# Quantitative Analyses of the Seven Isomeric 3,4- and 3,6-Dimethylcyclohexenes by Gas Chromatography

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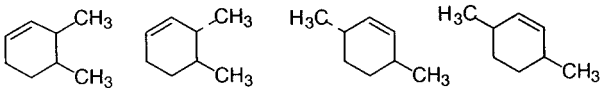
*Received June 23, 2000*

Quantitative analyses of mixtures of the seven isomeric 3,4- and 3,6-dimethylcyclohexenes have been achieved by gas chromatography. Correlations of structure and absolute stereochemistry with elution order have been made rigorously with the aid of authentic optically active samples all derived from (3*R*)-methylcyclohexanone.

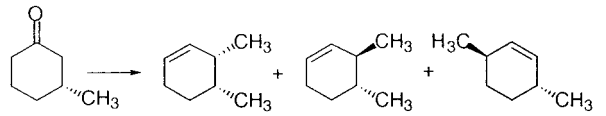
## Introduction

Accurate determinations of relative concentrations of the seven 3,4- and 3,6-dimethylcyclohexenes on a submilligram scale, an analytical capability required for a projected stereochemical investigation, might be achieved using enantioselective capillary columns based on modified cyclodextrins as chiral stationary phases.[1] To realize this objective would require the successful completion of several tasks: preparations of authentic samples of *cis*-3,4-dimethylcyclohexene ((±)-**1**), *trans*-3,4-dimethylcyclohexene ((±)-**2**), *trans*-3,6-dimethylcyclohexene ((±)-**3**), and the meso isomer *cis*-3,6-dimethylcyclohexene (**4**); demonstrations that they can be distinguished by capillary gas chromatography on achiral columns and that the pairs of enantiomers can be separated well on chiral columns; and conclusive correlations between absolute stereochemistry and elution order on chiral columns for each of the three pairs of enantiomers.




(±)-1 (±)-2 (±)-3 4

These tasks have all been accomplished. Two of the three pairs of enantiomers proved to be baseline resolvable on a CycloSil-B column, and the third pair of enantiomers could be resolved on a Cyclodex-B fused silica capillary column. The correlations of relative elution order with absolute stereochemistry were made using samples of (3*R*,4*R*)-**1**, (3*S*,4*R*)-**2**, and (3*R*,6*R*)-**3** prepared from (3*R*)-(+)-methylcyclohexanone, (3*R*)-**5**.




(3*R*)-5 (3*R*,4*R*)-1 (3*S*,4*R*)-2 (3*R*,6*R*)-3

With these synthetic, stereochemical, and analytical results in hand, and with equally secure absolute stereochemical assignments for the four isomers of 1-(*E*)-propenyl-2-methylcyclobutane now ascertained with the aid of X-ray crystallography,[2] one may address the complex kinetic situation posed by the simultaneous stereomutations, fragmentations, and conversions of these cyclobutanes to mixtures of seven isomeric dimethylcyclohexenes with confidence that the stereochemical characteristics of the vinylcyclobutane-to-cyclohexene isomerizations may be deciphered.

## Results

**Racemic and Meso Samples.** The literature recounts various preparations and characterizations of (±)-**1**, (±)-**2**, (±)-**3**, and **4**.[3−9] The synthetic routes adopted here utilized conveniently available starting materials and the stereochemical control one may achieve through the formation and deprotonation of 2,4,6-triisopropylbenzenesulfonyl hydrazones (trisylhydrazones).[10]

The 3,4-dimethylcyclohexenes (±)-**1** and (±)-**2** were prepared as outlined in Scheme 1. A mixture of isomeric 2,3-dimethyl-cyclohexanols (**6**) was oxidized to a mixture of *cis*- and *trans*-2,3-dimethylcyclohexanones[11,12] (**7**) with pyridinium chlorochromate (PCC) in $CH_2Cl_2$.[13] Condensation of these ketones with 2,4,6-triisopropylbenzenesulfonyl hydrazine (TrisylNHNH$_2$),[10,14] followed by a

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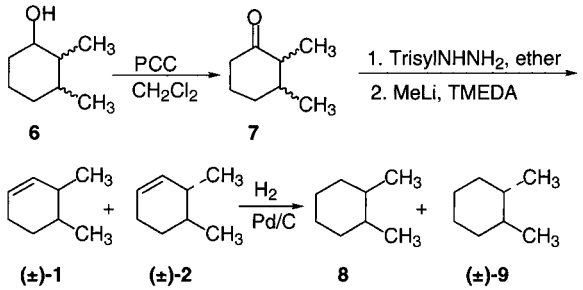
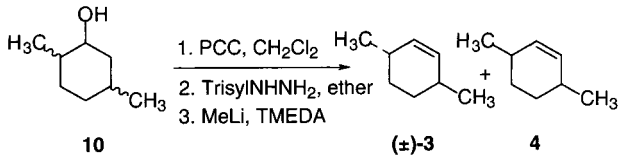
10.1021/jo000956s CCC: $19.00 
Published on Web 09/19/2000

**Scheme 1**




**Scheme 2**




Shapiro reaction,[15,16] gave as expected a mixture of the 3,4-dimethylcyclohexenes (±)-**1** and (±)-**2** as well as some 2,3-dimethylcyclohexene as a minor side product.

