Tetrahedron Letters,Vol.23,No.7,pp 775-778,1982 0040-4039/82/070775-04$03.00/0
Printed in Great Britain

A GENERAL REGIOSPECIFIC SYNTHESIS OF (±) 11-DEOXYANTHRACYCLINONES +

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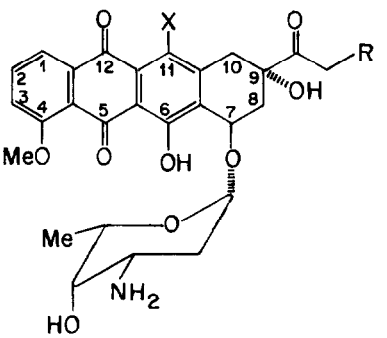
An elegant regiospecific approach for the synthesis of 11-deoxyanthracyclinones is described, involving the Diels-Alder reaction of an appropriate diene with a suitably substituted naphthalene C-D ring synthon.

The anthracycline antibiotics, daunomycin (1a) and adriamycin (1b) are presently of great interest because of their potent activity in the clinical treatment of a variety of human cancers [1] However, their main disadvantage of having severe dose limiting side effects[2] which include myelosuppression and cardiomyopathy have prompted the search for new anthracyclines that show decreased side effects and/or increased antitumor activity This has resulted in the isolation of new anthracycline antibiotics lacking a hydroxyl group at C-11 position [11-deoxydaunomycin (1c) and 11-deoxyadriamycin (1d) etc.[3]] related to aclacinomycin A,[4] which showed a low incidence of cumulative dose-dependent cardiotoxicity. In contrast to adriamycin,



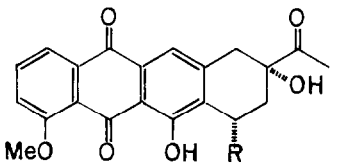
1a R=H , X=OH
1b R=X=OH
1c R=X=H
1d R=OH , X=H

aclacinomycin A selectively inhibits whole cellular RNA synthesis at concentration six to eight times lower than those required to inhibit DNA synthesis.[5] Although many elegant approaches for the total synthesis of the aglycones of daunomycin and its analogues have been developed,[6] only two recent reports have appeared on the synthesis of 7,11-dideoxydaunomycinone (2a)[7] and 11-deoxydaunomycinone (2b)[8] respectively. A very simple and regiospecific approach for the

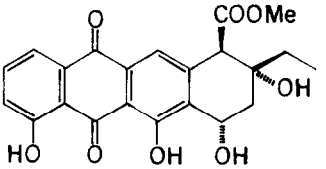
+ Dedicated to the memory of the late Prof. K. Venkataraman

synthesis of this compound (2) is now reported. Further, this approach can serve as an efficient regiospecific convergent route to other 11-deoxyanthracyclinones including aklavinone (3)[9], the aglycone of aclacinomycin A.

The main synthetic strategy is the Diels-Alder reaction between a suitably substituted naphthalene synthon such as 7 with a desired diene to give the D.A. adduct 8, which can be smoothly converted to the tetracyclic dione 10 and transforming the latter product to an appropriate 11-deoxyanthracyclinone.



