metallocyclobutane is preferred. For purposes of these arguments, a preference for either conformation would lead to retention of stereochemistry in degenerate metathesis. For discussions of the stereochemistry of the metathesis of internal alkenes, see (a) J. Wang and H. R. Menapace, *J. Org. Chem.*, **33**, 3794 (1968); (b) W. B. Hughes, *Chem. Commun.*, 431 (1969); (c) J. M. Basset, J. L. Bilhou, R. Mutin, and A. Theolier, *J. Am. Chem. Soc.*, **97**, 7376 (1975); (d) C. P. Casey, L. D. Albin, and T. J. Burkhardt, *ibid.*, 99, 2533 (1977); (e) J. L. Bilhou, J. M. Basset, R. Mutin, and W. F. Graydon, *ibid.*, **99**, 4033 (1977).

(10) Prepared by hydroalumination of 1-decyne-*1-d*$_1$ followed by H_2O quench. The decene was further purified by treatment with 5% ethanolic $AgNO_3$ to remove alkynes which were found to inhibit olefin metathesis.

(11) Prepared by $LiAlD_4$ reduction of ethyl caprylate, conversion of the resulting deuterated octanol to octyl formate and pyrolysis of the formate at 530 °C.

(12) The epoxidation of (*Z*)-1-decene-*1-d*$_1$ with *m*-$ClC_6H_4CO_3H$ was shown to be >99% stereospecific.

(13) GC analysis of the NMR sample indicated <0.1% 1-decene oxide.

(14) (a) Integrals of the oxirane protons were determined by planimetry. (b) The relative amount of monodeuterio oxide was determined by measuring for each NMR the ratio of protons in positions 1 and 2. The estimated error in the ratio of monodeuterated products is ±0.1. (c) In the 270-MHz FT NMR experiment the number of transients was limited to prevent imminent overflow during data collection. Thus all data were collected using the maximum number of bits to ensure maximum time domain range. (d) In a separate experiment a 99.9-s pulse delay was used in obtaining the 270-MHz FT NMR spectrum to ensure that this ratio was not caused by a significant difference in T_1's for the two isomers.

(15) This ratio represents a minimum value since no correction was made for the residual proton found in the starting 1-octene-*1, 1-d*$_2$ (see Figure 1).

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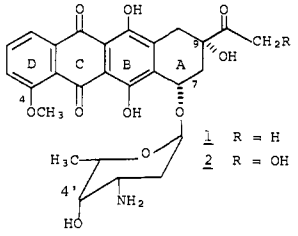
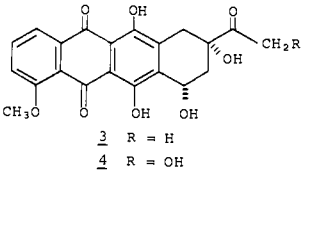
Total Synthesis of Adriamycinone. Regiospecific Synthesis of Anthracyclinones via Base-Catalyzed Cyclizations

Sir:

The anthracycline antibiotics, daunorubicin (**1**) and especially adriamycin (**2**), are widely used for the treatment of a



