COMMUNICATIONS

The Total Synthesis of Daunomycinone[1]

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The aglycone of the antitumor antibiotic daunomycin, daunomycinone **1**, has been synthesized along with its C-1 isomer.

On a synthétisé la daunomycinone **1**, aglycone de l'antibiotique antitumoriale daunomycine, ainsi que son épimère en C-1. [Traduit par le journal]

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Daunomycin is currently a very important drug for clinical treatment of leukemia (1). Mild acid hydrolysis of daunomycin gives an amino sugar daunosamine and the aglycone daunomycinone **1** (2).

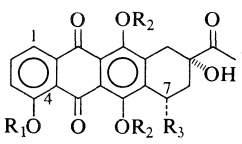
We wish to report a total synthesis of **1** fashioned in the CD → ABCD annelation sequence which has been successfully put to test in a model study (3). The synthesis of the antibiotic aglycone itself utilized also the bicyclic ketol **2**, obtained from 2,5-dimethoxybenzaldehyde in seven steps (**3**) or, preferably, **2** may be prepared as shown in Scheme 1.

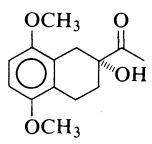
Condensation of **2** with 3-acetoxyphthalic acid monomethyl esters (isomeric mixture) in refluxing trifluoroacetic anhydride yielded a mixture of diaryl ketones which was directly saponified (2 *N* NaOH/ethanol) and subjected to HF cyclization at room temperature. The resulting quinones **3** and **4** (overall 19%; ν 3500, 1710, 1670, 1640 cm^{-1}; *m/e* 396) were then quantitatively methylated (Me_2SO_4–K_2CO_3–acetone)(*m/e* 410; δ 2.35 (3H, s, $COCH_3$), 3.85, 3.87, 3.88, 3.92, 3.97 (9H total, singlets, OCH_3).

Since separation of isomers was not feasible at this stage, introduction of the oxygen function at C-7 was next attempted. The side-chain ketone was protected as the dioxolane group (ethanediol–TsOH–benzene; 88%; *m/e* 454; 1.40 (3H, s, CH_3), 3.88, 3.92, 3.96, 4.02 (13H total, singlets, OCH_3 and acetal CH_2), bromination (NBS) was then achieved selectively at the desired position. Methanolysis of the bromoacetals permitted isolation of two compounds by preparative t.l.c. (silica, methanol–chloroform, 1:25; R_f 0.31, 0.51) which subsequently proved to be acetals having epimeric benzylic methoxy groups (**5**, R = OCH_3 at C-1 or C-4). Only after hydrolysis (HCl – aqueous THF) of the dioxolane function could the ring A isomers be finally resolved by preparative t.l.c. (silica, methanol – ethyl acetate 1:100). From the R_f 0.51 band, the more polar daunomycinone trimethyl ether (**6**, m.p. 185–186°; *m/e* 440; ν 3460, 1715, 1680 cm^{-1}; δ 2.40 (3H, s, $COCH_3$), 3.56 (3H, s, OCH_3), 3.89 (3H, s, $ArOCH_3$), 4.00 (6H, s, $ArOCH_3$)) and the less polar isodaunomycinone trimethyl ether (**7**, m.p. 226–227°; *m/e* 440; ν 3460, 1715, 1680 cm^{-1}; δ 2.40 (3H, s, $COCH_3$), 3.56 (3H, s, OCH_3), 3.93 (3H, s, $ArOCH_3$), 4.00 (6H, s, $ArOCH_3$)) were obtained in the ratio of *ca.* 1:1. The former compound has been identified by comparison with a specimen derived from natural daunomycin.

