responding methyl groups most often have the L configuration.

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Registry No. 4a, 65195-51-9; **4b**, 65195-53-1; **4c**, 65195-55-3; **4d**, 65195-57-5; acetic acid, 64-19-7; propionic acid, 79-09-4; carbon, 7440-44-0; oxygen, 7782-44-7.

Flexible New Synthetic Route to Daunomycinone, Adriamycinone, and Their 6-Deoxy Analogues[1]

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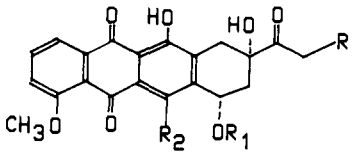
The total synthesis of naturally occurring anthracyclines and related analogue structures has been the subject of intense study since 1970, especially efforts directed toward preparation of the aglycones daunomycinone (**1**) and adriamycinone (**2**), which are

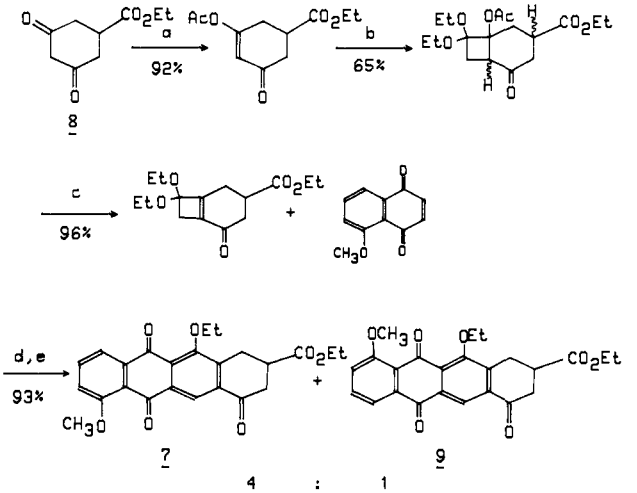


1, R = R_1 = H; R_2 = OH
2, R = OH; R_1 = H; R_2 = OH
3, R = H; R_1 = daunosamine; R_2 = OH
4, R = OH; R_1 = daunosamine; R_2 = OH
5, R = R_1 = R_2 = H
6, R = OH; R_1 = R_2 = H

components of the clinically useful antitumor agents daunorubicin (**3**) and adriamycin (**4**).[2,3] There remains, however, the need for synthetic routes that incorporate the oxygen function at C-7 at an early stage, since the existing methodology for this functionalization is inadequate especially with regard to scaleup to preparative levels.[3,4] It is, furthermore, desirable that these routes be inherently flexible permitting preparation of analogue structures differing in the substitution pattern in the anthraquinone nucleus.[4]

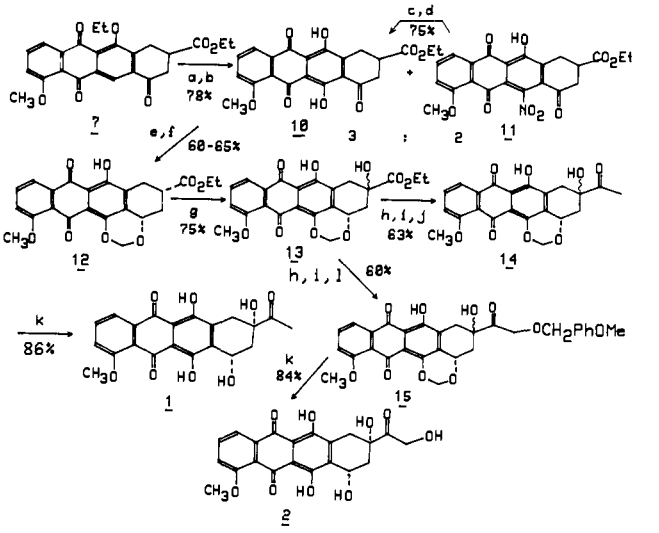
We have previously reported preliminary studies that defined the elements of a solution that meets the aforementioned criteria.[5] In the present paper, we describe the completion of our studies

Scheme I[a]



[a] Reagents: (a) Ac_2O, 70-80 °C, 16 h; (b) $CH_2=C(OEt)_2$ (4 equiv), Et_2O, *hν* (450-W Hanovia medium-pressure Hg lamp), room temperature, 40-48 h; (c) LiOEt (1 equiv), THF, room temperature, 1 h; (d) Δ (185-190 °C), mesitylene, 1.5 h; (e) NaOEt (catalyst), O_2, EtOH, room temperature, 10 min.

