TOTAL SYNTHESIS OF β-CHAMIGRENE

Thesis by

William Clinton Dow

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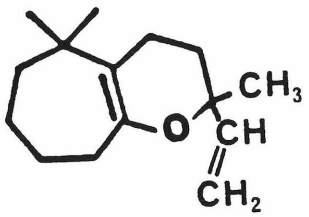
Abstract

A total synthesis of the sesquiterpene (±)-β-Chamigrene is described. A key step is the preparation of spiro-ketone *ii* through Claisen rearrangement of the vinyl-substituted cycloheptapyran *i*. A modified Meinwald-Cava ring contraction sequence is used for the intramolecular elaboration of a functionalized one-carbon unit at the hindered alpha flank of the spirocycle. This procedure affords ester *iii*. Alternate reaction pathways available to the reactive ketene intermediate are also discussed. These results are compared with observations made in a previously reported synthesis of aphidicolin.



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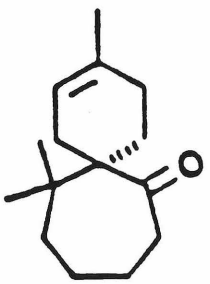

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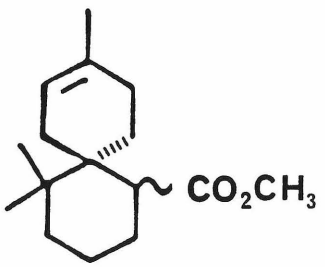

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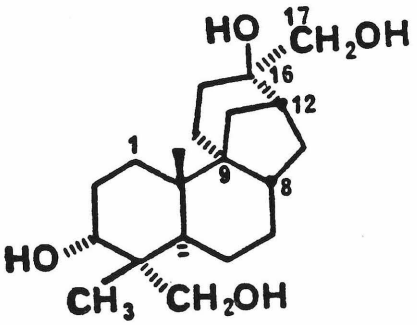
Preface

The tetracyclic diterpene aphidicolin (1) was isolated in 1972 from cultures of Cephalosporium aphidicola Petch.[1] This diterpene tetraol has attracted considerable interest for a number of reasons. Aphidicolin shows antiviral activity against DNA-containing viruses, such as Herpes simplex type I.[2] The antiviral activity is believed to be due to an inhibition of DNA synthesis. Aphidicolin also presents a challenging target for the synthetic chemist. The unusual ring system contains a bicyclo[3.2.1]octane moiety (4), a



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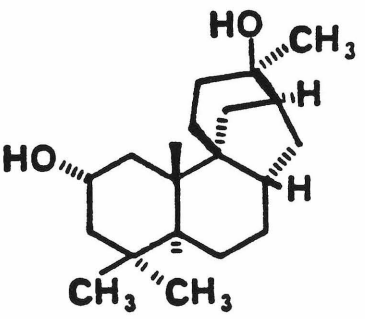

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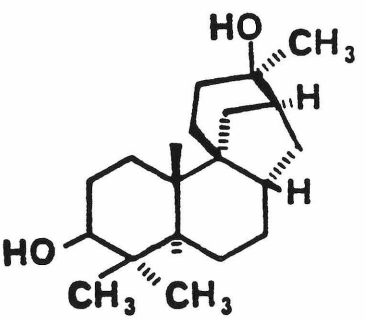

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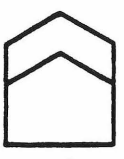

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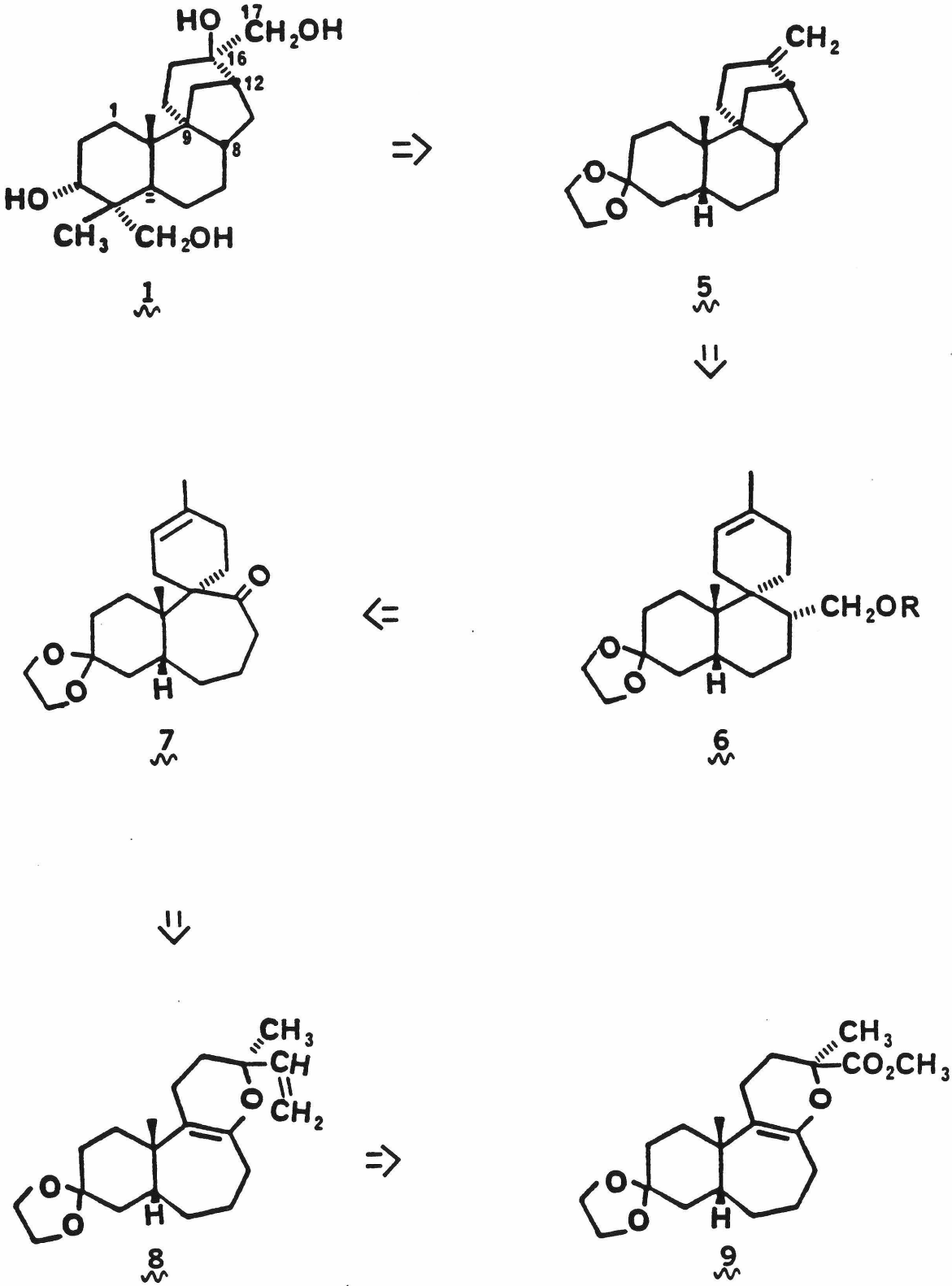
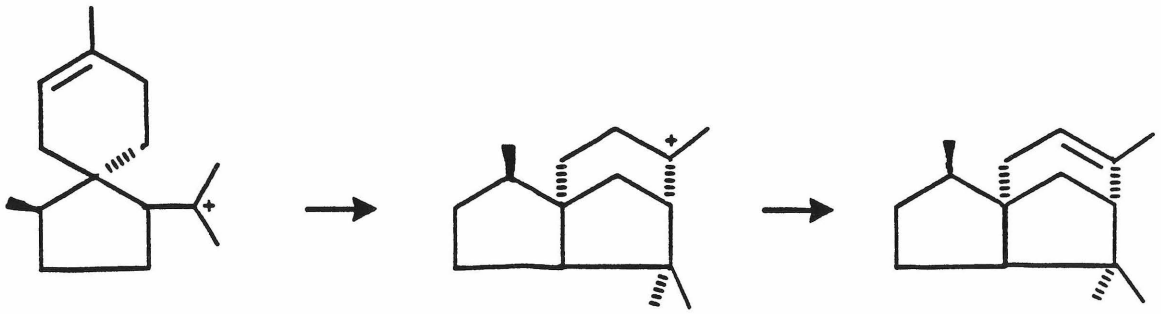
substructure common to many classes of diterpenes.[3] Diterpenes with a close structural similarity to aphidicolin were later isolated. Stemodin (2)[4] and maritimol (3)[5] are two examples. These compounds possess a ring system epimeric with aphidicolin at C-9 and C-12.

In 1979, Ireland and Aristoff described an approach to the synthesis of aphidicolane-type diterpenes, including the successful construction of the aphidicolin ring system.[6] Their approach is outlined in Scheme I. The plan called for elaboration of the A ring and the C-16, C-17 diol functionality late in the synthesis. A key step in this scheme was the closure of the final skeletal bond between C-12 and C-13. An efficient solvolytic approach to closure of a bicyclo[3.2.1]-octane system had been demonstrated in the syntheses of cedrene (10) reported by Corey and Lawton (Scheme II).[7] An attractive feature of the solvolytic π route is that selective entry into the aphidicolin or stemodin--maritimol ring systems was possible through control of the stereochemistry of the spiro center. The stereochemistry indicated for tricyclic intermediate 6 in Scheme I establishes the stereochemistry required for aphidicolin intermediate 5.

Scheme I. The Ireland Approach to Aphidicolin (1)[6]



Scheme II.[7]



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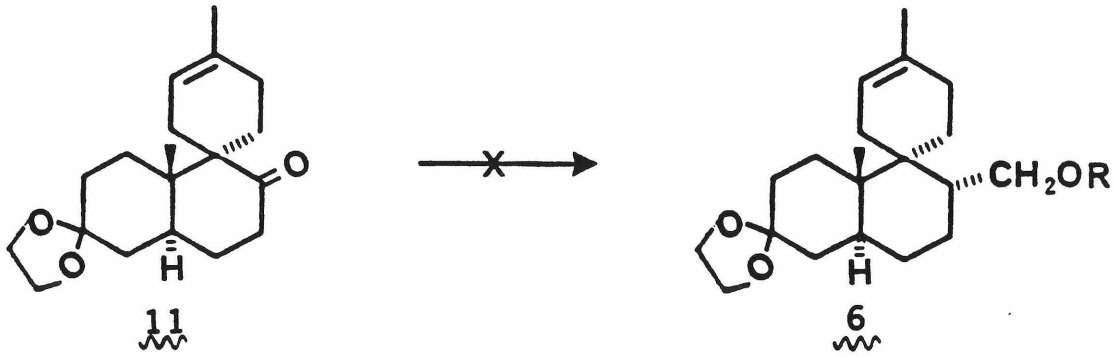
The spiroannelation procedure was an extension of work reported by Büchi and coworkers,[8] in which a hetero-Diels-Alder reaction generated a vinyldihydropyran which then underwent Claisen rearrangement to a substituted cyclohexene. Vinyldihydropyran 8 rearranged upon heating to provide spiroketone 7.

Spiroketone 7 was not a part of the original design. Initially, the plan was to prepare intermediate 6 by the addition of a functionalized one-carbon unit to spiroketone 11. This proved to be a serious problem when it was found that steric hindrance from the adjacent spirocyclic ring sufficiently blocks approach to the carbonyl carbon that enolization rather than addition occurred with a variety of nucleophilic reagents.



