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A VICARIOUS AROMATIC SUBSTITUTION APPROACH TO AKLAVINONE FROM CHRYSAZIN

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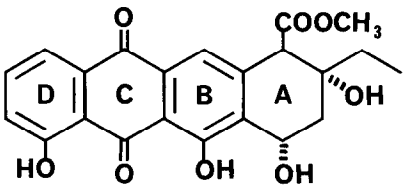
Abstract: The cheap, available dye-intermediate 1,8-dihydroxyanthraquinone (2) is converted efficiently to a useful aklavinone precursor (3). A Mitsunobu alkylation-Claisen rearrangement sequence and an unprecedented vicarious aromatic substitution on an anthraquinone are employed as key steps.



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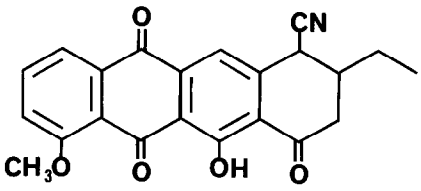

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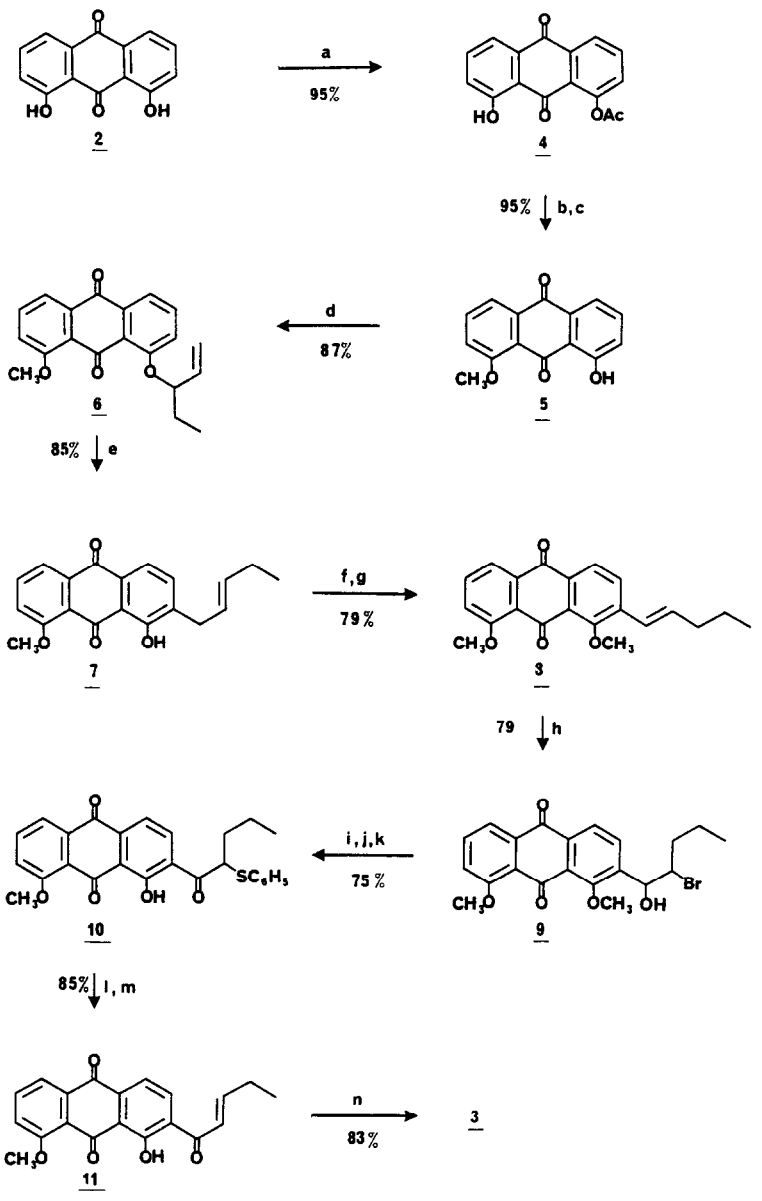
The anthracycline antibiotics have attracted a vast amount of synthetic interest in recent years because of their great therapeutic value.[1] Aklavinone (1), the aglycone portion of one of the most promising new anthracyclines, aclacinomycin,[2] has been synthesized by several different routes.[3a-d] All of these syntheses have relied on the construction of either the B or C ring as a key step. Our aim was to graft a suitably functionalized A ring onto an intact anthraquinone nucleus. Earlier we reported the synthesis of a tetracyclic model system lacking the hydroxyl in the D ring via a low yielding, multi-step sequence involving an experimentally complicated annulation reaction.[4] We now wish to report a considerably improved route starting from 1,8-dihydroxyanthraquinone (chrysazin) (2) and proceeding to the tetracyclic aklavinone precursor (3) in 22% overall yield. The final step in this sequence is a novel vicarious aromatic substitution reaction on an anthraquinone. Vicarious aromatic substitutions have been studied in simple aromatic systems,[5] but appear to have seen no use in natural product synthesis.

