1.52 g (21.6% from BOC-leucinal) of white crystals of the (2S,4S,5S) isomer **26β**, which was 99.2% pure by HPLC. Mp: 146-148 °C. $[\alpha]^{25}_D$: -39.4° (c 1, ethanol). ^{1}H NMR ($CDCl_3$): 4.55 (d, J = 9.5 Hz, NH), 4.45 (t, J = 6.1 Hz), 3.86 (br m), 2.58 (br m), 2.0-2.35 (m), 1.48 (s, 9 H), 0.96 (d, J = 5.6 Hz, 3 H), 0.94 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$): 179.0, 156.08, 80.74, 79.54, 51.68, 45.66, 41.77, 29.07, 28.21, 26.25, 24.67, 22.99, 21.77, 20.27, 18.32 ppm. IR (film): 3427, 3320, 1754, 1667, 1677, 1524, 1275, 1200, 1164, 1060, 1035, 675 cm^{-1}. Anal. Calcd for $C_{17}H_{31}O_4N$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.35; H, 9.92; N, 4.38.

(2R,4S,5S) Isomer 26α. Mp: 94-96 °C. $[\alpha]_D$: -32.4° (c 1, ethanol). ^{1}H NMR ($CDCl_3$): 4.51 (d, J = 10.0 Hz, NH), 4.32 (d of d, J = 6.1 Hz, Jj = 10.0 Hz), 3.85 (d of t, J = 5.3 Hz, J = 9.9 Hz), 2.6 (m), 2.17 (m), 1.89 (m), 1.65 (m), 1.43 (s, 9 H), 1.01 (d, J = 7.1 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 6 H), 0.88 (d, J = 9.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): 177.92, 155.96, 79.82, 79.44, 50.10, 46.36, 42.37, 28.34, 27.42, 25.83, 24.76, 22.97, 21.84, 20.50, 17.85 ppm. IR (film): 3348, 3336, 1763, 1681, 1523, 1368, 1272, 1161 cm^{-1}. Anal. Calcd for $C_{17}H_{31}O_4N$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.13, H, 9.87; N, 4.49.

(2S,4R,5S) Isomer 27α. Mp: 86-88.5 °C. $[\alpha]_D$: -56° (c 1, ethanol). ^{1}H NMR ($CDCl_3$): 4.65 (br d, J = 8.7 Hz, NH), 4.29 (br s), 3.78 (br s), 2.60 (m), 2.22 (m), 1.47 (s, 9 H), 1.07 (d, J = 6.7 Hz, 3 H), 0.95 (m, 9 H), ppm. ^{13}C NMR ($CDCl_3$): 177.52, 155.53, 80.46, 51.67, 46.51, 38.90, 28.23, 27.49, 26.78, 24.49, 23.52, 21.33, 20.45, 18.20 ppm. IR (film): 3339, 1785, 1696, 1675, 15.26, 1369, 1172, 1163, 930, 875 cm^{-1}. Found: C, 64.89; H, 9.99; N, 4.32.

The fourth isomer **27β** could not be obtained in pure form.

Keto ester **32** was obtained as a mixture of two diastereomers, from a different run of the sequence. ^{1}H NMR ($CDCl_3$): 5.08 (d, J = 7.6, NH), 5.00 (d, J = 7.2, NH), 4.10 (m, 1 H), 4.12 (m, CH_2O), 3.00 (m, 1 H), 2.79 (m, 1 H), 2.56 (d, J = 2.9 Hz), 2.49 (d, J = 2.9 Hz), 2.00 (m), 1.45 (s, t-Bu), 1.45 (s, t-Bu), 0.94 (m) ppm. ^{13}C NMR ($CDCl_3$): 209.18, 208.68, 174.37, 174.26, 155.45, 79.56, 60.25, 58.11, 57.44, 46.17, 45.73, 40.46, 40.33, 38.67, 37.37, 29.86, 28.20, 26.88, 24.82, 24.67, 23.24, 23.14, 21.68, 21.50, 20.05, 19.97, 19.51, 14.12 ppm. IR (film): 3350, 1720, 1705, 1510, 1365, 1250, 1170, 1010, 1020 cm^{-1}. Anal. Calcd for $C_{19}H_{35}O_5N$: C, 63.84; H, 9.87; N, 3.92. Found: C, 63.74; H, 10.07; N, 3.87.

4-[(*tert*-Butoxycarbonyl)amino]-6-methyl-1-hepten-3-one (23). A solution of 6.78 mmol of vinylmagnesium bromide in 20 mL of THF was cooled to -78 °C. A solution of 620 mg (2.26 mmol) of the amide in 5 mL of THF was then slowly added. After being stirred for 0.5 h, the mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into 40 mL of water and 2 mL of 2 N HCl and extracted with 4 × 20 mL of ethyl acetate. The combined ethyl acetate washes were dried over $MgSO_4$ and concentrated to afford an oil, which was chromatographed on silica gel with 15% EtOAc/hexane to afford 384 mg (70% yield) of the enone **23** along with 121 mg of the amine addition product. $[\alpha]_D$: -8.4°, (c 1.18, EtOH). ^{1}H NMR ($CDCl_3$): 6.40 (m, 2 H), 5.87 (d of d, J = 1.2 Hz, J = 9.85 Hz, 1 H), 5.16 (d, J = 8.0 Hz, 1 H), 4.63 (d of t, J = 3.9 Hz, J = 9.2 Hz, 1 H), 1.70 (m, 1 H), 1.50 (m, 2 H), 1.41 (s, 9 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): 199.14, 155.46, 133.34, 129.57, 79.57, 55.66, 41.37, 28.23, 24.80, 23.19, 21.77 ppm. IR (film): 3340, 1700, 1610, 1510, 1500, 1362, 1250, 1155, 1040, 1020, 970, 775 cm^{-1}.

***N*-Methyl-*N*-methoxy-2-[(*tert*-Butoxycarbonyl)-amino]-4-methylpentanamide (22).** A solution of 30 mL of CH_2Cl_2, 2.49 g (10.0 mmol) of BOC-leucine, 2.8 mL (20.0 mmol) of triethylamine, and 1.2 g (12.0 mmol) of *N,O*-dimethylhydroxylamine hydrochoride at room temperature was treated with 3.03 mL (20.0 mmol) of DEPC (diethyl phosphorocyanidate). This resulted in an exothermic reaction (>40 °C). The solution was allowed to cool and stir overnight at room temperature and was poured into water, and the product was isolated with methylene chloride (3 × 25 mL). The methylene chloride extracts were washed with sodium bicarbonate, dried over $MgSO_4$, and concentrated to afford 2.57 g (94%) of the amide. MS, *m/e* calcd for $C_{13}H_{26}N_2O_4$: 275.1971. Found: 279.1958. $[\alpha]_D$: -27° (c 9.36, EtOH). ^{1}H NMR ($CDCl_3$): 5.00 (d, J = 9 Hz, NH), 4.74 (m, 1 H), 3.75 (s, 3 H), 3.1. (s, 3 H), 1.43 (s, 9 H), 1.00 (d, J = 3 Hz, 3 H), 0.92 (d, J = 3 Hz, 3 H) ppm. IR (film): 3323, 1710, 1660, 1500, 1390, 1365, 1250, 1170, 1045, 1020, 990 cm^{-1}.

Reduction of Enone 23. Sodium borohydride (114 mg, 3.0 mmol) was added to a solution of the enone (30 mg, 1.25 mmol) and $CeCl_3$ (47 mg, 0.125 mmol) in 5 mL of methanol at room temperature. The addition resulted in the vigorous evolution of gas. After 10 min TLC showed the reaction to be complete. The mixture was poured into water, and the allylic alcohols were isolated with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford 290 mg (98% yield) of a viscous oil, which was identical with a sample of **9** prepared by the Grignard route except that the syn/anti ratio was 1:1 as determined by HPLC (1.5 mL/min, 15% EtOAc/hexane, silica gel, RI detector). The spectra data are identical with material prepared from the aldehyde.

