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ANTHRACYCLINES XVII

THE SYNTHESIS OF 2 - FLUORO AND 3 - FLUORO - 4-DEMETHOXYDAUNOMYCIN.

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Abstract: *2- Fluoro and 3 - fluoro-4-demethoxydaunomycinone have been prepared by phthalide annelation of the quinone monoacetal(10), which was in turn prepared from the previously described fully oxygenated ketone (1). Extensions of this approach to permit inclusion of a chiral induction step are also evaluated.The title compounds were prepared by glycosidation of the appropriate racemic aglycones and the merits of different methods of attaching the sugar are discussed.*

INTRODUCTION.

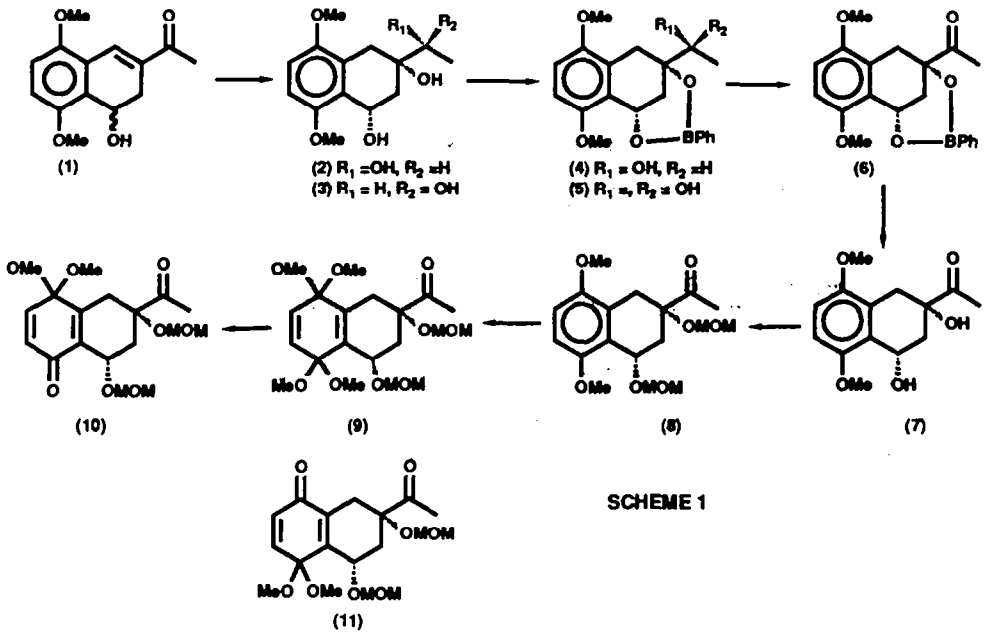
As part of an ongoing program to employ heteronuclear n.m.r. to probe the interaction of DNA with intercalating agents, we have prepared 2- fluoro and 3-fluoro-4-demethoxydaunomycin (34 and 37), thereby completing the series of D ring monofluorinated glycosides[1, 2]. In keeping with other endeavours in the synthesis of the rhodomycin group of anthracyclines[3,4,5] we have utilised the annelation of quinone monoacetals with the anions of 3-cyanophthalides in the key step of assembling the anthracyclinone. In this paper we report the preparation of dienones (10) and (11) and their subsequent conversion to the title compounds.

RESULTS AND DISCUSSION.

Synthetic approaches to anthracyclines of the rhodomycin group have developed to the point of multi-gram preparations of both racemic and optically pure products[3]. Further development in this area must therefore compete in terms of scale , minimised use of protecting groups, cheap reagents and optical purity. From the outset of this study we sought to develop strategies that would meet these challenges and provide the scope to incorporate optical activity without recourse to a classical resolution of a racemate. Of all the possible starting materials for the AB component of the aglycone, the Rodrigo ketone (1)[6,7] appeared to offer the most promise, as the presence of an α,β unsaturated ketone provided the capacity to induce optical activity by means of a chiral reduction along the lines used previously by Terashima[8,9] and ourselves[5] in the 7-deoxy series. The prospect of using the ketone (1) was somewhat daunting in that the products required eg (2) and (3) had previously been considered too unstable for use on a large scale[6]. However we can now refute these earlier claims and draw attention to the full potential of ketone (1) as a versatile starting point for anthracycline synthesis.

