H, s), and 7.34-7.80 (5 H, m); MS, m/z 281 and 283 ($M^+ + 1$). Anal. Calcd for $C_{14}H_{13}O_2SCl$: C, 59.89; H, 4.67. Found: C, 60.13; H, 4.72.

(*R*)-(+)-2-Chloro-2-phenylethyl *p*-chlorophenyl sulfone (3c): mp 84-85 °C; $[\alpha]^{25}_D$ +78° (c 4.4, chloroform); $[\theta]_{226}$ +19000 (c 7.1 × 10^{-3}, methanol); IR (KBr) 1325 and 1140 cm^{-1}; ^1H NMR δ ($CDCl_3$) 3.80-3.94 (2 H, m), 5.30 (1 H, t, J = 7.2 Hz), 7.17 (5 H, s), 7.30 (2 H, d, J = 9.0 Hz), and 7.60 (2 H, d, J = 9.0 Hz); MS, m/z 314 and 316 (M^+); HRMS, m/z 313.9885 ($C_{14}H_{12}O_2SCl_2$ requires 313.9935). Anal. Calcd for $C_{14}H_{12}O_2SCl_2$: C, 53.34; H, 3.84. Found: C, 54.44; H, 3.80.[11]

(*R*)-(+)-2-Chloro-2-phenylethyl *p*-methoxyphenyl sulfone (3d): mp 72-74 °C; $[\alpha]^{22}_D$ +48° (c 2.6, chloroform); $[\theta]_{226}$ +8900 (c 1.3 × 10^{-4}, methanol); IR (KBr) 1325, 1310, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77-3.90 (2 H, m), 3.80 (3 H, s), 5.29 (1 H, t, J = 7.2 Hz), 6.85 (2 H, d, J = 9.0 Hz), 7.23 (5 H, s), and 7.63 (2 H, d, J = 9.0 Hz); MS, m/z 310 and 312 (M^+). Anal. Calcd for $C_{15}H_{15}O_3SCl$: C, 57.97; H, 4.87. Found: C, 58.03; H, 4.78.

(*R*)-(+)-2-Chloro-2-phenylethyl methyl sulfone (10a): mp 119-121 °C; $[\alpha]^{23}_D$ +76° (c 0.76, chloroform); $[\theta]_{221}$ +9400 (c 1.0 × 10^{-4}, methanol); IR (KBr) 1320, 1305, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73 (3 H, s), 3.68 (1 H, d, J = 7.2 Hz), 3.75 (1 H, d, J = 7.2 Hz), 5.36 (1 H, t, J = 7.2 Hz), and 7.37 (5 H, s); MS, m/z 218 and 220 (M^+); HRMS, m/z 218.0111 ($C_9H_{11}O_2SCl$ requires 218.0169). Anal. Calcd for $C_9H_{11}O_2SCl$: C, 49.45; H, 5.04. Found: C, 46.69; H, 4.55.[11]

The authentic stereoisomers of compounds (-)-**3a-d** and (-)-**10a** were prepared by starting from an optically pure (*R*)-(-)-mandelic acid in a similar way.

(*S*)-(-)-2-Chloro-2-phenylethyl *p*-tolyl sulfone (3a): mp 92-93 °C; $[\alpha]^{26}_D$ -82° (c 3.4, chloroform); $[\theta]_{222}$ -24000 (c 1.1 × 10^{-4}, methanol); IR (KBr) 1320, 1305, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (3 H, s), 3.77-3.91 (2 H, m), 5.30 (1 H, t, J = 7.2 Hz), 7.23 (7 H, s), and 7.60 (2 H, d, J = 9.0 Hz); MS, m/z 294 and 296 (M^+). Anal. Calcd for $C_{15}H_{15}O_2SCl$: C, 61.11; H, 5.13. Found: C, 61.47; H, 5.15.

(*S*)-(-)-2-Chloro-2-phenylethyl phenyl sulfone (3b): mp 83-84 °C; $[\alpha]^{22}_D$ -83° (c 0.62, chloroform); $[\theta]_{218}$ -17000 (c 1.1 × 10^{-4}, methanol); IR (KBr) 1320, 1305, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80-3.90 (2 H, m), 5.32 (1 H, t, J = 7.2 Hz), 7.21 (5 H, s), and 7.33-7.80 (5 H, m); MS, m/z 280 and 282 (M^+). Anal. Calcd for $C_{14}H_{13}O_2SCl$: C, 59.89; H, 4.67. Found: C, 59.83; H, 4.31.

