Total Synthesis of *dl*-Cyclosativene by Cationic Olefinic and Acetylenic Cyclizations[1]

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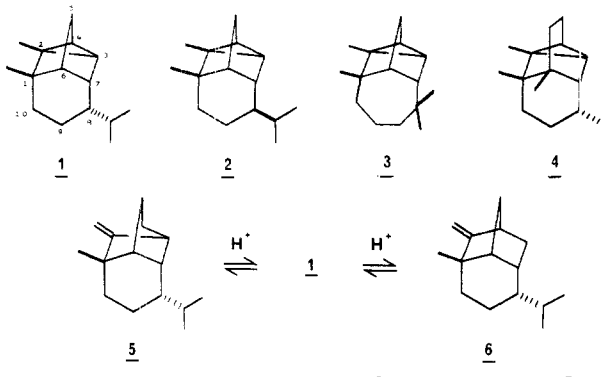
Racemic cyclosativene has been prepared stereospecifically by two routes each involving intramolecular capture of a homoallylic carbonium ion by a carbon–carbon multiple bond. Diels–Alder reaction between propynal and 2,3-dimethylcyclopentadiene followed by suitable elaboration of the product **15** gave the requisite norbornenyl tosylates **23** and **39** possessing endo-substituted alkene and alkyne side chains, respectively. Solvolysis of each in trifluoroethanol afforded tetracyclic products **25** and **40**, contaminated with tricyclic material in the case of **23**, demonstrating the superiority of the alkyne group in achieving complete cyclization. The conversions of **25** and **40** to cyclosativene were effected in five and six steps, respectively.

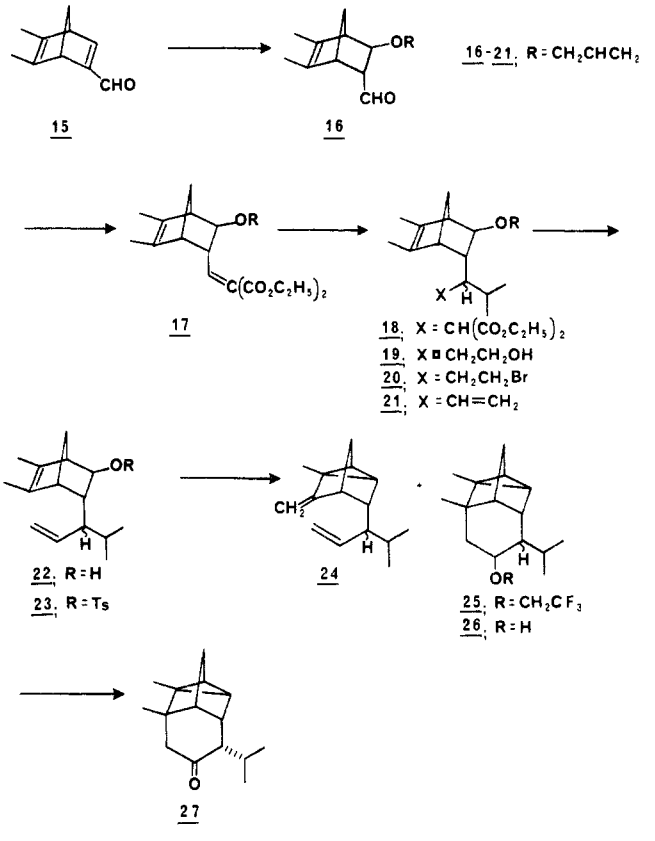
The tetracyclic sesquiterpenes comprise a select class of natural products of which cyclosativene (**1**),[2] cyclocopacamphene (**2**),[3] longicyclene (**3**),[4] and cycloseychellene (**4**) bear close structural resemblance.[5] Each is related to



a tricyclic sesquiterpene (sativene,[6] copacamphene,[7] longifolene,[8] and seychellene,[9] respectively) by virtue of an acid-catalyzed equilibration, illustrated for the interconversion of sativene (**5**), cyclosativene (**1**), and isosativene (**6**) as reported by Smedman[2] and McMurry.[10] In fact, because of these rearrangements, total syntheses of the tricyclic isomers also represent formal syntheses of their tetracyclic counterparts, although the generally unfavorable equilibria make such routes impractical by the usual criteria of efficiency.[11]

The complex molecular architecture of these tetracyclic sesquiterpenes has attracted several groups of synthetic

Scheme I



chemists, and to date all but cycloseychellene (**4**) have yielded to rational syntheses.[12,13] Each of the reported syntheses has utilized the intramolecular cycloaddition of a diazo compound (ketone or alkane) to an alkene to generate the cyclopropane of the tetracyclic products from bicyclic precursors.

It occurred to us several years ago that an alternative entry into the highly condensed nucleus of the tetracyclic sesquiterpenes **1**, **2**, and **3** might be available through the solvolysis of an appropriately substituted norbornenyl compound. By this scheme solvolysis of a suitable tosylate (e.g., **7**) would be expected to generate the homoallylic cation **8** which then could be captured intramolecularly by an attached *endo*-alkene side chain. Solvent capture of the ensuing cation **9** would yield the desired tetracyclic

(1) (a) Taken in part from the Ph.D. Thesis of J.C.T., Duke University, June 1975. (b) A portion of this work has appeared in preliminary form: Baldwin, S. W.; Tomesch, J. C. *Tetrahedron Lett.* **1975**, 1055. (c) Financial assistance from the Merck Foundation for Faculty Development and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. (d) We are indebted to Dr. David Rosenthal and Mr. Fred Williams of the Research Triangle Institute for Mass Spectrometry (supported by NIH Grant No. RR 00330) for mass spectral determinations.

(2) (a) Smedman, L.; Zavarin, E. *Tetrahedron Lett.* **1978**, 3833. (b) Smedman, L.; Zavarin, E.; Teranishi, R. *Phytochemistry* **1969**, *8*, 1457.

(3) Kido, R.; Sakuma, R.; Uda, H.; Yoshikoshi, A. *Tetrahedron Lett.* **1969**, 3169.

(4) Nayak, U. R.; Dev, S. *Tetrahedron Lett.* **1963**, 243. (b) Nayak, U. R.; Dev, S. *Tetrahedron* **1968**, *24*, 4099.

(5) (a) Terhune, S. J.; Hogg, J. W.; Lawrence, B. M. *Tetrahedron Lett.* **1973**, 4705. (b) Dhekne, V. V.; Paknikar, S. K. *Indian J. Chem.* **1974**, *12*, 1016.

(6) de Mayo, P.; Williams, R. E. *J. Am. Chem. Soc.* **1965**, *87*, 3275.

(7) (a) Kolbe-Haugwitz, M.; Westfelt, L. *Acta Chem. Scand.* **1970**, *24*, 1623. (b) Kolbe, M.; Westfelt, L. *Ibid.* **1967**, *21*, 585.

(8) Moffett, R. H.; Rogers, D. *Chem. Ind. (London)* **1953**, 916.

(9) Smedman, L.; Zavarin, E. *Tetrahedron Lett.* **1968**, 3833.

(10) McMurry, J. E. *Tetrahedron Lett.* **1969**, 55.

(11) The acid treatment of cyclocopacamphene provides entry to the sativene, cyclosativene, and isosativene manifolds rather than to that of cyclocopocamphene. McMurry, J. E. *J. Org. Chem.* **1971**, *36*, 2826.

(12) (a) Piers, E.; Britton, R. W.; Kiziere, R. J.; Smillie, R. D. *Can. J. Chem.* **1971**, *49*, 2623. (b) Piers, E.; Geraghty, M. B.; Soucy, M. *Synth. Commun.* **1973**, *3*, 401.

(13) (a) Welch, S. C.; Waters, R. L. *J. Org. Chem.* **1974**, *39*, 2665. Welch, S. C.; Waters, R. L. *Synth. Commun.* **1973**, *3*, 15.

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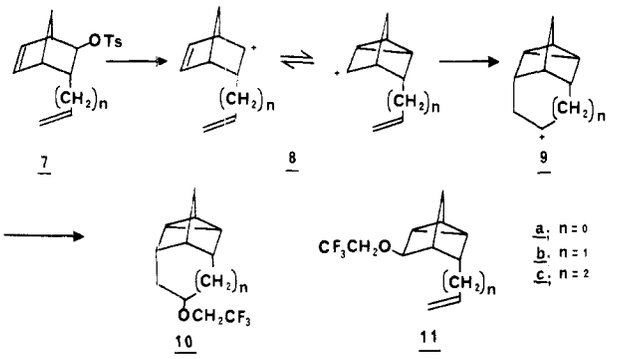


derivative **10** in a single step from readily accessible intermediates.

