Tetrahedron Vol. 40, No. 22, pp. 4789 to 4793, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00

HETEROANTHRACYCLINES—III

6,7,11-TRI-O-METHYL-4-DEMETHOXY-12-SULFONODAUNOMYCINONE [6,10,11-TRIMETHOXY-8-HYDROXY-8-ACETYL-7,8,9,10-TETRAHYDROBENZO(B)-THIOXANTHEN-12-ONE-5-DIOXIDE]

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(*Received in USA* 11 *May* 1984)

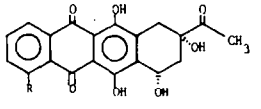
Abstract—The sulfone analogue of 6,7,11-tri-O-methyl-4-demethoxydaunomycinone, namely 6,7,11-tri-O-methyl-4-demethoxy-12-sulfonodaunomycinone (**12**) was synthesized using 5,8-dimethoxy-2-acetyltetralin (**13**) as starting material which can be prepared in large scale by hydrogen chloride catalysed cyclization of 3-(2,5-dimethoxybenzyl)-1,4-dioxopentane (**15**) in methylene chloride followed by hydrogenolysis thus shortening and simplifying our earlier procedures and eliminating the handling of large quantity of liquid hydrogen fluoride. The intermediate **15** can be easily prepared in large scale according to the procedure which we reported earlier.[13c]

Reaction of **13** with 2,2'-dithiosalicylic acid gave an isomeric mixture of **17** and **18** which were separated and their structure differentiated by dipole moment studies.[14] Isomer **17** was reduced by Zn dust to **22** and **23** which reacted with anhydrous methanol to form **24** and **25**. Both **24** and **25** as an isomeric mixture were oxidized to **28** and **29** by oxygen in basic N,N-dimethylformamide solution and finally to the stable sulfones **30** and **31** by *m*-chloroperoxybenzoic acid. These two isomeric sulfones were separated and fully characterized and then oxidized further to form **34** which was converted to the title compound **12** by free radical bromination and reaction with anhydrous methanol in the presence of silver trifluoromethanesulfonate. The structure of **12** was positively established by detailed analysis of its high field PMR spectrum (Fig. 1).

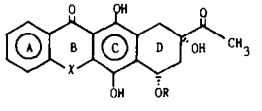
Since the early reports on the syntheses of derivatives of 4-demethoxydaunomycinone (**1**), daunomycinone (**2**) and carminomycinone (**3**),[1,2] a large number of excellent works appeared dealing with the syntheses and structure modification of the first generation anthracyclines. Of the numerous modified structures, 4-demethoxydaunomycin, 4-demethoxy-4'-deoxydaunomycin, 4-demethoxy-4'-epidaunomycin and their corresponding adriamycin analogues[3] are either more potent and or less toxic. The isolation and structure elucidation of aklavinones and aclacinomycins in the mid-1970's[4,5] and the favourable clinical report of aclacinomycin A[6] together with the finding that aclacinomycin Y had 10-fold greater antimicrobial activity over aclacinomycin A[7] prompted extensive works on the synthesis of aklavinones and its derivatives.[8] However, the structure-activity-cardiotoxicity relationship continues to be the very interesting and perplexing problem of the anthracycline antitumor drugs.

The absence of the 11-OH function seems to show favourable effect in cardiotoxicity as shown in the case of aclacinomycin A,[6] 11-deoxydaunomycin and the adriamycin analogues.[9] This information, together with those from 4-demethoxy-, 4'-deoxy- and 4'-epi-analogues[3] probably led to the syntheses of 4-demethoxy-11-deoxydaunomycin, -adriamycin, 4'-O-THP-adriamycin,[10] 4- and 6-O-methyl aclacinomycin A[11] and maybe eventually the 4-demethoxy-11-deoxy-4'-deoxy analogues.

