Highly Effective Asymmetric Synthesis of 11-Deoxydaunomycinone and Analogues[1]

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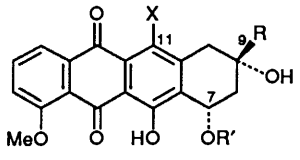
Optically active 11-deoxydaunomycinone and its 9-hydroxymethyl analogue were synthesized in ⩾95% e.e. by means of tandem Michael/Diels–Alder reaction as a key step in the tetracycle's formation. As a reagent, a chiral pentadienyltin was prepared without loss of optical purity from ethyl 2-[(*S*)-1-hydroxyethyl]pent-4-enoate, which was obtained in 97% e.e. by reduction (yeast) of the corresponding acetoacetate derivative. The chirality on the tin reagent was transferred to the C-9 of 11-deoxydaunomycinone *via* diastereoselective epoxidation in high efficiency. For the synthesis of the 9-hydroxymethyl analogue of 11-deoxydaunomycinone, enantioselective epoxidation was applied to the allylic alcohol moiety of the tetracyclic quinonoid compound to afford the corresponding optically active epoxide in high chemical and optical yield. Success in this highly efficient and enantioselective epoxidation was attributed to the protection of the phenolic hydroxy group in the substrate from competitive co-ordination to the Sharpless reagent.

Anthracyclines have been attracting considerable attention on account of their marked antitumour activities and characteristic linear, tetracyclic quinonoid skeletons. Therefore, a number of studies on their synthesis[2] and mechanism of action[3] have been made over more than a decade. In recent years, special interest has focused on the development of more active but less toxic anthracyclines; of these, 11-deoxyanthracyclines (*e.g.*, 11-deoxydaunomycin **1a**, 11-deoxyadriamycin **2a**, aclacinomycins, and nogalamycins) are considered promising.[4]

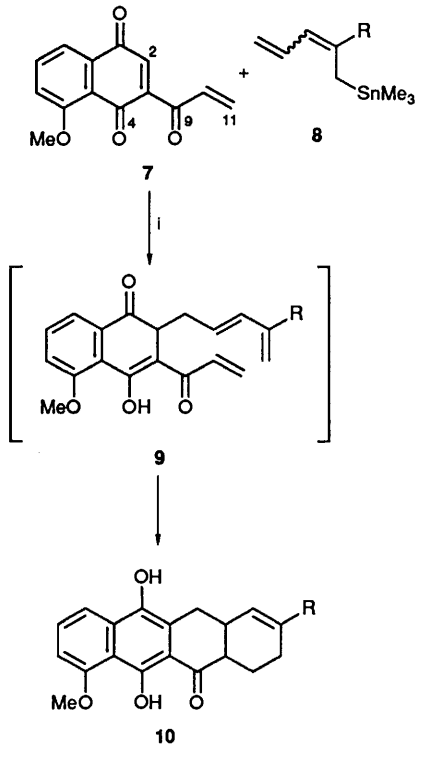


1 X = H, R = Ac (**a**; 11-Deoxydaunomycin)
2 X = H, R = $COCH_2OH$ (**a**; 11-Deoxyadriamycin)
3 X = H, R = CH_2OH
4 X = OH, R = Ac (**a**; Daunomycin)
5 X = OH, R = $COCH_2OH$ (**a**; Adriamycin)
6 X = OH, R = CH_2OH
a; R′ = Daunosaminyl
b; R′ = H

In spite of such importance, however, only a limited number of asymmetric syntheses have been reported,[5,6] Most of them include an inefficient optical-resolution step in the total synthesis. Thus, most of the reported methods concerning the racemic tetracycles are not adaptable enough to be extended to their asymmetric synthesis.

In our previous reports[7] we have described a novel and convenient method for the construction of the tetracyclic skeleton of 11-deoxyanthracyclinones; tandem Michael/Diels–Alder reaction, which consists of the initial Michael addition of a pentadienyltin (PDT) **8** to an acryloylquinone **7** nucleus and the subsequent and spontaneous intramolecular Diels–Alder cyclisation (Scheme 1). The keys to our efficient synthesis are the highly regioselective preparation of various 2-substituted PDTs **8**[8] and their well controlled reaction with quinone **7**. Therefore, various side-chains at the 9- position of the anthracyclinone moiety can be easily introduced to the tetracyclic framework from the tin reagent.

This success encouraged us to pursue the asymmetric synthesis. We planned to prepare a PDT bearing an optically

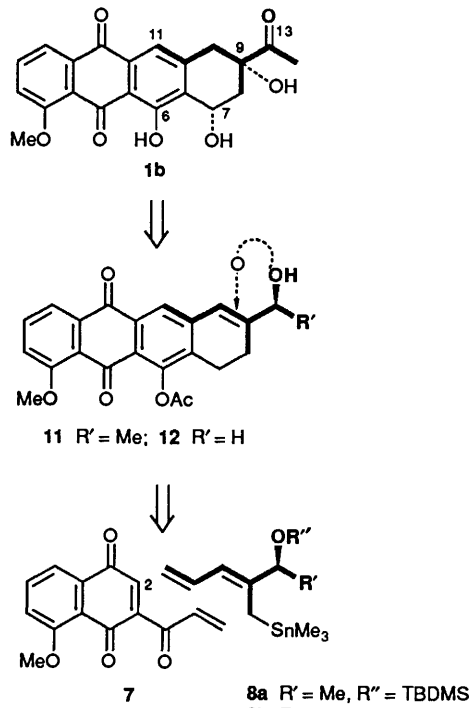


Scheme 1 Tandem Michael/Diels–Alder reaction. *Reagent:* i, $(Pr^iO)_3$-TiCl

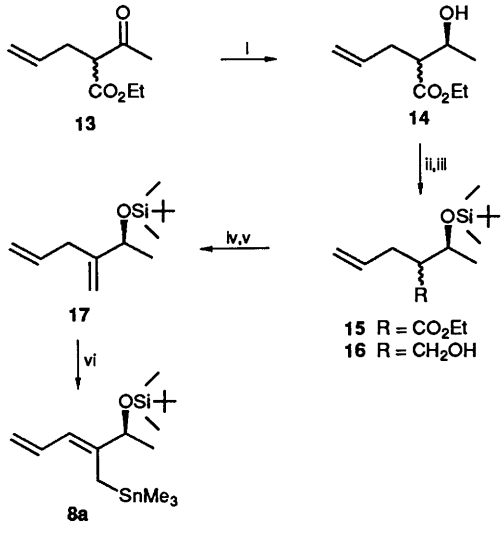
active carbon, and then to obtain the chirality at C-9 of 11-deoxydaunomycinone **1b** transferred from the oxygen functionality at C-13 on the side-chain, which would be derived from the substituent on the PDT (Scheme 2).

To realise this chirality transformation, the Sharpless diastereoselective[9] and enantioselective[10] epoxidations of allylic alcohols would be the most powerful tools, as is generally recognised. Both epoxidations would allow the chirality to be introduced to the tetracyclic quinonoid system at as late a step as possible (Scheme 2). Thus, the strategy is advantageous in respect of prevention of racemisation.

However, in previous examples[5c,6a] of the epoxidation of analogous tetracyclic quinonoid compounds, high enantiomeric excess (e.e.) was not attained; a couple of successful examples



Scheme 2



Scheme 3 Preparation of optically active PDT. *Reagents and conditions:* i, Baker's yeast; ii, Bu^{t}Me$_2$SiCl, imidazole, DMF; iii, DIBAL, hexane, 91% from compound **14**; iv, *p*-TsCl, pyridine, CH_2Cl_2; v, NaI, DMF, then DBU, 60% from compound **16**; vi, Bu^{t}OK, Bu^{n}Li, hexane, then Me_3SnCl in THF, 80%.

have been reported only in the epoxidation of bicyclic AB-ring synthons.[6c–e] Therefore, this was a challenging problem. We decided not to adopt a kinetic resolution method, but to adopt diastereoselective epoxidation of the optically active allylic alcohol **11** and enantioselective epoxidation of the appropriate *primary* alcohol **12** to eliminate the expected difficulty.

In this article, we give full details of this chemistry; the preparation of the highly optically active PDT as a key reagent, a successful asymmetric epoxidation of tetracyclic quinones, and a synthesis of optically active 11-deoxyanthracyclinones.

Results and Discussion

Preparation of an Optically Active PDT.—The first problem was how to prepare the optically active PDT as a chiral building block in high enantiomeric purity. Since simple 2-substituted PDTs were regioselectively prepared from the corresponding 2-substituted penta-1,4-dienes,[8] the chiral route can also follow this strategy.

