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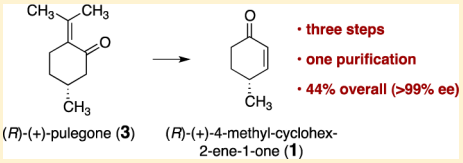
Synthesis of (*R*)-(+)-4-Methylcyclohex-2-ene-1-one

Maung Kyaw Moe Tun and Seth B. Herzon*

Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States

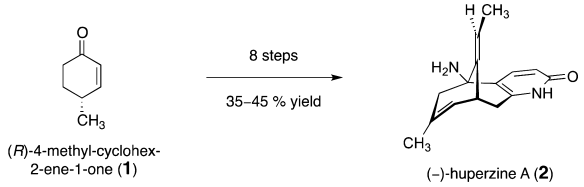
Supporting Information

ABSTRACT: A three-step synthesis of (*R*)-(+)-4-methylcyclohex-2-ene-1-one (**1**) from (*R*)-(+)-pulegone (**3**), proceeding in 44% overall yield, is described. The sequence comprises vinyl triflate formation, site-selective ozonolysis, and reduction. The route requires only one chromatographic purification and provides a convenient method to access multigram quantities of (*R*)-(+)-4-methylcyclohex-2-ene-1-one (**1**).



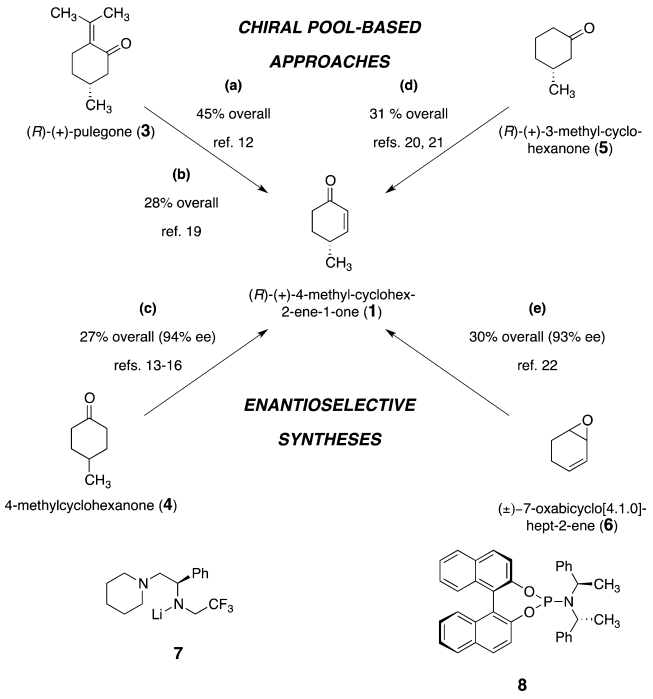
We recently described a synthesis of the natural neuroprotective agent (−)-huperzine A (**2**) that proceeds in eight steps and 35−45% overall yield from (*R*)-(+)-4-methylcyclohex-2-ene-1-one (**1**, Scheme 1).[1] (−)-Huperzine A (**2**) is a candidate for the treatment of a variety of neurological disorders,[2−5] and substantial resources have been devoted toward the development of an economical manufacturing route to **2**.[6] The reagent (*R*)-(+)-4-methylcyclohex-2-ene-1-one (**1**) has been employed in many synthetic sequences.[7−11] We obtained **1** by a chiral pool approach, developed by Lee et al.,[12] which begins with (*R*)-(+)-pulegone (**3**). This sequence was reproducibly executed in high overall yield on multigram scales, but several lateral manipulations were required (Scheme 2a). A more direct route to **1** that we have investigated comprises enantioselective deprotonation[13] of 4-methylcyclohexanone (**4**), trapping with chlorotrimethylsilane, and oxidation[14−16] (27%, Scheme 2c).[17] In this approach useful levels of stereoselectivity were obtained only if the deprotonation was conducted at −100 °C, a temperature not easily attained on large scales.

