Synthesis of Macrocyclic Terpenoid Hydrocarbons by Intramolecular Carbonyl Coupling: Bicyclogermacrene, Lepidozene, and Casbene

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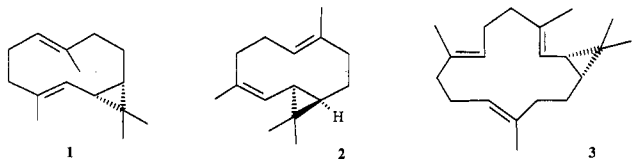
Total syntheses of two germacrane sesquiterpenes, bicyclogermacrene (1) and lepidozene (2), and of the cembrane sesquiterpene casbene (3) are discussed. Bicyclogermacrene and lepidozene were prepared in seven steps from geranylacetone by routes that involve titanium-induced cyclizations of *cis*- and *trans*-2,2-dimethyl-3-(3-methyl-7-oxo-3(*E*)-octenyl)cyclopropanecarbaldehyde, respectively. (+)-Casbene was prepared from (+)-2-carene and 6-methyl-5-hepten-2-one by a route whose key steps were the palladium-catalyzed cross-coupling of vinylic iodide **31** with homoallylic organozinc reagent **32** and the titanium-induced cyclization of *cis*-2,2-dimethyl-3-(3,7-dimethyl-11-oxo-3(*E*),7(*E*)-dodecadienyl)cyclopropanecarbaldehyde (**16**).

We have been involved for some years now in exploring applications of titanium-induced carbonyl-coupling reactions[1] to the synthesis of macrocyclic natural products. Among our efforts have been successful syntheses of flexibilene,[2] the only known 15-membered-ring diterpene, humulene,[3] an 11-membered-ring sesquiterpene, helminthogermacrene,[4] a 10-membered-ring sesquiterpene, and isocaryophyllene,[5] a 9-membered-ring sesquiterpene. We now report the details of our work[6] on the total syntheses of bicyclogermacrene (1) and lepidozene (2), two 10-membered-ring (germacrene) sesquiterpenes, as well as casbene (3), a 14-membered-ring (cembrane) diterpene.

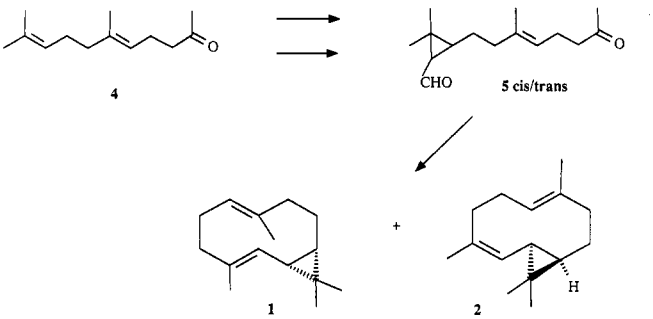


Syntheses of Bicyclogermacrene and Lepidozene

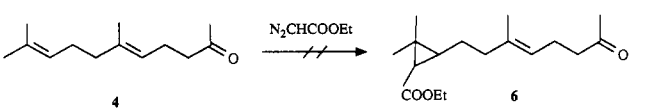
The two germacrene sesquiterpenes bicyclogermacrene (1) and lepidozene (2) differ only in that bicyclogermacrene contains a cis-fused dimethylcyclopropane ring and has two *E* double bonds, whereas lepidozene contains a trans-fused dimethylcyclopropane ring and has one *E* and one *Z* double bond. Bicyclogermacrene was first isolated in 1969[7] from the peel oil of the shrub *Citrus junos* and has since been identified as a constituent in a number of other plants. It has been suggested that bicyclogermacrene is a biogenetic precursor of a number of other sesquiterpenes containing a fused dimethylcyclopropane ring, such as maaliane, aristolane, and aromadendrane derivatives.

Lepidozene has not yet been found in nature but has been prepared[8] by degradation of lepidozenal, a sesquiterpene aldehyde present in the liverwort *Lepidozea vitrea*. This aldehyde was found to possess growth-inhibitory activity in the leaves and roots of rice seedlings and to function as an allomone in ecological systems.[9]

Bicyclogermacrene and lepidozene each have two potential 1,10-dicarbonyl precursors, depending on which double bond is formed in the final coupling step. If the choices are examined, however, it becomes clear that the most efficient option is to form the double bond nearest the cyclopropane ring by carbonyl coupling of **5**, because the starting material for such a path bears a strong resemblance to the commercially available geranylacetone (4). Furthermore, it should be simplest from a synthesis point of view to prepare **5c** and **5t** together and then separate the mixture. Cyclization of the cis isomer will lead to bicyclogermacrene, and cyclization of the trans isomer will lead to lepidozene.



Our initial thought for the preparation of **5** was to explore the potential cyclopropanation reaction of geranylacetone with ethyl diazoacetate to see if selectivity could be found for reaction at the terminal double bond. It is known, for example, that allylic C–H bond insertion[10] by Pd(II) shows selectivity for the desired double bond of geranylacetone and that cycloaddition of dichloroketene to ethyl geranyl-acetate shows selestivity for the analogous bond.[5] Although the desired reaction to yield **6** did indeed take place when geranylacetone was treated with ethyl diazoacetate, both in the presence of cupric sulfate and on photolysis (Hanovia high-pressure mercury lamp), low product yields were obtained and the route was therefore abandoned.



(1) (a) McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655. (b) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405.
(2) McMurry, J. E.; Matz, J. R.; Kees, K. L.; Bock, P. A. *Tetrahedron Lett.* **1982**, *23*, 1777.
(3) McMurry, J. E.; Matz, J. R. *Tetrahedron Lett.* **1982**, *23*, 2723.
(4) McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1985**, *26*, 2171.
(5) McMurry, J. E.; Miller, D. D. *Tetrahedron Lett.* **1983**, *24*, 1885.
(6) Preliminary reports on the syntheses of bicyclogermacrene and lepidozene have appeared: McMurry, J. E.; Bosch, G. K. *Tetrahedron Lett.* **1985**, *26*, 2167.
(7) Nishimura, K.; Shinoda, N.; Hirose, Y. *Tetrahedron Lett.* **1969**, 3097.
(8) Matsuo, A.; Kubota, N.; Nakayama, M.; Hayashi, S. *Chem. Lett.* **1981**, 1097.
(9) Whittacker, R.; Feeny, P. *Science (Washington, D.C.)* **1971**, *171*, 757.
(10) (a) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572. (b) McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1984**, *25*, 4187.

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Recalling our previous success in selectively adding dichloroketene to the terminal double bond of ethyl geranylacetate,[5] we next explored the analogous reaction with geranylacetone. If the cycloaddition were successful, it should be possible to convert the product dichlorocyclobutanone into the desired cyclopropanecarbaldehyde by Favorskii reaction.

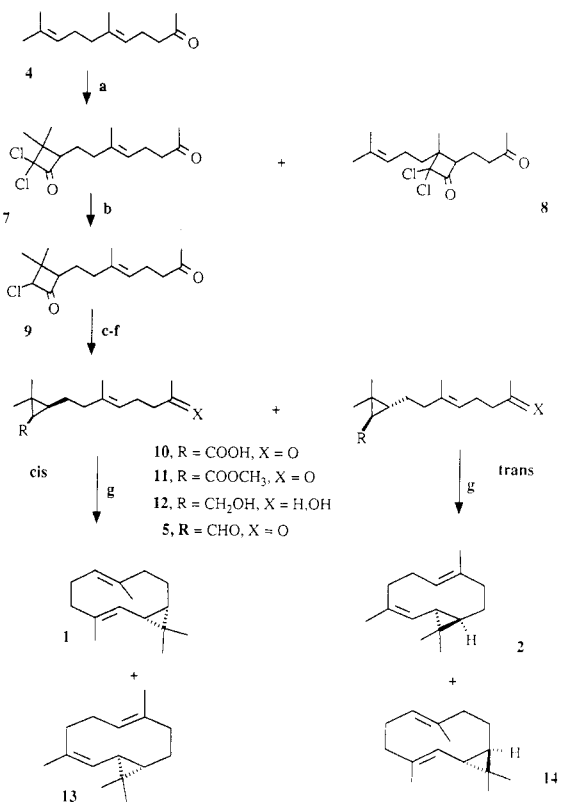
Reaction of geranylacetone with dichloroketene (generated from trichloroacetyl chloride and zinc–copper couple in the presence of phosphoryl chloride[11]) provided a 3:1 mixture of the desired terminal dichlorocyclobutanone **7** and its isomer **8** in 60% yield. Although these isomers proved difficult to separate, preparative HPLC (Waters Prep 500) with peak-shaving and recycling was successful. Alternatively, it also proved possible to carry the mixture through the synthesis and remove the unwanted byproduct at a later stage in the route.

Dichlorocyclobutanone **7** was reduced selectively to the monochlorocyclobutanone **9** by treatment with 1 equiv of zinc dust in glacial acetic acid to give a 2:1 mixture of the two stereoisomers in high yield. For characterization purposes, these isomers were separated by HPLC, but both were useful for the synthesis. Quasi-Favorskii rearrangement[12] of this mixture by treatment with aqueous sodium hydroxide gave a mixture of cis and trans cyclopropanecarboxylic acid isomers **10c/t**, which were esterified by treatment with iodomethane and potassium carbonate in refluxing acetone. The individual stereoisomers of the chlorocyclobutanone were also subjected to the same conditions to see if they could be stereoselectively converted into the corresponding cyclopropanecarboxylic acids, but rearrangement of either isomer resulted in the formation of the same mixture of isomeric acids.

Chromatographic separation of the cis and trans keto esters **11c/t** followed by reduction of each with lithium aluminum hydride provided the corresponding diols **12c/t**, and oxidation of the diols with pyridinium chlorochromate[13] in dichloromethane then gave the respective keto aldehydes **5c/t**. This oxidation was carried out initially in the absence of molecular sieves, in which case the reaction generally took in excess of 3 h to go to completion, and workup was generally unpleasant. In the presence of molecular sieves,[14] however, the oxidation was complete in less than 10 min, and workup was considerably facilitated. Structural assignments were made by analysis of the ^{1}H NMR coupling constants of the ring-fusion cyclopropane protons in **11c** and **11t**. As expected,[15] the coupling in the cis isomer **11c** (J = 8.8 Hz) is larger than that in the trans isomer **11t** (J = 5.5 Hz).

