Synthesis of the Enantiomers of 4-Vinylcyclohexene

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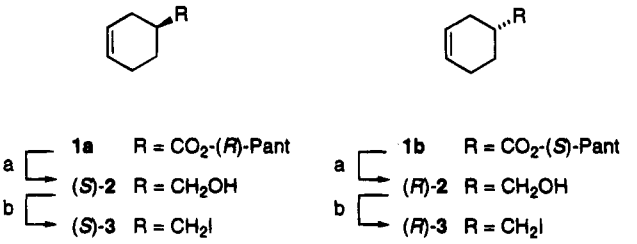
Racemic 4-vinylcyclohexene (4-VCH) is a volatile byproduct of butadiene rubber manufacture and processing[1] and is an intermediate in an industrially important synthesis of styrene.[2] There is concern that this hydrocarbon may pose a health risk to humans.[3] Preliminary investigations suggest that biological oxidation of 4-VCH leads to toxic mono- and diepoxide derivatives.[4] To facilitate a more detailed study of the biological oxidation and toxicity, we require supplies of both enantiomers of 4-VCH.

Previous preparations of enantiomerically enriched 4-VCH have involved rearrangement of optically enriched divinylcyclobutane,[5,6] rearrangement of butadiene or *rac*-divinylcyclobutane in the presence of optically active metal complexes,[7–11] resolution of 4-VCH using optically active metal complexes,[12,13] kinetic resolution by asymmetric hydroboration,[14] and synthesis from optically enriched precursors.[15] In order to provide material of high enantiomeric purity, we have explored routes for the asymmetric synthesis of the enantiomers of the title compound.

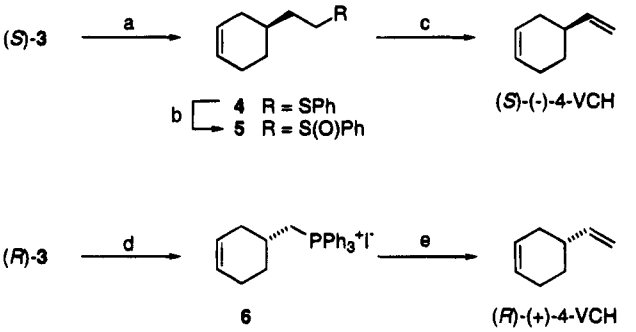
The diastereomerically pure pantolactone esters of 3-cyclohexene-1-carboxylic acid, **1a** and **1b** (Scheme 1), were prepared as reported by Helmchem.[16] The chiral auxiliary (*R*)-(−)-pantolactone was obtained from Aldrich Chemical Co. in >99% ee as determined by HPLC analysis on a Chiralcel OD column. The enantiomer, (*S*)-(+)-pantolactone, was prepared in >98% ee from (*R*)-(−)-pantolactone by the method of Corey.[17] The esters **1a** and **1b** were reduced with $LiAlH_4$ to give the corresponding (hydroxymethyl)cyclohexenes (*S*)-**2** and (*R*)-**2** in 95% yield.[18] The alcohols **2** were converted in 95% yield

Scheme 1[a]



[a] Conditions: (a) $LiAlH_4$, Et_2O; (b) I_2, PPh_3, imidazole, 25% CH_3CN/Et_2O.

Scheme 2[a]



[a] Conditions: (a) $PhSCH_3$, *n*-BuLi, DABCO, 0 °C; (b) *m*-CPBA; (c) DMSO, Δ; (d) PPh_3, toluene, 110 °C; (e) NaH, DMSO, CH_2O.

to iodides (*S*)-**3** and (*R*)-**3**,[19] which were used to prepare the enantiomers of 4-VCH via two different routes as described below.

Iodide (*S*)-**3** was reacted with the lithium salt of thioanisole[20] in THF at 0 °C to give phenyl thioether (*R*)-**4** in 70% yield (Scheme 2). Oxidation of (*R*)-**4** with *m*-chloroperbenzoic acid gave in 95% yield a 1:1 mixture of diastereomeric sulfoxides **5**. The sulfoxides **5** were heated in DMSO in a sealed tube at 185 °C to give (*S*)-(−)-4-VCH in 35% yield. The overall yield from (*S*)-**3** was 23%.

Compound (*R*)-**3** was converted to the phosphonium salt **6** in 93% yield. The corresponding phosphonium ylide was produced by deprotonation of **6** with 1.4 equiv of NaH in DMSO. The ylide was treated with an excess of paraformaldehyde to provide, in 44% yield, (*R*)-(+)-4-VCH. The overall yield from (*R*)-**3** was 41%.

