JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Asymmetric Intramolecular Carbolithiation of Achiral Substrates: Synthesis of Enantioenriched (*R*)-(+)-Cuparene and (*R*)-(+)-Herbertene

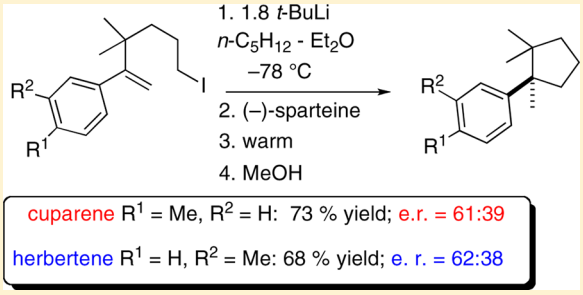
Matthew R. Luderer,[†] Michael J. Mealy,[‡,§] and William F. Bailey*[,‡]

[†]Department of Natural Science, Mathematics, and Engineering, University of Pittsburgh at Greensburg, Greensburg, Pennsylvania 15601, United States

[‡]Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269, United States

Supporting Information

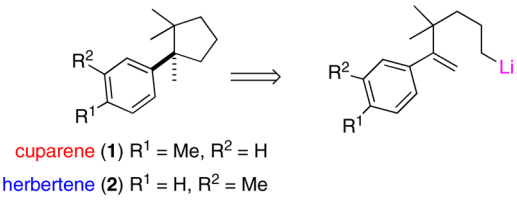
ABSTRACT: Concise syntheses of the sesquiterpenes (*R*)-(+)-cuparene and (*R*)-(+)-herbertene by asymmetric cyclization of achiral olefinic alkyllithium precursors in the presence of (−)-sparteine are reported. The quaternary stereogenic center in each product is set at the final step of the synthesis by enantioselective (er = 61:39) 5-*exo* ring closure.



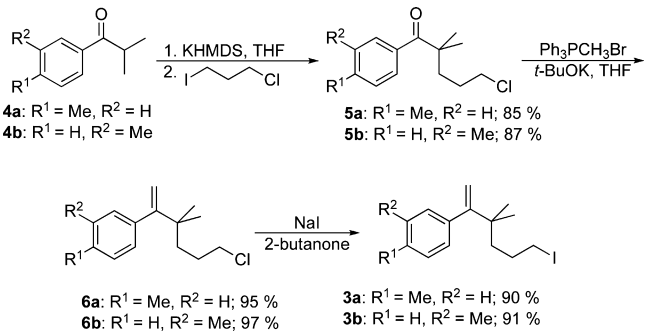
Some time ago, we[1] as well as Groth[2] reported that the cyclization of achiral olefinic organolithiums may proceed in an enantioselective fashion when conducted in the presence of an enantiopure chiral ligand such as (−)-sparteine or other lithiophilic ligands.[3] The enantioselectivity of the process is often high but it is quite substrate dependent.

It occurred to us that an enantioselective cyclization of suitably constituted achiral olefinic alkyllithiums, which in turn may be prepared from the corresponding iodides by low-temperature lithium−iodine exchange,[4] might offer a direct route to enantioenriched samples of the sterically encumbered, structurally related, sesquiterpenes cuparene (**1**) and herbertene (**2**). Both molecules feature contiguous quaternary centers.

Naturally occurring (*R*)-(+)-cuparene (**1**) was first isolated and characterized by Enzel and Erdtman[5] in 1958, and the (S)-(−) enantiomer of herbertene was reported in 1981 by Matsuo and co-workers[6] [(*R*)-(+)-herbertene (**2**) is depicted below]. The synthesis of racemic cuparene[7] and herbertene[8] has received a good deal of attention in the literature, including a preparation of racemic cuparene by us,[9] but syntheses of the enantioenriched compounds have been limited.[10,11] Moreover, all previously reported enantioselective syntheses of **1** or **2** (or their enantiomers) introduce the stereogenic quaternary carbon at an early stage of the synthesis, and virtually all of the asymmetric preparations incorporate the chiral center in the starting material. In contrast, the retrosynthesis depicted below, if reduced to practice, sets the quaternary stereogenic center in an enantioselective fashion at the final step of the synthesis.