(*S*)-(-)-2-Chloro-2-phenylethyl *p*-chlorophenyl sulfone (3c): mp 93-94 °C; $[\alpha]^{26}_D$ -80° (c 1.7, chloroform); $[\theta]_{226}$ -30000 (c 1.1 × 10^{-4}, methanol); IR (KBr) 1325 and 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80-3.93 (2 H, m), 5.30 (1 H, t, J = 7.2 Hz), 7.20 (5 H, s), 7.30 (2 H, d, J = 9.0 Hz), and 7.60 (2 H, d, J = 9.0 Hz); MS, m/z 314 and 316 (M^+). Anal. Calcd for $C_{14}H_{12}O_2SCl_2$: C, 53.34; H, 3.84. Found: C, 53.63; H, 3.61.

(*S*)-(-)-2-Chloro-2-phenylethyl *p*-methoxyphenyl sulfone (3d): mp 63-66 °C; $[\alpha]^{24}_D$ -55° (c 2.0, chloroform); $[\theta]_{226}$ -22000 (c 1.2 × 10^{-4}, methanol); IR (KBr) 1325, 1310, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (2 H, m), 3.83 (3 H, s), 5.29 (1 H, t, J = 7.2 Hz), 6.84 (2 H, d, J = 9.0 Hz), 7.20 (5 H, s), and 7.63 (2 H, d, J = 9.0 Hz); MS, m/z 310 and 312 (M^+). Anal. Calcd for $C_{15}H_{15}O_3SCl$: C, 57.97; H, 4.87. Found: C, 58.24; H, 4.88.

(*S*)-(-)-2-Chloro-2-phenylethyl methyl sulfone (10a): mp 116-118 °C; $[\alpha]^{22}_D$ -77° (c 1.7, chloroform); $[\theta]_{221}$ -11000 (c 1.3 × 10^{-4}, methanol); IR (KBr) 1320, 1305, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73 (3 H, s), 3.68 (1 H, d, J = 7.2 Hz), 3.75 (1 H, d, J = 7.2 Hz), 5.34 (1 H, t, J = 7.2 Hz), and 7.35 (5 H, s); MS, m/z 218 and 220 (M^+). Anal. Calcd for $C_9H_{11}O_2SCl$: C, 49.45; H, 5.04. Found: C, 49.67; H, 4.88.

Ring-Inversion Barriers for the 3- and 4-Cyclohexenyl Radicals in Solution[1]

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Ring-inversion barriers for the 3- and 4-cyclohexenyl radicals were investigated by an electron paramagnetic resonance (EPR) method and were found to be 7.0 ± 0.9 and 2.4 ± 0.5 kcal mol^{-1} in fluid solution. The inversion motions and the magnitudes of the barriers were closely related to those of the corresponding cyclohexenones and methylenecyclohexanes.

The effect of ring size on the inversion barriers for cycloalkyl radicals bears a crude relationship to the effect observed for inversions in the corresponding cycloalkanes.[2] For example, the barriers for ring inversions of the cyclopentyl,[3] cyclohexyl,[4] and cycloheptyl[2] radicals are 1.3, 4.9, and 3.4 kcal mol^{-1}, respectively, while those for the corresponding cycloalkanes are 0.6, 10, and 1-2 kcal mol^{-1}.[5] Partial unsaturation of the ring has the effect of lowering the barrier relative to that of the cycloalkane. For example, NMR studies of cyclohexene set the barrier at 5.3 kcal mol^{-1}, while infrared studies of the same system lead to the somewhat higher estimate of 7.4 kcal mol^{-1}.[6]

In cycloalkenyl radicals, the situation is somewhat more complex because the inversion barriers ought to depend upon the relative positions of the unpaired electron and the double bond. To explore this problem, we have investigated the inversion barriers for the 3- and 4-cyclohexenyl radicals.

Experimental Section

Materials. 4-Iodocyclohexene was prepared by a new method described below, which was found to be more convenient than those previously described.[7] All other materials were commercially available. Di-*tert*-butyl peroxide was washed with aqueous silver nitrate then with water. After drying over magnesium sulfate, it was finally passed through a column of activated alumina. Hexamethyldistannane was purified by vacuum distillation. Triethylsilane was used as received.

