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Synthesis of Tris[2-(dimethylamino)ethyl]amine with Regiospecific Deuterium Labels

Julian Sobieski,^[b] Illia Ruzhlyo,^[a] Grzegorz Szczepaniak,^[b] Adam Gorczyński,^[b,c] Krzysztof Matyjaszewski,^[b] Eric Manoury,^[a] and Rinaldo Poli^{*,[a,d]}

- [a] Dr. I. Ruzhlyo, Dr. E. Manoury, Prof. R. Poli
CNRS, LCC (Laboratoire de Chimie de Coordination),
Université de Toulouse, UPS, INPT
205 Route de Narbonne, BP 44099, F-31077, Toulouse Cedex 4, France
E-mail: rinaldo.poli@lcc-toulouse.fr
- [b] Mr. J. Sobieski, Dr. G. Szczepaniak, Dr. A. Gorczyński, Prof. K. Matyjaszewski
Department of Chemistry
Carnegie Mellon University
4400 Fifth Avenue, Pittsburgh, PA 15213, United States
- [c] Dr. A. Gorczyński
Faculty of Chemistry
Adam Mickiewicz University
Uniwersytetu Poznańskiego 8, Poznań, 61-614 Poland
- [d] Prof. R. Poli
Institut Universitaire de France
1, rue Descartes, 75231 Paris Cedex 05, France

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Abstract: Simple synthetic routes to regioselectively deuterated tris[2-(dimethylamino)ethyl]amine (Me_6TREN) variants are described. Imine formation with formaldehyde- d_2 from tris(2-aminoethyl)amine (TREN) and subsequent reductions with NaBD_4 afforded $\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{CD}_3)_2]_3$ or $d_{18}\text{-Me}_6\text{TREN}$ in 79% yield. A trisubstitution protocol from 2-bromo- N,N -dimethylacetamide and ammonium carbonate and subsequent reduction of the $\text{N}(\text{CH}_2\text{CONMe}_2)_3$ intermediate (**3**) by lithium aluminum deuteride has afforded $\text{N}[\text{CH}_2\text{CD}_2\text{N}(\text{CH}_3)_2]_3$ or ($d_6\text{-arm}$)- Me_6TREN in three steps and 52% overall yield. A similar protocol from 2-bromo- N,N -dimethyl- d_2 -acetamide, obtained in two steps from d_4 -acetic acid, with reduction of the $\text{N}(\text{CD}_2\text{CONMe}_2)_3$ intermediate by lithium aluminum hydride has afforded $\text{N}[\text{CD}_2\text{CH}_2\text{N}(\text{CH}_3)_2]_3$ or ($d_6\text{-cap}$)- Me_6TREN in four steps and 13% overall yield from CD_3COOD .

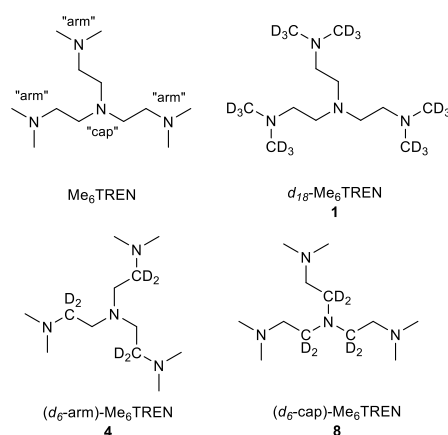


Figure 1. Structures of tris[2-(dimethylamino)ethyl]amine (Me_6TREN) and of the deuterium-labelled variants synthesized in this work.

Introduction

Tris[2-(dimethylamino)ethyl]amine (Me_6TREN) is a multidentate, neutral, tripodal, nitrogenous ligand used extensively in transition metal coordination chemistry and catalysis, notably to coordinate s - and d -block metal ions.^[1] Its purpose, among many ligands of its type, is to exert steric and electronic influences on the electronic structure, coordination geometry, redox properties and relative energy of metal complexes, thus profoundly influencing their optical, magnetic and reactivity properties. In particular, the energetic profile of stoichiometric and catalytic reactions is altered by the stabilization of reacting species and intermediates. Nevertheless, the free or coordinated ligand may also be directly implicated in elementary catalytic cycle steps, including but not limited to acid-base, hydrogen atom transfer, or proton-coupled electron transfer processes.^[2] Hence, the generation of families of deuterium-labelled ligands is desirable for wholly describing their role in catalytic systems.