Scheme 1. Preparation of Olefinic Alkyl Iodides



The requisite olefinic alkyl iodides **3a** and **3b** were prepared in straightforward fashion from 4-methylisobutyrophenone[12] (**4a**) or 3-methylisobutyrophenone[13] (**4b**) as illustrated in Scheme 1. These three-step syntheses proceeded efficiently to afford **3a** and **3b** in 73% and 74% overall yield, respectively. It is interesting to note that the Finkelstein reactions used to convert the primary chlorides (**6a** and **6b**) to the corresponding iodides (**3a** and **3b**) were unexpectedly slow. Indeed, the displacements were incomplete even after 5 d when performed in refluxing acetone; the use of 2-butanone as solvent led to complete conversion within 24 h at reflux.

Received: September 17, 2014
Published: October 10, 2014

Conversion of **3a** to the corresponding alkyllithium was effected under an atmosphere of argon by addition of 1.8 molar equiv of *t*-BuLi in heptane to approximately 0.1 M solutions of **3a** in dry *n*-C_5H_{12}–Et_2O (9:1 by vol) at −78 °C. It should be noted that slightly more than 2.0 molar equiv of *t*-BuLi is typically used to convert a primary alkyl iodide to an alkyllithium because the second molar equiv of *t*-BuLi consumes the cogenerated *tert*-butyl iodide.[4] In the present case, the alkyl iodides are styrene derivatives, and it is well-known that organolithiums such as *t*-BuLi add to the styrene double bond to give benzyllithium intermediates.[14] Fortunately, the lithium–iodine exchange is more rapid than the intermolecular addition to the styrene double bond. However, when excess *t*-BuLi is present after the exchange, addition to the styrene moiety does occur, particularly when reaction mixtures are warmed and/or when a lithiophilic Lewis base is present. The use of slightly less than the stoichiometric quantity of *t*-BuLi (in the present instance 1.8 molar equiv) circumvents the problem of intermolecular addition to the styrene double bond but there is a price to be paid: after the exchange there is a quantity of *t*-BuI remaining and this species serves as a proton source that leads to quench of the organolithium generated in the exchange. Thus, the yields of organolithiums derived from **3a** and **3b** are less than quantitative. In any event, as discussed below, the small amount of uncyclized alkene generated by quench of the organolithium by proton abstraction from *t*-BuI is easily removed from product mixtures.

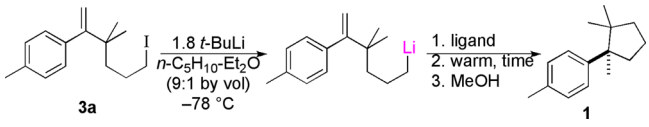
Exploratory cyclizations of the alkyllithium derived from **3a** were conducted to assess the effect of ligand structure and reaction temperature on the enantioselectivity of the ring-closure. The results of these experiments are summarized in Table 1.

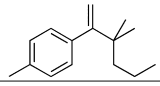
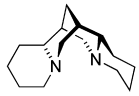
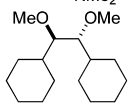
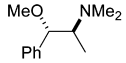
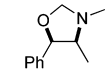
Not surprisingly, the organolithium derived from **3a** does not cyclize at room temperature in the absence of an added ligand; 3,3-dimethyl-2-*p*-tolyl-1-hexene is the sole product when reaction mixtures are quenched with MeOH (Table 1, entry 1). However, the intramolecular carbolithiation is accelerated and proceeds in an enantioselective manner when conducted at room temperature in the presence of 1.8 molar equiv of (−)-sparteine to afford an 86% yield of (*R*)-(+)-cuparene (**1**) with an enantiomeric ratio of 61:39 as adjudged by chiral stationary-phase gas chromatography (CSP-GC) and determination of the specific rotation of the sample (Table 1, entry 2). In an effort to improve the enantioselectivity of the ring closure, reactions were run at lower temperature for extended periods of time. Unfortunately, there was a dramatic decrease in yield but virtually no increase in enantioselectivity (Table 1, cf. entries 2–5). Cyclizations in the presence of other enantiopure, chiral ligands were also investigated (Table 1, entries 6–9) but none of the ligands examined afforded **1** in higher er than the benchmark ligand (−)-sparteine. Using the best conditions identified in the exploratory study, (*R*)-(+)-cuparene (**1**) and (*R*)-(+)-herbertene (**2**) were prepared as outlined in Scheme 2.

