Total Synthesis of (±)-Velloziolone

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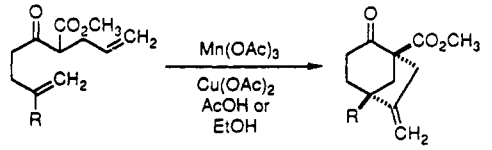
The first total synthesis of the 9,10-*seco*-kaurene velloziolone (**3**) has been accomplished using an atom transfer tandem free-radical cyclization to prepare the 6-methylenebicyclo[3.2.1]octan-2-one moiety. The known diol **11** is converted to iodo acetate **10** in three steps. Alkylation of β-keto ester **22** with **10** affords **33** that is converted to α-iodo ketone **7** in one pot by silylation, followed by palladium-catalyzed decarboxylation to give the tetrasubstituted silyl enol ether regiospecifically and iodination of the enol ether. Atom transfer cyclization at 150 °C, but not at 25 or 85 °C, provides a mixture of bicyclic iodides. Elimination of HI and hydrolysis of the acetate furnishes velloziolone.

Introduction

We recently found that Mn(III)-based oxidative tandem free-radical cyclization provides 6-methylenebicyclo-[3.2.1]octan-2-ones **2** from simple acyclic β-keto esters **1**.[1] Acetoacetate **1a** cyclizes to give 86% of **2a**; the yield of **2b** (43%) is lower since the first cyclization to the terminal alkene does not give exclusively the cyclohexyl radical. Tandem free-radical cyclizations of this type may prove useful for the synthesis of the tetracyclic kaurene and gibberellin diterpenes. For instance, oxidative cyclization of **1c** in EtOH affords 52% of **2c** containing the fully functionalized CD ring system of gibberellic acid.[1d] The ketone and ester groups provide the functionality needed for elaboration of the A and B rings.



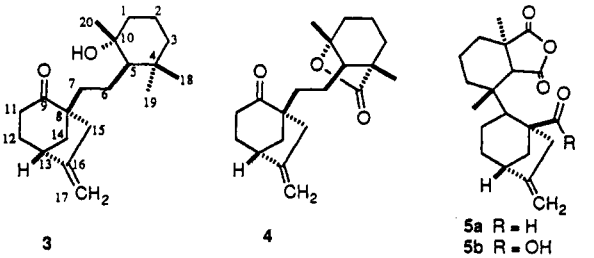
1a, R = Me
1b, R = H
1c, R = OMEM

2a, R = Me (86%)
2b, R = H (43%)
2c, R = OMEM (52%)

seco-Kaurenes, in which the B-ring has been cleaved, are simpler targets that are more suitable for the initial application of tandem free-radical cyclization to diterpene systhesis. Velloziolone[2] (**3**) and wedelia *seco*-kaurenolide[3] (**4**) are representative 9,10-*seco*-kaurenes while fujenal (**5a**) and fujenoic acid[4] (**5b**) are typical 6,7-*seco*-kaurenes. We chose velloziolone (**3**), isolated from Brazilian *Vellozia caputadeae*, as our target. Pinto and co-workers established its structure in 1982 by 1D and 2D ^1H NMR and ^{13}C NMR experiments and by comparison to other compounds isolated from the *Vellozia* species.[2] The stereochemistry was assigned based on the presumed biogenesis from kaurene.

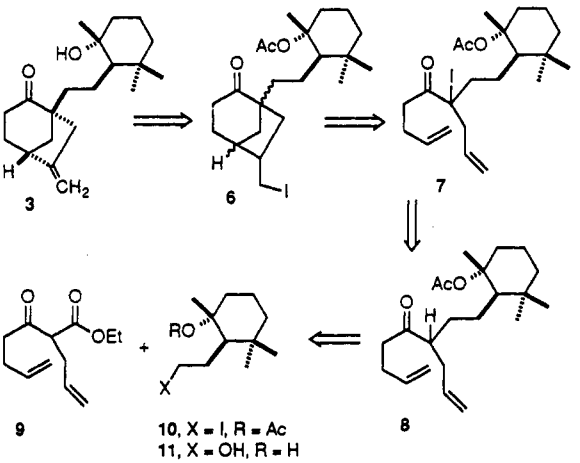
Results and Discussion

Retrosynthetic Analysis. Mn(III)-based oxidative cyclization is not suitable for the synthesis of velloziolone



3 **4** **5a** R = H, **5b** R = OH

since the initial radical must be generated by oxidation of a 1,3-dicarbonyl compound. Atom transfer cyclizations developed by Curran are more suitable for the synthesis of monocarbonyl compounds.[5] Diol **11** has been prepared by the mercury-mediated cyclization of homogeranic acid and $LiAlH_4$ reduction of the resulting lactone.[6] Alkylation of β-keto ester **9** with iodide **10**, prepared from diol **11**, followed by hydrolysis and decarboxylation of the α-dialkylated β-keto ester should give ketone **8**. Selective formation of the presumably more stable tetrasubstituted silyl enol ether and iodination should give α-iodo ketone **7**. Atom transfer tandem free-radical cyclization should give a mixture of iodides **6**; elimination and hydrolysis should provide velloziolone (**3**).



9 **10**, X = I, R = Ac; **11**, X = OH, R = H **8**

Atom transfer cyclization of unsaturated α-iodo ketones with the carbonyl group in the tether are regioselective for 6-endo cyclization.[5b] Curran has shown that irradiation

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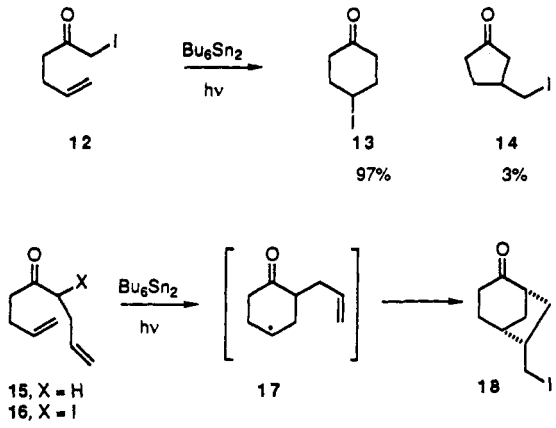
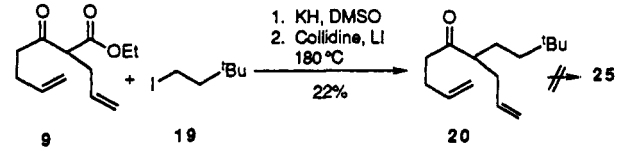
of α-iodo ketone **12** gives a 97:3 mixture of cyclohexanone **13** and cyclopentanone **14**.[5b] Therefore, the radical derived from iodide **16** should give cyclohexyl radical **17** selectively. Since iodine transfer is very fast,[5d] radical **17** might not cyclize faster than it abstracts iodine to give a cyclohexyl iodide. Recent results indicate that the second cyclization is faster than halogen transfer in the annulation of iodo malonates[5e] and tandem cyclization of α-bromo- and α-iodo acetoacetates.[7]



