partially at pH 9.4 and no more above pH 10.1. This observation seems consistent with the fact that the giant Hb is dissociated into smaller assembly at pH 9,[16] and thus it appears less likely that an electron donor is an exogeneous impurity. Recalling that human metHb was partially photoreduced by laser irradiation at 441.6 nm only for the low-affinity quaternary structure,[9] we suggest that the photoexcitation of electrons creates a hole in the heme, to which an electron is transferred from the protein moiety with the specific conformation. The very similar phenomena were also observed for another giant hemoprotein, chlorocruorin with $M_r = 3 \times 10^6$, for which the photoreduction ceased to occur at alkaline pH.[17] Therefore, such feature seems inherent in the extracellular giant Hb's. Kinetics of photoreduction of this giant Hb are under investigation with time-resolved RR spectroscopy.

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A Novel Route for Stereospecific Construction of the A Ring of Anthracyclinones: Total Synthesis of (±)-γ-Citromycinone

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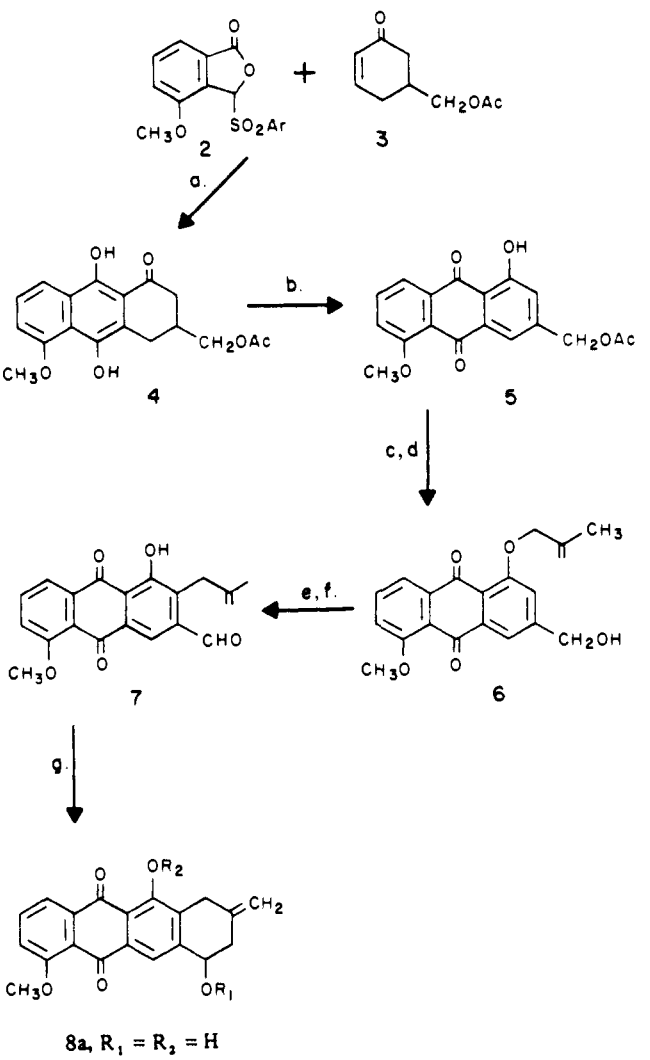
We have developed a conceptually new route for regio- and stereo-specific construction of the A ring of anthracyclinones with cis hydroxyl functionalities at C-7 and C-9.

The most commonly used sequence for constructing the A ring of such anthracyclinones has been to first fabricate an intermediate containing the 9-hydroxyl group then introduce the 7-hydroxyl through homolytic bromination and solvolysis.[1-3] The disadvantages associated with this procedure are well documented[4]—only moderate stereoselectivity is observed and the preparative value is frequently compromised by the low solubility of anthracyclinones in media that are compatible with the required bromination.

