Synthesis of a Cyclohexadiene Monoepoxide by Intramolecular Darzens Condensation. Efficient Synthesis of an A-Ring Anthracyclinone Precursor

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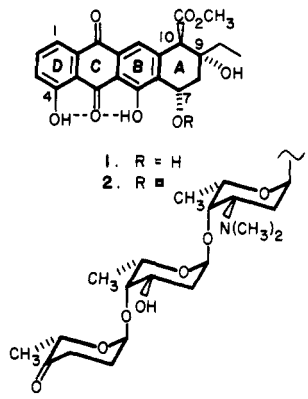
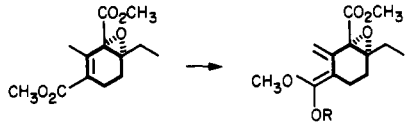
A convenient regiospecific synthesis of dimethyl 1,2-epoxy-2-ethyl-6-methylcyclohex-5-ene-1,5-dicarboxylate, a synthon for the A ring of aklavinone, is described. Michael addition–elimination of dimethyl ethylmalonate to methyl β-chlorocrotonate and its α-bromo and β-chloro derivatives was investigated, and the contrasting results are discussed. The key step in the preparation of the cyclohexadiene monoepoxide is a one-step Michael addition–elimination/intramolecular Darzens glycidic ester condensation between dimethyl (3-oxopentyl)malonate and methyl α,β-dichlorocrotonate leading to trimethyl 1,2-epoxy-2-ethyl-6-methylenecyclohexane-1,5,5-tricarboxylate. Solvent plays an important role in the course of this condensation. This epoxy triester is the exclusive product formed in polar aprotic solvents. Demethoxycarbonylation then completes the synthesis of the cyclohexadiene monoepoxide.

There is a great deal of interest in preparing aklavinone (1), the aglycon of the potent antitumor antibiotic aclacinomycin A (2) which is currently undergoing clinical tests. This interest has resulted in several total syntheses



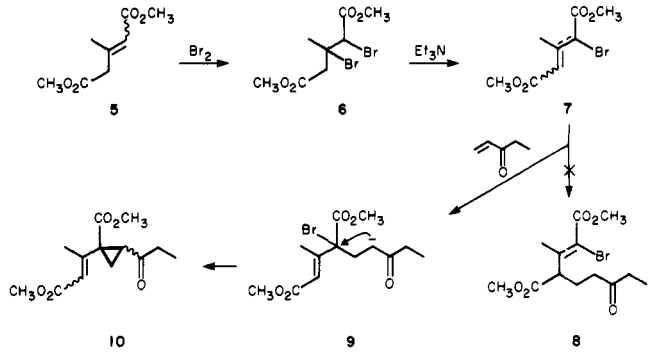
of 1 in recent years.[1-6] In our efforts to develop a short and highly convergent synthesis of 1, we have prepared the cyclohexadiene monoepoxide 3 which includes most of the functionality found in the A ring of aklavinone and is a suitable precursor to the vinyl ketene acetal 4. The highly



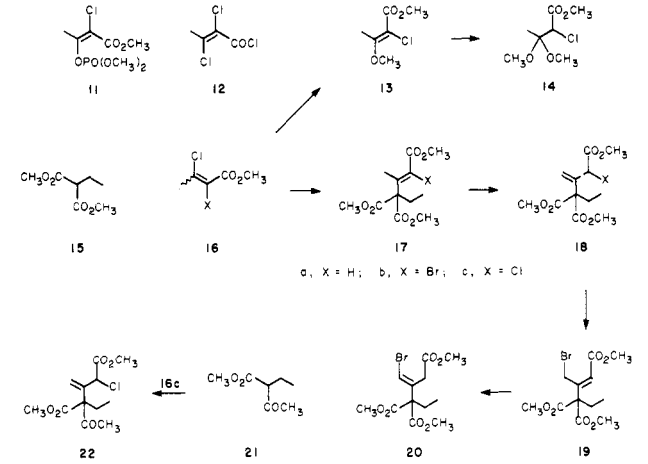
3 4

regioselective reaction of vinyl ketene acetals with juglone derivatives is a well documented route to 11-deoxyanthracyclinones[7,8] so that application of this quinone–vinyl ketene acetal reaction should lead to a convenient total synthesis of aklavinone. We now report a simple and convergent route to epoxide 3 which is based on an intramolecular Darzens condensation.

Scheme I. Michael Addition of Ethyl Vinyl Ketone to 2-Bromo-3-methylglutaconate (7)



Scheme II. Michael Addition to Halocrotonates 16



Results and Discussion

Dimethyl β-methylglutaconate (5)[9] was prepared in 85% yield as a mixture of cis and trans isomers by base-catalyzed methanolysis of methyl isodehydroacetate. Bromine addition to glutaconate 5 (Scheme I) afforded dibromo derivative 6 which could be dehydrobrominated by brief heating with triethylamine in ethyl ether to give 7 as a mixture of four isomers. No effort was made to separate these isomers since they would equilibrate during the next reaction. It was anticipated that the Michael addition of 7 to ethyl vinyl ketone would lead to the 2-bromo-3,4-dialkylglutaconate 8 which would then undergo an intra-

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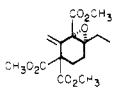
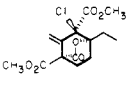
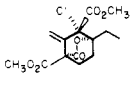
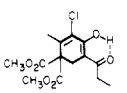
Table I. Product Distribution from Base-Catalyzed Reaction of Methyl 2,3-Dichlorocrotonate (16c) and Dimethyl (3-Oxopentyl)malonate (23)

	% yield of products			
				
conditn	**34**	**33**	**31**	**28**
NaH/DMF	65			
NaH/THF	15	40	20	
$NaOCH_3/CH_3OH/Et_2O$	35			40
KO-*t*-Bu/*t*-BuOH	60	10	trace	trace

molecular Darzens condensation to afford the epoxide **3**. However, this reaction took a different course, and the only product obtained was the cyclopropane **10** which was isolated as a mixture of stereoisomers. The initial Michael addition had occurred at the bromine-bearing carbon of **7** and the intermediate enolate ion **9** underwent an internal displacement of bromide ion and ring closed to cyclopropane **10**.

