrolysis apparatus. The elimination products, after initial cooling with a water condenser placed under the apparatus, were frozen down in a condenser cooled to −60 °C with acetone—dry ice mixture. Afterward, the cooling mixture was removed from the condenser and the stream of argon was passed through the apparatus for 30 min. The 5 mL of red liquid collected in the condenser contained (GC–MS) 70% of the deuterated acrylonitrile **11** as well as smaller amounts of deuterocyanic acid D–C≡N, hydrocyanic acid [CARE: highly toxic!] and the starting material. The reaction mixture was distilled, collecting fraction boiling at 25–80 °C (3.62 g). The colorless distillate, containing 86% [D_3(D_2)]acrylonitrile (**11**) (yield 47%) and some DCN, was processed in the next step (procedure 4.2.10) without further purification. MS: *m/z* (int.%): 56 (100, $M^{+\bullet}$), 54 (77); isotopic purity of **11** (MS): 74% [D_3]acrylonitrile and 26% [D_2]acrylonitrile.

*4.2.10. 4-Methyl-4-nitro[2,3,3-D$_3$]pentanenitrile (**1e**) (according to[11] with some modifications).* Crude [D_3(D_2)]acrylonitrile (**11**) (3.62 g containing 2.82 g (50.3 mmol) of pure compound **11**) was slowly added at room temperature to a stirred solution of 2-nitropropane (10.65 g, 10.8 mL, 120 mmol) and tetrabutylammonium hydroxide (40% in water, 1.2 mL) in dioxane (10 mL). The reaction mixture was stirred at room temperature for 12 h and heated to reflux for next 2 h. The cooled reaction mixture was poured in water (60 mL), and washed with ether (15 mL×4). The organic layer was washed with 3 M aqueous sodium hydroxide (20 mL), 3 M aqueous hydrochloric acid (20 mL), and water (20 mL×2), dried over magnesium sulfate, filtered, and the solvent was removed under vacuum. The residual oil was distilled at 76–78 °C/0.3 Torr, affording 4-methyl-4-nitro[2,3,3-D_3]pentanenitrile (**1e**) as a colorless liquid (4.15 g, 28.6 mmol) in 57% yield. FTIR (film): 2996 (C–H), 2252 (C≡N), 1536 (NO_2), 856 (C–N); ^{1}H NMR: 1.56 (s, 3H, CH_3CO), 2.32 (s, 1H, CHD); isotopic purity (NMR, MS): 70% D; MS, *m/z* (int.%): 99 (100, $[M-NO_2]^+$), 97 (6, $[M-DNO_2]^{+\bullet}$), 72 (32), 57(67), 43 (39).

*4.2.11. 4-Methyl-4-nitro[3,3-D$_2$]pentanenitrile (**1d**).* The D/H exchange was performed in a similar way as for compound **1c**, starting from 4-methyl-4-nitro[2,3,3-D_3]pentanenitrile (**1e**) (2 g, 13.8 mmol), ethyl ether (13.8 mL), water (5 g, 276 mmol), 38% aqueous sodium hydroxide (0.35 mL), and Aliquat 336™ (40% aqueous solution, 0.05 mL, one drop) at room temperature for 12 h (four reaction cycles). 4-Methyl-4-nitro[3,3-D_2]pentanenitrile (**1d**) (1.62 g) was obtained as a colorless liquid in 82% yield. Bp 76–77 °C/0.3 Torr. FTIR (film): 2996 (C–H), 2256 (C≡N), 1544 (NO_2), 856 (C–N); ^{1}H NMR: 1.64 (s, 3H, CH_3CO), 2.38 (s, 1H, CH_2); isotopic purity (NMR): 80% D; MS, *m/z* (int.%): 98 (100, $[M-NO_2]^+$), 96 (5, $[M-DNO_2]^{+\bullet}$), 71 (46), 57(96), 55 (55).