Scheme II[a]



[a] Reagents: (a) SbF_5 (10 equiv)-HF (100 equiv), CH_2Cl_2, -78 °C, 10 min; (b) anhydrous NH_4NO_3 (5 equiv), $(CF_3CO)_2O$ (20 equiv), CH_2Cl_2, room temperature, 1 h; (c) H_2, Pd-C, EtOAc; (d) $NaNO_2$, H_2SO_4, H_2O then Et_2NOH; (e) BH_3-THF (8 equiv), THF, 0 °C, 0.2 h; (f) $AgOSO_2CF_3$ (3 equiv), $ClCH_2OCH_3$ (3 equiv), CH_2Cl_2, room temperature, 0.5 h; (g) LDA (10 equiv), O_2, THF, -78 °C then $(EtO)_3P$ (2 equiv), -78 °C, 2 h; (h) 0.1% KOH, EtOH-H_2O (2:1), reflux, 0.5 h; (i) EtSH (3 equiv), 1,1'-carbonyldiimidazole (1.5 equiv), $Mg(OEt)_2$ (catalyst), DMF, room temperature, 16 h; (j) $LiCu(CH_3)_2$ (25 equiv), Et_2O-THF, 0 °C, 3 h; (k) CF_3COOH, room temperature, 4 h; then CH_3OH, reflux, 1 h; (l) $LiCu(CH_2OCH_2PhOCH_3)_2$ (25 equiv), THF, 0 °C, 3 h.

in this area which have culminated in the development of a highly flexible route to **1**, **2**, and related structures such as the potentially significant 6-deoxy series of aglycones **5** and **6**. The derived glycosides of **5** and **6**, along with their 11-deoxy counterparts, may possess reduced dose-dependent cardiotoxicity, which is a major problem associated with the clinical application of **3** and **4**.[6,7]

† Fellow of the A. P. Sloan Foundation 1976-1980; recipient of a Career Development Award (CA-00702) from the National Cancer Institute of the National Institutes of Health.

(1) Preliminary stages of this investigation were conducted in the Department of Chemistry, Wayne State University, Detroit, MI 48202.

(2) For a comprehensive referencing in this area, see: Kelly, T. R.; Vaya, J.; Anathasubramanian, L. *J. Am. Chem. Soc.* **1980**, *102*, 5983.

(3) (a) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263. (b) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *J. Chem. Soc., Chem. Commun.* **1982**, 158.

(4) Several such routes now exist; cf. ref 2 and 3 and papers cited therein. None permit access to 6-deoxy systems and other analogue series from common intermediates, and direct introduction of the C-7 and C-9 oxygen functions generally remains a problem. The recent work of Johnson et al. also utilizes a C-9 ketone as a means to introduce the C-9 oxygen at the stage of the tetracyclic system; however, only in the 7,11-deoxy series: Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, 103, 1561.

(5) (a) Boeckman, R. K., Jr.; Delton, M. H.; Nagasaka, T.; Watanabe, T. *J. Org. Chem.* **1977**, *42*, 2946. (b) Boeckman, R. K., Jr.; Delton, M. H.; Dolak, T. R.; Watanabe, T.; Glick, M. D. *Ibid.* **1979**, *44*, 4781.

(6) Chlewbowski, R. T. *West. J. Med* **1979**, *131*, 364 and references therein.

(7) For a related application of this strategy to the preparation of (±)-alkavinone see: Boeckman, R. K., Jr.; Sum, F.-W *J. Am. Chem. Soc.* **1982**, *104*, 4604.

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Our synthetic route focuses initially upon the preparation of the key tetracyclic ketone **7**, which is a common intermediate toward all target aglycones. Ketone **7** was obtained in four steps from dihydroresorcinol **8**[8] as shown in Scheme I. The mixture of tetracyclic ketones **7** and **9** was readily separable by fractional crystalization to provide pure **7** (mp 144–145 °C).[9-11]