As a chiral starting compound, we chose the easily accessible ethyl 2-[(*S*)-1-hydroxyethyl]pent-4-enoate **14**, which can be obtained by the reduction (yeast)[11] of the keto group of ethyl 2-acetylpent-4-enoate **13** (Scheme 3). The enantiomeric purity at the resulting alcoholic carbon of compound **14** was extremely high (see later) and its absolute configuration * was that desired (*S*), required for the natural anthracyclinone synthesis.

Protection of the hydroxy group was important for completion of the successive reaction. The protecting group should be inert under both anionic and Lewis acidic conditions and also capable of being removed specifically while keeping the optically active carbon intact. The t-butyldimethylsilyl (TBDMS) group was found to be the best choice on the whole. The siloxy ester **15** was then reduced to the corresponding siloxy alcohol **16** by diisobutylaluminium hydride (DIBAL) without cleavage of the silyl ether. Reduction by lithium aluminium hydride gave rise to deprotection of the silyl ether to some degree.

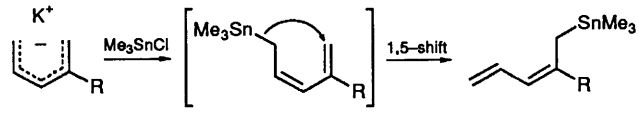
The chiral 1,4-diene **17** was obtained from ester **15** in 54% overall yield by application of the method of Wolff *et al.*[13] to the derived alcohol **16**; tosylation, iodination and dehydroiodination. The optical purity of compound **17** was determined to be as high as 97% from the ^{1}H NMR spectrum of the corresponding methoxy(trifluoromethyl)phenylacetic (MTPA) ester.

The optically active PDT **8a** could be prepared by trapping of the corresponding alkali metal salt of siloxy alkene **17** with Me_3SnCl. Initial attempts to prepare the pentadienyl salt with BuLi in tetrahydrofuran (THF) were found to be unsuccessful. A considerable amount of diene **17** was recovered, in spite of the applicability of the reaction conditions to other simple 1,4-dienes, presumably owing to the severe steric hindrance of the bulky protecting group.† Treatment of diene **17** with a stronger base, a Bu^{t}OK–BuLi mixture,[14] which is kinetically more favourable for anion formation, instantly afforded an orange precipitate of the corresponding potassium salt in hexane. It was quenched by Me_3SnCl in THF at −78 °C to give the 2-substituted (+)-(*S*)-(*Z*)-penta-2,4-dienyltin **8a** almost exclusively‡ among the four possible regio- and stereo-isomers in *ca.* 80% yield. Moreover, the high optical purity (≥95% e.e.) was preserved, fortunately even after such strongly basic conditions,§ as shown later. The PDT **8a** was used without

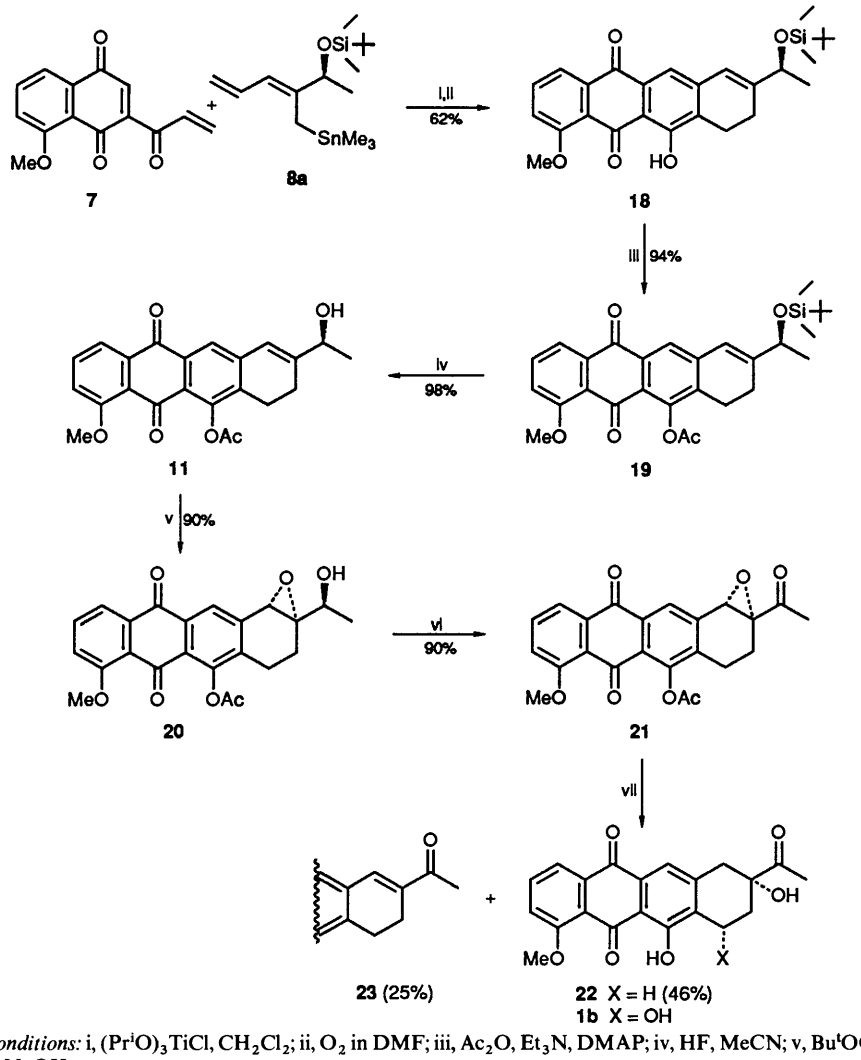
* The absolute configuration and the high enantiomeric purity were predicted from Prelog's rule: ref. 12.

† Protection by a methyl group instead of TBDMS did not interfere with the deprotonation.

‡ This high regio- and stereo-selectivity is explained by the conformation (U-shape for the potassium salts) of the pentadienyl anion and the 1,5-shift of the Me_3Sn group. On the other hand, when the same potassium salt was quenched by Me_3SiCl, a 4-substituted (*Z*)-pentadienylsilane was obtained exclusively. See refs. 7 and 8.



§ Allylic ethers are known to be easily deprotonated at their allylic position: see ref. 15.



Scheme 4 *Reagents and conditions:* i, $(Pr^iO)_3TiCl$, CH_2Cl_2; ii, O_2 in DMF; iii, Ac_2O, Et_3N, DMAP; iv, HF, MeCN; v, Bu^tOOH, $VO(acac)_2$, CH_2Cl_2; vi, PDC; vii, aq. $Na_2S_2O_4$, NaOH

purification owing to its sufficient purity and thermal instability upon distillation.

Synthesis of Optically Active 11-*Deoxydaunomycinones.*—The tandem Michael/Diels–Alder reaction between the acryloylquinone **7** and the chiral PDT **8a** proceeded without difficulty by the use of $(Pr^iO)_3TiCl$ as a Lewis acid. The chemo-, site-, regio- and stereo-selectivities were also high* like those observed in the reported reactions between compound **7** and simpler PDTs.[7c] The yield was good (62%) in two steps after aerial oxidation[7c,16] to afford the tetracyclic quinone **18** (Scheme 4).

The phenolic hydroxy group of compound **18** needed to be protected because the presence of an unprotected hydroxy group impairs the efficiency of the epoxidation in terms of both chemical and optical yield.[5c,6a] Acetylation of compound **18** with a mixture of acetic anhydride, triethylamine and 4-(dimethylamino)pyridine (DMAP) gave ester **19**. Acid-catalysed acetylation was unsuitable here owing to the cleavage of the silyl ether and racemisation.

Desilylation with dil. hydrofluoric acid in acetonitrile at 0 °C gave the highly optically active alcohol **11** in 98% chemical and 95% optical yield, determined as the corresponding MTPA ester. Higher reaction temperature and/or prolonged reaction time gave rise to partial racemisation, because of the ready formation of the stable allylic cation at C-13 under acidic conditions. Desilylation with tetrabutylammonium fluoride (TBAF) was so slow as to result in competing deacetylation because of its strong basicity.

Diastereoselective epoxidation of the tetracyclic quinonoid compound **11** according to the Sharpless method,[9] Bu^tOOH–$VO(acac)_2$, gave only one diastereoisomeric isomer of the corresponding epoxide **20**, detected by means of NMR spectroscopy. This indicates complete transfer of the chirality from C-13 to C-9. In a similar asymmetric epoxidation, the reverse combination of reagent–substrate, *i.e.* chiral reagent and racemic alcohol, was reported to give moderate optical purity (56% e.e.).[6a] This may be due to insufficient difference in the reactivity between the two enantiomeric alcohols in the kinetic resolution.

