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Polyene Cyclization Promoted by the Cross Conjugated α-Carbalkoxy Enone System. An Efficient Approach to Highly Functionalized Decalins

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The cross conjugated α-carbalkoxy enone system was found to be an excellent promoter for polyene cyclization. Under mild conditions, the reaction occurred readily with a high degree of regio- and stereoselectivity. Based on this facile process, an efficient method for the construction of highly functionalized decalin derivatives has been developed.

INTRODUCTION

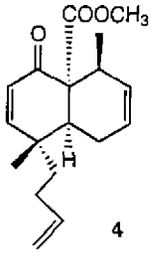
Polyene cyclization, also known as cationic cyclization, is a powerful synthetic tool for the preparation of alicyclic compounds. Its attractiveness lies in the potential control of stereochemistry and the readiness with which highly substituted carbon-carbon bonds may be formed. The synthetic application of this method has been the subject of several reviews.[1-4] In general, the success of the polyene cyclization process depends on the method of initiation, the nucleophilicity of the participating double bond(s), and the process of termination.[2]

The initiation of cyclization can be triggered by formation of a cation either by electrophilic addition to a double bond or by ionization, usually from an sp^3-hybridized carbon. Protonic and Lewis acids have been the most frequently used electrophiles. Protonation of the terminal olefinic bond was used in early attempts to initiate polyene cyclization. Unfortunately, these reactions resulted in complex mixtures of partially cyclized products.[5-7] The difficulties encountered were attributed to the lack of regioselectivity in the protonation process as well as the occurrence of competing reactions, such as addition and isomerization, due to the severe reaction conditions often required. Therefore, the use of an appropriately positioned functional group as an initiator is a common practice. Previously applied functional groups with various degrees of success include epoxide,[8-11] acetal,[3] allylic alcohol[12] and α,β-unsaturated carbonyl groups (aldehyde or ketone).[13-19]

After generation of the cationic center, the specific course of the cyclization depends on the initiator (functionality generating the carbocation) and the nucleophilicity of the double bond involved. However, some generalizations about the cyclization product have been established.[2] For example, where a double bond is 5,6 to the initiating center and electronically unbiased or substituted at C-5, then 6-*endo* cyclization (six-membered ring formation) is almost invariably favored over the 5-*exo* mode (five-membered ring formation).

From the synthetic point of view, a useful cationic cyclization must be terminated by one mechanism giving a single product. Termination can be achieved by elimination and/or attack by an internal or external nucleophile. Proton elimination is the most common termination mode for tertiary cations and also for secondary cations when the cyclizing reagent is a Lewis acid. With protonic acids, nucleophilic attack is often observed and usually stereoselective. The lack of predictability when alkenes terminate cyclization has led to the development of terminators whereby the products can be more precisely anticipated.[2,20]

During the course of our synthetic studies on *cis*-clerodanes, enone ester **1** was subjected to Diels-Alder reaction under Lewis acid catalysis. Interestingly, treatment of **1** and *trans*-piperylene in the presence of zinc chloride gave rise to cyclic compounds **2** and **3** (Scheme I), instead of the expected Diels-Alder adduct **4**. These observed products were apparently formed *via* intramolecular cyclization promoted by the cross conjugated α-carbomethoxy enone system. As a result of this serendipitous discovery, we have carried out



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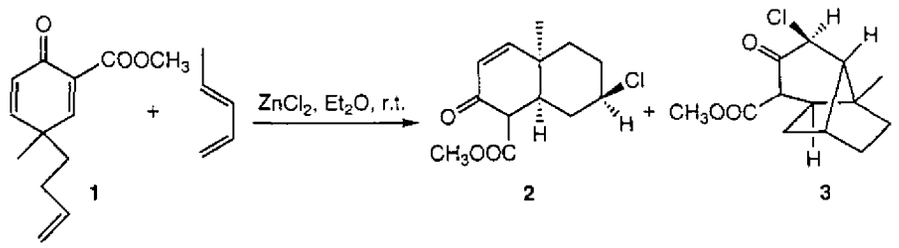
Scheme I



an extensive study on this polyene cyclization process. Accordingly, an efficient procedure for the construction of highly functionalized decalin derivatives has been developed. Details of this investigation are described herein.[21]

RESULTS AND DISCUSSION

Enone ester **1** was readily prepared from 3-ethoxy-6-methyl-2-cyclohexenone (**5**)[22] *via* a sequence involving four synthetic operations as shown in Scheme II. Stork-Danheiser alkylation[23] of enone **5** with lithium diisopropylamide (LDA) and 4-bromo-1-butene gave compound **6** in 84% yield. This compound was reduced with lithium aluminum hydride, followed by hydrolysis with dilute hydrochloric acid to give cyclohexenone **7** in 83% yield over two steps. The carbomethoxy group was introduced using sodium hydride and dimethyl carbonate (74% yield) or LDA and methyl cyanoformate[24] (93% yield) to give keto ester **8** as a mixture of three isomers (two epimers and an enol tautomer) in a ratio of 1:1:3 as indicated by the ^{1}H NMR spectrum. Subsequent oxidation of **8** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[25,26] in refluxing benzene gave the required enone ester **1** in 71% yield . Compound **1** could also be prepared in 76% yield using a bromination-dehydrobromination process by sequential treatment with *N*-bromosuccinimide (NBS) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

With enone ester **1** in hand, its cyclization was examined using a variety of Lewis acids and reaction conditions. The particular Lewis acids (zinc chloride, stannic chloride, aluminum chloride and zinc iodide) were chosen because they had been noted previously as appropriate catalysts for the related polyene cyclizations. The results are summarized in Table 1. When enone ester **1** was treated with anhydrous zinc chloride at room temperature in diethyl ether, compounds **2** and **3** were formed in 90% yield in 2.6:1 ratio. When zinc chloride was replaced by aluminum chloride, a remarkable enhancement of the reaction rate as well as selectivity was observed. The reaction occurred almost instantaneously even at -78 °C and the bicyclic compound **2** was produced exclusively in 75% yield. The use of zinc iodide as a reagent led to the formation of iodide **9** as the sole product in 85% yield. On the other hand, when stannic chlo-

