

## Research Article

# On the specific rotation of deuterium-containing isotopomers of 2-dimethylaminocyclohexyl-1-trimethylammonium iodide

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## Summary

The specific rotation of a variety of differential isotopomers is reported. The difference in their specific rotation appears to be greater than their percentage mass difference and each isotopomer seems to rotate (the plane of) plane-polarized light differently. Copyright © 2005 John Wiley & Sons, Ltd.

**Key Words:** deuterium; isotopomers; optical rotation; *quasi*-enantiomeric; specific rotation

## Introduction

Compounds that are chiral by virtue of deuterium labelling are known to have small but significant specific rotations,  $\{[\alpha]_D^T\}$ , in the order  $\pm 0.5\text{--}2^\circ$ .<sup>1–3, †</sup> However, in certain cases, the specific rotation can be extremely high ( $-367^\circ$ )<sup>4</sup> due to a cooperative deuterium effect, and in other cases undetectable.<sup>5</sup> The relative conformation of certain deuteriated substrates has been shown to have a remarkable influence on their specific rotation<sup>6</sup> and this has been documented in a number of other studies.<sup>4</sup>

The magnitude of rotation (of the plane) of plane-polarized light has been shown to be influenced by optically active chromophores, such as polarizable aromatic rings.<sup>7,8</sup> Whilst a C–D bond is shorter, and consequently has lower polarizability than its parent C–H bond;<sup>1b</sup> the result of which may give rise to

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† Liquid crystals have been shown to give increased sensitivity for molecules that owe their chirality due to isotopic substitution.<sup>2</sup>

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lower specific rotations for deuterium-containing chiral isotopomers. Within the literature, it is apparent that very little attention has been focussed on this area. Most notably, Paquette and Mason have observed a decrease in specific rotation of deuterium-labelled apoborenes relative to their unlabelled variants.<sup>1b</sup> Whereas, Meyer and Lobo have reported a 3% reduction in the magnitude of the peak and trough (in the Cotton Effect) for a series of camphor D-labelled isotopomers relative to their non-labelled parent substrates.<sup>9</sup> Closer inspection of the literature has revealed conflicting views; in some cases a moderate decrease in the specific rotation for a deuterium-containing isotopomer has been shown,<sup>10,11</sup> whereas, others have shown a marginal increase in specific rotation.<sup>10</sup> By comparison, both unlabelled and D-labelled chiral isotopomers have been reported to have similar optical rotatory dispersion properties.<sup>7,12, ‡</sup> Within the literature, it is evident that a significant amount of attention has been focussed on probing differential isotopomers using vibrational optical activity<sup>13</sup> and studying their theoretical optical rotation.<sup>14, §</sup>

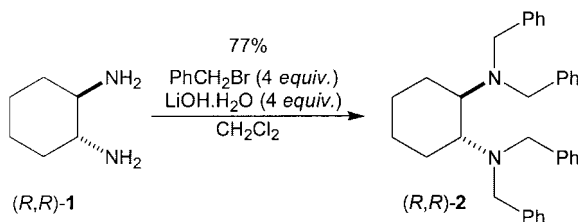
## Results and discussion

We have recently become interested in the synthesis of enantiomerically pure symmetrically *N,N'*-tetra-substituted 1,2-diamines, like (*R,R*)-**2**, through sequential alkylation of 1,2-diaminocyclohexane (*R,R*)-**1** mediated by lithium hydroxide monohydrate as the stoichiometric base (Scheme 1).<sup>15</sup> This methodology has been shown to be particularly versatile for S<sub>N</sub>2 active electrophiles, which are structurally related to benzyl bromide and allyl bromide.<sup>16</sup> Within a series of reports, we have extended this methodology towards related unsymmetrically *N,N'*-tetra-substituted 1,2-diamines derived from symmetrically *N,N'*-di-substituted 1,2-diamines.<sup>17</sup> Under these conditions, formation of the corresponding ammonium salt(s) through simple quaternatization of the resulting tertiary 1,2-diamine does not occur.<sup>18</sup>