The alcoholic moiety of the epoxide **20** was then oxidised to give the corresponding ketone **21** by pyridinium dichromate (PDC)[17] followed by reductive oxirane-ring opening under

* Chemoselectivity (Michael addition *vs.* intermolecular Diels–Alder cyclisation) is explained by the preferable *s-trans*-conformation of compound **8a**. From this conformation, the successive Diels–Alder reaction is not capable of proceeding. Site-selectivity of the nucleophilic addition to the acryloylquinone **7** is understood by the molecular orbital theory (Hückel calculation): the LUMO of compound has its largest coefficient at C-2 on the quinone nucleus. This tendency is enhanced by the chelation of the Lewis acid between the C-4 and C-9 carbonyls of compound **7**. The position C-11 on the acryloyl moiety, which is also expected to be a Michael acceptor, has a much smaller LUMO coefficient.

alkaline conditions[6a] to afford (*R*)-7,11-dideoxydaunomycinone **22**. At the latter reduction step, the dehydration product **23** was also formed.* Since the stereoselective introduction of the 7-OH group has already been established,[19] the total synthesis of the natural enantiomer of **1b** was completed.

Synthesis of Optically Active 11-Deoxydaunomycinone Analogues.[20]—The other attempt to acheive an efficient asymmetric synthesis of 11-deoxyanthracyclinones was the use of the primary allylic alcohol **12** as a substrate for enantioselective epoxidation avoiding kinetic resolution. The target compound in this synthesis was the 11-deoxydaunomycinone analogue **3b**, whose 11-oxy congener **6b** was reported by Arcamone[21] as the aglycone of the anthracycline **6a** possessing almost the same antitumour activity as the parent daunomycin **4a**.

Since we have already synthesized the racemic methyl ether **31** of **3b**,[7c] we employed the tetracyclic quinone **24** as the starting material in the present asymmetric synthesis (Scheme 5).

The first problem we had to solve here was selective demethylation† of the allylic methyl ether in the presence of the aryl methyl ether. Since the allylic ether was assumed to be more reactive than the other methyl ether, a nucleophile would preferentially attack the allylic carbon rather than the methyl carbon on acid catalysis.

Acetic anhydride in the presence of an acid catalyst can transform the ether to the allylic acetate. Some Lewis acids and protic acids were examined, and showed that the allylic ether was cleaved while the aryl methyl ether was left intact (Table 1). When the applied acid had a nucleophilic counteranion such as Cl^- in $FeCl_3$, the desired acetate **25** was accompanied by the corresponding allylic chloride **26**. Consequently, perchloric acid as a non-nucleophilic acid gave the best results, to afford acetate **25** in 85% yield. To be advantageous to the following epoxidation, the phenolic hydroxy group at C-6 was also acetylated at the same time.

The second problem was selective deacetylation of the allylic acetate at C-13 without deacetylation at C-6. After several attempts under various reaction conditions, acid-promoted ester exchange in methanol–acetone was the best choice to give the monoacetyl allylic alcohol **12** in 91% yield, while basic hydrolysis afforded the completely deacetylated product **27**.

Since we could obtain the suitable substrate **12**, it was subjected to Sharpless asymmetric epoxidation.[10] As expected, the reaction proceeded well with remarkably high optical (96% e.e.) and chemical (80%) yields to afford the epoxide **28** by employing (+)-diethyl tartrate (1.2 mol equiv.), $(Pr^iO)_4Ti$ (1.0 mol equiv.) and Bu^tOOH (2.2 mol equiv.) at −20 °C.

Table 1 Effect of acids on the demethylative acetylation of compound **24**[a]

Acid	Isolated yield (%)	
	25	**26**
BF_3·Et_2O	No reaction	
$FeCl_3$	49	28
$Fe(ClO_4)_3$·$6H_2O$	53	0
$MeSO_3H$	No reaction	
H_2SO_4	54	0
$HClO_4$	82	0

[a] All reactions were performed with an equimolar acid and substrate **24** in CH_2Cl_2–Ac_2O (1:1) at 0 °C.

The e.e. of epoxide **28** was also determined from analysis of the corresponding MTPA ester. As reported previously, the hydroxy group at C-6 inhibited the epoxidation almost completely, when diol **27** was subjected to reaction. Even a large excess of the reagents (5–10 mol equiv.) gave only a trace amount of the tetraol (two OH groups in ring A) **32** estimated by NMR spectroscopy after prolonged reaction period.

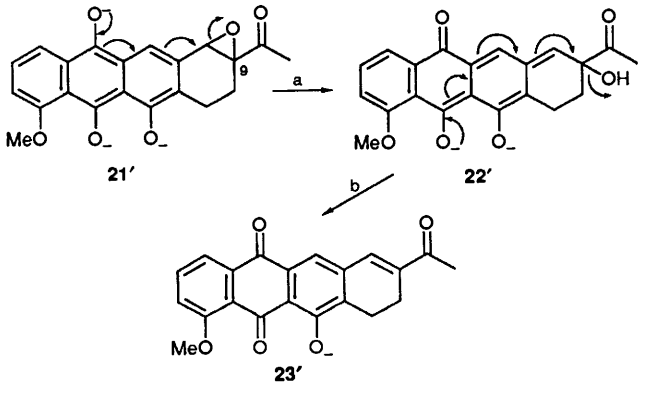
Reductive oxirane-ring opening of compound **28** was performed by treatment with alkaline $Na_2S_2O_4$[6a] to yield a (−)-(*R*)-7,11-dideoxydaunomycinone analogue, triol **29**. The acetate moiety was concomitantly hydrolysed to yield the free phenol, which was necessary this time for the introduction of the hydroxy group at C-7. The generally applied method,[5c,7c,22] catalytic hydrogenation in the presence of triethanolamine, gave a complex mixture.

For the stereoselective introduction of the 7-OH group by the bromination–alkaline hydrolysis sequence, it is considered that the 9-OH group plays an important role in determining the stereochemistry of the incoming 7-OH group presumably by means of hydrogen bonding. Therefore, the extra hydroxy group on the side-chain should be protected in order not to reduce the stereoselectivity.

When the hydroxy group on the side-chain was protected as the trifluoroacetate (compound **30b**) the stereoselectivity of hydroxylation at C-7 was decreased to give a considerable amount of the 7,9-*trans*-diol (*cis*:*trans* 3:1).‡ Because the trifluoroacetate was easily hydrolysed under the applied aqueous alkaline conditions, the regenerated hydroxy group at C-13 directed the 7-OH group to approach from the opposite direction. On the other hand, siloxy diol **30c** protected by an alkaline-proof TBDMS group showed a lower yield owing to the poor solubility of the corresponding bromide in the aqueous solution used for hydrolysis.

