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An Efficient Synthesis of Aklavinone and Related 11-Deoxyanthracyclinones

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Cycloaddition of the vinyl ketene acetal 1-ethyl-2-(methoxycarbonyl)-3-methylene-4-[((*tert*-butyldimethylsilyl)oxy)methoxymethylene]cyclohexane 1,2-epoxide (**4b**) with bromojuglones provides a convenient, flexible, and efficient synthesis of (±)-aklavinone (**1a**) and related 11-deoxyanthracyclinones. Aklavinone is obtained from 3-bromojuglone (**7b**) in five steps and 41% overall yield. Improved conditions for the bromoquinone–vinyl ketene acetal cycloaddition are described.

The 11-deoxyanthracyclinones are an important new family for antitumor antibiotics. The best known members of this group, aclacinomycin A and 11-deoxydaunomycin, are glycosides derived from aklavinone (**1a**) and 11-deoxydaunomycinone (**2a**). Early studies have shown that 11-deoxyanthracyclines possess high activity against a variety of human cancers and are less toxic than daunomycin and adriamycin, the anthracycline antitumor antibiotics currently being used clinically. These findings have inspired several total syntheses of aklavinone (**1a**)[1-8] and 11-deoxydaunomycin[9-13] in recent years.

In planning a total synthesis of 11-deoxyanthracyclinones, one must address two distinct problems. These are (1) regioselective preparation of the substituted anthraquinone moiety and (2) efficient and stereoselective introduction of the necessary A-ring functionality. Many elegant approaches have been employed to solve the first of these objectives. Efforts to elaborate the A ring of aklavinone (**1a**) have suffered from either a lack of convergence or a lack of stereoselectivity.

The regioselective reaction of juglones as bromojuglones with vinyl ketene acetals has been employed previously in the total synthesis of aklavinone (**1a**), 11-deoxydaunomycinone (**2a**), and related 11-deoxyanthracyclinones.[6,9,10] These reports have demonstrated the versatility of the vinyl ketene acetal approach in preparing 11-deoxyanthracyclinones with different D-ring substitution patterns. The full range of functional groups compatible with this reaction, however, has never been investigated. We now report the preparation of the highly functionalized vinyl ketene acetals **4a** and **4b** which incorporate most of the functionality present in ring A of aklavinone. We also describe improved conditions for the bromojuglone–vinyl ketene acetal cycloaddition which expand the scope and improve the efficiency of this reaction. These developments result in a flexible, convenient, and highly convergent route to aklavinone (**1a**) and related 11-deoxyanthracyclinones.

Results and Discussion

In an earlier report[14] we described a simple convergent route to epoxy diester **3**, which contains most of the functionality present in ring A of aklavinone. The α,β-unsaturated ester moiety in **3** makes it a suitable vinyl ketene acetal precursor. We initially prepared the trimethylsilyl vinyl ketene acetal **4a** by treating **3** with excess lithium diisoproylamide (LDA) and quenching the resulting dienolate with chlorotrimethylsilane. This vinyl ketene acetal proved too labile so we prepared the more stable *tert*-butyldimethylsilyl vinyl ketene acetal **4b** by a similar procedure. This material was much easier to handle and was stable in toluene even through an aqueous isolation. Thus **4b** was available in about 80% yield as a 1/1 mixture with toluene but free of inorganic salts and

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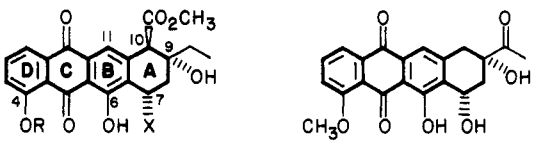
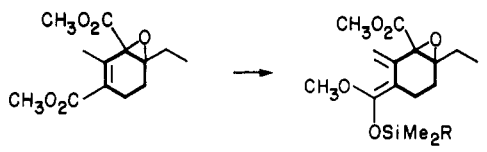


	R	X
1a	H	OH
1b	CH_3	H
1c	H	H

2



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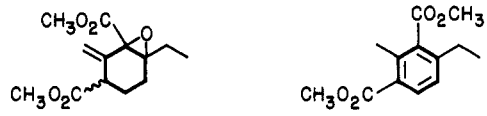
4a, R = Me
4b, R = Bu^t