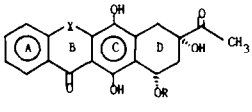
The removal of the 11-OH function reduces the electron affinity of the C-12 quinone CO function in the one electron transfer process during the reduction of quinone as can be seen in the reduction potential difference of 1,4-dihydroxy- and 1-hydroxyanthraquinones.[12] This and the fact that the 11-deoxyanthracyclines are generally less cardiotoxic, would further strengthen the hypothesis that cardiotoxicity and the



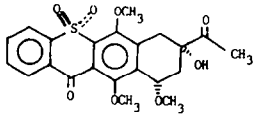
1 R= H, 2 R= OCH_3, 3 R= OH



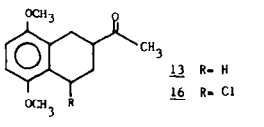
4 X= SO, R= H
5 X= SO_2, R= H
8 X= SO, R=daunosaminyl
9 X= SO_2, R=daunosaminyl



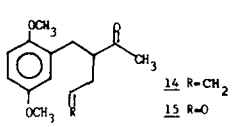
6 X= SO, R= H
7 X= SO_2, R= H
10 X=SO, R=daunosaminyl
11 X=SO_2, R=daunosaminyl



12

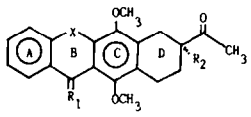


13 R= H
16 R= Cl

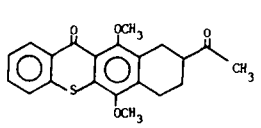


14 R=CH_2
15 R=O

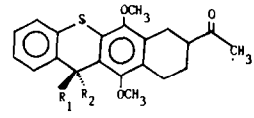
reduction potential of the quinone moiety are related. We therefore proposed the construction of 6,7,9,11-tetrahydroxy-9-acetyl - 7,8,9,10 - tetrahydrobenzo(b)thioxanthen - 12 - one - 5 - oxide (**4**), the -5-dioxide (**5**) and their corresponding regio-isomers (**6** and **7**). Glycoside formation with various aminosugars such as daunosamine or 4-deoxydaunosamine would lead to the 4-demethoxy or 4-demethoxy-4'-deoxydaunomycin sulfone and sulfoxide analogues such as **8**, **9**, **10**, **11**. These molecules together with their 11-deoxy compounds would be of great interest in the studies of structure–activity–toxicity relationship of anthracyclines. The successful synthesis of **12** demonstrated the easy access to the heteroaglycones **4**, **5**, **6**, **7** and many others.



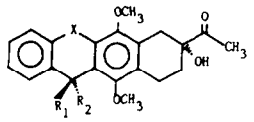
17 X=S, R_1=O, R_2=H
19 X=S, R_1=H_2, R_2=H
20 X=S, R_1=H_2, R_2=OH
21 X=SO_2, R_1=H_2, R_2=OH



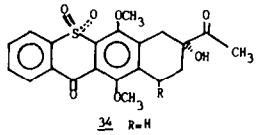
18



22 R_1=OH, R_2=H
23 R_1=H, R_2=OH
24 R_1=OCH_3, R_2=H
25 R_1=H, R_2=OCH_3
26 R_1=OC_2H_5, R_2=H
27 R_1=H, R_2=OC_2H_5



28 R_1=OCH_3, R_2=H, X=S
29 R_1=H, R_2=OCH_3, X=S
30 R_1=OCH_3, R_2=H, X=SO_2
31 R_1=H, R_2=OCH_3, X=SO_2
32 R_1=OC_2H_5, R_2=H, X=SO_2
33 R_1=H, R_2=OC_2H_5, X=SO_2



34 R=H
35 R=Br

RESULTS AND DISCUSSION

The title compound **12** was conveniently prepared in an acceptable overall yield starting with the versatile intermediate 5,8-dimethoxy-2-acetyltetralin (**13**). In our previous publications, we reported three different preparative processes for this intermediate.[13] The two early processes gave very good overall yields in large scale preparation but were somewhat restricted by a cyclization process where a large quantity of liquid hydrogen fluoride was needed. The third process involved a one-pot reaction for the preparation of 3 - (2,5 - dimethoxybenzyl) - 5 - hexen - 2 - one (**14**) which gave an excellent overall yield of **15** upon ozonolysis. In methylene chloride saturated with hydrogen chloride, **15** cyclized to the unstable **16** which was reduced by trimethylsilane to **13**. Unfortunately, a large quantity of trimethylsilane is required and reduction of the acetyl side chain cannot be excluded even in the presence of acetone. However, hydrogenolysis of **16** in ethanol in the presence of Pd/C immediately after removal of the methylene chloride at room temp gave good reproducible yields of **13**.

