

## CHIRAL SYNTHESIS OF REGIOSPECIFICALLY DEUTERATED 3-METHYLCYCLOHEXANONES

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### SUMMARY

The enantioselective synthesis of deuterated 3-methylcyclohexanones 1-4 is described.

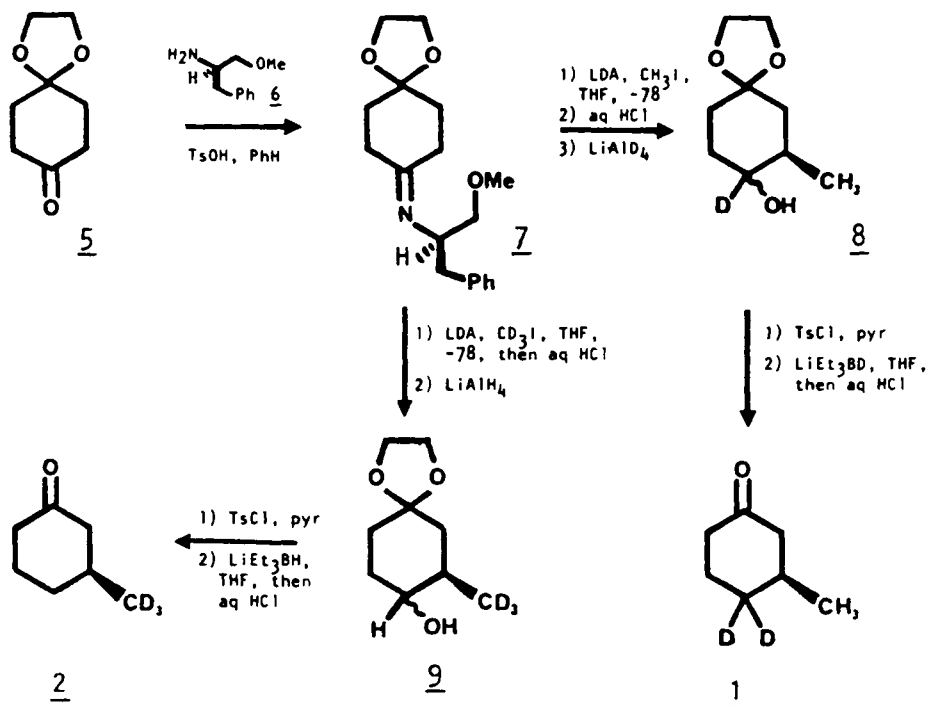
### KEY WORDS

Optically active, deuterated, 3-methylcyclohexanone

The deuterated 3-methylcyclohexanones 1-4 are of interest as substrates for spectroscopic and theoretical studies<sup>1,2</sup>. Recently, we reported the preparation of a series of racemic, deuterated 3-methylcyclohexanones, and the detailed assignment and interpretation of the Raman optical activity (ROA) spectrum of the parent compound.<sup>2</sup> Ongoing studies of C-H stretching vibrational circular dichroism and low-frequency ROA required the chiral series of deuterated 3-methylcyclohexanones 1-4. We now report the efficient, enantioselective synthesis of these compounds.

Chiral 3-methylcyclohexanones 1 and 2 were prepared as shown in Scheme 1. Alkylation of imine<sup>4</sup> 7, derived from 1,4-cyclohexanedione monoketal 5 and amine 6, with methyl iodide followed by hydrolysis and reduction with LiAlD<sub>4</sub> afforded alcohol 8 as a mixture of diastereomers. Using the sequence developed for the racemic series<sup>3</sup>, 8 was converted to (3R)-4-d<sub>2</sub>-methylcyclohexanone 1, identical in all respects (except optical rotation) to an authentic sample of racemic material. Based on the observed rotation of 1<sup>9</sup> we estimate the optical purity of our synthetic material to be greater than 60%.

