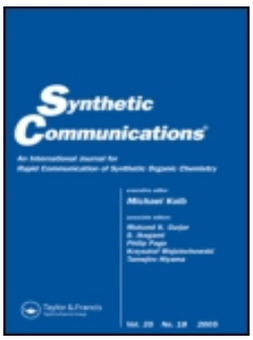

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Synthesis of three putative kairomones of the beech leaf-mining weevil *Orchestes fagi* (L.)

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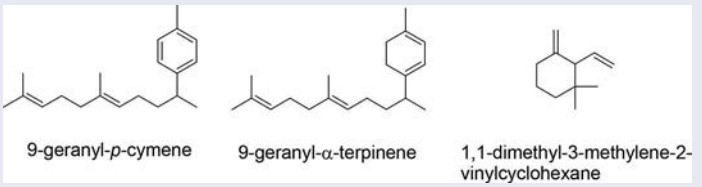
ABSTRACT

The beech leaf-mining weevil, *Orchestes fagi* (L.), also known as the beech flea weevil, is a common and widespread pest of beech, *Fagus sylvatica* L., in its native Europe. It now appears to be well established in Nova Scotia, Canada. We report a novel synthesis of 9-geranyl-p-cymene and syntheses of 9-geranyl-α-terpinene and 1,1-dimethyl-3-methylene-2-vinylcyclohexane, making partial use of known methods. All three of these compounds are found in beech leaf volatiles and/or wood and are putative kairomones of the beech leaf-mining weevil.

GRAPHICAL ABSTRACT



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Beech leaf-mining weevil; 1,1-dimethyl-3-methylene-2-vinylcyclohexane; 9-geranyl-*p*-cymene; 9-geranyl-α-terpinene; kairomones

Introduction

The beech leaf-mining weevil, *Orchestes fagi* (L.) (Curculionidae: Curculioninae: Rhamphini), also known as the beech flea weevil, is a common and widespread pest of beech, *Fagus sylvatica* L. (Fagaceae), in its native Europe. It now appears to be well established in Nova Scotia, Canada.[1] Adult insects and mating pairs appear to be attracted to beech buds just prior to bud burst. Examination of volatiles from eclosing beech buds has identified two possibly attractive diterpene compounds, 9-geranyl-*p*-cymene **1** and 9-geranyl-α-terpinene **2a** (see Scheme 1). A third compound, 1,1-dimethyl-3-methylene-2-vinylcyclohexane **3**, is an additional putative kairomone of the same insect, found in both beech leaf volatiles and wood, bearing a structural resemblance to published cyclohexylidene curculionid pheromones;[2] to the best of our knowledge, there is no precedence for its synthesis in the literature. There is a report, however, of **3** being a constituent of the volatiles of the plant *Melinis minutiflora*.[3]

There are only sparse literature examples detailing the synthesis of *E*-2,6-dimethyl-10-(*p*-tolyl)-2,6-undecadiene (9-geranyl-*p*-cymene, geracymene) **1**[4,5] and *E*-2,

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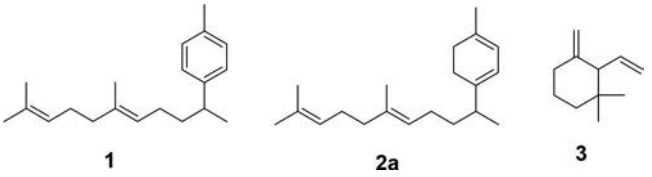
Supplemental data (full experimental details and ^{1}H and ^{13}C NMR spectra) can be accessed on the publisher's website.



Scheme 1. 9-Geranyl-*p*-cymene **1**, 9-geranyl-α-terpinene **2a**, and 1,1-dimethyl-3-methylene-2-vinylcyclohexane **3**.