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6

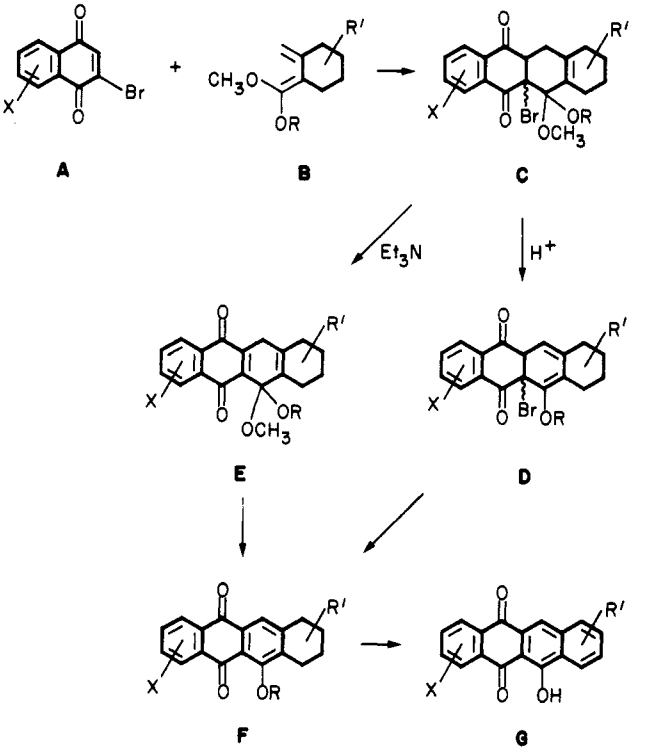
diisopropylamine. Attempts to further purify **4b** by chromatography caused complete hydrolysis; therefore the 1/1 toluene mixture was used in all subsequent reactions.

To take full advantage of the regioselective reaction of bromojuglones with vinyl ketene acetals we needed a number of 2- and 3-bromojuglone derivatives in isomerically pure form. Convenient routes to the methyl ethers **7a** and **8a** have been reported previously.[15] The methyl ethers, in turn, can be cleaved to the respective phenols **7b** and **8b** with $AlBr_3$. Methyl ether cleavage by other Lewis acids gave less satisfactory results. Partial substitution of chlorine for bromine was observed when $AlCl_3$ was used, and BBr_3 led to a mixture of polybromojuglones. The phenols **7b** and **8b** could not be separated by HPLC but acetylation provided **7c** and **8c**, respectively, which were easily separated, and each was shown to be greater than 99% isomerically pure. Thus no rearrangement had occurred during the methyl ether cleavage. Preparative quantities of isomerically pure 2-bromojuglone acetate (**8c**) were prepared from 1,5-diacetoxynaphthalene according to the literature procedure.[16]

Bromojuglone–Vinyl Ketene Acetal Cycloadditions. The initial step in the reaction of bromojuglones A with vinyl ketene acetals B (Scheme I) is cycloaddition to form a bromo ketal C. It is unclear whether this proceeds by a stepwise[10] or concerted mechanism but the regiochemical outcome of this reaction is well established. In the past, the unstable bromo ketal was never isolated but was hydrolyzed on silica gel to obtain the anthracyclinones F (R = H and alkyl). This hydrolysis is initiated by silica gel catalyzed cleavage of ketal C to diene D, which loses HBr to form F. The HBr then assumes the role of catalyst in the ketal cleavage. Generation of HBr is clearly not compatible with acid labile functionality in F. In addition, if ketal cleavage is initiated prior to completion of the cyclization reaction, the resulting HBr can destroy the vinyl ketene acetal B.

It is thus not surprising that our initial attempts to cyclize **4a** or **4b** with a variety of bromojuglones resulted

Scheme I. Bromojuglone–Vinyl Ketene Acetal Cycloaddition Intermediates and Products



primarily in decomposition of the vinyl ketene acetals. Without an acid scavenger present, only the vinyl ketene acetal decomposition products **3**, **5**, and **6** were isolable. Strontium carbonate has been used successfully as an acid scavenger in a related reaction involving 3-bromojuglone (**7b**).[2] When $SrCO_3$ was present during the cycloaddition reaction we observed much less decomposition of **4b** and the cycloadduct C, formed in good yield, was stable under the reaction conditions. Unfortunately, C (R = $SiMe_2$-*t*-Bu) proved very difficult to handle after the acid scavenger was removed. On chromatography, C decomposed very slowly to a mixture of anthracyclinones F (R = $SiMe_2$-*t*-Bu, H, and CH_3) and the corresponding dianhydroanthracyclinones G. Silica gel hydrolysis of cycloadduct C was clearly not a satisfactory route to F.