Model Studies. Atom transfer tandem cyclization of the simplest possible α-iodo dienone **16** was examined to demonstrate the validity of this approach. Claisen condensation of ethyl 4-pentenoate with ethanol-free sodium ethoxide[8] affords 61% of β-keto ester **9**.[9] Hydrolysis and decarboxylation gives 84% of the symmetrical dienone **15**.[9] Iodination[5b] of the silyl enol ether obtained from dienone **15** with NIS provides α-iodo dienone **16**. Irradiation of a 0.3 M solution of α-iodo dienone **16** in benzene with a sunlamp in the presence of 0.1 equiv of Bu_6Sn_2 furnishes a 2.8:1 mixture of bicyclic iodide **18**, as a ~4:1 mixture of exo and endo isomers, and dienone **15** as the two major products. Dienone **15** is probably derived from the initially formed α-keto radical by hydrogen atom abstraction, although the source of the hydrogen is not clear. Bicyclic iodide **18** is not stable to chromatography,[5b,7] and elimination of HI was not examined due to anticipated problems with the isolation of the volatile nine-carbon enone. Since atom transfer cyclization of **16** was successful, we turned our attention to more sophisticated models.

Since the preparation of tertiary α-iodo dienone **7** from the unsymmetrical dienone **8** was unprecedented, we carried out further model studies to develop procedures for the formation of unsymmetrical tertiary α-iodo ketones and to examine their atom transfer cyclizations. We chose 1-iodo-3,3-dimethylbutane[10] (**19**) as a model for hindered iodide **10**. Alkylation of β-keto ester **9** with **19** proved to be surprisingly difficult. No product is obtained using EtONa in EtOH, NaH in THF at reflux, or LDA and DMPU in THF. Eventually, we found that reaction of β-keto ester **9** with **19** using KH in DMSO[11] affords 95% of a 1.3:1 mixture of C- to O-alkylated products. Use of the potassium enolate and DMSO as solvent are required for reactivity. Unfortunately, these conditions also favor O-alkylation. Decarboxylation of the crude product with LiI in 2,4,6-collidine[12] at 180 °C provides 22% of ketone **20**.



To our surprise, we were unable to form the more substituted sily enol ether **25** that is required for the formation of the tertiary iodide **26**. We were initially optimistic since many procedures have been reported that lead selectively to the thermodynamically more stable tetrasubstituted silyl enol ether from 2-methylcyclohexanone.[13] Ratios as high as 97:3 favoring the more substituted, thermodynamically stable isomer have been reported. We subjected **20** to all the conditions reported to give the more substituted silyl enol ether from 2-methylcyclohexanone: TMSCl and Et_3N in DMF at 130 °C;[13a] TBDMSCl, KH, and DMPU in THF at −78 °C;[13b] TMSCl, diisopropylamine, MeMgBr, and DMPU in ether;[13c] TMSCl, KH, and BEt_3 in THF;[13d] TMSI and HMDS;[13e] TMSCl, Et_3N, and NaI in CH_3CN;[13f] and TMSOTf in Et_3N.[13g] All the procedures fail. Either there is no reaction, the undesired trisubstituted silyl enol ether is formed exclusively, or mixtures containing 10% or less of the desired tetrasubstituted silyl enol ether **25** are obtained. We had no choice but to abandon this route to **25**.

After extensive consideration of alternate routes to tetrasubstituted silyl enol ether **25**, we developed a successful route based on Tsuji's procedure for the regiospecific generation of allyl-substituted silyl enol ethers in 60–80% yield by palladium-catalyzed decarboxylation of silyl enol ethers of allyl acetoacetates.[14] Decarboxylation of **24** by Tsuji's procedure should give **25** regiospecifically.

Alkylation of the dianion of methyl acetoacetate with allyl bromide gives β-keto ester **21**.[15] Transesterification with excess allyl alcohol as solvent[16] affords allyl β-keto carboxylate **22** in 72% overall yield. This two-step procedure is necessary since alkylation of the dianion of allyl acetoacetate gives less than 20% of **22**, indicating that the reactive allyl ester is not compatible with dianion alkylation conditions. Alkylation of **22** with 1-iodo-3,3-dimethylbutane[10] (**19**) and KH in DMSO as described above affords 33% of β-keto ester **23**. Silylation of **23** with TMSI generated in situ[13f] gives 97% of silyl enol ether **24** as a single stereoisomer. The key decarboxylation–allylation step using catalytic $Pd_2(dba)_3$ and dppe in THF at room temperature provides 68% of the desired silyl enol ether **25** as a 1:1 mixture of *E* and *Z* isomers.[14] Iodination of **25** with NIS in THF[5b] at room temperature furnishes 92% of the desired tertiary α-iodo ketone **26**.

Once again, we ran into unanticipated problems. To our surprise, irradiation of 0.3 M solution of tertiary iodide **26** in benzene with a sunlamp in the presence of Bu_6Sn_2 at room temperature affords ketone **20** and only a trace of

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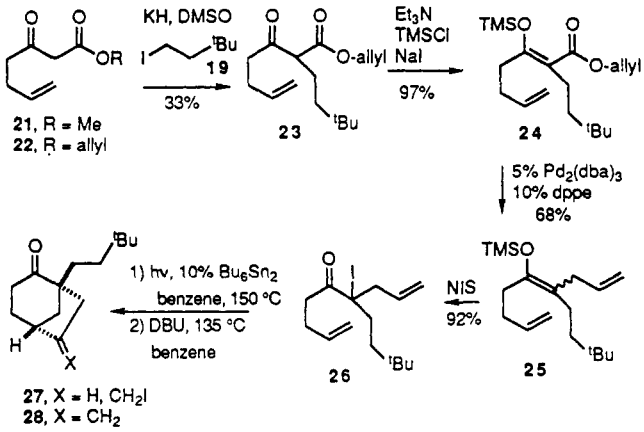

the desired bicyclic iodide **27**. Apparently, the tertiary α-keto radical abstracts a hydrogen atom much more rapidly than it cyclizes. This was particularly discouraging since **20** cannot be recycled.

Curran found that atom transfer cyclization of α-iodo esters to give butyrolactones proceeds in higher yield at 80 °C than at 25 °C.[5c] He suggested that the higher temperature allows the initially formed syn radical to adopt the anti configuration necessary for the cyclization to occur. Although conformational preferences of the radical are unlikely to be a factor with α-keto radicals, we examined the effect of temperature on the atom transfer cyclizations of **16** and **26**.

Initial results with the secondary α-iodo ketone **16** were encouraging. The ratio of bicyclic iodide **18** to dienone **15** increases from 2.8:1 at 25 °C to 3.5:1 at 85 °C and 4.8:1 at 150 °C. Varying the concentration of iodide, the amount of Bu_6Sn_2,[17] and addition of EtI[17] does not increase the yield of **18**.