Described herein is an improved synthetic preparation of both enantiomers of 4-VCH from a commercially available chiral auxiliary. The synthesis proceeds via several intermediates of high enantiomeric purity. These intermediates are configurationally stable and can be used in stereoselective preparation of putative oxidative metabolites. Toxicological studies with the enantiomers of 4-VCH are currently in progress and will be reported in due course.

Experimental Section

Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl. Dichloromethane, toluene, and dimethyl sulfoxide were distilled from CaH_2. Analytical thin-layer chromatography was performed on Merck precoated, glass-backed silica gel 60 F-254, 0.25 mm plates. Visualization of spots was

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effected by treatment of the plate with a solution of phosphomolybdic acid in ethanol followed by charring on a hot plate. Gas chromatography was performed using a 0.125 in. × 6 ft 15% Chromosorb on Carbowax W-HP column with helium as carrier and TCD detection. Pantolactone enantiomeric purity was determined on a 46 × 0.25 cm Chiralcel OD (cellulose) column, 10 μm particle size, with detection at 224 nm. NMR spectra of known compounds were identical with those of authentic samples. High resolution mass spectra were recorded at the Nebraska Center for Mass Spectrometry, Lincoln, NE. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

(*S*)-4-(Hydroxymethyl)cyclohexene ((*S*)-2).[18] To a well-stirred suspension of $LiAlH_4$ (1.8 g, 48 mmol) in freshly distilled ether (60 mL) was added dropwise a solution of 7.9 g (33 mmol) of cyclohexenoate ester **1a**[16] in ether (70 mL) over 1 h. After being stirred for 1 h at room temperature, the mixture was cooled to 0 °C and the reaction quenched by careful successive additions of water (1.8 mL), 4 N NaOH (1.8 mL), and water (5.5 mL). The white precipitate was removed by filtration and continuously extracted with ether for 3 h. The combined ether extracts were concentrated by distillation of solvent at ambient pressure through a Vigreux column and purified by column chromatography on 70–230 mesh silica gel 60 (125 g) eluted with 50% Et_2O/hexanes to give 3.5 g (31 mmol, 95%) of alcohol (*S*)-**2** as a colorless oil: R_f 0.24 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ −105° (*c* 3.5, CH_2Cl_2); IR (neat) 3326 (br), 1649 cm^{-1}; ^1H NMR δ 1.15–1.35 (1H, m), 1.64–1.88 (3H, m), 1.98–2.20 (3H, m), 3.15–3.35 (1H, m), 3.41–3.57 (2H, m), 5.60–5.73 (2H, m); ^{13}C NMR δ 24.5 (CH_2), 25.1 (CH_2), 28.0 (CH_2), 36.0 (CH), 67.3 (CH_2), 125.8 (CH), 126.9 (CH).

(*R*)-4-(Hydroxymethyl)cyclohexene ((*R*)-2):[18] $[\alpha]^{24}_D$ +112.8° (*c* 1.9, CH_2Cl_2).

(*S*)-4-(Iodomethyl)cyclohexene ((*S*)-3). Alcohol (*S*)-**2** (3.4 g, 31 mmol) was dissolved in 25% acetonitrile/ether (120 mL) at room temperature, and PPh_3 (9.7 g, 37 mmol) and imidazole (2.7 g, 40 mmol) were added. Iodine (9.4 g, 37 mmol) was added slowly over 30 min with periodic cooling. After being stirred for an additional 30 min, the reaction was quenched by addition of water (0.5 mL) and then adsorbed by rotary evaporation onto 70–230 mesh silica gel (40 g) in three portions. The material was purified by chromatography on 70–230 mesh silica gel 60 (300 g) eluted with pentane to give 6.5 g (29 mmol, 95%) of (*S*)-**3** as a colorless oil: R_f 0.64 (10% EtOAc/hexanes); $[\alpha]^{24}_D$ −50.6° (*c* 2.81, $CHCl_3$); IR (neat) 1649 cm^{-1}; ^1H NMR δ 1.25–1.42 (1H, m), 1.68–1.93 (3H, m), 2.00–2.32 (3H, m), 3.15–3.25 (2H, m), 5.59–5.60 (2H, m); ^{13}C NMR δ 15.0 (CH_2), 24.8 (CH_2), 29.2 (CH_2), 32.0 (CH_2), 35.9 (CH), 125.5 (CH), 126.8 (CH).

Anal. Calcd for $C_7H_{11}I$: C, 37.86; H, 4.99. Found: C, 37.64; H, 4.98.

