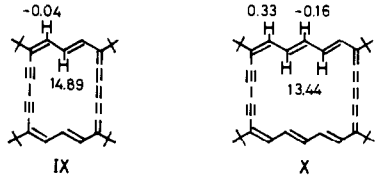
perchromism in VIII. The 100-MHz ^1H FT NMR spectrum in $CDCl_3$ of VIII exhibits inner proton (H^b) signals at τ 12.85 (dd, J = 13–14 Hz) and outer proton (H^a and H^c) signals at τ −0.64 (d, J = 14 Hz) and τ −0.06 (d, J = 13 Hz), respectively. An appreciable downfield shift of the *tert*-butyl signal (τ 7.81, s) was also observed. (The electronic spectrum of VIII and IX and the 100-MHz ^1H FT NMR spectrum of VIII in $CDCl_3$ will appear in the microfilm edition of the journal; see paragraph at end of paper regarding supplementary material.) The assignment of the outer protons was made using the tetradeuterio derivative of VIII which was prepared from I and acetone-d_6 by an analogous reaction sequence. The NMR spectrum indicates clearly that VIII sustains a strong diamagnetic ring current. Consequently, whether VIII is a perturbed peripheral [26]annulene or an annulenoannulene consisting of two 18π-electron systems becomes the most interesting problem.

The magnitude of a diamagnetic ring current, estimated approximately by the difference in chemical shifts ($\Delta\tau = \tau_i - \tau_o$) between inner ($\tau_i$) and outer ($\tau_o$) proton signals, in a series of conformationally stable tetra-*tert*-butyldidehydro[4n + 2]annulenes decreases markedly with increase of ring size (n = 3, $\Delta\tau$ = 13.76; n = 4, $\Delta\tau$ = 13.29; n = 4, $\Delta\tau$ = 9.99; n = 6, $\Delta\tau$ = 6.28; n = 7, $\Delta\tau$ = 4.0).[6] In view of the same trend observed in the tetradehydro[18]- (IX) ($\Delta\tau$ = 14.93)[2] and the tetradehydro[22]annulenes (X) ($\Delta\tau$ = 13.11–13.60),[7] the value found for VIII ($\Delta\tau$ = 12.91–13.49) seems to be larger than that anticipated for tetradehydro[26]annulene as well as for VIII as regarded as a perturbed peripheral [26]]annulene, in which the central diacetylene behaves only as a bridging chain. The downfield



shifts of all signals of VIII compared with IX and X can be reasonably ascribed to an additive diatropicity effect of both 18-membered rings; i.e., the protons H^a, H^b, and H^c in the ring A suffer a deshielding effect of the diamagnetic ring current of the ring B and vice versa. The ^1H NMR spectral behavior of VIII indicates that the bicyclic annulene (VIII) is a fused aromatic compound consisting of two 18π-electron systems being a hybrid of structures, $VIII_a$, $VIII_b$, and $VIII_c$. In other words, the annulenoannulene (VIII) can be represented most properly by the symmetrical formula, $VIII_d$.

Supplementary Material Available. The electronic spectrum of VIII together with that of IX and the 100 MHz ^1H-FT-nmr spectrum of VIII in $CDCl_3$ at 36° will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JACS-75-4424.

