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Construction of a Sterically Congested Carbon Framework via 5-Hexenyllithium Cyclization. Synthesis of (±)-Cuparene.

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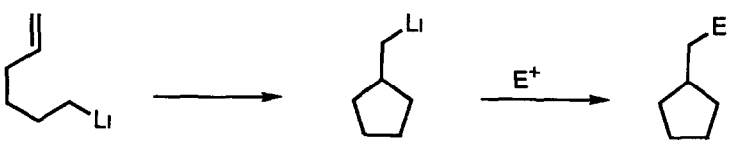
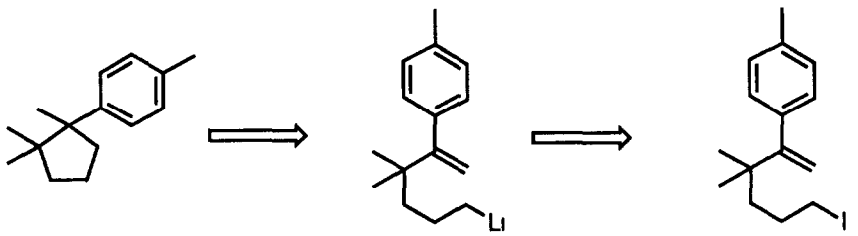
Abstract: The naturally occurring sesquiterpene (±)-cuparene [1,1,2-trimethyl-2-(4-methylphenyl)cyclopentane], which contains two contiguous quaternary centers, is produced in good yield by 5-exo-trig cyclization of the 5-hexenyllithium (**2**) generated from 6-iodo-3,3-dimethyl-2-(4-methylphenyl)-1-hexene (**3**) by low temperature lithium - iodine exchange In contrast, radical mediated cyclization of **3** proceeds via the 6-endo-trig mode to give 1,1-dimethyl-2-(4-methylphenyl)cyclohexane

Recently, we[1] and others[2] have reported on the facile cyclizations of substituted 5-hexenyllithiums as a route to functionalized five-membered ring-containing carbocycles This intramolecular insertion of an unactivated alkene into a C-Li bond is a totally regiospecific 5-exo-trig process that proceeds via a rigid cyclohexane-chair-like transition state in a highly *stereoselective manner*[3]



In view of the fact that this anionic route to five-membered rings can be used to prepare relatively strained molecules,[4] it was of interest to determine if the method might be applicable to the synthesis of sterically congested systems containing contiguous quaternary centers[5] Herein we report that the methodology may indeed be used for the preparation of such systems as demonstrated by the preparation of (±)-cuparene (**1**) via 5-exo-trig cyclization of the olefinic alkyllithium derived from iodide **3** In this connection it should be noted that, subsequent to the initiation of the work to be described below, Knief and Barbeaux reported on the synthesis of (±)-cuparene via a related route involving cyclization of the olefinic benzyllithium derived from 6-methyl-2-methylseleno-2-(4-methylphenyl)-6-heptene.[6]

The sesquiterpene cuparene, first isolated by Enzell and Erdtman[7] from the heartwood of conifers of the family *Cupressaceae*, has been prepared by a number of routes [8-13] The molecule, and related 2-aryl-1,1,2-trimethylcyclopentanes, pose an interesting challenge due to the presence of the two adjacent quaternary carbons Simple retrosynthetic analysis of **1** (Scheme 1) suggests that it should be possible to introduce the quaternary center bearing the *p*-tolyl substituent by 5-exo-trig cyclization of a 5-hexenyllithium (**2**) which, in turn, can be generated from iodide **3** by low-temperature lithium-iodine interchange [14]



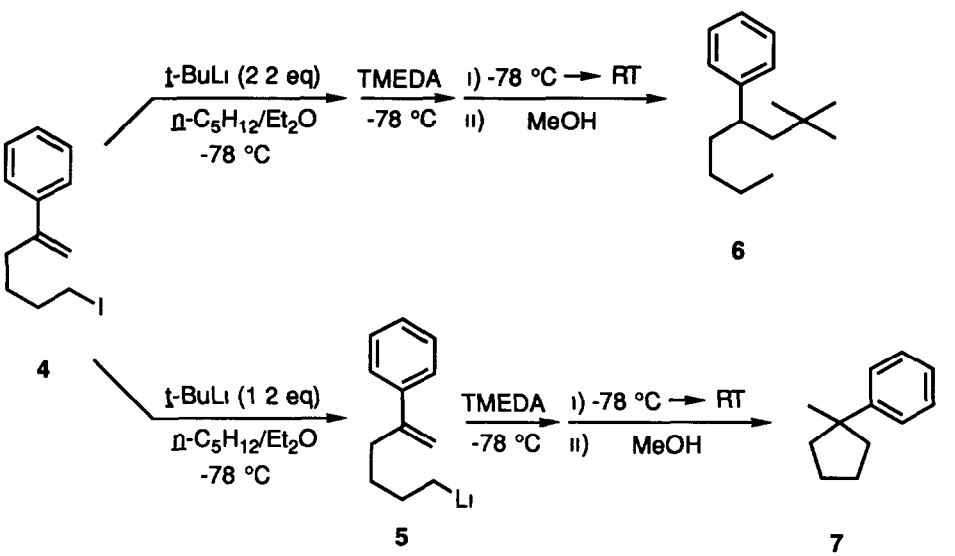
1 **2** **3**

Scheme 1

A potential difficulty with this approach to the synthesis of cuparene is the possibility that **2** would preferentially undergo 6-endo-trig cyclization to generate a less congested six-membered ring bearing a benzylic organolithium Such cyclization to the larger of the two possible rings would be the expected behavior[15] of the radical corresponding to **2** (vide infra) and for this reason it seemed prudent to initially investigate the cyclization of the readily available 6-iodo-2-phenyl-1-hexene (**4**)