Scheme 1. Route to (−)-Huperzine A (2) by Tun et al.[1]



Several other methods to prepare (*R*)-(+)-4-methylcyclohex-2-ene-1-one (**1**) have been disclosed, including two that begin with (*R*)-(+)-pulgeone (**3**). Condensation of (*R*)-(+)-pulegone (**3**) with trisylhydrazine, vinyllithium generation,[18] protonation, and selective ozonolysis of the resulting 1,3-diene provides **1** in 28% overall yield (Scheme 2b).[19] Although this route is efficient, trisylhydrazine is of high molecular weight and relatively expensive on a molar basis. The application of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as a co-solvent in the vinyllithium generation step[18] was also undesirable in large-scale experiments. Alternatively, degradation of (*R*)-(+)-pulegone (**3**) to (*R*)-(+)-3-methylcyclohexanone (**5**, 69%),[20] followed by a five-step sequence provides the target **1** (21% from **5**, Scheme 2d).[21] A recent strategy employs ring-opening kinetic resolution of (±)-7-oxabicyclo[4.1.0]hept-

Scheme 2. Published Routes to (*R*)-(+)-4-Methylcyclohex-2-ene-1-one (1)[a]



[a]Abbreviated Conditions: (a) (i) $NaBH_4$; (ii) O_3 then DMS; (iii) $HOCH_2CH_2OH$, CSA; (iv) Tf_2O, pyridine; (v) DBU; (vi) H_2SO_4, H_2O. (b) (i) $TrisNHNH_2$; (ii) *n*-BuLi; (iii) O_3 then DMS. (c) (i) **7**, TMSCl; (ii) $Pd(OAc)_2$. (d) (i) $TiCl_4$, pyrrolidine; (ii) B_2H_6 then H_2O_2, NaOH; (iii) H_2O_2, CH_3OH; (iv) 120 °C, (v) PDC. (e) (i) $Cu(OTf)_2$, **8**, $(CH_3)_2Zn$; (ii) PDC, CH_2Cl_2, 0 → 23 °C.

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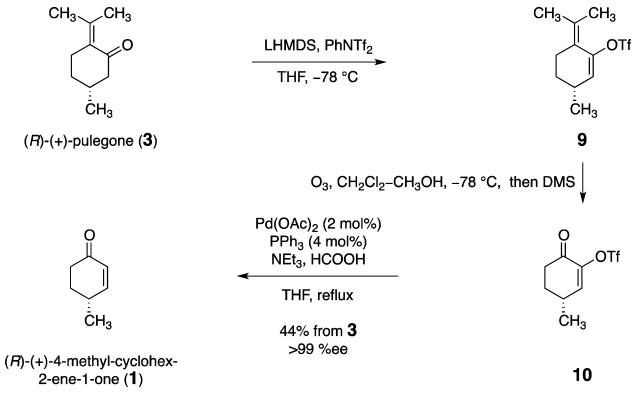
2-ene (**6**, prepared from 1,3-cyclohexadiene) with dimethylzinc, followed by oxidation (30%, Scheme 2e).[22]

We have developed an alternative and highly practical route to (*R*)-(+)-4-methylcyclohex-2-ene-1-one (**1**, Scheme 3).

Scheme 3. Improved Route to (*R*)-(+)-4-Methylcyclohex-2-ene-1-one (1) from (*R*)-(+)-Pulegone (3)