(*R*)-4-(Iodomethyl)cyclohexene ((*R*)-3): $[\alpha]^{24}_D$ +52.3° (*c* 7.01, $CHCl_3$).

(*R*)-2-(3-Cyclohexen-1-yl)ethyl Phenyl Sulfide ((*R*)-4). To a stirred solution of diazabicyclo[2.2.2]octane (0.21 g, 1.8 mmol) and thioanisole (0.23 g, 1.8 mmol) in THF (4 mL) at 0 °C was added a solution of *n*-BuLi (1.7 mmol) in hexanes. After being stirred for 45 min, the reaction was cooled to −30 °C and a solution of iodide (*S*)-**3** (0.34 g, 1.5 mmol) in THF (3 mL) was added via cannula. The cannula was rinsed with THF (2 × 1 mL). The mixture was allowed to warm to room temperature over 2 h and was then poured into water (30 mL) and extracted with ether (2 × 25 mL). The organic extracts were dried ($MgSO_4$), filtered, and evaporated to give a colorless oil which was purified by chromatography on 70–230 mesh silica gel 60 (50 g) eluted with 0–10% EtOAc/hexanes to give 0.25 g (1.1 mmol, 74%) of (*R*)-**4** as a colorless oil: R_f 0.15 (hexanes); $[\alpha]^{25}_D$ −55.2° (*c* 2.3, $CHCl_3$); IR (neat) 1649, 736, 690 cm^{-1}; ^1H NMR δ 1.12–1.30 (1H, m), 1.54–1.79 (5H, m), 1.98–2.17 (3H, m), 2.94 (2H, t, *J* = 7.6 Hz), 5.57–5.70 (2H, m), 7.08–7.35 (5H, m); ^{13}C NMR δ 24.9 (CH_2), 28.4 (CH_2), 30.9 (CH_2), 31.3 (CH_2), 32.7 (CH), 35.6 (CH_2), 125.5 (CH), 126.0 (CH), 126.9 (CH), 128.6 (CH), 128.7 (CH), 136.9 (C); EIMS (70 eV) *m*/*z* 218 (M^+), 137, 123, 110, 108 (100), 93, 80, 79, 67, 65, 55, 53, 51; HRMS calcd for $C_{14}H_{18}S$ 218.1130, found 218.1129.

2-(3-Cyclohexen-1-yl)ethyl Phenyl Sulfoxides (5). To a stirred solution of sulfide (*R*)-**4** (0.57 g, 2.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added a solution of *m*-chloroperbenzoic acid (2.6 mmol) in CH_2Cl_2 (12 mL) over 15 min. After 1 h, the reaction was quenched by addition of 10% Na_2SO_3 solution (2 mL). The mixture was poured into saturated $NaHCO_3$ solution (60 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to give a colorless oil which was purified by chromatography on 230–400 mesh silica gel 60 (35 g) eluted with 30% EtOAc/hexanes to give 0.60 g (2.5 mmol, 98%) of a mixture of sulfoxide diastereomers **5** as a colorless oil: R_f 0.20 (30% EtOAc/hexanes); $[\alpha]^{23}_D$ −56.6° (*c* 1.4, $CHCl_3$); IR (neat) 1649, 1040, 748, 693 cm^{-1}; ^1H NMR δ 1.13–1.32 (1H, m), 1.52–1.80 (5H, m), 1.98–2.17 (3H, m), 2.74–2.94 (2H, m), 5.55–5.70 (2H, m), 7.45–7.68 (5H, m); ^{13}C NMR δ 24.8 (CH_2), 24.8 (CH_2), 28.3 (CH_2), 28.4 (CH_2), 28.5 (CH_2), 31.3 (CH_2), 31.4 (CH_2), 32.7 (CH), 32.8 (CH), 54.9 (CH_2), 123.9 (CH), 125.7 (CH), 126.9 (CH), 127.0 (CH), 129.0 (CH), 130.8 (CH), 143.9 (C); EIMS (70 eV) *m*/*z* 234 (M^+), 217 (100), 126, 123, 109, 107, 93, 91, 81, 79, 78, 77, 67, 55, 53, 51; HRMS calcd for $C_{14}H_{18}OS$ 234.1079, found 234.1078.

