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A CONVERGENT SYNTHESIS OF (+)-4-DEMETHOXYDAUNOMYCINONE AND (+)-DAUNOMYCINONE

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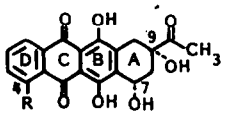
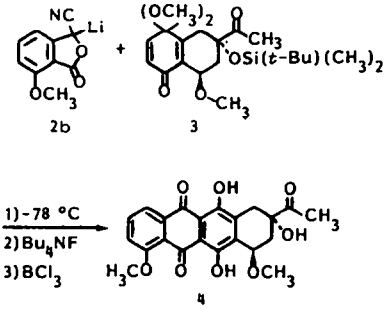
Abstract—A convergent synthesis of (+)-4-demethoxydaunomycinone and (+)-daunomycinone via annelation of a functionalized quinone monoketal with the anion of the corresponding 3-cyano-1(3H)isobenzofuranone is reported. The quinone monoketal, which serves as the AB-ring component in the sequence, was prepared without chromatography from 2,5-dimethoxybenzaldehyde in sixteen steps. The monoketal of proper absolute configuration was obtained by resolution of the imine from (−)-α-methylbenzylamine and 1,2,3,4,-tetrahydro - 5,8 - dimethoxy - 4 - oxo - 2 - acetyl - 2 - hydroxynaphthalene cyclic 4-(ethylene mercaptole). Two noteworthy aspects of the synthesis were the highly selective reduction of a bicyclic β-hydroxyketone to afford a diol with the required *cis*-stereochemistry at the eventual C-7 and C-9 positions of the anthracyclinone and the regioselective hydrolysis of the quinone bisketal to afford the monoketal of proper regiochemistry for the synthesis of (+)-daunomycinone. Thus, (+)-daunomycinone and (+)-4-demethoxydaunomycinone were prepared in nineteen steps from 2,5-dimethoxybenzaldehyde in respective overall yields of 3 and 5% (the overall yield for the racemic material was 13%). This synthetic strategy allows a convergent approach to a variety of D-ring analogs.

CONSIDERABLE effort over the last ten years has focused on synthetic routes to the rhodomycinone aglycons,[2] especially towards the synthesis of daunomycinone or its 4-demethoxy analog. While the latter aglycon is not naturally occurring, the symmetrical nature of the B-, C-, and D-rings simplifies the synthetic strategy to the molecule. Furthermore, preliminary reports indicate high biological activity for an anthracycline in which 4-demethoxydaunomycinone is the aglycon.[3] Wong[4a] reported the first synthesis of racemic daunomycinone from the 7-deoxy compound[5] by introducing the required 7-hydroxyl group via a bromination/solvolysis reaction sequence. A majority of the routes to these aglycons, including our regiospecific synthesis reported in 1977,[6] involved the preparation of the 7-deoxy compound with the anticipation that the 7-OH group could be introduced in the last step.[6,7a] However, difficulties in effecting this conversion on a reasonable scale led to the conclusion that the 7-deoxy compound was not useful for efficiently preparing the aglycon.[6,7b,8] Since our goal was not only the synthesis of the title compounds, but



1a, R = H, 4-demethoxydaunomycinone
b, R = OCH_3, daunomycinone

also to develop a synthetic strategy which would readily afford analogs, the uncertainty of successfully introducing the 7-OH group required for glycosylation in other analogs ruled out the respective 7-deoxy compounds as synthetic targets. Thus, our efforts focused on a convergent route to aglycons in which all of the A-ring functionality was present.[9] Previous work had established that coupling of the anion **2b** with the functionalized monoketal **3** produced **4** in excellent yield.[10] The tetracyclic **4** could be converted to a

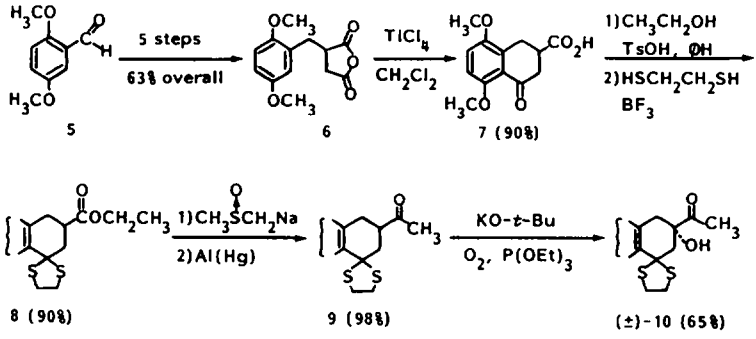


mixture of daunomycinone and epi-daunomycinone (OH groups at C-7 and C-9 trans) by solvolysis of **4** in trifluoroacetic acid; however, chromatographic separation of the two isomers was extremely tedious. This made the synthesis useful for the preparation of only a few hundred milligrams of pure material. This is currently a limitation of any synthesis that does not produce the proper stereochemistry of the OH groups at C-7 and C-9.

We report herein a useful convergent synthesis of (∓)-4-demethoxy-, (+)-4-demethoxy- and (+)-daunomycinone, employing the general synthetic strategy illustrated by the annelation reaction of **2b** with **3**.

Synthesis of the AB-ring system

Our objective was the preparation of an AB-ring segment which contained all of the functionality of the A-ring of daunomycinone with the proper absolute configuration.[11] This compound would then be reacted with a CD-ring portion to produce the completely functionalized tetracyclic system. The basic bicyclic system **6** was prepared by the general approach of Wong and Schwenk[4c] with several practical improvements. These procedures, detailed in the Experimental Section, allowed preparation of **6** in 63% overall yield with no purifications except a simple recrystallization in the final step. The liquid hydrogen fluoride

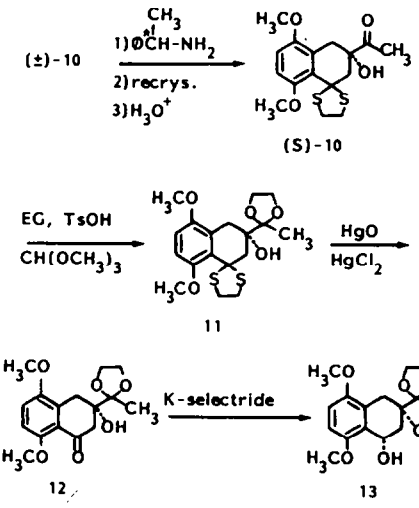


cyclization of the anhydride **6** to the tetralone **7**, while useful in small-scale work, was impractical for large-scale synthesis. Although a number of other Friedel–Crafts catalysts did not give good yields in the **6** to **7** conversion, titanium tetrachloride in methylene chloride effected the ring closure reproducibly on a 100 gram scale in 90% yield. With the tetralone acid **7** conveniently available in quantity, methods for introducing the required functionality of the anthracyclinone A-ring were explored.

