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HIGHLY EFFICIENT TERPENOID PHEROMONE SYNTHESES VIA REGIO- AND STEREOCONTROLLED PROCESSING OF ALLYLLITHIUMS GENERATED BY REDUCTIVE LITHIATION OF ALLYL PHENYL THIOETHERS

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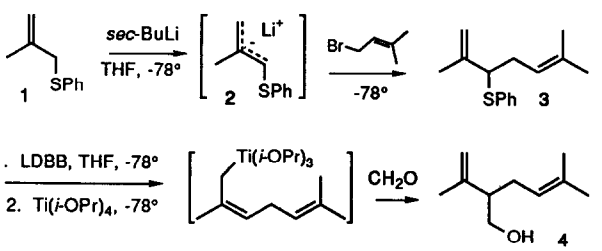
Abstract - Previous work had shown that reductive lithiation of allyl phenyl thioethers, followed by transmetallation, produces allylmetallics which react selectively with carbonyl compounds at the most or least substituted terminus; the latter results in mainly cis olefin. This technology allows extremely efficient syntheses of racemic versions of lavandulol (two-pot, 70% yield), the Comstock mealy bug pheromone (one-pot, 45% yield) and the California red scale pheromone (4-steps, 23% yield).

Recently, the first general preparative method for allyllithiums was announced.[1] The procedure involves reductive lithiation[2] of the readily available phenyl allyl sulfides by the use of aromatic radical anions. Furthermore, methods were revealed whereby considerable regiochemical control could be exercised in the case of unsymmetrical allyl anions with regard to which allylic terminus adds to the carbonyl group of aldehydes and ketones.[3] It was found that attack occurs exclusively at the most substituted terminus when the allyllithium is treated with titanium tetraisopropoxide before treatment with an aldehyde. However, the most novel finding was that treatment of the allyllithium instead with cerium(III) chloride results in predominant attack on the carbonyl group by the least substituted allylic terminus. In the latter case, the stereochemistry of the resulting olefin can be controlled.[3]

We now demonstrate the utility of this new technology by highly efficient syntheses of three terpenoid natural products which are used in insect communication. The synthesis of racemic lavandulol **4** utilizes titanium(IV) to realize attack at the most substituted terminus. The synthesis of the Comstock mealybug pheromone **9** demonstrates the ability of cerium(III) to direct attack to the least substituted terminus. Finally, the synthesis of the racemic AII component of the California red scale pheromone **10** uses both technologies and in the case of the use of cerium(III) a demonstration is given of the high selectivity for production of a Z-olefin.

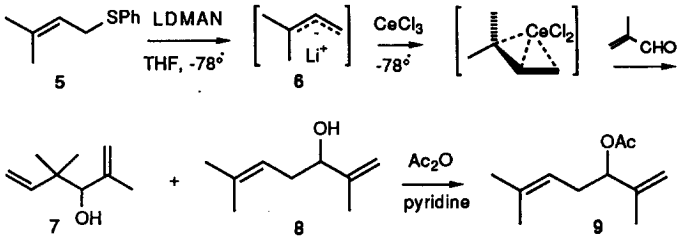
Lavandulol **4**, a monoterpene which has been prepared several times[4-7] since its initial isolation by Schinz[8] from lavender, has been used as a perfume additive in the cosmetic industry and has been recently isolated from the defensive secretion of the red-lined carrion beetle.[9] (±)-Lavandulol was prepared in 70% overall yield from commercial materials in a straightforward, two-pot procedure (Scheme 1) using the regiochemical attributes of the previously described allyltitanium chemistry.



Scheme 1

Methallyl phenyl sulfide **1** was deprotonated with *sec*-BuLi at -78 °C in THF and the resulting lithio derivative **2** (a Biellmann[10] anion) was alkylated with commercial prenyl bromide to produce 2,6-dimethyl-3-phenylthio-1,5-heptadiene **3** in 86% yield along with a small amount (10%) of the regioisomer resulting from γ-alkylation. Treatment of **3** with lithium *p,p'*-di-*tert*-butylbiphenylide (LDBB)[11] at -78 °C followed by transmetallation with $Ti(i\text{-}OPr)_4$ at -78 °C led to the formation of an allyltitanium intermediate which when treated in situ with gaseous CH_2O[12] produced a single regioisomeric product **4** in 81% yield; no trace of the regioisomer resulting from attack of CH_2O at the less substituted terminus of the allylic system was detected. The product, isolated via flash chromatography, was identified as lavandulol by comparison of ^1H NMR and FTIR spectral data with those reported.[5] By virtue of its high yield and brevity, this synthesis compares favorably with the most efficient reported syntheses of (±)-lavandulol.[6]

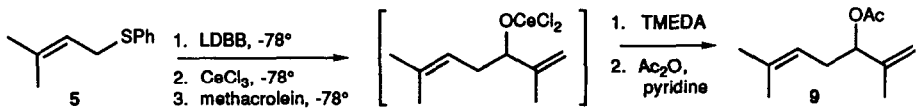
The Comstock mealybug is a citrus pest that causes great economic losses to fruit growers in many parts of the world.[13] There are a number of recorded syntheses of the Comstock mealybug sex pheromone **9**.[14-16] We have devised extremely efficient syntheses of the racemic material using the regiochemical attributes of allylcerium chemistry.[3] We first prepared **9** in a two-pot sequence from commercial prenyl phenyl sulfide **5** (Scheme 2).