*4.2.12. 4-Methyl-4-nitro[2,2,3,3-D$_4$]pentanenitrile (**1f**).* The H/D exchange was performed in a similar way as for compounds **1c** and **1d**, starting from 4-methyl-4-nitro[2,3,3-D_3]pentanenitrile (**1e**) (2 g, 13.8 mmol), ethyl ether (13.8 mL), deuterium oxide (5.6 g, 5 mL, 276 mmol), 40% solution of sodium deuteroxide (NaOD) in deuterium oxide (0.35 mL), and a catalytic amount of Aliquat 336™ (40% aqueous solution, 0.05 mL, one drop) at room temperature for 12 h (four reaction cycles). 4-Methyl-4-nitro[2,2,3,3-D_4]pentanenitrile (**1f**) (1.5 g)

was obtained as a colorless liquid in 73% yield. Bp 80 °C/0.4 Torr. FTIR (film): 2996 (C–H), 2252 (C≡N), 1544 (NO_2), 856 (C–N); ^{1}H NMR: 1.56 (s, 3H, CH_3CO); isotopic purity (NMR): 75% D; MS, *m*/*z* (int.%): 100 (100, $[M-NO_2]^+$), 98 (5, $[M-DNO_2]^{+\bullet}$), 73(21), 57(42).

*4.2.13. [D_6]Acetone oxime (**12**) (according to[12] with some modifications).* A solution of hydroxylamine hydrochloride (11 g, 0.158 mol) and sodium carbonate (17 g, 0.16 mol) in water (130 mL) was stirred at room temperature. Then, [D_6]acetone (9.37 g, 11.75 mL, 0.146 mol) was added slowly and stirred for the next 12 h at room temperature. Afterward, the reaction mixture was poured into water (100 mL), and washed with ether (25 mL×10). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent was removed using a vacuum evaporator at less than 25 °C. The residual solvent was removed under vacuum affording colorless crystals of [D_6]acetone oxime (**12**) (7.5 g, 0.0949 mol) in 65% yield. Mp 58.5–60 °C (lit.[12] 61.5 °C). FTIR (KBr pellet): 3050 (O–H), 2225, 2135 (C–D), 1670 (C=N); MS, *m*/*z* (int.%): 79 (100, $M^{+\bullet}$), 61 (60, $[M-CD_3]^+$), 44 (16), 42 (18); isotopic purity (MS): >98% D.

*4.2.14. 2-Bromo-2-nitro[D_6]propane (**13**) (according to[13] with some modifications).* A solution of [D_6]acetone oxime (**12**) (6.29 g, 79.6 mmol) in water/dioxane (1:1, 100 mL) was added during 15 min at room temperature to a stirred suspension of *N*-bromosuccinimide (50 g, 281 mmol) in water (750 mL) contained sodium hydrogen sulfate (23.5 g, 289 mmol). After stirring three days at room temperature, solid potassium hydroxide (16.2 g, 289 mmol) was added and after 30 min the reaction mixture was washed with methylene chloride (50 mL×5), the organic layer was washed with 3 M aqueous hydrochloric acid (50 mL×2), water (50 mL×2), dried over anhydrous magnesium sulfate, filtered, and the solvents removed under vacuum. The residual oil was distilled at 145–150 °C, affording 2-bromo-2-nitro[D_6]propane (**13**) as a colorless oil (7.62 g, 43.8 mmol) in 55% yield. FTIR (film): 1556 (NO_2), 843 (C–N); MS, *m*/*z* (int.%): 127 (69, $M-[NO_2]^+$), 107 (1), 85 (2), 79 (3), 46(100); isotopic purity (MS): >98% D.

*4.2.15. 4-[D_3]Methyl-4-nitro[5,5,5-D_3]pentanenitrile (**1g**) (according to[13] with some modifications).* A solution of 2-bromo-2-nitro-[D_6]propane (**13**) (6.16 g, 35.4 mmol) in 96% ethanol (150 mL) was cooled to −10 °C using an ice-salt bath. Then, a solution of sodium borohydride (7.3 g, 35.4 mmol) in 80% ethanol (200 mL) was slowly added with stirring. The cooling bath was removed and the stirring was continued for about 1 h as the temperature reached the room temperature. The reaction mixture was concentrated removing 150 mL of ethanol. To the cooled to −10 °C residue, acrylonitrile (2.48 g, 3.1 mL, 46.7 mmol) was slowly added with stirring and the reaction was continued for next 24 h at room temperature. Afterward, the reaction mixture poured into water (350 mL), washed with ether (20 mL×5), the combined organic layers washed with 3 M aqueous hydrochloric acid (10 mL), water (10 mL×2), dried over anhydrous magnesium sulfate, filtered, and the solvents removed under vacuum. The residual oil was distilled at 79–80 °C/0.4 Torr, affording 4-[D_3]methyl-4-nitro[5,5,5-D_3]pentanenitrile (**1g**) as a colorless oil (1.65 g, 11.14 mmol) in 31% yield. FTIR (film): 2937 (C–H), 2250 (C≡N), 1534 (NO_2), 845 (C–N); ^{1}H NMR: 2.24–2.44 (m, 4H, CH_2CH_2), 4.57 (s, 2H, CH_2NO_2); isotopic purity (NMR, MS): >98% D; MS, *m*/*z* (int.%): 102 (100, $M-[NO_2]^+$), 101 (7, $M-[HNO_2]^{+\bullet}$), 74 (27), 60 (38), 44(22).