The two CO groups of **7** were differentiated chemically by esterification followed by thioketalization to give **8**. Attempts to introduce the OH group alpha to the ester function in **8** were unsuccessful. Attempted oxygenation of the ester enolate of **8** with oxodiperoxymolybdenum(pyridine) (hexamethylphosphoric triamide), the $MoO_5 \cdot HMPA$ reagent,[13a] gave a complex mixture of products. Apparently, oxidation of the thioketal competes with enolate oxidation. Oxygenation of the ester enolate with oxygen in the presence of triethylphosphite gave primarily recovered starting material.[13b] This latter result is somewhat surprising in view of the high-yield oxygenation of the analogous ethylene glycol ketal of **8** reported subsequent to our studies.[12b]

Since oxygenation of the ester **8** proved difficult, it was converted to the methyl ketone using the Corey procedure.[14] This conversion was initially conducted on the methyl ester of **8**; however, the yields of the reaction were quite variable, and poor yields were obtained on larger scale (50 g) reactions. Surmising that part of the difficulty came from the high insolubility of the methyl ester in the solvent system, the reaction was then performed on the lower melting and more soluble ethyl ester. Using the ethyl ester **8**, the conversion to **9** was conducted routinely on a 100-gram scale in over 90% yield. The required tertiary hydroxyl group was then introduced via oxygenation of the ketone enolate. The yields for this oxygenation were only reproducible when freshly distilled dimethylformamide was employed as solvent and the oxygen uptake monitored. Otherwise, an induction period was often noted, and unless the reaction was quenched at the proper time, low yields of **10** resulted.

With racemic **10** available, its resolution was examined using α-methylbenzylamine. Since both antipodes of the amine are commercially available, a successful resolution would afford the molecule of natural absolute configuration. Reaction of **10** with (−)-α-methylbenzylamine followed by recrystallization from ethyl acetate afforded a 25% yield of optically pure imine which was hydrolyzed to a levorotatory hydroxy ketone, (−)-**10**. Our studies at this point were aided by



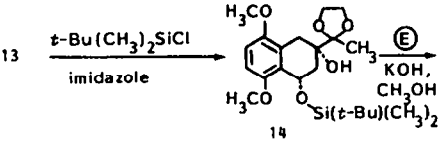
an X-ray determination of the absolute configuration of (−)-**10** conducted by the Hassall group[12c] which established that this hydroxy ketone had the natural (*S*) configuration of the A-ring in the anthracyclinones. While the yield of the resolution is only 25%, the enriched imine recovered from the initial resolution could be hydrolyzed, and the enriched (*R*)-**10** could be removed by utilizing the (+)-α-methlbenzylamine. Thus, hydrolysis of the imine mother liquors afforded hydroxy ketone enriched in (*R*)-**10** which was then reacted with (+)-α-methylbenzylamine to afford after resolution pure (*R*)-**10**. The mother liquors from this resolution were then resolved with (−)-α-methylbenzylamine to afford additional (*S*)-**10**. In practice, two such cycles gave a 35% yield of (*S*)-**10** from racemic **10**.

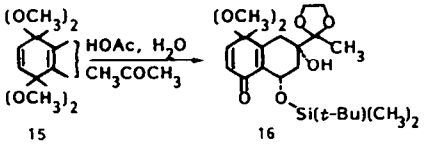
The major remaining problem was the efficient conversion of **10** to the *cis*-1,3-diol **13**. Ketalization of **10** under standard azeotropic conditions sometimes led to decomposition products as well as the desired ketal, but mild ketalization conditions employed in an earlier study[15] gave the ketal **11** in quantitative yield. Various methods for reduction of **12**, available from thioketal hydrolysis of **11**, afforded a difficultly separable *cis/trans* mixture of diols.[16] However, potassium tri-sec-butylborohydride reduction of **12** afforded almost exclusively the required *cis*-diol **13**.[17]

Coupling of the AB- and CD-ring segments

Previous studies on the coupling reaction of the model system, **3**, with 7-methoxy-3-(phenylsulfonyl)-1-(3H)-isobenzofuranone as the annelating reagent indicated that it was necessary to protect the tertiary

OH group to obtain good yields of tetracyclic product.[10] Since the benzylic OH group of **13** needed to be protected for the anodic oxidation step leading to the quinone bisketal, various methods for protecting both OH groups in **13** were examined.[18] While the benzylic hydroxyl group was easily functionalized, functionalization of both it and the tertiary OH group of **13** could

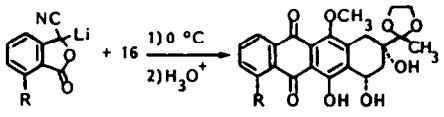




not be performed cleanly with either *t*-butyldimethylsilyl chloride[19] or chloromethylmethyl ether. Apparently, the steric bulk of the ethylene glycol ketal and the other *cis* oxygen substitutent hinders functionalization of the tertiary position. The difficulty in protecting both hydroxyl groups led to the examination of the chemistry of the monoblocked system **14**.

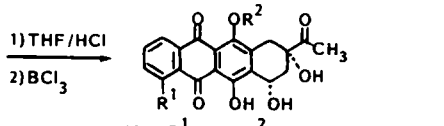
Anodic oxidation of **14** in a single cell produced in excellent yield the respective quinone bisketal, **15**, which was directly hydrolyzed to a mixture of two regioisomeric monoketals in a ratio of *ca* 83:17 as determined by HPLC analysis. The major isomer, which could be obtained in a pure form by recrystallization, was assigned as **16** by analogy to the directing effect of an allylic oxygen substitutent on model quinone bisketal hydrolyses.[20] This assignment was subsequently confirmed by the use of the monoketal in the synthesis of (+)-daunomycinone. While the regiochemistry of the quinone monoketal is of no importance for the synthesis of 4-demethoxydaunomycinone, it is of concern for the synthesis of certain anthracyclinones having D-ring substitutents. Fortunately, in the synthesis of (+)-daunomycinone *vida infra* the crude mixture of monoketals could be employed in the coupling step, and the major coupling product could be obtained free from impurities by fractional recrystallization.[21]

The coupling reaction of **16**, having an unprotected tertiary OH group, with the anion of 3-cyano-1(3H)-isobenzofuranone[22] was examined. Reaction of **2a** and **16** under conditions developed in our model studies[10] afforded the tetracyclic compound **17a** in 90% crude yield. The reason for the high yield of tetracyclic product from coupling of **16** *vs* the low yield obtained from the coupling reactions of other systems having a free tertiary OH group may be due to the different monoketal or different annelating reagent. Hydrolysis of the ketal and demethylation of the aromatic methoxyl group gave 4-demethoxydaunomycinone in excellent overall yield. It is not necessary to purify intermediates **17a** and **18a** since the boron trichloride demethylation to afford **19a** converts both regioisomers to the desired 4-demethoxydaunomycinone. A similar reaction sequence performed with the anion of 7 - methoxy - 3 - cyano - 1(3H) -



2a, R = H
b, R = OCH_3

17a, R = H (90%)
b, R = OCH_3 (64%)



18a, R^1 = H, R^2 = CH_3 (98%)
b, R^1 = OCH_3, R^2 = CH_3 (84%)
1a, R^1 = R^2 = H (98%)
b, R^1 = OCH_3, R^2 = H (86%)

isobenzofuranone[23] afforded (+)-daunomycinone in excellent yield. In this case the coupling was performed with the crude mixture of monoketals from hydrolysis of **15**, and the natural regioisomer **17b** was fractionally crystallized from the coupling reaction mixture.