Selective and regiospecific deuterium labelling of reaction components, coupled with NMR analysis of products and with the determination of possible kinetic isotope effects, is a powerful tool for mechanistic studies.^[3] Another common use of selectively deuterated ligands is to assist the assignment of the NMR resonances of paramagnetic compounds.^[4] However, deuterated variants of multidentate ligands, if not prohibitively expensive, are typically not commercially available. Specifically, selectively deuterated analogues of Me_6TREN have not been previously described, except for a single report of compound $\text{N}(\text{CH}_2\text{CH}_2\text{N}(\text{CD}_3)_2)_3$, which was indeed used to assist the interpretation of the ^1H NMR spectrum of a paramagnetic complex, $[\text{CoCl}_2(\text{Me}_6\text{TREN})]$.^[5] Thus, synthetic pathways to label three unique positions of Me_6TREN with deuterium labels were developed. These comprise two different methylene sites composing the ethylene bridges between the central “capping” and the peripheral “arm” amine groups, as summarized in Figure 1, and a new synthetic route to the isotope with perdeuteration at the methyl groups belonging to the “arm” amines.

Results and Discussion

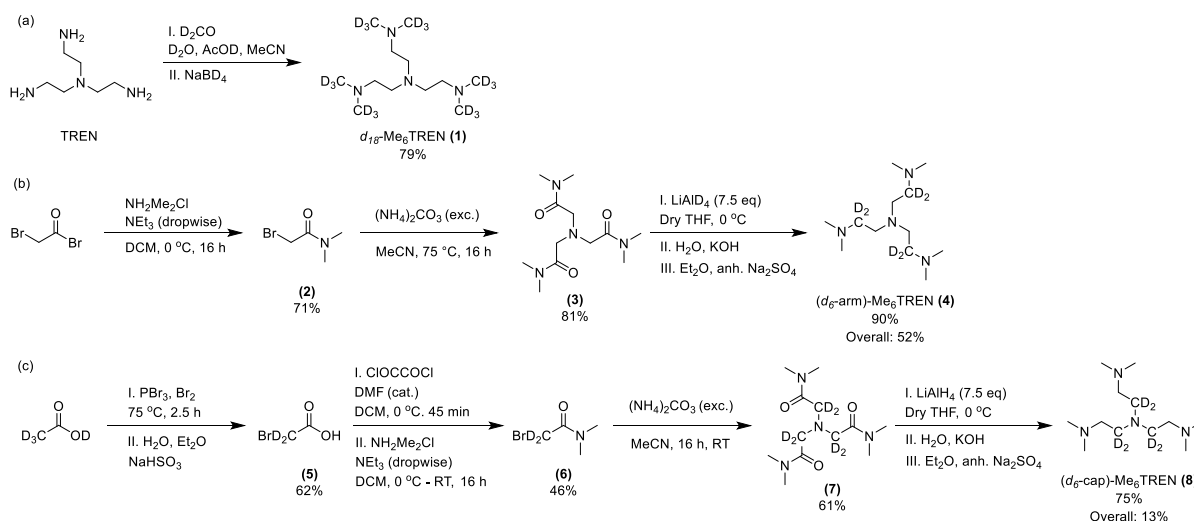
Me₆TREN can be synthesized in a facile manner from its precursor tris(2-aminoethyl)amine (TREN) by the Eschweiler–Clarke reaction.^[6] However, such methodology is best suited for large quantities that can be distilled for product isolation, which would be prohibitively expensive with deuterated reagents. Instead, a suitable small-scale synthesis proceeded by imine formation on the non-methylated tris(2-aminoethyl)amine (TREN) precursor scaffold by formaldehyde and subsequent reduction by NaBH₄ (Scheme 1a).^[7] This methodology was applied to synthesize *d*₁₈-Me₆TREN (**1**) in a 79% yield by replacing the formaldehyde solution with D₂CO in D₂O, followed by reduction with NaBD₄. This strategy is preferable to other methylation methods such as substitution, *e.g.* with CD₃I, as it avoids amine quaternization side-products. It also appears more convenient than the previously published synthesis of this compound, which involved refluxing a mixture of TREN, Et₃N and DCOOD (in large excess, 20 equivalents per TREN molecule) in DMSO-*d*₆ for 16 h at 150 °C, followed by tedious removal of excess Et₃N, DCOOD and DMSO-*d*₆ by distillation. Furthermore, the yield of this synthesis was not reported. Rather, the crude product was directly coordinated to CoCl₂, to yield the [CoCl₂(Me₆TREN)] product in small amounts (4.4% yield from TREN), the purity of which was not determined. Our synthesis, on the other hand, requires 1 h at room temperature for the first step and a few hours at 0 °C for the second one, followed by a simple work-up for the recovery of the pure product with a yield of 79% on a 300 mg scale (see details in the Experimental Section).