Deprotonation of (*R*)-(+)-pulegone (**3**, lithium hexamethylsilazide) and trapping of the resulting enolate with *N*-phenylbis(trifluoromethanesulfonimide) provided the vinyl triflate **9**.[23] The unpurified vinyl triflate **9** was selectively oxidized (ozone, dichloromethane−methanol, −78 °C) to form the α-(trifluoromethanesulfonyloxy)-α,β-unsaturated ketone **10**. Heating solutions of the unpurified α-(trifluoromethanesulfonyloxy)-α,β-unsaturated ketone **10** with palladium acetate (2 mol %), triphenylphosphine, triethylamine, and formic acid provided the target **1** (44%, >99% ee from **3**). This final step required significant optimization, as we have found that the α-(trifluoromethanesulfonyloxy)-α,β-unsaturated ketone **10** is susceptible to several decomposition pathways (including epimerization, aromatization, and dimerization) under basic reducing conditions. Overall, this sequence requires three manipulations and one chromatographic purification, employs inexpensive reagents and starting materials, and should be preferable to published procedures.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation at 30−33 °C. Flash-column chromatography was performed as described by Still et al.,[24] employing silica gel (60 Å, 40−63 μm particle size). Analytical thin layer chromatography (TLC) was performed using glass plates precoated with silica gel (1.0 mm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet (UV) light or/and submersion in aqueous potassium permanganate solution ($KMnO_4$), followed by brief heating on a hot plate (120 °C, 10−15 s).

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran was distilled from sodium−benzophenone under an atmosphere of nitrogen immediately before use. Triethylamine was distilled from calcium hydride under an atmosphere of nitrogen immediately before use. Commercial samples of 92% grade (*R*)-(+)-pulegone (**3**) and formic acid (>96% purity) were employed.

Instrumentation. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 or 500 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, coupling constant in Hertz, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 or 125 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$, δ 77.0). Distortionless enhancement by polarization transfer spectra [DEPT (135)] were recorded at 100 or 125 MHz at 24 °C, unless otherwise noted. ^{13}C NMR and DEPT (135) data are combined and represented as follows: chemical shift, carbon type [obtained from DEPT (135) experiments]. Fluorine nuclear magnetic resonance spectra (^{19}F NMR) were recorded at 282 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale), and are referenced indirectly to the ^{1}H frequency of $CHCl_3$. Attenuated total reflectance Fourier transform infrared spectra (ATR-FTIR) are referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). High-resolution mass spectrometry (HRMS) were obtained using an Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometer.

Synthesis of (*R*)-(+)-4-Methylcyclohex-2-ene-1-one (1). *Step 1: Synthesis of Vinyl Triflate 9.* (*R*)-(+)-Pulegone (**3**, 6.85 g, 45.0 mmol, 1 equiv) was added dropwise via syringe over 5 min to a stirred solution of lithium hexamethylsilazide (7.91 g, 47.3 mmol, 1.05 equiv) in tetrahydrofuran (45.0 mL) at −78 °C. Upon completion of the addition, the reaction mixture was stirred for 30 min at −78 °C. A solution of *N*-phenylbis(trifluoromethanesulfonimide) in tetrahydrofuran (1.00 M, 47.0 mL, 47.0 mmol, 1.05 equiv) was added dropwise via cannula over 10 min to the cold reaction mixture. Upon completion of the addition, the reaction mixture was warmed over 30 min to 24 °C. The warmed solution was stirred for 2 h at 24 °C. The warmed product mixture was diluted sequentially with ether (150 mL) and pentane (150 mL). The diluted solution was transferred to a separatory funnel that had been charged with 1.0 N aqueous sulfuric acid solution (150 mL). The layers that formed were separated. The organic layer was washed sequentially with 1.0 N aqueous sodium hydroxide solution (150 mL) and saturated aqueous sodium chloride solution (150 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford the vinyl triflate **9** as a pale yellow oil. ^{1}H and ^{13}C NMR spectroscopic data for **9** prepared in this way were in agreement with those reported.[23]

Step 2: Synthesis of α-(Trifluoromethanesulfonyloxy)-α,β-unsaturated Ketone 10. The residue obtained in the preceding step was dissolved in dichloromethane (220 mL) and methanol (54 mL), and the resulting solution was cooled to −78 °C. The cooled solution was treated with a continuous stream of ozone. Upon observation of a pale blue color (approximately 20 min), the addition of ozone was arrested, and the reaction mixture was purged with nitrogen (10 min) at −78 °C. Dimethyl sulfide (16.5 mL, 225 mmol, 5.00 equiv) was added, and the resulting mixture was warmed over 30 min to 24 °C. The warmed product mixture was concentrated to afford the α-(trifluoromethanesulfonyloxy)-α,β-unsaturated ketone **10** as a pale yellow oil. An analytically pure sample of the α-(trifluoromethanesulfonyloxy)-α,β-unsaturated ketone **10** was obtained by flash column chromatography (eluting with 20% ether−pentane).