On one occasion, the cycloadduct C derived from 2-bromojuglone acetate (**8c**) and **4b** was obtained as a stable, colorless, crystalline solid. This made it possible to study other conditions for the conversions of C to F. Under acidic conditions (95% formic acid, room temperature) C was very slowly converted to F as a mixture of the silyl ether, phenol, and methyl ether. As the concentration of HBr increased, F was cleaved completely to G. Fluoride ion cleaved C to F as a 5/1 mixture of methyl ether and phenol. The most selective method for converting the bromo ketal C to desired phenol F (R = H) was triethylamine (TEA). With TEA, dehydrobromination precedes ketal cleavage and the intermediate E loses methanol in preference to *tert*-butyldimethylsilanol. The anthracyclinone F was thus obtained as 10/1 (or greater) mixture of silyl ether (R = $SiMe_2$-*t*-Bu) and methyl ether (R = Me). These could be separated by chromatography or the mixture could be treated with tetrabutylammonium fluoride to cleave the silyl ether and convert the entire product to the desired phenol F (R = H).

These results indicated that TEA would be more suitable than $SrCO_3$ as the acid scavenger during the cyclization. In addition to improving the ratio of phenol and methyl ether, TEA offers several other advantages over

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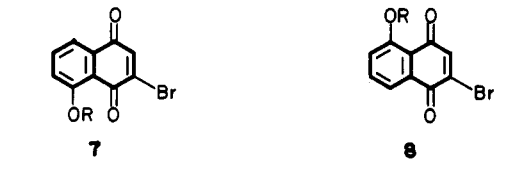
$SrCO_3$ as an acid scavenger during the bromojuglone–vinyl ketene acetal reaction. Its solubility in benzene avoids the difficulties associated with heterogeneous reactions. This makes it a more efficient acid scavenger, and no hydrolysis of the vinyl ketene acetal **4b** was observed even after heating at 55 °C for extended periods. Since the tertiary amine cleavage of the unstable cycloadduct C to the anthracyclinone F proceeds under alkaline conditions, no dianhydroanthracyclinone G is observed.

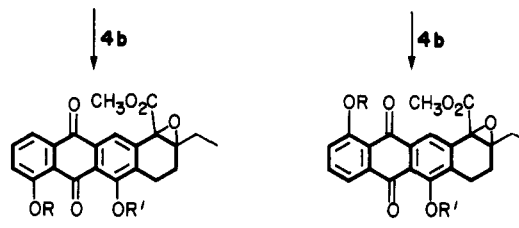
The presence of TEA during the cycloaddition reaction poses one minor problem. Methanol is generated as a byproduct when G is converted to the silyl ether F, and TEA can catalyze the addition of methanol to bromojuglones. For examples, 2-methoxyjuglone was observed as a minor side product in the cycloaddition involving 3-bromojuglone (**7b**). This problem can be overcome by adding 4-Å molecular sieves to the reaction mixture, thus removing the methanol as it is formed.

Using the above information, we were able to develop a convenient and reliable procedure for the reaction of vinyl ketene acetal **4b** with a number of bromojuglone derivatives. The following example will show the versatility of this approach in preparing aklavinone (**1a**) and a number of related anthracyclinones. With TEA present, the cycloaddition of 3-bromojuglone methyl ether (**7a**) with



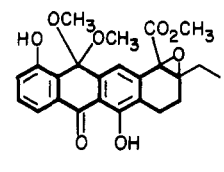
7 **8**

a, R = CH_3; **b**, R = H; **c**, R = $COCH_3$



9 **10**

	R	R′		R	R′
a	CH_3	$SiMe_2Bu^t$	**d**	H	$SiMe_2Bu^t$
b	CH_3	H	**e**	H	H
c	CH_3	CH_3	**f**	H	CH_3
			g	$COCH_3$	$SiMe_2Bu^t$



11

vinyl ketene acetal **4b** proceeded slowly but cleanly in benzene at room temperature. The reaction was terminated after 40 h, although it was far from complete. After an aqueous workup and isolation, the crude mixture containing silyl ether **9a** and methyl ether **9c** was treated with tetrabutylammonium fluoride in THF. Pure phenol **9b** and methyl ether **9c** were obtained in 12% and 2.4% yield, respectively, by chromatography and recrystallization. Stereospecific hydrogenolysis of the benzylic epoxide **9b** under established conditions (1 atom of H_2, $Pd/BaSO_4$, 1:1 ethanol/triethanolamine)[1,3] provided the known aklavinone precursor **1b**[4] in quantitative yield. Conditions for the cycloaddition were not optimized since a more direct route to aklavinone is described below.

Under identical conditions, 2-bromojuglone methyl ether (**8a**) was more reactive than **7a** toward vinyl ketene acetal **4b**. After cleavage of the silyl ether **10a**, we obtained phenol **10b** and methyl ether **10c** in 31% and 3.6% yield, respectively.