*4.2.16. 2-Nitro[2-D]propane (**14**)[2].* Sodium (2.35 g, 0.102 mol) was carefully added in several portions to anhydrous ethanol (30 mL) under an efficient fume hood to prevent auto-ignition. After sodium is dissolved, 2-nitropropane (9.07 g, 9 mL, 0,102 mol, freshly distilled over anhydrous calcium chloride) was added dropwise into the hot ethanolate solution with efficient stirring under reflux. The formation of a white precipitate of 2-nitropropane sodium salt is observed and after addition of all 2-nitropropane, the reaction mixture solidified. After cooling to room temperature, the precipitate was filtered, washed with dry ethyl ether (20 mL×2) and dried under vacuum over potassium hydroxide at room temperature, affording 2-nitropropane sodium salt (10.25 g, 91%) directly processed without further purification.

2-Nitropropane sodium salt (10, 25 g, 0.093 mol) was transferred into a three necked flask equipped with a reflux condenser, an efficient stirrer, and a dropping funnel. A hot solution of [D_3]phosphoric acid in D_2O (obtained in situ from deuterium oxide (99.8%, 9 mL) and phosphorus pentoxide, 2.9 g) was added dropwise with stirring under argon. The stirring was continued for next 30 min and allowed to cool to room temperature. Then sodium chloride (0.5 g) was added and the reaction mixture was washed with methylene chloride (20 mL×3), dried over magnesium sulfate, filtered, and distilled twice through a short Vigreux column, affording 4.0 g (48%) of 2-nitro[2-D]propane (**14**). Colorless liquid, bp 120–122 °C. FTIR (film): 2960, 2910, 2860 (C–H), 2230 (C–D), 1530 (NO_2 asym.), 1380 (NO_2 sym.); ^{1}H NMR: 1.52 (s, 6H, $2CH_3$), isotopic purity (NMR): >80% D.

4.2.17. 5-Methyl-5-nitro[3-D]hexan-2-one (1 h)[2]. Methyl vinyl ketone (2.83 g, 3.36 mL, 40.45 mmol) was added dropwise at room temperature to 2-nitro[2-D]propane (**14**) (3.76 g, 3.73 mL, 41.7 mmol) in dry ethyl ether (5 mL) containing 100 mg of dry tetrabutylammonium hydroxide (the water in the commercial 40% solution was removed using a vacuum evaporator and the residue dried under vacuum) and 0.2 mL of D_2O (to solubilize the quarternary base). The reaction mixture was heated to reflux for 1 h, cooled to room temperature, and diluted with dry ether (100 mL). The reaction mixture was washed subsequently with 5% deuterium chloride (DCl) in deuterium oxide (5 mL×2), with 5% sodium hydrogen carbonate in deuterium oxide (5 mL×2) and with saturated sodium chloride in deuterium oxide (5 mL×2). The organic layer dried over anhydrous calcium chloride, filtered, and ether was removed under vacuum. The yellow oil of crude nitro ketone **1h** (6.17 g, 91%) was distilled in vacuo yielding 4.26 g (64%) of 5-methyl-5-nitro[3-D]hexan-2-one (**1h**) as an uncolored liquid, bp 123–126 °C/15–16 Torr. FTIR (film): 2980, 2940 (C–H), 2160 (C–D), 1720 (C=O), 1535 (NO_2 asym.), 1350 (NO_2 sym.); ^{1}H NMR: 1.58 (s, 6H, $2CH_3$), 2.15 (s, 3H, $COCH_3$), 2.05–2.6 (m, 3H, CH_2CHD); isotopic purity (NMR): >80% D; MS, *m*/*z* (int.%): 114 (12, $[M-NO_2]^+$), 70 (21), 43 (100, $CH_3C{\equiv}O^+$).