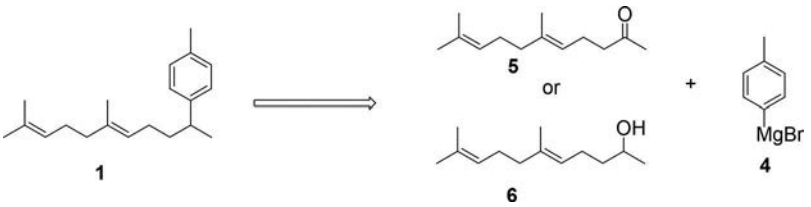
6-dimethyl-10-(4′-methyl-1′,3′-cyclohexadienyl)-2,6-undecadiene (9-geranyl-α-terpinene, geraterpinene) **2a**,[6] even though they are apparently relatively simple diterpenes. Compounds **1** and **2a** have been detected in the oils of various plants: compound **1** in *Sideritis trojana*,[7] *Sideritis cilicica*,[8] *Anthemis dispacea*,[9] *Anthemis rosea* ssp. carnea,[10] *Calamina pamphylica* ssp. *pamphylica*, *davisii*, and *alanyense*,[11] *Artemisia absinthium* from Tajikistan,[12] and *Cydonia oblonga* Miller.[13] Both compounds **1** and **2a** have been found together in the same plant, for instance, in *Artemisia absinthium* L.,[14] *Sideritis dichotoma*[15] and *Helichrysum* species.[16]

Discussion

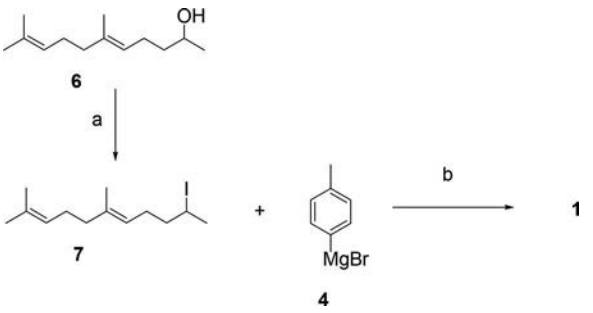
Retrosynthetically, **1** would seem the simpler of the two diterpenes to synthesize because the *p*-tolyl moiety could be readily obtained from the Grignard reagent *p*-tolylmagnesium bromide **4**, and the 13-C chain could also be easily obtained from geranylacetone **5** or fuscumol[17] **6** (see Scheme 2).

Examination of compound **2a** suggested that it would be more challenging to synthesize, as a reagent that could deliver a 4-methyl-1,3-cyclohexadien-1-yl group is not readily known. Consequently, the cyclohexadiene ring of **2a** would need to be synthesized *de novo*.

With this in mind, efforts were focused first on synthesis of **1** with two methods being targeted. The first involved a very simple cuprate coupling of commercially available *p*-tolylmagnesium bromide **4** with *E*-10-iodo-2,6-dimethyl-2,6-undecadiene **7**, itself available by a straightforward iodination of commercially available racemic fuscumol[17] **6** (*E*-2-hydroxy-6,10-dimethyl-5,9-undecadiene, see Scheme 3). The cuprate coupling proceeded with only 3% yield, after separation from the byproduct bis(*p*-tolyl), which was accomplished with a silver nitrate/silica gel cartridge. Given that unactivated secondary alkyl iodides are only borderline substrates for alkylation reactions, the low yield of this cuprate coupling was not surprising.



Scheme 2. Retrosynthesis of 9-geranyl-*p*-cymene **1**.



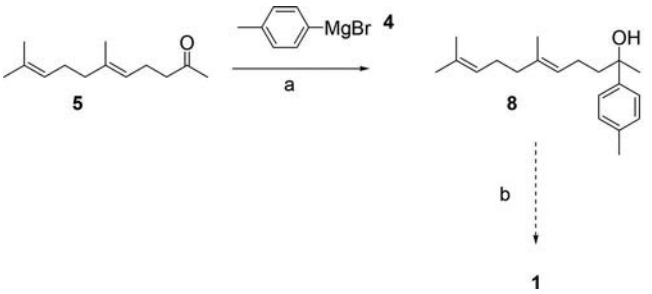
Scheme 3. (a) I_2, PPh_3, imidazole, 1:3 CH_3CN/Et_2O, rt, 98%. (b) Li_2CuCl_4, *p*-tolylmagnesium bromide, THF, −78 °C–rt, 3% after purification.