The phenols **9b** and **10b** are nearly identical by NMR, IR, UV, and TLC. They differ most noticeably in the chemical shift of their chelated phenolic protons. This proton appears as a sharp singlet at δ 12.76 for **10b**. The peri methoxyl group strengthens the chelation effect in **9b**, causing a 0.5 ppm downfield shift to δ 13.25 for phenol **9b**. In $CDCl_3$ these signals vary less than 0.1 ppm over a wide range of concentrations. The dimethyl ethers **9c** and **9d** can be distinguished by TLC or NMR, but the respective structures can only be assigned on the basis of the known regioselectivity of the bromojuglone–vinyl ketene acetal cycloaddition reaction.

3-Bromojuglone (**7b**) is the most reactive juglone derivative toward **4b**. This is due to the combined polarizing effect of the bromine and peri hydroxyl group. At room temperature the reaction between **7b** and **4b** can be monitored by NMR and is complete within 2 h. After the crude silyl ether **9d** was cleaved with fluoride ion, the known diphenol **9e** was isolated in 61% yield. None of the regioisomer **10e** could be detected, and only a trace of the methyl ether **9f** was obtained after chromatography. Spectral data for **9e** were consistent with those reported for authentic material,[1,3] but this was insufficient for positive identification. Additional evidence for **9e** was obtained from its IR spectrum, which showed two distinct quinone carbonyl absorptions (1665 and 1620 cm^{-1}), confirming that both phenols are chelated to the same carbonyl. As further proof, hydrogenolysis of benzylic epoxide **9e** provided racemic 7-deoxyaklavinone (**1c**) which was identical with authentic material. Since **1c** has been converted to aklavinone our route will provide aklavinone (**1a**) in five convenient steps and 41% overall yield from 3-bromojuglone (**7b**).

The cycloaddition of **4b** with 2-bromojuglone acetate (**8c**) was carried out at room temperature in benzene with TEA and 4-Å molecular sieves. Acetate **8c** is less reactive than 3-bromojuglone (**7b**) but more reactive than ethers **7a** or **8a**, so the reaction was complete in 24 h. After an aqueous isolation the crude acetate silyl ether **10g** was treated with fluoride ion in THF followed by the addition of methanol and K_2CO_3. This sequence cleaved both the silyl and acetate, but the major product was ketal **11** (or a regioisomer of **11**). By NMR **11** shows two new *O*-methyl singlets (δ 2.9 and 3.0) and only a single chelated phenol (δ 13.1). The unstable ketal **11** was hydrolyzed with aqueous acetic acid to obtain the desired diphenol **10e**, which was isolated in 56% yield from **8c**. Regioisomer **9e** and methyl ether **10f**, each formed in about 1% yield, were easily separated from **10e** by chromatography.

Molecular sieves are particularly important during cycloaddition reactions with **8c**. Acetate **8c** is susceptible to both transesterification and halogen displacement by methanol and TEA. Transesterification of **8c** generates 2-bromojuglone (**8b**), which reacts rapidly but not regioselectively with vinyl ketene acetal **4b**. Without molecular sieves present during the cyclization of **8c** and **4b** the diphenols **9e** and **10e** were isolated in 6% and 35% yield, respectively, and 3-methoxyjuglone was detected by NMR.

The new diphenol **10e** is indistinguishable from the aklavinone precursor **9e** by NMR except for the chemical

shift of the chelated phenolic protons. For **10e** these signals appear at δ 12.58 and 12.93, or about 0.6 ppm downfield from those of **9e**, because the phenolic protons of **10e** are not chelated to the same carbonyl. From the IR spectrum the single quinone carbonyl absorption at 1635 cm^{-1} confirms that both carbonyls are chelated.

Ultraviolet visualization of TLC slides is a valuable tool for distinguishing between anthracyclinones that have different oxygen substituents, especially when they have very similar R_f values. Under a long-wavelength UV lamp all compounds **9** and **10** with both oxygens substituted (**a**, **c**, **d**, and **g**) show no fluorescence. All of the monophenols (**b** and **f**) are fluorescent orange. The diphenol **10e** is also fluorescent orange but the aklavinone precursor **9e** is fluorescent yellow. None of these compounds are fluorescent under a short-wavelength UV lamp; however, they do quench the fluorescent indicator present on the silica gel. This provides a rapid and reasonable estimate of the relative abundance of different species. The dianhydroanthracyclinones such as **8** and **20** are fluorescent yellow under both short- and long-wavelength UV lamps regardless of th eoxygen substituents.