To complete the synthesis, **6** was reacted with aluminum chloride at ambient temperature to give 4-O-demethyl-7-O-methyldaunomycinone (**8**, m.p. 246–250°; *m/e* 398; ν 3440, 1715, 1600 cm^{-1}) which was oxidized to the unstable diquinone **9** (ν 3460, 1715, 1685 cm^{-1}) by lead tetraacetate and immediately remethylated (Me_2SO_4–K_2CO_3–acetone, 25°) to provide 7-O-methyldaunomycinone (**10**; ν 3460, 1720, 1620, 1585 cm^{-1}, 10%). The benzylic methoxy was replaced by the trifluoroacetoxy group with trifluoroacetic acid (25°, 2 h), resulting in **12** (ν 3480, 1785, 1720, 1620, 1580 cm^{-1}). Treatment

[1]Part II of Synthetic Studies of Hydronaphthacenic Antibiotics.





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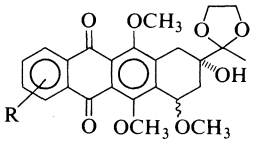
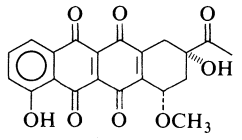


5

1 $R_1 = CH_3$, $R_2 = H$, $R_3 = OH$
3 $R_1 = R_3 = H$, $R_2 = CH_3$
6 $R_1 = R_2 = CH_3$, $R_3 = OCH_3$
8 $R_1 = R_2 = H$, $R_3 = OCH_3$
10 $R_1 = CH_3$, $R_2 = H$, $R_3 = OCH_3$
12 $R_1 = CH_3$, $R_2 = H$, $R_3 = OCOCF_3$ (epimer)



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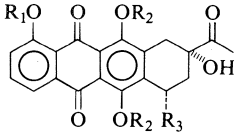
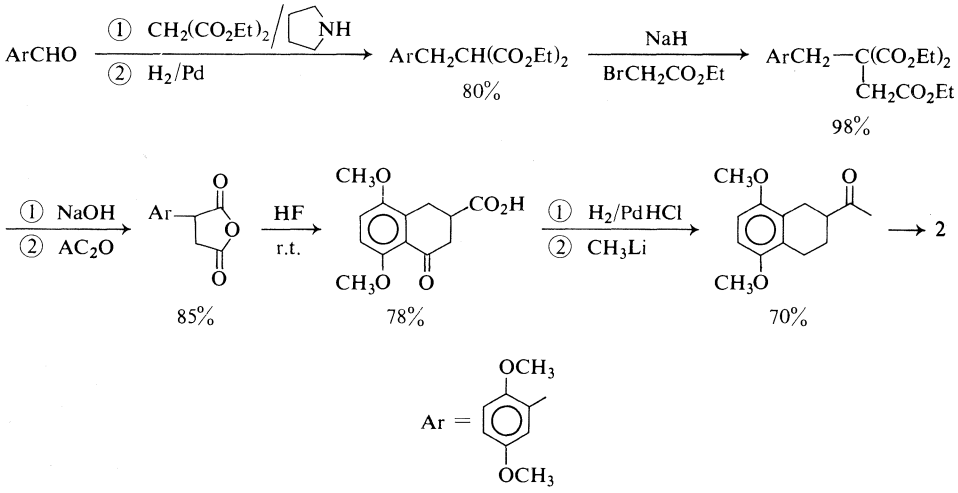


4 $R_1 = R_3 = H$, $R_2 = CH_3$
7 $R_1 = R_2 = CH_3$, $R_3 = OCH_3$
11 $R_1 = CH_3$, $R_2 = H$, $R_3 = OH$



SCHEME I

of **12** with ammonium hydroxide in boiling acetone furnished daunomycinone (ν 3480, 1715, 1620, 1585 cm^{-1}). These latter two compounds are identical with samples derived from natural daunomycin.

Parallel experiments performed on isodaunomycinene trimethyl ether **7** gave isodaunomycinone (**11**, m.p. 216–218°; *m/e* 398; ν 3480, 1715, 1620, 1580 cm^{-1}). All key synthetic intermediates exhibit spectral properties consistent with assigned structures and correct elemental analyses or exact mass molecular ion.

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