The second method, closely related to the syntheses published by Pietsch et al.[4] and Sabharwal et al.,[5] involved treating geranylacetone **5** (*E*-6,10-dimethyl-5,9-undecadien-2-one) with *p*-tolylmagnesium bromide **4** to give *E*-6,10-dimethyl-2-hydroxy-2-(*p*-tolyl)-5,9-undecadiene **8** (quantitative yield), which could then be deoxygenated to give **1** (see Scheme 4).

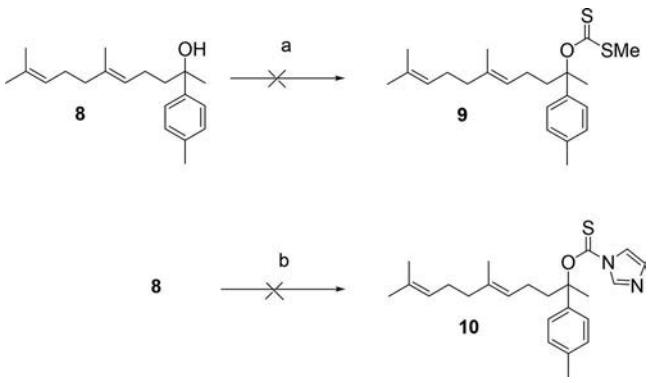
Several deoxygenation methods were attempted before a satisfactory one was found. Two direct deoxygenations of **8** were attempted; these were catalytic hydrogenolysis with Lindlar's Pd[18] and catalytic hydrogenolysis with P2 nickel,[19] both of which resulted in no reaction. The well-known Barton and McCombie deoxygenation[20] failed to produce any 9-geranyl-*p*-cymene **1** because the intermediate xanthate esters **9** or **10** could not be generated from **8** by either of the two methods shown in Scheme 5.

Despite these failures, it was found that protection of **8** with ethyl vinyl ether (EVE), which proceeded in 78% yield, and then treatment of **11** with lithium naphthalenide[21] cleanly gave **1** in 75% yield (see Scheme 6). This is similar to the syntheses of **1** reported by Pietsch et al. in 2003[4] and Sabharwal et al. in 1990;[5] however, their methods involved a one-pot Grignard reaction and dissolving metal reduction in liquid ammonia to generate **1**.

Success in the synthesis of **2a** was obtained by modifying the first three steps of the synthesis previously reported by Vig.[6] Our work is shown in Schemes 7 and 8. Geranyl acetone **5** was treated with the commercially available Grignard reagent, 4-methoxyphenyl-magnesium bromide **12,** to give **13** in 69% yield.



Scheme 4. (a) Et_2O, rt, quantitative. (b) Deoxygenation.

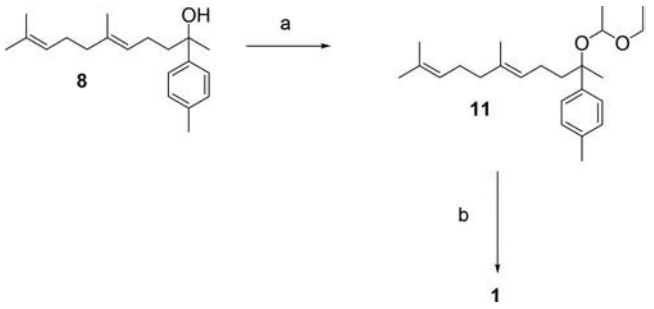


Scheme 5. (a) (i) NaH, THF, HMPA, rt; (ii) CS_2, rt–reflux; (iii) MeI, reflux. (b) 1,1′-Thiocarbonyldiimidazole, CH_2Cl_2, rt.