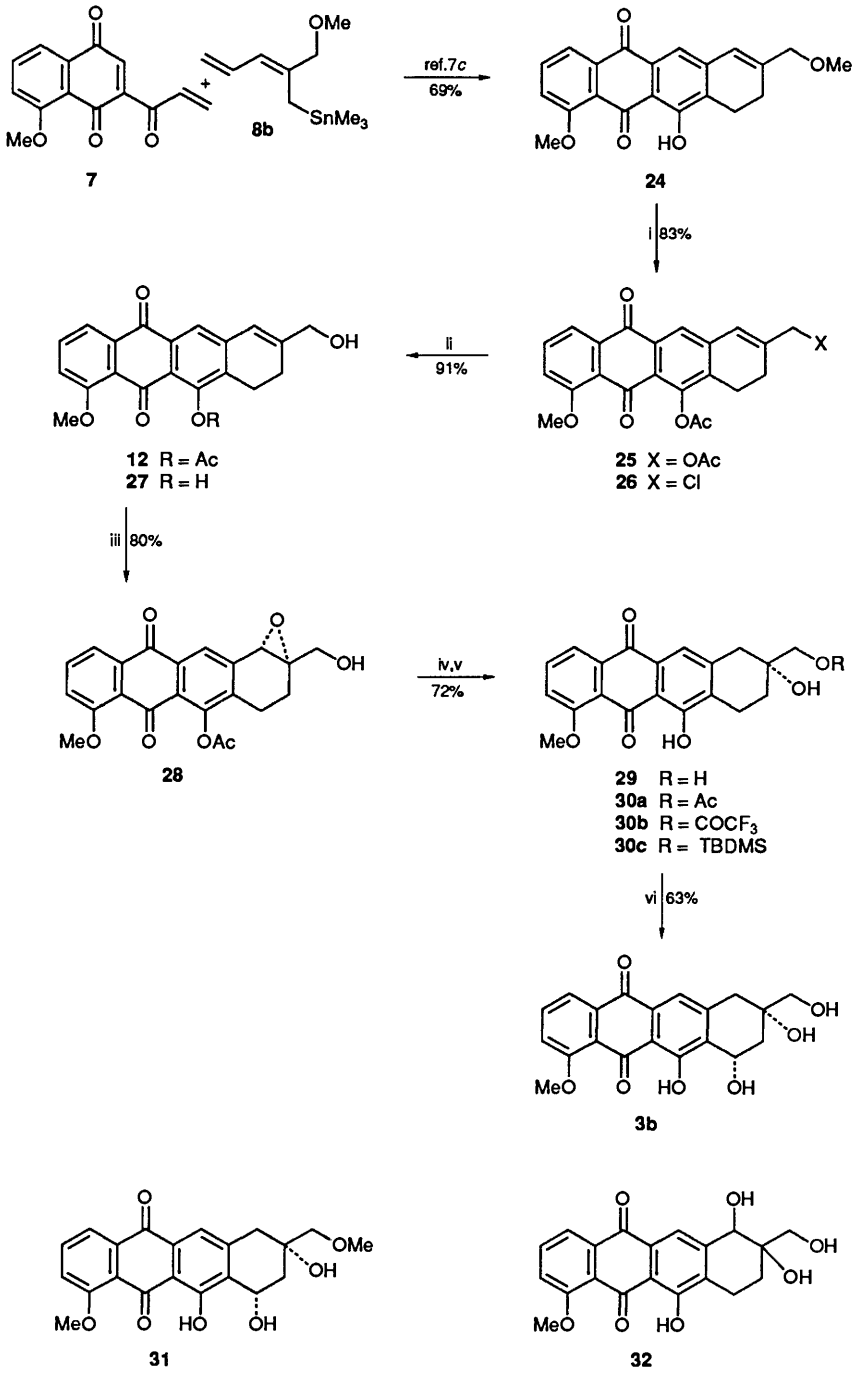
After all this, acetyl protection resulted in excellent stereoselectivity. The usual acetylation method, acetic anhydride and pyridine, was applied to triol **29** to afford acetate **30a** as the sole product, which was exposed to the bromination–hydrolysis sequence. To optimise the reaction, the control of the stoichiometry by Br_2 was delicate; 1.75–2.0 mol equiv. of Br_2 gave the best yield of tetraol **3b**. A smaller amount of Br_2 left some of the acetate **30a** unchanged and a larger amount of Br_2 halogenated both of the benzylic positions, C-7 and C-10. The highly enantiomeric 11-deoxydaunomycinone analogue [(+)-

* This unfavourable dehydration may be due to the inductive effect of the acetyl group at C-9. Reductive oxirane-ring opening would proceed *via* path *a* to afford the intermediate **22′**, which would protonate to give compound **22**. However, the acetyl group promoted the further reaction *via* path *b* (S_N2-like) to give the dehydration product **23′**. Concerning rate enhancement by electron-withdrawing groups in S_N2 reactions, see ref. 18.



† Although the methyl ether as a protecting group is the most stable and withstands deprotection, utilisation of more easily removed protecting groups (*e.g.*, methoxymethyl, t-butyl and TBDMS, which was successful in PDT **8a**) was unsuccessful because the corresponding PDT reagents were incapable of being prepared in sufficient yield. This is presumably due to the instability of the corresponding pentadienyl anions.

‡ In feudomycinone syntheses, excellent stereoselectivity has been obtained by the use of trifluoroacetate; see refs. 7*c* and 23.



Scheme 5 *Reagents and conditions:* i, Ac_2O, $HClO_4$, CH_2Cl_2; ii, H_2SO_4, MeOH–acetone; iii, Bu^{t}OOH, $(Pr^iO)_4Ti$, (+)-diethyl tartrate; iv, aq. $Na_2S_2O_4$, NaOH; v, Ac_2O, pyridine; vi, Br_2, CCl_4, then aq. NaOH

3b] was thus obtained stereoselectively in 63% yield from triol **29** and in 27% total yield from the tetracyclic quinone **24**.

Having applied the tandem Michael/Diels–Alder reaction, highly optically active 11-deoxyanthracyclinones were synthesized successfully. This strategy makes the best advantage of PDT reagents: easy access to functionalised PDTs, highly regioselective preparation of 2-substituted PDTs, and highly controlled reaction toward the acryloylquinone. In particular, a chiral group could be introduced on the pentadienyl moiety with high enantiomeric purity. This evidence emphasises those PDT reagents capable of more versatile application.

The chirality originally produced by the yeast reduction was brought into the anthracyclinone skeleton through PDT as a chiral reagent without any loss of its optical purity, and then was transferred to C-9 of the anthracyclinone *via* Sharpless epoxidation with excellent efficiency even in the tetracyclic quinonoid system. Similarly, enantioselective epoxidation of the suitable tetracyclic quinone was also found to be very effective. In such a procedure, intra- and inter-molecular chirality transfer was performed at a later step in the synthesis. This is advantageous in respect of prevention of racemisation. Therefore, the present method is one of the most promising routes to optically active 11-deoxyanthracyclinones.

Experimental

Experimental protocols are shown in the previous paper.[7c] NMR *J*-values are given in Hz. Optical rotations were recorded on a JASCO DIP-181 polarimeter. Hexane was distilled from lithium aluminium hydride and stored over

sodium wire. Baker's yeast was purchased from Oriental Yeast Co.

Ethyl 2-[(S)-1-*Hydroxyethyl*]*pent*-4-*enoate* **14**.—Keto ester **13** (5.0 g, 29.4 mmol) was added to a stirred mixture of baker's yeast (100 g), sucrose (20 g), and water (500 cm^3) at 30–35 °C. Further aliquots of sucrose (20 g) were added every 6 h during 2 days. After filtration of the mixture through Celite, the filtrate, saturated with NaCl, was extracted with diethyl ether. The extract was dried and the solvent was removed. The residual liquid was purified by distillation to give hydroxy ester **14** (3.0 g, 60%) as a diastereoisomeric mixture (*ca.* 6:4), liquid; b.p. 73–75 °C/2 mmHg; ν_{max}(neat)/cm^{-1} 3400, 1720 and 1640; $\delta_H(CDCl_3)$ (major diastereoisomer) 1.20 (3 H, d, *J* 6.4), 1.24 (3 H, t, *J* 7.0), 2.35–2.50 (4 H, m, overlapped), 3.90 (1 H, quintet, *J* 6.4), 4.14 (2 H, q, *J* 7.0), 5.00 (1 H, br d, *J* 10.1), 5.06 (1 H, br d, *J* 17.1) and 5.72 (1 H, ddt, *J* 17.1, 10.1 and 6.7); (minor diastereoisomer) 1.18 (3 H, d, *J* 6.4), 1.23 (3 H, t, *J* 7.0), 2.35–2.50 (4 H, m, overlapped), 3.97 (1 H, quintet, *J* 6.4), 4.13 (2 H, q, *J* 7.0), 4.98 (1 H, br d, *J* 10.1), 5.05 (1 H, br d, *J* 17.1) and 5.76 (1 H, ddt, *J* 17.1, 10.1 and 6.7).

2-[(S)-1-(*t-Butyldimethylsiloxy*)*ethyl*]*pent*-4-*enol* **16**.—To a dimethylformamide (DMF; 15 cm^3) solution of the optically active hydroxy ester **14**[11] (5.50 g. 32 mmol) at 0 °C were added t-butyldimethylsilyl chloride (5.24 g, 35 mmol) and imidazole (4.58 g, 67 mmol). The solution was gradually warmed and stirred at 40 °C overnight. After the mixture had been poured into water–hexane and shaken, the organic phase was separated and the aqueous phase was extracted again with hexane. The combined organic phases were treated as usual to afford siloxy ester **15** as a liquid, which was subjected immediately to the next reduction.

To a solution of ester **15** in dry hexane (50 cm^3) at 0 °C was added a 1 mol dm^{-3} hexane solution of DIBAL (75 cm^3) through a dropping funnel during 1 h under nitrogen and the resulting solution was stirred for an additional 4 h at the temperature. After the consumption of the ester was confirmed (IR spectroscopy), the reaction was quenched by addition of methanol (10 cm^3) and water (5 cm^3) to give precipitates which were filtered off through Celite. The filter was washed with diethyl ether and methanol. The combined filtrate and washings were concentrated under reduced pressure and partitioned between diethyl ether and brine. After the usual treatment, alcohol **16** (7.10 g, 29 mmol) was obtained as a liquid.