4.3. General procedure for reduction of nitro compounds 1a–g and 15 to corresponding hydroxylamines or nitrones 2a–h with aluminum amalgam

4.3.1. Aluminum amalgam (modified procedure[15]). Commercial aluminum foil (0.255 g, 9.58 mmol) was cut into ca. 20 strips, and each strip was rolled into a cylinder about 5 mm in diameter using a glass tube. Each of the aluminum foil cylinders was degreased by immersing it in ethyl ether, dried in air for several seconds, and amalgamated by immersing one by one for 15 s in a solution of mercury (II) chloride (0.07 g) in water (4 mL). Each amalgamed cylinder was then quickly transferred into a three neck flask containing tetrahydrofuran (15 mL) and water (0.13 mL). The reaction mixture was stirred vigorously for 30 min at room temperature before the reduction was carried out.

4.3.2. Aluminum amalgam reduction. The solution of the appropriate nitro compound **1a–d**, **f–g** or **15** (5 mmol) in diethyl ether (5 mL) was added dropwise to the flask containing Al(Hg) at such a rate that the solvent refluxed briskly. The reaction mixture was stirred for 0.5–7 h at room temperature until all the starting

material was consumed. Cellulose powder (Whatman, 0.1 g) was subsequently added into resulted white-gray suspension and the reaction mixture was filtered through a cellulose bed. The alumina precipitate was washed in the case of nitro ketones with ethyl ether (5 mL×5), and in the case of nitro nitriles subsequently with ethyl ether (5 mL×2), dichloromethane (5 mL×2) and dichloromethane/methanol 1:1 (v/v) (5 mL×3). The solvent was removed under vacuum, and the obtained crude products were purified by distillation (compound **2b**), crystallization (compounds **2c**, **d**, **f**, **g**), or flash chromatography (compound **2h**).

*4.3.3. 3-Hydroxylamino-3-methyl[2,2-D_2]butanenitrile (**2a**) (starting from compound **1a** according to the general procedure 4.3).* A solution of 3-methyl-3-nitro[2,2-D_2]butanenitrile (**1a**, 650 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminum foil and mercury (II) chloride, following the general procedure. Yield of the *title compound* **2a** 429 mg (74%), a bluish oil, directly processed into the corresponding β-nitroso nitrile **3a**. FTIR (film): 3260 (O–H, N–H), 2970 (C–H), 2250 (C≡N), 2200, 2110 (C–D); ^{1}H NMR: 1.24 (s, 6H, $2CH_3$); MS, *m*/*z* (int.%): 116 (0.2, M^+•), 101 (5, $[M-CH_3]^+$), 84 (14), 74 (100), 56 (49); isotopic purity (MS): 95% D.

*4.3.4. 2,2-Dimethyl-5-[D_3]methyl-1-oxy-3,4-dihydro-2H-[4,4-D_2]pyrrole (**2b**) (starting from compound **1b** according to the general procedure 4.3).* A solution of 5-methyl-5-nitro[1,1,1,3,3-D_5]hexan-2-one (**1b**, 820 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminum foil and mercury (II) chloride, following the general procedure. Yield of the *title compound* **2b** 515 mg (78%), a bluish oil, after distillation in vacuo (bp 50 °C/1 Torr) colorless oil. FTIR (film): 2971 (C–H), 2202, 2115 (C–D), 1596 (C=N), 1234 (N–O); ^{1}H NMR: 1.35 (s, 6H, $2CH_3$), 1.93 (s, 2H, $C(3)H_2$); MS, *m*/*z* (int.%): 132 (100, M^+•), 117 (40, $[M-CH_3]^+$), 100 (32), 71 (35), 56 (26), 46 (71); isotopic purity (MS): 93% D (70% [D_5], 27% [D_4], 3% [D_2] compound).