Cyclization of tertiary α-iodo ketone **26** at elevated temperature is equally successful. Irradiation of a 0.3 M solution of iodide **26** in benzene in the presence of Bu_6Sn_2 at 150 °C affords a ~2.5:1 mixture of bicyclic iodide **27**, as a mixture of exo and endo isomers, and ketone **20** as the only major products. The model study was completed by treatment of the reaction mixture with DBU in benzene at 135 °C[7] to provide 49% of **28** and 20% of ketone **20**. The ^{13}C NMR data of the 6-methylenebicyclo[3.2.1]octan-2-one portion of **28** correspond closely to the data reported by Pinto for velloziolone.[2] In this model study, we developed a regiospecific route to the tertiary α-iodo ketone **26** and established that the atom transfer tandem cyclization proceeds in high yield at elevated temperature.

The reasons for the temperature dependence of the yield of the cyclizations of **16** and **26** are not obvious. Curran has previously observed that the cyclization of primary α-keto radicals to form cyclohexanones is slow.[5b,c] If the cyclization is slow, hydrogen atom abstraction can compete more effectively. Our studies with secondary and tertiary α-keto radicals derived from **16** and **26** suggest that steric hindrance by the alkyl substituents retards cyclization more than it retards hydrogen abstraction to give **15** and **20**. Hydride abstraction becomes the exclusive pathway with tertiary α-keto radicals at 25 °C. The temperature effect on the yield of the cyclization may be due to entropic factors. Cyclization is a unimolecular reaction and should therefore have a smaller negative $\Delta S^{\ddagger}$ than bimolecular hydrogen abstraction. Therefore, raising the temperature should improve the yield of cyclic products since the rate of cyclization will increase faster than the rate of hydrogen abstraction.

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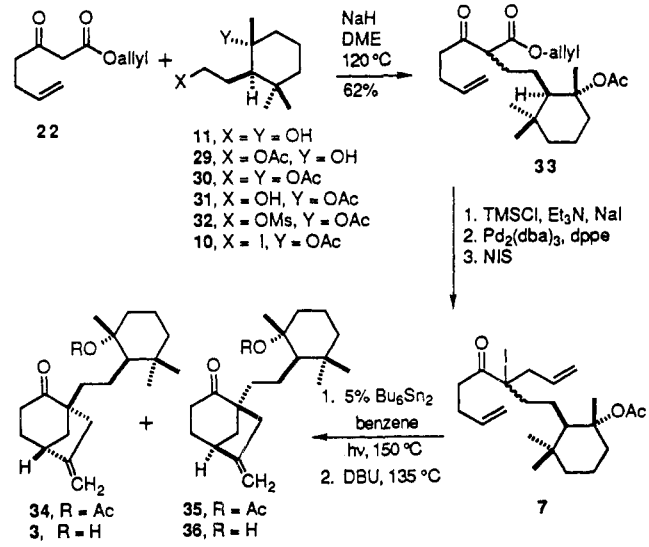
Preparation of Iodide 10. The next problem to be faced was the preparation of the iodide **10** from the known diol **11**, which was prepared by a modification of Hoye's procedure.[6] Mercuric trifluoroacetic-mediated cyclization of homogeranic acid yields the crude mercury-substituted lactone.[6a,b] Reduction of both the carbon–mercury bond and the lactone is accomplished with $LiAlH_4$ in THF at rt.

We planned to convert diol **11** into diacetate **30** and to selectively hydrolyze[18] the less hindered primary acetate to give acetoxy alcohol **31**, which could be converted to iodo acetate **10**. Formation of diacetate **30** proved to be remarkably difficult. Initial attempts using standard techniques, including stoichiometric DMAP,[19] failed. Primary acetate **29** forms easily, but does not react further. Fortunately, treatment of diol **11** with *N,N*-diethylaniline and AcCl in $CHCl_3$ at reflux[20a] affords 83% of the desired diacetate **30**. Selective hydrolysis of the primary acetate using excess K_2CO_3 in 3:1 MeOH–H_2O at 0 °C[18b] provides 50% of acetoxy alcohol **31**, which slowly isomerizes to primary acetate **29** on standing, and 43% of diol **11**, which can be recycled. Finally, treatment of **31** with MsCl and Et_3N gives **32**, which reacts with NaI in acetone to provide the required iodide **10** in 71% yield.



Completion of the Synthesis of Velloziolone. Alkylation of the potassium enolate of β-keto ester **22** with iodide **10** in DMSO is unsuccessful even though these conditions had been developed using the hindered iodide **19** as a model for **10**. Fortunately, alkylation of β-keto ester **22** with iodide **10** proceeds smoothly using NaH in DME at 120 °C[21] to form 62% of **33** as a 1:1 mixture of diastereomers. One-pot silylation, palladium-induced decarboxylation–allylation, and iodination affords 41% (from **33**) of tertiary iodide **7**.

Tandem free-radical cyclization of **7** and elimination of HI from the bicyclic iodide proceed exactly as in the model study. Irradiation of a 0.3 M solution of **7** in benzene with 10% Bu_6Sn_2 at 150 °C for 15 min followed by treatment with DBU in benzene at 135 °C provides 37% of a 1:1 mixture of velloziolone acetate **34** and *epi*-velloziolone

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acetate **35**. Careful flash chromatography furnishes pure **34** followed by a 4:1 mixture enriched in the more polar isomer **35**. Hydrolysis of **34** in 10% KOH in MeOH at reflux affords 72% of pure velloziolone (**3**). Hydrolysis of the 4:1 mixture provides 89% of a 4:1 mixture of *epi*-velloziolone (**36**) and **3**, which could not be separated chromatographically.

The spectral data for both **3** and **36** are similar to the partial ^{1}H NMR data and full ^{13}C NMR reported for (−)-velloziolone by Pinto.[2] Since the two sets of stereochemical centers are separated by an ethylene chain, major spectral differences are neither expected nor observed. All ^{13}C NMR resonances for alcohol **3**, derived from the less polar acetate **34**, are within 0.3 ppm of those reported for natural (−)-velloziolone. The data for alcohol **36**, derived from the more polar acetate **35**, do not match as well. Carbons 14 (+2.0 ppm), 3 (−1.1 ppm), 12 (+0.5 ppm) and 10 (+0.5 ppm) differ significantly from those of the diastereomer **3** and natural velloziolone.

The ^{1}H NMR data confirm the assignment. The resonances for alcohol **3**, derived from the less polar acetate **34**, correspond to the data reported for velloziolone except that our data are shifted ~0.03 ppm downfield, possibly due to a referencing error. If the data is corrected for this shift, all the resonances are within 0.01 ppm; the data for alcohol **36** do not match as well. The difference separating the chemical shifts of the two exomethylene protons is diagnostic; in synthetic and natural **3** the separation of ~0.1 ppm, while in **36** it is 0.08 ppm.

