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A CONVENIENT APPROACH TO THE TOTAL SYNTHESIS OF (±) 4-DEMETHOXYDAUNOMYCINONE

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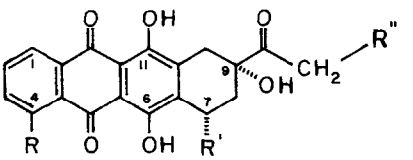
Abstract - A convenient and most practical approach to the synthesis of (±) 4-demethoxydaunomycinone starting from 2-methylhydroquinone is described.

In the last decade perhaps no family of chemotherapeutic agents has attracted so much world wide attention as the group of anthracycline antibiotics for the treatment of cancer. Chief among them are daunomycin (1) and adriamycin (2) which have shown remarkable effectiveness in combating a variety of human cancers.[1] Their primary site of action is considered to be at the tumor cell level through an interference with DNA synthesis and functionality. Adriamycin (2) is in particular of considerable clinical value because of its effectiveness on a number of solid tumors and it appears to be the most effective single agent among all antitumor agents presently in use. However, like other anticancer agents, these compounds also display some side effects, the most serious being the cumulative dose-dependent cardiotoxicity. These compounds are presently made by microbiological fermentation and the yields of these products are very low, thus making these drugs rather inacessible and expensive. In addition, it has been shown that a small structural change in 1 and 2 appears to have better therapeutic ratio. For these reasons, there has been a continued interest aimed at the total synthesis of these antibiotics including one of its analogues, 4-demethoxydaunomycin (3), which has now assumed considerable clinical importance as it is found to be 8 to 10 times more active than daunomycin and adriamycin.[2] Further, 4-demethoxydaunomycin (3) is orally active. As there is no possibility of obtaining 3 by fermentation and as many suitable methods for the synthesis of L-daunosamine[3] and its coupling to the aglycone of 3 [4-demethoxydaunomycinone (5)] have already been



1, R = OMe, R' = O-daunosaminyl, R" = H

2, R = OMe, R' = O-daunosaminyl, R" = OH

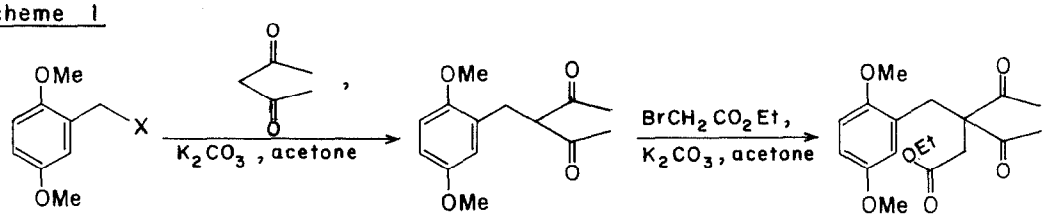
3, R = H, R' = O-daunosaminyl, R" = H

4, R = OMe, R' = OH, R" = H

accomplished,[4] our main efforts have been directed towards evolving a convenient synthesis of the aglycone moiety, 4-demethoxy-daunomycinone (5). Several synthetic approaches have been developed for the synthesis of both daunomycinone (4) and its 4-demethoxy derivative (5), utilising Friedel-Crafts acylation[5,6] and Diels-Alder reactions.[7,8] Yet, the versatile method first employed by Wong *et al.*[5] for the assemblage of tetracyclic system AB + CD coupling seems to be most appropriate. It involves the preparation of a tetraline derivative, such as 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (6) representing final AB rings and its condensation by acylation with a phthalic acid derivative, corresponding to CD rings in tetracyclic system. Various methods have since been reported for the synthesis of 6 which can be smoothly converted to 4-demethoxy-7-deoxy-daunomycinone (7). The conversion of 7 to 5 has been well established.[2a] Although various methods have since been reported for the synthesis of 6 (including those of ours[7]) none has been found to be suitable for the preparation of 6 in multi-gram quantities. We now report an efficient and a much simpler approach starting from 2-methylhydroquinone, employing easily accessible organic intermediates and reagents. Precise experimental procedures for the successful elaboration of these products have been outlined in view of their interesting application for the synthesis of other anthracyclinones.