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Total Synthesis of Sesquiterpenes via Intramolecular Ketene Cycloadditions: Isocomene and α-*cis*- and α-*trans*-Bergamotenes, an Approach to Seychellene

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Cyclobutanone **2**, a late intermediate in Wenkert's isocomene synthesis, was prepared by a six-step sequence in 10% overall yield. Carroll rearrangement of acetoacetate **9** gave ketone **10**. Peterson olefination with ethyl (trimethylsilyl)propionate followed by hydrolysis gave acid **12** as a mixture of double bond position isomers. Addition of the corresponding acid chlorides **13** to Et_3N in toluene at reflux gave cyclobutanone **4**. Isomerization of the double bond of **4** with hydriodic acid gave **2**. Isomerization of β-bergamotenes with hydriodic acid in benzene provided an effective route to the α-bergamotenes. Tricyclic ketone **28** was prepared by oxy-Cope rearrangement of allylic alcohol **27**. Oxy-Cope rearrangement of propargylic alcohol **32** gave cyclooctadienone **33**. Under some reaction conditions **33** was converted to cyclooctatrienolate **35**, which was protonated to give **36** and underwent electrocyclic ring opening to give **38**.

Stereospecific intramolecular cycloaddition of ketenes to alkenes has been extensively developed recently as a general method for the synthesis of polycyclic cyclobutanones.[2-4] Since this reaction proceeds in optimal yield

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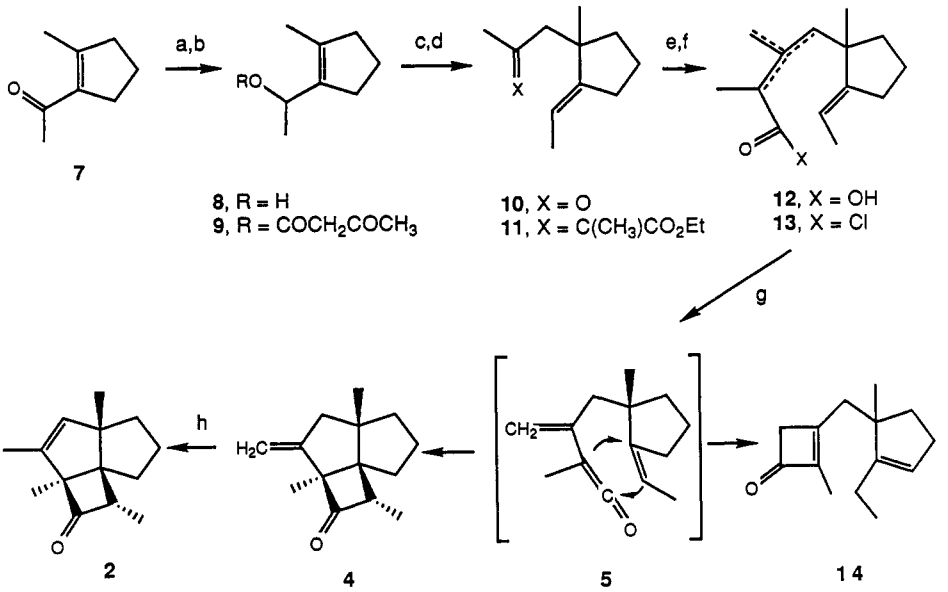
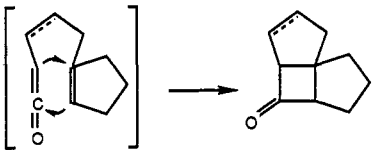
Scheme I[a]



[a] (a) $NaBH_4$; (b) diketene, DMAP; (c) 2 equiv of LDA, THF, reflux and then CCl_4 reflux; (d) $(CH_3)_3SiCH(CH_3)CO_2Et$, LDA; (e) NaOH, EtOH, reflux; (f) oxalyl chloride; (g) Et_3N, toluene, reflux; (h) HI, benzene.

with a three-atom tether, it has been applied with good success to the synthesis of tricyclo[5.3.0.$0^{1,5}$]decan-6-ones, which are potential intermediates for the synthesis of angularly substituted triquinane sesquiterpenes (eq 1).[2l,3l,5] These sesquiterpenes, such as isocomene (**1**), silphinene, and pentalenene, have been the subject of intense synthetic effort during the last decade.[6] We report here the application of an intramolecular ketene cycloaddition to the synthesis of cyclobutanone **2**, a late intermediate in Wenkert's isocomene synthesis.[7]



(1)

In addition, we envisioned a possible route to the tricyclic sesquiterpene seychellene that would also utilize an intramolecular cycloaddition as a key step. We report here our work on a closely related model system, which was studied to establish the feasibility of such a route.

Results and Discussion

Formal Synthesis of Isocomene (1). Cyclobutanone **2** should be formed readily from ketene **3**. Unfortunately, the stereospecific synthesis of the α,β-unsaturated ketene of **3** is a challenging problem that has not been adequately solved. Cyclobutanone **2** should also be available by isomerization of cyclobutanone **4**, which should be formed readily from ketene **5**. We have shown that deprotonation of α,β-unsaturated acid chlorides occurs at the least substituted γ-carbon regardless of the stereochemistry of the double bond.[2g,h] Therefore, treatment of acid chloride **6** with Et_3N should give ketene **5**, which should undergo cycloaddition to give **4**. Acid chloride **6** should be readily available from ketone **10**, which, in turn, should be available from acetoacetate **9** by a Carroll rearrangement.

Reduction of 1-acetyl-2-methylcyclopentene (**7**) with $NaBH_4$ in methanol for 2 h at 25 °C and 1 h at 35 °C gave alcohol **8**[8] in 91% yield. Reaction of **8** with diketene and a catalytic amount of 4-(dimethylamino)pyridine in ether at −20 to 25 °C gave acetoacetate **9** in 83% yield. Carroll rearrangement was accomplished by Wilson's procedure.[9]

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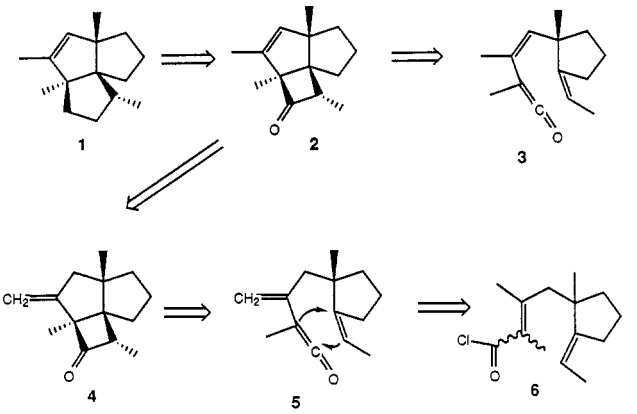

Acetoacetate **9** was converted to the dianion with 2 equiv of LDA in THF at −78 °C. The resulting solution was stirred for 4 h at −78 °C and heated at reflux for 1 h to give the crude β-keto acid, which was immediately decarboxylated by heating at reflux in CCl_4 for 14 h to produce ketone **10** in 72% yield from **9** (Scheme I). The Carroll rearrangement leading to **10** is stereospecific, giving only the *E* isomer, since there is a severe steric interaction between the two methyl groups in the Carroll rearrangement transition state leading to the *Z* isomer.