2-[(S)-1-(*t-Butyldimethylsiloxy*)*ethyl*]*penta*-1,4-*diene* **17**.—The optically active alcohol **16** (7.10 g) was dissolved in dichloromethane (30 cm^3) and toluene-*p*-sulphonyl chloride (7.97 g, 42 mmol) and pyridine (4.6 cm^3, 58 mmol) were added to the solution at 0 °C. After the mixture had been swirled, it was kept overnight at −20 °C and diethyl ether and water were added. The organic layer was washed successively with 5% aq. HCl, saturated aq. $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and the solvent was evaporated off to give the corresponding sulphonate.

A mixture of the sulphonate and NaI (10.87 g, 72.5 mmol) in DMF (60 cm^3) was stirred under N_2 for 5 h at *ca.* 55 °C, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (6.5 cm^3, 43 mmol) was added to the mixture which was then stirred for an additional 3 h at *ca.* 85 °C before being poured onto ice and extracted with hexane (×3), and the combined extracts were washed successively with 5% aq. HCl and saturated aq. $NaHCO_3$, and treated as usual. The residue was purified by distillation (Kugelrohr) to afford the optically active 1,4-diene **17** (3.91 g, 17.3 mmol) as a liquid in 60% yield from *alcohol* **16**; b.p. 113–117 °C/17 mmHg (Found: M^+, 226.1746. $C_{13}H_{26}OSi$ requires M, 226.1753); $[\alpha]_D^{24}$ +21° (*c* 1.1, CCl_4); ν_{max}(neat)/cm^{-1} 1825m and 1640; $\delta_H(CDCl_3)$ 0.03 (3 H, s, diastereotopic Me on Si), 0.05 (3 H, s, diastereotopic Me on Si), 0.89 (9 H, s, Bu^t), 1.22 (3 H, d, *J* 6.4), 2.74 (1 H, dd, *J* 16.5 and 7.3), 2.84 (1 H, dd, *J* 16.5 and 6.4), 4.25 (1 H, q, *J* 6.4), 4.75 (1 H, s), 5.04 (1 H, s), 5.03–5.08 (2 H, m) and 5.82 (1 H, dddd, *J* 17.1, 10.4, 7.3 and 6.4).

The enantiomeric purity of product **17** was determined as follows. The silyl protecting group was cleaved by TBAF in THF to give the corresponding alcohol, which was converted into the (*R*)-MTPA ester by reaction with the MTPA chloride and pyridine. The ratio of the MTPA esters (^{1}H NMR) was [(*S*)-**17**; δ_H 1.44 (d, *J* 6.4)]:[(*R*)-**17**; δ_H 1.38 (d, *J* 6.7)] 98.5:1.5.

Optically Active PDT **8a**.—To a suspension of Bu^tOK (350 mg, 3.1 mmol) and BuLi (1.4 mol dm^{-3} in hexane; 2.2 cm^3, 3.1 mmol) in dry hexane (10 cm^3) at 0 °C was added diene **17** (226 mg, 3.0 mmol) dropwise under nitrogen immediately to yield a reddish brown precipitate of the corresponding anion salt. After the solvent had been replaced by THF (10 cm^3), the resulting dark red solution was cooled to −78 °C and treated with a solution of Me_3SnCl (598 mg, 3.0 mmol) in THF (2 cm^3), whereupon it turned pale yellow. After being stirred for 30 min, the solution was poured into water and extracted with diethyl ether (×3). The combined extracts were treated as usual to give the PDT **8a** (950 mg, 80%), which was employed immediately in the following tandem Michael/Diels–Alder reaction without purification owing to its sufficient purity and its instability: $[\alpha]_D^{24}$ +79° (*c* 1.98, CCl_4); ν_{max}(neat)/cm^{-1} 1795m, 1635 and 1600; $\delta_H(CDCl_3)$ 0.03 (3 H, s, diastereotopic Me on Si), 0.05 (3 H, s, diastereotopic Me on Si), 0.12 (9 H, s, J_{HSn} 51 and 53), 0.90 (9 H, s), 1.22 (3 H, d, *J* 6.4), 1.83 (1 H, d, *J* 11.9), 1.91 (1 H, d, *J* 11.9), 4.14 (1 H, q, *J* 6.4), 4.96 (1 H, dd, *J* 10.4 and 2.1), 5.07 (1 H, dd, *J* 16.8 and 2.1), 5.90 (1 H, d, *J* 11.0) and 6.41 (1 H, ddd, *J* 16.8, 11.0 and 10.4).

9-[(S)-1-(*t-Butyldimethylsiloxy*)*ethyl*]-7,8-*dihydro*-6-*hydroxy*-4-*methoxynaphthacene*-5,12-*dione** **18**.—The tandem Michael/Diels–Alder reaction between the acryloylquinone **7** (1 mmol) and the chiral PDT **8a** (1.2 mmol) was performed in a similar way to that reported.[7c] After completion of the reaction (TLC; *ca.* 1 h), the reaction mixture was washed successively with 5% aq. HCl (×2) and with water, and was treated as usual. The tetracyclic hydroquinone **10** [R = CH(OTBDMS)Me] was detected (TLC, silica gel) as a bright yellow spot (benzene or dichloromethane as the developer).

The viscous residue obtained above was dissolved in DMF and submitted to oxidation under oxygen as described in the literature.[7c] After chromatographic purification (5% ethyl acetate in dichloromethane as the eluent), *compound* **18** (287 mg, 62% from 1.0 mmol of **7**) was obtained as orange needles (from diethyl ether–hexane); m.p. 137–139 °C (Found: C, 69.7; H, 7.0. $C_{27}H_{32}O_5Si$ requires C, 69.80; H, 6.94%); $[\alpha]_D^{24}$ −50° (*c* 0.46, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3440, 1670, 1650, 1620 and 1585; $\delta_H(CDCl_3)$ 0.07 (3 H, s), 0.09 (3 H, s), 0.92 (9 H, s), 1.30 (3 H, d, *J* 6.7), 2.27 (1 H, dt, *J* 16.7 and 8.3), 2.40 (1 H, dt, *J* 16.7 and 8.3), 2.93 (2 H, t, *J* 8.3), 4.05 (3 H, s), 4.41 (1 H, q, *J* 6.7), 6.48 (1 H, br s), 7.32 (1 H, dd, *J* 8.3 and 1.2), 7.46 (1 H, s), 7.69 (1 H, dd, *J* 8.3 and7.5), 7.92 (1 H, dd, *J* 7.5 and 1.2) and 13.25 (1 H, s); *m/z* 464 (M^+, 33%), 449 (10), 407 (100), 392 (13), 389 (34), 379 (12) and 333 (86).

6-*Acetoxy*-9-[(S)-1-(*t-butyldimethylsiloxy*)*ethyl*]-7,8-*dihydro*-4-*methoxynaphthacene*-5,12-*dione* **19**.—To a solution of compound **18** (461 mg, 0.994 mmol) in dichloromethane (10 cm^3) were added acetic anhydride (0.4 cm^3), triethylamine (0.44 cm^3), and DMAP (20 mg) at room temperature under nitrogen

* The carbon numbering of the parent anthracyclines is adopted to that of the synthetic tetracyclic intermediates.

and the mixture was stirred overnight. After being stirred for an additional 1 h with water (10 cm^3), the mixture was extracted with dichloromethane and the extract was washed successively with 5% aq. HCl and saturated aq. $NaHCO_3$, and then was treated as usual. Purification with column chromatography (5% ethyl acetate in benzene as the eluent) gave the *acetate* **19** (473 mg, 94%) as yellow crystals (from hexane); m.p. 137–141 °C (Found: M^+, 506.2125. $C_{29}H_{34}O_6Si$ requires M, 506.2125); ν_{max}(KBr)/cm^{-1} 1770, 1665 and 1585; δ_H($CDCl_3$) 0.05 (3 H, s), 0.07 (3 H, s), 0.90 (9 H, s), 1.27 (3 H, d, *J* 6.4), 2.25 (1 H, dt, *J* 17.1 and 8.2), 2.38 (1 H, dt, *J* 17.1 and 8.2), 2.49 (3 H, s), 2.79 (2 H, br), 3.96 (3 H, s), 4.40 (1 H, q, *J* 6.4), 6.54 (1 H, s), 7.25 (1 H, d, *J* 8.2), 7.59 (1 H, dd, *J* 8.2 and 7.9), 7.79 (1 H, s) and 7.82 (1 H, d, *J* 7.9); *m/z* 506 (M^+, 74%), 449 (100), 425 (37), 424 (40), 407 (58), 389 (62) and 333 (74).