As an alternate route to an intramolecular Darzens condensation precursor such as **8**, we chose to study Michael addition–elimination reactions with β-chlorocrotonates as shown in Scheme II. Our first objective was to determine the most efficacious crotonate and nucleophile. Dimethyl ethylmalonate (**15**) was chosen as the nucleophile for the initial studies. The addition of **15** to methyl β-chlorocrotonate (**16a**) was accomplished with NaH in DMF and gave a 1/4 mixture of the isomeric adducts, **17a** and **18a**, in 60% combined yield. Equilibration of this mixture with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to a 20/1 mixture favoring the conjugated isomer **17a**, but attempts to introduce into **17a** the halogen necessary for a Darzens condensation were completely unsuccessful.

The halogen, however, could be introduced before the Michael reaction by bromination of **16a** followed by dehydrobromination with TEA. This afforded methyl 2-bromo-3-chlorocrotonate (**16b**) in 77% yield as a 3/2 mixture of *Z* and *E* isomers. Michael addition of malonate **15** to **16b** did not lead to the expected product **17b** or to **18b**, but instead gave the rearranged bromide **20** as the only adduct, obtained in 58% yield. This can be explained by an allyl bromide rearrangement of **18b** to **19** followed by a proton shift to give the vinyl bromide **20**. The structure of compound **20** is supported by NMR. The ^1H spectrum shows a singlet at δ 3.37 (2 H) and another singlet at δ 6.70 (1 H) while the ^{13}C spectrum shows a doublet and a singlet in the vinyl region, indicating that the double bond is trisubstituted.

Allyl bromides are known to undergo rearrangement of this type but allyl chlorides do not,[10] so methyl 2,3-dichlorocrotonate (**16c**) was prepared. This was first accomplished by treating **16a** with chlorine gas followed by dehydrochlorination with TEA which afforded **16c** in 66% yield, or 26% overall from methyl acetoacetate. A more convenient route to **16c** is to treat methyl α-chloroacetoacetate with excess phosphorus pentachloride followed by a methanol isolation. This sequence affords **16c** in 65% distilled yield (60% from methyl acetoacetate) as an 8/1 mixture of cis and trans isomers along with the higher boiling enol phosphate **11** in about 5% yield. Without the methanol quench, the distilled crotonate **16c** was always contaminated with 10–20% of the corresponding acyl chloride **12** which survived an aqueous isolation.

In contrast to the reaction with the bromochlorocrotonate **16b**, addition of malonate **15** to dichlorocrotonate **16c** gave the stable allylic chloride **18c** as the only adduct. In its ^1H NMR spectrum, **18c** shows three downfield signals for protons in the allyl moiety, and ^{13}C NMR shows a singlet and a triplet for the two vinyl carbons. This confirms the presence of a geminally disubstituted double bond. Since triester **18c** has a halogen α to the ester, it is suitable for a Darzens glycidic ester condensation.

Michael additions to dichlorocrotonate **16c** are difficult to drive to completion because **16c** and adduct **18c** decompose slowly in strong base. Decomposition of **16c** can be minimized by using a hindered protic solvent such as *tert*-butyl alcohol. Small nucleophiles such as methoxide add rapidly to **16c** to give the vinyl ether **13** if less than 100 mol % of base is used, but a slight excess of base leads to the ketal **14**. Other nucleophiles can also be added. For example, addition of the β-keto ester **21** to **16c** is best accomplished with potassium carbonate in DMF and leads to **22** as a mixture of diastereomers in 36% yield. This addition is much slower than addition of the malonate **15** to **16c** so decomposition of **16c** and **22** is a more serious complication. With stronger bases, only decomposition is observed.

Based on these preliminary experiments, the addition of dimethyl (3-oxopentyl)malonate (**23**) to methyl 2,3-dichlorocrotonate (**16c**) was chosen as the best route to the precursor for an intramolecular Darzens condensation. With two highly functionalized reactants such as **16c** and **23**, many base-catalyzed reactions are possible. Scheme III outlines the major reactions that were observed under a variety of reaction conditions. The number and types of products obtained depended on the solvent, base, and addition order of the reactants as shown in Table I. For small scale work it was possible to adapt the NaH procedure used in the model studies by increasing the amount of NaH. In DMF, the epoxide **34** was obtained in 60% yield as the only adduct and chromatography followed by careful crystallization from cold ethyl ether afforded pure epoxide **34**. By ^1H NMR, **34** shows a triplet at δ 0.94 for the alkyl methyl group, three 2 H multiplets between δ 1.7 and 2.3 for the three methylene groups, three methyl ester singlets (δ 3.74, 3.75, and 3.78), and two vinyl doublets at δ 5.31 and 5.45. In addition, ^{13}C NMR shows two vinyl carbons as a singlet and a doublet indicating a geminally disubstituted carbon–carbon double bond. Cleavage of the epoxide ring of **34** with wet TFA leads to the γ-lactone **35**, and further proof of the structure **34** was obtained by subsequent reactions.

The Michael–Darzens reaction could not be driven to completion with NaH in DMF and some unreacted **23** always remained. Use of excess dichlorocrotonate **16c** and excess NaH led mostly to decomposition of **16c** and formation of an insoluble black tar. This decomposition was less of a problem when the reaction was carried out in THF, but two lactones, **31** and **33**, were formed in addition to epoxide **34** and again the reaction did not go to completion.