Attempted Horner–Emmons–Wittig reaction of **10** with triethyl 2-phosphonopropionate was unsuccessful despite the reported preparation of tetrasubstituted acrylates by this procedure.[10] More remarkably, Horner–Emmons–Wittig reaction of **10** with triethyl phosphonoacetate was also unsuccessful despite the fact that **10** appeared to be relatively unhindered. On closer consideration, however, Newman's rule of six predicts that ketone **10** is indeed quite hindered since β-substituents retard attack at a carbonyl group more than α-substituents.[11] Peterson olefination has been successful in cases where the Horner–Emmons reaction fails.[12] We were delighted to find that reaction of **10** with the lithium salt of ethyl 2-(trimethylsilyl)propionate[13] in THF for 1 h at −78 °C, 1 h at 25 °C, and 12 h at reflux gave ester **11** as a mixture of isomers. The crude product was hydrolyzed with excess sodium hydroxide in ethanol at reflux for 9 h to give a 75% yield (98% based on recovered **10**) of **12** as a complex mixture of the eight possible α,β- and diastereomeric β,γ-unsaturated acids. The two α,β-unsaturated isomers and the two β,γ-unsaturated isomers with a 1,1-disubstituted double bond will be converted to ketene **5**. Two other diastereomeric β,γ-unsaturated isomers with a *Z* trisubstituted double bond will be converted to ketene **3**, which should give cyclobutanone **2** directly. Examination of the NMR spectrum of crude **12** indicated that the β,γ-unsaturated isomers with a 1,1-disubstituted double bond were major components of the mixture. The crude product was therefore used without purification.

The mixture of acids **12** were converted to a mixture of acid chlorides **13** by treatment with excess oxalyl chloride in benzene at 25 °C for 2 h and 55 °C for 1 h. The acid chloride was added over 30 min to 3 equiv of Et_3N in toluene at reflux followed by heating for 3 h to give the desired cyclobutanone **4** in 31% overall yield from **10** (41% based on recovered **10**) and cyclobutenone **14** in 4.5% yield. As expected, cycloadduct **4** is formed as a single regio- and stereoisomer. Addition to the double bond should be stereospecifically cis, and the carbonyl group of the ketene should add to the less substituted end of the double bond.[4] The structure of **4** was proven by conversion to **2**.

The minor product **14** is formed by closure of the α,β-unsaturated ketene to give the cyclobutenone and isomerization of the exocyclic double bond into the ring. We have shown that reversible ring closure of α,β-unsaturated ketenes is a facile process for α,β-unsaturated ketenes containing a substituent on both the ketene and α-carbon and a β-unsubstituted carbon.[2j] If isomerization of the exocyclic double bond into the ring occurs during either acid chloride or ketene preparation, a ketene will be formed, which should close to **14** rather than undergoing a less favorable [2 + 2] cycloaddition with the endocyclic double bond.

Isomerization of the double bond of **4** to give **2** in the presence of a reactive cyclobutanone was a challenging problem. Isomerization over palladium catalysts with hydrogen, which we have previously used in the synthesis of chrysanthenone,[2h] proved unsuccessful. A variety of acid-catalyzed isomerizations either gave no reaction or complex mixtures of products. Finally, we found that treatment of **4** with excess concentrated hydriodic acid[14] in benzene for 3.5 h at 25 °C isomerized the double bond into the ring without extensive side reactions to give **2** in 51% yield. The structure of **2** was established by comparison of IR and ^1H and ^{13}C NMR spectral data with those of an authentic sample.[7]

Since Wenkert has converted **2** to isocomene,[7] this completes a formal total synthesis. Cyclobutanone **2** was prepared from commercially available ketone **9** in only six steps in 10% overall yield.

Synthesis of α-Bergamotenes (16). The conditions for the successful isomerization of **4** to **2**, concentrated hydriodic acid in benzene, have also been found to be effective with other acid-sensitive alkenes. Treatment of β-*trans*-bergamotene (**15a**)[2g] with a hydriodic acid in benzene for 2.5 h at 25 °C gave α-*trans*-bergamotene (**16a**)[15] in 54% yield. Similar treatment of β-*cis*-bergamotene (**15b**)[2g] gave α-*cis*-bergamotene (**16b**)[15] in 55% yield. This isomerization procedure makes the α-bergamotenes readily available since the β-bergamotenes can be prepared easily by using intramolecular ketene cycloadditions.[2b,g,3c] This isomerization with strong acid is successful despite the propensity to rearrangement of the intermediate cation.[16,17] β-Pinene (**15c**) has been isomerized to α-pinene (**16c**) with benzoic acid in β-pinene as solvent for 48 h at reflux.[17c] However, treatment of β-pinene with acid generally results in rearrangement of the carbon skeleton.

Attempted Synthesis of Seychellene (17). Seychellene (**17**) is a tricyclic sesquiterpene that has been the subject of much synthetic attention.[18] Our analysis sug-

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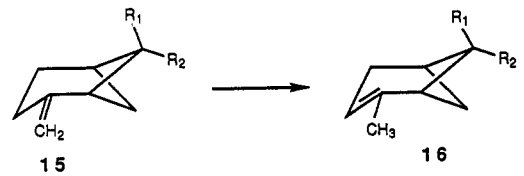
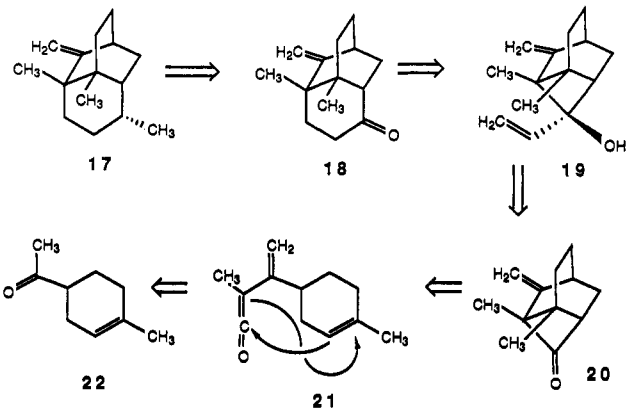


15 16

a, $R_1 = CH_3$, $R_2 = CH_2CH_2CH{=}C(CH_3)_2$
b, $R_1 = CH_2CH_2CH{=}C(CH_3)_2$, $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$

gested that seychellene could be prepared from ketone **18**, which might be prepared by a 1,3-sigmatropic rearrangement of 1-vinylcyclobutanol **19**. Cyclobutanol **19** could be prepared from cyclobutanone **20**, which should be easily prepared by intramolecular cycloaddition of ketene **21**. Since **21** can be prepared easily from 4-acetyl-1-methylcyclohexene (**22**), this route was attractive.



17 18 19 22 21 20

Base-catalyzed 1,3-sigmatropic rearrangements of 1-vinylcyclobutanols with an anion-stabilizing substituent at the 2-carbon have been developed as a route to cyclohexanones,[19] indicating that the proposed conversion of **19** to **18** is plausible. Base-catalyzed oxy-Cope rearrangements of 1,2-divinylcyclobutanols have been developed by Gadwood, Paquette, and others as a route to cyclooctenones.[20] It was not clear, a priori, whether the steric constraints imposed by the tricyclic framework of **19**, which would force the formation of a *trans*-cyclooctene, would permit the oxy-Cope reaction to occur. If the oxy-Cope rearrangement did not occur, the desired 1,3-sigmatropic rearrangement to give **18** was a plausible outcome of generation of the alkoxide of **19**.

We chose to prepare **26** as a model for **20** since the absence of the methyl group should facilitate the preparation of the α,β-unsaturated acid **23** and increase the yield of the cycloaddition.[21] Reaction of **22** with the sodium salt of triethyl phosphonoacetate in THF for 2 days at 25 °C followed by hydrolysis with aqueous barium hydroxide at reflux for 12 h gave crystalline acid **23**[21] in 70% yield as the *E* isomer. Reaction of acid **23** with excess oxalyl chloride in benzene at 25 °C for 3 h and 55 °C for 1 h gave acid chloride **24**, which was added over 2 h to 3 equiv of Et_3N in toluene at reflux followed by heating at reflux for 3 h to give the desired cycloadduct **26** in 59% yield from 23 (Scheme II).

Addition of **26** to vinyllithium in THF at −78 °C followed by quenching at −78 °C with acetic acid gave **27** in quantitative yield. The stereochemistry of **27** is tentatively assigned as shown, since vinyllithium should attack from the less hindered α-face, as has been observed in related additions to chrysanthenone.[22] Alcohol **27** could not be purified since it rearranged on silica gel.

