stereochemistry between the C(13) methyl and vinyl chain at C(17) in both **13** and **14** was confirmed on the basis of ^{1}H NOE.[14]

The stereoselective introduction of the methyl group at C(20) from the allyl alcohol **13** was carried out in the following way. The vinyl ether of **13** was prepared [$Hg(OAc)_2$, CH_2=$CHOEt$ at reflux; recovered alcohol **13**, 37%], and the Claisen rearrangement of the resulting vinyl ether **15** gave the single product **16**[15] in quantitative yield. Decarbonylation of the aldehyde **16** with $Rh(PPh_3)_3Cl$ in refluxing benzene for 90 min gave the enone **3**[16] in 64% yield. The same treatment of the C(23)-epimer **14**, as above, gave also the single product **17**.[16] For an examination of the relative stereochemistry among C(13), C(17), and C(20), the enone **17** derived from **14** was converted to the ketone **18** which was identical in all respects (NMR, IR, HPLC)[3] with an authentic sample of **18**.[17] These results revealed that the initial 1,4 addition of **9** to **5** led predominantly to the relative stereochemistry between C(17) and C(23) as shown in **13**, and the high degree of stereoselectivity of Claisen rearrangement on **13** and **14** provided the asymmetric center at 20β-H and 20α-H, respectively.

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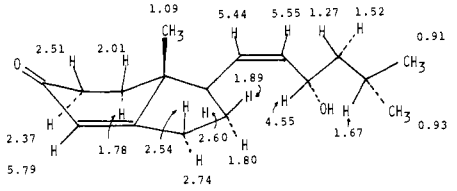
3% isopropyl alcohol in hexane). ^{1}H NMR (400 MHz) data of the enone **14** are shown in the following diagram.



IR (neat) 3400 and 1660 cm^{-1}; R_f = 0.36 (1:2 hexane–AcOEt); HPLC retention time, 10.5–12.4 min (3% isopropyl alcohol in hexane). We thank Iwao Miura (Otsuka Pharmaceutical Co.) for his help in the interpretation of the NMR spectra.

(14) The irradiation of the C(13)-methyl caused a significant increase (17% in **13**, 25% in **14**) of the absorption due to the olefinic protons.

(15) The careful examination of the reaction mixture by TLC and HPLC indicated that Claisen rearrangement of **15** proceeded via one transition state. Aldehyde **16**: NMR (CCl_4, 90 MHz) δ 0.87 (3 H, d, J = 6 Hz, $C(CH_3)_2$), 0.89 (3 H, d, J = 6 Hz, $C(CH_3)_2$), 1.12 (3 H, s, CH_3), 5.0–5.75 (2 H, m, olefinic), 5.62 (1 H, s, enone), 9.72 (1 H, t, J = 2 Hz, CHO); IR (neat) 1720 and 1665 cm^{-1}.

(16) C(20)α-methyl resonances are 0.08 ppm higher field in NMR spectrum than C(20)β-methyl. Enone **3**: NMR ($CDCl_3$, 100 MHz) δ 0.91 (6 H, d, J = 6.35 Hz, $-C(CH_3)_2$), 1.02 (3 H, d, J = 7.3 Hz, CH_3), 1.00 (3 H, s, CH_3), 5.23 (1 H, dd, J = 16.2 and 8.7 Hz, CC*H*=CH—), 5.29–5.59 (1 H, m, CCH=C*H*—), 5.74 (1 H, s, enone); IR (neat) 1670 and 975 cm^{-1}; HPLC retention time, 10.0–10.8 min (Si-60-5μm, 4 o.d. × 250 mm, 5 mL/min, 3.7% AcOEt in hexane. Enone **17**: NMR ($CDCl_3$, 100 MHz) δ 0.91 (6 H, d, J = 6.3 Hz, $-C(CH_3)_2$), 1.10 (3 H, d, J = 7.8 Hz, CH_3), 1.13 (3 H, s, CH_3), 5.26 (1 H, dd, J = 15.2 and 7.0 Hz, CC*H*=CH—), 5.29–5.62 (1 H, m, CCH=C*H*—), 5.76 (1 H, s, enone); IR (neat) 1675 and 975 cm^{-1}; HPLC retention time 11.0–12.1 min (3.7% AcOEt in hexane).

