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A CONVERGENT SYNTHESIS OF (±)DAUNOMYCINONE

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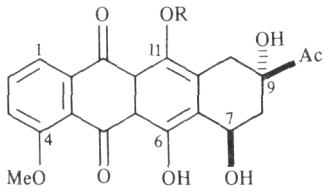
Abstract—A convergent AB + CD synthesis of (±)daunomycinone **1** in 14% overall yield from hydroxy phthalan **10** is described. Methyl vinyl ketone reacts with 4,7-dimethoxy isobenzofuran (generated from **10**) to provide the adduct **16** which is developed into the AB synthon **30**. The cyanophthalide **32**, the CD half of the molecule, is attached with good regiocontrol and a subsequent tetracyclic C_6-C_7 acetonide **40**, oxygenated at C-9 to eventually produce a 5:6 mixture **1** and its C-7 epimer **8**.

INTRODUCTION

The anthracyclinones[1] have attracted the intense interest of organic chemists for the past twenty years. Their efforts, described in this symposium and elsewhere have resulted not only in the development of many synthetic routes to these compounds but also in the generation of much innovative chemistry. By the early eighties most of the synthetic problems previously recognised[2] had been solved and almost every conceivable manner of assembling the tetracyclic skeleton explored, in many cases with remarkable ingenuity.

Our interest in the synthesis of daunomycinone **1**, originating from studies of isobenzofurans[3] was maintained by the success of model experiments depicted below (Scheme 1). The dimethyl acetal of 6-bromoveratraldehyde was converted by standard procedures into the isobenzofuran precursor[3] (hydroxyphthalan **2**) which provided the Diels–Alder adduct **3** with methyl vinyl ketone. The latter underwent a base-catalysed reverse-Michael cleavage, a general 5-endo-*trig* reversal of 7-oxabicyclo[2.2.1]heptenes[4] to afford enone **4** in high yield. Reduction of the double bond with sodium amalgam provided a 1:1 mixture of diastereomers **5** and protection of its hydroxyl group gave the butyl dimethyl silyl ether **6**. Oxygenation of **6** by the Gardner procedure[5] was smooth and reproducible and **7** resulted as a mixture of stereoisomers. Thus **7** was available in *ca* 25% overall yield from veratraldehyde by this sequence.



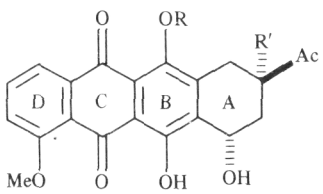
8 R = H
42 R = Me

We saw in the success of these model studies an opportunity to make a worthwhile contribution to the synthesis of the AB half of daunomycinone, in particular to the emplacement of the C-7 hydroxyl group (anthracyclinone numbering) recognized as a "difficult" function in the rubric of existing methodology. We report herein the successful completion of this task[6] and the extension of these endeavours to a convergent synthesis of (±)daunomycinone **1**, (±)7-epi-daunomycinone **8** and (±)-deoxydaunomycinone **9**.

RESULTS AND DISCUSSION

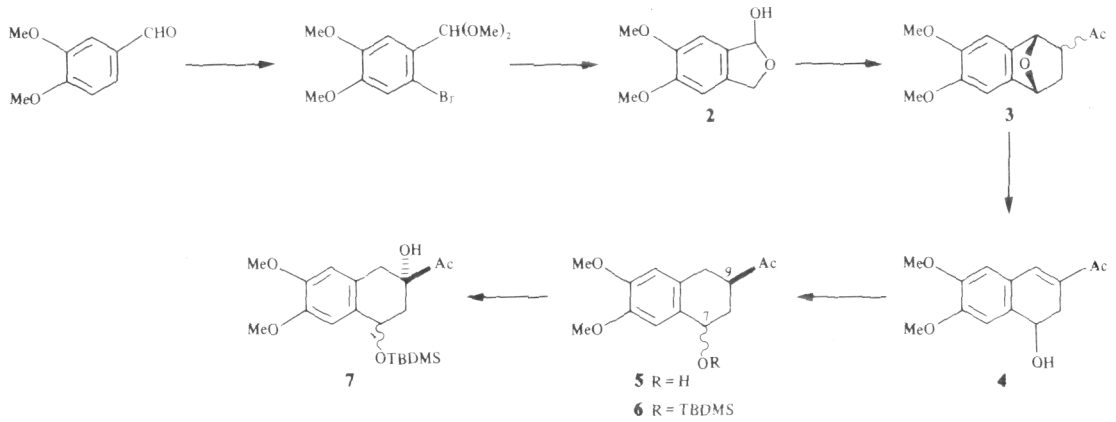
(1) *Synthesis of the AB segment of daunomycinone*

To parallel the model studies just described the lactol **10** was required as our isobenzofuran precursor for the synthesis of the AB half. This compound had been previously prepared[7] from 2,3-dicyanohydroquinone, a substance no longer commercially available. Its laboratory synthesis in our hands from benzoquinone[8] proved to be inefficient, irreproducible and generated large quantities of cyanide waste. Two other routes to the required lactol were therefore devised. The first, beginning with 2,5-dimethoxy-2,5-dihydrofuran provided **10** in 27% overall yield after five unexceptional steps. The major problem here was the strong tendency of 2-methoxyfuran to polymerise under the conditions of its formation (TsOH, 260°) and thereby reduce the yield of this step to only 35%. The second method provided **10** in 21% overall yield from 2,5-dimethoxybenzyl alcohol (**14**, R = H) but it was more direct, easily scaled up and required much less time. The lithiation of this alcohol had been reported[9] to take place on both sides of the 5-methoxy group (C-4 and C-6) and our attempt to intercept such lithio species with dimethyl formamide did provide **10** albeit in low yield



1 R = H, R' = OH
9 R = R' = H
43 R = Me, R' = OH

as an inseparable constituent of a complex mixture of products. Various derivatives of the alcohol were therefore prepared and tested in lithiations. These included the tetrahydropyranyl ether (**14**, R = THP), the NN-dimethylurethane (**14**, R = $CONMe_2$) and the acetal (**14**, R = CH(Me)OEt) but the best results were

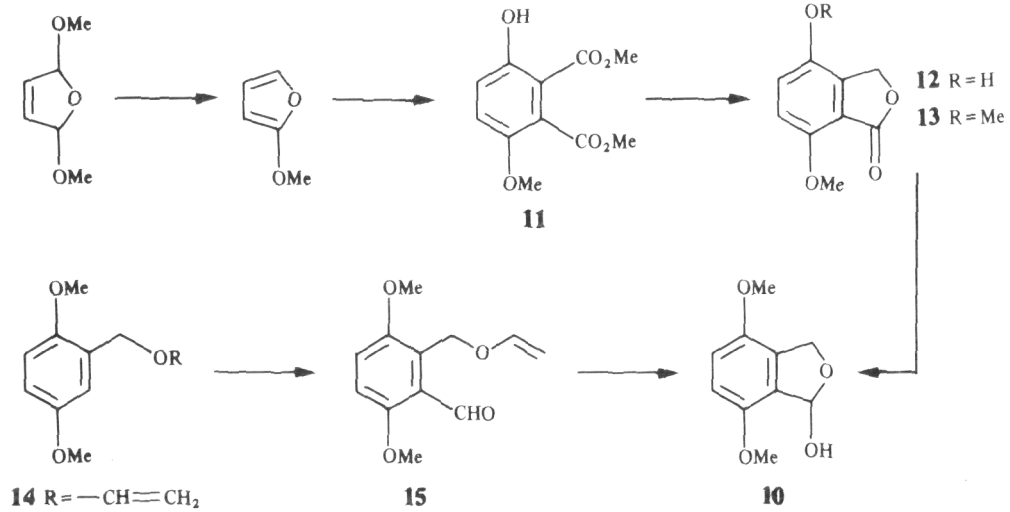


Scheme 1. Model experiments.

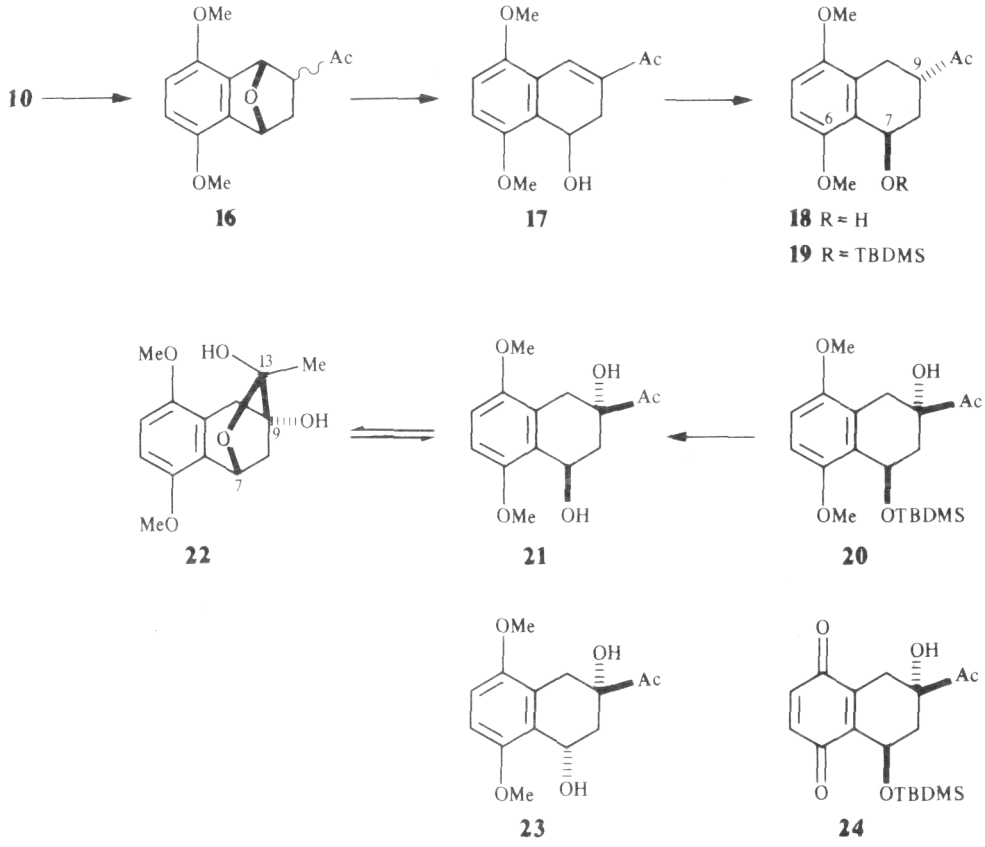
obtained with the vinyl ether **14** prepared and lithiated as described[10] in a timely publication. Quenching the resulting anion with dimethyl formamide again produced a complex mixture, but the desired product **15** could be obtained by distillation (30%). Hydrolysis of the latter provided[3] the required hydroxy phthalan **10** (Scheme 2).