The lactones **31** and **33** are similar to epoxide **34** by ^1H NMR but show only two methyl esters and small differ-

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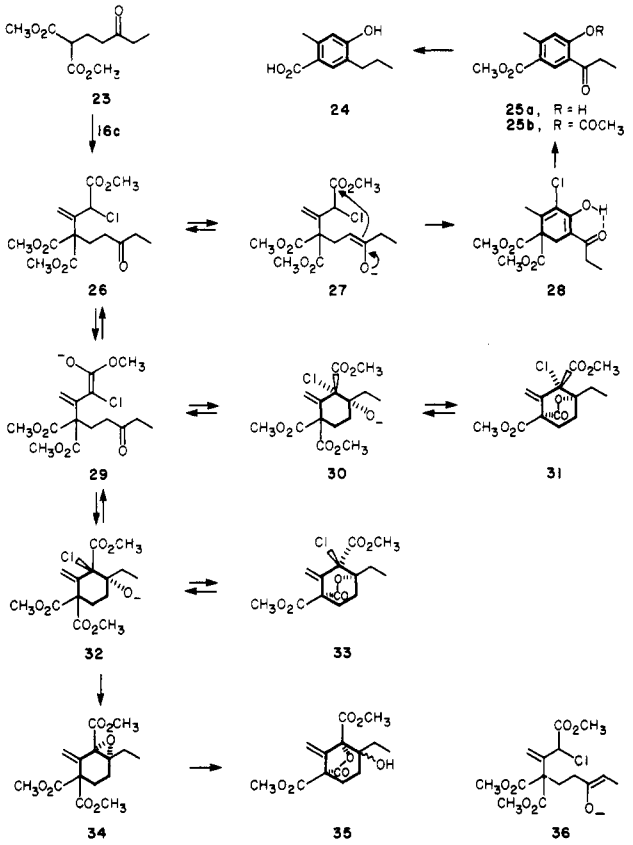
Scheme III. Base-Catalyzed Reaction of Methyl 2,3-Dichlorocrotonate (16c) and Dimethyl (3-Oxopentyl)malonate (23)



ences in the other signals. These lactones can be separated by chromatography and the relative stereochemistry of each was determined by treating them with sodium methoxide. Methoxide opens the lactone ring and leads to an equilibrium among the intermediates **26**, **27**, **29**, **30**, and **32**, and a mixture of enol–ketone **28** and epoxide **34** is produced. Since lactone **31** has a cis relationship between the halogen and the lactone bridge, it must undergo a ring-opening step before it can be converted to the epoxide **34**. On the other hand, lactone **33** can be converted to **34** via alkoxide **32** without ring opening, so it leads to less of the Dieckmann product **28**. In parallel reactions, **31** led to a 3/2 ratio of epoxide **34** and enol–ketone **28**, while **33** led to a 4/1 ratio of these products. The enol–ketone **28** was also obtained as the major adduct when **16c** and **23** were condensed with sodium methoxide in ether–methanol. However, methoxide addition to **16c** was a significant side reaction.

The structure of **28** was assigned on the basis of its ^1H NMR spectrum but since most of the signals appear as singlets this provides no information about the relationships among the functional groups. Further evidence for this structure was obtained by demethoxycarbonylation of **28** by heating with LiCl in Me_2SO.[11] This led to phenolic ketone **25a** which shows a chelated aromatic ketone (1640 cm^{-1}) by IR while the acetate **25b** has a free aromatic ketone (1690 cm^{-1}). Catalytic hydrogenation–hydrogenolysis of **25a** followed by ester hydrolysis afforded the *p*-hydroxybenzoic acid **24**, whose structure was confirmed by UV spectroscopy.

The desired epoxide **34** can be obtained most efficiently by condensing dichlorocrotonate **16c** and keto malonate **23** with potassium *tert*-butoxide in *tert*-butyl alcohol.

(11) Krapcho, A. P. *Synthesis* **1982**, 805.

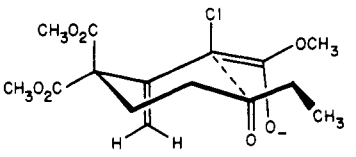


Figure 1. Transition state for **29** in polar solvents leading to epoxide **34** via the chair conformation.

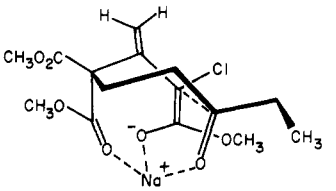


Figure 2. Transition state for **29** in nonpolar solvents leading to lactone **33** via the boat conformation.

Under these conditions the desired Michael addition–Darzens condensation can be driven to completion with only a slight excess of the crotonate and the results are reproducible on increasing the scale. Thus 50-g quantities of epoxide **34** can be obtained after kugelrohr distillation in 70% yield. This material contains trace quantities of the lactones **31** and **33** and is suitable for the next reaction.

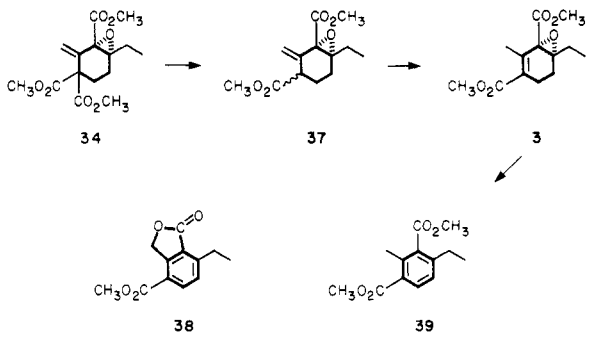
As we have seen, the solvent plays a very important role in determining the fate of the initial Michael adduct **26** in this reaction. Methanol, a good hydrogen bonding solvent, stabilizes the ketone enolate **27** relative to the more delocalized ester dienolate **29** and leads to **28** as the major product. The less hindered ketone enolate **36** must also be stabilized by a protic solvent but no products derived from this enolate have been observed, most likely because the malonate esters, six carbon atoms away, are sterically too crowded.

