(2) These isomers may be prepared in a pure state by an alternative method. Their interconversion has been studied in detail, and the results will be published elsewhere. In addition to rate law evidence, the close similarity of the rates of reaction of **3** and **4** with $Ph_3P$ (to produce **1**) to their rates of isomerization strongly supports the suggested mechanism.
(3) The synthesis of this intermediate has been claimed[4] and its existence has frequently been cited in the literature.[5] These claims are all erroneous and we have established that the putative **2** is in fact $P_2(CO)_2IrH$, as previously suspected by Yagupsky and Wilkinson.[6] Since the compound **2** has not been isolated, its stereochemistry is unknown, a fact which contributes some uncertainty to the interpretation placed on the results reported herein.
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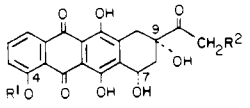
## Benzocyclobutenedione Monoketal. A 1,4-Dipole Equivalent for Anthracyclinone Synthesis. Synthesis of (±)-4-Demethoxydaunomycinone

*Sir:*

The clinical activity[1] of the anthracyclinone antibiotics daunomycin, adriamycin, and carminomycin has inspired much synthetic work on the aglycones of these molecules, **1a–c,**

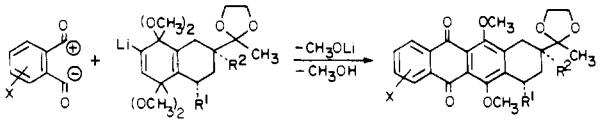


**1a**, $R^1=CH_3$, $R^2=H$
**b**, $R^1=CH_3$, $R^2=OH$
**c**, $R^1=R^2=H$

and their analogues. The 4-demethoxy system, first prepared by Wong,[2] has also proven especially promising in clinical trials,[3] and several publications regarding the synthesis of this tetracyclinone have resulted.[4]

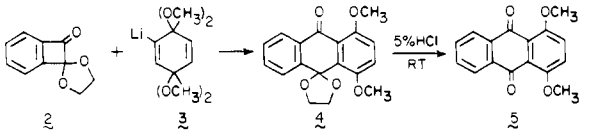
Our anionic approach to anthracyclinones via coupling of an AB ring to a D-ring precursor would be equally applicable to the synthesis of the 4-demethoxy system.[5] However, the synthesis of a 7- or a 7,9-deoxy analogue, followed by subsequent introduction of the remaining A-ring oxygen substituent(s), affords only an alternative to Wong's[2,6] original and quite acceptable synthesis of these deoxygenated species. In fact, current work on both the 4-demethoxy and naturally occurring systems has involved introduction of the 7- or 7,9-hydroxyl group(s) after formation of the tetracyclic ring by methods that proceed in modest yields at best,[2,3a,6] two exceptions being the elegant use of a trimethylsilyl group as a latent 7-oxygen function[4d] and the Diels–Alder route of Krohn.[4f] As outlined earlier, we conceived of quinone bisketals

**Scheme I.** General Outline for One-Step Construction of Anthracyclinone Systems

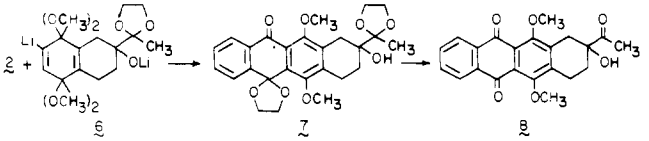


serving as key moieties in mild procedures for one-step formation of anthracyclinones in which a completely functionalized, optically active AB-ring system is linked with a D-ring precursor.[5,8] We report studies which utilize benzocyclobutenedione monoketal as a 1,4-dipole equivalent[9,12] (Scheme I) culminating in the synthesis of (±)-4-demethoxydaunomycinone.