Model studies[14] partially verified our predictions when it was discovered that **7b** was converted to a 2:3 mixture of **10b** and **11b** on exposure to trifluoroethanol at room temperature.[15] In the instances of **7a** and **7c**, solvolysis yielded only tricyclic ethers **11a** and **11c**, with no trace of tetracyclic material (**10a** and **10c**) being detectable. It thus appeared that this general route would be applicable to syntheses of cyclosativene (**1**) and cyclocopacamphene (**2**) but not to longicyclene (**3**). The results described herein detail two total syntheses of cyclosativene based on these conclusions.[1a]

The preparation of the bicyclic norbornenyl tosylate **23** required for trifluoroethanolysis in a cyclosativene synthesis is shown in Scheme I. By this plan the two methyl groups on the norbornane ring of cyclosativene were to be incorporated in a Diels–Alder reaction with 2,3-dimethylcyclopentadiene (**14**). This compound has previously been prepared by dehydration of 1,2-dimethylcyclopent-2-en-1-ol,[16] but large-scale preparation of this material by several methods[17] proved to be impractical in our hands. Alternatively, allylic alcohol **13**, prepared by $LiAlH_4$ reduction of unsaturated ketone **12**,[18] could be readily dehydrated to give the desired diene **14**.[19] Although **14** prepared in this fashion could be isolated by careful distillation, it was found to be more convenient to generate **14** in the presence of propynal. In this manner one could isolate adduct **15** as an unstable oil possessing the expected spectral properties. Dissolution of crude **15** in excess allyl alcohol containing potassium carbonate then led to aldehyde **16** as a single homogeneous substance in 28% overall yield from alcohol **13**. The net result of this three-step process is the facile generation of a substituted norbornene possessing groups suitable for differentiation and further elaboration. The synthetic logic of nucleophilic addition to an activated alkene to specifically generate contiguous asymmetry (as in **15** → **16**) has been previously noted[20] but is of insufficient utility to merit mention. Presumably the stereochemical outcome of this reaction is the result of initial attack of allyl alcohol at the β-carbon of the enol from the more accessible exo face followed by thermodynamic protonation.

After some initial experimentation, elaboration of the aldehyde group of **16** could be accomplished routinely. Titanium tetrachloride catalyzed addition of diethyl malonate[21] afforded Knoevenagel product **17**, and copper acetate catalyzed conjugate addition of isopropylmagnesium bromide[22] gave diester **18** as a mixture of diastereomers.[23] Conversion of **18** to primary alcohol **19** was accomplished by standard procedures as was the subsequent formation of bromide **20**. The elimination of hydrogen bromide from **20** proved to be rather difficult since a variety of basic reagents mainly afforded products of substitution contaminated with lesser amounts of the desired alkene **21**. Eventually use of sodium hydroxide in a dimethyl sulfoxide–water system[24] produced a 1:1 mixture of alkene **21** and alcohol **20** from which pure **21** was isolated in 41% yield after chromatography and distillation. Recycling recovered alcohol **20** further increased the efficiency of this process. Reductive cleavage of the allyl ether of **21** proceeded smoothly to give alcohol **22**, which upon esterification with *p*-toluenesulfonyl chloride yielded the necessary tosylate **23**, still as a mixture of diastereoisomers at the isopropyl group.

Dissolution of tosylate **23** in trifluoroethanol then led to an essentially instantaneous reaction to generate a fairly complex mixture of products as determined by GLC analysis. The two major peaks (50% of the total volatile material), present in essentially equal amounts, were separated by careful column chromatography and were assigned structures **24** and **25**, respectively, by detailed analysis of their spectral characteristics.

Of special interest in the NMR spectrum of **25** were signals for the two quaternary methyl groups (δ 0.80 and 1.01), in general agreement with expectations.[2] The absence of vinyl protons in the NMR spectrum coupled with an absorption at 3050 cm^{-1} in the IR spectrum also indicated the presence of a cyclopropane. This essentially 1:1 ratio of tetracyclic/tricyclic products is generally consistent with the model studies described earlier (**7** → **8** → **9**).[14]

With the basic ring system and all the carbon atoms of cyclosativene in hand, it only remained to remove the trifluoroethyl ether and equilibrate the isopropyl group to the more stable equatorial configuration of cyclosativene to achieve the total synthesis of the natural product. Unfortunately the first of these processes proved to be unduly difficult. By analogy with the cleavage of trichloroethyl ethers, **25** was exposed to a variety of reductive reaction conditions (Zn/H^+, Na/NH_3), all without success. In addition, attempted oxidation of the trifluoroethyl ether to the trifluoroacetate with ruthenium tetraoxide[25] gave no indication of reaction.

The failure of the above methods led us to use the only published procedure for the cleavage of trifluoroethyl alkyl ethers as initially developed by Sargent.[26] Thus, exposure of **25** to a 500 molar excess of sodium naphthalenide for 5 days was successful in bringing about the desired cleavage, but the presence of the overwhelming excess of

(14) Baldwin, S. W.; Tomesch, J. C. *Synth. Commun.* **1975**, *5*(6), 445. Experimental details are available on request.

(15) A survey of several solvents revealed the superiority of trifluoroethanol in achieving total cyclization to the tetracyclic material. For leading references concerning trifluoroethanol as a solvolysis medium, see: Raber, D. J.; Dukes, M. D.; Gregory, J. *Tetrahedron Lett.* **1974**, 667.

(16) Mironov, V. A.; Sobolev, E. V.; Elizaroa, A. N. *Tetrahedron* **1963**, *19*, 1939.

(17) A recent report describes the efficient preparation of diene **14** by this route. Fischli, A.; Klause, M.; Mayer, H.; Schonoholzer, R.; Ruegg, R. *Helv. Chim. Acta* **1975**, *58*, 564.

(18) 2,3-Dimethylcyclopent-2-en-1-one (**12**) was prepared in 54% yield by the conversion of 5-nitro-2-heptanone to 2,5-heptanedione via a modified Nef reaction[18a] followed by base-catalyzed cyclization.[18b] (a) Black, D. S. C. *Tetrahedron Lett.* **1972**, 1331. (b) Hunsdiecker, H. U.S. Patent 2 387 587, 1945; *Chem. Abstr.* **1946**, *40*, 3131. (c) Al-Jallo, H. N. A.; Waight, E. S. *J. Chem. Soc. B* **1966**, 75.

(19) This route to 2,3-dimethylcyclopentadiene parallels that of: McLean, S.; Haynes, P. *Tetrahedron* **1965**, *21*, 2313.

(20) An earlier description of this general synthetic procedure has appeared. Baldwin, S. W.; Tomesch, J. C. *J. Org. Chem.* **1974**, *39*, 2382.

(21) Lehnert, W. *Tetrahedron Lett.* **1970**, 4723.

(22) Marshall, J. A.; Roebke, H. *J. Org. Chem.* **1966**, *31*, 3109.

(23) This compound was carried through the remaining steps of the synthesis as a mixture of diastereoisomers at the isopropyl group.

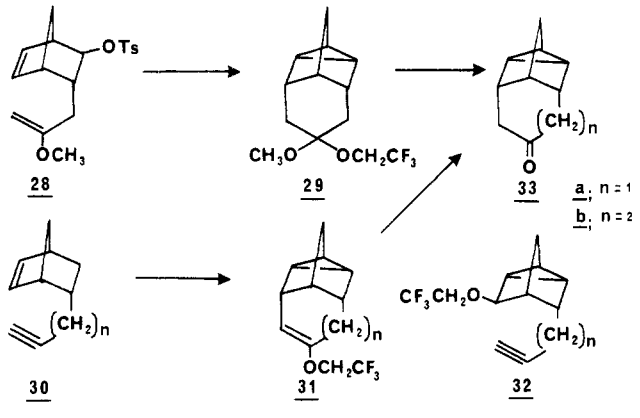
(24) Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc. C* **1967**, 1115.

(25) Berkowitz, L. M.; Rylander, P. Z. *J. Am. Chem. Soc.* **1958**, *80*, 6682.

(26) Sargent, D. *J. Am. Chem. Soc.* **1971**, *93*, 5268.

naphthalene and naphthalene-derived products made isolation of alcohol **26** extremely tedious and inefficient. Finally, repeated crystallizations (saving the mother liquors) and chromatography produced alcohol **26** as a 1:1 mixture with aromatic contaminants. Oxidation of this mixture with Collins reagents[27] allowed final chromatographic purification of ketone **27** in 27% yield from the trifluoroethyl ether. Ketone **27** exhibited two peaks by GLC analysis, but extended equilibration of the mixture with sodium methoxide afforded a single isomer, assumed to have the more stable α orientation of the isopropyl side chain. The conversion of **27** to cyclosativene will be discussed subsequently.

A critical evaluation of the preceding chemistry reveals that although the cationic olefinic cyclization route to tetracyclic sesquiterpenes is conceptually valid, several problems detract significantly from the overall process. The most conspicuous of these is the production of significant amounts of tricyclic material in the solvolysis step. In addition are the difficulties encountered in cleaving the alkyl trifluoroethyl ether of the tetracyclic products. It occurred to us that the first of these difficulties might be overcome if we could somehow render the carbon side chain more nucleophilic, that is, more efficient in capturing the intermediate homoallylic cation (e.g., **8**). Two such possibilities were apparent. Several years ago Felkin[28] reported that placement of an alkoxy group on the double bond involved in cationic ring closure led to enhanced solvolysis rates and increases in fully cyclized material. As applied to our model for a cyclosativene synthesis, the above considerations suggested that **28** should be more



efficient in producing tetracyclic products than was unsubstituted **7b**. A second method for increasing side-chain nucleophilicity was found in the work of Peterson,[29] who demonstrated that the alkyne is an effective cationic carbon nucleophile. Since then, many examples of the utility of alkynes in related cyclizations have been recorded.[30] For the present problem alkyne **30** would serve as an effective model. It should be noted that the tetracyclic products from trifluoroethanolysis of either **28** or **30a** would be ketone derivatives and thus subject to ready hydrolysis to the carbonyl compound.

Primarily because of the relative ease of synthesis of the two models, alkyne **30** was prepared (Scheme II) and subjected to trifluoroethanolysis.[14] In a very clean reaction, compounds **31** and **32** were produced in a 2:1 ratio, and after purification, tetracyclic **31** was smoothly hydrolyzed to ketone **33** with aqueous acid. It is interesting that alkyne **30b**, which would give rise to the seven-membered ring of longicyclene, still afforded only the tricyclic product **32b** on trifluoroethanolysis.