The synthesis was completed by the slow addition of each individual keto aldehyde to a refluxing slurry of low-valent titanium, generated from titanium trichloride and zinc–copper couple in dimethoxyethane. Cyclization of the cis keto aldehyde **5c** gave bicyclogermacrene (**1**) and isobicyclogermacrene (**13**) in 60% yield as a 3:1 mixture, along with a small amount of lepidozene. The lepidozene probably results from epimerization of the starting cis keto aldehyde by Lewis acidic zinc chloride at a rate competitive with its cyclization. Both (±)-bicyclogermacrene and (±)-isobicyclogermacrene were identified by comparison of their IR and NMR spectra with those of authentic samples.[16]

Scheme I[a]



[a] (a) Cl_3COCl, $POCl_3$, Zn–Cu, ether, 65%; (b) Zn, CH_3COOH, H_2O, 98%; (c) KOH, H_2O, room temp, 92%; (d) CH_3I, K_2CO_3, acetone, 85%; (e) $LiAlH_4$, ether, 98%; (f) pyridinium chlorochromate; NaOAc, mol sieves, CH_2Cl_2, 76%; (g) $TiCl_3$, Zn–Cu, dimethoxyethane, reflux, 30-h addition, 60% (**5c**) and 78% (**5t**).

A similar cyclization of the trans keto aldehyde **5t** gave a readily separable 2:3 mixture of lepidozene (**2**) and isolepidozene (**14**) in 78% yield. (±)-Lepidozene was identified by comparison of its IR and NMR spectra with those of an authentic sample,[17] while the previously unknown (±)-isolepidozene was characterized spectroscopically (see Experimental Section). The successful synthetic work is summarized in Scheme I.

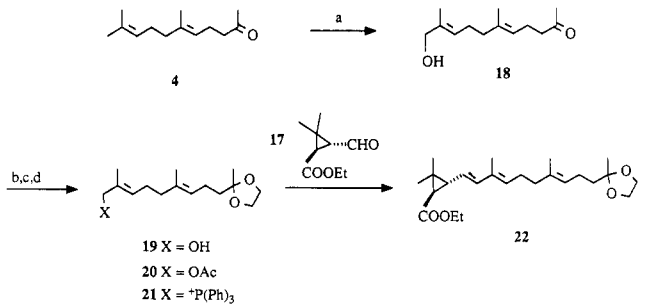
Attempted Syntheses of Casbene

Casbene (**3**), a diterpene hydrocarbon first isolated from seedlings of the caster bean *Ricinus cummunis* by Robinson and West in 1970,[18] is structurally analogous to bicyclogermacrene, except that it contains an additional isoprene unit. The compound has biological activity as an antifungal agent and phytoalexin, and its production can be enhanced by employment of fungal elicitors.[19]

Three syntheses of casbene have been reported. The first, carried out by Crombie in 1980,[20] used a nickel-induced cyclization of a bis-allylic dibromide as the key step. The second, developed by Toma,[21] used an intramolecular carbenoid insertion reaction to form the 14-membered ring. The third, reported by Malamas in an unpublished Ph.D.

(11) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879.
(12) Bak, D. A.; Brady, W. T. *J. Org. Chem.* **1979**, *44*, 107.
(13) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(14) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561.
(15) Bramwell, A. F.; Crombie, L.; Hemesley, P.; Pattenden, G.; Elliot, M.; Janes, N. F. *Tetrahedron* **1969**, *25*, 1727.
(16) We thank Dr. K. Nishimura, Suntory Limited,for providing copies of the IR spectra of (+)-bicyclogermacrene and (+)-isobicyclogermacrene.
(17) We thank Dr. A. Matsuo, Hiroshima University, for providing copies of the IR and ^{1}H NMR spectra of (−)-lepidozene.
(18) Robinson, D.; West, C. *Biochemistry* **1970**, *9*, 70.
(19) Sitton, D.; West, C. *Phytochemistry* **1975**, *14*, 1921.
(20) Crombie, L.; Kneen, G.; Pattenden, G.; Whybrow, D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1711.
(21) Toma, K.; Miyazaki, E.; Murae, T.; Takahashi, T. *Chem. Lett.* **1982**, 863.

Scheme II[a]



[a] (a) (ref 23) Benzoquinone, $Pd(CF_3COO)_2$, *o*-methoxyacetophenone, CH_3COOH, then KOH; (b) $HOCH_2CH_2OH$, $(COOH)_2$, PhH; (c) (ref 24) Ac_2O, pyridine; (d) Ph_3P, LiBr, $(Ph_3P)_4Pd$.

thesis,[22] used an intramolecular Horner–Emmons reaction.

The most straightforward carbonyl-coupling route for a synthesis of casbene would be by a direct adaptation of the procedure used in the bicyclogermacrene/lepidozene work. In other words, addition of dichloroketene to farnesylacetone (**15**), followed by Favorskii rearrangement, should yield keto aldehyde **16**, which might then be converted into casbene by titanium-induced cyclization.

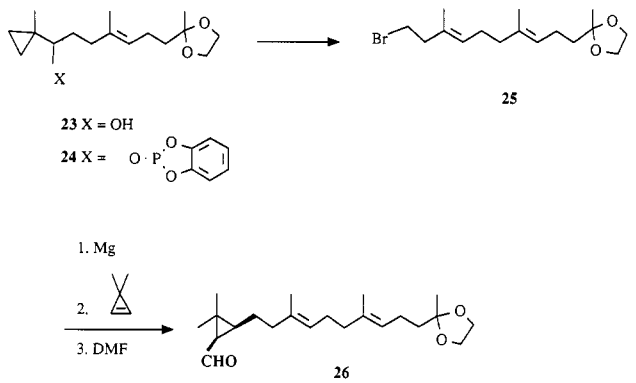
Unfortunately, when the cycloaddition reaction of dichloroketene with **15** was attempted under the conditions used in the bicyclogermacrene/lepidozene work, a nearly inseparable mixture of the three possible double-bond adducts was formed. Thus, another route to keto aldehyde **16** was sought.

A second possibility that occurred to us is the short route shown in Sheme II. Starting again from farnesylacetone (**15**), terminal oxidation, followed by a Wittig reaction with aldehyde **17** obtained by oxidation of ethyl chrysanthemate, should give triene **22**. Selective reduction at the disubstituted double bond would then yield **16**. The advantages of this route are that it should provide access to a single ring-fusion isomer, depending on the starting material, and that the synthesis could be a chiral one. Although triene **22** could in fact be obtained without incident, we were unfortunately forced to abandon the route when we were unable to carry out the selective reduction step.

A further possibility for preparing **16**, shown in Scheme III, was suggested by the observation of Lehmkuhl[25] that Grignard reagents add to cyclopropenes to form cyclopropyl Grignard reagents, which can in turn react with electrophiles to yield cis-disubstituted cyclopropanes. Thus, we thought that reaction of the Grignard reagent prepared from homoallylic bromide **25** with 3,3-dimethylcyclopropene, followed by quenching with dimethylformamide, might provide the desired aldehyde **16** as its ethylene acetal **26**.

Although the necessary homoallylic bromide **25** could be prepared smoothly by treatment[26] of **24** with anhydrous zinc bromide in ether solution,[27] all attempts to convert either the homoallylic bromide or its related iodide to the

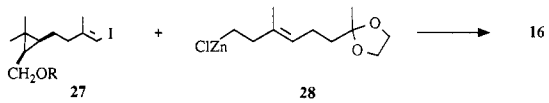
Scheme III



corresponding Grignard reagent failed. Treatment of **25** with magnesium turnings in tetrahydrofuran using a variety of initiators, treatment with Rieke magnesium, and treatment with lithium metal all gave the dimer resulting from Wurtz coupling as the predominant product. This reluctance of homoallylic halides to form stable Grignard reagents was also observed later during our successful synthesis of casbene.

A Successful Synthesis of Casbene

Our final, and ultimately successful, attempt at preparing casbene precursor **16** made use of Negishi's method[28] for carrying out the palladium-catalyzed coupling of a vinylic iodide with a homoallylzinc reagent. In essence, we planned to construct vinylic iodide **27** by carbo-



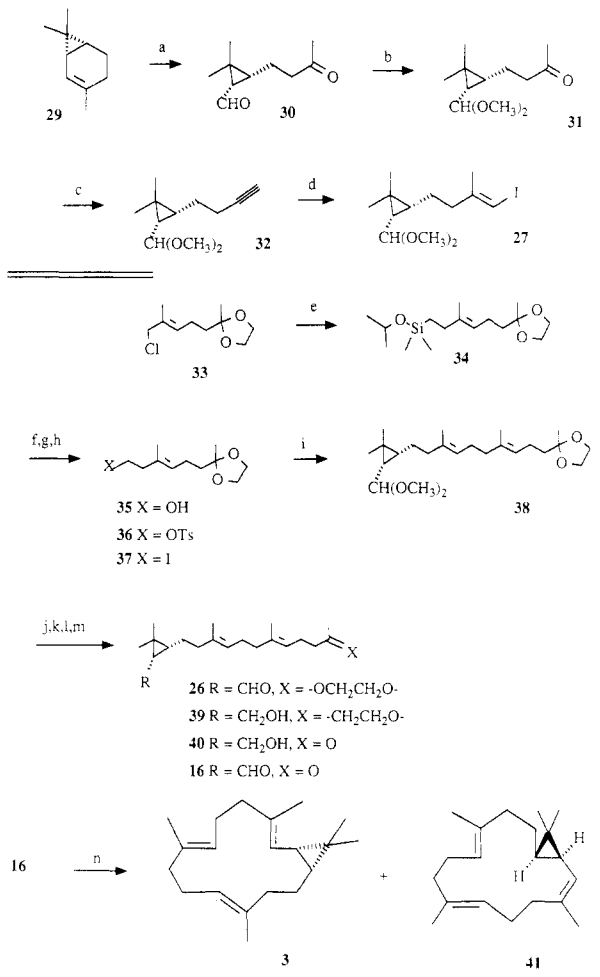
cupration of the corresponding terminal alkyne and then couple with the approriate homoallylic organometallic reagent **28**. Though longer than the other routes we had tried, this method has the advantage of leading to a chiral product if the proper starting material is chosen.