2a R = H
2b R = OH



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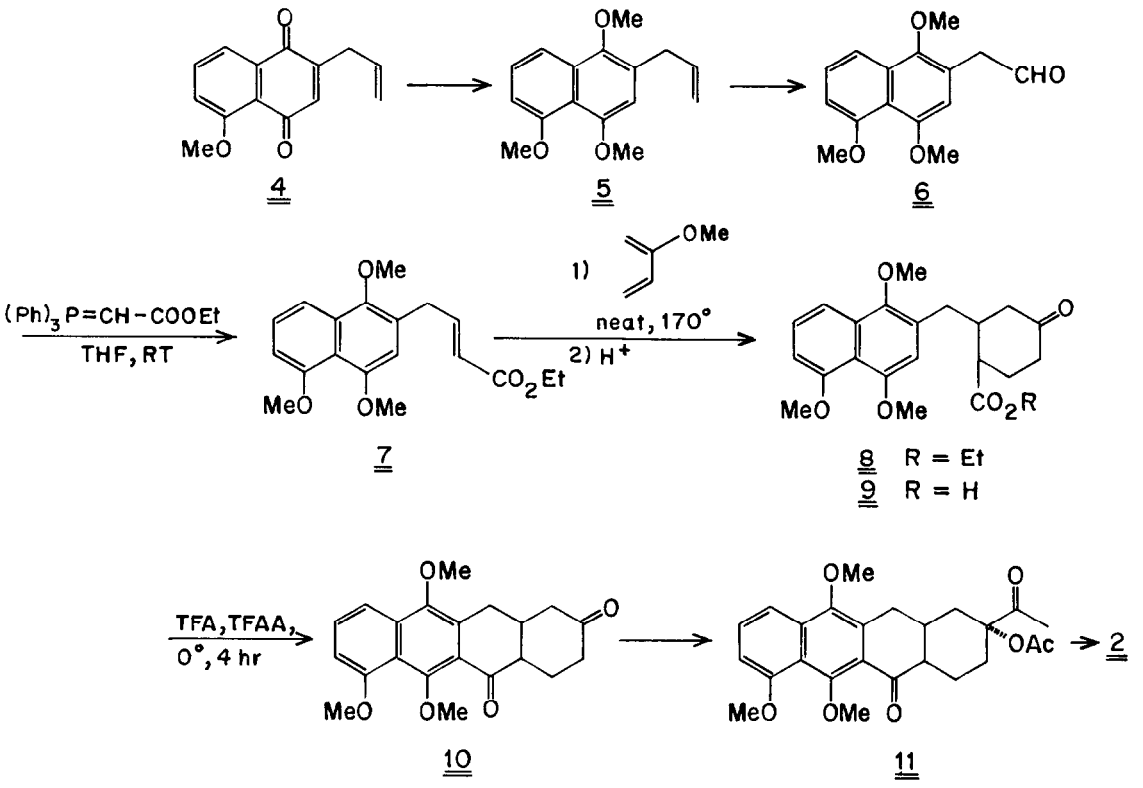
Our regiospecific synthesis of 11-deoxyanthracyclinones involve the preparation of the dienophile 7 and an appropriate diene as precursors. The obvious intermediate for the synthesis of 7 is 1,4,5-trimethoxynaphthalene-2-acetaldehyde (6) which was prepared starting from 2-allyl-5-methoxynaphthoquinone (4).[10] Reduction of the quinone (4) to the corresponding hydroquinone with sodium hydrosulphite followed by methylation (DMS,K_2CO_3, acetone) afforded the trimethyl ether 5 (80%). Oxidation of the olefin 5, using an osmium tetroxide-potassium chlorate system to give the corresponding diol which is converted directly to the aldehyde 6 with sodium periodate[11] or by lead tetraacetate in benzene.[12]

Wittig condensation of the aldehyde 6 with triphenylcarboethoxymethylene phosphorane[13] in THF at room temperature afforded 7 in 70% yield [PMR ($CDCl_3$) δ 7.55 (dd, J=8 and 1.5 Hz, 8-H), 7.31 (t, J=8Hz, 7-H), 7.08 (m, CH=), 6.77 (dd, J=8 and 1.5 Hz, 6-H), 6.46 (s, 3-H), 5.75 (m, CH=), 4.11 (q, O-CH_2-), 3.91, 3.86, 3.77 (3s, 3OMe), 3.64 (q, Ar$\underline{CH_2}$-), 1.24 (t, CH_2-$\underline{CH_3}$), M^+ 330]. Treatment of 7 with 2-methoxybutadiene at 170° (sealed tube) for 48 hr gave exclusively the desired adduct which on acid work up (aq.HCl) and silica gel chromatographic purification gave 8 in 60% yield. Alkaline hydrolysis (2N, NaOH in MeOH, r.t.) gave 9 (90%) which was subjected to cyclisation by treating with a mixture of $(CF_3CO)_2O$ and CF_3COOH (2.1) at 0° for 4 hr to give

the tetracyclic dione 10 (85%),[14] m.p. 217-218° [PMR: ($CDCl_3$) δ 7.66 (dd, J=8, 1.5 Hz, 1-H), 7.49 (t, J=8 Hz, 2-H) 6.89 (dd, J=8, 1.5 Hz, 3-H), 4.00, 3.92 and 3.86 (3s, 3OMe), 3.37 (m, $ArCH_2$-), 2.00-2.88 (m, $3CH_2$ and 2CH-); M^+ 354][15].



Sih and his coworkers[7] have converted the dione 10 to 11 by treatment with HC≡CMgBr followed by $Hg(OAc)_2$-H_2S. The latter product converted to 2a by ceric ammonium nitrate oxidation followed by bromination and dehydrobromination and finally deacetylation with NaOMe in MeOH. The conversion of 2a to 2b has been carried by the wellknown procedure.[8]

This approach to 11-deoxyanthracyclinones is more elegant and regiospecific. The possibility of extending this approach to other anthracyclinones, in particular, the synthesis of aklavinone, utilizing a more highly functionalised A ring synthon is under investigation[16]

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12. The overall yield of the aldehyde 6 from the olefin 5 by either of the methods is 35%. Alternate method for the synthesis of 6 from 1,5-hydroxynaphthalene is being looked into.

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14. The compound gave satisfactory elemental analysis and spectroscopic data.

15. The physical and spectral data of this compound is identical with the product (10) reported by Sih et al (see Ref.7).

16. This work was assisted partly by a grant from the Science and Technology Cell, Education and Youth Services Department, Maharashtra State.

NCL Communication No.2912

(Received in UK 3 December 1981)