4-Iodocyclohexene. To a stirred mixture of 50 g (0.30 mol) of potassium iodide in 20 mL of 85% phosphoric acid was added dropwise 13 mL (11 g, 0.14 mol) of 1,4-cyclohexadiene. The resulting mixture was heated at 85 °C for 16 h, after which time

(1) National Research Council of Canada. Issued as NRCC publication 27764.
(2) Burkey, T. J.; Griller, D.; Sutcliffe, R.; Harding, C. J. *J. Org. Chem.* **1985**, *50*, 1138.
(3) Lloyd, R. V.; Wood, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 8269.
(4) Ogawa, S.; Fessenden, R. W. *J. Chem. Phys.* **1964**, *41*, 994. Bonnazola, L.; Leray, N.; Marx, R. *Chem. Phys. Lett.* **1974**, *24*, 88.
(5) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. In *Conformational Analysis*; Wiley: New York, 1965. Brookeman, J. R.; Rushworth, F. A. *J. Phys. C* **1976**, *9*, 1043.
(6) Anet, F. A. L.; Haq, M. Z. *J. Am. Chem. Soc.* **1965**, *87*, 3147. Durig, J. R.; Carter, R. O.; Carreira, L. A. *J. Chem. Phys.* **1974**, *60*, 3098.
(7) Lambert, J. B.; Marko, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 7978 and references cited therein.

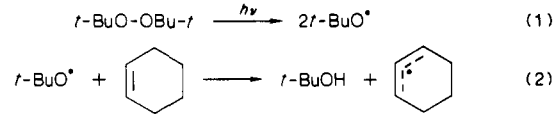
0022-3263/87/1952-3316$01.50/0

100 mL each of Et_2O and H_2O were added. The layers were separated, and the aqueous layer was extracted once with 20 mL of Et_2O. The combined ether layers were then decolorized with 20% sodium thiosulfate solution, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo to yield 14 g of yellow liquid, which consisted of 4-iodocyclohexene, iodocyclohexane, and various diiodides. A portion of the crude material (2.35 g) was purified by chromatography on silica gel, eluting with pentane to yield 1.22 g of the 4-iodocyclohexene (TLC analysis, pentane, R_f 0.44, UV identification). A pure sample was also obtained by preparative VPC (25% β,β'-oxydipropionitrile on Chromosorb P AW, 7 ft × $^1/_4$ in., 100 °C, He flow 60 mL/min). The resulting iodide was sensitive to light. The ^1H and ^{13}C NMR spectra were in agreement with previous reports:[7] ^1H NMR (250 MHz, $CDCl_3$) δ 5.77 (m, 1 H), 5.50 (m, 1 H), 4.48 (quintet, 1 H), 2.6–2.9 (m, 2 H), 2.14 (m, 4 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 125.7, 124.7, 37.6, 34.2, 26.5, 25.7; IR (CCl_4) 3030, 2925, 2839, 1651, 654 cm^{-1}; mass spectrum (70 eV), m/e 210 (M^+), 127, 81 (base peak).

Apparatus. Radicals were generated in the cavity of a Varian E-104 electron paramagnetic resonance (EPR) spectrometer by continuous photolysis of appropriate precursors using a 1000-W mercury–xenon arc lamp. Samples, were prepared by dissolving the reagents in propane, cyclopropane, or isopentane/cyclopentane (4:1 v/v) and were sealed in Suprasil tubes after degassing by several freeze–pump–thaw cycles.

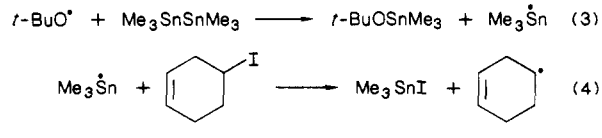
Results and Discussion

Photolysis of a cyclopropane solution containing cyclohexene (3% v/v) and di-*tert*-butyl peroxide (10% v/v) in the cavity of an EPR spectrometer gave clean spectra of the 3-cyclohexenyl radical (eq 1 and 2). Abstraction at

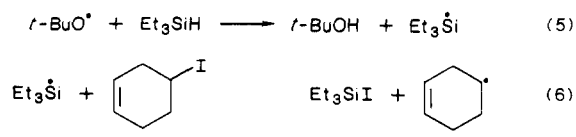


the allylic position was evidently quite efficient since there was no detectable contribution to the spectrum from the 4-cyclohexenyl radical or from that derived by *tert*-butoxyl addition to the double bond.[8] Spectra of sufficient quality for analysis were obtained between −90 and −20 °C.