As detailed in Scheme IV, the necessary vinylic iodide **27** was easily prepared from (+)-2-carene (**29**). Ozonolysis followed by reduction with dimethyl sulfide gave cis keto aldehyde **30**, which was selectively protected by reaction with trimethyl orthoformate and lanthanum chloride in methanol[29] to give the keto acetal **31**. This protected keto acetal **31** was then converted to the corresponding terminal alkyne **32** by using conditions devised by Negishi.[30] Thus, the kinetic enolate of **31**, generated by treatment with lithium 2,2,6,6-tetramethylpiperidide, was converted to the terminal enol phosphate by reaction with diethyl chlorophosphate. Without isolation of the intermediate, selective elimination was induced by treatment with a further 2 equiv of lithium tetramethylpiperidide to form the terminal alkyne **32** in 56% yield. The possible allenic byproduct was not observed.

A number of experiments were carried out to find the best conditions for the conversion[31] of alkyne **32** to the corresponding vinylic iodide **27**. The major source of variation in the success of this carbometalation was the source and purity of the cuprous halide used. When freshly prepared cuprous bromide was used, 50% or more

(22) Malamas, M. *Diss. Abstr. Int., B* **1985**, *45*, 2161.
(23) McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1984**, *25*, 4187.
(24) Tsukahara, Y.; Kinoshita, H.; Inomata, K.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3013.
(25) Lehmkuhl, H.; Muller, K. *Liebigs Ann. Chem.* **1978**, 1841.
(26) Corey, E. J.; Anderson, J. E. *J. Org. Chem.* **1967**, *32*, 4160.
(27) Johnson, W. S.; Li, T.; Faulkner, D. J.; Campbell, S. F. *J. Am. Chem. Soc.* **1968**, *90*, 6225.
(28) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298.
(29) Luche, J. L.; Gemal, A. L. *J. Chem. Soc.* **1978**, 976.
(30) Negishi, E.; King, A. O.; Klima, W. L. *J. Org. Chem.* **1980**, *45*, 2526.
(31) Westmijze, H.; Meijer, J.; Bos, J. J. T.; Vermeer, P. *Recl. J. R. Natl. Chem. Soc.* **1976**, *95*, 304.

Scheme IV[a]



[a] (a) O_3, then $(CH_3)_2S$, 99%; (b) $(CH_3)_3CH$, $LaCl_3$, CH_3OH, 87%; (c) LiTMP, then $ClPO(OEt)_2$, then LiTMP, 56%; (d) $(CH_3)_3Cu_2MgCl\cdot 6LiBr$, then ICN, 60%; (e) $(i\text{-PrO})(CH_3)_2SiCH_2MgCl$, CuI, 90%; (f) H_2O_2, Na_2CO_3, CH_3OH, 75%; (g) TsCl, pyridine, 66%; (h) NaI, acetone, 90%; (i) Mg, $ZnCl_2$, THF, then $(Ph_3)_4Pd$, 70%; (j) H_3O^+; (k) $NaBH_4$, CH_3OH, 83%; (l) H_2O, CH_3COOH, 91%; (m) pyridinium chlorochromate mol sieves, CH_2Cl_2, 83%; (n) $TiCl_3$/Zn–Cu, dimethoxyethane; 75%.

of dimeric product was formed at the expense of the desired vinylic iodide. Use of either freshly prepared or high-quality commercial cuprous iodide improved the reaction to some extent, although significant amounts (10–20%) of dimeric products were generally obtained. The best results were achieved by using a commercial cuprous bromide/dimethyl sulfide complex that had been recrystallized from dimethyl sulfide/hexane.[32] Under optimum conditions, none of the dimeric product was observed and vinylic iodide **27** was obtained in 60% yield.

The next step was to prepare the homoallylic organozinc compound necessary for the coupling reaction with vinylic iodide **27**. Initial attempts to prepare this compound involved treatment of allylic chloride **33** with nucleophiles, followed by conversion to the homoallylic alcohol. We found, for example, that **33** could be alkylated with the anion of 1,3-dithiane, but attempts at hydrolysis to the corresponding aldehyde under various conditions were unsuccessful. Similarly, **33** could be converted into the corresponding nitrile by reaction with KCN, but hydrolysis to yield the carboxylic acid could not be effected.

The successful route involved the use of (chloromethyl)isopropoxydimethylsilane as a nucleophilic hydroxymethyl anion equivalent. The Grignard reagent of this compound had previously been reported to be an efficient hydroxymethyl anion equivalent for converting ketones and aldehydes to the corresponding glycols.[33] In the present instance, allylic chloride **33** was treated with [(isopropoxydimethylsilyl)methyl]magnesium chloride in the presence of CuI catalyst to give **34**, which was converted to the homoallylic alcohol **35** by treatment with hydrogen peroxide in refluxing tetrahydrofuran/methanol buffered with potassium carbonate.[34] Alcohol **35** was then converted into the corresponding homoallylic iodide **37** by treatment with *p*-toluenesulfonyl chloride in pyridine, followed by reaction with sodium iodide in acetone.

Conversion of iodide **37** into an organozinc reagent was a matter of some concern at this point, given our previous experience in trying to convert a homoallylic bromide to the corresponding Grignard reagent. Indeed, when the conversion was attempted by sonication of a tetrahydrofuran solution of **37** with magnesium turnings, rapid reaction was observed, leading to the Wurtz-coupled dimer as the major product. Fortunately, however, when the reaction was carried out in the presence of slightly more than 1 molar equiv of dry zinc chloride, dimerization was almost completely suppressed, although the reaction was considerably more sluggish.

The coupling of an organometallic reagent derived from iodide **37** with vinylic iodide **27** was accomplished by using conditions described by Negishi.[35] Reaction of **37** with Mg in the presence of dry $ZnCl_2$, followed first by addition of tetrakis(triphenylphosphine)palladium and then by addition of iodide **27**, resulted in the formation of a 70% yield of the coupled product **38**. When simultaneous removal of both protecting groups was attempted under a variety of conditions, however, only a low yield of keto aldehyde **16** was obtained. Evidently the cyclopropanecarboxaldehyde grouping in **16** is unstable to the acidic conditions necessary for hydrolysis of the ethylene acetal.

Further experimentation showed that the dimethyl acetal protecting group could be removed cleanly by treatment of **38** with dilute hydrochloric acid in aqueous tetrahydrofuran for short periods of time. Without isolation, the aldehyde acetal **26** was reduced to the corresponding alcohol **39** by treatment with sodium borohydride, and the ethylene acetal was cleaved by treatment with aqueous acetic acid to give keto alcohol **40**. Keto alcohol **40** was then oxidized with pyridinium chlorochromate in the presence of powdered molecular sieves to give pure keto aldehyde **16**.

Completion of the synthesis was accomplished by slow addition of **16** to a refluxing slurry of $TiCl_3$/Zn–Cu to give a 75% yield of cyclized products consisting of (+)-4-(*E*),8(*E*),12(*E*)-casbene (**3**) and its 12*Z* isomer **41** in a ratio of approximately 2:1, along with minor amounts of trans-fused isomers. (+)-Casbene was identified by comparison of its ^1H NMR spectrum with that of natural casbene, and by comparison of its ^1H and ^{13}C NMR spectra with those published by Toma[21] in his total synthesis. As far as we are aware, the absolute configuration and optical

(32) The relative merits of cuprous bromide, cuprous iodide, and cuprous bromide–dimethyl sulfide complex as sources of cuprous ion in the reactions of lithium dimethylcuprate have recently been discussed. The authors found cuprous iodide to be the best reagent, followed closely by recrystallized cuprous bromide–dimethyl sulfide complex: (a) Lipshutz, B. H.; Whitney, S.; Kozlowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1986**, *27*, 4273. (b) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197.

(33) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4245.

(34) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249.

(35) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298.

rotation of natural casbene are not known, though our synthetic material may well be enantiomeric with the natural product in light of Crombie's arguments,[20] based on the known absolute configurations of related diterpenes, that casbene should be of 1*S*,3*R* configuration.

Concluding Remarks

We have accomplished the total synthesis of three natural products, two of them for the first time and the third in chiral form. Most important, however, we have demonstrated several simple methods for the preparation of isoprenoid α,Ω-dicarbonyl compounds and have shown for the first time how the titanium-induced carbonyl coupling reaction can be used in the synthesis of germacranoid and cembranoid terpenes. We are continuing our work with the goal of preparing more complex molecules.

Experimental Section

General Methods. All reactions were carried out under argon in glassware that had been dried at 120 °C or that had been evacuated and flame-dried prior to refilling with argon. The phrase "worked up in the usual manner" refers to extraction of the crude product with ether or dichloromethane, washing the organic layers with water and with saturated brine, drying over anhydrous sodium sulfate, filtration, and concentration by solvent removal at the rotary evaporator. The purity of all intermediates was established to be >95% by ^{13}C NMR and/or capillary GC unless stated otherwise.