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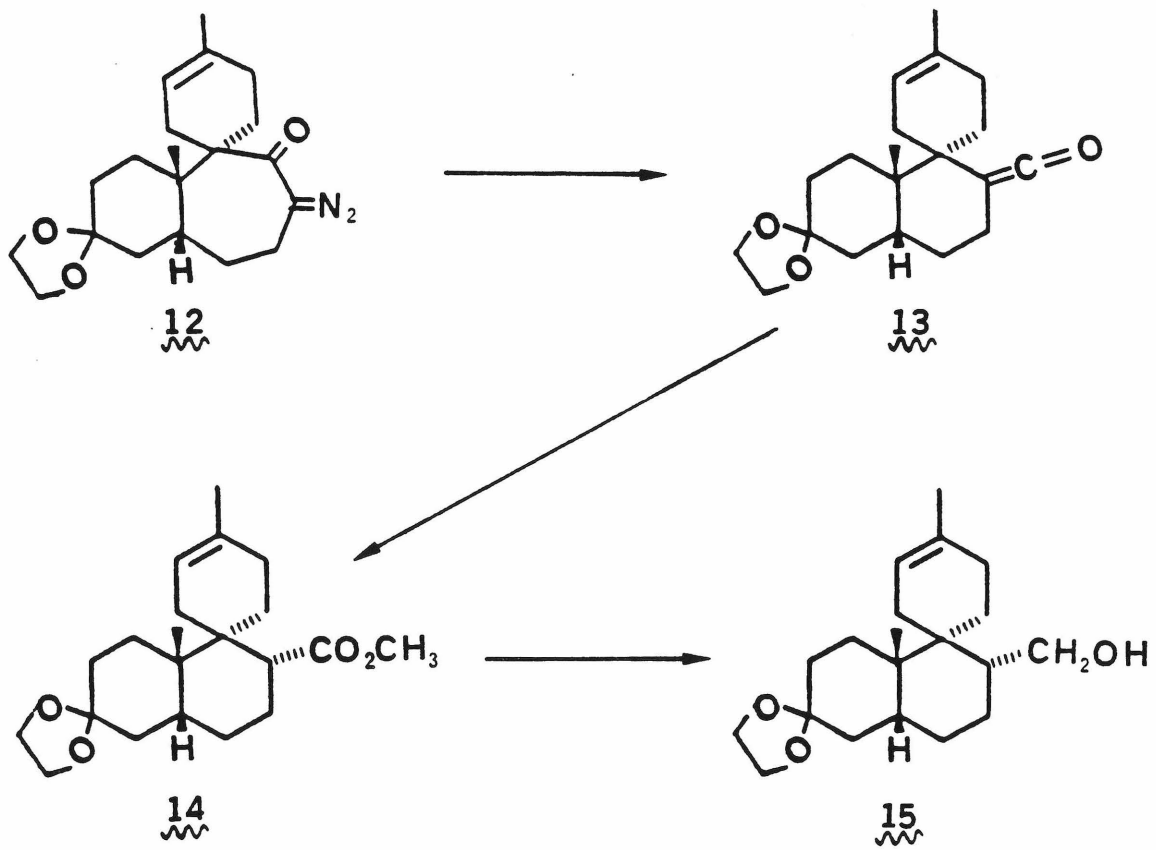
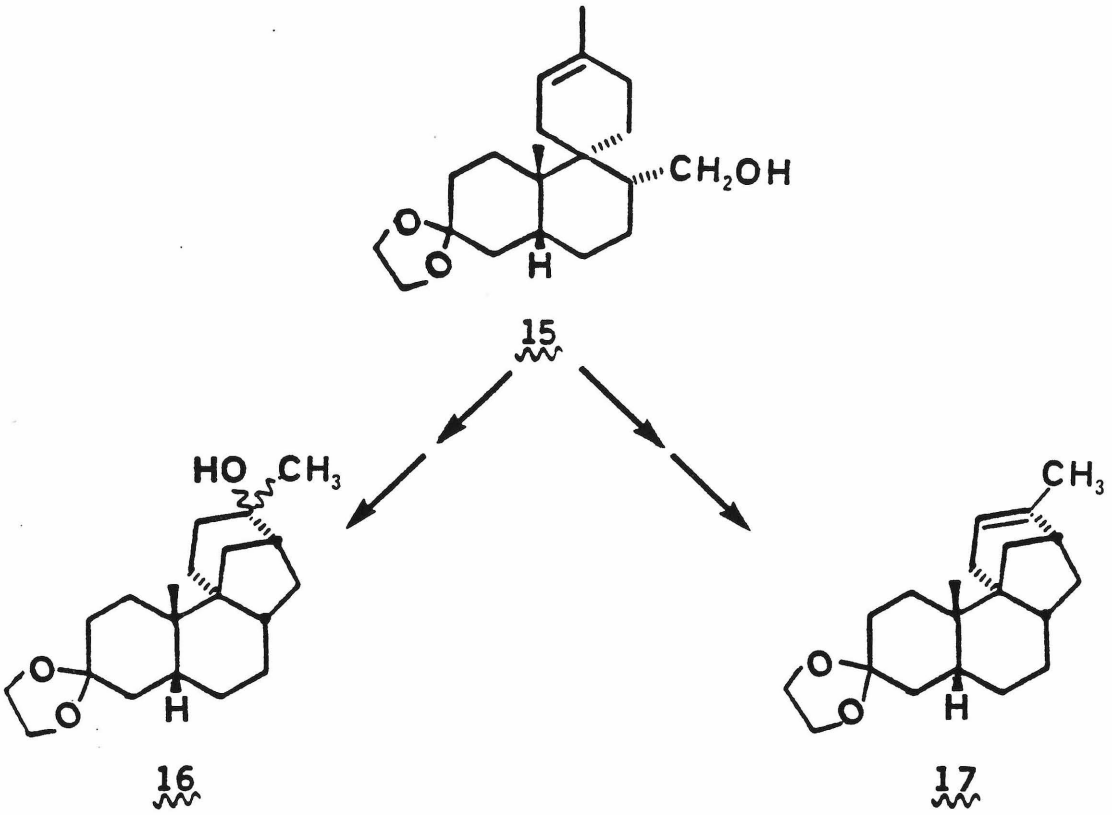
The decision of Ireland and Aristoff was to avoid the need for intermolecular addition at the hindered center through modification of the synthetic route. A promising alternative was in intramolecular elaboration of a functionalized one-carbon unit from a precursor which already contained the carbon. The Meinwald-Cava ring contraction sequence[9] was viewed as a means of effecting the needed transformation. B-homo spiroketone 7 was therefore prepared by Claisen rearrangement of vinyldihydropyran 8. Spiroketone 7 was then converted to the α-diazoketone 12 (Scheme III). Low temperature photolysis produced the reactive ketene 13,

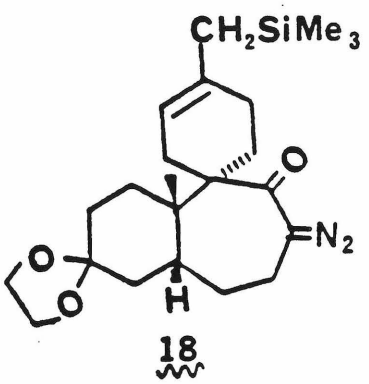
which was trapped *in situ* by sodium methoxide. This provided the ring-contracted ester 14, which was then converted to alcohol 15. After derivatization, alcohol 15 underwent efficient solvolytic closure to the aphidicolin ring system, forming the epimeric alcohols 16 or the endocyclic olefin 17 depending on experimental conditions.[6,10] Conditions leading to useful quantities of olefin 5, the exocyclic olefinic isomer of olefin 17, were not found.

Scheme III. Ring Contraction





At this point, all of the key elements in the synthetic plan had been reduced to practice, but some method of directing the solvolysis so as to afford the exocyclic olefin was still needed. Silicon has been shown to exert a directive effect in elimination reactions.[11] Accordingly, diazoketone 18 was prepared[12] by minor modification of the procedure used in the preparation of the de(trimethylsilyl)diazoketone 12. Photolysis of diazoketone 18 led



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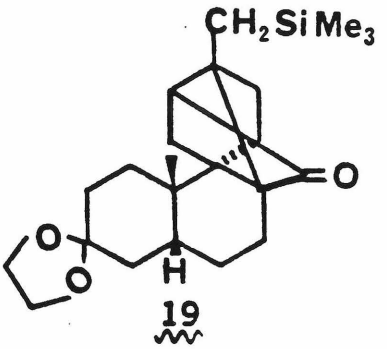

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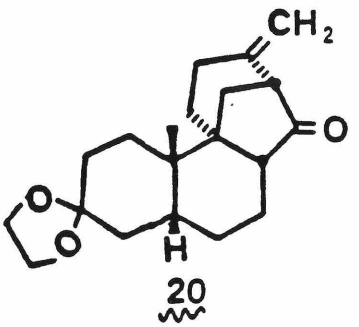

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almost exclusively to cyclobutanone 19, even under conditions where the de-silyl system provided the methyl ester. This was considered a setback until it was found that cyclobutanone 19 underwent rearrangement to exocyclic olefinic ketone 20 under mild acid catalysis (silica gel). This fortuitous result thus provided the aphidicolin framework. These efforts soon culminated in the total synthesis of

aphidicolin, which was reported by Ireland, Godfrey, and Thaisrivongs in early 1981.[12]

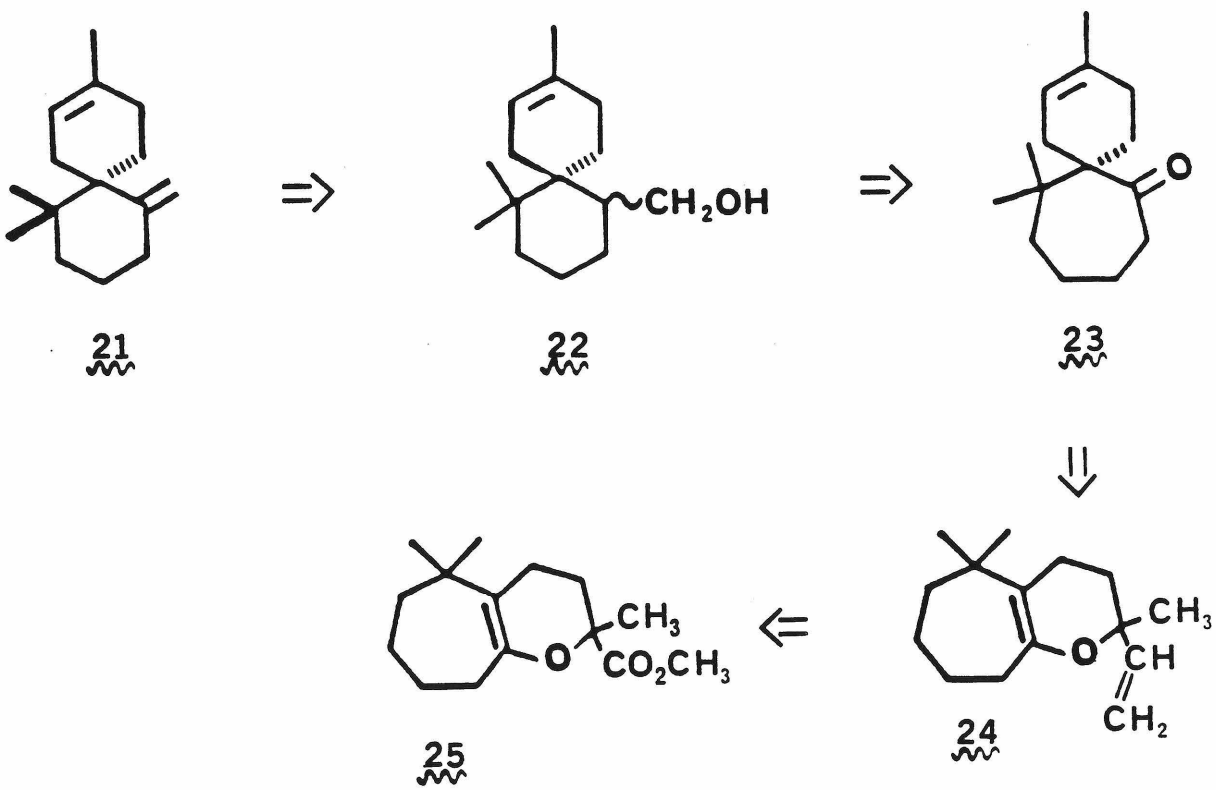
The methodology developed in the course of the aphidicolin synthesis is expected to prove useful in other applications. Of particular promise, in terms of efficiency and versatility, are the new spiroannelation procedure and the use of ring contraction to introduce functionalized one-carbon units at a hindered position.

β-Chamigrene (21) is a sesquiterpene first isolated in 1967 from the leaves of Chamaecyparis taiwanensis Masam.[13] It has also been isolated from a variety of higher plants[14] as well as from algae and bryophyta (mosses and liverworts).[15] β-Chamigrene possesses many of the structural features found in aphidicolin, and the concepts used in the total synthesis of β-chamigrene reflect this similarity. The approach is outlined in Scheme IV. Spiroannelation to form the spiro[5.6]dodecane system 23 was accomplished through hetero-Diels-Alder reaction and Claisen rearrangement, much as already described for aphidicolin. Further transformations, including ring contraction, provided the alcohol 22. This intermediate is a spiro[5.5]undecane system with a functionalized one-carbon unit adjacent to the spiro center. Conversion of the

one-carbon unit (i.e., the primary alcohol) to an exocyclic olefin completed the synthesis of β-chamigrene.

Aphidicolin and β-chamigrene were pursued concurrently within the Ireland research group. β-Chamigrene was viewed as a related synthetic target, rather than as merely a model compound for aphidicolin. In fact, many interesting differences in reactivity between the aphidicolin and β-chamigrene systems were revealed during the course of this work. These are discussed in the next section.