Addition of vinyllithium to **26** at −78 °C followed by warming the lithium alkoxide to 25 °C gave the oxy-Cope rearrangement product **28** in 62% yield from **26**. Oxy-Cope rearrangements of 1,2-divinylcyclobutanols occur quite readily due to relief of ring strain. Related rearrangements of lithium alkoxides have occurred at temperatures as low as −80 °C.[20c,d] *trans*-Cyclooctenes have occasionally been obtained.[20d,e] The two double bonds of **27** are favorably oriented for oxy-Cope rearrangement to give **28** despite the fact that the product has a trans double bond in an eight-membered ring.

Fragmentation becomes the favored process with slight modification of geometry. Addition of vinyllithium to **29** followed by quenching with acetic acid at −78 °C gave **30**[22] in 83% yield. Treatment of **30** with KH in THF at 0 °C presumably resulted in fragmentation to give the vinyl ketone **31**, which polymerized under the basic reaction conditions (Scheme III).

Gadwood has developed the oxy-Cope rearrangement of 1-alkynyl-2-alkenylcyclobutanols as a route to cyclooctadienones.[20c,f] We therefore decided to examine the base induced reactions of enynol **32**. Addition of lithium acetylide, prepared by Midland's procedure,[23] to **26** in THF at −20 °C for 2.5 h gave a 3:1:1 mixture of **32**, oxy-Cope rearrangement product **33**, and **34**, the product of lithium acetylide addition to **33**. Alcohol **34** is formed because oxy-Cope rearrangement of the lithium salt of **32** to give **33** occurs at a rate comparable to the addition of lithium acetylide to **26** at −20 °C. Unfortunately, acetylide addition to **26** did not occur at lower temperatures. Oxy-Cope rearrangement of **32** was completed by heating the mixture of **32** and **33** in THF at reflux for 2 h to give a 33% isolated yield of **33** (Scheme IV).

Addition of sodium acetylide[24] to **26** was examined since addition of lithium acetylide to **26** could not be accomplished without concomitant oxy-Cope rearrangement. Addition of sodium acetylide to **26** in THF occurred only at reflux to give a 25% yield of **36** and a 17% yield of **38**. Under these reaction conditions the sodium salt of **32** rearranges to give oxy-Cope product **33**. Enone **33** reacts in the presence of base to give trienolate **35**, which reacts further to give both **36** and **38**. Protonation at the α-position gives **36**. The ^1H and ^{13}C NMR spectra of **33** and **36** do not permit unambiguous assignment of their structure. The double-bond position can be unambiguously determined by examination of the IR spectra. The

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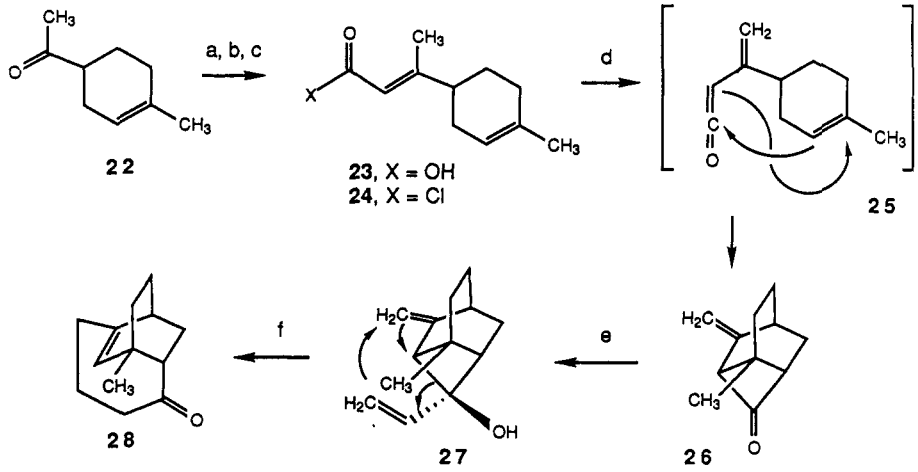
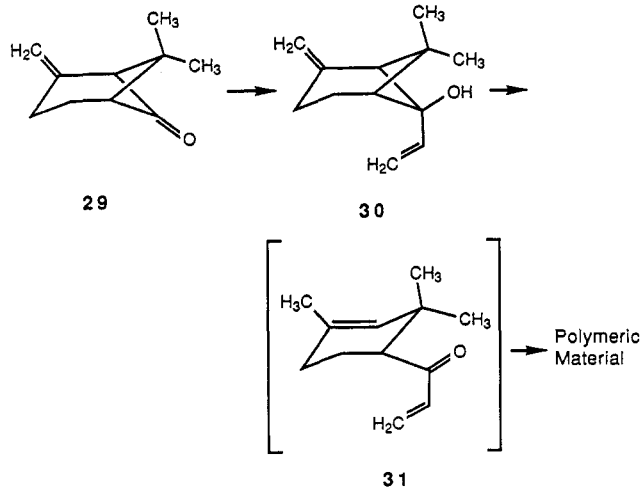
Scheme II[a]



[a] (a) LDA, $EtOCOCH_2PO(OEt)_2$; (b) $Ba(OH)_2$, H_2O, reflux; (c) oxalyl chloride; (d) Et_3N, toluene, reflux; (e) CH_2=CHLi, −78 °C; (f) CH_2=CHLi on **26**, −78 to 25 °C.

Scheme III



unconjugated carbonyl group at **36** absorbs at 1677 cm^{-1}, while the conjugated carbonyl group of **33** absorbs at 1650 cm^{-1}.

Trienolate **35** is a cyclooctatriene, which can undergo conrotatory electrocyclic ring opening[25] to give **37**, which will be protonated to give trienone **38**. It is possible that ring opening is accelerated by the presence of the alkoxide. However, relief of strain also plays a role in facilitating the rearrangement, and it is impossible to determine the significance of the various factors favoring electrocyclic ring opening.

These results demonstrate that oxy-Cope rearrangements can be carried out efficiently to yield **28** and **33** and suggest that it will not be possible to carry out the 1,3-sigmatropic rearrangement necessary for the proposed synthesis of seychellene.

Experimental Section

Materials and Methods. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ, ppm downfield from internal tetramethylsilane. Coupling constants are reported in hertz. Analytical gas chromatography was performed on a 25-m bonded OV-225B capillary column. Melting points are uncorrected. High-resolution mass spectra were obtained at the University of Connecticut.

Benzene, diisopropylamine, and triethylamine were dried by distillation from calcium hydride. Benzene was deoxygenated by bubbling nitrogen through the solvent. Diethyl ether and THF were dried by distillation from sodium benzophenone ketyl. All commercial reagents were used without further purification. Vinyllithium was obtained from Lachat Chemicals, Inc. Anhydrous toluene, 1-acetyl-2-methylcyclopentene, 4-acetyl-1-methylcyclohexene, *n*-butyllithium, diketene, hydriodic acid, and sodium acetylide were purchased from Aldrich Chemical Co. Ethyl 2-(trimethylsilyl)propionate was prepared by alkylation of ethyl trimethylsilylacetate by the procedure of Crimmin, O'Hanlon, and Rogers.[12a]

All air- and moisture-sensitive reactions were run under an inert atmosphere in flame-dried glassware with magnetic stirring. Reagents were added via oven-dried syringes through rubber septa.