In conclusion, we have completed the first synthesis of the 9,10-*seco*-kaurene velloziolone in only nine steps from the β-keto ester **21** and diol **11** using an atom transfer tandem free-radical cyclization to form the 6-methylenebicyclo[3.2.1]octan-2-one. This approach should be useful for the synthesis of other 9,10-*seco*-kaurenes, such as wedelia *seco*-kaurenolide (**4**).

Experimental Section

General Methods. All reactions were carried out in flame-dired glassware under N_2. THF, diethyl ether, and DME were distilled from sodium–benzophenone ketyl before use. CH_2Cl_2, CH_3CN, diisopropylamine, and benzene were distilled from calcium hydride before use. HMPA, DMPU, DMSO, and Et_3N were distilled from calcium hydride and stored over 4A molecular sieves. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ with TMS as an internal reference unless otherwise noted. Chemical shifts are reported in parts per million downfield from TMS (δ); coupling constants are reported in Hz. Carbon multiplicities were determined by APT experiments. IR spectra are reported in cm^{-1}. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI.

Ethyl 2-(2-Propenyl)-3-oxohept-6-enoate (9). Ethanol-free sodium ethoxide[8] (prepared from 480 mg (20.8 mmol) of Na) and ethyl 4-pentenoate (6.00 g, 41.6 mmol) were heated at 170 °C for 1 h in a flask fitted with a short distillation column to remove ethanol formed during the reaction. The reaction was cooled, diluted with ether, washed with water, dried ($MgSO_4$), and concentrated in vacuo to afford 3.94 g (90%) of crude **9**. Distillation (80–90 °C, 1 Torr) afforded 2.66 g (61%) of **9**: ^{1}H NMR 5.86–5.65 (m, 2), 5.13–4.94 (m, 4), 4.18 (q, 2, J = 7), 3.53 (t, 1, J = 7), 2.78–2.52 (m, 4), 2.40–2.28 (m, 2), 1.28 (t, 3, J = 7).

1,8-Nonadien-5-one (15). Keto ester **9** (7.50 g, 36.0 mmol) was dissolved in 5% NaOH solution (50 g, 63 mmol). The solution was stirred for 6 h, acidified with 6 N HCl, and extracted with ether (200 mL). The ether layer was dried ($MgSO_4$) and concentrated in vacuo to afford 6.54 g (99%) of crude keto acid. Distillation (5 Torr, 75–80 °C) with concomitant decarboxylation afforded 4.18 g (84%) of ketone **15** whose ^{1}H NMR and IR spectra are identical to those previously described:[9] ^{13}C NMR 209.3, 137.0 (2 C), 115.1 (2 C), 41.7 (2 C), 27.6 (2 C).

4-Iodo-1,8-nonadien-5-one (16). To LDA (4.37 mmol) in 30 mL of THF at −78 °C was added ketone **15** (503 mg, 3.64 mmol) in 10 mL of THF. The solution was stirred for 15 min, and TMSCl (480 mg, 4.37 mmol) was added. The solution was quenched with water and extracted with ether. The ether layer was washed with saturated $NaHCO_3$ solution, dired ($MgSO_4$), and concentrated in vacuo to afford 730 mg (95%) of the corresponding silyl enol ether. To the silyl enol ether (182 mg, 617 mmol) in 10 mL of THF in a foil-wrapped flask was added NIS (980 mg, 4.37 mmol) in 10 mL of THF.[5b] The solution was stirred for 45 min and was diluted with 10% $Na_2S_2O_3$ and extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 703 mg (92%) of light-sensitive **16**: ^{1}H NMR 5.82 (tdd, 1, J = 6, 10, 17), 5.76–5.64 (m, 1), 5.14 (br d, 1, J = 10), 5.12 (br d, 1, J = 17), 5.07 (br d, J = 1, 17), 5.01 (br d, 1, J = 10), 4.47 (t, 1, J = 7), 2.96 (ddd, 1, J = 7, 7, 18), 2.86–2.76 (m, 1), 2.74–2.62 (m, 2), 2.44–2.34 (m, 2); ^{13}C NMR 203.5, 136.6, 135.0, 118.4, 115.6, 38.5, 38.3, 30.3, 28.2.

Atomic Transfer Cyclization of 16. A benzene solution (2.6 mL, 0.1 M) of α-iodo ketone **16** (38 mg, 0.08 mmol) and Bu_6Sn_2 (5 mg, 0.01 mmol) in an NMR tube at 25 °C was irradiated with a 275-W sunlamp placed ~15 cm away.[5a,b] The ^{1}H NMR spectrum of the crude product showed a ~4:1 mixture of exo and endo isomers by integration of the resonances corresponding to the iodomethyl protons of *exo*-**18** at δ 3.26 (dd, 1, J = 8.0, 9.2) and 3.17 (dd, 1, J = 7.7, 9.2) and one of the two resonances for the iodomethyl proton of *endo*-**18** at δ 3.37 (dd, 1, J = 8, 9). Analysis of the ^{1}H NMR spectrum indicated that a 2.8:1 mixture of **18** and **15** was present. Analogous reactions irradiated at 85 and 150 °C afforded 3.5:1 and 4.8:1 mixtures of **18** and **15**, respectively.

4-(3,3-Dimethylbutyl)-1,8-nonadien-5-one (20). To KH (464 mg, 11.6 mmol) in DMSO (10 mL), was added keto ester **9** (2.03 g, 9.65 mmol) in 10 mL of DMSO.[11] After H_2 evaluation ceased (10 min), 1-iodo-3,3-dimethylbutane[10] (2.45 g, 11.57 mmol) was added and the solution was stirred for 20 h. The reaction was quenched with 10% HCl, diluted with water, and extracted with hexane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 2.70 g (95%) of a 1.3:1 mixture of C- to O-alkylated material. The crude alkylation product (1.40 g, 4.90 mmol) and $LiI{\cdot}2H_2O$ (1.96 g, 14.6 mmol) in 20 mL of 2,4,6-collidine were heated at 180 °C for 8 h.[12] The mixture was cooled, diluted with water (300 mL) and extracted with ether (300 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 551 mg (50%) of crude **20**. Flash chromatography (100:1 hexane–EtOAc) afforded 234 mg (22%) of **20**: ^{1}H NMR 5.82 (tdd, 1, J = 6, 10, 17), 5.70 (tdd, 1, J = 6, 10, 17), 5.18 (br d, 1, J = 10), 5.09 (br d, 1, J = 17), 4.95 (br d, 1, J = 17), 4.83 (br d, 1, J = 10), 2.54–2.45 (m, 3), 2.35–2.26 (m, 3), 2.22–2.12 (m, 1), 1.64–1.51 (m, 1), 1.46–1.33 (m, 1), 1.08 (AA′ portion of AA′BB′, 2, $J_{AA'} \approx J_{BB'}$ = 13, $J_{AB} = J_{A'B'}$ = 10, $J_{AB'} = J_{A'B}$ = 4), 0.85 (s, 9); ^{13}C NMR 212.3, 137.4, 135.3, 116.8, 115.0, 52.4, 41.7, 41.1, 35.9, 30.2, 29.2 (3 C), 27.6, 26.0; IR (neat) 1720, 990, 910.