In aprotic solvents the more delocalized ester dienolate **29** is more stable than the ketone enolates **27** or **36**. Polar aprotic solvents such as DMF or Me_2SO strongly solvate the counter ion so steric factors determine the conformation of **29** and the transitions states leading to **30** or **32**. Molecular models indicate that steric hindrance is minimized when **29** exists in the *Z* s-cis conformation, and the lowest energy transition state for the aldol condensation leads to **32** as shown in Figure 1. The alkoxide **32** is formed in a chair conformation with the halogen and alkoxide in antiperiplanar trans axial positions as needed for epoxide formation. Thus the epoxide **34** is the only product observed.

In THF or ethyl ether, the dienolate **29** exists as a tight ion pair with the sodium ion so chelation of the sodium ion by the ketone and ester carbonyls can overcome steric hindrance in the *Z* s-trans dienolate. This also controls the conformation of the transition state in the aldol condensation as shown in Figure 2 and leads to **32** in a boat conformation. Since the alkoxide and halogen are not antiperiplanar, lactone formation is preferred over halogen displacement, and **33** is the major product. Chelation is less effective at stabilizing the transition states leading to **31** and **34**, thus smaller amounts of these products are observed.

The epoxy triester **34** is best converted to epoxy diester **3** by heating in strong sodium methoxide (Scheme IV). Under the vigorous conditions required to drive the reaction to completion some of the product is dehydrated to the isophthalate **39**. Column chromatography affords pure **3** in 35–45% yield, depending on the scale. The ^1H NMR spectrum of **3** shows a new allylic methyl signal at δ 2.07 and only two methyl ester signals (δ 3.70 and 3.78). The LiCl/Me_2SO procedure[10] proved to be less effective

Scheme IV. Conversion of Epoxy Triester 34 to Cyclohexadiene Monoepoxide 3



for converting **34** to **3**. This procedure required careful prior purification of **34** and led to a mixture of **3** and **37** in 45% yield; however, these could not be separated from lactone **38** which was always a minor side product.

Conclusion

The 2,3-dihalocrotonates **16b** and **16c** are useful, highly functionalized intermediates which can be prepared easily from methyl acetoacetate. Although **16b** and **16c** are similar in structure, they lead to very different Michael adducts when treated with hindered nucleophiles such as substituted malonates. The Michael–Darzens condensation of dimethyl (3-oxopentyl)malonate (**23**) with **16c**, which combined two multifunctional intermediates, can lead to a variety of products depending on the conditions used for the condensation. Despite the complexity of this reaction it can be controlled to provide a convenient, economical, and convergent route to the epoxide **3** which is a useful synthon for ring A of aklavinone. A total synthesis of aklavinone based on **3** following established vinyl ketene acetal methodology will be reported in a subsequent communication.

Experimental Section

General Methods. Unless otherwise specified all reactions were magnetically stirred and carried out at room temperature under a nitrogen atmosphere. After quenching and solvent extraction, all solutions were dried over $MgSO_4$, filtered, and evaporated under reduced pressure on a Berkeley rotary evaporator. Anhydrous ethyl ether was used as obtained (Mallinckrodt), methanol was distilled from magnesium methoxide, tetrahydrofuran was distilled from sodium benzophenone, dimethyl formamide was decanted from molecular sieves, and dichloromethane and chloroform were distilled from P_2O_5. All ^1H NMR spectra were obtained as $CDCl_3$ solutions with 1% Me_4Si as internal standard and, unless specified, were obtained on a Varian EM-390 90 MHz spectrometer; others were taken with the Berkeley UCB-200 or UCB-250 instruments. All ^{13}C NMR spectra were taken as $CDCl_3$ solutions at 25.14 MHz on a Nicolet TT-23 spectrometer. Infrared spectra were obtained with a Perkin-Elmer 137 spectrophotometer. UV spectra were obtained on a Varian Cary 219 or Perkin-Elmer 552A spectrophotometer. Melting points are uncorrected.

Methyl 2-Bromo-3-chlorocrotonate (16b). By syringe, 3.0 mL of bromine (56 mmol) was added to a solution of 5.00 g of methyl β-chlorocrotonate[12] (**16a**, 37.2 mmol) in 20 mL of chloroform. The deep red solution was heated to reflux overnight, then cooled to room temperature, and poured into 300 mL of dichloromethane. The organic solution was washed sequentially with 10% aqueous $Na_2S_2O_3$ (2 × 50 mL), water (50 mL), and brine (200 mL) and then dried. Evaporation of the solvent left 11.0 g (100%) of methyl 3-chloro-2,3-dibromobutyrate as a mixture of stereoisomers: ^1H NMR δ 2.56 (s, 3 H), 3.80 (s, 3 H), 4.89, 4.95 (2 s, 1 H).

The crude trihalobutyrate was dissolved in 100 mL of anhydrous ether and 13 g of triethylamine (130 mmol) was added. A precipitate formed immediately and the mixture was stirred overnight. The mixture was then filtered, the precipitate was washed with 100 mL of ether, and the filtrate was washed sequentially with 1 N HCl (100 mL), water (200 mL), and brine (150 mL) and then dried. After evaporation of the ether and kugelrohr distillation, 6.1 g (71%) of **16b** were obtained as a mixture of stereoisomers: bp 105–115 °C (20 mmHg); ^1H NMR δ 2.36, 2.53 (2 s, 3 H), 3.81, 3.83 (2 s, 3 H); IR (neat) 3000, 1730, 1600 cm^{-1}. Anal. Calcd for $C_5H_6O_2BrCl$: C, 28.1; H, 2.8; Br, 37.4; Cl, 16.6. Found: C, 28.6; H, 2.9; Br, 35.9; Cl, 16.9.