The 4-cyclohexenyl radical was generated by two methods,[9] both of which involved iodine abstraction from 4-iodocyclohexene. In the first, the radical was obtained by photolysis of cyclopropane or isopentane/cyclopentane solutions containing the parent iodide (3% v/v), hexamethyldistannane (10% v/v), and di-*tert*-butyl peroxide (10% v/v)[9] (eq 1, 3, and 4). In the second method, pro-



pane solutions of di-*tert*-butyl peroxide, triethylsilane, and 4-iodocyclohexene were photolyzed in the EPR cavity and gave excellent spectra of the 4-cyclohexenyl radical between −150 and −30 °C (eq 1, 5, and 6).



Inversion barriers can be measured by EPR spectroscopy if spectra can be obtained where the inversion of the

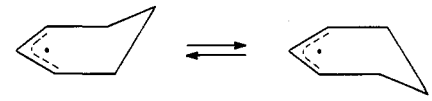


Figure 1. Inversion of the 3-cyclohexenyl radical.

radical is "frozen" at low temperatures and is rapid, with respect to the EPR time scale, at high temperatures. The spectral parameters obtained at these limits can be used in the standard exchange treatment[10] to simulate spectra and thus to determine inversion rate constants, in the intermediate temperature range.

The inversion barrier for the 3-cyclohexenyl radical was determined by this method. At −65 °C in cyclopropane solvent the radical adopted a frozen conformation and the EPR parameters were $a^{H_{1,3}} = 14.5$ G, $a^{H_2} = 3.5$ G, $a^{H_{4,6}} = 26.2$ G, $a^{H_{4',6'}} = 8.4$ G, and $a^{H_5} = 0.94$ G in excellent agreement with the literature values.[11] The hyperfine splittings due to the hydrogens at the 1-, 2-, and 3-positions are typical of those for allylic radicals.[12] At −20 °C these remained unchanged but the hydrogen atoms at the 4- and 6-positions became magnetically equivalent and their hyperfine splitting (17.3 G) was the average of those observed at the low-temperature limit. These observations imply that the radical is fairly rigid in the allylic region at all temperatures and that the motion which makes the hydrogens at the 4- and 6-positions magnetically equivalent is an inversion of the methylene group at the 5-position through the C_1–C_2–C_3 plane (Figure 1).

Analysis of the spectra obtained between −65 and −20 °C led to the Arrhenius expression for the inversion process given in eq 7, where the stated uncertainties represent 2 standard deviations and $\theta = 2.30RT$ kcal mol^{-1}. These

$$\log (k/s^{-1}) = (13.1 \pm 0.8) - (7.0 \pm 0.9)/\theta \qquad (7)$$

results are in very good agreement with those obtained by Pratt and de Tannoux[11] who studied the inversion of 3-cyclohexenyl in adamantane-d_{16} and obtained log (A/s^{-1}) = 13.1 and E_a = 7.3 kcal mol^{-1}. Clearly, the matrix did not perturb the inversion motion in that case although this has been known to occur in adamantane for radicals of similar size.[13]

The EPR spectrum of the 4-cyclohexenyl radical showed that rapid inversion was taking place at temperatures >−70 °C and the spectral parameters under these conditions were $a^{H_4} = 21.5$ G (H), $a^{H_5} = 24.8$ G (2 H), and $a^{H_3} = 29.7$ G (2 H). The basis for the assignments of a^{H_5} and a^{H_3} is described below. Unfortunately, the spectrum for the radical in its frozen conformation could not be obtained at the lowest accessible temperature (−150 °C). Nevertheless, by using simulation methods we were able to estimate the spectral parameters for this conformation, and these were used in the calculation of the Arrhenius parameters for the radical inversion. As we will show, the Arrhenius parameters are very insensitive to the choice of these hyperfine splittings.