The reaction of **2**[13] with **3** at −65 °C for 30 min, followed by warming to room temperature and then heating at reflux for 3 h, afforded after standard workup a yellow solid, which was crystallized from methylene chloride–ether to afford yellow needles (70%, mp 198.5–199.5 °C). Hydrolysis of a

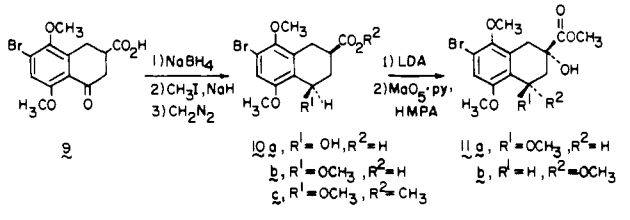


heterogeneous mixture of **4** and 5% hydrochloric acid at room temperature for 15 h afforded a quantitative yield of **5,** which was identical with the methylation product of quinizarin. Likewise, coupling of **2** with **6** (prepared from the requisite bromo alcohol by treatment with 2 equiv of butyllithium) afforded **7** (47%, mp 245–247 °C from $CH_2Cl_2$–ether), which was quantitatively hydrolyzed (THF–3 M HCl, 15:8, 20 h, room temperature) to **8,** mp 183.5–186 °C (lit.[4c] mp 184–186 °C).

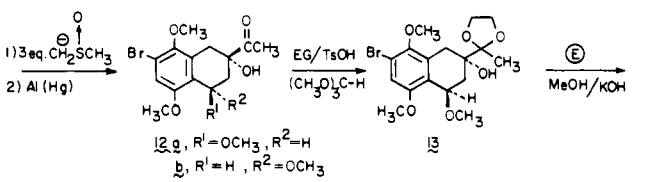


There now remained the application of this mild ring formation method to the fully oxygenated AB-ring precursor. The appropriately functionalized AB-ring system **12** was readily available as outlined in Scheme II;[14] only the salient points will

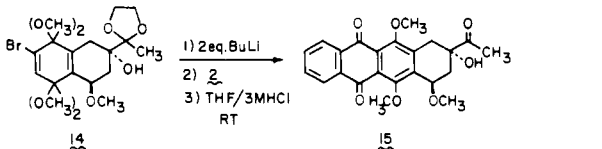
**Scheme II.** Synthesis and Coupling Reactions of the AB-Ring System



**9**
**10a**, $R^1=OH$, $R^2=H$
**b**, $R^1=OCH_3$, $R^2=H$
**c**, $R^1=OCH_3$, $R^2=CH_3$
**11a**, $R^1=OCH_3$, $R^2=H$
**b**, $R^1=H$, $R^2=OCH_3$



**12a**, $R^1=OCH_3$, $R^2=H$
**b**, $R^1=H$, $R^2=OCH_3$
**13**



**14**
**15**

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be noted here. The reduction of **9** with sodium borohydride at −15 °C afforded a mixture of the *cis*- and *trans*-hydroxy acid (99%, ca. 80:20). The pure cis compound was obtained by lactonization of the reaction mixture (165 °C, 20 min), extraction of the trans acid, and hydrolysis of the pure lactone (mp 118–119.5 °C). Methylation (93%) and esterification (95%) afforded **10c.** Application of Vedejs'[15] procedure for ester enolate hydroxylation yielded, after silica gel chromatography, **11** (74%). This was smoothly converted to a mixture of ketones that could readily be separated by silica gel chromatography to afford **12a** (55%) and its isomer **12b** (7%). Since a chromatographic separation was required at this stage, we have carried the steps **9** → **12** without separation of isomers (overall yield 32% from **9**). While ketalization methods involving heating proved unacceptable owing to partial aromatization and epimerization of **12a,** a mixture of ethylene glycol and trimethyl orthoformate at room temperature for 16 min afforded **13** with minimal aromatization or epimerization of the methoxy group.[16] Execution of the same reaction sequence as for **6** afforded **15** in 63% overall yield after recrystallization from methanol. This compound was identical in melting point and spectroscopic properties with those previously reported.[2] Since **15** is readily converted to 4-demethoxydaunomycinone,[2,3,6] this completes the synthesis.