(17) We are indebted to Professor P. A. Grieco for providing an authentic sample of **18**.[1d]

A Novel Methoxy-Directed Ketal Hydrolysis and Its Application to a Convergent, Regiospecific Synthesis of (±)-Daunomycinone

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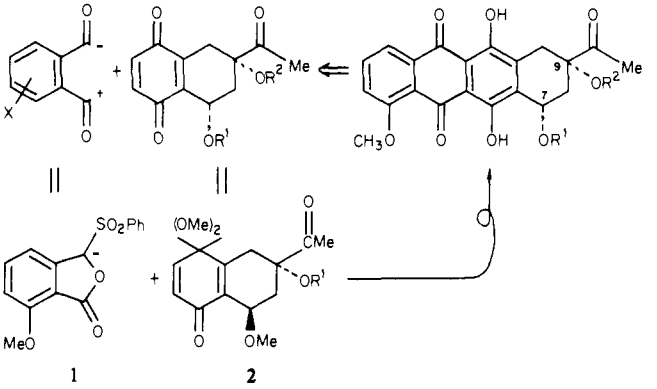
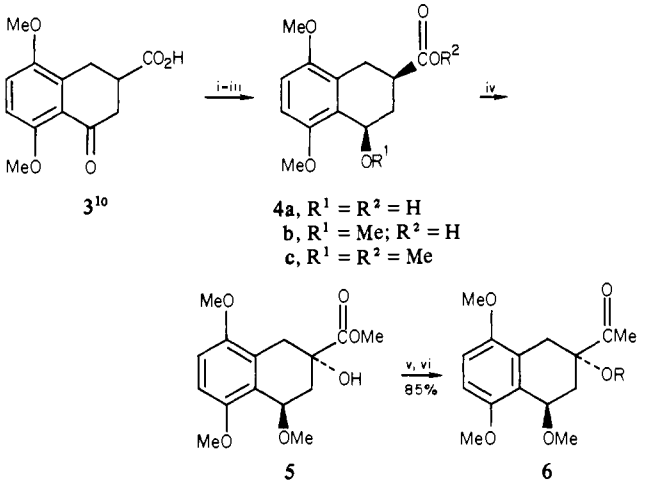
Quinone monoketals, readily available via anodic oxidation of 1,4-dimethoxy aromatic systems followed by monohydrolysis, are of demonstrated utility in organic synthesis.[1] However, the hydrolyses of quinone bisketals to the respective monoketals usually show only poor to moderate regioselectivity unless a suitable substituent (i.e., Br, OMe, SMe) is unsymmetrically substituted on the molecule.[1,2] Recent studies have established the utility of quinone monoketals in the regiospecific synthesis of anthrones[3] and anthraquinones.[4] Thus, a combination of any one of the available 1,4-dipole equivalents[3-5] with an appropriate quinone monoketal (i.e., **2**) would effect a one-step synthesis of an anthracyclinone fully functionalized in the A ring (Scheme I). The latter consideration is especially important since, in spite of a number of excellent syntheses of 7,9-dideoxy- and 7-deoxyanthracyclinones,[6] procedures for introduction of the 7,9-dioxygen[7] or 7-oxygen[8] substituents are less than adequate, especially for

Scheme I. 1,4-Dipole–Quinone Strategy for Anthracyclinone Synthesis



1 2

Scheme II.[a] Synthesis of A,B-Ring Fragment



[a] (i) $NaBH_4$, EtOH; (ii) NaH, MeI; (iii) CH_2N_2; (iv) LiCA, MoOPH; (v) Me_3SiCl, HMDS, Py; (vi) $LiCH_2SOMe$, KF, Al(Hg)

† Conoco Oil Fellow, 1980–1981.

‡ The Ohio State University Presidential Fellow, 1980–1981.