A 40:60 mixture of (±)-**1** and (±)-**2** was reduced with hydrogen over a palladium catalyst to form, respectively, *meso-cis*-1,2-dimethylcyclohexane (**8**) and the racemic trans isomer ((±)-**9**). The stereochemical assignments for the 1,2-dimethylcyclohexanes, and thus of the 3,4-dimethylcyclohexenes, were confirmed by spectroscopy, chromatographic comparisons with authentic samples, and chiral gas chromatography. *trans*-1,2-Dimethylcyclohexane ((±)-**9**) was resolved on a CycloSil B column to two equal-area peaks corresponding to its distinct enantiomeric forms.

The 3,6-dimethylcyclohexenes (±)-**3** and **4** were made through a similar route from a commercially available mixture of 2,5-dimethylcyclohexanols (**10**) as summarized in Scheme 2. Again, the reaction sequence from ketones to arylsulfonylhydrazones to cyclohexenes gave olefinic products with high regioselectivity; little 1,4-dimethylcyclohexene was formed.

Pure samples of (±)-**3** and **4** were collected by preparative GC and the structural assignments were made through NMR spectroscopy. The assignments were confirmed by chiral GC on a CycloSil B column: (±)-**3** gave two equal-intensity peaks while cis isomer **4** showed but a single peak.

**Achiral GC Separations**. The four samples (±)-**1**, (±)-**2**, (±)-**3**, and **4** were well separated on an achiral phenylmethyl silicone capillary GC column. The relative concentrations of [(+)-**1** + (−)-**1**], [(+)-**2** + (−)-**2**], [(+)-**3** + (−)-**3**], and **4** in samples containing the seven isomers in any proportions may thus be determined conveniently.[17]

Using a $\beta,\beta'$-oxydipropionitrile (ODPN) column, mixtures of [(+)-**1** + (−)-**1**], [(+)-**2** + (−)-**2**], [(+)-**3** + (−)-**3**], and **4** could be readily separated on a small preparative scale into the four distinct structural and diastereomeric components. Thus, for a complete analysis of a mixture of the seven dimethylcyclohexene isomers under consideration, it remained only to separate quantitatively the three pairs of enantiomers and to establish correlations between elution order and absolute stereochemistry.

**Chiral GC Separations**. Initial attempts to separate samples of (±)-**1**, (±)-**2**, and (±)-**3** with chiral capillary GC columns were not encouraging. Trials with the chiral columns on hand (Cyclodex-B (10.5% heptakis(2,3,6-tri-*O*-methyl)-$\beta$-cyclodextrin in DB-1701), 30 m, purchased in 1991 from J&W; Chiraldex G-BP (octakis(3-*O*-butyryl-2,6-di-*O*-methyl)-$\gamma$-cyclodextrin), 20 m, from Advanced Separation Technologies; Lipodex C (heptakis(2,3,6-tri-*O*-pentyl)-$\beta$-cyclodextrin), 50 m glass, Macherey-Nagel) failed to give any resolutions, or gave slightly broadened peaks, or, at best, partial resolutions. Three new columns were secured. The first (Hydrodex $\beta$-3P (heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-$\beta$-cyclodextrin in OV-1701), 25 m, Macherey-Nagel) did not solve the impasse, but the second and third, under carefully defined temperature, pressure, and flow-rate conditions, proved to give satisfactory resolutions (Figure 1). A CycloSil B column resolved the enantiomers of (±)-**2** and of (±)-**3**, and a new Cyclodex B column separated the enantiomers of (±)-**1**. The baseline character of these separations may be judged from the chromatograms visually or, more clearly, from the relative integrated intensities of the pairs of peaks. For the three separations shown in Figure 1, the (first enantiomer):(second enantiomer) proportions were measured to be 49.7:50.3, 50.1:49.9, and 49.8:50.2, close to the theoretically expected 50:50 balance.

**Chiral Samples from (3*R*)-(+)-Methylcyclohexanone.** Authentic samples of either enantiomer of **1**−**3** were needed to correlate absolute stereochemistry with elution order for these dimethylcyclohexenes. All three reference samples required for these correlations were derived from (3*R*)-methylcyclohexanone, (3*R*)-**5**, as shown in Schemes 3 and 4.

