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A CLAISEN REARRANGEMENT ROUTE TO THE VINEOMYCINS

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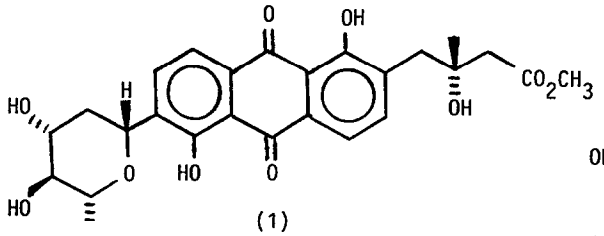
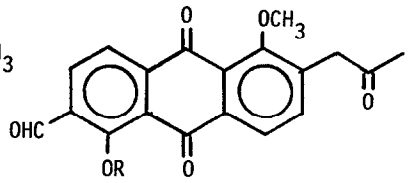
Summary: Anthrarufin is converted by a high yield route involving sequential Claisen rearrangements to an intermediate (3) suitable for the synthesis of vineomycins.

The vineomycin subgroup of anthracycline antibiotics may hold special promise as antitumour agents because their C-glycosyl moieties should be less vulnerable to deactivating deglycosylation than the equivalent O-glycosyl moieties of the clinically used anti-cancer agents adriamycin and daunomycin. Recently,[1] Danishefsky and coworkers reported a synthesis of vineomycinone B_2 methyl ester (1) via the substituted anthraquinone (2) which was itself prepared by two routes in overall yields of 20 and 42%. With a view to developing syntheses of vineomycinone analogues we sought to improve the availability of the key anthraquinone intermediates. We now report the synthesis of compound (3) in 80% overall yield from the 1,5-bis(chloroallyl)ether (4) of the commercially available hydroxyanthraquinone anthrarufin (5).

Reductive Claisen rearrangement ($Na_2S_2O_4$/DMF/H_2O/2.5 h)[2] of the bis ether (4) gave a 98% yield of the product (6) of single rearrangement which was converted (96%) into the anthrafuran (7) by treatment with 0.6% ethanolic potassium hydroxide (25% mol excess/reflux/5 h).[3] Reductive Claisen rearrangement of the anthrafuran (7) gave the hydroxyanthrafuran (8) in 98% yield. Methylation (Me_2SO_4/K_2CO_3/Me_2CO/5 h) gave (96%) the methyl ether (9). Mercuration[2] ($Hg(TFA)_2$/TFA/HCO_2H/18 h) gave the furanoketone (10) (73%) and the diketone (11) (22%). The diketone could be cyclised ($MeSO_3H$/P_2O_5, 10:1, 1 h) to give (10) (94%) thereby raising the overall yield of (10) to 94%. Ozonolysis of (10) in CH_2Cl_2 (-78°/1 h) followed by reductive workup (Me_2S) gave compound (3) in 96% yield. The overall yield (80%) of (3) compares most favourably with those reported by Danishefsky and coworkers for synthesis of the analogous dimethyl ether.

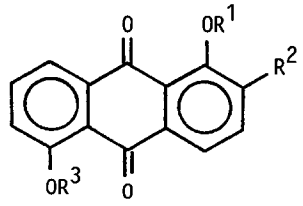


(1)



(2) R = CH_3

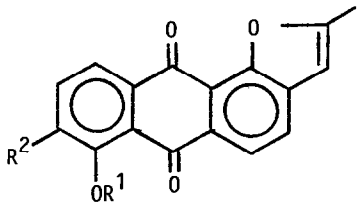
(3) R = $COCH_3$



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

(5) $R^1 = R^2 = R^3 = H$

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

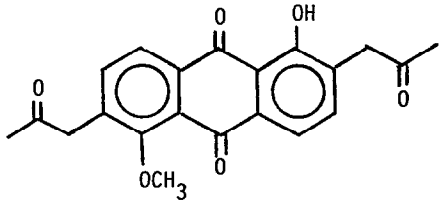


(7) $R^1 = CH_2C(Cl)=CH_2$, $R^2 = H$

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

(9) $R^1 = CH_3$, $R^2 = CH_2C(Cl)=CH_2$

(10) $R^1 = CH_3$, $R^2 = CH_2COCH_3$



(11)

With such unsymmetrical 2,6-disubstituted-1,5-dihydroxyanthraquinone derivatives now available, the way is opened for synthesis of novel vineomycinones and vineomycins.

References

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