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Intramolecular Carbolithiation as a Route to a Sterically Congested Cyclopentene: Synthesis of the Longtailed Mealybug Pheromone

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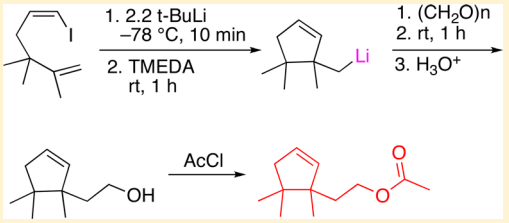
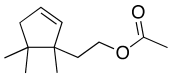
Supporting Information

ABSTRACT: A concise preparation of the pheromone secreted by the female longtailed mealybug [viz., 2-(1,5,5-trimethylcyclopent-2-en-1-yl)ethyl acetate] (**1**) is described. The key step in the synthesis of **1** involves 5-exo-trig ring closure of the vinyllithium derived from (*Z*)-1-iodo-4,4,5-trimethyl-1,5-hexadiene by lithium−iodine exchange.



Several years ago, Millar and co-workers reported the isolation and characterization of the pheromone secreted by the female longtailed mealybug (*Pseudococcus longispinus*).[1] The structure of this unusual monoterpene (**1**) features contiguous quaternary centers in a cyclopentene framework, and any synthesis of **1** must address the problem posed by this congested architecture.[2]



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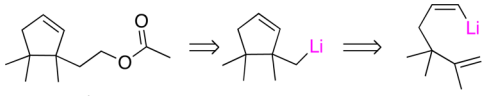
Three syntheses of racemic **1** have been reported by Millar's group, and each sets the adjacent quaternary centers in the cyclopentene ring at an early stage in the process.[1,3,4] It occurred to us that intramolecular carbolithiation might offer a straightforward route to the pheromone: the retrosynthesis is depicted below. The approach suggests that the challenge posed by the quaternary centers in **1** might be addressed in the penultimate step of the synthesis via a 5-exo-trig ring closure of a vinyllithium tethered to a suitably functionalized alkene. The vinyllithium, in turn, would be derived from the corresponding vinyl iodide by lithium−iodine exchange.[5,6]



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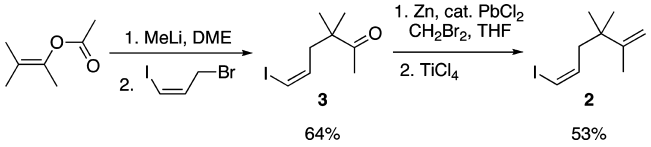
The requisite vinyl iodide (**2**) was prepared in two steps as illustrated in Scheme 1. Alkylation of the lithium enolate derived from 3-methylbut-2-en-2-yl acetate[7] with (*Z*)-3-bromo-1-iodopropene[8] following House's protocol[9] proceeded uneventfully to give ketone **3**. Attempts to convert **3** to **2** using standard Wittig chemistry resulted in a mixture of products including an unacceptably large quantity of alkyne generated by dehydrohalogenation of the vinyl iodide moiety. Fortunately, Utimoto's olefination procedure,[10] employing a CH_2Br_2−$TiCl_4$−Zn system containing catalytic $PbCl_2$, cleanly afforded isomerically pure **2**.

Scheme 1. Preparation of Vinyl Iodide 2



It was clear from our previous experience constructing less congested cylopentanoids, such as (±)-cuparene[11] and (±)-laurene,[12] that intramolecular carbolithiation of the vinyllithium derived from **2** would require warming the organolithium in the presence of TMEDA to facilitate the cyclization. Consequently, all reactions involving organolithiums were conducted under an atmosphere of argon using scrupulously dry and oxygen-free solvents and reagents.

