for such a correlation and leads to a parametric barrier equation (eq 9) which is isomorphic with the empirical correlation (eq 6). The physical significance of the correlation is shown then to derive from the notion that the activation process is a deformation that is required to overcome the vertical electron transfer energy gap. A relationship between the N^+ equation and the present correlation can be drawn in terms of the above physical picture.

Greater insight into the problem can be achieved when more necessary vertical data becomes available and when full VB computations[9] are carried out for these reactions. Both goals appear to be attainable.[9,24,28]

Acknowledgment. Discussions with C. D. Ritchie and his "healthy dose of skepticism" were incentives of this research which began during my leave of absence to Queen's University. The Natural Sciences and Engineering Research Council of Canada is thanked for an International Exchange Award and S. Wolfe is thanked for the kind hospitality which enabled the leave of absence in Queen's. Cathy Turney and Shirley Smith from the University of Alabama—Huntsville are thanked for the typing.

Registry No. F^-, 16984-48-8; Cl^-, 16887-00-6; Br^-, 24959-67-9; I^-, 20461-54-5; HO^-, 14280-30-9; CH_3O^-, 3315-60-4; HOO^-, 14691-59-9; $CF_3CH_2O^-$, 24265-37-0; PrS^-, 20733-14-6; PhS^-, 13133-62-5; N_3^-, 14343-69-2; CN^-, 57-12-5; SO_3^{2-}, 14265-45-3; $CH_3CO_2^-$, 71-50-1; H_2O, 7732-18-5; $PrNH_2$, 107-10-8; N_2H_4, 302-01-2; piperidine, 110-89-4; pyronin cation, 17817-77-5.

Synthesis of Terpenes Containing the Bicyclo[3.1.1]heptane Ring System by the Intramolecular [2 + 2] Cycloaddition Reaction of Vinylketenes with Alkenes. Preparation of Chrysanthenone, β-Pinene, β-*cis*-Bergamotene, β-*trans*-Bergamotene, β-Copaene, and β-Ylangene and Lemnalol

Yashwant S. Kulkarni, Maho Niwa, Eyal Ron, and Barry B. Snider*[1]

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254

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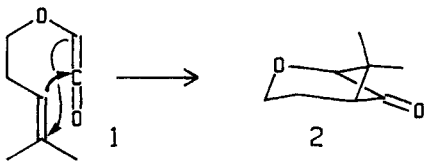
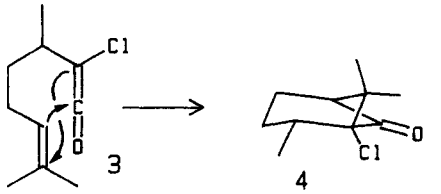
Treatment of geranoyl chloride (**20**) with triethylamine in toluene at reflux gave the vinylketene **21** which underwent a [2 + 2] cycloaddition to give 7,7-dimethyl-2-methylenebicyclo[3.1.1]heptan-6-one (**24**) in 43% yield. Isomerization over Pd gave chrysanthenone (**6**) in quantitative yield. Wolff–Kishner reduction gave β-pinene (**5**) in 70% yield. A similar sequence of reactions starting from (*Z,E*)- and (*E,E*)-farnesoyl chloride gave ketones **51** and **57**, which were converted to β-*cis*-bergamotene (**8**) and β-*trans*-bergamotene (**9**), respectively. β-Copaene (**10**) and β-ylangene (**11**) were prepared from **57** by a three-step sequence. Treatment of the imidazolide **59** with tri-*n*-butyltin hydride in toluene at reflux gave a 46% yield of a 1:1 mixture of **10** and **11**. Selenium dioxide oxidation of **11** gave the antitumor agent lemnalol. The mechanisms of the regiospecific ketene generation and the [2 + 2] cycloaddition reaction have been explored, and the reactivity of the novel bicyclo[3.1.1]heptanones has been examined.

The stereospecific [2 + 2] cycloaddition of ketenes to alkenes is a valuable method for the synthesis of cyclobutanones and compounds that can be derived from them; it is one of the few general methods for the carbofunctionalization of alkenes. We have recently initiated a program to develop the intramolecular [2 + 2] cycloaddition of ketenes to alkenes into a general synthetic method.[2-5] Initial studies indicated that electronic effects of substituents on the alkene rather than the connectivity pattern controls the regiochemistry of the cycloaddition. Specifically, ketenes **1** and **3**, in which the terminal carbon of the double bond is more highly substituted, cyclize regiospecifically to the bicyclo[3.1.1]heptan-6-ones **2** and **4**.[2]





Several mono- and sesquiterpenes contain the bicyclo[3.1.1]heptane ring system. Numerous monoterpenes, including the readily available essential oil β-pinene (**5**), chrysanthenone (**6**),[6] and the monoterpenoid glycoside paeonoflorin (**7**),[7] which was isolated from the traditional

(1) Camille and Henry Dreyfus Teacher-Scholar, 1982–1987.

(2) (a) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194. (b) Kulkarni, Y. S.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 2809. (c) Kulkarni, Y. S.; Burbaum, B. W.; Snider, B. B. *Tetrahedron Lett.* **1985**, *26*, 5619. (d) Snider, B. B.; Kulkarni, Y. S. *Tetrahedron Lett.* **1985**, *26*, 5675. (e) Snider, B. B.; Hui, R. A. H. F. *J. Org. Chem.* **1985**, *50*, 5167. (f) Snider, B. B.; Kulkarni, Y. S., submitted for publication in *J. Org. Chem.*

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(5) For preliminary communications describing a portion of this work, see ref 2b and 2d.

(6) Kotake, M.; Nonaka, H. *Liebigs Ann. Chem.* **1957**, *607*, 153.

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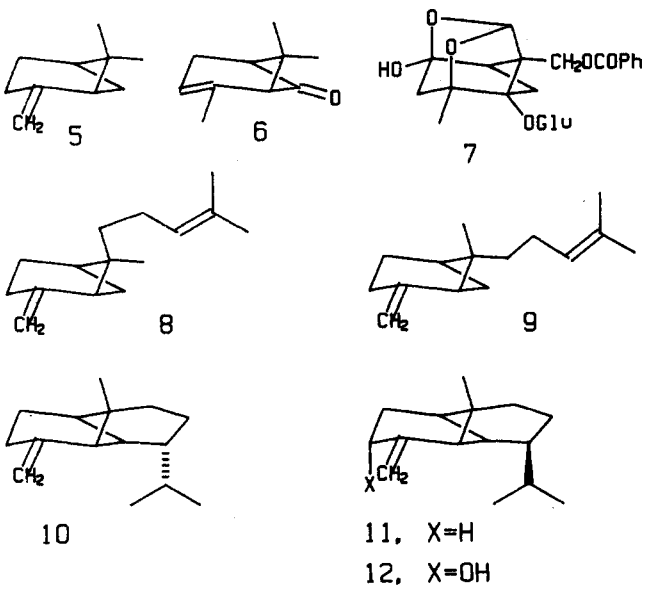
0022-3263/87/1952-1568$01.50/0



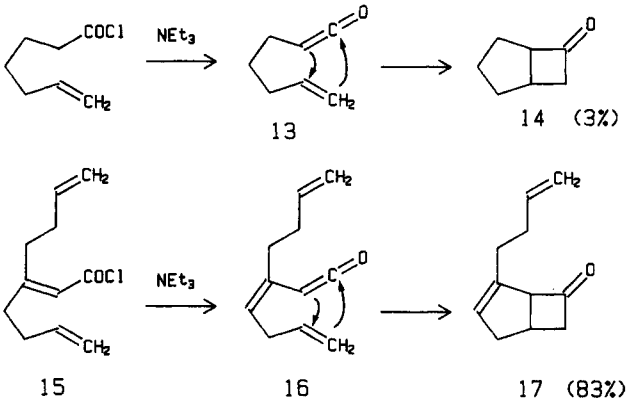
oriental drug *Paeonia albifora*, possess the pinane skeleton. Sesquiterpenes containing this ring system include β-*cis*-bergamotene (**8**),[8] β-*trans*-bergamotene (**9**),[8,9] and their α isomers. In addition, several tricyclic sesquiterpenes including the essential oils β-copaene (**10**)[10,11] and β-ylangene (**11**)[11,12] and the antitumor agent lemnalol (**12**)[13] contain a bicyclo[3.1.1]heptane ring system with an additional ring fused to it.

The synthesis of these molecules has been a challenging problem, caused largely by the difficulty of preparing the carbon skeleton. β-Pinene has been synthesized from acyclic precursors.[14] Chrysanthenone has been prepared by partial synthesis by the photolysis of natural verbenone.[15] α-*cis*- and β-*cis*-bergamotene have been prepared by Gibson and Erman in 12 steps starting from β-pinene.[16] Corey, Cane, and Libit have prepared α-*trans*- and β-*trans*-bergamotene in 21 steps from geranyl acetate.[17] Larsen and Monti have prepared α-*trans*- and α-*cis*-bergamotene in 13 steps.[14c] Heathcock et al. have prepared α-copaene and α-ylangene in 17 steps,[18] and Corey and Watt have prepared α- and β-copaene and α- and β-ylangene in 18 steps.[19]

The successful conversions of ketenes **1** and **3**, which were prepared in situ from the readily available acid chlorides, to bicyclo[3.1.1]heptan-6-ones prompted us to extend the reaction to ketenes suitable for preparation of these terpenes. Our earlier results established that simple alkylketenes did not undergo the cycloaddition reaction; the presence of the chlorine of **3** as an activating group is necessary. We therefore turned out attention to other activating groups that would allow the cycloaddition to proceed and provide more suitable functionality than the chlorine of **4** for conversion to the double bond present in the 3-carbon bridge of these terpenes.