Condensation of **13** with 2,2'-dithiosalicylic acid in concentrated sulfuric acid at room temp gave a mixture of two regioisomers **17** and **18** which were separated by chromatography over silica. The first isomer recovered from the column was assigned structure **17** whose calculated dipole moment was 3.2 D and the experimental value was 3.5 D. The second isomer was assigned structure **18** the calculated dipole moment of which was 4.7 D and the experimental value was 4.9 D. Dipole moments were calculated using the reported basic dipole moment of thioxanthone of 2.75 D and published values for benzene soln group moments.[14]

Oxidation of vinylogous thioesters to sulfoxides and sulfones by oxidizing reagents such as hydrogen peroxide, selenium dioxide or *m*-chloroperoxybenzoic acid are known. Attempts to effect the same oxidation on **17** by a variety of oxidizing reagents either failed or was accompanied by aromatization of the D-ring or ester formation in the side chain via a Baeyer-villiger oxidation. Thus it seems that the removal of the C-5 CO function is needed before the S atom can be oxidized to sulfoxide or sulfone. Heating an ammonium hydroxide–tetrahydrofuran solution of **17** in the presence of Zn dust and cupric sulfate overnight resulted in the selective reduction of the C-5 CO group to form **19** in almost quantitative yield. However, the conversion of **19** to **12** via **20** and **21** resulted in the aromatization of the D-ring possibly due to the failure to selectively oxidize the C-5 or the C-7 positions. When the reduction was carried out at room temp for only 45 min, the product was a mixture of isomers **22** and **23**. These two isomers seemed to exist in a slow equilibrium at room temp. Attempted separation by thin layer chromatography on silica showed the presence of two compounds. However, equilibrium seemed to re-establish after their isolation. Thus the isomeric mixture was converted to the methyl ethers **24** and **25** quantitatively by anhydrous methanol and 2,2-dimethoxypropane. Oxidation of these by oxygen in N,N-dimethlformamide in the presence of t-butyl alcohol and potassium t-butoxide under anhydrous condition gave **28** and **29**. All of these compounds are relatively unstable and attempts to separate one isomer from the other and induce crystallization failed. Their presence were indicated only by routine spectroscopies. Further oxidation of **28** and **29** by *m*-chloroperoxybenzoic acid gave the stable sulfones **30** and **31**. Separation of these from each other was accomplished by preparative HPLC on Partisil column. Since both will be converted to **34** for further development, large scale separation is not necessary. The PMR spectrum of the first isomer collected from the column shows the C_5—H at $\delta = 5.57$, C_{11}—OCH_3 at $\delta = 4.02$, C_6—OCH_3 at $\delta = 3.86$, C_5—OCH_3 at $\delta = 3.12$ and $COCH_3$ at $\delta = 2.38$ while the second isomer shows the C_5—H at $\delta = 5.64$, C_{11}—OCH_3 at $\delta = 4.04$, C_6—OCH_3 at $\delta = 3.93$, C_5—OCH_3 at $\delta = 3.12$ and $COCH_3$ at $\delta = 2.32$. Both the C_5—H and C_6—OCH_3 of the second isomer appeared in significantly lower field than those of the first isomer, assignment based on this difference is inconclusive. Their IR spectra were almost identical except that the first isomer shows a

strong doublet at 1080 cm^{-1} with $\Delta\nu = 10\ cm^{-1}$ and the second isomer has a sharp strong peak at 1080 cm^{-1}. The first isomer was tentatively assigned structure **30** and the second isomer was assigned **32** based solely on their polarity difference.

It is of interest to observe that the alcohols **22** and **23** were converted partly to the ethyl ethers **26** and **27** when solvents containing ethanol such as ethyl acetate were used for their extraction. Separation of **26** and **27** from **24** and **25** is very difficult. Their presence, confirmed only by PMR and mass spectra, complicated the formation of **34** with much higher proportion of D-ring aromatized products due to possibly slower rate of oxidation of **32** and **33** to **34** than that of **30** and **31**.