In an attempt to probe the scope and limitation of this methodology,<sup>15–17,19</sup> we were interested in the use of methyl iodide as our S<sub>N</sub>2 active electrophile. Using our standard protocol,<sup>15</sup> addition of five equivalents of methyl iodide to a stirred solution of 1,2-diaminocyclohexane (*R,R*)-**1** and lithium hydroxide monohydrate (four equivalents) in dichloromethane, gave exclusively the ammonium iodide (*R,R*)-**3** in 87% yield (Scheme 1). This process must proceed via methylation of the corresponding tetramethyl-1,2-diamino cyclohexane (*R,R*)-**4**. This pathway was shown to be particularly efficient since addition of methyl iodide to a stirred solution of tetramethyl-1,2-diaminocyclohexane

‡By using optical rotatory dispersion.<sup>12</sup>

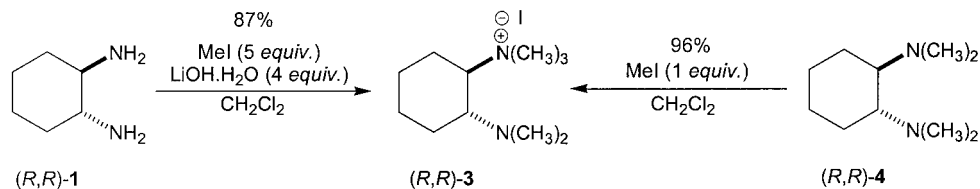
§For a quantum mechanical account of optical activity, see Rosenfeld.<sup>14c</sup>

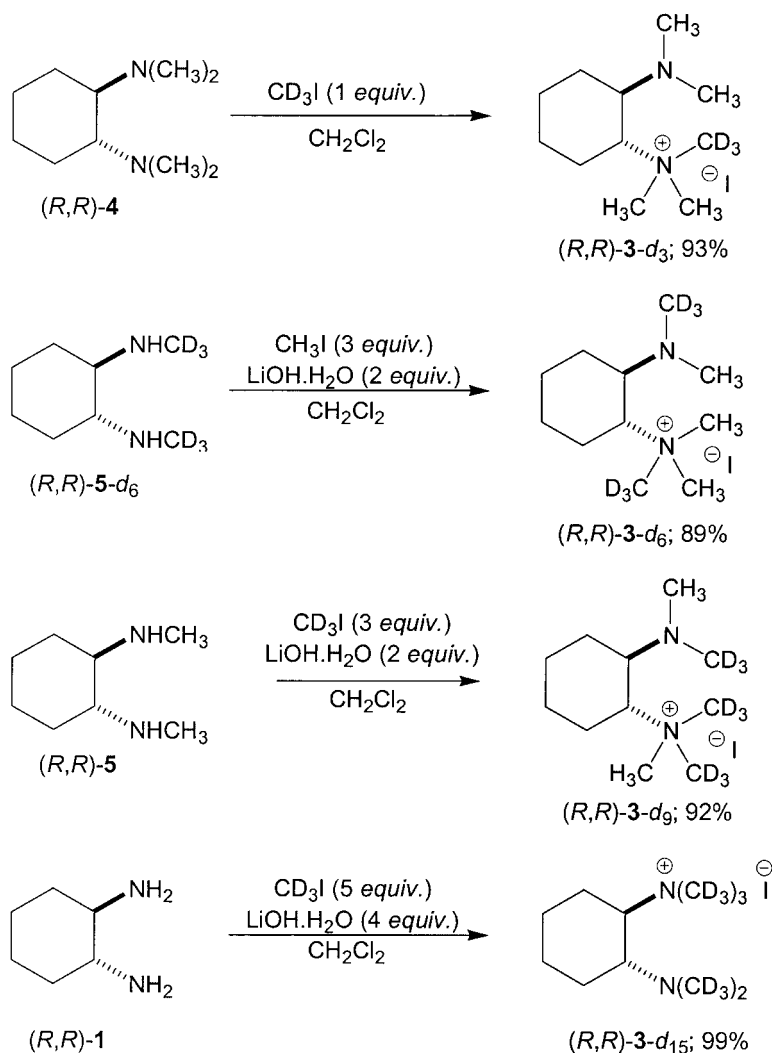
**Scheme 1.**

(*R,R*)-**4** in dichloromethane gave, the required ammonium iodide (*R,R*)-**3** in 96% yield (Scheme 2).