SUMMARY

The chemistry reported herein comprises a highly convergent route to anthracyclinones. (+)-Daunomycinone and (+)-4-demethoxydaunomycinone have been prepared in nineteen steps from 2,5-dimethoxybenzaldehyde in respective overall yields of about 3% and 5%, (overall yield for the racemic material is 13%). The synthesis requires no chromatography, and the individual reactions do not have severe scale limitations. In fact, this chemistry has been used to prepare over 25 grams of racemic 4-demethoxydaunomycinone. An additional advantage of this approach to anthracyclinone synthesis is the ready availability of analogs by performing the coupling step with modified CD- or AB-ring segments. We plan to report on the synthesis and biological testing of these modified anthracyclinones at a later date. In principle, the preparation of ^{14}C-ring labeled anthracyclinones to aid in tissue distribution and metabolism studies of the anthracyclinones[15] would also be feasible via use of a ^{14}C-labeled CD-ring segment. Thus, the synthesis reported herein satisfies the major goals we set six years ago.

EXPERIMENTAL[24]

Dimethyl-(2,5-dimethoxybenzylidene)malonate. A mixture of 2,5-dimethoxybenzaldehyde (300 g, 1.8 mol), dimethylmalonate (240 ml, 262 g, 1.98 mol), piperidine (9.0 ml), HOAc (3 ml), and benzene (300 ml) was heated to reflux in an apparatus equipped with a Dean-Stark trap (34 ml of lower phase was collected over 14 hr). The mixture was diluted with an equal volume of Et_2O and washed with 100 ml-portions of 5% HCl, 5% $NaHCO_3$, and brine. Concentration *in vacuo* yielded a yellow oil which was diluted with Et_2O/H and cooled to give dimethyl-(2,5-dimethoxybenzylidene)malonate (471 g, 93%) as yellow crystals suitable for use in the next step. A sample recrystallized from Et_2O showed: m.p. 59–60°; IR 2950 (m), 1740 (s), 1725 (s), 1620 (m), 1500–1400 (m, structured), 1272–1150 (s, structured); ^{1}H-NMR (60 MHz, CCl_4) 7.80 (s, 1H), 6.78 (m, 3H), 3.75 (overlapping s, 6H), 3.68 (s, 3H), 3.60 (s, 3H); exact mass calc for $C_{14}H_{16}O_6$ *m/e* 280.0947, obsd 280.0936.

Trimethyl - 3 - (2,5 - dimethoxyphenyl) - 1,2,2 - propanetricarboxylate. A mixture of the product from above (100 g, 0.36 mol) and 10% Pt-C (2.0 g) in THF (225 ml) was hydrogenated in a Parr apparatus (initial pressure 59 lb/in.^{2}, final pressure 27 lb/in.^{2}) for 5 hr. The soln was filtered through Celite, and the colorless filtrate was used directly in the next step. Distillation of a portion of the material through a short-path head afforded 90% of a colorless viscous oil: b.p. 172–174°/0.6 mm; IR (neat) 2970 (s), 1740 (s), 1500 (s), 1440 (s), 1280 (s), 1230 (s), 1160 (s), 1050 (s); ^{1}H-NMR (60 MHz, CCl_4) 6.60 (m, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 3.65 (s, 6H), 3.58 (obscured, 1H), 3.10 (d, J = 7.5 Hz, 2H).

The hydrogenation soln was diluted with sufficient THF to make the total volume about 1 l and then placed in a 2-l, 3-necked flask under N_2 while NaH (17 g, 60% by weight) in mineral oil was added over 1hr. After H_2 evolution ceased, methyl bromoacetate (59.8 g) was added over 15 min. The soln was heated to reflux for 5 hr, and then the THF was removed *in vacuo* to afford a white oily solid (a mixture of product, NaBr, mineral oil, and unknown impurities). This material was used directly in the next step. Standard workup of a portion of the material followed by recrystallization of the product from Et_2O/PE gave the triester as a white crystalline solid: m.p. 102.5–104.0°; IR 1730 (s), 1495 (s), 1426 (s), 1310 (s), 1280 (s), 1220 (s), 1190 (s), 1040 (s); ^{1}H-NMR (60 MHz, CCl_4), 6.60 (br d, 2H), 6.42 (br d, 1H), 3.55–3.70 (overlapping s, 15H), 3.32 (s, 2H), 2.70 (s, 2H); exact mass calc for $C_{17}H_{22}O_8$ *m/e* 354.1315, obsd 354.1305.

(2,5-Dimethoxybenzyl)succinic anhydride **6**. The crude triester from two runs as described above [200 g of starting dimethyl-(2,5-dimethoxybenzylidene)malonate] was dissolved in hot EtOH (600 ml), water (1200 ml) and KOH (360 g) were added, and the homogeneous soln was heated to a gentle reflux for 14 hr. The resulting orange soln was cooled and then extracted with $CHCl_3$ (2 × 400 ml). The light orange aqueous phase was cooled in ice and slowly acidified with conc HCl (600 ml). After 5 hr at 0°, the solid was collected and dried to constant weight under vacuum to afford 182.2 g (81% overall from Knoevenagel product) of white powdery solid.

The crude triacid (182.2 g, 0.584 mol) was added to Ac_2O (1.0 l), and the soln was slowly heated to reflux. The solid gradually dissolved, and CO_2 evolution was apparent. After heating for 2 hr, the soln was concentrated by distillation at atmospheric pressure (~ 500 ml of distillate was collected). The resulting cloudy soln was filtered (3.4 g of white solid, probably NaBr, was collected), and the remaining Ac_2O was removed *in vacuo* at about 80°. The dark brown oil was then poured into a 1-l flask, and the flask was rinsed, using a minimum amount of $CHCl_3$. The solution was rapidly swirled while hexane (about 350 ml) was added, and then the product was allowed to crystallize. After collection of the solid and drying, white anhydride (122 g, 84% from the crude acid) was obtained: m.p. 74–76° (lit.[4d] m.p. 75–76°); IR 1860 (s), 1780 (s), 1500 (s), 1220 (s), 1170 (s), 1140 (s), 928 (s), 915 (s); ^{1}H-NMR 6.69 (2 s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.20–2.74 (m, 5H).

1,2,3,4 - Tetrahydro - 5,8 - dimethoxy - 4 - oxo - 2 - naphthoic acid **7**. The anhydride (106 g, 0.42 mol) in CH_2Cl_2 (500 ml) was added to a stirred soln of $TiCl_4$ (111 ml, 191 g, 1.0 mol) in CH_2Cl_2 (1600 ml) at room temp over a period of 20 min. A slight warming of the mixture was noted, and the soln was then stirred at room temp for 1 hr. The mixture was then cooled in ice, and the CH_2Cl_2 layer was poured onto ice (300 g). Some product precipitated and was collected; however, the majority of material remained as a reddish oily solid on the walls of the reaction flask. Water (850 ml) was added to the flask, and the soln was vigorously stirred until the reddish-brown material was converted into a light yellow solid. This material was filtered, combined with the previous solid, washed with water, and dried (first in the air and then under vacuum) to obtain the ketoacid (95.4 g, 90%), m.p. 199–201° (lit.[4d] m.p. 207–208°), suitable for use directly in the next step; IR 1740 (s), 1680 (s), 1475 (s), 1280 (s), 1270 (s), 1260 (s), 1170 (s), 1080 (s); ^{1}H-NMR 6.90 (AB q, Δν = 15.6 Hz, J = 9 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.6–2.7 (m, 5H).