Condensation of (3*R*)-**5** with ethyl formate gave mostly 2-formyl-5-methylcyclohexanones (**11**), along with much smaller amounts of 2-formyl-3-methyl isomers.[18−21] This mixture of isomers, without separation, was converted into the corresponding *n*-butylthiomethylene derivatives[22] and then on to the α-methyl ketones with W-2 Raney nickel.[23] The desired chiral *trans*-3,6-dimethylcyclohexene (3*R*,6*R*)-**3** was then readily obtained by way of the trisylhydrazone and a methyllithium-promoted elimination.[24]

The crude mixture of α-formyl ketones **11** (Scheme 3) served just as well as a precursor for (3*R*,4*R*)-**1** and (3*S*,4*R*)-**2** (Scheme 4). Conversion of **11** to a mixture of dianions, using two equivalents of LDA in THF, followed by methylation with methyl iodide and hydrolytic removal of the formyl functions,[25] gave (2,3*R*) isomers of 2,3-dimethylcyclohexanone ((3*R*)-**7**). It was converted into a mixture of (3*R*,4*R*)-**1** and (3*S*,4*R*)-**2** (Scheme 4) without difficulty, and the two optically active hydrocarbon products were separated and purified by preparative GC.

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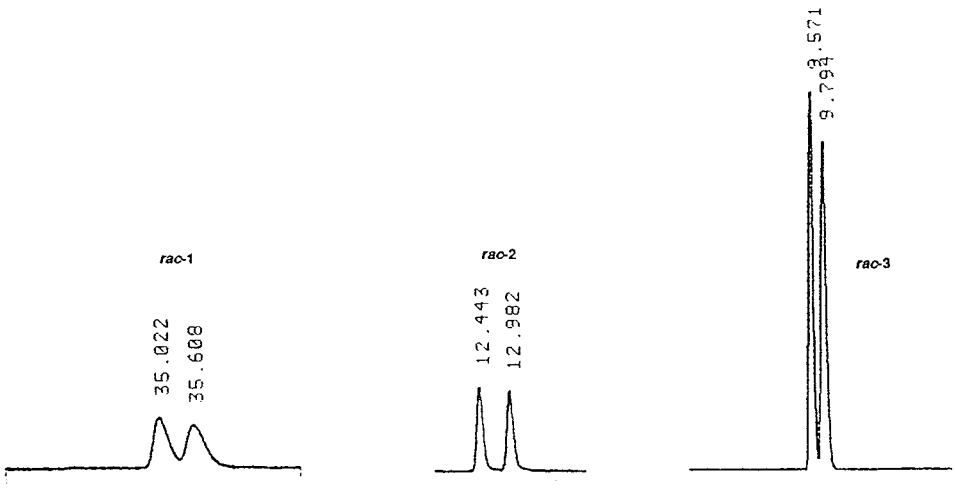
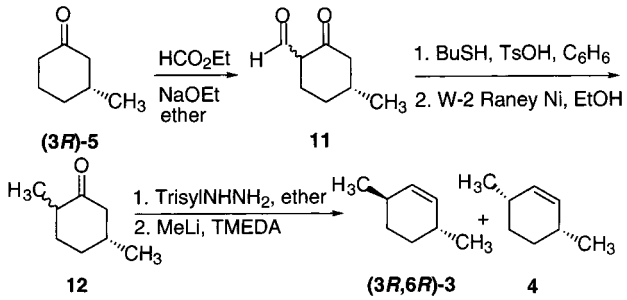
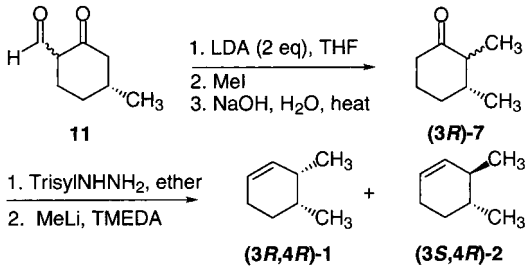



**Figure 1.** Chiral chromatographic separations of enantiomers of (±)-**1**, (±)-**2**, and (±)-**3** on modified cyclodextrin columns.

**Scheme 3**




**Scheme 4**




Specific rotations for very small samples of GC-purified (3*R*,4*R*)-**1**, (3*S*,4*R*)-**2**, and (3*R*,6*R*)-**3** were measured, in duplicate, using a 2-mL volumetric flask and a 1-mL 10-cm length micro polarimeter cell. The values obtained were none too precise: for (3*R*,4*R*)-**1**, $[\alpha]_D$ +200 and +240; for (3*S*,4*R*)-**2**, $[\alpha]_D$ −46 and −57; and for (3*R*,6*R*)-**3**, $[\alpha]_D$ +180 and +240 (in reagent-grade hexanes, with 0.2- to 7-mg samples). Such uncertainties in specific rotations, given the balances employed and the limited qualities of hydrocarbons invested, seem unsurprising. The observed lack of high precision in measuring specific rotations for these very small samples underscores the advantages of the alternative chiral GC methodology for determinations of enantiomeric excess!