Scheme 2

Treatment of **5** with lithium 1-(dimethylamino)naphthalenide (LDMAN)[17] at -78 °C resulted in the allyllithium **6** which, when treated with anhydrous $CeCl_3$ followed by methacrolein, led to alcohol **8** (54%) along with regioisomeric alcohol **7** (17%) resulting from attack of methacrolein at the most substituted terminus of the allylic system. The preference for attack of methacrolein at the least substituted terminus of the allylcerium, as indicated by the 3.2 : 1 ratio of **8** to **7**, is similar to that reported for the reaction of prenylcerium with other carbonyl compounds but inferior to those that have been attained in our laboratory for the addition of carbonyl compounds to other allylceriums.[3,18] Treatment of **8** with acetic anhydride in pyridine produced **9** in 85% yield. The ^1H NMR and FTIR spectral data for **9** were identical to those previously reported for the Comstock mealybug pheromone.[14,15]

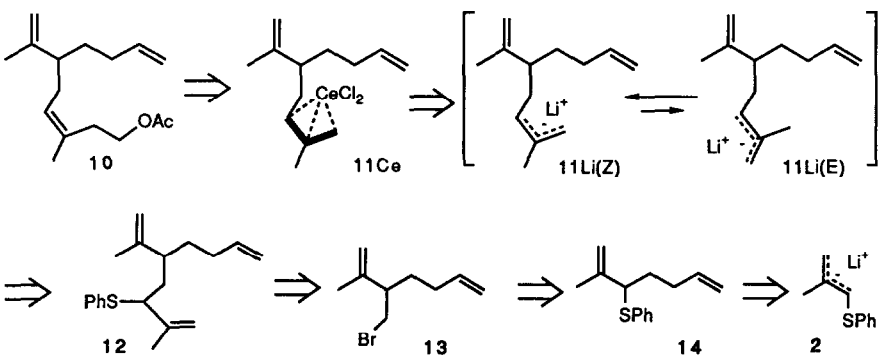
This two-pot reaction sequence was then condensed to a still more efficient one-pot synthesis (eq 1). Reductive lithiation of prenyl phenyl sulfide **5** in the same manner followed by consecutive treatment of the allyllithium intermediate **6** with anhydrous $CeCl_3$, methacrolein, tetramethylethylenediamine (TMEDA),[19] and acetic anhydride / pyridine yielded **9** in 45% yield after chromatography. Less than 2% of the unacetylated alcohol **8** was recovered. In a related earlier synthesis by Mori,[15] allyl alcohol **8** was generated from the reaction of prenyl bromide with methacrolein in the presence of lithium and the pheromone was obtained in 9% overall yield, after acetylation; the poor yield in this two step process is presumably due largely to the tendency of allyllithiums to react with carbonyl compounds at the most substituted terminus.[3]



(1)

The California red scale, *Aonidiella aurantii* (Maskell), is a serious citrus pest in many parts of the world, particularly in California, Australia, and the Mediterranean countries. Tashino and Chambers[20] discovered that the female red scale produces a sex pheromone that is used to attract male red scales. The structures of the components of this pheromone were first elucidated by Roelofs *et al.*[21] and several syntheses have been reported.[7b,22,23] The synthetically most interesting component **10**, designated AII, features a homoallylic acetate that includes a trisubstituted Z olefin; the other component lacks this olefinic group. The norsesquiterpene structures represent interesting biosynthetic pathways since they do not merely involve head-to-tail coupling of isoprenoid units.

