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A CONVERGENT REGIOSPECIFIC ROUTE TO THE AKLAVINONE RING SYSTEM†

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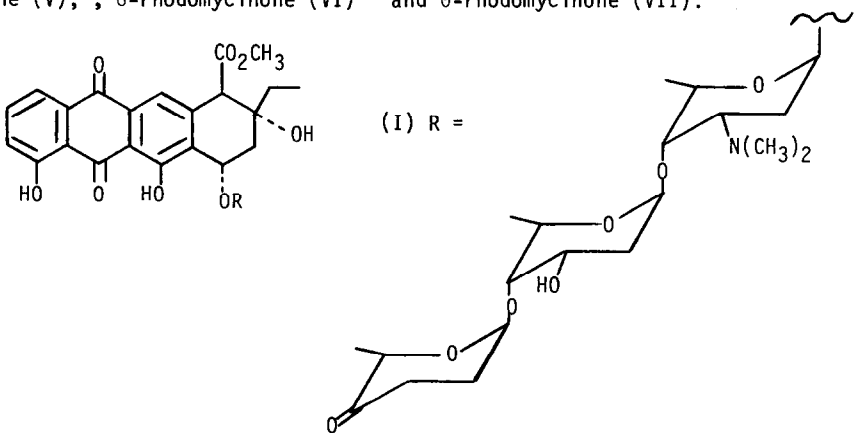
ABSTRACT: A convergent regiospecific route to the aklavinone (II) ring system is described.

During the past decade, the anthracycline antibiotics adriamycin and daunomycin have emerged as important chemotherapeutic agents for the treatment of cancer. Their cardiotoxic side effect, however, imposes a serious restriction on their clinical application[1] and has prompted intense global efforts in the search for a better tolerated substitute. Aclacinomycin A (I)[2] was discovered in 1975 in Japan and was subsequently found to be similarly efficacious in its antineoplastic activity, but to possess a reduced level of cardiotoxicity in both animal[3] and clinical studies,[4] in comparison with adriamycin and daunomycin.

These findings have aroused considerable interest among synthetic chemists in searching for an efficient route[5] for the preparation of the aglycone of aclacinomycin, aklavinone (II).[6] Bearing a methoxycarbonyl group at the C-10 position, aklavinone belongs to a subgroup of the anthracyclinones which includes ε-rhodomycinone (III),[7] ε-isorhodomycinone (IV),[8] ε-pyrromycinone (V),[9], δ-rhodomycinone (VI)[10] and θ-rhodomycinone (VII).[11]



(II) R = H

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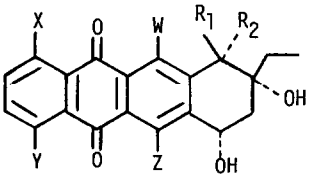


(III) $R_1 = CO_2CH_3$, $R_2 = H$
X = H, Y = Z = W = OH

(IV) $R_1 = CO_2CH_3$, $R_2 = H$
X = Y = Z = W = OH

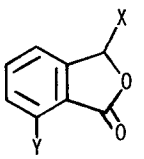
(V) $R_1 = CO_2CH_3$, $R_2 = H$
X = Y = Z = OH, W = H

(VI) $R_1 = CO_2CH_3$, $R_2 = H$
X = Y = W = OH, Z = H

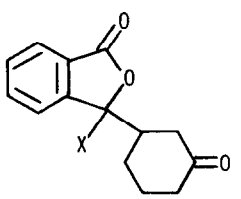
(VII) $R_1 = H$, $R_2 = CO_2CH_3$
X = H, Y = Z = W = OH

It is desirable to develop a methodology which will produce the tetracyclic anthraquinone skeleton with the 4,6-dihydroxy-10-methoxycarbonyl functionalities, features unique to the aklavinone structure. We now report a convergent strategy which is centered on a connective annelation reaction that delivers all the functional groups regiospecifically.[12]

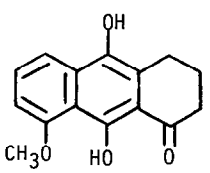
Hauser,[13] Kraus[14] and van Leusen[15] have demonstrated that a suitably substituted phthalide anion undergoes conjugated addition to an unsaturated α,β-unsaturated ketone, e.g. cyclohexenone, resulting in a hydroquinone product. We prepared a series of substituted phthalides[13,16] and reinvestigated the addition of their anions to cyclohexenone.[14] Using the simple phthalides (VIIIa) and (VIIIb), only the Michael products (IX) and (IXb) were obtained under the mild conditions we had chosen. However, use of the methoxysulfonylphthalide (VIIIc) led to the desired hydroquinone (X) in moderate yield. Furthermore, a much cleaner reaction occurred with the anion of the cyanophthalide (IXd), and (X) was isolated as crystals (mp 172° C) in 80% yield.