*4.3.5. 5,5-Dimethyl-1-oxy-4,5-dihydro-3H-[3,3-D_2]pyrrol-2-ylamine (**2c**) (starting from compound **1c** according to the general procedure 4.3).* A solution of 4-methyl-4-nitro[2,2-D_2]pentanenitrile (**1c**, 720 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminum foil and mercury (II) chloride, following the general procedure. Yield of the *title compound* **2c** 546 mg (84%), a colorless oil that solidified into white plates. Mp 215–218 °C (dec). FTIR (KBr pellet): 3180 (N–H), 2975 (C–H), 2110 (C–D), 1680 (C=N), 1200 (N–O); ^{1}H NMR (CD_3OD): 1.31 (s, 6H, $2CH_3$), 1.96 (s, 2H, $C(4)H_2$); isotopic purity (NMR): 95% D; MS, *m*/*z* (int.%): 130 (100, M^+•), 115 (76, $[M-CH_3]^+$), 113 (38), 98 (88), 84 (18), 71 (20).

*4.3.6. 5,5-Dimethyl-1-oxy-4,5-dihydro-3H-[4,4-D_2]pyrrol-2-ylamine (**2d**) (starting from compound **1d** according to the general procedure 4.3).* A solution of 4-methyl-4-nitro[3,3-D_2]pentanenitrile (**1d**, 720 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminum foil and mercury (II) chloride, following the general procedure. Yield of the *title compound* **2d** 520 mg (80%), a colorless oil that solidified on standing in white plates. Mp 214–216 °C (dec). FTIR (KBr pellet): 3175 (N–H), 2970 (C–H), 2220, 2110 (C–D), 1680 (C=N), 1195 (N–O); ^{1}H NMR (CD_3OD): 1.31 (s, 6H, $2CH_3$), 4.69 (s, 2H, $C(3)H_2$); isotopic purity (NMR): 95% D; MS, *m*/*z* (int.%): 130 (100, M^+•), 115 (73, $[M-CH_3]^+$), 113 (36), 98 (79), 84 (26), 71 (31).

*4.3.7. 5,5-Dimethyl-1-oxy-4,5-dihydro-3H-[3,3,4,4-D_4]pyrrol-2-ylamine (**2f**) (starting from compound **1f** according to the general procedure 4.3).* A solution of 4-methyl-4-nitro[2,2,3,3-D_4]pentanenitrile (**1f**, 720 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminum foil and mercury (II) chloride, following the general procedure. Yield of the *title compound* **2f** 475 mg (72%), a colorless oil that solidified into white plates. Mp 213–216 °C (dec). FTIR (KBr pellet): 3190 (N–H), 2970 (C–H), 2225, 2110 (C–D), 1680 (C=N), 1195 (N–O); ^{1}H NMR (CD_3OD): 1.31 (s, 6H, $2CH_3$); isotopic purity (NMR): 75% D; MS, *m*/*z* (int.%): 132 (100, M^+•), 117 (53, $[M-CH_3]^+$), 115 (28), 90 (69), 84 (8), 72 (22).

*4.3.8. 5,5-Bis([D_3]methyl)-1-oxy-4,5-dihydro-3H-pyrrol-2-ylamine (**2g**) (starting from compound **1g** according to the general procedure 4.3).* A solution of 4-[D_3]*methyl*-4-*nitro*[5,5,5-D_3]*pentanenitrile* (**1g**, 730 mg, 5 mmol) in diethyl ether (5 mL) was added dropwise with stirring to a flask containing Al(Hg) freshly prepared from aluminum foil and mercury (II) chloride, following the general procedure. Yield of the *title compound* **2g** 670 mg (75%), a colorless oil that solidified on standing in white plates. Mp 212–215 °C (dec). FTIR (KBr pellet): 3180 (N–H), 2960 (C–H), 2215, 2110 (C–D), 1690 (C=N), 1195 (N–O); ^{1}H NMR (CD_3OD): 1.96 (t, 2H, *J* 8 Hz, $C(4)H_2$), 2.65 (t, 2H, *J* 8 Hz, $C(3)H_2$); isotopic purity (NMR): 95% D; MS, *m*/*z* (int.%): 134 (72, M^+•), 116 (100, $[M-CD_3]^+$), 100 (81), 98 (38), 80 (2), 75 (17).