2,2-Dichloro-3,3-dimethyl-4-(3-methyl-7-oxo-3(*E*)-octenyl)cyclobutanone (7). A solution of trichloroacetyl chloride (14.19 g, 78 mmol) and phosphoryl chloride (12.0 g, 78.3 mmol) in ether (60 mL) was added to a mixture of geranylacetone (10.00 g, 51.4 mmol) and zinc–copper couple (5.37 g, 82.1 mmol) in ether (100 mL) over a period of 4.5 h. After being stirred at room temperature for an additional 8 h, the mixture was filtered through a pad of Celite on a sintered glass funnel. The filtrate was diluted with pentane and stirred for 15 min, resulting in the separation of a yellow gum. The pentane layer was decanted and the gum was dissolved in acetone (75 mL). This solution was diluted with water (200 mL) and was extracted with pentane (3 × 100 mL). The combined pentane extracts were washed with water (2 × 250 mL), saturated sodium bicarbonate solution (4 × 100 mL), and brine and then concentrated to give 15.8181 g of crude product. Chromatography on silica gel (20% ether–hexane) yielded 10.2148 g (65%) of a 3:1 mixture of the regioisomeric dichlorocyclobutanones **7** and **8**. This mixture was normally used without further purification since the byproducts could be removed later in the synthesis. If desired, however, it could be purified by HPLC on a Waters Prep 500 chromatograph using two silica gel cartridges (8% ethyl acetate in hexane) to give nearly pure **7**: IR (film) 2975, 2940, 1805, 1720, 1445, 1360, 1160, 860, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.10 (t, J = 6 Hz, 1 H), 3.33 (t, J = 10 Hz, 1 H), 2.46 (t, J = 7.8 Hz, 2 H), 2.25 (m, 2 H), 2.12 (s, 3 H), 2.03 (m, 2 H), 1.75 (m, 2 H), 1.59 (s, 3 H), 1.48 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 207.74, 196.01, 134.21, 123.96, 91.50, 62.64, 44.58, 43.03, 37.08, 29.51, 23.96, 22.53, 22.00, 20.75, 15.33.

2-Chloro-3,3-dimethyl-4-(3-methyl-7-oxo-3(*E*)-octenyl)cyclobutanone (9). Zinc dust (0.148 g, 2.25 mmol) was added to a solution of **7** (0.6878 g, 2.253 mmol) in 90% acetic acid (10 mL) at 0 °C. The resulting grey suspension was stirred at 0 °C for 30 min and then at room temperature for 4 h until most of the zinc had dissolved. The mixture was diluted with ether (15 mL) and was washed with water (3 × 30 mL), saturated sodium bicarbonate (30 mL), and brine. The organic layer was dried (Na_2SO_4) and concentrated to give 0.5977 g (98.3%) of **9** as a mixture of diastereomers that could be separated by HPLC (silica gel, 10% ethyl acetate–hexane). **9c**: IR (film) 2980, 2920, 2870, 1780, 1710, 1445, 1355, 1160, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.06 (t, J = 9 Hz, 1 H), 4.7 (d, J = 3.1 Hz, 1), 2.85 (dt, J = 7.7, 3.1 Hz, 1 H), 2.45 (t, J = 8 Hz, 2 H), 2.25 (m, 2 H), 2.12 (s, 3 H), 2.02 (m, 2 H), 1.7 (m, 2 H), 1.59 (s, 3 H), 1.45 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 2.49 MHz) δ 207.57, 200.41, 134.33, 123.48, 68.36, 61.69, 42.86, 36.96, 35.35, 29.21, 27.36, 21.88, 17.65, 15.15. **9t**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.08 (t, J = 9 Hz, 1 H), 4.55 (d, J = 2.9 Hz, 1 H), 2.79 (td, J = 8.4, 2.4 Hz, 1 H), 2.44 (t, J = 7.5 Hz, 2 H), 2.24 (m, 2 H), 2.01 (m, 2 H), 1.70 (m, 2 H), 1.57 (s, 3 H), 1.28 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 208.40, 204.05, 134.69, 123.96, 69.91, 64.78, 43.39, 37.43, 35.88, 29.86, 24.91, 24.68, 22.24, 21.76, 15.74.

***cis*- and *trans*-2,2-Dimethyl-3-(3-methyl-7-oxo-3(*E*)-octenyl)cyclopropanecarboxylic Acids (10c/t).** Chlorocyclobutanone **9** was treated at room temperature for 16 h with aqueous potassium hydroxide solution (50 mL, 0.57 N) to give a homogeneous solution. The solution was then extracted with dichloromethane (2 × 30 mL) to remove neutral byproducts, and the aqueous layer was acidified to pH 0 with dilute hydrochloric acid. Workup in the usual manner gave 1.4366 g (92.3%) of a mixture of **10c** and **10t** that was used without further purification: IR (film) 2800–3600, 1710, 1680, 1440, 1360, 1220, 1160, 1110, 950 cm^{-1}.

Methyl *cis*- and *trans*-2,2-Dimethyl-3-(3-methyl-7-oxo-3-(*E*)-octenyl)cyclopropanecarboxylate (11c/t). A refluxing solution of **10** (1.3343 g, 5.288 mmol) in acetone (35 mL) containing potassium carbonate (1.29 g, 9.3 mmol) was treated during 2 h with methyl iodide (2 mL, 32 mmol). The solvent was removed on the rotary evaporator, and the residue was partitioned between water (30 mL) and ether (30 mL), followed by workup in the usual manner to give a pale yellow oil. Chromatography on silica gel (50% ether–pentane) gave 1.1964 g (84.9%) of a 65:45 mixture of **11t** and **11c** as a colorless oil. The isomers were separated by preparative HPLC (silica gel, 25% ether–hexanes). **11t**: IR (film) 2930, 2915, 1725, 1440, 1180, 1160, 1195, 1180, 1160, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.06 (t, J = 8 Hz, 1 H), 3.65 (s, 3 H), 2.43 (t, J = 7.4 Hz, 2 H), 2.23 (m, 2 H), 2.11 (s, 3 H), 2.00 (t, J = 7.5 Hz, 2 H), 1.58 (s, 3 H), 1.44 (m, 2 H), 1.25 (m, 1 H), 1.17 (s, 3 H), 1.13 (d, J = 5.5 Hz, 1 H), 1.11 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 207.33, 172.41, 134.80, 122.83, 50.54, 42.92, 38.80, 32.84, 32.07, 29.21, 26.88, 26.23, 21.82, 20.63, 20.27, 15.27. **11c**: IR (film) 2930, 2915, 1725, 1440, 1175, 1165, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.06 (t, J = 8 Hz, 1 H), 3.62 (s, 3 H), 2.43 (t, J = 7.6 Hz, 2 H), 2.23 (m, 2 H), 2.11 (s, 3 H), 1.93 (t, J = 7.5 Hz, 2 H), 1.70 (m, 2 H), 1.39 (d, J = 8.8 Hz, 1 H), 1.19 (s, 3 H), 1.11 (s, 3 H), 1.03 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 208.04, 171.81, 135.70, 122.59, 50.54, 43.33, 39.28, 33.20, 29.51, 28.67, 28.08, 25.16, 22.12, 21.46, 15.56, 13.96.

***cis*-8-(2-(Hydroxymethyl)-3,3-dimethylcyclopropyl)-5-methyl-5(*E*)-octen-2-ol (12c).** Lithium aluminum hydride (0.070 g, 1.84 mmol) was added to a solution of cis keto ester **11c** (0.3020 g, 1.134 mmol) in ether (20 mL). After stirring at room temperature for 20 min, the reaction was quenched by addition of 0.1 mL of H_2O, 0.1 mL of 0.1 N NaOH, and 0.3 mL of H_2O. The resulting suspension was filtered through a pad of Celite, dried ($Na_2S_2O_4$), and concentrated to give 0.2688 g (98.6%) of the diol **12c** as a colorless oil: IR (film) 3340, 2915, 1505, 1375, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.14 (t, J = 7.0 Hz, 1 H), 3.79 (m, 1 H), 3.63 (m, 2 H), 1.95–2.10 (m, 4 H), 1.60 (s, 3 H), 1.35–1.55 (m, 4 H), 1.17 (d, J = 6.2 Hz, 3 H), 1.05 (s, 3 H), 1.00 (s, 3 H), 0.80 (m, 1 H), 0.57 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 135.34, 124.08, 67.47, 59.72, 40.17, 38.98, 29.09, 28.37, 26.94, 24.20, 23.19, 22.95, 17.77, 15.86, 14.61.

***cis*-2,2-Dimethyl-3-(3-methyl-7-oxo-3(*E*)-octenyl)cyclopropanecarbaldehyde (5c).** Diol **12c** (0.2688 g, 1.118 mmol) in dichloromethane (5 mL) was added to a well-stirred suspension of pyridinium chlorochromate (0.7930 g, 3.679 mmol), sodium acetate (81.1 mg, 0.99 mmol), and powdered molecular sieves (3 Å, 0.50 g) in dichloromethane (15 mL). After being stirred at room temperature for 45 min, the mixture was diluted with ether (20 mL), stirred an additional 15 min, and filtered through a pad of Florisil. Concentration afforded a pale yellow oil that was chromatographed (Florisil, 50% ether–hexane) to yield 0.2003 g (75.8%) of the cis keto aldehyde **5c** as a colorless oil: IR (film) 2920, 2720, 1720, 1700, 1420, 1380, 1360, 1160, 1120, 1060, 990 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.45 (d, J = 8 Hz, 1 H), 5.08 (t, J = 7.5 Hz, 1 H), 2.44 (t, J = 7.8 Hz, 2 H), 2.24 (m, 2 H), 2.12 (s, 3 H), 1.99 (m, 2 H), 1.80 (m, 2 H), 1.60 (s, 3 H), 1.31 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 208.62, 202.05, 135.46, 123.37, 43.64, 39.74, 38.83, 37.46, 29.92, 29.80, 29.08, 22.83, 22.37, 16.00, 15.22.

(±)-Bicyclogermacrene and (±)-Isobicyclogermacrene (1 and 13). A mixture of titanium trichloride (3.81 g, 24.7 mmol)

and zinc–copper couple[36] (5.40 g, 83.9 mmol) in dimethoxyethane (100 mL) was refluxed for 7 h, and cis keto aldehyde **5c** (0.2515 g, 1.064 mmol) in dimethoxyethane (100 mL) was added to the resulting black slurry over a period of 42 h via syringe pump. After being refluxed for an additional 2 h, the reaction mixture was cooled, diluted with pentane (200 mL), and filtered through Florisil. The solvents were removed by atmospheric pressure distillation and brief exposure of the residue to vacuum at 0 °C to give a yellow oil. Chromatography (Florisil, pentane) yielded 0.1385 g of a colorless oil consisting of 71% (45% yield) bicyclogermacrene (**1**) and 22% (14% yield) isobicyclogermacrene (**13**), as determined by GC analysis. A small amount of lepidozene was also detected. The products were separated by HPLC (silica gel, hexanes predried by passage through a column of neutral activity I alumina).