One of the hydroxy groups of 1,8-dihydroxyanthraquinone (2) was selectively acetylated using a procedure employed by Mitscher[6] in the aloe-emodin series. Methylation followed by removal of the acetate with sodium hydroxide gave 1-hydroxy-8-methoxyanthraquinone (5) in 90% overall yield.[7]



a) $B(OH)_3$, Ac_2O, 90°C b) K_2CO_3, Me_2SO_4, acetone c) NaOH, H_2O, 60°C d) 1-penten-3-ol, diethylazodicarboxylate, $P\emptyset_3$, THF 0° - rt e) $Na_2S_2O_4$, DMF-H_2O, 70°C f) K_2CO_3, Me_2SO_4, acetone g) $RhCl_3$, EtOH h) NBS, H_2O, acetone i) Jones oxidation j) $AlCl_3$, CH_2Cl_2, rt k) ØSH, NaOH, ØH-H_2O, cetyltrimethylammonium bromide l) $NaIO_4$, HOAc-H_2O m) CCl_4, 70°C n) $PhSCH_2CN$, $NaCH_2SOCH_3$, DMSO.

The formation of a pure substituted allylic ether such as (6) proved to be a problem in earlier anthraquinone syntheses.[8] Alkylations using bromides more complicated than allyl bromide gave low yields due to substitution a both α and γ positions. The Mitsunobu-type alkylation reaction[9] totally eliminated this problem as ether (6) was obtained pure in 87% yield using 1-penten-3-ol. Reductive Claisen rearrangement of ether (6) was carried out with sodium dithionite (1.3 eq, 70°C) to yield (7) in 85% yield.[10] The elaboration of the alkenyl sidechain in (7) to the hydroxyenone (11) was carried out as follows. Isomerization of the double bond from the 2 to the 1 position with $RhCl_3$ in refluxing absolute ethanol (100/1 catalytic ratio) followed by methylation of the phenol gave (8) in 79% for the two steps.[8] Regioselective formation of bromohydrin (9) was accomplished in 83% yield. Jones oxidation, selective demethylation with $AlCl_3$ in CH_2Cl_2, and phase-transfer catalysed displacement[14] of the α bromide gave α-phenylthioketone (10) in 79% for the three steps. Oxidation to the sulfoxide and pyrolysis gave enone[11] (11) in 85% for the two steps.

The key step in our approach was a tandem Michael-vicarious aromatic substitution ring closure. This was carried out most auspiciously using $PhSCH_2CN$ as Michael donor and dimsylsodium-DMSO as base-solvent system. The hydroxyenone (11) was added dropwise as a DMSO solution to the preformed anion (3.5 eg $NaCH_2SOCH_3$-DMSO) and the solution allowed to stir at room temperature for approx. 2 hrs. The reaction mixture was neutralized with HOAc, diluted with CH_2Cl_2, washed with H_2O, and column chromatographed on silica gel (ss 2-1: hexane-ethyl acetate) to yield yellow crystalline (3)[12] (mp 138-140) in 83%. This tetracyclic ketone-nitrile obtained in 22% overall yield from chrysazin contains much useful functionalization in the A ring. Studies on the conversion of this intermediate to aklavinone are presently underway in our laboratories.

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7. 1-hydroxy-8-acetoxyanthraquinone (4) gave poor yield in the Mitsunobu alkylation.

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11. hydroxyenone (11): mp 119-121°C; mass spectrum [m/e 336, 321, 307, 282 and 281]; nmr [δ 13.67 (s, 1H); 7.97 (d, 1H); 7.87 (d, 1H); 7.78 (m, 1H); 7.39 (d, 1H); 7.06 (m, 1H); 6.92 (d, 1H); 4.04 (s, 3H); 2.32 (m, 2H); 1.15 (t, 3H).

12. tetracyclic keto-nitrile (3): mp 138-140°C; high resolution mass spectrum, calcd. for $C_{22}H_{17}O_5N$ m/e 375.1107, observed m/e 375.1114; mass spectrum [m/e 375, 358, 346, 319, 301 and 289]; nmr [δ 14.20 (s, 1H); 7.90 (s, 1H); 7.84 (m, 2H); 7.39 (d, 1H); 4.15 (d, 1H); 4.07 (s, 3H) 2.88; (m, 2H); 2.49 (m, 1H); 1.73 (m, 2H); 1.05 (t, 3H).

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