*4.3.9. 2,2-Dimethoxy-5-hydroxylamino-5-methyl[3-D]hexane (**2h**)[2].* A solution of 5-methyl-5-nitro[3-D]hexan-2-one (**1h**) (4.14 g, 0.026 mol) in a large excess of dry methanol (250 mL) was stirred at room temperature with Amberlite IR-120 ion exchange resin (0.5 g) and dry molecular sieves 3 Å (3 g) for 15 h. The reaction mixture was filtered and the methanol was evaporated from the filtrate affording a yellow oil. Flash chromatography on silica with hexane/diethyl ether (1:1, v/v) yielded 2.76 g (52%) of the protection product, intermediate dimethyl ketal – 2,2-dimethoxy-5-methyl-5-nitro[3-D]hexane (**15**). FTIR (film): 2830 (C–H sym. in $-OCH_3$ groups), 2150 (C–D), 1535 (NO_2 asym.), 1345 (NO_2 sym.), 1115, 1055 (C–O); ^{1}H NMR ($CDCl_3$): 1.25 (s, 3H, $C(1)H_3$), 1.60 (s, 6H, $C(CH_3)_2$), 1.58, 1.98 (2m, 3H, CH_2CHD), 3.14 (s, 6H, $2OCH_3$); isotopic purity (NMR): 80% D.

2,2-Dimethoxy-5-methyl-5-nitro[3-D]hexane (**15**) (2.61 g) was treated with aluminum amalgam according to the general procedure 4.3, affording 2,2-dimethoxy-5-hydroxylamino-5-methyl[3-D]-hexane (**2h**). The crude product was purified by flash chromatography on silica, first with hexane/diethyl ether (1:1, v/v), then with hexane/diethyl ether/methanol (3:3:2 v/v/v). Colorless oil, yield 1.39 g (57%). FTIR (film): 3360 (NH, OH), 2830 (C–H sym. in $-OCH_3$ groups), 2150 (C–D), 1120, 1055, 1040 (C–O, C–N). ^{1}H NMR (CD_3OD): 1.00 (s, 6H, $C(CH_3)_2$), 1.21 (s, 3H, $C(1)H_3$), 1.4–1.55 (2 m, 3H, CH_2CHD), 3.12 (s, 6H, $2OCH_3$), 4.9 (broad m, 2H, N–H, O–H); isotopic purity (NMR): 80% D.

4.4. Oxidation with *m*-CPBA

*4.4.1. 5-Methyl-5-nitroso[1,1,1,3,3-D_5]hexan-2-one dimer (**3b**) (according to[17] with some modifications).* To a cooled to 0 °C solution of 2,2-Dimethyl-5-[D_3]methyl-1-oxy-3,4-dihydro-2*H*-[4,4-D_2]pyrrole (**2b**) (0.39 g, 3.07 mmol) in chloroform (10 mL), a solution of *m*-chloroperbenzoic acid (purity 85%, 0.69 g, 3.40 mmol) in cold (0 °C) chloroform was slowly added with stirring. The reaction mixture was stirred at 0 °C for next 2 h, diluted with chloroform (10 mL), and washed with 5% aqueous sodium hydroxide (10 mL×3) and water (10 mL×2). The organic phase was dried over anhydrous magnesium sulfate, and filtered through a short column filled with silica gel. The blue solution was concentrated affording a deep blue oil (0.335 g) that solidified on standing to a colorless solid, 5-methyl-5-nitroso[1,1,1,3,3-D_5]hexan-2-one dimer (**3b**) in 76%

yield. Mp 59–60 °C (hexane), lit.[6] 58–60 °C. FTIR (KBr pellet): 2990 (C–H), 1700 (C=O), 1240 (N_2O_2 of nitroso compound dimer); ^{1}H NMR: 1.12 (s, 6H, $2CH_3$, monomer), 1,56 (s, 6H, $2CH_3$, dimer), 2.30 (s, 2H, CH_2, monomer and dimer); isotopic purity (NMR): 90% D; MS, *m*/*z* (int.%): 150 (1.1, MD^+), 118 (21), 100 (11), 55 (8), 46 (100).

4.5. General procedure for oxidation of nitrones or hydroxylamines 2a,c,d,f,g to nitroso compounds 3a,c,d,f,g with sodium periodate (according to[16] with some modifications)

A solution of the appropriate hydroxylamine or nitrone **2a**,**c**,**d**,**f**,**g** (1.95 mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL) was placed in a flask protected against light with an aluminum foil. Then, a solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL) was slowly added with stirring at room temperature. In the case of β-hydroxylamino nitrile **2a**, the oxidation product was a blue oil. After 30 min, the reaction mixture was washed with hexane (10 mL×6), the combined organic layers dried over anhydrous magnesium sulfate and filtered, affording a blue solution of nitroso nitrile monomers **3a**. In the case of all the other compounds (**2c**,**d**,**f**,**g**), the solid precipitate of oxidation products was filtered off after 1 h, washed with water (5 mL×3), and dried under vacuum. The resulting grayish precipitate, containing some inorganic salts was washed with hot chloroform (50 °C, 5 mL×3) and filtered. In all cases, the blue solution containing the appropriate nitroso nitrile monomers **3a**,**c**,**d**,**f**,**g** was filtered through a layer of silica gel for chromatography, and the solvent was removed under vacuum at room temperature, affording a deep blue oil of nitroso compound monomers, that solidified quickly into colorless dimers. The products were purified by re-crystallization.