Allyl 3-Oxohept-6-enoate (22). Crude methyl 3-oxohept-6-enoate[15] (**21**) (19.0 g, 0.12 mol) and allyl alcohol (25 mL) were heated at 160 °C for 21 h in a flask fitted with a short distillation column to remove methanol formed during the reaction.[16] The solution was concentrated in vacuo and distilled (65–70 °C, 0.3 Torr) to afford 15.8 g (72% from methyl acetoacetate) of **22** as a clear liquid: ^{1}H NMR 5.89 (tdd, 1, J = 7, 10, 17), 5.82 (tdd, 1, J = 7, 10, 17), 5.35 (td, 1, J = 1.4, 17), 5.27 (td, 1, J = 1.4, 10), 5.04 (br d, 1, J = 17), 4.99 (br d, 1, J = 10), 4.64 (ddd, 2, J = 1.4, 1.4, 6.8), 3.49 (s, 2), 2.66 (t, 2, J = 7), 2.36 (app q, 2, J = 7); ^{13}C NMR 201.7, 166.7, 136.4, 131.5, 118.8, 115.5, 65.9, 49.1, 42.0, 27.3; IR (neat) 1740, 1720, 990, 910. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.01; H, 7.86.

Allyl 2-(3,3-Dimethylbutyl)-3-oxohept-6-enoate (23). To KH (242 mg, 6.04 mmol) in DMSO (10 mL) was added keto ester **22** (1.00 g, 5.49 mmol) in 5 mL of DMSO.[11] After H_2 evolution ceased (10 min), 1-iodo-3,3-dimethylbutane[10] (1.16 g, 5.49 mmol) was added and the solution was stirred for 20 h. The reaction was quenched with 10% HCl, diluted with water, and extracted with hexane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 1.46 g (99%) of a 3:2 mixture of C- to O-alkylated material. Flash chromatography (20:1 hexane–EtOAc) afforded 487 mg (33%) of pure **23**: ^{1}H NMR 5.90 (tdd, 1, J = 6, 10, 17), 5.79 (tdd, 1, J = 6, 10, 17), 5.32 (tdd, 1, J = 1.5, 1.5, 17), 5.25 (tdd, 1, J = 1.5, 1.5, 10), 5.03 (tdd, 1, J =

1.5, 1.5, 17), 4.98 (tdd, 1, J = 1.5, 1.5, 10), 4.62 (ddd, 2, J = 1.5, 1.5, 6), 3.40 (t, 1, J = 7), 2.74–2.50 (m, 2), 2.32 (app q, 2, J = 6), 1.89–1.78 (m, 2), 1.18–1.08 (m, 2), 0.89 (s, 9); ^{13}C NMR 204.4, 169.5, 136.7, 131.5, 118.9, 115.4, 65.8, 59.7, 41.5, 41.0, 30.3, 29.1 (3 C), 27.4, 23.6; IR (neat) 1750, 1720, 990, 910. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.84.

Allyl 2-(3,3-Dimethylbutyl)-3-[(trimethylsilyl)oxy]hepta-2,6-dienoate (24). To neat keto ester **23** (250 mg, 0.94 mmol) were added Et_3N (120 mg, 1.18 mmol) and TMSCl (130 mg, 1.18 mmol) followed by NaI in CH_3CN (1.18 mL, 1.0 M, 1.18 mmol).[13f] The mixture was stirred for 10 min, and ice-cold pentane and saturated $NaHCO_3$ solution were added. The layers were separated, and the aqueous layer was extracted with pentane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 308 mg (97%) of a single stereoisomer of silyl enol ether **24**: ^{1}H NMR 5.95 (tdd, 1, J = 6, 10, 17), 5.82 (tdd, 1, J = 6, 10, 17), 5.33 (tdd, 1, J = 1.5, 1.5, 17), 5.21 (tdd, 1, J = 1.5, 1.5, 10), 5.02 (tdd, 1, J = 1.5, 1.5, 17), 4.98 (br d, 1, J = 10), 4.60 (ddd, 2, J = 1.5, 1.5, 6), 2.70 and 1.22 (AA'BB', 4, $J_{AA'} \approx J_{BB'}$ = 13, $J_{AB} = J_{A'B'}$ = 10, $J_{AB'} = J_{A'B}$ = 4), 2.32–2.20 (m, 4), 0.90 (s, 9), 0.26 (s, 9); ^{13}C NMR 168.9, 163.9, 137.6, 132.8, 117.4, 114.8, 114.7, 64.5, 42.9, 34.1, 32.0, 30.4, 29.3 (3 C), 22.3, 0.9 (3 C); IR (neat) 1710, 1610, 990, 910. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.40; H, 10.12. Found: C, 67.57; H, 10.26.

4-(3,3-Dimethylbutyl)-5-[(trimethylsilyl)oxy]-1,4,8-nonatriene (25). To a burgundy-colored mixture of $Pd_2(dba)_3$ (42 mg, 0.05 mmol) and dppe (36 mg, 0.10 mmol) in 2.5 mL of THF was added silyl enol ether **24** (308 mg, 0.91 mmol) in 2.5 mL of THF.[14] The solution was stirred for 45 min, and the resultant olive-green mixture was concentrated in vacuo to one quarter of its volume and filtered through a plug of deactivated silica gel (hexane) to afford 182 mg (68%) of a 1:1 mixture of E and Z isomers of **25**: ^{1}H NMR 5.92–5.78 (m, 1), 5.78–5.65 (m, 1), 5.08–4.92 (m, 4), 2.78 (br d, 0.5 × 2, J = 6.7), 2.68 (ddd, 0.5 × 2, J = 1.5, 1.5, 6.7), 2.29–2.12 (m, 4), 1.96 and 1.19 (AA'BB', 0.5 × 4, $J_{AA'} \approx J_{BB'}$ = 13, $J_{AB} = J_{A'B'}$ = 10, $J_{AB'} = J_{A'B}$ = 4), 1.88 and 1.19 (AA'BB', 0.5 × 4, $J_{AA'} \approx J_{BB'}$ = 13, $J_{AB} = J_{A'B'}$ = 10, $J_{AB'} = J_{A'B}$ = 4), 0.88 (s, 0.5 × 9), 0.87 (s, 0.5 × 9), 0.19 (s, 0.5 × 9), 0.18 (s, 0.5 × 9); ^{13}C NMR (145.2, 144.8), (138.4, 138.3), (137.4, 137.3), (117.0, 116.9), (114.8, 114.5), (114.5, 114.4), (43.4, 41.8), (34.7, 33.9), 31.9, 31.8, 30.4, (29.3, 29.2) (3 C), (25.0, 24.4), (0.7, 0.6) (3 C); IR (neat) 1670, 1250, 990, 910.