Scheme II

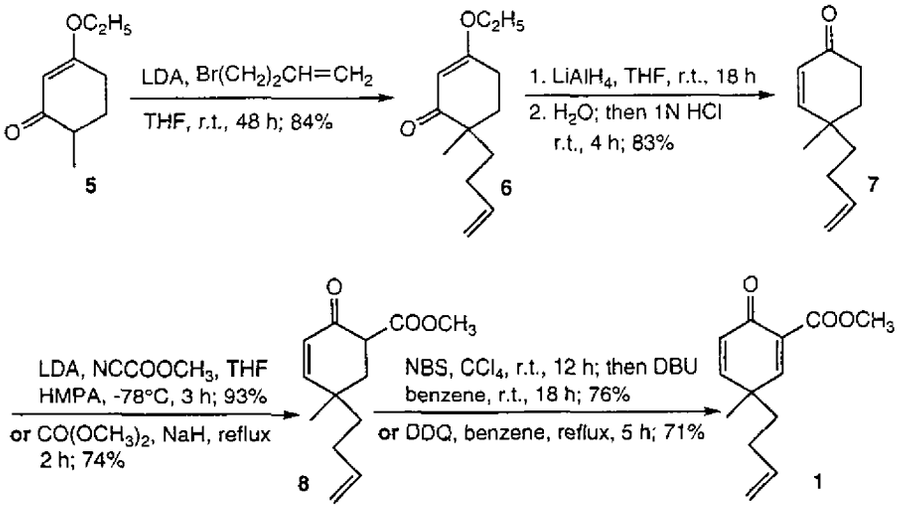
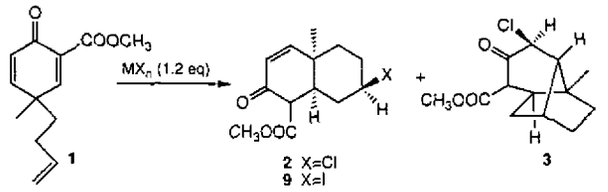


Table 1. Polyene Cyclization of Compound 1 Using Various Lewis Acids



Lewis acid	solvent	temp (°C)	time	yield (%)	ratio (2:3)
$ZnCl_2$	Et_2O	25	3 h	90	2.6:1
$AlCl_3$	Et_2O	-78	15 min	75	1:0
$EtAlCl_2$	CH_2Cl_2	-78	1 h	78	2.1:1
$TiCl_4$	CH_2Cl_2	-78	2 min	86	3:1
$SnCl_4$	CH_2Cl_2	-78	5 min	92	1:2.5
ZnI_2	Et_2O	25	3 days	85	9 only

ride was used as a reagent and dichloromethane as a solvent, a rapid cyclization took place giving the tricyclic compound **3**, instead of the bicyclic compound **2**, as the predominant product. Two other Lewis acids, ethylaluminum chloride and titanium tetrachloride, were also examined. These reagents were found to be also effective, but the product selectivity in favor of the bicyclic compound was inferior to that using aluminum chloride.

Compound **2** was obtained as an inseparable mixture of isomers due to the presence of the highly enolizable and epimerizable β-keto ester moiety. The regiochemistry and stereochemistry of this compound was assigned as follows. Treatment of compound **2** with acetic anhydride in pyridine gave rise to the corresponding enol acetate **10** whose structure was confirmed by spectroscopic methods, especially NMR spectroscopy with the assistance of NOE experiments. In the ^1H NMR spectrum, the splitting pattern (ddd, J = 12.5, 4.5, 2 Hz) observed for the C_6 proton at δ 2.62 suggested that this compound was *cis*-fused. The additional coupling (2 Hz) was due to the long range *w*-coupling with H_2 at δ 5.97 (dd, J = 10, 2 Hz). This type of coupling is possible only for the *cis* system. The *cis* ring junction of compound **10** was further confirmed by NOE experiments which also provided useful information for assigning the stereochemistry of C_8. As shown in Fig. 1, irradiation of the C_1 methyl at δ 1.04 resulted in enhancements of H_6 (9.3%) and H_8 (0.7%). Based on the above spectral data, structures **2** and **10** could be assigned to the bicyclic compound and the corresponding enol acetate, respectively.

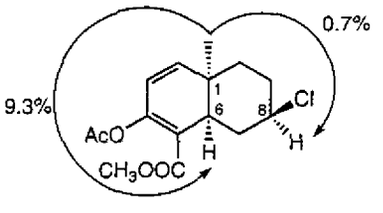
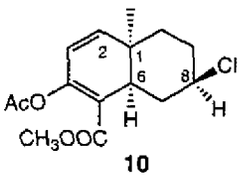


Fig. 1. NOE data of compound **10**.



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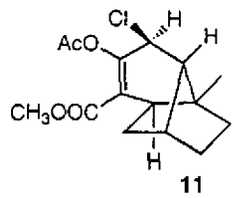
Similarly acetylation of the tricyclic compound **3** afforded enol acetate **11**. Its structure was also verified spectroscopically. The complete assignment of the ^1H NMR spectrum (see the experimental section) was assisted by extensive ^1H NMR decoupling experiments. The stereochemistry of enol acetate **11** was also assigned on the basis of NOE experiments (Fig. 2). Irradiation of the C_9 methyl at δ 1.15 resulted in enhancements of H_5 (5.0%), H_4 (6.2%) and H_1 (5.1%). Thus, the tricyclic compound and its acetate were assigned to structures **3** and **11**, respectively. The iodo compound was assigned to structure **9** based on structure **12** of its acetate, which was established by spectroscopic methods. Again, the all-*cis* relationship of H_6, H_8 and the angular methyl group was deduced by NOE experiments. As shown in Fig. 3, irradiation of the C_1 methyl at δ 0.95 resulted in enhancements of H_6 (7.3%) and H_8 (2.5%), whereas irradiation of H_6 led to an 8.0% enhancement of H_8.