*4.5.1. 3-Methyl-3-nitroso[2,2-D_2]butanenitrile dimer (**3a**) (starting from deuterium labeled hydroxylamine **2a** according to the general procedure 4.5).* A solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL) was slowly added with stirring at rt to a solution of 3-hydroxylamino-3-methyl[2,2-D_2]butanenitrile (**2a**) (226 mg, 1.95-mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL), following the general procedure. Yield of the *title compound* **3a** 33 mg (15%), a deep blue oil that solidified into white plates. Mp 59–61 °C (10% chloroform/hexane). FTIR (KBr pellet): 2995 (C–H), 2250 (C≡N), 1260 (N_2O_2); ^{1}H NMR: 1.47 (s, 6H, $2CH_3$, monomer), 1.59 (s, 6H, $2CH_3$, dimer); MS,[3] *m*/*z* (int.%): 115 (0.6, MH^+), 114 (0.4, $M^+\bullet$), 84 (74, $[M-NO]^+$), 72 (21), 58 (15), 57 (100), 56 (39), 55 (33), 42 (27), 40 (21), 39 (26); isotopic purity (MS): 95% D.

*4.5.2. 4-Methyl-4-nitroso[2,2-D_2]pentanenitrile dimer (**3c**) (starting from deuterated nitrone **2c** according to the general procedure 4.5).* A solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL) was slowly added with stirring at rt to a solution of 5,5-dimethyl-1-oxy-4,5-dihydro-3*H*-[3,3-D_2]pyrrol-2-ylamine (**2c**) (254 mg, 1.95 mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL), following the general procedure. Yield of the *title compound* **3c** 75 mg (30%), a deep blue oil that solidified into white plates. Mp 56–58 °C (10% chloroform/hexane). FTIR (KBr pellet): 2985 (C–H), 2240 (C≡N), 1255 (N_2O_2); ^{1}H NMR: 1.17 (s, 6H, $2CH_3$, monomer), 1.62 (s, 6H, $2CH_3$, dimer), 2.41 (s, 2H, CH_2); isotopic purity (NMR): 95% D; MS,[3] *m*/*z* (int.%): 129 (0.1, MH^+), 98 (40, $[M-NO]^+$), 71 (32), 70 (19), 57 (29), 56 (23), 55 (100), 43 (36), 42 (38), 41 (28), 39 (24).

*4.5.3. 4-Methyl-4-nitroso[3,3-D_2]pentanenitrile dimer (**3d**) (starting from deuterated nitrone **2d** according to the general procedure 4.5).* A solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL) was slowly added with stirring at rt to a solution of 5,5-dimethyl-1-oxy-4,5-dihydro-3*H*-[4,4-D_2]pyrrol-2-ylamine (**2d**) (254 mg, 1.95 mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL), following the general procedure. Yield of the *title compound* **3d** 74 mg (30%), a deep blue oil that solidified on standing in white plates. Mp 56–58 °C (10% chloroform/hexane). FTIR (KBr pellet): 2990 (C–H), 2240 (C≡N), 1260 (N_2O_2); ^{1}H NMR: 1.17 (s, 6H, $2CH_3$, monomer), 1.55 (s, 6H, $2CH_3$, dimer), 2.27 (s, 2H, CH_2);; isotopic purity (NMR): 80% D; MS,[3] *m*/*z* (int.%): 129 (0.3, $MH^+\bullet$), 128 (0.5, $M^+\bullet$), 98 (70, $[M-NO]^+$), 71 (36), 70 (22), 57 (100), 56 (48), 55 (24), 43 (34), 42 (69), 41 (44), 39 (16).