With adequate supplies of our isobenzofuran precursor in hand the reactions of Scheme 1 were then undertaken. Treatment of **10** with methyl vinyl ketone and a few drops of glacial acetic acid in refluxing carbon tetrachloride produced a 3:1 (*endo–exo*) mixture of bridged adducts **16** in 91% yield from which the *endo* isomer could be crystallized. Both isomers suffered reverse-Michael cleavage with methanolic sodium methoxide to afford the enone **17** (94%) which was reduced with 2% sodium amalgam in ethanol (95%) to the hydroxyketone **18** as a single diastereomer. Silylation then provided a single silyl ether **19** diastereomerically pure by 400 MHz NMR (Tables 1 and 2). The H-7 signal (daunomycinone numbering) of this compound at 5.15 δ was a narrow triplet ($\nu_{1/2}$ = 5.8 Hz)[11] with equal coupling constants (2.8 Hz) to the neighbouring axial and equatorial protons at C-8, thus signifying an axial disposition for the bulky *O*-silylether moiety. The acetyl substituent at C-9 must be equatorially oriented because H-9, appearing as a multiplet at 3.16–3.24 δ, was observed to have diaxial coupling constants, 12.90 Hz (H_8-axial) and 12.1 Hz (H_{10}-axial), and equatorial-axial coupling constants 1.0 Hz (H_8-equatorial) and 6.1 Hz (H_{10}-equatorial). Since alcohol **18** had $\nu_{1/2}$ = 8 Hz for its H-7 signal it follows that the sodium amalgam reduction produces only one diastereomer here, in contrast to the reduction of model compound **4** when a 1:1 mixture of C_7—C_9 *cis* and C_7—C_9 *trans* diastereomers was obtained. The C_6 methoxy group present in **17** but not in **4** must be responsible; steric interaction (or dipolar repulsion) between it and the C-7 hydroxyl group is probably of enough significance to favour the production of diastereomer **18**, under the alkaline conditions of the sodium amalgam reduction.

The ready availability of **19** by this simple four step sequence from **10** (69% overall) required that a plan for regiocontrolled CD attachment be formulated and the intermediate **19** be refined accordingly. Some exploratory experiments with **19** were therefore conducted. Oxygenation under the Gardner conditions as before produced a single stereoisomer **20** in 70% yield. The C-7 silyl ether moiety was axial (H-7, $\nu_{1/2}$ = 8.1 Hz) as was the C-9 acetyl group (confirmed by X-ray analysis[12]) indicating that oxygenation of the C-9



Scheme 2. The synthesis of hydroxyphthalan **10**.



Scheme 3.

enolate had taken place exclusively on the face opposite to the bulky C-7 substituent. Removal of the silyl group with fluoride provided chemical confirmation of the relative stereochemistry; the *trans* diol **21** so resulting existed in equilibrium with the hemi-ketal **22**. The IR spectrum of the product (in KBr) had only a weak carbonyl stretching absorption and the pmr spectrum of a freshly prepared solution (in $CDCl_3$) revealed an 8:3 ratio of **22**:**21**; H-7 of **22** was a clean doublet at 5.43 ppm ($J_{6\beta,7} = 5.5$ Hz, $J_{6\alpha,7} \approx 0$ Hz) and the C_{13}-methyl group appeared as a sharp singlet at 1.3 ppm. Slow equilibration reverses this ratio. After one hour the spectrum of the same sample shows a 9:1 ratio in favour of **21**. The synthesis and transformations of **19** with the H-7 signal now a broad triplet ($\nu_{1/2}$ = 18.6 Hz after D_2O exchange) and the acetyl methyl a sharp singlet at 2.36 ppm, implying that a conformational inversion had occurred placing the C_7-hydroxyl and C_9-acetyl groups equatorial. The question of the configuration at C-13 in **22** was not conclusively settled. Many attempts to form a C_{13}—C_9 acetonide[13] failed, probably because the hydroxyl groups are *anti* as shown (Scheme 3). The C_{13} methyl group is definitely less crowded when located *syn* to the C_9 hydroxyl function and this perhaps, is the configuration that actually exists in **22**. Treatment of **20** or **21** with trifluoroacetic acid–acetic acid–water at 0° produced a 3:2 mixture of diols **23** and **21** in 80% yield. The *cis*-diol **23** separated by column chromatography displayed the H-7 signal in its pmr spectrum at 5.20 ppm with $\nu_{1/2}$ = 6.4 Hz (after D_2O treatment) indicating an axial C_7-hydroxyl group and therefore the C_7—C_9 *cis* dihydroxy stereochemistry shown. Quinone **24**, an attractive intermediate for the synthesis of 4-demethoxy daunomycinone, was obtained (92%) by oxidation of **20** with ceric ammonium nitrate in aqueous acetonitrile.

Although **20**, **23** and **24** were easily prepared and provided us with some experience of A-ring chemistry which subsequently proved valuable, their sensitivity to acidic and basic conditions precluded the use of any one of them as our AB synthon for regiospecific CD attachment without extensive and wasteful protection and deprotection sequences. Among the available methods for such CD annelation, the addition-cyclisation techniques of Kraus[14] and Hauser[15] for anthraquinone synthesis attracted our attention because they had already been adapted[16,17] to regiospecific anthracyclinone synthesis. Acting on the belief that yields in the coupling reaction could be substantially improved by the elimination of acidic hydrogen atoms and redundant carbonyl functions we embarked on the process of refining **19** into a suitable substrate for such regiospecific annelation. Reduction with DIBAL-H provided (90%) a mixture of isomers **25** which were subjected to anodic oxidation[18] to afford bis-ketals **26** in 93% yield. Selective hydrolysis of the latter produced, on average, a 9:2 ratio of monoketals **27** and **28**. This was achieved with a pH 5 acetate buffer and no quinone **29** was detected by TLC or pmr; the use of acetic acid under other conditions[17] of dilution, time and temperature did not improve on this result but produced varying amounts of quinone **29**. The two constituents of the monoketal mixture were separated

by flash chromatography on silica gel but since *ca* 4.5% of the material was lost as the quinone **29** during the process, the mixture was carried through and separation of resulting regioisomers postponed for a more opportune stage of the synthesis. The structures of **27** and **28** were assigned at this stage however; comparison of the chemical shifts of H-7 in the monoketals (4.88 ppm in **27** and 4.77 ppm in **28**) bisketal **26** (4.63 ppm) and quinone **29** (4.90 ppm) revealed the slight deshielding influence of the C-6 carbonyl group on H-7 in **27** and **29**. The monoketal mixture was then silylated (95%) to produce the mixture of ethers **30** and **31**. This completed the synthesis of the AB segment (in 38% yield from phthalan **10**) free of acidic hydrogen atoms and redundant carbonyl groups and ready for CD annelation by the Kraus method.

Synthesis of the CD segment

The cyanophthalide **32** chosen as our CD synthon had been used[16] in a similar role before. We prepared it by deprotonation[19] of m-anisaldehyde dimethyl acetal followed by carboxylation of the anion to hydroxyphthalide **33**. The latter upon treatment with aqueous potassium cyanide and subsequently with dilute hydrochloric acid produced a solid, presumably the cyanohydrin which cyclised to **32** upon crystallisation from methanol.