It should be noted that the sesquiterpenes were isolated in pure form without the need for chromatography. The only significant impurity in the crude reaction mixtures was a quantity of alkene formed by protonation of the organolithium prior to cyclization by *t*-BuI cogenerated in the exchange reaction, and this material was easily removed by washing a pentane solution of the reaction mixtures with concentrated sulfuric acid.

In summary, the preparation of (*R*)-(+)-cuparene (**1**) and (*R*)-(+)-herbertene (**2**), which features asymmetric 5-*exo* ring closure of achiral, olefinic alkyllithiums as the final step of the syntheses, proceeds with modest enantioselectivity when conducted in the presence of (−)-sparteine.

Table 1. Exploratory Cyclizations of the Alkyllithium Derived from 3a



entry	ligand	temp (°C)	time (h)	products, yield, %[a]		
					**1**	er[b]
1	none	+20	2	100	0	–
2		+20	2	14	86	61:39
3		0	2	77	23	62:38
4		0	6	55	45	62:38
5		−20	6	90	10	63:37
6		0	3	12	88	58:42
7		+20	2	39	61	53:47
8		+20	2	49	51	50:50
9		+20	2	100	0	–

[a]Yields were determined by capillary GC. [b]Enantiomeric ratio: in all cases, the *R*-(+) absolute configuration of **1** was obtained.

EXPERIMENTAL SECTION

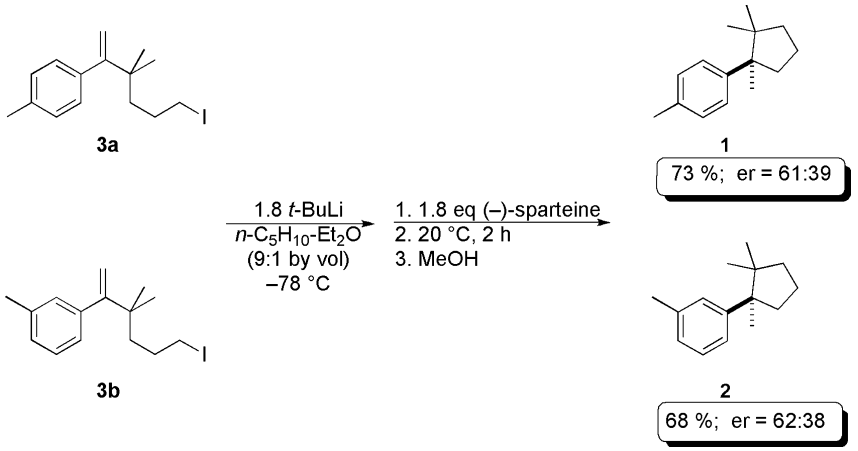
General Procedures. CAUTION: Organolithium compounds are extremely pyrophoric, and they should only be handled by individuals trained in their proper and safe use.[15] All manipulations of *t*-BuLi were performed in carefully flame-dried glassware under oxygen-free argon using standard cannula and syringe techniques.[15,16]

The concentration of *t*-BuLi in heptane was determined immediately prior to use by titration with a standard solution of 2-butanol in xylenes using 1,10-phenanthroline as indicator.[17] Dry diethyl ether and THF were freshly distilled from dark-purple solutions of sodium and benzophenone; dry, alkene-free *n*-pentane was obtained by repetitive washing of technical grade pentane with concentrated sulfuric acid until the acid layer remained clear, followed by successive washings with water, saturated sodium bicarbonate, and water. The pentane was dried ($MgSO_4$) and freshly distilled from a dark purple solution of sodium/benzophenone/tetraglyme. The ligands used in the experiments summarized in Table 1 were available from a prior study.[3] Enantiomeric ratios (er) were determined by CSP-GC on a 30 m × 0.25 mm × 0.25 μm Chiraldex *β*-DM column.