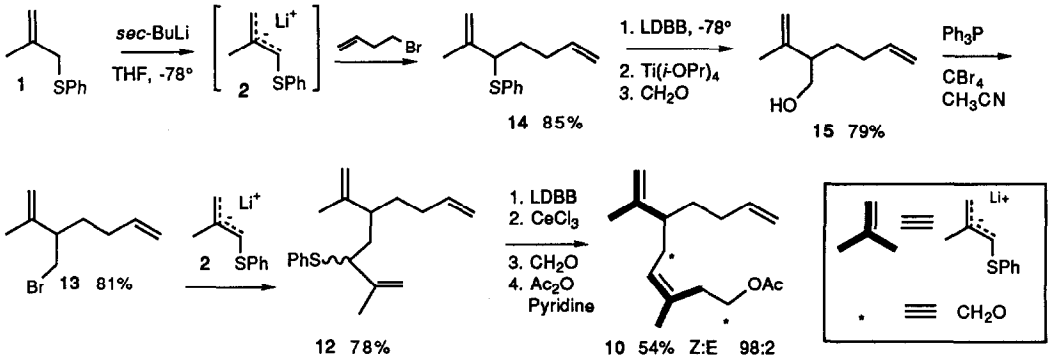
The most challenging aspect of the synthesis of **10** is the establishment of the trisubstituted Z-olefin. This task seemed ideally suited for the allylcerium chemistry since it had been shown that the predominantly cis *disubstituted* allyllithiums generated by reductive lithiation are captured by cerium trichloride with retention of configuration and that cis olefins are therefore the major product from attack of aldehydes and ketones on allylceriums generated in this way. The methyl group at the central carbon atom of the requisite allyl system (see **11**, Scheme 3) could only enhance the tendency of the precursor allyllithium to exist in the Z-conformation since 11Li(E) is destabilized by repulsion between that methyl group and the large substituent on the terminus of the allyl system; there is dramatic experimental confirmation of this notion in the field of allylpotassiums.[24] As indicated in the retrosynthetic analysis (Scheme 3), the allylic nucleophile **11** would be available by reductive lithiation of the allyl phenyl sulfide **12** which, in turn, would be generated by alkylation of the Biellmann anion **2** arising by deprotonation[10] of the commercially available methallyl phenyl sulfide. The alkylating agent **13** would arise from the corresponding alcohol which could be prepared from the allyltitanium derived from **14** by reductive lithiation followed by transmetallation. Finally, **14** would be available by alkylation of the same Biellmann anion **2** by the commercially available 4-bromo-1-butene.



Scheme 3

In the event (Scheme 4), 2-methyl-3-phenylthio-1,6-heptadiene **14**, the precursor of the first reductively produced allyl anion, was prepared in 85% yield by deprotonation of methallyl phenyl sulfide with *sec*-BuLi followed by the projected alkylation. The desired regioisomer resulting from α-alkylation was separated by flash

chromatography from a small amount of a 1 : 1 cis : trans mixture of regioisomers resulting form γ-alkylation. Allyl sulfide **14** was reductively lithiated with LDBB producing an allyllithium which was treated in situ with $Ti(i\text{-}OPr)_4$ followed by gaseous formaldehyde. Alcohol **15**, obtained as the only regioisomer, resulted from attack of CH_2O on the most-substituted terminus of the allylic system. As in the synthesis of lavandulol, there was no detection of the regioisomer which would have resulted from attack of CH_2O at the less-substituted terminus of the allylic skeleton. The ^1H NMR spectrum of **15** exhibited a one proton multiplet at δ 2.31 which was assigned as the C3 methine proton; in addition, the spectrum exhibited another multiplet at δ 3.50 that was assigned as the carbinol protons and two broad singlets at δ 4.83 and 4.94 that were assigned as the C1 geminal olefinic protons. Alcohol **15** was converted to bromide **13** in 81% yield using Ph_3P and CBr_4 in CH_3CN at 0 °C.[25] The ^1H NMR spectrum of **13** exhibited a multiplet at δ 2.45 which was assigned as the C3 methine proton; in addition, the spectrum exhibited a doublet at δ 3.38 (J = 7.2 Hz) that was assigned as the bromomethyl protons and two broad singlets at δ 4.80 and 4.92 that were assigned as the terminal geminal olefinic protons.



Scheme 4

Regioselective α-alkylation of sulfur - stabilized allyllithium **2** with bromide **13** led in 78% yield to a mixture of diastereomeric sulfides **12** and a small amount of a 1 : 1 mixture of the regioisomers resulting from γ-alkylation. The next step of the synthesis involves the construction, in both a regio- and stereocontrolled fashion, of the trisubstituted Z-double bond from allyl sulfides **12**. Treatment of **12** with LDBB at -78 °C produced an allyllithium intermediate which was treated with anhydrous $CeCl_3$ followed by gaseous formaldehyde. Treatment of the crude reaction mixture with acetic anhydride and pyridine produced (±)-**10** in 54% yield from **12** along with 9% of a diastereomeric mixture of regioisomeric acetates.