2-Methylhydroquinone dimethyl ether (8)[9] was converted to 2,5-dimethoxybenzylbromide (9) by treatment with N-bromosuccinimide in boiling carbon tetrachloride in 80% yield. Condensation of (9) with 2,4-pentanedione in acetone in presence of anhydrous pot. carbonate at room temperature gave 3-acetyl-4-(2',5'-dimethoxyphenyl)-2-butanone (10) in 70% yield. Alkylation of 10 with ethyl bromoacetate under very mild condition using anhydrous pot.carbonate in acetone at room temperature gave the keto ester (11) in 75-80% yield. Earlier Wong *et al.*[5] did the same alkylation using sodium hydride in refluxing THF under strictly anhydrous conditions to give 11. In fact both the alkylations can be carried out as one pot reaction employing anhydrous potassium carbonate in acetone at room temperature without affecting the overall yield of 11 from 9 (scheme 1). Hydrolysis of 11 with aqueous sodium hydroxide underwent a reversed Claisen followed by the hydrolysis of the ester and gave the keto acid 12 in 95% yield. Operationally the conversion of methyl hydroquinone to the keto acid (12) can be smoothly carried out in an overall yield of 36%. Attempts were made to convert the keto acid

Scheme 1



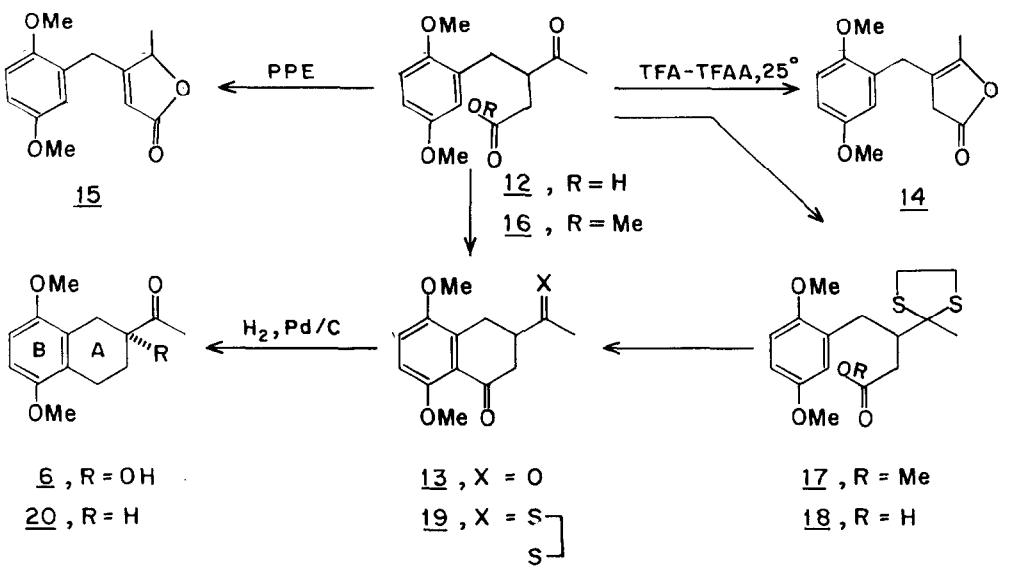
8 , X = H
9 , X = Br

10

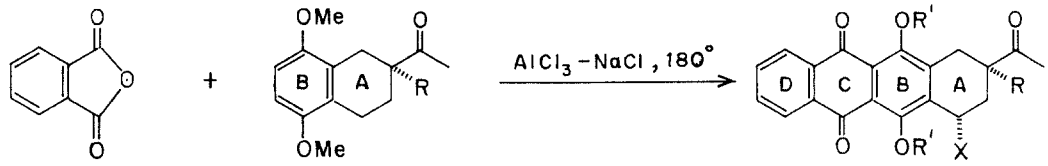
11

(12) to 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-4one (13) by a variety of reagents (see scheme 2). Our first attempt of this conversion with conc. sulphuric acid at room temperature met with failure and 12 was recovered unchanged. Employing an equal quantity of trifluoroacetic acid and trifluroacetic anhydride at room temperature for 8 hr and usual workup resulted in the formation of a product whose IR and PMR spectra clearly indicated that it is a lactone,14. [ν max. 1780 cm^{-1} lactone C=O) : δ $CDCl_3$ 2.0 (3H, bs, CH_3), 2.83 (2H, bs, $\underline{CH_2}$-CO), 3.33 (2H, s, Ar$\underline{CH_2}$-)]. Treatment of 12 with polyphosphate ester (P_2O_5, Et_2O, $CHCl_3$) at reflux temperature resulted in the formation of an isomeric lactone 15 in more than 80% yield. [ν max. 1760 cm^{-1} (lactone C=O); $CDCl_3$ δ 1.46 (3H, d, J=6Hz, CH_3), 4.9 (1H, q, -$\underline{CH}$-Me), 5.50 (1H, bt, $\underline{CH}$=), 3.53 (2H, s, Ar-$\underline{CH_2}$)]. To surmount this obstacle, it appeared necessary to protect the acetyl carbonyl group so that the lactone formation can be avoided totally. Although, ketalisation is the obvious choice of protecting the ketone, we preferred thio-ketalisation for reasons of its stability during cyclisation under acid conditions. Thus the keto-acid 12 was first converted to its ester by diazomethane and the resultant ester 16 was then treated with ethane dithiol in presence of small amount of BF_3 etherate to give the thioketal derivative (17). Alkaline hydrolysis of 17 gave the corresponding acid (18) which was then subjected to cyclisation with polyphosphate ester to obtain 19. Dethioketalisation of 19 by treatment with mercuric oxide and mercuric chloride in boiling acetonitrile[10] resulted in the formation of the desired tetralone (13). However, 13 can be obtained from the keto-acid (12) by subjecting it to hydrofluoric acid cyclisation in 60-65% yield.[5] Catalytic hydrogenation of the tetralone (13) using 10% Pd/C gave the desired synthon, 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (20) in 95% yield.