Oxidation of both **30** and **31** by oxygen in N,N-dimethylformamide and t-butyl alcohol soln in the presence of potassium t-butoxide for six min followed by the addition of dilute hydrochloric acid and trimethyl phosphite regenerated the C_5-carbonyl function to form **34**. Reaction of **34** with N-bromosuccinimide in carbon tetrachloride heated under reflux and irradiation by UV light gave a good yield of the unstable product **35** which without detailed characterization was converted to the title compound **12** by stirring it in anhydrous methanol in the presence of silver trifluoromethanesulfonate. A mass spectrum recorded by a conventional electron impact ionization instrument gave only a molecular ion of 396 corresponding to the D-ring aromatized product. The aromatization was confirmed by observing the progressive disappearance of the 1710 cm^{-1} peak and the increase of the 1680 cm^{-1} peak after heating the compound in a 180° oil bath. The molecular ion peak of 446.1 plus a very strong and characteristic peak at 469.1 ($M^+ + Na$) was observed in the Manitoba Time-Of-Flight Mass Spectrometer for secondary ion mass spectra.[15] This newly designed instrument uses bursts of alkali metal ions of ~ 10 ns duration to strike a thin layer of organic material deposited on a metallic surface producing secondary ions of the organic compound at ambient temperature. The high field PMR spectrum (Fig. 1) shows all the structural details of this molecule. Thus the C_4—H and C_1—H appear at $\delta = 8.23$ and $\delta = 8.15$ both as doublet of a doublet with $J_{4,3} = 7.5$ Hz, $J_{4,2} = 1.3$ Hz, $J_{1,2} = 7.5$ Hz, $J_{1,3} = 1.2$ Hz. The C_2—H and C_3—H appear at $\delta = 7.85$ and $\delta = 7.75$ as double doublet of a doublet with $J_{2,1} = 7.5$ Hz, $J_{2,3} = 7.5$ Hz, $J_{2,4} = 1.2$ Hz, $J_{3,2} = 7.5$ Hz, $J_{3,4} = 7.5$ Hz, $J_{3,1} = 1.2$ Hz. The C_9—OH is seen at $\delta = 4.967$ as a sharp singlet which disappears after deuterium exchange. The C_7—H appears at $\delta = 4.817$ showing coupling to the C_8—H_2 with $J_{7e,8a} = 3.6$ Hz, $J_{7e,8e} = 2,2$ Hz. These small coupling constants clearly indicate that the C_7—H_e bisects the H—C_8—H angle forming a H_{7e}—C_7—C_8—H_{8a} dihedral angle of 45° and a H_{7e}—C_7—C_8—H_{8e} dihedral angle of 65° in the quasi-chair D-ring and this a *cis*-geometry for the C_7—OCH_3 and C_9—OH.

EXPERIMENTAL

All m.ps were recorded on a Fischer–Johns apparatus and are uncorrected. NMR spectra were recorded on Brucker WH-90 or Brucker AM-300 spectrometers using TMS as internal standard. IR spectra were recorded on a Perkin–Elmer 710 infracord spectrometer and dipole moments were taken on a DMO1 Kahl dipolometer. Mass spectra were recorded on a Finnigan 1015 or an A.E.I. MS-50 or a Manitoba Time-Of-Flight[15] spectrometer. Elemental analyses were performed by Canadian Microanalytical Services.