The syntheses of both selectively arm-labelled *d*₆ variants utilized a trisubstitution protocol at the central amine starting from acyl-based substrates. For (*d*₆-arm)-Me₆TREN (**4**) a 3-step synthesis was employed (Scheme 1b) beginning with commercially available bromoacetyl bromide, which underwent a condensation with dimethylamine generated *in-situ* to form the dimethylbromoacetamide substrate (**2**) needed for the trimerization step. Heating (**2**) in acetonitrile in the presence of excess ammonium carbonate in a tightly sealed pressure tube efficiently substituted the three protons of the *in situ*-generated ammonia to yield an amine bearing three amide functionalities (**3**).

Finally, amide reduction by LiAlD₄ gave the product (*d*₆-arm)-Me₆TREN (**4**). This synthetic approach for the synthesis of amines has been described on an old patent,^[8] but has not been previously applied to the generation of CD₂-labelled amines with use of LiAlD₄, to the best of our knowledge.

To synthesize the variant bearing deuterium labels on the methylene groups near the capping amine of Me₆TREN (**8**), acetic acid-*d*₄ was used as a commercially available, deuterated starting material (Scheme 1c). A Hell–Volhard–Zelinsky reaction^[9] with Br₂ and PBr₃ was employed to afford **5** after aqueous work up. Sodium bisulfite was found more convenient than sodium thiosulfate to remove residual liquid bromine, because workup with the former generated gases and NaBr while the latter additionally produced solids including solid sulfur that complicated subsequent gravity filtration. Then, an *in-situ* generation of deuterated bromoacetyl chloride by oxalyl chloride catalyzed by DMF and subsequent amidation by the same methodology used for the synthesis of **2** was carried out to synthesize **6** without the need to isolate the deuterated bromoacetyl halide intermediate. This paved the way for a similar tri-substitution, as per the conversion of **2** to **3**, yielding tris((*N,N*-dimethylaminocarbonyl)-*d*₂-methyl)amine (**7**), with the deuterium atoms installed prior to the final reduction. Reduction of the deuterated triamide intermediate **7** was carried out with LiAlH₄ to produce the labelled variant **8**.

In theory, the α methylene position in **3** should allow deprotonation and then deuteration in the presence of a solvent with mobile deuterons such as D₂O. This could then provide a more convenient route to **8** by a common intermediate. However, attempts at using base yielded either no appreciable exchange or degradation of the amide functionalities. Using potassium hydroxide as base in D₂O, especially with heating at 50 °C, degraded the amide functionalities, whereas potassium carbonate as base afforded negligible exchange regardless of temperature, albeit no degradation. It is worth noting that **3** dissolved in D₂O alone and held at 50 °C for 16 h did not degrade but afforded no exchange.



Scheme 1. Synthesis of Me₆TREN variants bearing regiospecific deuterium labels.

Should a fully-deuterated ethylene bridge be desired (i.e. d_{12} -Me₆TREN), this additional labelled product would be accessible by reduction of the deuterated triamide intermediate **7** with LiAlD₄. All above methodologies, however, do not suffice to achieve partial or full deuteration of the bridge in conjunction with deuterated methyl groups (i.e. d_{24} or d_{30} variants), should these more complex variants be desired, without the use of additional deuterated reagents.