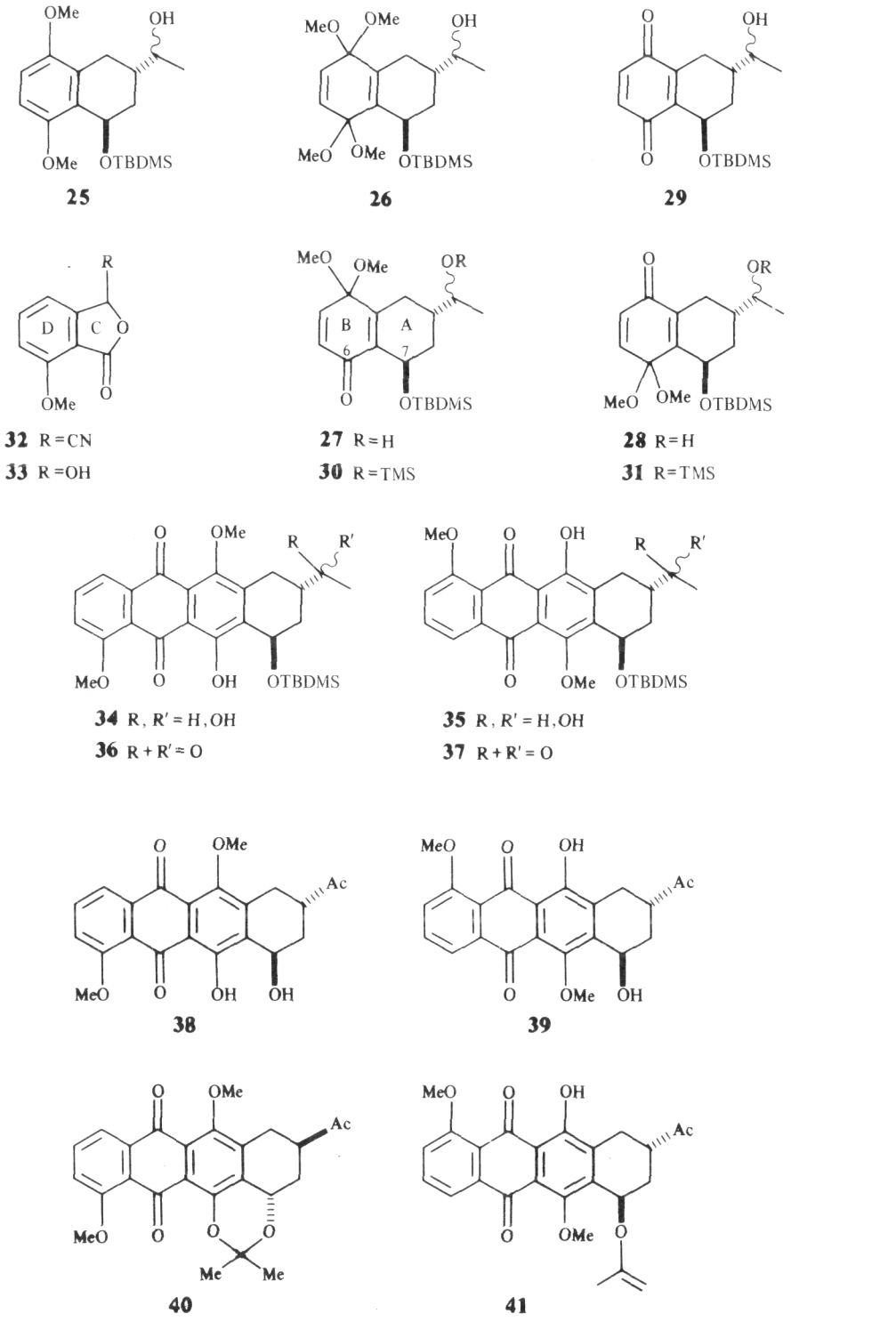
Coupling of the AB and CD segments

The cyanophthalide **32** was deprotonated quantitatively (as determined by methylation of the anion with excess methyl iodide) when treated with 1.1 equivalents of LDA in tetrahydrofuran-hexamethyl phosphoramide at −78°. Addition of the monoketal mixture (**30**+**31**) to the orange anion at this temperature was followed by warming to room temperature over 2 hr and stirring with 20% aqueous acetic acid overnight. An 87% yield of anthraquinones **34** and **35** was obtained, amply justifying the precautions taken earlier to remove acidic hydrogen atoms and non-essential carbonyl groups from the AB synthon. The mixture of anthraquinones was oxidized with PDC in DMF to produce ketones **36** and **37** (85%). The same sequence carried out with pure **30** afforded pure **36** in similar yield. The stereochemistry of **36** was established by examination of its 400 MHz pmr spectrum; the OTBDMS group at H-7 is axial ($\nu_{1/2}$ = 4.7 Hz for H-7) and the C_9-acetyl group equatorial because the proton at C-9 showed two diaxial (13.1 and 11.9 Hz),[20] and two axial-equatorial interactions (3.0 and 4.8 Hz). Chemical confirmation of the structure and stereochemistry of **36** came from its conversion into (±) 9-deoxydaunomycinone **9**. Desilylation of **36** with acetic acid-trifluoroacetic acid-water produced alcohol **38** (85%) which was selectively demethylated at C-11 with boron trichloride at −78° to produce **9** in 85% yield. Spectra of our product matched the published data[21] and its 400 MHz spectrum showed that the C_7-hydroxyl group was axial ($\nu_{1/2}$ = 5.8 Hz for H-7) and the C-9 acetyl group equatorial.

With the success of the coupling process assured, we turned our attention to the remaining problems of C-9 hydroxylation and separation of regioisomers **36** and **37**. Experience acquired earlier in oxygenations of **6**, **19** and related intermediates persuaded us to seek a tetracyclic substrate with no free hydroxyl functions. Regioisomers **38** and **39**, the products of desilylation of the mixture **36**+**37** (with aqueous acetic acid-trifluoracetic acid) possess a significant and useful structural difference; **38** but not **39** contains "peri" hydroxyl groups at C-6 and C-7. Subjecting this mixture to ketalisation with 2-methoxypropene and p-toluene sulfonic acid produced the expected outcome—acetonide **40** from **38** and vinyl ether **41** from **39**. This was a crucial result, for not only did it provide (in **40**) a suitable substrate for C_9-oxygenation but also permitted the separation of the derivatised regioisomers by simple column chromatography. This was achieved on silica gel in ethyl acetate–ligroin, 7:3 with **40** (R_f = 0.64) and **41** (R_f = 0.42) isolated in the original 9:2 ratio (Scheme 4). The 400 MHz pmr spectrum of **40** showed that a conformational inversion in ring A had occurred; H-7 was now axial ($\nu_{1/2}$ = 17.5 Hz) and the C-9 proton had four moderate coupling constants of 4.0, 6.8, 8.0 and 6.5 Hz implying that the C-9 acetyl group was quasi-axial and the C-7 acetonide equatorial[21] in contrast to the silyl ether **36**. Oxygenation of **40** by the modified Gardner procedure tested earlier on **6** and **19** proceeded smoothly and reproducibly in 77% yield to afford this time a 6:5 mixture of *trans* and *cis* diols (**42** and **43** respectively) after hydrolysis of the acetonide with p-toluene sulfonic acid in wet methylene chloride. In contrast to the oxygenation of **19**, the C-7 substituent of **40**, constrained in an equatorial orientation by formation of the acetonide, has little influence on the steric course of this oxygenation. The C-7 epimers **42** and **43** were separated by column chromatography and the 400 MHz pmr spectra of the individual isomers revealed the ring A stereochemistry of each. The H-7 signal of **43** is much narrower ($\nu_{1/2}$ = 6.6 Hz) than that of **42** ($\nu_{1/2}$ = 16.1 Hz) as shown in Fig. 1, implying a *cis* diaxial arrangement of the C_7—C_9 hydroxyl groups in **43** and a *trans* equatorial-axial orientation in **42**. The spectra also showed significant long range coupling (2.2 Hz) between the H_8 and H_{10} equatorial protons in both epimers.[22] Demethylation of each product was effected selectively at C-11 in 85% yield with boron trichloride in dry methylene chloride at −78° to produce (±)daunomycinone **1** (from **43**) and (±)7-epidaunomycinone **8** (from **42**). The m.p. and spectra of our synthetic sample of **1** were identical with published[22,23,24] data. The pmr spectrum of pure **8** could not be obtained because of solubility problems and a tendency on its part to partially epimerise to **1** in solution; its IR and mass spectra however were similar to published[22,24] data. Since 7-epidaunomycinone has been previously isomerised to daunomycinone[25] the present synthesis provides racemic daunomycinone in *ca* 14% yield from phthalan **10**.

EXPERIMENTAL

M.ps were determined on a Buchi model SMP-20 apparatus and are uncorrected. Elemental analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario and/or Canadian Microanalytical Service, Vancouver, British Columbia. NMR spectra were determined, unless otherwise stated, in $CDCl_3$ containing 1% TMS on either a Bruker WP-80 or Bruker WH-400 spectrometer. Coupling constants were measured directly and confirmed by decoupling where necessary. Spectra are reported in the following manner: chemical shift (δ) in ppm, multiplicity, number of protons, coupling constants, assignment. Infrared spectra were determined on a Beckmann model IR-10 or Acculab 10



Scheme 4. Coupling of the AB and CD segments and separation of the regioisomers.

spectrophotometer, in KBr or in 0.1 mm NaCl cells with $CHCl_3$ as a solvent or in the case of liquids between NaCl plates. High resolution mass spectra were determined on a Varian VG 7070F instrument and are reported in the following manner; ion (relative intensity, assignment). Column chromatography was performed with silica gel (Merck, 0.063–0.20 mm, 70–230 mesh ASTM) or where better resolution was required with Merck 0.04–0.063 mm, 230–400 mesh ASTM under positive pressure. Cooling baths used were prepared by the following combinations of solvents—coolants: −23°, CCl_4–dry ice; −78°, MeOH–dry ice.

