

# SYNTHESIS OF DEUTERATED 3-METHYLCYCLOHEXANONES

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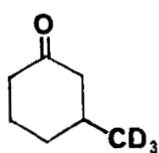
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## SUMMARY

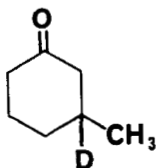
The efficient, regiospecific preparation of the series of deuterated 3-methylcyclohexanones is described.

Key words: deuterated cyclohexanones

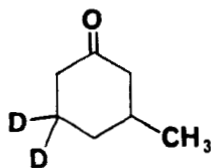
The deuterated 3-methylcyclohexanones 1-4 are of interest for the detailed assignment of the vibrational spectra and determination of the vibrational force field.<sup>1</sup> The nature of these studies requires material labeled with a high degree of regiospecificity and isotopic purity. We report herein the efficient, regiospecific preparation of the title compounds.



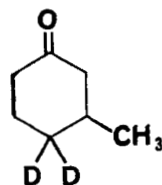
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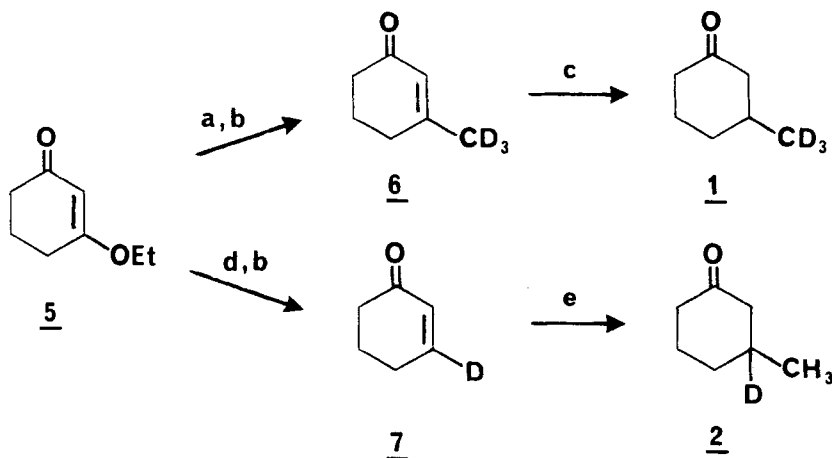


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Compounds 1 and 2 were prepared from 3-ethoxycyclohexenone 5 by the route shown in Scheme 1. Treatment of 5 with the Grignard reagent derived from  $^2\text{H}_3$ -methyl iodide<sup>2</sup> followed by acid-catalyzed elimination affords cyclohexenone 6. Our attempts to reduce this compound by hydrogenation using several catalyst systems were complicated by allylic hydrogen exchange which resulted in deuterium loss at the methyl group. Reduction of 6 using lithium in liquid ammonia afforded the desired 3-( $^2\text{H}_3$ -methyl)cyclohexanone 1 in 73% overall yield from 5.

Deuterated 3-methylcyclohexanone 2 has been previously prepared by dissolving metal reduction of the corresponding cyclohexenone in the presence of a deuterated amine.<sup>3</sup> This procedure requires the synthesis and purification of the requisite amine solvent; consequently we investigated a more efficacious route to 2. Reduction of 5 with  $\text{LiAlD}_4$  and acid-catalyzed elimination gave the  $\beta$ -deuterated cyclohexenone 7.<sup>4</sup> Treatment of this intermediate with lithium dimethylcuprate afforded 3- $^2\text{H}_1$ -3-methylcyclohexanone 2.