*4.5.4. 4-Methyl-4-nitroso[2,2,3,3-D_4]pentanenitrile dimer (**3f**) (starting from deuterated nitrone **2f** according to the general procedure 4.5).* A solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL) was slowly added with stirring at rt to a solution of 5,5-dimethyl-1-oxy-4,5-dihydro-3*H*-[3,3,4,4-D_4]pyrrol-2-yl-amine (**2f**) (257 mg, 1.95 mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL), following the general procedure. Yield of the *title compound* **3f** 71 mg (30%), a deep blue oil that solidified into white plates. Mp 57–58 °C (10% chloroform/hexane). FTIR (KBr pellet): 2995 (C–H), 2240 (C≡N), 1255 (N_2O_2); ^{1}H NMR: 1.17 (s, 6H, $2CH_3$, monomer), 1.55 (s, 6H, $2CH_3$, dimer); isotopic purity (NMR): 80% D; MS,[3] *m*/*z* (int.%): 131 (0.4, MH^+), 130 (0.5, $M^+\bullet$), 100 (81, $[M-NO]^+$), 73 (34), 72 (29), 59 (29). 58 (30), 57 (100), 56 (47), 44 (50), 43 (56), 42 (36), 41 (20), 39 (16).

*4.5.5. 4-([D_3]Methyl)-4-nitroso[5,5,5-D_3]pentanenitrile dimer (**3g**) (starting from deuterated nitrone **2g** according to the general procedure 4.5).* A solution of sodium periodate (0.59 g, 2.75 mmol) in water (10 mL) was slowly added with stirring at rt to a solution of 5,5-bis([D_3]methyl)-1-oxy-4,5-dihydro-3*H*-pyrrol-2-ylamine (**2g**) (261 mg, 1.95 mmol) and sodium hydrogen carbonate (0.25 g, 2.97 mmol) in water (7.5 mL), following the general procedure. Yield of the *title compound* **3g** 118 mg (46%), a deep blue oil that solidified on standing in white plates. Mp 64–65 °C (10% chloroform/hexane). FTIR (KBr pellet): 2972 (C–H), 2247 (C≡N), 1279 (N_2O_2); ^{1}H NMR: 2.23–2.48 (m, 4H, CH_2CH_2); isotopic purity (NMR): 95% D; MS, *m*/*z* (int.%): 134 (1.1, MD^+), 133 (0.5, MH^+), 132 (0.3, $M^+\bullet$), 102 (98, $[M-NO]^+$), 75 (15), 74 (44), 61 (20), 60 (100), 59 (16), 58 (26), 45 (22), 44 (46), 43 (28), 42 (17); isotopic purity (NMR): 95% D.

4.6. Sodium hypobromite oxidation

*4.6.1. 5-Methyl-5-nitroso[3-D]hexan-2-one dimer (**3h**) (according to[2,15] with some modifications).* Bromine (1.60 g, 0.516 mL, 10.058 mmol) was added dropwise with stirring at rt to a solution of sodium hydroxide (0.811 g, 20.275 mmol) in water (7.5 mL). The resulting sodium bromate (I) solution was cooled to −10 °C and 2,2-dimethoxy-5-hydroxylamino-5-methyl[3-D]hexane (**2h**) was added dropwise with stirring. After 15 min at −10 °C the reaction mixture was washed with methylene chloride (15 mL×3). The organic solution was washed with aqueous saturated sodium chloride solution (10 mL×2), dried (magnesium sulfate), filtered and the solvent was evaporated under vacuum affording a blue oil that solidified into white plates of 5-methyl-5-nitroso[3-D]hexan-2-one dimer (**3h**). Yield 0.837 g (87%), mp 50–55 °C (pentane). FTIR ($CHCl_3$): 2980, 2940 (C–H), 2300 (C–D), 1705 (C=O), 1535 (NO), 1270 (N_2O_2);. ^{1}H NMR: 1.12 (s, 6H, $2CH_3$, monomer), 1.55 (s, 6H, $2CH_3$, dimer), 2.11 (m, 3H, CH_2CHD), 2.29, 2.50 (2s, 3H, $COCH_3$ monomer and dimer). MS, *m*/*z* (int.%): 146 (7.1, MD^+), 145 (9.4, MH^+), 144 (5.8, $M^+\bullet$), 116 (34), 115 (93), 114 (94, $[M-NO]^+$), 113 (93), 43 (95, $CH_3C{\equiv}O^+$), 44 (100); isotopic purity (MS): 75% D.

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