Treatment of a solution of **4** in n-pentane - diethyl ether (3 2 by volume) with 2 2 equivalents of t-BuLi at -78 °C according to our general protocol for lithium - iodine exchange[14] followed by the addition of 2 2 equivalents of N,N,N',N'-tetramethylethylenediamine (TMEDA) and warming to room temperature led unexpectedly to the formation of 2,2-dimethyl-4-phenyloctane (**6**) as the major product of the reaction (Scheme 2) Apparently the intermolecular addition of excess t-BuLi to the conjugated double bond to give a benzylic anion is more facile than cyclization of the 5-phenyl-5-hexenyllithium (**5**) generated in the exchange reaction Indeed, the ease with which t-BuLi adds to styrenes, particularly in the presence of a coordinating amine such as TMEDA, has been noted previously [16] Fortunately, the lithium - halogen exchange reaction is complete well before the intermolecular addition of t-BuLi to the carbon - carbon double bond ensues Thus, the formation of **6** could be easily circumvented by the simple expedient of employing only 1 2 equivalents of t-BuLi for the lithium - iodine interchange Under these conditions, as shown in Scheme 2, iodide **4** is converted to **5** which then undergoes regiospecific 5-exo-trig cyclization to give 1-methyl-1-phenylcyclopentane (**7**) as the major product (52%) along with a significant quantity of 2-phenyl-1-hexene (48%), there was no trace of product arising from 6-endo-trig cyclization It might be noted that ~2 equivalents of t-BuLi are normally used to effect lithium - iodine exchange so as to consume

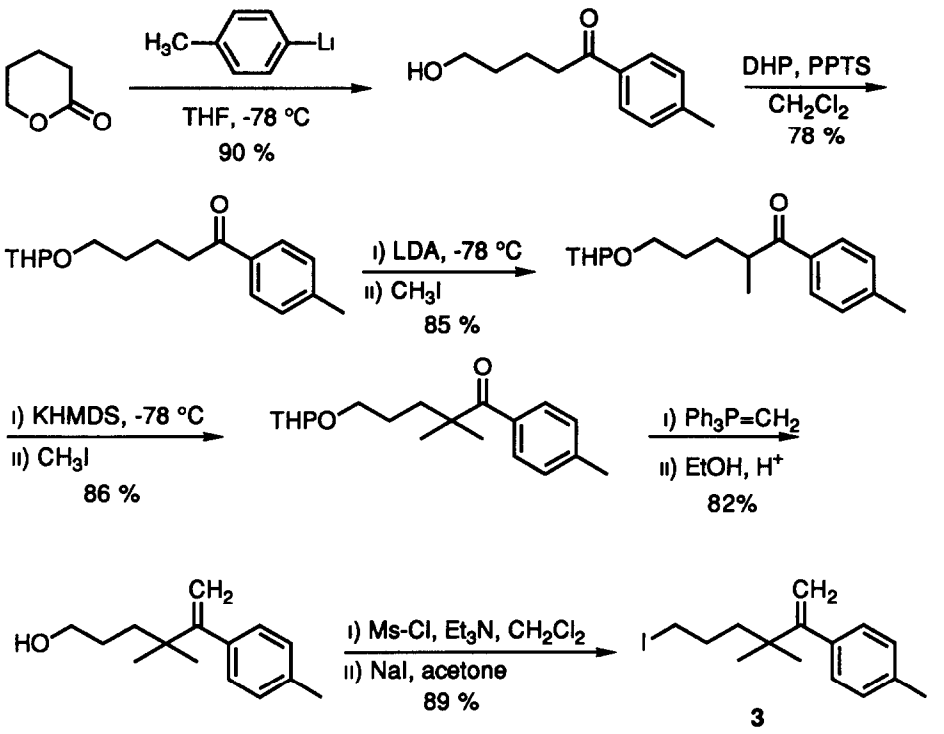
the equivalent of cogenerated t-butyl iodide and thereby minimize quench of the organolithium by proton abstraction from the t-BuI [14] The use of only 1 equivalent in this instance is no doubt responsible for the formation of a sizeable amount of 2-phenyl-1-hexene through protonation of **5** by the t-BuI



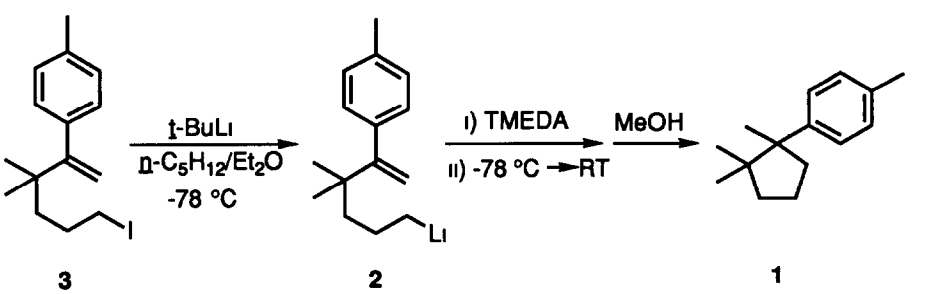
Scheme 2

The preparation of iodide **3** required for the synthesis of cuparene was accomplished in a straightforward if somewhat circuitous fashion as outlined in Scheme 3 The more direct route, involving ring-opening of α,α-dimethyl-δ-valerolactone with *p*-tolyllithium, proved unsuccessful in our hands and led to a mixture of products Hence, it was necessary to introduce the gem-dimethyl groups following the ring-opening of the parent lactone with *p*-tolyllithium