Scheme 2



Having obtained 20, which constitutes the AB synthon, our next step was to introduce the tertiary hydroxyl group either at this stage or to build the anthracyclinone skeleton and subsequently introduce the tert. hydroxyl at 9-position. We preferred the latter course as in our experience introduction of tert. hydroxyl employing the method described by Wong et al.[5] by oxidation in t-butanol with



6 R = OH
20 R = H

5 R = X = OH, R' = H
7 R = OH, R' = X = H
21 R = R' = X = H
22 R = OH, R' = X = H
23 R = X = H, R' = Me
24 R = OH, R' = Me, X = H

t-butoxide and oxygen followed by reduction with zinc gave the hydroxyketone (6) together with substantial quantities of 2-acetyl-5,8-dimethoxynaphthalene due to the aromatisation of the A-ring. We have recently demonstrated that 2-acetyl-5,8-dimethoxynaphthalene by metal-ammonia reduction gives 20 in more than 80% yield.[7c]

Earlier it was shown that condensing 20 or 6 with phthalic acid monomethyl ester in trifluoroacetic acid and trifluoroacetic anhydride solution followed by basic hydrolysis and then cyclisation led to the corresponding anthracyclinone (21 or 22). The same can be achieved by fusing an intimate mixture of 20 with phthalic anhydride in $AlCl_3$-NaCl (5:1) melt maintained at 180-190° for 3 to 5 min.[7a] By this approach, we could obtain 4-demethoxy-7,9-dideoxydaunomycinone (21) in 76% yield. Methylation of 21 with dimethyl sulphate in presence of anhydrous pot.carbonate in boiling acetone gave the dimethyl ether (23) m.p. 145-47°[8c] (80% yield). Hydroxylation of C-9 in 23 was achieved via a four-step reaction sequence which was commonly employed for the introduction of C-17 hydroxyl group in steroids[11] and the same was adopted by Sih and his colleagues[6b] for the synthesis of 7-deoxydaunomycinone. This involved the preparation of enol acetate (PTS acid, Ac_2O), followed by epoxidation and the resultant epoxy acetate was then treated successively by base and acid to ensure complete hydrolysis and rearrangement to give (±) 7-deoxy-4-demethoxydaunomycinone dimethyl ether (24), which after chromatographic purification resulted in 55% overall yield from 23. As the method for the demethoxylation of 24 and introduction of hydroxyl function at C-7 have already been described,[5,8c] this route formally constitutes a total synthesis of (±) 4-demethoxydaunomycinone (5).[12]

EXPERIMENTAL

MPs are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded in nujol or chloroform or neat in a Perkin Elmer Model 683 spectrophotometer with sodium chloride optics. PMR spectra were obtained on Varian A-60 or Bruker WH-90 spectrometer

in $CDCl_3$ or CCl_4 solutions containing TMS as an internal standard with chemical shift (δ) expressed in ppm downfield from TMS. Mass spectra were run on AEI MS30 double beam mass spectrometer, or CEC 21-110B spectrometer. All solvents and reagents were purified and dried by standard techniques.