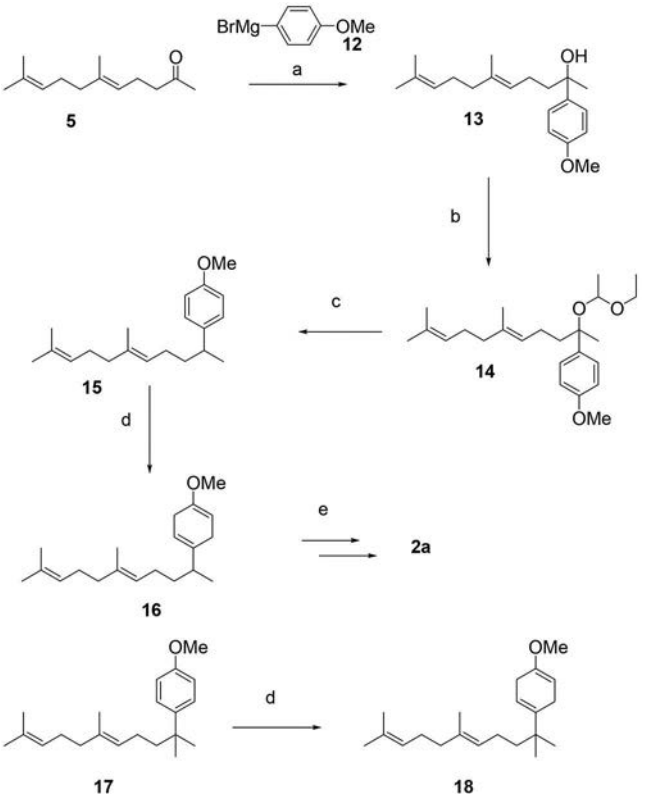
Subsequent ethyl vinyl ether protection of **13** was carried out to give **14** in 95% yield, followed by deoxygenation under Birch conditions to give **15** in 79% yield. Further Birch reduction of **15** gave **16**, which was then converted to **2a** using a slight modification of the method reported by Vig,[6] namely the use of *p*-toluenesulfonic acid in refluxing wet tetrahydrofuran (THF). This provided a much higher yield for the hydrolysis of the methyl enol ether in **16**. The spectral data of the intermediates **19** and **20** in this process closely correlated with those reported by Vig;[6] however, as well as **2a**, gas chromatography / mass spectrometry (GC/MS), ^{1}H NMR, and ^{13}C NMR revealed the presence of isomers **2b** and a trace amount of **2c** (structures tentatively assigned) in the product mixture.

A lithium naphthalenide deoxygenation of **14** was also attempted, as this method conveniently did not require liquid ammonia. However, the drawback of this method was the formation of a significant amount of **17** (~50% of the product, see Scheme 7). This presumably occurred by the anion initially formed from **14** abstracting a methyl group from the methoxy functionality of another molecule of **14**. Anisole **17** could then undergo Birch reduction to give **18**, which would react in the same way as **16** throughout the remaining steps of the synthesis. However, it was found that the use of Birch conditions on **14** cleanly gave **15** as previously mentioned, so this problem was accordingly circumvented.

Two routes to diene **3** achieved success (see Schemes 9, 10, and 11). The first route, considerably shorter than the other, involved deconjugation of commercially available

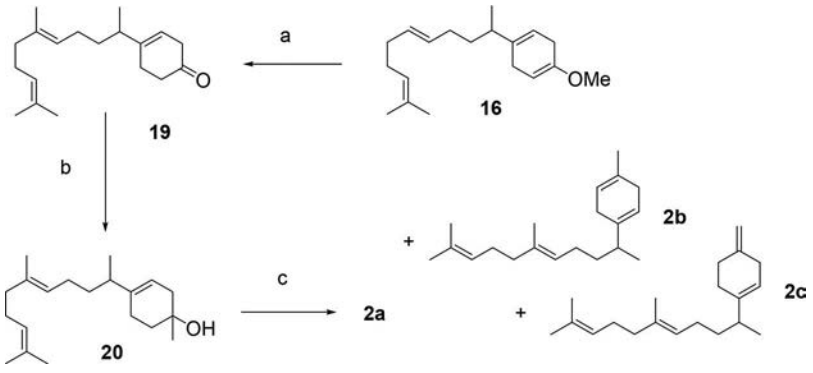


Scheme 6. (a) Ethyl vinyl ether, PPTS, CH_2Cl_2, rt, 78%. (b) Li/naphthalene, THF, rt, 75%.