Conversion of **7** to **1** and **2** was initiated by selective deprotection of the C-11 oxygen with SbF_5–HF in CH_2Cl_2 at −78 °C (93% yield) as shown in Scheme II.[12] Introduction of the C-6 oxygen was accomplished by treatment of the resulting phenol with $NO_2^+CF_3CO_2^-$ in CH_2Cl_2, which afforded a mixture of **10** (mp 190–193 °C) and the related nitro compound **11** (3:2) in 84% yield.[13] Nitro ketone **11** could be efficiently converted (75% overall yield) to **10** by reduction (H_2/Pd–C/EtOAc) and diazotization ($NaNO_2/H_2SO_4/H_2O$). Reduction of **10** by diborane in THF followed by protection of the C-6,7 hydroxyl groups (CH_3OCH_2Cl-$AgOSO_2CF_3/CH_2Cl_2$) afforded the ester **12** (mp 210–212 °C) as a single diastereomer (60–65%). Ester **12** was then oxidized ($LDA/O_2/(EtO)_3P$) to provide the C-9 hydroxylated esters **13** as a 1:1 mixture of diastereomers (75%).[14]

This mixture is of no consequence since subsequent equilibration of the C-7 hydroxyl establishes the required stereorelationship between C-7 and C-9. Hydroxy esters **13** can be directly converted to either **1** or **2** by ester hydrolysis, conversion to the thioester (1,1′-carbonyldiimidazole, EtSH, $Mg(OEt)_2$) and treatment with an excess of the appropriate lithium dialkylcuprate reagent ($(CH_3)_2CuLi$ or $(p\text{-}CH_3OPhCH_2OCH_2)_2CuLi$)[15] to provide the ketones **14** and **15** in 63% and 60% yield, respectively. Hydrolysis of the protecting groups in **14** and **15** with concomitant isomerization of C-7 (CF_3CO_2H) then affords **1** (mp 278–280 °C) and **2** (mp 284–287 °C) in good yield (86% and 84%, respectively) identical in all respects with authentic materials (NMR, MS, TLC).[16,17]

The C-6 deoxy systems **5** and **6** were prepared from **7** by a series of transformations analogous to those shown in Scheme II. In the case of the 6-deoxy series, the C-7 oxygen function was protected as a methoxy methyl ether.[9,18] Conversion of the 6-deoxy analogue of **12** to the two analogues of daunomycinone, **5** (mp 267–269 °C), and adriamycinone, **6** (mp 293–295 °C), was accomplished along the lines of the natural series including the stereochemical equilibration at C-7, which proceeded stereospecifically.[19,20]

Thus, the synthetic route to adriamycinone and daunomycinone presented above comprises 13 steps and proceeds in ~8% overall yield. Besides convergency, the route offers substantial flexibility for production of analogues by substitution in the naphthoquinone unit as well as analogues in the 6-deoxy series.

Acknowledgment. This investigation was generously supported by research grants (CA-28897 and CA-29108) from the National Cancer Institute of the National Institutes of Health, to whom we are grateful.

Supplementary Material Available: Scheme for preparation of **5** and **6** and partial NMR data for **7** and **9–15** (3 pages). Ordering information is given on any current masthead page.