2,5-Dimethoxybenzylbromide (9)

2,5-Dimethoxytoluene (15.2 g., 0.1 mole) in carbontetrachloride (200 ml) and N-bromo-succinimide (26.5 g., 0.15 mole) was refluxed for 2.5 hr. in the presence of a catalytic amount of benzoyl peroxide. The succinimide was filtered off, the residue was washed with carbontetrachloride and the combined organic solution distilled off. The resulting yellowish solid (18.5 g., 80%) was crystallised from hexane containing a few drops of benzene to give 2,5-dimethoxybenzyl bromide as colourless needles, m.p. 76-8° : NMR δ (CCl_4) 3.65 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.35 (s, 2H, CH_2Br), 6.55 (m, 3H, aromatic). Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.75; H, 4.76. Found : C, 46.67; H, 4.79%.

3-Acetyl-4-(2', 5'-dimethoxyphenyl)-2-butanone (10)

An acetone solution (250 ml) containing 2,5-dimethoxybenzyl bromide (13.86 g., 60 m mol), 2,4-pentanedione (7.2 g., 72 m mol) and anhydrous potassium carbonate (69 g., 0.5 mole) was stirred at room temperature for 12 hr. in a 500 ml flask fitted with a mechanical stirrer. The acetone was then distilled off and water was added to dissolve the inorganic salts. It was then extracted with chloroform, washed with water and dried (Na_2SO_4). Removal of solvent under reduced pressure gave a viscous oil which slowly solidified to give a pale yellow solid which was crystallised from methanol (yield : 10.6 g, 70%), m.p.63-8° (lit.[5] m.p. 63-8°). IR (film) 1700 and 1720 cm^{-1} (>C=O); NMR (CCl_4) 6.60 (m, 3H, aromatic), 3.80 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.50 (s, 2H, benzylic), 2.10 (s, 3H, -COMe), 2.0 (s, 3H, COMe). Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.2; H, 7.2. Found : C, 66.84; H, 7.26%.

Ethyl-3,3-diacetyl-4-(2', 5', - dimethoxy-phenyl) - butanoate (11)

An acetone solution (250 ml) containing 3-acetyl-4-(2', 5' - dimethoxyphenyl)-2-butanone (10) (12 g., 48 m mol), ethyl bromo-acetate (8 g., 52 m mol) and anhydrous potassium carbonate (40 g., 0.3 mole) was stirred at room temperature for 10-12 hr. Work up as above gave a viscous oil which soon solidified to a colourless solid. Recrystallisation from methanol yielded pure (11), m.p. 68-71° (lit.[5] m.p. 66-7°), in 77%yield (12.5 g). IR ($CHCl_3$) 1760 (ester), 1720 (ketone); NMR ($CDCl_3$) 6.65 (m, 3H, aromatic), 4.10 (q, 2H, $COOCH_2CH_3$), 3.60 (s, 3H, OMe), 3.50 (s, 3H, OMe), 3.20 (s, 2H, benzylic), 2.85 (s, 2H, CH_2- COOEt), 2.20 (s, 6H, COMe), 1.25 (t, 3H, COOEt). Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.28; H, 7.14, Found : C, 63.83; H, 7.08%).

3-Acetyl-4-(2', 5'-dimethoxyphenyl)-butanoic acid (12)

The keto ester (11) (12.5 g; 37 m mol) was hydrolysed by heating in a sodium hydroxide solution (8%, 78 ml) at 65-70° for 3 hr. The basic solution was then washed with benzene and acidified with cold conc. HCl. The precipitated keto acid (12) was filtered, dried and crystallised from methanol, m.p. 105-7° (lit.[5] m.p. 106-107°), yield 9.75 g. (98%); IR ($CHCl_3$) 1730 (>C=O); NMR ($CDCl_3$) 8.60 (s, 1H, COOH), 6.72 (m. 3H, aromatic), 3.75 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3-2.2 (m, 5H), 2.10 (s, 3H, COMe). Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.16; H, 6.76. Found : C, 62.86; H, 7.15%.