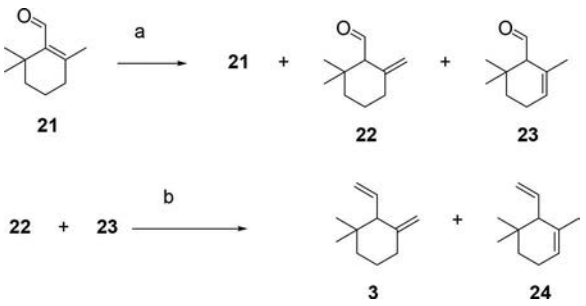


Scheme 7. (a) THF, 0 °C–rt, 69%. (b) Ethyl vinyl ether, PPTS, CH_2Cl_2, rt, 95%. (c) Li, naphthalene, THF, rt, 58%, or Li, NH_3, EtOH, Et_2O, −78 °C–rt, 79%. (d) Li, NH_3, EtOH, Et_2O, −78 °C–rt, yield not determined. (e) See Scheme 8.

β-cyclocitral **21** using strong base (NaHMDS). Although complete deconjugation was not realized, separation of conjugated from unconjugated compounds by silica-gel chromatography could be realized. Unfortunately, an inseparable mixture of deconjugated isomers



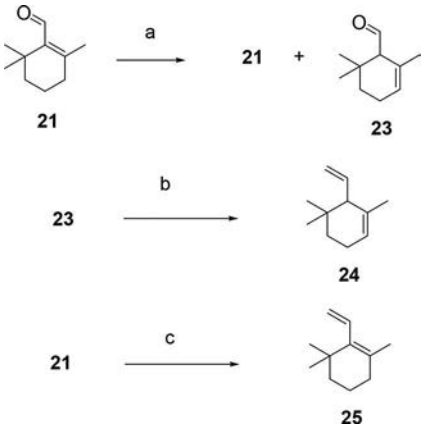
Scheme 8. (a) 0.1 M aqueous TsOH, THF, reflux. (b) MeMgI, Et_2O, rt–reflux, 18% over three steps. (c) $POCl_3$, pyridine, 0 °C–rt, 70%.



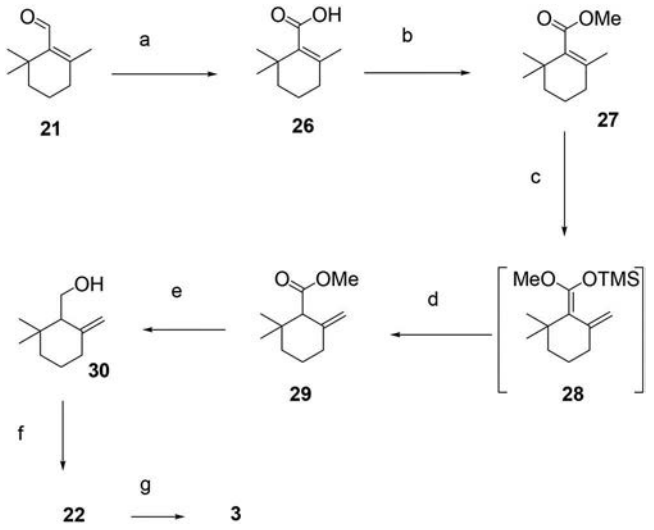
Scheme 9. (a) NaHMDS, THF, 0 °C, 18% yield of aldehydes **22** and **23** after removal of recovered **21** by silica gel column chromatography. (b) CH_3PPh_3Br, NaHMDS, THF, −78 °C–rt, 8% yield of a 4:1 mixture of **3** and **24** after purification. **3** and **24** are partially separable by silica-gel column chromatography.