Scheme IV. The Approach to β-Chamigrene



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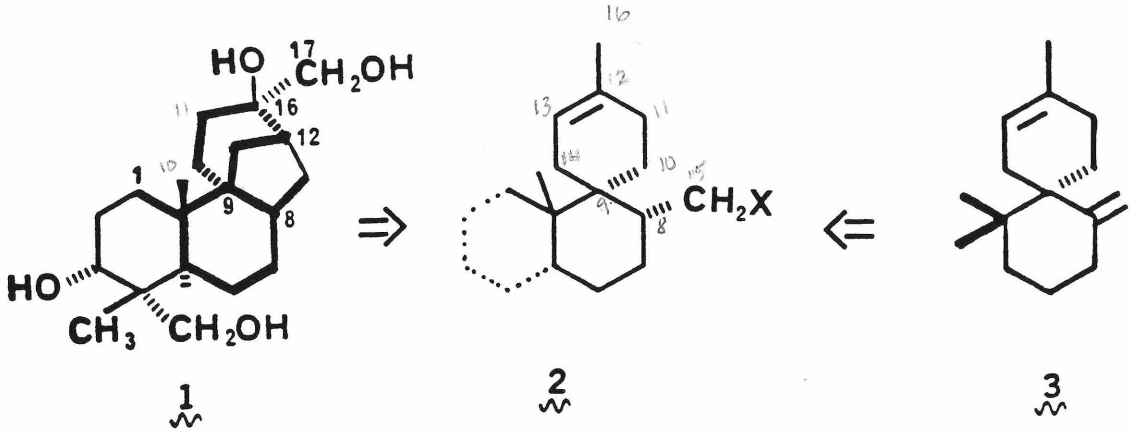
Results and Discussion

Successful execution of the recently reported synthesis of (±)-aphidicolin[2] (1) required the development of methodology for a stereocontrolled spiroketone synthesis and for the subsequent introduction of a functionalized one carbon unit adjacent to the spiro center. Such methodology should prove useful in a variety of contexts. Another such situation was envisaged to be the total synthesis of (±)-β-chamigrene (3). This terpene was the first-isolated[3] of an interesting class of sesquiterpenes possessing a spiro[5.5]undecane skeleton. β-Chamigrene and the endocyclic olefinic isomer α-chamigrene[4] are constituents of the essential oils of a variety of higher plants[3,5] as well as algae and bryophyta.[6] In addition, a number of halogenated derivatives have been isolated from marine sources.[7] Alpha- and beta-chamigrene have been implicated as key links in the biosynthesis of thujopsene, widdrol, cuparene, and related sesquiterpenes.[8] A number of acid-catalyzed interconversions within this group have been noted.[9]

The similarity between the retrosynthetic analysis used for β-chamigrene and aphidicolin stemmed from the observation that both molecules can be proposed to



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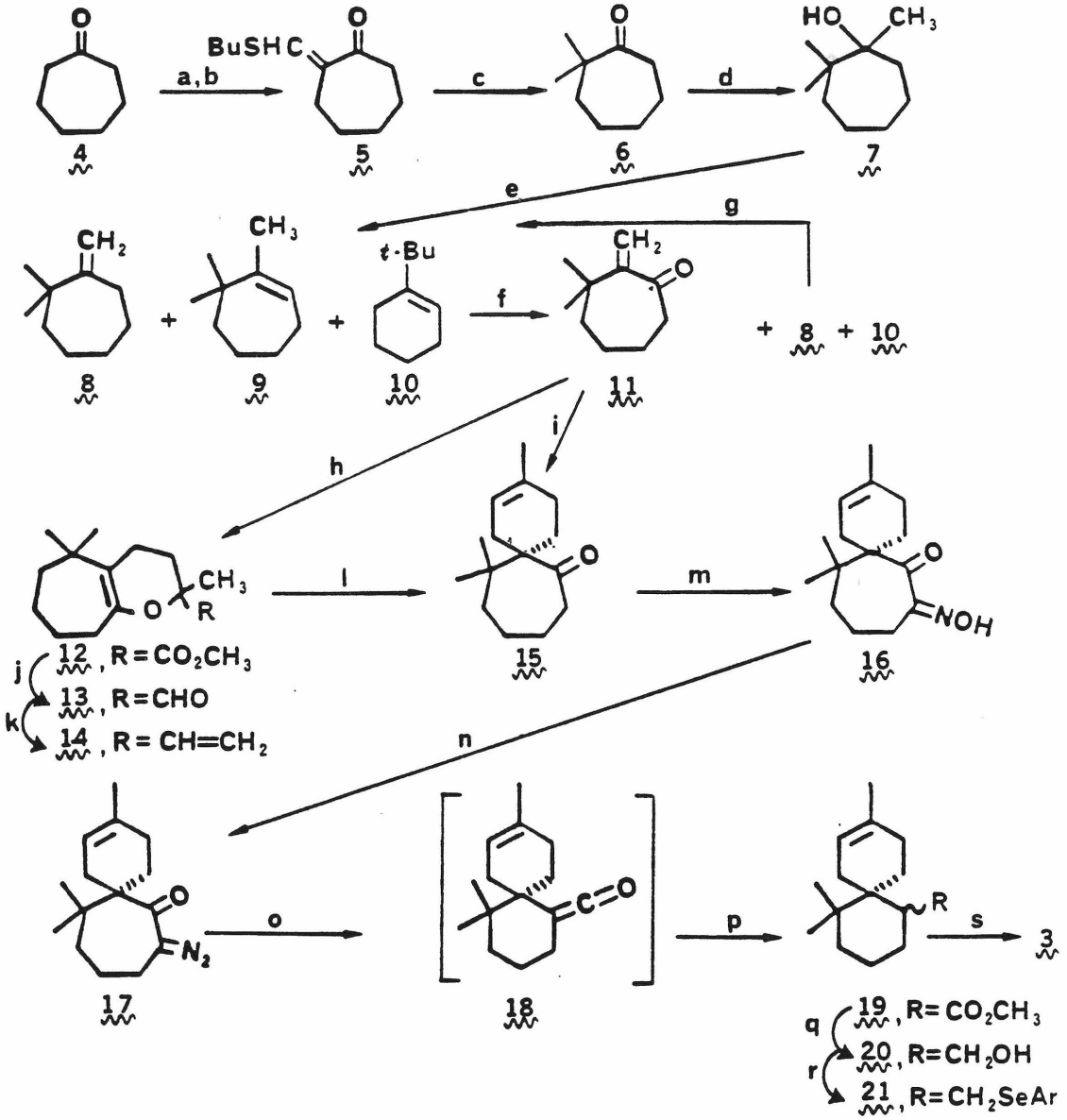
arise from a spiro[5.5]undecane moiety with a functionalized one-carbon unit adjacent to the spiro center. A solvolytic π-route[10] in a suitably-functionalized tricyclic intermediate 2 would serve to knit together the bicyclo[3.2.1]octane BCD ring system required for aphidicolin, whereas the elimination of the generalized HX from a corresponding bicyclic intermediate would lead to β-chamigrene. The present successful application of these concepts to the synthesis of β-chamigrene, coupled with the success of the previously reported aphidicolin synthesis,[2] underscores the utility of such a plan. This approach is markedly different from a previous synthesis of β-chamigrene[11] and from the

numerous routes to α-chamigrene which have been recorded.[12]

Geminal dimethylation of cycloheptanone was accomplished in 73% yield by reduction--alkylation[13] of thioenol ether 5,[14] which is available in 76% yield from cycloheptanone (Scheme I). These procedures could be conveniently carried out on a 300- to 500-millimolar scale. Corey's[15] route to ketone 6 via pinacolic coupling of cyclohexanone and acetone was also investigated. Technical problems (see Experimental Section) and the nontrivial separation of the byproduct 1-acetyl-1-methylcyclohexane from ketone 6 precluded the convenient application of this procedure on the scale described above. Alcohol 7, prepared by standard methods (97% yield), was treated with thionyl chloride in pyridine (-45°C). This provided a 3:2:1 mixture of olefins 8, 9, and 10 in 77% yield. The geminal methyl substitution exerts a two-fold effect on this system. Compared with the unsubstituted methylcycloheptene--methylenecycloheptane system,[16] the endocyclic olefin 9 is destabilized relative to exocyclic olefin 8. The geminal methyl substitution also facilitates ring contraction and rearrangement to t-butylcyclohexene[17] (10). Dehydration at higher temperatures led to increased proportions of

Scheme I. Synthesis of β-Chamigrene (3)[a]



[a] a) HCO_2Et, NaOMe, toluene; b) n-BuSH, p-TsOH, PhH,Δ; c) Li, NH_3, H_2O, THF, Et_2O, then CH_3I; d) CH_3Li, Et_2O; e) $SOCl_2$, Pyr, -45°C; f) hν, O_2, hematoporphyrin, EtOAc, Pyr, then Ac_2O; g) I_2, 120°C; h) methyl methacrylate, xylenes, hydroquinone, 195°C; i) isoprene, Me_2AlCl, CH_2Cl_2; j) DIBAL-H, hexane--DME, -78°C; k) $Ph_3P=CH_2$, THF; l) quinoline, 170°C; m) n-BuLi, THF, then i-AmONO; n) NH_2Cl, Et_2O; o) hν, -85°C, MeOH; p) NaOMe, MeOH, -85°C; q) $LiAlH_4$, Et_2O; r) (o-NO_2)PhSeCN, $(n\text{-}Bu)_3P$, THF; s) 90% TBHP, CH_2Cl_2.

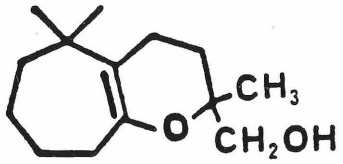
t-butylcyclohexene, and acidic dehydration procedures (e.g., $KHSO_4$/heat or p-toluenesulfonic acid--benzene) gave t-butylcyclohexene as sole product.[18]

The olefin mixture, carried on without separation, was subjected to photosensitized oxygenation with acetic anhydride workup. Enone 11 was obtained in 92% yield, based on the amount of endocyclic olefin 9 present in the starting material. Exocyclic olefin 8 and t-butylcyclohexene were recovered unchanged. A 1,3-quasidiaxial relationship between one of the methyl groups and the allylic quasiaxial proton in exocyclic olefin 8 prevents the overlap which is necessary for reaction.[19] Treatment of the recovered olefin mixture at 120°C with a catalytic amount of freshly sublimed iodine provided a mixture which again contained ca. 35% endocyclic olefin 9. The olefin mixture could then be recycled through the photooxygenation procedure. Potassium 3-aminopropylamide (KAPA),[20] usually an effective reagent for olefin isomerization under basic conditions, was not effective in the isomerization of exocyclic olefin 8 to endocyclic olefin 9.

Following essentially the same strategy as reported in the aphidicolin series,[2b] Diels-Alder reaction of enone 11 with excess methyl methacrylate afforded

dihydropyran--ester 12 in 50% yield (93% based on recovered and reusable enone). Efforts to improve the conversion by manipulation of conditions proved fruitless. Substitution of the radical scavenger 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy radical[21] for hydroquinone improved the yield of ester 12 to 64%, but also resulted in considerable (and unexplained) decrease in recovered enone (7%).

An interesting, but troublesome, difference in reactivity between ester 12 and the corresponding tricyclic esters in the aphidicolin and stemodin series[2] was observed in their reduction to aldehydes. Reduction of ester 12 to aldehyde 13 with diisobutylaluminum hydride (DIBAL-H) in ether at -78°C was accompanied by considerable overreduction to the primary alcohol 22, even when less than one equivalent of DIBAL-H was used in a low-conversion experiment. The value of dimethoxyethane (DME) as a cosolvent for the partial reduction of esters to aldehydes with DIBAL-H has been reported.[22] When applied to this system, optimum results in the reduction of ester 12 were achieved with 2 equivalents of 1 M DIBAL-H in hexane, precomplexed with an equal volume of dimethoxyethane. This corresponds to roughly 10 equivalents of DME per equivalent of DIBAL-H. With this procedure, the reduction



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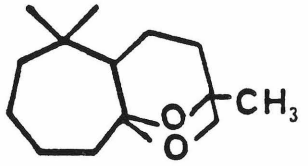

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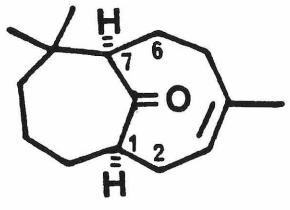
of ester 12 to aldehyde 13 proceeded smoothly. Wittig olefination of the aldehyde provided vinyldihydropyran 14 in 92% yield from the ester.

Earlier attempts at oxidation of the alcohol 22 back to the aldehyde 13 met with consistent failure. Alcohol 22 demonstrated a proclivity toward cyclization to the bicyclic ketal 23. Such cyclizations in dihydropyran systems have been noted previously.[23] Treatment of alcohol 22 with buffered pyridinium chlorochromate (PCC)[24] or pyridinium dichromate[25] led to the bicyclic ketal; no trace of aldehyde 13 was observed in either case. Collins reagent[26] produced a complex mixture.

Initial experiments on the Claisen rearrangement of vinyldihydropyran 14 as a neat oil in sealed, base washed glass ampoules provided variable amounts of

spiroketone 15 and an isomeric product which has been fully characterized as the bicyclic ketone 24. The mechanism by which this material is formed has not been determined, but the intermediacy of the isomerized vinyldihydropyran 25 or perhaps the ring opened species 26 would seem possible. The cis- fusion of bicyclic ketone 24 was assigned after 500 MHz ^{1}H NMR studies established that both bridgehead protons are quasiaxial. The methyne proton at C-7 shows couplings to the C-6 protons of 4.0 and 12.5 Hz, the latter only consistent with a quasidiaxial relationship. With the aid of decoupling, it was found that the C-1 methyne proton is coupled to the allylic protons on C-2 with J = 5.5 and ca. 6 Hz. A control experiment verified that



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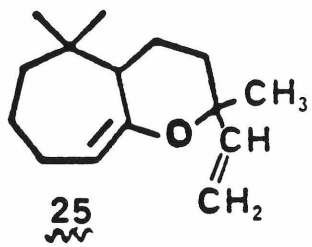

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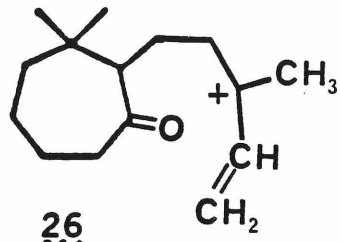

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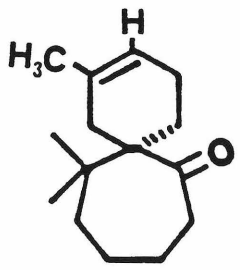
spiroketone 15 and bicyclic ketone 24 do not interconvert under the conditions used for the neat rearrangement of vinyldihydropyran 14. Desired spiroketone 15 was the exclusive product, obtained in 80% yield, when the Claisen rearrangement was performed at 170°C in quinoline.