**Absolute Stereochemical Assignments for Chiral GC Peaks**. The GC-purified (3*R*,4*R*)-**1**, (3*S*,4*R*)-**2**, and (3*R*,6*R*)-**3** samples gave single peaks on chiral GC colums under conditions known to separate (±)-**1**, (±)-**2**, and (±)-**3** into pairs of peaks representing the two enantiomers, a conformation of the essentially 100% ee character of the (3*R*)-**5** used in the preparations of Schemes 3 and 4, and of the lack of stereochemically compromising reactions at the original C3 $sp^3$ center as (3*R*)-**5** was converted into (3*R*,4*R*)-**1**, (3*S*,4*R*)-**2**, and (3*R*,6*R*)-**3**. Mixtures of (±)-**1** with (3*R*,4*R*)-**1**, (±)-**2** with (3*S*,4*R*)-**2**, and (±)-**3** with (3*R*,6*R*)-**3** were prepared and analyzed by chiral GC to secure the assignments: (3*S*,4*S*)-**1** elutes on the new Cyclodex B column before (3*R*,4*R*)-**1**; (3*R*,4*S*)-**2** elutes on the CycloSil B column before (3*S*,4*R*)-**2**; and (3*S*,6*S*)-**3** elutes on the CycloSil B column before (3*R*,6*R*)-**3** (Figure 2). Thus the associations of specific chromatographic peaks in these chiral GC chromatograms with specific stereoisomers of the chiral 3,4- and 3,6-dimethylcyclohexenes were demonstrated.

With the relative concentrations of any pair of enantiomers of **1**, **2**, and **3** in whatever proportions and of the meso isomer **4** known from achiral capillary GC analyses, and the relative concentrations of each enantiomer of **1**, **2**, and **3** available from chiral GC separations on one or another modified cyclodextrin capillary column, the relative concentrations of each of the seven isomers of 3,4- and 3,6-dimethylcyclohexene in a sample may be calculated.

## Conclusions

The results attained demonstrate that one may analyze an unknown mixture of the seven dimethylcyclohexenes under consideration on the scale and with the precision and accuracy associated with capillary GC. The various isomers may be separated using standard analytical and preparative GC and chiral GC methods, and the structural and absolute stereochemical assignments with chromatographic peak elution order have been made in a rigorous fashion. The power of chiral GC, in conjunction with other chromatographic methods and with efficient synthetic routes to reference compounds of known structure and absolute stereochemistry, have been combined in this instance to pave the way for detailed stereochemical investigations[2] that, in the recent past, would have seemed too daunting for serious engagement.

## Experimental Section

The two 30-m × 0.25 id fused silica chiral GC columns which gave satisfactory resolutions (CycloSil-B (30% heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-*β*-cyclodextrin in DB-1701) and Cyclodex-B (10.5% heptakis(2,3,6-tri-*O*-methyl)-*β*-