Pheromone component **10** was characterized by comparison of the ^1H NMR spectral data with those previously reported[7b,21,26] and also by comparison of retention times from a gas chromatogram of an authentic sample consisting of a 1 : 1 mixture of Z-and E- isomers.[27] The retention time for **10** is identical with that of the more mobile Z-component of the 1 : 1 mixture of Z- and E-isomers of **10**. The ^1H NMR spectrum of **10** exhibits a methyl singlet at δ 1.65 which was an indication of the presence of the methyl group at C3 of the Z-isomer; the methyl singlet at C3 of the E-isomer occurs at higher field (δ 1.56). Gratifyingly, the Z : E ratio obtained for synthetic **10** was 98 : 2 as measured by gas chromatography. The complex AII component of the California red scale pheromone was thus prepared in six steps in 23% overall yield. This efficient, reagent conservative, synthesis involves two allyl anions both produced by reductive lithiation of the alkylation product of the same Biellmann anion

2. Both of the allyl anions were captured by formaldehyde, one at the most substituted terminus after treatment with $Ti(i\text{-}OPr)_4$ and the other at the least substituted terminus by the use of allylcerium chemistry. The latter case is an interesting demonstration of the use of this new technology in the regio- and stereochemically controlled formation of a Z-double bond.

In summary, the regioselective addition of allyltitanium intermediates, as well as the regioselective and stereoselective addition of allylcerium intermediates to enals and aldehydes has been successfully applied toward the stereocontrolled syntheses of racemic versions of lavandulol, the Comstock mealybug pheromone, and the California red scale pheromone. These three syntheses are highly competitive in both brevity and yield with the most efficient of those reported. An important aspect of these syntheses that would become important in industrial settings is that few expensive reagents are used. It should be emphasized that lithium metal is far less expensive per equivalent than any organolithium compounds and the thiophenol and di-*tert*-butylbiphenyl can be recycled.

EXPERIMENTAL

All reactions involving organometallics were performed under an argon atmosphere with pre-dried (minimum 110 °C, 12 h) glassware. Thin layer chromatograms were performed on glass-backed 250 μ silica gel GF plates (Analtech uni-plates). Flash chromatography[28] was performed using 40-63 μm silica gel 60 (Merck) and standard techniques. Analytical HPLC was performed on a Waters model 590 fitted with a U6K injector, a differential UV detector, a differential refractometer, and a 1 mm x 25 mm column pre-packed with 5 μ Lichrosorb (Analtech). Semi-preparative HPLC was performed using 3-5 (8 mm x 30 mm) columns in tandem, each packed with 10 μ Lichrosorb (Analtech). Capillary gas chromatographic analyses were performed on a Hewlett-Packard 5890 gas chromatograph utilizing a 0.20 mm fused silica capillary column with a Carbowax® 20M stationary phase. Infrared spectra were recorded using an IBM IR/32 FTIR spectrometer using the IR/305 V2.00 program and are reported in reciprocal centimeters (cm^{-1}) along with relative intensity (w = weak, m = medium, s= strong absorption). ^1H and ^{13}C nuclear magnetic (NMR) spectra were recorded either on a Bruker WH-300 spectrometer or a Bruker AF-300 spectrometer while using either deuterated chloroform or deuterated benzene as the solvent. Chemical shifts are reported in units of δ (ppm) relative to tetramethylsilane used as an internal standard. ^1H NMR data are reported as follows: chemical shift; multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet); coupling constant; and integration. High resolution mass spectra were recorded either on a Varian MAT CH-5 double-focussing mass spectrometer or on a VG 70-SE.

Lithium *p,p'*-di-*tert*-butylbiphenylide (LDBB). A typical procedure follows. To a dry three-necked flask, which was continually purged with argon and equipped with a glass-coated stirring bar, was added THF (22 mL) and *p,p'*-di-*tert*-butylbiphenyl (1.11 g, 4.18 mmol). The mixture was cooled to 0 °C with an ice bath and lithium ribbon (29.0 mg, 4.18 mmol), which was cut into small strips, was inserted into the reaction mixture. The blue-green color of the radical anion appeared within 5 min, and the LDBB was completely formed after 5 h of rapid stirring at 0°. During the generating period, the glass wall of the reaction vessel was washed periodically with dry THF to flush down any adhered lithium pieces.

Lithium 1-(dimethylamino)naphthalenide (LDMAN).[1] To a flame dried three-neck flask, which was continually purged with argon and equipped with a glass-coated stirring bar, was added THF (30 ml) and 1-(dimethylamino)naphthalene (3.04 mL, 3.16 g, 18.5 mmol). The mixture was cooled to -45 °C with a 1-hexanol/dry ice bath and lithium ribbon (128 mg, 18.5 mmol), which was cut into small strips, was inserted into the

reaction mixture. The dark green color of the radical anion appeared within 5 min, and the LDMAN was completely formed after 3.5 h of rapid stirring. During the generating period, the glass wall of the reaction vessel was washed periodically with dry THF to flush down any adhered lithium pieces.