An alternate preparation of spiroketone 15 by Diels-Alder reaction of enone 11 with isoprene under Lewis acid catalysis (dimethylaluminum chloride[27]) proved effective, providing the spiroketone in 69% yield. While the observed regioisomer would be expected to predominate,[28] it is noteworthy that regioisomer 27 was not detected in the reaction mixture.



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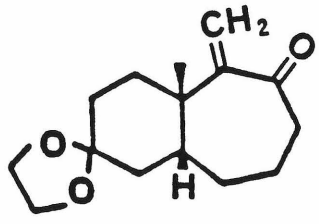

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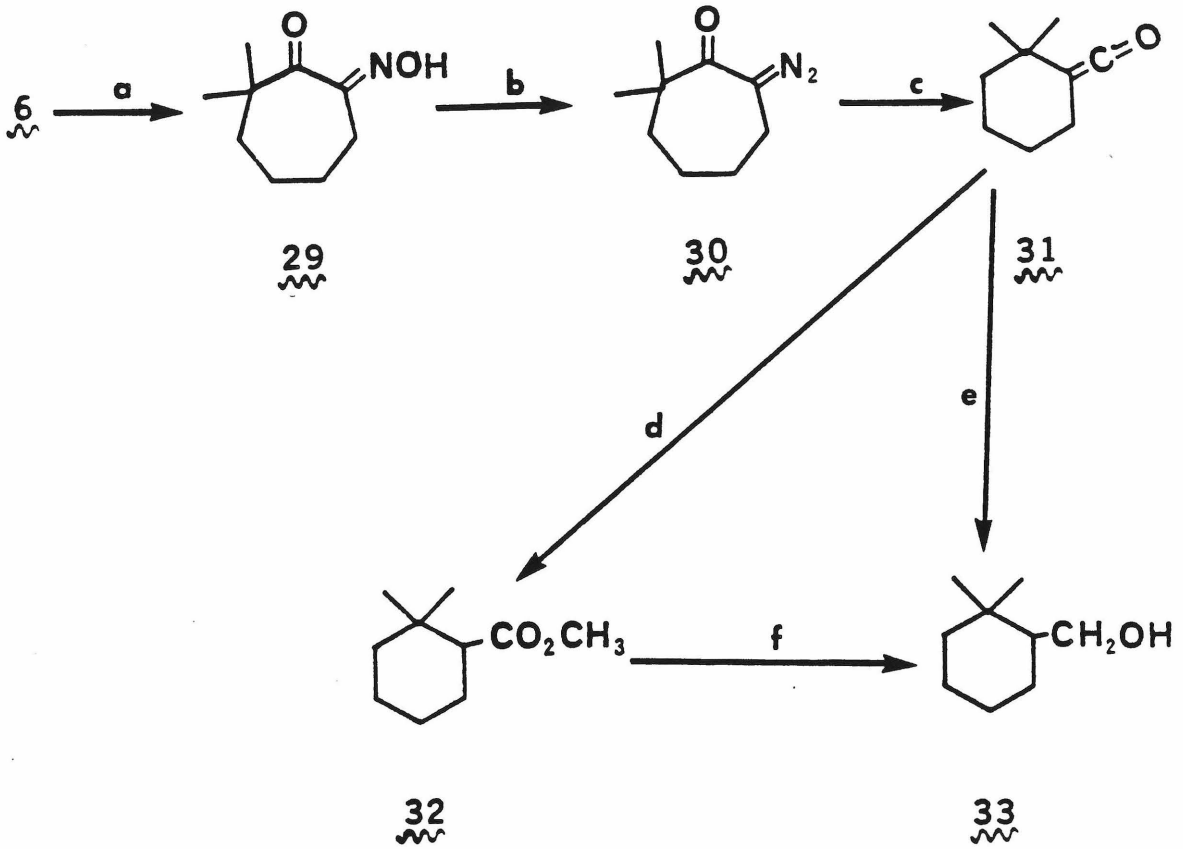
Similar conditions proved unsuccessful with enone 28 from the aphidicolin synthesis.[2b] Accessibility to the olefin is blocked on one face by the angular methyl, and the other face is within the concave region of a cis-fused system. The steric obstacle is more significant here, where the enone must function as the dienophile, than in the previous case[2b] where enone 28 served as the diene. Thus, steric hindrance as well as the acid-labile ketal functionality may explain the difference in reactivity of enones 11 and 28 in this reaction.

Model studies on ring contraction (Scheme II) were encouraging. Of particular note is the direct preparation of alcohol 33 by *in situ* reduction of ketene intermediate 31.

The α-oximinoketone 16 was prepared by enolization of spiroketone 15 followed by trapping with i-amylnitrite (75% yield at 60% conversion). Treatment with ethereal chloramine[29] provided the diazoketone 17, which was routinely used without chromatographic purification. Irradiation of the diazoketone in 0.4 M sodium methoxide--methanol at -85°C ensured that ketene 18 was trapped as the methyl ester 19 (62% yield from α-oximinoketone 16). The homogeneity of ester 19 by 500 MHz ^{1}H NMR and ^{13}C NMR suggests a strong predominance of one diastereomer, but this was not conclusively

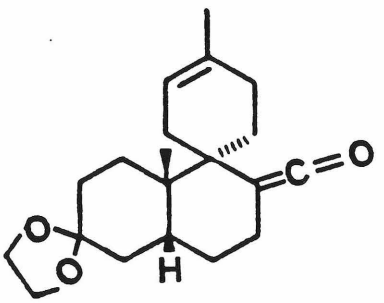
Scheme II. Model Studies on Ring Construction[a]



[a] a) t-BuOK, t-BuOH, i-AmONO, 40°C; b) aq. NaOH, NH_4Cl, 5% NaOCl, THF; c) hν, MeOH, -85°C; d) NaOMe, MeOH, -85°C; e) $NaBH_4$; f) $LiAlH_4$, Et_2O.

established. High selectivity in this transformation has precedent; under similar conditions ketene 34 was found to provide a 5:1 mixture of esters 35a and 35b in 70% yield.[2b,30]

The reactivity of ketene 18 was further studied with respect to new synthetic applications. Photolysis of diazoketone 17 at higher temperatures led to the preparation of increasing amounts of cyclobutanone 36. The cyclobutanone was prepared cleanly by photolysis in ether at 0°C with no methoxide present (quantitative yield). This observation of a facile, but avoidable, intramolecular [π2s + π2a] cycloaddition parallels results from the de-silyl aphidicolin series.[2b] Cyclobutanone 36 proved stable to silica gel, in contrast to (trimethyl-



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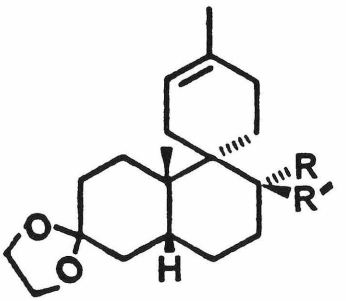
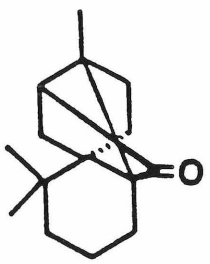


35a; R=CO_2CH_3, R'=H

35b; R=H, R'=CO_2CH_3



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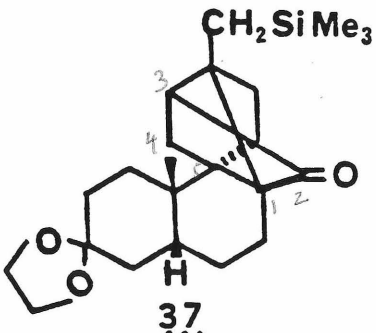

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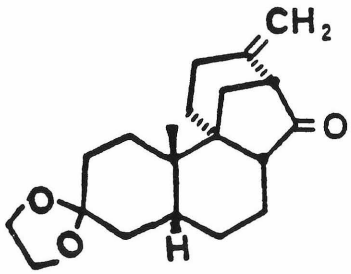

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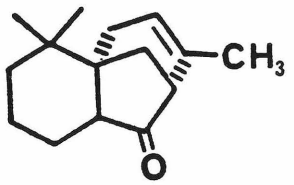
silyl)cyclobutanone 37 from the aphidicolin synthesis[2a] which underwent ready rearrangement to keto--olefin 38. Rearrangement of cyclobutanone 36 was observed, however, when it was treated with p-toluenesulfonic acid monohydrate. This provided the keto--olefin 39 and keto--alcohol 40 in modest yields (24 and 31 percent, respectively). Selection for either product through manipulation of experimental conditions should be possible, based on previous work;[2b,30] however, this was not pursued.

In spite of earlier success with model ketene 31, in situ reduction of ketene 18 to alcohol 20 was not observed. Alcohol 20 was therefore prepared, in 96%



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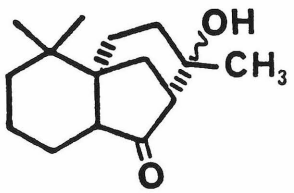

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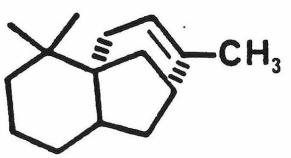
yield, by the reduction of ester 19 with lithium aluminum hydride. All that remained for completion of the synthesis of β-chamigrene was to effect elimination to the exocyclic olefin. This task was approached with some concern, however, for two reasons. First, it would require transformations in the hindered region adjacent to the spiro center, and second, the olefin in the other ring is favorably positioned for remote participation in transformations at the exocyclic carbon. Such remote participation was central to the formation of the aphidicolin framework, but in the present context it would spell disaster. A syn-elimination, involving intramolecular removal of the hindered ring proton adjacent to the spiro center, seemed to meet the

necessary criteria. Accordingly, o-nitrophenylselenide[31] 21 was prepared by the one-pot procedure (in THF) of Grieco and coworkers.[32] Selenide 21, obtained in 66% yield, was accompanied by lesser amounts of endocyclic olefin 41 and exocyclic olefin 42 (approximately 20 and 10 percent, respectively, from alcohol 20). Preparation of the selenide by the same procedure, but in pyridine, led to greater amounts of the olefinic byproducts, which presumably arise from intramolecular displacement in the postulated[32] oxaphosphonium species 43. Endocyclic olefin 41 was also obtained from the attempted preparation of the methanesulfonate ester of alcohol 20.



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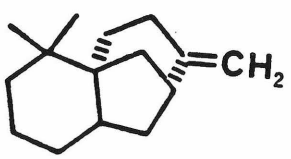

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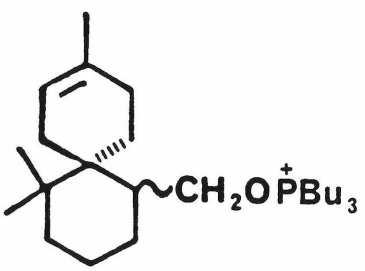

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Syn- elimination of the selenoxide (prepared from selenide 21 with 90% t-butyl hydroperoxide in dichloromethane) afforded (±)-β-chamigrene in 49% yield after chromatography. The documented[33] difficulties in the elimination of β,β-dialkylselenides make the outcome of this elimination quite gratifying. Spectral data for synthetic β-chamigrene are in good agreement with published values[3] for the natural product.

Experimental Section[34]

2-[Butylthiomethylene]-cycloheptanone(5). A modification of the procedures of Johnson and Posvic[35] and Ireland and Marshall[14] was used. To a mechanically stirred suspension of 188 g (3.5 mol) sodium methoxide in 3.5 L dry toluene at 0°C were added 259 g (3.49 mol) ethyl formate and 183 g (1.63 mol) cycloheptanone over 10 min. The ice bath was removed and the thick white reaction mixture stirred at room temperature for 10.5 h. The reaction vessel was then repositioned in an ice bath and 500 mL ice water added. The organic layer was separated and extracted with 5% aqueous sodium hydroxide solution (5 x 600 mL). The combined aqueous extracts were washed with ether (1 x 100 mL) and then acidified to pH 4 with conc hydrochloric acid. After saturating the aqueous solution with solid sodium chloride, extraction with ether (5 x 600 mL) was performed. The combined organic layers were washed with brine (1 x 100 mL) and dried ($MgSO_4$). Concentration under reduced pressure afforded 223 g crude hydroxymethylenecycloheptanone[36] as a red oil. This was used directly in the next experiment without further purification.

The crude product was combined with 183 g (2 mol) n-butanethiol and 400 mL dry benzene in a 1 L round

bottom flask equipped with reflux condenser and Dean-Stark trap. A trace of p-toluenesulfonic acid monohydrate was added and the reaction mixture heated under reflux for 25 h. The reaction mixture was cooled to room temperature and washed with saturated aqueous sodium bicarbonate (2 x 50 mL). Solvents were removed by distillation ($\leqslant$ 100°C, 1 atm) to provide a red brown oil. Distillation afforded 265 g (76% from cycloheptanone) of the known[37] thiomethylene compound 5 as a yellow oil: bp 125-135°C (0.005 mm).