Encouraged by the results from the solvolysis of **30a** we began another preparation of cyclosativene which eventually proved to be very successful. Aldehyde **16** was successively converted to alcohol **34** and bromide **35**. Nucleophilic displacement of bromide with the lithium acetylide/ethylenediamine complex[31] then gave alkyne **37** and elimination product **36** in a 3:1 ratio from which pure **37** could be isolated in 47% yield by careful distillation. It was possible to reductively remove the allyl ether protecting group in the presence of the alkyne by prior generation of the acetylide anion followed by treatment with sodium/ammonia. This means of protecting terminal alkynes during reductive procedures is very effective[32] and should find other synthetic applications. The alcohol **38** so produced was then converted to the corresponding oily tosylate **39**.

Solvolysis of **39** in trifluoroethanol was complete after several minutes as determined by GLC analysis. Isolation of the product gave an 85% yield of material which was essentially homogeneous (GLC) and which was unequivocally assigned the structure of the desired enol ether **40** by spectral analysis. Particularly diagnostic were sharp methyl resonances at δ 0.91 and 1.05 and the presence of a single vinyl resonance at δ 4.35. Further confirmation of **40** was obtained by the formation of ketone **41** on acidic hydrolysis (57% yield of purified material from tosylate **39**).

The next task in the synthesis of cyclosativene was the regiospecific introduction of the isopropyl group. Although ketone **41** is flanked by two methylene groups which might prove difficult to differentiate, we were encouraged by the report[33] that similarly substituted 3,3,5-trimethylcyclohexanone reacts with ethyl formate exclusively at C-6, an acylation analogous to that desired in the present instance. In the event, ketone **41** formed a semicrystalline formyl compound which was smoothly acylated with acetic anhydride to give a single enol acetate. This acetate clearly possessed the desired structure **42** by NMR analysis. Of particular interest were absorptions at δ 2.90 (allylic methine proton) and an AB quartet at δ 2.32 attributed to the isolated methylene group adjacent to the ketone carbonyl.

Conversion of **42** to the isopropyl derivative **27** was accomplished by a low-temperature addition–elimination–addition with lithium dimethylcuprate as developed by Coates[34] and Casey.[35] The product, **27**, formed in 71% yield, was a single homogeneous substance that proved to be identical in all respects with compound **27** prepared by Scheme I. Thus, although **27** could be prepared in two

(27) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(28) (a) Felkin, H.; Lion, C. *J. Chem. Soc., Chem. Commun.* **1968**, 60. (b) Felkin, H.; Lion, C. *Tetrahedron* **1971**, *27*, 1387. (c) Felkin, H.; Lion, C. *Ibid.* **1971**, *27*, 1403.
(29) (a) Peterson, P. E.; Kamat, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 4521. (b) Peterson, P. E.; Kamat, R. J. *Ibid.* **1966**, *88*, 3152. (c) Peterson, P. E.; Vidrine, D. W. *J. Org. Chem.* **1979**, *44*, 891.
(30) (a) Volkmann, R. A.; Andrews, G. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 4777. (b) Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Meyers, R. F.; Bryson, T. A.; Miles, D. H. *Ibid.* **1971**, *93*, 4330 (and accompanying communication). (c) Markezich, R. L.; Willy, W. E.; McCarry, B. E.; Johnson, W. S. *Ibid.* **1973**, *95*, 4414 (and accompanying communications). (d) Closson, W. D.; Roman, S. A. *Tetrahedron Lett.* **1966**, 6015. (e) Stutz, H.; Hanack, M. *Ibid.* **1974**, 2457. (f) Sekera, M. H.; Weissman, B.; Bergman, R. G. *J. Chem. Soc., Chem. Commun.* **1973**, 679.
(31) (a) Smith, W. N.; Beumel, O. F., Jr. *Synthesis* **1974**, 441. (b) Gibson, W. F.; Erman, W. F. *J. Am. Chem. Soc.* **1969**, *91*, 4771.
(32) The protection of a terminal alkyne as its sodium salt during the Na/NH_3 reduction of an internal alkyne has been reported. Dobson, N. A.; Raphael, J. *J. Chem. Soc.* **1955**, 3558.
(33) Richer, J. C.; MacDougall, W. A. *Can. J. Chem.* **1968**, *46*, 3703.
(34) Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 1027.
(35) (a) Casey, C. P.; Marten, D. F.; Boggs, R. A. *Tetrahedron Lett.* **1973**, 2071. (b) Casey, C. P.; Marten, D. F. *Synth. Commun.* **1973**, *3*, 321.

different ways, the latter method involving cationic acetylenic cyclization proved to be vastly superior to the cationic olefinic route.

The final stages of the synthesis of cyclosativene were accomplished in routine fashion. Reduction of the ketone carbonyl with $LiAlH_4$ followed by acylation with methanesulfonyl chloride gave mesylate **43**. Reaction of the mesylate with potassium *tert*-butoxide in dimethyl sulfoxide[36] produced a mixture of alkenes **44** which on catalystic hydrogenation gave pure *dl*-cyclosativene (**1**).[31] Attempted direct displacement of the mesylate with the mixed copper hydride reagent developed by Masamune[38] gave a mixture of alkene and cyclosativene which also yielded pure cyclosativene on catalytic hydrogenation. Spectra derived from the cyclosativene produced in this manner were identical in all respects with published data for the natural material.[2]

Experimental Section[39]

2-Formyl-5,6-dimethylbicyclo[2.2.1]hepta-2,5-diene (15). In a 3-L flask equipped with an addition funnel, mechanical stirrer, and nitrogen inlet and cooled in an ice–water bath were placed 1.1 L of reagent-grade benzene, 56.6 g (0.471 mol) of $MgSO_4$, 25.4 g (0.471 mol) of propynal,[40] and 0.80 g (4.7 mmol) of *p*-toluenesulfonic acid. To the stirring solution maintained between 3 and 10 °C was added over 2.5 h 52.7 g (0.471 mol) of 2,3-dimethylcyclopent-2-en-1-ol (**13**)[41] in 500 mL of benzene. The mixture was allowed to stir at this temperature for 4 h and then warmed to room temperature. After 3 g of K_2CO_3 and a spatula full of hydroquinone were added, the solution was filtered and concentrated in vacuo (<40 °C) to give an oil which was characterized as aldehyde **15** from NMR and IR data: IR (CCl_4) 2800 and 2710 (CHO), 1668 cm^{-1} (C=O); NMR (CCl_4) δ 1.71 (s, 6 H, C-5 CH_3 and C-6 CH_3), 2.04 (m, 2 H, C-7 H), 3.43 (s, 1 H, C-1 H or C-4 H), 3.65 (s, 1 H, C-1 or C-4 H), 7.81 (d, J = 3 Hz, 1 H, C-3 H), 9.72 (s, 1 H, CHO).

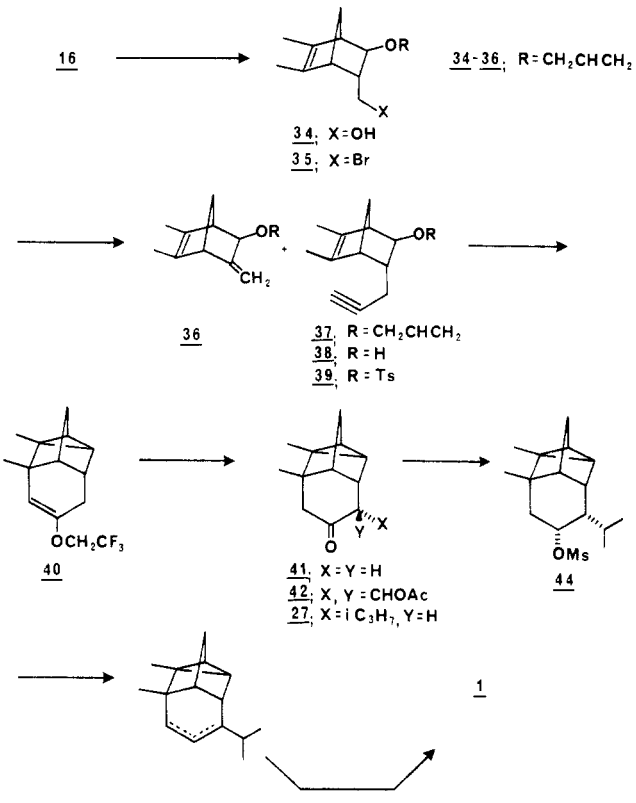
Further purification of this material was not possible due to extensive decomposition.

***endo*-2-Formyl-*exo*-3-(allyloxy)-5,6-dimethylbicyclo[2.2.1]hept-5-ene (16).** The above unpurified α,β-unsaturated aldehyde **15** was stirred with 325 mL of allyl alcohol containing 3 g of K_2CO_3 for 18 h at 0 °C. After filtration, hydroquinone was added and the solution concentrated in vacuo. The resulting oil was distilled through a 6-in. vacuum-jacketed Vigreux column, the fraction boiling between 75 and 82 °C (0.15 mm) yielding 27.34 g (28% from **13**) of aldehyde **16**. An analytical sample was prepared by column chromatography (silica gel, 5% ether/benzene) followed by evaporative distillation to give pure aldehyde **16**: NMR (CCl_4) δ 1.58 (6 H, C-5 CH_3 and C-6 CH_3), 2.60 (m, 2 H, C-7 H), 2.60 (2 H, C-2 H and C-1 H or C-4 H), 2.82 (1 H, C-1 H or C-4 H), 3.67 (1 H, C-3 H), 9.49 (d, J = 2 Hz, 1 H, CHO).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 75.69; H, 8.80. Found: C, 75.51; H, 9.06.