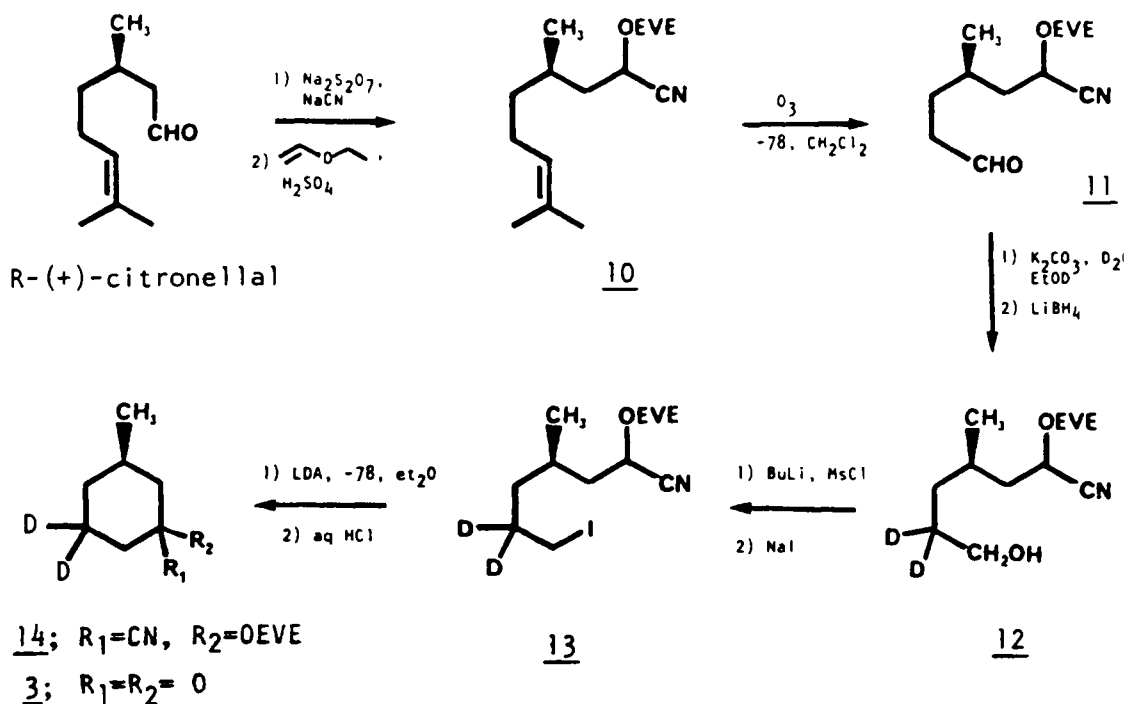
## Scheme 1



A similar series of transformations was used to prepare (3*S*)-**2**. Alkylation of imine **7** with  $d_3$ -methyl iodide followed by hydrolysis and reduction with  $\text{LiAlH}_4$  afforded alcohol **9**. Tosylation, reduction and deketalization gave (3*S*)-**2** (64% enantiomeric excess) identical to racemic material by IR and proton NMR.

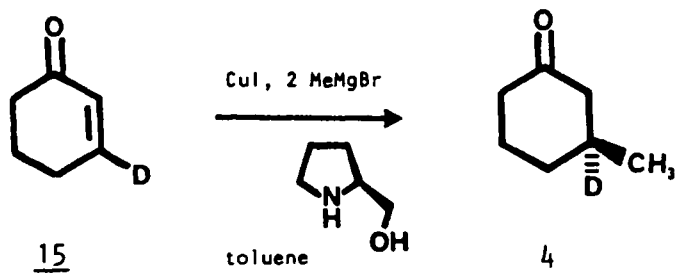
Methylcyclohexanone **3** was prepared from commercially available R-(+)-citronellal by the seven step sequence outlined in Scheme 2. Formation of the protected cyanohydrin **10** followed by ozonolysis gave aldehyde **11**. Introduction of deuterium was accomplished by base-catalyzed exchange; after two cycles, the level of incorporation was greater than 98% based on the disappearance of the  $^1\text{H}$  NMR signal at 2.3  $\delta$  and the collapse of the aldehydic proton resonance to a singlet. Alcohol **12** was transformed to the corresponding iodide **13** by standard procedures, whereupon cyclization to **14** was effected by treatment with lithium diisopropylamide in ether<sup>5</sup>. Deprotection of **14** gave the desired

## Scheme II



( $\underline{3R}$ )- $\underline{3}$  (enantiomeric excess >90% based on the optical purity of starting citronellal).

## Scheme III



Finally, deuterated methylcyclohexanone  $\underline{4}$  was prepared by asymmetric cuprate addition to the readily available  $\beta$ -deuterocyclohexenone  $\underline{15}$ <sup>3,6</sup> using the protocol of Leyendecker.<sup>7</sup> Addition of  $\underline{15}$  to the organocopper species formed from L-prolinol, copper(I) iodide and two equivalents of methyl Grig-

nard reagent<sup>8</sup> afforded the desired (3S)-4 in 10% enantiomeric excess. While the optical purity of material obtained by this route is low, the expedience of this procedure for large scale preparation of 4 is well-suited for our anticipated spectroscopic studies.