Preparation of the dienones(10) and (11).

We have previously demonstrated[10] that the double bond in ketone (1) is activated by the homoallylic alcohol and may be epoxidised with *tert*- butyl hydroperoxide in the presence of a vanadium catalyst to afford an epoxide in which the ether ring is *cis* to the alcohol . Direct reduction of the epoxide with lithium aluminium hydride yields a mixture of triols (2)



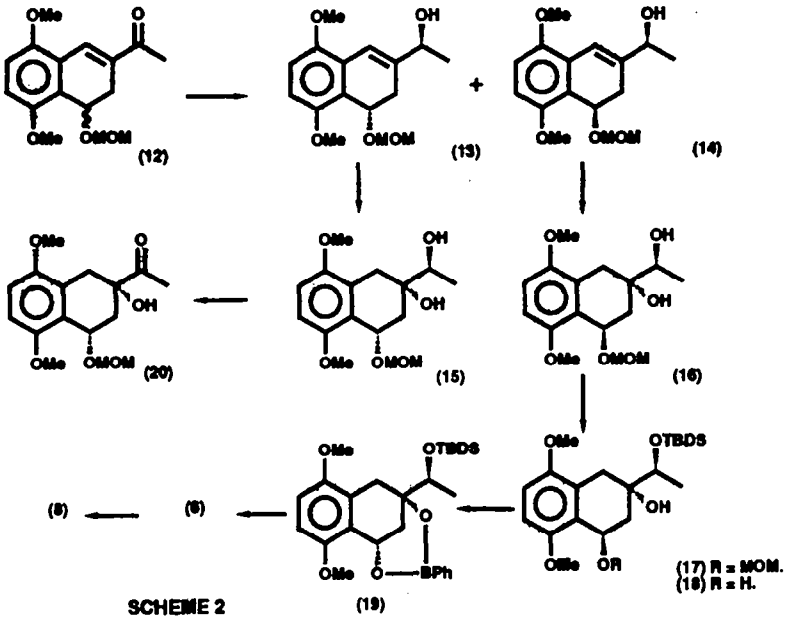
SCHEME 1

and (3) with the C 7 and C 9 hydroxyls (anthracycline numbering) in the *cis* configuration. A number of alternatives for elaborating these triols were considered but the difficulty of cheaply oxidising the 1,2 diol system in the analogous 7-deoxy series [5,8] dictated that the best strategy would be to simultaneously protect the latent A ring hydroxyls and to oxidise the free side chain alcohol. This was achieved by the formation of the phenyl boronates (4) and (5) and subsequent oxidation with pyridinium chlorochromate to afford the ketone (6) in 88% yield . Deprotection of (6) was effected cleanly with 2-methylpentane-2,4-diol[11] and acetic acid to yield the dihydroxy ketone (7). Since free unhindered hydroxyl groups can not be tolerated in the formation of the aglycone by phthalide anion annelation some further protection of the dihydroxy ketone (7) was required. Furthermore, as the annelation sequence ultimately required the removal of a methyl ether derived from the dienone component (Scheme 3) it was appropriate to constrain possible protecting goups to those which could be cleaved with boron trichloride and thereby restrict the deprotection sequence to one step. We accordingly selected the methoxymethyl (MOM) group and employed this for the present study. Electrolysis of the ketone (8) followed by controlled hydrolysis of the intermediate ketal (9) afforded the dienones (10) and (11) in a 87:13 ratio.

This sequence provided a rapid entry to a racemic AB dienone which could be utilised on a scale of 50g, and required minimal chromatography.

Introduction of chirality to dienones (10) and (11).