(8) Kuehne, M. E.; Lambert, B. F. *J. Am. Chem. Soc.* **1959**, *81*, 4278.
(9) All new compounds had satisfactory spectroscopic data (IR, NMR) and acceptable high-resolution mass spectroscopic or combustion analytical data. A listing of NMR spectral data can be found in the supplementary material.
(10) Prepared by Jones oxidation of 1,4,5-trimethoxynaphthalene in 70% yield. For the preparation of 1,4,5-trimethoxynaphthalene: Jackson, D. K.; Swenton, J. S. *Synth. Commun.* **1977**, 333.
(11) The mixture was crystallized from acetone–hexane to effect the separation of the majority of **7**. The residual material could be separated by chromatography.
(12) (a) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1980**, *21*, 3351. (b) Gesson, J. P.; Giusto, L. D.; Jacquesy, J. C. *Tetrahedron* **1978**, 1715.
(13) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056.
(14) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(15) Prepared from the lithium reagent in the usual way. The lithium reagent was prepared from the corresponding tributylstannane by transmetalation with *n*-BuLi. This particular dialkylcuprate reagent shows markedly higher thermal stability than other related cuprate reagents and alkyllithium reagents (cf.: Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481). A further description of the utility of this reagent as a methanol carbanion equivalent will be reported in due course.
(16) We thank Professor Andrew Kende for an authentic sample of racemic **1** and Dr. Daniel Lednicer of Adria Laboratories for an authentic sample of optically active **2**.
(17) Steric factors that favor attack from the pseudoaxial direction upon the half-chair cyclohexyl ring of the intermediate carbonium ion or protonated acetal in the precursors to **1** and **2** (the C-6 OH) are enhanced in the cyclic acetals **17** and **18**, leading exclusively to the natural C-7 configuration; cf. for a similar case: Kende, A. S.; Belletire, J.; Bentley, T. J.; Hume, E.; Airey, J. *J. Am. Chem. Soc.* **1975**, *97*, 4425.
(18) A scheme describing these transformations may be found in the Supplementary Material.
(19) ^1H NMR spectral data (400 MHz, $CDCl_3$). **5**: δ 12.95 (s, 1 H), 7.99 (d, J = 7.7 Hz, 1 H), 7.95 (s, 1 H), 7.74 (t, J = 8.0 Hz, 1 H), 7.37 (d, J = 8.3 Hz, 1 H), 4.93 (dd, J_1 = 10.0 Hz, J_2 = 3.6 Hz, 1 H), 4.45 (s, 1 H), 4.06 (s, 3 H), 4.02 (d, J = 10.0 Hz, 1H), 3.11 (d, J = 17.9 Hz, 1 H), 2.98 (d, J = 17.9 Hz, 1 H), 2.41 (s, 3 H), 2.37–2.26 (m, 2 H). **6**: δ 12.91 (s, 1 H), 8.00 (d, J = 7.7 Hz, 1 H), 7.84 (s, 1 H), 7.76 (t, J = 8.1 Hz, 1 H), 7.39 (d, J = 8.6 Hz, 1 H), 5.09 (m, 1 H), 4.80 (dd, J_1 = 20.6 Hz, J_2 = 5.2 Hz, 1 H), 4.71 (dd, J_1 = 20.6 Hz, J_2 = 5.2 Hz, 1 H), 4.46 (s, 1 H), 4.06 (s, 3 H), 3.27 (d, J = 18.0 Hz, 1 H), 3.02 (d, J = 18.0 Hz, 1 H), 2.39 (d, J = 14.6 Hz, 1 H), 2.24 (dd, J_1 = 14.6 Hz, J_2 = 4.3 Hz, 1 H).
(20) The unexpectedly high stereospecificity of the equilibration in the 6-deoxy series is apparently related to delivery of the nucleophile (H_2O) from the pseudoaxial direction with assistance of the C-9 axial hydroxyl group. Concurrent with our studies, an Italian group observed similar selectivity in the 4-demethoxy compound: Penco, S.; Angelucci, F.; Arcamone, F.; Ballabio, M.; Barchielli, G.; Francheschi, F.; Franchi, G.; Suarato, A.; Vanotti, E. *J. Org. Chem.* **1983**, *48*, 405.

Short, Stereocontrolled Synthesis of [4]Peristylane

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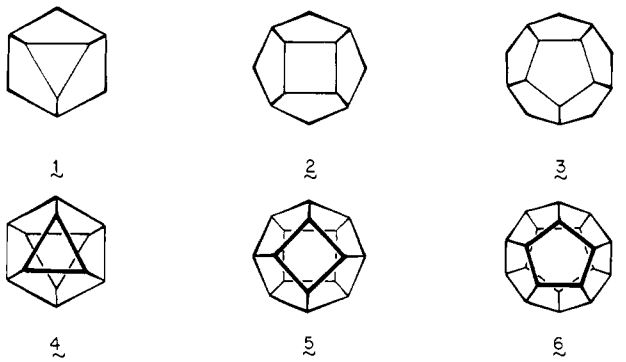
The peristylanes (**1–3**) are attracting growing interest because



of their unusual hemispherical topology and their obvious relationship to highly symmetric $(CH)_{2n}$ polyhedral systems (e.g., **4–6**).[1] The original synthesis of [3]peristylane (**1**) by Nickon and Pandit[2] in 1968 has been followed by the design of two alternative routes in Garratt's laboratory.[1] Concurrently, the group headed by Eaton succeeded in devising an elegant pathway to [5]peristylane (**3**).[3] To date, however, the central compound of this series (**2**) has remained elusive. Our interest in [4]peristylane and select functionalized derivatives of this hydrocarbon was

(1) Garratt, P. J.; White, J. F. *J. Org. Chem.* **1977**, *42*, 1733.
(2) Nickon, A.; Pandit, G. D. *Tetrahedron Lett.* **1968**, 3663.
(3) Eaton, P. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 1014. Eaton, P. E.; Mueller, R. H.; Carlson, G. R.; Cullison, D. A.; Copper, G. F.; Chou, T.-C.; Krebs, E.-P. *Ibid.* **1977**, *99*, 2751.

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