5-Chloro-2,2-dimethyl-1-*p*-tolylpentan-1-one (5a). A flame-dried, 500 mL three-necked round-bottom flask was charged with 2.00 g (49.9 mmol) of oil-free potassium hydride and 160 mL of dry THF under an atmosphere of nitrogen. The contents of the flask were stirred at room temperature, 12.8 mL (60.7 mmol) of 1,1,1,3,3,3-hexamethyldisilazane was added dropwise with a syringe, and the turbid solution was stirred until all evidence of hydrogen evolution had ceased. The off-white mixture was then cooled to −78 °C, and a solution of 6.65 g (41.3 mmol) of **4a** in 20 mL of dry THF was added

dx.doi.org/10.1021/jo502139m | J. Org. Chem. 2014, 79, 10722–10726

Scheme 2. Preparation of 1 and 2



dropwise. The yellow-green solution was stirred at −78 °C for 1 h, and a solution of 7.10 mL (66.1 mmol) of 1-chloro-3-iodopropane in 20 mL of dry THF was added dropwise. The cooling bath was removed, and the reaction mixture was allowed to warm and stir at room temperature for 12 h. The yellow-green color was noted to disappear accompanied by the formation of a white precipitate. The reaction mixture was poured into 200 mL of 10% aqueous hydrochloric acid, the organic layer was separated, and the aqueous phase was extracted with 150 mL portions of ether until the acid layer became a light yellow color. The combined organic extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was dissolved in 150 mL of ether and washed with 100 mL of 10% aqueous sodium thiosulfate and then 100 mL of brine. After drying ($MgSO_4$), the solution was filtered and concentrated by rotary evaporation, and the residual oil was purified by flash chromatography on silica gel (R_f = 0.31; 5% EtOAc–hexanes) to afford 8.30 g (85%) of a clear colorless oil: ^{1}H NMR δ 1.33 (s, 6H), 1.66–1.74 (m, 2H), 1.87–1.91 (m, 2H), 2.37 (s, 3H), 3.46 (t, J = 6.48 Hz, 2H), 7.19 (d, J = 8.29 Hz, 2H), 7.64 (d, J = 8.29 Hz, 2H); ^{13}C NMR δ 21.5, 26.4, 28.3, 38.6, 45.5, 47.4, 128.2, 129.0, 135.9, 141.8, 207.6. Anal. Calcd for $C_{14}H_{19}OCl$: C, 70.43; H, 8.02. Found: C, 70.77; H, 8.09.

5-Chloro-2,2-dimethyl-1-*m*-tolylpentan-1-one (5b). A flame-dried, 500 mL, three-necked round-bottom flask was charged with 1.55 g (38.7 mmol) of oil-free potassium hydride and 140 mL of dry THF under an atmosphere of nitrogen. The contents of the flask were stirred at room temperature, 10.2 mL (48.2 mmol) of 1,1,1,3,3,3-hexamethyldisilazane was added dropwise with a syringe, and the turbid solution was stirred until all evidence of hydrogen evolution had ceased. The off-white mixture was then cooled to −78 °C, and a solution of 5.21 g (32.1 mmol) of **4b** in 20 mL of dry THF was added dropwise. The yellow-green solution was stirred at −78 °C for 1 h and a solution of 5.52 mL (51.4 mmol) of 1-chloro-3-iodopropane in 20 mL of dry THF was added dropwise. The cooling bath was removed, and the reaction mixture was allowed to warm and stir at room temperature for 12 h. The yellow-green color was noted to disappear accompanied by the formation of a white precipitate. The reaction mixture was poured into 200 mL of 10% aqueous hydrochloric acid, the organic layer was separated, and the aqueous phase was extracted with 150 mL portions of ether until the acid layer became a light yellow color. The combined organic extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was dissolved in 150 mL of ether and washed with 100 mL of 10% aqueous sodium thiosulfate and then 100 mL of brine. After drying ($MgSO_4$), the solution was filtered and concentrated by rotary evaporation, and the residual oil was purified by flash chromatography on silica gel (R_f = 0.30; 5% EtOAc–hexanes) to afford 6.64 g (87%) of a clear, colorless oil: ^{1}H NMR δ 1.33 (s, 6H), 1.70–1.76 (m, 2H), 1.86–1.90 (m, 2H), 2.38 (s, 3H), 3.48 (t, J = 6.45 Hz, 2H), 7.26–7.30 (m, 2H), 7.44–7.47 (m, 2H); ^{13}C NMR δ 21.9, 26.6, 28.6, 38.7, 45.8, 47.8, 124.9, 128.4, 128.6, 132.1, 138.4, 139.4, 209.3; HRMS-FAB $[M + H]^+$ calcd for $C_{14}H_{19}OCl$ 239.1203, found 239.1202.