Bicyclogermacrene (1): IR ($CHCl_3$) 2920, 2860, 1435, 1375, 1150, 985, 850, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.81 (m, 1 H), 4.33 (d, J = 12 Hz, 1 H), 2.40 (dt, J = 13, 3.4 Hz, 1 H), 2.20 (m, 1 H), 1.68–2.13 (m, 6 H), 1.65 (s, 3 H), 1.46 (s, 3 H), 1.1–1.3 (m, 2 H), 1.07 (s, 3 H), 1.01 (s, 3 H), 0.59 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 140.76, 127.89, 126.46, 124.79, 41.19, 37.25, 30.04, 29.21, 26.94, 26.82, 26.05, 20.86, 19.85, 16.57, 15.44; mass spectrum (electron impact), m/e (relative intensity) 204 (37.9), 121 (100), 93 (72). Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.59; H, 11.65.

Isobicyclogermacrene (13): IR ($CHCl_3$) 2920, 2865, 1440, 1380, 1130, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (isobicyclogermacrene could not be isolated free from some contaminating lepidozene) δ 5.03 (m), 4.96 (d, J = 10 Hz), 1.71 (s, 3 H), 1.40 (s, 3 H), 1.03 (s, 3 H), 0.98 (s, 3 H), 0.40 (m, 1 H).

***trans*-8-(2-(Hydroxymethyl)-3,3-dimethylcyclopropyl)-5-methyl-5(*E*)-octen-2-ol (12t).** Lithium aluminum hydride (0.2050 g, 5.40 mmol) was added to a solution of trans keto ester **11t** (0.8869 g, 3.330 mmol) in ether (75 mL). After stirring at room temperature for 30 min, the reaction was quenched by the addition of about 0.2 mL of H_2O, 0.2 mL of 0.1 N NaOH, and 0.6 mL of H_2O. The resulting suspension was filtered through a pad of Celite, the filtrate was dried ($Na_2S_2O_4$), and the solvent was evaporated to give 0.7995 g (99.9%) of the diol **12t** as a colorless oil: IR (film) 3340, 2965, 2920, 2860, 1450, 1375, 1130, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.14 (t, J = 6.8 Hz, 1 H), 3.78 (m, 1 H), 3.58 (m, 1 H), 2.04 (m, 4 H), 1.60 (s, 3 H), 1.20–1.55 (m, 4 H), 1.17 (d, J = 6.2 Hz, 3 H), 1.06 (s, 3 H), 1.05 (s, 3 H), 0.54 (m, 1 H), 0.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 135.28, 124.08, 67.29, 63.23, 39.94, 38.98, 32.61, 28.97, 27.12, 24.14, 23.13, 21.64, 21.52, 19.61, 15.68.

***trans*-2,2-Dimethyl-3-(3-methyl-7-oxo-3(*E*)-octenyl)-cyclopropanecarbaldehyde (5t).** Trans-diol **12t** (0.6781 g, 2.821 mmol) in dichloromethane (5 mL) was added to a well-stirred suspension of pyridinium chlorochromate (2.00 g, 9.28 mmol) and sodium acetate (0.20 g, 2.4 mmol) in dichloromethane (45 mL). After being stirred at room temperature for 4 h, the mixture was diluted with ether (50 mL) and stirred an additional 15 min. The suspension was then filtered through a pad of Florisil, and the product was eluted with ether. Concentration afforded 0.5397 g (81%) of the trans keto aldehyde **5t** as a pale yellow oil: IR (film) 2920, 2870, 2730, 1680, 1375, 1360, 1115, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.27 (d, J = 7.6 Hz, 1 H), 5.06 (t, J = 7.5 Hz, 1 H), 2.44 (t, J = 7.8 Hz, 2 H), 2.24 (m, 2 H), 2.12 (s, 3 H), 2.03 (m, 2 H), 1.30–1.50 (m, 4 H), 1.28 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 208.40, 201.37, 135.16, 123.36, 43.39, 43.27, 39.04, 35.29, 30.76, 29.75, 26.47, 22.24, 22.06, 21.22, 15.68.

(±)-Lepidozene and (±)-Isolepidozene (2 and 14). A mixture of titanium trichloride (4.77 g, 30.9 mmol) and zinc–copper couple (4.18 g, 63.9 mmol) in dimethoxyethane (100 mL) was refluxed for 3 h, and a solution of trans keto aldehyde **5c** (0.2371 g, 1.003 mmol) in dimethoxyethane (100 mL) was added to the resulting black suspension over a period of 46 h via syringe pump. After being refluxed for an additional 2.5 h, the reaction mixture was cooled, diluted with pentane (200 mL), and filtered through Florisil. The solvents were removed by atmospheric pressure distillation, and the residue was briefly exposed to vacuum at 0 °C to give a yellow oil. Chromatography (Florisil, pentane) yielded 0.1716 g of a colorless oil consisting of 56% (47% yield) isolepidozene (**2**), and 37% (31% yield) lepidozene (**14**) as determined by GC analysis. The isomers were separated by HPLC (silica gel, hexanes predried by passage through a column of neutral activity I alumina).

Lepidozene (2): IR ($CHCl_3$) 2960, 2910, 2840, 1445, 1375, 1125, 970, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.19 (t, J = 8.2 Hz, 1 H), 5.00 (d, J = 9 Hz, 1 H), 1.6–2.5 (m, 8 H), 1.73 (s, 3 H), 1.61 (s, 3 H), 1.06 (s, 3 H), 0.98 (s, 3 H), 0.70 (m, 1 H), 0.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 133.31, 132.90, 126.84, 125.33, 40.41, 33.98, 31.95, 31.12, 26.05, 24.80, 24.08, 22.35, 21.82, 18.96, 15.44; mass spectrum (electron impact, 70 eV), m/e (relative intensity) 204 (27.7), 121 (98.4), 93 (71.3). Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.12; H, 11.42.

Isolepidozene (14): IR ($CHCl_3$) 2960, 2910, 2850, 1640, 1440, 1375, 850, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.82 (d, J = 14 Hz, 1 H), 4.56 (d, J = 11.7 Hz, 1 H), 1.80–2.55 (m, 8 H), 1.61 (s, 3 H), 1.50 (s, 3 H), 1.12 (s, 3 H), 1.05 (s, 3 H), 0.78 (m, 1 H), −0.10 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 134.92, 132.06, 131.94, 127.18, 42.26, 41.13, 40.41, 36.24, 39.33, 24.92, 24.26, 23.01, 21.88, 17.29, 16.34; mass spectrum (electron impact, 70 eV), m/e (relative intensity) 204 (55.8), 121 (99.9), 119 (100), 93 (86). Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.51; H, 11.61.

(+)-*cis*-2,2-Dimethyl-3-(3-oxobutyl)cyclopropanecarbaldehyde (30). A solution of (+)-2-carene (**29**) (4.31 g, 31.6 mmol) in methanol (10 mL) and dichloromethane (25 mL) was treated at −78 °C with a stream of ozone for 32 min, and the solution was purged with argon for 5 min. Dimethyl sulfide (35 mL) was then added, and the mixture was allowed to warm gradually to room temperature. After 3 h, the mixture was diluted with ether (100 mL) and washed with dilute ice-cold sodium bicarbonate solution (100 mL), water, and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated to give keto aldehyde **30** (5.27 g, 99%) as a colorless oil: IR (film) 2950, 2920, 2870, 2730, 1710, 1690, 1410, 1370, 1165, 1120, 980, 755 cm^{-1}; ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 207.57, 201.25, 43.09, 38.09, 36.66, 29.80, 29.63, 28.67, 18.30, 14.61; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.53 (d, J = 5.7 Hz, 1 H), 2.46 (t, J = 7.3 Hz, 2 H), 2.13 (s, 3 H), 2.00 (m, 2 H), 1.61 (dd, J = 7.3 Hz, 10.6 Hz, 1 H), 1.37 (m, 1 H), 1.31 (s, 3 H), 1.17 (s, 3 H); $[\alpha]^{22}_D$ +58.8°.

(+)-*cis*-1-(Dimethoxymethyl)-2,2-dimethyl-3-(3-oxobutyl)cyclopropane (31). Lanthanum chloride hexahydrate (7.865 g, 22.26 mmol) was added to a solution of **30** (5.2704 g, 31.33 mmol) in methanol (50 mL). Trimethyl orthoformate (16 mL) was then added, and the mixture was stirred at room temperature for 70 min. After the colorless solution was poured into an ice cold solution of 24 g sodium bicarbonate in 300 mL of water, workup in the usual manner gave a pale yellow oil. Chromatography (silica gel, 25% hexane–ethyl acetate) yielded keto acetal **31** (6.2031 g, 87%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.15 (d, J = 8.2 Hz), 3.32 (s, 3 H), 3.30 (s, 3 H), 2.51 (m, 2 H), 2.13 (s, 3 H), 1.60 (m, 2 H), 1.06 (s, 3 H), 1.04 (s, 3 H), 0.86 (t, J = 9.2 Hz, 1 H), 0.63 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 208.28, 101.68, 51.97, 51.43, 43.39, 29.69, 28.61, 27.30, 26.17, 19.14, 17.83, 14.97; $[\alpha]^{22}_D$ +4.0°; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 123 (74), 183 (100), 213 (1), 215 (1).