Treatment of a 0 1 M solution of iodide **3** in n-pentane - diethyl ether (3 2 by vol) at -78 °C with 1 2 equiv of t-BuLi served to cleanly generate the corresponding 5-hexenyllithium (**2**) as demonstrated by the fact that quench of the reaction mixture at -78 °C with deoxygenated methanol affords the open-chain alkene, 3,3-dimethyl-2-(4-methylphenyl)-1-hexene, in virtually quantitative yield Addition of 1 2 equiv of dry, deoxygenated TMEDA to the cold (-78 °C) solution of **2** followed by removal of the cooling bath and allowing the reaction mixture to stand at ambient temperature (ca +24 °C) for 2 h resulted in clean 5-exo-trig cyclization (Scheme 4) Quench of the reaction mixture with methanol and analysis by GC revealed that (±)-cuparene (**1**) had been produced in 82% yield The only other material present in the crude reaction mixture was ~18% of the isomeric open-chain alkene Careful washing of the reaction mixture with concentrated sulfuric acid served to remove the alkene and pure (±)-cuparene was isolated in 76% yield following chromatography on silica gel (Scheme 4)



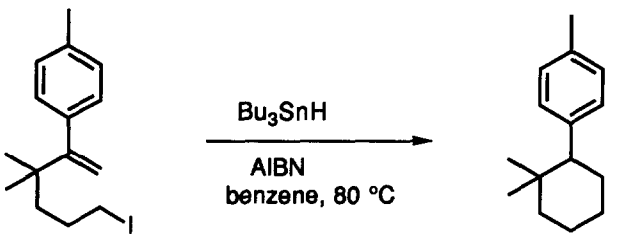
Scheme 3



Scheme 4

For purposes of comparison, we also explored the radical-mediated cyclization of iodide **3** (tributyltin hydride, AIBN in benzene at 80 °C) As expected,[15] the 5-hexenyl radical generated from **3** underwent 6-endo-trig cyclization to give 90% of 1,1-dimethyl-2-(4-methylphenyl)-

cyclohexane as the exclusive carbocyclic product (Scheme 5) The same behavior has recently been reported for the radical-mediated cyclization of the bromide corresponding to **3** [17]



3

Scheme 5

In conclusion, the results presented above demonstrate that regiospecific 5-exo-trig cyclization of a suitably constituted 5-hexenyllithium provides a synthetically useful route to sterically congested cyclopentane-ring containing frameworks The exclusively 5-exo isomerization observed for the 5-hexenyllithium contrasts with the 6-endo closure of the analogous 5-hexenyl radical and serves to underscore the often complementary behavior of these two modes of ring closure

EXPERIMENTAL SECTION

Proton and carbon-13 NMR spectra were recorded as solutions in $CDCl_3$ on an IBM AF-270 NMR instrument Proton chemical shifts (δ) were referenced with respect to the residual proton resonance in the $CDCl_3$ solvent (δ = 7 25) and carbon-13 chemical shifts were referenced with respect to the center line of the $CDCl_3$ resonance (δ = 77 05) but all chemical shifts are reported in ppm from Me_4Si A Perkin-Elmer Series 1600 FTIR instrument was used to record infrared spectra Purity of the starting materials and reaction products was assessed by analytical gas-liquid chromatography (GC) using a Hewlett-Packard model 5890 chromatograph equipped with a flame-ionization detector and a 25-m x 0 20-mm cross-linked methyl silicone (0 33-mm film thickness) fused-silica capillary column High resolution mass spectra were obtained by EI at 70 eV Thin-layer chromatography (TLC) was performed on E Merck precoated (0 2 mm) silica gel 60 F_{254} plates visualization was accomplished by spraying with 10 % ethanolic phosphomolybdic acid and heating Reaction products were purified by flash chromatography using Universal Scientific 32-60 μm silica gel

All reactions involving alkyllithiums were performed in flame-dried glassware using standard syringe/cannula techniques under an atmosphere of dry, oxygen-free argon that had been passed

through a 5-cm x 50-cm glass column containing activated BASF R3-11 copper catalyst Diethyl ether and tetrahydrofuran were freshly distilled from dark-purple solutions of sodium/benzophenone Dry, olefin-free n-pentane was obtained by repeated washings of commercial n-pentane with concentrated sulfuric acid until the acid layer remained clear, followed by washing successively with several portions of water, saturated aqueous sodium bicarbonate, and water, drying ($MgSO_4$) and distillation of the purified pentane under nitrogen from lithium aluminum hydride N,N,N',N'-tetramethylethylenediamine (TMEDA, bp 120 - 122 °C) and 1,1,1,3,3,3-hexamethyldisilazane (bp 125 °C) were distilled under nitrogen from calcium hydride. Methylene chloride was distilled under nitrogen from calcium hydride Acetone (Baker, analytical grade) used in the preparation of iodides was dried over calcium sulfate and distilled Sodium iodide was dried at 100 °C (ca 5 mm) for 8-10 h in a vacuum oven A solution of *p*-tolyllithium in diethyl ether was prepared from lithium metal and *p*-bromotoluene following the literature procedure for phenyllithium [18] The concentrations of commercial solutions of t-BuLi in n-pentane (Aldrich) and *p*-tolyllithium in diethyl ether were determined immediately prior to use by titration with sec-butanol in xylene using 1,10-phenanthroline as indicator [19]

