spectrum with that in the Sadtler index. *o*-MePhSPh and *m*-MePhSPh were identified by the analogy of their GC retention times and methyl group ^{1}H NMR chemical shifts (δ 2.29 and 2.37, respectively) with those for the corresponding ethers (Table II). The sulfide aromatic proton absorptions in the NMR, unlike those of the ethers, are not essentially first order at 250 MHz and consist of many lines in the δ 7.1–7.4 range.

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Registry No. PhOH, 108-95-2; PhI, 591-50-4; *o*-MePhI, 615-37-2; *p*-MePhI, 624-31-7; *m*-MePhOH, 108-39-4; *p*-MePhOH, 106-44-5; PhSH, 108-98-5; PhOPh, 101-84-8; *o*-MePhOPh, 3991-61-5; *m*-MePhOPh, 3586-14-9; *p*-MePhOPh, 1706-12-3; PhSPh, 139-66-2; *o*-MePhSPh, 13963-35-4; *m*-MePhSPh, 13865-48-0; potassium *tert*-butoxide, 865-47-4; benzyne, 462-80-6.

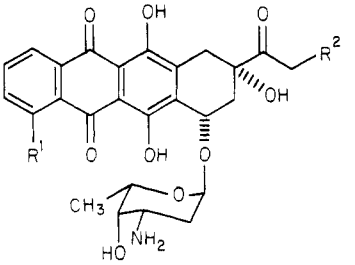
Communications

A New General Regiocontrolled Synthesis of Anthracyclinones Using Cycloaddition of Homophthalic Anhydrides to 2-Chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-Ethanediyl Acetal

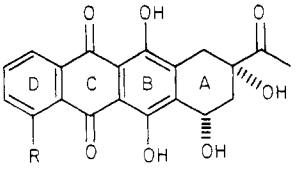
Summary: The cycloaddition of 2-chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-ethanediyl acetal (**10**) with homophthalic anhydrides **6** and **9** furnished the adducts **19** and **25**, which were readily converted into 5,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione (**23**) and 6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione (**27**), late stage precursors to 4-demethoxydaunomycinone (**4**) and daunomycinone (**5**).

Sir: The anthracycline antibiotics daunomycin (**1**), adriamycin (**2**), and carminomycin (**3**) are effective antineoplastic agents against a variety of experimental tumors and some types of human cancer.[1] Over the past several years several elegant regiospecific syntheses of their aglycones have been reported.[2] We now communicate our recent work in this area, which provides a novel and potentially useful route to 4-demethoxydaunomycinone (**4**) and daunomycinone (**5**).

Recently we reported that condensation of homophthalic anhydride **6** with juglone (**7**) produced the tetracyclic compound **8** as the sole product (Scheme I).[3] We have now used this regiospecific cycloaddition for the synthesis of anthracyclinones **4** and **5**. Thus, our synthetic strategy to **4** and **5**, which is outlined in Scheme II, centers on the one-step construction of a linear tetracycle bearing oxygen functionalities (hydroxy or oxo group) in both B and C rings through cycloaddition of homophthalic anhydrides



1, $R^1 = OCH_3$; $R^2 = H$
2, $R^1 = OCH_3$; $R^2 = OH$
3, $R^1 = OH$; $R^2 = H$



4, R = H
5, R = OCH_3

6 and **9** to the appropriately functionalized quinone **10**.

The preparation of the chloroquinone acetal **10** was achieved in 65% overall yield from commercially available[4] 2,6-dichlorobenzoquinone (**11**) by the three-step sequence shown in Scheme III. Diels–Alder reaction of 2-[(trimethylsilyl)oxy]butadiene (**12**)[5] with **11** (ether or benzene, 35–60 °C, 3–6 h, under argon) led to the adduct **13**.[6] Mild acetalization[7] of **13** by the method of Larson[8] (ethylene

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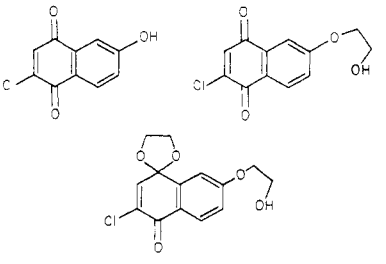
(3) Tamura, Y.; Wada, A.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1981**, *22*, 4283.

(4) The reagent is available from Tokyo Kasei Chemical Co., of Japan, and Aldrich Chemical Co.