(+)-*cis*-1-(3-Butynyl)-2-(dimethoxymethyl)-3,3-dimethylcyclopropane (32). Lithium tetramethylpiperidide (LiTMP) was prepared by treating a solution of tetramethylpiperidine (2.50 mL, 14.8 mmol) in tetrahydrofuran (27 mL) at 0 °C with *n*-butyllithium (9.70 mL, 1.50 M in hexane) with stirring for 1 h to complete formation of the salt. The resulting pale yellow solution was cooled to −78 °C, and keto acetal **31** (2.9775 g, 13.89 mmol) in tetrahydrofuran (9 mL) was added over 1 h. After stirring for 1 h, diethyl chlorophosphate (2.24 mL, 17.1 mmol) was added. The mixture was stirred at −78 °C for 30 min and then was allowed to warm to room temperature for 1 h. The resulting yellow solution was added over 1 h to a second batch of LiTMP (32.7 mmol) in tetrahydrofuran (54 mL) at −78 °C and was allowed to warm gradually to room temperature with stirring for 18 h. The resulting black solution was quenched with water (2 mL), the solvent was evaporated, and the residue was dissolved in ether (50 mL). After washing the solution with ice-cold HCl (100 mL, 0.5 N), workup in the usual manner gave a yellow residue that was chromatographed (silica gel, 15% ether–hexane) to give

(36) The zinc/copper couple was prepared as described in McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3264.

alkyne **32** as a colorless oil (1.5241 g, 56%): IR (film) 3300, 2930, 2820, 2110, 1445, 1375, 1155, 1120, 1100, 1050, 955, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.14 (d, J = 8.6 Hz, 1 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 2.25 (m, 2 H), 1.93 (t, J = 2.7 Hz, 1 H), 1.60 (m, 2 H), 1.07 (s, 3 H), 1.04 (s, 3 H), 0.92 (t, J = 9.0 Hz, 1 H), 0.78 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 101.91, 84.39, 68.18, 52.09, 51.79, 28.79, 27.60, 26.29, 24.56, 18.66, 18.24, 15.32; $[\alpha]^{22}_D$ +7.8°; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 165 (100), 195 (2), 197 (2). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.08.

(+)-*cis*-1-(4-Iodo-3-methyl-3(*E*)-butenyl)-2-(dimethoxymethyl)-3,3-dimethylcyclopropane (27). Methylmagnesium chloride (3.48 mL, 2.75 M in tetrahydrofuran, 9.57 mmol) was added to a colorless solution of lithium bromide (1.65 g, 19.0 mmol) and cuprous bromide/dimethyl sulfide complex (1.34 g, 6.52 mmol) in tetrahydrofuran (16 mL) at −10 °C. A greenish yellow precipitate formed in the course of the addition, redissolving near the end to give a cloudy brown solution. After stirring at −10 to 0 °C for 10 min, alkyne **32** (0.6182 g, 3.140 mmol) in tetrahydrofuran (2 mL) was added. The solution gradually became black and was stirred for 44 h at −2 to 0 °C. After cooling to −45 °C, cyanogen iodide (1.60 g, 10.5 mmol) in tetrahydrofuran (4 mL) was added, and the mixture was allowed to warm to room temperature for 2 h. The red-brown mixture was heated with concentrated ammonium hydroxide (3 mL) and saturated ammonium chloride (3 mL), and the suspension was partitioned between dilute sodium thiosulfate solution (100 mL) and pentane. The aqueous layer was extracted with pentane (3 × 30 mL), and the organic layer was washed with dilute ammonium chloride solution (50 mL), water, and brine. The organic layer was then dried (Na_2SO_4) and concentrated to give a yellow oil. Chromatography (silica gel, 10% ether–hexanes) afforded the vinyl iodide **27** (0.6260 g, 59%) as a colorless oil: IR (film) 2930, 2820, 1440, 1375, 1270, 1100, 1055, 955, 910, 770, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.87 (m, 1 H), 4.13 (d, J = 8.6 Hz, 1 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 1.83 (d, J = 0.8 Hz, 3 H), 2.25 (m, 2 H), 1.50 (m, 2 H), 1.05 (s, 3 H), 1.01 (s, 3 H), 0.87 (t, J = 8.8 Hz, 1 H), 0.59 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 147.74, 101.85, 74.68, 52.03, 51.61, 39.70, 28.85, 27.42, 26.47, 23.84, 23.55, 18.06, 15.27; $[\alpha]^{22}_D$ +5.2°; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 75 (100), 337 (1).

7-Chloro-6-methyl-5(*E*)-hepten-2-one Ethylene Acetal (33). The ethylene acetal of 6-methyl-5-hepten-2-one (28.84 g, 169.4 mmol) was added over a period of 30 min to a solution of selenium dioxide (8.85 g, 79.8 mmol) and *tert*-butyl hydroperoxide (36 mL, 90%) in dichloromethane (110 mL) at 0 °C. The mixture was stirred at 0 °C for an additional 4 h, and the pale yellow solution was washed with water (2 × 200 mL), dilute NaOH solution (2 × 100 mL), water, and brine. The organic layer was then dried (Na_2SO_4) and concentrated to give a pale yellow oil that was dissolved in methanol (100 mL), cooled to 0 °C, and treated with sodium borohydride (3.5 g). After stirring at room temperature for 30 min, the solvent was evaporated and the residue was partitioned between ether (100 mL) and water (100 mL). Workup in the usual manner gave an oil that was chromatographed (silica gel, 25% ethyl acetate–hexane) to yield 23.05 g (73%) of the allylic alcohol as a colorless oil: IR (film) 3400, 2970, 2920, 2870, 1445, 1380, 1220, 1135, 1055, 950, 865 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.39 (t, J = 7.5 Hz, 1 H), 3.97 (s, 2 H), 3.92 (m, 4 H), 2.1 (m, 2 H), 1.6 (m, 2 H), 1.65 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 134.48, 124.25, 109.18, 67.49, 63.98, 38.14, 23.12, 21.66, 12.89; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 87 (56), 169 (100), 185 (1.5), 187 (1.2). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.50; H, 9.74. Found: C, 64.36; H, 9.82.

According to the method of Meyers,[37] methanesulfonyl chloride (5.66 mL, 73.1 mmol) was added to a solution of the allylic alcohol (9.8888 g, 53.1 mmol), lithium chloride (5.50 g, 130 mmol), and 2,4,6-collidine (9.26 mL, 70.1 mmol) in dry dimethylformamide (100 mL) at 0 °C. The resulting white suspension was stored at 0 °C overnight and then diluted with ice water (300 mL). The product was extracted into pentane (3 × 100 mL) and the organic layer was washed successively with water, saturated cupric nitrate solution, water, and brine. The organic layer was then dried (Na_2SO_4) and concentrated to give 10.1176 g (93%) of allylic chloride **33** as a pale yellow oil: IR (film) 2970, 2930, 2870, 1440, 1380, 1260, 1210, 1135, 1055, 940, 865, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.53 (t, J = 7.6 Hz), 4.00 (s, 2 H), 3.91 (m, 4 H), 2.11 (m, 2 H), 1.73 (s, 3 H), 1.70 (m, 2 H), 1.31 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 131.53, 130.28, 109.42, 64.49, 52.15, 38.15, 23.67, 22.53, 13.84; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 169 (100), 203 (2), 205 (3).

8-(Isopropoxydimethylsilyl)-6-methyl-5(*E*)-octen-2-one Ethylene Acetal (34). A solution of (chloromethyl)isopropoxydimethylsilane (5.75 g, 34.47 mmol) in tetrahydrofuran (25 mL) was added to magnesium turnings (0.92 g, 38 mmol) over 2 h at room temperature. The reaction was initiated by addition of 2 mL of the silane solution to the turnings, addition of a crystal of iodine and 20 μL of dibromoethane, and brief heating with a heat gun until the iodine color had disappeared. The reaction temperature was then moderated by application of a water bath at 20 °C. After all of the chloromethylsilane solution had been added, the pale brown solution was heated at 40 °C for 1 h. After cooling, the solution was added to cuprous iodide (0.59 g, 3.1 mmol) at 0 °C, and the resulting suspension was cooled to −78 °C while allylic chloride **33** was added over 15 min. The solution was allowed to gradually warm to room temperature and was stirred overnight, after which it was quenched by addition of water (2 mL) and was concentrated. The residue was diluted with saturated ammonium chloride (50 mL), concentrated ammonium hydroxide (5 mL), and extracted into pentane. The organic layer was washed successively with water, dilute hydrochloric acid, sodium bicarbonate, and brine, then dried (Na_2SO_4), and concentrated. Chromatography (silica gel, 25% ether–pentane) afforded 6.6441 g (90%) of the alkylsilane **34** as a colorless oil: IR (film) 2960, 2860, 1445, 1375, 1250, 1170, 1130, 1055, 1025, 940, 840, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.10 (t, J = 7.5 Hz, 1 H), 3.95 (m, 1 H), 3.92 (m, 4 H), 1.90–2.10 (m, 4 H), 1.64 (m, 2 H), 1.58 (s, 3 H), 1.30 (s, 3 H), 1.12 (d, J = 6 Hz, 6 H), 0.64 (m, 2 H), 0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.57 MHz) δ 137.65, 122.38, 109.95, 64.75, 64.66, 39.09, 32.91, 25.81, 23.81, 22.64, 15.72, 15.17, −1.54; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 117 (100), 161 (76), 298 (1), 299 (2), 300 (1).

8-Hydroxy-6-methyl-5(*E*)-octen-2-one Ethylene Acetal (35). Silane **34** (2.6486 g, 8.814 mmol) was dissolved in a mixture of methanol (20 mL), tetrahydrofuran (20 mL), and sodium bicarbonate (2.52 g), and the mixture was brought to reflux. Hydrogen peroxide (90%, 8 mL) was added in 2-mL increments at 15-min intervals to the refluxing suspension. The white suspension was cooled, diluted with ether (50 mL), filtered through a pad of Celite, and concentrated. The residue was partitioned between ether (50 mL) and water (100 mL), followed by workup in the usual manner to give a colorless oil. Chromatography (silica gel, ether) afforded 1.3131 g (74%) of the alcohol **35** as a colorless oil: IR (film) 3400, 2930, 2870, 1380, 1270, 1060, 950, 860, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.24 (t, J = 7.5 Hz, 1 H), 3.91 (m, 4 H), 3.63 (t, J = 6.1 Hz, 2 H), 2.22 (t, J = 6.1 Hz, 2 H), 2.12 (t, J = 7.9 Hz, 2 H), 1.7 (m, 2 H), 1.63 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 131.05, 126.88, 109.66, 64.25, 59.96, 42.32, 38.51, 23.31, 22.53, 15.50; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 87 (100), 200 (3).