6-Iodo-2-phenyl-1-hexene (4). A suspension of 2 20 g (5 60 mmol) of methyltriphenylphosphonium bromide in 10 mL of dry THF was cooled to 0 °C in a three-necked, round-bottomed flask equipped with a mechanical stirrer and rubber septa With stirring, a solution of potassium hexamethyldisilazide (KHMDS) in THF, prepared from 0 23 g (5.60 mmol) of oil-free potassium hydride and 1 20 mL (5 60 mmol) of 1,1,1,3,3,3-hexamethyldisilazane, was added in a dropwise manner via a teflon cannula The bright yellow suspension was stirred at 0 °C for 15 min and then at room temperature for 1 h The ylide mixture was recooled to 0 °C and a solution of 0 40 g (2 25 mmol) of 5-hydroxy-1-phenyl-1-pentanone[20] in 2 mL of dry THF was then added The resulting mixture was stirred at 0 °C for 0 5 h and at ambient temperature overnight The reaction mixture was poured into 10 mL of 10% aqueous hydrochloric acid and extracted with two 25-mL portions of diethyl ether The combined ether extracts were washed with water, dried ($MgSO_4$), and concentrated to afford an oil that was purified by flash chromatography on silica gel (25% ethyl acetate-hexanes) to give 0 25 g (63%) of **5-phenyl-5-hexen-1-ol** R_f 0 06 (25% ethyl acetate-hexanes), ^1H NMR δ 7 45-7 28 (m, 5H), 5 30 and 5 09 (AB pattern, J_{AB} = 1 39 Hz, 2H), 3 65 (t, J = 6 28 Hz, 2H), 2 56 (t, J = 6 82 Hz, 2H), 1 66-1 37 (m, 5H), ^{13}C NMR δ 148 23 (C(5)), 141 12 (C(1')), 128 18 (C(3',5')), 127 24 (C(4')), 126 01 (C(2',6')), 112 28 (C(6)), 62 48 (C(1)), 34 97 (C(4)), 32 19 (C(2)), 24 28 (C(3)) A portion of this alcohol (0 19 g, 1 10 mmol) was converted to its mesylate following the general procedure of Crossland and Servis[21] and added to a solution of 0 21 g (1 38 mmol) of anhydrous sodium iodide in 2 mL of dry acetone The resulting mixture was stirred overnight under an atmosphere of nitrogen Inorganic salts were then removed by filtration and the filtrate was concentrated by rotary evaporation The residue was taken up in pentane and washed successively with 10% aqueous sodium thiosulfate, water and brine After drying ($MgSO_4$), the solution was concentrated at reduced pressure and the residue was purified by chromatography on silica gel using hexanes as eluent to afford 0 20 g (62% from the alcohol) of pure title iodide R_f 0 25 (hexanes), ^1H NMR δ 7 43-7 26 (m, 5H), 5 30 and 5 08 (AB pattern, J_{AB} = 1 25 Hz, 2H), 3 18 (t,

J = 7.03 Hz, 2H), 2 54 (t, J = 7 47 Hz, 2H), 1 89-1.81 (m, 2H), 1 63-1 54 (m, 2H); ^{13}C NMR δ 147 81 (C(2)), 140.95 (C(1')), 128 29 (C(3',5')), 127 40 (C(4')), 126 08 (C(2',6')), 112.67 (C(1)), 34 16 (C(3)), 33 03 (C(5)), 28 96 (C(4)), 6 58 (C(6)) Mass spectroscopic molecular weight calcd for $C_{12}H_{15}I$ 286 0219, found 286 0227

Reaction of 6-Iodo-2-phenyl-1-hexene with t-BuLi. A 0 1 M solution of 6-iodo-1-phenyl-1-hexene (56.5 mg, 0.20 mmol) in n-pentane-diethyl ether (3 2 by volume) was cooled to -78 °C and 0 25 mL of a 1 72 M solution of t-BuLi (0 43 mmol) in pentane was added dropwise over a period of about 5 min The pale yellow-red reaction mixture was stirred at -78 °C for 5 min and then 0 07 mL (0 43 mmol) of dry, deoxygenated TMEDA was added The addition of TMEDA resulted in the formation of a yellow precipitate and the reaction solution became distinctly red After 5 min at -78 °C, the cooling bath was removed, the reaction mixture was allowed to warm to room temperature (during this period the reaction mixture became progressively more red) and stand for 1 h under an atmosphere of argon at ca +24 °C The mixture was then hydrolyzed by addition of 1 0 mL of deoxygenated MeOH, washed with water, dried ($MgSO_4$) and analyzed by GC-MS Analysis revealed that 2,2-dimethyl-4-phenyloctane was the major product formed by intermolecular addition of excess t-BuLi to the double bond, only small amounts of 2-phenyl-1-hexene and 1-methyl-1-phenylcyclopentane (5-exo-trig product) were detected (Scheme 2) When the same experiment was conducted using 1 2 molar equivalents of t-BuLi, no 2,2-dimethyl-4-phenyloctane was generated As shown in Scheme 2, the major products of the reaction were 1-methyl-1-phenylcyclopentane (52%) and 2-phenyl-1-hexene (48%)