Ethyl-1,2,3,4-tetrahydro-5,8-dimethoxy-4-oxo-2-naphthoate cyclic 4-(ethylene mercaptole), **8**

A mixture of the keto acid from above (142 g, 0.57 mol), abs EtOH (100 ml), benzene (550 ml), and *p*-TsOH (0.5 g) was heated to reflux under a 39 cm-Vigreux column and a Dean-Stark trap. The pot temp was adjusted so that the benzene/EtOH/H_2O azeotrope distilled, and the reaction was allowed to proceed for 24 hr. Conventional workup afforded 95% of the ester as a light tan solid. Recrystallization of this material from EtOH afforded the ethyl ester as a white solid: m.p. 96–98°; IR 1730 (s), 1680 (s), 1585 (s), 1475 (s), 1255 (br s), 1085 (s); ^{1}H-NMR (60 MHz) 6.88 (AB q, Δν = 15 Hz, J = 9 Hz, 2H), 4.23 (q, J = 6 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.39–2.82 (m, 5H), 1.23 (t, J = 6.5 Hz, 3H); exact mass calc for $C_{15}H_{18}O_5$ *m/e* 278.1154, obsd 278.1162.

More conveniently, the solvent from the crude esterification mixture was distilled at atmospheric pressure, and the solid residue was dried under vacuum for several hours. To this mixture were added benzene (1.5 l), 1,2-ethanedithiol (48 ml), and $BF_3 \cdot Et_2O$ (0.5 ml). This mixture was heated to reflux under a Dean-Stark trap for 12 hr, and then the solvent was distilled at atmospheric pressure until the volume of the reaction mixture was about 150 ml. The cooled mixture was then diluted with an equal volume of PE and cooled in ice. The title compound, obtained as a tan solid (184 g, 90%, m.p. 107–109°), was used directly in the next step. A sample recrystallized from benzene/H gave white crystalline material: m.p. 114–116°; IR 2950 (m), 2930 (m), 1725 (s), 1590 (m), 1475 (s), 1460 (s), 1285 (s), 1255 (s), 1065 (s); ^{1}H-NMR (90 MHz) 6.75 (s, 2H), 4.21 (q, J = 7.6 Hz, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.57–3.41 (m, 4H), 3.2–2.3 (m, 5H), 1.31 (t, J = 7.5 Hz, 3H); exact mass calc for $C_{17}H_{22}O_4S_2$ *m/e* 354.0960, obsd 354.0970.

1,2,3,4-Tetrahydro-5,8-dimethoxy-4-oxo-2-acetylnaphthalene cyclic 4-(ethylene mercaptole), **9**

To a 3-l, round-bottomed flask equipped with a stirrer and condenser and maintained under N_2 was added NaH (37.8 g of a 60% oil dispersion, 0.95 mol). The NaH was washed with PE (2 × 25 ml), and DMSO (400 ml) was added. The material was slowly heated to 65–70° and maintained at this temp until H_2 evolution ceased (2 hr). The mixture was cooled to 0°, and THF (400 ml) was added. The crude product from the previous step (134 g, 0.38 mol) was dissolved in THF (535 ml) and added to the rapidly stirred soln. The ice bath was removed, and the brownish-red soln was stirred for 1 hr and then poured into water (4 l). This mixture was carefully acidified to pH 4 by dropwise addition of conc HCl, and the soln was extracted with CH_2Cl_2 (4 × 750 ml). The extracts were combined and washed with water (2 × 2500 ml), the bulk of the solvent was removed by distillation at atmospheric pressure, and the remaining volatiles were removed from the thick yellow oil by vacuum drying for 14 hr. The crude ketosulfoxide showed: ^{1}H-NMR 6.78 (s, 2H), 4.00 (s, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.51–3.39 (m, 4H), 3.20–3.00 (m, 5H), 2.71 (s, 3H).

The material was dissolved in THF and divided into two batches for the Al/Hg reduction. Aluminum foil (57 g, 1-in. squares) was placed in a 5-l, 3-necked, round-bottomed flask equipped with an efficient condenser and an overhead stirrer, and 2% aqueous $HgCl_2$ (1.0 l) was added. The soln was swirled for 30 sec, then the $HgCl_2$ soln was poured off, and a soln of the compound in THF (2400 ml) was added, followed by addition of water (250 ml).

Note: The Al is very reactive after amalgamation, and these steps must be done rapidly since a fire could result. The reaction must be monitored closely since it becomes sufficiently exothermic that cooling must be employed; however, the reaction temp should be maintained above 50°. After 2 hr, the H_2 evolution ceased, and the mixture was filtered through Celite. The THF was removed *in vacuo* and then used to wash the aluminum salts; this process was repeated three times. The product solidified upon concentration to afford 98 g (80%) of light yellow solid, m.p. 124–129°, which was used directly in the next step. The yield of product varied from 80% to as high as 95% on 50-gram runs. A sample recrystallized from EtOAC/H

showed: m.p. 128–130°; IR 1710 (br s), 1600 (m), 1475 (br s), 1435 (s), 1280 (s), 1255 (s), 1090 (s); ^{1}H-NMR (90 MHz) 6.75 (s, 2H), 3.38 (s, 3H), 3.74 (s, 3H), 3.6–3.39 (m, 4H), 3.1–2.45 (m, 5H), 2.26 (s, 3H); exact mass calc for $C_{16}H_{20}O_3S_2$ *m/e* 324.0854, obsd 324.0861.

1,2,3,4-*Tetrahydro*-5,8-*dimethoxy*-4-*oxo*-2-*acetyl*-2-*hydroxynaphthalene cyclic* 4-(*ethylene mercaptole*), **10**

To a stirred −24° soln of the ketone (8.9 g, 27.4 mmol), t-BuOH (23 ml), freshly distilled DMF (71 ml), and $(EtO)_3P$ (5 ml, 27.4 mmol) maintained under N_2 was added a −50° soln of t-BuOK (6.2 g, 55.2 mmol) in DMF (26 ml). O_2 was introduced into the system and after 15 min one equivalent of O_2 (670 ml) was absorbed. The light orange mixture was then quenched by addition of HOAc (5 ml) affording a light yellow mixture. Two such runs were combined and concentrated at 60°/0.2 mm and the residue worked up as usual to afford a light yellow syrup. The majority of remaining volatiles were removed at room temp/10^{-3} mm over 24 hr. Trituration of the resulting semi-solid with Et_2O/EtOAc afforded in two crops 12.2 g (65%) of light yellow solid, m.p. 143–147° suitable for use in the next step. Recrystallization of this material from EtOAc gave in three crops 10.6 g (56%) of crystalline hydroxy ketone, m.p. 148–150°. The analytically pure material showed m.p. 151–153° (lit.[12c] m.p. 152.5–153.0°).