This chemistry effects the formation of the C ring of the anthracyclinone system from an AB- and D-ring component under sufficiently mild conditions that the thermally and acid-labile A ring can be incorporated directly into a tetracyclic framework. By using modified AB- and D-ring components, the route would afford convergent syntheses of a variety of anthracyclinone analogues. Finally, the strategy documented herein may be applicable to the syntheses of related antibiotic aglycones: aklavinones, citromycinones, and even olivomycins.

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(14) All new compounds afforded acceptable combustion analyses or exact mass measurement. The melting points (°C) of the compounds follow: **10a,** 139–141; **10b,** 135–136; **10c,** 91.5–93; **11a,** 115–116; **12a,** 79–80; **13,** 105–106; **14,** 190–191 °C.
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(16) We express our appreciation to Professor Paul Dowd for bringing the procedure to our attention and for supplying experimental details of the method.
(17) We have found boron trichloride in methylene chloride at −70 °C for 30 min to be the reagent of choice for demethylation of **15** to 4-demethoxy-7-deoxy-7-methoxyepidaunomycinone (94%). The procedure of Arcamone[6] was then utilized for conversion to a mixture of 4-demethoxydaunomycinone and its epi isomer.

(18) We wish to thank the National Science Foundation (CHE76-80381 A81) and the National Institutes of Health (CA 17712-01A2) for generous support. D.K.J. is an Ohio State University Dissertation Fellow (1978–1979); L.N. is an American Oil Fellow (1977–1978). Our thanks to C. M. Wong for an authentic sample of **15** and R. B. Garland (G. D. Searle Co.) for authentic samples of 4-demethoxydaunomycinone and its 7-epi isomer.

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## Novel Copper–Pyridine Catalyzed Ring Opening Reactions of Aryl Oxiranes. An Asymmetric Synthesis of (+)-Indene 1,2-Oxide and (+)-*cis*-1,2-Indandiol

*Sir:*

Aryl oxiranes have proved to be important intermediates in synthetic chemistry,[1] and certain of their hydroxylated derivatives have been described as the ultimate carcinogens of aromatic compounds.[2] While their behavior in acidic and basic media is reasonably well understood,[3] their reactivity under neutral conditions has been little investigated. Kinetic studies in several laboratories[4] have shown that these compounds undergo spontaneous ring opening reactions at pH 7, producing materials of unknown stereochemistry. Recently, Hanzlik and Michaely[5] reported on the rate of $Cu^{2+}$-catalyzed oxirane opening of 2-pyridylethylene oxide and on the products formed. While the pH optimum for the catalyzed process was 4.5, the rate was still significant at pH 7. Hoping to effect aryl oxirane ring opening under neutral conditions, we examined the reactivity of indene oxide (**1**) in the presence of $CuSO_4$ in an aqueous phosphate buffer (pH 7). Under these conditions, the oxirane was rapidly destroyed, but no diols were formed. The potent effect of $CuSO_4$ prompted us to explore the possibility that the nitrogen atom in 2-pyridylethylene oxide complexed with copper, with formation of a species that can promote hydration of an aryl oxirane. When **1** was added to an aqueous solution containing pyridine and $CuSO_4$ buffered with phosphate buffer at pH 7, *cis*-1,2-indandiol formed rapidly and cleanly (i.e., without detectable quantities of the trans isomer or other products). The results of a study of the effect of the absence of one or more components in the reaction mixture are summarized in Table I. The study also established that the presence of NaCl or NaBr increases the reaction rate. The successful hydration of **1** under these very mild conditions stimulated us to explore the copper–pyridine catalyzed reactivity of several oxiranes with methanol, water, and chloride ion. The results of this study (summarized in Table II) demonstrate that aryl oxiranes react regioselectively at the benzylic carbon to yield exclusively or predominantly cis products: glycols, glycol monomethyl ethers, and chlorohydrins. This regioselectivity differs from that noted by Hanzlik and Michaely[5] for 2-pyridylethylene oxide, where reaction occurred at the less substituted carbon. Alkyl oxiranes do not react under

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