The NMR and mass spectrometry analyses attest the isotopic purity of the three Me₆TREN isotopomers. The ¹H spectra (Figure 2a) reveal no significant proton resonance at the deuterated positions. Likewise, the ¹³C{¹H} NMR spectra (Figure 2b) show weak multiplet resonances for the CD₂ groups of **4** and **8** and for the CD₃ group of **1**. The expected patterns for these resonances are a 1:2:3:2:1 quintet for CD₂ and a 1:3:6:7:6:3:1 septet for CD₃. There is no evidence for the presence of significant amounts of CHD (in **4** and **8**) and CHD₂ (in **1**) isotopomers, which would yield an isotopically shifted 1:1:1 triplet and 1:2:3:2:1 quintet, respectively, with enhanced intensities due to the Overhauser effect of the H saturation.

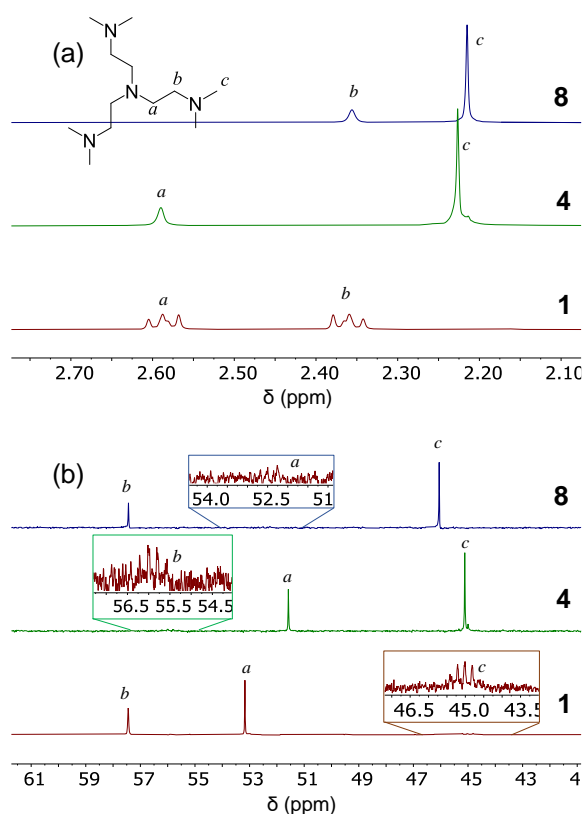


Figure 2. Expansions of the ¹H (a) and ¹³C{¹H} (b) NMR spectra in CDCl₃ of the three Me₆TREN isotopomers **1**, **4** and **8**. The full spectra are provided in the SI.

Conclusion

Herein, we have reported the syntheses of three Me₆TREN variants possessing regioselective deuterium labels either on all *N*-methyl groups of the peripheral amines or in each of the two different ethylene linker positions, using commercially accessible reagents, including relatively inexpensive deuterated reagents.

The synthesis of the d_{18} -Me₆TREN variant proceeded by imine formation with formaldehyde- d_2 as a solution in D₂O and subsequent reduction by NaBD₄, while the d_6 variants utilized a trisubstitution protocol by ammonium carbonate in a sealed pressure tube and subsequent reduction by lithium aluminum hydride/deuteride.

Experimental Section

Instrumentation. ¹H NMR (400 MHz) and ¹³C{¹H} NMR (101 MHz) spectra were recorded on Bruker Avance 400 and Avance III 400 instruments in CDCl₃. The chemical shifts are reported as δ (ppm) downfield from TMS, as calculated from the residual CHCl₃ and ¹³CDCl₃ resonances, respectively, as the internal standard. High resolution mass spectra (HRMS) were obtained from dichloromethane solutions with a Xevo G2 Q TOF spectrometer.