6-*Acetoxy*-7,8-*dihydro*-9-[(S)-1-*hydroxyethyl*]-4-*methoxynaphthacene*-5,12-*dione* **11**.—To an acetonitrile solution (2 cm^3) of siloxy compound **19** obtained above, at 0 °C, was added a solution of HF (47%; 0.5 cm^3) in acetonitrile (9.5 cm^3) under nitrogen and the resulting solution was stirred at this temperature. As soon as the reaction was complete (*ca.* 1 h; TLC), cold water–chloroform was added to the mixture and the organic layer was treated as usual to give the *allylic alcohol* **11** (360 mg, 98%) as yellow needles (from dichloromethane–diethyl ether); m.p. 211–214 °C (Found: M^+, 392.1251. $C_{23}H_{20}O_6$ requires M, 392.1260); $[\alpha]_D^{24}$ −13.4° (*c* 1.0, 1,4-dioxane); ν_{max}(KBr)/cm^{-1} 3490, 1760, 1660 and 1580; δ_H($CDCl_3$) 1.36 (3 H, d, *J* 6.4), 2.30 (1 H, dt, *J* 16.8 and 8.3), 2.41 (1 H, dt, *J* 16.8 and 8.3), 2.51 (3 H, s), 2.81 (2 H, br), 4.00 (3 H, s), 4.45 (1 H, q, *J* 6.4), 6.57 (1 H, br s), 7.30 (1 H, dd, *J* 8.3 and 0.8), 7.64 (1 H, dd, *J* 8.3 and 7.5), 7.78 (1 H, s) and 7.87 (1 H, d, *J* 7.5); *m/z* 392 (M^+, 11%), 374 (38), 350 (41), 332 (100), 314 (50) and 307 (67).

The enantiomeric purity of the product **11** was determined by a similar method to that for compound **17**. The ratio of the corresponding MTPA esters (^1H NMR signals) was [(*S*)-**10**; δ_H 1.52 (d, *J* 6.7)]: [(*R*)-**10**; δ_H 1.46 (d, *J* 6.7 Hz)] 97.5:2.5.

Diastereoselective Epoxidation of the Chiral Allylic Alcohol **11**. *Synthesis of* (9S, 10S)-6-*Acetoxy*-9,10-*epoxy*-7,8,9,10-*tetrahydro*-9-[(S)-1-*hydroxyethyl*]-4-*methoxynaphthacene*-5,12-*dione* **20**.—The alcohol **11** (136 mg, 0.347 mmol) was dissolved in dichloromethane (10 cm^3) and to the solution cooled to −20 °C were added $VO(acac)_2$ (10 mg) and Bu^tOOH (4 mol dm^{-3} in dichloromethane; 0.17 cm^3, 0.68 mmol) under nitrogen. After being stirred for 1 h, the reaction mixture was kept in a freezer (−20 °C) overnight. The reaction was stopped by addition of water and extracted with chloroform; the extract was treated as usual. The residue was chromatographed (5% ethyl acetate in chloroform containing a trace of ethanol as the eluent) to afford pure *epoxide* **20** (128 mg, 90%) as yellow needles (from dichloromethane–diethyl ether); m.p. 224–226.5 °C (Found: M^+, 408.1201. $C_{23}H_{20}O_7$ requires M, 408.1209); $[\alpha]_D^{24}$ −159° (*c* 1.05, 1,4-dioxane); ν_{max}(KBr)/cm^{-1} 3400, 1760, 1665 and 1580; δ_H($CDCl_3$) 1.32 (3 H, d, *J* 6.4), 1.87 (1 H, ddd, *J* 14.3, 13.1 and 5.5), 2.24 (1 H, dd, *J* 14.6 and 6.7), 2.26 (1 H, br s), 2.52 (3 H, s), 2.53 (1 H, m), 2.88 (1 H, br), 4.01 (3 H, s), 4.10 (1 H, s), 4.13 (1 H, qd, *J* 6.4 and 1.5), 7.32 (1 H, dd, *J* 8.2 and 0.9), 7.69 (1 H, dd, *J* 8.2 and 7.6), 7.89 (1 H, dd, *J* 7.6 and 0.9) and 8.20 (1 H, s); *m/z* 408 (M^+, 19%), 390 (10), 366 (60), 348 (71), 338 (29) and 322 (100).

Only one diastereoisomer of compound **20** was detected by ^1H NMR spectroscopy.

Oxidation of the Epoxy Alcohol **20** *to* (9R,10S)-6-*Acetoxy*-9-*acetyl*-9,10-*epoxy*-7,8,9,10-*tetrahydro*-4-*methoxynaphthacene*-5,12-*dione* **21**.—To a solution of the epoxy alcohol **20** (120 mg, 0.294 mmol) in dichloromethane (15 cm^3) were added PDC (330 mg, 0.877 mmol) and pyridinium trifluoroacetate (30 mg),[17] and the mixture was stirred at room temperature under nitrogen for 2 days and then filtered through Celite. The filtrate was washed with 5% aq. HCl and treated as usual. The residue was chromatographed (0.5% methanol in chloroform) to obtain the epoxy ketone **21**[24] (108 mg, 90%): $[\alpha]_D^{25}$ −100° (*c* 0.5, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1770, 1710, 1670 and 1585; δ_H ($CDCl_3$) 2.20 (3 H, s and 1 H, m), 2.40–2.48 (2 H, m), 2.50 (3 H, s), 2.94 (1 H, br), 3.98 (3 H, s), 4.18 (1 H, s), 7.30 (1 H, d, *J* 8.5), 7.66 (1 H, dd, *J* 8.5 and 7.6), 7.85 (1 H, d, *J* 7.6) and 8.22 (1 H, s); *m/z* 406 (M^+, 17%), 382 (9), 364 (100), 346 (40), 336 (18), 328 (15), 322 (98) and 321 (52).

(R)-7,11-*Dideoxydaunomycinone* **22**.—Under nitrogen, a cold aq. solution (20 cm^3) of $Na_2S_2O_4$ (1 g) and NaOH (0.6 g) was added to the epoxy ketone **21** (100 mg, 0.246 mmol) and the mixture was stirred at 0 °C for 4 h. Cold, 5% aq. HCl was added gradually to the reaction mixture to the point where the colour turned to reddish orange from dark brown. After extraction with chloroform, the extract was treated as usual. Chromatographic separation (1% methanol in chloroform as the eluent) of the residue afforded compound **22** (41 mg, 46%) and its dehydration product **23** (21 mg, 25%). For *compound* **22**: orange needles (from dichloromethane–diethyl ether); m.p. 217.5–219 °C (for racemic **22**: lit.,[19a] 218–219.5 °C;[25] 208–210 °C;[24,26] 209–211 °C) (Found: M^+, 366.1111. $C_{21}H_{18}O_6$ requires M, 366.1103); $[\alpha]_D^{22}$ −28° (*c* 0.26, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3510, 3450, 1710, 1670, 1625 and 1585; δ_H ($CDCl_3$) 1.96 (1 H, ddt, *J* 13.1, 6.7 and 2.4), 2.06 (1 H, ddd, *J* 13.1, 11.5 and 6.4), 2.36 (3 H, s), 2.79 (1 H, dd, *J* 17.1 and 2.4), 2.92 (1 H, ddd, *J* 18.5, 11.5 and 6.7), 3.12 (1 H, ddd, *J* 18.5, 6.4 and 2.4), 3.31 (1 H, d, *J* 17.1), 3.69 (1 H, br), 4.08 (3 H, s), 7.36 (1 H, dd, *J* 8.3 and 1.2), 7.50 (1 H, s), 7.73 (1 H, dd, *J* 8.3 and 7.5), 7.95 (1 H, dd, *J* 7.5 and 1.2) and 13.40 (1 H, s); *m/z* 366 (M^+, 19%), 348 (7), 323 (100) and 305 (25). The spectroscopic data of compound **22** agreed with those reported previously.[19a,22–24]

For compound **23**: δ_H($CDCl_3$) 2.47 (3 H, s), 2.64 (2 H, t, *J* 9), 2.98 (2 H, t, *J* 9), 4.08 (3 H, s), 7.37 (1 H, d, *J* 8), 7.39 (1 H, s), 7.68 (1 H, s), 7.76 (1 H, t, *J* 8), 7.97 (1 H, d, *J* 8) and 13.24 (1 H, s).