α,2-Dimethyl-1-cyclopentene-1-methanol (8). A solution of sodium borohydride (1.01 g, 26.69 mmol) in 15 mL of ice water was added slowly via pipette over 5 min to a stirred solution of 1-acetyl-2-methylcyclopentene (**7**) (3.00 g, 24.16 mmol) in 30 mL of methanol at 10 °C. The reaction mixture was slowly warmed to 20 °C, stirred for 2 h, and then heated at 35 °C for an additional 1 h. Methanol was removed in vacuo, and the aqueous residue was extracted with diethyl ether (4 × 15 mL). The combined ethereal extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to give 2.78 g (91%) of **8** as a yellow oil: ^1H NMR δ 4.70 (q, 1, J = 6.4), 2.30–2.54 (m, 2), 2.24–2.33 (m, 2), 1.72–1.85 (m, 2), 1.66–1.68 (br s, 3), 1.53 (br s, OH), 1.25 (d, 3, J = 6.4); ^{13}C NMR δ 137.7, 133.9, 64.3, 38.8, 30.3, 21.6, 21.5, 13.6; IR (neat) 3350, 2970, 2950, 2930, 2895, 2840, 1678, 1445, 1380, 1365, 1335, 1290, 1185, 1069, 1055, 1011, 983, 880 cm^{-1}. The data are identical with those previously described.[8]

1-(2-Methyl-1-cyclopentenyl)ethyl 3-Oxobutanoate (9). A catalytic amount of 4-(dimethylamino)pyridine (18.0 mg, 0.14 mmol) was added to a solution of diketene (1.96 mL, 2.10 g, 25.0 mmol) and **8** (2.75 g, 21.8 mmol) in 70 mL of anhydrous diethyl ether at −20 °C under argon. The reaction was stirred for 30 min at −20 °C and then warmed to room temperature and stirred for an additional 11 h. The reaction mixture was then washed with 0.1% aqueous NaOH (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo to give 4.58 g of crude product as a yellow oil. Purification of a 1.00-g portion by flash column chromatography on silica gel (19:2 hexane–ethyl acetate) gave 828 mg (83%) of pure **9** as a 23:1 mixture of keto and enol tautomers: ^1H NMR δ 12.16 (s, 1, enol), 5.77 (q, 1, J = 6.6), 4.96 (q, 1, J = 0.75 Hz, enol), 3.41 (q, 2, J = 0.45), 2.20–2.47 (m, 4), 2.26 (t, 3, J = 0.45), 1.94 (t, 3, J = 0.75, enol), 1.73–1.84 (m, 2), 1.69–1.73 (m, 3), 1.31 (d, 1, J = 6.6); ^{13}C NMR δ 200.7, 166.4, 136.6, 133.2, 68.8, 50.3, 38.6, 30.9, 29.9, 21.4, 18.8, 13.8; IR (neat) 2990, 2960, 2940, 2850, 1745, 1720, 1650, 1450, 1415, 1360, 1310, 1266, 1242, 1190, 1152, 1065, 1048, 973, 944, 850, 800 cm^{-1}; mass spectrum, m/z (relative

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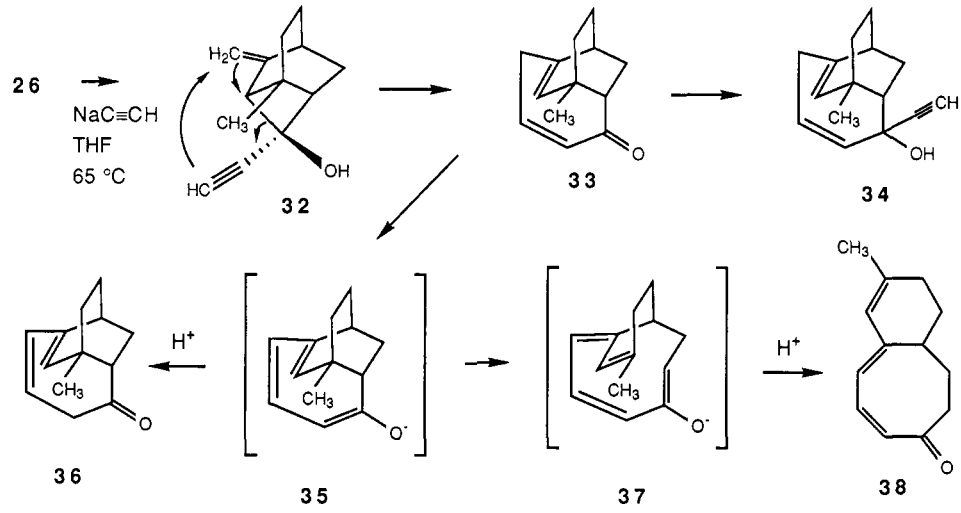
Scheme IV



intensity) 108 (47), 93 (100), 91 (47), 79 (28), 77 (40), 44 (26), 43 (29), 39 (17).

1-(2(*E*)-Ethylidene-1-methylcyclopentyl)propan-2-one (10). Lithium diisopropylamide was prepared by the slow addition of *n*-butyllithium (28.7 mL, 2.5 M in hexanes, 71.8 mmol) to a solution of diisopropylamine (10.31 mL, 7.44 g, 73.5 mmol) in 35 mL of anhydrous THF at −78 °C under N_2. After being stirred for 30 min at −78 °C, the lithium amide solution was warmed to room temperature and added dropwise over 40 min to a solution of **9** (7.22 g, 34.3 mmol) in 150 mL of anhydrous THF at −78 °C under N_2. The reaction mixture was stirred at −78 °C for 30 min, at room temperature for 4 h, and at reflux for 1 h. After the mixture was cooled to room temperature, the solvent was removed in vacuo without heating. The residue was dissolved in 75 mL of diethyl ether and extracted with water (1 × 30 mL) and 0.1% aqueous NaOH (3 × 35 mL). The aqueous extracts were combined and washed with diethyl ether (2 × 30 mL). Following the addition of 40 mL of diethyl ether to the aqueous phase, the solution was acidified to pH <2 with 4 M HCl while being stirred rapidly, the layers were quickly separated, and the aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined ethereal extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting crude β-keto acid was dissolved in 125 mL of carbon tetrachloride and heated at reflux for 14 h to effect decarboxylation. Solvent removal in vacuo and evaporative distillation (0.10 Torr, 85 °C) gave 4.12 g (72%) of **10** as a yellow oil: ^{1}H NMR δ 5.16 (qdd, 1, J = 6.6, 2.6, 2.6), 2.51 (d, 1, J = 14.7), 2.43 (d, 1, J = 14.7), 2.16–2.41 (m, 2), 2.09 (s, 3), 1.58 (ddd, 3, J = 6.6, 1.6, 1.6), 1.54–1.81 (m, 4), 1.10 (s, 3); ^{13}C NMR δ 208.9 (C=O), 150.7 (=C), 113.8 (=CH), 53.7 (CH_2), 44.1 (C), 39.5 (CH_2), 32.2 (CH_3), 28.9 (CH_2), 26.8 (CH_3), 22.3 (CH_2), 14.7 (CH_3); IR (neat) 3040, 2960, 2875, 1723, 1711, 1453, 1435, 1405, 1357, 1200, 1157, 1010, 970, 940, 815 cm^{-1}; mass spectrum, m/z (relative intensity) 166 (1.5, M^+), 109 (75), 108 (100), 93 (98), 91 (24), 81 (33), 79 (26), 77 (29), 67 (45), 43 (64). Anal. Calcd for $C_{11}H_{18}O$ 166.1358, found 166.1358.