As we have shown, the new vinyl ketene acetal **4b** provides a very convenient synthetic educt for anthracyclinones possessing the AB-ring substitution pattern of aklavinone (**1**). This minimizes the number of steps required to elaborate the A ring of aklavinone once the anthracyclinone skeleton has been constructed. The versatility of this approach has been demonstrated by preparing anthracyclinones **9** and **10** with different D-ring substitution patterns. Any of these can be elaborated by established methods[1,3] to anthracyclinone with the A-ring substitution patterns of aklavinone. Under the mild conditions of our modified cycloaddition procedure it should be possible to incorporate more complex functionality into the juglone component and thus prepare a wide variety of aklavinone analogues.

Experimental Section

General Methods. Unless otherwise specified all reactions were carried out in oven-dried flasks at room temperature under an argon atmosphere with magnetic stirring. After quenching and solvent extraction, solutions were dried over $MgSO_4$, filtered, and evaporated under reduced pressure on a rotary evaporator. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Dichloromethane, diisopropylamine, and triethylamine (TEA) were distilled from CaH_2. Other solvents were obtained from Mallinckrodt and were used without further purification. Molecular sieves (4 Å, $^1/_{16}$-in. pellets) were activated at 450 °C for 12 h prior to use. All NMR spectra were obtained on $CDCl_3$ solutions with Me_4Si as internal standard, infrared spectra were obtained as KBr pellets, and UV spectra were obtained as solutions in 95% ethanol. HPLC was performed on a 4.6 mm × 25 cm column packed with 5-μm Microsorb silica with 19/1 isooctane/ethyl acetate at a flow rate of 1 mL/min and was monitored by UV at 279 nm. Detection limits of <1% were verified by doping experiments in all cases. The epoxide **3**[14] and bromojuglones **7a**,[15] **8a**,[15] and **8c**[16] were prepared as described.

3-Bromojuglone (7b) and 3-Bromojuglone Acetate (7c). A solution containing 3.62 g (13.3 mol) of 3-bromojuglone methyl ether (**7a**) in 40 mL of dichloromethane was added via syringe over 5 min to a stirred slurry of $AlBr_3$ (14.5 g, 54 mmol) in 120 mL of dichloromethane. After the mixture was stirred for an additional 25 min, the reaction was quenched by *cautiously* adding 30 mL of 1 M H_3PO_4 in small portions until the vigorous exothermic reaction subsided. The reaction mixture was poured into 50 mL of 1 M H_3PO_4. The bromojuglone was extracted from the resulting aqueous suspension by washing repeatedly with dichloromethane (5 × 100 mL), and the combined organic extracts were then washed sequentially with water (3 × 100 mL) and brine (100 mL) and dried. The solution was filtered and then concentrated until a precipitate formed. This concentrated solution was filtered through a 20-g column of silica gel eluted with dichloromethane to obtain 2.58 g (75% yield) of 3-bromojuglone (**7b**): mp 169–170 °C from 95% ethanol (lit.[17] mp 172 °C); ^1H NMR δ 7.1–7.8 (m, 4 H), 11.68 (s, 1 H).

The isomeric purity of this material could not be established by HPLC on either silica gel or reverse-phase columns. Acetylation according to the described procedure[17] provided 3-bromojuglone acetate (**7c**) in 90% yield. This material was 99% isomerically pure by HPLC: mp 146–149 °C (lit.[17] mp 151 °C); HPLC t_R 19.5 min.

2-Bromojuglone acetate (8c) was prepared from 2-bromojuglone methyl ether (**8a**) by the above sequence or according to the literature procedure.[16] By either method, **8c** was greater than 99% isomerically pure: mp 154–155 °C (lit.[17] mp 158 °C); HPLC t_R 18.15 min.