The introduction of the correct chirality into the two optical centres of dienones (10) and (11) could in principal be accomplished by chiral reduction of the ketone in (1) followed by diastereoselective epoxidation of the double bond as outlined for the analogous 7-deoxyanthracyclinones[5,8,9]. In the latter case the epoxidation was controlled by the chiral allylic alcohol . However we have shown in the case of ketone (1) that the homoallylic alcohol was dominant in directing the stereochemical outcome of the epoxidation[10]. Accordingly it was essential to firstly protect the benzylic alcohol function and this was conveniently achieved by use of the methoxymethyl ether (see above). This choice of protecting group was consistent with the philosophy discussed previously but in the present context it is also significant that a wide variety of alternative groups *inter alia* trimethylsilyl, t-butyldimethylsilyl, methyl, benzyl, 4-methoxybenzyl and 2-(trimethylsilyl)-ethoxymethyl all failed for one reason or another to permit the chemistry outlined in Scheme 2 to be accomplished efficiently. Operating initially at the racemic level , it was possible to reduce the ketone (12) with sodium borohydride to afford two isomeric alcohols (13) and (14) and convert these without separation to the diols (15) and (16). The former of these two products was converted directly by oxidation with Fetizon's reagent[13] to ketone (20), which upon protection of the tertiary alcohol afforded the ether (8). In contrast the alcohol (16) required inversion of the benzylic ether which was accomplished in 61% overall yield by the uneventful sequence shown in Scheme 2.



SCHEME 2

Having established the basic strategy required for the synthesis of dienone (10) at the achiral level we next examined the reduction of the ketone (12) with chiral reducing agents. The reagents chosen were those based on $LiAlH_4$ modified with (-)-N-methylephedrine and an aromatic amine[9]. The resultant reduction products , the allylic alcohols (13) and (14), were epoxidised and reduced to yield a mixture of the diols (15) and (16). These were separated and the required diol (15) oxidised to the ketone (20) with Fetizon's reagent. The optical purity of the chiral ketone was then evaluated by ^1H n.m.r. analysis in the presence of the chiral shift reagent *tris*- [3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato] europium (III). The results of a series of experiments (see table) indicate that the optical purity of the ketone (20) was poor especially when compared with results obtained in the 7- deoxy series using this reaction protocol. The current series of compounds could not be separated by chiral phase chromatography[14] which was a serious drawback in regard to the rapid evaluation of the optical integrety of this series of reactions. Furthermore the ketone (20) could not be obtained in an optically pure form by repeated recrystallization of optically enriched samples. From a practical point of view, chiral reduction of the ketone (20) was not a satisfactory solution to the preparation of chiral anthracycline precursors. The low solubility of the the ketone in ether at -78°, coupled to its sluggish reactivity towards chirally modified hydrides precluded its use on a large scale and compounded the problem of poor chiral induction. Accordingly we have not persued this approach and at this time simply note that alternative strategies based on the ketone (1) appear more promising.

Achiral amine.	Optical purity of ketone (20) % ee
N-ethylaniline	35
N,N-diphenylamine	60
N-phenyl-1-naphthylamine	7
N-phenyl-2-naphthylamine	35

Table 1: All reductions carried out in diethyl ether at -78° using a ratio of ketone (12):$LiAlH_4$:(-)N-methylephedrine:achiral amine of 1:3.3:3.4:6.8.

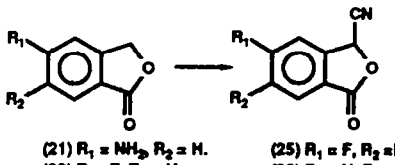
Preparation of the aglycones (28) and (30).

The preparation of the aglycones (28) and (30) was accomplished by annelating the dienones (10) with the fluorinated 3-cyanophthalide derivatives (25) and (26) respectively. Although the minor dienone (11) could be separated and independently annelated with its appropriate modal partner, there was no practical advantage in this approach unless decagram quantities were involved. The reaction yields of 94% for the tetracycles (27) and (29) respectively are typical of those previously recorded in our laboratories for similar reactions and further highlight the efficiency of this reaction sequence. Deprotection of the condensation products was achieved using boron trichloride in dichloromethane, although good yields were obtained only with freshly prepared solutions of the reagent and rigorous attention to the work up conditions. For large scale preparations there was no requirement to isolate any intermediates and the final products could be obtained in pure form simply by recrystallisation.

Synthesis of the glycosides.