4-Iodo-4-(3,3-dimethylbutyl)-1,8-nonadien-5-one (26). To silyl enol ether **25** (182 mg, 0.61 mmol) in 10 mL of THF in a foil-wrapped flask was added NIS (174 mg, 0.77 mmol) in 5 mL of THF.[5b] The solution was stirred for 45 min, diluted with 10% $Na_2S_2O_3$, and extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 197 mg (92%) of light-sensitive **26**: ^{1}H NMR 5.87 (tdd, 1, J = 6, 10, 17), 5.83–5.68 (m, 1), 5.20 (br d, 1, J = 10), 5.18 (br d, 1, J = 17), 5.10 (tdd, 1, J = 1.5, 1.5, 17), 5.02 (br d, 1, J = 10), 3.12 (td, 1, J = 7, 16), 2.96–2.81 (m, 2), 2.71 (dd, 1, J = 7, 16), 2.44 (m, 2), 2.21–1.98 (m, 2), 1.34–1.21 (m, 1), 1.02 (ddd, 1, J = 4, 13, 13), 0.89 (s, 9); ^{13}C NMR 204.4, 137.1, 134.1, 119.1, 115.5, 59.9, 42.8, 40.4, 34.7, 30.3, 29.2 (3 C), 29.0, 28.9; IR (neat) 1705, 990, 910.

1-(3,3-Dimethylbutyl)-6-methylenebicyclo[3.2.1]octan-2-one (28). A benzene solution (1.6 mL, 0.3 M) of α-iodo ketone **26** (167 mg, 0.48 mmol) and Bu_6Sn_2 (3 mg, 0.05 mmol) in a resealable tube was immersed in an oil bath at 150 °C while being irradiated from above and to the side with a 275-W sunlamp (to avoid irradiating through the oil bath) for 15 min.[5b] The resultant mixture was concentrated in vacuo. The ^{1}H NMR spectrum of the crude product showed a mixture of exo and endo isomers and resonances corresponding to the iodomethyl protons of **27** at δ 3.37–3.12 and that a ~2.5:1 mixture of **27** and **20** was present. An analogous reaction irradiated at 85 °C gave a ~1:2.5 mixture of **27** and **20**.

A benzene solution (5.7 mL) of crude primary iodide **27** and DBU (260 mg, 1.7 mmol) in a resealable tube was immersed in an oil bath at 135 °C for 2 h.[7] The mixture was cooled, diluted with ether, washed with 10% HCl, dried ($MgSO_4$), and concentrated in vacuo to afford 127 mg of crude alkene **28** and **20**. Flash chromatography (50:1 hexane–EtOAc) afforded 25 mg (20%) of ketone **20**, followed by 16 mg (13%) of a 6:1 mixture of **28** and **20**, followed by 40 mg (38%) of **28**: ^{1}H NMR 5.04 (br s, 1), 4.95 (br s, 1), 2.85 (m, 1), 2.48–2.23 (m, 6), 1.90–1.76 (m, 2), 1.68–1.52 (m, 1), 1.44 (ddd, 1, J = 4.5, 12.5, 12.5), 1.22 (ddd, 1, J = 4.5, 12.5, 12.5), 1.10 (ddd, 1, J = 4.5, 12.5, 12.5), 0.89 (s, 9); ^{13}C NMR 213.7, 153.0, 106.5, 56.9, 43.3, 42.4, 41.8, 39.0, 36.1, 33.7, 30.2, 29.2 (3 C), 28.7; IR (neat) 1710, 890.

***trans*-2-(2-Hydroxyethyl)-1,3,3-trimethylcyclohexan-1-ol (11).** Mercuric trifluoroacetate-mediated cyclization of crude homogeranic acid and ligand exchange using saturated KBr solution by the procedure of Hoye[6] afforded the crude mercury lactone. A solution of the mercury lactone (16.5 g, 35.7 mmol) in 200 mL of THF was added slowly to $LiAlH_4$ (100 mL, 1.0 M in THF, 100 mmol) in 200 mL of THF over 1 h, and the solution was stirred for 18 h. The unreacted $LiAlH_4$ was quenched by sequentially adding 3.8 mL of water, 3.8 mL of 15% NaOH solution, and 11.4 mL of water. The resultant solution was filtered and concentrated in vacuo to afford 7.38 g of crude product. Recrystallization (2:1 hexane–EtOAc) afforded 2.29 g (20% overall yield in six steps from geraniol) of **11**.[6]

***trans*-1-Acetoxy-2-(2-acetoxyethyl)-1,3,3-trimethylcyclohexane (30).** To diol **11** (1.93 g, 10.4 mmol) in 90 mL of chloroform at 0 °C was added *N,N*-diethylaniline (7.73 g, 51.8 mmol) and acetyl chloride (4.06 g, 51.8 mmol).[17a] The solution was heated at reflux for 7 h, diluted with water (700 mL), and extracted with CH_2Cl_2. The combined organic layers were washed with 10% HCl and saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo to give 3.53 g of a blue oil. Flash chromatography (15:1 hexane–EtOAc) afforded 2.33 g (83%) of pure diacetate **30**: ^{1}H NMR 4.26 (ddd, 1, J = 6, 9.5, 10.5), 4.08 (ddd, 1, J = 7, 9, 10.5), 2.60–2.50 (m, 1), 2.06 (s 3), 1.96 (s, 3), 1.82–1.44 (m, 8), 1.51 (s, 3), 0.97 (s, 3), 0.85 (s, 3); ^{13}C NMR 170.9 (C), 170.0 (C), 86.8 (C), 65.6 (CH_2), 50.1 (CH), 40.5 (CH_2), 37.4 (CH_2), 35.1 (C), 32.5 (CH_3), 25.7 (CH_2), 22.8 (CH_3), 21.8 (CH_3), 21.0 (CH_3), 20.0 (CH_3); 19.6 (CH_2); IR (neat) 1745, 1250. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.74; H, 9.62.

***trans*-1-Acetoxy-2-(2-hydroxyethyl)-1,3,3-trimethylcyclohexane (31).** To diacetate **30** (750 mg, 2.77 mmol) in 50 mL of 3:1 MeOH–H_2O at 0 °C was added K_2CO_3 (1.92 g, 13.9 mmol).[18b] The solution was stirred for 4.5 h, neutralized with 10% HCl, and extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a mixture of primary monoacetate **31** and diol **11**. Flash chromatography (2:1 hexane–EtOAc) afforded 315 mg (50%, 87% based on recovered diol **11**) of pure monoacetate **31**, followed by 220 mg (43%) of diol **11**.