2,2-Dimethylcycloheptanone(6). A. From thioenol ether (5). The following is a modification of the procedure of Coates and Sowerby.[13] To a refluxing solution of 8.28 g (1.2 mol) lithium in 3 L ammonia (distilled and passed through a drying tower of potassium hydroxide) was added a solution of 43.9 g (0.21 mol) thioenol ether (5), 7.2 g (0.40 mol) water, 150 mL THF, and 400 mL ether dropwise over 20 min. The reaction mixture was stirred 2.5 h. Additional ether (100 mL) was added, followed by the dropwise addition of 150 mL (2.41 mol) iodomethane in 100 mL ether over 15 min. The ammonia was allowed to evaporate over several hours, and 500 mL 5% aqueous sodium hydroxide was then added. The reaction mixture

was extracted with ether (4 x 1 L), and the combined organic extracts washed with water (2 x 100mL). The resulting solution was dried ($MgSO_4$) and concentrated under reduced pressure to afford 33.5 g pale yellow oil. Distillation afforded 21.15 g (73%) dimethyl ketone (6) as a colorless liquid: bp 94-96°C (ca. 45 mm); R_f = 0.78 (6:1 petroleum ether-ether); IR (neat) 1705 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.08 (s, 6H, 2 x CH_3), 2.45-2.65 (m, 2H, $-CH_2CO-$), Lit.[38] (CCl_4) δ 1.13 (s, 6H).

B. From pinacolic coupling and rearrangement. To a mechanically stirred solution of 30 g (110 mmol) mercuric chloride in 500 mL THF at 0°C was added 96 g (4 mol) 70-80 mesh magnesium (Fisher Scientific) over 5 min. The mixture was stirred 20 min, then the turbid gray supernatant liquid was aspirated from the flask and replaced with 2.5 L THF. The resulting suspension at -5 to 0°C was carefully treated dropwise with 210 mL (1.91 mol) titanium tetrachloride, initially producing a thick, yellow-green mixture. After 10 mL of the reagent had been added (ca. 10 min), the reaction mixture abruptly turned black and became less viscous. The remainder of the titanium tetrachloride was added over 1.5 h.

Caution: When this procedure is performed on a

scale greater than that previously reported,[15] it is very important to add only a small portion of the required titanium tetrachloride prior to the change in color from yellow-green to purple-black. This change, which has a variable initiation period, presumably signals the onset of reduction of Ti(IV) to Ti(II) which is highly exothermic. The original work, particularly in the preparation of their compounds 9 and 14, unfortunately conveys the impression that the color change occurs later, upon addition of the ketones. Addition of the entire quantity of titanium tetrachloride prior to the initiation of reduction on the scale reported here results in a violent reaction with vaporization of much of the THF.

After the addition of titanium tetrachloride was complete, the walls of the flask were washed with 500 mL THF and the reaction mixture stirred 25 min. A solution of 53 mL (515 mmol) cyclohexanone and 80 mL (1.08 mol) acetone in 200 mL THF was added dropwise over 45 min while the cooling bath was maintained at -20 to -10°C (the addition is exothermic). The black mixture was stirred 90 min at -20 to -10°C and then cautiously quenched with 300 mL 10% aqueous sodium hydroxide, added over 10 min to minimize heating and foaming. The reaction mixture was stirred 3 h at room temperature

before the solution was decanted from the black precipitate. The precipitate was washed with 1 L ether, and this solution was combined with the first to provide ca. 4 L organic extract, which was washed with 5% aqueous sodium hydroxide (4 x 500 mL) and brine (2 x 500 mL). The combined aqueous layers were extracted with ether (2 x 800 mL); these organic layers were combined with the main organic extract after washing with brine (1 x 50 mL). The solution was dried ($MgSO_4$) and concentrated under reduced pressure, followed by dilution with benzene and additional concentration under reduced pressure to remove the last traces of water. This gave 65 g (80%) crude pinacol product[15] as a pale yellow oil. This material was routinely used for the subsequent rearrangement without further purification.

To a stirred solution of 3.15 g crude pinacol product in 5 mL THF at room temperature was added 10 mL 60% perchloric acid. The reaction mixture was stirred 12 h, then diluted with 50 mL water and extracted with ether (3 x 75 mL). The combined organic layers were washed with saturated aqueous sodium carbonate (1 x 10 mL) and with brine (2 x 10 mL). The resulting solution was dried ($MgSO_4$) and concentrated under reduced pressure to afford a yellow oil which was

purified by flash chromatography (6 x 20 cm, 16:1 petroleum ether--ether) to afford 0.55 g ketone 6 in pure form and another 0.28 g in mixed fractions. The total yield of ketone 6 was 0.83 g (ca. 25% from cyclohexanone).

1,2,2-Trimethylcycloheptanol(7). To a stirred solution of 13 mL (22.1 mmol) of 1.6 M methyllithium in ether at 0°C was added 1.56 g (11.1 mmol) ketone 6 in 30 mL ether dropwise over 5 min. The ice bath was removed and the reaction mixture stirred at room temperature for 1 h. The mixture was then carefully diluted with 50 mL water and the organic layer removed. The aqueous layer was extracted with ether (2 x 75 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 1.68 g (97%) of the alcohol 7, sufficiently pure for further transformation: R_f = 0.36 (6:1 petroleum ether-ether); IR 3450 cm^{-1} (-OH); ^1H NMR ($CDCl_3$) δ 0.90, 0.97 (2s, 2 x 3H, gem CH_3), 1.17 (s, 3H, CH_3-C-OH), Lit.[17] ($CDCl_3$) δ 0.90, 0.95, 1.15.

1,1-Dimethyl-2-methylenecycloheptane(8) and 2,3,3-trimethylcycloheptene(9). To a stirred solution of 1.65 g (10.6 mmol) alcohol 7 in 50 mL pyridine at

-45°C (bath temperature) was added 3 mL (41 mmol) thionyl chloride dropwise over 5 min. The reaction mixture was stirred an additional 1 h at -45 to -50°C, then poured into 200 mL ice water. The resulting mixture was extracted with ether (3 x 100 mL), and the combined organic layers washed with 5% aqueous hydrochloric acid (4 x 50 mL), saturated aqueous sodium bicarbonate (1 x 50 mL), and water (1 x 50 mL). The resulting solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on 40 g silica gel with 250 mL n-pentane to afford 1.40 g (77%) of a mixture of olefins 8, 9, and t-butylcyclohexene (10)[39] in the approximate ratio of 3:2:1, as judged by VPC (10% SE-30, 100°C). The olefin mixture was routinely used for subsequent transformation without separation. An analytically pure sample of endocyclic olefin 9 was prepared by preparative VPC (10% SE-30, 90°C): IR ($CHCl_3$) nondescript; ^1H NMR ($CDCl_3$) δ 1.07 (s, 6H, gem CH_3), 5.45 (bt, 1H, J = 7 Hz, vinyl).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.97; H, 12.84.

An analytically pure sample of exocyclic olefin 8 was prepared as described below.

1,1,-Dimethyl-2-methylenecycloheptanone(8) from Wittig olefination. To a stirred suspension of 19.8 g (55.4 mmol) methyltriphenylphosphonium bromide in 60 mL THF at -78°C was added 24.7 mL (56.8 mmol) of 2.3 M n-butyllithium in hexane. The reaction mixture was warmed to room temperature and stirred for 30 min. A solution of 2.0 g (14.3 mmol) 2,2-dimethylcycloheptanone 6 in 7 mL THF was added and the reaction mixture stirred an additional 13 h. The reaction mixture was then heated under reflux for 7.5 h after TLC indicated that some starting material remained. The reaction mixture was then cooled and 5 mL methanol added. The resulting white suspension was filtered through a short pad of silica gel with ether to provide 2.5 g yellow oil. This material was chromatographed on 50 g silica gel with n-pentane to afford 1.6 g (81%) exocyclic olefin 8 as a colorless oil. Analytically pure olefin was obtained by preparative VPC (10% SE-30, 100°C): IR ($CHCl_3$) 3095 cm^{-1} ($=CH_2$), 1631 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.08 (s, 6H, 2 x CH_3), 2.05-2.20 (m, 2H, allylic), 4.70, 4.77 (2d, 2 x 1 H, J = 2 Hz, vinyl).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.74; H, 13.10.

3,3-Dimethyl-2-methylenecycloheptanone(11). A solution of 8.6 g (62 mmol) of olefins 8, 9, and 10 (27% olefin 9 by VPC at 90°C) prepared as described above, 50 mg hematoporphyrin dihydrochloride, 10 mL pyridine, and 25 mL of ethyl acetate was irradiated for 2 h with a 650-W tungsten filament lamp in a Pyrex jacket cooled by tap water while oxygen was bubbled through the solution. The solution was added to 30 mL acetic anhydride and stirred 2 h at room temperature. The brown mixture was carefully poured into a 2 L Erlenmeyer flask containing an ice cold, magnetically stirred solution of saturated aqueous sodium carbonate (300 mL). Additional solid sodium carbonate was added in portions over 20 min until gas evolution had ceased and the solution was saturated. This mixture was extracted with ether (4 x 500 mL), and the combined organic layers washed with brine (2 x 50 mL) and concentrated under reduced pressure. The crude product was diluted with 100 mL n-heptane and again concentrated under reduced pressure (azeotropic removal of pyridine) to provide 9.4 g brown oil. Chromatography on 250 g Florisil with petroleum ether provided 5.1 g recovered olefin (a mixture of 8 and 10 by ^{1}H NMR) and subsequent elution with 1:1 petroleum ether--ether afforded 2.36 g (92% yield based on olefin 9) of the desired enone. A

portion of this material was rechromatographed on Florisil and then evaporatively distilled at 100-110°C (ca. 45 mm) to obtain analytically pure 11: R_f = 0.30 (10:1 petroleum ether--ether); IR (neat) 1687 cm^{-1} (C=O), 1608 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.13 (s, 6H, 2 x CH_3), 2.35-2.60 (m, 2H, allylic), 5.08, 5.27 (2s, 2H, vinyl).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.09; H, 10.54.

Equilibration of olefin mixture with iodine. To 0.89 g (6.4 mmol) olefin mixture (recovered from photooxygenation; approximately 3:1 ratio of olefin 8 and t-butylcyclohexene (10)) at 120°C was added 7 mg (0.028 mmol) freshly sublimed iodine with stirring. After 30 min, the reaction mixture was cooled and 5 mL 10% aqueous sodium thiosulfate added. The resulting mixture was extracted with n-pentane (3 x 75 mL) and the combined organic layers concentrated under reduced pressure to a brown oil. Chromatography of the oil on 20 g silica gel with n-pentane afforded 0.82 g (92%) colorless oil, shown by NMR and VPC (10% SE-30, 90°C) to be a mixture of olefins 8, 9, and 10 in the approximate ratio 41:36:23. Material prepared in this manner was used for the photooxygenation procedure without further purification.

2,5,5-Trimethyl-3,4,6,7,8,9-hexahydrocyclohepta[b]-pyran-2-carboxylic acid, methyl ester (12). A. Diels-Alder reaction with hydroquinone inhibitor. A solution of 10.2 g (67 mmol) enone 12, 102 g (1 mol) methyl methacrylate, and 100 mg hydroquinone in 100 mL xylenes was sealed in a 750 mL teflon lined autoclave (Berghof) after bubbling argon through the solution. The reaction mixture was heated to 195°C over 2 h, then maintained at 195°C for an additional 69 h. The autoclave was then cooled and ca. 200 mL of an amber, free flowing liquid was removed and slowly added to 1500 mL rapidly stirred ether in an open flask. This served to precipitate polymeric material as a flocculent white solid, facilitating product isolation. The solution was decanted and concentrated under reduced pressure at 45°C to afford 185 g amber liquid. The polymer was then dissolved in 150 mL chloroform and slowly added to 1500 mL rapidly stirred ether as before. Decantation and concentration of the solution under reduced pressure afforded an additional 28 g yellow oil which was combined with the main fraction. Removal of xylenes by distillation under reduced pressure (ca. 50 mm), followed by filtration of the pot residue through silica gel with ether and concentration under reduced pressure, afforded 49 g yellow

oil. The material was divided into two portions and each was purified by flash chromatography (5 x 25 cm, 20:1 petroleum ether--ether) to afford a total of 8.5 g (50%) Diels-Alder adduct as a colorless oil: R_f = 0.44 (10:1 petroleum ether--ether); IR (neat) 1752 cm^{-1}, 1730 cm^{-1} (C=O), 1660 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.97, 1.02 (2s, 6H, gem CH_3), 1.41 (s, 3H, C-2 CH_3), 3.67 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 20.3, 23.4, 24.4, 25.3, 27.0, 29.1, 30.7, 31.4, 35.9, 39.8, 51.4, 75.6, 112.7, 148.7, 174.2. Analytically pure material was prepared by rechromatography as above of a portion of the ester, followed by evaporative distillation at 125-135°C (ca. 45 mm).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.52; H, 9.63

Further elution provided 3.9 g (46%) of recovered enone.