The two sets of β hyperfine splittings for the rapidly inverting 4-cyclohexenyl radical tend toward the values observed for the cyclohexyl (22.5 G)[4] and cyclopentyl

(8) Wong, P. C.; Griller, D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 5106.
(9) Griller, D. *Magn. Reson. Rev.* **1979**, *5*, 1.
(10) Heizner, J. *Quantum Chemistry Program Exchange*, Indiana University, Program 209.
(11) De Tannoux, N. M.; Pratt, D. W. *J. Chem. Soc., Chem. Commun.* **1978**, 394.
(12) Fischer, H.; Paul, H. In *Landolt-Börstein*; Fischer, H., Hellwege, K.-H., Eds.; Springer-Verlag: New York, 1977; New Series, Group II, Vol. 9, Part b.
(13) Griller, D.; Ingold, K. U.; Krusic, P. J.; Fischer, H. *J. Am. Chem. Soc.* **1978**, *100*, 6750 and references cited therein.

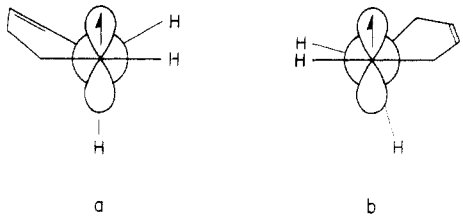


Figure 2. Newman projections for the conformation of β-hydrogens in the 4-cyclohexyl radical.

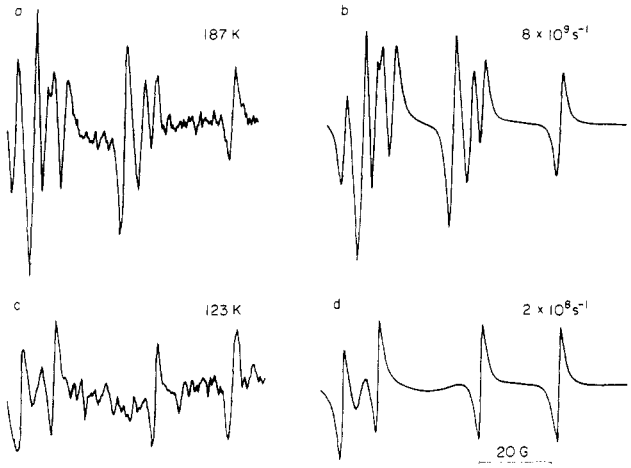


Figure 3. Experimental (high-field half) and computer-simulated spectra for the 4-cyclohexenyl radical at 187 (a,b) and 123 K (c,d); the appropriate rate constants for inversion are given in the figure.

radicals (33.5 G).[3] Inspection of models of the half-chair conformation of 4-cyclohexenyl radical shows the origin of this effect. Carbon atoms 1–3 are held rigidly in a plane by the double bond and cause the hydrogen atoms at C_3 to adopt the conformation shown in Figure 2a, which is similar to that adopted by the β-hydrogens in cyclopentyl. By contrast, flexibility in the remainder of the molecule allows the hydrogens at C_5 to take up more exaggerated axial and equatorial positions (Figure 2b) as is the case for cyclohexyl.

A very simple approach was used to estimate the hyperfine splittings for the frozen conformation of the 4-cyclohexenyl radical. We began with the equation developed by Ogawa and Fessenden[4] that crudely[14,15] describes the relationship between the β hyperfine splittings of the cyclohexyl radical and the dihedral angle, ϕ, between the axis of the p orbital and the C_β–H bond (eq 8). In this

$$a^{H_\beta} = A \cos^2 \phi + B \qquad (8)$$

equation A and B are constants equal to 40.5 and 4.5 G, respectively. We applied the constraint that the dihedral angle between the β-hydrogens was 120° and calculated values of hyperfine splittings which averaged to those observed for 4-cyclohexenyl at the high temperature limits. The values were 42.3 and 7.3 G for the β hyperfine splittings that averaged to 24.8 G while the values for the remaining pair were 44.8 and 14.6 G (average 29.7 G). These data were used as a starting point for the computer simulations and were refined until the optimum quality of fit was obtained. The best values were $a^{H_5} = 42.3$ G, $a^{H_{5'}} = 7.3$ G, $a^{H_3} = 40.8$, and $a^{H_{3'}} = 18.6$ G with $a^{H_4} = 21.5$ G. Representative spectra are shown in Figure 3, and the

Table I. Inversion Barriers for Cyclohexenyl Radicals and Cyclohexene Derivatives

	barrier, kcal mol^{-1}
3-cyclohexenyl radical	7.0[a] (7.3)[b]
4-cyclohexenyl radical	2.4[a]
cyclohexene	5.3,[c] 7.6[d]
3-methylenecyclohexene	6.0[e]
4-methylenecyclohexene	6.3[e], 4.2[e]
2-cyclohexenone	10.4[f]
3-cyclohexenone	1.3[f]

[a] This Work. [b] Reference 11; (EPR, adamantane matrix). [c] Reference 6; (NMR, solution). [d] Reference 6 (Raman, gas phase). [e] Reference 16 (infrared, gas phase). [f] Reference 17 (infrared, gas phase).