References and Notes

(1) For a review, see M. Nakagawa, "Topics in Nonbenzenoid Aromatic Chemistry", Vol. 1, Hirokawa Publishing Co., Tokyo, 1974, p 191.
(2) T. Katakami, S. Tomita, K. Fukui, and M. Nakagawa, *Chem. Lett.*, 225 (1972).
(3) The ir, NMR, and mass spectral data of all new compounds described in this communication are consistent with the assigned structures.
(4) In contrast, the low melting isomer (VI) gave no VII upon attempted oxidative coupling under the same reaction conditions, and only starting material was recovered in 62% yield. The failure to intramolecularly cyclize this isomer of VI is attributable to the inaccessible mutual disposition of the ethynyl groups in the molecule of trans structure with respect to the ethynyl and the hydroxyl groups (VI_b). On this basis, we assign the cis structure (VI_a) to the high melting isomer in which the ethynyl groups are favorably positioned for intramolecular oxidative coupling.
(5) The authors wish to propose this abbreviated name for the condensed annulene, although according to IUPAC rules, VIII is 5,10,18,23-tetra-*tert*-butylbicyclo[12.12.4]triaconta-1,3,11,13,15,17,23,25-octaene-6,8,19,21,27,29-hexayne. The authors are grateful to Dr. K. Hirayama, Fuji Photo Film Co. Ltd. and Mr. K. Fukui, Mitsui Petrochem. Ind. Co. Ltd. for their valuable suggestions with regard to annulenoannulene nomenclature.
(6) M. Nakagawa, presented at the 2nd International Symposium on the Chemistry of Nonbenzenoid Aromatic Compounds, Lindau, Germany, Sept 23–27, 1974 and will be published in *Pure Appl. Chem.*
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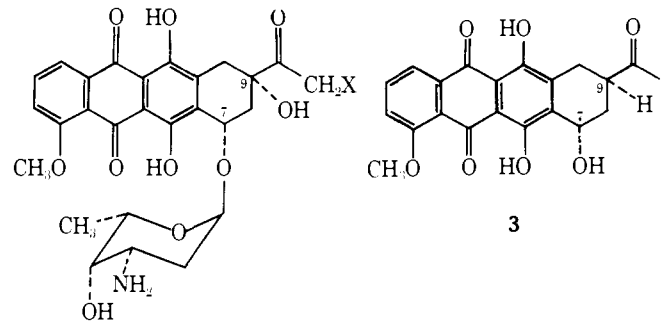
Regiospecific Total Synthesis of (±)-9-Deoxydaunomycinone

Sir:

The anthracycline antibiotics daunomycin (**1**) and adriamycin (**2**) are antineoplastic agents of established clinical utility.[1] Their scarcity has led to continuing efforts toward their total synthesis, and recent progress in that direction has been reported.[2] We wish to describe a short, mild, and completely regiospecific approach to antibiotics of this class which has resulted in the first total synthesis of (±)-9-deoxydaunomycinone (**3**).

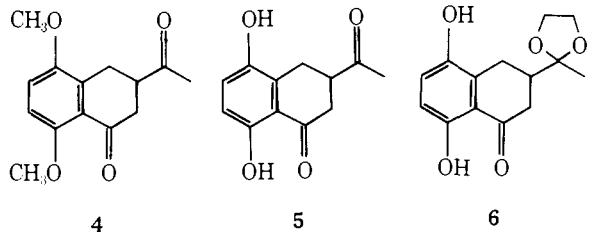


1 X = H
2 X = OH

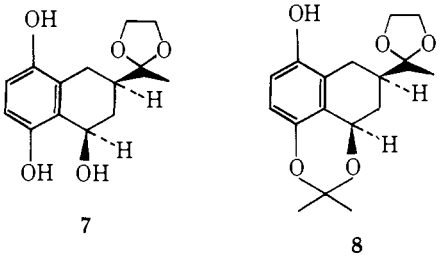
3

The reaction which maintains regiospecificity in our synthetic sequence is the photochemical Fries rearrangement of the *o*-cyanobenzoate ester **9**. This crystalline intermediate was prepared in 54% overall yield by a five-step route from the dihydroxytetralone (**5**), itself available in 76% yield by BBr_3 demethylation (CH_2Cl_2, −78° to 0°, 25 min) of the known[3] dimethyl ether **4**. The corresponding ketal **6** (ethylene glycol, *p*-TSA, C_6H_6, 4 hr reflux, 91%) was reduced by sodium borohydride in dry tetrahydrofuran (reflux, 16 hr) to give 83% of trihydroxy ketal **7**, which was

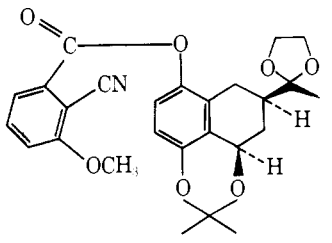
converted in neat 2,2-dimethoxypropane (catalyst *p*-TSA, 25°, 2 hr) to the highly sensitive ketal acetonide **8**, mp 143–144°, in 88% yield. Acylation of the free phenol of **8** with 3-methoxy-2-cyanobenzoic acid by the Brewster–Ciotti method[4] gave 77% of the key photo-Fries precursor **9**, mp 179–181°.