B. Alternate Diels-Alder procedure. A solution of 168 mg (1.1 mmol) enone 11, 1.1 mL (10.3 mmol) methyl methacrylate, and ca. 5 mg (0.03 mmol) 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy radical[21] in 0.5 mL benzene was sealed in a flame dried and base washed heavy walled Pyrex tube after three cycles of freezing and thawing. The tube was then heated at

180°C for 48 h. After cooling, the tube was opened and the yellow oil was slowly added to 700 mL rapidly stirred ether in an open flask. A few drops of chloroform were used for the transfer. The resulting white suspension was filtered through a short pad of silica gel with ether and the filtrate concentrated under reduced pressure to afford 749 mg yellow oil. This was purified by flash chromatography (5 x 15 cm, 9:1 petroleum ether--ether) to provide 164 mg ester in pure form and 15 mg in mixed fractions for a total of 179 mg (64%). Additional elution provided 11 mg (7%) starting enone. This procedure was repeated with a similar low mass recovery.

2-Ethenyl-2,5,5-trimethyl-3,4,6,7,8,9-hexahydrocyclohepta[b]pyran (14). To a stirred solution of 106 mg (0.42 mmol) ester 12 in 3 mL hexane at -78°C was added dropwise over 1.5 min 1.5 mL (0.75 mmol) 0.5 M diisobutylaluminum hydride (DIBAL-H) in 1:1 hexane--dimethoxyethane (prepared by the addition of 1 M DIBAL-H in hexane to an equal volume of DME). After stirring 45 min at -78°C, another 0.2 mL (0.10 mmol) 0.5 M DIBAL-H in hexane--DME was added. The reaction mixture was treated with 1 mL methanol 5 min later, and then warmed to room temperature. The gelatinous

reaction mixture was then diluted with 20 mL ether and 5 mL 0.5 M aqueous sodium potassium tartrate solution. Two distinct layers developed upon stirring for several minutes. The organic layer was removed, and the aqueous layer extracted with ether (3 x 50 mL). The combined organic layers were washed with brine (1 x 10mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 104 mg crude aldehyde 13 as an oil: IR (neat) 2820 cm^{-1}, 2725 cm^{-1} (-CHO), 1740 cm^{-1} (C=O), 1660 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.96, 1.01 (2s, 2 x 3H, gem dimethyl), 1.20 (s, 3H, C-2 CH_3), 9.45 (d, 1H, J = 2 Hz, CHO). This material was used directly for the following experiment.

To a suspension of 1.25 g (3.5 mmol) methyltriphenylphosphonium bromide in 10 mL THF at room temperature was added dropwise 1.4 mL (3.1 mmol) 2.20 M n-butyllithium in hexane. After 1 h, the crude aldehyde in 2 mL THF was added. The reaction mixture was stirred 5 h and then filtered through a short pad of silica gel with 300 mL 1:1 petroleum ether--ether. The filtrate was concentrated under reduced pressure and immediately purified by flash chromatography (3 x 20 cm, 50:1 petroleum ether--ether) to afford 85 mg (92% from 12) allyl vinyl ether 14 as a colorless oil: R_f = 0.80 (20:1 petroleum ether--ether); IR ($CHCl_3$) 1691 cm^{-1} (C=C);

^{1}H NMR ($CDCl_3$) δ 0.98, 1.03 (2s, 2 x 3H, gem dimethyl), 1.23 (s, 3H, C-2 CH_3), 2.15-2.40 (m, 2H, allylic), 4.95 (dd, 1H, J = 1.8, 10.2 Hz, vinyl), 5.05 (dd, 1H, J = 1.8, 16.8 Hz, vinyl), 5.72 (dd, 1H, J = 10.2, 16.8 Hz, vinyl). Analytically pure material was obtained by rechromatography of a portion of the olefin followed by evaporative distillation at 55-65°C (0.25 mm).

Anal. Calcd for $C_{15}H_{24}O$: C, 81,76; H, 10.98. Found: C, 81.57; H, 10.91.

3,12,12-Trimethylspiro[5.6]-2-dodecen-7-one (15). A. By Claisen rearrangement of 14 in quinoline. A stirred solution of 114 mg (0.52 mmol) 14 in 10 mL quinoline was heated at 170°C for 4 h. The cooled reaction mixture was diluted with 300 mL ether and washed with 5% aqueous hydrochloric acid (2 x 100 mL), saturated aqueous sodium bicarbonate (1 x 50 mL), and brine (1 x 50 mL). The ethereal solution was dried ($MgSO_4$) and concentrated under reduced pressure to provide 174 mg black oil, which was purified by flash chromatography (3 x 15 cm, 40:1 petroleum ether--ether) to afford 91 mg (80%) spiroketone 15 as a colorless oil which soon crystallized: mp 68-70°C; R_f = 0.32 (20:1 petroleum ether--ether); IR (neat) 1695 cm^{-1} (C=O), 1402, 1382 cm^{-1} (gem dimethyl); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 0.85, 0.87 (s, 2 x 3H, gem dimethyl), 1.55 (s, 3H, allylic CH_3), 5.38 (dd, 1H, J = 6.2, 5.1 Hz, vinyl); ^{13}C NMR ($CDCl_3$) δ 22.3, 22.9, 23.4, 24.2, 25.1, 26.1, 27.8, 28.4, 35.8, 39.7, 40.7, 56.1, 120.1, 133.9, 214.8; mass spectrum (16 eV) m/e (intensity) 220 (100), 205 (20), 164 (22), 149 (95), 138 (19), 136 (53). Analytically pure material, mp 68-70°C, was prepared by crystallization from n-pentane--ether.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.60; H, 10.90.

B. Attempted preparation by neat Claisen rearrangement of 14. After 3 cycles of freezing and thawing, 89 mg (0.40 mmol) allyl vinyl ether 14 was sealed in a base washed and flame dried Pyrex ampoule and heated at 165°C for 2 h. The tube was cooled and the contents removed with ether. Concentration under reduced pressure afforded 85 mg (96%) bicyclic ketone 24 as a pale yellow oil: R_f = 0.23 (20:1 petroleum ether--ether): IR (neat) 1710 cm^{-1} (C=O), 1395, 1375 cm^{-1} (gem dimethyl); ^1H NMR (500 MHz, $CDCl_3$) δ 0.82, 0.92 (2s, 2 x 3H, gem dimethyl), 1.67 (s, 3H, allylic CH_3), 2.87 (dd, 1H, J = 12.5, 4.0 Hz, C-7 methyne), 5.38 (bt, 1H, J = 9 Hz, vinyl); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.1, 22.4, 25.1, 29.2, 29.3, 30.4, 32.5, 33.9, 46.4, 55.3, 56.1, 122.6, 139.5, 217.4; mass spectrum (16 eV) m/e (intensity)

220 (100), 205 (20), 187 (6), 151 (15), 138 (31). A portion of the material was rechromatographed and evaporatively distilled at 80-85°C (0.25 mm) to afford analytically pure material.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.82; H, 10.94.

In many runs this procedure provided a mixture of spiroketone 15 and bicyclic ketone 24 in variable proportion.

C. Preparation from enone 11 by Diels-Alder reaction. To a stirred solution of 4.31 g (28.3 mmol) enone 11 and 8.5 mL (84.9 mmol) isoprene in 20 mL dichloromethane at -10°C was added 19 mL (ca. 33.9 mmol) 25% dimethylaluminum chloride in hexane (Alfa; used without standardization) over 5 min. The solution was then warmed to room temperature and stirred 4 h. The reaction mixture was then poured into 100 mL ice water (with foaming) and the resulting mixture extracted with ether (3 x 500 mL). The ethereal extracts were washed with brine (1 x 50 mL), combined, and dried ($MgSO_4$). Concentration under reduced pressure afforded 6.27 g oily crystals which were purified by flash chromatography (7 x 15 cm, 20:1 petroleum ether--ether) to provide 4.33 g (69%) spiroketone 15 as colorless

crystals, identical by mp, TLC, and 500 MHz ^{1}H NMR to material prepared via the Claisen rearrangement of allyl vinyl ether 14.

Attempted interconversion of ketones 15 and 24. After freezing and thawing, 1 mg spiroketone 15 was sealed in a base washed and flame dried ampoule. A similar ampoule containing 1 mg bicyclic ketone 24 was prepared. The ampoules were placed in an oil bath preheated to 171°C for 1 h, then removed and opened after cooling. TLC (20:1 petroleum ether--ether) indicated that both compounds were recovered without discernible change.

Preparation of α-oximinoketone 16 from ketone 15. A. Deprotonation with n-butyllithium. To a stirred solution of 166 mg (0.75 mmol) spiroketone 15 in 10 mL THF at 0°C was added 0.6 mL (1.43 mmol) 2.38 M n-butyllithium in hexane. The reaction mixture was warmed to room temperature and stirred 20 min before the addition of 0.6 mL (4.5 mmol) i-amylnitrite. The resulting solution was stirred 4 h and then acidified to ca. pH 4 with 10 mL 1% aqueous hydrochloric acid. The reaction mixture was then extracted with ether (3 x 100 mL) and the combined organic layers washed with brine (1 x 25 mL) and dried ($MgSO_4$). Concentration

under reduced pressure afforded an oil which was purified by flash chromatography (3 x 25 cm, 6:1 petroleum ether--ether) to afford 63 mg (40%) starting material. Further elution with 3:1 petroleum ether--ether provided 84 mg (45%) oximinoketone as a pale yellow solid: R_f = 0.11 (3:1 petroleum ether--ether); IR ($CHCl_3$) 3590 cm^{-1}(s), 3300 cm^{-1} (br) (-OH), 1700 cm^{-1} (C=O), 1625 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.93 (s, 6H, gem dimethyl), 5.25 (s, 1H, $w_{\frac{1}{2}}$ = 9 Hz, vinyl). A portion of this material was recrystallized from ether--petroleum ether to afford analytically pure material: mp 152-154°C dec.

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30. Found: C, 72.18; H, 9.24.

B. Deprotonation with potassium t-butoxide. A stirred solution of 30 mg (0.14 mmol) spiroketone 15 and 100 mg (0.89 mmol) potassium t-butoxide in 2 mL t-butanol was heated at 40°C for 1.5 h, at which point 0.2 mL (1.5 mmol) i-amylnitrite was added. Another 0.2 mL (1.5 mmol) i-amylnitrite was added 4 h later, and another 0.4 mL (3.0 mmol) 2.5 h after the second addition. The reaction mixture was stirred an additional 12 h and then cooled, acidified to ca. pH 4 with 1% aqueous hydrochloric acid, and extracted

with ether (3 x 75 mL). The combined organic layers were washed with brine (2 x 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 42 mg yellow oil. Flash chromatography (3 x 15 cm, 3:1 petroleum ether--ether) provided 6 mg (20%) starting material with minor impurities, followed by 12 mg (34%) oximinoketone 16.

Preparation of ester 19. In modification of the procedure of Theilacker and Wegner,[29] ethereal chloramine was prepared just prior to use by the addition of 2.3 mL (35 mmol) 15 M aqueous ammonium hydroxide to a stirred solution of 50 mL (36 mmol) 5.25% aqueous sodium hypochlorite solution in 50 mL ether at 0°C. To a stirred solution of 426 mg (1.70 mmol) oximinoketone 16 and 0.42 mL (1.68 mmol) 4 N aqueous sodium hydroxide in 35 mL ether at 10°C was added 25 mL (ca. 4 mmol) ethereal chloramine over 3 min. After 30 min, another 9 mL (ca. 1.5 mmol) chloramine solution was added and the reaction mixture stirred for an additional 80 min. The mixture was then diluted with 25 mL water and extracted with ether (3 x 200 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 481 mg

crude diazoketone 17 as a yellow solid: R_f = 0.75 (3:1 petroleum ether--ether); IR ($CHCl_3$) 2085 cm^{-1} (N_2), 1615 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.90, 0.95 (2s, 2 x 3H, gem dimethyl), 5.33 (bd, 1H, $w_{1/2}$ = 9 Hz, vinyl). This material was used directly in the following experiment without further purification.

A solution of 481 mg of the above diazoketone and 584 mg (10.8 mmol) sodium methoxide in 25 mL methanol was photolyzed under argon for 1 h at -90 to -85°C (liquid nitrogen--methanol bath) with a Hanovia medium-pressure mercury vapor lamp and a Pyrex filter. The reaction mixture was maintained at -85°C for 30 min, then warmed to room temperature over 30 min. The yellow solution was then poured into 50 mL ice water and extracted with dichloromethane (3 x 200 mL). The combined organic extracts were washed with brine (1 x 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 394 mg yellow oil. The crude product was purified by flash chromatography (3 x 20 cm, 20:1 petroleum ether--ether) to afford 244 mg (57% from 16) ester 19 as a pale yellow oil. Mixed fractions afforded an additional 21 mg ester for a total yield of 265 mg (62% from oximinoketone 16): R_f =0.60 (10:1 petroleum ether--ether); IR ($CHCl_3$) 1723 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.85, 0.93 (2s,

2 x 3H, gem dimethyl), 2.62 (dd, 1H, J = 5, 14 Hz, >CH-CO_2), 3.57 (s, 3H, ester), 5.33 (m, 1H, $w_{1/2}$ = 9 Hz, vinyl); ^{13}C NMR ($CDCl_3$) δ 20.9, 22.9, 23.3, 25.6, 26.0, 28.5, 29.6, 37.3, 39.2, 47.4, 51.0, 122.0, 132.0, 176.9; mass spectrum (70 eV) m/e (intensity) 250 (6), 218 (15), 135 (49), 133 (18), 44 (46), 40 (100). Analytically pure material was prepared by rechromatography and evaporative distillation at 70-80°C (1 mm) of a portion of the material. This material later crystallized: mp 77-80°C.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.76; H. 10.45.