5-Hydroxy-1-(4-methylphenyl)-1-pentanone. Following the general procedure of Rosenblum and Bihovsky[20] for the reaction of aryllithiums with lactones, a solution of 2 00 g (20 0 mmol) of δ-valerolactone in 20 0 mL of dry THF was cooled to -78 °C and 20 2 mL of a 0 99 M solution of *p*-tolyllithium (20 0 mmol) in diethyl ether was added dropwise over a period of about 0 5 h The reaction mixture was stirred at -78 °C under nitrogen for 20 min, 2 0 mL of water was then added, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature with stirring An additional 20 mL of water was then added, the organic phase was separated and the aqueous phase was extracted with 25 mL of fresh diethyl ether The combined organic phases were dried ($MgSO_4$) and solvents were removed by rotary evaporation to afford an oil Purification by column chromatography on silica gel (30% ethyl acetate-hexanes) gave 3 50 g (90%) of pure keto-alcohol R_f 0 056 (30% ethyl acetate-hexanes), IR (neat) 3393, 3022, 1671, 1603, 807 cm^{-1}, ^{1}H NMR δ 7 86-7 83 (m, 2H), 7 25-7 22 (m, 2H), 3 65 (t, J = 3 29 Hz, 2H), 2 98 (t, J = 7 01 Hz, 2H), 2 39 (s, 3H), 1 89-1 57 (m, 5H), ^{13}C NMR δ 200 15 (C(1)), 143 78 (C(1')), 134 43 (C(4')), 129 23 (C(2',6')), 128 16 (C(3',5')), 62 27 (C(5)), 37 97 (C(2)), 32 23 (C(4)), 21 59 (CH_3), 20 30 (C(3)) Mass spectroscopic molecular weight calcd for $C_{12}H_{14}O$ (M^+-H_2O) 174 1045, found 174 1043

5-[(Tetrahydropyranyl)oxy]-1-(4-methylphenyl)-1-pentanone. A solution of 3 50 g (18 3 mmol) of 5-hydroxy-1-(4-methylphenyl)-1-pentanone, 2 50 mL (27 5 mmol) of 3,4-dihydro-2H-

pyran and 0 46 g (0 18 mmol) of pyridinium *p*-toluenesulfonate in 125 mL of dry methylene chloride was stirred at room temperature for 6 h (the reaction was monitored by TLC) At the end of the time period, the reaction mixture was diluted with 75 mL of diethyl ether and washed with 100 mL of half-saturated brine After drying ($MgSO_4$), solvents were removed to afford a yellow liquid Purification by flash chromatography (20% ethyl acetate-hexanes) gave 4 00 g (78%) of the pure THP-ether R_f 0 26 (20% ethyl acetate-hexanes), IR (neat) 1679, 1603, 1072, 1027 cm^{-1},^1H NMR δ 7 83 (apparent d, J = 8 14 Hz, 2H), 7 21 (apparent d, J = 8 14 Hz, 2H), 4 55 (m, 1H), 3.89-3 71 (m, 2H), 3 51-3 35 (m, 2H), 2 95 (t, J =7 28 Hz, 2H), 2 37 (s, 3H), 1 87-1 41 (m, 10H), ^{13}C NMR δ 199 84, 143 57, 134 54, 129 18, 128 13, 98 81, 67 18, 62.27, 38.14, 30 71, 29 31, 25.45, 21.55, 21 25, 19 59 Mass spectroscopic molecular weight calcd for $C_{17}H_{24}O_3$ 276.1725, found 276 1717

5-[(Tetrahydropyranyl)oxy]-2-methyl-1-(4-methylphenyl)-1-pentanone. A 50-mL, three-necked, round-bottomed flask, equipped with a condenser and a pressure-equalizing addition funnel, was flame-dried under nitrogen and charged with 1 96 mL (14 0 mmol) of dry diisopropylamine and 5 00 mL of dry THF The flask was cooled to 0 °C in an ice-bath and 5 10 mL of a 2 63 M solution of n-butyllithium (13.4 mmol) in hexanes was then added dropwise The resulting solution was stirred at 0 °C for 15 min and then cooled to -78 °C in a dry ice-acetone bath A solution of 3 10 g (11 2 mmol) of 5-[(tetrahydropyranyl)oxy]-1-(4-methylphenyl)-1-pentanone in 6 mL of dry THF was then added over a period of about 0 5 h and the reaction mixture was stirred at -78 °C for an additional 0 5 h A solution of 1 39 mL (22 4 mmol) of iodomethane in 3 mL of dry THF was then added, the cooling bath was removed, the reaction mixture was allowed to warm to room temperature, and it was heated at gentle reflux for 2 h After cooling to room temperature, the reaction mixture was poured into 20 mL of saturated aqueous ammonium chloride The organic phase was separated and the aqueous phase was extracted with two 25-mL portions of diethyl ether The combined organic extracts were dried ($MgSO_4$) and concentrated The residue was taken up in 25 mL of diethyl ether and washed successively with 10-mL portions of 10% aqueous hydrochloric acid, 10% aqueous sodium thiosulfate and brine After drying ($MgSO_4$), the solution was concentrated and the crude product was purified by flash chromatography on silica gel (20% ethyl acetate-hexanes) to afford 2 74 g (85%) of the title compound R_f 0 28 (20% ethyl acetate-hexanes), IR (neat) 1679, 1603, 1451, 1375, 1345, 1027, 973 cm^{-1},^1H NMR δ 7.90-7 82 (m, 2H), 7 29-7 21 (m, 2H), 4 58-4 50 (m, 1H), 3.92-3 67 (m, 2H), 3 56-3 30 (m, 3H), 2 40 (s, 3H), 1 94-1 42 (m, 10H), 1 18 (d, J = 6 87 Hz, 3H), ^{13}C NMR δ 203 61, 143 35, 133 95, 129 09, 128 23, 98 61, 67 13, 62 14, 39 89, 30 55, 30 20, 27 31, 25 30, 21 37, 19 49, 17 21 Mass spectroscopic molecular weight calcd for $C_{18}H_{26}O_3$ 290 1882, found 290 1877