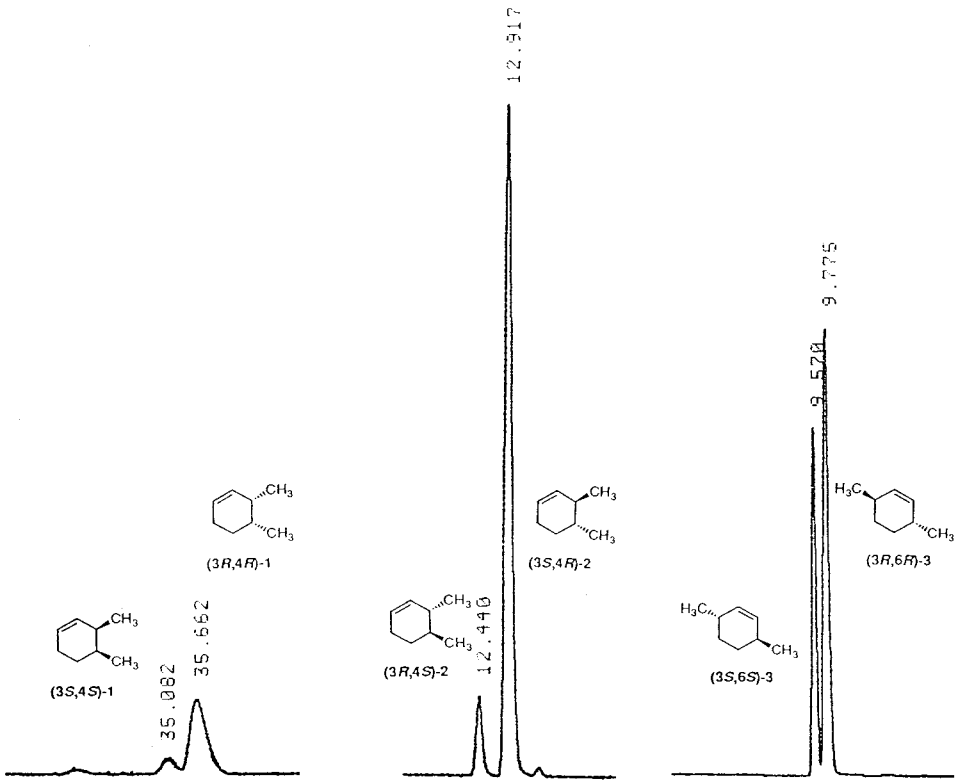



**Figure 2.** Mixtures of (±)-**1** with (3*R*,4*R*)-**1**, (±)-**2** with (3*S*,4*R*)-**2**, and (±)-**3** with (3*R*,6*R*)-**3** analyzed on modified cyclodextrin capillary GC columns.

cyclodextrin in DB-1701) were obtained from J&W Scientific, Folsom, CA 95630. The instrumentation and standard procedures used in this work have been detailed elsewhere.[1b,26−27]

**2,3-Dimethylcyclohexanones (7).** Oxidation of a mixture of *cis*- and *trans*-2,3-dimethylcyclohexanols (**6**; Aldrich, 2.02 g, 15.8 mmol) with PCC[13] (5.04 g, 23.4 mmol) in dry $CH_2Cl_2$ (30 mL), followed by a conventional workup and column chromatography (silica gel, hexanes/ethyl acetate, 9:1), gave 1.96 g (99%) of **7** as a clear oil, a 1:2.1 mixture (analytical GC on a phenylmethyl silicone column) of the known trans and cis isomers For *trans*-2,3-dimethylcyclohexanone: MS *m*/*z* (rel intensity) 126 (40, $M^+$), 111 (11), 98 (28), 83 (47), 82 (58), 69 (70), 55 (100), 41 (70); for the cis isomer: MS *m*/*z* (rel intensity) 126 (26, $M^+$), 111 (12), 98 (23), 83 (50), 82 (50), 69 (38), 55 (100), 41 (61).

**3,4-Dimethylcyclohexenes ((±)-1, (±)-2).** To a 50-mL round-bottomed flask were added dry ether (30 mL), 2,4,6-triisopropylbenzenesulfonyl hydrazide[28] (2.61 g, 8.73 mmol), and the mixture of 2,3-dimethylcyclohexanones (1.05 g, 7.93 mmol). The reaction mixture was stirred under argon for 7 h at room temperature, then concentrated and dried under vacuum for 1 h to give 3.17 g of off-white solid. This crude triisopropylbenzenesulfonyl hydrazone, TMEDA (18 mL, freshly distilled from KOH), and 1.4 M MeLi (11.7 mL, 16.4 mmol) were added to a 50-mL three-necked flask at −78 °C;[16] the reaction mixture was allowed to warm to room temperature and was stirred for 24 h under argon. The resultant orange solution was cooled to 0 °C and was quenched carefully with water (40 mL). The aqueous layer was extracted with pentane (3 × 25 mL), and the combined organic layers were then washed with HCl (2 M, 3 × 20 mL), NaOH (3 M, 20 mL), and water (20 mL). The organic material was dried ($MgSO_4$), filtered, and concentrated by distillation to give 0.62 g (71% for the two steps) of the 3,4-dimethylcyclohexenes, a 1.1:1 mixture (analytical GC) of the trans (7.7 min) and cis (9.2 min) isomers. Preparative GC afforded pure samples of the two isomers; these separations, and all other preparative GC work with dimethylcyclohexenes, employed a 2.3-m × 6.4-mm 20% $\beta,\beta'$-oxydipropionitrile (ODPN) on Chromasorb P-NAW column at 45 °C.

For *cis*-3,4-dimethylcyclohexene ((±)-**1**): $^1$H NMR $\delta$ 5.52−5.64 (m, 2 H), 2.12−2.23 (m, 1 H), 1.95−2.04 (m, 2 H), 1.74−1.88 (m, 1 H), 1.33−1.53 (m, 2 H), 0.87 (d, $J$ = 6.86 Hz, 3 H), 0.86 (d, $J$ = 7.41 Hz, 3 H); $^{13}$C NMR $\delta$ 133.2, 125.6, 33.6, 31.4, 26.6, 24.5, 16.9, 15.8 (lit.[7] $\delta$ 133.0, 125.5, 34.2, 32.1, 27.2, 24.9, 17.0, 16.0); MS *m*/*z* (rel intensity) 110 (47, $M^+$), 95 (90), 81 (71), 67 (100), 53 (26), 41 (54). Analytical GC on a new chiral Cyclodex B column at 30 °C and 15 psi (Figure 1) gave two peaks with retention times (relative peak areas) of 35.0 min (49.8%) and 35.6 min (50.2%).