Cyclisation of keto acid (12)

(a) With hydrofluoric acid :

The keto acid (12) (10 g, 0.376 mol) was added with stirring into a polythene reaction flask containing anhydrous hydrofluoric acid (100 ml). After stirring for 3 hr. at 15-20°C, the remaining hydrofluoric acid was evaporated and the brownish residue was diluted with water. It was then exhaustively extracted with chloroform, the chloroform solution washed with sodium bicarbonate solution and dried (Na_2SO_4). The solvent was evaporated and the resultant light yellow solid (13) (5.7 g., 61%) was crystallised from methanol, m.p. 120-22° (lit.[5] m.p. 123-5°): IR ($CHCl_3$) 1710 (>C=O), 1680 (Ar-C=O).NMR ($CDCl_3$) 2.30 (s, 3H, COMe), 2.50-3.50 (m, 5H) 3.90 (s, 6H, OCH_3), 6.70 (d (J=9Hz), 1H, 6-H) 6.95 (d (J=9Hz), 1H, 7-H) : MS m/e : 248 (M+), 205 (M-COMe). Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found : C, 67.75; H, 6.73%.

(b) With trifluoroacetic acid and trifluoroacetic anhydride

The keto acid (1 g, 37 m mol) was treated with trifluoroacetic acid (5 ml) and trifluoroacetic anhydride (5 ml) at 0° and the resultant mixture was stirred at R.T. for 8-10 hrs. The reaction mixture was poured into crushed ice, extracted with chloroform. The chloroform solution was washed with $NaHCO_3$, water and dried. Evaporation of the solvent gave a viscous liquid which upon purification by silica gel chromatography gave the lactone (14) (0.6 g., 65%) as pale yellow liquid; IR (nujol) 1780 (lactone); NMR (CCl_4) : 6.75 (m, 3H, aromatic), 3.80(s, 3H, OMe), 3.75 (s, 3H, -OMe), 3.33 (s, 2H, $ArCH_2$), 2.83 (bs, 2H, $-CH_2-CO$), 2.0 (bs, 3H, Me) : Mass (m/e) : 248 (M^+).

(c) With polyphosphate ester (PPE) :

The keto acid (0.5 g, 18.8 m mol) and PPE (15 ml, from 15 g. P_2O_5, 20 ml ether and 40 ml chloroform) were refluxed together for 4-6 hrs. The solvent was distilled off and the residual reddish liquid was purified by silica gel column chromatography. The lactone (15) (0.38 g, 81.5%) was obtained as a viscous yellow liquid : IR (nujol) : 1760 (lactone) NMR ($CDCl_3$) : 6.70 (m, 3H, aromatic), 5.50 (bs, 1H, =CH-CO), 4.90 (q, 1H, -CHMe) :

3.73 (s, 6H, -OMe), 3.53 (bs, 2H, Ar-CH_2), 1.46 (d, J = 6Hz, 3H, -CHMe).

Methyl-3-acetyl-4-(2', 5'-dimethoxyphenyl)-butanoate (16)

The keto acid (1.5 g)in methanol (10 ml) was treated with excess of an ethereal solution of diazomethane. Work up in the usual fashion and purification by silica gel column chromatography gave the methyl ester (16) as a light yellow oil in 89% yield (1.4 g). IR (nujol) 1740 (ester), 1718 (ketone). NMR (CCl_4) : 6.50 (m, 3H, aromatic), 3.73 (s, 3H, OMe)- 3.63 (s, 3H, OMe), 3.50 (s, 3H, COOMe), 3.0 to 2.2 (m, 5H), 2.03 (s, 3H, Ac). Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.28; H,7.14. Found : C, 63.89; H, 7.23%.