Resolution of (±)-**10**. A mixture of (±)-**10** (4.8 g, 0.014 mol), benzene (100 ml), Linde 4A sieves (10 g), and (+)-α-methylbenzylamine (3.6 ml, 0.028 mol) was heated to reflux overnight in an apparatus equipped with a Dean-Stark trap. The mixture was then filtered through a Celite pad and concentrated *in vacuo* to afford, after trituration with Et_2O, the diastereomeric imines as an off-white powder, m.p. 165–178°. The ratio of the diastereomeric imines can be determined by integration of the Me groups at *ca* δ 1.35 in the 200 MHz ^{1}H-NMR spectrum. In a typical run this crude product was dissolved in boiling EtOAc (40 ml), and then the volume was reduced to 25 ml. Slow cooling to room temp gave clear crystals which were filtered, washed with EtOAc (10 ml) and Et_2O (15 ml), and dried to yield 1.55 g (25%) of colorless needles: m.p. 195–195.5°; $[\alpha]_D^{20}$ (dioxane) = −29.5°; IR(KBr) 3240 (m), 1660 (s), 1475 (s), 1460 (s), 1435 (s), 1260 (s), 1250 (s), 1080 (s); ^{1}H-NMR (200 MHz, C_6D_6) 7.25–7.00 (m, 5H), 6.51 (AB q, J = 4.4 Hz, Δv = 12.9 Hz, 2H), 4.37 (q, J = 6 Hz, 1H), 3.55 (s, 3H), 3.4–3.3 (m, 2H), 3.29 (s, 3H), 3.17–2.75 (m, 7H), 1.42 (s, 3H), 1.25 (d, J = 6 Hz, 3H); exact mass calc for $C_{24}H_{29}NO_3S_2$ *m/e* 443.1588, obsd 443.1600.

The combined mother liquors were concentrated *in vacuo* and then hydrolyzed to enriched (*S*)-**10** by adding THF (30 ml) and 5% aqueous HCl (7 ml). This solution was stirred at room temp for 0.5 hr, and then the THF was removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 ml), and the combined organic phases were worked up as usual to afford an oil which crystallized on standing. This hydroxy ketone enriched in (*S*)-**10** was reacted as described above except with (−)-α-methylbenzylamine to yield 1.81 g (29%) of imine: m.p. 195–195.5°; $[\alpha]_D^{20}$ (dioxane) = +29.5°. Note that this latter imine is the compound having the natural configuration of the anthracyclinone A-ring.

A solution of 5% aqueous HCl (25 ml) was added to a stirred solution of the imine above (3.05 g, 8.9 mmol) in THF (110 ml). The resulting light yellow soln was stirred for 10 min at room temp and then concentrated *in vacuo* to remove the majority of the THF. The residue was extracted with CH_2Cl_2 (3 × 30 ml) and worked up as usual to afford the levorotatory hydroxy ketone, (*S*)-**10**. Recrystallization of this material from EtOAc gave 2.05 g (89%) of white product: m.p. 178.5–179.5°; $[\alpha]_D^{20}$ ($CHCl_3$) = −24.4° {lit.[12c] m.p. 178.5–179.5°, $[\alpha]_D^{20}$ ($CHCl_3$) = −24.4°}.

1,2,3,4-*Tetrahydro*-5,8-*dimethoxy*-4-*oxo*-2-*acetyl*-2-*hydroxynaphthalene cyclic* 4-(*ethylene mercaptole*), *cyclic* 2-*ethyleneglycol ketal*, **11**

A mixture of ketone **10** (61.7 g, 0.18 mol), distilled ethylene glycol (312 ml), commercial trimethylorthoformate (240 ml), and anhyd *p*-TsOH (1 g) was combined in the above order and stirred in an oil bath at 37–40° for 24 hr. The heterogeneous soln (white solid in a blue liquid) was poured into 20% KOH (1200 ml) and stirred for 1.5 hr in an ice bath. The soln was then diluted with water (2 l), stirred for an additional hour, and then filtered. Drying the white solid overnight *in vacuo* gave the ketal as a cream-colored solid (69 g, 100%), m.p. 163–166° (lit.[12b] m.p. 162.4–163°).

For (*S*)-**11** the homogeneous mixture was poured into 20% CH_3OH/KOH, and after 30 min, ice was added to precipitate the crude solid. The optically pure material showed: m.p. 130–131°, $[\alpha]_D^{20}$ ($CHCl_3$) −38.0°, {lit.[12c] m.p. 144–146°, $[\alpha]_D^{20}$ ($CHCl_3$) = −42.4°}.

Compound **13**.[25] The thioketal **11** (22.0 g, 57.3 mmol) was dissolved in CH_3OH (3200 ml) and water (400 ml), and to the vigorously stirred mixture were added $HgCl_2$ (22 g, 81 mmol) and yellow HgO (16.6 g, 77 mmol). The progress of the reaction was monitored by TLC (Et_2O, phosphomolybdic acid spray, starting material is blue with R_f 0.4 and product is much less intense with R_f 0.1), and the reaction was judged complete after 20 min. The soln was filtered through Celite and concentrated at *ca* 50–55° *in vacuo* until the volume was about 500 ml. The filtered Hg- salts were slurried with CH_2Cl_2 (3 × 300 ml), and this solvent was used for extraction of the product from the concentrated aqueous soln. Workup gave 15.4 g (88%) of the β-hydroxy ketone as a light yellow solid which was used directly in the next step, m.p. 173–176° (lit.[12b] m.p. 177.5–178.0°).

The optically pure material showed: m.p. 182–183°, $[\alpha]_D^{20}$ ($CHCl_3$) = +13.9° {lit.[12c] m.p. 182.5–184.0°, $[\alpha]_D^{20}$ ($CHCl_3$) = +14.0°}.

A slurry of the crude hydroxy ketone (15.4 g, 0.05 mol) from above in THF (500 ml) was cooled in dry ice for about 0.5 hr, and then potassium tri-sec-butylborohydride (100 ml of a 1M THF soln, 0.1 mol) was added dropwise over 0.5 hr. The soln was stirred for 1 hr at dry ice temp and then for 2 hr at room temp. The homogeneous yellow soln was cooled in ice, and 20% KOH (225 ml) was added cautiously, followed by dropwise addition of 30% H_2O_2 (48.6 ml). The soln was stirred at room temp for 1 hr, and then the excess peroxide was destroyed by addition of sodium thiosulfate. After concentration *in vacuo*, the aqueous soln was extracted with CH_2Cl_2 (3 × 200 ml). Workup and trituration with Et_2O gave a light yellow crystalline solid. This material was crystallized from CH_2Cl_2/Et_2O to give 13.7 g (89%) of diol, m.p. 125–126.5°.

The optically pure material showed: m.p. 141–143°, $[\alpha]_D^{20}$ ($CHCl_3$) = +5.3°; IR 3530 (br s), 3430 (br s), 1495 (s), 1280 (s, sh), 1275 (s), 1110 (s), 1095 (s), 1080 (s); ^{1}H-NMR (200 MHz, D_2O wash) 6.66 (s, 2H), 5.14 (br, 1H), 4.03 (s, 4H), 3.81 (s, 3H), 3.75 (s, 3H), 3.08 (dd, J = 17.7, 2.4 Hz, 1H), 2.65 (d, J = 17.7 Hz, 1H), 2.36 (d of t, J = 2.4, 2.4, 18.9 Hz, 1H), 1.92 (dd, J = 4.9, 18.9 Hz, 1H), 1.42 (s, 3H); exact mass for $C_{16}H_{22}O_6$ calc *m/e* 310.1416, obsd 310.1423.