For *trans*-3,4-dimethylcyclohexene ((±)-**2**): $^1$H NMR $\delta$ 5.58−5.67 (m, 1 H), 5.41−5.49 (m, 1 H), 1.96−2.05 (m, 2 H), 1.61−1.82 (m, 2 H), 1.14−1.36 (m, 2 H), 0.98 (d, $J$ = 7.13 Hz, 3 H), 0.97 (d, $J$ = 6.04 Hz, 3 H); $^{13}$C NMR $\delta$ 133.4, 129.5, 37.7, 35.9, 30.6, 25.2, 20.3, 20.1 (lit.[7] $\delta$ 133.5, 125.7, 38.1, 36.4, 31.0, 25.6, 20.3 (both Me); MS *m*/*z* (rel intensity) 110 (48, $M^+$), 95 (92), 81 (76), 67 (100), 53 (28), 41 (56). Analytical gas chromatography on a chiral CycloSil B column at 50 °C and 15 psi (Figure 1) gave two peaks with retention times (relative peak areas) of 12.4 min (50.1%) and 13.0 min (49.9%).

**1,2-Dimethylcyclohexanes (8** and (±)-**9**) were obtained by reducing a small sample of a 40:60 mixture of (±)-**1** and (±)-**2** with hydrogen over palladium on carbon. Analytical GC on a capillary phenylmethyl silicone column at 40 °C showed a 60:40 mixture of trans ((±)-**9**, 7.1 min) and cis (**8**, 9.1 min) isomers of 3,4-dimethylcyclohexane. Authentic samples (Philips 66) of the 3,4-dimethylcyclohexanes had analytical GC retention times of 7.1 min for the trans and 9.1 min for the cis isomers. Analytical GC on a new CycloSil B column at 50 °C and 15 psi gave two peaks with retention times (relative peak areas) of 11.1 min (50.0%) and 12.0 min (50.0%) for (±)-**9** and one peak (16.9 min) for **8**.

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**3,6-Dimethylcyclohexenes ((±)-3, 4).** A mixture of 2,5-dimethylcyclohexanones[29] was prepared by oxidizing 2,5-dimethyl-cyclohexanols (**10**; TCI America, 2.05 g, 16.0 mmol) with PCC in dry $CH_2Cl_2$. A conventional workup and column chromatography (silica gel, hexanes:ethyl acetate, 9:1) gave 1.91 g (95%) of the ketones as a clear oil. The two isomers had essentially identical mass spectra: MS *m/z* (rel intensity) 126 (33, $M^+$), 111 (7), 98 (18), 82 (48), 69 (100), 56 (55), 41 (58−64).

A portion of this mixture of isomeric ketones (1.06 g, 7.94 mmol), dry ether (30 mL), and 2,4,6-triisopropylbenzenesulfonyl hydrazide (2.63 g, 8.74 mmol) were combined in a 50-mL round-bottomed flask, and the reaction mixture was stirred under argon for 7 h at room temperature. Concentration and drying under vacuum gave 3.58 g of a white solid, which was subjected to the Shapiro reaction protocol detailed above to give 0.56 g (64% for the two steps) of a mixture of the cis and trans isomers of 3,6-dimethylcyclohexenes, along with a small amount of 1,4-dimethylcyclohexene. Analytical GC showed a 1:1.7 mixture of the trans (6.9 min) and cis (7.3 min) 3,6-dimethylcyclohexenes. Small samples of each were collected by preparative GC.

For *trans*-3,6-dimethylcyclohexene ((±)-**3**): $^1$H NMR $\delta$ 5.46 (s, 2 H), 2.05−2.21 (m, 2 H), 1.74−1.87 (m, 2 H), 1.09−1.21 (m, 2 H), 0.96 (d, $J$ = 6.59 Hz, 6 H); $^{13}$C NMR $\delta$ 132.7, 31.5, 30.5, 21.9 (lit.[7] $\delta$ 133.6, 31.9, 30.9, 22.1); MS *m/z* (rel intensity) 110 (32, M+), 95 (81), 81 (29), 68 (100), 67 (88), 55 (40), 39 (41). Analytical GC on a CycloSil B column at 50 °C and 15 psi gave two peaks with retention times (relative peak areas) of 9.6 min (49.7%) and 9.8 min (50.3%).