Selective Demethylative Acetylation of Compound **24**. 6-*Acetoxy*-9-*acetoxymethyl*-7,8-*dihydro*-4-*methoxy*-5,12-*naphthacene*-5,12-*dione* **25**.—70% $HClO_4$ (0.06 cm^3) was added to a suspension of tetracyclic quinone **24** (226 mg, 0.645 mmol) in dichloromethane (10 cm^3)–acetic anhydride (10 cm^3) at 0 °C, which mixture was then stirred for 5 min and then poured into water. The organic layer was treated as usual. The residue was purified by column chromatography to give *compound* **25** (226 mg, 83%) as orange-yellow needles (from dichloromethane–diethyl ether); m.p. 189–192 °C (Found: C, 68.5; H, 4.7. $C_{24}H_{20}O_7$ requires C, 68.57; H, 4.79%); ν_{max}(KBr)/cm^{-1} 1765, 1740, 1660 and 1590; δ_H($CDCl_3$) 2.15 (3 H, s), 2.35 (2 H, t, *J* 7.9), 2.52 (3 H, s), 2.86 (2 H, br), 4.00 (3 H, s), 4.71 (2 H, s), 6.59 (1 H, br s), 7.30 (1 H, dd, *J* 8.5 and 0.9), 7.65 (1 H, dd, *J* 8.5 and 7.6), 7.83 (1 H, s) and 7.87 (1 H, dd, *J* 7.6 and 0.9); *m/z* 420 (M^+, 20%), 378 (15), 377 (11), 376 (13), 360 (22) and 318 (100).

Selective Deacetylation of Diacetate **25**. 6-*Acetoxy*-7,8-*dihydro*-9-*hydroxymethyl*-4-*methoxynaphthacene*-5,12-*dione* **12**.—The diacetate **25** (197 mg, 0.469 mmol) was suspended in a mixture of acetone (10 cm^3) and methanol (5 cm^3) and to the mixture was added a solution of sulphuric acid (50 mg) in methanol (5 cm^3). After the suspension had been degassed with nitrogen, it was refluxed for 4 h, cooled, poured onto ice–water, and extracted with chloroform (×3). The residual mass obtained after the usual treatment of the combined extracts was chromatographed (10% ethyl acetate in dichloromethane) to

afford the *allylic alcohol* **12** (162 mg, 91%) as orange-yellow needles (from dichloromethane–diethyl ether); m.p. 211–215 °C (Found: C, 69.6; H, 4.75. $C_{22}H_{18}O_6$ requires C, 69.83; H, 4.79%); ν_{max}(KBr)/cm^{-1} 3480, 1750, 1660 and 1585; δ_H($CDCl_3$) 1.80 (1 H, br), 2.30 (2 H, dd, *J* 8.3 and 7.5), 2.52 (3 H, s), 2.82 (2 H, br), 4.00 (3 H, s), 4.27 (2 H, br s), 6.59 (1 H, br s), 7.30 (1 H, dd, *J* 8.3 and 1.0), 7.65 (1 H, dd, *J* 8.3 and 7.5), 7.79 (1 H, s) and 7.87 (1 H, dd, *J* 7.5 and 1.0); *m/z* 378 (M^+, 29%) and 336 (100).

Enantioselective Epoxidation of the Primary Allylic Alcohol **12**. *Synthesis of* (9S,10S)-6-*Acetoxy*-9,10-*epoxy*-7,8,9,10-*tetrahydro*-9-*hydroxymethyl*-4-*methoxynaphthacene*-5,12-*dione* **28**.—To a solution of $(Pr^iO)_4Ti$ (0.32 mmol) in dichloromethane (3 cm^3) at −20 °C containing powdered molecular sieves 4 Å (0.2 g) were added (+)-diethyl tartrate (79.3 mg, 0.38 mmol) and Bu^{t}OOH (0.69 mmol; as a dichloromethane solution) under nitrogen. After the mixture had been stirred for 30 min, a cold (−20 °C) solution of compound **12** (120 mg, 0.317 mmol) in dichloromethane (6 cm^3) was added and the mixture was stirred for 2 h, then kept in a freezer (*ca.* −20 °C) overnight. Water was then added to the mixture. The resulting precipitates and the molecular sieves were filtered off through a Celite pad. The usual treatment of the filtrate afforded a residue, which could be employed to the following reaction after certification of the complete consumption of substrate **12** by NMR spectroscopy. When purified with column chromatography (1% ethanol in chloroform), compound **28** (100 mg, 80%) was obtained as orange-yellow crystals; δ_H($CDCl_3$) 1.78 (1 H, ddd, *J* 14.4, 13.4 and 5.5), 2.35 (1 H, dd, *J* 13.1 and 7.0), 2.51 (3 H, s and 1 H, m), 2.87 (1 H, br), 3.87 (1 H, dd, *J* 12.5 and 8.2), 3.99 (1 H, dd, *J* 12.5 and 4.3), 4.00 (3 H, s), 4.07 (1 H, s), 7.31 (1 H, dd, *J* 8.4 and 0.9), 7.67 (1 H, dd, *J* 8.4 and 7.6), 7.87 (1 H, dd, *J* 7.6 and 0.9) and 8.15 (1 H, s).

Enantiomeric purity of compound **28** was determined by means of NMR spectroscopic analysis of the corresponding (*R*)-MTPA ester to be 96% e.e., *i.e.* [(9*S*,10*S*)-**28**; δ_H 4.43 (d, *J* 12.2)]:[(9*R*,10*R*)-**28**; δ_H 4.50 (d, *J* 12.2)] 98:2.

(R)-9-*Deacetyl*-7,11-*dideoxy*-9-*hydroxymethyldaunomycinone* **29**.—A similar method to that mentioned above for the synthesis of compound **22** was applied to epoxide **28**. The epoxide **28** (89 mg, 0.226 mmol) gave *compound* **2a** (58 mg, 72%) as orange needles (from THF–diethyl ether); m.p. 245–250 °C (decomp.) (Found: M^+, 354.1110. $C_{20}H_{18}O_6$ requires M, 354.1103); $[\alpha]_D^{22}$ −10.6° (*c* 0.6, 1,4-dioxane); ν_{max}(KBr)/cm^{-1} 3510, 3360, 1665, 1620 and 1580; δ_H($CDCl_3$) 1.81 (1 H, dt, *J* 13.1 and 7.9), 2.03 (1 H, dt, *J* 13.1 and 6.7), 2.95 (4 H, m), 3.62 (2 H, s), 4.08 (3 H, s), 7.36 (1 H, d, *J* 7.9), 7.53 (1 H, s), 7.74 (1 H, t, *J* 7.9), 7.97 (1 H, d, *J* 7.9) and 13.41 (1 H, s); *m/z* 354 (M^+, 74%), 336 (17), 323 (84) and 305 (100).

(7S,9S)-9-*Deacetyl*-9-*hydroxymethyl*-11-*deoxydaunomycinone* **3b**.—A solution of compound **29** (62 mg, 0.176 mmol), acetic anhydride (0.15 cm^3), and pyridine (0.05 cm^3) in dichloromethane (3 cm^3) was stirred under nitrogen at room temperature overnight. The solution was washed successively with water, 5% aq. HCl, and saturated aq. $NaHCO_3$, and then was treated as usual to give compound **30a** (60 mg, 0.151 mmol).

Monoacetate **30a** was dissolved in tetrachloromethane (150 cm^3) and hydroxylation at C-7 was performed by the reported method [7c] with bromine (43 mg, 0.27 mmol) to give *compound* **3b** (41 mg, 63% from compound **29**) after chromatography (3% methanol in chloroform) as orange-yellow flakes (from THF–diethyl ether); m.p. 224–228 °C (decomp.) (Found: M^+, 370.1042. $C_{20}H_{18}O_7$ requires M, 370.1052); $[\alpha]_D^{24}$ +126° (*c* 0.15, 1,4-dioxane); ν_{max}(KBr)/cm^{-1} 3420, 1660, 1620 and 1580; δ_H($CDCl_3$) 1.81 (1 H, dd, *J* 14.7 and 4.8), 2.26 (1 H, br), 2.52 (1 H, dt, *J* 14.7 and 2.0), 2.80 (1 H, d, *J* 17.5), 3.06 (1 H, dd, *J* 17.9 and 2.0), 3.42 (1 H, br), 3.55 (1 H, d, *J* 10.7), 3.67 (1 H, d, *J* 11.1), 4.08 (3 H, s), 5.38 (1 H, m), 7.38 (1 H, dd, *J* 8.3 and 1.0), 7.59 (1 H, s), 7.76 (1 H, dd, *J* 8.3 and 7.9), 7.97 (1 H, dd, *J* 7.9 and 1.0) and 13.65 (1 H, s); *m/z* 370 (M^+, 100%), 352 (40), 334 (33), 322 (43) and 321 (74).