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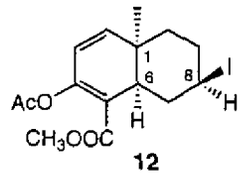

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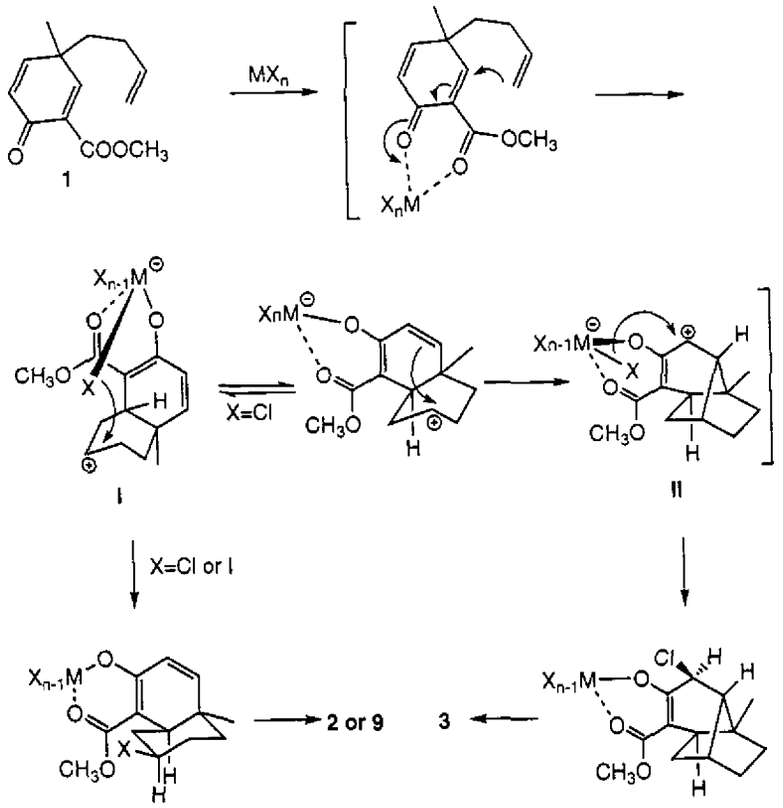
In addition to its high efficiency, the regio- and stereoselectivity observed for the above cyclization process as well as the unusual mode of termination *via* halide formation are of considerable interest. A mechanistic rationale is depicted in Scheme III. It is conceivable that halide formation with the specific stereochemistry in all cases **2**, **3** and **9** is a result of intramolecular transfer of the halide ion from

Scheme III



the metal to the incipient carbocation **I** or **II**. It is also noteworthy that the formation of tricyclic compound **3** requires the participation of the β-carbon of the conjugated enone system. This is rather unusual, but could be explained by invoking the intermediacy of the allyl carbocation **II**. The ratio between the bicyclic and tricyclic compounds produced depends on the Lewis acid used. It is probable that, when zinc iodide or aluminum chloride is used as a reagent, the intermediate **I** rapidly delivers a halide to the carbon cation in an intramolecular fashion. Thus, the bicyclic compound is produced as the sole product. On the other hand, when stannic chloride is used, the corresponding intermediate delivers the chloride somewhat less effectively, allowing participation of the β-carbon of the conjugated enone system leading eventually to the preferential formation of the tricyclic compound.

At this point, we became interested in evaluating the potential influence of the additional carbon-carbon double bond present in enone ester **1** on the observed facile cyclization. Towards this end, enone ester **13** was prepared and its cyclization investigated.

The preparation of enone ester **13** started with reduction of the conjugated carbon-carbon double bond of enone **7** (Scheme IV). The most popular method, catalytic hydrogenation, was not suitable, as the isolated carbon-carbon double bond would be reduced indiscriminately. Hydrosilylation using Wilkinson's catalyst and dissolving metal reduction were then considered to selectively reduce the conjugated double bond. Unfortunately, complicated results were observed in both cases. We then turned to a useful reducing agent, the hexamer of (triphenylphosphine) copper hydride $(Ph_3PCuH)_6$.[27] It was reported that the reagent was

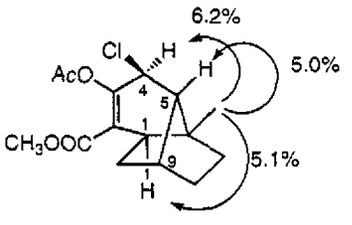


Fig. 2. NOE data of compound **11**.

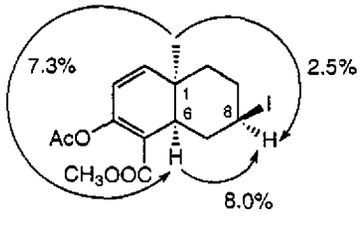
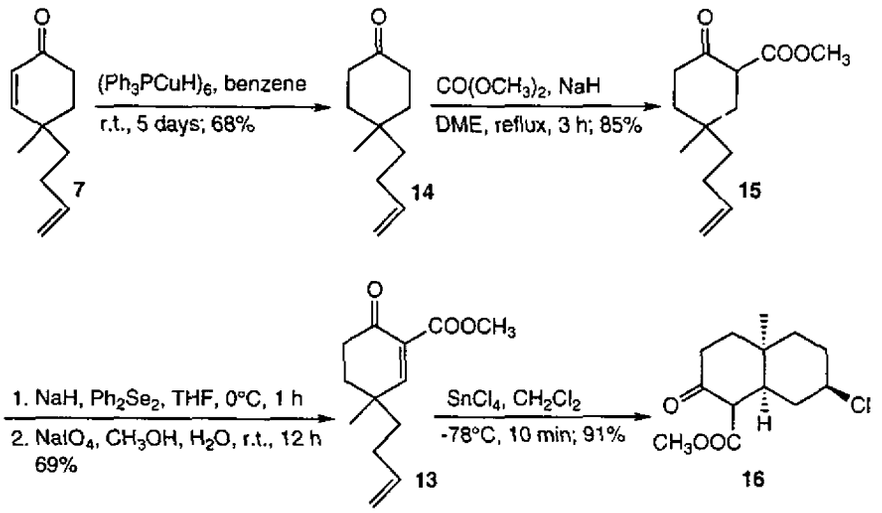


Fig. 3. NOE data of compound **12**.