Ethyl 2-(Ethoxycarbonyl)-3-[*exo*-3-(allyloxy)-5,6-dimethyl-*endo*-bicyclo[2.2.1]hept-5-en-2-yl]propenoate (17). According to the general procedure of Lehnert,[21] a solution of 24.2 mL (0.22 mol) of $TiCl_4$ in 55 mL of CCl_4 was added dropwise to a flask containing 450 mL of dry THF. Upon completion of the addition, 17.60 g (0.11 mol) of diethyl malonate and 22.15 g (0.11 mol) of aldehyde **16** in 55 mL of dry THF was added dropwise over 20 min to the slurry, the solution turning from bright yellow to dark brown. After the mixture was stirred for 10 min, 75 mL of dry pyridine was added dropwise, and the reaction was stirred for 10 h at 0 °C followed by an additional 36 h at room tem-

Scheme II



(36) Snyder, C. H.; Soto, A. R. *J. Org. Chem.* **1964**, *29*, 742.

(37) The stereochemical outcome of the hydrogenation was anticipated on the basis of steric ease of approach to the catalyst surface and the results of a similar hydrogenation in the sativene series by de Mayo.[6]

(38) Masamune, S.; Rossy, P. A.; Bates, G. S. *J. Am. Chem. Soc.* **1973**, *95*, 6452.

(39) Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected; boiling points are uncorrected. Infrared spectra (IR) were determined either on a Perkin-Elmer 237 or on a Perkin-Elmer 137 spectrometer using 0.1-mm cavity cells and polystyrene calibration bands as references. Nuclear magnetic resonance (NMR) spectra were determined on a JEOL MH 100 spectrometer in either CCl_4 or $CDCl_3$ solution containing 1% Me_4Si as an internal standard. Many of the compounds possess the allyl ether group, and rather than repeat NMR absorptions for this group many times, representative values are given here: δ 4.00 (m, $W_{1/2}$ = 9 Hz, 2 H, OCH_2CHCH_2), 5.10 (m, $W_{1/2}$ = 28 Hz, 2 H, OCH_2CHCH_2), 5.80 (m, $W_{1/2}$ = 25 Hz, 1 H, OCH_2CHCH_2). Gas–liquid chromatographic analyses (GLC) were performed on a Hewlett-Packard Model 700 chromatograph equipped with dual hydrogen flame detectors and using nitrogen (25 mL/min) as the carrier gas through columns (6 ft × $^1/_8$ in.) packed with 5% SE-30 on Chromosorb P. Preparative GLC separations were carried out on an F&M Model 700 chromatograph equipped with dual thermal conductivity detectors. A flow of helium (60 mL/min) through columns (6 ft × $^1/_4$ in.) packed with 3% SE-30 on Chromosorb P was employed. High-resolution mass spectra were collected at the Research Triangle Institute for Mass Spectrometry. Analytical thin-layer chromatography (TLC) was performed on microscope slides coated with silica gel H (Brinkmann Instruments Inc.) with components visualized by the $Ce(NH_4)_2(NO_3)_6$/char technique. Preparative thick-layer chromatography (PTLC) was performed on 20 cm × 20 cm plates coated with a 1-mm layer of silica gel H and HF 254 (Brinkmann Instruments Inc.). Column chromatography employing graded alumina activities refers to Woelm neutral aluminum oxide, distributed by Waters Associates, which was deactivated according to the supplied instructions. Silical gel absorbents are either 60–200 mesh grade 950 for gas chromatography (Grace Davison) or 100–200 mesh grade 923 (Grace Davison). Anhydrous solvents were dried immediately prior to use. Tetrahydrofuran (THF), dimethoxyethane (DME), and diethyl ether (ether) were distilled from lithium aluminum hydride ($LiAlH_4$). Dimethyl sulfoxide (Me_2SO) and pyridine were distilled from calcium hydride (Me_2SO at reduced pressure) and stored over 3A molecular sieves. Acetonitrile was distilled from phosphorus pentoxide, benzene was dried over sodium wire, and 2,2,2-trifluorethanol was purchased from Aldrich Chemical Co. and used as received. Petroleum ether refers to that hydrocarbon fraction boiling between 30 and 60 °C. The terms "concentration" and "concentrated at reduced pressure" refer to evaporation on a rotary evaporator connected to an aspirator system until constant weight was obtained. Bulb to bulb distillation and evaporative distillation refer to distillation using a Büchi Kugelrohr apparatus. All compounds described in this work containing an asymmetric carbon atom are racemic; the prefix "*dl*" has been omitted. Elemental analyses were performed by M-H-W Laboratories and are within acceptable limits (±0.3%).

(40) Sauer, J. C. In "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 813.

(41) Alcohol **13** was obtained in 98% yield from the routine $LiAlH_4$ reduction of 2,3-dimethylcyclopent-2-enone.[18]

perature. The reaction mixture was then poured into 400 mL of water and worked up as usual with ether. The resulting oil was distilled (short path), with the fraction distilling between 145–152 °C (0.40 mm) being collected to yield 20.83 g (54.5%) of compound **17**. A 0.20-g sample of the compound was purified by PTLC (5% acetone–petroleum ether; two times). The band with R_f 0.42 was collected and Kugelrohr distilled at 128 °C (0.10 mm) to give the analytical sample as a colorless oil: IR (CCl_4) 3038 (=CH_2), 1730 (C=O), 1640 (C=C), 930 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 1.30 and 1.33 (t, J = 7 Hz, 6 H, OCH_2CH_3), 1.67 (8 H, C-7 H, C-5 CH_3, and C-6 CH_3), 2.58 (2 H, C-1 H and C-4 H), 2.75 (d, J = 11 Hz, 1 H, C-2 H), 3.25 (1 H, C-3 H), 4.24 (m, 4 H, 2 OCH_2CH_3), 6.42 (d, J = 11 Hz, 1 H, $CH=C(CO_2Et)_2$).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.12; H, 7.91.

Ethyl 2-(Ethoxycarbonyl)-4-methyl-3-[*exo*-3-(allyloxy)-5,6-dimethyl-*endo*-bicyclo[2.2.1]hept-5-en-2-yl]pentanoate (18). In a variation of the procedure of Marshall,[22] isopropylmagnesium bromide was prepared in the normal manner from 19.0 mL (25.1 g, 0.204 mol) of isopropyl bromide and 4.96 g (0.204 mol) of magnesium in 350 mL of dry diethyl ether in a 500-mL three-necked flask fitted with a bottom stopcock (with glass wool in the exit tube) for use as an addition funnel. In a 1-L three-necked flask connected to the above flask and equipped with a magnetic stirrer, nitrogen inlet, and low-temperature thermometer were placed 400 mL of dry THF, 3.90 g (0.0195 mol) of $Cu(OAc)_2 \cdot H_2O$, and 20.83 g (0.06 mol) of ester **17** to which was then added the Grignard solution over 1.5 h (−20 to −25 °C). The reaction was maintained at −20 to −25 °C for an additional 0.5 h and then allowed to warm slowly to 15 °C. It was then poured slowly into a cold rapidly stirring saturated solution of NH_4Cl, about 300 mL of additional ether was added, and the reaction was worked up as usual with ether. The resulting oil was then Kugelrohr distilled (145 °C, 0.17 mm) to yield 17.78 g (75.6%) of diester **18** which was used in the subsequent reaction without further purification. A small amount of **18** was purified by PTLC (5% acetone–petroleum ether; two times). The band with R_f 0.35 was collected and distilled in the Kugelrohr manner (145 °C, 0.17 mm) to produce the analytical sample:[23] IR (CCl_4) 3080 (=CH_2), 1755, 1730 (br, C=O), 935 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 0.91 (6 H, $CH(CH_3)_2$), 1.26 (6 H, OCH_2CH_3), 1.49–1.89 (br, 4 H, C-7 H, $CHCH(CH_3)_2$), 1.63 (s, 6 H, C-5 CH_3 and C-6 CH_3), 2.06 (br, 1 H, C-2 H), 2.50 (2 H, C-1 H and C-4 H), 3.16 (1 H, C-3 H), 3.46 (d, J = 4 Hz, 1 H, $CH(CO_2Et)_2$), 4.15 (4 H, OCH_2CH_3).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found: C, 70.16; H, 9.12.