4-(2(*E*)-Ethylidene-1-methylcyclopentyl)-2,3-dimethylbut-2-enoic and 4-(2(*E*)-Ethylidene-1-methylcyclopentyl)-2-methyl-3-methylenebutanoic Acids (12). Lithium diisopropylamide was prepared by the slow addition of *n*-butyllithium (2.36 mL, 2.67 M in hexanes, 6.30 mmol) to a solution of diisopropylamine (0.92 mL, 6.33 mg, 6.55 mmol) in 25 mL of anhydrous THF at −78 °C under N_2. After being stirred for 15 min at −78 °C, the lithium amide solution was warmed briefly (30 min) to room temperature, returned to −78 °C, treated over 15 min with a solution of ethyl 2-(trimethylsilyl)propionate[13b] (1.00 g, 5.74 mmol) dissolved in 10 mL of anhydrous THF, and stirred for 1.5 h at −78 °C. A solution of **10** (760 mg, 4.57 mmol) in 10 mL of anhydrous THF was then added dropwise over 10 min to the solution. The reaction mixture was stirred at −78 °C for 1 h, at room temperature for 1 h, and at reflux for 12 h. After the mixture was cooled to room temperature, the reaction was quenched with 15 mL of saturated aqueous NH_4Cl solution, the layers were separated, and the organic layer was washed with water (2 × 10 mL). The aqueous washes were extracted with ethyl acetate (4 × 10 mL), the organic phases were combined, and the solvent was removed in vacuo to give crude **11**. Crude **11** and sodium hydroxide (1.00 g, 25 mmol) were dissolved in 20 mL of absolute ethanol, and the solution was heated at reflux under N_2 for 9 h to effect hydrolysis. After the solution was cooled to room temperature, the solvent volume was reduced 50% in vacuo, followed by the addition of 20 mL of diethyl ether and 20 mL of water. The layers were separated, the aqueous phase was extracted with diethyl ether (4 × 10 mL), and the ethereal extracts were washed with water (4 × 10 mL). The combined ethereal extracts were dried (Na_2SO_4), and the solvent was removed in vacuo to give 175.8 mg of recovered **10**. The aqueous layers were combined and acidified to pH <2 with concentrated hydrochloric acid and extracted with methylene chloride (4 × 10 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield 770.3 mg (75%, 98% based upon recovered starting material) of **12** as a complex mixture of double bond position isomers and stereoisomers as indicated by the resonances in the ^{1}H NMR spectrum at δ 4.92, 5.06, and 5.08. The crude mixture was used without further purification or characterization.

2α,4α,7β-Trimethyl-5-methylenetricyclo[5.3.0.0^{1,4}]decan-3-one (4). Oxalyl chloride (1.48 mL, 2.20 g, 17.32 mmol) was added dropwise to a solution of crude **12** (770.3 mg total, 3.46 mmol) in 20 mL of anhydrous benzene at 7 °C under N_2. The reaction mixture was stirred at room temperature for 2 h and at 55 °C for an additional 1 h. The benzene was then removed in vacuo, and the residual orange-yellow acid chloride **13** was taken up in 7 mL of anhydrous toluene and added slowly over 30 min to a solution of Et_3N (1.44 mL, 1.05 g, 10.36 mmol) in 60 mL of anhydrous toluene at reflux. The reaction mixture was heated at reflux for 3 h, cooled to room temperature, and filtered through a pad of Celite to remove the precipitated triethylamine hydrochloride. The filter cake was washed with hexane (5 × 10 mL), the filtrates were combined, and the solvent was removed in vacuo. Flash column chromatography of the residue on silica gel (25:1 hexane–ethyl acetate) gave 297.3 mg (31% from **10**, 41% based on recovered **10**) of **4** as a viscous, pale yellow oil, which crystallized upon cooling, and 46.2 mg (6%) of **14**.

An analytical sample of **4** was prepared by three recrystallizations of a 127.0-mg sample from pentane at −78 °C under N_2 to give 77.3 mg of white crystals: mp 47.2–48.0 °C; ^{1}H NMR δ 4.99 (dd, 1, J = 2.0, 2.0), 4.95 (dd, 1, J = 2.0, 2.0), 3.08 (q, 1, J = 7.7), 2.45 (dd, 2, J = 2.0, 2.0, 1.69–1.84 (m, 3), 1.46–1.62 (m, 2), 1.26–1.44 (m, 1), 1.15 (s, 3), 1.06 (d, 3, J = 7.7), 1.02 (d, 3, J = 0.5); ^{13}C NMR δ 212.7 (C=O), 151.7 (C=), 109.2 (=CH_2), 74.6 (C), 59.4 (C), 53.0 (CH), 51.0 (C), 44.8 (CH_2), 37.5 (CH_2), 24.3 (CH_2), 21.3 (CH_3), 20.4 (CH_2), 15.54 (CH_3), 10.87 (CH_3); IR ($CDCl_3$) 2955, 2930, 2870, 1763, 1695, 1455; mass spectrum, m/z (relative intensity) 204 (0.5, M^+), 189 (1), 176 (3), 161 (10), 148 (50), 133 (100). Anal. Calcd for $C_{14}H_{20}O$ 204.1515, found 204.1512.

Spectral data for **14**: ^{1}H NMR δ 5.33 (dq, 1, J = 2.1, 2.1),

3.04–3.18 (m, 2), 2.63 (dq, 1, J = 13.8, 0.7), 2.51 (dq, 1, J = 13.8, 1.0), 2.19–2.30 (m, 2), 1.80–1.99 (m, 2), 1.58–1.77 (m, 2), 1.63 (dddd, 3, J = 0.7, 1.0, 2.3, 2.4), 1.11 (s, 3), 1.10 (t, 3, J = 7.3); ^{13}C NMR δ 172.2, 151.5, 145.7, 122.1, 51.1, 50.3, 38.9, 37.7, 29.4, 26.2, 19.4, 12.1, 7.5, carbonyl resonance not observed; IR ($CDCl_3$) 3065, 2970, 2940, 2925, 2880, 2860, 1753, 1646, 1457, 1379, 1331, 1316 cm^{-1}.

2α,4$a\alpha$,5,7β-Tetramethyltricyclo[5.3.0.0^{1,4}]dec-5-en-3-one (2). A solution of 4 (33.6 mg, 0.164 mmol) in 6 mL of deoxygenated benzene was treated with concentrated hydriodic acid (57%, 110 mg) at room temperature under N_2. The solution was stirred vigorously, and the reaction was monitored by GC. After 30 min the solution was pink in color with a small amount of a yellow aqueous phase. After 60 min the solution was once again colorless and apparently homogeneous; GC analysis indicated a 3:1 ratio of starting material to product in the reaction mixture. After 3.5 h, GC analysis indicated that all starting material had been consumed. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 mL), the layers were separated, and the benzene layer was washed with an additional portion of saturated aqueous $NaHCO_3$ (0.5 mL). The combined aqueous layers were then back-extracted with benzene (2 × 1 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo to give 29.9 mg of crude product. Flash column chromatography on silica gel (35:1 pentane–diethyl ether) gave 17.3 mg (51%) of pure **2**, which exhibited IR, ^{1}H NMR, and ^{13}C NMR spectra identical with those previously reported:[7] ^{1}H NMR δ 5.28 (q, 1, J = 1.5), 3.28 (q, 1, J = 7.7), 1.61 (d, 3, J = 1.5), 1.28–1.80 (m, 6), 1.13 (s, 3), 1.12 (s, 3), 1.06 (d, 3, J = 7.7); ^{13}C NMR δ 137.2 (=C), 136.5 (=CH), 79.6 (C), 56.7 (C), 56.4 (C), 53.3 (CH), 40.9 (CH_2), 27.2 (CH_2), 24.5 (CH_2), 22.6 (CH_3), 13.5 (CH_3), 13.2 (CH_3), 11.01 (CH_3), carbonyl resonance not detected; IR ($CDCl_3$) 3030, 2970, 2870, 1764, 1455 cm^{-1}.