5-[(Tetrahydropyranyl)oxy]-2,2-dimethyl-1-(4-methylphenyl)-1-pentanone. A 50-mL, three-necked, round-bottomed flask, equipped with a condenser and a pressure-equalizing addition funnel, was flame-dried under nitrogen atmosphere and 0 50 g (12 4 mmol) of oil-free potassium hydride and 15 0 mL of dry THF were added The contents of the flask were stirred at room temperature and 2 70 mL (12 9 mmol) of dry 1,1,1,3,3,3-hexamethyldisilazane was added

dropwise with a syringe The turbid solution was stirred under nitrogen until evolution of hydrogen gas ceased The mixture was then cooled to -78 °C and a solution of 3.00 g (10 3 mmol) of 5-[(tetrahydropyranyl)oxy]-2-methyl-1-(4-methylphenyl)-1-pentanone in 6 00 mL of dry THF was added over a period of 0 5 h The reaction mixture was stirred at -78 °C for 0 5 h and then 1 30 mL (20 6 mmol) of iodomethane was added The cooling bath was removed, the reaction mixture was allowed to warm and stir at room temperature for 5 h followed by heating at gentle reflux for 1 h At the end of the time period, the reaction mixture was cooled to room temperature and poured into 10 0 mL of 10% aqueous hydrochloric acid The organic layer was separated and the aqueous phase was extracted with 25 mL of fresh diethyl ether. The combined organic extracts were dried ($MgSO_4$), concentrated by rotary evaporation and the residue was dissolved in 30 mL of diethyl ether The ethereal solution was washed with 15-mL portions of 10% aqueous sodium thiosulfate and brine After drying ($MgSO_4$), the solution was concentrated by rotary evaporation and the residual oil was purified by flash chromatography on silica gel (20% ethyl acetate-hexanes) to afford 2 71 g (86%) of the dialkylated product R_f 0 32 (20% ethyl acetate-hexanes), IR (neat) 1671, 1611, 1451, 1072, 1027, 814 cm^{-1},^{1}H NMR δ 7.61 (apparent d, J = 8 13 Hz, 2H), 7 15 (apparent d, J = 8 13 Hz, 2H), 4 48 (m, 1H), 3 78-3 28 (series of m, 4H), 2 34 (s, 3H), 1 87-1 44(m, 10H), 1 29 (s, 6H), ^{13}C NMR δ 208 08, 141 31, 135 95, 128 67, 127 99, 98 59, 67 51, 62 23, 47 49, 37 47, 30 66, 26 21, 26 18, 25.43, 25 18, 21 36, 19 55 Mass spectroscopic molecular weight calcd for $C_{19}H_{28}O_3$ 304 2038, found 304 2034

6-[(Tetrahydropyranyl)oxy]-3,3-dimethyl-2-(4-methylphenyl)-1-hexene. Potassium t-butoxide(1 00 g ,9 00 mmol), 3 23 g (9 00 mmol) of methyltriphenylphosphonium bromide and 16 mL of dry benzene were heated at reflux with stirring for 1 h under an atmosphere of nitrogen A solution of 2 50 g (8.22 mmol) of 5-[(tetrahydropyranyl)oxy]-2,2-dimethyl-1-(4-methylphenyl)-1-pentanone in 5 mL of dry benzene was then added and the mixture was heated at reflux for an additional 0 5 h The mixture was cooled to room temperature and 20 mL of hexanes and 10 mL of water were added with stirring The organic layer was separated and the aqueous phase was extracted with two 10-mL portions of hexanes The combined organic phases were dried ($MgSO_4$) and concentrated at reduced pressure to afford an oil which was diluted with 20 mL of fresh hexanes and the mixture was cooled in an ice-bath The precipitated triphenylphosphine oxide was removed by filtration, the filtrate was concentrated by rotary evaporation, and the residue was purified by flash chromatography (10% ethyl acetate-hexanes) to afford 2 13 (85%) of the title compound R_f 0 47 (20% ethyl acetate-hexanes), IR (neat) 3082, 1618, 1504, 1451, 1133, 1110, 1027, 898, 822 cm^{-1},^{1}H NMR δ 7 12-7 01 (m, 4H), 5 11 and 4 84 (AB pattern, J_{AB} = 1 74 Hz, 2H), 4 58-4 55 (m, 1H), 3 90-3 30 (m, 4H), 2 33 (s, 3H), 1 90-1 34 (m, 10H), 1 08 (s, 6H), ^{13}C NMR δ 157 38, 140 43, 135 75, 128 72, 128 01, 113 52, 98 72, 67 97, 62 20, 39 06, 37 05, 30 75, 27 74, 25 52, 25 21, 21 05, 19 60 Mass spectroscopic molecular weight calcd for $C_{20}H_{30}O_2$ 302 2246, found 302 2235