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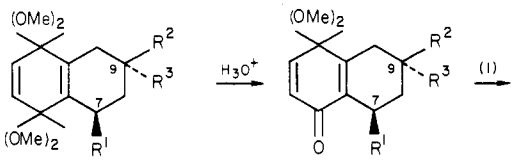
reasonable-scale preparation of the compounds. While three recent routes to 4-demethoxydaunomycinone[9] have permitted the direct synthesis of the fully oxygenated aglycon, only recently has this methodology been incorporated together with the regiochemical control required by the naturally occurring aglycon.[6] After exploratory studies on the suitability of the known systems which would serve as 1,4-dipole equivalents in reaction with quinone monoketals, the "Hauser anion"[5a] (**1**) was deemed most appropriate. We report herein an interesting and useful directing effect of a neighboring methoxy group on the monohydrolysis of several functionalized bisketals and the utilization of this chemistry in a convergent, regiospecific synthesis of anthracyclinones.

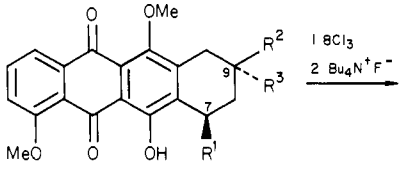
The required systems for study were prepared as outlined in Scheme II.[10] While the intermediates shown were purified and characterized, it is most expedient to proceed directly from **3** to **5** without purification and to isolate **5** (45% from **3**) by silica gel chromatography [11% of the cis isomer (OH, OMe) of **5** was also obtained]. The anodic oxidation of **4c**, **5**, and **6** [R = *t*-Bu(Me)$_2$Si][11] gave the corresponding bisketals **7b**, **7c**, and **7d** in yields of 92%, 85%, and 96%, respectively.

Two critical questions remained to be answered: (1) would the methoxy group at C_7[13] influence the monohydrolysis of bisketals such as **7** and (2) would the oxygen substituents at C_7 and C_9 survive the annelation reaction conditions? Monohydrolysis of

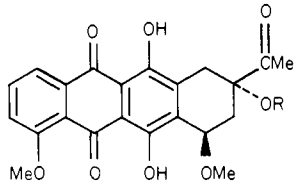


7 **8**

a, $R^1 = R^3 = H$; $R^2 = CO_2Me$
b, $R^1 = OMe$; $R^2 = CO_2Me$; $R^3 = H$
c, $R^1 = OMe$; $R^2 = CO_2Me$; $R^3 = OH$
d, $R^1 = OMe$; $R^2 = COMe$; $R^3 = OTDS$



9



10a, R = *t*-BuMe$_2$Si
b, R = H

bisketals **7b–d** was especially clean, affording the respective monoketals **8b** (90%), **8c** (92%), and **8d** (79%) with >95% regioselectivity.[14] By contrast, hydrolysis of **7a** gave ca. 55:45 mixture (NMR analysis) of two monoketals. While the 7-methoxy group of **8b** survived the cyclization conditions nicely giving **9b** in 49% yield, attempts to couple the monoketals having a free hydroxyl group at C_9 gave poor yields of tetracyclic products, perhaps due to a competing fragmentation reaction. However, protection of the C_9 hydroxyl [**8c** (R^3 = OMe_3Si), **8d**] gave the tetracyclic compounds **9c** (37%) and **9d** (50%)[15] in moderate yield after silica gel chromatography. The structure of **9d** was rigorously established by methylation at the C_6-OH group [$(Me)_2SO_4$, K_2CO_3, MeCOMe], desilylation ($Bu_4N^+F^-$, THF), and comparison of this material with an authentic sample synthesized via our bisketal route.[9c] Since the annelation is regiospecific,[3,4] this establishes the structure of **8d** and, by inference, **8b,c** and **9b,c**. In some systems, we observed higher yields when the annelation step was conducted in dimethyl sulfoxide–tetrahydrofuran (homogeneous conditions) using dimsyl anion as the base. In this manner, reaction of **1** with **8d** followed by boron trichloride demethylation gave **10a** in 47% yield over the two steps.