2,3-*Dicarbomethoxy*-4-*methoxyphenol* (**11**)

To a mixture of dibutyl phthalate (10 ml) and *p*-toluenesulfonic acid (100 mg), preheated to 260°, 2,5-dimethoxy-2,5-dihydrofuran (14 ml), was added drop-wise, by

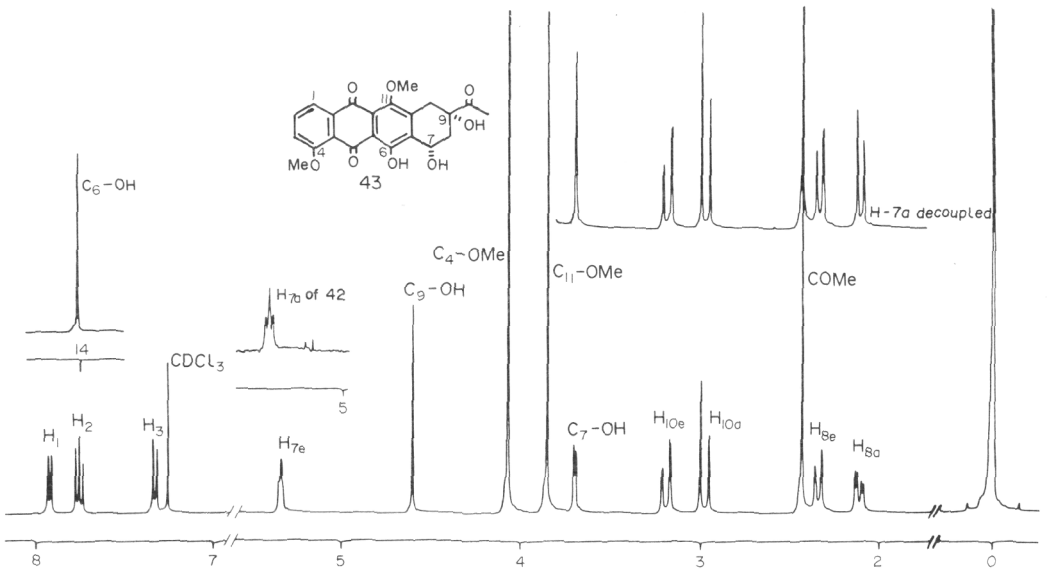


Fig. 1. The 400 MHz ^{1}H-NMR spectrum of **43** in $CDCl_3$.

means of syringe pump. The flask was connected to a Claisen head column, condenser, and receiving flask containing dimethyl acetylenedicarboxylate (14 ml). The rate of addition was adjusted so that the methoxy furan distilled as formed. Once the addition was complete, the receiving flask was warmed for 2 hr to 60°, cooled and the dimethyl acetylenedicarboxylate removed *in vacuo*. The remaining thick oil crystallized upon the addition of methanol (35%). M.p. 120–121°; IR($CHCl_3$) 3200, 1740, 1690 cm^{-1}; ^{1}H-NMR (80 MHz) 3.81 (s, 3H, Ar—OMe), 3.92 (s, 6H, 2 × CO_2Me), 7.00, 7.17 (ABq, 1H each, J = 9.1 Hz, Ar), 10.48 (s, 1H, exchanges with D_2O, —OH); mass spectrum, 240 (44, $M^{\cdot+}$), 208 (100, $M^{\cdot+}$ − OMe—H). (Found: C, 54.93; H, 4.98. Calc for $C_{11}H_{12}O_6$; C, 55.00; H, 5.04%).

4-*Hydroxy*-7-*methoxyphthalide* (**12**)

To a soln of borane-dimethylsulfide complex (0.3 ml, 1.5 eq) in dry THF (10 ml) under N_2, was added a soln of phenol **11** (100 mg) in dry THF (1 ml). The soln was refluxed 4 hr, cooled and the THF removed *in vacuo*. NaOH (10 ml of 10%) and just enough MeOH to dissolve the residue was added. The soln was warmed on a steam bath for 15 min and the MeOH removed. The residual oil was acidified (2N HCl) extracted into $CHCl_3$ (2 × 25 ml), dried (Na_2SO_4) and the $CHCl_3$ removed *in vacuo* to leave a solid. Recrystallization from MeOH gave phthalide **12** (90%). M.p. 200–201°; IR(KBr) 3300, 1740 cm^{-1}; ^{1}H-NMR (acetone-d_6, 80 MHz) 3.85 (s, 3H, —OMe), 5.16 (s, 2H, —CH_2O—), 6.90 and 7.11 (ABq, 1H each, J = 8.8 Hz, Ar); mass spectrum, 180 (90, $M^{\cdot+}$), 151 (100, $M^{\cdot+}$ − CHO). (Found: C, 60.36; H, 4.52. Calc for $C_9H_8O_4$: C, 60.00; H, 4.48%).

4,7-*Dimethoxyphthalide* (**13**)

The phthalide **12** (2.25 g), iodomethane (20 ml), anhyd K_2CO_3 (5.2 g) and acetone (100 ml) were refluxed 24 hr under N_2. The soln was filtered and the acetone removed *in vacuo*. The resulting oil was extracted into $CHCl_3$ (3 × 25 ml), washed with water (10 ml), NaOH (10 ml of 10%), water (10 ml), dried (Na_2SO_4) and the $CHCl_3$ removed *in vacuo* to leave a solid. Recrystallization from MeOH gave **13** (95%). M.p. 169–170° (lit.[7] 168–170°); IR($CHCl_3$) 1760 (C=O) cm^{-1}, ^{1}H-NMR (80 MHz) 3.86, 3.94 (s, 3H each, 2 × OMe), 5.17 (s, 2H, —CH_2O—), 6.85 and 7.06 (Abq, 1H each, J = 8.8 Hz, Ar).

2-*Acetyl*-1,4-*epoxy*-1,2,3,4-*tetrahydro*-5,8-*dimethoxy naphthalene* **16**

Phthalan **10**[3] (3.82 g), glacial AcOH (3.3 ml), methyl vinyl ketone (10.7 ml, 7 eq. freshly distilled and 1% hydroquinone added) were dissolved in CCl_4 (100 ml). The mixture was refluxed at 80° for 20 hr. Sat $NaHCO_3$ aq was added to neutralise the acid and the organic layer separated, dried (Na_2SO_4) and the solvent removed *in vacuo* to leave an oil. The *endo* isomer crystallised upon addition of ether and the combined yield of both isomers was 91%. *Endo* **16**: m.p. 140–141°; IR($CHCl_3$) 1700 cm^{-1}. ^{1}H-NMR (80 MHz); 1.9–2.3 (m, 2H, H-3), 2.18 (s, 3H, $COCH_3$), 3.35–3.6 (m, 1H, H-2) 3.75, 3.79 (s, 3H each, 2 × OMe), 5.57 (dt, 1H, H-4, $J_{3\beta,4}$ = 4.6 Hz, $J_{3\alpha,4}$ = 0.8 Hz, $J_{1,4}$ = 0.8 Hz), 5.8 (dd, 1H, H-1, $J_{1,2}$ = 5.2 Hz, $J_{1,4}$ = 0.8 Hz), 6.62, 6.63 (s, 1H each, ArH, a collapsed AB). MS; 248 (12, $M^{\cdot+}$) 178 (100, $M^{\cdot+}$ − CH_2=CH—$COCH_3$, retro Diels–Alder). (Found: C, 67.33; H, 6.43. Calc for $C_{14}H_{16}O_4$; C, 67.73; H, 6.50%).

3-*Acetyl*-1,2-*dihydro*-1-*hydroxy*-5,8-*dimethoxynaphthalene* **17**

Adduct **16** (2.0 g) was suspended in abs MeOH (20 ml) under N_2 and cooled to 0°. NaOMe (1 g of Na in 20 ml of abs MeOH) was added slowly over 20 min. The soln was warmed to room temp and stirred for 4 hr. Water was added and CO_2 bubbled through until neutral to litmus. The soln was poured into saturated brine (100 ml) and extracted with $CHCl_3$ (5 × 30 ml). The extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave a solid which crystallised from ether-CH_2Cl_2 (95%) m.p. 114–115°; IR(KBr) 3300, 1645 cm^{-1}. ^{1}H-NMR (80 MHz); 1.94 (d, disappears with D_2O, 1H, J = 3.3 Hz), 2.40 (ddd, 1H, H-2α, J_{gem} = 18.5 Hz, $J_{1,2\alpha}$ = 6.3 Hz, $J_{2\alpha,4}$ = 2.7 Hz), 2.47 (s, 3H, $COCH_3$), 3.24 (dd, 1H, H-2β, J_{gem} = 18.5 Hz, $J_{1,2\beta}$ = 2.3 Hz), 3.86 (s, 6H, 2 × OMe), 5.34 (dd, after D_2O exchange, 1H, H-1) 6.80 (d, 1H, ArH, J = 9 Hz) 6.96 (d, 1H, ArH), 7.90 (d, 1H, H-4, $J_{2\alpha,4}$ = 2.7 Hz). MS; 248 (11, $M^{\cdot+}$), 230 (80, $M^{\cdot+}$ − H_2O), 215 (100, $M^{\cdot+}$ − H_2O—Me); HRMS; (Found: 248.1051. Calc for $C_{14}H_{16}O_4$: 248.1049).

1,3-trans-3-*Acetyl*-1,2,3,4-*tetrahydro*-1-*hydroxy*-5,8-*dimethoxynaphthalene* **18**

Dihydronaphthalene **17** (500 mg) was dissolved in abs EtOH (27 ml) under N_2. Na-amalgam (9.2 g of Na 2% weight, 5 eq.) was added and the soln stirred vigorously for 5 hr. Water was added and CO_2 bubbled through until the soln was neutral to litmus. The soln was decanted to separate the Hg and the EtOH removed *in vacuo*. Extraction of the residue with $CHCl_3$ (3 × 10 ml) was followed by washing with brine (20 ml) and water (2 × 20 ml) and drying (Na_2SO_4). Removal of the $CHCl_3$ left an oil which crystallised on standing and was recrystallised from MeOH m.p. 100–101.5°; IR($CHCl_3$) 3600, 1710 cm^{-1}; ^{1}H-NMR (80 MHz) 1.4–3.4 (m, 5H, H-2, 3 and 4),

2.25 (s, 3H, $COCH_3$) 3.80, 3.88 (s, 3H each, 2 × OMe), 5.1 (q, 1H, H-1, $v_{1/2}$ = 8 Hz after D_2O exchange), 6.7 (s, 2H, ArH). MS: 250 (87, $M^{\cdot+}$), 189 (100, $M^{\cdot+} - H_2O$—$COCH_3$). (Found: C, 66.71; H, 7.17. Calc for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%).