We next focussed our attention on synthesizing a series of non-racemizable deuterium-containing isotopomers (*R,R*)-**3-*d*<sub>3</sub>**, *d*<sub>6</sub>, *d*<sub>9</sub> and *d*<sub>15</sub> based on the parent ammonium iodide (*R,R*)-**3** in attempt to probe their specific rotations. We were interested in these particular derivatives due to their ease of synthesis, configurational stability, rich abundance of deuterium atoms and differential molecular masses. We first synthesized the isotopomeric ammonium iodides (*R,R*)-**3-*d*<sub>3</sub>**, (*R,R*)-**3-*d*<sub>9</sub>**, (*R,R*)-**3-*d*<sub>15</sub>**, and (*R,R*)-**3-*d*<sub>6</sub>** by simple addition of trideuteriomethyl iodide to the corresponding 1,2-diamines (*R,R*)-**4**, (*R,R*)-**5** and (*R,R*)-**1**, respectively (Scheme 3), and by addition of methyl iodide to the *N,N'*-di-(trideuteriomethyl)-diaminocyclohexane (*R,R*)-**9-*d*<sub>6</sub>**. These reactions proceeded efficiently giving a wide range of deuterium-containing enantiomerically pure isotopomeric ammonium iodides (*R,R*)-**3-*d*<sub>3</sub>**, (*R,R*)-**3-*d*<sub>6</sub>**, (*R,R*)-**3-*d*<sub>9</sub>** and (*R,R*)-**3-*d*<sub>15</sub>** in good yields (Scheme 3). By <sup>13</sup>C NMR spectroscopy, it is interesting to note the relative C–N chemical shifts for these parent isotopomers; the <sup>13</sup>C NMR chemical shift for the CH<sub>3</sub>–N<sup>+</sup> signal appears downfield relative to the CH–N signal—e.g. for (*R,R*)-**3-*d*<sub>3</sub>**, the chemical shifts for C–N<sup>+</sup>, CH–N, CH<sub>3</sub>–N<sup>+</sup> and CH<sub>3</sub>–N appear at 71.8, 64.5, 53.8 and 40.0 ppm, respectively.

With these isotopomers in hand, it was interesting to discover that their specific rotations differed considerably (Table 1). We had initially expected the

**Scheme 2.**



Scheme 3.

specific rotations to be marginally lower on increasing deuterium incorporation due to its dependence on concentration (g/ml)<sup>†,‡</sup> by assuming each

<sup>†</sup> Based on the difference in molarity, the specific rotation of a deuterium-labelled isotopomer is equal to  $[\alpha]_D^T$  (of the unlabelled substrate)  $\times (M_{d_0}/M_{d_n})$ , where  $M_{d_0}$  is the molecular mass of the unlabelled substrate and  $M_{d_n}$  is the molecular mass of the D-labelled substrate. From this, the assumed specific rotation for 3-*d*<sub>3</sub>, 3-*d*<sub>6</sub>, 3-*d*<sub>9</sub> and 3-*d*<sub>15</sub> is -42.37, -41.97, -41.60 and -40.8, respectively (based on the unlabelled ammonium iodide 3-*d*<sub>0</sub>) and -42.14, -41.45, -40.18 and -39.59, respectively (based on the unlabelled ammonium ion itself).