4 5 6

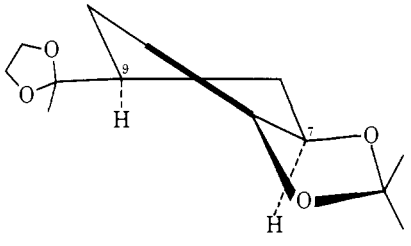


7 8



9

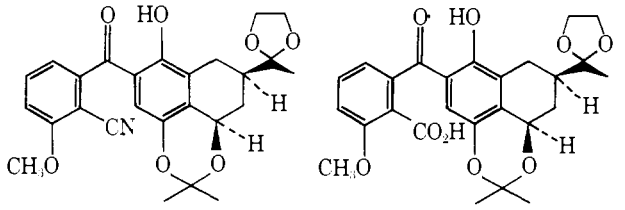
A 100-MHz NMR analysis of the benzylic >C*H*OR hydrogen in compounds **7**, **8**, and **9** revealed in each case the X signal of an ABX quartet with J_{AX} = 12 Hz and J_{BX} = 4 Hz, requiring a pseudoequatorial orientation of the benzylic oxygen in each of these intermediates. In view of the known preference[5] for large β-substituents in tetralin systems to adopt the equatorial conformation, the above NMR results indicate the (side-view) stereoformula **10** for these intermediates.



10

The critical photorearrangement of *o*-cyanobenzoate ester **9** was best achieved by direct irradiation with a 450-W medium pressure Hanovia source (1% solution of **9** in freshly LAH-distilled dioxane, 70°, quartz vessel) and carried to half-disappearance of starting material.[6] Chromatography over silica gel (C_6H_{12}–EtOAc, 1:1) gave the bright yellow photo-Fries ketone **11**, mp 198–200°, $\lambda_{max}^{CHCl_3}$ 395 and 283 nm, ε 2400 and 6600, in 48% yield based on ester consumed, plus 47% recovered starting material. The hindered cyano function in **11** was quantitatively hydrolyzed[7] by 10% aqueous sodium hydroxide (10% EtOH, reflux, N_2, 90 min) to the yellow keto acid **12** which on the basis of ir appeared to exist mainly in the open form and which still retained the acetonide (δ 1.48 and 1.52, s, 6 H) and ethylenedioxy (δ 4.0, 4 H, s) groups.

Formation of the anthracyclinone system was effected by treatment of the acid **12** with liquid hydrogen fluoride at 20° for 15 min. When the purple reaction mixture was poured onto a vigorously stirred, cold (−60°) mixture of chloroform and sodium carbonate solution, warmed to 20°,



11 12

and the chloroform extract washed with bicarbonate then chromatographed on silica gel (TLC, 3% MeOH in CH_2Cl_2) there was obtained in 23% yield a homogeneous red solid, mp 208–210°, which gave a single R_f on TLC or LLC, showed an electronic spectrum superimposable with that of authentic daunomycinone, and gave a clean mass spectrum, *m/e* 382 (M^+, 100%), 362 (71%), 339 (55%), 321 (86%), 284 (67%), identifying its gross structure as a 9-deoxydaunomycinone.

Unambiguous confirmation of the structure and stereochemistry of the cyclization product **3** was obtained by comparison of the distinctive signals of its proton magnetic resonance spectrum (δ2.33, s, 3 H (C-14); 4.09, s, 3 H (OCH_3); 5.24, m, 1 H (C-7); 13.33 and 13.99, s, 1 H ea., (phenolic OH)) with those of the very similar spectrum of daunomycinone itself. In particular, the C-7 benzylic proton of **3** exhibits a narrow multiplet ($\nu_{1/2}$ = 5 Hz) corresponding to that observed at δ 5.33 ($\nu_{1/2}$ = 7 Hz) for natural daunomycinone. Both signal widths are in sharp contrast to the values of 13–17 Hz reported for other anthracyclinones epimeric at C-7 and indicate pseudoequatorial C-7 hydrogen.[8] We conclude therefore that total synthesis of the (±)-9-deoxydaunomycinone epimer (**3**) having the "natural" relation between the C-7 and C-9 substituents has been completed.[9] Elaboration of other highly functionalized anthracyclinones by our photochemical route is under investigation.