In summary, the chiral, deuterated 3-methylcyclohexanones 1-4 have been prepared by short, enantioselective synthetic sequences. As in the previously reported synthesis of the racemic series, deuterium incorporation in each case is high (>98%) and completely regiospecific. The overall efficiency of our synthetic routes is readily amenable to the preparation of multi-gram quantities of the title compounds. The use of these substrates for vibrational circular dichroism and low-frequency Raman studies is in progress and will be reported elsewhere.

#### 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. Preparative gas chromatography of analytical samples was performed on a Varian 3700 using a 50 cm OV-101 column.

Deuterated reagents were obtained as follows:  $d_3$ -methyl iodide (99% gm/atm D, Aldrich) lithium triethyldeuteroborate (Super Deuteride, Aldrich), lithium aluminum deuteride (98% gm/atm D, Chemalog), ethanol  $d_1$  (99.5% gm/atm D, Aldrich).

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

A solution of cyclohexane-1,4-dione monoketal<sup>10</sup> (4.30 g, 26 mM) in 60 mL of dry benzene was refluxed for 8 h with azeotropic H<sub>2</sub>O removal. Concentration under reduced pressure afforded the crude imine 7 as a pale oil (IR (plate): 1650 cm<sup>-1</sup>) which was taken up in 20 mL of dry THF and the resulting solution added dropwise to a solution of lithium diisopropylamide (27.6 mM) in 60 mL of THF at -20°C. After stirring for 1 h, the reaction mixture was cooled

to  $-78^\circ\text{C}$  and a solution of methyl iodide (4.00 g, 28 mM) in 15 mL of THF was added. The resulting mixture was stirred 3 h at  $-78^\circ$  and quenched by addition of 10 mL of methanol. Solvent was removed by rotary evaporation and the residual oil was dissolved in 200 mL of ether, washed with three 50 mL portions of 1 M HCl, 50 mL portions of  $\text{H}_2\text{O}$  and brine and dried over  $\text{NaSO}_4$ . Concentration under reduced pressure gave a pale oil which was dissolved in 10 mL of dry ether and added dropwise to a stirred suspension of  $\text{LiAlD}_4$  (0.48 g, 11 mM) in 50 mL of ether at  $0^\circ\text{C}$ . Workup and purification as described previously<sup>3</sup> gave alcohol 8 as a mixture of diastereomers (2.81 g, 62% from 5). NMR and IR spectra were identical to those of an authentic sample of racemic 8.<sup>3</sup>

(3R)-4,4- $^2\text{H}_2$ -3-methylcyclohexanone (1).

Using the sequence described previously for the racemic series<sup>3</sup>, alcohol 8 was transformed to (3R)-3-methylcyclohexanone 1 which was identical to an authentic sample of racemic material by NMR and IR. The optical rotation of an analytical sample ( $[\alpha]_D^{22}$  9.01,  $c$  4.28,  $\text{CHCl}_3$ ) indicated an optical purity of 61%.<sup>9</sup>

(7R)-7-( $^2\text{H}_3$ -methyl)-8-hydroxy-1,4-dioxaspiro[4.5]decane (9).

Imine 7 (7.61 g, 25 mM) was alkylated with  $d_3$ -methyl iodide using the procedure described above for preparation of 8. Hydrolysis of the crude imine and reduction with  $\text{LiAlH}_4$  afforded alcohol 9 as a diastereomeric mixture. Flash chromatography (silica gel, 2:1 hexane:ethyl acetate) and bulb-to-bulb distillation (oven temperature  $185^\circ\text{C}$ ) afforded 9 as a pale oil (2.75 g, 62% from 5). IR(plates): 3600, 2185 (w)  $\text{cm}^{-1}$ . NMR ( $\text{CDCl}_3$ ):  $\delta$  = 3.95 (s,4H), 3.4-3.65 (m,1H), 2.97 (bs,1H, exchanges with  $\text{D}_2\text{O}$ ), 2.20-1.55 (m,7H).

(3S)-3-( $^2\text{H}_3$ -methyl)cyclohexanone (2).