Materials. Anhydrous THF was obtained from an Innovative PURESOLV Solvent Purification System equipped with 4Å MS columns. Dimethyl ammonium chloride (99 %), oxalyl chloride (98 %), triethylamine (99 %, Acros Organics); bromine (99 %), phosphorus tribromide (98 %), ammonium carbonate (ACS grade ($\geq 95\%$), Sigma Aldrich); sodium sulfate (99 %, Carlo Erba Reagents); potassium hydroxide (86.7 %, Fisher Chemicals) and sodium bisulfate (p.a., Janssen) were purchased from commercial sources and used without further purification. LiAlH₄ was purchased and used as-is in a 1.0 M THF solution from Sigma-Aldrich. LiAlD₄ (98 atom % D) was purchased in a solid form from Aldrich Chemical Company and stored in a glovebox. Commodity solvents dichloromethane (DCM), acetonitrile (MeCN) and dimethyl formamide (DMF) were purchased from Carlo Erba Reagents, while Et₂O and MeOH were obtained from VWR Chemicals and used without further purification. Deuterated chemicals acetic acid- d_4 (99.5 atom % D), acetic acid- d_1 (99 atom % D), formaldehyde- d_2 (20 wt. % in D₂O, 98 atom % D) and NaBD₄ (98 atom % D) were purchased from Sigma-Aldrich and used as supplied.

Tris(2-(d_6 -*N,N*-dimethylamino)ethyl)amine (1). d_{18} -Me₆TREN was synthesized according to a modified literature procedure.^[7] In a 100 mL round-bottom flask, tris(2-aminoethyl)amine (232 mg, 1.6 mmol) was added to a solution of acetic acid- d_1 (10 mL) in MeCN (50 mL), followed by the addition of aqueous formaldehyde- d_2 (8.2 mL, 51.0 mmol, 20 wt. % in D₂O). The resulting mixture was stirred for 1 h at room temperature and then cooled to 0 °C. Subsequently, NaBD₄ (1.0 g, 23.3 mmol) was added in 5 portions (200 mg every 30 min). After stirring the reaction mixture at room temperature for 48 h, the solvent was removed. Aqueous sodium hydroxide (3 M) was then added to the residue until pH > 11 was achieved. The resulting solution was extracted with DCM (5 x 50 mL). The DCM extracts were combined, dried over MgSO₄, and the solvent was removed *in vacuo* to give the target compound as a pale-yellow oil (305 mg, 79%). HRMS (DCI-CH₄) *m/z*: [M+H]⁺ calcd for C₁₂H₁₃D₁₈N₄ 249.3679, found: 249.3678. ¹H NMR (400 MHz, CDCl₃): δ 2.59 (dd, *J* = 8.8, 5.9 Hz, 6H, 3x(CD₃)₂NCH₂CH₂), 2.36 (dd, *J* = 8.8, 5.9 Hz, 6H, 3x(CD₃)₂NCH₂CH₂). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 57.44 (3x(CD₃)₂NCH₂CH₂), 53.17 (3x(CD₃)₂NCH₂CH₂), 45.01 (m, 3x(CD₃)₂N).

2-Bromo-*N,N*-dimethylacetamide (2). In a 100 mL round-bottom flask, bromoacetyl bromide (4.00 g, 19.5 mmol) was added to a slurry of dimethylamine hydrochloride (2.43 g, 29.8 mmol) in DCM (35 mL) at 0 °C, followed by dropwise addition of triethylamine (3.5 g, 35 mmol, 4.8 mL). The resulting mixture was stirred overnight and filtered. The mother liquor was concentrated *in vacuo* to give a tan solid, which was extracted with diethyl ether (3 x 30 mL). The solvent was removed *in vacuo* to give 2.33 g of a brown oil (71 %) sufficiently pure to be used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 4.10 (s, 2H), 3.12 ppm (s, 3H), 3.01 ppm (s, 3H).