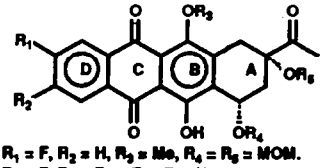
Glycosidation of anthracycline aglycones has commonly been accomplished by Koenigs - Knorr methodology using either the glycosyl chloride[11] or bromide[12]. An alternative procedure involving the coupling of equimolar quantities of the glycosyl *p*-nitrobenzoate (31) and 4-demethoxydaunomycinone in the presence of molecular sieve and trimethylsilyl triflate (TMS triflate) has been reported by Terashima[15] to afford an exceptionally high yield of the required α–anomer. Accordingly this coupling reaction was our first choice in the current study.

Using the previously described conditions, which included particular attention being paid to the physical state of the molecular sieve employed, we found that the racemic aglycone (30) afforded a mixture containing the optically pure glycosides (35) 17%, (41) 31%, (45) 15%, unreacted (30) 33% and a mixture of the β–analogues of (35) and (41) 4%, all of which were assigned structures by comparison of the spectral and chiroptical properties with those of the 4-demethoxy analogues.[11] These results were discouraging in view of the 99% yield of α-glycoside obtained by Terashima from optically pure 4-demethoxydaunomycinone. Lowering the reaction temperature to -30°, and increasing the ratio of sugar to aglycone resulted,in the case of the 2-fluoro derivative (28), in an increase in the yield of the correct antipode (32) 28%, which was obtained together with glycoside (38) 28%, unreacted (28) 7%, the analogous bis-*O*-daunosaminyl derivative (44), and a mixture of the β–glycosides (1%). The disparity between our results for the TMS triflate promoted glycosidations and those reported by Terashima[15] has yet to be explained although we believe we have ruled out the possible adverse effects due to protic solvents used as solvent stabilisers. It has been noted [16] that the physical state of the molecular sieve employed in the reaction, together with the ratio of diethyl ether to dichloromethane used as solvent

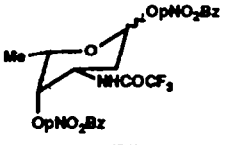


(21) R_1 = NH_2, R_2 = H.
(22) R_1 =F, R_2 = H.
(23) R_1 =H, R_2 = NH_2.
(24) R_1 =H, R_2 = F.

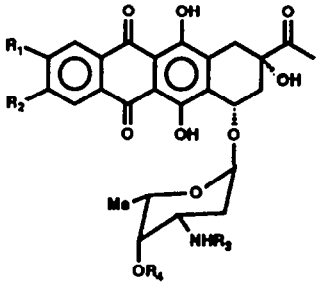
(25) R_1 = F, R_2 =H.
(26) R_1 = H, R_2 =F.



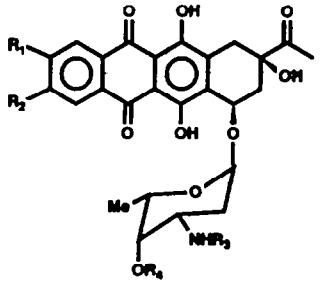
(27) R_1 = F, R_2 = H, R_3 = Me, R_4 = R_5 = MOM.
(28) R_1 = F, R_2 = R_3 = R_4 =R_5 =H.
(29) R_1 = H, R_2 =F, R_3 = Me, R_4 = R_5 = MOM.
(30) R_1 = R_3 = R_4 = R_5 =H, R_2 = F.



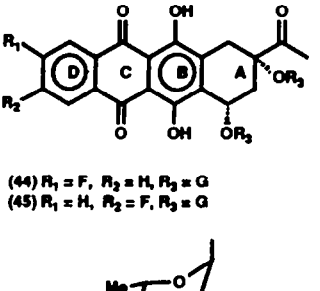
(31)



(32) R_1 = F, R_2 =H, R_3 = $COCF_3$, R_4 =pNO_2Bz.
(33) R_1 = F, R_2 = R_4 = H, R_3 = $COCF_3$.)
(34) R_1 =F, R_2 = R_4 = H, R_3 = H.HCl.
(35) R_1 = H, R_2 = F, R_3 = $COCF_3$, R_4 =pNO_2Bz.
(36) R_1 = R_4 = H, R_2 = F, R_3 = $COCF_3$.
(37) R_1 = R_4 = H, R_2 = F, R_3 = H.HCl.