1,3-trans-3-*Acetyl*-1-*t-butyldimethylsilyloxy*-1,2,3,4-*tetrahydro*-5,8-*dimethoxynaphthalene* **19**

Hydroxy ketone **18** (1.73 g), Et_3N (4.82 ml, 5 eq.) and N,N-dimethylaminopyridine (0.93 g, 1.1 eq.) were dissolved in dry CH_2Cl_2 (30 ml) under N_2. The flask was cooled and t-butyl dimethylsilyl chloride (5.2 g, 5 eq.) added dropwise in CH_2Cl_2 (10 ml) over 15 min. The soln was stirred for two days under N_2, then poured into water (50 ml) and the organic layer separated, washed with water (3 × 30 ml) and dried (Na_2SO_4). The solvent was removed and the residual oil filtered through a column in EtOAc-ligroin (1:4). The fraction of R_f 0.9 contained the product which was crystallised from hexane (85%) m.p. 94–95°; IR($CHCl_3$) 1705, 1250 cm^{-1}. See Tables 1 and 2 for ^{1}H-NMR. MS: 364 (1, $M^{\cdot+}$)m, 307 (83, $M^{\cdot+}$ − Bu), 189 (100, $M^{\cdot+}$ − HOSiMe_2Bu—$COCH_3$). (Found: C, 65.74; H, 8.63. Calc for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85%).

3-(1,3-cis)*Acetyl*-1-*t-butyldimethylsilyloxy*-1,2,3,4-*tetrahydro*-3-(1,3-trans)*hydroxy*-5,8-*dimethoxynaphthalene* **20**

Potassium t-butoxide (77.9 mg, freshly sublimed), trimethyl phosphite (0.14 ml, distilled from calcium hydride) and dry dimethylformamide (DMF) (4 ml) were placed in a flask under N_2 and cooled to −23°. The soln was saturated with dry O_2 (after bubbling for 5 min.) and silyl ether **19** (84.4 mg) in dry tetrahydrofuran (THF) (1 ml) added. O_2 was again passed through the mixture for 14 min at which time TLC showed no starting material. Water (5 ml) was added and CO_2 bubbled through until neutral to litmus. The water and DMF were removed *in vacuo* and the residue extracted with hexane. Removal of the solvent left a solid which was crystallized from hexane (70%). M.p. 102.5–103°; IR(KBr) 3510, 1720 cm^{-1}; see Tables 1 and 2 for ^{1}H-NMR. MS: 380 (12, $M^{\cdot+}$), 323 (27, $M^{\cdot+}$ − Bu), 248 (15, $M^{\cdot+}$ − BuMe$_2$SiOH), 205 (48, $M^{\cdot+}$ − BuMe$_2$SiOH—$COCH_3$), 75 (100, Me_2SiOH). (Found: C, 63.31; H, 8.42. Calc for $C_{20}H_{32}O_5Si$: C, 63.12; H, 8.48).

3-*Acetyl*-1,2,3,4-*tetrahydro*-1,3-trans-*dihydroxy*-5,8-*dimethoxynaphthalene* **21** *and hemiketal* **22**

Silyl ether **20** (200 mg) THF (10 ml) and tetrabutylammonium fluoride (3.15 ml of a 1N soln, 6 eq.) were refluxed under N_2 for 8 hr. Water was added and the solvent removed. The resulting aqueous material was extracted with $CHCl_3$ (2 × 10 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to leave an oil which was filtered through a column with EtOAc–ligroin (1:1). The product was crystallised from ether (75%) m.p. 97–100°. IR(KBr), 3400, 1700 (weak) cm^{-1}. ^{1}H-NMR (80 MHz, selected absorptions only) **21**; 2.36 (s, 3H, $COCH_3$), 3.78, 3.87 (s, 3H each, 2 × OCH_3), 5.3 (1H, broad t; after D_2O exchange, H-1, $v_{1/2}$ = 18.6 Hz), 6.75 (s, 2H, ArH). **22**; 1.3 (s, 3H, ketal Me), 3.78, 3.80 (s, 3H each, OCH_3), 5.43 (d, 1H, H-1, $J_{1,2\beta}$ = 5.5 Hz), 6.7 (2H, s, ArH). MS: 266 (11, $M^{\cdot+}$), 248 (10, $M^{\cdot+} - H_2O$), 230 (16, $M^{\cdot+} - 2H_2O$), 205 (100, $M^{\cdot+}$ − H_2O—$COCH_3$). (Found: C, 62.82; H, 6.69. Calc for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81%).

3-*Acetyl*-1,2,3,4-*tetrahydro*-1,3-cis-*dihydroxy*-5,8-*dimethoxynaphthalene* **23**

Silyl ether **20** (100 mg) was dissolved in THF (1 ml) and a mixture of AcOH and water (3 ml, 2:1) was added. The soln was cooled to 0° and trifluoracetic acid (5 drops) added. After stirring for 6 hr the soln was neutralized with sat $NaHCO_3$ aq. The mixture was extracted with CH_2Cl_2 (2 × 10 ml) and the extract dried (Na_2SO_4) and solvents removed *in vacuo* to leave an oil (80%). Column chromatography in EtOAc-ligroin, 1:1 provided **23** (R_f = 0.28, 60%) and **22** (R_f = 0.20, 40%). The *cis*-diol **23** resisted crystallisation. IR neat, 3400, 1705 cm^{-1}; ^{1}H-NMR (80 MHz) see Tables 1 and 2. MS: 266 (35, $M^{\cdot+}$), 248 (5, $M^{\cdot+} - H_2O$), 230 (56, $M^{\cdot+} - 2H_2O$), 215 (58, $M^{\cdot+}$ − $2H_2O$—CH_3), 205 (84, $M^{\cdot+} - H_2O$—$COCH_3$), 177 (100, $M^{\cdot+} - H_2O$—$COCH_3$—CO). (Found: C, 63.06; H, 6.98. Calc for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81%).

Treatment of the *trans*-diol **22** under identical conditions again provided a 3:2 mixture of *cis* (**23**) and *trans* (**22**) diols.

3-(1,3-cis)*Acetyl*-1-*t-butyldimethylsilyloxy*-1,2,3,4-*tetrahydro*-3-(1,3-trans)*hydroxynaphtha*-5,8-*dione* **24**

Silyl ether **20** (25.7 mg) in acetonitrile (0.5 ml) was treated with ceric ammonium nitrate 3 eq, 111 mg) in water (1 ml). After 5 min water (5 ml) was added and the soln extracted with CH_2Cl_2, the extracts dried and the solvents removed *in vacuo* to leave an oil which was filtered through a column of silica gel in EtOAc-ligroin (1:4). Crystallisation from ether provided quinone **24** (92%) m.p. 94–97°; IR(KBr); 3500, 1710, 1650 cm^{-1}. ^{1}H-NMR (80 MHz); 0.2 (s, 6H, $SiMe_2$), 0.87 (s, 9H, Si—Bu^t), 1.8–2.3 (m, 2H, H-2), 2.7 (qd, 2H, H-4, J_{gem} = 18.7 Hz, J_{14} = 2.3 Hz), 5.07 (broad triplet, 1H, H-1), 6.75 (s, 2H, quinone H). MS: Chemical Ionisation 351 (50, $M^{\cdot+}$ + 1), Electron Impact; 293 (20, $M^{\cdot+}$ − Bu^t), 275 (100, $M^{\cdot+}$ − Bu^t—H_2O). (Found: C, 62.01; H, 7.31. Calc for $C_{18}H_{26}O_5Si$: C, 61.68; H, 7.48%).

1,3-trans-1-*t-Butyldimethylsilyloxy*-1,2,3,4-*tetrahydro*-3-(1-*hydroxy-ethyl*)-5,8-*dimethoxynaphthalene* **25**

The ketone **19** (39.3 mg) was dissolved in CH_2Cl_2 (5 ml) under N_2 and cooled to −78°. Diisobutyl aluminum hydride (0.15 ml of 25% weight in toluene, 2 eq) was added slowly after 5 min methanol (2 ml) was added. The solution was warmed to room temp and poured into $CHCl_3$ (20 ml), washed with brine, dried (Na_2SO_4) and the solvents removed *in vacuo* to leave an oil (90%) which was a mixture of diastereomers. IR (neat) 3410 cm^{-1}. ^{1}H-NMR (80 MHz); 0.1, 0.2 (s, 2 × 3H, $SiMe_2$), 0.88 (s, 9H, SiBu^t), 1.3 (d, 3H, CH_3, J = 6.3 Hz), 1.4–3.3 (complex m, 5H, H-2, H-3, H-4), 3.8 (broad s, 7H, 2 × OMe + C<u>H</u>OH), 5.2 (t, 1H, H-1), 6.65 (AB, q, 2H, aromatic H, J_{AB} = 8.4 Hz). MS: 366 (0.5, $M^{\cdot+}$), 309 (100, $M^{\cdot+}$ − Bu^t). HRMS (base peak mass matched). (Found: 309.1510. Calc for $C_{16}H_{25}O_4Si$: 309.1523.

1,3-trans-1-*t-Butyldimethylsilyloxy*-1,2,3,4,5,8-*hexahydro*-3-(1-*hydroxy-ethyl*)-5,5,8,8-*tetramethoxynaphthalene* **26**

Anodic oxidation of **25** was carried out in a standard H-cell apparatus having compartments of 5.0 and 4.5 cm diam (anode and cathode compartments) separated by a medium porosity fritted disk. The compartments had volumes of 160 and 130 ml each. The smaller cathode compartment contained 2% KOH in MeOH (69 ml) while the anode compartment had **25** (1.45 g) dissolved in 85 ml of the same soln. The oxidation was carried out at a constant potential of 1.7 V vs. a Pt reference electrode (70 V applied) at 15–25° with a current of 0.6 A for 3 hr. The progress of the reaction was monitored by following the decrease in intensity of the UV maximum at 290 nm (in **25**) to about 5% of its original value. The methanol was removed *in vacuo* and the oil extracted into ether, washed with water (3 × 30 ml), dried and the solvents removed to leave an oil which did not crystallise (90%). IR (neat) 3500 cm^{-1}. ^{1}H-NMR (80 MHz) 0.2 (s, 6H, $SiMe_2$), 0.85 (s, 9H, Si—Bu^t), 1.15 (d, 3H, CH_3, J = 6.5 Hz), 1.35–2.65 (complex m, 5H, H-2, H-3 and H-4), 3.10, 3.13, 3.22 (s, 12H, 4 × OMe), 3.70 (complex m, 1H, C<u>H</u>OH), 4.63 (broad t, 1H, H-1), 6.1 (AB q, 2H ArH, J_{AB} = 9 Hz). MS chemical ionization; 429 ($M^{\cdot+}$ + 1), Electron impact; 397 (0.5, $M^{\cdot+}$ − OMe), 265 (63, $M^{\cdot+}$ − OMe—Me_2Bu^tSiOH), 247 (100, $M^{\cdot+}$ − OMe—Me_2Bu^tSiOH—H_2O). HRMS (base peak mass matched). (Found: 247.1270. Calc for $C_{15}H_{19}O_3$: 247.1335).