4,4-Dimethyl-5-(4-methylphenyl)-5-hexen-1-ol. Dilute (10%) aqueous hydrochloric acid was added to a solution of 1 30 g (4 30 mmol) of 6-[(tetrahydropyranyl)-oxy]-3,3-dimethyl-2-(4-

methylphenyl)-1-hexene in 25 mL of absolute ethanol until the pH of the solution was ~3 and the solution was heated on a steam bath for 15 min After cooling to room temperature, 25 mL of cold water was added and the mixture was extracted with three 25-mL portions of diethyl ether The combined organic extracts were dried ($MgSO_4$), concentrated at reduced pressure, and the residue was purified by flash chromatography (20% ethyl acetate-hexanes) to give 0 90 g (96%) of the pure title alcohol R_f 0 16 (20% ethyl acetate-hexanes), IR (neat) 3325, 3082, 1618, 1512, 1451, 1049, 898, 814 cm^{-1}, ^1H NMR δ 7 09-6.99 (m, 4H), 5 12 and 4.85 (AB pattern, J_{AB} = 1 70 Hz, 2H), 3 59 (t, J = 6 63 Hz, 2H), 2 33 (s, 3H), 1 67-1 32 (m, 5H), 1 10 (s, 6H), ^{13}C NMR δ 157 42 (C(5)), 140 34 (C(1')), 135 85 (C(4')), 128 62 (C(3',5')), 128 07 (C(2',6')), 113 55 (C(6)), 63.41 (C(1)), 38 94 (C(4)), 36 75 (C(2)), 28 14 (C(3)), 27 74 (4-CH_3), 21 02 (p-CH_3) Mass spectroscopic molecular weight calcd for $C_{15}H_{22}O$ 218 1671, found 218 1660

3,3-Dimethyl-6-iodo-2-(4-methylphenyl)-1-hexene (3). The mesylate of 4,4-dimethyl-5-(4-methylphenyl)-5-hexen-1-ol, prepared from 0 750 g (3 41 mmol) of the alcohol following the general procedure of Crossland and Servis,[21] was added to a solution of 0 640 g (4 26 mmol) of anhydrous sodium iodide in 6 5 mL of dry acetone and the mixture was heated at gentle reflux with stirring for 4 h under an atmosphere of nitrogen The mixture was then cooled to room temperature, filtered, and the inorganic salts were washed with several portions of fresh acetone The combined filtrate and washings were concentrated by rotary evaporation The residue was taken up in 20 mL of hexanes and the solution was washed successively with 10-mL portions of 10% aqueous sodium thiosulfate, water and brine After drying ($MgSO_4$), the solution was concentrated and the crude iodide was purified by column chromatography on silica gel (hexanes as eluent) to afford 1 10 g (89%) of the title iodide R_f 0 30 (hexanes), IR (neat) 3082, 1618, 1512, 1451, 898, 814 cm^{-1}, ^1H NMR δ 7 14 (apparent d, J = 8 05 Hz, 2H), 7 03 (apparent d, J = 8 05 Hz, 2H), 5 14 and 4.88 (AB pattern, J_{AB} = 1 59 Hz, 2H), 3 14 (t, J = 7 07 Hz, 2H), 2 36 (s, 3H), 1 93-1 81 (m, 2H), 1.50-1.40 (m, 2H), 1 12 (s, 6H), ^{13}C NMR δ 157 15 (C(2)), 140.11 (C(1')), 136 00 (C(4')), 128 61 (C(3',5')), 128 18 (C(2',6')), 113 79 (C(1)), 41 96 (C(5)), 38 96 (C(3)), 29 25 (C(4)), 27 87 (3-CH_3), 21 09 (p-CH_3), 7.39 (C(6)) Mass spectroscopic molecular weight calcd for $C_{15}H_{21}I$ 328 0690, found 328 0685

Reaction of 3,3-Dimethyl-6-iodo-2-(4-methylphenyl)-1-hexene with t-BuLi and Quench at Low Temperature: Preparation of 3,3-Dimethyl-2-(4-methylphenyl)-1-hexene. A 0 1 M solution of 3,3-dimethyl-6-iodo-2-(4-methylphenyl)-1-hexene (86 7 mg, 0 26 mmol) in n-pentane-diethyl ether (3 2 by volume) was cooled to -78 °C under an atmosphere of dry, oxygen-free argon and 0 16 mL of a 2 02 M solution of t-BuLi (0.32 mmol) in pentane was added dropwise over a period of 5 min The solution was stirred at -78 °C for 5 min and then 0 5 mL of dry, deoxygenated MeOH was added at the same temperature The reaction mixture was allowed to warm to room temperature with stirring, washed with water, and dried ($MgSO_4$) Analysis of the product mixture by GC showed that it was essentially one component Evaporation of the solvents and purification of the residue by flash chromatography on silica gel (hexanes as eluent) gave the title alkene in virtually quantitative yield R_f 0 30 (hexanes), ^1H NMR δ 7 13-6 98