Methyl 2,3-Dichlorocrotonate (16c). Methyl α-chloroacetoacetate (304 g, 2.02 mol) was added over 30 min to an ice cooled suspension of PCl_5 (610 g, 2.95 mol) in 1.2 L of chloroform. This mixture was mechanically stirred at 0 °C for 8 h and then the chloroform solution was carefully decanted into a separatory funnel containing 1 kg of ice. The two phases were shaken vigorously and additional ice was added as needed to moderate the exothermic reaction. After the phases were separated, the chloroform solution was washed with cold water (2 × 300 mL) then shaken vigorously with saturated sodium bicarbonate until the final wash was neutral (4 × 300 mL). Finally the organic layer was washed with brine (2 × 200 mL), dried, and filtered. Methanol (600 mL) was added to the chloroform solution, and this was stirred overnight and then evaporated. Distillation afforded **16c** as a 10/1 mixture of *Z* and *E* isomers, contaminated with a small amount of methyl α,α-dichloroacetoacetate, suitable for further reactions: 280 g, 73% yield; bp 76–80 °C (25 mmHg); ^1H NMR δ 2.35 and 2.51 (2 s, 3 H), 3.81 (s, 3 H); IR (neat) 3000, 1740, 1610 cm^{-1}; GC/MS, *m/e* (assignment, relative intensity) 170 (M + 2, 35), 168 (M^+, 56), 137 (M − OCH_3, 76), 133 (M − Cl, 100).

Continued distillation of the pot residue afforded 24 g (5%) of the enolphosphate **11**, a portion of which was further purified by column chromatography and kugelrohr distillation: bp 110–113 °C (0.1 mmHg); ^1H NMR (250 MHz) δ 2.35 (d, 3 H, J = 2 Hz), 3.82 (s, 3 H), 3.89 (d, 6 H, J = 12 Hz); IR (neat) 3000, 1730, 1630 cm^{-1}; MS, *m/e* (assignment, relative intensity) 260 (M + 2, 8), 258 (M^+, 23), 223 (M − Cl, 54), 127 ($P(OH)_2(OCH_3)_2^+$, 100). Anal. Calcd for $C_7H_{12}O_6ClP$: C, 32.5; H, 4.7. Found: C, 32.4; H, 4.7.

In a similar reaction the product was distilled prior to the addition of methanol. This afforded a small forerun which contained the acyl chloride **12** as a 6/1, *Z*/*E* mixture of isomers: bp 104–105 °C; ^1H NMR δ 2.40 and 2.53 (2 s, 3 H); IR (neat) 1760, 1570 cm^{-1}; GC/MS, *m/e* (assignment, relative intensity) 176 (M + 4, 5), 174 (M + 2, 15), 172 (M^+, 15), 137 (M − Cl, 100).

1-Chloro-3-pentanone was prepared by a modification of the literature procedure.[13] Dichloromethane was used in place of nitrobenzene, then after the aqueous quench a pinch of hydroquinone was added, and the dichloromethane was evaporated. The residue was then distilled at atmospheric pressure into a flask containing a pinch of hydroquinone. This afforded a 20/1 mixture of 1-chloro-3-pentanone and ethyl vinyl ketone in 73% yield, which was used without further purification: bp 120–125 °C (lit.[13] bp 32.3–33.3 °C (2.5 mmHg)). **1-Chloro-3-pentanone**: ^1H NMR δ 1.03 (t, 3 H), 2.47 (q, 2 H), 2.89 (t, 2 H), 3.73 (t, 2 H). **Ethyl vinyl ketone**: ^1H NMR δ 1.09 (t, 3 H), 2.61 (q, 2 H), 5.78 (dd, 1 H, J = 3, 9 Hz), 6.26 (d, 1 H, J = 3 Hz), 6.30 (d, 1 H, J = 9 Hz).

Dimethyl (3-Oxopentyl)malonate (23). A solution of dimethyl malonate (279 g, 2.11 mol) dissolved in 200 mL of anhydrous ether was added over 15 min to an ice cooled solution of sodium methoxide prepared by dissolving 30.4 g (1.36 mol) of sodium metal in 600 mL of anhydrous methanol. The solution was mechanically stirred for 15 min, then a solution of 1-chloro-3-pentanone (122 g, 1.02 mol) in 600 mL of ether was added over 2 h, and after another 2 h the reaction mixture was acidified with 6 M HCl and divided into two portions. Each portion was diluted with 200 mL of ether and poured into 200 mL of brine and 400 mL of water. Each aqueous phase was washed with 200 mL of ether and the combined ether extracts were washed sequentially with 400 mL of water, 400 mL of bicarbonate, and 400 mL of brine and dried. Evaporation of the solvent and distillation

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of the residue afforded 98 g of recovered dimethyl malonate and 160 g (74%) of **23**: bp 108–110 °C (0.5 mmHg); ^{1}H NMR δ 1.00 (t, 3 H), 1.9–2.5 (m, 6 H), 3.35 (t, 1 H), 3.65 (s, 6 H); IR (neat) 3000, 1740, 1720 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.5; H, 7.5. Found: C, 55.4; H, 7.3.

Michael Addition–Elimination Reactions with β-Chlorocrotonates. Typical Procedure. A solution of dimethyl ethylmalonate (**15**, 3.1 mmol) dissolved in 2.0 mL of DMF was added over 2 min to an ice cooled suspension of NaH (2.5 mmol) in 5 mL of DMF. After hydrogen evolution subsided, a solution of the crotonate (**16**, 3.0 mmol) in 2.0 mL of DMF was added over 5 min and the mixture was stirred for 2 h at 0 °C and then poured into 50 mL of ether and 20 mL of 1 M HCl. The ether phase was washed sequentially with bicarbonate (2 × 10 mL), water (10 mL), and brine (50 mL) and dried. Evaporation of the solvent and kugelrohr distillation afforded the addition product.