Results and Discussion

Synthesis of β-Pinene and Chrysanthenone. Vinylketene **21** was a potentially attractive precursor since the available evidence indicated that vinylketenes undergo both intermolecular and intramolecular cycloadditions more readily than simple alkylketenes. The intermolecular [2 + 2] cycloadditions of vinylketenes occur only with activated alkenes and cyclopentadiene, but nevertheless much more readily than alkyl ketenes.[20] Marko et al. have found that the vinylketene **16** cyclizes to **17** in 83% yield while the simple alkylketene **13** cyclizes to **14** in only 3% yield.[3a] One role for the double bond in these cycloadditions may be to restrict rotational freedom, resulting in a less negative entropy of activation for the cycloaddition. However, it is likely that the role of the double bond is more significant.



Vinylketene **21** can be prepared by treatment of the geranoyl chloride (**20**) with triethylamine. Unfortunately, vinylketenes **22** and **23** can also be formed in this reaction. It should be noted that the vinylketenes studied by Marko et al. were all prepared from acid chlorides such as **15**, which were presumably chosen since only a single vinylketene can be formed. Bedoukian and Wolinsky have shown that treatment of **20** with triethylamine and methanol in benzene gives methyl γ-geranoate (**26**) in 85% yield presumably via the intermediacy of vinylketene **21**.[21] This precedent suggested that vinylketene **21** would be formed selectively from **20**. The intramolecular cycloaddition of **21** would give **24**, which can easily be converted to β-pinene (**5**) and chrysanthenone (**6**).

Treatment of geranic acid (**19**) with excess oxalyl chloride in toluene gave the acid chloride **20**, which was dissolved in toluene and added slowly to a solution of triethylamine in toluene at reflux. The solution (0.03 M) was heated at reflux for 3 h and worked up to give a 43% yield of 7,7-dimethyl-2-methylenebicyclo[3.1.1]heptan-6-one (**24**), a 2% yield of **6**, and a 7% yield of **25**. Reaction in more concentrated solution is necessary to scale up this

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(9) Cane, D. E.; King, G. G. S. *Tetrahedron Lett.* **1976**, 4737. We thank Prof. Cane for providing us with spectra of β-*trans*-bergamotene. Noyoe, S.; Kobayashi, H.; Morisaki, N. *Ibid.* **1976**, 4625.
(10) Buttery, R. G.; Teranishi, R.; Mon, T. R.; Ling, L. C. *J. Sci. Food Agric.* **1969**, *20*, 721.
(11) Westfelt, L. *Acta Chem. Scand.* **1967**, *21*, 152.
(12) Hunter, G. L. K.; Brogden, W. B., Jr. *J. Org. Chem.* **1964**, *29*, 2100.
(13) Kikuchi, H.; Tsukitani, Y.; Yamada, Y.; Iguchi, K.; Drexler, S.; Clardy, J. *Tetrahedron Lett.* **1982**, *23*, 1063. Kikuchi, H.; Manda, T.; Kobayashi, K.; Yamada, Y.; Iguchi, K. *Chem. Pharm. Bull.* **1983**, *31*, 1086.
(14) For previous syntheses of α- or β-pinene see: (a) Crowley, K. J. *Tetrahedron* **1965**, *21*, 1001. (b) Thomas, M. T.; Fallis, A. G. *J. Am. Chem. Soc.* **1976**, *98*, 1227. (c) Larsen, S. D.; Monti, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 8015.
(15) (a) Hurst, J. J.; Whitham, G. H. *J. Chem. Soc.* **1960**, 2864. (b) Erman, W. F. *J. Am. Chem. Soc.* **1967**, *89*, 3828.
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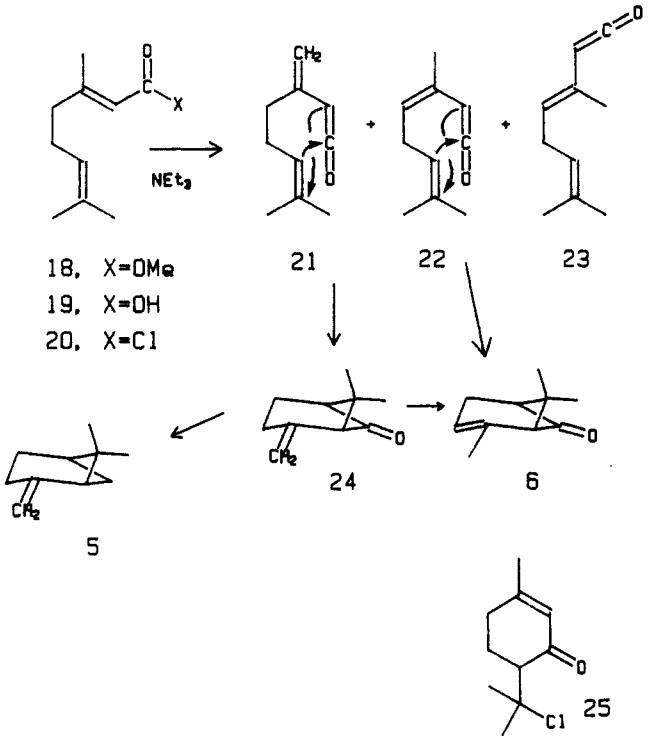
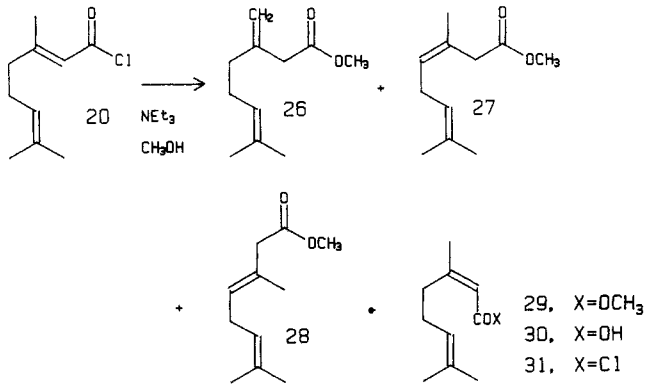
(17) Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7016.
(18) Heathcock, C. H.; Badger, R. A.; Patterson, J. W., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 4133.
(19) Corey, E. J.; Watt, D. S. *J. Am. Chem. Soc.* **1973**, *95*, 2303. Watt, D. S. Ph.D. Thesis, Harvard University, Cambridge, MA, 1972.
(20) Jackson, D. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 2330. Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943. Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670 and ref 7 therein.
(21) Bedoukian, R. H.; Wolinsky, J. *J. Org. Chem.* **1975**, *40*, 2154.



reaction economically. Only a slight decline in yield resulted from carrying out the reaction in 0.1 M solution (40% of **24**, 5% of **6**). In 0.5 M solution the yield decreased noticeably as did the selectivity for **24** (30% of **24**, 11% of **6**). We found that toluene and/or benzene were optimal solvents for the intramolecular cycloadditions of alkoxyketenes since triethylamine hydrochloride, which catalyzes the decomposition of ketenes, precipitated from solution as it was formed.[2e] The choice of solvent is determined empirically on the basis of the optimal temperature for the reaction.

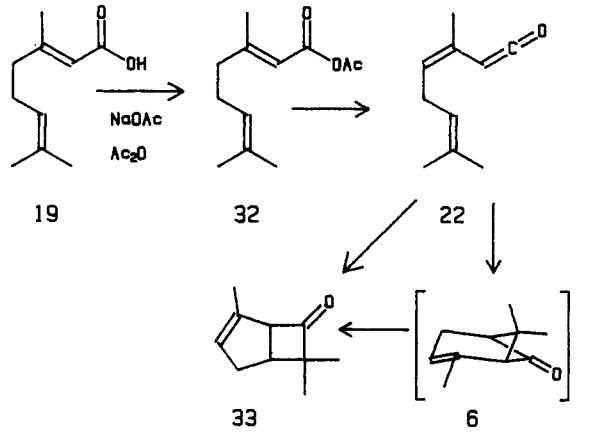
These results suggest that vinylketene **21** is formed selectively from **20**. This was confirmed by repeating Bedoukian and Wolinsky's trapping experiment[21] and carefully analyzing the mixture of products. Treatment of **20** with triethylamine and methanol in benzene at 0 °C gave a 9:1 mixture of **26** and **18**, with only traces of **27**, **28**, and **29**. The formation of **18** could be due to isomerization of the β,γ-unsaturated esters **26–28** to the α,β-unsaturated ester **18** but is much more likely due to the formation of **18** without the intermediacy of the ketene.[22]



There are two possible reasons for the selective formation of the *exo*-methyleneketene **21**. Katzenellenbogen and Crumrine have shown that kinetic deprotonation of related α,β-unsaturated acids occurs on the methyl group regardless of the double-bond geometry.[23] More recently, Harris and Weiler have shown, by the use of labeled substrates that deprotonation of methyl 3-methyl-2-butenoate or 3-methyl-2-butenoic acid with lithium amide bases occurs regioselectively on the methyl group syn to the acid function under kinetic conditions.[24] Since coordination of the lithium to the oxygen may be responsible for the regioselectivity, this result may not be applicable to the observed selectivity of ketene formation from treatment of acid chlorides with triethylamine. Treatment of the *Z* acid chloride **31** with triethylamine in toluene gave a 15% yield of **24** uncontaminated with **6**. The low yield of **24** is due largely to the instability of the *Z* acid chloride, which spontaneously undergoes an ene reaction.[25] In other cases where the ene reaction is not possible, both *E* and *Z* acid chlorides give identical yields of cyclobutanones.[22] Therefore, the selective formation of **21** is due to the greater kinetic acidity of the methyl protons rather than the *E* geometry of the double bond. Consequently, the stereochemistry of the α,β-unsaturated ester has no effect on the reaction so that mixtures of isomers can be used.