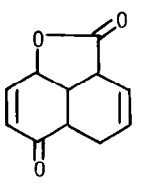
(VIIIa) X = SPh, Y = H
(VIIIb) X = SO_2Ph, Y = H
(VIIIc) X = SO_2Ph, Y = OCH_3
(VIIId) X = CN, Y = OCH_3



(IXa) X = SPh
(IXb) X = SO_2Ph



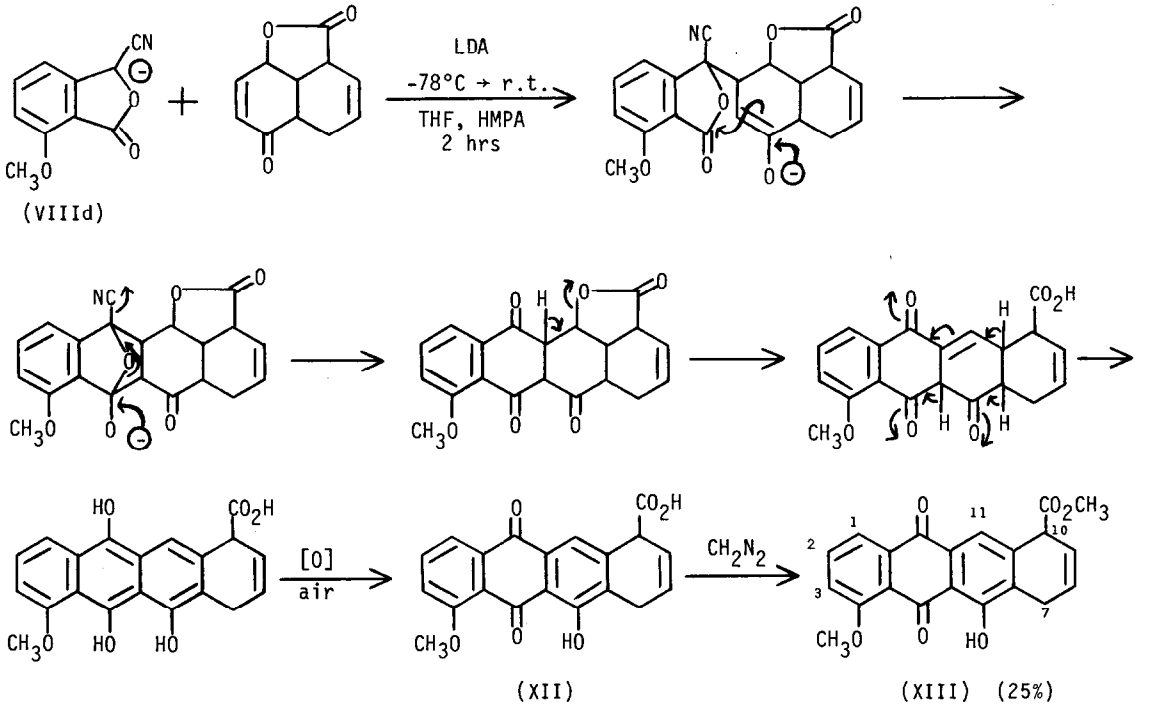
(X)



(XI)

We reasoned that an additional heteroatom substitution on the cyclohexenone ring would raise its oxidation state and hence provide a potential source for the phenolic moiety of the anthracycline B-ring from the initial annelation product. Furthermore, an A-ring carrying a properly positioned carboxyl group might be attached to the cyclohexenone starting material, and thus the lactone (XI) appears to be an ideal model compound satisfying both requirements in the annelation studies. The lactone (XI) has been described in Woodward's reserpine synthesis[17] and is readily available in three steps from benzoquinone and the methyl ester of vinylacrylic acid.

Treatment of the lithio anion of cyanophthalide (VIIId) with the enone lactone (XI) gave the quinone (XII). A plausible pathway is the initial Michael addition of the phthalide anion to the enone system, followed by attack of the resulting enolate anion on the phthalide carbonyl group and subsequent loss of cyanide ion, establishing the tetracyclic skeleton in the form of a trione intermediate. Opening of the lactone ring followed by a series of enolizations under the basic conditions gave a hydroquinone which was oxidized during isolation. This cascade of events led to quinone (XII), which possessed the desired 4,6-dihydroxy-10-carboxy substitution pattern with complete regiospecificity. The crude product was converted into its methyl ester (XIII) with diazomethane, and the crystalline product (XIII) (mp 214-215° C)[18] was isolated in 25% yield.



(VIIId)

(XII)

(XIII) (25%)

The above experimental results demonstrated the feasibility of our original strategy. In a subsequent communication, we shall report the total synthesis of aklavinone using the methodology described in this communication.

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16) Phthalide (VIIId) was prepared from N,N-diethyl-6-formyl-anisamide (NaCN, TsOH, aq. THF, 0° C - r.t.; 95%, mp 120-121° C).

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18) NMR δ 3.45 (bq, 2, H_7), 3.72 (s, 3, OCH_3), 4.07 (s, 3, CO_2CH_3), 4.53 (bd, 1, H_{10}), 6.07 (bq, 2, $\overset{H}{\diagdown}C{=}C\overset{H}{\diagup}$), 7.37 (dd, 1, H_3), 7.66 (s, 1, H_{11}), 7.8 (dd, 1, H_2), 8.0 (dd, 1, H_1). UV (MeOH) 223, 259, 395, 416, 436 nm (log ε 4.57, 4.47, 3.99, 4.06, 3.97); IR (KBr) 1730, 1670, 1630, 1580 cm^{-1}; MS 364 (M^+); 305 (M^+-CO_2CH_3). Anal. Calcd.: C, 69.22; H, 4.43. Found: C, 69.46; H, 4.42.

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