***α-trans*-Bergamotene (16a).** To a solution of 12.0 mg (0.059 mmol) of *β-trans*-bergamotene (**15a**) in 3 mL of benzene under N_2 was added concentrated hydriodic acid (57%, 36 mg). The mixture was stirred for 2.5 h and quenched by slow addition of 3 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with benzene (2 × 3 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated to give 12.1 mg of crude material. Flash chromatography on silica gel (hexane) gave 6.5 mg (54%) of pure **16a**: ^{1}H NMR δ 5.20 (m, 2), 2.20 (m, 1), 2.15 (m, 2), 2.00 (m, 3), 1.70 (s, 3), 1.66 (br s, 3), 1.63 (s, 3), 1.60 (m, 3), 1.17 (d, 1, J = 8.6), 0.83 (s, 3); ^{13}C NMR δ 144.5, 131.0, 125.3, 116.5, 45.4, 41.1, 39.0, 38.6, 31.6, 29.7, 25.7, 23.8, 23.0, 17.6, 17.4. The spectral data are identical with those previously described.[15]

***α-cis*-Bergamotene (16b).** To a solution of 16.6 mg (0.081 mmol) of *β-cis*-bergamotene (**15b**) in 4 mL of deoxygenated benzene under N_2 was added concentrated hydriodic acid (57%, 48 mg). Reaction for 1 h and workup as described above gave 19 mg of crude product. Flash chromatography on silica gel (hexane) gave 9.2 mg (55%) of pure **16b**: ^{1}H NMR δ 5.20 (m, 1), 5.07 (br t, 1, J = 7), 2.34 (ddd, 1, J = 5.3, 8.3, 11.1), 2.18 (m, 2), 1.98 (br dt, 1, J = 1.3, 5.3), 1.69 (m, 2), 1.67 (d, 3, J = 1.2), 1.59 (s, 3), 1.55 (s, 3), 1.26 (s, 3), 1.15 (d, 1, J = 8.3), 1.1–1.6 (m, 3); ^{13}C NMR δ 143.7, 130.7, 125.4, 116.6, 46.1, 40.5, 40.4, 33.9, 31.6, 29.7, 25.7, 23.1, 23.1, 22.9, 17.5. The spectral data are identical with those previously described.[15]

3-(4-Methyl-3-cyclohexen-1-yl)-but-2(*E*)-enoic acid (23)[21] was prepared by a modification of the literature procedure. Reaction of triethyl phosphonoacetate (8.20 g, 36.6 mmol) with **22** gave 7.1 g of crude ester, which was hydrolyzed without purification.

The ester was added to a solution of barium hydroxide octahydrate (14.2 g, 45 mmol) in 100 mL of water and heated at reflux overnight. The solution was cooled to 25 °C and washed twice with ether. The aqueous phase was acidified by the dropwise addition of concentrated hydrochloric acid until the pH was <1 and all solids had dissolved. The solution was extracted with five portions of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give 6.5 g of crude **23** as yellow crystals. Recrystallization from hexane gave 3.80 g (70%) of pure (*E*)-**23** as white crystals: mp 104.7–105 °C (lit.[21] mp 108–109 °C); ^{1}H NMR δ 5.72 (br s, 1), 5.41 (br s, 1), 1.5–2.4 (m, 7), 2.17 (s, 3), 1.66 (br s, 3); ^{13}C NMR δ 172.5, 167.3, 133.9, 119.8 (=CH), 113.9 (=CH), 44.5, 30.2, 30.2, 27.2, 23.4, 17.5. The spectral data are identical with those previously described.[21]

2-Methyl-6-methylenetricyclo[3.3.1.0^{2,7}]nonan-8-one (26). Oxalyl chloride (2.66 mL, 3.96 g, 31.2 mmol) was added slowly to a solution of **23** (1.11 g, 6.16 mmol) in 15 mL of anhydrous benzene at 8 °C under N_2. The solution was stirred for 3 h at room temperature and then heated at 55 °C for an additional 1 h. The solvent was removed in vacuo, the bright yellow acid chloride was taken up in 40 mL of anhydrous toluene, and the resulting solution was added over 2 h to Et_3N (2.60 mL, 1.88 g, 18.6 mmol) in 120 mL of anhydrous toluene at reflux under N_2. The reaction mixture was heated at reflux for 3 h, cooled to room temperature, and filtered through a pad of Celite to remove the precipitated triethylamine hydrochloride. The filter cake was rinsed with hexane (4 × 20 mL), the filtrates were combined, and the solvent was removed in vacuo to give 1.13 g of a dark brown liquid. Flash column chromatography on silica gel (20:1 hexane–ethyl acetate) gave 659.9 mg (66%) of **26** as a pale yellow liquid. Evaporative distillation (75 °C, 2.0 Torr) of a 572.4-mg sample of this material gave 507.0 mg (59% from **23**) of pure **26** as a clear, colorless liquid: ^{1}H NMR δ 4.78 (br s, 1, $W_{1/2}$ = 2.4 Hz), 4.71 (dd, 1, J = 1.0, 1.0), 3.35 (d, 1, J = 7.7), 2.78 (ddd, 1, J = 7.7, 6.0, 2.1), 2.50 (br s, 1, $W_{1/2}$ = 8.3 Hz), 1.97–2.12 (m, 2), 1.76–1.95 (m, 4), 1.14 (s, 3); ^{13}C NMR δ 206.1 (C=O), 151.2, 106.8, 73.4, 61.8, 34.6, 33.2, 32.3, 30.8, 25.4, 24.4; IR (neat) 3080, 2950, 2865, 1779, 1647, 1450, 1381, 1252, 1200, 1089, 1031, 1021, 996, 890, 878 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O$ 162.1045, found 162.1039.

8-Ethenyl-2-methyl-6-methylenetricyclo[3.3.1.0^{2,7}]nonan-8-ol (27). A solution of **26** (50.7 mg, 0.31 mmol) in 1 mL of anhydrous THF was added slowly over 4 min to a solution of vinyllithium (0.27 mL, 1.68 M in THF, 0.45 mmol) in 3 mL of anhydrous THF at −78 °C under N_2. During the addition the tip of the syringe needle was kept below the solvent surface to chill the ketone before it reacted with the vinyllithium. The reaction mixture was stirred at −78 °C for 1.5 h and quenched with 0.08 mL of glacial acetic acid. The solution was warmed to room temperature, and 2 mL of saturated aqueous $NaHCO_3$ was added. The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 2 mL). The combined ethereal layers were dried ($MgSO_4$) and concentrated in vacuo to give **27** in quantitative yield as a white crystalline solid. An analytical sample was prepared by precipitation from pentane upon the addition of water: mp 77.5–79.0 °C; ^{1}H NMR δ 6.17 (dd, 1, J = 17.4, 10.9), 5.31 (dd, 1, J = 17.4, 1.8), 5.15 (dd, 1, J = 10.9, 1.8), 4.79 (d, 1, J = 1.8), 4.60 (d, 1, J = 1.8), 2.68 (d, 1, J = 6.6), 2.30–2.38 (m, 1), 2.21 (dd, 1, J = 6.6, 5.7), 2.02 (ddd, 1, J = 13.0, 5.5, 2.3), 1.45–1.78 (m, 5), 1.54 (s, 3), 1.26 (br s, 1, OH); ^{13}C NMR δ 155.7, 141.2, 114.3, 106.2, 78.9, 60.8, 50.8, 39.7, 34.6, 33.6, 30.5, 29.4, 26.5; IR ($CDCl_3$) 3700, 3600, 2924, 2870, 1605, 1200–1000 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O$: C, 82.05; H, 9.53; 190.1358. Found: C, 81.49; H, 9.44; 190.1361.

1-Methyltricyclo[6.4.0.0^{3,10}]dodec-2-en-7-one (28). A solution of **26** (50.7 mg, 0.31 mmol) in 1 mL of anhydrous THF was added slowly over 4 min to a solution of vinyllithium (0.27 mL, 1.68 M in THF, 0.45 mmol) in 3 mL of anhydrous THF at −78 °C under N_2. During the addition the tip of the syringe needle was kept below the solvent surface to chill the ketone before it reacted with the vinyllithium. The reaction mixture was stirred at −78 °C for 1.5 h and allowed to warm slowly to room temperature over 3 h. The solution was stirred at 25 °C for 3 h and quenched with 2 mL of saturated aqueous sodium bicarbonate solution. The layers were separated, and the aqueous layers were extracted with three portions of ether. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 60.7 mg of crude ketone **28**. Flash chromatography on deactivated silica gel (20:1 hexane–EtOAc) gave 36.7 mg (62%) of pure **28**. An analytical sample was prepared by evaporative distillation (110 °C, 0.1 Torr): mp 41.5–43 °C; ^{1}H NMR δ 5.61 (s, 1), 2.59 (br s, 1), 2.25–2.45 (m, 2), 2.05–2.20 (m, 1), 1.85–2.03 (m, 2), 1.50–1.75 (m, 4), 1.25–1.40 (m, 2), 1.05–1.25 (m, 2), 1.14 (s, 3); ^{13}C NMR δ 213.3 (CO), 148.4 (=C), 132.7 (=CH), 64.7 (CH), 44.8 (CH_2), 40.5 (C), 36.2 (CH_2), 34.9 (CH), 29.1 (CH_2), 27.9 (CH_2), 25.5 (2 CH_2), 23.5 (CH_3); IR ($CDCl_3$) 2924, 2870, 1670 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O$ 190.1358, found 190.1363.