The data for **31**: ^{1}H NMR 3.69 (t, 2, J = 7), 2.61 (m, 1), 1.96 (s, 3), 1.76–1.68 (m, 2), 1.63–1.54 (m, 3), 1.52 (s, 3), 1.48–1.37 (m, 2), 1.30–1.21 (m, 2), 0.96 (s, 3), 0.87 (s, 3); ^{13}C NMR 169.8 (C), 87.4 (C), 63.9 (CH_2), 50.4 (CH), 40.5 (CH_2), 37.5 (CH_2), 35.3 (C), 32.5 (CH_3), 29.7 (CH_2), 22.9 (CH_3), 21.8 (CH_3), 20.0 (CH_3), 19.7 (CH_2); IR (neat) 3500, 1750. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60. Found: C, 68.38; H, 10.55.

***trans*-1-Acetoxy-2-[[(methylsulfonyl)oxy]ethyl]-1,3,3-trimethylcyclohexane (32).** To primary alcohol **31** (315 mg, 1.38 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added Et_3N (210 mg, 2.07 mmol) and MsCl (17 mg, 1.52 mmol). The solution was stirred for 0.5 h and poured into ice–water, which was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ solution, dired ($MgSO_4$), and concentrated in vacuo to afford crude mesylate **32**, which was used immediately: ^{1}H NMR 4.38 (ddd, 1, J = 6.5, 9.5, 9.5), 4.21 (ddd, 1, J = 7, 9.5, 9.5), 3.02 (s, 3), 2.60–2.50 (m, 1), 1.97 (s, 3), 1.90–1.81 (m, 2), 1.63–1.20 (m, 6), 1.52 (s, 3), 0.97 (s, 3), 0.86 (s, 3).

***trans*-1-Acetoxy-2-(2-iodoethyl)-1,3,3-trimethylcyclohexane (10).** Crude mesylate **32** was dissolved in 20 mL of acetone containing NaI (1.10 g, 7.30 mmol). The mixture was heated at reflux for 18 h, cooled, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were washed with 10% $Na_2S_2O_3$ solution, dried ($MgSO_4$), and concentrated in vacuo to afford 333 mg (71%) of **10** as a clear viscous oil: ^{1}H NMR 3.36 (ddd, 1, J = 6, 9, 10.5), 3.21 (ddd, 1, J = 7, 9, 10.5), 2.58 (m, 1), 2.08–1.98 (m, 2), 1.96 (s, 3), 1.65–1.18 (m, 6), 1.51 (s, 3), 0.97 (s, 3), 0.84 (s, 3); ^{13}C NMR 170.6, 87.6, 50.8, 41.2, 38.2, 36.0, 33.2, 33.1, 23.7, 22.8, 20.9, 20.3, 8.5; IR (neat) 1750. Anal. Calcd for $C_{13}H_{23}IO_2$: C, 46.16; H, 6.85; I, 37.52. Found: C, 46.30; H, 6.88; I, 37.59.

Allyl 2-[(*trans*-2-Acetoxy-2,6,6-trimethylcyclohexyl)-ethyl]-3-oxohept-6-enoate (33). To NaH (76 mg, 60% oil dis-

persion, 3.17 mmol) in 5 mL of DME in a resealable tube were added allyl alcohol in DME (0.50 mL, 1.0 M, 0.05 mmol) and keto ester **22** (614 mg, 3.37 mmol) in 5 mL of DME.[21] After H_2 evolution ceased (15 min), iodide **10** (670 mg, 2.00 mmol) in 5 mL of DME was added and the tube was immersed in an oil bath at 120 °C for 22 h. The mixture was cooled, diluted with water, neutralized with 10% HCl, and extracted with ether. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (40:1 hexane–EtOAc) afforded 484 mg (62%) of **33** as a 1:1 mixture of diastereomers: ^{1}H NMR 5.93 (tdd, 1, J = 6, 10, 17), 5.79 (tdd, 1, J = 6, 10, 17), 5.33 (tdd, 1, J = 1.5, 1.5, 17), 5.26 (tdd, 1, J = 1.5, 1.5, 10), 5.03 (tdd, 1, J = 1.5, 1.5, 17), 4.93 (tdd, 1, J = 1.5, 1.5, 10), 4.62 (ddd, 2, J = 1.5, 1.5, 6), 3.48 (dd, 0.5 × 1, J = 4.3, 6.2), 3.46 (dd, 0.5 × 1, J = 4.3, 6.2), 2.74–2.58 (m, 2), 2.55–2.44 (m, 1), 2.38–2.24 (m, 2), 2.18–2.00 (m, 2), 1.96 (s, 0.5 × 3), 1.95 (s, 0.5 × 3), 1.94–1.79 (m, 1), 1.68–1.17 (m, 8), 1.46 (s, 3), 0.95 (s, 3), 0.81 (s, 3); ^{13}C NMR 204.2 (C), (170.2, 170.1) (C), 169.4 (C), 136.7 (CH), 131.5 (CH), 119.0 (CH_2), 115.5 (CH_2), 87.3 (C), 65.8 (CH_2), 59.7 (CH), (53.7, 53.5) (CH), (40.9, 40.8) (CH_2), 40.5 (CH_2), 37.4 (CH_2), (35.5, 35.4) (C), 32.5 (CH_3), (30.5, 30.3) (CH_2), 27.4 (CH_2), 24.7 (CH_2), 22.9 (CH_3), 22.0 (CH_3), 20.7 (CH_3), 19.7 (CH_2); IR (neat) 1730, 990, 910.

4-[(*trans*-2-Acetoxy-2,6,6-trimethylcyclohexyl)ethyl]-4-iodo-1,8-nonadien-5-one (7). To keto ester **33** (106 mg, 0.27 mmol) in 1 mL of pentane were added Et_3N (33 mg, 0.32 mmol), TMSCl (35 mg, 0.32 mmol), and NaI in CH_3CN (1.18 mL, 1.0 M, 1.18 mmol).[13f] The solution was stirred for 20 min and worked up as described above for the preparation of **24** to afford 101 mg (89%) of silyl enol ether that was added directly to a burgundy colored mixture of $Pd_2(dba)_3$ (11 mg, 0.01 mmol) and dppe (10 mg, 0.02 mmol) in 2 mL of THF.[14] The solution was stirred for 45 min, NIS (135 mg, 0.60 mmol) in 4 mL of THF was added to the resultant olive-green mixture, and the flask was wrapped in foil. The solution was stirred for 1 h and worked up as described above for the preparation of **26** to afford crude light-sensitive **7**. Flash chromatograph (40:1 hexane–EtOAc) afforded 47 mg (41%) of pure α-iodo ketone **7** as a 1:1 mixture of diastereomers: ^{1}H NMR 5.86 (tdd, 1, J = 6, 10, 17), 5.72 (tdd, 1, J = 6, 10, 17), 5.20 (br d, 1, J = 10), 5.18 (br d, 1, J = 17), 5.09 (tdd, 1, J = 1.5, 1.5, 17), 5.02 (tdd, 1, J = 1.5, 1.5, 10), 3.14–2.82 (m, 4), 2.60–2.51 (m, 1), 2.42 (app q, 2, J = 7), 2.18 (ddd, 1, J = 3, 10, 15), 2.16 (ddd, 1, J = 3, 10, 15), 1.99 (s, 0.5 × 3), 1.95 (s, 0.5 × 3), 1.71–1.18 (m, 8), 1.52 (s, 0.5 × 3), 1.48 (s, 0.5 × 3), 0.99 (s, 0.5 × 3), 0.94 (s, 0.5 × 3), 0.86 (s, 0.5 × 3), 0.84 (s, 0.5 × 3); ^{13}C NMR 204.3, 136.9, 134.0, 119.1, (115.6, 115.5), (87.5, 87.6), (60.3, 60.2), 53.9, 43.6, 41.4, 40.7, 37.6, (36.4, 36.3), 35.9, 35.7, 32.7, 28.9, 24.2, 23.2, 21.9, 20.2, 19.7; IR (neat) 1740, 1705, 990, 910.