Preparation of 5,8-dimethoxy-2-acetyltetralin (**13**). To

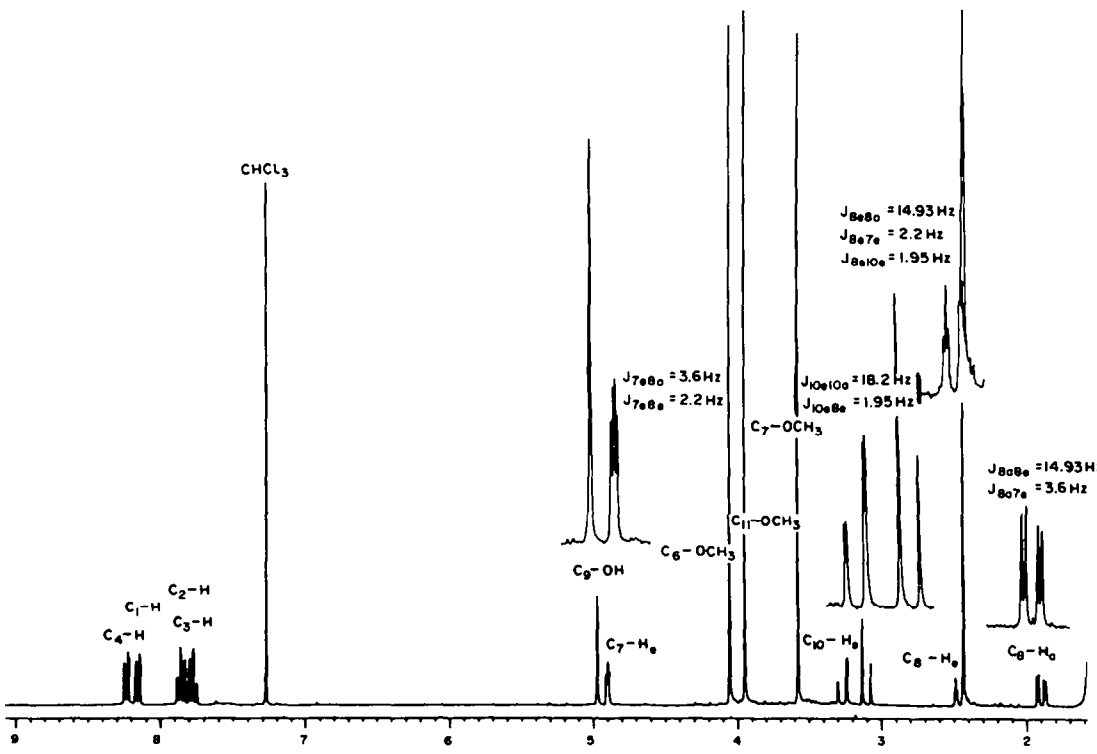


Fig. 1. Brucker AM-300 ^{1}H-NMR spectrum of **12**.

anhyd CH_2Cl_2 (400 ml) saturated with dry HCl at −30°, **15** (30 g) was added within 2 min and with vigorous stirring. The soln which turned dark red immediately, was stirred for a period of 20 min keeping the temp at −30°. Removal of the CH_2Cl_2 by evaporation at room temp under reduced pressure gave a dark brown syrupy residue which was immediately dissolved in EtOH (600 ml) and subjected to hydrogenolysis in the presence of Pd/C (5%) (4 g) under atmospheric pressure for a period of 4 hr. Removal of the catalyst by filtration and evaporation of the alcohol under reduced pressure gave a clear colorless residue which crystallized upon addition of ether and MeOH. The crystal (14.2 g) collected was identical to the tetralin **13** prepared previously by other processes. The mother liquor, after chromatography on silica gave an additional amount of crystalline **13** (7.5 g).

Preparation of **17** and **18**. To an ice-cooled stirred conc H_2SO_4 soln (250 ml) of 2,2'-dithiosalicylic acid (15 g) was added the tetralin **13** (5 g). The soln was stirred for a period of 6 hr at room temp and then poured into ice-water (1.5 l) and extracted exhaustively with EtOAc (4 × 300 ml). The combined extracts, washed with water, $NaHCO_3$ aq and dried over $MgSO_4$, were evaporated to dryness under reduced pressure to give an orange solid residue (6.2 g) which was a mixture of mainly **17** and **18** together with a small amount of demethylated products. This crude product was then dissolved in acetone (200 ml) to which was added finely pulverized K_2CO_3 (10 g) and MeI (10 ml). The soln was stirred at 40° for a period of 16 hr, cooled, filtered and evaporated to dryness to give a semi-solid residue which was purified by pressurized column chromatography on silica to give the crystalline products **17** (2.3 g) and **18** (2.1 g).