6-Methyl-8-(*p*-toluenesulfonyloxy)-5(*E*)-octen-2-one Ethylene Acetal (36). A solution of alcohol **35** (1.596 g, 7.969 mmol) in pyridine (4 mL) was cooled to 0 °C, *p*-toluenesulfonyl chloride (1.60 g, 8.39 mmol) was added, and the mixture was stirred for 10 min. After being stored in a refrigerator at 0 °C for 16 h, the mixture was diluted with ether (50 mL), washed with ice-cold dilute HCl (160 mL), and worked up in the usual manner to give an oily residue. Chromatography (silica gel, ethyl acetate–hexane 1:3) gave 1.8718 g (66%) of the tosylate **36** as a colorless oil: IR (film) 2970, 2880, 1600, 1445, 1360, 1180, 1100, 1060, 960, 910, 820, 775, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.76 (d, J = 7.5 Hz, 2 H), 7.32 (d, J = 7.5 Hz, 2 H), 5.11 (t, J = 7.3 Hz, 1 H), 4.05 (t, J = 7.1 Hz, 2 H), 3.92 (m, 4 H), 2.43 (s, 3 H), 2.28 (t, J = 7.1 Hz, 2 H), 2.03 (m, 2 H), 1.60 (m, 2 H), 1.51 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 144.40, 133.02, 129.56, 129.32, 127.59, 109.42, 68.72, 64.37, 38.51, 38.33, 23.55, 22.41, 21.34, 15.56; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 87 (89), 121 (88), 139 (94), 183 (100), 355 (25), 356 (5), 357 (2).

(37) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

8-Iodo-6-methyl-5(*E*)-octen-2-one Ethylene Acetal (37). Sodium iodide (1.3 g, 8.7 mmol) was added to a solution of tosylate **36** in acetone (5 mL). After stirring for 24 h, the resulting brown suspension was concentrated, and the residue was partitioned between ether and water. The aqueous phase was extracted with pentane (3 × 30 mL), and the combined organic phase was washed with dilute sodium thiosulfate solution, water, and brine. The organic layer was dried (Na_2SO_4), the solution was concentrated, and the residue was chromatographed (silica gel, ether–hexane 15:85) to afford 1.1183 g (88%) of iodide **37** as a colorless oil: IR (film) 2970, 2870, 1445, 1375, 1245, 1220, 1170, 1130, 1055, 950, 865 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.19 (t, J = 7.3 Hz, 1 H), 3.92 (m, 4 H), 3.19 (t, J = 7.6 Hz, 2 H), 2.496 (t, J = 7.6 Hz), 2.07 (m, 2 H), 1.70 (m, 2 H), 1.60 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 133.25, 126.76, 109.42, 64.37, 43.45, 38.51, 23.61, 22.41, 15.03, 4.72; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 87 (100), 121 (88), 183 (69), 310 (4), 311 (18), 312 (2).

(+)-*cis*-12-(2-(Dimethoxymethyl)-3,3-dimethylcyclopropyl)-6,10-dimethyl-5(*E*),9(*E*)-dodecadien-2-one Ethylene Acetal (38). A mixture of homoallylic iodide **37** (0.8102 g, 2.612 mmol), magnesium turnings (0.070 g, 2.8 mmol), and zinc chloride (0.367 g, 2.7 mmol) in tetrahydrofuran (5.4 mL) was placed in a small thin-walled septum-sealed test tube. The mixture was then sonicated at maximum power for 45 min by using a Bransonic sonifier Model 350 equipped with a Model 431A cup horn transducer, cooled by a flow of water. The reaction was initiated with 1,2-dibromoethane (20 μL), followed by 10-μL additions of 15-min intervals. The temperature was maintained near reflux by adjustment of cooling-water flow. A white precipitate formed after about 5 min, which redissolved to give a nearly colorless solution after about 30 min. This solution was added to tetrakis(triphenylphosphine)palladium(0) (136 mg, 0.118 mmol) to give a yellow solution, and vinylic iodide **27** (0.6675 g, 1.974 mmol) in tetrahydrofuran (3 mL) was then added. After 10 min, a white precipitate began to form, and the mixture was stirred at room temperature for 20 h. The resulting white suspension was diluted to 50 mL with pentane and washed with ice-cold 50% saturated ammonium chloride (50 mL). Workup in the usual manner gave a yellow oil that was chromatographed (silica gel, 20% ether–hexane) to yield the coupled product **38** (0.5416 g, 70%) as a pale yellow oil: IR (film) 2970, 2920, 1445, 1380, 1200, 1100, 1055, 955, 910, 870 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.10 (t, J = 6.7 Hz, 2 H), 4.15 (d, J = 8.7 Hz, 1 H), 3.92 (m, 4 H), 3.32 (s, 3 H), 3.30 (s, 3 H), 1.9–2.2 (m, 8 H), 1.25–1.75 (m, 4 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.30 (s, 3 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.85 (m, 1 H), 0.64 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 135.16, 134.92, 124.32, 109.89, 102.21, 64.61, 52.33, 51.61, 39.94, 39.64, 39.10, 28.97, 27.54, 26.88, 26.59, 23.78, 22.65, 18.00, 15.92, 15.33; $[\alpha]^{22}_D$ +10.7°; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 75 (84), 112 (100), 269 (67), 393 (1).

(+)-*cis*-12-(2-(Hydroxymethyl)-3,3-dimethylcyclopropyl)-6,10-dimethyl-5(*E*),9(*E*)-dodecadien-2-one Ethylene Acetal (39). Acetal **38** (0.5416 g, 1.380 mmol) was dissolved in a 80:20:0.1 mixture of tetrahydrofuran, water, and hydrochloric acid (4 mL), and the mixture was stirred at room temperature for 6 min. The solution was cooled to 0 °C, and methanol (4 mL) was added. Sodium borohydride (0.20 g, 5.3 mmol) was added, and the mixture was stirred at room temperature for 15 min. The solution was then diluted with ether to 50 mL, washed with water (50 mL), and worked up in the usual manner to give a pale yellow oil that was chromatographed (silica gel, 25% ethyl acetate–hexanes) to obtain alcohol **39** (0.4021 g, 83%) as a colorless oil: IR (film) 3400, 2980, 2930, 1445, 1380, 1255, 1220, 1140, 1060, 1020, 950, 920, 870, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.09 (t, J = 7.3 Hz, 2 H), 3.92 (m, 4 H), 3.62 (dd, J = 1 Hz, 7.6 Hz), 1.9–2.1 (m, 8 H), 1.6–1.75 (m, 2 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.35–1.45 (m, 2 H), 1.05 (s, 3 H), 1.00 (s, 3 H), 0.80 (m, 1 H), 0.59 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 134.98, 134.86, 124.32, 123.90, 109.84, 64.55, 60.02, 40.23, 39.52, 39.04, 29.21, 28.55, 27.06, 26.41, 23.67, 23.19, 22.59, 17.88, 15.98, 15.80, 14.67; $[\alpha]^{22}_D$ +6.4°; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 87 (100), 163 (65), 349 (1), 350 (1).

Acetal aldehyde **26** could also be isolated prior to reduction if desired: IR (film) 2910, 1690, 1445, 1380, 1215, 1130, 1060, 865 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.43 (d, J = 5.8 Hz, 1 H), 5.10 (t, J = 7.3 Hz, 2 H), 3.92 (m, 4 H), 1.60–2.15 (m, 12 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.32 (s, 3 H), 1.30 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 201.73, 134.80, 133.79, 124.85, 123.90, 109.66, 64.43, 39.64, 39.40, 38.92, 38.62, 37.31, 29.57, 28.91, 26.41, 23.61, 22.77, 22.47, 15.80, 15.03; $[\alpha]^{22}_D$ +27.1°; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 87 (100), 347 (2), 348 (3), 349 (2).

(+)-*cis*-12-(2-(Hydroxymethyl)-3,3-dimethylcyclopropyl)-6,10-dimethyl-5(*E*),9(*E*)-dodecadien-2-one (40). Acetal **39** (0.1280 g, 0.365 mmol) was dissolved in 80% aqueous acetic acid (1 mL) and the mixture was heated at 65 °C for 1 h and then cooled and diluted with excess cold sodium bicarbonate solution. The product was extracted into ether (3 × 15 mL) and worked up in the usual manner, giving a residue that was chromatographed (silica gel, 33% ethyl acetate–hexane) to obtain 0.1021 g (91%) of keto alcohol **40** as a colorless oil: IR (film) 3400, 2910, 1710, 1440, 1360, 1245, 1155, 1020, 915, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.01 (m, 2 H), 3.57 (dd, J = 2 Hz, 7.6 Hz, 2 H), 2.39 (t, J = 6.4 Hz, 2 H), 2.19 (m, 2 H), 2.07 (s, 3 H), 1.8–2.05 (m, 6 H), 1.54 (s, 3 H), 1.52 (s, 3 H), 1.3–1.4 (m, 2 H), 1.00 (s, 3 H), 0.95 (s, 3 H), 0.75 (m, 1 H), 0.52 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 208.82, 136.17, 134.98, 124.14, 122.47, 60.02, 43.63, 40.23, 39.52, 29.80, 29.21, 28.55, 27.06, 26.41, 23.13, 22.35, 17.88, 15.92, 14.67; $[\alpha]^{22}_D$ +7.59°; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 163 (100), 305 (1).