4-Methyl-3-[*exo*-3-(allyloxy)-5,6-dimethyl-*endo*-bicyclo-[2.2.1]hept-5-en-2-yl]pentanol (19). In an adaptation of the procedure of Henkel and Spurlock,[42] a solution of 17.78 g (0.045 mol) of diester **18**, 100 mL of ethanol, and 100 mL of 20% NaOH was heated at reflux for 9 h after which the flask was cooled in an ice bath and acidified with cold 6 N HCl to pH 1. The solution was then saturated with NaCl and worked up with ether. The resulting diacid was dissolved in 150 mL of pyridine and heated at reflux for 5 h after which the solution was poured into 200 mL of ice–water, acidified to pH 1 with cold 6 N HCl, and worked up with ether. The crude monoacid was directly reduced by its addition as an ether solution (55 mL) to a stirring slurry of 2.64 g (0.070 mol) of $LiAlH_4$ in 270 mL of ether. After the mixture was stirred for 12 h, the reaction was worked up by the slow addition of 2.64 mL of water, followed by 2.64 mL of 15% NaOH solution and finally 7.92 mL of water. The solution was filtered from the crystalline precipitate which was then washed with an additional 250 mL of ether. The combined ethereal extracts were then concentrated at reduced pressure to yield an oil which was Kugelrohr distilled (120-140 °C, 0.05 mm) to give 9.52 g of the crude alcohol. TLC of the alcohol (10% ether–benzene) showed one major component (R_f 0.24) and several more polar minor components. The alcohol was purified by column chromatography (200 g of silica gel). Elution with 250 mL of benzene followed by 1.25 L of 10% ether–benzene effected the separation of the alcohol from the more polar impurities. Concentration yielded 6.74 g of pure alcohol **19** after Kugelrohr distillation (135 °C, 0.07 mm): 53.4% yield from diester **18**; IR (CCl_4) 3630 and 3350 (OH), 3080 (=CH_2), 925 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 0.93 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 1.64, 1.72 (s, 6 H, C-5 CH_3 and C-6 CH_3), 2.54 (2 H, C-1 H and C-4 H), 3.01 (2 H, C-3 H and OH), 3.60 (m, 2 H, CH_2OH).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.83; H, 10.67.

4-Methyl-3-[*exo*-3-(allyloxy)-5,6-dimethyl-*endo*-bicyclo-[2.2.1]hept-5-en-2-yl]-1-bromopentane (20). According to an adaptation of the procedure of Schaefer,[43] 1.39 mL (4.36 g, 0.027 mol) of bromine was added dropwise to a solution of 7.65 g (0.029 mol) of triphenylphosphine in 40 mL of dry acetonitrile. The addition funnel was washed down with several milliliters of dry acetonitrile, and the flask was removed from the ice–water bath and stirred for 10 min at room temperature. To the white slurry was added dropwise a solution of 2.36 mL (2.31 g, 0.024 mol) of pyridine, 6.74 g (0.024 mol) of alcohol **19**, and 25 mL of dry acetonitrile. After being stirred 5 min, the solution was heated to reflux briefly, cooled to room temperature, and filtered. The solution was concentrated in vacuo to yield an oil which upon the addition of pentane produced a solid (triphenylphosphine oxide) which was broken up and washed with petroleum ether (2 × 150 mL). All washings were combined, filtered, and concentrated in vacuo. Kugelrohr distillation (134 °C, 0.25 mm) yielded 7.31 g (88.6%) of bromide **20** which was used in the subsequent reaction without further purification. A small amount was purified by PTLC (10% acetone–petroleum ether), Kugelrohr distillation of which gave the analytical sample: IR (CCl_4) 1080 (C—O), and 925 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 0.89 (d, J = 7 Hz, 3 H, $CH(CH_3)_2$), 0.96 (d, J = 7 Hz, 3 H, $CH(CH_3)_2$), 1.62 and 1.71 (6 H, C-5 CH_3 and C-6 CH_3), 2.48 (2 H, C-1 H and C-4 H), 3.02 (1 H, C-3 H), 3.38 (distorted t, J = 8 Hz, 2 H, CH_2Br); high-resolution mass spectrum, calcd for $C_{18}H_{29}OBr$ m/e 340.1401, found, 340.1407.

4-Methyl-3-[*exo*-3-(allyloxy)-5,6-dimethyl-*endo*-bicyclo-[2.2.1]hept-5-en-2-yl]pentene (21). In an adaptation of the procedure of Norman,[24] a mixture of 13.5 g (0.337 mol) of NaOH, 8.6 mL of water, and 77 mL of Me_2SO was heated at 85 °C for 15 min, whereupon 7.31 g (0.021 mol) of bromide **20** was added. After being stirred 13 h, the reaction mixture was cooled, poured into 75 mL of water, and worked up with ether. Kugelrohr distillation of the resulting oil (135 °C, 0.05 mm) yielded 4.59 g of a 1:1 mixture of alcohol **19** and alkene **21**. The alcohol–alkene mixture was separated by column chromatography (250 g of silica gel). Elution with benzene (535 mL) afforded alkene **21** which was distilled in the Kugelrohr manner to give 2.26 g (41%) of pure alkene **21**: IR (CCl_4) 3090 (=CH_2), 1640 cm^{-1} (C=C); NMR (CCl_4) δ 0.84 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 1.71 (s, 6 H, C-5 CH_3 and C-6 CH_3), 2.35 (1 H, C-1 H or C-4 H), 2.50 (1 H, C-1 H or C-4 H), 3.00 (1 H, C-3 H); high-resolution mass spectrum, calcd for $C_{18}H_{28}O$ m/e 260.2140, found 260.2134.

Further elution of the column with benzene (3.5 L) produced alcohol **19**, which after evaporative distillation (120–130 °C, 0.10 mm) gave 1.52 g (26%) alcohol **19** suitable for recycling.

4-Methyl-3-(*exo*-3-hydroxy-5,6-dimethyl-*endo*-bicyclo-[2.2.1]hept-5-en-2-yl)pentene (22). In a 100-mL flask equipped with a magnetic stirrer, serum cap, NH_3 inlet, and dry ice condenser protected from atmospheric moisture with a drying tube was placed 2.25 g (0.0098 mol) of allyl ether **21** and 5 mL of dry THF. After 60 mL of NH_3 was condensed in the flask, 0.398 g (0.017 mol) of sodium plus a large excess was added in small pieces until the blue color persisted for 2 h. Solid NH_4Cl was added to discharge the blue color, and the NH_3 was allowed to evaporate. After 20 mL of saturated NaCl was added, the aqueous material was worked up with ether to afford an oil which on Kugelrohr distillation (103 °C, 0.05 mm) resulted in 1.38 g (73%) of alcohol **22**: IR (CCl_4) 3640 (OH), 3080 (=CH_2), 1640 (C=C), 1000 and 905 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 0.81 (d, J = 7 Hz, 3 H, $CH(CH_3)_2$), 0.84 (d, J = 7 Hz, 3 H, $CH(CH_3)_2$), 1.60 (s, 6 H, C-5 CH_3 and C-6 CH_3), 2.24 (1 H, C-1 or C-4 H), 2.34 (1 H, C-1 or C-4 H), 3.30 (1 H, C-3 H), 4.90 (m, 2 H, $CHCH=CH_2$), 5.45 (m, 1 H, $CHCH=CH_2$); high-resolution mass spectrum, calcd for $C_{15}H_{24}O$ m/e 220.1827, found 220.1832.

(42) Henkel, J. G.; Spurlock, L. A. *J. Am. Chem. Soc.* **1973**, *95*, 8339.

(43) Schaefer, J. P.; Higgins, J. G.; Shenov, P. K. In "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 249.

4-Methyl-3-[*exo*-3-(*p*-toluenesulfonyloxy)-5,6-dimethyl-*endo*-bicyclo[2.2.1]hept-5-en-2-yl]pentene (23). To a cold solution of 1.39 g (0.006 mol) of alcohol **22** in 25 mL of dry pyridine was added 2.40 g (0.0126 mol) of *p*-toluenesulfonyl chloride, and the stoppered flask was placed in the refrigerator for 36 h whereupon the reaction mixture was poured into 60 mL of ice–water and extracted with ether. The solution was filtered and concentrated in vacuo at room temperature to yield 1.21 g (56%) of tosylate **23**, which occasionally was slightly contaminated by tricyclic olefin **24**. For **23**: NMR (CCl_4) δ 0.85 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 1.64 (s, 6 H, C-5 CH_3 and C-6 CH_3), 2.51 (s, 3 H, $-ArCH_3$), 4.04 (1 H, C-3 H), 5.02 (m, 2 H, $CH=CH_2$), 5.64 (m, 1 H, $CHCH=CH_2$), 7.22, 7.90 (AA'BB', J = 8.5 Hz, 4 H, aromatic).

No further analytical data were obtained due to the instability of the compound.

Solvolysis of Tosylate 23. To 25 mL of 2,2,2-trifluoroethanol in a 50-mL flask was added 0.105 g (0.105 mol) of sodium metal, and the contents were allowed to stand until all the sodium had dissolved. Addition of this solution to a 50-mL flask equipped with a magnetic stirrer and under a N_2 atmosphere which contained 0.94 g (0.0025 mol) of tosylate **23** led to the formation of a cloudy white solution. After 10 min the trifluoroethanol solution was worked up with petroleum ether to yield 0.71 g of crude product. GLC at 180 °C showed five small peaks and two major peaks (retention times of 1.75 and 3.25 min, ratio approximately 1:1, total 50% of the peak area). TLC (hexane) indicated three major spots (R_f 0.63, 0.25, and 0.06). Separation of these components was effected on a 2.5-cm-diameter column packed with 70 g of silica gel (60–200 mesh) in hexane and was monitored by GLC. Elution with hexane yielded between the 50th and the 125th mL of eluent 0.150 g (30%) of the least polar spot, corresponding to the peak with a retention time of 1.75 min on GLC. This was identified as tricyclic alkene **2-methyl-3-methylene-5-*endo*-(2-methyl-4-buten-3-yl)nortricyclene (24)** by spectral considerations: IR (CCl_4) 3050 ($=CH_2$ and cyclopropane CH), 1670 (C=C), 920 ($CHCH_2$), 875 cm^{-1} ($=CH_2$); NMR (CCl_4) δ 0.80 and 0.83 (6 H, $CH(CH_3)_2$), 0.70–2.50 (m, 11 H, all unassigned), 4.45 and 4.60 (s, 2 H, exocyclic $C=CH_2$), 4.91 (m, 2 H, $CHCH=CH_2$), 5.42 (m, 1 H, $CHCH=CH_2$); high-resolution mass spectrum, calcd for $C_{15}H_{22}$ m/e 202.1721, found 202.1718.