References

1 Part 23 of the series Synthesis of Naturally Occurring Quinones. Part 22; Y. Naruta, Y. Nishigaichi and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1989, 1203.

2 W. A. Remers, *The Chemistry of Antitumor Antibiotics*, Wiley, New York, 1979, p. 221; F. Arcamone, *Anticancer Agents Based on Natural Product Models*, ed. J. M. Cassady and J. D. Douros, Academic, New York, 1980, p. 1; W. A. Remers, *Anticancer Agents Based on Natural Product Models*, 1980, p. 131; S. Terashima, *J. Synth. Org. Chem. Jpn.* (*Yuki Gosei Kagaku Kyokaishi*), 1982, **40**, 20; M. J. Broadhurst, C. H. Hassall and G. J. Thomas, *Chem. Ind.* (*London*), 1985, 106; K. Krohn, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 790; T. R. Kelly, *Tetrahedron* (*Symposia-in-Print No. 17*), 1984, **40**, 4537; R. H. Thomson, *Naturally Occurring Quinones, III*, Chapman and Hall, London, 1987, p. 527, and references cited therein.

3 B. R. J. Abdella and J. Fisher, *Environ. Health Perspect.*, 1985, **64**, 3; J. R. Brown and S. H. Imam, *Prog. Med. Chem.*, 1984, **21**, 169, and references cited therein.

4 *Anthracycline Antibiotics*, ed. H. S. El Khadem, Academic, New York, 1982.

5 Asymmetric syntheses of 11-deoxyanthracyclinones: (*a*) H. Sekizaki, M. Jung, J. M. McNamara and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 7372; (*b*) J. M. McNamara and Y. Kishi, *Tetrahedron*, 1984, **40**, 4685; (*c*) J. P. Rizzi and A. S. Kende, *Tetrahedron*, 1984, **40**, 4693; (*d*) E. Broser and K. Krohn, *Tetrahedron Lett.*, 1984, **25**, 2463; (*e*) M. Suzuki, Y. Kimura and S. Terashima, *Tetrahedron Lett.*, 1985, **26**, 6481; (*f*) M. Kawasaki, F. Matsuda and S. Terashima, *Tetrahedron*, 1988, **4**, 5727.

6 Asymmetric syntheses of 11-oxyanthracyclinones: (*a*) D. Dominguez and M. P. Cava, *J. Org. Chem.*, 1983, **48**, 2820; (*b*) K. Tomioka, M. Nakajima and K. Koga, *J. Am. Chem. Soc.*, 1987, **109**, 6213; (*c*) M. Sodeoka, T. Iimori and M. Shibasaki, *Tetrahedron Lett.*, 1985, **26**, 6497; (*d*) N. Tanno and S. Terashima, *Chem. Pharm. Bull.*, 1983, **31**, 821; (*e*) A. V. Rama Rao, J. S. Yadav, K. Bal Reddy and A. R. Mehendale, *Tetrahedron*, 1984, **40**, 4643; (*f*) R. A. Russell, R. W. Irvine and R. N. Warrener, *J. Org. Chem.*, 1986, **51**, 1595; (*g*) S. Jew, S. Terashima and K. Koga, *Chem. Pharm. Bull.*, 1979, **27**, 2351; (*h*) R. C. Gupta, P. A. Harland and R. J. Stoodley, *Tetrahedron*, 1984, **40**, 4657; (*i*) Y. Tamura, H. Annoura, H. Yamamoto, H. Kondo, Y. Kita and H. Fujioka, *Tetrahedron Lett.*, 1987, **28**, 5709; (*j*) S. Qureshi, G. Shaw and G. E. Burgess, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1557; (*k*) K. Krohn and U. Müller, *Tetrahedron*, 1986, **42**, 6635; (*l*) J. C. Florent, J. Ughetto-Monfrin and C. Monneret, *J. Org. Chem.*, 1987, **52**, 1051.

7 (*a*) Y. Naruta, M. Kashiwagi, Y. Nishigaichi, H. Uno and K. Maruyama, *Chem. Lett.*, 1983, 1687; Y. Naruta, Y. Nishigaichi and K. Maruyama, (*b*) *Chem. Lett.*, 1986, 1703; (*c*) *J. Org. Chem.*, 1988, **53**, 1192.

8 Y. Naruta, Y. Nishigaichi and K. Maruyama, *Chem. Lett.*, 1988, 135; *J. Org. Chem.*, in the press.

9 K. B. Sharpless and T. R. Verhoeven, *Aldrichim. Acta*, 1979, **12**, 63.

10 B. E. Rossiter, *Asymmetric Synthesis*, ed. J. D. Morrison, Academic, New York, 1985, vol. 5, p. 193; M. G. Finn and B. E. Sharpless, *Asymmetric Synthesis*, 1985, vol. 5, p. 247.

11 G. Fráter, *Helv. Chim. Acta*, 1979, **62**, 2825. For reviews, see: *Asymmetric Catalysis*, ed. B. Bosnich, Martinus Nijhoff, Lancaster, 1986, p. 100; J. B. Jones, *Asymmetric Synthesis*, ed. J. D. Morrison, Academic, New York, 1985, vol. 5, p. 309.

12 V. Prelog, *Pure Appl. Chem.*, 1964, **9**, 119.

13 S. Wolff, M. E. Huecas and W. C. Agosta, *J. Org. Chem.*, 1982, **47**, 4358.

14 L. Lochmann, J. Pospíšil and D. Lím, *Tetrahedron Lett.*, 1966, 257; M. Schlosser, *J. Organomet. Chem.*, 1967, **8**, 9; J. J. Bahl, R. B. Bates and B. Gordon, III, *J. Org. Chem.*, 1979, **44**, 2290.

15 D. A. Evans, G. C. Andrews and B. Buckwalter, *J. Am. Chem. Soc.*, 1974, **96**, 5560; W. C. Still and T. L. Macdonald, *J. Am. Chem. Soc.*, 1974, **96**, 5561.

16 F. M. Hauser and D. Mal, *J. Am. Chem. Soc.*, 1983, **105**, 5688.

17 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.

18 *Advanced Organic Chemistry*, ed. J. March, Wiley-Interscience, New York, 1985, p. 298.

19 (*a*) Y. Tamura, S. Akai, H. Kishimoto, M. Sasho, M. Kirihara and Y. Kita, *Chem. Pharm. Bull.*, 1988, **36**, 3897; (*b*) K. Tamoto, M. Sugimori and S. Terashima, *Tetrahedron*, 1984, **40**, 4617.
20 For a preliminary report, see: Y. Naruta, Y. Nishigaichi and K. Maruyama, *Tetrahedron Lett.*, 1989, **30**, 3319.
21 M. B. Naff, J. Plowman and V. L. Narayanan, ref. 4, p. 1; S. Penco, F. Angelucci and F. Arcamone, *Ger. Offen*, 2 757 057, 1978 (*Chem. Abstr.*, 1978, **89**, P197892j). The related 4-demethoxy compound was also synthesized; M. J. Broadhurst, C. H. Hassal and G. J. Thomas, *Eur. Pat. Appl.*, EP44 954, 1982 (*Chem. Abstr.*, 1982, **96**, 218189x). Also, see: A. Genot, J. C. Florent and C. Monneret, *J. Org. Chem.*, 1987, **52**, 1057, and references therein.
22 H. Brockmann, J. Niemeyer, H. Brockmann, Jr. and H. Budzikiewicz, *Chem. Ber.*, 1965, **98**, 3785; F. M. Hauser, S. Prasanna and D. W. Combs, *J. Org. Chem.*, 1983, **48**, 1328.
23 K. Krohn and W. Priyana, *Tetrahedron*, 1984, **40**, 4609.
24 J.-M. Tornare and P. Vogel, *Helv. Chim. Acta*, 1985, **68**, 1069.
25 E. Ghera and Y. Ben-David, *J. Org. Chem.*, 1988, **53**, 2972.
26 A. A. Abdallah, J.-P. Gesson, J.-C. Jacquesy and M. Mondon, *Bull. Soc. Chim. Fr.*, 1986, 93; A. V. Rama Rao, A. R. Mehendale and K. Bal Reddy, *Indian J. Chem., Sect. B*, 1984, **23**, 1154.

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