1-Ethyl-2-(methoxycarbonyl)-3-methylene-4-[((*tert*-butyldimethylsilyl)oxy)methoxymethylene]cyclohexane 1,2-Epoxide (4b). Butyllithium (3.7 mL, 1.58 M in hexane) was added to a solution of diisopropylamine (0.90 mL) in 20 mL of THF at 0 °C. After 10 min this solution was cooled to −78 °C, and a solution containing 1.00 g (3.94 mmol) of freshly distilled **3** dissolved in 10 mL of THF was added by syringe over 10 min. After the addition was complete the bath temperature was raised to −20 °C over 20 min. After 5 min at −20 °C, 3.25 g (21.6 mmol) of *tert*-butyldimethylchlorosilane was added and the cooling bath was removed. When the reaction flask had warmed to room temperature, the solvent was evporated at 30 °C, the residue was dissolved in 100 mL of toluene, and the toluene solution was shaken briefly with 5% $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL) and dried over K_2CO_3. The solution was filtered, and the toluene was evaporated at 30 °C to obtain 1.56 g of light brown oil which was a 1/1 mixture of toluene and **4b** by NMR. This represents an 80–85% yield of **4b** and was used immediately in the cycloaddition reactions. **4b**: ^1H NMR δ 0.18 (s, 6 H), 1.01 (s, 6 H), 1.05 (t, 3 H), 1.4–2.5 (m, 6 H), 3.68 (s, 3 H), 3.84 (s, 3 H), 5.36 (s, 1 H), 5.76 (s, 1 H); MS *m/e* (relative intensity) 368 (9, M^+), 339 (12), 312 (9), 73 (100).

General Procedure for Cycloaddition of 4b with Bromojuglones. Vinyl ketene acetal **4b** (1.56 g), prepared as above, was dissolved in 16 mL of benzene and 1.6 mL of TEA. The bromojuglone and 1.3 g of 4-Å molecular sieves were added and the mixture was stirred at room temperature for 2–40 h. The benzene solution was then decanted from the molecular sieves, poured into 100 mL of benzene, washed sequentially with water (50 mL), 1 M HCl (2 × 50 mL), bicarbonate (50 mL), and brine (100 mL), dried, and evaporated. The residue was dissolved in 20 mL of THF, and 3 mL of 1 M tetrabutylammonium fluoride in THF was added. After 5 min the deep purple reaction mixture was poured into 100 mL of benzene, washed sequentially with water (3 × 50 mL) and brine (100 mL), and dried. After the benzene was evaporated, the residue was chromatographed on a 50-g column of silica gel, eluting with dichloromethane containing 0–5% ethyl acetate. Each anthracyclinone was further purified by dissolving it in a minimum amount of chloroform and adding methanol to precipitate the anthracyclinone.

Cycloaddition of 4b with 3-Bromojuglone Methyl Ether (7a). The cycloaddition was carried out following the general procedure with 0.80 g (3.0 mmol) of **7a** and was quenched after 40 h. After treatment with fluoride, chromatography, and recrystallization, 0.15 g (12%) of **9b** and 0.03 g (2.4%) of **9c** were obtained.

9b: mp 185–187 °C; R_f 0.09; ^1H NMR δ 1.08 (t, 3 H), 1.6–2.1 (m, 3 H), 2.2–2.7 (m, 2 H), 3.1–3.5 (m, 1 H), 3.96 (s, 3 H), 4.03 (s, 3 H), 7.31 (dd, 1 H), 7.65 (t, 1 H), 7.70 (s, 1 H), 7.92 (dd, 1 H), 13.25 (s, 1 H); IR 2950, 1730, 1660, 1625, 1580 cm^{-1}; UV λ_{max} (relative absorbance) 230 (1.0), 260 (0.60), 419 (0.27). Anal. Calcd for $C_{23}H_{20}O_7$: C, 67.6; H, 4.9. Found: C, 67.4; H, 4.7.

9c: mp 159–161 °C; ^1H NMR δ 1.12 (t, 3 H), 1.6–2.0 (m, 3 H), 2.3–2.7 (m, 2 H), 3.2–3.35 (m, 1 H), 3.93 (s, 3 H), 4.00 (s, 3 H), 4.03 (s, 3 H), 7.32 (dd, 1 H), 7.67 (t, 1 H), 7.85 (dd, 1 H), 7.96 (s, 1 H); IR 2980, 2950, 1730, 1675, 1585 cm^{-1}; UV λ_{max} (relative absorbance) 223 (1.00), 261 (0.88), 378 (0.19); HRMS, *m/e* calcd for $C_{24}H_{22}O_7$ 422.1366, found 422.1358.

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Cycloaddition of 4b with 2-Bromojuglone Methyl Ether (8a). The cycloaddition was carried out according to the general procedure with 0.80 g (3.0 mmol) of **8a** and was quenched after 40 h. After treatment with fluoride, chromatography, and recrystallization, 0.38 g (31%) of **10b** and 46 mg (3.6%) of **10c** were obtained.