Compound **14**.[25] A mixture of the diol **13** (20 g, 0.065 mol), imidazole (20 g, 0.29 mol), t-butyldimethylsilyl chloride (20 g, 0.13 mol) dissolved in dry DMF (200 ml) was stirred at 45° for 24 hr, after which time TLC (*ca* 80% Et_2O/H) showed no starting diol. The bulk of the DMF was removed at 45°/1 mm, and the residue was partitioned between CH_2Cl_2 (45 ml) and sat. $NaHCO_3$ (200 ml). Standard workup gave a thick oil which solidified to give the protected diol (27 g, 96%) which was used directly in the next step. The analytical sample of the material was obtained by recrystallization from CH_3OH/H_2O and showed: m.p. 106–107°; IR 3440 (m), 1600 (m), 1480 (s), 1465 (m), 1260 (s), 1075 (s), 1045 (m), 980 (m), 850 (m), 780 (m); ^{1}H-NMR (200 MHz) 6.7 (center of AB, J = 8.7 Hz, Δv = 21.4 Hz, 2H), 5.33 (unresolved t, 1H), 5.19 (s, 1H), 4.03 (s, 4H), 3.76 (s, 6H), 3.12 (dd, J = 2, 16 Hz, 1H), 2.70 (d, J = 16 Hz, 1H), 2.30 (d of poorly resolved t, J = 14 Hz, 1H), 1.81 (dd, J = 3.5, 14 Hz, 1H), 1.46 (s, 3H), 0.86 (s, 9H), 0.25 (s, 3H), 0.08 (s, 3H); exact mass for $C_{22}H_{36}O_6Si$ calc *m/e* 424.2281, obsd 424.2259.

The optically pure compound showed: m.p. 126–127°, $[\alpha]_D^{20}$ ($CHCl_3$) = +7.9°.

Compound **15**.[25,26] A slurry of protected diol, **14**, (14 g) and 1% KOH/CH_3OH (600 ml) was anodically oxidized using the macro Pt electrode and the Pt sheet anode in a thermostated cell held at *ca* 0° with a current of 1A. The reaction was followed by UV analysis at 290 nm, and the electrolysis was terminated after the initial optical density decreased to 1% of its initial value (*ca* 3 hr). The mixture was then neutralized with solid CO_2 and concentrated on the rotary evaporator. Concentration and drying of the product gave a quantitative yield of bisketal which was hydrolyzed directly to the monoketal. Recrystallization of a sample of the bisketal from Et_2O/H gave a white crystalline compound: m.p. 79–81°.

The optically pure compound showed: m.p. 103–104°; $[\alpha]_D^{20}$ ($CHCl_3$) = −18.7°; IR 3470 (s), 2960 (s), 2940 (s), 1110–1080 (vs, br), 1032 (s), 1042 (s), 985 (s); ^{1}H-NMR ($CCl_4 \cdot CH_2Cl_2$) 6.06 (s, 2H), 4.73 (distorted t, 1H), 4.58 (s, 1H), 3.87 (s, 4H), 3.12 (s, 3H), 3.09 (s, 3H), 3.06 (s, 6H), 1.8–2.3 (m, 3H), 1.43 (dd, J = 3, 14 Hz, 1H), 1.23 (s, 3H), 0.87 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR 139.8, 133.8, 132.5, 131.5, 111.8, 95.7, 95.2, 74.8, 65.3, 65.2, 63.9, 61.9, 51.2, 50.8, 50.4 (3 C), 34.8, 31.7, 25.9, 18.5, 17.9, −4.8, −4.7.

A −20° soln of 8% HOAc/acetone (75 ml: 300 ml) was added to the crude bisketal, and the homogeneous soln was stored at −20° for 48 hr. The soln was then poured into sat. $NaHCO_3$ (150 ml), and the majority of the acetone was removed on the rotary evaporator. The heterogeneous suspension was extracted with CH_2Cl_2 (2 × 250 ml), and the organic phase was washed with sat. $NaHCO_3$ (150 ml). The soln was dried and concentrated to give an amber oil which crystallized after being dried under vacuum. The sample was dissolved in boiling Et_2O (50 ml), and the Et_2O was replaced with low-boiling PE (50 ml). The material was allowed to crystallize at room temp to afford 9.5 g (64%) of monoketal (TLC and 300 MHz ^{1}H-NMR analysis showed that this was a 91 : 9 mixture of regioisomers), m.p. 108–110°, suitable for use in the coupling step. A pure sample of monoketal was obtained by careful recrystallization from EtOAc/H: m.p. 117–119°; IR 3480 (m), 1660 (s), 1090 (s), 1060 (s), 1045 (s); ^{1}H-NMR (80 MHz) 6.57 (AB q, J = 10 Hz, Δv = 27.5 Hz, 2H), 5.07 (distorted t, J ~ 2.6 Hz, overlapping s, 2H), 4.00 (s, 4H), 3.23 (s, 6H), 2.55 (AB q, Δv = 31 Hz, J = 19 Hz with lower field doublet having J = 1 Hz, 2H), 2.17 (d of distorted t, J = 19 Hz, 1H), 1.67 (dd, J = 3, 19 Hz, 1H), 1.41 (s, 3H), 0.84 (s, 9H), 0.26 (s, 3H), 0.13 (s, 3H); ^{13}C-NMR [$(CD_3)_2CO$] 183.7, 153.0, 144.5, 135.8, 132.3, 112.4, 95.5, 76.6 (2 C), 66.0, 64.0, 50.8, 34.6, 33.4, 26.1 (3 C), 18.9, 18.5, −4.6, −4.9 (1 C missing). (Found: C, 59.82; H, 8.21. Calc for $C_{22}H_{36}O_7$: C, 60.00; H, 8.18%).

The mother liquors were a mixture of regioisomeric monoketals which were used in the synthesis of 4-demethoxydaunomycinone with a 10–15% reduction in yield relative to the crystalline material.

Compound **17a**.[25] To a 0° soln of DMSO (52 ml) and THF (130 ml) was added dropwise CH_3Li (17 ml of a 1.6 M soln). After 5 min the cyanophthalide **2a** (4.3 g, 27.2 mmol) in DMSO (20 ml) was added over about 1 min. After stirring for 5 min, the soln was cooled to about −40°, and the monoketal **16** (10 g, 22.2 mmol) in THF (30 ml) was added rapidly via syringe. The soln turned black, then red, and finally a royal purple. The cooling bath was removed, and the mixture was stirred for 2 hr at room temp. After addition of 10% HCl (250 ml), the THF was removed on the rotary evaporator, and acetone (300 ml) was added. After stirring at 30° for 14 hr, the TLC (2% $CH_3OH/CHCl_3$) showed that deblocking of the t-butyldimethylsilyl group was complete, and the heterogeneous reaction soln was cooled in ice. The ppt was washed with water and dried to afford yellow microcrystalline solid (8.4 g, 87%, m.p. 228–234 °) which was used directly in the next step. The analytically pure compound was obtained by recrystallization from CH_2Cl_2: m.p. 243.5–244.5 °; IR 3500–3340 (br, m), 1671 (s), 1630 (s), 1595 (s), 1455 (s), 1432 (s), 1420 (s), 1382 (s), 1362 (s), 1255 (s), 1234 (s), 1067 (s), 1045 (s), 990 (s): ^{1}H-NMR (200 MHz) 8.47–8.35 (m, 2H), 7.85–7.79 (m, 2H), 5.08 (s, overlapping m, 2H), 3.75 (m, 4H), 3.56 (s, 3H), 2.89 (dd, J = 20, 2.6 Hz, 1H), 2.35 (d, J = 20 Hz, 1H), 2.0 (d of poorly defined t, J = 17 Hz, 1H), 1.45 (dd, J = 17, 5.6 Hz, 1H), 0.91 (s, 3H). (Found: C, 64.93; H, 5.16. Calc for $C_{23}H_{22}O_8$: C, 64.79; H, 5.16%).