6-Chloro-3,3-dimethyl-2-*p*-tolylhex-1-ene (6a). A suspension of 11.5 g (32.2 mmol) of methyltriphenylphosphonium bromide and 3.06 g (27.3 mmol) of potassium *tert*-butoxide in 230 mL of dry THF was stirred under an atmosphere of nitrogen for 1 h prior to the dropwise addition of a solution of 5.40 g (22.7 mmol) of **5a** in 20 mL of dry THF. The yellow color was noted to disappear accompanied by the formation of a white precipitate. The resulting mixture was stirred at room temperature for 16 h and then filtered and concentrated by rotary evaporation. The residue was dissolved in 150 mL of pentane, washed with 100 mL of water and 100 mL of brine, and dried ($MgSO_4$). Filtration through a pad of silica gel, followed by concentration using rotary evaporation, yielded 5.06 g (95%) of a clear, colorless oil: ^{1}H NMR δ 1.10 (s, 6H), 1.43–1.47 (m, 2H), 1.75–1.83 (m, 2H), 2.32 (s, 3H), 3.47 (t, J = 6.78 Hz, 2H), 4.87 (d, J = 1.61 Hz, 1H), 5.12 (d, J = 1.61 Hz, 1H), 7.00 (d, J = 7.98 Hz, 2H), 7.07 (d, J = 7.98 Hz, 2H); ^{13}C NMR δ 21.2, 28.0, 28.5, 38.5, 39.2, 45.8, 114.0, 128.4, 128.8, 136.2, 140.4, 157.4. Anal. Calcd for $C_{15}H_{21}Cl$: C, 76.09; H, 8.94. Found: C, 75.72; H, 8.55.

6-Chloro-3,3-dimethyl-2-*m*-tolylhex-1-ene (6b). A suspension of 9.75 g (27.3 mmol) of methyltriphenylphosphonium bromide and 2.82 g (25.2 mmol) of potassium *tert*-butoxide in 250 mL of dry THF was stirred under an atmosphere of nitrogen for 1 h prior to the dropwise addition of a solution of 5.00 g (21.0 mmol) of **5b** in 20 mL of dry THF. The yellow color was noted to disappear accompanied by the formation of a white precipitate. The resulting mixture was stirred at room temperature for 16 h and then filtered and concentrated by rotary evaporation. The residue was dissolved in 150 mL of pentane, washed with 100 mL of water and 100 mL of brine, and dried ($MgSO_4$). Filtration through a pad of silica gel, followed by concentration using rotary evaporation, yielded 4.66 g (94%) of a clear, colorless oil: ^{1}H NMR δ 1.12 (s, 6H), 1.41–1.51 (m, 2H), 1.79–1.87 (m, 2H), 2.35 (app d, J = 1.95 Hz, 3H), 3.51 (td, J = 6.78, 1.85 Hz, 2H), 4.89 (app t, J = 1.96 Hz, 1H), 5.14 (app t, J = 1.96 Hz, 1H), 6.92–6.95 (m, 2H), 7.08 (d, J = 7.00 Hz, 1H), 7.18 (td, J = 7.52, 2.07 Hz, 1H); ^{13}C NMR δ 21.7, 28.1, 28.5, 38.4, 39.2, 46.0, 113.9, 126.0, 127.4, 127.5, 129.7, 137.2, 143.3, 157.5. Anal. Calcd for $C_{15}H_{21}Cl$: C, 76.09; H, 8.94. Found: C, 75.70; H, 8.58.