2,6-Dimethyl-3-phenylthio-1,5-heptadiene (3). To a stirred solution of methallyl phenyl sulfide (1.69 g, 10.3 mmol) in 60 mL of THF at -78 °C was added *sec*-butyllithium (8.08 mL, 10.5 mmol, 1.30 M) producing a yellow-colored allyllithium. After 1 h of stirring, prenyl bromide (1.69 g, 1.32 mL, 11.3 mmol) was added and the reaction mixture was stirred for an additional 2 h. The THF was removed *in vacuo*, and the resulting residue was taken up in 150 mL of ether. The organic layer was washed once with water and once with saturated NaCl solution. Na_2CO_3 was used for drying and the solvent was removed *in vacuo*. Column chromatography (R_f = 0.25; hexanes) yielded 2.06 g of the olefin as a clear liquid (86% yield): ^{1}H NMR ($CDCl_3$) δ 7.38 - 7.13 (m, 5H), 5.12 (t, J = 7.0 Hz, 1H), 4.73 (s, 1H), 4.64 (s, 1H), 3.64 (dd, J_1 = 6.9 Hz, J_2 = 8.5 Hz, 1H), 2.39 (m, 2H), 1.78 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.76, 135.61, 133.44, 132.47, 128.63, 126.91, 121.28, 113.65, 56.48, 31.67, 25.81, 18.21, 18.05; IR (neat, NaCl) 3075 (w), 3060 (w), 2971 (m), 2915 (m), 2857 (w), 1642 (w), 1584 (w), 1479 (m), 1439 (s), 1376 (m), 1026 (w), 894 (m), 894 (m), 743 (s), 691 (s) cm^{-1}; high resolution mass spectrum calculated for $C_{15}H_{20}S$ 232.1286, measured 232.1285.

(±)-Lavandulol (4). To a stirred solution of LDBB (4.18 mmol) in THF (30 mL) at -78 C° was added sulfide 3 (405 mg, 1.74 mmol) dropwise, over a period of 5 min; the resulting mixture was allowed to stir for 10 min. Titanium(IV) isopropoxide (0.995 g, 1.04 mL, 3.48 mmol) was added dropwise to the reaction mixture at -78°and the solution was stirred for an additional 20 min. Gaseous formaldehyde[12] was then passed through the reaction mixture over a period of 45 min. The reaction was quenched with saturated NH_4Cl solution (5 mL) and diluted with ether (100 mL); the resulting titanium precipitate was removed by filtration. The etheral solution was washed with 5% NaOH solution (2 x 30 mL), 5% HCl solution (2 x 30 mL), H_2O (30 mL), and saturated NaCl solution (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (R_f = 0.15; 10% ethyl acetate in hexanes) afforded 217 mg of a clear, colorless liquid (81% yield): ^{1}H NMR ($CDCl_3$) δ 5.08 (dt, J_1 = 1.4 Hz, J_2 = 6.5 Hz, 1H), 4.92 (dd, J_1 = 1.4 Hz, J_2 = 1.0 Hz, 1H), 4.81 (d, J = 1.0 Hz, 1H), 3.50 (m, 2H), 2.28 (m, 1H), 2.07 (m, 2H), 1.70 (s, 6H), 1.61 (s, 4H); IR (neat, NaCl) 3360 (m), 3074 (w), 2968 (s), 2918 (s), 2882 (s), 1645 (m), 1450 (m), 1444 (m), 1377 (m), 1039 (s), 890 (s) cm^{-1}. The spectral characteristics were identical to those previously reported.[5]

2,6-Dimethyl-1,5-heptadien-3-ol (8). To a stirred solution of LDMAN (18.5 mmol) in THF (30 ml) at -78° was added sulfide **201** (1.50 mg, 8.41 mmol) dropwise over a period of 5 min; the resulting mixture was allowed to stir for 10 min. The reaction mixture was then transferred *via* cannula to a slurry of anhydrous cerium(III) chloride (3.45 g, 9.25 mmol) in THF (10 mL) at -78 °C. After 3 h of stirring at -78°, the orange-colored solution was treated with freshly distilled methacrolein (1.18 g, 1.39 mL, 16.8 mmol). A 5% HCl solution was then added dropwise until the resulting white precipitate dissolved, and the solvent was then removed *in vacuo*. The residue was dissolved in ether (50 mL) and the resulting etheral solution was washed with 5% HCl (2 x 20 mL), 5% NaOH (2 x 20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (R_f = 0.26; 6.5% ethyl acetate in hexanes) afforded 637 mg (54% yield) of **8** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.13 (t, J = 7.2 Hz, 1 H), 4.85 (s, 1 H), 4.97 (s, 1 H), 4.06 (t, J = 6.4 Hz, 1 H), 2.28 (dd, J_1 = 6.4 Hz, J_2 = 6.8 Hz, 2 H), 1.79 (s, 1 H), 1.75 (s, 3 H), 1.74 (s, 3 H), 1.65 (s, 3 H); ^{13}C NMR ($CDCl_3$) 147.16, 135.13, 119.83, 110.83, 75.63, 34.23, 25.93, 16.05; IR (neat, NaCl) 3378 (s), 3073 (w), 2971