(5) Girard, C.; Amice, P.; Barnier, J. P.; Conia, J. M. *Tetrahedron Lett.* **1974**, 3329.

(6) Although the stereochemistry of **13** could not be determined with certainly, the endo adduct is expected as the major product from consideration of similar cycloadditions.[9]

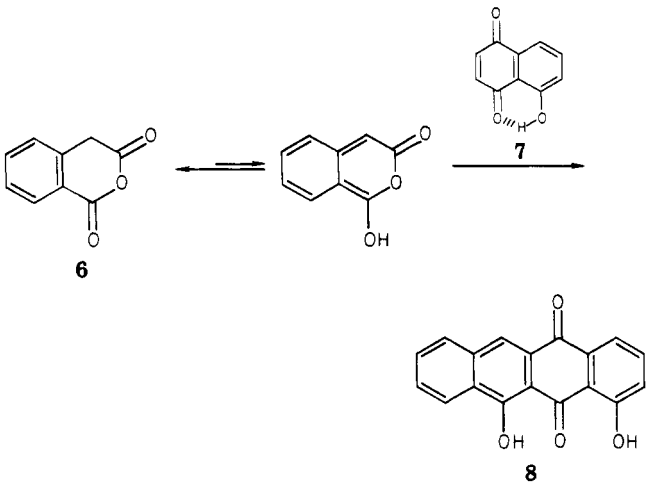
(7) Normal acetalization condition (ethylene glycol–*p*-TsOH in refluxing benzene) of **13** or acetalization after dehydrochlorination of **13** readily caused aromatization and preferentially gave the naphthoquinones shown below.



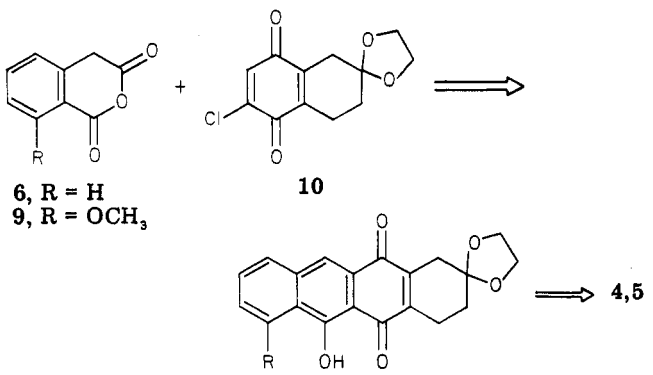
(8) (a) Larson, G. L.; Hernandez, A. *J. Org. Chem.* **1973**, *38*, 3935. (b) *Synth. Commun.* **1974**, *4*, 61.

