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A CONVENIENT INTERMEDIATE FOR 4-DEMETHOXYANTHRACYCLINONE SYNTHESIS

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Summary Quinizarin is converted by high yielding steps into an acetoxyanthraquinone possessing acetal and methyl acetate substituents in the 2- and 3-positions. This compound is analogous to key intermediates in recent syntheses of aklavinone, 11-deoxydaunomycinone, and related compounds.

Recently, Kishi and co-workers reported elegant asymmetric syntheses of aklavinone,[1] 11-deoxydaunomycinone,[2] and related compounds[2] in which the key intermediates were hydroxyanthraquinones with acetal and methyl acetate substituents in the 2- and 3-positions.

We report here a 70% conversion of the commercially available 1,4-dihydroxyanthraquinone (quinizarin) (1) into an analogous intermediate (4) for the synthesis of 4-demethoxydaunomycinone (5). Reductive Claisen rearrangement ($Na_2S_2O_4$/DMF/H_2O/2.5 h)[3] of the 1,4-bis(chloroallyl)ether (2) of quinizarin gave a 96% yield of the product (3) of single rearrangement, which was converted (99%) into the anthrafuran (6) by treatment with 2.6% ethanolic potassium hydroxide (20% molar excess/reflux/25 min).[4] Reductive Claisen rearrangement of the anthrafuran (6)[3] gave the hydroxyanthrafuran (7) in 94% yield. Methylation (Me_2SO_4/K_2CO_3/Me_2CO/5 h) afforded (96%) the methyl ether (8) which in a one-pot reaction involving ozonolysis in CH_2Cl_2 (-78°/2 h), reductive work-up (Me_2S), and treatment of the product with trimethyl orthoformate, methanol, and p-toluenesulfonic acid (reflux/15 min) gave the acetoxyacetal (4) in 82% yield. The latter product is analogous to the intermediates of Kishi and the present sequence shows that contrary to a recent report,[5] synthetic strategies for the formation of anthracyclinone antibiotics based on Claisen rearrangements show considerable promise.

In an alternative synthesis of the hydroxyanthrafuran (6) [affording (4) in 51% overall yield], treatment of quinizarin with ethyl acetoacetate in triethylamine (reflux/72 h)[6] gave the 3-ethoxycarbonylanthrafuran (9) (72%) which was hydrolysed in 94% yield to the acid (10) by heating under reflux (30 h) with methanesulfonic acid in aqueous formic acid. Decarboxylation with copper chromite in quinoline under N_2 gave the anthrafurandione (11) (83%) which on

allylation with 2,3-dichloroprop-1-ene and anhydrous potassium carbonate in dry acetone gave the intermediate (6) in quantitative yield.

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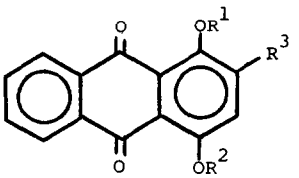
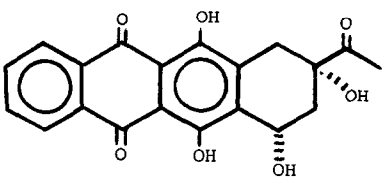
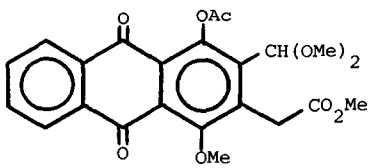


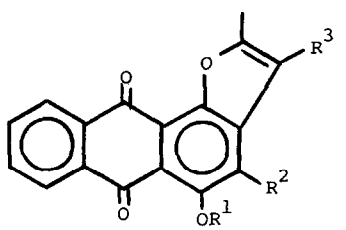
(1) $R^1 = R^2 = R^3 = H$
(2) $R^1 = R^2 = CH_2C(Cl)=CH_2$, $R^3 = H$
(3) $R^1 = H$, $R^2 = R^3 = CH_2C(Cl)=CH_2$



(5)



(4)



(6) $R^1 = CH_2C(Cl)=CH_2$, $R^2 = R^3 = H$
(7) $R^1 = R^3 = H$, $R^2 = CH_2C(Cl)=CH_2$
(8) $R^1 = Me$, $R^2 = CH_2C(Cl)=CH_2$, $R^3 = H$
(9) $R^1 = R^2 = H$, $R^3 = CO_2Et$
(10) $R^1 = R^2 = H$, $R^3 = CO_2H$
(11) $R^1 = R^2 = R^3 = H$

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