The synthesis of chrysanthenone (**6**) was completed by isomerization of the exocyclic double bond into the ring in quantitative yield with hydrogen and palladium on calcium carbonate.[26] The synthesis of β-pinene was completed by the Huang-Minlon modification of the Wolff–Kishner reduction in 70% yield.[27] Although **24** undergoes ring opening in basic media,[28] the hydrazone can be formed from hydrazine hydrate in ethylene glycol at 110 °C in the absence of potassium hydroxide and fortunately, and somewhat surprisingly, is reduced faster than it undergoes ring opening in ethylene glycol containing potassium hydroxide at reflux. The intramolecular cycloaddition of **21** to give **24** is thus the key step in three-step syntheses of chrysanthenone (43%) and β-pinene (30%).

Beereboom reported that treatment of geranic acid (**19**) with acetic anhydride and sodium acetate at reflux gave a 28% yield of filifolone (**33**).[29,30] Erman et al. have



(22) Snider, B. B.; Ron, E., unpublished results.

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(26) Widmark, G. *Acta Chem. Scand.* **1955**, *9*, 941. Brown, C. A. *Synthesis* **1978**, 754 and references cited therein.

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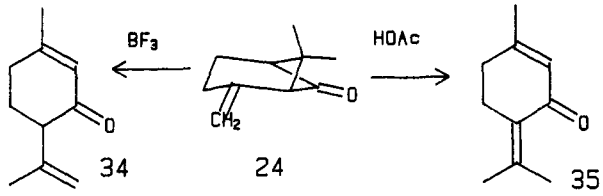
(30) For a similar reaction carried out on farnesol see: Corbella, A.; Gariboldi, P.; Gil-Quintero, M.; Jommi, G.; St. Pyrek, J. *Experientia* **1977**, *33*, 703. Bernasconi, S.; Gariboldi, P.; Jommi, G.; Sisti, M.; Fava, G. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 995.

studied the mechanism of this reaction.[31] They proposed that **19** is converted to the mixed anhydride **32**, which loses acetic acid to give **22**, cyclizing to give chrysanthenone (**6**). Under the reaction conditions chrysanthenone is not stable but rearranges to filifolone (**33**) by a series of Wagner–Meerwein shifts initiated by protonation of the carbonyl group. In support of this mechanism they showed that treatment of **6** with acetic acid or boron trifluoride etherate led to a mixture containing a significant amount of **33**.

We therefore considered the possibility that **21** and **24** are intermediates in Beerboom's filifolone synthesis. Treatment of cyclobutanone **24** with boron trifluoride etherate in methylene chloride gave a 95% yield of isopiperitenone (**34**). Heating a solution of **24** in acetic acid

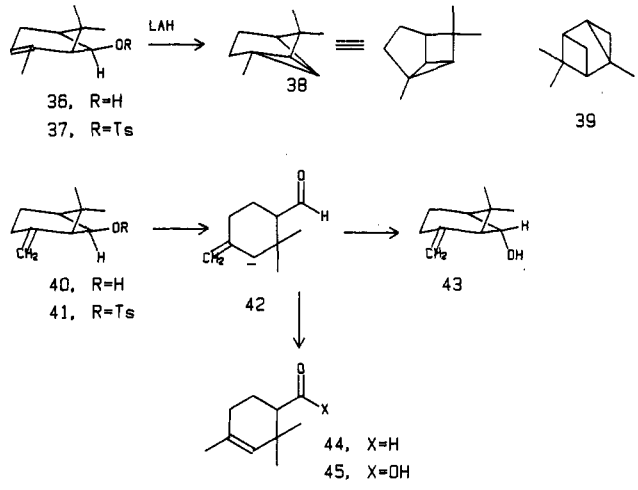


34 24 35

at 110 °C for 4 h gave a complex mixture containing piperitenone (**35**) as the major product. No chrysanthenone was present. To approximate the reaction conditions for the synthesis of filifolone, **24** was dissolved in a mixture of sodium acetate, acetic acid, and acetic anhydride and heated at reflux for 2 h. As before, a complex mixture containing piperitenone (22%) but not filifolone was obtained. These results establish that **24** is not a competent intermediate for the formation of filifolone. Apparently, acid-catalyzed rearrangements of **24** are initiated by protonation of the reactive exocyclic double bond while acid-catalyzed rearrangements of **6** are initiated by protonation of the carbonyl group rather than the unreactive endocyclic double bond.

The apparently selective formation of vinylketene **22** from mixed-anhydride **32** but vinylketene **21** from acid chloride **20** is puzzling. The formation of **21** from **20** is probably irreversible, especially since the reaction conditions were chosen so that triethylamine hydrochloride precipitates from solution as it is formed. The formation of vinylketenes from **32** in a mixture containing acetic acid is probably readily reversible. The cyclization of vinylketene **22** to **6** may be faster than the cyclization of **21** to **24** since it will have a lower entropy of activation. If this is the case, it is possible that all three possible vinylketenes **21**–**23** are formed and rapidly revert to **32** but that only the cyclization of **22** to **6** is competitive with reversion to **32**.

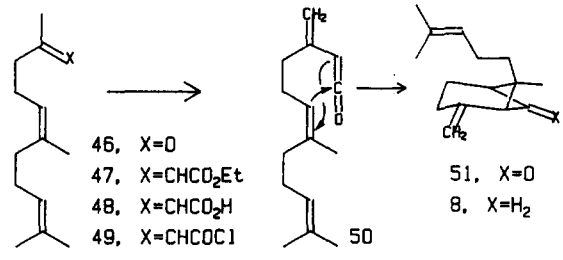
Chrysanthenol (**36**) has also been isolated from natural sources.[32] Dembitskii and co-workers have isolated **36** and reported that reduction of the tosylate **37** with LAH gave **39**, which they called cyclopinene.[32b] Since this structure seemed mechanistically implausible, we have reexamined this reaction. Reduction of tosylate **37** with LAH in ether at reflux gave a 41% yield of a tricyclic hydrocarbon whose spectral data are consistent with the plausible structure **38**. We have carried out a similar sequence on **24**. Reduction of **24** with LAH gave a 77% yield of **40**, which was converted to tosylate **41** in 98% yield. Tosylate **41** did not react with LAH in ether at reflux or with diisobutylaluminum hydride in either ether or hexane at reflux. The

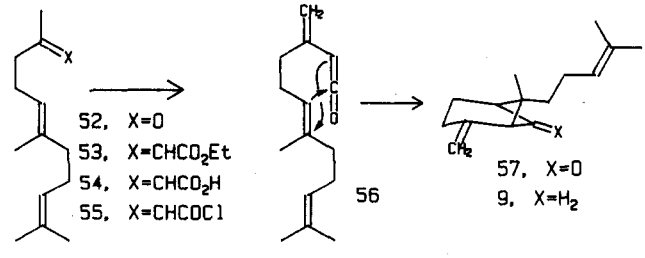


relative stabilities of **37** and **41** are consistent with these observations. Tosylate **41** is stable for several months at 0 °C. Tosylate **37** decomposes with a half-life of 5 h at −20 °C in dilute hexane solution under nitrogen. Examination of molecular models indicates that the π-orbitals of the double bond of **37** are properly oriented to participate in solvolysis of the tosylate, leading to a tricyclic cyclopropylcarbinyl cation that is reduced to give **38**. On the other hand, examination of models indicates that the π-orbitals of the double bond of **41** are not properly oriented to participate in solvolysis of the tosylate.

Chrysanthenone (**6**) and **36** undergo base-catalyzed cleavage of the cyclobutane to give cyclohexenecarboxylic acid (**45**) and cyclohexenecarboxaldehyde (**44**), respectively.[15a,28] We have found that treatment of alcohol **40** with sodium hydride in THF at reflux for 2.5 h gave a 40% yield of the isomeric alcohol **43**. This unusual rearrangement probably proceeds by cleavage to give the aldehyde carbanion **42**, which in the absence of a proton source recloses to **40** or the more stable alcohol **43**. Aldehyde **44** and products derived from it are also formed.

Synthesis of β-Bergamotenes. This intramolecular cycloaddition reaction offered a very attractive route to *β-cis*-bergamotene (**8**) and *β-trans*-bergamotene (**9**). Nerylacetone (**46**) was converted to a 9:1 mixture of (*E*,*Z*)-





and (*Z*,*Z*)-farnesic acid (**48**) by a Horner–Emmons Wittig reaction[33] followed by basic hydrolysis in 78% yield. The crude acid **48** was converted to the acid chloride **49**, which

(31) Erman, W. F. *J. Am. Chem. Soc.* **1969**, *91*, 779. Erman, W. F.; Treptow, R. S.; Bazukis, P.; Wenkert, E. *J. Am. Chem. Soc.* **1971**, *93*, 657.
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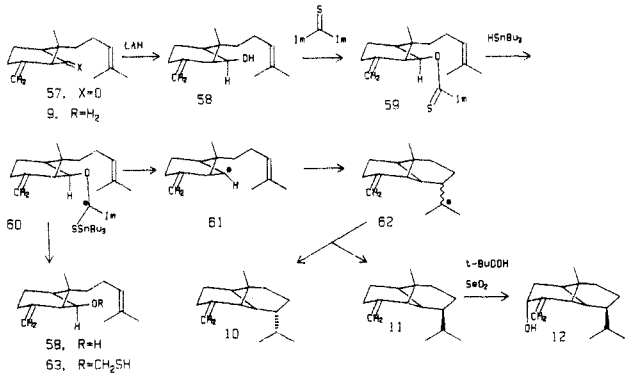
(33) Vig, O. P.; Kapur, J. C.; Khurana, C. K.; Vig, B. *J. Indian Chem. Soc.* **1969**, *46*, 505.

was added to triethylamine in toluene at reflux to give a 39% yield of **51** uncontaminated with **57**. Wolff–Kishner reduction of **51** gave a 65% yield of β-*cis*-bergamotene (**8**) whose spectral data are identical with those previously reported.[8a,16] This completes a five-step synthesis of β-*cis*-bergamotene from nerylacetone in 19% overall yield.