<sup>‡</sup> By assuming the rotation of the plane of plane-polarized light is unaltered by the presence of an isotopic label (or the change is negligible); the observed rotation of a labelled substrate can approximated to  $\alpha_{\text{obs(L)}} = \alpha_{\text{obs(U)}} \times RMM_U/RMM_L$  when all other variables are constant. Obviously,  $[\alpha]_D^T$  (labelled) =  $\alpha_{\text{obs(L)}}/c_1l_1$  and  $[\alpha]_D^T$  (unlabelled) =  $\alpha_{\text{obs(U)}}/c_2l_2$ . However,  $l_1 = l_2$  for the same polarimeter cell, and  $c_1 = g_{(L)}/ml_{(L)}$  and  $c_2 = g_{(U)}/ml_{(U)}$ . If we assume that  $ml_{(L)} = ml_{(U)}$ , and  $g_{(L)} = g_{(U)}$ , then  $c_1 = c_2$ . Therefore  $[\alpha]_D^T$  (labelled) =  $\alpha_{\text{obs(L)}}/c_1l_1 = (\alpha_{\text{obs(U)}} \times RMM_U/RMM_L)/c_2l_2 = [\alpha]_D^T$  (unlabelled)  $\times (RMM_U/RMM_L)$ .

**Table 1.**

Ammonium salt	$[\alpha]_{\text{D}}^{24}$
<b>3</b>	-42.8 ( <i>c</i> 1.5, CHCl <sub>3</sub> )
<b>3-<i>d</i><sub>3</sub></b>	-41.4 ( <i>c</i> 1.5, CHCl <sub>3</sub> )
<b>3-<i>d</i><sub>6</sub></b>	-35.7 ( <i>c</i> 1.5, CHCl <sub>3</sub> )
<b>3-<i>d</i><sub>9</sub></b>	-35.5 ( <i>c</i> 1.5, CHCl <sub>3</sub> )
<b>3-<i>d</i><sub>15</sub></b>	-26.6 ( <i>c</i> 1.2, CHCl <sub>3</sub> )

isotopomer had a similar magnitude of rotation (of the plane) of plane-polarized light. However, closer inspection<sup>¶</sup> revealed that each isotopomer intrinsically rotated (the plane of) plane-polarized light differently than its non-isotopomeric counterpart (*R,R*)-**3** due to their larger than expected differences in specific rotations. This presumably is due to the subtle differences between the deuterium atom (within a C–D bond) and the hydrogen atom (within a C–H bond), and the resulting properties these intrinsically play on their ability to rotate (the plane of) plane-polarized light. Increasing the relative abundance of deuterium labels present with a particular isotopomer could potential magnify this effect.<sup>1b,4</sup> However, due to the limited number of reported studies within this area and their conflicting outcomes, it is difficult to conclude to what degree this effect influences the specific rotation.

In conclusion, we report a novel and efficient procedure for the synthesis of isotopomeric pentamethyl ammonium salts (*R,R*)-**3-*d*<sub>3</sub>**, (*R,R*)-**3-*d*<sub>6</sub>**, (*R,R*)-**3-*d*<sub>9</sub>** and (*R,R*)-**3-*d*<sub>15</sub>**, derived from 1,2-diaminocyclohexane (*R,R*)-**1**, and have shown that these differential isotopomers rotate (the plane of) plane-polarized light differently. This perhaps is due to a number of factors;

- (a) the concentration effect (g/ml) and;
- (b) differential enantiomers rotate (the plane of) plane-polarized light differently.

Within our laboratory, we are currently exploring this phenomenon and these studies will be reported in due course.

## Experimental

All reactions were carried out under nitrogen using oven-dried glassware. Proton and carbon NMR spectra were recorded on a Bruker AM 400 Fourier transform spectrometer using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield from tetramethylsilane. Infrared spectra were recorded on a Shimadzu 8300 FTIR machine. The levels of D-incorporation were determined by a combination of mass and proton NMR spectra. The specific rotations were measured on a Jasco P-1010 polarimeter between 24.1 and 24.8°C. Each sample was subject to three

separate optical rotations ( $\alpha_{\text{obs}}$ ) and the average of these three readings ( $\alpha_{\text{ave}}$ ) were used to calculate the specific rotation. For consistency, the same volumetric flask (2 ml) and analytical balance were used in each operation. For mass spectrometry, samples were sent to the EPSRC national Mass Spectrometry Service Centre, Swansea.