In contrast, our methodology directly generates the 7-hydroxyl group first, during the course of constructing the A ring, then utilizes this functionality to guide the stereospecific introduction of the second hydroxyl group at the 9-position. The key step in this sequence is the intramolecular ene reaction of the olefinic aldehyde **7** to regiospecifically furnish the *exo*-methylene alcohol **8a**.

As a demonstration of the efficacy of this methodology, we have performed the first total synthesis of γ-citromycinone. Because only small quantities of this rare anthracyclinone were originally

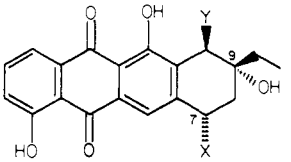
Scheme I



8a, $R_1 = R_2 = H$

[a] LiO-*t*-Bu, THF. [b] O_2, DMF, 100 °C, 12 h; 55% overall from **2**. [c] 2-(Chloromethyl)propene, K_2CO_3, KI, acetone; 95%. [d] NaOH, H_2O-THF; 98%. [e] $Na_2S_2O_4$, DMF, Δ; 94%. [f] $BaMnO_4$, CH_2Cl_2; 92%. [g] $SnCl_4 \cdot 5H_2O$, CH_2Cl_2; 93%.

isolated, a definitive structural assignment was not possible and two structures, **1a** and **1b**, were initially postulated.[5] Two groups[6,7]



1a, X = OH; Y = H
b, X = H; Y = OH

independently prepared **1b**; however, the mass spectral fragmentation pattern was inconsistent with that of γ-citromycinone, and the structure was revised to **1a**.[6,8,9]

The regiospecific preparation of the ene product **8a**, which serves

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(9) Introduction of the 7-hydroxyl group in 4,6,7-trideoxydaunomycinone was accomplished in modest yield using the bromination procedure. The product was converted to the 4,6-dideoxy analogue of daunorubicin and shown to have anticancer activity comparable with daunorubicin. Penco, S.; Angelucci, F.; Arcamone, F.; Ballabio, M.; Barchielli, G.; Francheschi, G.; Franchi, G.; Suarato, A.; Vanotti, E. *J. Org. Chem.* **1983**, *48*, 405.

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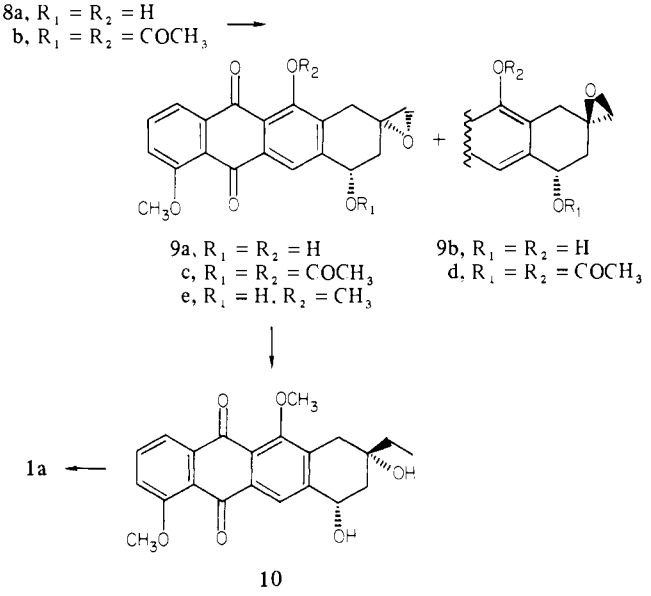
Scheme II



as an intermediate to γ-citromycinone (**1a**), is shown in Scheme I. Condensation[10] of the phthalidylsulfone **2**[11] (3 equiv of LiO-*t*-Bu, THF; initially at −78 °C and then at reflux) with **3**[12] gave the regiospecifically constructed tetrahydronaphthacene **4** which was directly transformed to the anthraquinone **5**[13] (55% overall yield) upon heating in DMF under an oxygen atmosphere[14] (100 °C, 12 h). Reaction of **5** with 2-(chloromethyl)propene (K_2CO_3, acetone; 95%) gave the allyl ether intermediate that was deacetylated (NaOH, H_2O–THF; 98%) to furnish the hydroxymethylanthraquinone **6**. Claisen rearrangement[15] of **6** ($Na_2S_2O_4$, DMF; 94%) followed by oxidation[16] of the hydroxymethyl group ($BaMnO_4$, CH_2Cl_2; 92%) gave the olefinic aldehyde **7**.