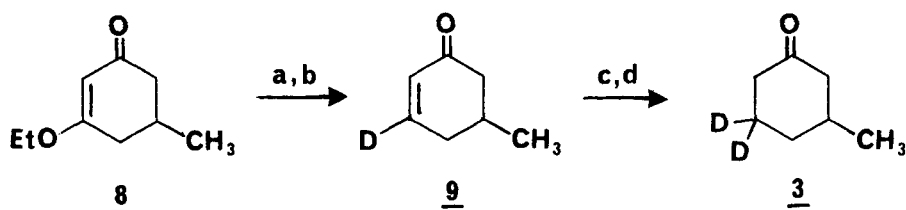
Scheme 1



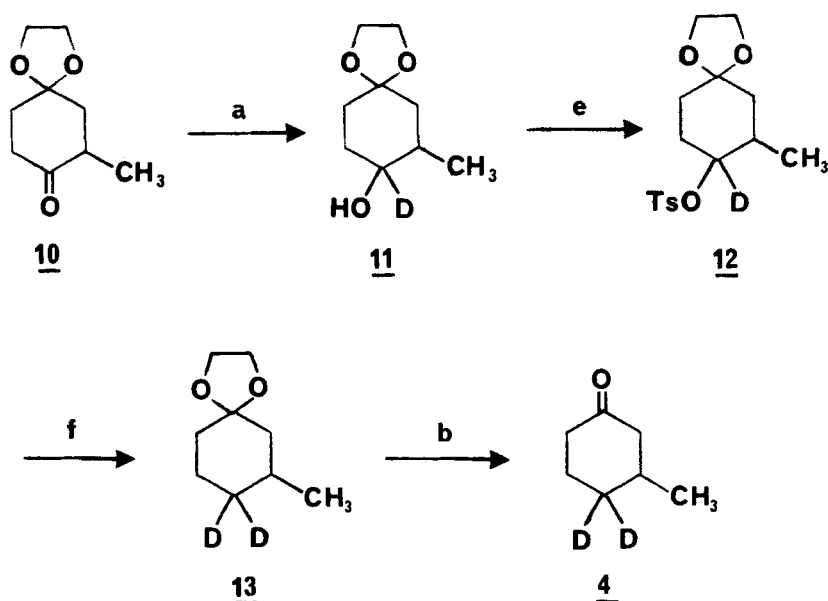
- a)  $\text{CD}_3\text{MgI}$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ$ ; b)  $1\text{ N HCl}$ ,  $\text{H}_2\text{O}$ , THF; c)  $\text{Li}$ ,  $\text{NH}_3$ ; d)  $\text{LiAlD}_4$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ$ ; e)  $(\text{CH}_3)_2\text{CuLi}$ ,  $\text{Et}_2\text{O}$ ,  $-78^\circ$ .

The bis-deuterated 3 was prepared from 3-ethoxy-5-methylcyclohexenone 8<sup>5</sup> by the sequence illustrated in Scheme 2. Reduction of 8 with  $\text{LiAlD}_4$  and acidic workup yielded cyclohexenone 9. Conjugate reduction<sup>6</sup> followed by treatment with base (to wash deuterium from the  $\alpha$ -position) afforded 5,5- $^2\text{H}_2$ -3-methylcyclohexanone 3.

Scheme 2



Scheme 3



a)  $\text{LiAlD}_4$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ$ ; b)  $1\text{ N HCl}$ ,  $\text{H}_2\text{O}$ ,  $\text{THF}$ ; c)  $\text{Na}_2\text{Fe}(\text{CO})_4$ ,  $\text{Fe}(\text{CO})_5$ ,  $\text{CH}_3\text{CO}_2\text{D}$ ; d)  $\text{K}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ ; e)  $\text{TsCl}$ ,  $\text{pyr}$ ,  $0^\circ$ ; f)  $\text{LiEt}_3\text{BD}$ ,  $\text{THF}$ ,  $0^\circ$ .