The first isomer **17** was purified by recrystallization from $CHCl_3$ and ether, m.p. 142–144°; IR(cm^{-1}): 1710 (acetyl), 1640 (phenone); PMR(δ ppm): 8.48 (m, 1H, C_4—H), 7.32–7.61 (m, 3H, C_1—H, C_2—H, C_3—H), 3.91 (s, 3H, OCH_3), 2.15–1.55 (m, 2H, C_8—H_2); high resolution MS calc for $C_{21}H_{20}O_4S$: 368.1084; Found: 368.1087; dipole moment Calc: 3.2 D; Found: 3.5 D; Anal ($C_{21}H_{20}O_4S$) C.H.S.

The second isomer **18** was further purified by recrystallization from $CHCl_3$-ether; m.p. 160–162°; IR(cm^{-1}): 1710 (acetyl), 1640 (phenone); PMR (δ ppm): 8.44 (m, 1H, C_1—H), 7.33–7.62 (m, 3H, C_2—H, C_3—H, C_4—H), 3.92 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.70–3.44 (m, 5H, C_7—H_2, C_9—H, C_{10}—H_2), 2.08–2.35 (m, 2H, C_8—H_2), 2.30 (s, 3H, $COCH_3$); high resolution MS Calc for $C_{21}H_{20}O_4S$: 368.1084; Found: 368.1088; dipole moment Calc 4.7 D; Found: 4.9 D.

Preparation of **22** *and* **23**. To a soln of a THF (250 ml), NH_4OH (250 ml) and **17** (4 g) at ambient temp was added Zn dust (40 g) and $CuSO_4$ (600 mg). The mixture was stirred at room temp for 45 min. The Zn dust was removed by filtration, washed with acetone (80 ml), diluted with water (200 ml) and extracted with CH_2Cl_2 (4 × 250 ml). The combined extracts were washed with water, dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give almost quantitative recovery of the products **22** and **23**; IR (cm^{-1}) 3580 (—OH), 1710 ($COCH_3$), 1590 (aromatic); PMR (δ ppm), 7.27 (m, 2H, C_1—H, C_4—H), 7.14 (m, 2H, C_2—H, C_3—H), 6.13 and 6.09 (2 singlets, 1H, C_5—H for 22 and 23), 3.09–3.86 (5 singlets, 7H, C_6—OCH_3, C_{11}—OCH_3 and C_5—OH of 22 and 23), 2.89 (m, 5H, C_7—H_2, C_9—H, C_{10}—H_2), 2.32 (s, 3H, $COCH_3$), 2.18 (m, 2H, C_8—H_2); high resolution MS Calc for $C_{21}H_{22}O_4S$; 370.1239; Found: 370.1228.

Preparation of **30** *and* **31**. The crude mixture of **22** and **23** (3.8 g) was dissolved and heated under reflux in anhyd MeOH (200 ml) and 2,2-dimethoxypropane (10 ml) for a period of 8 hr. Removal of the MeOH by evaporation under reduced pressure gave a light coloured syrupy reside which was shown by TLC on silica to consist of two major components. Attempts to separate these two components by preparative TLC were unsuccessful. The IR revealed the complete disappearance of the 3580 cm^{-1} peak and the mass spectrum showed a molecular ion of 384 in agreement with the proposed structures **24** and **25**. The mixture was then dissolved in anhyd N,N-dimethylformamide (320 ml), t-BuOH (30 ml) and trimethyl phosphite (6 ml). To this soln, cooled in a dry-ice bath at −30° was added t-BuOK (3 g) and dry O_2 introduced through a gas dispersion tube for ½ hr. The soln was then neutralized to pH = 6–7 with dil HCl and stirred for an additional ½ hr at room temp, diluted with water (500 ml) and extracted with CH_2Cl_2 (3 × 500 ml). The combined CH_2Cl_2 extracts were washed with water, dried and the CH_2Cl_2 was removed by evaporation under reduced pressure to give an orange syrupy residue. Part of the residue (400 mg) containing some N,N-dimethylformamide was separated by preparative TLC on silica to give a mixture of **28** and **29**. Separation of **28** from **29** was unsuccessful and their presence were only detected by the appearance of a new peak at 3500 cm^{-1} and the molecular ion M^+ = 400 in the mass spectrum. The residue containing **28** and **29** was dissolved in CH_2Cl_2 (150 ml) to which was added *m*-chloroperoxybenzoic acid (3.4 g). The soln was stirred at room temp for ½ hr, washed with Na_2CO_3 aq, dried and evaporated to dryness to give a crude mixture of isomers **30** and **31** (3.5 g) which are stable and can be separated. Since both isomers will eventually be converted to **34** for further development, only a small amount (210 mg) were separated by preparative HPLC on a Partisil column. The first isomer recovered from the column (45 mg) was recrystallized from CH_2Cl_2-ether; m.p. 228–231°; IR(cm^{-1}) 3500 (OH), 1710 ($COCH_3$), 1590 (aromatic), 1160, 1140 (sulfone); PMR (*vide supra*); high resolution MS. Calc for $C_{22}H_{24}O_7S$; 432.1243, Found: 432.1235; anal ($C_{22}H_{24}O_7S$) C, H.