In a similar manner, geranylacetone (**52**) was converted to a 9:1 mixture of (*E*,*Z*)- and (*Z*,*E*)-farnesic acid (**54**) and thence to **57** in 38% overall yield. Initial attempts at Wolff–Kishner reduction of **57** to give **9** with hydrazine hydrate were unsuccessful due to the increased steric bulk of the larger side chain. Fortunately, the hydrazone could be prepared with anhydrous hydrazine. Wolff–Kishner reduction gave a 40% yield of β-*trans*-bergamotene (**9**) whose spectral data are identical with those previously reported.[8a,9,17] This completes a five-step synthesis of β-*trans*-bergamotene from geranylacetone in 15% overall yield.

Concurrently with our preliminary paper, Corey and Desai reported a synthesis of β-*trans*-bergamotene via the cyclization of **56** to **57**. They prepared vinylketene **56** from the less readily available β,γ-unsaturated acid that was prepared in moderate yield by a Wittig reaction on the unstable β-keto acid.[3c]

Synthesis of β-Copaene and β-Ylangene. The bicyclo[3.1.1]heptanone **57** appeared to be a very attractive intermediate for the synthesis of β-copaene (**10**) and β-ylangene (**11**) since completion of the synthesis would only require formation of a bond between the carbonyl carbon and proximal end of the double bond with a concomitant four-electron reduction. The Barton–McCombie method[34,35] for the deoxygenation of secondary alcohols appeared to offer an attractive method to accomplish this transformation. This procedure should generate the cyclobutyl radical **61**, which should cyclize to **62** faster than it is reduced by $(n\text{-Bu})_3SnH$ to **9**. The cyclization of radicals generated by the Barton–McCombie procedure has been reported.[36] The cyclization of a radical to a similar double bond has been observed by Bakuzis et al. in a synthesis of sativene and copacamphene.[37]



Reduction of **57** with LAH gave **58** in 84% yield, which was converted to the thiocarbonyl imidazolide **59** in 76% yield. A solution of **59** and 3 equiv of $(n\text{-Bu})_3SnH$ in toluene was heated at reflux for 3 h to give a 15% yield of a 1:1 mixture of β-copaene (**10**) and β-ylangene (**11**), accompanied by a 25% yield of alcohol **58** and a 40% yield of hemithioacetal **63**. β-*trans*-Bergamotene, which would be formed by the direct reduction of **61** was not formed, indicating that cyclization of **61** is faster than reduction. Since **63** can be hydrolyzed to alcohol **58** in good yield in 1:1:1 THF–H_2O–HOAc for 48 h, the yield of **10** and **11** is 43% based on recovered starting material.

The relatively low yields of **10** and **11** in the Barton deoxygenation are probably a result of the instability of the strained cyclobutyl radical **61**, which slows down fragmentation of **60**, allowing competing reduction of **60** to give **58** and **63** to become important side reactions. Barton has reported the formation of hemithioacetals related to **63** from primary thiocarbonyl imidazolides since fragmentation of the intermediate corresponding to **60** to give an unstable primary radical is also slow compared to reduction of the radical intermediate. They were able to solve this problem by carrying out the reduction at higher temperatures, which favors fragmentation.[38] Unfortunately, reduction of the imidazolide **59** in xylene at reflux or the xanthate in toluene at reflux gave no better results.

We have explored other reaction conditions designed to favor fragmentation of **60** over direct reduction to **58** and **63**. Since reduction of **60** is a bimolecular reaction, it should be slowed down relative to fragmentation to **61** if the $(n\text{-Bu})_3SnH$ concentration is low. Optimal results were obtained by addition of a mixture of **59**, 2 equiv of $(n\text{-Bu})_3SnH$, and 0.1 equiv of AIBN in toluene to a solution of toluene at reflux over 12 h. After 18 h an additional 2 equiv of $(n\text{-Bu})_3SnH$ and 0.1 equiv of AIBN in toluene were added over 6 h. These reaction conditions gave a 46% yield of a 1:1 mixture of β-copaene (**10**) and β-ylangene (**11**), accompanied by a 34% yield of alcohol **58** and a 28% yield of hemithioacetal **63**. Only a 20% yield of **10** and **11** was obtained if AIBN was omitted. Use of Ph_3SnH instead of $(n\text{-Bu})_3SnH$ gave an 18% yield of **10** and **11**.

Other methods of generating radical **61** have been unsuccessful. Reduction of the phenyl thionocarbonate ester[39] gave no tricyclic products. Photolysis of secondary acetates in wet HMPA has been reported to give the hydrocarbon in excellent yield.[40] Unfortunately, photolysis of the acetate of **58** in wet HMPA gave no β-copaene or β-ylangene.

β-Copaene and β-ylangene were readily separated by preparative GC on XF-1150 (a silicone nitrile) at 90 °C. This is marked improvement over previously reported procedures for the separation of these compounds[19] and their α isomers.[18,19] The spectral data are identical with those previously reported.[19] This procedure makes β-copaene and β-ylangene readily available from geranylacetone in seven steps in 12% overall yield.

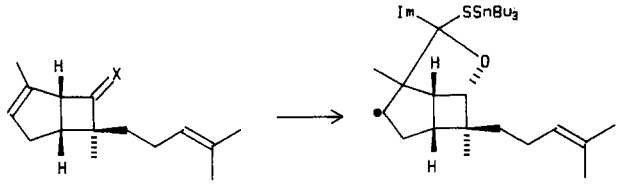
We attempted to isomerize a mixture of **10** and **11** to a mixture of α-copaene and α-ylangene with hydrogen and palladium on calcium carbonate as reported for the conversion of β-pinene to α-pinene[26] and used above for the synthesis of chrysanthenone. Unfortunately, the only products isolated were the saturated hydrocarbons. No reaction occurred with palladium on barium sulfate or on lead-poisoned palladium on calcium carbonate.

Synthesis of Lemnalol. The antitumor agent lemnalol (**12**) has recently been isolated from the soft coral *Lemnalia tenuis* Verseveldt, a source markedly different from

(34) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans 1* **1975**, 1574. We thank Professor Barton for valuable suggestions on improving the yield of the reductive cyclization.
(35) For a review see: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.
(36) Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1983**, *47*, 4403. Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313 and ref 8 therein.
(37) Bakuzis, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261.
(38) Barton, D. H. R.; Motherwell, W.; Stange, A. *Synthesis* **1981**, 743.
(39) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.
(40) Pete, J.-P.; Portella, C.; Monneret, C.; Florent, J.-C.; Khuong, Huu, Q. *Synthesis* **1977**, 774. Deshayes, H.; Pete, J.-P.; Portella, C.; Scholler, *J. Chem. Soc., Chem. Commun.* **1975**, 439. Deshayes, H.; Pete, J.-P.; Portella, C. *Tetrahedron Lett.* **1976**, 2019.

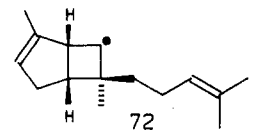
the essential oils from which β-ylangene has been isolated.[13] Oxidation of β-ylangene with SeO_2 and *t*-BuOOH[41] gave a 76% yield of lemnalol (**12**), which was identical with an authentic sample by spectroscopic and chromatographic comparison.[42] The selective formation of the axial alcohol was anticipated from related results obtained in the oxidation of β-pinene.[41]

Attempted Synthesis of α-Bourbonene. The tricyclic sesquiterpene α-bourbonene (**70**) has been prepared with photochemical [2 + 2] cycloaddition as the key step.[43]

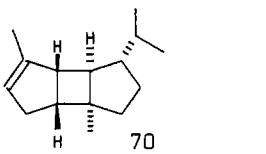


64, X=O
65, X=αOH, H
66, X=αOCSIm, H
67, X=αOCCIm, H
SSnBu3
68, X=βOH, H
69, X=Br, H

71



72

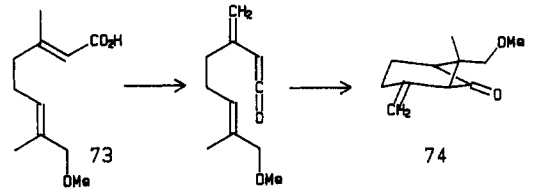


70

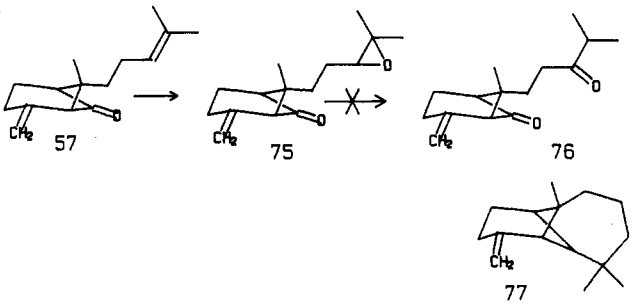
Corbella et al. have prepared sesquifilifolone (**64**) from (*E,E*)-farnesic acid by Beereboom's procedure and reduced it to **65**.[30] They tried unsuccessfully to convert **65** to α-bourbonene by solvolysis in acid.[30b] Reductive cyclization of thiocarbonyl imidazolide **66** appeared to offer an attractive route to α-bourbonene. However, no tricyclic product was obtained, and the NMR spectrum of the crude product suggested that the side-chain double bond was intact and the cyclopentene double bond had reacted. Presumably the radical **67** cyclizes, prior to fragmentation to **72**, to give **71** or its regioisomer as has been observed by Angoh and Clive in a related example.[44] We therefore turned our attention to alternative methods to generate the cyclobutyl radical **72**.

Initially we attemped to prepare the more stable β-alcohol **68**, which will give a radical epimeric to **67** that cannot add to the cyclopentane double bond. Unfortunately, dissolving metal reduction of **64** under a variety of conditions gave a complex mixture of products. We then turned our attention to the conversion of **65** to compounds such as **69** that can serve as a precursor to the cyclobutyl radical **72**. Attempted preparation of the mesylate of **65** with methanesulfonyl chloride and triethylamine in dichloromethane even at −30 °C led to a complex mixture of products. In view of the reactivity of **37**, the instability of a homoallylic cyclobutyl mesylate is not surprising. This approach to α-bourbonene was therefore abandoned.