Regioselective hydrolysis of **26**

The bis-ketal **26** (1.39 g) dissolved in acetone (10 ml) was treated with a pH 5 acetate buffer (200 mmol strength) until two solvent layers were formed in the mixture. After 20 hr at room temp, sat $NaHCO_3$ aq (10 ml) was added and the mixture extracted with $CHCl_3$ (2 × 10 ml). The $CHCl_3$ extracts were washed with water (1 × 10 ml), dried and the solvents removed to leave an oil (86%) which showed two spots on TLC

Table 1. Proton chemical shift assignments for daunomycinone and synthetic precursors

Compound	Field strength	Proton(s) Chemical shift in ppm 1	2	3	4	6	7e	7a	8e	8a	9e	9a	10e	10a	11	14	t-Bu	Me_2Si	C_7-OH	C_9OH
19*	400 MHz	6.61	6.68			3.75	5.15		2.17	1.53		3.16–3.24	3.04	2.50	3.75	2.25	0.85	0.18, 0.02		
20*	80 MHz	6.61	6.81			3.77	5.36		2.37	1.94			2.83	3.22	3.78	2.35	0.82	−0.05, 0.11		3.73
23*	80 MHz	6.75	6.75			3.77	5.20		2.0–2.25				3.06	2.72	3.86	2.37			2.0–2.25	
36	400 MHz	7.93	7.73	7.32	4.07	13.97	5.30		2.26	1.56		3.23	3.21	2.78	3.87	2.30	0.88	0.25, 0.12		
38	80 MHz	7.94	7.74	7.32	4.07	14.03	5.24			1.5–1.9		← 2.2–3.6 plus 8e →			3.88	2.32				
9	400 MHz	8.04	7.79	7.39	4.09	13.33	5.23		2.41	1.78		3.10	3.23	2.64	14.00	2.33			4.00	
40	400 MHz	7.75	7.61	7.24	4.00			4.70	2.52	1.83	3.04		3.19	2.88	3.90	2.62	acetonide methyl	(1.62, 1.68)		
42	400 MHz	7.94	7.76	7.34	4.08	14.40		5.39	2.35	2.18			2.92	3.13	3.85	2.40			4.31	3.79
43	400 MHz	7.92	7.75	7.33	4.08	14.07	5.33		2.34	2.12			3.19	2.98	3.86	2.44			3.70	4.61
1	400 MHz	8.05	7.80	7.40	4.10	14.01	5.34		2.36	2.16			3.20	2.95	13.31	2.43			3.70	4.53
39	400 MHz	4.08	7.34	7.76	7.95	3.98	5.17		2.41	1.76		3.09	3.27	2.63	13.88	2.32			2.84	
41	400 MHz	4.07	7.33	7.74	7.95	3.87	5.64		2.59–2.67	1.50		3.03	3.35	2.59–2.67	13.89	2.31	vinyl ether	(1.83, 4.13, 4.20)		

* *Daunomycinone numbering* is used for compounds **19**, **20** and **23** except for aromatic protons (H-1 and H-2).

Table 2. Proton NMR coupling constants for daunomycinone and synthetic precursors

Compound	1,2	1, 3	2, 3	7a, 8a	7a, 8e	7e, 8a	7e, 8e	C_7-$\nu_{1/2}$	8a, 9a	8a, 9e	8e, 9a	8e, 9e	8e, 10e	9a, 10a	9a, 10e	8_{gem}	10_{gem}	9e, 10a	9e, 10e	7e, OH	7a, OH
								Coupling constants (Hz)													
19*	ABq	J = 8.8				2.8	2.8	5.8	12.9		1.0			12.1	6.1	12.9	17.9				
20*	ABq	J = 8.9				4.6	3.3	8.1								14.5	16.0				
23*						4.1	2.2	6.4					1.4			OM	17.6				
36	8.2	1.0	8.2			2.3	2.3	4.7	13.1		3.0			11.9	4.8	13.1	19.0				
38	7.9	1.8	7.9	← not measurable →				9.0	← not measurable →												
9	8.1	0.8	8.1			4.0	2.1	5.8	13.0		1.8			11.4	4.7	13.0	18.6				
40	7.7	1.0	7.7	10.4	6.2			17.5		8.0		4.0				13.1	16.9	6.5	6.8		
42	8.0	1.1	8.0	9.3	6.8			16.1					2.2			12.8	17.3				2.1
43	8.1	1.0	8.1			4.7	1.9	6.6					2.2			14.5	18.3			3.8	
1	7.9	1.1	7.9			4.9	2.1	7.5					1.9			14.7	18.6			4.9	
	2, 3	2, 4	3, 4																		
39	7.8	1.1	7.8			4.0	2.8	5.5	13.5		2.0			11.6	4.8	13.5	18.6				
41	8.0	1.1	8.0			3.0	3.0	6.5	13.6		NM			NM	5.0	13.6	18.5				

* Daunomycinone numbering is used for **19**, **20** and **23** except the aromatic protons (H-1 and H-2).
OM—overlapping multiplet.
NM—not measurable.

in EtOAc-ligroin (1 : 1). Flash chromatography of the mixture provided (in order of elution) quinone **29** (40 mg), monoketal **28** (155 mg) and monoketal **27** (710 mg). This separation was not performed routinely. It is more convenient to separate the regioisomers at a later stage.

Quinone **29**, oil, $R_f = 0.5$. IR (neat) 3420, 1650 cm^{-1}. ^{1}H-NMR (80 MHz); 0.1, 0.2 (s, 2 × 3H, $SiMe_2$), 0.8 (s, 9H, Si—Bu^t), 1.2 (d, 3H, CH_3, J = 6.4 Hz), 1.6–3.0 (complex m, 5H, H-2, H-3, and H-4), 3.75 (m, 1H, CHOH), 4.90 (broad t, 1H, H-1), 6.7 (s, 2H, quinone H). This spectrum showed some signals of the other diastereomer as well. MS: chemical ionization, 337 ($M^{\cdot+}$ + 1), 319 ($M^{\cdot+}$ + 1-H_2O); electron impact, 261 (100, $M^{\cdot+}$ − H_2O—Bu^t).

Monoketal **28**, oil, $R_f = 0.44$; IR (neat), 3420, 1665, 1638, 1615 cm^{-1}. ^{1}H-NMR (80 MHz); 0.2 (s, 6H, $SiMe_2$), 0.9 (broad s, 9H, Si—Bu^t), 1.3 (d, 3H, CH_3, J = 6.3 Hz), 1.4–2.8 (complex m, 5H, H-2, H-3 and H-4), 3.20 and 3.25 (s, 3H each, 2 × OMe), 3.76 (broad m, 1H, CHOH), 4.77 (t, 1H, H-1), 6.4 and 6.75 (ABq, 2H, enone H, J_{AB} = 10.5 Hz). MS: chemical ionization, 383 (2, $M^{\cdot+}$ + 1), 351 (100, $M^{\cdot+}$ + 1-CH_3OH); electron impact, 307 (100, $M^{\cdot+}$ − H_2O—Bu^t). HRMS (base peak mass matched). (Found: 307.1352. Calc for $C_{16}H_{23}O_4Si$: 307.1366).

Monoketal **27**, oil, $R_f = 0.40$; IR (neat) 3450, 1670, 1640, 1618 cm^{-1}. ^{1}H-NMR (80 MHz); 0.08, 0.18 (s, 3H each, $SiMe_2$), 0.8 (s, 9H, Si—Bu^t), 1.28 (d, 3H, CH_3, J = 6.3 Hz), 1.4–2.6 (complex m, 5H, H-2, H-3 and H-4), 3.2 (s, 6H, 2 × OMe), 3.75 (broad m, 1H, CHOH), 4.88 (t, 1H, H-1), 6.4, 6.75 (ABq, 2H enone H, J_{AB} = 10.5 Hz), MS: chemical ionization, 383 (2, $M^{\cdot+}$ + 1), 365 (14, $M^{\cdot+}$ + 1-H_2O), 351 (100, $M^{\cdot+}$ + 1-CH_3OH); electron impact, 307 (100, $M^{\cdot+}$ − H_2O—Bu^t): HRMS (base peak mass matched). (Found: 307.1350. Calc for $C_{16}H_{23}O_4Si$: 307.1366).

1,3-trans-1-*t-Butyldimethylsilyloxy*-1,2,3,4,5,8-*hexahydro*-5,5-*dimethoxy*-3-(1-*trimethylsilyloxyethyl*) *naphthalene*-8-*one*, **30**

Alcohol **27** (50 mg) in pyridine (1 ml, anhyd) was treated with trimethylsilyl chloride (1 ml) under N_2. The pyridine and excess reagent were removed *in vacuo* after 1 hr and the residual oil rapidly filtered through a pressure column in EtOAc-ligroin (1 : 1). The solvents were removed to leave an oil (95%) which was stored under vacuum until required for the next step. IR (neat); 1667, 1638, 1610 cm^{-1}. ^{1}H-NMR (80 MHz); 0.06, 0.15 (s, 3H each, $SiMe_2$), 0.10 (s, 9H, $SiMe_3$), 0.81 (s, 9H, Si—Bu^t), 1.17 (d, 3H, CH_3, J = 6.2 Hz), 1.2–2.6 (m, 5H, H-2, H-3 and H-4), 3.19 (s, 6H, 2 × OMe), 3.7 (broad m, 1H, CHOH), 4.83 (t, 1H, H-1), 6.38 and 6.7 (ABq, 2H, enone H, J_{AB} = 10.4 Hz). MS: chemical ionisation, 455 (1, $M^{\cdot+}$ + 1); electron impact, 397 (14, $M^{\cdot+}$ − Bu^t), 307 (100, $M^{\cdot+}$ − $SiMe_2$Bu^{t}OH—Me), HRMS (base peak mass matched). (Found: 307.1353. Calc for $C_{16}H_{23}O_4Si$: 307.1366).