Table 1. 360 MHz NMR spectra of 3-methylcyclohexanones a,b

	H <sub>2a</sub>	H <sub>2e</sub>	H <sub>3</sub>	H <sub>4a</sub>	H <sub>4e</sub>	H <sub>5a</sub>	H <sub>5e</sub>	H <sub>6a</sub>	H <sub>6e</sub>	H <sub>7</sub>
3-methylcyclohexanone	2.36, bt, J=13 Hz (2H) <sup>a</sup>	2.01, t, J=12.6 Hz	1.90, m J=19.4, 11.6, 3.7 Hz	1.32, ddd, J=11.4 Hz	1.85, m (2H) <sup>a,b</sup>	2.08, m	1.66, m	2.35, bt, J=13 Hz (2H) <sup>a</sup>	2.23, dt, J=13, 5.8 Hz	1.01, d J=6.2 Hz (3H)
3-(d <sub>3</sub> -methyl)cyclohexanone (1)	2.36, bt, J=13 Hz (2H) <sup>a</sup>	2.00, t, J=13.2 Hz	1.87, m (2H) <sup>a,b</sup>	1.32, bq, J=11.4 Hz	1.87, m (2H) <sup>a,b</sup>	2.03, m	1.65, m	2.36, bt, J=13 Hz (2H) <sup>a</sup>	2.23, dt, J=13.6, 1 Hz	---
3-d <sub>1</sub> -3-methylcyclohexanone (2)	2.35, bt, J=13.9 Hz (2H) <sup>a</sup>	1.99, bd, J=12.9 Hz	---	1.32, bt, J=12 Hz	1.84, bd, J=12 Hz	2.05, m	1.66, m	2.35, bt, J=13.9 Hz (2H) <sup>a</sup>	2.23, dt, J=13.9, 6 Hz	1.01, s (3H)
5,5-d <sub>2</sub> -3-methylcyclohexanone (3)	2.36, bt, J=12 Hz	2.01, t, J=12 Hz	1.91, m	1.32, t, J=11.7	1.85, bd, J=11.7	---	---	2.33, d, J=14.3 Hz	2.22, d J=14.3 Hz	1.02, d, J=6.3 Hz (3H)
4,4-d <sub>2</sub> -3-methylcyclohexanone (4)	2.35, bt, J=15 Hz (2H) <sup>a</sup>	2.01, t, J=12.5 Hz	1.89, m	---	---	2.05, m	1.64, m	2.35, bt, J=15 Hz (2H) <sup>a</sup>	2.23, dt, J=13.6, 2 Hz	1.01, d, J=6.3 Hz (3H)

a) chemical shifts are reported in ppm downfield from internal TMS.

b) asterisk (\*) denotes overlapping or interchangeable assignments.

Finally, the synthesis of 4,4- $^2\text{H}_3$ -3-methylcyclohexanone 4 was achieved as shown in Scheme 3. Reduction of the readily available ketone 10<sup>7</sup> with  $\text{LiAlD}_4$  afforded alcohol 11 as a mixture of diastereomers. Tosylation of 11 gave 12 which was subsequently reduced with lithium triethyldeuteroborate<sup>8</sup> to give 13. Deketalization of 13 afforded the desired product 4 in 52% overall yield from 10.

The individual proton resonances of 1-4 were clearly resolved at 360 MHz (Table 1). Based on NMR and mass spectral analysis and the isotopic purities of the starting materials, we estimate the isotopic purity of the deuterated products to be greater than 95% in each case. In summary, the regioselectively deuterated 3-methylcyclohexanones 1-4 have been prepared in good yield and with high isotopic purity. The preparation of 1-4 in optically pure form will be the subject of a future communication from these laboratories.

### Experimental

Infrared spectra were determined on a Beckman 4220 spectrometer. Nuclear magnetic resonance spectra were measured on a Bruker WM-360 and a Varian Associates T-60. All chemical shifts are reported in parts per million ( $\delta$ ) downfield from internal tetramethylsilane. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Gas chromatographic analyses were performed on a Varian 3700 using a 50 cm OV-101 column.

Deuterated reagents were obtained as follows:  $\text{d}_3$ -methyl iodide (99% gm/atm D, Aldrich) lithium triethyldeuteroborate (Super Deuteride, Aldrich), lithium aluminum deuteride (98% gm/atm D, Chemalog), methanol  $\text{d}_4$  (99.5% gm/atm D, Merck), acetic acid- $\text{d}_1$  (98% gm/atm D, Aldrich).

#### 3-( $^2\text{H}_3$ -methyl)-2-cyclohexenone (6)

Deuterated methyl Grignard reagent was prepared by slow addition of 10.0 g (69 mM)  $\text{d}_3$ -methyl iodide to a stirred suspension of Mg metal (1.65 g, 69 mM) in

100 mL of dry ether at 0°. To the resulting ice-cold solution was added 3-ethoxy-2-cyclohexenone 5 (8.01 g, 57 mM) in 15 mL of dry ether. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. After cooling to 0°, the reaction mixture was quenched by the careful addition of 5 mL of H<sub>2</sub>O. The resulting solution was filtered, combined with 75 mL of 1 N HCl and stirred 2 h at room temperature. The organic layer was separated and the aqueous layer was extracted with two 50 mL portions of ether. The combined organic layers were washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Distillation of the residue under aspirator pressure (bp 88-94°) afforded cyclohexenone 6 as a pale oil, 5.22 g, 82%. IR (plate): 2240(w), 1690 cm<sup>-1</sup>.

NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.90 (bs, 1H), 2.2-1.8 (m, 6H).