With a view toward the preparation of paeonoflorin (**7**), we have briefly explored the effect of oxygen substituents on the cycloaddition. Hydroxylation of methyl geranoate with SeO_2 and *t*-BuOOH[41] followed by methylation of the alcohol with silver oxide and methyl iodide and hydrolysis of the ester gave the methoxy acid **73**. Acid **73** was converted to the acid chloride, which was treated with triethylamine to give a 30% yield of **74** as a single stereoisomer, indicating that allylic oxygen functionality is compatible with the cycloaddition.



73 74



57 75 76

77

Epoxidation of **57** with 1 equiv of *m*-chloroperbenzoic acid in a two-phase mixture of methylene chloride and aqueous sodium bicarbonate for 2 h at 25 °C gave a 94% yield of **75** as a ~1:1 mixture of diastereomers. The trisubstituted double bond is much more reactive than the exocyclic double bond. With excess peracid, Baeyer–Villiger oxidation became a major side reaction. Unfortunately, we could not isomerize the epoxide of **75** to the ketone **73**, which would be a potential precursor for longipinene (**77**).

Conclusion

These results clearly indicate the power of the intramolecular [2 + 2] cycloaddition of ketenes to generate bi- and tricyclic terpenes containing the bicyclo[3.1.1]heptane ring system that are otherwise inaccessible. We are continuing to explore the scope and mechanism of these reactions and are exploiting them in total synthesis.

Experimental Section

Materials and Methods. NMR spectra were recorded on Varian EM-390 and XL-300 spectrometers in $CDCl_3$. Chemical shifts are reported (ppm) downfield from tetramethylsilane (δ) for proton and carbon with tetramethylsilane as a standard for proton spectra and $CDCl_3$ (triplet centered at δ 77.00) as a standard for carbon spectra. Coupling constants are reported in hertz. IR spectra were obtained on a Perkin-Elmer 683 spectrometer. Combustion analyses were performed by Galbraith Laboratories, Inc. MPLC refers to medium-pressure liquid chromatography on a Merck Lobar silica gel column. All air-sensitive reactions were run under nitrogen in flame-dried glassware with magnetic stirring. Reagents were added via oven-dried syringes through septa. All solvents for air- or moisture-sensitive reactions were dried by standard procedures.

7,7-Dimethyl-2-methylenebicyclo[3.1.1]heptan-6-one (24). Oxalyl chloride (3.81 g, 30 mmol) was added dropwise to a cooled solution of (*E*)-3,7-dimethyl-2,6-octadienoic acid (**19**; 1.00 g, 6 mmol) in 10 mL of dry benzene. The resulting solution was allowed to warm to 25 °C, stirred for 2 h, and heated at 45 °C for 30 min. The solvent and unreacted oxalyl chloride were removed in vacuo to give 1.12 g (100%, 90% pure) of acid chloride **20**: NMR 1.6 (br s, 3), 1.70 (br s, 3), 2.10 (s, 3), 1.90–2.30 (m, 4), 5.02 (br t, 1, J = 6), 6.00 (br s, 1); IR (neat) 1770, 1615 cm^{-1}.

Crude acid chloride **20** (1.12 g, 6 mmol) dissolved in 50 mL of dry toluene was added dropwise with stirring to a solution of

(41) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.
(42) We thank Dr. Tsukitani for an authentic sample of lemnalol.
(43) White, J. D.; Gupta, D. N. *J. Am. Chem. Soc.* **1966**, *88*, 5364. Brown, M. *J. Org. Chem.* **1968**, *33*, 162.
(44) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 980.

triethylamine (1.82 g, 18 mmol) in 100 mL of toluene at reflux. The solution was heated at reflux for 3 h, cooled to 25 °C, and filtered to remove the precipitated triethylamine hydrochloride. The solid residue was washed with 4 × 25 mL of hexane. The filtrate was evaporated in vacuo to give a red oil, which was purified by flash chromatography on silica gel (95:5 hexane–EtOAc) to give 0.39 g (43%) of pure **24** and 0.02 g (2%) of **6** followed in later fractions by 0.08 g (7%) of 6-(1-chloro-1-methylethyl)-3-methyl-2-cyclohexen-1-one (**25**).

Spectral data for **24**: NMR 1.07 (s, 3), 1.20 (s, 3), 2.05–2.35 (m, 4), 2.62 (ddd, 1, J = 7.2, 5.7, 2.5, H_5), 3.15 (d, 1, J = 7.2, H_1), 4.63 (br, 1), 4.80 (br, 1); ^{13}C NMR 17.4, 24.8, 25.2, 27.1, 31.9, 62.4, 74.3, 109.7, 148.2, 209.2; IR (neat) 1780, 1645 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.66; H, 9.24.

Spectral data for **25**: NMR 1.66 (s, 3), 1.91 (s, 3), 1.94 (br s, 3), 2.35–2.45 (m, 2), 2.55–2.68 (m, 2), 2.70 (dd, 1, J = 5.0, 5.0), 5.79 (br s, 1); ^{13}C NMR 23.6, 26.0, 28.1, 31.6, 33.7, 56.8, 73.1, 127.5, 160.8, 197.8; IR (neat) 1670, 1640 cm^{-1}. The spectral data are identical with those previously described.[45]

A similar reaction sequence carried out on 9.0 g (55 mmol) of **19** using 550 mL of toluene for the cyclization gave a 40% yield of **24**, 5% yield of **6**, and a 7% yield of **25**. A similar reaction sequence carried out on 11.8 g (65 mmol) of **19** using 130 mL of toluene for the cyclization gave a 30% yield of **24**, 11% yield of **6**, and a 7% yield of **25**.

Chrysanthenone (6). Hydrogen was bubbled through a solution of ketone **24** (1.20 g, 8 mmol) and 5% Pd on $CaCO_3$ (60 mg) in 3 mL of hexane for 10 min at 25 °C. The flask was sealed and stirred for 75 min. The solution was filtered to remove the catalyst, and the filtrate was evaporated in vacuo to give 1.15 g (95%) of pure **6**. The NMR, ^{13}C NMR, and IR spectra are identical with those previously reported.[46]

β-Pinene (5). A mixture of ketone **24** (0.10 g, 0.67 mmol) and hydrazine monohydrate (0.34 g, 6.7 mmol) in 3 mL of triethylene glycol was heated at 110 °C for 30 min and then at 150 °C to remove water. The reaction mixture was cooled, and solid, powdered KOH (0.75 g, 13.4 mmol) was added. The mixture was heated at 185 °C for 1 h, cooled, and poured over ice water. The mixture was extracted with ether (4 × 10 mL). The combined ether fractions were dried and evaporated at atmospheric pressure to give crude β-pinene. Evaporative distillation gave 0.062 g (68%) of pure β-pinene. The NMR, ^{13}C NMR, and IR spectra are identical with those previously reported.[46]

Isopiperitenone (34). Boron trifluoride etherate (0.1 mL, 0.9 mmol) was added to a solution of ketone **24** (25 mg, 0.17 mmol) in 1 mL of dry 1,2-dichloroethane. The solution was stirred at 25 °C for 30 min and quenched by addition of ice. Normal workup followed by flash chromatography on silica gel (95:5 hexane–EtOAc) gave 19 mg (95%) of pure **34**: NMR 1.73 (s, 3), 1.93 (s, 3), 1.95–2.45 (m, 4), 2.94 (t, 1, J = 8.0), 4.77 (m, 1), 4.94 (m, 1), 5.89 (m, 1); IR (neat) 1675, 1450, 1380 cm^{-1}. The spectral data are identical with those of an authentic sample.[47]

Piperitenone (35). A solution of ketone **24** (90 mg, 0.6 mmol, 1 equiv), sodium acetate (37 mg, 0.45 mmol, 0.75 equiv), acetic anhydride (60 mg, 0.6 mmol, 1 equiv), and acetic acid (71 mg, 1.2 mmol, 2 equiv) was refluxed for 12 h. Water (1 mL) was added to the dark red solution, which was cooled to 25 °C and stirred overnight. Normal workup gave 46.2 mg of crude product. Purification by flash chromatography (silica gel, 5–50% ether in pentane) gave 20 mg (22%) of piperitenone: NMR 1.86 (s, 3), 1.94 (br, 3), 2.10 (s, 3), 2.18 (t, 1, J = 2.0), 2.66 (t, 2, J = 6.3), 5.90 (q, 1, J = 1.4).

***exo*-2,7,7-Trimethylbicyclo[3.1.1]hept-2-en-6-ol (36).** Ketone **24** (0.40 g, 2.67 mmol) in 6 mL of THF was added to a slurry of LAH (0.31 g, 8 mmol) in 5 mL of THF. The reaction mixture was stirred overnight at 25 °C and quenched by the addition of methanol (2 mL), water (2 mL), 10% NaOH (4 mL), and water (2 mL) with cooling. Normal workup followed by flash chromatography on silica gel (85:15 hexane–EtOAc) gave 0.270 g (67%) of pure **36**: NMR 0.89 (s, 3), 1.56 (s, 3), 1.65 (br s, 3), 1.98 (m, 2), 2.15–2.35 (m, 2), 3.04 (br s, 1, OH), 3.95 (s, 1), 5.19 (m, 1); ^{13}C NMR 22.6, 23.0, 27.2, 32.0, 37.0, 46.6, 53.3, 78.2, 117.5, 142.5; IR (neat) 3400, 1445 cm^{-1}. The spectral data are identical with those previously described.[48]

***exo*-2,7,7-Trimethylbicyclo[3.1.1]hept-2-en-6-yl Tosylate (37).** Tosyl chloride (0.32 g, 1.7 mmol) was added to a solution of **36** (0.206 g, 1.36 mmol) in 2 mL of dry pyridine at −5 °C. The solution was stirred overnight at 0 °C and quenched by the addition of 0.1 mL of water to hydrolyze unreacted tosyl chloride. After 1 h, the solution was diluted with 20 mL of water and worked up to give 0.400 g (98%) of pure **37**: mp 47–49 °C; NMR 0.85 (s, 3), 1.42 (s, 3), 1.56 (d, 3, J = 1.8), 2.00 (d, 1, J = 7.2), 2.10–2.18 (m, 1), 2.24 (m, 2), 2.45 (s, 3), 4.45 (s, 1), 5.21 (br s, 1), 7.36 (d, 2, J = 8.4), 7.77 (d, 2, J = 8.4); ^{13}C NMR 21.6, 22.3, 26.4, 31.8, 37.4, 45.7, 51.5, 86.1, 118.1, 127.8, 129.7, 134.2, 141.3, 144.6.