Treatment of an approximately 0.1 M solution of **2** in *n*-pentane/diethyl ether (9:1 by vol) at −78 °C with 2.2 molar equiv of *tert*-butyllithium (*t*-BuLi) served to cleanly generate the corresponding vinyllithium as demonstrated by the outcome of the synthesis of **1** depicted in Scheme 2: there was no evidence of alkyne formation in the course of the lithium−iodine exchange when conducted using these conditions.[13] Addition of 2.2 molar equiv of TMEDA at −78 °C, removal of the cooling bath, and allowing the reaction mixture to warm and stand at room temperature for 1 h effected the ring closure. The reaction mixture was recooled to −78 °C, and the (1,5,5-trimethylcyclopent-2-enyl)methyllithium product was trapped by reaction with dry paraformaldehyde[14] to afford alcohol **4** in 65% isolated yield (Scheme 2). Acylation of **4** following Millar's procedure[1,3] completed the synthesis of **1**.

The concise synthesis of racemic **1** presented in Schemes 1 and 2 is arguably the most direct preparation of the pheromone that has been reported to date. More generally, the three-step

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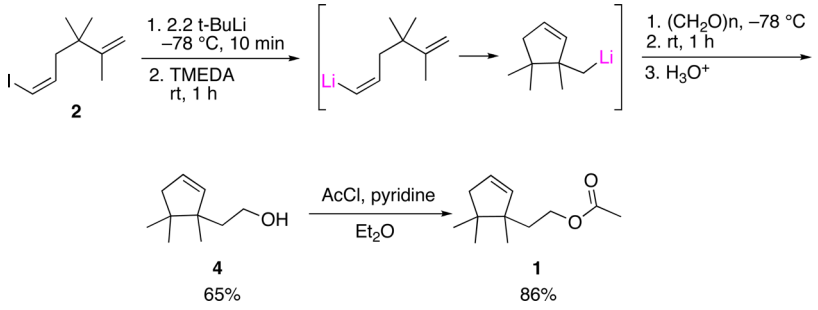
Scheme 2. Intramolecular Carbolithiation Route to 1



2 4 65% 1 86%

(exchange−cyclization−trapping), one-pot conversion of **2** to **4** in 65% yield illustrates the efficiency of intramolecular carbolithiation as a route to congested carbocyclic systems.

EXPERIMENTAL SECTION

General Procedures. Spectroscopic and chromatographic procedures, methods used for the purification of reagents and solvents, as well as precautions regarding the manipulation of organolithiums have been previously described.[15] Paraformaldehyde was dried with P_2O_5 for 2 days under vacuum in a drying pistol heated with refluxing methanol.

(*Z*)-6-Iodo-3,3-dimethylhex-5-en-2-one (3). Following the general procedure of House and co-workers,[9] a flame-dried, round-bottomed flask was charged under argon with 10 mg of 2,2-bipyridyl and 37 mL of a 1.4 M solution of methyllithium (52 mmol) in diethyl ether. The solution was stirred under a flow of argon at room temperature for 30 min to evaporate some of the diethyl ether. Dry 1,2-dimethoxyethane (60 mL) was then added, the solution was cooled to 0 °C in an ice bath, and 3.33 g (26 mmol) of 3-methylbut-2-en-2-yl acetate[7] was added dropwise with a syringe until the color of the solution changed from a dark red-purple to a light red-orange (indicating the presence of a slight excess of methyllithium). (*Z*)-3-Bromo-1-iodopropene[8] (6.90 g, 27.9 mmol) was added rapidly; the resulting solution was stirred for 45 min at 0 °C and then 30 min at room temperature. Pentane (60 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added and the layers separated. The aqueous phase was saturated with NaCl and then extracted with additional pentane. The combined organic layers were dried ($MgSO_4$) and concentrated to yield 4.52 g (64%) of the title iodoketone as a clear oil: ^{1}H NMR (400 MHz) δ 6.33 (dt, J = 7.5 Hz, J = 1.3 Hz, 1H), 6.07 (q, J = 7.1 Hz, 1H), 2.38 (dd, J = 6.9 Hz, J = 1.3 Hz, 2H), 2.15 (s, 3H), 1.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 137.4, 85.4, 47.9, 44.2, 25.4, 24.5; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_8H_{14}IO$, 253.0089; found, 253.0105.