Velloziolone Acetate (34) and (1*S,5*R**)-1-[((1*R**,2*R**)-2-Acetoxy-2,6,6-trimethylcyclohexyl)ethyl]-6-methylenebicyclo[3.2.1]octan-2-one (35).** A benzene solution (1.2 mL, 0.3 M) of α-iodo ketone **7** (38 mg, 0.08 mmol) and Bu_6Sn_2 (5 mg, 0.01 mmol) was irradiated at 150 °C as described above for the preparation of **26**. Benzene (1.2 mL) and DBU (37 mg, 0.24 mmol) were added, and the tube was immersed in an oil bath at 135 °C for 3 h.[7] Workup as described above for the preparation of **28** afforded a 1:1 mixture of **34** and **35**. Flash chromatography (40:1 petroleum ether/EtOAc) afforded 3 mg (11%) of **34**, followed by 3 mg (11%) of a 1:1 mixture of **34** and **35**, followed by 4 mg (15%) of a 4:1 mixture of **35** and **34**.

The data for **34**: ^{1}H NMR 5.06 (br s, 1), 4.98 (br s, 1), 2.87 (m, 1), 2.53–2.21 (m, 8), 1.97 (s, 3), 1.92–1.16 (m, 11), 1.47 (s, 3), 1.01 (s, 3), 0.84 (s, 3); ^{13}C NMR 213.4, 170.4, 152.8, 106.6, 87.7, 57.1, 54.3, 43.8, 42.4, 41.8, 40.3, 37.5, 37.3, 36.1, 35.6, 33.8, 32.4, 23.0, 22.5 (2 C), 20.5, 19.8.

The data for **35** (determined from the mixture): ^{1}H NMR 5.06 (br s, 1), 4.97 (br s, 1), 2.87 (m, 1), 2.52–2.23 (m, 8), 1.98 (s, 3), 1.92–1.16 (m, 11), 1.47 (s, 3), 0.99 (s, 3), 0.84 (s, 3); ^{13}C NMR 213.3, 170.4, 152.8, 106.6, 87.6, 57.1, 54.1, 43.3, 42.3, 42.0, 40.3, 37.3, 37.1, 36.1, 35.6, 33.7, 32.5, 23.0, 22.4 (2C), 20.5, 19.8.

(±)-Velloziolone (3). The less polar acetate **34** (2 mg, 0.006 mmol) in 0.5 mL of 10% KOH in MeOH was heated reflux for 2 h. The mixture was cooled, concentrated in vacuo to one quarter of its volume, neutralized with 10% HCl, and extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (10:1 hexane–EtOAc) afforded 1.3 mg (72%) of pure **3**: ^{1}H NMR 5.06 (br s, 1), 4.96 (br s, 1), 2.87 (m, 1), 2.49–2.24 (m, 8), 1.92–1.15 (m, 11), 1.19 (s, 3), 0.95 (s, 3), 0.77 (s, 3); ^{13}C NMR 213.7 (C-9), 152.5 (C-16), 106.6 (C-17), 73.6 (C-10), 58.1 (C-5), 57.5 (C-8), 43.0 (C-14), 42.6 (C-1), 42.3 (C-13), 42.2 (C-3), 41.4 (C-15), 38.2 (C-7), 35.9 (C-11), 35.3 (C-4), 33.7 (C-12), 32.6 (C-19), 23.6 (C-20), 22.0 (C-6), 21.2 (C-18), 20.4 (C-2); IR (neat) 3490, 2920, 1710, 880; MS (EI) m/e (rel intensity) 304.2 (M^+, 34), 286.2 (29), 268.2 (28), 253.2 (15), 225.2 (15), 177.1 (20), 163.1 (20), 135.1 (100), 109.1 (35). The spectral data are identical to those reported for the natural product.[2]

(1*S,5*R**)-1-[((1*R**,2*R**)-2-Hydroxy-2,6,6-trimethylcyclohexyl)ethyl]-6-methylenebicyclo[3.2.1]octan-2-one (36).** The 4:1 mixture of **35** and **34** (2 mg, 0.006 mmol) was treated as described above for **34**. Flash chromatography (10:1 hexane–EtOAc) afforded 1.6 mg (89%) of a 4:1 mixture of **36** and **3**.

The data for **36** were determined from the mixture: ^{1}H NMR 5.07 (br s, 1), 4.99 (br s, 1), 2.87 (m, 1), 2.49–2.24 (m, 8), 2.04–1.10 (m, 11), 1.19 (s, 3), 0.93 (s, 3), 0.76 (s, 3); ^{13}C NMR 213.7 (C-9), 152.7 (C-16), 106.7 (C-17), 74.4 (C-10), 58.0 (C-5), 57.5 (C-8), 44.7 (C-14), 42.3 (C-13), 41.8 (C-1), 41.4 (C-15), 41.0 (C-3), 38.3 (C-7), 36.2 (C-11), 35.3 (C-4), 34.1 (C-12), 32.6 (C-19), 23.7 (C-20), 22.1 (C-6), 21.1 (C-18), 20.3 (C-2).

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **3**, **7**, **16**, **20**, **25**, **26**, **28**, and **33–36** (22 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthetic Studies on Wortmannin and 11-Desacetoxywortmannin

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This report describes the first synthesis of the highly reactive furanocyclohexadienone lactone subunit of the natural products wortmannin (**1**) and 11-desacetoxywortmannin (**2**). The simplified wortmannin analogue **6** was prepared by acid treatment of aminomethylene lactone **22** in analogy to the known conversion of lactone **3** into wortmannin. Compound **22** was, in turn, prepared from the readily accessible lactone **18** through sequential oxidations and introduction of the aminomethylene unit using tris(dimethylamino)methane.

Wortmannin (**1**)[1] and its desacetoxy derivative **2**[2] are antifungal antibiotics isolated from the culture filtrates of several *Penicillium* and *Myrothecium* species. Both **1** and **2** are potent antiinflammatory agents, a fact first

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