2,6,6-Trimethyltricyclo[3.2.0.0^{2,7}]heptane (38). A solution of tosylate **37** (0.30 g, 1 mmol) in 2 mL of dry ether was added to a slurry of LAH (0.057 g, 1.5 mmol) in 4 mL of dry ether. The mixture was heated at reflux for 5 h and worked up by the addition of 0.5 mL of methanol, 0.5 mL of water, 1.0 mL of 10% NaOH, and 1 mL of water. The ether layer was separated, and the aqueous layer was washed with several portions of ether. The combined ether layers were dried, and the solvent was removed at atmospheric pressure with gentle heating. The residue was distilled at 65 °C (25 torr) to give 55 mg (41%) of pure **38**: NMR 0.75 (s, 3), 1.05 (s, 3), 1.10 (dd, 1, J = 3.0, 5.0, H_1 or H_7), 1.19 (s, 3), 1.50 (dd, 1, J = 9.0, 11.5, H_4), 1.69 (dddd, 1, J = 3.7, 6.4, 11.5, 11.5, $H_{4\beta}$), 1.79 (dd, 1, J = 11.5, 11.5, $H_{3\beta}$), 1.85 (m, 1, H_5), 1.95 (dd, J = 3.0, 5.0, H_7 or H_1), 2.06 (ddd, 1, J = 6.4, 9.0, 11.5, H_3); ^{13}C NMR 18.9 (C_6-Me at 1.05), 22.0 (C_6-Me at 0.75), 29.9 (C_4), 31.1 (C_2-Me), 31.8 (C_3), 31.9 (C_1 or C_7), 34.3 (C_7 or C_1), 36.6, 49.1 (C_5), one quaternary carbon was not seen, even with added Cr(AcAc)$_2$; IR (neat) 2810–3030, 1450, 1360 cm^{-1}. The data are identical with those described for cyclopinene.[32b]

***exo*-7,7-Dimethyl-2-methylenebicyclo[3.1.1]heptan-6-ol (40).** Reduction of ketone **24** (450 mg, 3 mmol) with LAH as described above for the preparation of **36** gave 0.35 g (77%) of pure **40**: mp 43–45 °C; NMR 0.76 (s, 3), 1.53 (s, 3), 1.85–1.95 (m, 2), 1.95–2.05 (m, 1), 2.15–2.30 (m, 1), 2.37 (dddd, 1, J = 2.2, 2.2, 9.0, 9.0), 2.49 (d, 1, J = 6.0), 2.50 (br s, 1, OH), 4.11 (s, 1), 4.58 (m, 1), 4.64 (m, 1); ^{13}C NMR 23.5, 23.8, 23.9, 28.1, 39.8, 46.4, 58.1, 75.2, 106.7, 151.0; IR ($CHCl_3$) 3600, 1640 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.62; H, 10.47.

***exo*-7,7-Dimethyl-2-methylenebicyclo[3.1.1]heptan-6-yl Tosylate (41).** Reaction of **40** (0.3 g, 2 mmol) with tosyl chloride as described above for the preparation of **37** gave 0.60 g (98%) of **41**: NMR 0.71 (s, 3), 1.38 (s, 3), 1.80–1.95 (m, 2), 2.07–2.17 (m, 1), 2.18–2.19 (m, 1), 2.30–2.45 (m, 1), 2.45 (s, 3), 2.48 (d, 1, J = 6.4), 4.52 (m, 1), 4.56 (s, 1), 4.67 (m, 1), 7.33 (d, 2, J = 8.4), 7.78 (d, 2, J = 8.4); ^{13}C NMR 21.6, 23.0, 23.1, 23.6, 27.1, 40.1, 45.5, 56.2, 83.7, 108.5, 128.0, 129.7, 134.1, 144.7, 148.4; IR (neat) 1640, 1600, 1360, 1180 cm^{-1}.

***endo*-7,7-Dimethyl-2-methylenebicyclo[3.1.1]heptan-6-ol (43).** A solution of alcohol **40** (85 mg, 0.56 mmol) was added to a suspension of hexane-washed NaH (67 mg of 60% dispersion in mineral oil, 0.7 mmol) in 3 mL of dry THF containing a trace of imidazole under nitrogen. The resulting mixture was heated at reflux for 2.5 h and quenched with water. Normal workup followed by flash chromatography on silica gel (85:15 hexane–EtOAc) gave 34 mg (40%) of **43** as a pale yellow oil: NMR 0.83 (s, 3), 1.18 (s, 3), 1.65–1.98 (m, 2), 2.16–2.24 (m, 1), 2.26–2.40 (m, 1), 2.42–2.56 (m, 1), 2.76 (dd, 1, J = 5.4, 5.9), 4.53 (dd, 1, J = 5.9, 5.9), 4.71 (m, 1), 4.82 (m, 1); ^{13}C NMR 19.4, 20.8, 23.9, 26.9, 33.0, 46.1, 59.0, 67.3, 110.4, 148.2; IR (neat) 3310, 1640, 1450 cm^{-1}.

(2*E*,6*Z*)-3,7,11-Trimethyl-2,6,10-dodecatrienoic acid (48) was prepared from nerylacetone (**46**; 1.94 g, 10 mmol) as described below for the preparation of **54**. Reaction with the sodium salt of triethyl phosphonoacetate gave 2.64 g (100%) of crude **47** as a 9:1 mixture of *E*,*Z* and *Z*,*Z* isomers: NMR 2.15 (br s, 3). The minor isomer could be detected by peaks at 1.88 (br s, 3) and 2.65

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(t, 2, J = 8.0). Hydrolysis of **47**, as described below, gave 2.2 g (93%) of a 9:1 mixture of **48** and the 2(Z) isomer which was used without purification: NMR 1.61 (br s, 3), 1.69 (br s, 6), 2.04 (m, 4), 2.17 (d, 3, J = 1.2), 2.18 (m, 4), 5.10 (m, 2), 5.68 (br s, 1). The 2(Z) isomer was assigned on the basis of peaks at 1.93 (d, 3, J = 1.5) and 2.65 (t, 2, J = 8.2).

***syn*-7-Methyl-2-methylene-7-(4-methyl-3-pentenyl)bicyclo[3.1.1]heptan-6-one (51).** (2E,6Z)-3,7,11-Trimethyl-2,6,10-dodecadienoic acid (**48**; 1.89 g, 8 mmol, 85% pure) was converted to the acid chloride **49** and thence to **51** as described below for the preparation of **57**. Purification as described above gave 0.58 g (39% based on 85% pure acid) of pure **51**: NMR 1.18 (s, 3), 1.45 (m, 2), 1.60 (s, 3), 1.69 (s, 3), 1.90–2.40 (m, 6), 2.68 (br dd, 1, J = 6.6, 6.2), 3.21 (d, 1, J = 6.6), 4.63 (m, 1), 4.83 (m, 1), 5.12 (t, 1, J = 7.3); ^{13}C NMR 17.5, 23.2, 23.9, 24.1, 25.4, 25.7, 31.1, 34.5, 62.2, 73.9, 110.3, 124.1, 131.6, 147.6, 209.1; IR (neat) 1780, 1645 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O$: C, 82.50; H, 10.00. Found: C, 80.70; H, 10.16.

The isomer with an endocyclic double bond (0.045 g, 3%) was isolated from later chromatographic fractions: NMR 1.19 (s, 3), 1.40–1.60 (m, 2), 1.62 (s, 3), 1.70 (s, 3), 1.74 (d, 3, J = 1.6), 1.80–2.0 (m, 2), 2.63 (m, 4), 5.13 (m, 1), 5.37 (m, 1); ^{13}C NMR 17.5, 22.9, 24.2, 24.5, 25.7, 28.0, 32.4, 37.5, 62.4, 66.9, 118.9, 124.2, 131.7, 137.6, 206.3; IR (neat) 1780, 1450, 1375 cm^{-1}.