After this fraction a volatile impurity was present in all cuts which could be removed either by preparative GLC or by subjecting the contaminated samples to reduced pressure (0.01 mm) for 30 min. The material corresponding to the spot with R_f 0.25 was collected in the 550th and 775th mL of eluent. Concentration yielded 0.330 g (42%) of tetracyclic ether **25** slightly contaminated by the volatile material. Preparative gas–liquid chromatography of about 100 mg of this material led to the isolation of 12 mg of compound identified as tetracyclic ether **1,2-dimethyl-8-isopropyl-9-trifluoroethoxytetracyclo[4.4.0.0^{2,4}.0^{3,7}]decane (25)** (retention time of 3.7 min at 130 °C). The remainder of this oil was subjected to a vacuum of 0.01 mm for 30 min which removed the volatile material (and some desired product) to give a total of 0.114 g (15.1%) of tetracyclic ether **25**. GLC of this showed one major peak (80% of the total) at a retention time of 3.25 min (180 °C) accompanied by several smaller ones: IR (CCl_4) 3050 (cyclopropane CH), 1280 (CF), 970 and 860 cm^{-1} (nortricyclene ring); NMR (CCl_4) δ 0.80 (s, 3 H, CH_3), 0.91 (m, 6 H, $CH(CH_3)_2$), 1.01 (s, 3 H, CH_3), 0.66–2.30 (m, all unassigned H), 3.63 (m, 3 H, $CHOCH_2CF_3$); high-resolution mass spectrum, calcd for $C_{17}H_{25}OF_3$ m/e 302.1861, found 302.1863.

The chromatography column was stripped with 300 mL of 5% ether–hexane which on concentration gave material corresponding to the most polar TLC spot. NMR showed that this contained a mixture of unreacted tosylate, some uncleaved allyl ether from the previous step, and the volatile impurity.

1,2-Dimethyl-8-isopropyltetracyclo[4.4.0.0^{2,4}.0^{3,7}]decan-9-ol. (26) and Its Conversion to 1,2-Dimethyl-8α-isopropyltetracyclo[4.4.0.0^{2,4}.0^{3,7}]decan-9-one (27). The trifluoroethyl ether was cleaved by following the general procedure of Sargent.[26] To a stirring solution of 21.6 g (0.168 mol) of naphthalene (Fisher certified) in 175 mL of freshly dried DME under a N_2 atmosphere was added 3.86 g (0.168 mol) of sodium. After a few minutes the solution took on the characteristic dark green color and was allowed to stir for 4 h. To the solution of sodium naphthalenide was added 0.102 g (0.34 mmol) of trifluoroethyl ether **25** in 2 mL of freshly dried glyme, and the resulting mixture was allowed to stir for 5.5 days whereupon air was blown over the solution until it became tan and viscous. Additional glyme was added along with 50 mL of a saturated solution of NH_4Cl and the organic layer separated and worked up with ether. The resulting solid was recrystallized from 50 mL of methanol, the solid naphthalene being separated, and the mother liquor was set aside. This naphthalene was again recrystallized from methanol and its mother liquor combined with that from the first recrystallization. The combined mother liquors were then concentrated at reduced pressure to yield 8.64 g of material which was mostly naphthalene plus a minute amount of product as shown by GLC. Column chromatography (300 g of silica gel) of this residue yielded naphthalene after 1200 mL of benzene and then product (contaminated with naphthalene) after 500 mL of 15% ether–petroleum ether. Concentration of the solution containing the product afforded an oil which was further purified by chromatography on 15 g of silica gel. Elution of the product with 15% ether–petroleum ether was followed by a third chromatography on 20 g of silica gel. After 60 mL of 5% ether–petroleum ether and 200 mL of 10% ether–petroleum ether, the product was eluted with 70 mL of 15% ether–petroleum ether. GLC at 200 °C of this solution showed that it consisted of two major components in a ratio of 1:1 with retention times of 1.5 and 2.6 min. TLC also showed the presence of two components (R_f 0.37 and 0.52, 20% ether–hexane, two times), and NMR indicated that the impurity was aromatic. In an adaptation of the procedure of Ratcliffe and Rodehorst,[27] 0.24 g (0.0024 mol) of CrO_3 was added to a stirring solution of 0.38 g (0.388 mL, 0.0048 mol) of pyridine in 6 mL of dry methylene chloride in a flask equipped with a drying tube. This solution was stirred for 15 min, and then impure tetracyclic alcohol **26** from above was added in 1 mL of dry CH_2Cl_2. A black tarry precipitate formed, and the solution was allowed to stir for 15 min whereupon the solution was decanted from the precipitate which was washed with ether. All the organic extracts were combined and washed with 10% NaOH (3 × 5 mL), 10% HCl (2 × 5 mL), and finally a saturated solution of $NaHCO_3$ (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The oil which resulted was subjected to column chromatography through a 1-cm-diameter column packed with 10 g of silica gel (100–200 mesh) in 10% ether–petroleum ether. Elution with this solvent mixture yielded the product between the 10th and 80th mL of eluent. Concentration at reduced pressure led to the isolation of 0.20 g of the tetracyclic ketone (27% yield from trifluoroethyl ether **25**). This possible mixture of isopropyl epimers was subjected to equilibration in a solution of excess sodium methoxide in methanol for 6 weeks which then gave one peak at a retention time of 1.9 min when analyzed by GLC at 225 °C; TLC showed one spot (R_f 0.73, 20% ether–hexane, two times). The IR spectrum showed a C=O stretch at 1710 cm^{-1} as well as other data (TLC, GLC, NMR) identical with those obtained for tetracyclic ketone **27** produced by an alternate route (vide infra).

***endo*-2-(Hydroxymethyl)-*exo*-3-(allyloxy)-5,6-dimethylbicyclo[2.2.1]hept-5-ene (34).** To a stirring mixture of 5.23 g (0.138 mol) of $LiAlH_4$ in 200 mL of dry ether was added dropwise 22.6 g (0.11 mol) of aldehyde **16** in 50 mL of ether over 30 min. Following completion of the addition, the mixture was allowed to stir for 1.5 h, and then the reaction was quenched by the slow addition of 5.4 mL of 15% NaOH and 16.2 mL of water. The ethereal solution was filtered, the solid washed with ether (3 × 200 mL), and the ethereal material combined and concentrated in vacuo. The resulting oil was Kugelrohr distilled (114 °C, 0.03 mm) to yield 21.99 g (96%) of alcohol **34**: IR (CCl_4) 3400 (OH), 3080 ($=CH_2$), 1645 (C=C), 1080 and 1020 (C—O—C), 925 cm^{-1} ($CH=CH_2$); NMR (CCl_4) δ 1.63 (8 H, C-7 H, C-5 CH_3 and C-6 CH_3), 2.02 (1 H, C-2 H), 2.53 (2 H, C-1 H and C-4 H), 2.98 (m, 1 H, C-3 H), 3.43 (m, 3 H, CH_2OH).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 74.96; H, 9.68. Found: C, 75.13; H, 9.88.

***endo*-2-(Bromomethyl)-*exo*-3-(allyloxy)-5,6-dimethylbicyclo[2.2.1]hept-5-ene (35).** According to the method of Schaefer,[43] to a cold slurry of 35.3 g (0.136 mol) of triphenylphosphine in 170 mL of dry acetonitrile was added 20.2 g (6.47 mL, 0.127 mol) of bromine, and the contents were allowed to warm to room temperature. A solution of 23.30 g (0.112 mol) of alcohol **34**, 10.7 g (10.9 mL, 0.135 mol) of pyridine, and 15 mL of dry

acetonitrile was added over 10 min to the white suspension, and the resulting orange slurry was allowed to stir for 5 min and was then heated to reflux for 1 min. The dark brown solution was stirred for 5 min and cooled in an ice–water bath, whereupon the solution was filtered and concentrated to give an oil which solidified. The solid was broken up and washed with petroleum ether (4 × 150 mL). Concentration of the combined petroleum ether solutions gave an oil which was Kugelrohr distilled (88 °C, 0.08 mm) to afford 23.23 g (77%) of bromide **35** pure by GLC: IR (CCl_4) 930 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 1.69 (m, 2 H, C-7 H), 1.66 and 1.77 (s, 6 H, C-5 CH_3 and C-6 CH_3), 2.31 (m, 1 H, C-2 H), 2.62 and 2.70 (br, 2 H, C-1 H and C-4 H), 2.95 (br, 1 H, C-3 H), 3.02–3.57 (m, 2 H, CH_2Br); high-resolution mass spectrum, calcd for $C_{13}H_{19}OBr$, *m/e* 270.0169; found 270.0164.