17a and **18a**: 60% yield; by ^{1}H NMR the crude product was a 1/4 mixture of **17a**/**18a**; separated by column chromatography. **17a**: ^{1}H NMR δ 0.92 (t, 3 H), 2.09 (q, 2 H), 2.16 (m, 3 H), 3.68 (s, 3 H), 3.74 (s, 6 H), 5.90 (m, 1 H); IR (neat, mixture) 3000, 1730, 1645 cm^{-1}. **18a**: ^{1}H NMR δ 0.89 (t, 3 H), 2.06 (q, 2 H), 3.13 (s, 2 H), 3.58 (s, 3 H), 3.64 (s, 6 H), 5.25 (s, 2 H).

20: 43% yield; bp 130–145 °C (0.5 mmHg); ^{1}H NMR δ 0.90 (t, 3 H), 2.15 (q, 2 H), 3.37 (s, 2 H), 3.67 (s, 3 H), 3.70 (s, 6 H), 6.70 (s, 1 H); ^{13}C NMR δ 9.0 (q), 26.6 (t), 38.0 (t), 51.6 (q), 52.4 (q, 2 C), 64.5 (s), 113.8 (d), 133.5 (s), 169.1 (s, 3 C). Anal. Calcd for $C_{12}H_{17}O_6Br$: C, 42.6; H, 5.1; Br, 23.7. Found: C, 42.9; H, 5.1; Br, 23.6.

18c: 34% yield; bp 110–135 °C (1.0 mmHg); ^{1}H NMR δ 0.89 (t, 3 H), 2.16 (q, 2 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 3.78 (s, 3 H), 4.96 (s, 1 H), 5.69 (s, 1 H), 6.02 (s, 1 H); ^{13}C NMR δ 8.7 (q), 26.5 (t), 52.1 (q), 52.3 (q), 52.6 (q), 54.9 (d), 63.3 (s), 123.2 (t), 139.6 (s), 168.1 (s), 169.4 (s, 2 C); IR (neat) 3000, 1730, 1660 cm^{-1}.

Michael–Darzens Condensation of Methyl 2,3-Dichlorocrotonate (16c) and Dimethyl (3-Oxopentyl)malonate (23). General Procedure with NaH. A solution of **23** (1.00 g, 4.6 mmol) in 2 mL of THF was added over 2 min to a suspension of NaH (0.33 g, 13.8 mmol) in 5 mL of THF. After the vigorous hydrogen evolution subsided, the mixture was cooled to 0 °C and a solution of **16c** (1.56 g, 9.2 mmol) dissolved in THF (5 mL) was added over 15 min. The resulting dark mixture was stirred at 0 °C for 3 h then poured into 100 mL of dilute bicarbonate and 100 mL of ether. The ether extract was washed sequentially with bicarbonate (3 × 50 mL) and brine (100 mL) and dried. After the solvent was evaporated the residue was heated to 110 °C (0.2 mmHg) for 15 min to remove most of the unreacted **16c** and **23** and the remaining oil, a mixture of **31**, **33**, and **34**, was chromatographed over silica gel, eluting with 7/3, isooctane/ethyl acetate. Lactone **33** was eluted first and was further purified by recrystallization from methanol: 240 mg, 16% yield; mp 111.5–113 °C; ^{1}H NMR δ 1.00 (t, 3 H), 1.7–2.6 (m, 6 H), 3.78 (s, 3 H), 3.89 (s, 3 H), 5.40 (d, 1 H, J = 2 Hz), 5.71 (d, 1 H, J = 2 Hz); IR (CCl_4) 3000, 1775, 1750 cm^{-1}. Anal. Calcd for $C_{14}H_{17}O_6Cl$: C, 53.1; H, 5.4. Found: C, 53.2; H, 5.4.

The second compound eluted was lactone **31** and it was further purified by recrystallization from methanol: 120 mg, 8% yield; mp 115–116 °C; ^{1}H NMR δ 0.97 (t, 3 H), 1.4–1.8 (m, 2 H), 2.1–2.5 (m, 4 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 5.4–5.5 (m, 2 H); IR (CCl_4) 3010, 1780, 1750 cm^{-1}; HRMS, m/e calcd for $C_{14}H_{17}O_6Cl$ 316.0714, found 316.0708.

The third compound eluted was epoxide **34** (200 mg, 14% yield), which was kugelrohr distilled to obtain an analytical sample of **34** as a thick oil and crystallized by dissolving in a small amount of hot anhydrous ether and cooling in an ice bath: bp 145–150 °C (0.3 mmHg); mp 59–61 °C; ^{1}H NMR (200 MHz) δ 0.94 (t, 3 H, J = 7.5 Hz), 1.3–1.6 (m, 2 H), 1.6–1.8 (m, 2 H), 1.9–2.2 (m, 2 H), 3.74 (s, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 5.31 (d, 1 H, J = 1.2 Hz), 5.45 (d, 1 H, J = 1.2 Hz); ^{13}C NMR δ 8.51 (q), 23.3 (t), 25.5 (t), 27.0 (t), 52.0 (q), 52.4 (q, 2C), 58.7 (s), 65.1 (s), 65.6 (s), 121.1 (t), 137.5 (s), 168.3 (s), 169.7 (s), 169.9 (s); IR (neat) 2950, 1770 cm^{-1}; UV (methanol) λ_{max} 240 nm (ϵ 730). Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.7; H, 6.4. Found: C, 57.6; H, 6.4.