***β-cis*-Bergamotene (8).** Wolff–Kishner reduction of **51** (96 mg, 0.44 mmol) as described above for the preparation of **5** gave crude product. Flash chromatography on silica gel (hexane) gave 54 mg (60%) of pure **8**: NMR 1.11 (m, 2), 1.23 (s, 3), 1.42 (d, 1, J = 9.9), 1.58 (s, 3), 1.66 (s, 3), 1.79–1.98 (m, 4), 2.05–2.14 (m, 1), 2.29–2.43 (m, 2), 2.52 (br dd, 1, J = 5.1, 5.1), 2.5–2.6 (m, 1), 4.58 (m, 1), 4.65 (m, 1), 5.07 (br t, 1, J = 7.2); ^{13}C NMR 17.5, 21.9, 22.6, 23.1, 23.7, 25.7, 26.7, 35.2, 40.1, 43.0, 51.2, 106.4, 125.3, 130.7, 151.7; IR (neat) 2910, 1640, 1450, 1370 cm^{-1}. The H NMR and IR spectral data are identical with those of an authentic sample.[8,16]

(2*E*,6*E*)-3,7,11-Trimethyl-2,6,10-dodecatrienoic Acid (54). Triethyl phosphonoacetate (2.7 g, 12 mmol) in 5 mL of DME was added to a suspension of hexane-washed NaH (0.48 g, 60% dispersion in mineral oil, 12 mmol) in 25 mL of DME. The solution was stirred for 30 min, cooled to 0 °C in an ice–salt bath, and treated with geranylacetone (**52**; 1.94 g, 10 mmol) in 5 mL of dry DME. The solution was slowly warmed to 25 °C and stirred for 3 h. It was then heated at reflux for 30 min, cooled, and worked up to give 2.64 g (100%) of crude **53** as a 9:1 mixture of E,E and E,Z isomers: NMR 2.15 (d, 3, J = 1.5). The minor isomer could be detected by peaks at 1.90 (d, 3, J = 1.5) and 2.70 (t, 2, J = 8.0). Ester **53** was added to 50 mL of 10% aqueous NaOH solution, and the resulting mixture was heated at reflux overnight. The solution was cooled, washed with hexane, and carefully neutralized with concentrated hydrochloric acid, taking care to keep the reaction mixture at 0 °C. The aqueous layer was extracted with several portions of ether that were dried and evaporated to give 2.2 g (93%) of a 87:13 mixture of **54** and the 2(Z) isomer, which was used without purification: NMR 1.60 (br s, 6), 1.68 (br s, 3), 1.98 (t, 2, J = 7.5), 2.05 (dt, 2, J = 7.5, 7.5), 2.17 (d, 3, J = 1.2), 2.15–2.26 (m, 4), 5.08 (m, 2), 5.69 (br s, 1). The 2(Z) isomer was assigned on the basis of peaks at 1.92 (d, 3, J = 1.5) and 2.65 (t, 2, J = 8.0).

Alternatively, **54** was prepared by oxidation of commercial (E,E)-farnesol to farnesal with pyridinium dichromate, followed by oxidation of farnesal to **54** with silver oxide.[49]

***anti*-7-Methyl-2-methylene-7-(4-methyl-3-pentenyl)bicyclo[3.1.1]heptan-6-one (57).** (2E,6E)-3,7,11-Trimethyl-2,6,10-dodecatrienoic acid (**54**; 1.89 g, 8 mmol, 85% pure) in 10 mL of dry benzene was added cautiously to a suspension of hexane-washed NaH (0.32 g of 60% dispersion in mineral oil, 8 mmol) in 5 mL of dry benzene. The mixture was stirred for 15 min at 25 °C at which time hydrogen evolution had ceased. The solution was treated with oxalyl chloride (2.0 g, 16 mmol) and stirred for 1.5 h at 25 °C and 0.5 h at 40 °C. The solvent and excess oxalyl chloride were removed in vacuo to give a quantitative yield of crude acid chloride **55**: NMR 1.60 (br s, 6), 1.68 (br s, 3), 1.90–2.35 (m, 8), 2.13 (br s, 3), 5.09 (m, 2), 6.03 (br s, 1); IR (neat) 1770, 1610 cm^{-1}.

The crude acid chloride was dissolved in 80 mL of dry toluene and added dropwise with vigorous stirring to a solution of triethylamine (2.4 g, 24 mmol) in 160 mL of toluene at reflux. The resulting mixture was heated at reflux for 1 h, cooled, and worked up to give a red oil. Flash chromatography on silica gel (95:5 hexane–EtOAc) gave 0.73 g (49% based on 85% pure acid) of pure **57**: NMR 1.02 (s, 3), 1.45 (m, 2), 1.60 (s, 3), 1.68 (br s, 3), 1.90–2.03 (m, 2), 2.06–2.16 (m, 2), 2.26–2.38 (m, 2), 2.72 (ddd, 1, J = 2.9, 2.9, 7.5, H_5), 3.21 (d, 1, J = 7.0, H_1), 4.64 (m, 1), 4.81 (m, 1), 5.08 (t, 1, J = 7.0); ^{13}C NMR 14.3, 17.6, 23.5, 24.8, 25.4, 25.6, 35.4, 40.0, 67.0, 73.2, 110.1, 123.7, 131.9, 148.1, 209.4; IR (neat) 1775, 1642, 1450, 1378 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O$: C, 82.50; H, 10.00. Found: C, 82.15; H, 10.16.

***β-trans*-Bergamotene (9).** A solution of ketone **57** (0.11 g, 0.5 mmol) and anhydrous hydrazine (0.16 g, 5 mmol) in 2.5 mL of diethylene glycol was heated at 105 °C for 3 h and at 155 °C for 0.5 h. The solution was cooled, treated with freshly powdered KOH (0.56 g, 10 mmol), and heated at 190 °C for 2 h. The solution was cooled and worked up as described above for the preparation of β-pinene. Flash chromatography on silica gel (hexane) gave 41 mg (40%) of pure **9**: NMR 0.71 (s, 3), 1.44 (d, 1, J = 9.9), 1.63 (s, 3), 1.53–1.70 (m, 3), 1.70 (s, 3), 1.76–1.88 (m, 1), 1.96 (br td, 2, J = 7.2, 7.2), 2.00–2.10 (m, 1), 2.20–2.37 (m, 2), 2.53 (br dd, 1, J = 5.2, 5.2), 2.5–2.6 (m, 1), 4.57 (m, 1), 4.64 (m, 1), 5.17 (t, 1, J = 6.9); ^{13}C NMR 17.6, 18.6, 23.5, 23.8, 25.7, 27.1, 31.6, 38.2, 38.7, 43.8, 50.2, 106.0, 125.1, 131.1, 152.1; IR (neat) 2910, 1640, 1450, 1370 cm^{-1}. The H NMR and IR spectral data are identical with those of an authentic sample.[8,17]

***exo,anti*-7-Methyl-2-methylene-7-(4-methyl-3-pentenyl)bicyclo[3.1.1]heptan-6-ol (58).** Reduction of **57** (287 mg, 1.3 mmol) with LAH as described above for the preparation of **36** gave, after purification, 240 mg (84%) of pure **58**: NMR 0.77 (s, 3), 1.62 (s, 3), 1.68 (s, 3), 1.85–2.12 (m, 8), 2.23 (br dd, 1, J = 8.2, 18.2), 2.33–2.50 (m, 1), 2.56 (d, 1, J = 7.2), 4.12 (s, 1), 4.59 (m, 1), 4.65 (m, 1), 5.17 (t, 1, J = 7.0); ^{13}C NMR 17.6, 20.4, 23.2, 23.7, 23.9, 25.7, 40.0, 42.9, 44.8, 56.7, 75.8, 106.9, 125.3, 130.9, 150.9; IR (neat) 3340, 1640, 1450, 1370 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O$: C, 81.75; H, 10.98. Found: C, 81.19; H, 11.23.

Imidazolide (59). A solution of alcohol **58** (0.220 g, 1 mmol) and thiocarbonyldiimidazole (0.33 g, 2 mmol) in 5 mL of dry dichloromethane was stirred overnight at 25 °C. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel (4:1 hexane–EtOAc) to give 0.25 g (76%) of pure **59**: NMR 0.85 (s, 3), 1.53 (s, 3), 1.65 (s, 3), 1.79 (br t, J = 8.8), 1.92–2.08 (m, 3), 2.08–2.22 (m, 1), 2.33–2.45 (m, 1), 2.50–2.66 (m, 2), 3.00 (d, 1, J = 6.9), 4.74 (m, 1), 4.82 (m, 1), 5.08 (br t, 1, J = 7.5), 5.20 (s, 1), 7.06 (s, 1), 7.65 (s, 1), 8.35 (s, 1); ^{13}C NMR 17.4, 19.9, 23.2, 23.4 (2 carbons), 25.6, 39.6, 43.0, 43.7, 54.1, 86.0, 109.0, 117.1, 124.3, 130.8, 131.5, 136.7, 148.0, 182.8; IR (neat) 1642, 1460, 1380, 1230 cm^{-1}.

β-Copaene (10) and β-Ylangene (11). (n-Bu)$_3$SnH (0.39 g, 1.35 mmol) in 4 mL of dry toluene was added to a solution of imidazolide **59** (150 mg, 0.45 mmol) dissolved in 3 mL of dry toluene. The solution was heated at reflux for 3 h, cooled, and evaporated in vacuo. Flash chromatography on silica gel (hexane) gave 14 mg (15%) of a 1:1 mixture of **10** and **11**. Elution with 98:2 hexane–EtOAc gave 48 mg (40%) of hemithioacetal **63**. Elution with 85:15 hexane–EtOAc gave 25 mg (25%) of recovered alcohol **58**. The mixture of **10** and **11** was separated by GC ($^1/_4$ in. × 6 ft 10% XF-1150 on Chromosorb PNAW, 50 mL/min, 90 °C).

A solution of imidazolide **59** (44 mg, 0.13 mmol), (n-Bu)$_3$SnH (0.14 mL, 0.268 mmol), and AIBN (2 mg, 0.013 mmol) in 3.5 mL of dry toluene was added to 5 mL of toluene at reflux over the course of 12 h by the use of a syringe infusion pump. After an additional 2 h, TLC showed that **59** was still present. A solution of (n-Bu)$_3$SnH (0.14 mL, 0.26 mmol) and AIBN (5 mg, 0.03 mL) in 3 mL of toluene was then added slowly over the course of 6 h by a syringe infusion pump to the reaction mixture at reflux. Workup and chromatography as described above gave 12.6 mg (46%) of a mixture of **10** and **11**, 9.7 mg (28%) of **63**, and 10.2 mg (34%) of **58**.