Thioketal of 16

The above keto ester (16) (1.4 g., 5 m mol) in chloroform (5 ml) was stirred at 0° and treated with ethanedithiol (0.5 ml, 6 m mol) and BF_3etherate (0.5 ml). The mixture was stirred at r.t. for 6-8 hr. The chloroform solution was washed thrice with 2% NaOH, water and dried. Evaporation of the solvent yielded a gummy solid (17) which was crystallised from methanol as white crystals, m.p. 79-80°, yield (1.475 g, 83%) : IR (nujol) : 1730 (ester). NMR (CCl_4) : 6.63 (s, 3H, aromatic), 3.80 (s, 6H, OMe), 3.70 (s, 3H, COOMe), 3.26 (s, 4H, $2XCH_2S$), 3.20-1.85 (m, 5H), 1.40 (s, 3H, Me). Anal. Calcd. for $C_{17}H_{24}O_4S_2$: C, 57.30; H, 6.74. Found : C, 57.34; H, 6.49%.

Cyclisation with PPE

(a) The above protected ester (1.32 g, 3.7 m mol) in methanol (10 ml) was heated with 8% NaOH (10 ml) at 80-90° for 4 hr. Methanol was distilled off, water was added to residue and acidified with conc. HCl. The crude acid (18) (0.85 g., 67%) was crystallised from methanol, m.p. 109-112°; IR (nujol) : 1700 (C=O). Anal Calcd. for $C_{16}H_{22}O_4S_2$: C, 56.14 : H, 6.43. Found : C, 56.21; H, 6.55%.

(b) The above acid (18; 1g, 3 m mol) and PPE (10 ml) (from 15 g. P_2O_5, 20 ml ether and 40 ml chloroform) were heated at 60-65°for 10-12 hr. The reaction mixture was poured into crushed ice, the product extracted with chloroform, washed and dried. Distillation of the solvent gave a reddish liquid which was purified by silica gel colum chromatography. Crystallisation from methanol gave (19) as colourless needles, m.p.143-5° in 50% yield (0.47 g.). IR (nujol) : 1670 (C=O). NMR ($CDCl_3$) : 6.86 (q, 2H, aromatic), 3.86 (s, 6H, OMe), 3.33 (s, 4H, $2XCH_2$), 3.0-2.2 (m, 5H), 1.86 (s, 3H, CH_3). MS (m/e) 324 (M^+). Anal. Calcd. for $C_{16}H_{20}O_3S_2$: C, 59.25; H, 6.17. Found : C, 58.69; H. 6.17%.

2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-naphthalene-4-one (13)

Desulfurisation of the above monoketone was effected by reacting 800 mg. (2.4 m mol) of it in aq. acetonitrile (80%, 100 ml) with mercuric oxide (650 mg, 2.7 m mol) and mercuric chloride (1.6 g., 5.8 m mol) and stirring the mixture at 90° for 4 hr. It was cooled, solid filtered off and washed with chloroform several times. The combined chloroform solution was washed with water, then with 6M ammonium acetate, brine and dried. Evaporation of the solvent and purification of the residue by silica gel column chromatography yielded the diketone (13), m.p. 120-2° in 50% yield. The product was identical in all respects with the HF cyclisation product.

2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-naphthalene (20)

A solution of the tetralone (13) (5 g., 20 m mol), ethyl alcohol (200 ml), concentrated hydrochloric acid (5 ml), water (20 ml) and 10% Pd/C (1 g) was hydrogenated at room temperature and at atmospheric pressure with mechanical shaking for 7 hr. The catalyst was filtered, washed with a little ethyl alcohol and the combined alcohol solution evaporated to dryness under reduced pressure. The colourless residue was crystallised from ethyl alcohol and petroleum ether to give the monoketone (20) (4.475 g, 94.8%), m.p. 82-83° (lit.[5] m.p. 81-2°). IR ($CHCl_3$) 1710 (C=O); NMR : ($CDCl_3$) 2.20 (s, 3H,$COCH_3$), 3.75 (s, 6H, OCH_3), 6.50 (s, 2H, aromatic); MS m/e : 234 (M^+). Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.8; H, 7.69. Found : C, 71.57; H, 7.68%.