Scheme IV



effective and selective in reducing the carbon-carbon double bonds of conjugated ketones, aldehydes, esters, nitriles and sulfones in the presence of isolated olefins, carbonyls, halogens and typical oxygenated functionalities. When enone **7** was treated with 0.5 equi-mole of $(Ph_3PCuH)_6$ at room temperature for 5 days, a 68% yield of ketone **14** was obtained along with the recovered starting material. Carbomethoxylation of **14** with dimethyl carbonate and sodium hydride afforded keto ester **15** in 85% yield as a mixture of keto and enol forms in a ratio of 1:2 as indicated by its ^{1}H NMR spectrum. Phenylselenenylation using diphenyl diselenide and sodium hydride, followed by oxidative elimination with sodium periodate furnished enone ester **13** in 69% yield. When compound **13** was treated with stannic chloride in methylene chloride at -78 °C for 10 min, it cyclized readily to give compound **16** in a 91% yield. The ^{1}H NMR spectrum indicated that this compound existed exclusively in the enol form showing an enol proton at δ 12.3 as a singlet.

For comparison, enones **7** and **8** were also subjected to similar treatment with stannic chloride. No reaction was observed for the former compound even after 24 h at room temperature. In the latter case, the starting material was intact at low temperature. At room temperature, a complex mixture was formed upon complete consumption of the starting material, which took about 2 h.

CONCLUSION

In conclusion, the results described above illustrate that the cross conjugated β-keto ester system can serve as a highly effective promoter for cationic cyclization, which occurs readily with high regio- and stereoselectivity and also with an unusual termination process involving halogen atom incorporation when a metal halide is used as the reagent. In essence, this cyclization process allows for expeditious construction of the decalin system with a high level of functionalization suitable for further elaboration leading to a variety of naturally occurring compounds. This is evident from the recently reported total synthesis of dehydrochamaecynenol,[28] which made use of compound **9** as a key intermediate.

EXPERIMENTAL

Combustion elemental analyses were performed by the microanalytical laboratory of the University of Alberta. Fourier transform infrared spectra were recorded on a Nicolet 7199 or Nicolet MX-1 FTIR spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker WH-200, Bruker WH-300, Bruker WH-400 or Bruker AM-400 spectrometer using deuteriochloroform as solvent. Coupling constants are reported to ±0.5 Hz. Chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WH-300 (75 MHz) spectrometer as solutions in deuteriochloroform as the internal standard, setting the central peak at 77.00 ppm. Carbon-13 multiplicities were derived from Carr-Purcell-Meiboom-Gill spin echo *J*-modulated experiments (APT or Attached Proton Test). Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuteriochloroform signal,

whereas methylene groups, quaternary carbons and carbonyl groups appear in phase (p) with it. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer substracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing an antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with argon for 10 min prior to use. High resolution electron impact mass spectra (hrms) were recorded using an A.E.I. model MS-50 mass spectrometer. Spectral data are reported as *m/z* values. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. Concentrations of solvent systems used in column chromatography are given by volumes, e.g., ethyl acetate/hexane (20:80) means 20 parts of ethyl acetate by volume to 80 parts of hexane by volume. Unless otherwise stated, all materials used are commercially available. All compounds made are racemic. Solvents were distilled under argon from appropriate drying agents before use. Tetrahydrofuran (THF), ether and 1,2-dimethoxyethane (DME) were freshly distilled from a blue or purple solution of sodium benzophenone ketyl. Diisopropylamine was obtained by distillation from sodium hydroxide or potassium hydroxide. Pyridine, benzene, hexamethylphosphoric triamide (HMPA), dichloromethane and carbon tetrachloride were distilled from calcium hydride. Reactions requiring anhydrous conditions were performed using oven or flame-dried glassware, assembled and allowed to cool while being purged with argon. Argon was passed through a column of 4 Å molecular sieves, with a self-indicating silica gel (coarse grained) as the indicator. Flash chromatography was used routinely for purification and separation of product mixtures, using silica gel (Merck) of 230-400 mesh. All solvents were distilled prior to use for chromatography. Analytical thin layer chromatography (TLC) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt). Ultraviolet active materials were detected by visualization under a UV lamp. For TLC, the visualization of the chromatograms was completed by dipping in an ethanol solution of vanillin (5%, w/v) and sulfuric acid (5%, v/v), followed by careful charring on a hot plate.

6-(3-Butenyl)-3-ethoxy-6-methyl-2-cyclohexenone (6)

To a solution of diisopropylamine (12.1 mL, 84.1 mmol) in THF (60 mL) at 0 °C under an argon atmosphere, was added *n*-BuLi (52.5 mL, 1.6 M in hexane, 84 mmol) slowly. The mixture was stirred at 0 °C for 15 min and then cooled to -78 °C. A solution of enone **5** (10 g, 64.9 mmol) in THF (20 mL) was added dropwise over a period of 15 min. The resulting mixture was stirred at -78 °C for 1 h and 4-bromo-1-butene (13.5 mL, 134 mmol) was added in one portion. The mixture was allowed to warm slowly to room temperature and stirred for 2 days. Saturated aqueous ammonium chloride was added and the mixture was extracted with ether (3 × 50 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration followed by flash chromatography using ethyl acetate/hexane (5:95) as an eluent gave rise to compound **6** (8.9 g, 66% yield): IR (CH_2Cl_2 cast) 1650 (C=O, enone) cm^{-1}; ^1H NMR (200 MHz) δ 5.67 (dddd, *J* = 17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.12 (s, 1H, C**H**=COEt), 4.87 (dddd, *J* = 17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=C**H**H), 4.79 (dddd, *J* = 10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**H**H), 3.78 (q, J = 7 Hz, 2H, OCH_2), 1.25 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 2.35 (m, 2H), 1.70-2.20 (m, 3H), 1.35-1.70 (m, 3H), 1.00 (s, 3H, CH_3); ^{13}C NMR (75 MHz) δ 203.3 (p), 175.3 (p), 138.6 (a), 114.1 (p), 101.1 (a), 63.9 (p), 42.9 (p), 35.9 (p), 31.9 (p), 28.2 (p), 25.8 (p), 22.1 (a), 13.9 (a); hrms M^+ 208.1460 (calcd. for $C_{13}H_{20}O_2$: 208.1463). Anal. calcd. for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 75.10, H 9.79.