R_f = 0.25 (20% ether−pentane, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, 1H, J = 3.2, 1.2 Hz, H_1), 2.90−2.79 (m, 1H, H_2), 2.75−2.65 (m, 1H, H_4), 2.57−2.49 (m, 1H, H_4), 2.22−2.14 (m, 1H, H_3), 1.82−1.72 (m, 1H, H_3), 1.26 (d, 3H, J = 7.2 Hz, H_5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6 (C), 144.2 (CH), 143.7 (C), 118.5 (C, J_{C-F} = 323 Hz), 36.4 (CH_2), 31.3 (CH), 29.9 (CH_2), 19.9 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.9. IR (ATR-FTIR), cm^{-1} 2968 (br), 1705 (s), 1421 (s), 1166 (s), 1137 (s), 1103 (s), 1085 (s). HRMS-CI(m/z) $[M + H]^+$ calcd for $C_8H_{10}F_3O_4S$, 259.0246; found, 259.0244.

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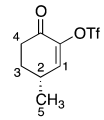

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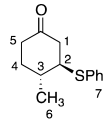
Step 3: (R)-(+)-4-Methylcyclohex-2-ene-1-one (1). A 500-mL round-bottomed flask was charged with the unpurified α-(trifluoromethanesulfonyloxy)-α,β-unsaturated ketone **10** obtained in the preceding step. The residue was dried by azeotropic distillation with benzene (10.0 mL), and the dried residue was dissolved in tetrahydrofuran (60 mL). Palladium acetate (202 mg, 900 μmol, 0.02 equiv) and triphenylphosphine (472 mg, 1.80 mmol, 0.04 equiv) were then added in sequence, and the resulting solution was stirred for 15 min at 24 °C. A solution of triethylamine (7.03 mL, 50.4 mmol, 1.12 equiv) and formic acid (1.87 mL, 49.5 mmol, 1.10 equiv) in tetrahydrofuran (120 mL) was then added dropwise via cannula over 5 min to the reaction mixture. The reaction vessel was fitted with a reflux condenser and then placed in an oil bath that had been preheated to 85 °C. The reaction mixture was stirred and heated for 12 h at 85 °C. The product mixture was cooled over 30 min to 24 °C. The cooled product mixture was diluted sequentially with ether (360 mL) and pentane (360 mL). The diluted solution was transferred to a separatory funnel that had been charged with saturated aqueous sodium chloride solution (100 mL). The layers that formed were separated, and the organic layer was washed with saturated aqueous sodium chloride solution (2 × 100 mL). The washed organic layer was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 30% ether−pentane) to provide (*R*)-(+)-4-methylcyclohex-2-ene-1-one (**1**) as a pale yellow oil (2.20 g, 44% from **3**). Spectroscopic data for **1** prepared in this way were in agreement with those reported.[12] The (*R*)-(+)-4-methylcyclohex-2-ene-1-one (**1**) prepared in this way was determined to be of >99% ee by chiral stationary phase HPLC analysis of the thiophenol 1,4-addition products **11** and **12** (see below).