*(-)-N,N,N,N',N'-2-Dimethylaminocyclohexyl-1-trimethylammonium iodide (R,R)-3*

Methyl iodide (0.24 g, 0.11 ml, 1.7 mmol) was added to a stirred solution of *(-)-N,N,N,N'-tetramethyl-1,2-diaminocyclohexane (R,R)-4* (0.29 g, 1.7 mmol) in dichloromethane (5 ml). The solution was stirred for 30 min. The solvent was removed under reduced pressure to give *(-)-N,N,N,N',N'-2-dimethylaminocyclohexyl-1-trimethylammonium iodide (R,R)-3* (0.46 g, 87%) as a white solid;  $R_F$  [(chloroform/diethyl ether/acetone) 1:1:1] 0.10;  $[\alpha]_{\text{D}}^{24} = -48.8$  ( $c$  1.5,  $\text{CHCl}_3$ ); mp  $126^\circ\text{C}$ ;  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  3390, 2939 and 1454;  $\delta_{\text{H}}$ (270 MHz,  $\text{CDCl}_3$ ) 4.13 (1 H, td,  $J = 11.0$  and 3.7 Hz,  $\text{N}^{\oplus}\text{CH}$ ), 3.44 (9 H, s,  $3 \times \text{N}^{\oplus}\text{CH}_3$ ), 2.68 (1 H, td,  $J = 11.0$  and 3.2 Hz, NCH), 2.37 (1 H, m, CH), 2.26 (6 H, s,  $2 \times \text{NCH}_3$ ), 1.97–1.72 (2 H, m,  $2 \times \text{CH}$ ) and 1.62–1.15 (5 H, m,  $5 \times \text{CH}$ );  $\delta_{\text{C}}$ (100 MHz,  $\text{CDCl}_3$ ) 71.8 ( $\text{N}^{\oplus}\text{-C}$ ), 64.5 (NC), 53.8 ( $\text{N}^{\oplus}\text{-CH}_3$ ), 40.0 ( $\text{N-CH}_3$ ), 27.1, 24.9, 23.9 and 22.5 ( $4 \times \text{CH}_2$ ) [found  $(\text{M-I})^+$  185.2010,  $\text{C}_{11}\text{H}_{25}\text{N}_2$  requires M-I, 185.2018].

*(-)-N,N,N,N'-2-Dimethylaminocyclohexyl-1-dimethyltrideuterioammonium iodide (R,R)-3-d<sub>3</sub>*

Methyl iodide- $d_3$  (0.19 g, 0.08 ml, 1.3 mmol) was added to a stirred solution of *(-)-N,N,N,N'-tetramethyl-1,2-diaminocyclohexane (R,R)-4* (0.22 g, 1.3 mmol) in dichloromethane (5 ml). The solution was stirred for 30 min. The solvent was removed under reduced pressure to give *(-)-N,N,N,N'-2-dimethylaminocyclohexyl-1-dimethyltrideuterioammonium iodide (R,R)-3-d<sub>3</sub>* (0.38 g, 93%) as a white solid;  $R_F$  [(chloroform/diethyl ether/acetone) 1:1:1] 0.10;  $[\alpha]_{\text{D}}^{24} = -41.4$  ( $c$  1.5,  $\text{CHCl}_3$ ); mp  $126^\circ\text{C}$ ;  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  3390, 2939, 2100 (CD) and 1454;  $\delta_{\text{H}}$ (270 MHz,  $\text{CDCl}_3$ ) 4.13 (1 H, td,  $J = 11.0$  and 3.7 Hz,  $\text{N}^{\oplus}\text{-CH}$ ), 3.46 (6 H, s,  $2 \times \text{N}^{\oplus}\text{CH}_3$ ), 2.68 (1 H, td,  $J = 11.0$  and 3.2 Hz, NCH), 2.37 (1 H, m, CH), 2.26 (6 H, s,  $2 \times \text{NCH}_3$ ), 1.97–1.72 (2 H, m,  $2 \times \text{CH}$ ) and 1.62–1.15 (5 H, m,  $5 \times \text{CH}$ );  $\delta_{\text{C}}$ (100 MHz,  $\text{CDCl}_3$ ) 71.8 ( $\text{N}^{\oplus}\text{C}$ ), 64.5 (NC), 53.8 ( $2 \times \text{N}^{\oplus}\text{CH}_3$ ), 52.9 (1 C, septet,  $^1J_{\text{C-D}} \sim 20$  Hz;  $\text{N}^{\oplus}\text{CD}_3$ ), 40.0 ( $\text{NCH}_3$ ), 27.1, 24.9, 23.9 and 22.5 ( $4 \times \text{CH}_2$ ) [found  $(\text{M-I})^+$  188.2200,  $\text{C}_{11}\text{H}_{12}\text{D}_3\text{N}_2$  requires M-I, 188.2201].