4-(3-Butenyl)-4-methyl-2-cyclohexenone (7)

To a suspension of lithium aluminum hydride (2.81 g, 74 mmol) in THF (20 mL) at room temperature under an argon atmosphere, was added dropwise a solution of enone **6** (7 g, 33.7 mmol) in THF (10 mL). The resulting mixture was stirred at 0 °C for 1 h and then at room temperature overnight. To this mixture, cooled to 0 °C, was added water to destroy excess lithium aluminum hydride. The resulting mixture was stirred for another hour and then acidified with 1 N HCl. The resulting solution was stirred for 4 h. After the hydrolysis was complete, the mixture was extracted with ether (3 × 50 mL). The extracts were combined and washed with saturated aqueous sodium bicarbonate (30 mL), water (50 mL) and brine (50 mL). After being dried over magnesium sulfate, the solution was filtered and concentrated to give the crude product, which was subjected to flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give enone **7** (4.58 g, 92% yield): IR (CH_2Cl_2 cast) 1684 (C=O, enone) and 1646 (C=C) cm^{-1}; ^1H NMR (200 MHz) δ 6.70 (d, *J* = 10 Hz, 1H, C**H**=CHCO), 5.90 (d, *J* = 10 Hz, 1H, CH=C**H**CO), 5.80 (dddd, *J* = 17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.04 (dddd, *J* = 17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=C**H**H), 4.96 (dddd, *J* = 10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**H**H), 2.45 (m, 2H), 2.15-1.87 (m, 3H), 1.87-1.70 (m, 1H), 1.60-1.48 (m, 2H), 1.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz) δ 197.2 (p), 157.1 (a), 138.7 (a), 127.8 (a), 114.6 (p), 40.2 (p), 35.2 (p), 34.3 (p), 33.5 (p), 28.7 (p), 24.6 (a); hrms

M^+ 164.1199 (calcd. for $C_{11}H_{16}O$: 164.1201). Anal. calcd. for $C_{11}H_{16}O$: C 80.44, H 9.82; found: C 80.30, H 9.83.

4-(3-Butenyl)-6-carbomethoxy-4-methyl-2-cyclohexenone (8)

Using Dimethyl Carbonate

To a stirred suspension of sodium hydride (116 mg, 95%, 4.6 mmol) in dimethyl carbonate (15 mL) at room temperature under an argon atmosphere, was added a solution of enone **7** (300 mg, 1.8 mmol) in dimethyl carbonate (3 mL). The reaction mixture was refluxed under an argon atmosphere for 2 h and cooled to 0 °C. A 1 N aqueous HCl solution (10 mL) was then added cautiously to the mixture. The resulting aqueous solution was extracted with ether (3 × 50 mL), and the combined extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to afford keto ester **8** (301 mg, 74% yield) as a mixture of three isomers (two epimers and an enol) in a ratio of 1:1:3: IR (CH_2Cl_2 cast) 3450 (OH, enol), 1747 (C=O, ester), 1694 (C=O, ketone), 1662 (C=O, enol ester) and 1626 (C=C, enol) cm^{-1}; ^1H NMR (200 MHz) δ 11.87 (s, 0.6H, **OH**), 6.70 (dd, *J* = 10, 1.5 Hz, 0.2H, **CH**=CHCO), 6.69 (dd, *J* = 10, 1.5 Hz, 0.2H, **CH**=CHCO), 6.05 (d, *J* = 10 Hz, 0.6H, **CH**=CHCO, enol form), 5.91 (d, *J* = 10 Hz, 0.2H, CH=**CH**CO), 5.86 (d, *J* = 10 Hz, 0.6H, CH=**CH**CO, enol form), 5.73 (d, *J* = 10 Hz, 0.2H, CH=**CH**CO), 5.66-5.85 (m, 1H, **CH**=CH_2), 4.90-5.15 (m, 2H, CH=**CH_2**), 3.76, 3.75 (s, 3H, **OCH_3**), 3.65-3.45 (m, 0.4H, COC**H**COOMe), 2.50-1.85 (m, 4H), 1.75-1.35 (m, 2H), 1.18, 1.15 (both s, 0.6H each, **CH_3** (keto forms)), 1.02 (s, 1.8H, **CH_3** (enol form)); hrms M^+ 222.1256 (calcd. for $C_{13}H_{18}O_3$: 222.1256). Anal. calcd. for $C_{13}H_{18}O_3$: C 70.24, H 8.16; found: C 70.20, H 8.25.

Using Methyl Cyanoformate

n-Butyllithium (9.4 mL, 1.6 M in hexane, 15 mmol) was added to a stirred solution of diisopropylamine (2.3 mL, 16 mmol) in THF (20 mL) at 0 °C under an atmosphere of argon. After 30 min, the temperature was lowered to -78 °C and a solution of enone **7** (1.85 g, 11.3 mmol) in THF (10 mL) was added dropwise over a period of 15 min. Stirring was continued at 0 °C for 1 h. The temperature was lowered again to -78 °C and then HMPA (2.2 mL, 12.4 mmol) was introduced. This was followed by the addition of methyl cyanoformate (1.1 mL, 13.5 mmol) in one portion. After stirring for 1 h at -78 °C, the mixture was warmed to room temperature and treated with ice-cold water (10 mL). The product was extracted into ether (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (5:95) as an eluent gave compound **8** (2.5 g, 93% yield).

4-(3-Butenyl)-2-carbomethoxy-4-methyl-2,5-cyclohexadienone (1)

Direct Oxidation with DDQ

To a solution of keto ester **8** (200 mg, 0.9 mmol) in benzene (5 mL) at room temperature under an argon atmosphere, was added DDQ (407 mg, 1.8 mmol). The mixture was stirred for 15 min and then refluxed for 5 h. The reaction mixture was concentrated. Chloroform (15 mL) was added to the residue and the precipitate was removed by filtration. The filtrate was concentrated and the residue was subjected to flash chromatography using ethyl acetate/hexane (20:80) as an eluent to give enone ester **1** (141 mg, 71% yield): IR (CH_2Cl_2) 1742 (C=O, ester), 1665 (C=O, ketone) and 1638 (C=C) cm^{-1}; ^1H NMR (200 MHz) δ 7.50 (d, *J* = 3 Hz, 1H, **CH**=CCOOMe), 6.75 (dd, *J* = 10, 3 Hz, 1H, **CH**=CHCO), 6.32 (d, *J* = 10 Hz, 1H, CH=**CH**CO), 5.70 (dddd, *J* = 17, 10, 6.5, 6.5 Hz, 1H, **CH**=CH_2), 4.97 (dddd, *J* = 17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=C**HH**), 4.95 (dddd, *J* = 10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**HH**), 3.87 (s, 3H, **OCH_3**), 1.95-1.75 (m, 4H), 1.31 (s, 3H, **CH_3**); ^{13}C NMR (75 MHz) δ 181.6 (p), 165.2 (p), 160.6 (a), 153.6 (a), 137.2 (a), 131.8 (p), 129.7 (a), 115.5 (p), 52.4 (p), 42.1 (a), 39.7 (a), 29.3 (a), 25.7 (p); hrms M^+ 220.1098 (calcd. for $C_{13}H_{16}O_3$: 220.1099). Anal. calcd. $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.57, H 7.41.