The second isomer **31** (16 mg) was recrystallized from methylene-ether; m.p. 234–7°; IR and PMR (*vide supra*); high resolution MS for $C_{22}H_{24}O_7S$; Found: 432.1233.

Preparation of **34**. The crude isomeric mixture of **30** and **31** (3 g) was dissolved in N,N-dimethylformamide and t-BuOH (20 ml). To the soln, cooled in a dry-ice bath of −30°, was added t-BuOK (2.5 g) and O_2 introduced through a gas dispersion tube for 6 min. The dark blue basic soln was adjusted to pH = 6–7 by adding dropwise dil HCl, followed by trimethyl phosphite (6 ml), stirred for 1 hr at room temp and diluted with water (300 ml). The aqueous soln was extracted with $CHCl_3$ (3 × 300 ml) and the combined $CHCl_3$ extracts washed with water, dried and evaporated to dryness under reduced pressure to give an orange oily residue which was subjected to separation by column chromatography on silica. The crude crystalline product **34** (900 mg) was recrystallized from methylene-ether; m.p. 194–6°; IR(cm^{-1}): 3500 (OH), 1715 ($COCH_3$), 1680 (phenone), 1590, 1560 (aromatic), 1160, 1135 (sulfone); high resolution MS Calc for $C_{21}H_{20}O_7S$: 416.0930; Found: 416.0946; PMR(δ ppm): 8.14 (m, 2H, C_1—H, C_4—H), 7.76 (m, 2H, C_2—H, C_3—H), 4.01 (s, 3H, C_6—OCH_3), 3.89 (s, 3H, C_{11}—OCH_3), 3.68 (s, 1H, C_9—OH), 3.04 (m, 4H, C_7—H_2, C_{10}—H_2), 2.35 (s, 3H, $COCH_3$), 1.94 (m, 2H, C_8—H_2).

Preparation of 6.7,11 - *tri* - O - *methyl* - 4 - *demethoxy* - 12 - *sulfonodaunomycinone* (**12**). A soln of CCl_4 (400 ml), N-bromosuccimide (190 mg), the sulfone **34** (400 mg) was heated under reflux and irradiation with a Hanovia medium pressure mercury lamp for 3/4 hr while the progress of the reaction was monitored by TLC until the starting material disappeared. The soln was then stirred for 2 hr at room temp, filtered and the CCl_4 was removed by evaporation under reduced pressure. The residue was subjected to a fast pressurized chromatography on silica to remove the residual succinimide which was eluted out by $CHCl_3$ after most of the unstable bromination product **35** was recovered. The fractions free of succinimide (330 mg) were dissolved in anhyd MeOH (30 ml) to which was added silver trifluoromethanesulfonate (165 mg). The soln was stirred at room temp for a period of 4 hr, concentrated under reduced pressure, diluted with water (30 ml) and extracted with CH_2Cl_2 (2 × 50 ml). The combined extracts, dried over $MgSO_4$ were evaporated to dryness to give an orange oily residue which was separated by preparative TLC on silica. The major product **12** (124 mg) was purified by recrystallization from methylene-ether; m.p. 171–4°; IR(cm^{-1}): 3470 (OH), 1720 ($COCH_3$), 1680 (phenone), 1590, 1560 (aromatic), 1160, 1140 (sulfone); MS 446.1 (M^+), 469.1 ($M^+ + Na$)[16]; PMR: (Fig. 1) *vide supra*.

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