*(-)-N,N',N'-2-Methyltrideuterioaminocyclohexyl-1-dimethyltrideuterioammonium iodide (R,R)-3-d<sub>6</sub>*

Methyl iodide (0.30 g, 0.13 ml, 2.1 mmol) was added to a solution of *(-)-N,N'-dimethyl-d<sub>6</sub>-1,2-diaminocyclohexane (R,R)-9-d<sub>6</sub>* (0.12 g, 0.7 mmol) in dichloro-

omethane (5 ml). The solution was stirred for 30 min. Lithium hydroxide monohydrate (58 mg, 1.4 mmol) was added and stirring continued for another hour. The mixture was decanted from inorganic solids and solvent was removed to give (-)-*N,N',N'*-2-methyltrideuterioaminocyclohexyl-1-dimethyltrideuterioammonium iodide (*R,R*)-**3-d<sub>6</sub>** (0.24 g, 89%) as a white solid;  $R_F$  [(chloroform/diethyl ether/acetone) 1:1:1] 0.10;  $[\alpha]_D^{24} = -35.7$  (*c* 1.5, CHCl<sub>3</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3390, 2939 and 2100 (CD) and 1454;  $\delta_H(270 \text{ MHz, CDCl}_3)$  4.14 (1 H, td,  $J = 11.0$  and 3.7 Hz, N<sup>⊕</sup>CH), 3.43 (6 H, s, 2 × N<sup>⊕</sup>CH<sub>3</sub>), 2.68 (1 H, td,  $J = 11.0$  and 3.2 Hz, NCH), 2.39 (1 H, m, CH), 2.26 (3 H, s, NCH<sub>3</sub>), 2.04–1.76 (2 H, m, 2 × CH) and 1.58–1.17 (5 H, m, 5 × CH);  $\delta_C(100 \text{ MHz, CDCl}_3)$  72.1 (N<sup>⊕</sup>C), 64.9 (NC), 53.0 (2 × N<sup>⊕</sup>CH<sub>3</sub>), 52.9 (1 C, septet,  $^1J_{C-D} \sim 20 \text{ Hz; N}^{\oplus}\text{CD}_3$ ), 40.1 (NCH<sub>3</sub>), 40.0 (1 C, septet,  $^1J_{C-D} \sim 20 \text{ Hz; NCD}_3$ ), 27.1, 24.9, 23.9 and 22.5 (4 × CH<sub>2</sub>) [found (M-I)<sup>+</sup> 191.2389, C<sub>11</sub>H<sub>19</sub>D<sub>6</sub>N<sub>2</sub> requires M-I, 191.2389].

*(-)-N,N'*-2-Methyltrideuterioaminocyclohexyl-1-methylditrideuterioammonium iodide (*R,R*)-**3-d<sub>9</sub>**