(±)4-Demethoxy-7,9-dideoxydaunomycinone (21)

A mixture of 5.65 g. (45 m mol) of anhydrous aluminium chloride and 2 g. (40 m mol) of sodium chloride was heated in a beaker at 180-190° for 4-5 minutes. To this melt was added 2.53 g. (17.5 m mol) of phthalic anhydride and the tetralin (20) (1 g., 4 m mol) and this mixture was stirred for 7 min. at 180-90°. After cooling, the reaction mixture was digested with a saturated solution of oxalic acid by heating on a steam bath for 1 hr. It was cooled, extracted with chloroform (4 x 50 ml), the combined chloroform extract was washed with 5% $NaHCO_3$, brine and dried. The residue after evaporation of solvent gave a red solid (1.1 g, 76.5%) which upon crystallisation from methanol yielded (21) as red needles m.p. 177-79° (lit.[6b] m.p. 180-2°); IR ($CHCl_3$) 3300 (chelated-OH), 1700 (ketone), 1680 (quinone), 1600 (aromatic); NMR ($CDCl_3$); 14.10 (s, 1H, OH), 14.0 (s, 1H, -OH), 8.58 (m, 2H, aromatic), 7.80 (m,2H, aromatic), 3.0 to 2.50 (m, 7H) 2.30 (s, 3H, Ac); MS (m/e) : 336 (M^+). Anal. Calcd. for : $C_{20}H_{16}O_5$: C, 70.14; H, 4.76. Found : C, 69.90; H, 5.00%.

(±) 4-Demethoxy-7-deoxydaunomycinone dimethyl ether (24)

(a) The above hydroxyanthracyclinone (336 mg, 1 m mol) was methylated with dimethyl sulphate (1.5 g., 5 m mol), potassium carbonate (1.35 g, 5 m mol), and acetone (50 ml) in the usual manner. Work up in the usual manner and purification of the methyl ether by crystallisation from methanol gave a yellow crystalline solid (23) (290 mg, 80%), m.p. 145-7° (lit.[8c] m.p. 145-7°); NMR ($CDCl_3$) : 8.30 (m, 2H, 1,4-H), 7.80 (m, 2H, 2,3-H), 4.0 (s, 3H, OMe), 3.96 (s, 3H, OMe), 2.30 (s, 3H, Ac). Anal.Calcd. for $C_{22}H_{20}O_5$, C, 72.52, H, 5.48. Found : C, 72.41, H, 5.86%

(b) To 200 mg (0.55 m mol) of the above methyl ether in 50 ml of acetic anhydride was added 670 mg (4.9 m mol) of p-toluene-sulphonic acid (monohydrate). Continuous slow distillation of acetic anhydride and acetic acid was carried out over 6-7 hr. A further quantity of 120 mg of p-toluene sulfonic acid was added and the distillation continued over 3-4 hr. The residual acetic anhydride was removed in vacuo and the brownish yellow mass was partly purified over silicagel column. This yellow solid (200 mg) was epoxidised with m-chloroperbenzoic acid in dichloromethane. After stirring for 1 hr at room temperature (25°C), it was worked up to give 180 mg (90%) of the crude epoxide as a yellow viscous oil. The latter was treated with 7.5 ml of 0.3N sodium hydroxide in 50% ethyl alcohol for 35 min. at room temperature. After acidification and extraction with dichloromethane, the residue was treated with 10 ml of a solution containing 6 ml of glacial acetic acid, 1 ml of conc. sulfuric acid and 3 ml of water for 1 hr. After dilution with water, the reaction mixture was extracted with dichloromethane, washed with water, dried and evaporated to yield 180 mg of crude red solid. Silica gel column chromatography of this crude material (elution with hexane : acetone, 97:3) gave 4-Demethoxy-7-deoxydaunomycinone dimethyl ether (24) which crystallised from methanol : hexane as yellow needles (110 mg, 55%), m.p. 187-8° (lit[8c] m.p. 184-6°); NMR ($CDCl_3$) : 8.25 (m, 2H, 1,4-H), 7.75 (m, 2H, 2,3-H), 4.0 (s, 3H, OMe), 3.90 (s, 3H, OMe), 2.25 (s, 3H, Ac). MS (m/e) 380 (M^+), 362 ($M-H_2O$), 337 (M-Ac). Anal. Calcd. for : $C_{22}H_{20}O_8$: C, 69.47; H, 5.26. Found : C, 68.95; H, 5.13%. The sample was identical in all respects with an authentic sample.[7a]

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