#### 3-(<sup>2</sup>H<sub>3</sub>-methyl)-cyclohexanone (1)

To a vigorously stirred solution of lithium (.67 g, 96 mM) in 140 mL distilled ammonia was added 3-(<sup>2</sup>H<sub>3</sub>-methyl)-cyclohexanone 6 (5.20 gm, 46 mM) in 20 mL of dry ether. The reaction mixture was stirred 1/2 h at ammonia reflux and then quenched by addition of solid NH<sub>4</sub>Cl. The ammonia was allowed to evaporate and the residue was taken up in 100 mL of ether, washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub> and concentrated at reduced pressure. Flash chromatography of the crude product (silica gel, 10:1 pentane:ether) followed by bulb-to-bulb distillation (oven temperature 180°) afforded 4.71 g (89%) of cyclohexanone 1 as a water-white oil. IR(plate): 2205, 1713 cm<sup>-1</sup>.

MS (EI, 70 eV): m/e 72 (100%), 97 (13%), 115 (m<sup>+</sup>, 31%).

#### 3-<sup>2</sup>H<sub>1</sub>-5-methyl-2-cyclohexenone (9)

To a stirred suspension of LiAlD<sub>4</sub> (1.00 gm, 24 mM) in 100 mL of anhydrous ether at 0° was added dropwise cyclohexenone 8 (6.80 gm, 44 mM) in 30 mL of ether. Following completion of the addition, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The reaction was

quenched by the careful addition of 1 mL of  $\text{H}_2\text{O}$ , 1 mL of 15%  $\text{NaOH}$  and 3 mL of  $\text{H}_2\text{O}$ . The mixture was filtered, combined with 30 mL of 1 *N*  $\text{HCl}$  and stirred for 1 h. The organic layer was separated, washed with 75 mL portions of saturated  $\text{NaHCO}_3$  and brine and dried over  $\text{MgSO}_4$ . Filtration and concentration at reduced pressure afforded 4.33 g of cyclohexenone 9 as a pale oil. The product so obtained was of sufficient purity to allow further transformation without additional purification. An analytical sample was prepared by flash chromatography (silica gel, 5:1 pentane:ether) and bulb-to-bulb distillation (oven temperature  $220^\circ$ ) which gave 9 as a water-white oil. IR (plate): 2235, 1680,  $1605\text{ cm}^{-1}$ .

NMR (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.95 bs, (1H), 2.90-1.90 (m, 5H), 1.05 (d,  $J$  = 6 Hz, 3H).

#### 5,5- $^2\text{H}_2$ -3-methylcyclohexanone (3)

$\text{Na}_2\text{FeCO}_4$  (6.01 g, 28 mM) and  $\text{d}_1$ -acetic acid (3.70 g, 61 mM) were combined in 50 mL of dry THF. To the resulting deep purple solution was added cyclohexenone 9 (2.23 g, 20 mM) in 5 mL of THF. After stirring for 24 h the reaction mixture was diluted with 150 mL of ether and carefully poured into 150 mL of an ice-cold solution of 5%  $\text{NaOCl}$ . The aqueous layer was extracted with an equal volume of ether and the combined organic layers were washed with  $\text{H}_2\text{O}$  and brine, and dried over  $\text{MgSO}_4$ . Concentration under reduced pressure afforded a dark oil which was combined with 40 mL of 5% aqueous  $\text{K}_2\text{CO}_3$ . The resulting mixture was stirred at reflux for 6 h. After cooling, the mixture was extracted with three 50 mL portions of ether and the combined organic layers were washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residual oil was subjected to flash chromatography (10:1 pentane:ether) followed by bulb-to-bulb distillation (oven temperature  $180^\circ$ ) to give cyclohexanone 3 (1.80 g, 79%) as a water-white oil. IR (plate): 2208,  $1713\text{ cm}^{-1}$ .

MS (EI, 70 eV):  $m/e$  = 69 (100%), 99 (9%), 114 ( $\text{M}^+$ , 26%).

#### 3- $^2\text{H}_1$ -3-methylcyclohexanone (2)

A solution of lithium dimethylcuprate was prepared from 9.77 g (51 mM)

of cuprous iodide and 60 mL of methyllithium (108 mM, 1.8 M in ether) in 180 mL of anhydrous ether and cooled to  $-78^{\circ}$ . Added dropwise over 1/4 h was cyclohexenone 7<sup>4</sup> (3.50 g, 36 mM) in 10 mL of ether. The resulting bright yellow mixture was warmed to  $0^{\circ}$  over 1 h and stirred an additional hour at  $0^{\circ}$ . The reaction mixture was poured into an ice-cold solution of saturated  $\text{NH}_4\text{Cl}$  and stirred vigorously for 1/4 h. The aqueous layer was extracted with three 75 mL portions of ether and the combined organic layers were washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Distillation of the residual oil afforded 3.42 g (84%) of cyclohexanone 2 as a water-white oil (b.p.  $168-170^{\circ}$ ). IR (plate): 2205, 1715  $\text{cm}^{-1}$ .