0022-3263/82/1947-4376$01.25/0

Scheme I



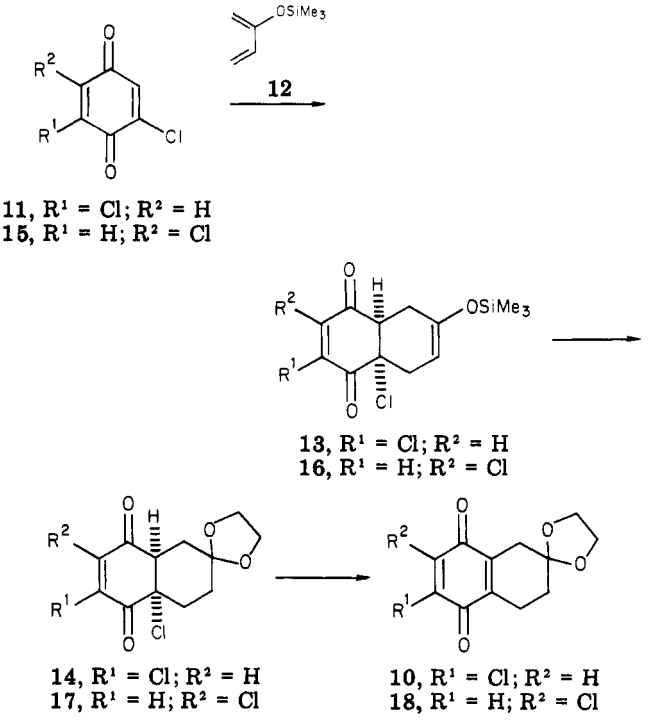
Scheme II



glycol–catalytic amount of concentrated HCl, ether, room temperature, 5 h) gave a high yield of the acetal **14**, which was subsequently dehydrochlorinated (Et_3N, room temperature, 2 h) to **10** (mp 149.5–150 °C from benzene–hexane). The preparation of **10** from **11** was readily performed in one pot within 10 h. When the same sequence of reactions was carried out with 2,5-dichlorobenzoquinone (**15**) as the starting material, the isomeric chloroquinone acetal **18** was obtained (56% overall yield from **15**, mp 98–98.5 °C from benzene–hexane) via the intermediates **16** and **17**. The orientation of the Diels–Alder reaction of **12** with **11** and **15** was readily assigned by the fact that the nucleophilic end of the diene systems selectively reacts at the unsubstituted olefinic site of the chlorobenzoquinones.[9,10]

From our previous results[3] it was expected that the nucleophilic end (C-4 position) of the homophthalic anhydride **6** would attack on the more positive site of dienophile. The reaction of **6** with an equimolar amount of **10** (bromobenzene, 100–110 °C, 1–2 h) regiospecifically gave the 6-hydroxynaphthacenone **19** (43%, mp 229.5–230.5 °C

Scheme III



from $CHCl_3$) and with **18** under the same conditions gave the isomeric 11-hydroxynaphthacenone **20** (50%, mp 214–216 °C from $CHCl_3$).[11] The isolated regioisomers **19** and **20** were distinguishable by the chemical shift of the phenolic protons in their respective ^1H NMR spectra. In this Diels–Alder reaction, employment of the known[11] naphthoquinone acetal **21** instead of the acetals **10** and **18** gave an inseparable mixture (3:2) of **19** and **20** in 19% yield. The use of the lithium salt of **6** in the cycloaddition dramatically improved the yield of the adduct **19**. Thus, lithiation of **6** with lithium diisopropylamide (LDA) followed by treatment with **10** (THF, –78 °C for 20 min and allowed to warm to room temperature, under argon) gave

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(12) The mechanism for the addition of the lithium salt to **10** has not been finalized yet.