(s), 2917 (s), 1651 (w), 1447 (m), 1375 (m), 1049 (m), 1026 (m), 899 (m) cm^{-1} The spectral characteristics were identical to those previously reported.[14b,15]

2,6-Dimethyl-1,5-heptadien-3-ol acetate (9) from Acetylation of 8. Freshly distilled acetic anhydride (2.5 ml) was added to a stirred solution of **85** (234 mg, 1.67 mmol) in dry pyridine (5.0 ml). The mixture was left to stir overnight at room temperature. The reaction mixture was then poured into ice-water and extracted with ether (2 x 30 ml). The ether solution was washed with saturated $NaHCO_3$ solution (2 x 30 ml) , saturated NaCl solution (2 x 30 ml), dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (R_f = 0.45; 6.5% ethyl acetate in hexanes) afforded 258 mg of a clear oil (85% yield): ^1H NMR ($CDCl_3$) δ 5.15 (*t*, *J* = 6.8 Hz, 1H), 5.04 (*t*, *J* = 7.0 Hz, 1H), 4.94 (s, 1H), 4.89 (s, 1H), 2.34 (m, 2H), 2.05 (s, 3H), 1.73 (s, 3H), 1.69 (s, 3H), 1,62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.28, 143.12, 134.29, 119.04, 112.68, 77.08, 31.62, 25.76, 22.68, 18.37, 17.92; IR (neat, NaCl) 3082 (w), 2974 (m), 2921 (m), 2860 (w), 1742 (s), 1653 (w), 1448 (m), 1371 (m), 1239 (s), 1111 (w), 1045 (m), 1021 (m), 955 (w), 903 (m), 845 (w) cm^{-1}. The spectral characteristics were identical to those previously reported.[14,15]

2,6-Dimethyl-1,5-heptadien-3-ol Acetate (9). One-pot preparation. To a stirred solution of LDBB (5.91 mmol) in THF (20 mL) at -78 C° was added prenyl sulfide **5** (458 mg, 2.57 mmol) dropwise over a period of 5 min; the resulting mixture was allowed to stir for 10 min. The reaction mixture was then transferred *via* cannula to a slurry of anhydrous cerium(III) chloride (1.44 g, 3.85 mmol) in THF (10 mL) at -78°. After 3 h of stirring at -78°, the orange-colored solution was treated with freshly distilled methacrolein (0.59 g, 0.70 mL, 8.5 mmol). After 15 min of stirring at -78°, TMEDA (2.39 g, 3.10 mL, 20.6 mmol) was added and the resulting mixture was stirred for 15 min. Pyridine (1.42 g, 1.45 mL, 18.0 mmol) and freshly distilled acetic anhydride (0.92 g, 0.85 mL, 8.99 mmol) were then added at -78° and the reaction mixture was allowed to warm to room temperature where stirring was maintained overnight. The mixture was poured into ice-water and extracted with ether (2 x 25 mL). The ether solution was washed with saturated $NaHCO_3$ solution (2 x 25 mL) , saturated NaCl solution (2 x 25 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (R_f = 0.45; 6.5% ethyl acetate in hexanes) afforded 211 mg of **9** as a clear oil (45% yield).

2-Methyl-3-phenylthio-1,6-heptadiene (14). To a stirred solution of methallyl phenyl sulfide (1, 6.60 g, 40.2 mmol) in 120 mL of THF at -78 °C was added *sec*-butyllithium (38.4 mL of a 1.10 M, 42.2 mmol) producing a yellow-colored allyllithium. After 1 h of stirring, 4-bromo-1-butene (5.43 g, 4.08 mL solution, 40.2 mmol) was added and the reaction mixture was stirred for an additional 2 h. The workup was identical to that for **3**. Column chromatography (R_f = 0.17; hexanes) yielded 7.46 g of the olefin as a clear liquid (85% yield): ^1H NMR ($CDCl_3$) δ 7.38 - 7.13 (m, 5H), 5.59 (m, 1H), 5.02 (d, *J* = 17.2 Hz, 1H), 4.98 (d, *J* = 10.1 Hz, 1H), 4.73 (s, 1H), 4.61 (s, 1H), 3.64 (t, *J* = 8.1 Hz, 1H), 2.14 (dt, J_1 = 7.2 Hz, J_2 = 7.1 Hz, 2H), 1.77 (s, 3H), 1.85 - 1.67 (m, 2H); IR (neat, NaCl) 3075 (s), 2975 (m), 2936 (s), 2853 (m), 1640 (s), 1584 (m), 1480 (s), 1374 (m), 1090 (w), 1067 (w), 1024 (m), 994 (m), 912 (s), 897 (s), 745 (s), 691 (s) cm^{-1}; high resolution mass spectrum calculated for $C_{14}H_{18}S$ 218.1129, measured 218.1129.

