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THE VINYLKETENE ACETAL ROUTE TO AKLAVINONE AND 11-DEOXYDAUNOMYCINONE

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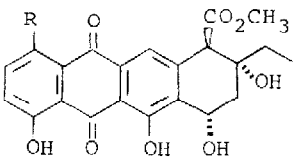
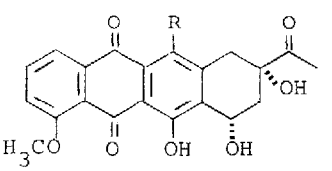
Summary: 11-Deoxyanthracyclinone precursors 6a and 6b have been prepared regiospecifically by the reaction of bromojuglone methyl ethers 4a and 4b with vinylketene acetal 5, prepared from the Hagemann's ester ketal 7a.

In the past decade a number of potentially clinically useful 6-deoxy- and 11-deoxyanthracyclines have been isolated. The most promising of these is aclacinomycin A,[1,2,3] the aglycone of which is aklavinone (1a). Aglycones of other antitumor antibiotics include ε-pyrromycinone (1b),[2] 11-deoxydaunomycinone (2a),[4] α-citromycinone (3a)[5] and α_2-rhodomycinone (3b).[5]



1a, R=H
1b, R=OH



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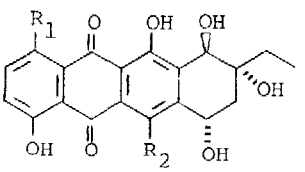
2b, R=OH



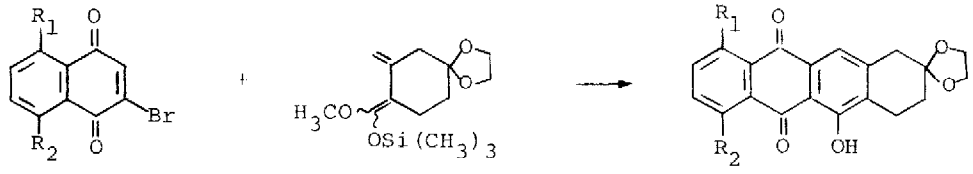
3a, R_1=R_2=H
3b, R_1=OH, R_2=H
3c, R_1=H, R_2=OH

With this growing interest[6] in aclacinomycin A, it has become desirable to develop an efficient route to aklavinone, preferably one that also can be adapted to analogous structures such as 1b, 2a, 3a, and 3b. Although a number

of syntheses of daunomycinone (2b) have been reported[7,8,9,10] they are not readily adaptable to the 6- or 11-deoxyanthracyclinones. Our route to these systems uses the reaction of mixed vinylketene acetals with halonaphthoquinones which has been used previously to synthesize a variety of anthraquinones.[11] This reaction is regiospecific and offers the flexibility of incorporating a variety of peripheral substitution patterns.

We now report the synthesis of anthracyclinone precursors 6a and 6b from readily available starting materials as shown in Scheme I. The vinylketene

Scheme I



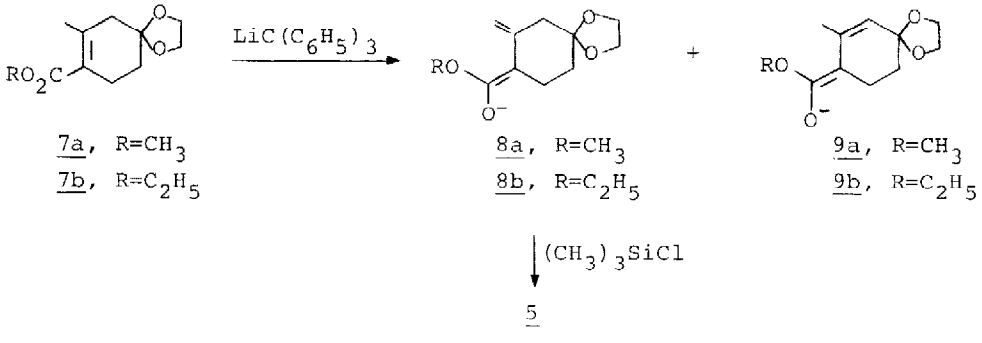
4a, R_1=OCH_3, R_2=H
4b, R_1=H, R_2=OCH_3

5

6a, R_1=OCH_3, R_2=H
6b, R_1=H, R_2=OCH_3

acetal 5 is formed directly from the ethylene ketal of Hagemann's ester (7a) as shown in Scheme II. 2- and 3-Bromojuglone methyl ethers (4a and 4b) are

Scheme II



7a, R=CH_3
7b, R=C_2H_5

8a, R=CH_3
8b, R=C_2H_5

9a, R=CH_3
9b, R=C_2H_5

5

available by regiospecific routes[12] from 1,5-dimethoxynaphthalene. The key step is formation of the exo vinylketene acetal. Although Gesson[13] reported a low yield of anions 8b and 9b when 7b was treated with $LiC(C_6H_5)_3$ and an unfavorable ratio of 8b to 9b when hindered amide bases were used, we have observed yields of 5 as high as 90% by the treatment of 7a with a three fold excess of $LiC(C_6H_5)_3$ followed by chlorotrimethylsilane. Crude 5 [^{1}H-NMR (CCl_4) δ 1.75 (2H, t), 2.30 (2H, t), 2.33 (2H, s), 3.55 (3H, s, 3.90 (4H, s), 4.95 (2H, m)[14]] is unstable to heat, moisture and acid and is used immediately

without isolation. The fate of the undesired isomeric anion 9a has not been determined.