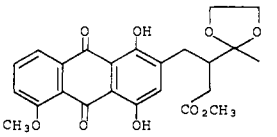
1 R = H
2 R = OH



3 R = H
4 R = OH

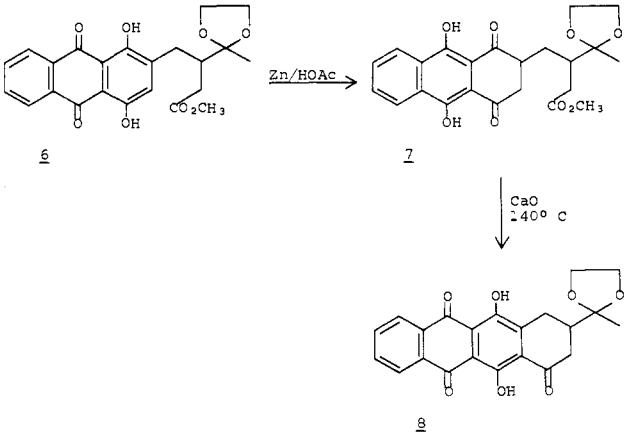
variety of human cancers.[1] Total syntheses of the aglycone (anthracyclinone) portion of these antibiotics have been a topic of considerable interest in recent years owing to the lack of an efficient biosynthetic process[2] and epimerization of the C-4′ hydroxyl in daunosamine[3] that may result in analogues with apparent reduced cardiotoxicities. Although several synthetic approaches to (±)-daunomycinone (**3**) or (±)-adriamycinone (**4**) have already been described,[4-6] invariably these routes require the separation of regioisomers (orientation of rings A and D substituents) at some stage. Notable exceptions are the BA → DCBA schemes of Kende[7] and Swenton.[8] Herein, we disclose a fundamentally different regiospecific synthesis of anthracyclinones from an appropriately substituted anthraquinone derivative. The construction of the alicyclic A ring was achieved via intramolecular Marschalk- and Claisen-type condensations.

Retrosynthetic analysis of the anthracyclinone molecule reveals that **5** could serve as a plausible precursor, but the



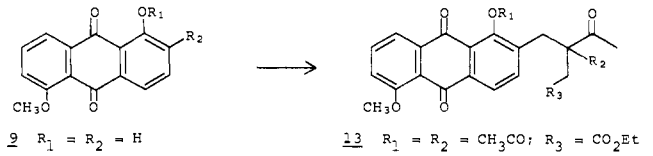
5

success of this approach is dependent on the availability of a suitable method for ring A closure. Owing to the strong electron-withdrawing property of the anthraquinone system, **5** resisted cyclization when treated with a variety of conventional strongly acidic or basic reagents.[9] A possible solution to this recalcitrant problem was indicated in our recent model studies.[9] The substituted anthraquinone, **6**, was first transformed into its leuco form, **7**, which underwent cyclization under the



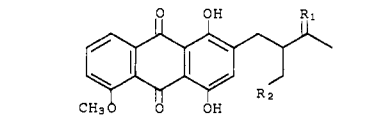
6 **7** **8**

following rigid experimental condition: CaO or BaO as base, Zn as reducing agent to suppress back-oxidation of **7** to **6**, and ethylene glycol as solvent.[10] The successful development of this model ring closure reaction[11] prompted us to turn our attention to the synthesis of **5**. Marschalk methylation[12] of 1-hydroxy-5-methoxyanthraquinone[13] (**9**) gave **10**,[14] mp 185-186 °C, in 60% yield. After quantitative conversion of **10** into **11** (Ac_2O, H_2SO_4, 3 h), mp 195-197 °C, **11** was treated with 1.3 equiv



9 $R_1 = R_2 = H$
10 $R_1 = H$; $R_2 = CH_3$
11 $R_1 = Ac$; $R_2 = CH_3$
12 $R_1 = Ac$; $R_2 = CH_2Br$

13 $R_1 = R_2 = CH_3CO$; $R_3 = CO_2Et$
14 $R_1 = R_2 = H$; $R_3 = COOH$



15 $R_1 = O$; $R_2 = COOH$
16 $R_1 = O$; $R_2 = COOCH_3$
17 $R_1 = OCH_2CH_2O$; $R_2 = COOH$
18 $R_1 = OCH_2CH_2O$; $R_2 = COOCH_2CH_2OH$

of NBS to yield bromide **12** (60%), mp 213-216 °C, which was alkylated (NaH, DMF, 0 °C) with 3-acetyllevulinic acid ethyl ester to afford **13**, mp 181-182 °C, in 96% yield. Hydrolysis of the ester grouping and cleavage of the β-diketone (reverse Claisen) were simultaneously effected by reaction of **13** with 5% aqueous NaOH at 65 °C for 5 h to give **14** (90%), mp 197-200 °C. Elbs oxidation[15] of **14** gave 40% **15**, mp 124-126