1,3-*Dihydro*-3-*hydroxy*-7-*methoxyisobenzofuran*-1-*one* **33**

A stirred soln of *m*-anisaldehyde dimethyl acetal (1.0 g) in dry diethyl ether (10 ml) was cooled to −78° and treated with BaLi (1.1 eq) under N_2. The soln was warmed to 0°, stirred for 1 hr and dry CO_2 (dried by passage through two $CaCl_2$ towers) bubbled through. 10% NaOH aq (10 ml) was added and the aqueous layer washed with diethyl ether (3 × 10 ml), acidified with 2N HCl and extracted with $CHCl_3$ (3 × 20 ml). The extracts were dried (Na_2SO_4) and the $CHCl_3$ removed *in vacuo* to leave a solid which crystallised from $CHCl_3$ (20%) m.p. 152–152.5° (lit.[26] 151–153°): IR(KBr), 3340, 1750 cm^{-1}. ^{1}H-NMR (80 MHz), 4.0 (s, 3H, OMe), 4.10 (broad d, 1H, J = 7.2 Hz, disappears with D_2O, OH), 6.52 (d, 1H, J = 7.2 Hz, collapses to a singlet with D_2O, CH—OH), 7.01 (d, 1H, J = 8.2 Hz, ArH), 7.17 (d, 1H, J = 7.6 Hz, ArH), 7.57 (dd, 1H, ArH). MS: 180 (100, $M^{\cdot+}$).

3-*Cyano*-1,3-*dihydro*-7-*methoxyisobenzofuran*-1-*one* **32**

An aqueous soln of KCN (0.72 g in 5 ml) was added to **33** (0.79 g) at room temp. After 20 min the soln was acidified with 2N HCl and stirred for 12 hr. The resulting ppt was filtered (0.71 g, 78%) and ^{1}H-NMR showed it was the cyanohydrin of **32**. The solid was dissolved in MeOH, heated on a steam bath for 15 min and allowed to cool. The crystals that were deposited in cooling were filtered to provide **33** m.p. 155° (lit.[16] 155°). IR(KBr); 1780 cm^{-1}. ^{1}H-NMR (80 MHz); 4.04 (s, 3H, OMe), 6.01 (s, 1H, CHCN), 7.09 (d, 1H, J = 8.6 Hz, ArH), 7.21 (d, 1H, J = 8.6 Hz, ArH), 7.8 (t, 1H, J = 8.6 Hz, ArH). MS: 189 (100, $M^{\cdot+}$).

7,9-trans-7-(*t-Butyldimethylsilyloxy*)-7,8,9,10-*tetrahydro*-6-*hydroxy*-9-(1-*hydroxyethyl*)-4,11-*dimethoxy*-5,12-*naphthacenedione* **34**

A 3-necked flask containing anhyd THF (5 ml) and diisopropylamine (0.25 ml, 1.8 mmol) was cooled to −78° and n-BuLi (1.04 ml of 1.7N soln, 1.8 mmol) added slowly. After stirring at 0° for 10 min the soln was again cooled to −78° and HMPA (0.56 ml, 3.4 mmol) added slowly. Cyanophthalide **33** (278 mg, 1.5 mmol) in tetrahydrofuran (7 ml) was added 5 min later and the soln turned orange. The soln was warmed to −23°, maintained at this temp for 10 min and cooled to −78° when the monoketal **30** (660 mg, 1.5 mmol) in THF (7 ml) was added slowly. The mixture was allowed to warm to room temp over 2 hr and aqueous AcOH (20%, 10 ml) added and the soln stirred overnight. The soln was neutralized with $NaHCO_3$ aq and the THF removed *in vacuo*. The aqueous residue was extracted into ether (3 × 10 ml) and the ether removed to leave a solid (87%) recrystallized from hexane m.p. 141–142°; IR($CHCl_3$); 3600, 1660, 1615 cm^{-1}. ^{1}H-NMR (80 MHz); 0.10, 0.22 (s, 3H each, $SiMe_2$), 0.84 (s, 9H, Si—Bu^t), 1.35 (d, 3H, CH_3, J = 6.7 Hz), 1.4–3.4 (complex m, 5H, H-8, H-9 and H-10), 3.9, 4.1 (s, 3H each 2 × OMe), 3.8 (m, 1H, CHOH), 5.3 (t, 1H, H-7, $v_{1/2}$ = 8 Hz), 7.33 (dd, 1H, H-3, $J_{2,3}$ = 8 Hz, $J_{1,3}$ = 1.8 Hz), 7.75 (t, 1H, H-2, $J_{1,2} = J_{2,3}$ = 8 Hz), 7.95 (dd, 1H, H-1), 13.95 (s, 1H) (C_6-OH). MS: 512 (13, $M^{\cdot+}$), 380, (100, $M^{\cdot+}$ − $SiMe_2$Bu^{t}OH). (Found: C, 65.10; H, 7.33. Calc for $C_{28}H_{36}O_7Si$: C, 65.59; H, 7.08%). The same reaction was conducted with the ketal mixture (**30** + **31**) and the mixture of regioisomers carried through two further steps to form **38** + **39** which were separated by derivatisation (see below).

7,9-trans-9-*Acetyl*-7-*t-butyldimethylsilyloxy*-7,8,9,10-*tetrahydro*-6-*hydroxy*-4,11-*dimethoxy*-5,12-*naphthacenedione* **36**

Alcohol **34** (1.4 g) was placed in dry DMF (15 ml) under N_2. Pyridinium dichromate (4 eq) was added and the soln stirred at room temp for 8 hr. The mixture was poured into water (150 ml) and extracted with $CHCl_3$ (4 × 50 ml). The solvents were removed and the resulting solid taken up in ether (100 ml) and washed with brine (5 × 20 ml), dried and the ether removed. The resulting solid was filtered through a column in EtOAc-ligroin (1 : 1). Recrystallization of the product from ether provided **36** (85%). M.p. 154–155°; IR(KBr) 3440, 1705, 1660, 1620 cm^{-1}. ^{1}H-NMR see Tables 1 and 2. MS: Chemical Ionisation 511 (32, $M^{\cdot+}$ + 1); electron impact; 495 (2, $M^{\cdot+}$ − Me), 453 (100, $M^{\cdot+}$ − Bu^t). (Found: C, 66.17; H, 7.04. Calc for $C_{28}H_{34}O_7Si$: C, 65.86; H, 6.71%).

7,9-trans-9-*Acetyl*-7,8,9,10-*tetrahydro*-6,7-*dihydroxy*-4,11-*dimethoxy*-5,12-*naphthacenedione* **38**

Ketone **36** (0.5 g) was suspended in aqueous AcOH (50%, 2 ml), trifluoroacetic acid (1 ml) added and the mixture stirred at room temp for 1 hr. The soln was neutralized with sat $NaHCO_3$ aq and extracted into $CHCl_3$ (20 ml). The extract was dried and the solvent removed to leave a solid which was crystallized from ether-CH_2Cl_2 (85%) m.p. 210–212°; IR(KBr) 3500, 3450, 1695, 1655, 1618 cm^{-1}. ^{1}H-NMR (80 MHz); 1.5–1.9 and 2.2–3.6 (complex m, 5H, H-8, H-9 and H-10), 2.32 (s, 3H, $COCH_3$), 3.88, 4.07 (s, 3H each, 2 × OMe), 5.24 (m, 1H, H-7, $v_{1/2}$ = 9.0 Hz after D_2O exchange), 7.32 (dd, 1H, H-3, $J_{2,3}$ = 7.9 Hz, $J_{1,3}$ = 1.8 Hz), 7.74 (t, 1H, H-2, $J_{2,3} = J_{1,2}$ = 7.9 Hz), 7.94 (dd, 1H, H-1), 14.03 (s, 1H, C_7-OH disappears with D_2O). MS: 396 (28, $M^{\cdot+}$), 376 (100, $M^{\cdot+}$ − H_2—H_2O). (Found: C, 66.28; H, 5.13. Calc for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09%).

(±)9-*Deoxydaunomycinone* **9**

Alcohol **38** (50 mg, 0.12 mmol) in dry CH_2Cl_2 (10 ml) under N_2 was cooled to −78° and BCl_3 (1.89 ml, 15 eq of 1N soln) added quickly. After 0.5 hr MeOH (5 ml) was added and the soln allowed to warm to room temp. The solvents were removed *in vacuo* and the remaining solid recrystallized from CH_2Cl_2-ether to afford **9** (85%) m.p. 230–232°; IR(KBr); 3480, 1700, 1655, 1605 cm^{-1}. ^{1}H-NMR; see Tables 1 and 2. MS: 382 (5, $M^{\cdot+}$), 321 (100, $M^{\cdot+} - H_2O—COCH_3$).

Derivatisation and separation of regioisomers **38** and **39**. *Formation of acetonide* **40** *and vinyl ether* **41**

The mixture of regioisomers **38** and **39** (1 g) was dissolved in dry CH_2Cl_2 (10 ml) under N_2 and 2-methoxypropene (4 ml) and *p*-toluenesulfonic acid (5 crystals) added. The mixture was stirred at room temp for 1 hr, solid K_2CO_3 (1 g) added and stirring continued for a further 3 hr. The soln was filtered the filtrate evaporated to dryness *in vacuo*. The resulting oil was chromatographed (fine silica gel, under positive pressure, in EtOAc-ligroin, 7:3) on a column and the two products (R_f = 0.64, **40** and R_f = 0.42, **41**) separated. The overall yield was 85% and the ratio of **40**:**41** was 9:2.