1-Methyltricyclo[6.4.0.0^{3,10}]dodeca-2,5-dien-7-one (33). Acetylene gas was bubbled through a solution of *n*-butyllithium (0.87 mL, 2.54 M in hexane, 0.34 mmol) in 2 mL of anhydrous

THF at −78 °C for 5 min. Acetylene was then passed over the solution to maintain an acetylene atmosphere. A solution of **26** (50.7 mg, 0.31 mmol) in 1 mL of THF was added. The solution was warmed to −20 °C and stirred for 2.5 h. The reaction was quenched with 2 mL of saturated aqueous sodium bicarbonate solution. Normal workup gave 66.7 mg of crude product. Examination of the NMR spectrum indicated that 3:1:1 mixture of **32**, **33**, and **34** was present: ^{1}H NMR (**32**) δ 4.83 (d, 1, J = 1.8), 4.69 (d, 1, J = 1.8); (**34**) δ 6.07 (s, 1), 5.63 (ddd, 1, J = 12, 3.5, 3.5), 5.32 (ddd, 1, J = 12, 2.5, 2.5).

Evaporative distillation (100 °C, 0.2 Torr) of the crude product gave 41.2 mg of a 1:3 mixture of propargylic alcohol **32** and dienone **33** indicating that the oxy-Cope rearrangement of **32** occurred on heating. Alcohol **34** remained in the pot under these distillation conditions. A solution of the distillate in THF was heated at reflux for 2 h and concentrated in vacuo. Flash chromatography of the residue on silica gel (20:1 hexane–EtOAc) gave 19.4 mg (33%) of pure **33**: ^{1}H NMR δ 6.08 (ddd, 1, J = 12.0, 4.5, 2.9), 5.84 (br s, 1, $W_{1/2}$ = 2.4 Hz), 5.46 (dddd, 1, J = 12.0, 2.8, 2.3, 1.9), 3.09 (ddd, 1, J = 18.9, 2.8, 2.8), 2.76 (ddd, 1, J = 18.9, 4.5, 2.3), 2.65 (br s, 1), 2.41 (br s, 1), 1.20–1.75 (m, 6), 1.32 (s, 3); ^{13}C NMR δ 206.9 (CO), 144.4 (=C), 141.4 (=CH), 136.9 (=CH), 130.8 (=CH), 63.3, 43.1 (C), 38.2, 36.3, 29.0, 27.8, 27.1, 23.4; IR ($CDCl_3$) 3010, 2941, 2870, 1650, 1603 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$ 188.1202, found 188.1207.

1-Methyltricyclo[6.4.0.0^{3,10}]dodeca-2,4-dien-7-one (36) and 10-Methylbicyclo[6.4.0]dodeca-5,7,9-trien-4-one (38). A solution of **26** (80.6 mg, 0.50 mmol) in 1 mL of THF was added to a suspension of sodium acetylide (24.6 mg, 0.51 mmol) in THF at 25 °C. The solution was heated at reflux for 2 h, cooled to room temperature, and quenched with 5 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous phase was extracted with five portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 90 mg of crude product. Flash chromatography on silica gel (20:1 hexane–EtOAc) gave 23.2 mg (25%) of **36** followed by 15.3 mg (17%) of **38**.

Spectral data for **36**: ^{1}H NMR δ 6.36 (br d, 1, J = 9.4), 5.71 (s, 1), 5.34 (ddd, 1, J = 9.4, 4.1, 4.1), 2.96 (br s, 2), 2.73 (br s, 1), 2.36 (d, 1, J = 6.6), 1.23–1.85 (m, 6), 1.32 (s, 3); ^{13}C NMR δ 211.6 (CO), 147.4 (=C), 136.8 (=CH), 130.6 (=CH), 129.1 (=CH), 63.9, 47.0, 46.7 (C), 37.6, 28.4, 27.3, 24.3, 23.7; IR ($CDCl_3$) 3020, 2950, 2870, 1677, 1630, 1605 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$ 188.1202, found 188.1199.

Spectral data for **38**: ^{1}H NMR δ 6.56 (dd, 1, J = 12.3, 6.3), 6.00 (br s, 1), 5.96 (d, 1, J = 6.3), 5.88 (dd, 1, J = 12.3, 1.7), 2.65–2.85 (m, 2), 1.45–2.25 (m, 7), 1.85 (s, 3); ^{13}C NMR δ 206.3, 148.5, 142.5, 138.7, 129.6, 125.3, 122.4, 38.4, 35.9, 32.8, 26.4, 26.4, 24.1; IR ($CDCl_3$) 3015, 2930, 2865, 2835, 1650, 1633, 1570, 1450, 1435, 1410, 1130, 819 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$ 188.1202, found 188.1207.

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Regio- and Stereospecific Syntheses of 4-Deoxyadriamycinone and 4,6-Dideoxyadriamycinone from a Common Intermediate

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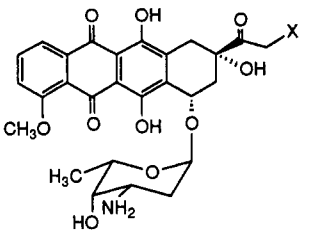
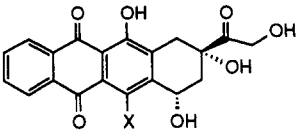
Regio- and stereospecific total syntheses of (±)-4-deoxyadriamycinone (**2a**) and (±)-4,6-dideoxyadriamycinone (**2b**) from commercially available quinizarin (**3**) are described. A key feature of these preparations was the delineation of conditions for Claisen rearrangement of **4c** to furnish specifically either **5a** or **6a**.

Adriamycin (**1a**) has the widest spectrum of activity of any anticancer agent in clinical use and is less toxic than the structurally similar daunorubicin (**1b**).[1] Recently, we reported the first methodology for regio- and stereospecific synthesis of the A-ring fragment present in adriamycinone and, in conjunction with that work, described the total synthesis of (±)-6-deoxyadriamycinone.[2] Unlike previous preparations of the A-ring substitution pattern present in **1a**,[3] our synthesis was not predicated upon the intermediacy of a methyl ketone intermediate.

In order to establish the potential of this methodology for synthesis of adriamycinone and also to explore its potential for providing a practical route to 4-deoxyadriamycinone (**2a**), we undertook the reaction sequence shown in part in Scheme I. Conversion of commercially available quinizarin (**3**) to the substituted anthraquinone **4c**, via the intermediacy of **4a** and **4b**, was accomplished through sequential monoetherification with 2-chloromethyl-1-butene[4] (K_2CO_3, DMF; 50%), hydroxymethylation[5] (CH_2=O, $Na_2S_2O_4$, NaOH, H_2O–CH_3OH; 67–78%), and methylation ($DMSO_4$, K_2CO_3, acetone; 95%).



1a. X = OH Adriamycin
1b. X = H Daunorubicin



2a. X = OH, 4-Deoxyadriamycinone
2b. X = H, 4,6-Dideoxyadriamycinone

Claisen rearrangement of **4c** in DMF–water in the presence of sodium dithionite[6] did not give the desired product **6a**, but instead solely furnished **5a** from regios-

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