Acknowledgment. We are grateful to the American Cancer Society (institutional award IN-18M to John Belletire) and the National Cancer Institute, USPHS (Grants CA 11326 and 5F02 GM 51 050 02), for support of this research.

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(6) Overirradiation results in destruction of product. The use of benzene or acetonitrile as solvent, of Pyrex vessels, of triplet quenchers or photolysis on a silica gel support has given no improvement in chemical yield.
(7) This facile hydrolysis may proceed by neighboring carbonyl group participation (through a gem-diol).
(8) Cf. H. Brockmann and J. Niemeyer, *Chem. Ber.*, **100**, 3578 (1967). Our proton spectra were taken in $CDCl_3$ solution (internal Me_4Si) using a Jeolco PFT-100 Fourier transform magnetic resonance spectrometer.

(9) The mechanistic implications of the generation of the "natural" configuration at C-7 will be discussed in our full paper.

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Novel Rearrangements during Dehydration of Nucleophile Adducts of Arene Oxides. A Reappraisal of Premercapturic Acid Structures

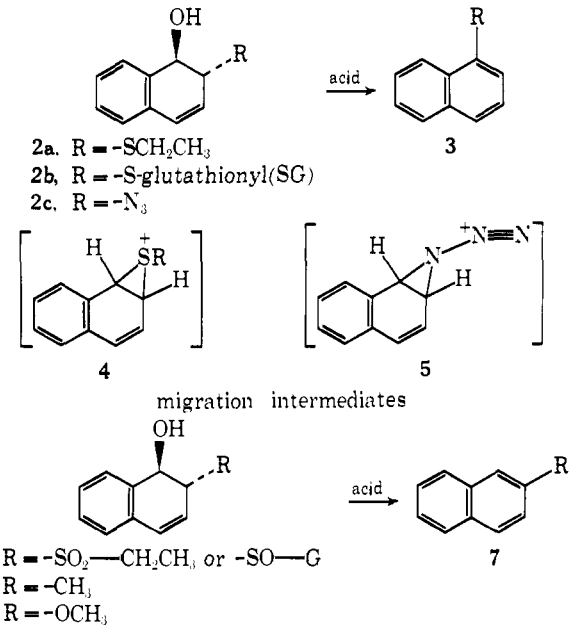
Sir:

Covalent binding of environmental agents to cellular entities such as protein and nucleic acid has been proposed as a prerequisite for the chemical induction of cancer.[1] For the polycyclic aromatic hydrocarbon class of carcinogens, metabolically formed arene oxides have emerged as the most viable candidates to account for this binding.[2] Structural information on the nature of arene oxide adducts, thus, acquires special significance. The present study establishes that the structures of arene oxide adducts must be determined prior to dehydration since unanticipated rearrangements can accompany aromatization.

The most common binding reaction of arene oxides within the cell consists of opening of the oxirane ring by the thiol group of the tripeptide glutathione to form a premercapturic acid.[2,3] Reaction of arene oxides with glutathione occurs both spontaneously and enzymatically with glutathione-*S*-epoxide transferase.[4,5] For naphthalene 1,2-oxide (**1**), the adduct prepared chemically or enzymatically has been assigned the structure 1-*S*-glutathionyl-2-hydroxy-1,2-dihydronaphthalene based primarily on the observations[6,7] that dehydration results in a C-1 substituted naphthalene ring. The ^{1}H NMR spectrum of the chemically synthesized adduct[6] (D_2O at 220 MHz) *suggests that sulfur is attached at C-2 rather than C-1.* Partial coincidence of signals from the peptide residue with the critical signals from the dihydronaphthalene ring, however, prevent rigorous assignment of sulfur substitution at C-2 in the adduct. Dehydration of *trans*-1-hydroxy-2-thioethyl-1,2-dihydronaphthalene[8] (**2a,** Scheme I) was, therefore, examined as a simpler model. Treatment of **2a** with 5% trifluoroacetic acid in methanol at room temperature caused rapid dehydration to 1-thioethylnaphthalene[9] (**3a**), *via* migration of the thioethyl residue.