Arrhenius parameters obtained in this approach are given in eq 9, where the stated errors again represent 2 standard deviations and where $\theta = 2.30RT$ kcal mol^{-1}.

$$\log (k/s^{-1}) = (12.6 \pm 0.8) - (2.4 \pm 0.5)/\theta \qquad (9)$$

Major changes in the values chosen for the β hyperfine splittings in the frozen conformation did little to affect the results, which validates the approach. For example, changing the β hyperfine splittings to 34.8, 14.8 G and 34.9, 24.5 G led to a substantial decrease in the quality of fit but barely changed the barrier to inversion, which was found to be 2.6 ± 0.8 kcal mol^{-1}. Indeed, similar calculations showed that changing the parameters for the frozen conformation had an effect on the A factor for inversion but did little to alter the barrier.

We now return to the question of whether the inversions of the 3- and 4-cyclohexenyl radicals are similar to the motions of related molecules. Clearly, both radicals have a certain degree of planarity which is imposed by the presence of the double bond and the radical center. Sensible comparisons can therefore only be made with molecules which themselves have two groups that impose similar constraints. In this sense, methylenecyclohexenes and cyclohexenones are obvious choices for comparison.

The inversion barriers for methylenecyclohexenes,[16] cyclohexenones[17] and related molecules are given in Table I together with the barriers for the 3- and 4-cyclohexenyl radicals.

At first sight the data appear to be confusing in that two barriers are reported for cyclohexene[6] and 4-methylenecyclohexene.[16] However, sensitivity to the method of measurement is to be expected in some instances. This is because infrared and Raman methods derive barriers by looking at specific molecular motions which lead to inversion. For example, in the infrared study of 4-methylenecyclohexene[16] it was possible to measure barriers for two distinct inversion modes. However, while infrared and Raman methods look directly at specific molecular motions, NMR and EPR methods determine the barrier for the minimum energy pathway which leads to inversion and cannot specifically say whether this represents a single mode or a combination of modes. Hence, the lowest barriers obtained by infrared and Raman experiments should generally be compared with the barriers obtained by magnetic resonance techniques.

The inversion barriers for 3-cyclohexenyl, 3-methylenecyclohexene, and 2-cyclohexenone are higher than that in cyclohexene. Inclusion of the radical center or of functional groups which impose planarity close to the double bond causes a large part of the molecule to become

(14) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1976**, *8*, 13.
(15) Ingold, K. U.; Nonhebel, D. C.; Wildman, T. A. *J. Phys. Chem.* **1984**, *88*, 1675.
(16) Smithson, T. L.; Ibrahim, N.; Wieser, H. *Can. J. Chem.* **1983**, *61*, 442.
(17) Wieser, H.; Smithson, T. L.; Krueger, P. J. *J. Mol. Spectrosc.* **1982**, *96*, 368.

planar and rigid. Inversion then has to be achieved by motion of the most distant methylene through the plane defined by the double bond and neighboring group, c.f. Figure 1. This motion is a true inversion and requires a high activation energy. By contrast, the 4-cyclohexenyl radical, 4-methylenecyclohexene, and 3-cyclohexenone have inversion barriers that are significantly less than that in cyclohexene. In these cases, a methylene separates the planar group and the double bond and leaves two adjacent methylenes in the remainder of the structure. These molecules are far less rigid than those of the first group and "inversion" can be achieved by low-energy twisting or pseudorotation pathways.

Conclusion. The ring inversions of the 3- and 4-cyclohexenyl radicals bear a close relationship to inversions of the related cyclohexenones and methylenecyclohexenes.