For *cis*-3,6-dimethylcyclohexene (**4**): $^1$H NMR $\delta$ 5.51 (d, $J$ = 1.1 Hz, 2 H), 2.08−2.21 (m, 2 H), 1.59−1.72 (m, 2 H), 1.26−1.39 (m, 2 H), 0.97 (d, $J$ = 7.14 Hz, 6 H); $^{13}$C NMR $\delta$ 132.5, 29.6, 28.2, 21.5 (lit.[7] $\delta$ 132.7, 30.0, 28.6, 21.7); MS *m/z* (rel intensity) 110 (30, $M^+$), 95 (86), 81 (25), 68 (100), 67 (95), 55 (39), 39 (41). Analytical GC on the CycloSil B column at 50 °C and 15 psi gave one peak with a retention time of 12.2 min.

**Achiral analytical gas chromatographic separations** of **1**, **2**, **3**, and **4** on the capillary phenylmethyl silicone column at 40 °C gave the elution sequence **3** (6.9 min), **4** (7.3 min), **2** (7.7 min) and **1** (9.2 min).[17] Preparative separations on the ODPN column gave the dimethylcyclohexenes at 7.29 min (**3**), 8.18 min (**4**), 9.11 min (**2**) and 11.34 min (**1**).

**2-Formyl-(5*R*)-methylcyclohexanone (11)** was prepared by condensing (3*R*)-methylcyclohexanone (**(3*R*)-5**; Aldrich; 2.9 g) with ethyl formate.[18−21] A conventional workup led to 4.2 g of a yellow oil. Analytical GC indicated an 8.8:1 preponderance of **11** (16.0 min) over the 2-formyl-3-methyl isomer (16.1 min). A small sample of both isomers was purified by preparative GC (10% SE-30, 100 °C): $^1$H NMR $\delta$ 9.94 (d, $J$ = 2.19 Hz), 9.71 (s), 8.74 (d, $J$ = 3.02 Hz), 8.68 (d, $J$ = 2.74 Hz), 2.60−2.70 (m), 2.27−2.49 (m), 1.94−2.06 (m), 1.71−1.68 (m), 1.41−1.49 (m), 1.17−1.33 (m), 1.14 (d, $J$ = 6.86 Hz), 1.02 (d, $J$ = 6.59 Hz); MS *m/z* (rel intensity) 140 (100, $M^+$), 125 (30), 111 (43), 97 (36), 79 (28), 70 (84), 55 (64), 39 (60).

**2,(5*R*)-Dimethylcyclohexanones (12).** Crude intermediate **11** (2.10 g, 14.9 mmol), dry benzene (70 mL), butanethiol (2.08 mL, 1.75 g, 19.4 mmol), and *p*-TsOH (40 mg) were combined and heated to reflux for 20 h as 1.7 mL of water was removed by azeotropic distillation.[19,22] The prescribed workup led to a red oil, which was distilled (bp 100−120 °C (1−2 mm)) to give 1.76 g of the butylthiomethylene intermediate[19] as a yellow oil: *m/z* (rel intensity) 212 (16, $M^+$), 179 (6), 155 (100), 113 (7), 93 (10), 85 (11), 69 (7), 55 (10), 41 (20). This intermediate was reduced in ethanol at 55 °C under argon with W-2 Raney Ni; 12 g of Raney Ni were added in 3 g portions over a 50-min period.[23] The reaction mixture was stirred for 16 h at 55 °C under argon and then cooled and filtered through Florisil. The Florisil was washed with 200 mL of ethanol and the combined ethanolic material was concentrated by distillation to give a yellow oil. Column chromatography (silica gel, hexanes:ethyl acetate, 9:1) gave 0.48 g (29% from (3*R*)-**5**) of **12** as a clear oil. Analytical GC showed there was a 4.4:1 trans (12.5 min):cis (13.0 min) mixture of 2,(5*R*)-dimethylcyclohexanones and some 10% of the 2,(3*R*)-dimethylcyclohexanones.

**(3*R*,6*R*)-*trans*- and *cis*-3,6-Dimethylcyclohexenes ((3*R*, 6*R*)-3 and 4).** The mixture of ketones prepared immediately above was combined with 2,4,6-triisopropylbenzenesulfonyl hydrazide (1.25 g, 4.19 mmol) and dry ether (15 mL); the formation of the trisylhydrazone and its decomposition through a Shapiro reaction was conducted as detailed above to give 0.14 g (33% for the two steps) of (3*R*,6*R*)-**3** and **4**, and a small amount of the 3,(4*R*)-dimethylcyclohexenes. Analytical GC showed a 4:1 mixture of (3*R*,6*R*)-**3** (6.7 min) and **4** (7.2 min) isomers. Preparative GC afforded pure samples of each.