10b: mp 166–168 °C; R_f 0.06; ^{1}H NMR 1.08 (t, 3 H), 1.6–2.0 (m, 3 H), 2.3–2.6 (m, 2 H), 3.1–3.3 (m, 1 H), 3.97 (s, 3 H), 4.05 (s, 3 H), 7.36 (dd, 1 H), 7.71 (s, 3 H), 7.73 (t, 1 H), 7.96 (dd, 1 H), 12.76 (s, 1 H); IR 2950, 1750, 1735, 1660, 1630, 1580 cm^{-1}; UV λ_{max} (relative absorbance) 229 (1.00), 257 (0.68), 285 (0.24), 414 (0.28); HRMS, m/e calcd for $C_{23}H_{20}O_7$ 408.1209, found 408.1205.

10c: mp 197–199 °C; ^{1}H NMR δ 1.08 (t, 3 H), 1.6–2.0 (m, 3 H), 2.3–2.7 (m, 2 H), 3.2–3.4 (m, 1 H), 3.88 (s, 3 H), 3.98 (s, 3 H), 4.04 (s, 3 H), 7.30 (dd, 1 H), 7.72 (t, 3 H), 7.90 (dd, 1 H), 8.40 (s, 1 H); IR 2940, 1750, 1730, 1665, 1580 cm^{-1}; UV λ_{max} (relative absorbance) 221 (1.00), 260 (0.93), 387 (0.21); HRMS, m/e calcd for $C_{24}H_{22}O_7$ 422.1366, found 422.1383.

Cycloaddition of 4b with 3-Bromojuglone (7b). The cycloaddition reaction was carried out according to the general procedure with 0.51 g (2.0 mmol) of **7b** and was quenched after 2 h. After treatment with fluoride, chromatography, and recrystallization, 0.48 g (61%) of **9e** and 0.01 g (1%) of **9f** were obtained.

9e: mp 224–226 °C (lit.[1] mp 221–224 °C, lit.[3] mp 229–230 °C); R_f 0.22; ^{1}H NMR δ 1.13 (t, 3 H), 1.65–2.05 (m, 3 H), 2.35–2.60 (m, 2 H), 3.15–3.3 (m, 1 H), 4.00 (s, 3 H), 7.28 (dd, 1 H), 7.68 (t, 1 H), 7.71 (s, 1 H), 7.79 (dd, 1 H), 11.99 (s, 1 H), 12.37 (s, 1 H); IR 2990, 1730, 1665, 1620, 1590 cm^{-1}; UV λ_{max} ($\epsilon \times 10^{-4}$) 230 (3.9), 258 (2.5), 293 (0.81), 434 (1.2).

9f: mp 175–176 °C; R_f 0.16; ^{1}H NMR δ 1.10 (t, 3 H), 1.5–2.1 (m, 3 H), 2.2–2.8 (m, 2 H), 3.1–3.5 (m, 1 H), 3.88 (s, 3 H), 3.98 (s, 3 H), 7.29 (dd, 1 H), 7.61 (t, 1 H), 7.74 (dd, 1 H), 8.04 (s, 1 H), 12.08 (s, 1 H); IR 2960, 1720, 1660, 1630, 1580 cm^{-1}; UV λ_{max} (relative absorbance) 223 (1.00), 260 (0.94), 283 (0.29), 392 (0.20), 410 (0.21); HRMS, m/e calcd for $C_{23}H_{20}O_7$ 408.1209, found 408.1198.

Cycloaddition of 4b with 2-Bromojuglone Acetate (8c). The cycloaddition was carried out as above with 0.89 g (3.0 mmol) of **8c** and was quenched after 24 h. When the reaction with fluoride was complete, 10 mL of methanol and 1.5 g of K_2CO_3 were added to the THF solution and stirring was continued. After 2 h at room temperature, the solution was decanted from the remaining K_2CO_3, poured into 100 mL of benzene, and neutralized with 1 M HCl. The benzene solution was washed sequentially with bicarbonate (2 × 50 mL) and brine (50 mL), dried, and filtered. The benzene was evaporated, the residue was dissolved in 15 mL of glacial acetic acid and 1 mL of water, and this mixture was stirred overnight and then poured into 100 mL of benzene. The benzene solution was washed sequentially with water (3 × 50 mL), bicarbonate (2 × 50 mL), and brine (50 mL) and dried. Chromatography and recrystallization provided 0.66 g (56%) of **10e**, 0.01 g (1%) of **9e**, and 0.01 g (1%) of **10f**.

10e: mp 160–161 °C; R_f 0.31; ^{1}H NMR δ 1.14 (t, 3 H), 1.65–2.05 (m, 3 H), 2.35–2.6 (m, 2 H), 3.15–3.3 (m, 1 H), 4.01 (s, 3 H), 7.30 (dd, 1 H), 7.66 (t, 1 H), 7.71 (s, 1 H), 7.80 (dd, 1 H), 12.58 (s, 1 H), 12.93 (s, 1 H); IR 2960, 1750, 1630, 1600, 1570 cm^{-1}; UV λ_{max} ($\epsilon \times 10^{-4}$) 231 (4.2), 259 (3.0), 295 (1.0), 436 (1.3).