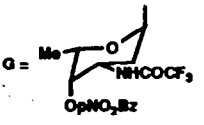


(38) R_1 = F, R_2 = H, R_3 = $COCF_3$, R_4 =pNO_2Bz.
(39) R_1 = F, R_2 = R_4 = H, R_3 = $COCF_3$.
(40) R_1 = F, R_2 = R_4 = H, R_3 = H.HCl.
(41) R_1 = H, R_2 = F, R_3 = $COCF_3$, R_4 =pNO_2Bz.
(42) R_1 = R_4 = H, R_2 = F, R_3 = $COCF_3$.
(43) R_1 = R_4 = H, R_2 = F, R_3 = H.HCl.



(44) R_1 = F, R_2 = H, R_3 = G
(45) R_1 = H, R_2 = F, R_3 = G

G =



SCHEME 3

has a profound influence on the outcome, and in this context we have found that in our hands, racemic 4-demethoxydaunomycinone has behaved similarly to the fluoro analogues. Whilst separation of the optically pure diastereoisomers of the major glycosides obtained from both anthracyclinones was easily performed by chromatography, removal of traces of the β-glycosides and the bis-*O*-daunosaminyl derivatives proved tedious. For this reason, we turned to the Koenigs - Knorr method of glycosidation as an alternative approach. In the case of both aglycones (28) and (30) glycosidation by this method, using the glycosyl chloride, afforded mixtures of α-glycosides as the only sugar containing products. Thus, for example, anthracyclinone (28) afforded the glycosides (32) (38%), (38)(39%), and unreacted (28) (19%). However it should be noted that improved yields of the required glycosides were obtained only by employing a large excess of the expensive sugar (31). In contrast reactions employing the glycosyl bromide gave better yields of the desired compounds but were accompanied by small amounts of the β-isomers.

Deprotection of the glycosides (32) , (35) , (38) and (41) was accomplished in two steps by standard methods. Isolation of the final products as the pure hydrochlorides was complicated by the instability of the free amines towards acid and by their poor solubility. Indeed the hydrochlorides (34), (37), (40), (43) appeared to aggregate in aqueous solution, possibly as a result of hydrogen bonding, and exhibited an uncharacteristically low solubility compared with daunomycin hydrochloride. The potential of these molecules to intercalate with DNA and other oligonucleotides is being examined by n.m.r. methods and will be reported elsewhere.

EXPERIMENTAL

General procedures: These have been reported previously.[5,9]

(±)-(1RS,3RS,1'RS)-and (1RS,3RS,1'SR)-3-(1'-Hydroxyethyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1,3-diol (3) and (2).

To a solution of the unsaturated ketone (1) (248 mg) in dry benzene (25 ml) under an argon atmosphere was added vanadium(IV)bis(2,4-pentanedionate)oxide (25 mg). The mixture was stirred at room temperature and a solution of *t*-butyl hydroperoxide (3 M, 667 µl, 2 equiv) in dry benzene added. After stirring for 2 h at room temperature the mixture was added dropwise to a stirred suspension of lithium aluminium hydride (266 mg, 7 equiv) in dry ether (150 ml) under an argon atmosphere at 0°. The suspension was stirred at room temperature for 2 h, cooled to 0°, and the excess hydride neutralized with ethyl acetate, and then methanol. The mixture was poured into a mixture of brine (100 ml) and water (100 ml), and the aqueous phase extracted with ethyl acetate (3x100 ml). The combined organic phase was washed with brine (2x100 ml), dried and the solvent evaporated. [The residue may be used directly in the next step.] Alternatively, crystallization from ether and centrifugal thin layer chromatography of the mother liquors (5% methanol in dichloromethane) afforded a mixture of *the title compounds* (243 mg, 91.3%). Partial seperation of this mixture was effected during chromatography (above). The less polar isomer (2), was crystallized from a mixture of ethyl acetate and light petroleum to give colorless prisms, m.p. 115-6° (Found: C, 62.6; H, 8.0. $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%). I.r. ν_{max} 3570 m, 3480 m, 2940 s, 2905 m, 2840 m, 1603 m, 1454 s, 1380 s, 1365 s, 1339 s, 1260 m, 1085 vs, 1060 vs, 959 m, 898 m cm^{-1}. ^1H n.m.r. δ 1.24, d, *J* 6.6 Hz, 3H, H 2'; 1.76, dd, *J* 4.8, 14.6 Hz, 1H, H 2; 2.33, ddd, *J* 1.8, 2.1, 14.6 Hz, 1H, H 2; 2.50, d, *J* 18.0 Hz, 1H, H 4; 2.89, bs, 1H, C(1')OH; 2.97, dd, *J* 2.1, 18.0 Hz, 1H, H 4; 3.24, bs, 1H, C(1)OH; 3.77, s, 3H, OCH_3; 3.79, q, *J* 6.6 Hz, 1H, H 1'; 3.86, s, 3H, OCH_3; 4.48, bs, 1H, C(3)OH; 5.24, dd, *J* 1.8, 4.8 Hz, 1H, H 1; 6.75, ABq, *J* 8.0 Hz, 2H, H 6, H 7. Mass spectrum m/z 268 (M, 31%), 206 (20), 205 (74), 180 (12), 178 (15), 177 (100), all other peaks less than 10%.