(*R*)-(3-Cyclohexen-1-ylmethyl)triphenylphosphonium Iodide ((*R*)-6). A solution of triphenylphosphine (11.3 g, 43.0 mmol) and iodide (*R*)-**3** (6.37 g, 28.7 mmol) in toluene (30 mL) was heated to 110 °C. After 36 h, the solid white product was collected by filtration, washed with toluene, and dried under vacuum for 8 h. The filtrate was concentrated by rotary evaporation and again heated to reflux. Additional product was collected after 60 and 68 h to give a total of 12.9 g (26.6 mmol, 93%) of (*R*)-**6** as a fine white powder: mp 243–246 °C; $[\alpha]^{22}_D$ +11.2° (*c* 2.7, MeOH); ^1H NMR δ 1.51–2.18 (7H, m), 3.70 (2H, ddm, *J* = 13.0 Hz), 5.46 (1H, dm, *J* = 10.0 Hz), 5.61 (1H, dm, *J* = 10.0 Hz), 7.68–7.94 (15H, m); ^{13}C NMR δ 24.4 (CH_2), 28.3 (d, *J* = 49.2 Hz, CH_2), 29.2 (d, *J* = 3.5 Hz, CH), 29.8 (d, *J* = 8.3 Hz, CH_2), 32.6 (d, *J* = 8.7 Hz, CH_2), 118.5 (d, *J* = 86.5 Hz, C), 124.8 (CH), 126.7 (CH), 130.5 (d, *J* = 12.8 Hz, CH), 133.5 (d, *J* = 10.8 Hz, CH), 135.1 (CH).

Anal. Calcd for $C_{25}H_{26}IP$: C, 61.99; H, 5.41. Found: C, 61.65; H, 5.40.

(*S*)-(−)-4-Vinylcyclohexene (from 5). A solution of sulfoxide **5** (4.84 g, 20.6 mmol) was dissolved in DMSO (13 mL) and sealed in a tube under vacuum. The tube was heated to 185 °C for 45 min. After cooling, the tube was opened, poured into 5% K_2CO_3 solution (100 mL), and extracted with pentane (2 × 50 mL). The pentane was dried ($MgSO_4$), filtered, and evaporated by distillation at ambient pressure through a Vigreux column. The resulting residue was purified by chromatography on 230–400 mesh silica gel 60 (40 g) eluted with pentane and then distilled at reduced pressure to give 0.77 g (7.15 mmol, 35%) of (*S*)-(−)-4-VCH as a colorless liquid containing 6% by weight pentane: R_f 0.50 (hexanes); t_R 3.0 min (80 °C, 23 mL/min); $[\alpha]^{24}_D$ −98° (*c* 0.8, $CHCl_3$); ^1H NMR δ 1.28–1.50 (1H, m), 1.72–1.94 (2H, m), 2.03–2.38 (4H, m), 4.91–5.08 (2H, m), 5.51–5.74 (2H, m), 5.84 (1H, ddd, *J* = 17.2, 10.4, 6.7 Hz); ^{13}C NMR δ 24.8 (CH_2), 28.3 (CH_2), 30.9 (CH_2), 37.5 (CH), 112.3 (CH_2), 126.1 (CH), 126.9 (CH), 143.8 (CH).

(*R*)-(+)-4-Vinylcyclohexene (from (*R*)-6). Pentane-washed sodium hydride (1.0 g, 42 mmol) was suspended in DMSO (70 mL). The mixture was stirred and heated to 60 °C for 2 h until gas evolution ceased. To the resulting clear brown solution was added phosphonium iodide (*R*)-**6** (12.9 g, 27 mmol) all at once. The dark orange mixture was stirred for 20 min, and paraformaldehyde (1.6 g, 53 mmol, dried under vacuum over P_2O_5) was added. The mixture was stirred at room temperature for 1 h and then at 50 °C for 30 min, after which time the orange color had dissipated. The reaction was cooled to room temperature, poured into water (400 mL), and extracted with pentane (4 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and filtered and volatiles removed by distillation at ambient pressure through a Vigreux column. The resulting residue was purified by chromatography on 230–400 mesh silica gel 60 (100 g) eluted with pentane and then distilled at reduced pressure to give 1.3 g (11.9 mmol, 44%) of (*R*)-(+)-4-VCH as a colorless liquid: R_f 0.50 (hexanes); t_R 3.0 min (80 °C, 23 mL/min); $[\alpha]_D$ +119° (*c* 1.31, $CHCl_3$), $[\alpha]_D$ +114° (*c* 0.9, toluene), $[\alpha]_D$ +117° (*c* 1.7, CCl_4) (lit.[15] $[\alpha]_D$ +115° (*c* 0.2–1.0, CCl_4)); EIMS (70 eV) *m*/*z* 108 (M^+), 104, 103, 93, 91, 80, 79, 78, 77, 67, 66, 54 (100); HRMS calcd for C_8H_{12} 108.0940, found 108.0939.

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Supporting Information Available: Proton and ^{13}C NMR spectra for all new compounds reported (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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