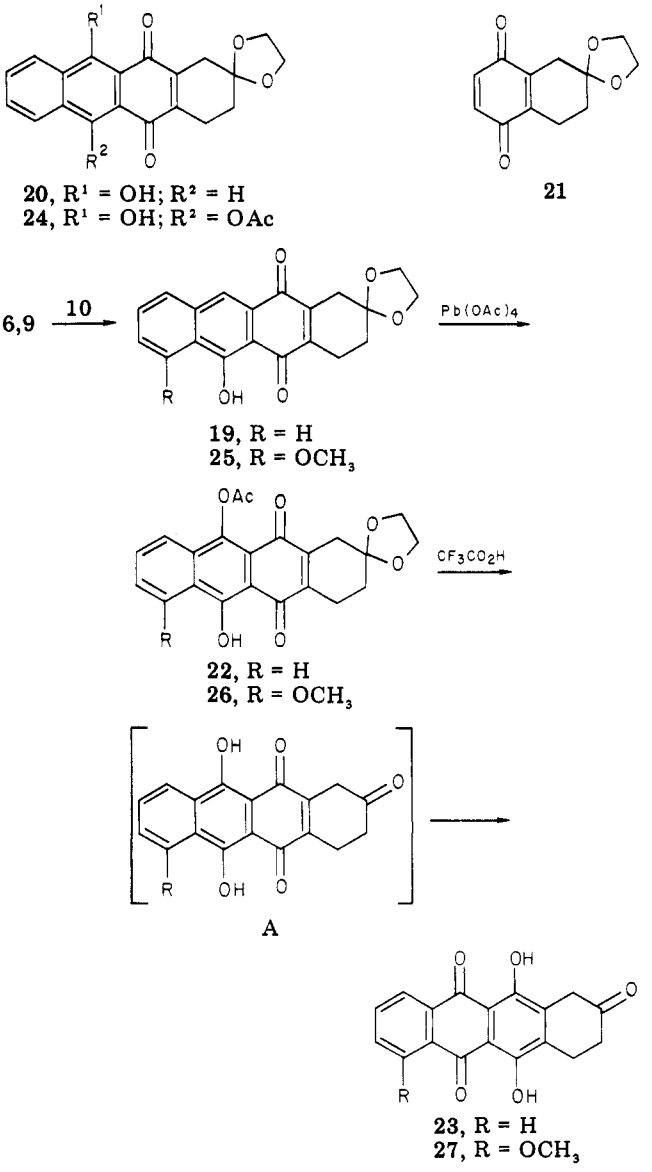
(13) The ^1H NMR spectra were taken in $CDCl_3$ with a Hitachi R-20A (60 MHz) or R-22 (90 MHz) spectrometer with Me_4Si as an internal standard. The IR spectra were taken with a Shimazu-IR-27G spectrometer. Spectral data are as follows. **10**: ^1H NMR δ 6.82 (s, 1 H), 4.0 (s, 4 H), 2.9–2.5 (m, 4 H), 1.86 (t, 2 H); IR 1670, 1655, 1595, 1125 cm^{-1}. **13**: ^1H NMR δ 6.89 (s, 1 H), 4.8–4.6 (m, 1 H), 3.8–2.2 (m, 5 H), 0.17 (s, 9 H); IR 1720, 1690, 1670, 1585, 1250 cm^{-1}. **14**: ^1H NMR δ 6.88 (s, 1 H), 4.2–3.8 (m, 1 H), 3.99 (s, 4 H), 3.0–2.5 (m, 4 H), 1.84 (t, 2 H); IR 1710, 1670, 1655, 1590, 1125 cm^{-1}. **16**: ^1H NMR δ 7.01 (s, 1 H), 4.9–4.7 (m, 1 H), 3.67 (t, 1 H), 3.3–2.4 (m, 4 H), 0.21 (s, 9 H); IR 1690, 1665, 1585, 1245 cm^{-1}. **17**: ^1H NMR δ 6.93 (s, 1 H), 3.71 (s, 4 H), 4.2–2.4 (m, 7 H); IR 1690, 1680, 1655, 1590, 1130 cm^{-1}. **18**: ^1H NMR δ 6.89 (s, 1 H), 4.0 (s, 4 H), 2.8–2.5 (m, 4 H), 1.82 (t, 2 H); IR 1650, 1600, 1120 cm^{-1}. **19**: ^1H NMR δ 14.06 (s, 1 H), 8.55–8.35 (m, 1 H), 8.01 (s, 1 H), 7.95–7.5 (m, 3 H), 4.02 (s, 4 H), 3.1–2.8 (m, 4 H), 1.92 (t, 2 H); IR 1655, 1630, 1605 cm^{-1}. **20**: ^1H NMR δ 13.97 (s, 1 H), 8.6–8.3 (m, 1 H), 8.01 (s, 1 H), 8.0–7.5 (m, 3 H), 4.02 (s, 4 H), 3.1–2.8 (m, 4 H), 1.92 (t, 2 H); IR 1655, 1630, 1605 cm^{-1}. **22**: ^1H NMR δ 13.56 (s, 1 H), 8.2–7.9 (m, 2 H), 7.7–7.4 (m, 2 H), 3.98 (s, 4 H), 3.02 (t, 2 H), 2.83 (s, 2 H), 2.47 (s, 3 H), 1.95 (t, 2 H); IR 1760, 1655, 1630 cm^{-1}. **23**: ^1H NMR δ 13.48 (s, 1 H), 13.37 (s, 1 H), 8.4–8.2 (m, 2 H), 7.9–7.6 (m, 2 H); 3.76 (s, 2 H), 3.40 (t, 2 H); IR 1710, 1610, 1580 cm^{-1}. **24**: ^1H NMR δ 13.57 (s, 1 H), 8.4–8.0 (m, 2 H), 7.8–7.5 (m, 2 H), 4.02 (br s, 4 H), 3.00 (s, 2 H), 2.81 (t, 2 H), 2.48 (s, 3 H), 1.93 (t, 2 H); IR 1760, 1655, 1630 cm^{-1}. **25**: ^1H NMR δ 15.11 (s, 1 H), 7.93 (s, 1 H), 7.7–6.9 (m, 3 H), 4.0 (br s, 7 H), 3.0–2.75 (m, 4 H), 1.89 (t, 2 H); IR 1650, 1630, 1600, 1575 cm^{-1}. **26**: ^1H NMR δ 13.84 (s, 1 H), 7.9–7.2 (m, 3 H), 4.04 (s, 3 H), 4.03 (s, 4 H), 3.04 (t, 2 H), 2.84 (br s, 2 H), 2.46 (s, 3 H), 1.93 (t, 2 H); IR 1760, 1660, 1630, 1590 cm^{-1}. **27**: ^1H NMR δ 13.89 (s, 1 H), 13.38 (s, 1 H), 8.1–7.2 (m, 3 H), 4.07 (s, 3 H), 3.60 (s, 2 H), 3.26 (t, 2 H); IR 1715, 1615, 1590 cm^{-1}.