The optically pure compound showed: m.p. 228–229.5° $[\alpha]_D^{20}$ = +25.4°.

Compound **18a**. A mixture of THF (500 ml) and concentrated HCl (135 ml) was cooled to 0°, and the tetracyclic ketal **17a** (8.4 g, 20 mmol) was added as a slurry in THF (500 ml). The ice bath was removed, and the soln was stirred at room temp for 12 hr. After addition of water (250 ml), the acid was neutralized with solid $NaHCO_3$. The layers were separated, and the THF layer was concentrated to a yellow mushy solid. The resulting solid was refluxed with CH_3OH, cooled, and filtered to afford a beautiful yellow–orange solid (7.8 g, 98%): m.p. 206–208°; ^{1}H-NMR (300 MHz) 13.8 (s, 1H), 8.24–8.21 (m, 2H), 7.78–7.72 (m, 2H), 5.27 (br d, 1H), 3.82 (s, 3H), 3.15 (dd, J = 18, 2 Hz, 1H), 2.94 (d, J = 18 Hz, 1H), 2.37 (s, 3H), 2.29 (d of poorly defined t, J = 15 Hz, 1H), 2.08 (dd, J = 5, 15 Hz, 1H). (Found: C, 64.99; H, 5.34.[28a] Calc for $C_{21}H_{18}O_7$: C, 65.96; H, 4.96%).

4-Demethoxydaunomycinone. A mixture of the tetracyclic ketone **18a** (10.0 g, 26 mmol) in CH_2Cl_2 (1 l) was cooled to −78°, and BCl_3 (200 ml of a 1M soln in CH_2Cl_2) was added over a period of about 5 min. The soln was stirred at this temp for 2.5 hr, and then CH_3OH (300 ml) was added. The soln was concentrated on the rotary evaporator until a red solid in a nearly colorless supernatant liquid (about 150 ml) resulted. This material was filtered, washed with CH_3OH, and dried to give an orange solid. The ^{1}H-NMR (300 MHz) spectrum of this solid showed a doubling of peaks as if some boron were still complexed to the molecule. The material was slurried in CH_3OH (500 ml), and the soln was heated to reflux for 2 hr. The soln was then cooled, filtered, and dried for 8 hr at 76° to give a bright red solid (9.5 g, 99%), showing a 500 MHz ^{1}H-NMR spectrum identical with that of an authentic sample. The m.p. of the product was variable and was not a good criterion for purity. Typically, the material had a two-degree m.p. in the range 146–150°. Slow recrystallization of the material from $CH_3OH/CHCl_3$ gave beautiful red crystals, m.p. 183–185° (lit.[12b] variable m.p.).

The optically pure compound[28] showed m.p. 182–188°, $[\alpha]_D^{20}$ ($CHCl_3$) = 148° (lit.[4b] $[\alpha]_D^{20}$ = 165°, lit.[12c] $[\alpha]_D^{20}$ = 164.5°, lit.[3a] $[\alpha]_D^{20}$ = 140°, lit.[27] $[\alpha]_D^{20}$ = 153°, showing spectroscopic properties identical to those reported previously).[15]

Compound **17b**. A soln of dry THF (10 ml) and dry DMSO (3 ml) was cooled to 0°, and CH_3Li (0.95 ml of a 1.6M soln in Et_2O) was added dropwise. The cloudy anionic soln was stirred for 5 min, and then 7 - methoxy - 3 - cyano - 1(3H) - isobenzofuranone[23] (0.285 g, 1.5 mmol) in DMSO (3 ml) was added. The resulting orange soln was stirred for 5 min, and crude **16** (530 mg, 1.25 mmol), dissolved in THF (5 ml), was added. The soln became dark purple after 1 min and was stirred at 0° for 0.5 hr and then at room temp for 1.25 hr. The reaction was quenched with 5% HCl (2 ml), concentrated *in vacuo*, and extracted with CH_2Cl_2 (3 × 45 ml). Workup and concentration afforded a semi-solid which was dissolved in acetone (35 ml) and 5% aqueous HCl (15 ml). After stirring at room temp for 1 hr, TLC (1% $CH_3OH/CHCl_3$) showed complete desilylation. Cold water (50 ml) was slowly added, and the soln was cooled to 0° and filtered to yield, after vacuum drying, 290 mg (57%) of a light orange solid, **17b** (m.p. 217–220°, with shrinking). The aqueous filtrate was extracted with CH_2Cl_2 (2 × 40 ml) and then purified by flash chromatography on a silica gel column (12 × 1.5 cm) with 2% CH_3OH/CH_2Cl_2 to yield an additional 55 mg of pure product, for a total yield of 345 mg (67%). An analytical sample was obtained by recrystallization from CH_2Cl_2/Et_2O to yield **17b** as orange needles: m.p. 220–222°, $[\alpha]_D^{20}$ ($CHCl_3$) = +25.0°; IR 3500–3380 (br s), 1680 (s), 1630 (s), 1590 (s), 1430 (br s), 1385 (br s), 1285 (s), 1230 (s), 1220 (s), 990 (s); ^{1}H-NMR (200 MHz), 14.03 (s, 1H), 7.93 (d, J = 8 Hz, 1H), 7.8 (t, J = 8 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 5.03 (m, 1H), 4.04 (s, 4H), 3.85 (s, 6H), 3.24 (dd, J = 2.2, 18.4 Hz, 1H), 2.78 (d, J = 18.4 Hz, 1H), 2.43 (d of distorted t, J

= 12.6 Hz, 1H), 1.95 (dd, J = 5.2, 12.6 Hz, 1H), 1.45 (s, 3H). (Found: C, 62.48; H, 5.35. Calc for $C_{24}H_{24}O_9$: C, 63.16; H, 5.26%).

Compound **18b**. To a stirred soln of **17b** (340 mg) and THF (110 ml) was added 30% aqueous HCl (50 ml). The soln was stirred at room temp for 42 hr, after which time TLC analysis showed no starting material. The mixture was extracted with CH_2Cl_2 (3 × 80 ml) and worked up as usual to give 300 mg of an orange solid. This was recrystallized from CH_3OH/Et_2O to yield 225 mg (73%) of **18b** as orange needles, m.p. 205–205.5°. The mother liquors were concentrated, and a second crop of orange needles (32 mg, m.p. 202.5–203.5°) was isolated for a total recrystallized yield of 257 mg (85%), $[\alpha]_D^{20}$ ($CHCl_3$) = +82°; IR 3550–3350 (br s), 1710 (s), 1665 (s), 1625 (s), 1585 (s), 1440 (s), 1385 (s), 1030 (s); ^{1}H-NMR (200 MHz) 14.1 (s, 1H), 7.92 (d, J = 8 Hz, 1H), 7.74 (t, J = 8 Hz, 1H), 7.34 (d, J = 8 Hz, 1H), 5.34 (m, 1H), 4.50 (s, 1H), 4.00 (s, 3H), 3.84 (s, 3H), 3.15 (br s, 1H), 3.19 (dd, J = 2.1, 18 Hz, 1H), 2.96 (d, J = 18 Hz, 1H), 2.40 (s, 3H), 2.37 (partially obscured d of distorted t, 1H), 2.09 (dd, J = 4.8, 15 Hz, 1H). (Found: C, 63.09; H, 5.12.[28a] Calc for $C_{22}H_{20}O_8$: C, 64.07; H, 4.85%).