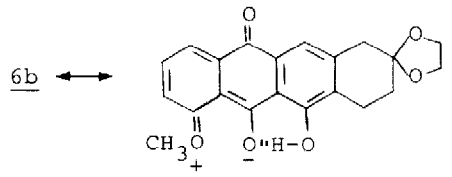
The anthracyclinone precursor 6a was obtained by stirring 3-bromojuglone methyl ether (4a) with crude ketene acetal 5 in dry benzene for two days. Upon silica gel chromatography, 6a coeluted with a side product to give a dark green oil. Trituration in cold methanol resulted in 6a as a yellow powder (17% isolated yield); recovered starting material was also obtained. Recrystalization from benzene/methanol gave 6a with mp 218-221°C: IR (KBr) 1675, 1630 cm^{-1}; UV (MeOH) 227, 263, 411 nm; ^{1}H-NMR ($CDCl_3$) δ 1.91 (2H, t), 2.88 (2H, t), 2.96 (2H, s), 3.91, 3.94 (7H, 2xs), 7.1-7.9 (4H, m), 12.70 (1H, s); HRMS, $C_{21}H_{18}O_6$ requires m/e 366.1103, found 366.1091.

The isomeric anthracyclinone precursor 6b was prepared by combining 5 with 3-bromojuglone methyl ether (4b) as described above. In this case silica gel chromatography gave 6b in 53% yield, mp 220-222°C after recrystallization from benzene/methanol: IR (KBr) 1675, 1630 cm^{-1}; UV (MeOH) 227, 260, 416 nm; ^{1}H-NMR ($CDCl_3$) δ 1.92 (2H, t), 2.89 (2H, t), 2.93 (2H, s), 3.94 (7H, s), 7.1-7.9 (4H, m), 13.21 (1H, s); HRMS, $C_{21}H_{18}O_6$ requires m/e 366.1103, found 366.1101.

The regioisomers 6a and 6b are easily distinguishable by TLC.[15] Structural assignments are based on the work of Savard and Brassard[11] as well as our own data from model systems and are supported by UV and ^{1}H-NMR data. Isomer 6b has a UV spectrum consistent with that of 11-deoxydaunomycinone (2a)[4] and shows a visible absorption at slightly longer wavelength than 6a in agreement with the absorptions of 1-hydroxy-8-methoxyanthraquinone and 1-hydroxy-5-methoxyanthraquinone.[16]

Although the chemical shifts of the phenolic protons are somewhat concentration dependent, the difference between them is reproducible. Under identical conditions the phenolic proton of 6b is downfield from that of 6a due to a small contribution from resonance structure 10 which strengthens the intramolecular hydrogen-bond, thus deshielding the proton. No such resonance structure is possible for the isomer 6a. This trend can also be seen in isomeric hydroxymethoxyanthraquinones.[11]

Hydrolysis of the ketal functions in 6a and 6b will give ketones 11a and 11b, respectively. Since elaboration has been reported of the related ketone



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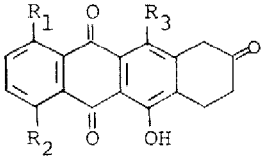

11a, R_1=OCH_3, R_2=R_3=H
11b, R_1=R_3=H, R_2=OCH_3
11c, R_1=H, R_2=OCH_3, R_3=OH

11c into both daunomycinone (2b)[8] and β-rhodomycinone (3c),[17] these methods should be adaptable to the preparation of a number of anthracyclinone analogues from both 11a and 11b, including 11-deoxydaunomycinone (2a) and aklavinone (1a). Other anthracyclines in which ring B is mono-oxygenated should be readily prepared by this regiospecific reaction between vinylketene acetals and bromonaphthoquinones, and their syntheses are being pursued.

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14. The resonance of the silyl group is obscured by $(CH_3)_3SiC(C_6H_5)_3$ derived from the base. The resonances of $HC(C_6H_5)_3$ do not interfere.
15. Silica gel slides eluted with 19/1 chloroform ethyl acetate: 6a, R_f=0.23; 6b, R_f=0.30. Both show an orange fluorescence when visualized with a Blak Ray UVL-21 Long Wavelength ultraviolet lamp.
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