6-Iodo-3,3-dimethyl-2-*p*-tolylhex-1-ene (3a). To a stirred suspension of 24.0 g (160 mmol) of anhydrous sodium iodide in 250 mL of dry 2-butanone was added 4.71 g (19.9 mmol) of **6a**, and the resulting mixture was heated at gentle reflux under an atmosphere of nitrogen for 24 h. After cooling, the slightly yellow mixture was filtered through a sintered glass funnel and concentrated by rotary evaporation, and the residue was partitioned between 150 mL of pentane and 150 mL of water. The aqueous phase was discarded, and the organic portion was washed with 100 mL of 10% (w/v) sodium thiosulfate and then 100 mL of brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue was passed through a

dx.doi.org/10.1021/jo502139m | J. Org. Chem. 2014, 79, 10722–10726

short column of alumina, which was eluted with pentane. Concentration by rotary evaporation afforded 5.87 g (90%) of the previously reported iodide:[9] ^{1}H NMR δ 1.10 (s, 6H), 1.40−1.44 (m, 2H), 1.81−1.89 (m, 2H), 2.34 (s, 3H), 3.13 (t, J = 7.08 Hz, 2H), 4.86 (d, J = 1.58 Hz, 1H), 5.12 (d, J = 1.58 Hz, 1H), 7.00 (d, J = 7.94 Hz, 2H), 7.09 (d, J = 7.94 Hz, 2H); ^{13}C NMR δ 7.5, 21.3, 28.1, 29.5, 39.2, 42.2, 114.0, 128.4, 128.8, 136.2, 140.3, 157.4.

6-Iodo-3,3-dimethyl-2-*m*-tolylhex-1-ene (3b). A stirred suspension of 17.7 g (118 mmol) of anhydrous sodium iodide in 200 mL of dry 2-butanone was treated with 3.50 g (14.8 mmol) of **6b** ,and the resulting mixture was heated at gentle reflux under an atmosphere of nitrogen for 24 h. After cooling, the slightly yellow mixture was filtered through a sintered glass funnel and concentrated by rotary evaporation, and the residue was partitioned between 150 mL of pentane and 150 mL of water. The aqueous phase was discarded, and the organic portion was washed with 100 mL of 10% (w/v) sodium thiosulfate and then 100 mL of brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue was passed through a short column of alumina which was eluted with pentane. Concentration by rotary evaporation afforded 4.42 g (91%) of a clear, colorless oil: ^{1}H NMR δ 1.10 (s, 6H), 1.41−1.45 (m, 2H), 1.78−1.92 (m, 2H), 2.34 (s, 3H), 3.13 (t, J = 7.02 Hz, 2H), 4.87 (d, J = 1.54 Hz, 1H), 5.12 (d, J = 1.54 Hz, 1H), 6.90−6.93 (m, 2H), 7.06 (d, J = 7.54 Hz, 1H), 7.17 (t, J = 7.54 Hz, 1H); ^{13}C NMR δ 7.7, 21.7, 28.1, 29.4, 39.2, 42.2, 113.9, 126.0, 127.4, 127.6, 129.7, 137.2, 143.2, 157.6. Anal. Cacld for $C_{15}H_{21}I$: C, 54.89; H, 6.45. Found: C, 55.17; H, 6.84.