Determination of Enantiomeric Excess. *Conjugate Addition of Thiophenol to (R)-(+)-4-Methylcyclohex-2-ene-1-one (1).* Triethylamine (50.0 μL, 490 μmol, 0.49 equiv) was added to a stirred solution of (*R*)-(+)-4-methylcyclohex-2-ene-1-one (**1**, 110 mg, 1.00 mmol, 1 equiv) and thiophenol (112 μL, 1.10 mmol, 1.10 equiv) in chloroform (10 mL) at 0 °C. Upon completion of the addition, the reaction mixture was warmed over 5 min to 24 °C. The warmed solution was stirred for 30 min at 24 °C. Additional portions of triethylamine (50.0 μL, 490 μmol, 0.49 equiv) and thiophenol (112 μL, 1.10 mmol, 1.10 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred for an additional 30 min at 24 °C. The product mixture was diluted with ether (20 mL). The diluted solution was transferred to a separatory funnel that had been charged with 1.0 N aqueous sodium hydroxide solution (10 mL). The layers that formed were separated, and the organic layer was washed sequentially with 1.0 N aqueous sodium hydroxide solution (10 mL) and saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford a mixture of the thiophenol addition products **11** and **12** (1.5:1 mixture of diastereomers). The addition products were purified by flash column chromatography (eluting with 20% ether−pentane) to afford separately the *anti*-1,4 addition product **11** as a colorless oil (65.0 mg, 30%) and the *syn*-1,4 addition product **12** as a white crystalline solid (31.1 mg, 14%, mp 84−86°).

anti-Addition product **11**: R_f = 0.34 (20% ether−pentane, $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.43−7.40 (m, 2H, H_7), 7.35−7.38 (m, 3H, H_7), 3.00 (ddd, 1H, *J* = 11.2, 9.8, 4.6, H_2), 2.69−2.64 (ddd, 1H, *J* = 14.5, 4.5, 1.8, H_1), 2.43−2.27 (m, 3H, H_1/H_5), 2.20−2.10 (m, 1H, H_4), 1.93−1.82 (m, 1H, H_3), 1.55−1.42 (m, 1H, H_4), 1.27 (d, 3H, *J* = 8.0 Hz, H_6). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1 (C), 133.7 (CH), 132.8 (C), 129.0 (CH), 127.9 (CH), 52.8 (CH), 47.5 (CH_2), 40.2 (CH_2), 35.5 (CH), 32.8 (CH_2), 19.6 (CH_3). IR (ATR-FTIR), cm^{-1} 2957 (s), 1715 (s), 1456 (m), 1322 (m), 1248 (w), 1183 (w), 1008 (m), 937 (w), 749 (s), 692 (s). HRMS-CI(*m*/*z*) $[M + Na]^+$ calcd for $C_{13}H_{16}NaOS$, 243.0814; found, 243.0810.



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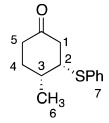
syn-Addition product **12**: R_f = 0.22 (20% ether−pentane, $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.43−7.41 (m, 2H, H_7), 7.33−7.25 (m, 3H, H_7), 3.62−3.59 (m, 1H, H_2), 2.57−2.55 (m, 2H, H_1), 2.50−2.25 (m, 3H, H_3/H_5), 2.00−1.80 (m, 2H, H_4),1.25 (d, 1H, *J* = 8.5 Hz, H_6). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7 (C), 133.9 (C), 133.0 (CH), 129.1 (CH), 127.5 (CH), 52.6 (CH), 45.5 (CH_2), 38.9 (CH_2), 33.6 (CH), 30.2 (CH_2), 16.4 (CH_3). IR (ATR-FTIR), cm^{-1} 2924 (s), 1715 (s), 1580 (m), 1453 (m), 1326 (w), 1186 (m), 1086 (w), 1020 (w), 905 (w), 740 (s), 700 (s). HRMS-CI(*m*/*z*) $[M + Na]^+$ calcd for $C_{13}H_{16}NaOS$, 243.0814; found, 243.0810.



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The addition products **11** and **12** were determined to be of >99% ee by chiral stationary phase HPLC analysis (see Supporting Information).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H, ^{13}C, and ^{19}F NMR for all new compounds and HPLC chromatograms. This material is free of charge via the Internet at http://pubs.acs.org/.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: seth.herzon@yale.edu.

Notes

The authors declare no competing financial interest.

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