Acetonide **40**. Foam not crystallized: IR(KBr); 700, 1663, 1615 cm^{-1}. ^{1}H-NMR: see Tables 1 and 2. MS: chemical ionisation, 437 (10, $M^{\cdot+}+1$) electron impact, 418 (8, $M^{\cdot+} - H_2O$), 378 (35, $M^{\cdot+} - C_3H_6O$), 335 (100, $M^{\cdot+} - C_3H_6O—COCH_3$). HRMS (base peak mass matched. (Found: 335.0917. Calc for $C_{20}H_{15}O_5$: 335.0920).

Vinyl ether **41** crystallized from ether m.p. 172–174°; IR(KBr) 3400, 1695, 1652, 1615 cm^{-1}. ^{1}H-NMR; see Tables 1 and 2. MS: 436 (4, $M^{\cdot+}$), 379 (100, $M^{\cdot+} - C_3H_5O$), 335 (72, $M^{\cdot+} - CH_3H_6O—COCH_3$). HRMS. (Found: 436.1528. Calc for $C_{25}H_{24}O_7$: 436.1522.)

7,9-trans-9-*Acetyl*-7,8,9,10-*tetrahydro*-7,11-*dihydroxy*-1,6-*dimethoxy*-5,12-*naphthacenedione* **39**

Vinyl ether **41** (0.2 g) was dissolved in wet CH_2Cl_2 (5 ml) and *p*-toluenesulfonic acid (1 crystal) added. After 1 hr solid K_2CO_3 (0.1 g) was added and stirring continued for 1 hr. The soln was filtered, the solvent removed *in vacuo* and the residue recrystallized from ether-CH_2Cl_2 (90%). M.p. 118–120°; IR(KBr) 3450, 1690, 1650, 1620 cm^{-1}. ^{1}H-NMR; see Tables 1 and 2. MS: 396 (100, $M^{\cdot+}$), 381 (32, $M^{\cdot+} - CH_3$), 363 ($M^{\cdot+} - CH_3—H_2O$). HRMS. (Found: 396.1211. Calc for $C_{22}H_{20}O_7$: 396.1209.)

11-*Methyldaunomycinone* **43** and 11-*methyl epidaunomycinone* **42**

Acetonide **40** (132 mg, 0.292 mmol) trimethyl phosphite (0.3 ml) dry t-BuOH (10.5 ml) and THF (5.2 ml) were cooled to −23° under N_2. O_2 was bubbled through for 5 min and a mixture of t-BuOK (freshly sublimed, 105 mg, 3.2 eq) in t-BuOH-tetrahydrofuran (5.25 ml, 1.71 ml resp.) was added quickly and the O_2 bubbled through again for 15 min. Water (2 ml) was added and CO_2 bubbled through until the soln was neutral to litmus. The solvents were removed *in vacuo* and the residue extracted into $CHCl_3$ (2 × 20 ml), dried and the $CHCl_3$ removed to leave a solid. The solid was filtered through a column in CH_2Cl_2—MeOH (97:3) and the resulting product hydrolysed in wet CH_2Cl_2 (5 ml) with *p*-toluenesulfonic acid (2 crystals) at room temp. After 0.5 hr the mixture was washed with sat $NaHCO_3$ aq (2 × 5 ml), the organic phase dried and the solvent removed *in vacuo* to leave a mixture of **42** and **43** (87% total). The mixture was chromatographed on a column (fine silica gel, positive pressure, CH_2Cl_2—MeOH, 97:3) to provide **43** (R_f = 0.1) and **42** (R_f = 0.03) in a 5:6 ratio. **43** crystallized from CH_2Cl_2 m.p. 219–221°. IR(KBr) 3300, 1695, 1645, 1605 cm^{-1}; ^{1}H-NMR; see Fig. 1 and Tables 1 and 2. MS: 412 (76, $M^{\cdot+}$), 394 (10, $M^{\cdot+} - H_2O$), 376 (37, $M^{\cdot+} - 2H_2O$), 351 (100, $M^{\cdot+} - H_2O—COCH_3$). HRMS. (Found: 412.1156. Calc for $C_{22}H_{20}O_8$: 412.1158.) **42**; crystallized from CH_2Cl_2 m.p. 243–245°; IR(KBr); 3420, 1690, 1650, 1610 cm^{-1}. ^{1}H-NMR; see Tables 1 and 2. MS: 412 (8, $M^{\cdot+}$), 394 (54, $M^{\cdot+} - H_2O$), 376 (100, $M^{\cdot+} - 2H_2O$). HRMS. (Found: 412.1154. Calc for $C_{22}H_{20}O_8$: 412.1158.)

(±)*Daunomycinone* **1**

The methyl ether **43** (50 mg) in dry CH_2Cl_2 (15 ml) under N_2 was cooled to −78° and BCl_3 (1.8 ml of 1N soln, 15 eq.) added and the soln stirred for 0.5 hr. Sat $NaHCO_3$ aq (3 ml) was added, the soln warmed to room temp, the CH_2Cl_2 layer separated and the aqueous layer which contained a red solid extracted further with CH_2Cl_2 until the extracts were colourless. The combined extracts were dried and the solvent removed to leave a deep red solid crystallized from THF-MeOH (85%) m.p. 275–278° (lit.[22] 280°). IR(KBr); 3540, 1695, 1640, 1612 cm^{-1}. ^{1}H-NMR; see Tables 1 and 2. MS: 398 (34, $M^{\cdot+}$), 380 (20, $M^{\cdot+} - H_2O$), 362 (100, $M^{\cdot+} - 2H_2O$), 337 (50, $M^{\cdot+} - 2H_2O$), 337 (50, $M^{\cdot+} - H_2O—COCH_3$).

(±)7-*Epidaunomycinone* **8**

Prepared by the same procedure for **42** in 83% yield. m.p. 255–260° (lit.[22] 269°). IR(KBr): 3400–3500, 1692, 1648, 1610 cm^{-1}. ^{1}H-NMR not obtainable due to solubility problems and epimerisation to daunomycinone. MS: 398 (8, $M^{\cdot+}$), 380 (9, $M^{\cdot+} - H_2O$), 362 (49, $M^{\cdot+} - 2H_2O$), 337 (100, $M^{\cdot+} - H_2O—COCH_3$).

3-*Acetyl*-1,2,3,4-*tetrahydro*-1-*hydroxy*-6,7-*dimethoxynaphthalene* **5**

Dihydronaphthalene **4**[3,4] (1 g) was dissolved in abs EtOH (54 ml) under N_2, NaHg (18.4 g of 2.5% sodium, 5 eq) added and the soln stirred vigorously for 5 hr. Water (40 ml) was added and CO_2 bubbled through the soln until neutral to litmus. The soln was decanted from the Hg and the EtOH removed *in vacuo* to leave an oil (900 mg). Column chromatography in benzene-acetone (4:1) provided the *cis* and *trans* isomers.

Compound **5** (1,3-cis). M.p. 111–112.5° (ether); IR($CHCl_3$); 3500, 1690 cm^{-1}. ^{1}H-NMR (80 MHz); 1.6–2.6 (broad m, 3H, H-2 and H-3), 2.25 (s, 3H, $COCH_3$), 2.95 (broad s, 2H, H-4), 3.85, 3.87 (s, 3H each 2 × OMe), 4.6–5.0 (broad m, 1H, H-1) 6.60, 7.02 (s, 1H each, ArH). MS: 250 (8, $M^{\cdot+}$), 232 (20, $M^{\cdot+} - H_2O$), 189 (100, $M^{\cdot+} - H_2O—COCH_3$). (Found: C, 67.42; H, 7.11. Calc for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%).

Compound **5** (1,3-trans). M.p. 101–103° (ether); IR($CHCl_3$); 3500, 1690 cm^{-1}. ^{1}H-NMR (80 MHz); 1.6–3.1 (broad m, 5H, H-2, H-3 and H-4), 2.25 (s, 3H, $COCH_3$), 3.83, 3.85 (s, 3H each, 2 × OMe), 4.75–4.95 (broad q, 1H, H-1), 6.60, 6.85 (s, 1H each, ArH). MS: 250 (3, $M^{\cdot+}$), 232 (32, $M^{\cdot+} - H_2O$), 189 (100, $M^{\cdot+} - H_2O—COCH_3$). (Found: C, 67.21; H, 7.11. Calc for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%).

3-*Acetyl*-1-*t*-*butyldimethylsilyloxy*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-*naphthalene* **6**

The mixture of *cis* and *trans* isomers **5** was silylated as before (see procedure for **19**) to provide a mixture of isomers in similar yield. These were not separated but only characterised by ^{1}H-NMR and mass spectroscopy. MS: 364 (3, $M^{\cdot+}$), 189 (100, $M^{\cdot+} - OSiMe_2Bu^t—COCH_3$). The ^{1}H-NMR spectrum was complex but showed an approximately 1:1 mixture of *cis* and *trans* diastereomers.

3-*Acetyl*-1-*t*-*butyldimethylsilyloxy*-1,2,3,4-*tetrahydro*-3-*hydroxy*-6,7-*dimethoxynaphthalene* **7**

The mixture of silyl ethers **6** was oxygenated as before (see procedure for **20**) to provide a mixture of diastereomers **7** in similar yield. The isomers were not separated. MS: 380 (5, $M^{\cdot+}$), 323 (33, $M^{\cdot+} - Bu^t$), 248 (10, $M^{\cdot+} - Me_2Bu^tSiOH$), 75 (100, Me_2SiOH).

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