Attempted preparation of alcohol 20 by in situ reduction of ketene 18. A solution of crude diazoketone 17, prepared from 24 mg (0.096 mmol) oximinoketone 16, in 10 mL methanol was photolyzed as described in the preparation of ester 19 for 90 min at -90 to -85 C. A solution of 35 mg (0.93 mmol) sodium borohydride in 4 mL methanol at -10°C was then added dropwise over 4 min while the photolysis vessel was maintained at -85°C. The reaction mixture was maintained at -85 to -80°C for 1 h, then warmed to room temperature over 1 h. The reaction mixture was diluted with 10 mL 1% aqueous hydrochloric acid and extracted with dichloromethane (3 x 100 mL).

The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 29 mg yellow oil. The crude product was shown by ^1H NMR and TLC (several solvent systems) to be a complex mixture of no preparative value.

11-Hydroxymethyl-3,7,7-trimethylspiro[5.5]undec-2-ene (20). To a stirred solution of 141 mg (0.56 mmol) ester 19 in 10 mL ether at 0°C was added 80 mg (2.1 mmol) lithium aluminum hydride. The ice bath was removed, and the reaction mixture stirred 1.5 h at room temperature. Excess reagent was quenched by the addition of 80 μL water, followed by 80 μL 4 N aqueous sodium hydroxide, and 320 μL water. The resulting mixture was dried ($MgSO_4$) and concentrated under reduced pressure to afford 119 mg (96%) alcohol 20 as a colorless oil which crystallized upon standing. This material was generally used for subsequent transformations without additional purification. Analytically pure material was obtained by recrystallization from ether: mp 84-85°C; R_f = 0.27 (4:1 petroleum ether--ether); IR ($CHCl_3$) 3640 cm^{-1},

3480 cm^{-1} (OH), 1395 cm^{-1}, 1370 cm^{-1} (gem dimethyl); ^1H NMR ($CDCl_3$) δ 0.82, 0.85 (2s, 2 x 3H, gem dimethyl), 3.4-3.85 (m, 3H, $-CH_2O$), 5.30 (m, 1H, $w_{½}$ = 8 Hz, vinyl); mass measured molecular ion calcd for $C_{15}H_{26}O$: 222.1985; found, 222.1980.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.13; H, 11.80.

Preparation of selenide 21 (and olefins 41 and 42). A. In pyridine. Following the procedure of Grieco and coworkers,[32] a stirred solution of 38 mg (0.17 mmol) alcohol 20 and 197 mg (0.87 mmol) o-nitrophenyl selenocyanate[31] in 0.3 mL pyridine at room temperature was treated dropwise with 0.21 mL (0.85 mmol) tri-n-butylphosphine. The reaction mixture was stirred 1 h, then purified, without additional workup, by flash chromatography (3 x 15 cm, 100:1 petroleum ether--ether) to afford 21 mg (30%) selenide 21 as a yellow oil: R_f = 0.36 (25:1 petroleum ether--ether); ^1H NMR (CCl_4) δ 0.90, 0.95 (2s, 2 x 3H, gem dimethyl), 2.5-3.3 (m, 2H, CH_2-Se), 5.33 (m, 1H, $w_{½}$ = 7 Hz, vinyl), 7.1-8.3 (m, 4H, o-nitrophenyl). This material was used directly for subsequent experiments.

Prior to elution of the desired selenide, there was obtained 22 mg of an oil which by TLC and VPC (10% SE-30, 160°C) was a mixture with three components. This material was chromatographed on 5 g silica gel impregnated with 25% (w/w) silver nitrate with n-pentane.

Component I (4 mg) (R_f = 0.91, n-pentane) was a simple hydrocarbon not investigated further.

Component II (9 mg) (R_f = 0.83) was the bridged olefin 41: IR ($CHCl_3$) 1625 cm^{-1} (C=C), 1390 cm^{-1}, 1370 cm^{-1} (gem dimethyl), 815 cm^{-1} (C=CH); ^1H NMR (CCl_4) δ 0.84, 0.90 (2s, 2 x 3H, gem dimethyl), 4.85 (m, 1H, $w_{1/2}$ = 6 Hz, vinyl). Analytically pure material was obtained by preparative VPC (10% SE-30, 160°C).

Anal. Calcd for $C_{15}H_{24}$: C, 88.33; H, 11.67. Found: C, 88.38; H, 11.66.

Component III (3 mg) (R_f = 0.77) was the bridged exocyclic olefin 42: IR ($CHCl_3$) 1648 cm^{-1} (C=C), 1388 cm^{-1}, 1370 cm^{-1} (gem dimethyl), 888 cm^{-1} ($C=CH_2$); ^1H NMR (CCl_4) δ 0.85, 0.92 (2s, 2 x 3H, gem dimethyl), 4.25, 4.32 (2d, 2 x 1H, J = 3 Hz, vinyl). Analytically pure material was obtained by preparative VPC (10% SE-30, 160°C).

Anal. Calcd for $C_{15}H_{24}$: C, 88.33; H, 11.67. Found: C, 88.19; H, 11.55.

B. Selenide Preparation in THF. To a stirred solution of 40 mg (0.18 mmol) alcohol and 184 mg (0.81 mmol) o-nitrophenyl selenocyanate in 0.4 mL THF was added 0.23 mL (0.93 mmol) tri-n-butylphosphine. After stirring 1.5 h at room temperature, the THF was removed under reduced pressure and the residue chromatographed as in Part A to afford 48 mg (66%) selenide 21 as a yellow oil and 12 mg of a colorless oil which by ^1H NMR was identified as a 2:1 mixture of olefins 41 and 42 (33%).

Attempted mesylation of alcohol 20. To a stirred solution of 23 mg (0.10 mmol) alcohol 20 in 0.5 mL pyridine at -10°C was added 40 µL (0.52 mmol) methanesulfonyl chloride. The reaction mixture was stirred 2 h at 0°C, then warmed to room temperature and stirred an additional 5 h until the alcohol was no longer visible by TLC (R_f = 0.27, 4:1 petroleum ether--ether). The reaction mixture was then poured into 5 mL ice water and extracted with ether (1 x 20 mL). The ethereal extract was washed with water (1 x 5 mL) and brine (1 x 5 mL), dried ($MgSO_4$), concentrated

under reduced pressure, and the residue filtered through 5 g alumina (Neutral, Activity III) with 50 mL ether. Concentration under reduced pressure afforded 20 mg oil. There was no evidence of mesylate formation by ^{1}H NMR. TLC (petroleum ether) revealed two main products with R_f = 0.89 and 0.82. These components were separated on 15 g silica gel impregnated with 25% (w/w) silver nitrate with n-pentane.

Compound I (3 mg) (R_f = 0.89) was a simple hydrocarbon not investigated further.

Compound II (6 mg) was shown to be olefin 41 by ^{1}H NMR and TLC.

(±)-β-Chamigrene (3). To a stirred solution of 41 mg (0.10 mmol) selenide 21 in 0.5 mL dichloromethane at room temperature was added 310 μL (3 mmol) 90% t-butyl hydroperoxide. The reaction mixture was stirred 24 h at room temperature, then diluted with 29 mL n-pentane and washed with brine (2 x 1 mL). The resulting solution was dried $MgSO_4$) and concentrated under reduced pressure. Chromatography of the resulting oil on 10 g silver nitrate-impregnated silica gel (25% w/w) with n-pentane afforded 10 mg (49%) (±)-β-chamigrene with ^{1}H NMR and IR in excellent agreement with published data.[3] Analytically pure material was

prepared by preparative VPC (10% SE-30, 160°C) followed by evaporative distillation at 80-90°C (1.2 mm), lit.[3] bp 110-113°C (13 mm).

Anal. Calcd for $C_{15}H_{24}$: C, 88.33; H, 11.67. Found: C, 88.04; H, 11.62.

Preparation of bicyclic ketal 23. To a stirred solution of 67 mg (0.27 mmol) ester 12 in 0.5 mL ether at room temperature was added 26 mg (0.69 mmol) lithium aluminum hydride. After stirring for 15 min, the excess reagent was quenched by the addition of 25 μL water, 25 μL 4 N aqueous sodium hydroxide, and 100 μL water. The mixture was diluted with 2 mL ether and ca. 0.5 g anhydrous magnesium sulfate added. Investigation by TLC (3:1 petroleum ether--ether) revealed partial conversion of the alcohol 22 (R_f = 0.22) to a pair of spots corresponding to less polar materials: a heavy spot (R_f = 0.67) and a lighter spot (R_f = 0.77). The reaction mixture was filtered, the ether removed under reduced pressure, and the residue dissolved in 1 mL chloroform and ca. 1 mg p-toluensulfonic acid monohydrate

added. Within 10 min, the alcohol was no longer visible by TLC and what had been the minor product (R_f = 0.77) became predominant. The chloroform was removed under reduced pressure and the residue chromatographed on 10 g silica gel with 50:1 pentane--ether to afford 52 mg (86%) bicyclic ketal 23 as a mixture of diastereomers: IR ($CHCl_3$) nondescript; ^1H NMR ($CDCl_3$) δ 0.82, 0.90 (2s, 2 x 3H, gem dimethyl, major isomer), 0.90, 0.99 (2s, 2 x 3H, gem dimethyl, minor isomer), 1.27 (s, 3H, CH_3), 3.37, 3.74 (2d, 2 x 1H, J = 6 Hz, $-CH_2-O$, major isomer), 3.30 (m, 1H, $-CH_2-O$, minor isomer), 3.73 (d, 1H, J - 7H, $-CH_2-O$, minor isomer). Analytically pure material (a mixture of diastereomers) was obtained by evaporative distillation at 115-125°C (45 mm).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.88. Found: C, 74.70; H, 10.75.

Attempted PCC oxidation of alcohol 22. To a stirred solution of 43 mg (0.17 mmol) ester 12 in 2 mL pyridine at 0°C was added 17 mg (0.45 mmol) lithium aluminum hydride. The reaction mixture was stirred 20 min, followed by the addition of 0.17 mL water and 0.5 mL 10% aqueous sodium hydroxide. The reaction mixture was warmed to room temperature and extracted with ether (3 x 30 mL). The combined organic extracts were washed

with brine (1 x 10 mL) and concentrated under reduced pressure to afford 86 mg crude alcohol 22 and residual pyridine. To a stirred suspension of 39 mg (0.18 mmol) pyridinium chlorochromate (PCC)[24] and 12 mg (0.14 mmol) anhydrous sodium acetate in 3 mL dichloromethane at room temperature was added 29 mg (ca. 0.06 mmol) crude alcohol--pyridine mixture in 2 mL dichloromethane. After 45 min, the reaction mixture was filtered through a short pad of Florisil and concentrated under reduced pressure to afford 14 mg oil, which was shown by TLC (3:1 petroleum ether--ether) and ^{1}H NMR to be a mixture of bicyclic ketal diastereomers 23 with no evidence of aldehyde formation.

Attempted PDC oxidation of alcohol 22. To a stirred solution of 22 mg (0.09 mmol) ester 12 in 1 mL ether at room temperature was added 9 mg (0.24 mmol) lithium aluminum hydride. After 10 min, 0.1 mL water, 0.1 mL 4 N aqueous sodium hydroxide, and 0.3 mL water were added. The reaction mixture was then diluted with 5 mL ether and dried (Na_2SO_4/K_2CO_3). Concentration under reduced pressure afforded 21 mg crude alcohol 22. To this material was added 1 mL dichloromethane, followed by 59 mg (0.16 mmol) pyridinium dichromate (PDC)[25] with stirring. After 4 h, the reaction mixture was filtered

through a short pad of anhydrous magnesium sulfate with ether and concentrated under reduced pressure to afford an oil shown by TLC and NMR to contain several components including ketal 23, but with no evidence of desired aldehyde 13.

Attempted preparation of 2,2(1H)-(ethylenedioxy)-4′, 4aβ-dimethyl-3,4,4a,8,9,9aβ-hexahydrospiro[5H-benzocycloheptene-5,1′-cyclohex-3β-en]-6(7H)-one.[2b] To a stirred solution of 62 mg (0.25 mmol) 2,2(1H)-(ethylenedioxy)-4aβ-methyl-5-methylene-3,4,4a,7,8,9aβ-hexahydro-9H benzocyclohepten-6(5H)-one (28)[2b] and 100 µL (1 mmol) isoprene in 0.2 mL dichloromethane at -10°C was added 0.28 mL (ca. 0.50 mmol) 25% dimethylaluminum chloride in hexane (Alfa; used without standardization) over 1 min. The ice bath was removed and the reaction mixture stirred 1 h, then 1 mL water and 20 mL ether were added. The organic layer was separated, washed with brine (1 x 1 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford 60 mg yellow oil. ^1H NMR and TLC (1:1 petroleum ether--ether) indicated that the crude product was a complex mixture not of preparative value. This reaction was not further pursued.