To an ice-cold solution of 9 (2.74 g, 16 mM) in 30 mL of dry pyridine was added a solution of tosyl chloride (3.30 g, 17 mM) in 10 mL of pyridine. The reaction mixture was allowed to warm to room temperature and stirred for 17 h. The resulting mixture was diluted with ether (200 mL), washed with 75 mL por-

tions of saturated  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$  and brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residual yellow oil was taken up in 30 mL of THF and added dropwise to a solution of  $\text{LiEt}_3\text{BH}$  (24 mM) in 50 mL of THF and the resulting mixture was stirred at reflux for 2 h. After cooling, the reaction was quenched by addition of  $\text{H}_2\text{O}$  (9 mL), 3 N  $\text{NaOH}$  (9 mL) and 30%  $\text{H}_2\text{O}_2$  (9 mL). The organic layer was separated and concentrated under reduced pressure. The residual oil was dissolved in 20 mL of ether, 10 mL of 1 M  $\text{HCl}$  was added and the mixture was stirred at room temperature for 5 h. The aqueous layer was separated and extracted with three 20 mL portions of ether; the combined organic layers were washed with  $\text{H}_2\text{O}$  and brine, and dried over  $\text{MgSO}_4$ . Concentration under reduced pressure and distillation gave cyclohexanone 2 as a water-white oil (b.p 158-160°, 805 mg, 45% from 9). IR and NMR spectra of 2 were identical to those of racemic material<sup>3</sup>. Optical rotation of an analytical sample ( $[\alpha]_{\text{D}}^{22}$  9.23,  $c$  7.91,  $\text{CHCl}_3$ ) indicated an optical purity of 64%.<sup>9</sup>

(4R)-2-(1-ethoxy)ethoxy-4,8-dimethyl-nonanenitrile (10).

To a solution of sodium metabisulfite (28.5 g, 0.15 M) in 250 mL of  $\text{H}_2\text{O}$  was added R-(+)-citronellal (Fluka,  $[\alpha]_{\text{D}}^{20}$  + 13.0°, 38.0 g, 0.25 M). The resulting mixture was stirred 1/2 h, washed with 200 mL ether, and then sodium cyanide (14.0/g, 0.29M) in 50 mL of  $\text{H}_2\text{O}$  was added. After stirring for 1/4 h, the cyanohydrin separated from the aqueous layer as an oil. The mixture was extracted with three 200 mL portions of ether. Two drops of concentrated sulfuric acid were added to the combined organic layers and solvent was removed by rotary evaporation to give the cyanohydrin as a yellow oil. The crude cyanohydrin was cooled to 0° and ethyl vinyl ether (28.0 g, 0.39 M) was added at a rate sufficient to maintain a gentle reflux. Following the addition, the reaction mixture was stirred 1 h at 25°C, diluted with 200 mL of ether and washed rapidly with 100 mL portions of saturated  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$  and brine. After drying over  $\text{Na}_2\text{SO}_4$  and removal of solvent, the protected cyanohydrin 10 was obtained as a yellow oil. Attempts to purify this material by

distillation resulted in extensive decomposition; however, the crude cyanohydrin (53 g) was of sufficient purity to be ozonized directly. A small sample was subjected to flash chromatography (silica gel, 3:1 hexane: ethyl acetate) to give the diastereomeric cyanohydrins 10 as a pale oil. IR (plates):  $2235\text{ cm}^{-1}$ . NMR ( $\text{CDCl}_3$ ):  $\delta = 5.05$  (bt, 1H), 5.00-4.30 (m, 2H), 3.98-3.70 (m, 2H), 2.42-1.80 (m, 2H) 1.78 (bs, 3H), 1.65 (bs, 3H), 1.70-1.30 (m, 1H), 1.05 (bd, 3H).

(4R)-2-(1-ethoxy)ethoxy-4-methyl-7-oxo-heptanenitrile (11).

Protected cyanohydrin 10 (19.7 g, 78 mM) was dissolved in 150 mL  $\text{CH}_2\text{Cl}_2$  cooled to  $-78^\circ$  and treated with ozonized oxygen gas until a faint blue color persisted. Dimethyl sulfide (5 mL) was added and the mixture was allowed to warm to room temperature over 1 h. The resulting solution was washed with 100 mL portions of  $\text{H}_2\text{O}$  and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude aldehyde was filtered through a silica gel plug (3:1 hexane: ethyl acetate) which gave 11 as a pale oil (14.6 g, 69% from R-(+)-citronellal). An analytical sample was further purified by flash chromatography (5:1 hexane:ethyl acetate) to give 11 as a water-white oil. IR (plates):  $2235, 1720\text{ cm}^{-1}$ . NMR ( $\text{CDCl}_3$ ):  $\delta = 9.85$  (t,  $J=1.5\text{ Hz}$ , 1H), 5.05-4.70 (m, 1H), 4.65-4.20 (m, 1H), 4.93-3.25 (m, 2H), 2.45 (bt,  $J=7\text{ Hz}$ , 2H), 2.02-1.15 (m, 11H), 1.05 (bd, 3H).