(m, 4H), 5 14-5 08 (m, 1H), 4 87-4 80 (m, 1H), 2 35 (s, 3H), 1 43-1 22 (m, 4H), 1.08 (s, 6H), 0 95-0 82 (m, 3H), ^{13}C NMR δ 157.99, 140 65, 135 76, 128 73, 128.04, 113.13, 43 34, 39 38, 27 76, 21 09, 17 95, 14 66 Mass spectroscopic molecular weight calcd for $C_{15}H_{22}$ 202 1721, found 202 1716

(±)-Cuparene (1). A 0 1 M solution of 3,3-dimethyl-6-iodo-2-(4-methylphenyl)-1-hexene (315 6 mg, 0 96 mmol) in n-pentane-diethyl ether (3 2 by volume) was cooled to -78 °C under an atmosphere of dry, oxygen-free argon and 0 55 mL of a 2.10 M solution of t-BuLi (1 15 mmol) in pentane was added dropwise over a period of 5 min The reaction mixture was stirred at -78 °C for 5 min and then 170 μL (1 15 mmol) of dry, deoxygenated TMEDA was added dropwise via syringe Addition of TMEDA resulted in the formation of a thick, yellow precipitate The mixture was stirred for 5 min -78 °C, the cooling bath was then removed, and the solution was allowed to warm and stand at room temperature under argon for 2 h before addition of 1 0 mL of deoxygenated MeOH The reaction mixture was washed with water and then with small portions of concentrated sulfuric acid until GC analysis of the reaction mixture revealed that the open-chain alkene had been completely removed The mixture was then washed with saturated, aqueous sodium bicarbonate, dried ($MgSO_4$) and solvents were carefully removed by rotary evaporation. The virtually pure product was chromatographed on silica gel using hexanes as eluent to give 147 7 mg (76%) of pure (±)-cuparene R_f 0 43 (hexanes), ^{1}H NMR δ 7 28-7 21 (m, 2H), 7 13-7 05 (m, 2H), 2 31 (s, 3H), 1 85-1 48 (m, 6H), 1 25 (s, 3H), 1 05 (s, 3H), 0 55 (s, 3H) [lit [12] ^{1}H NMR δ 7 4-7 1 (m, 4H), 2 25 (s, 3H), 1 65 (br, 6H), 1 22 (s, 3H), 1 04 (s, 3H), 0 54 (s, 3H)], ^{13}C NMR δ 144 59, 134 74, 128 23, 126 96, 50 28, 44 24, 39 78, 36 89, 26 49, 24 44, 24 31, 20 86, 19 78. These ^{13}C shifts are virtually identical to those reported by Reetz et al[11] for this compound [lit [11] ^{13}C NMR δ 144 4, 134 7, 128 2, 126 9, 50 3, 39 8, 36 9, 26 4, 24 4, 24 3, 20 8, 19 7] but the carbon at δ = 44 24 was not listed in this report

Radical Cyclization of 3,3-Dimethyl-6-iodo-2-(4-methylphenyl)-1-hexene: Preparation of 1,1-Dimethyl-2-(4-methylphenyl)cyclohexane. A solution of 178 9 mg (0 55 mmol) of 3,3-dimethyl-6-iodo-2-(4-methylphenyl)-1-hexene in 25 mL of freshly distilled, dry benzene was heated to reflux under an atmosphere of nitrogen and 5 60 mL of a solution containing 177 5 mg (0 61 mmol) tri-n-butyltin hydride and 5 mg of AIBN was added via a syringe over about 0 5 h After heating at reflux for a further 1 h (no unreacted iodide was found by TLC), the reaction mixture was cooled to room temperature and concentrated by rotary evaporation Analysis of the crude product by gas-liquid chromatography showed that the reaction had proceeded in a 6-endo fashion to give 1,1-dimethyl-2-(4-methylphenyl)cyclohexane, only a trace amount (< 2%) of 3,3-dimethyl-2-(4-methylphenyl)-1-hexene was detected Purification by column chromatography on silica gel (hexanes as eluent) afforded 100 4 mg (90%) of 1,1-dimethyl-2-(4-methylphenyl)cyclohexane R_f 0 44 (hexanes), ^{1}H NMR δ 7 11-7 03 (m, 4H), 2 36 (m, 1H), 2 34 (s, 3H), 1 94-1 80 (m, 2H), 1 65-1 24 (m, 6H), 0 82 (s, 3H), 0 78 (s, 3H) [lit [16] ^{1}H NMR 7 06 (d, J = 7 Hz, 2H), 7 02 (d, J = 7 Hz, 2H), 2 34 (m, 1H), 2 32 (s, 3H), 2 0 - 1 7 (m, 2H), 1 6 - 1 4 (m, 4H), 1 4 - 1 2 (m, 2H), 0 79 (s, 3H), 0 75 (s, 3H)], ^{13}C NMR δ 141 11, 135 19, 129 15, 128 14, 53 44, 42 30, 34 11,

31 42, 28 61, 27 42, 22 65, 21 02, 19 69. Mass spectroscopic molecular weight calcd for $C_{15}H_{22}$ 202 1721, found 202 1721

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