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Palladium-Catalyzed Reactions in the Synthesis of 3- and 4-Substituted Indoles. 3.[1] Total Synthesis of (±)-Aurantioclavine

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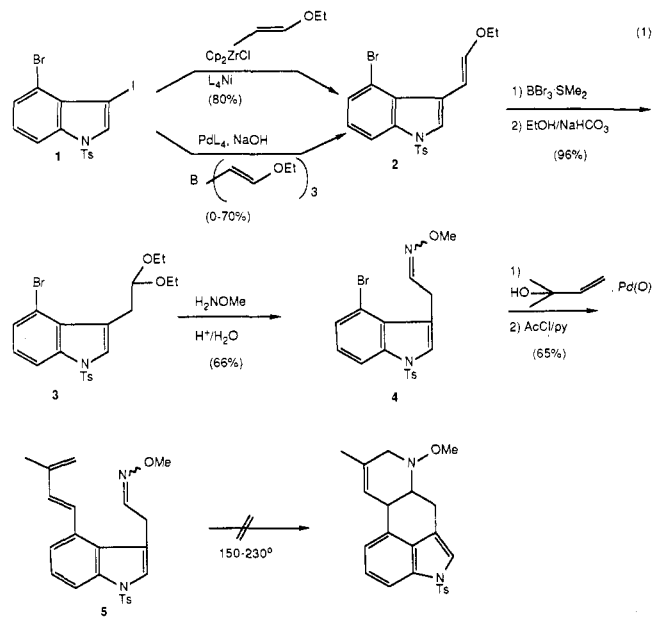
(±)-Aurantioclavine (**9**) was synthesized in overall 23% yield and 13 steps from commercially available starting materials. The synthesis involved palladium(II)-catalyzed indole ring formation, nickel(0)/zirconium(IV)-assisted introduction of one side chain, palladium(0)-catalyzed introduction of the other side chain, acid-catalyzed cyclization to form the seven-membered ring, and photolytic reductive detosylation to produce **9**.

Introduction

A general approach to the synthesis of 3,4-disubstituted indoles involving palladium(II)-catalyzed formation of 3-iodo-4-bromoindole **1** and sequential introduction of carbon side chains at the 3- and 4-positions using palladium(0) catalysis has recently been developed in these laboratories.[1] The use of this chemistry in the synthesis of derivatives of the ergot alkaloid clavicipitic acid has recently been reported.[2] The ease of introduction of highly functionalized side chains at the 3- and 4-positions of the indole nucleus suggested that this methodology would provide efficient routes to substrates suitable for intramolecular heteroatom Diels–Alder cyclizations to produce tetracyclic ergot alkaloid ring systems.[3] The results of studies directed toward this end are detailed herein.

Results and Discussion

The planned approach to the ergot alkaloid ring system involves synthesis of the requisite diene–aldehyde via palladium(0)-catalyzed chemistry, conversion of the aldehyde to an electron-deficient imine, and finally a reverse-electron-demand intramolecular heteroatom Diels-Alder reaction. The first attempt, patterned directly after Oppolzer's synthesis of lysergic acid methyl ester[3] is outlined in eq 1. The most direct route from **1** to **2**—palladium(0)-catalyzed alkylation of the 3-position by oxidative addition/insertion of methyl vinyl ether[4]—gave the undersired regioisomer (alkylation α to the methoxy group) as the major product. Palladium(0)-catalyzed oxidative addition–transmetalation from boron[5] was next attempted. For some reason this process was very sensitive to the purity of the boron reagent and to the freshness of the catalyst and yields were variable from run to run. The most reliable method proved to be nickel(0)-catalyzed oxidative addition–transmetalation from zirconium,[6] which consistently gave **2** in yields of 75–80%. Since the enol ether was somewhat resistant to hydrolysis and since the aldehyde was somewhat sensitive, hydrolysis using $BBr_3 \cdot SMe_2$ was immediately followed by acetalization to give **3** in excellent yield. Treatment with *O*-methylhydroxylamine under acidic conditions gave oxime **4** as a



(1) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. For an early report of the use of Pd(0) catalysis for the alkylation of 4-bromoindole, see: Somei, M.; Tsuchiya, M. *Chem. Pharm. Bull.* **1981**, *29*, 3145.

(2) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.*, in press.

(3) Oppolzer, W.; Francotte, E.; Battig, K. *Helv. Chim. Acta* **1981**, *64*, 478.

(4) Hallberg, A.; Westfelt, L.; Holm, B. *J. Org. Chem.* **1981**, *46*, 5414.

(5) Miyaura, N.; Maeda, K.; Suginome, H.; Suzuki, A. *J. Org. Chem.* **1982**, *47*, 2117.

(6) Negishi, E-i.; VanHorne, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168.

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