22 (γ-cyclocitral) and **23** (α-cyclocitral) were obtained. Regardless, Wittig reaction of the inseparable mixture of deconjugated isomers **22** (γ-cyclocitral) and **23** (α-cyclocitral) gave a mixture of **3** and **24**, which were partially separable by silica-gel chromatography (see Scheme 9). Consequently a 4:1 mixture of **3** and **24** was readily obtained by this method and used for trapping studies of *O. fagi*. Subsequently, it was found that α-cyclocitral **23** could be prepared exclusively from β-cyclocitral **21** by equilibration with potassium hexamethyldisilylamide (KHMDS). Following removal of unconverted **21** by silica-gel column chromatography, diene **24** could then be made very easily in 100% purity by Wittig homologation of **23** (see Scheme 10). This brings to mind the fact that if γ-cyclocitral **22**, although not commercially available, could be obtained in complete isomeric purity, **3** could easily be obtained by Wittig homologation of **22**.

To complete the series of isomers of **3**, the conjugated diene **25** was obtained by a straightforward Wittig homologation of **21** (see Scheme 10), albeit with ~1% of **3** and ~1% of **24** present (as determined by GC/MS) as an inseparable mixture; this is not surprising in light of the fact that under basic conditions **21** isomerizes to **22** and/or **23**.



Scheme 10. KHMDS, THF, 0 °C, 17% of **23** after removal of recovered **21** by silica-gel column chromatography. (b) CH_3PPh_3Br, NaHMDS, THF, −78 °C–rt, 57%. (c) CH_3PPh_3Br, NaHMDS, THF, −78 °C–rt, 41%.



Scheme 11. (a) Air, CH_2Cl_2, rt, 54%. (b) CH_3I, K_2CO_3, acetone, reflux, 63%. (c) (i) ^nBuLi, THF, −10 °C–rt; (ii) TMSCl, −30 °C–rt, **28** not isolated. (d) HCl, H_2O, rt, 34% over 2 steps. (e) $LiAlH_4$, THF, 0 °C–rt, 39%. (f) PCC, CH_2Cl_2, rt, 47%. (g) CH_3PPh_3Br, NaHMDS, THF, −78 °C–rt, 60%.

The intended target, however, remained molecule **3**; it was realized by the use of a previously reported method that gave an intermediate ester (compound **29**, Scheme 11) that could easily be converted to **3**. Fehr and Galindo[22,23] report that methyl γ-cyclogeranate **29** can be obtained with complete regioselectivity by deprotonation of methyl β-cyclogeranate **27** with butyllithium, trapping with TMSCl (chlorotrimethylsilane) to give **28** and subsequent protonation (see Scheme 11). Also noteworthy is the synthesis of **29** as separate enantiomers by the same authors.[22] Acid **26** can be prepared readily by air oxidation of β-cyclocitral **21**. Methylation of **26** gives **27**, according to the method of Fehr and Galindo.[22] Reduction of **29** with lithium aluminum hydride, then pyridinium chlorochromate (PCC) oxidation of **30** and Wittig homologation of **22** (γ-cyclocitral) was found to yield **3** in 100% purity.

Consequently, the synthetic targets **1** (three steps, 59% overall yield), **2a** (seven steps, 6.5% overall yield), and **3** (seven steps, 1.3% overall yield) were obtained in a straightforward manner and used in field-trapping studies with *Orchestes fagi*, the complete results of which are still pending.

Experimental

Diterpene 1

In a flame-dried, round-bottom flask with a glass-coated stir bar, naphthalene (1.99 g, 15.5 mmol), THF (20 mL), and lithium (130 mg, 18.7 mmol) were added. The lithium was broken into pieces with a clean, dry metal scoop after addition. After 30 min of stirring at rt, the characteristic dark green color of lithium naphthalenide appeared, and the reaction was allowed to stir at rt for a further 3.5 h. Another flame-dried round-bottom flask equipped with a glass-coated stir bar was charged with acetal **11** (265 mg, 0.740 mmol) and THF (10 mL) and stirred at rt. The lithium naphthalenide solution was added to acetal