(4R)-2-(1-ethoxy)ethoxy-4-methyl-6- $^2\text{H}_2$ -7-hydroxy-heptanenitrile (12).

Aldehyde 11 (10.0 g, 44 mM) was combined with 180 mL of ethanol- $d_1$ , 10 mL of  $\text{D}_2\text{O}$  and 1.10 g anhydrous  $\text{K}_2\text{CO}_3$  and stirred 24 h at  $25^\circ\text{C}$ . The mixture was filtered and concentrated under reduced pressure to give a pale oil. This material was redissolved in 150 mL of ethanol- $d_1$  and the above procedure was repeated to give the deuterated aldehyde as a pale oil (NMR ( $\text{CDCl}_3$ ):  $\delta = 9.85$  (s, 1H), no resonance at 2.45).

The crude deuterated aldehyde was dissolved in 30 mL of THF and the resulting solution was added to  $\text{LiBH}_4$  (0.315 g, 14 mM) in 70 mL of THF at  $0^\circ$ . After 1/2 h the reaction mixture was quenched with  $\text{H}_2\text{O}$ , washed with 100 mL portions

H<sub>2</sub>O and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Rotary evaporation gave a pale oil; flash chromatography (2:1 hexane: ethyl acetate) afforded alcohol 12 as a water-white oil (8.5 g, 84% from 11). IR (plates): 3540, 2240 cm<sup>-1</sup>. NMR (CDCl<sub>3</sub>):  $\delta$  = 5.05-4.72 (m,1H), 4.70-4.25 (m,1H), 3.93-3.40 (m,2H), 3.81 (bs, 2H), 2.58 (bs,1H, exchanges with D<sub>2</sub>O), 2.17-1.80 (m,5H), 1.78-0.98(m,9H).

(3R)-3-methyl-5-<sup>2</sup>H<sub>2</sub>-cyclohexanone (3).

To solution of alcohol 12 (1.75 g, 7.5 mM) in 50 mL of dry ether at 0° was added 3.0 mL of BuLi (2.6 M in hexane, 1.05 eq) followed by methanesulfonyl chloride (0.85 g, 1.2 eq). After stirring 1/2 h at 0°, the reaction mixture was filtered and concentrated to give the crude mesylate as a yellow oil. (NMR (CDCl<sub>3</sub>):  $\delta$  = 2.98 (s,3H)). This material was dissolved in 80 mL of dry acetone, sodium iodide (3.0 g, 20 mM) was added and the mixture was stirred at reflux for 12 h. The mixture was cooled, filtered and concentrated to give the iodide 13 as a dark brown oil. The crude iodide was taken up in 10 ml of dry ether and added dropwise to a solution of LDA (from 0.25 g diisopropylamine and 0.8 mL n-BuLi (2.6 M in hexane)) in refluxing ether (40 mL). After 2 h the reaction mixture was cooled and washed with 40 mL of H<sub>2</sub>O. Added was 20 mL of 5% HCl and the two-phase mixture was stirred vigorously for 1/2 h. The organic layer was separated and washed with three 40 mL portions of 1 M NaOH, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting dark oil was flash chromatographed (6:1 pentane:ether) to give 3-methylcyclohexanone 3 identical by IR and NMR to an authentic racemic sample. Optical rotation ( $[\alpha]_D^{22} + 13.2^\circ$ ,  $c$  .11, CHCl<sub>3</sub>) of an analytical sample indicated an optical purity of 92%.<sup>9</sup>

(3S)-3-<sup>2</sup>H<sub>1</sub>-3-methylcyclohexanone (4).

To a stirred suspension of copper(I) iodide (10.22 g, 52.5 M) in 100 mL of dry toluene at -30° was added a solution of MeMgBr (34 mL, 3.1 M in ether, 105 mM). The resulting mixture was warmed to -0° and a solution of (2S)-pyrrolidinemethanol (Aldrich, 5.44 g, 53 mM) in 10 mL of toluene was added. After 1 h at 0°, the mixture was cooled to -30° and a solution of  $\beta$ -deutero-



cyclohexenone 15<sup>6</sup> was added. The reaction mixture was warmed to 0° over ½h and quenched by addition of saturated NH<sub>4</sub>Cl. The reaction mixture was worked up by washing with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub> and concentrated by distillation of the solvent. The resulting pale oil was purified by flash chromatography (10:1 pentane:ether) to give methylcyclohexanone 4 as a water-white oil, identical by NMR and IR to an authentic sample of racemic material, having an optical purity ( $[\alpha]_D^{22}$  -1.46,  $c$  1.0, CHCl<sub>3</sub>) of 10%.<sup>9</sup>

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