7,7-Dimethyl-2-oximinocycloheptanone(29). A stirred solution of 354 mg (2.5 mmol) 2,2-dimethycycloheptanone (6) and 1.5 g (13 mmol) potassium t-butoxide in 7 mL t-butanol was heated at 40°C for 1.5 h, at which point 0.7 mL (5 mmol) i-amylnitrite was added. Heating was continued for 6 h, and the reaction mixture was then cooled, acidified to pH 4 with 5% aqueous hydrochloric acid, and extracted with ether (3 x 100 mL). The combined organic layers were washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered through a short pad of silica gel, and concentrated under reduced pressure to afford 3.6 g yellow oil. This was purified by flash chromatography (3 x 25 cm, 5:2 petroleum ether--ether) followed by removal of i-amyl alcohol at 0.05 mm to afford 326 mg yellow oil which by ^1H NMR was a mixture of the desired oxime and i-amyl alcohol in the molar ratio 3.3:1. The calculated yield of oximinoketone was 282 mg (67%). The oximinoketone was routinely used without further purification, but rechromatography and evaporative distillation at 80-90°C (0.35 mm) provided analytically pure material: R_f = 0.19 (4:1 petroleum ether--ether); IR (neat) 3595 cm^{-1}(s), 3280 cm^{-1} (br) (OH), 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.16 (s, 6H, gem dimethyl), 1.45-1.75 (m, 6H), 2.45-2.65 (m, 2H).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93. Found: C, 63.78; H, 8.87.

2-Diazo-7,7-dimethylcycloheptanone 30. To a stirred solution of 188 mg of the oximinoketone--i-amyl alcohol mixture described above (0.97 mmol 29), 5.6 mL (22.4 mmol) 4 N aqueous sodium hydroxide, 1.8 mL (27 mmol) aqueous ammonium hydroxide, and 50 mL THF at 5°C was added 5 mL (3.6 mmol) 5.25% aqueous sodium hypochlorite solution over 5 min. The reaction mixture was stirred 1 h at 10°C, then 6 h at 20°C. Another 1 mL (0.71 mmol) 5.25% aqueous sodium hypochlorite was added, and the reaction mixture stirred 2 h. The mixture was then diluted with 25 mL water and extracted with ether (3 x 300 mL). The organic layers were washed with brine (1 x 10 mL), combined, and dried (Na_2CO_3). Concentrations under reduced pressure followed by flash chromatography (2 x 15 cm, 5:1 petroleum ether--ether) afforded 56 mg (35%) diazoketone 30 as a yellow oil: R_f = 0.49 (3:1 petroleum ether--ether); IR (neat) 2090 cm^{-1} (N_2), 1700 cm^{-1} (w) (C=O), 1600 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 1.17 (s, 6H, gem dimethyl), 2.45-2.70 (m, 2H, CH_2-CN_2). This material was used without further purification for the experiments described below.

Further elution led to the recovery of 35 mg (22%) starting material.

(2,2-Dimethylcyclohexane)carboxylic acid, methyl ester (32). A solution of 8 mg (0.048 mmol) diazoketone 30, 0.9 mL (0.45 mmol) 0.5 M sodium methoxide in methanol, and 10 mL methanol was photolyzed under argon for 2 h at -85 to -80°C (liquid nitrogen--methanol bath) with a Hanovia medium pressure mercury vapor lamp and a Pyrex filter. The reaction mixture was then warmed to room temperature, diluted with 10 mL water, and extracted with dichloromethane (3 x 75 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 7 mg (86%) ester 32 as a colorless oil, homogeneous by TLC, IR, ^1H NMR, and VPC (10% SE-30, 100°C): R_f = 0.33 (6:1 petroleum ether--ether); IR (neat) 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.97, 0.99 (2s, 2 x 3H, gem dimethyl), 2.18 (t, 1H, J = 6 Hz, >CH-CO_2), 3.60 (s, 3H, OCH_3).

(2,2-Dimethylcyclohexane)methanol (33). A. From in situ ketene reduction. A solution of 7 mg (0.042 mmol) diazoketone 30 in 10 mL methanol was photolyzed in the apparatus described previously for 2 h at -88 to -80°C. After the irradiation, 20 mg (0.53 mmol) sodium borohydride (solid) was added. After 10 min, the reaction mixture was warmed to room temperature for 1 h before the addition of 10 mL 1% aqueous hydrochloric acid. The mixture was

then extracted with dichloromethane (3 x 75 mL), and the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure to afford 9 mg crude alcohol 33.

B. From hydride reduction of ester 32. A solution of 2 mg ester 32 in 1 mL ether was treated with excess lithium aluminum hydride, which was quenched after 30 min by the addition of water. The resulting mixture was dried ($MgSO_4$) and concentrated under reduced pressure to afford an oil which by VPC (10% SE-30, 100°C) had an identical retention time (by coinjection) to material prepared by Method A.

C. From olefination-hydroboration of 2,2-dimethylcyclohexanone. A suspension of 586 mg (12 mmol) 50% sodium hydride dispersion (pentane washed) and 4.6 g (13 mmol) methyltriphenylphosphonium bromide in 15 mL dimethyl sulfoxide was stirred 2 h at room temperature before 543 mg (4.3 mmol) 2,2-dimethylcyclohexanone[14] in 2 mL dimethyl sulfoxide was added. The reaction mixture was stirred 3 h at room temperature, followed by the addition of 1 mL methanol and filtration of the mixture through a short pad of silica gel with n-pentane. Concentration under reduced pressure and purification by

flash chromatography (3 x 20 cm, petroleum ether) afforded 261 mg (49%) 1,1-dimethyl-2-methylenecyclohexane.[40] To a stirred solution of 157 mg (1.26 mmol) of the olefin in 15 mL THF at 0°C was added 0.87 mL (0.87 mmol) 1 M borane--THF complex dropwise over 2 min. The cooling bath was removed and the reaction mixture stirred 1 h at room temperature, followed by the addition of 1 mL water and then 0.5 mL 4 N aqueous sodium hydroxide. The reaction mixture was again cooled to 0°C and 0.35 mL (3 mmol) 30% hydrogen peroxide added. The mixture was then stirred at room temperature for 1.5 h, followed by dilution with 5 mL brine and extraction with ether (2 x 200 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 186 mg colorless oil. Purification by flash chromatography (2 x 15 cm, 3:1 petroleum ether--ether) afforded 96 mg (54%) alcohol 33, identical with material prepared by the other routes. An analytically pure sample was prepared by preparative VPC (10% SE-30, 110°C): R_f = 0.20 (4:1 petroleum ether--ether); IR (neat) 3620 cm^{-1} 3420 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 0.80, 0.97 (2s, 2 x 3H, gem dimethyl), 3.2-3.9 (m, 2H, $-CH_2O-$).

Anal. Calc for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: C, 75.83; H, 12.70.

Preparation of cyclobutanone 36. A yellow solution of 62 mg (0.25 mmol) diazoketone 17 in 5 mL ether was photolyzed for 2 h at 0°C in the apparatus previously described. The now colorless solution was warmed to room temperature and concentrated under reduced pressure to afford 55 mg (100%) crude cyclobutanone 36 as a colorless oil which crystallized upon standing. A portion of the material was purified by flash chromatography (2 x 20 cm, 25:1 petroleum ether--ether) followed by crystallization from n-pentane at -10°C to afford analytically pure material: mp 47.5-49.0°C; R_f = 0.62 (9:1 petroleum ether--ether); IR ($CHCl_3$) 1755 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.82, 0.87 (2s, 2x 3H, gem dimethyl), 1.01 (s, 3H, CH_3), 2.47 (bd, 1H, J = 2.5 Hz, methyne).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.29; H, 9.97.

Acid-catalyzed rearrangement of cyclobutanone 36. A. Attempted rearrangement with silica gel. A slurry of 25 mg (0.11 mmol) cyclobutanone 36 and 1 g silica gel (E. Merck No. 7734) in 3 mL ether was stirred 25 h at room temperature. The silica gel was then

removed by filtration, and the filtrate concentrated under reduced pressure to afford 21 mg colorless oil which was shown by TLC and ^{1}H NMR to be starting material.

B. Rearrangement with p-toluenesulfonic acid. To a solution of 21 mg cyclobutanone 36 in 0.5 mL deuterochloroform in an NMR tube was added ca. 1 mg p-toluenesulfonic acid monohydrate. The disappearance of resonances attributed to cyclobutanone 36 and the development of new resonances were monitored by ^{1}H NMR, and judged complete after 5 days at room temperature. The reaction mixture was then diluted with 10 mL chloroform, washed with saturated aqueous sodium bicarbonate (1 x 1 mL) and brine (1 x 1 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 34 mg oil. This was purified by flash chromatography (2 x 15 cm, 9:1 n-pentane--ether) to afford 5 mg (24%) rearranged ketone 39 as a colorless oil. Rechromatography and evaporative distillation at 95-105°C (0.8 mm) provided analytically pure material: R_f = 0.29 (9:1 petroleum ether--ether); IR ($CHCl_3$) 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.93, 1.00 (2s, 2 x 3H, gem dimethyl), 2.1-2.4 (m, 3H, 2 allylic + -CH-C=O), 2.60 (bd, 1H, J = 5 Hz, allylic α-keto), 5.28 (m, 1H, $w_{1/2}$ = 9 Hz, vinyl).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.50, H, 10.07.

Further elution with ether provided 7 mg (31%) of keto-alcohol 40. This was filtered through a short pad of silica gel with 2:1 n-pentane--ether and evaporatively distilled at 105-115°C (0.6 mm) to afford analytically pure material: R_f = 0.18 (2:1 petroleum ether--ether); IR ($CHCl_3$) 3605 (s), 3450 (br) cm^{-1} (-OH), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.93, 0.98 (2s, 2 x 3H, gem dimethyl), 1.29 (s, 3H, -O-C-CH_3).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.98; H, 10.18.

References and Notes

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(34) All synthetic intermediates are racemic. Boiling points are uncorrected. Melting points were determined using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on Perkin-Elmer 737B or 3010 spectrometers. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM-390

spectrometer, except where "500 MHz" denotes spectra recorded on the Bruker WM-500 (Southern California Regional NMR Facility, Caltech). A JEOL FX-90Q spectrometer was used for carbon nuclear magnetic resonance (^{13}C NMR) spectra. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as internal standard, in the solvent specified.

Analytical gas-liquid chromatography (VPC) was performed on a Hewlett-Packard 5750 gas chromatograph with flame ionization detector, using helium carrier gas at 60 mL/min. The indicated stationary phase was adsorbed on 60-80 mesh Chromosorb WAW DMCS. Preparative VPC was performed on a Varian 930 gas chromatograph equipped with a thermal conductivity detector. The helium carrier gas was set to 60 mL/min, and the stationary phase and oven temperature are specified for each separation.

Thin-layer chromatography (TLC) was conducted on precoated plates of silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co. Silica gel column chromatography was performed on E. Merck silica gel 60, 70-230 mesh ASTM. Flash chromatography was performed on E. Merck

silica gel 60, 230-400 mesh ASTM, according to published procedure (Still, W. C.; Kahn, M.; MItra, A. J. Org. Chem. 1978, 43, 2923-2925) with column dimensions and eluting solvent given for each application. Alumina refers to the Brockmann Activity I-Neutral material manufactured by M. Woelm, which was adjusted to Activity III where indicated by the addition of 6% water prior to use. Silver nitrate inpregnated silica gel was prepared by dissolving silver nitrate (25% by weight of silica gel) in excess acetonitrile, adding the silica gel, and removing the solvent from the resulting slurry at room temperature (1 mm) for 12 h in a light-protected flask.

Solvents for reactions were prepared shortly before use as indicated. Benzene, toluene, pyridine, n-hexane, t-butanol, and dimethyl sulfoxide were distilled from calcium hydride. Tetrahydrofuran (THF), n-pentane, and dimethoxy-ethane (DME) were distilled under argon from sodium with sodium benzophenone ketyl as an indicator. Ether refers to anhydrous diethyl ether supplied by Mallinckrodt, used from freshly opened cans or after distillation under argon from sodium with sodium benzophenone ketyl as indicator. Iodomethane

and dichlormethane were distilled from phosphorus pentoxide. Ammonia was distilled through a drying tower filled with potassium hydroxide. Quinoline was distilled at reduced pressure from zinc dust. Methanol was distilled from magnesium turnings.

Other reagents were purified as follows: thionyl chloride was distilled from quinoline, then from boiled linseed oil. Methyl methacrylate was distilled from calcium hydride and stored over 1% hydroquinone. Iodine was freshly resublimed. Isoprene was distilled from sodium. i-Amylnitrite was washed with brine, dried over anhydrous magnesium sulfate, and distilled. Methanesulfonyl chloride was distilled under reduced pressure. All other reactants and solvents were "Reagent Grade" except as noted. "Petroleum ether" refers to the "Analyzed Reagent," bp 35-60°C, sold by J. T. Baker.

All reactions were performed under a positive pressure of argon except for the photooxygenations and reactions performed in sealed ampoules or NMR tubes. Glassware was oven dried at 140°C except where an aqueous reaction mixture was involved.

"Brine" refers to a saturated aqueous solution of sodium chloride. Solutions were dried by the addition of the specified anhydrous reagent followed by filtration to remove the reagent. "Removal of solvents under reduced pressure" refers to use of a rotary evaporator connected to a water aspirator with the heating bath temperature at 20-30°C unless indicated otherwise.

Mass spectral analyses were performed by the UCLA Mass Spectrometry Laboratory, Los Angeles, California. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

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