3-[*exo*-3-(Allyloxy)-5,6-dimethyl-*endo*-bicyclo[2.2.1]-hept-5-en-2-yl]propyne (37). According to the general procedures of Smith[31a] and Erman,[31b] in a 250-mL flask equipped with a magnetic stirrer and a nitrogen inlet was placed 56 mL of dry Me_2SO and 10.50 g (0.113 mol) of lithium acetylide/ethylenediamine complex. The stirring slurry was cooled at 9 °C, and 25.53 g (0.094 mol) of bromide **35** was dropwise over 1 h. The temperature was maintained between 8 and 9 °C for an additional 1 h following the completion of the addition. When GLC analysis of an aliquot after 6 h showed that some alkyl bromide remained, an additional small amount of lithium acetylide/ethylenediamine complex was added. After 8 h (total) the reaction was worked up with petroleum ether and the resulting oil Kugelrohr distilled (82 °C, 0.18 mm) to give 14.91 g of product shown by GLC to contain alkene **36** and alkyne **37** in a ratio of 1:3. This mixture was then distilled through a heated 40-cm concentric tube column. Material boiling between 30 and 45 °C (0.01 mm) consisted mainly of alkene **36**: NMR (CCl_4) δ 1.61 (s, 6 H, C-5 CH_3 and C-6 CH_3), 1.52–1.94 (m, 2 H, C-7 H), 2.64 (1 H, C-1 H or C-4 H), 2.73 (1 H, C-1 or C-4 H), 3.64 (1 H, C-3 H), 4.89 and 4.99 (2 s, 2 H, exocyclic =CH_2). No further analytical data were obtained due to difficulty in purification.

The fraction boiling between 45 and 50 °C (0.01 mm) was collected to yield 9.76 g (47%) of pure alkyne **37**. IR (CCl_4) 3310 (≡CH), 3080 (=CH_2), 2130 (RC≡CH), 990 and 925 cm^{-1} (C-H=CH_2); NMR (CCl_4) δ 1.20–2.34 (m, 12 H), 2.50 and 2.56 (2 H, C-1 H and C-4 H), 3.42 (1 H, C-3 H); high-resolution mass spectrum, calcd for $C_{15}H_{20}O$ *m/e* 216.1514, found 216.1518.

3-[*exo*-3-Hydroxy-5,6-dimethyl-*endo*-bicyclo[2.2.1]hept-5-en-2-yl]propyne (38). The allyl ether group was cleaved in the presence of the 1-alkyne by an adaptation of the combined procedures of Baldwin[20] and Raphael.[32] In a 500-mL flask equipped with a magnetic stirrer, serum cap, dry ice condenser fitted with a drying tube, and NH_3 inlet were placed 5.50 g (0.0254 mol) of allyl ether **37** and several crystals of triphenylmethane. After 250 mL of NH_3 had been condensed in the flask, 42.45 mL (0.0762 mol) of 1.8 M methyllithium solution was added slowly by syringe. This solution was stirred for 1 h whereupon 1.18 g (0.051 mol) of sodium in small pieces was added until the solution maintained a permanent blue color. After an additional 1 h of stirring, solid NH_4Cl was added, the NH_3 was allowed to evaporate, and 100 mL of saturated NaCl was added cautiously. This aqueous solution was extracted with ether (3 × 200 mL), and the combined extracts were dried ($MgSO_4$) and concentrated to afford an oil which was Kugelrohr distilled (83 °C, 0.05 mm) to yield 3.98 g (90%) of alcohol **38**: IR (CCl_4) 3620 and 3380 (OH), 3310 (≡CH), 2130 (R≡CH), 1670 cm^{-1} (tetrasubstituted C=C); NMR (CCl_4) δ 1.54–2.66 (m, 14 H, all unassigned), 3.31 (1 H, C-3 H); high-resolution mass spectrum, calcd for $C_{12}H_{16}O$ *m/e* 176.1201, found 176.1201.

3-(*exo*-3-(*p*-Toluenesulfonyloxy)-5,6-dimethyl-*endo*-bicyclo[2.2.1]hept-5-en-2-yl)propyne (39). To a stirred solution of 2.52 g (0.0143 mol) of alcohol **38** in 29 mL of dry pyridine cooled in an ice bath was added 5.45 g (0.0286 mol) of *p*-toluenesulfonyl chloride. After all components were dissolved, the flask was placed in the refrigerator and allowed to stand for 36 h whereupon the reaction was quenched with ice–water and worked up with ether to afford 4.36 g (92%) of the oily tosylate **39**: NMR (CCl_4) δ 1.46–2.80 (m, 8 H, all unassigned), 1.60 and 1.70 (s, 6 H, C-5 CH_3 and C-6 CH_3), 2.46 (s, 3 H, $ArCH_3$), 3.85 (1 H, C-3 H), 7.56 and 7.80 (AA'BB', 4 H, *J* = 8 Hz, aromatic).

No further analytical data were obtained.

Solvolysis of Tosylate 39. In a 200-mL flask equipped with a magnetic stirrer and a N_2 inlet and surrounded by a water bath was placed 5.3 g (0.016 mol) of tosylate **39** to which was added a solution of 2.53 g (0.032 mol) of pyridine in 60 mL of trifluoroethanol. After being stirred for 1 h, the solution was diluted with water and worked up with petroleum ether to yield 3.5 g (85%) of product. This material was shown to be 95% pure **1,2-dimethyl-9-trifluoroethoxytetracyclo[4.4.0.0^{2,4}.0^{3,7}]dec-9-ene (40)** by GLC and was not further purified at this step: IR (CCl_4) 3050 (cyclopropane CH and =CH), 1660 (C=C), 1278 (CF), 1175 (=COC), 975 (=CH), 875 and 860 (nortricyclene), 840 cm^{-1} (=CH); NMR (CCl_4) δ 0.71 (d, *J* = 5 Hz, 1 H, cyclopropane H), 0.80–2.60 (m, 7 H), 0.91 (s, 3 H, C-1 CH_3 or C-2 CH_3), 1.05 (s, 3 H, C-1 or C-2 CH_3), 3.98 (q, *J* = 8 Hz, 2 H, OCH_2CF_3), 4.35 (1 H, CH=C); high-resolution mass spectrum, calcd for $C_{14}H_{17}OF_3$ *m/e* 258.1235, found 258.1234.

1,2-Dimethyltetracyclo[4.4.0.0^{2,4}.0^{3,7}]decan-9-one (41). A solution of of 5.0 g (0.019 mol) of enol ether **40** in 600 mL of acetone and 20 mL of 1.2 N HCl was stirred at room temperature for 30 min whereupon the reaction was quenched by the addition of 20 mL of saturated $NaHCO_3$. After the acetone was removed in vacuo, the remaining aqueous layer was worked up with ether to give an oil which was Kugelrohr distilled (105 °C, 3.4 mm) to yield 2.30 g (67 or 57% overall from tosylate **39**) of ketone **41**: IR (CCl_4) 3060 (cyclopropane CH), 1722 (C=O), 870 and 845 cm^{-1} (nortricyclene); NMR (CCl_4) δ 0.80–2.60 (m, all unassigned), 0.88 (s, 3 H, C-1 or C-2 CH_3), 1.01 (s, 3 H, C-1 or C-2 CH_3); high-resolution mass spectrum, calcd for $C_{12}H_{16}O$ *m/e* 176.1201, found 176.1201.

1,2-Dimethyl-8-(acetoxymethylene)tetracyclo-[4.4.0.0^{2,4}.0^{3,7}]decan-9-one (42). Preparation of the 8-hydroxymethylene compound was accomplished by following an adaptation of the procedure of Johnson.[44] In a 25-mL flask equipped with a magnetic stirrer and a N_2 inlet and cooled in an ice bath was placed 6 mL of dry benzene and 0.648 g (0.012 mol) of $NaOCH_3$. To this stirring slurry were added dropwise 1.06 g (0.006 mol) of ketone **41** and 0.974 mL (0.888 g, 0.012 mol) of freshly distilled ethyl formate. The flask was then removed from the ice–water bath and allowed to stir at room temperature for 28 h whereupon 10 mL of ice–cold water was added along with additional benzene. The aqueous layer was then separated and the benzene layer extracted with cold 15% NaOH (2 × 20 mL). All aqueous extracts were combined and washed with 50 mL of ether whereupon 200 mL of ether was added and the solution brought to pH 2 by the slow addition of 1.2 N HCl. The ethereal layer was separated and the aqueous layer extracted with ether (2 × 200 mL). All ethereal extracts were combined, dried ($MgSO_4$), filtered, and the concentrated in vacuo to yield 0.83 g (66%) of an oil which solidified to a light yellow solid, essentially pure by GLC (225 °C, 2.1 min). A solution of 0.795 g (0.0039 mol) of crude hydroxymethylene compound from above, 65 mL of dry pyridine, and 5.5 mL (14-fold excess) of acetic anhydride **45** was stirred under a N_2 atmosphere for 20 h. The solvent and excess acetic anhydride were then removed at room temperature (reduced pressure), leaving a tan solid which was dissolved in 25 mL of ether and washed with brine (10 mL). After being dried ($MgSO_4$) and filtered, the solution was concentrated in vacuo to yield 0.889 g (93%) of tan solid which was recrystallized from a solution of 10 mL of ether and 4 mL of petroleum ether to yield 0.542 g (56.4% from the hydroxymethylene compound) of analytically pure enol acetate **42** as cream colored crystals: mp 116–117 °C; IR (CCl_4) 1755 (acetate C=O), 1705 (ketone C=O), 1635 (C=C), 1145, 1055, 945, 870 cm^{-1} (nortricyclene); NMR (CCl_4) δ 0.90 (s, 3 H, C-1 CH_3), 1.02 (s, 2 H, C-3 and C-4 H), 1.08 (s, 3 H, C-2 CH_3), 1.41 and 1.88 (2 H, AB, *J* = 11 Hz, C-5 H), 1.67 (s, 1 H, C-6 H), 2.20 (s, 3 H, $COCH_3$), 2.15 and 2.46 (2 H, AB, *J* = 19 Hz, C-10 H), 2.90 (s, 1 H, vinyl H).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.43; H, 7.57.