Tris((*N,N*-dimethylaminocarbonyl)methyl)amine (3). A 120 mL Schlenk flask with o-ring sealed screwable top was charged with crude 2-bromo-*N,N*-dimethylacetamide (**2**) (2.33 g, 14.0 mmol) and a stir bar. A 30 mL aliquot of MeCN was added, followed by ammonium carbonate (6.71 g, 69.8 mmol), in that order to prevent solid from aggregating on the bottom and preventing stirring. Then, another 30 mL aliquot of MeCN was added to rinse any debris off the walls of the vessel. The vessel was sealed tightly, and the contents were stirred at 75 °C for 16 h. During initial heating, significant bubbles appeared, with periodic bubbling afterwards. The resulting mixture was allowed to cool to room temperature, opened slowly, and filtered. The solid mass was rinsed with 20 mL acetonitrile. The solvent was removed *in vacuo* to give a brown oil, which was purified by silica column chromatography (eluent DCM/methanol – gradient 100:0 to 90:10, v/v. $R_f = 0.8$ for DCM/MeOH 9:1). The fractions containing pure product were combined and solvent was evaporated to give a crude product. Due to the hygroscopic nature of the product, it was again dissolved in diethyl ether (75 mL), dried with anhydrous Na₂SO₄, and filtered. The solvent was removed *in vacuo* to give 1.03 g (81%) of pure compound **3** as an odorless pale-gold oil. ¹H NMR (400 MHz, CDCl₃): δ 3.70 (s, 6H, 3xCH₂), 3.06 (s, 9H, 3xN-CH₃), 2.94 (s, 9H, 3xN-CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 169.34 (3xC(O)N(CH₃)₂), 55.72 (3xCH₂), 36.57 (3xCH₃), 35.42 (3xCH₃).

Tris(2-(*N,N*-dimethylamino)-2,2'-d₂-ethyl)amine (4). A 100 mL two-necked round bottom flask was charged with solid LiAlD₄ (73.3 mg, 1.75 mmol) in a glovebox under argon atmosphere. The sealed flask was taken out and connected to a Schlenk line. Under positive argon flow, a reflux condenser was installed and 10 mL of dry THF was added. Separately in an open-air vial, a solution of triamide intermediate **3** (74.0 mg, 272 μmol) in anhydrous THF (15 mL) was prepared, quickly drawn into a syringe, and inserted into a septum-outfitted neck. The solution was then added dropwise through the septum under argon flow to the flask containing LiAlD₄ under stirring. An additional amount of THF (5 mL) was used to rinse the vial and likewise added dropwise to insure a complete transfer of reagent. Gas evolution was observed, which intensified upon heating a solution to reflux, alongside the odor of amine. After 2 h, the gas evolution significantly subsided, and after an additional 4 h of reaction time, the mixture was allowed to cool to room temperature. The traces of remaining LiAlD₄ were quenched with deionized water (0.1 mL), followed by 15 wt% aqueous KOH (0.2 mL) and deionized water (0.1 mL), each of which were added dropwise. Then, the reaction mixture was diluted with diethyl ether (50 mL) and anhydrous Na₂SO₄ was added under stirring until the disappearance of the aqueous phase. After another 15 min of stirring, the resulting suspension was filtered and the mother liquor was concentrated *in vacuo* to give 58 mg (90 % step, 52% overall) of final product **4** as a pale-yellow liquid. HRMS (DCI-CH₄) m/z: [M+H]⁺ calcd for C₁₂H₂₅D₆N₄ 237.2925, found: 237.2917. ¹H NMR (400 MHz, CDCl₃): δ 2.59 (s, 6H, 3x(CH₃)₂NCD₂CH₂), 2.23 (s, 18H, 3x(CH₃)₂N), ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 56.02 (m, 3x(CH₃)₂NCD₂CH₂), 51.58 (3x(CH₃)₂NCD₂CH₂), 45.12 (3x(CH₃)₂N).

2-Bromoacetic-2,2-d₂ acid (5). Hell–Volhard–Zelinsky reaction conditions were adapted from the literature.^[10] A three-necked flask was charged with a stir bar, acetic acid-d₄ (4.00 g, 62.4 mmol), and PBr₃ (18 g, 66.6 mmol), and outfitted with a reflux condenser and septa. After cooling to 0 °C over an ice bath with stirring, liquid bromine (22.9 g, 143 mmol) was added dropwise by syringe. After the HBr evolution had ceased and the reaction mixture was additionally stirred at room temperature for 15 min, the reaction mixture was heated over a water bath at 75 °C for 3 h. After cooling to 0 °C, the reaction was quenched by the addition of deionized water (10 mL). Subsequently, 1 M sodium bisulfite solution was added until the color disappeared, and the sample became clear. The water layer was extracted four times with 100 mL of diethyl ether. The organic layers were combined, dried with anhydrous Na₂SO₄, and evaporated to yield a crystalline white solid (5.71 g, 40.5 mmol, 62%), which was directly used in the next step.