Treatment of **7** in methylene chloride with stannic chloride pentahydrate (0.5 equiv) resulted in instantaneous formation of **8a** as the sole regioisomer of reaction in 93% yield. The *exo*-methylene protons in the ^1H NMR spectrum of **8a** appeared as two singlets centered at 5.08 and 5.15 ppm. The C-7 proton at 4.75 ppm became a triplet (J = 4 Hz) upon exchange (D_2O) indicating that the C-7 hydroxyl group is axially oriented and therefore antiperiplanar with respect to the aromatic fragment.

The use of the seven hydroxyl group to effect stereocontrolled manipulation of the C-9, 13 olefinic group was straightforwardly realized as shown in Scheme II. Epoxidation of **8a** and the diacetate derivative **8b** with MCPBA (CH_2Cl_2; 89%) gave a 4:1 and 1:1 ratio of the corresponding *cis*- (**9a,c**) and *trans*-epoxides (**9b,d**), respectively. Ultimately, Sharpless epoxidation[17] of **8a** ($VO(AcAc)_2$, *t*-BuOOH, CH_2Cl_2) furnished **9a** as the sole stereoisomer of reaction (66%[18]).

Methylation of **9a** (Me_2SO_4, K_2CO_3, acetone; 91%) gave the methyl ether intermediate **9e**,[19] which was reacted with excess methyl copper[20] (2CuCN, 12MeLi; THF, 0 °C; 84%) to construct the ethylcarbinol fragment from the epoxide and furnished **10**. Demethylation of **10** (BCl_3, CH_2Cl_2, 86%) completed the synthesis of γ-citromycinone (**1a**). A direct comparison with an authentic sample was not possible due to its rarity; however, the mass spectrum of the synthetic material[21] was in excellent agreement with that reported for natural γ-citromycinone.[6]

Studies to establish the generality of this plan as a route for enantio- and stereospecific synthesis of other classes of anthracyclinones are being conducted.

Acknowledgment. We thank Dr. Bruce Lipschutz for helpful discussions. This work was generously supported by the National Cancer Institute of the National Institutes of Health (Grant 18141).