11 via syringe, and the reaction was stirred for 19 h at rt. Water (30 mL) was added, the layers were separated, and the aqueous layer was extracted with hexanes (2 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried ($MgSO_4$). Column chromatography on silica gel (hexanes > 20% EtOAc–hexanes as eluent) and removal of solvent in vacuo yielded **1** as a colorless, transparent liquid (150 mg, 0.56 mmol, 75%). ^{1}H NMR for **1** matched closely with that reported by Pietsch.[4] ^{13}C NMR was identical to that reported by Pietsch,[4] and the IR spectrum determined in our laboratory was identical with that reported by Sabharwal.[5] For bp and elemental analysis data, see Sabharwal's report.[5] For ^{1}H and ^{13}C NMR, as well as infrared (IR) and low-resolution mass spectrometry (LRMS), see the supporting information.

Diterpene 2a

In a flame-dried, round-bottom flask, alcohol **20** (12 mg, 0.041 mmol) and pyridine (anhydrous, 5 mL) were added. The reaction mixture was cooled to 0 °C, and $POCl_3$ (0.10 mL, 1.1 mmol) was added. After stirring for 23 h at 0 °C, water (20 mL) was added, and the reaction mixture was extracted with Et_2O (4 × 15 mL). The combined extractions were washed with brine (30 mL) and dried ($MgSO_4$). Column chromatography on silica gel (hexanes as eluent) yielded **2a** (inseparable from **2b** and **2c**, 7.7 mg, 0.028 mmol, 70%, as a colorless, transparent liquid) in a ratio of approximately 0.36:0.60:0.04 as determined by GC/MS. For ^{1}H and ^{13}C NMR, and IR spectral data of **2a** / **2b** / **2c**, as well as LRMS data of **2a**, see the supporting information. For literature IR and ^{1}H NMR spectral data, and elemental analysis data of **2a**, see Vig.[6]

Diene 3

A flame-dried, round-bottom flask was charged with methyltriphenylphosphonium bromide (1.90 g, 5.33 mmol) and THF (30 mL) and cooled to 0 °C. NaHMDS (5.3 mL, 1.0 M in THF, 5.3 mmol) was added dropwise over 3 min, and the reaction was stirred for 30 min at 0 °C and then 1 h at rt. The solution was then cooled to −78 °C, and aldehyde **22** (54 mg, 0.36 mmol) in THF (2 mL) was added via syringe with rinsing with THF (2 × 2 mL). The reaction mixture was allowed to warm to rt overnight, water (20 mL) was added, and the solution was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo and then filtration through a plug of silica using Et_2O as eluent removed excess methyltriphenylphosphonium bromide and triphenylphosphine oxide. Silica-gel column chromatography (pentane as eluent) and removal of solvent at 60 mbar and 5 °C yielded diene **3** (32 mg, 0.21 mmol, 60%) as a colorless, transparent liquid. R_f (hexanes) = 0.84. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.93 (dt, 1H, J = 16.9, 10.3 Hz), 5.08 (dd, 1H, J = 10.3, 2.3 Hz), 5.03 (dd, 1H, J = 17.0, 2.2 Hz), 4.74 (br. s, 1H), 4.58 (br. s, 1H), 2.42 (d, 1H, J = 9.6 Hz), 2.27 (m, 1H), 2.04 (m, 1H), 1.43–1.62 (m, 3H), 1.34 (m, 1H), 0.90 (s, 3H), 0.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.2, 137.7, 116.4, 108.3, 59.0, 39.1, 34.9, 34.6, 29.4, 23.4, 23.2. IR (neat, cm^{-1}): 3073 (w), 2927 (s), 2866 (m), 2863 (m), 1644 (w), 1458 (w), 1436 (w), 1385 (w), 1364 (w), 1005 (w). LRMS (EI, 70 eV) *m/z* (main peaks): 53, 55, 57, 65, 67, 69 (base peak), 77, 79, 81, 91, 93, 94, 107, 121, 135, 150 (M^+). HRMS: $[C_{11}H_{18}Ag]^+$ calc. 257.0454; found 257.0446. Mass measurement error: −3.29 ppm.

Acknowledgments

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