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# A SIMPLE SYNTHESIS OF (±) 4-DEMETHOXYDAUNOMYCINONE

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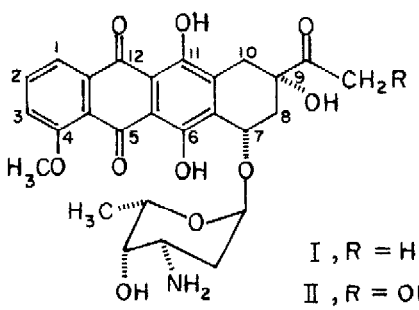
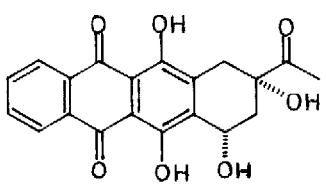
*A new and simple synthesis of 4-demethoxy-7-deoxydaunomycinone has been carried out essentially in three steps starting from 1,4-dimethoxy-6-tetralone.*

The anthracycline antibiotics daunomycin (I) and adriamycin (II) are of topical interest because of their potent activity against various types of experimental tumors as well as a variety of human cancers.[1] The compounds, however, suffer from a very serious drawback of having cumulative dose dependent cardiotoxicity.[2] Much effort has been directed towards obtaining new derivatives that show decreased side effects and/or increased anticancer activity. Recently it has been shown that 4-demethoxydaunomycin is four to eight times more active than daunomycin and the results of its clinical trials are reported to be very promising.[3] These factors have stimulated the development of numerous approaches to the synthesis of anthracyclinones.[4] We wish to report a very simple and efficient synthesis of the aglycone - 4-demethoxydaunomycinone (III).



I , R = H

II , R = OH



III

Our main strategy is to prepare the desired tetralin - 1,4-dimethoxy-6-acetyl-6-hydroxytetralin (VII) - starting from easily accessible 1,4-dimethoxy-6-tetralone[5] by a two carbon homologation, using an acyl anion equivalent such as 2-lithio-2-methyl-1,3-dithiane and transforming the resultant intermediate by conventional operations to get required product.

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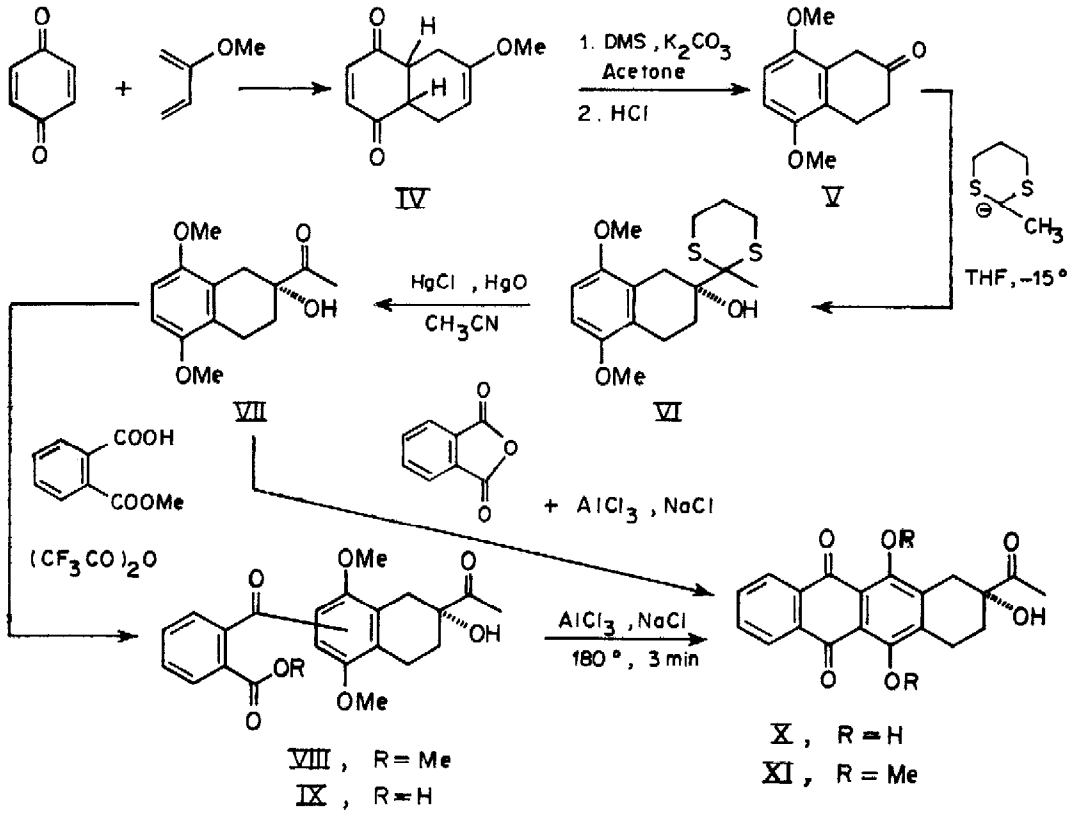
1,4-Dimethoxy-6-tetralone (V) was prepared by a slightly modified procedure. The Diels-Alder adduct (IV), obtained from benzoquinone and 2-methoxybutadiene[6] (sealed tube reaction in benzene at 90°, 12 hr) was methylated in boiling acetone ($Me_2SO_4$, $K_2CO_3$), followed by acid work up (HCl) of the acetone filtrate to give the tetralone (V) (75% overall yield from benzoquinone). Reaction of 2-lithio-1,3-dithiane in THF (prepared from 2-methyl-1,3-dithiane[7] with 1.1 eq. of n-BuLi - 15°, 3 hr.) with 1,4-dimethoxy-6-tetralone (-15°, 3 hr., then 0°, 18 hr.) and usual work up gave a mixture which can be easily separated on silica gel column (benzene-acetone mixture as eluent) to the desired thioketal derivative (VI) [NMR ($CDCl_3$) δ 1.83 (3H, s, $CH_3$), 1.8 to 2.2 (4H, m, 2 x $CH_2$), 2.96 (2H, bs, $ArCH_2$), 2.5 to 3.1 (6H, m, ($S-CH_2$)$_2$ and $ArCH_2$-] 3.73 (6H, s, 2 x OMe), 6.43 (2H, s, 2 x ArH); $M^+$ 340] in 59% yield and the rest as starting material.[8] Hydrolysis of the thioacetal (VI) in aqueous acetonitrile with mercuric chloride and mercuric oxide for 2.5 hr. afforded 1,4-dimethoxy-6-acetyl-6-hydroxytetralin (VII) in 80% yield, m.p. 99° (lit.[9] m. p. 97°). IR ($CHCl_3$) 3200 (OH), 1685 (C=O), 1600 (Ar) and 1230 $cm^{-1}$ (C-O-C); NMR ($CDCl_3$), δ 1.85 (2H, t, $CH_2$), 2.30 (3H, s, COMe), 2.80 (2H, bs, $ArCH_2$), 2.76 (2H, t, $ArCH_2$), 3.40 (1H, s, OH), 3.66 and 3.73 (2 x 3H, 2s, 2 x OMe) 6.60 (2H, s, 2 x ArH); mass spectrum, $M^+$ 250.