Data for β-ylangene (**11**): t_R 23 min; NMR 0.70 (s, 3), 0.86 (d, 3, J = 6.6), 0.87 (d, 3, J = 6.6), 1.45–1.70 (m, 7), 1.80–1.88 (m, 2), 2.00 (s, 1), 2.20–2.30 (m, 1), 2.40–2.55 (m, 1), 2.55 (d, 1, J = 5.9), 4.58 (m, 1), 4.67 (m, 1); ^{13}C NMR 19.6, 19.9, 20.0, 21.9, 23.0,

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24.2, 32.4, 36.7, 41.0, 42.8, 44.0, 48.2, 48.4, 106.2, 151.6; IR (neat) 3070, 2915, 2870, 1640, 1450, 1370 cm^{-1}; MS m/e (rel intens, %) 204 (12), 189 (8), 161 (88), 147 (15), 133 (26), 120 (67), 119 (39), 105 (95), 91 (100). The spectral data are identical with those previously reported.[19]

Data for β-copaene (**10**): t_R 26 min; NMR 0.69 (s, 3), 0.86 (d, 3, J = 6.6), 0.87 (d, 3, J = 6.6), 1.45–1.70 (m, 7), 1.80–1.88 (m, 2), 2.00–2.10 (m, 2), 2.16–2.30 (m, 1), 2.40–2.56 (m, 1), 4.56 (m, 1), 4.65 (m, 1); ^{13}C NMR 19.6, 19.9, 20.0, 21.7, 22.3, 24.3, 32.4, 36.5, 36.6, 40.7, 43.1, 43.7, 59.7, 105.8, 152.0; IR (neat) 3070, 2915, 2870, 1640, 1370 cm^{-1}; MS m/e (rel intens, %) 204 (15), 189 (2), 161 (100), 147 (10), 135 (25), 120 (20), 119 (42), 105 (73), 91 (65). The spectral data are identical with those previously reported.[19]

Data for **63**: NMR 0.77 (s, 3), 1.62 (s, 3), 1.69 (s, 3), 1.80–2.05 (m, 6), 1.99 (dd, 1, J = 9.3, 9.3, SH), 2.08–2.13 (m, 1), 2.13–2.23 (m, 1), 2.40–2.55 (m, 1), 2.72 (d, 1, J = 6.4), 4.01 (s, 1), 4.62 (m, 1), 4.69 (m, 1), 4.74 (dd, 1, J = 9.3, 11.3), 4.80 (dd, 1, J = 9.3, 11.3), 5.15 (m, 1); ^{13}C NMR 17.6, 20.2, 23.2, 23.7, 23.9, 25.7, 39.3, 42.6, 43.3, 53.7, 65.3, 80.1, 107.4, 125.2, 130.9, 150.3; IR (neat) 2530, 1640, 1440, 1070 cm^{-1}.

Dithiocarbonate of 58. A solution of alcohol **58** (44 mg, 0.2 mmol) in 1 mL of THF was cooled to −78 °C and treated with butyllithium (0.1 mL of 2.05 M, 0.2 mmol). The solution was warmed to 0 °C and treated with carbon disulfide (76 mg, 1 mmol). The mixture was stirred for 15 min at 25 °C and 15 min at 50 °C and cooled to 25 °C. Methyl iodide (142 mg, 1 mmol) was added, and the solution was stirred at 50 °C for 20 min. Normal workup followed by flash chromatography on silica gel (98:2 hexane–EtOAc) gave 63 mg (94%) of pure dithionocarbonate: NMR 0.80 (s, 3), 1.62 (s, 3), 1.68 (s, 3), 1.75–2.65 (m, 10), 2.56 (s, 3), 4.68 (m, 1), 4.75 (m, 1), 5.15 (br t, 1, J = 7.0), 5.18 (s, 1); ^{13}C NMR 17.6, 18.9, 20.0, 23.3, 23.4, 23.5, 25.7, 39.4, 42.8, 43.7, 54.3, 86.7, 108.4, 124.8, 131.2, 148.8, 214.1; IR (neat) 1640, 1450, 1210, 1070 cm^{-1}.

Lemnalol (12). A solution of β-ylangene (1.1 mg, 0.005 mmol; **11**), *tert*-butyl hydroperoxide (0.81 mg, 0.009 mmol, 90%, dried over $MgSO_4$ and dissolved in hexane), and selenium dioxide (0.34 mg, 0.003 mmol) in 0.4 mL of dry hexane was stirred for 4 h at 25 °C. The mixture was diluted with 5 mL of hexane, washed with 5 mL of 10% aqueous KOH, dried, and evaporated. Chromatography on silica gel (9:1 hexane–EtOAc) gave 0.9 mg (76%) of pure **12**: NMR 0.61 (s, 3), 0.84 (d, 6, J = 6.6), 1.40–1.75 (m, 8), 1.85 (ddd, 1, J = 1.5, 4.0, 14), 2.23 (s, 1), 2.23 (ddd, 1, J = 1.9, 7.8, 14), 2.62 (d, 1, J = 6.1), 4.42 (br d, 1, J = 7.8), 4.86 (br s, 1), 5.04 (br s, 1); ^{13}C NMR 19.5, 20.0, 20.2, 21.5, 32.4, 33.8, 36.5, 42.0, 42.5, 44.3, 47.1, 47.5, 66.9, 111.6, 155.2; IR ($CDCl_3$) 3605, 2750–3000, 1650 cm^{-1}. The spectral data are identical with those previously reported.[13,42]

Imidazolide 66. A solution of alcohol **65**[30] (294.4 mg, 1.34 mmol) and 1,1′-thiocarbonyldiimidazole in 6 mL of dry CH_2Cl_2 was stirred overnight. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (silica gel, 4:1 pentane–ether) to give 136.5 mg (0.4 mmol, 31%) of imidazolide **66**: NMR 1.10 (s, 3), 1.59 (s, 3), 1.60 (s, 3), 1.65 (br, 3), 1.68 (m, 2), 1.95 (m, 2), 2.31 (s, 1), 2.46 (m, 2), 3.60 (br, 1), 5.09 (m, 1), 5.53 (s, 1), 5.58 (d, 1, J = 7.5), 7.03 (t, 1, J = 1.5), 7.61 (t, 1, J = 1.5), 8.32 (s, 1); ^{13}C NMR 14.8, 16.5, 17.5, 22.9, 25.6, 34.0, 40.9, 43.1, 45.7, 50.6, 84.4, 117.7, 124.0, 129.7, 130.7, 131.5, 136.5, 138.9, 183.4.

(*E*)-8-Methoxy-3,7-dimethyl-2,6-octadienoic Acid (73). Oxidation of methyl 3,7-dimethyl-2,6-octadienoate with selenium dioxide and *tert*-butyl hydroperoxide by the procedure of Umbreit and Sharpless[41] gave methyl (*E*)-8-hydroxy-3,7-dimethyl-2,6-octadienoate in 57% yield. The spectral data are identical with those previously reported.[50]

The alcohol (0.48 g, 2.4 mmol) was dissolved in 12 mL of methyl iodide that was warmed to 50 °C and treated with silver oxide (1.76 g, 7.6 mmol).[51] The solution was heated at reflux for 1 h and stirred at 25 °C overnight. The mixture was filtered and the residue washed well with ether. The combined filtrates were evaporated to give 0.46 g (92%) of methyl (*E*)-8-methoxy-3,7-dimethyl-2,6-octadienoate. Hydrolysis of the ester (0.42 g, 2.0 mmol) with barium hydroxide (0.77 g, 2.4 mmol) in 20 mL of water at 100 °C overnight followed by normal workup gave 0.33 g (85%) of pure **73**: NMR 1.65 (br s, 3), 2.17 (br s, 3), 1.67–2.17 (m, 4), 3.19 (s, 3), 3.80 (s, 2), 5.33 (br, 1), 5.67 (s, 1).

***anti*-7-(Methoxymethyl)-7-methyl-2-methylenebicyclo[3.1.1]heptan-6-one (74).** (*E*)-8-Methoxy-3,7-dimethyl-2,6-octadienoic acid (**73**; 0.31 g, 1.56 mmol) was converted to the acid chloride and thence to **74** as described above for the preparation of **57** to give 0.30 g of crude product. Purification by flash chromatography on silica gel (98:2 pentane–EtOAc) gave 0.085 g (30%) of pure **74**: NMR 1.08 (s, 3), 2.10–2.17 (m, 2), 2.29–2.36 (m, 2), 2.71 (m, 1), 3.29 (s, 2), 3.31 (d, 1, J = 6.4), 3.39 (s, 3), 4.69 (br s, 1), 4.84 (br s, 1); ^{13}C NMR 13.3, 24.5, 25.3, 36.8, 59.1, 59.3, 63.7, 79.1, 110.7, two carbons were not observed; IR ($CDCl_3$) 1775 cm^{-1}.

***anti*-7-Methyl-2-methylene-7-(4-methyl-3,4-oxidopentyl)bicyclo[3.1.1]heptan-6-one (75).** *m*-Chloroperbenzoic acid (35 mg, 0.17 mmol) dissolved in 2 mL of methylene chloride was added to a solution of ketone **57** (0.038 g, 0.17 mmol) in 1.5 mL of methylene chloride and 1.2 mL of 0.5 M aqueous sodium bicarbonate. The two-phase mixture was stirred for 2.5 h at 25 °C, and the layers were separated. The organic layer was washed with 1 M sodium hydroxide and water and dried (Na_2SO_4) to give 41 mg of crude **75**. Flash chromatography on silica gel (9:1 hexane–EtOAc) gave 0.037 g (94%) of pure **75** as a ≈1:1 mixture of diastereomers: NMR 1.018, 1.022 (2 s, 3), 1.265, 1.272 (2 s, 3), 1.31 (s, 3), 1.40–1.72 (m, 4), 2.09–2.16 (m, 2), 2.29–2.36 (m, 2), 2.67–2.75 (m, 2), 3.21, 3.23 (2 d, 1, J = 7.3), 4.66 (br s, 1), 4.83 (br s, 1); ^{13}C NMR (14.30, 14.32), 18.6, (24.58, 24.59), 24.7, 24.8, 25.3, 35.2, (36.42, 36.45), 58.3, (60.8, 61.2), 63.9, (73.0, 73.3), (110.4, 110.3), (147.7, 147.9), 208.9; IR ($CDCl_3$) 1780, 1645, 1460, 1385 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 76.85; H, 9.62.

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