Methyl iodide-*d*<sub>3</sub> (0.90 g, 0.40 ml, 6.3 mmol) was added to a stirred solution of (-)-*N,N'*-dimethyl-1,2-diaminocyclohexane (*R,R*)-**9** (0.30 g, 2.1 mmol) in dichloromethane (5 ml). The solution was stirred for 30 min. Lithium hydroxide monohydrate (0.15 g, 4.2 mmol) was added and stirring continued for another hour. The mixture was decanted from inorganic solids and solvent was removed to give (-)-*N,N'*-2-methyltrideuterioaminocyclohexyl-1-methylditrideuterioammonium iodide (*R,R*)-**3-d<sub>9</sub>** (0.61 g, 92%) as a white solid;  $R_F$  [(chloroform/diethyl ether/acetone) 1:1:1] 0.10;  $[\alpha]_D^{24} = -35.5$  (*c* 1.5, CHCl<sub>3</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3390, 2939 and 2100 (CD) and 1454;  $\delta_H(270 \text{ MHz, CDCl}_3)$  4.11 (1 H, td,  $J = 11.0$  and 3.7 Hz, N<sup>⊕</sup>CH), 3.43 (3 H, s, N<sup>⊕</sup>CH<sub>3</sub>), 2.67 (1 H, td,  $J = 11.0$  and 3.2 Hz, NCH), 2.38 (1 H, m, CH), 2.26 (3 H, s, NCH<sub>3</sub>), 1.96–1.76 (2 H, m, 2 × CH) and 1.58–1.17 (5 H, m, 5 × CH);  $\delta_C(100 \text{ MHz, CDCl}_3)$  72.0 (N<sup>⊕</sup>C), 64.9 (NC), 52.8 (N<sup>⊕</sup>CH<sub>3</sub>), 52.5 (2 C, br septet,  $^1J_{C-D} \sim 20 \text{ Hz; 2} \times \text{N}^{\oplus}\text{CD}_3$ ), 40.2 (NCH<sub>3</sub>), 40.1 (1 C, septet,  $^1J_{C-D} \sim 20 \text{ Hz; NCD}_3$ ), 27.1, 24.9, 23.9 and 22.5 (4 × CH<sub>2</sub>) [found (M-I)<sup>+</sup> 194.2578, C<sub>11</sub>H<sub>16</sub>D<sub>9</sub>N<sub>2</sub> requires M-I, 194.2577].

*(-)-N,N,N',N',N'*-2-Ditrideuterioaminocyclohexyl-1-tri(trideuterio)ammonium iodide (*R,R*)-**3-d<sub>15</sub>**

Methyl iodide-*d*<sub>3</sub> (1.05 g, 0.47 ml, 7.5 mmol) was added to a stirred solution of (-)-1,2-diaminocyclohexane (*R,R*)-**1** (0.17 g, 1.5 mmol) in dichloromethane (5 ml). The solution was stirred for 30 min. Lithium hydroxide monohydrate (0.30 g, 7.5 mmol) was added sequentially over 2 h. The mixture was then decanted from inorganic solids and solvent was removed to give (-)-*N,N,N',N',N'*-ditrideuterioaminocyclohexyl-1-tri(trideuterio)ammonium

iodide (*R,R*)-**3-d**<sub>15</sub> (0.46 g, 99%) as a white solid;  $R_F$  [(chloroform/diethyl ether/acetone) 1:1:1] 0.10;  $[\alpha]_D^{24} = -26.6$  ( $c$  1.2, CHCl<sub>3</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2048 (C–D);  $\delta_H(270 \text{ MHz, CDCl}_3)$  4.08 (1 H, td,  $J = 11.0$  and 3.7 Hz, N<sup>⊕</sup>CH), 2.67 (1 H, td,  $J = 11.0$  and 3.2 Hz, NCH), 2.35 (1 H, m, CH), 1.96–1.79 (2 H, m, 2 × CH) and 1.58–1.17 (5 H, m, 5 × CH);  $\delta_C(100 \text{ MHz, CDCl}_3)$  72.0 (N<sup>⊕</sup>C), 64.8 (NC), 52.5 (3 C, br septet,  $^1J_{C-D} \sim 20 \text{ Hz}$ ; 3 × N<sup>⊕</sup>CD<sub>3</sub>), 40.1 (3 C, br septet,  $^1J_{C-D} \sim 20 \text{ Hz}$ ; 2 × NCD<sub>3</sub>), 27.1, 24.9, 23.9 and 22.5 (4 × CH<sub>2</sub>) [found (M–I)<sup>+</sup> 200.2951, C<sub>11</sub>H<sub>10</sub>D<sub>15</sub>N<sub>2</sub> requires M–I, 200.2954].

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