The dimethoxytetralin (VII) was condensed with excess of methyl hydrogen phthalate in refluxing trifluroacetic anhydride (40 hr) to give a mixture of isomeric keto-esters (VIII) in almost equal ratio (NMR) and was directly saponified (8% KOH, MeOH, RT) to yield the corresponding isomeric keto-acids (IX) in 63% yield from VII. Earlier, the ring closure to give anthracyclinone derivatives was accomplished using either $H_2SO_4$[10] or commonly with anhydrous HF[11] in poor yield. The cyclisation of IX is now best achieved by intimately mixing it with a ten-fold mixture of $AlCl_3$ - NaCl (5:1) heating at 180° for 3 min., and treating the resultant reddish mass with a saturated solution of oxalic acid to give 4-demethoxy-7-deoxydaunomycinone (X) in 80% yield. Methylation of X with $Me_2SO_4$ in presence of $K_2CO_3$ in refluxing acetone gave the dimethyl ether (XI) in almost quantitative yield, m.p. 184-86° (lit.[12] m.p. 184-86°). NMR ($CDCl_3$) δ 1.9 (2H, t, $CH_2$), 2.33 (3H, s, $COCH_3$) 2.97 (2H, s, $Ar-CH_2$), 3.04 (2H, t, $ArCH_2$) 3.80 and 3.83 (2 x 3H, 2s, 2 x OMe), 7.53 (2H, m, 1,4-ArH) and 8.00 (2H, m, 2,3-ArH). $M^+$ 380.




The dimethoxytetralin (VII) can be best converted directly to 4-demethoxy-7-deoxydaunomycinone (X) by fusing with an intimate mixture of phthalic anhydride (2.0 eq.), $AlCl_3$ - NaCl (5:1, ten fold excess) at 180° for 3 min. and treating the resultant reddish mass with a saturated solution of oxalic acid.[13] Extraction with chloroform and chromatography over silica gel column (benzene containing 2% acetone as eluent) and usual work up gave the desired product (X) (reddish plates; 70% yield), m.p. 212-15° (lit.[14] m.p. 210-212°).

As the conversion of (X) to 4-demethoxydaunomycinone (III) has already been described[11,15] we consider that our new synthesis of (X) can in effect constitute a total synthesis of III.[16]

References and Notes

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