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(13) Compounds **1a**, **5**, **6**, **7**, **8a**, **9a**, and **10** gave satisfactory combustion analyses (C ≤ 0.2%; H ≤ 0.3%). Melting points and ^1H NMR spectra of selected intermediates are given below. **5**: mp 178–180 °C; ^1H NMR ($CDCl_3$) δ 12.43 (s, 1 H), 7.98 (d, 1 H, J = 8.0 Hz), 7.73 (t, 1 H, J = 8.0 Hz), 7.72 (s, 1 H), 7.30 (d, 1 H, J = 8.0 Hz), 7.2 (s, 1 H), 5.18 (s, 2 H), 4.04 (s, 3 H), 2.16 (s, 3 H). **6**: ^1H NMR ($CdCl_3$) δ 7.88 (dd, 1 H, J = 7.5, 1.3 Hz) 7.73 (s, 1 H), 7.67 (t, 1 H, J = 7.5 Hz), 7.28 (s, 1 H), 7.23 (dd, 1 H, J = 7.5, 1.3 Hz), 5.35 (br s, 1 H), 5.06 (br s, 1 H), 4.78 (s, 1 H), 4.56 (s, 1 H), 4.01 (s, 3 H), 2.6 (br s, 1 H), 1.90 (s, 3 H). **7**: mp 187–189 °C; ^1H NMR ($CDCl_3$) δ 12.93 (s, 1 H), 10.32 (s, 1 H), 8.26 (s, 1 H), 8.00 (d, 1 H, J = 7.5 Hz), 7.76 (t, 1 H, J = 7.5 Hz), 7.40 (d, 1 H, J = 7.5 Hz), 4.82 (br s, 1 H), 4.39 (br s, 1 H), 4.07 (s, 3 H), 3.88 (br s, 2 H), 1.89 (s, 3 H). **8a**: mp 199–201 °C; ^1H NMR ($CDCl_3$) δ 12.81 (s, 1 H), 7.96 (dd, 1 H, J = 7.5, 1.3 Hz), 7.86 (s, 1 H), 7.71 (t, 1 H, J = 7.5 Hz), 7.35 (dd, 1 H, J = 7.5, 1.3 Hz), 5.15 (br s, 1 H), 5.08 (br s, 1 H), 4.8 (m, 1 H), 4.04 (s, 3 H), 3.53 (s, 2 H), 2.69 (unresolved dd, 2 H), 2.22 (d, 1 H, J = 8.0 Hz). **9a**: ^1H NMR ($CDCl_3$) δ 12.79 (s, 1 H), 7.91 (dd, 1 H, J = 7.9, 1.3 Hz), 7.90 (s, 1 H), 7.71 (t, 1 H, J = 7.9 Hz), 7.36 (dd, J = 7.9, 1.3 Hz), 4.99 (br s, 1 H), 4.05 (s, 3 H), 3.12 (d, 1 H, J = 19 Hz), 2.86 (s, 2 H), 2.82 (d, 1 H, J = 19 Hz), 2.26 (dd, 1 H, J = 14.0, 4.8 Hz), 2.02 (dd, 1 H, J = 14.0, 4.8 Hz). **10**: mp 167–170 °C; ^1H NMR ($CDCl_3$) δ 8.15 (s, 1 H), 7.84 (d, 1 H, J = 8.0 Hz), 7.65 (t, 1 H, J = 8.0 Hz), 7.25 (d, 1 H, J = 8.0 Hz), 4.92 (m, 1 H), 4.24 (d, 1 H, J = 8.0, D_2O exchangeable), 4.00 (s, 3 H), 3.88 (s, 3 H), 3.16 (br d, 1 H, J = 18.4 Hz), 3.00 (s, 1 H, D_2O exchangeable), 2.64 (d, 1 H, J = 18.4 Hz), 2.31 (br d, J = 16.0 Hz), 1.84 (unresolved dd, 1 H, J = 16.0, 4.4 Hz), 1.68 (q, 2 H, J = 7.0 Hz), 1.06 (t, 3 H, J = 7.0 Hz). **1a**: mp 215 °C dec; ^1H NMR (pyridine-d_5) δ 13.2 (br s, 2 H, D_2O exchangeable), 8.42 (s, 1 H), 7.88 (dd, 1 H, J = 7.5, 1.3 Hz), 7.61 (t, 1 H, J = 7.5 Hz), 7.35 (dd, 1 H, J = 7.5, 1.3 Hz), 5.11 (t, 1 H, J = 4.8 Hz), 5.10 (br s, 2 H, D_2O exchangeable), 3.40 (d, 1 H, J = 18.0 Hz), 2.97 (d, 1 H, J = 18.0 Hz), 2.46 (dd, 1 H, J = 14.5, 4.8 Hz), 2.22 (dd, 1 H, J = 14.5, 4.8 Hz), 1.79 (q, 2 H, J = 7.0 Hz), 1.16 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 354 (6.4), 326 (30), 318 (5.5), 307 (12), 282 (37), 280 (100), 279 (22), 254 (21).
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Mechanism of Hydroboration of Alkenes with Borane–Lewis Base Complexes. Evidence That the Mechanism of the Hydroboration Reaction Proceeds through a Prior Dissociation of Such Complexes

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Ever since our discovery that ether solvents powerfully catalyze the hydroboration of alkenes with diborane,[2] we have been interested in understanding the mechanism of this reaction and the actual role of the ether solvents on the mechanism.[3-10] Unfor-

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