Bromination-dehydrobromination

Keto ester **8** (500 mg, 2.3 mmol) was dissolved in carbon tetrachloride (8 mL) and the reaction vessel was protected from light. NBS (1.1 g, 6.2 mmol) was added. After 16 h at room temperature, the reaction mixture was filtered. The filtrate was concentrated to give the crude bromide (800 mg) which, without purification, was dissolved in benzene (10 mL). DBU (0.8 mL) was added. After stirring at room temperature for 4 h, the reaction mixture was filtered. The filtrate was diluted with ether (60 mL) and successively washed with 5% hydrochloric acid (2 × mL), water, saturated aqueous sodium bicarbonate solution and brine (10 mL each). Drying ($MgSO_4$), filtration and concentration gave the crude product which was subjected to flash chromatography. Elution with ethyl acetate/hexane (20:80) gave enone ester **1** (385 mg, 76% yield from **8**).

(1S*,6S*,9R*)-2-Carbomethoxy-9-chloro-6-methylbicyclo[4.4.0]-dec-4-en-3-one (2) and (1S*,4S*,5S*,9S*)-2-carbomethoxy-4-chloro-9-methyltricyclo[4.3.1.$0^{5,9}$]decan-3-one (3)

To a suspension of zinc chloride (770 mg, 5.7 mmol),

flame-dried under an argon atmosphere, in ether (110 mL), was added dropwise a solution of enone ester **1** (500 mg, 2.3 mmol) in ether (20 mL) at 0 °C. The resulting mixture was stirred under an atmosphere of argon at room temperature for 3 h. Water was then added to quench the reaction and the organic layer was separated. The aqueous layer was extracted with ether (3 × 30 mL). The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (2:98) as an eluent to afford compounds **2** (376 mg, 65% yield) and **3** (144 mg, 25% yield). Compound **2** (a mixture of keto and enol forms in a ratio of 1:4): IR (CH_2Cl_2 cast) 3180 (OH, enol), 1653 (C=O, enol ester) and 1626 (C=C, enol) cm^{-1}; ^1H NMR (300 MHz) δ 11.85 (s, 0.8H, **OH**), 5.90-6.15 (m, 2H, **CH=CH**), 3.75, 3.70 (s, 3H, OCH_3), 3.60-3.80 (m, 1.2H, CHCl and COCHCOOMe), 2.40 (ddd, J = 12, 4, 1.5 Hz, 1H, ring junction proton), 2.00-2.20 (m, 2H), 1.70 (m, 1H), 1.30-1.65 (m, 3H), 1.10, 0.90 (s, 3H, CH_3); hrms M^+ 256.0868, 258.0844 (calcd. for $C_{13}H_{17}ClO_3$: 256.0866, 258.0837). Compound **3** (a mixture of keto and enol forms in a ratio of 1:1): IR (CH_2Cl_2 cast) 3210 (OH, enol), 1747 (C=O, ester), 1731 (C=O, ketone), 1657 (C=O, enol ester) and 1618 (C=C, enol) cm^{-1}; ^1H NMR (400 MHz) δ 11.62 (s, 0.5H, **OH**), 4.80 (d, J = 7.0 Hz, 1H, **CHCl**), 3.70-3.85 (m, 3.5H, OCH_3 and COCHCOOMe), 2.62 (m, 1H), 2.45 (m, 1H), 2.00-2.20 (m, 2H), 1.20-1.70 (m, 5H), 1.10, 1.05 (s, 3H, CH_3); hrms M^+ 256.0872, 258.0839 (calcd. for $C_{13}H_{17}ClO_3$: 256.0866, 258.0837).

The preparation of compounds **2** and **3** was also carried out using stannic chloride, titanium tetrachloride, ethylaluminum chloride and aluminum chloride as reagents *via* the general procedure illustrated below with stannic chloride. Yield, time and temperature of each reaction are shown in Table 1.

A solution of enone ester **1** (50 mg, 0.23 mmol) in 10 mL of dichloromethane (ether for aluminum chloride) was cooled to -78 °C under an argon atmosphere. Stannic chloride (0.04 mL, 88 mg, 0.34 mmol) was added and the mixture was stirred under the same conditions. After 5 min, the starting material was completely consumed. Water was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic solutions were washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (2:98) as an eluent to give compounds **2** (15 mg, 26% yield) and **3** (39 mg, 66% yield).

(1S*,6S*,9R*)-2-Carbomethoxy-9-iodo-6-methylbicyclo-[4.4.0]dec-4-en-3-one (9)

To a stirred suspension of anhydrous zinc iodide (804 mg, 2.5 mmol) in ether (40 mL) at room temperature under an atmosphere of argon, was added a solution of enone ester **1** (460 mg, 2.1 mmol) in ether (15 mL). The reaction mixture was protected from light and stirred for 3 days at room temperature, followed by quenching with 1 N hydrochloric acid. The aqueous solution was extracted with ether (3 × 50 mL). The combined extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give compound **9** (621 mg, 85% yield; a mixture of three isomers in a ratio of 1:1:4.7): IR (CH_2Cl_2 cast) 3200 (OH, enol), 1733 (C=O, ester), 1683 (C=O, ketone), 1652 (C=O, enol ester) and 1625 (C=C, enol) cm^{-1}; ^1H NMR (300 MHz) δ 11.85 (s, 0.7H, **OH**), 6.10-5.95 (m, 2H, **CH=CH**), 4.00 (dddd, J = 12, 12, 4, 4 Hz, 1H, **CHI**), 3.70-3.85 (m, 3.3H, OCH_3 and COCHCOOMe), 2.30-2.50 (m, 2H), 1.80-2.15 (m, 2H), 1.30-1.65 (m, 3H), 1.08, 1.02, 0.95 (s, 3H, CH_3); ^{13}C NMR (75 MHz) for the enol form, δ 172.4 (p), 165.0 (p), 147.9 (a), 123.2 (a), 97.9 (p), 51.6 (a), 42.0 (a), 41.9 (p), 40.7 (p), 37.7 (p), 36.2 (p), 26.7 (a), 25.9 (a); hrms M^+ 348.0222 (calcd. for $C_{13}H_{17}IO_3$: 348.0223).