2-Methyl-3-hydroxymethyl-1,6-heptadiene (15). To a stirred solution of LDBB (5.56 mmol) in THF (30 mL) at -78 °C was added sulfide 14 (600 mg, 2.75 mmol) dropwise, over a period of 5 min; the resulting mixture was allowed to stir for 10 min. Titanium(IV) isopropoxide (1.59 g, 1.67 mL, 5.56 mmol) was added dropwise to the reaction mixture at -78 C°and the solution was stirred for an additional 20 min. Gaseous formaldehyde was passed through the reaction mixture over a period of 45 min. The reaction was quenched with

saturated NH_4Cl solution (5 mL) and workup was identical to that for **4**. Flash chromatography (R_f = 0.19; 13% ethyl acetate in hexanes) afforded 305 mg of **15** as a clear, colorless liquid (79% yield): ^1H NMR ($CDCl_3$) δ 5.80 (m, 1H), 5.00 (dd, J_1 = 1.6 Hz, J_2 = 17.5 Hz, 1H), 4.96 (d, J = 10 Hz, 1H), 4.95 (s, 1H), 4.83 (s, 1H), 3.51 (m, 2H), 2.30 (m, 1H), 2.04 (m, 3H), 1.68 (s, 3H) 1.44 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 144.83, 138.46, 114.71, 113.95, 63.99, 49.30, 31.31, 28.39, 18.73; IR (neat, NaCl) 3351 (m), 3075 (m), 2975 (m), 2928 (s), 1642 (m), 1441 (m), 1375 (w), 1046 (m), 995 (m), 909 (s), 893 (s) cm^{-1}; high resolution mass spectrum calculated for M - CH_2OH (C_8H_{13}) 109.1017, measured 109.1017.

2-Methyl-3-bromomethyl-1,6-heptadiene (13). To a stirred solution of alcohol **15** (137 mg, 0.98 mmol) and carbon tetrabromide (384 mg, 1.17 mmol) in dry acetonitrile (4 mL) at 0° under an argon atmosphere, was added triphenyl phosphine (307 mg, 1.17 mmol) dissolved in acetonitrile (1.5 mL). After 12 h of stirring, TLC analysis indicated total consumption of alcohol **15** and the formation of a new spot (R_f = 0.38; hexanes). After removal of the acetonitrile *in vacuo*, ether was added to the organic residue and the resulting mixture was filtered; the ether was removed *in vacuo* producing a yellow oil. Flash chromatography afforded 161 mg (81% yield) of bromide **13** as a clear, colorless liquid: ^1H NMR ($CDCl_3$) δ 5.79 (m, 1H), 5.02 (dd, J_1 = 17.3 Hz, J_2 = 1.4 Hz, 1H), 4.94 (d, J = 10.5 Hz, 1H), 4.92 (s, 1H), 4.80 (s, 1H), 3.38 (d, J = 7.2 Hz, 2H), 2.45 (m, 1H), 2.01 (m, 2H), 1.67 (s, 3H), 1.66 (m, 1H), 1.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 144.83, 138.14, 115.03, 113.81, 48.68, 36.46, 31.35, 30.83, 18.86; IR (neat, NaCl) 3073 (w), 2974 (m), 2927 (s), 1641 (m), 1440 (m), 1220 (s), 909 (m), 894 (m) cm^{-1}; high resolution mass spectrum calculated for $C_9H_{15}Br$ 202.0357, measured 202.0367.