(*Z*)-1-Iodo-4,4,5-methyl-1,5-hexadiene (2). A flamed-dried, round-bottomed flask was charged under an atmosphere of argon with 7.02 g (108 mmol) of activated Zn dust,[16] 100 mg of $PbCl_2$, and 60 mL of dry THF. Dibromomethane (10.44 g, 60 mmol) was added, the mixture was stirred at 25 °C for 30 min, and then cooled to 0 °C before 15 mL of a 1.0 M solution of $TiCl_4$ in dichloromethane (15 mmol) was added. The resulting mixture was stirred at 25 °C for 30 min before 3.02 g (12.0 mmol) of **3** dissolved in 30 mL of THF was added dropwise with a cannula. After stirring for 1 h at room temperature, the reaction mixture was diluted with ether (30 mL), washed with 1 M HCl (60 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. Purification by column chromatography [50 g of silica gel, using pentane as eluent (R_f = 0.65)] gave 1.60 g (53%) of the title compound as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (d, J = 5.8 Hz, 1H), 6.04 (apparent q, J = 6.8 Hz, 1H), 4.77 (s, 1H) 4.72 (s, 1H), 2.21 (d, J = 6.6 Hz, 2H), 1.74 (s, 3H), 1.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 139.0, 110.2,83.7, 45.6, 39.1, 27.3, 19.7; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_9H_{16}I$, 251.0297; found, 251.0285.

2-(1,5,5-Trimethylcyclopent-2-en-1-yl)ethanol (4). A flame-dried, round-bottomed flask was charged with 500 mg (2.00 mmol) of **2** in 20 mL of a 9:1 (by vol) ratio of dry n-C_5H_{12}/Et_2O. The solution was cooled to −78 °C, and 2.0 mL of a 2.19 M solution of *t*-BuLi in pentane (4.4 mmol) was added dropwise. The solution was stirred at −78 °C for 10 min, and then 0.60 mL (4.0 mmol) of dry TMEDA was added. The resulting mixture was removed from the cold bath and stirred in a desiccator until it turned bright yellow (∼1 h). The mixture was then recooled to −78 °C, and 90 mg (3.0 mmol) of dry paraformaldehyde in 1 mL of diethyl ether was added. The bath was again removed, and the solution was stirred at room temperature until the reaction mixture turned white (∼1.5 h). Saturated ammonium chloride (2 mL) was added to quench the reaction; 10 mL of brine was added, and the layers were separated. The organic layer was dried ($MgSO_4$), concentrated, and the residue was purified by column chromatography [40 g of silica gel using 0−20% Et_2O/n-C_5H_{12}; R_f (20% Et_2O/n-C_5H_{12}) = 0.15] to give 200 mg (65%) of the title compound as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63−5.61 (m, 1H), 5.58−5.55 (m, 1H), 3.77−3.69 (m, 2H), 2.12 (q, J = 2.2 Hz, 2H), 1.70−1.63 (m, 1H), 1.57−1.50 (m, 1H), 0.96 (s, 3H), 0.93 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 128.3, 61.0, 49.7, 47.1, 44.3, 39.5, 25.0, 24.2, 19.7; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{10}H_{19}O$ 155.1436; found, 155.1415.

2-(1,5,5-Trimethylcyclopent-2-en-1-yl)ethyl acetate (1). Under argon, 0.21 mL of acetyl chloride (3.0 mmol) was added to a stirring solution of 310 mg (2.01 mmol) of **4** and 0.32 mL of pyridine in 10 mL of dry Et_2O at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 4 h. Water (10 mL) and pentane (10 mL) were added and the layers separated. The organic layer was washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography [30 g of silica gel using 0−10% Et_2O/n-C_5H_{12} (R_f (10% Et_2O/n-C_5H_{12}) = 0.42)] gave 340 mg (86%) of **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63−5.62 (m, 1H), 5.56−5.54 (m, 1H), 4.22−4.16 (m, 1H), 4.12−4.05 (m, 1H), 2.13 (apparent s, 2H), 2.04 (s, 3H), 1.72−1.66 (m, 1H), 1.60−1.54 (m, 1H), 0.95 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 139.0, 128.5, 63.0, 49.7, 47.1, 44.3, 34.8, 24.9, 24.3, 21.4, 19.6; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{12}H_{21}O_2$ 197.1542; found, 197.1555. These NMR data were identical to those reported for this compound.[1,3]

ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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