10f: mp 167–169 °C; R_f 0.16; ^{1}H NMR δ 1.10 (t, 3 H), 1.5–2.1 (m, 3 H), 2.2–2.8 (m, 2 H), 3.1–3.5 (m, 1 H), 3.87 (s, 3 H), 3.99 (s, 3 H), 7.22 (dd, 1 H), 7.63 (t, 1 H), 7.76 (dd, 1 H), 8.06 (s, 1 H), 12.40 (s, 1 H); IR 2950, 1735, 1670, 1635, 1580 cm^{-1}; UV λ_{max} (relative absorbance) 222 (0.97), 259 (1.000), 286 (0.28), 391 (0.21), 404 (0.21); HRMS, m/e calcd for $C_{23}H_{20}O_7$ 408.1209, found 408.1198.

Registry No. (±)-**1a**, 78821-97-3; (±)-**1b**, 80173-04-2; (±)-**1c**, 78821-96-2; (±)-**3**, 95935-63-0; (±)-**4b**, 95935-64-1; **7a**, 69833-10-9; **7b**, 52431-65-9; **7c**, 77197-58-1; **8a**, 69833-09-6; **8c**, 77189-69-6; (±)-**9a**, 95935-65-2; (±)-**9b**, 95935-66-3; (±)-**9c**, 95935-67-4; (±)-**9d**, 95935-68-5; (±)-**9e**, 95374-66-6; (±)-**9f**, 95935-69-6; (±)-**10a**, 95935-70-9; (±)-**10b**, 95935-71-0; (±)-**10c**, 95935-72-1; (±)-**10e**, 95935-73-2; (±)-**10f**, 95935-74-3; (±)-**10g**, 95935-75-4; (±)-**11**, 95935-76-5.

Copper(I)-Induced Reactions of the Adducts Formed from Cyclopropyl Ketones and [Tris(methylthio)methyl]lithium

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The products obtained from the reaction of $CuClO_4 \cdot 4CH_3CN$ with the adducts formed from acyclic and cyclic cyclopropyl ketones and [tris(methylthio)methyl]lithium can be rationalized via the intervention of epoxide intermediates. Under the reaction conditions, cleavage of the C–O bond in the epoxide occurs in the direction that leads to a cyclopropylcarbinyl carbocation. This bond scission is accompanied by the migration of a thiomethyl group. For example, treatment of the lithium salt of 2-cyclopropyl-2-hydroxy-1,1,1-tris(methylthio)propane with $CuClO_4 \cdot 4CH_3CN$ in toluene gave only *S*-methyl 2-cyclopropyl-2-(methylthio)propanethioate. If geometric restrictions hinder the cyclopropyl substituent from effectively stabilizing an adjacent electron-deficient center, then cleavage of the alternative C–O bond in the epoxide becomes competitive. For example, reaction of $CuClO_4 \cdot 4CH_3CN$ with the adduct formed from nortricyclanone and [tris(methylthio)methyl]lithium provided 4,4-bis(methylthio)tricyclo[3.2.1.0^{2,7}]octan-3-one and *S*-methyl 3-(methylthio)tricyclo[2.2.1.0^{2,6}]heptane-3-carbothioate in yields of 72 and 27%, respectively.

Knapp and his co-workers have reported recently a sequence of reactions for the ring expansion of cyclobutanones and cyclopentanones to the corresponding 1-keto 2-thioketals.[1] According to this procedure, a solution of the ketone in tetrahydrofuran is treated initially with [tris(methylthio)methyl]lithium at −78 °C, and the resulting adduct **1** is isolated (Scheme I). In a subsequent step, a solution of the lithium salt **2** in toluene is prepared from **1** by reacting **1** with *n*-butyllithium at −78 °C. At this point, an excess of tetrakis(acetonitrile)copper(I) perchlorate or tetrafluoroborate is added. Heating this reaction mixture at 75 °C for 2–4 h provides 1-keto 2-thioketal **5**. Knapp has suggested that **2** → **5** may take place via epoxide **3**.[1] Cleavage of bond a in **3** would give **4** and 1,2-alkyl migration in **4** would afford **5**. However,

(1) Knapp, S.; Trope, A. F.; Theodore, M. S.; Hirata, N.; Barchi, J. J. *J. Org. Chem.* **1984**, *49*, 608–614.

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