2-Methyl-3-phenylthio-5-isopropenyl-1,8-nonadiene (12). To a stirred solution of methallyl phenyl sulfide (1, 110 mg, 0.670 mmol) in 1.5 mL of THF at -78 °C was added *sec*-butyllithium (542 μl of 1.30 M solution, 0.704 mmol,) producing a yellow-colored allyllithium. After 1 h of stirring, bromide **13** (136 g, 0.670 mmol) was added and the reaction mixture was stirred for an additional 2 h. The workup was identical to that for **3**. Column chromatography (1% ethyl acetate in hexanes) yielded 36 mg (19% yield) of a *cis/trans* mixture of regioisomers resulting from alkylation at the γ-position (R_f = 0.38 and 0.36), as well as 87 mg of a diastereomeric mixture of **12** (R_f = 0.26 and 0.20), and pure fractions of each diastereomer of **12** in amounts of 36 mg (R_f = 0.26) and 24 mg (R_f = 0.20); the total yield of **12** was 78%. Data for the more mobile diastereomer of **12** (R_f = 0.26) are as follows: ^1H NMR ($CDCl_3$) δ 7.40 - 7.15 (m, 5H), 5.81 (m, 1H), 4.99 (d, J = 17.1 Hz, 1H), 4.94 (d, J = 10.8 Hz, 1H), 4.84 (s, 1H), 4.81 (s, 1H), 4.65 (s, 1H), 4.53 (s, 1H), 3.62 (t, J = 7.3 Hz, 1H), 2.15 (m, 1H), 2.00 (m, 2H), 1.78 (s, 3H), 1.64 (dd, J_1 = 7.4 Hz, J_2 = 7.3 Hz, 2H), 1.60 (s, 3H), 1.42 (dt, J_1 = 7.7 Hz, J_2 = 7.6 Hz, 2H); IR (neat, NaCl) 3074 (m), 3019 (w), 2973 (m), 2929 (s), 2855 (m), 1642 (m), 1584 (w), 1439 (s), 1417 (w), 1375 (m), 1089 (w), 1067 (w), 1025 (m), 995 (m), 909 (m), 893 (s), 742 (s), 691 (s), 668 (w), 655 (w) cm^{-1}. Data for the less mobile diastereomer of **12** (R_f = 0.20) are as follows: ^1H NMR ($CDCl_3$) δ 7.38 - 7.13 (m, 5H), 5.77 (m, 1H), 4.97 (d, J = 17.6 Hz, 1H), 4.92 (d, J = 10.8 Hz, 1H), 4.80 (s, 1H), 4.77 (s, 1H), 4.66 (s, 1H), 4.61 (s, 1H), 3.57 (t, J = 7.4 Hz, 1H), 2.47 (m, 1H), 1.98 (m, 2H), 1.76 (s, 3H), 1.70 (m, 2H), 1.54 (s, 3H), 1.41 (dt, J_1 = 7.6 Hz, J_2 = 7.4 Hz, 2H); IR (neat, NaCl) 3073 (m), 3018 (w), 2970 (m), 2929 (s), 2855 (m), 1640 (m), 1580 (w), 1440 (s), 1417 (w), 1375 (m), 1089 (w), 1066 (w), 1024 (m), 996 (m), 908 (m), 893 (s), 742 (s), 690 (s), 668 (w), 655 (w) cm^{-1}. High resolution mass spectrum calculated for $C_{19}H_{26}S$ 286.1755, measured 286.1759.

(*Z*)-3-Methyl-6-isopropenyl-3,9-decadien-1-ol Acetate (10). To a stirred solution of LDBB (3.66 mmol) in THF (25 mL) at -78 °C was added sulfide **12** (498 mg, 1.74 mmol) dropwise over a period of 15

min. The resulting allyllithium was allowed to warm to -45° where stirring was maintained for 1 h. The allyllithium was then cooled to -78° prior to transfer *via* cannula to slurry of anhydrous $CeCl_3$ (1.30 g, 3.49 mmol) in THF (10 mL) at -78°. After 1 h of stirring, the orange-colored allylcerium was treated with gaseous formaldehyde[12] over a period of forty-five minutes. The orange color of the allylcerium solution gradually dissipated, and the solution became colorless after thirty minutes. A 5% HCl solution was then added dropwise until the resulting white precipitate dissolved, and the solvent was then removed *in vacuo*. The residue was dissolved in ether (50 mL) and the resulting etheral solution was washed with 5% HCl (2 x 20 mL), 5% NaOH (2 x 20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. TLC analysis of the crude reaction mixture indicated the formation of three spots (R_f = 0.40, 0.37, 0.30; 10% ethyl acetate in hexanes). In lieu of separation of the mixture of probably regioisomeric alcohols, the crude reaction mixture was acetylated directly by treatment with freshly distilled acetic anhydride (2.5 mL) and dry pyridine (5.0 mL). The resulting mixture was left to stir overnight at room temperature. The reaction mixture was then poured into ice-water and extracted with ether (2 x 20 mL). The ether solution was washed with saturated $NaHCO_3$ solution (2 x 20 mL) , saturated NaCl solution (2 x 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. TLC analysis of the crude reaction mixture indicated the formation of three spots (R_f = 0.38, 0.35, 0.26; 5% ethyl acetate in hexanes). Flash chromatography (5% ethyl acetate in hexanes) afforded 39 mg (9% yield) of a diastereomeric mixture of acetates resulting from the attack of formaldehyde at the most substituted terminus and 235 mg of **10** as a clear oil (54% yield). Capillary GC analysis of **10** (130 °C, 1 mL/min): 98% *Z* isomer (t_R = 9.06 min), 2% *E* isomer (t_R = 10.37 min), identical with those of an authentic mixture of these isomers.[27] ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 1H), 5.22 (t, *J* = 5.9 Hz, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 4.77 (s, 1H), 4.70 (s, 1H), 4.12 (t, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 2.1 - 1.9 (m, 5H), 1.65 (s, 3H), 1.60 (s, 3H), 1.47 (m, 2H); IR (neat, NaCl) 3074 (w), 2969 (m), 2927 (m), 2858 (m), 1744 (s), 1643 (m), 1450 (m), 1445 (m), 1380 (m), 1366 (m), 1238 (s), 1042 (m), 995 (w), 910 (m), 891 (m) cm^{-1}. The spectral characteristics were identical to those previously reported.[7b,21,26]

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