MS (EI, 70 eV):  $m/e$  = 70 (100%), 98 (11%), 113 ( $\text{M}^+$ , 32%).

8-<sup>2</sup>H<sub>1</sub>-8-hydroxy-7-methyl-1,4 dioxaspiro[4.5]decane (11)

A suspension of  $\text{LiAlD}_4$  (.680 g, 16 mM) in 120 mL of dry ether was cooled to  $0^{\circ}$ . Added dropwise over 1/2 h was a solution of 5.55 g (32 mM) of ketone 10 in 20 mL ether. The reaction mixture was allowed to warm to room temperature and stirred an additional 1 hr, at which time the mixture was quenched by careful addition of .6 mL of  $\text{H}_2\text{O}$ , .6 mL of 15% NaOH and 2 mL of  $\text{H}_2\text{O}$ . The reaction mixture was filtered, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . Concentration under reduced pressure followed by flash chromatography of the residual oil (silica gel, 2:1 hexane: ethyl acetate) and bulb-to-bulb distillation (oven temperature  $170^{\circ}$ ) afforded 5.20 g (92%) of alcohol 11 as a pale oil. IR (plate): 3600, 2180(w)  $\text{cm}^{-1}$ .

NMR (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.90 (s, 4H), 3.05 (bs, 1H) 1.95-1.20 (m, 7H) 1.02, 1.05 (2 overlapping d, 3H).

8-<sup>2</sup>H<sub>1</sub>-8-(p-toluenesulfonyl)-7-methyl-1,4-dioxaspiro[4.5]decane (12)

To an ice-cold solution of alcohol 11 (3.0 g, 17 mM) in 30 mL of dry pyridine was added p-toluenesulfonyl chloride (3.56 g, 1.1 eq) in 7 mL of pyridine. The reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. The mixture was diluted with 100 mL of ether, washed



with 75 mL portions of 5%  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$ , filtered and stripped. The resulting brown oil was subjected to flash chromatography (eluted with 4:1 hexane:ethyl acetate) which afforded tosylate 12 as a pale oil (4.56 g, 82%) which solidified on standing to give a white amorphous solid, m.p. 48-52°. IR (KBr pellet): 1610, 1380, 1160  $\text{cm}^{-1}$ .

NMR (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.42 (AB q, 4H), 3.84 (bs, 4H), 2.20 (s, 3H), 2.10-1.30 (m, 7H), 0.94, 0.98 2 overlapping d (3H).

4,4- $^2\text{H}_2$ -3-methylcyclohexanone (4)

To an ice-cold solution of tosylate 12 (1.98 g, 6.1 mM) in 25 mL of THF was added 13 mL of lithium triethylborodeuteride (1.0 M in THF, 2 eq). The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 hr. Excess hydride was decomposed by careful addition of 5 mL of  $\text{H}_2\text{O}$ , followed by addition of 5 mL of 3 N NaOH and 5 mL of 30% aqueous  $\text{H}_2\text{O}_2$ . The organic layer was separated and the aqueous layer was extracted with three 25 mL portions of ether. The combined organic layers were washed with brine and concentrated. The resulting pale oil was taken up in 20 mL of ether. Added was 10 mL of 1 N HCl and the two-phase mixture was stirred vigorously for 6 h. The ether layer was separated and the aqueous layer was extracted with three 15 mL portions of ether. The combined organic layers were washed with 20 mL of brine, dried over  $\text{MgSO}_4$ , filtered and stripped. The resulting pale oil was subjected to flash chromatography (10:1 pentane:ether) followed by bulb-to-bulb distillation (oven temperature, 180°) to give deuterated methylcyclohexanone 4 as a water-white oil (506 mg, 73%). IR (plate): 2197, 1714  $\text{cm}^{-1}$ . MS: (EI, 70 eV): m/e = 69 (100%), 99 (10%), 114 ( $\text{M}^+$ , 30%)

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