a near quantitative yield of the naphthacenone **19**.[12]

Attention was then focused on the oxidation of **19** at C(11) by means of the previously introduced 6-OH group. Although initial attempts to effect a direct para hydroxylation leading to the intermediate A under various conditions ($O_2/h\nu$, $NaOH/O_2$, $CrO_3/AcOH$, *m*-CPBA/CH_2Cl_2, and $H_2O_2/NaOH$) were unsuccessful, further investigation revealed a two-step sequence that resulted in the desired transformation. Treatment of **19** with lead tetraacetate [$AcOH-CH_2Cl_2$ (2:1), room temperature, 16 h] gave the para-acetoxylated ketone **22** (80%, mp 215–217 °C from MeOH). Acid treatment of **22** [$CF_3CO_2H-H_2O$ (2:1), 50 °C, 0.5 h] caused deacetalization, deacetylation, and enol–keto isomerization in B/C rings at the same time to give the desired naphthacenone **23**[13] [95%, mp 296–298 °C dec from MeOH (lit.[14] mp 310 °C, lit.[15] mp 300 °C)]. All spectral data were identical with those reported[14,15] and the ketone **23** was also shown to be identical with the sample obtained from **20** by the same sequence of reactions via the 6-acetoxy ketone **24** (mp 226–228 °C from MeOH). Since the conversion of **23** to (±)-4-demethoxydaunomycinone (**4**) has already been described,[15] our synthesis of **23** constitutes a new route to **4**.

For the synthesis of (±)-daunomycinone (**5**), 8-methoxyhomophthalic anhydride **9**[16] was reacted with **10** (bromobenzene, 110 °C, 0.5 h) to give regiospecifically the adduct **25** in low yield. The use of the lithium salt of **9** (THF, −78 °C, 20 min and allowed to warm to room temperature, under argon) afforded a good yield of the same adduct **25**, regiospecifically (65%, mp 252–254 °C from CH_2Cl_2–MeOH).[12] The conversion of **25** to the final ketone **27** was accomplished by the same method described for the conversion of **19** to **23**. Oxidation of **25** [$Pb(OAc)_4$, $AcOH-CH_2Cl_2$, room temperature, 16 h] gave the acetoxy ketone **26** (61%, mp 244.5–246 °C from CH_2Cl_2–MeOH), which underwent acid hydrolysis [$CF_3CO_2H-H_2O$ (2:1), 50 °C, 6 h] and enol–keto isomerization in situ to form **27**[13] [95%, mp 252–256 °C dec from AcOH, lit.[17] mp 248–250 °C, lit.[2e,18] mp 251–255 °C, lit.[2h] mp 252–256 °C], which was in all respects identical with a sample generously provided by Dr. Frank M. Hauser. Since **27** has been converted to **5**,[17] this comprises a regiospecific synthesis of **5**. The synthetic sequence presented here (Scheme IV) furnished **23** and **27**, late-stage precursors to **4** and **5**, from homophthalic anhydrides **6** and **9** in three steps and high overall yields (76% and 38% overall yields, respectively). A similar, but inverted approach that furnishes a 9-keto-11-deoxy product has recently been described by Jung et al.[19] and similar regiospecific Diels–Alder reactions with halogenated quinones that provide an 11-deoxyanthracyclinone have been described by Gesson et al.[20] and Rapoport et al.[21] The present method using modified homophthalic anhydride and chloroquinone components provides a potentially useful convergent synthesis of a variety of anthracyclinone analogues.

Scheme IV



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Registry No. (±)-**4**, 58924-49-5; (±)-**5**, 59367-20-3; **6**, 703-59-3; **6** Li, 83043-95-2; **9**, 74794-52-8; **9** Li, 83043-99-6; **10**, 83043-87-2; **11**, 697-91-6; **12**, 38053-91-7; (±)-**13**, 83043-88-3; (±)-**14**, 83043-89-4; **15**, 615-93-0; (±)-**16**, 83043-90-7; (±)-**17**, 83043-91-8; **18**, 83043-92-9; **19**, 83043-93-0; **20**, 83043-94-1; **21**, 66947-63-5; **22**, 83043-96-3; **23**, 58977-09-6; **24**, 83043-97-4; **25**, 83043-98-5; **26**, 83044-00-2; **27**, 59325-97-2.

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