Since a cyclic sulfonium ion (**4,** Scheme I) is implicated as the intermediate during dehydration and rearrangement of **2a,** decrease in the electron density at sulfur should inhibit migration without preventing dehydration. Treatment of **2a** with H_2O_2 and tungstic acid[10] in water led to a 90:10 mixture of 2- and 1-naphthyl ethyl sulfone,[11] respectively. Application of this technique to inhibit migration during dehydration of **2b** was also successful. An aqueous solution of the peptide conjugate was treated with 15% H_2O_2 at pH 7 and 0° for 6 hr. After destruction of excess H_2O_2 with catalase, the oxidized conjugate (λ_{max} 269 nm) was made strongly acidic and heated at 100° for 5 min to effect dehydration. The product consists principally of **7a** based on a λ_{max} of 276 nm with minor peaks at 265, 282, and 321 nm, a spectrum typical of the 2-substituted naphthalenes employed for this study.[12] Dehydration without oxidation gave a λ_{max} of 298 nm.

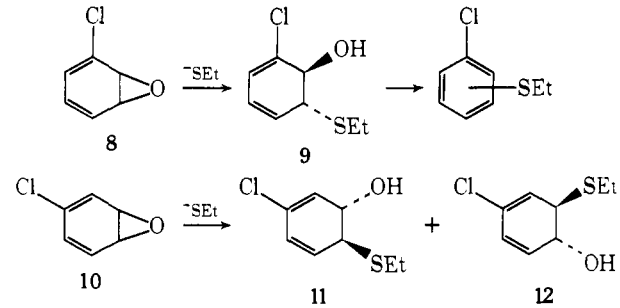
Scheme I



2a. R = -SCH_2CH_3
2b, R = -S-glutathionyl(SG)
2c. R = -N_3

6a. R = -SO_2—CH_2CH_3 or -SO—G
6b. R = -CH_3
6c, R = -OCH_3

Scheme II



The facility of migration for groups other than thioethers was then examined. *trans*-1-Hydroxy-2-methyl-1,2-dihydronaphthalene (**6b**) is known to dehydrate without migration of the methyl group to produce 2-methylnaphthalene[8] (**7b**). Addition of methoxide to **1** provided *trans*-1-hydroxy-2-methoxy-1,2-dihydronaphthalene (**6c**)[13] which decomposed (concentrated HCl in $CHCl_3$, 100° for 5 min) into 1-naphthol and 2-methoxynaphthalene (GLC–MS, 15% QF-1, 170°) in a ratio of 10:3, respectively. While other products were present, neither 2-naphthol nor 1-methoxynaphthalene (10% Carbowax 20 M, 150°) could be detected. Thus for **6c,** migration of the hydroxy group to C-2 or of the methoxy group to C-1 does not occur. In contrast, *trans*-1-hydroxy-2-azido-1,2-dihydronaphthalene[8] (**2c**) dehydrates ($t_{1/2} \sim 11$ min, 1 *N* HCl, 50°) to 1-azidonaphthalene (**2c**) with essentially complete migration of the azido group.[14] The facility with which intermediate **5** may be formed from a carbonium ion accounts for the facile migration. Evidently, only those substituents which readily stabilize positive charge (-SR, $-N_3$) undergo migration. The directed isomerization of **1** to form 1-naphthol,[15] the preferential ring opening of **1** by attack of nucleophiles at C-2, and the direction of migration during dehydration of these adducts all point to the greater stability of the carbonium ion at C-2.

Decomposition of the thiol adducts from 3- and 4-chlorobenzene oxides[16] (**8** and **10,** Scheme II) is also accompanied by migration of the thioether group. The adducts were prepared by allowing 0.2 m*M* solutions of the oxides in methanol to stand for 2 hr at 0° in the presence of 3 equiv each of ethanethiol and KOH. The reactions went to completion and were not accompanied by the production of phenols.