Enol–Ketone 28. A solution of sodium methoxide, prepared by dissolving 2.58 g (112 mmol) of sodium metal in 60 mL of anhydrous methanol, was added over 80 min with stirring to an ice cooled solution of **16c** (9.36 g, 55.4 mmol) and **23** (6.00 g, 27.8 mmol) in 120 mL of anhydrous ether. After the addition, the mixture was stirred an additional 2 h at 0 °C then poured into 200 mL of water, acidified with 1 M HCl, and extracted with 200 mL of ether. The ether phase was then washed sequentially with water (50 mL), bicarbonate (2 × 50 mL), and brine (100 mL) and dried. Evaporation of the ether left 12.0 g of light yellow oil which was kugelrohr distilled to give a mixture of the enol ether **13** and ketal **14** by NMR. Enol ether **13** crystallized from the mixture upon cooling in a dry ice/acetone bath and was recrystallized from ether–hexane: mp 43–46 °C; ^{1}H NMR δ 2.50 (s, 3 H), 3.77 (s, 3 H), 3.85 (s, 3 H). Ketal **14** was isolated by column chromatography: ^{1}H NMR δ 1.49 (s, 3 H), 3.22 (s, 3 H), 3.25 (s, 3 H), 3.75 (s, 3 H), 4.44 (s, 1 H).

The fraction boiling at 140–180 °C (0.5 mmHg) was collected and found to be a 8/7 mixture of **28**/**34**. Upon standing, coarse yellow-green crystals of **28** were deposited. These were separated from the oil to obtain 3.4 g, 40% yield of **28**: mp 83–85 °C from methanol; ^{1}H NMR δ 1.15 (t, 3 H), 2.15 (s, 3 H), 2.42 (q, 2 H), 3.12 (s, 2 H), 3.78 (s, 6 H), 15.6 (s, 1 H); IR ($CHCl_3$) 3000, 1730, 1590 cm^{-1}; UV (methanol) λ_{max} nm (ϵ) 230 (5500), 256 (7700), 337 (8000). Anal. Calcd for $C_{14}H_{17}O_6Cl$: C, 53.1; H, 5.4. Found: C, 53.1; H, 5.4.

Trimethyl 1,2-Epoxy-2-ethyl-6-methylenecyclohexane-1,5,5-tricarboxylate (34). Large Scale Synthesis. A solution of potassium *tert*-butoxide, prepared by refluxing potassium metal (27.6 g, 0.71 mol) in 700 mL of *tert*-butyl alcohol for 48 h, was added over 2 h to a solution of **16c** (61.3 g, 0.28 mol) and **23** (64.7 g, 0.38 mol) in 500 mL of *tert*-butyl alcohol with vigorous mechanical stirring. The dark mixture was stirred for an additional 1 h then divided into two portions. Each portion was poured into 1 L of ether with 300 mL of water and acidified with 20 mL of 6 M HCl. The aqueous phases were discarded and the organic phases were combined, washed sequentially with water (300 mL), bicarbonate (3 × 200 mL), water (200 mL), and brine (200 mL), and dried. Evaporation of the solvent and kugelrohr distillation of the residue afforded 64.4 g, 73% yield, of light yellow oil, bp 120–170 °C (0.5 mmHg), which was about 90% **34** and 10% **33** by NMR. This was suitable for subsequent reactions.

Methyl 4-Hydroxy-2-methyl-5-propionylbenzoate (25a). The enol–ketone **28** (290 mg, 0.92 mmol), LiCl (90 mg, 2.1 mmol), and water (80 mg, 4.4 mmol) were dissolved in Me_2SO (2 mL) and placed in a 150 °C oil bath. After 30 min the mixture was cooled to room temperature, poured into 50 mL of water, and extracted into ether (2 × 30 mL). The ether extracts were washed sequentially with water (30 mL), bicarbonate (2 × 10 mL), and brine (30 mL), dried, and evaporated to leave 0.19 g, 93% yield, of **25a**: mp 84–86 °C from methanol; ^{1}H NMR δ 1.21 (t, 3 H), 2.60 (s, 3 H), 3.04 (q, 2 H), 3.88 (s, 3 H), 6.79 (s, 1 H), 8.43 (s, 1 H), 12.85 (s, 1 H); IR ($CHCl_3$) 3000, 1720, 1640 cm^{-1}; UV (methanol) λ_{max} nm (ϵ) 235 (40000), 258 (14000), 318 (3600). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.8; H, 6.4. Found: C, 64.7; H, 6.4.

Acetate **25b**: mp 63–65 °C; ^{1}H NMR δ 1.14 (t, 3 H), 2.32 (s, 3 H), 2.61 (s, 3 H), 2.91 (q, 2 H), 3.89 (s, 3 H), 6.97 (s, 1 H), 8.38 (s, 1 H); IR ($CHCl_3$) 3000, 1760, 1720, 1690 cm^{-1}.

4-Hydroxy-2-methyl-5-propylbenzoic Acid (24). The keto phenol **25a** (100 mg, 0.45 mmol) was hydrogenated at 55 psi for 18 h with 30 mg of 10% Pt/C in 5 mL of acetic acid and resulted in 80 mg, 80% yield, of methyl 4-hydroxy-2-methyl-5-propylbenzoate: mp 133–134 °C from benzene; ^{1}H NMR δ 0.95 (t, 3 H), 1.63 (sextet, 2 H), 2.52 (s, 3 H), 2.59 (t, 2 H), 3.89 (s, 3 H), 6.02 (s, 1 H), 6.68 (s, 1 H), 7.82 (s, 1 H); IR ($CHCl_3$) 3700, 3000, 1710 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7. Found: C, 69.0; H, 7.7.

Methyl 4-hydroxy-2-methyl-5-propylbenzoate (40 mg, 0.2 mmol) was stirred overnight with 0.2 g of KOH in 5 mL of water, then poured into 10 mL of 1 M HCl, and extracted with 20 mL of ether. The ether was washed with 20 mL of brine, dried, and then evaporated to a residue of 20 mg, 54% yield, of acid **24**: mp 118–119 °C from 4/1, water/methanol; ^{1}H NMR δ 0.95 (t, 3 H), 1.36 (sextet, 2 H), 2.55 (s, 3 H), 2.56 (t, 2 H), 6.60 (s, 1 H), 7.88 (s, 1 H); IR ($CHCl_3$) 3650, 3000, 1680 cm^{-1}; UV λ_{max} (methanol) 265, (KOH, methanol) 273 nm. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3. Found: C, 67.9; H, 7.1.