For **(3*R*,6*R*)-*trans*-dimethylcyclohexene** ((3*R*,6*R*)-**3**), GC on the CycloSil B column at 50 °C and 15 psi gave one peak with a retention time of 9.9 min. Samples of (±)-**3** and (3*R*,6*R*)-**3** were combined and analyzed under same conditions; the two peaks observed (Figure 2) had retention times (relative peak areas) of 9.6 min (30.8%) and 9.8 min (69.2%). Two specific rotation determinations (2-mL volumetric flask, 10-cm path length 1-mL polarimeter cell, reagent-grade hexanes as solvent) gave $[\alpha]_D$ values of +180 (*c* 0.36) and +240 (*c* 0.20).

The cis isomer **4** on the CycloSil B column gave one peak with a retention time of 12.2 min.

**2,(3*R*)-Dimethylcyclohexanones ((3*R*)-7).** To a 100-mL three-necked flask were added diisopropylamine (2.94 g, 29.0 mmol), dry THF (20 mL), and 1.4 M MeLi (20.7 mL, 29.0 mmol) at −78 °C. The mixture was warmed to 0 °C, stirred for 15 min under argon, and cooled again cooled to −78 °C. Intermediate **11** (2.10 g, 14.9 mmol), prepared as described above and used without purification, was added dropwise in THF (10 mL).[25] After the addition was complete, the reaction mixture was warmed to 0 °C and stirred for 1 h. It was then cooled to −78 °C and MeI (2.68 g, 18.9 mmol, 1.17 mL) was added; the reaction mixture was allowed to warm to room temperature and was stirred for 9 h. It was quenched with water (30 mL) and acidified with 2 M HCl; the organic layer was removed and the aqueous layer was extracted with ether (4 × 25 mL). The combined organic material was dried ($MgSO_4$), filtered, and concentrated. The oily concentrate and 32 mL of 0.4 M NaOH were then heated to reflux for 6 h.[25] The hydrolysis reaction mixture was cooled to room temperature, acidified with 2 M HCl, and extracted with ether (4 × 25 mL). The combined organic material was washed with 1 M HCL (4 × 15 mL), dried ($MgSO_4$), filtered, and concentrated. Column chromatography (silica gel, hexanes:ethyl acetate, 9:1) gave 0.54 g (33% from (3*R*)-methylcyclohexanone) of 2,3-dimethylcyclohexanones as a slightly yellow oil. Analytical GC showed there was a 4.1:1 mixture of the trans (13.1 min) and cis (13.6 min) 2,(3*R*)-dimethylcyclohexanone isomers, and 13% of the 2,(5*R*)-dimethylcyclohexanones.

This mixture of ketones was converted into cyclohexenes by way of the trisylhydrazones, following the protocols described above. The product mixture (0.28 g, 33% for the two steps) contained the 3,(4*R*)-dimethylcyclohexenes, a 4.2:1 mixture of the trans (7.6 min) and cis (9.1 min) isomers according to analytical GC, and small amounts of two 3,6-dimethylcyclohexenes. Preparative GC provided pure samples of the cis and trans isomers (3*R*,4*R*)-**1** and (3*S*,4*R*)-**2.**

**(3*R*,4*R*)-*cis*-Dimethylcyclohexene** ((3*R*,4*R*)-**1**) had measured $[\alpha]_D$ values of +200 (*c* 0.01) and +240 (*c* 0.03). Analytical GC on a new chiral Cyclodex B column at 30 °C and 15 psi gave one peak with a retention time of 35.4 min. Samples of (±)-**1** and (3*R*,4*R*)-**1** were then mixed together and analyzed under the same conditions; the two peaks observed had retention times (relative peak areas) of 35.1 min (3.1%) and 35.7 min (96.9%) (Figure 2).

**(3*S*,4*R*)-*trans*-Dimethylcyclohexene** ((3*S*,4*R*)-**2**) had measured $[\alpha]_D$ values of −46 (*c* 0.20) and −57 (*c* 0.27). Analytical GC on the CycloSil B column at 50 °C and 15 psi gave one peak with a retention time of 12.9 min. Samples of (±)-**2** and (3*S*,4*R*)-**2** were mixed and analyzed under the same conditions;

(29) Bartlett, P. D.; Schueller, K. E. *J. Am. Chem. Soc.* **1968**, *90*, 6077−6082.

the two GC peaks seen (Figure 2) had retention times (relative peak areas) of 12.4 min (9.7%) and 12.9 min (90.3%).

**Acknowledgment.** We thank the National Science Foundation for supporting this work through Grant CHE 95-32016.

**Supporting Information Available:** Copies of $^{1}H$ and $^{13}C$ NMR spectra for (±)-**1**, (±)-**2**, (±)-**3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000956S