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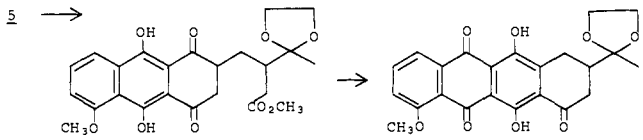
°C, along with 38% recovered **14,** which was conveniently separated from the product and recycled. After methylation of **15** with diazomethane, **16** (96%), mp 147–148 °C, was converted into the ketal **5** (ethylene glycol, *p*-TsA, 4 h, reflux): 90%; mp 164–165 °C; NMR δ 13.30 (s, 1 H), 13.19 (s, 1 H), 7.93 (dd, J_1 = 7.8, J_2 = 1.2 Hz, 1 H), 7.68 (dd, $J_1 = J_2$ = 7.8 Hz, 1 H), 7.30 (dd, J_1 = 7.8, J_2 = 1.2 Hz, 1 H), 7.13 (s, 1 H), 4.04 (s, 3 H), 4.00 (s, 4 H), 3.52 (s, 3 H), 3.13 (dd, J_1 = 12, J_2 = 3 Hz, 1 H), 2.0–3.0 (m, 4 H), 1.41 ppm (s, 3 H).

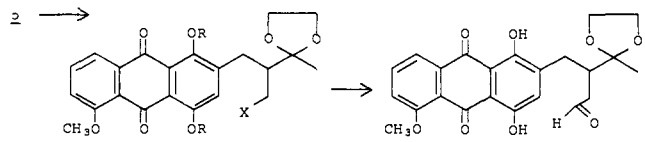
In contrast to **6, 5** was only sluggishly[16] reduced into its leuco form, **19,** using Zn/HOAc, but was found to be smoothly converted to **19** in 85% yield with basic dithionite (5% NaOH,



19 20

$Na_2S_2O_4$, dioxane, 1 h, 25 °C). When we subjected **19** to the same cyclization condition (Zn, ethylene glycol, CaO, 140 °C), successfully employed in the 4-demethoxy series, contrary to our expectations, the major products formed were **17** and **18** and only traces of **20** were detected. After an exhaustive study of the influence of a variety of bases and solvents on this ring-closure reaction, for it is well known that C-alkylation of ambident anions are heavily solvent dependent,[10] it was found that a 5–7% yield of **20** (mp 234–236 °C; δ 14.33 (s, 1 H), 13.10 (s, 1 H), 7.98 (dd, 1 H, J_1 = 7.8, J_2 = 1.2 Hz), 7.73 (t, 1 H, J = 7.8 Hz), 7.35 (dd, 1 H, J_1 = 7.8, J_2 = 1.2 Hz), 4.05 (s, 4 H), 3.98 (s, 3 H), 1.5–3.6 (m, 5 H), 1.39 ppm (s, 3 H)) was obtained if glycerol-H_2O (8:2) was substituted for ethylene glycol. Thus, it appears that the presence of the 4-methoxyl[17] group markedly altered the electronic properties[18] of **19** compared with **7,** accentuating the vicissitude of synthetic planning. This unexpected turn of events compelled us to devise yet another type of ring A cyclization.