Hydroxy Lactone 35. The epoxide **34** (100 mg) was dissolved in 0.5 mL of TFA and stirred for 30 min at room temperature. The TFA was evaporated to leave an oil which crystallized slowly

upon standing and was recrystallized from methanol to afford the γ-lactone **35**: mp 120–123 °C; ^{1}H NMR δ 0.98 (t, 3 H), 1.4–2.5 (m, 6 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 4.27 (bs, 1 H), 5.27 (s, 1 H), 5.30 (s, 1 H); IR (CCl_4) 3550, 3000, 1775, 1745, 1725 cm^{-1}.

Dimethyl 1,2-Epoxy-2-ethyl-6-methylcyclohex-5-ene-1,5-dicarboxylate (3). The epoxy triester **34** (52.3 g, 0.168 mol) was dissolved in a solution of sodium methoxide prepared by dissolving 11.81 g (0.52 mol) of sodium metal in 500 mL of anhydrous methanol. The solution was then heated to reflux, after 40 h the reaction mixture was cooled and poured into 1 L of ether and 500 mL of brine, and the phases were separated. The organic phase was first washed with two 300-mL portions of 5% aqueous NaOH to remove traces of methyl 4-hydroxy-2-methylbenzoate and **25a**, both derived from lactone **33** via **28**. Then the organic phase was washed sequentially with 300 mL of water and 500 mL of brine and dried. Evaporation of the ether left 25.1 g of crude **3** which contained about 15% of **39** and several minor components by ^{1}H NMR. These were separated by chromatography on silica gel eluted with 9/1, isooctane/ethyl acetate to afford 2.6 g, 7% yield, of isophthalate **39** as a colorless oil which was kugelrohr distilled: bp 115–125 °C (0.3 mmHg); ^{1}H NMR δ 1.20 (t, 3 H), 2.48 (s, 3 H), 2.59 (q, 2 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 7.11 (d, 1 H), 7.83 (d, 1 H); IR (neat) 3000, 1730, 1610 cm^{-1}; UV (methanol) λ_{max} nm (ε) 234 (12000), 277 (850). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8. Found: C, 66.1; H, 6.7.

Continued chromatography afforded 14.8 g, 35% yield, of the epoxy diester **3** as a clear oil which was kugelrohr distilled: bp 135–150 °C (0.75 mmHg); ^{1}H NMR (200 MHz) δ 1.00 (t, 3 H, J = 7.5 Hz), 1.3–1.4 (m, 2 H), 1.4–1.7 (m, 2 H), 2.06 (s, 3 H), 2.2–2.5 (m, 2 H), 3.70 (s, 3 H), 3.78 (s, 3 H); IR (neat) 2950, 1760, 1725 cm^{-1}; UV (methanol) λ_{max} 232 nm (ε 7100). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.4; H, 7.1. Found: C, 61.4; H, 7.1.

Pyridylseleno Group in Organic Synthesis. Preparation and Oxidation of α-(2-Pyridylseleno) Carbonyl Compounds Leading to α,β-Unsaturated Ketones and Aldehydes

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α-(2-Pyridylseleno) carbonyl compounds (A) were prepared by the reaction of ketones or aldehydes with 2-pyridylselenenyl bromide under various conditions (acidic, basic, or after conversion to silyl enol ethers) in good to excellent yields. Oxidation of A thus prepared affords α,β-unsaturated carbonyl compounds in excellent yields even in the cases where satisfactory results were not obtained by the oxidation of the corresponding α-phenylseleno carbonyl compounds. These results indicate that the 2-pyridylseleno group is a better leaving group than the phenylseleno group in selenoxide elimination leading to enones.

Among the useful chemistry of organoselenium compounds, preparation of α,β-unsaturated carbonyl compounds by the oxidation of α-phenylseleno carbonyl compounds belongs to one of the most important and widely used reactions.[1-3] However, several examples have been reported where satisfactory results were not obtained by this methodology. We have previously reported that a 2-pyridylseleno group is a better leaving group than phenylseleno in selenoxide elimination to give terminal olefins.[4] Here, we report that oxidation of α-(2-pyridylseleno)carbonyl compounds affords enones in excellent yields, even in cases where satisfactory results were not obtained by the oxidation of the corresponding α-phenylseleno carbonyl compounds. We have also found that α-(2-pyridylseleno) carbonyl compounds can be prepared by the reaction of ketones or aldehydes with 2-pyridylselenenyl bromide under various conditions (acidic, basic, or after conversion to silyl enol ethers) in good to excellent yields. These two reactions may well provide an improved method for dehydrogenation of ketones and aldehydes.[5]

Results and Discussion

2-Pyridylselenenyl bromide and chloride were prepared by the reaction of 2,2′-dipyridyl diselenide with bromine and sulfuryl chloride, respectively, and were used without isolation in the following reactions. If necessary they can be isolated as completely odorless powders and stored almost indefinitely. Alkyl 2-pyridyl selenides and 2,2′-dipyridyl diselenide are also odorless compounds in contrast to the corresponding phenylseleno derivatives.

2,2′-Dipyridyl diselenide is a known compound but reported preparation procedures have been somewhat troublesome.[6] Our improved procedure consists of a one-pot synthesis of 2,2′-dipyridyl diselenide from 2-bromopyridine, selenium powder, and sodium borohydride and isolation by column chromatography. This procedure is suitable for laboratory-scale preparation (see Experimental Section).

Preparation of α-(2-Pyridylseleno) Carbonyl Compounds. α-(2-Pyridylseleno)cyclohexanone (1) was produced by the reaction of cyclohexanone with 2-pyridylselenenyl bromide. The yield of 1, however, was unsatisfactory (11–34%) when the reaction was carried out without the addition of a reagent to facilitate the enolization of cyclohexanone. Acidic conditions were examined first and the addition of 5 equiv of aqueous hydrochloric

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