(1R*,6R*,8R*)-4-Acetoxy-5-carbomethoxy-8-chloro-1-methybicyclo[4.4.0]deca-2,4-diene (10) and (1R*,4S*,5S*,9R*)-3-acetoxy-2-carbomethoxy-4-chloro-9-methyltricyclo[4.3.1.$0^{5,9}$]dec-2-ene (11)

A 2.6:1 mixture of chlorides **2** and **3** (100 mg, 0.39 mmol) was dissolved in pyridine (5 mL). Acetic anhydride (1 mL) was added. The reaction mixture was stirred at room temperature under an argon atmosphere overnight. The solvent was removed under reduced pressure. Water was added and the resulting mixture extracted with ether (3 × 20 mL). The extracts were washed with 1 N hydrochloric acid and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (5:95) as an eluent gave enol acetates **10** (76 mg, 65% yield) and **11** (29 mg, 25% yield). Compound **10**: IR (CH_2Cl_2 cast) 1766 (CH_3COO) and 1711 ($COOCH_3$) cm^{-1}; ^1H NMR (200 MHz) δ 5.97 (dd, J = 10, 2.0 Hz, 1H, **CH**=CHCO), 5.70 (d, J = 10 Hz, 1H, CH=**CH**CO), 3.80 (s, 3H, OCH_3), 3.67 (m, 1H, CHCl), 2.62 (ddd, J = 12.5, 4.5, 2 Hz, 1H, ring junction proton), 2.22 (dddd, J = 13, 4, 4, 2 Hz, 1H, $\mathbf{H}_{7e}$), 2.17 (s, 3H, $\mathbf{CH}_3$CO), 2.05 (dddd, J = 14, 3, 3, 1.5 Hz, 1H, $\mathbf{H}_{9e}$), 1.72 (ddd, J = 14, 3, 3 Hz, 1H, $\mathbf{H}_{10e}$), 1.50-1.65 (m, 2H, $\mathbf{H}_{7a}$ and $\mathbf{H}_{9a}$), 1.35 (ddd, J = 14, 14, 3, 1H, $\mathbf{H}_{10a}$), 1.04 (s, 3H, CH_3);

^{13}C NMR (75 MHz) δ 168.5 (p), 165.4 (p), 151.6 (p), 145.0 (a), 123.8 (a), 116.2 (p), 56.5 (a), 51.9 (a), 42.4 (a), 38.1 (p), 37.0 (p), 35.9 (p), 34.4 (p), 25.3 (a), 20.9 (a); hrms M$^+$ 298.0982, 300.0941 (calcd. for $C_{15}H_{19}ClO_4$: 298.0972, 300.0942). Anal. calcd. for $C_{15}H_{19}ClO_4$: C 60.30, H 6.41; found: C 60.24, H 6.46. Compound **11**: IR (CH_2Cl_2 cast) 1765 (CH_3COO) and 1719 ($COOCH_3$) cm^{-1}; ^{1}H NMR (300 MHz) δ 4.90 (d, J = 7 Hz, 1H, **H$_4$**), 3.75 (s, 3H, OCH_3), 2.65 (m, 1H, **H$_6$**), 2.55 (dd, J = 7.5, 2 Hz, 1H, **H$_1$**), 2.20 (s, 3H, CH_3CO), 2.08 (dd, J = 7, 1 Hz, 1H, **H$_5$**), 1.20-1.90 (m, 6H), 1.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz) δ 168.6 (p), 164.8 (p), 149.6 (p), 130.7 (a), 60.1 (a), 55.9 (a), 52.1 (a), 50.7 (p), 43.7 (a), 41.3 (a), 40.6 (p), 35.9 (p), 31.1 (p), 20.8 (a), 16.7 (a); hrms M$^+$ 298.0963 (calcd. for $C_{15}H_{19}O_4Cl$: 298.0972).

(1R*,6R*,8R*)-4-Acetoxy-5-carbomethoxy-8-iodo-1-methylbicyclo[4.4.0]deca-2,4-diene (12)

Using the same procedure as described above, acetylation of iodide **9** (100 mg, 0.29 mmol) with pyridine (5 mL) and acetic anhydride (1 mL) afforded acetate **12** (100 mg, 89% yield): IR (CH_2Cl_2 cast) 1765 (CH_3CO) and 1709 ($COOCH_3$) cm^{-1}; ^{1}H NMR (200 MHz) δ 6.00 (dd, J = 9.5, 1.5 Hz, 1H, C**H**=CHCO), 5.80 (d, J = 9.5 Hz, 1H, CH=C**H**CO), 4.00 (dddd, J = 12, 12, 4, 4 Hz, 1H, C**H**I), 3.75 (s, 3H, OCH_3), 2.60 (ddd, J = 12, 4, 1.5 Hz, 1H, ring junction proton), 2.50 (m, 1H, **H$_{7e}$**), 2.36 (m, 1H, **H$_{9e}$**), 2.20 (s, 3H, CH_3CO), 1.82-2.10 (m, 2H, **H$_{7a}$** + **H$_{10e}$**), 1.58 (m, 1H, **H$_{9a}$**), 1.43 (m, 1H, **H$_{10a}$**), 0.95 (s, 3H, CH_3); ^{13}C NMR (75 MHz) δ 168.5 (p), 165.4 (p), 151.6 (p), 145.0 (a), 123.8 (a), 116.2 (p), 56.5 (a), 51.9 (a), 42.4 (a), 38.1 (p), 37.0 (p), 35.9 (p), 34.4 (p), 25.3 (a), 20.9 (a); hrms M$^+$ 390.0325 (calcd. for $C_{15}H_{19}IO_4$: 390.0328). Anal. calcd. for $C_{15}H_{19}IO_4$: C 60.30, H 6.41; found: C 60.24, H 6.46.