For completion of the synthesis, **9d** was demethylated (BCl_3, −70 °C, >90%) and desilylated (90%) to afford (±)-epi-7-methoxy-7-deoxydaunomycinone (**10b**). This can be converted by solvolysis[16] to (±)-daunomycinone. An especially attractive feature of the synthesis is the facile, regiospecific demethylation at the C_{11}-methoxy group without the complications usually associated with demethylations when C_6 and C_{11} both bear methoxy groups.[16,17] This chemistry then serves as an efficient, regiospecific, convergent route to rhodomycinone aglycons and analogues easily adaptable to large-scale preparation of these molecules. Furthermore, deoxygenation at C_6 would afford an entry into 6-deoxyrhodomycinone and citromycinone aglycons. Finally, the easy synthesis of quinone monoketals such as **8**, together with available 1,4-dipole equivalents,[5] presents a versatile and general entry into anthraquinone-type ring systems.[18,19]

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for support and Mr. G. Larson for the 200-MHz spectra.

Supplementary Material Available: NMR spectra (16 pages). Ordering information is given on any current masthead page.

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(10) This route closely follows that of ref 9c.
(11) The *tert*-butyldimethylsilyl protecting group[12] was formed in 75% yield from the ketone, *tert*-butyldimethylsilyl chloride (5 equiv), and imidazole (10 equiv) in DMF at 100 °C for 3 days.
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(13) The numbering refers to the positions in the anthracyclinone derived from these AB-ring precursors.
(14) Hydrolysis conditions were as follows (see ref 1 for more details): **7b** (0.5 g), 5 mL of 8% HOAc, 10 mL of acetone, 25 °C, 5 min; **7c** (0.28 g), 4.0 mL of 8% HOAc, 8 mL of acetone, 25 °C, 5 min; **7d** (1.35 g), 16.5 mL of 4% HOAc, 33 mL of acetone, 0 °C, 1 h.
(15) In the coupling of **8** (R^1–R^3 = H) with **1**, a colorless side product was obtained after acid workup which was established as 1,2,3,4-tetrahydro-5,8-dihydroxy-6-(phenylsulfonyl)naphthalene. This reasonably arises by addition of phenyl sulfinate liberated in the cyclization step with unreacted **8**. Suppression of this reaction would enhance the yield of the annelation.
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(18) All new compounds showed acceptable spectroscopic and analytical properties; the melting points (°C) are as follows: **4a**, 155–156; **4b**, 113–114; **4c**, 87–89; **5**, 108–109; **6** [R = H], 114–116; **6** (R = *t*-BuMe$_2$Si), 115–117; **7b**, 69–71; **8b**, 108–110; **7c**, 99–100; **8c**, 145–147; **8d**, 92–93; **9b**, 195–197; **9c**, 218–219; **9d**, 235–238; **10a**, 230–231; **10b**, 274–275. **7a**, **8a**, and **7d** were utilized as oils.
(19) The following procedure is representative of these annelations. To a mixture of 20 mL of THF and 20 mL of Me_2SO at 0 °C was added 1.53 mL of 1.59 N BuLi in hexane (2.43 mmol) to form the dimsyl anion. To this solution was added dropwise a solution of 0.74 g (2.43 mmol) of the sulfone and 1.0 g (2.43 mmol) of **8d** in 10 mL of Me_2SO. The reaction was stirred for 10 min at 0 °C (deep red color) and then at room temperature for 3 h (purple solution). The solution was cooled, acidified to pH 2 with 4 mL of 1 N HCl, and concentrated in vacuo. The residue was treated with 75 mL of CH_2Cl_2, filtered, and washed with water. After workup the orange residue was chromatographed on silica gel (0.5% MeOH/CH_2Cl_2 as eluant) to afford after recrystallization **9d** as orange needles, mp 236–238 °C. However, more conveniently, the crude residue from the annelation step was dissolved in 190 mL of CH_2Cl_2 and cooled to −78 °C under a N_2 atmosphere. To the solution was added 29 mL of 1 N BCl_3 in CH_2Cl_2 over 15 min, followed by stirring the reaction mixture for 45 min at −78 °C. After quenching the reaction by dropwise addition of MeOH at −78 °C, workup, and recrystallization (MeOH/CH_2Cl_2), 0.57 g of pure **10a** was obtained. Chromatography (as for **9d**) of the mother liquors gave an additional 0.044 g, for a total yield of 0.614 g (47%) over two steps; mp 230–231 °C.