1,2-Dimethyl-8α-isopropyltetracyclo[4.4.0.0^{2,4}.0^{3,7}]decan-9-one (27). According to the combined procedures of Coates[34] and Casey,[35] 11.90 mL (0.016 mol) of a 1.34 M methyllithium/ether

(44) Johnson, W. S.; Posvic, H. *J. Am. Chem. Soc.* **1947**, *69*, 1361.
(45) Spencer, T. A.; Smith, R. A. J.; Storm, L.; Villarica, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 4856.

solution was added to a cold (−20 °C) suspension of 1.52 g (0.008 mol) of CuI in 12 mL of dry ether. The solution was allowed to stir for 30 min at −20 °C and then 0.492 g (0.002 mol) of **42** in 15 mL of dry ether was added dropwise over 20 min. The solution was stirred an additional 2 h and then poured slowly into a rapidly stirring mixture of NH_4Cl, HCl, and ice–water. After the addition of NH_4OH, the ethereal layer was separated, the aqueous layer was extracted with ether (2 × 100 mL), and the combined ethereal extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Kugelrohr distillation of the resulting oil (80 °C, 0.04 mm) yielded 0.309 g (71%) of semicrystalline ketone **27**, homogeneous by GLC (225 °C, 1.9 min; 210 °C, 2.1 min) and TLC analyses (R_f 0.73, 20% ether–petroleum ether, two times): IR (CCl_4) 3050 (cyclopropane CH), 1710 (C=O), 870 cm^{-1} (nortricyclene); NMR (CCl_4) δ 0.87 (s, 3 H, C-1 CH_3), 0.90 (2 d, 6 H, $CH(CH_3)_2$), 1.00 (br s, 7 H, C-2 CH_3, C-3 and C-4 cyclopropane H, C-7 H, and $CH(CH_3)_2$), 1.26 (d, J = 10 Hz, 1 H, C-5 H), 1.72 (d, J = 10 Hz, 1 H, C-5 H), 1.67 (1 H, C-6 H), 2.00–2.30 (m, 3 H, C-8 and C-10 H).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.37; H, 9.99.

This material was identical in all respects with ketone **27** produced in the previous route.

1,2-Dimethyl-8α-isopropyltetracyclo[4.4.0.0^{2,4}.0^{3,7}]decan-9α-ol (43). To 0.100 g (0.0026 mol) of stirred $LiAlH_4$ in 5 mL of anhydrous ether was added 0.088 g (0.0004 mol) of ketone **27** in 1 mL of anhydrous ether. The reaction was allowed to stir for 2 h and was then quenched by the slow addition of 0.1 mL of 15% NaOH and 0.3 mL of water. After 10 mL of additional ether was added, the solution was filtered and the solid washed twice with 10 mL of ether. All ethereal washings were combined and concentrated at reduced pressure, with the resulting oil being subjected to bulb to bulb distillation (95 °C, 0.03 mm) to yield 0.80 g (91%) of alcohol **43**: IR (CCl_4) 3625 (OH), 3060 (cyclopropane CH), 870 and 850 cm^{-1} (nortricyclene); NMR (CCl_4) δ 0.70–1.98 (m, all unassigned H), 0.80 (s, 3 H, C-1 CH_3), 0.96 (6 H, $CH(CH_3)_2$), 1.15 (s, 3 H, C-2 CH_3), 3.80 (s, 1 H, C-9 β-H); high-resolution mass spectrum, calcd for $C_{15}H_{24}O$ m/e 220.1827, found 220.1826.

1,2-Dimethyl-8α-isopropyltetracyclo[4.4.0.0^{2,4}.0^{3,7}]decan-9α-ol Methanesulfonate (44). To 0.065 g (0.003 mol) of alcohol **43** dissolved in 1 mL of dry pyridine was added 0.046 mL (0.006 mol, 0.068 g) of methanesulfonyl chloride. After the mixture was stirred for several minutes, the flask was placed in the refrigerator for 24 h whereupon the pyridine solution was poured into 2 mL of ice–water and worked up with ether (3 × 10 mL) to afford 0.089 g (100%) of methanesulfonate **44**.

Cyclosativene (1). Removal of the mesyloxy group was effected by the method of Masamune.[38] To a stirred slurry of 76 mg (2.0 mmol) of $LiAlH_4$ in 2 mL of doubly distilled THF cooled in an ice–water bath was added dropwise 192 mg (6.0 mmol, 0.24 mL) of reagent-grade methanol. The solution was allowed to stir for 30 min at 0 °C. This solution of $LiAlH(OCH_3)_3$ was then taken up in a syringe and added dropwise to 190 mg (9.10 mmol) of CuI under a N_2 atmosphere in a 10-mL flask cooled in an ice–water bath. A thick black slurry formed which was allowed to stir for 30 min, after which time was added 45 mg (0.5 mmol) of **44** dissolved in 1 mL of doubly distilled THF. The reaction was stirred for 15 min at 0 °C followed by an additional 8 h at room temperature whereupon the slurry was poured into 5 mL of a cold solution of NH_4Cl, and 1 mL of concentrated NH_4OH was added. After the mixture was stirred, the blue solution was worked up with ether to afford a mixture of olefins and cyclosativene (determined by NMR). This was passed through 2 g of no. 1 alumina, eluting with petroleum ether, and then subjected without further characterization to catalytic hydrogenation (3 mL of ethyl acetate, 5 mg of 5% Pd/C, 1 atm of H_2). After 2 h hydrogenation was complete and yielded 7 mg (27% from the alcohol)[46] of cyclosativene (1).

The elimination of methanesulfonic acid could also be effected by using the method of Snyder.[36] To 45 mg (0.15 mmol) of the mesylate was added 113 mg (1 mmol) of potassium *tert*-butoxide dissolved in 1 mL of dry Me_2SO. The yellow solution was allowed to stir for 30 min, and then 3 mL of petroleum ether was added. The contents of the flask were poured into 5 mL of cold water and extracted with petroleum ether (3 × 15 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil which on the basis of NMR data, was believed to be a mixture of the di- and trisubstituted olefins. This mixture was passed through 2 g of no. 1 alumina and eluted with petroleum ether to remove any polar impurities. Hydrogenation of the alkene mixture following the above conditions led to a mixture of cyclosativene and unreduced trisubstituted olefin. This was resubmitted to hydrogenation but no further hydrogenation occurred, presumably due to poisoning of the catalyst by some contaminant from the Me_2SO. The mixture was subjected to bulb distillation at 85 °C (aspirator pressure) to give an oil which was then readily hydrogenated to yield cyclosativene (1) under the above conditions. The nonoptimized yield was comparable to that obtained by the copper(I) complex method.[46] Cyclosativene so obtained had a GLC retention time of 2.6 min at 175 °C: IR (CCl_4) 3050 (cyclopropane CH), 1390 and 1375 cm^{-1} ($CH(CH_3)_2$); NMR (CCl_4) δ 0.66 (d, J = 5.5 Hz, 1 H, C-3 or C-4 cyclopropane H), 0.76 (s, 3 H, C-1 CH_3), 0.78 (1 H, partly unresolved C-3 or C-4 cyclopropane H), 0.88 (d, J = 6 Hz, 3 H, $CH(CH_3)_2$), 0.91 (d, J = 6 Hz, 3 H, $CH(CH_3)$), 0.99 (s, 3 H, C-2 CH_3), 1.05–1.75 (m, unresolved, 10 H); high-resolution mass spectrum, calcd m/e 204.1878, found 204.1879.

Registry No. (±)-**1**, 30541-92-5; **12**, 1121-05-7; (±)-**13**, 72784-76-0; (±)-**15**, 56775-40-7; (±)-**16**, 56775-41-8; (±)-**17**, 72784-77-1; **18**, isomer 1, 72784-78-2; **18**, isomer 2, 72843-41-5; **19**, isomer 1, 72784-79-3; **19**, isomer 2, 72843-42-6; **20**, isomer 1, 72784-80-6; **20**, isomer 2, 72843-43-7; **21**, isomer 1, 72784-81-7; **21**, isomer 2, 72843-44-8; **22**, isomer 1, 72784-82-8; **22**, isomer 2, 72843-45-9; **23**, isomer 1, 72784-83-9; **23**, isomer 2, 72843-46-0; **24**, isomer 1, 72784-84-0; **24**, isomer 2, 72843-47-1; **25**, 72784-85-1; **26**, 72784-86-2; (±)-**27**, 56775-47-4; (±)-**34**, 72784-87-3; (±)-**35**, 72784-88-4; (±)-**36**, 72784-89-5; (±)-**37**, 56775-42-9; (±)-**38**, 72784-90-8; (±)-**39**, 56775-43-0; (±)-**40**, 56775-44-1; (±)-**41**, 56775-45-2; (±)-**42**, 56775-46-3; (±)-**43**, 72843-48-2; (±)-**44**, 72784-91-9; **45**, 108-24-7; allyl alcohol, 107-18-6; diethyl malonate, 105-53-3; isopropylmagnesium bromide, 920-39-8; ethyl formate, 109-94-4; (±)-1,2-dimethyl-8-(hydroxymethylene)tetracyclo[4.4.0.0^{2,4}.0^{3,7}]decan-9-one, 72784-92-0.

(46) The low yield of this reaction can likely be ascribed to the difficult manipulation of relatively small samples of volatile materials. The homogeneity of the product obtained suggests that the chemical efficiency and specificity are in fact quite high.