(*R*)-(+)-Cuparene (1). A solution of 630 mg (1.92 mmol) of **3a** in 17.3 mL of dry *n*-pentane and 1.9 mL of dry diethyl ether was cooled to −78 °C under an atmosphere of argon, and 1.87 mL of a 1.85 M solution of *t*-BuLi (3.46 mmol) in heptane was added dropwise via syringe over ca. 5 min. The mixture was allowed to stir for 15 min at −78 °C, and 822 mg (3.51 mmol) of dry, deoxygenated (−)-sparteine was then added dropwise via syringe. Upon complete addition, the reaction mixture was allowed to warm and stir at room temperature for 2 h before addition of 1 mL of deoxygenated, anhydrous methanol. The reaction mixture was washed with 25 mL of 10% aqueous sulfuric acid, 25 mL of water, 25 mL of saturated aqueous sodium bicarbonate, and 25 mL of brine. The organic portion was dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was dissolved in 15 mL of dry, alkene-free pentane and was washed with 10 mL portions of concentrated sulfuric acid until GC analysis revealed that the open-chain alkene had been removed. The organic layer was then washed with 25 mL of water, 25 mL of saturated aqueous sodium bicarbonate, and 25 mL of brine, dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was passed through a short pad of silica using pentane as eluent and, after concentration using rotary evaporation, afforded 283 mg (73%) of the pure sesquiterpene: ^{1}H NMR δ 0.56 (s, 3H), 1.06 (s, 3H), 1.25 (s, 3H), 1.51−1.58 (m, 1H), 1.64−1.71 (m, 2H), 1.73−1.82 (m, 2H), 2.31 (s, 3H), 2.45−2.52 (m, 1H), 7.08 (d, J = 8.16 Hz, 2H), 7.24 (d, J = 8.16 Hz, 2H); ^{13}C NMR δ 20.0, 21.1, 24.5, 24.6, 26.7, 26.7, 37.1, 40.0, 44.5, 50.5, 127.2, 128.4, 135.0, 144.8; $[\alpha]^{22}_D$ = +16.6 (c 0.25, $CHCl_3$) [lit.[5] $[\alpha]^{22}_D$ = +65 (c 5.0, $CHCl_3$)]. The product was found to have an er of 61:39 (favoring the (*R*)-enantiomer) by CSP-GC: the minor (*S*)-enantiomer eluted after 32.0 min followed by the major (*R*)-enantiomer at 33.9 min.

(*R*)-(+)-Herbertene (2). A solution of 503 mg (1.53 mmol) of **3b** in 13.8 mL of dry *n*-pentane and 1.5 mL of dry diethyl ether was cooled to −78 °C under an atmosphere of dry argon, and 1.49 mL of a 1.85 M solution of *t*-BuLi (2.76 mmol) in heptane was added dropwise via syringe over ca. 5 min. The mixture was allowed to stir for 15 min at −78 °C, and 621 mg (2.65 mmol) of dry, deoxygenated (−)-sparteine was then added dropwise via syringe. Upon complete addition, the reaction mixture was allowed to warm and stir at 20 °C for 2 h before addition of 1 mL of deoxygenated, anhydrous methanol. The reaction mixture was washed with 25 mL of 10% aqueous sulfuric acid, 25 mL of water, 25 mL of saturated aqueous sodium bicarbonate, and 25 mL of brine. The organic portion was dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was dissolved in 15 mL of dry, alkene-free pentane and was washed with 10 mL portions of concentrated sulfuric acid until GC analysis revealed that the open-chain alkene had been removed. The organic layer was then washed with 25 mL of water, 25 mL of saturated aqueous sodium bicarbonate, and 25 mL of brine, dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was passed through a short pad of silica using pentane as eluent and, after concentration using rotary evaporation, afforded afforded 138 mg (68%) of the pure sesquiterpene: ^{1}H NMR δ 0.56 (s, 3H), 1.07 (s, 3H), 1.26 (s, 3H), 1.52−1.59 (m, 1H), 1.64−1.82 (m, 4H), 2.34 (s, 3H), 2.45−2.54 (m, 1H), 6.92 (m, 1H), 7.13−7.19 (m, 3H); ^{13}C NMR δ 20.0, 22.1, 24.6, 24.7, 26.8, 37.1, 40.1, 44.5, 50.8, 124.4, 126.3, 127.6, 128.1, 137.0, 147.8; $[\alpha]^{22}_D$ = +13.8 (c 1.98, $CHCl_3$) [$[\alpha]_D$ (no temp reported) for the (−)-enantiomer, lit.[6] −48.3 (c 1.31, $CHCl_3$)]. The product was found to have an er of 62:38 (favoring the (*R*)-enantiomer) by CSP-GC: the minor (*S*)-enantiomer eluted after 16.9 min followed by the major (*R*)-enantiomer at 17.3 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: william.bailey@uconn.edu.

Present Address

[§]H. Lundbeck A/S, Chemical Production Development, Oddenvej 182, 4500 Nykøbing Sj., Denmark.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Terry L. Rathman of Optima Chemical, Douglas, GA, for generous gifts of *t*-BuLi in heptane. This work was supported by a grant from the Process Chemistry Division, H. Lundbeck A/S, Copenhagen, Denmark, and by the Mark A. Nordenberg Chancellor's Distinguished Teaching Award from the University of Pittsburgh to M.R.L.