(+)-*Daunomycinone*. A soln of **18b** (225 mg, 0.55 mmol) dissolved in CH_2Cl_2 (100 ml) was cooled to −78°, and BCl_3 (5.2 ml of a 1M soln in CH_2Cl_2) was added dropwise. The resulting purple soln was stirred at −78° for 20 min and then quenched with CH_3OH (5 ml). Concentration *in vacuo* gave a crude bright red solid which was dissolved in $CHCl_3$ and washed with water. Workup afforded a red solid which, upon recrystallization from hot CH_3OH with slow cooling, yielded 125 mg of beautiful dark red crystals, m.p. 210–212°. The mother liquors were chromatographed on silica gel (9 × 2 cm column, 1.5% $CH_3OH/CHCl_3$ as eluant) to yield 50 mg of red crystals, m.p. 211–212°. The total recrystallized yield was 175 mg (86%): m.p. 210–212° (lit.[29] m.p. 212–213°), $[\alpha]_D^{20}$ (dioxane) = +175.0° {lit.[29] $[\alpha]_D^{20}$ (dioxane) = +183.0°}.

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[10] B. L. Chenard, M. G. Dolson, A. D. Sercel and J. S. Swenton, *J. Org. Chem.* **49**, 318 (1984).

[11] A preliminary discussion of this synthesis of (±)-**13** was given in ref. 2.

[12] A related approach to a fully functionalized AB-ring segment was published while our work was in progress, [a] M. J. Broadhurst, C. H. Hassall and G. J. Thomas, *J. Chem. Soc.* Chem. Commun. 1958 (1982); [b] *Ibid.* Perkin Trans. I. 2239 (1982); [c] *Ibid.* 2249 (1982).

[13a] E. Vedejs, D. A. Engler and J. E. Telschow, *J. Org. Chem.* **43**, 188 (1978); [b] Oxidation of the thioketal linkage via hydroperoxide intermediates generated in the enolate oxygenation could be a problem in this reaction. However, the ester enolate appeared unreactive under our conditions.

[14] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1345 (1965).

[15] J. S. Swenton, D. K. Anderson, D. K. Jackson and L. Narasimhan, *J. Org. Chem.* **46**, 4825 (1981).

[16] An alternative procedure for obtaining *cis*-stereochemistry is to treat the *cis/trans*-diol mixture with phenyl boronic acid.[12c]

[17] The *trans*-isomer was not detected in the crude reaction mixture.

[18] The cyclic phenylboronate ester of **13**[12b] does not survive anodic oxidation in a single cell and thus was not further explored as a protecting group.

[19] E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.* **94**, 6190 (1972); K. K. Ogilive and D. J. Iwacha, *Tetrahedron Lett.* 317 (1973).

[20] The extent of regiocontrol of bisketal hydrolysis by an allylic oxygen substituent is dependent upon the nature of the group. This will be reported separately.

[21] Similar fractional crystallizations have proven successful in isolating other D-ring analogs of anthracyclinones employing this coupling.

[22] G. A. Kraus and H. Sugimoti, *Tetrahedron Lett.* 2263 (1978); G. A. Kraus, H. Cho, S. Crowley, B. Roth, H. Sugimoto and S. Prugh, *J. Org. Chem.* **48**, 3439 (1983).

[23] T. Li ahd Y. Wu, *J. Am. Chem. Soc.* **103**, 7007 (1981); B. A. Keay and R. Rodrigo, *Can. J. Chem.* **61**, 637 (1983).

[24] The following abbreviations have been used throughout the Experimental: n-BuLi, $CHCl_3$, cyclohexane, DMF, DMSO, EtOH, Et_2O, hexanes (H), HCl, lithium diisopropylamide, CH_3OH, CH_2Cl_2, petroleum ether (PE), THF. All m.ps below 220° were taken with a Thomas-Hoover capillary m.p. apparatus and are uncorrected. Measurements with standard samples indicate that the reported m.ps are probably 1–2° lower than the correct value. M.ps greater than 220° were recorded on a hot-stage apparatus. IR spectra were taken primarily on a Perkin-Elmer Model 283B grating spectrometer with some spectra being recorded on a Perkin-Elmer Infracord spectrometer. ^{1}H-NMR spectra were recorded at 90 MHz in $CDCl_3$ unless otherwise noted. Apparent multiplicities are reported, and in some cases, signals reported as triplets are in fact closely

spaced doublet of doublets. ^{13}C-NMR spectra (TMS reference) were recorded on a Bruker WP-80 instrument at 20 MHz in $CDCl_3$. The 200- and 300-MHz ^{1}H-NMR spectra were recorded by Mr. C. Engelman and Dr. G. Larson. Mass spectra and exact mass measurements were obtained by Mr. C. R. Weisenberger on a Kratos MS-30 mass spectrometer connected to a DS-55 data system. UV spectra were recorded on a Carey Model 15 instrument. The maxima are reported in nanometers with the extinction coefficients in parentheses. Rotations were obtained on a Perkin-Elmer Model 241 Polarimeter in the indicated solvent. Concentrations were 1 g/100 ml for bicyclic molecules and 0.1 g/100 ml for tetracyclic systems. THF was freshly distilled from benzophenone/Na prior to use. All other solvents used for reactions were freshly dried and distilled. All reactions were run under N_2 or argon atmosphere. Analytical samples were analyzed by Scandinavian Microanalytical Laboratory. Aluminum oxide and silica gel were from E. Merck Co. "Workup as usual" consisted of extraction of the product (CH_2Cl_2 or Et_2O), drying over $CaSO_4$ or Na_2SO_4, and concentration *in vacuo*, followed by drying under vacuum.

[25] The experimental procedure and yield for the optically active system was essentially identical to that reported for the racemic compound.

[26] For complete details on the electrochemical oxidations, see D. R. Henton, R. L. McCreery and J. S. Swenton, *J. Org. Chem.* **45**, 369 (1980).

[27] S. Terashima, N. Tanno and K. Koga, *Tetrahedron Lett.* **21**, 2749, 2753 (1980).

[28a] Two combustion analyses on different samples gave essentially identical results which were outside of acceptable limits for **18a** and **18b**. The analysis is within experimental error for the demethylation compound, and perhaps this accounts for the error in these two analogous systems. [b] Optical rotations are not totally reliable criteria for optical purity (ref. 27). Dr. W. Priebe has coupled our (+)-4-demethoxydaunomycinone to 3,4 - di - O - acetyl - 2,6 - dideoxy - α - L - *lyxo* - hexapyranosyl chloride and did not observe any diastereomeric coupling product in which 5% could have been detected. We thank Dr. Priebe for informing us of this result.

[29] F. Arcamone, G. Cassinelli, G. Franceshi, R. Mondelli, P. Orezzi and S. Penco, *Gazz. Chim. Ital.* **100**, 949 (1970).