The ketal **5** was transformed to **25** via a five-step reaction sequence involving benzylation ($PhCH_2Br$, K_2CO_3/acetone, 95% yield), hydrolysis (10% aqueous NaOH, dioxane, 90%), reduction (BH_3, THF, 25 °C, 80%), debenzylation (H_2, $Pd/BaSO_4$, ethyl acetate, 90%), and oxidation (PCC, CH_2Cl_2, 25 °C, 75%). Cyclization of **25** was achieved as follows. To 12

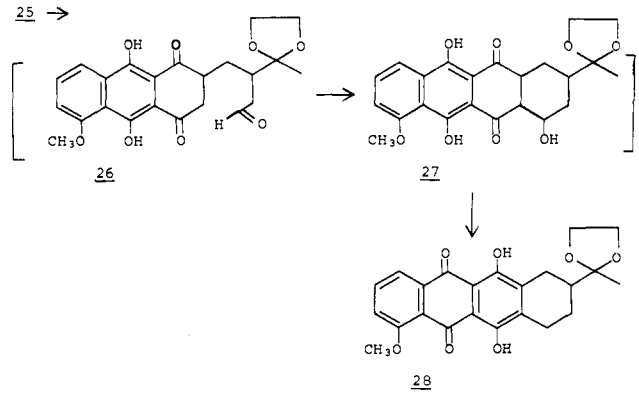


21 R = $CH_2Ø$; X = CO_2CH_3
22 R = $CH_2Ø$; X = CO_2H
23 R = $CH_2Ø$; X = CH_2OH
24 R = H; X = CH_2OH

25

mg of **25** in 0.2 mL of dioxane was added 0.4 mL of 5% NaOH and 120 mg of sodium dithionite. After stirring at 25 °C for 30 min (color turned from purple to yellow after 5 min), the reaction mixture was heated at 90 °C for 1 h. Additional sodium dithionite (20 mg) was then added and the heating was continued for another 30 min. After usual workup, **28** (6 mg, 52%; mp 177–178.5 °C; δ 13.82 (s, 1 H), 13.48 (s, 1 H), 8.00 (dd, 1 H, J_1 = 7.8, J_2 = 1.2 Hz), 7.71 (t, 1 H, J = 7.8 Hz), 7.33 (dd, 1 H, J_1 = 7.8, J_2 = 1.2 Hz), 4.05 (s, 4 H), 4.00 (s, 3 H), 3.14 (brd, 2 H, J = 18.0 Hz), 1.6–2.8 (m, 5 H), 1.38 ppm (s, 3 H)) was obtained by preparative TLC ($CHCl_3$–acetone, 95:5) on silica gel plates.

This intramolecular Marschalk cyclization reaction used in the transformation of **25** into **28** proceeds via the intermediates **26** and **27.** Deketalization (5% H_2SO_4, THF, 3 h, 50 °C) of **28** afforded (±)-7,9-dideoxydaunomycinone,[6] **29** (92%). As methods for the introduction of hydroxyl functions at C-7,[4,5] C-9[6] and C-14[4,5] have already been described, this route formally constitutes a regiospecific snythesis of adriamycinone. Equally significant, these modes of base-catalyzed cyclization will probably prove of general utility in other DCB → DCBA syntheses of anthracyclinone tetracycles. Further refinement of this synthetic sequence and in particular the cyclization conditions to accumulate diastereomers of **27** are currently in progress; preliminary results are very encouraging.



26 27 28

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(10) Hydroxylic solvents (e.g., H_2O, trifluoroethanol, etc.) favors C- vs. O-alkylation (see N. Kornblum et al., *J. Am. Chem. Soc.*, **85,** 1141, 1148 (1963); and P. G. Duggan and W. S. Murphy, *J. Chem. Soc., Perkin Trans. 2,* 1291 (1975)). As intramolecular acylation reaction requires high activation energy, polyhydroxylic solvent with high boiling point such as ethylene glycol was thus selected as solvent.
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(14) All intermediates gave C, H analyses and/or mass spectra and IR and NMR spectra consistent with the assigned structures. The yields reported are unoptimized and melting points were uncorrected. Unless stated otherwise, NMR spectra (δ) were taken in $CDCl_3$ solution.
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(16) Complete reduction of **5** into its leuco form using Zn in HOAc occurred only after 24 h compared with 30 min for **6.**
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(18) The 4-methoxyl group may also sterically interfere with the proper chelation of the Ca metal during cyclization.

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