■ REFERENCES

(1) Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787.

(2) Gil, G. S.; Groth, U. M. *J. Am. Chem. Soc.* **2000**, *122*, 6789.

(3) Mealy, M. J.; Luderer, M. R.; Bailey, W. F.; Sommer, M. B. *J. Org. Chem.* **2004**, *69*, 6042.

(4) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (b) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847.

(5) Enzell, C.; Erdtman, H. *Tetrahedron* **1958**, *4*, 361.

(6) Matsuo, A.; Yuki, S.; Nakayama, M.; Hayashi, S. *J. Chem. Soc., Chem. Commun.* **1981**, *16*, 864.

(7) For select preparations of (±)-cuparene, see: (a) Srikrishma, A.; Satanarayana, G.; Prasad, K. R. *Synth. Commun.* **2007**, *37*, 1511. (b) Secci, F.; Frongia, A.; Ollivier, J.; Piras, P. P. *Synthesis* **2007**, *7*, 999. (c) Srikrishma, A.; Satnanrayana, G. *Indian J. Chem.* **2006**, *45B*, 2465. (d) Cohen, T.; Kreethadumrongdat, T.; Liu, X.; Kulkarni, V. *J. Am. Chem. Soc.* **2001**, *123*, 3478. (e) Krief, A.; Barbeau, P. *Synlett* **1990**, 511.

(8) For select preparations of (±)-herbertene, see: (a) Bernard, A. M.; Frongia, A.; Secci, F.; Piras, P. P. *Chem. Commun.* **2005**, 3853. (b) Gupta, P. D.; Pal, A.; Roy; Mukherjee, D. *Tetrahedron Lett.* **2000**, *41*, 7563. (c) Ho, T.-L. *J. Chem. Soc., Perkin. Trans. 1* **1999**, 2479. (d) Mandelt, K.; Fitjer, L. *Synthesis* **1998**, 1523.

(9) Bailey, W. F.; Khanolkar, A. D. *Tetrahedron* **1991**, *47*, 7727.

(10) For asymmetric syntheses of cuparene, see: (a) Graninger, R. S.; Patel, A. *Chem. Commun.* **2003**, 1072. (b) Nayek, A.; Drew, M. G. B.; Ghosh, S. *Tetrahedron* **2003**, *59*, 5175. (c) Aavual, B. R.; Cui, Q.; Mash, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4681. (d) Fuganti, C.;

Serra, S. *J. Org. Chem.* **1999**, *64*, 8728. (e) Ichiba, T.; Higa, T. *J. Org. Chem.* **1986**, *51*, 3364.
(11) For asymmetric syntheses of herbertene, see: (a) Nayek, A.; Ghosh, S. *Tetrahedron Lett.* **2002**, *43*, 1313. (b) Abad, A.; Agullo, C.; Cunat, A. C.; Perni, R. H. *J. Org. Chem.* **1999**, *64*, 1741. (c) Tori, M.; Miyako, T.; Sono, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2731. (d) Takano, S.; Moriya, M.; Ogassawara, K. *Tetrahedron Lett.* **1992**, *33*, 329.
(12) Parker, W.; Ramage, R.; Raphael, R. *J. Chem. Soc.* **1962**, 1558.
(13) Pickard, V. *J. Am. Chem. Soc.* **1950**, *72*, 876.
(14) (a) Wei, X.; Johnson, P.; Taylor, R. J. K. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 1109 and references cited therein. (b) Fraenkel, G.; Russell, J. G.; Chen, Y. *J. Am. Chem. Soc.* **1973**, *95*, 3208.
(15) For the safe handling of organolithium compounds, see: Rathman, L.; Schwindeman, J. A. *Org. Process Res. Dev.* **2014**, *18*, 1192.
(16) Shriver, D. F.; Drezdon, M. A. *The Manipulation of Air-Sensitive Compounds*, 2nd ed.; Wiley: New York, 1986.
(17) Watson, S. C.; Eastham, J. F. J. *J. Organomet. Chem.* **1967**, *9*, 165.

dx.doi.org/10.1021/jo502139m | *J. Org. Chem.* 2014, 79, 10722−10726