2-Bromo-2,2'-d₂-*N,N*-dimethylacetamide (6). A one-pot synthesis was performed in a 100 mL round bottom flask which was charged with a stir

bar, 2-bromoacetic-2,2-d₂ acid (5.71 g, 40.5 mmol), and 30 mL of DCM. The flask was capped with a septum, outfitted with a venting needle, and cooled to 0 °C over an ice bath. Oxalyl chloride (6.17 g, 48.6 mmol) was added dropwise by syringe under stirring, followed by 0.5 mL of DMF. The mixture was removed from the ice bath and allowed to stir for 1 h, at which gas evolution ceased. Then, the mixture was again cooled to 0 °C. Under stirring, dimethylamine hydrochloride (4.0 g, 49 mmol) was added and stirred for 10 min. Then, triethylamine (10.0 mL, 7.26 g, 71.7 mmol) was added dropwise. The mixture was brought to room temperature and allowed to stir, sealed, over the melting ice bath overnight, eventually reaching room temperature, over a course of 16 h. The mother liquor was concentrated *in vacuo* to give a tan solid, which was extracted with diethyl ether (3 x 30 mL). The solvent was removed *in vacuo* to give 3.10 g (18.44 mmol) of a gold oil (46%), which was sufficiently pure to be used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 3.06 (s, 3H, CH₃), 2.94 (s, 3H, CH₃).

Tris((*N,N*-dimethylaminocarbonyl)-d₂-methyl)amine (7). The procedure was identical to that of **3.5**, the exception being that 2-bromo-*N,N*-dimethylacetamide-d₂ (3.100 g, 18.44 mmol) was used instead of 2-bromo-*N,N*-dimethylacetamide alongside the corresponding quantity of ammonium carbonate (8.8 g, 92 mmol). The product was isolated from the otherwise identical column chromatography procedure as a pale-gold oil (1.05 g, 3.77 mmol, 61% yield). HRMS (DCI-CH₄) m/z: [M+H]⁺ calcd for C₁₂H₁₉D₆N₄O₃ 279.2303, found: 279.2306. ¹H NMR (400 MHz, CDCl₃): δ 3.04 (s, 9H, 3xCH₃), 2.92 (s, 9H, 3xCH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 169.85 (3xC(O)N(CH₃)₂), 55.03 (3xCD₂), 36.71 (3xCH₃), 35.47 (3xCH₃).

Tris(2-(*N,N*-dimethylamino)-1,1'-d₂-ethyl)amine (8). The procedure was identical to that of **3.6**, except that **7** (196 mg, 704 μmol) was used instead of **3**, and LiAlH₄ (200.4 mg, 5.280 mmol) was used instead of LiAlD₄. The final product after extraction and drying was obtained as a pale-gold oil (125 mg, 75% step, 13% overall). HRMS (DCI-CH₄) m/z: [M+H]⁺ calcd for C₁₂H₂₅D₆N₄: 237.2925, found: 237.2918. ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 6H, 3x(CH₃)₂NCH₂CD₂), 2.22 (s, 18H, 3x(CH₃)₂N), ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 57.43 (m, 3x(CH₃)₂NCH₂CD₂), 52.25 (3x(CH₃)₂NCH₂CD₂), 46.05 (3x(CH₃)₂N).

Supporting Information Summary

Characterization data (NMR and Mass spectra) for compounds **1**, **3**, **4**, **7** and **8** (10 pages).

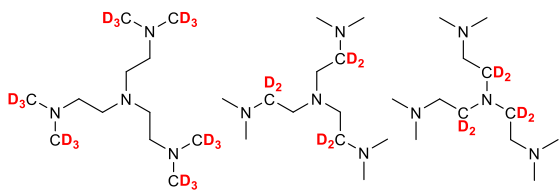
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Keywords: Deuterium labels • Regioselective deuteration • Tripodal ligand • Tris[2-(dimethylamino)ethyl]amine

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Simple synthetic routes to regioselectively deuterated variants of the common tris[2-(dimethylamino)ethyl]amine (Me₆TREN) ligand are described, where the deuterium labels are located either on the six methyl groups, on the three methylene groups adjacent to the NMe₂ arms or on the three methylene groups adjacent to the capping N atom.

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