4-(3-Butenyl)-4-methylcyclohexanone (14)

A solution of enone **7** (100 mg, 0.61 mmol) in benzene (15 mL) was added to the hexamer of (triphenylphosphine)copper hydride (600 mg, 0.31 mmol). The reaction mixture was stirred at room temperature under an argon atmosphere for 5 days and then exposed to the atmosphere and stirred for 20 min. The mixture was filtered through a short column of silica gel, using ether/hexane (50:50) as an eluent. The filtrate was concentrated. The residue was subjected to flash chromatography with ethyl acetate/hexane (2:98) to afford ketone **14** (38 mg, 68% yield based on the consumed starting material) along with the recovered starting material (45 mg). Compound **14**: IR (CH_2Cl_2 cast) 1716 (C=O) cm^{-1}; ^{1}H NMR (300 MHz) δ 5.83 (dddd, J = 17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH$_2$), 5.30 (dddd, J = 17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 4.95 (dddd, J = 10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 2.25-2.40 (m, 4H), 1.95-2.15 (m, 2H), 1.60-1.70 (m, 4H), 1.40-1.50 (m, 2H), 1.08 (s, 3H, CH_3); ^{13}C NMR (75 MHz) δ 212.5 (p), 139.1 (p), 114.4 (p), 39.8 (p), 37.6 (p, 2 × C), 37.3 (p, 2 × C), 32.3 (a), 28.3 (p), 23.9 (a); hrms M$^+$ 166.1358 (calcd. for $C_{11}H_{18}O$: 166.1358).

4-(3-Butenyl)-2-carbomethoxy-4-methylcyclohexanone (15)

To a stirred suspension of sodium hydride (38 mg, 95%, 1.5 mmol) in DME (3 mL) at room temperature under an argon atmosphere, were added dimethyl carbonate (0.4 mL) and a solution of enone **14** (100 mg, 0.6 mmol) in DME (2 mL). The mixture was refluxed for 3 h and cooled to 0 °C. A 1 N HCl solution (10 mL) was added cautiously to the mixture. The resulting solution was extracted with ether (3 × 50 mL). The combined extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to afford keto ester **15** (115 mg, 85% yield; a mixture of keto and enol forms in a ratio of 1:2): IR (neat) 3200 (OH, enol), 1745 (C=O, ester) and 1718 (C=O, ketone), 1659 (C=O, enol ester), 1641 (C=C) and 1617 (C=C, enol) cm^{-1}; ^{1}H NMR (300 MHz) δ 12.12 (s, 0.67 H, O**H**), 5.80 (m, 1H, C**H**=CH$_2$), 4.85-5.10 (m, 2H, CH=C**H$_2$**), 4.48-4.78 (m, 0.33 H, COC**H**COOCH$_3$), 3.75, 3.74, 3.72 (s, 3H, OCH_3), 2.25 (m, 1H), 1.90-2.15 (m, 4H), 1.65 (m, 1H), 1.20-1.50 (m, 4H), 0.95, 0.93, 0.90 (s, 3H, CH_3); hrms M$^+$ 224.1409 (calcd. for $C_{13}H_{20}O_3$: 224.1413).

4-(3-Butenyl)-2-carbomethoxy-4-methyl-2-cyclohexenone (13)

To a stirred solution of keto ester **15** (100 mg, 0.45 mmol) in THF (15 mL) at 0 °C under an argon atmosphere, were added sodium hydride (29 mg, 95% yield, 1.1 mmol) and a solution of diphenyl diselenide (167 mg, 0.54 mmol) in THF (5 mL). The reaction mixture was stirred at 0 °C for 1 h and then 1 N hydrochloric acid (5 mL) was added. The resulting mixture was extracted with ether (3 × 10 mL). The extracts were combined, washed with water and concentrated. The residue was dissolved in THF (5 mL), and a solution of $NaIO_4$ (286 mg, 1.3 mmol) in MeOH-H_2O (7:3, 12 mL) was added dropwise at room temperature. The resulting mixture was stirred overnight. Water was added and the resulting aqueous solution extracted with ether (3 × 50 mL). The extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give enone ester **13** (69 mg, 69% yield): IR (CH_2Cl_2

cast) 1745 (C=O, ester) and 1686 (C=O, ketone) cm^{-1}; ^1H NMR (400 MHz) δ 7.40 (s, 1H, C**H**=CCOOMe), 5.80 (dddd, *J* = 17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.05 (dddd, *J* = 17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=C**H**H), 4.99 (dddd, *J* = 10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.70 (s, 3H, OCH_3), 2.50-2.60 (m, 2H), 1.90-2.20 (m, 2H), 1.80 (m, 1H), 1.55-1.65 (m, 3H), 1.22 (s, 3H, CH_3).

(1S*,6S*,9R*)-2-Carbomethoxy-9-chloro-6-methylbicyclo[4.4.0]decan-3-one (16)

A solution of enone ester **13** (50 mg, 0.23 mmol) in dry dichloromethane (10 mL) was cooled to -78 °C under an argon atmosphere. Stannic chloride (0.03 mL, 0.27 mmol) was added, and the mixture was stirred at the same temperature for 10 min. Water (10 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give compound **16** (53 mg, 91% yield) existing completely in the enol form: IR (CH_2Cl_2 cast) 3600 (OH, enol), 1652 (C=O, enol ester) and 1614 (C=C, enol) cm^{-1}; ^1H NMR (300 MHz) δ 12.3 (s, 1H, O**H**), 3.80 (m, 1H, C**H**Cl), 3.75 (s, 3H, OCH_3), 2.50-2.60 (m, 3H), 1.90-2.20 (m, 2H), 1.65-1.85 (m, 2H), 1.35-1.65 (m, 3H), 1.05-1.35 (m, 1H), 0.90 (s, 3H, CH_3); ^{13}C NMR (75 MHz) δ 172.8 (p), 172.0 (p), 100.6 (p), 59.1 (a), 51.6 (a), 41.5 (p), 40.7 (a), 39.8 (p), 32.7 (p), 29.8 (p), 26.3 (p), 26.2 (a), 25.8 (p); hrms M^+ 258.1020, 260.0998 (calcd. for $C_{13}H_{19}ClO_3$: 258.1023, 260.0993).

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Polyene cyclization; Cross conjugated α-carbalkoxy enone system; Highly functionalized decalin derivatives.

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