(+)-*cis*-2,2-Dimethyl-3-(3,7-dimethyl-11-oxo-3(*E*),7(*E*)-dodecadienyl)cyclopropanecarbaldehyde (16). Keto alcohol **40** (0.1930 g, 0.631 mmol) in dichloromethane (6 mL) was added to a vigorously stirred suspension of pyridinium chlorochromate (131 mg, 0.608 mmol), powdered molecular sieves (4 Å, 131 mg), and sodium acetate (20 mg, 0.24 mmol) in dichloromethane (6 mL). After 10 min, ether (12 mL) was added, and the mixture was stirred a further 10 min. Filtration through a pad of Celite on a sintered glass funnel, concentration, and chromatography (silica gel, 25% ethyl acetate–hexanes) afforded 160.3 mg (83%) of the keto aldehyde **16** as a colorless oil: IR (film) 2910, 1710, 1690, 1440, 1410, 1370, 1230, 1055, 985, 915, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.43 (d, J = 6.2 Hz, 1 H), 5.06 (m, 2 H), 2.44 (t, J = 7.0 Hz, 2 H), 2.18 (m, 2 H), 2.11 (s, 3 H), 1.60–2.05 (m, 8 H), 1.60 (s, 3 H), 1.57 (s, 3 H), 1.32 (s, 3 H), 1.40 (m, 1 H), 1.15 (s, 3 H), 1.0 (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 208.52, 201.85, 136.06, 133.97, 124.79, 122.53, 43.57, 39.70, 39.46, 38.68, 37.37, 31.47, 29.66, 28.97, 26.41, 22.83, 22.53, 22.35, 15.86, 15.09; $[\alpha]^{22}_D$ +32.4°; mass spectrum (chemical ionization, CH_4), m/e (relative intensity) 109 (92), 121 (89), 139 (74), 161 (100), 287 (70), 305 (28), 306 (6).

(+)-Casbene (3). The active titanium reagent was prepared by refluxing a mixture of titanium trichloride (3.57 g, 20.6 mmol) and zinc–copper couple (4.17 g, 63.8 mmol) in dimethoxyethane (65 mL) for 4 h, and a solution of keto aldehyde **16** (0.1603 g, 0.5266 mmol) in dimethoxyethane (50 mL) was added to the resulting black suspension over a period of 38 h via syringe pump. After being refluxed for 3 additional h, the reaction mixture was cooled and diluted with pentane (100 mL). The solution was filtered through a pad of Florisil and concentrated to a pale yellow oil. Chromatography (silica gel, pentane) yielded 107.5 mg (75%) of a mixture of casbene isomers as a colorless oil. GC analysis of this mixture showed it to contain 57% of (+)-casbene (**3**), together with 26% of (−)-4(*E*),8(*E*),12(*Z*)-casbene (**45**), 12% of *trans*-(*E*,*E*,*E*)-casbene, and 5% of *trans*-(*E*,*E*,*Z*)-casbene. The isomers were separated by using semipreparative HPLC with a C18 reversed-phase column and acetonitrile as the eluant. Samples were injected as an ether solution, due to the relatively low solubility of the mixture in acetonitrile.

(+)-Casbene (3): IR (film) 2900, 1440, 1380, 1165, 1130, 880, 870, 840, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.95 (t, J = 7.5 Hz, 1 H), 4.87 (m, 2 H), 1.65–2.33 (m, 12 H), 1.64 (s, 3 H), 1.56 (s, 3 H), 1.54 (s, 3 H), 1.21 (apparent t, J = 8.7 Hz, 1 H), 1.04 (s, 3 H), 0.92 (s, 3 H), 0.56 (apparent t, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 136.04, 135.41, 133.27, 125.51, 123.42, 121.17, 40.34, 39.51, 39.31, 30.63, 28.88, 25.71, 24.98, 24.00, 19.81, 16.44, 16.25, 15.77; $[\alpha]^{22}_D$ +201.1°; mass spectrum (electron impact, 70 eV) calcd for $C_{20}H_{32}$ 272.2504, found 272.2503, m/e (relative intensity) 93

(76), 107 (63), 121 (100), 272 (26), 273 (6). Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.41; H, 11.98.

(−)-4(*E*),8(*E*),12(*Z*)-Casbene (45): IR (film) 3010, 2890, 1440, 1375, 1260, 1155, 1125, 1055, 945, 870, 840, 10 cm^{-1}; ^1H NMR (300 MHz) δ 5.05 (m, 2 H), 4.87 (d, J = 10.9 Hz, 1 H), 2.59 (dt, J = t 13.3 Hz, d 4.1 Hz), 1.80–2.35 (m, 9 H), 1.70 (s, 3 H), 1.58 (s, 3 H), 1.53 (s, 3 H), 1.25–1.45 (m, 3 H), 1.02 (s, 3 H), 0.88 (s, 3 H), 0.43 (m, 1 H (dt, J(t) = 9.0 Hz, J(d) = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 133.80, 133.22, 124.15, 123.81, 123.08, 40.24, 38.78, 31.27, 29.90, 29.17, 26.49, 25.42, 24.59, 23.17, 20.10, 19.91, 16.64, 16.10, 15.81; $[\alpha]^{22}_D$ −277.2°; mass spectrum calcd for $C_{20}H_{32}$ 272.2504, found 272.2503, m/e (relative intensity) 93 (81), 107 (60), 121 (100), 272 (37), 273 (9).

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Inducibility of an Enone Reductase System in the Fungus *Beauveria sulfurescens*: Application in Enantioselective Organic Synthesis

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Microbiological reduction of α,β-unsaturated carbonyl compounds is studied. Inducibility of the enone reductase system of *Beauveria sulfurescens* is reported. The best inducer is shown to be cyclohex-2-en-1-one. An appropriate procedure using induced resting mycelium is developed to reduce substituted cyclohexenones that are shown to be unable to induce the reducing enzyme. Optically pure *trans*-(2*R*,6*R*)-(−)-2,6-dimethylcyclohexan-1-one and *trans*-(2*R*,6*R*)-(−)-2,6-dimethylcyclohexan-1-ol are obtained from (±)-2,6-dimethylcyclohex-2-en-1-one along with optically pure (6*S*)-(−)-2,6-dimethylcyclohex-2-en-1-one.

In previous papers, we reported that the reduction of α,β-unsaturated carbonyl compounds is widespread among living organisms. Aerobic[1] and anaerobic bacteria,[2] fungi,[3] protozoan,[4] and plant[5] and animal[6] cells were all shown to reduce the carbon–carbon double bond. The stereochemical characteristics of this reaction are identical for all the organisms, while the reduction of the carbonyl group, when occurring, leads to either an *R* or *S* alcohol, depending on the cell involved.

According to those findings, one could predict the absolute configuration of substituted saturated ketones obtained via microbial reduction. Yet, the synthetic applications of the stereochemical rule proposed by our group for the reduction of C–C double bonds by a fungus *Beauveria sulfurescens*[3a] have been shown to be limited: the reaction occurs only on small molecules bearing a small α-substituent and a hydrogen atom in the β-position. Thus, many compounds of synthetic interest could not be reduced by the fungus under the conditions generally used.

In the hope of extending the scope of the reaction, we studied the reducing activity of the fungus under various growing conditions. The results reported here describe an efficient procedure developed to reduce rapidly and enantiospecifically prochiral substrates previously shown to remain untransformed.

Results and Discussion

Before describing our results, it would be appropriate to mention how we intended to explore the biology of *B. sulfurescens*. When working on the reduction of prochiral disubstituted cyclohexenones, we noticed that some of them could not be reduced by the fungus, even after 6–10 days of reaction.[3a] Beside enzymatic hindrances, cell permeation effects were thought to be involved. For these experiments, bioconversions had been performed in situ, the compound to be reduced being added to a 24-hour-old culture and incubated at least 48 h in the growth medium. No reducing activity could be detected in the growth medium free of mycelium leading us to assume that the reducing enzymes might be endocellular.

To support this assumption and to clarify whether or not cell permeation of the substrate was involved, we investigated the reducing activity of the fungus in mycelium homogenates. As a model experiment, we studied the reduction of cyclohex-2-en-1-one (cyclohexenone), shown to be thoroughly reduced, first into saturated ketone and then into saturated alcohol, in previous experiments.[3a]

The harvested mash of a 24-hour-old culture of *B. sulfurescens* was disrupted with an X-Press (freeze-pressing principle), resuspended in a buffer, and centrifuged to yield a supernatant that was immediately incubated with cyclohexenone and various cofactors.

The first results showed that no activity could be evidenced in cell-free extracts whatever the cofactor added. Saturated cyclohexanone could be detected only in experiments where the growth medium had been supplemented with the substrate. Thus, prior to any cofactor requirement, the reducing system must have been induced.

Following these results, we carried out a study on induction. We found it much easier, and cheaper, to work with resting mycelium, instead of homogenates, to study the influence of various inducers on the time course changes of cyclohexenone and to study applications in enantioselective synthesis.

B. sulfurescens was grown in conical flasks containing a glucose/peptone medium. After 24 h on a gyratory shaker, each flask received an aliquot of cyclohexenone. The induction time varied from 20 min to 24 h. After incubation, the mycelium of each flask was removed by filtration. Cyclohexenone reduction was followed by GPC

(1) Kergomard, A.; Renard, M. F.; Veschmabre, H. *Agric. Biol. Chem.* **1985**, *49*(5), 1499.
(2) (a) Bostmembrun-Desrut, M.; Kergomard, A.; Renard, M. F.; Veschambre, H. *Agric. Biol. Chem.* **1983**, *47*(9), 1997. (b) Desrut, M.; Kergomard, A.; Renard, M. F.; Veschambre, H. *Biochem. Biophys. Res. Commun.* **1983**, *110*(3), 908.
(3) (a) Kergomard, A.; Renard, M. F.; Veschambre, H. *J. Org. Chem.* **1982**, *47*, 792. (b) Kergomard, A.; Renard, M. F.; Veschambre, H. *Agric. Biol. Chem.* **1982**, *46*(1), 97.
(4) Kergomard, A.; Renard, M. F.; Veschambre, H.; Groliere, C. A.; Dupy-Blanc, J. *Agric. Biol. Chem.* **1986**, *50*(2), 487.
(5) Kergomard, A.; Renard, M. F.; Veschambre, H.; Courtois, D.; Petiard, V. *Phytochemistry*, in press.
(6) Fauve, A., unpublished data.

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