The more polar isomer (3), was crystallized from a mixture of ethyl acetate and light petroleum to give colorless needles: m.p. 156-9° (Found: C, 62.8; H, 7.5. $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%). I.r. ν_{max} 3680 m, 3490 m, 2940 s, 2845 m, 1602 m, 1455 s, 1378 s, 1330 s, 1260 m, 1088 vs, 962 m, 901 s cm^{-1}. ^1H n.m.r. δ 1.29, d, *J* 6.4 Hz, 3H, H 2'; 1.73, ddd, *J* 1.6, 4.8, 14.6 Hz, 1H, H 2; 2.39, d, *J* 17.9 Hz, 1H, H 4; 2.43, d, *J* 7.2 Hz, 1H, C(1')OH; 2.47, ddd, *J* 2.0, 2.3, 14.6 Hz, 1H, H 2; 3.05, dd, *J* 2.3, 17.9 Hz, 1H, H 4; 3.15, dd, *J* 1.6, 2.7 Hz, 1H, C(1)OH; 3.67, dq, *J* 6.4, 7.2 Hz, 1H, H 1'; 3.79, s, 3H, OCH_3; 3.86, s, 3H, OCH_3; 4.22, s, 1H, C(3)OH; 5.24, ddd, *J* 2.0, 2.7, 4.8 Hz, 1H, H 1; 6.75, ABq, *J* 8.9 Hz, 2H, H 6, H 7. Mass spectrum m/z 268 (M, 31%), 206 (22), 205 (76), 178 (16), 177 (100), 175 (10), all other peaks less than 10%.

(±)-(1RS,3RS)-3-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-1,3-diylbenzeneboronate (6).

A mixture of the triols (2) and (3) (353 mg) was dissolved in dry toluene (30 ml) by warming in an oil bath (100°). The solution was cooled to room temperature under an argon atmosphere, phenylboronic acid (214 mg) and *p*-toluenesulphonic acid (15 mg) added, and the mixture stirred for 2 h at room temperature. The solution was diluted with ether (80 ml), washed successively with 10% sodium bicarbonate solution (30 ml), brine (30 ml), dried, and the solvent evaporated. The residue was dissolved in dry dichloromethane (15 ml) and stirred at 30° under an argon atmosphere with pyridinium chlorochromate (1.10 g, 4 equiv) and powdered 3Å molecular sieve (1.25 g) for 1 h. The suspension was cooled, diluted with anhydrous ether (75 ml), stirred at room temperature for 15 min, and filtered through a short silica column. The column was eluted with ether (3x100 ml) and the combined eluant concentrated to give compound (6) (406 mg, 87.5%). Crystallization from a mixture of ether and light petroleum gave colorless needles, m.p. 101-3° (Found: C, 68.2; H, 6.0. $C_{20}H_{21}BO_5$ requires C, 68.2; H, 6.0%). I.r. ν_{max} 2960 m, 2940 m, 2840m, 1719 s, 1601 m, 1482 s, 1463 m, 1438 m, 1392 m, 1366 s, 1317 s, 1261 m, 1135 s, 1104 s, 1084 s, 908 m cm^{-1}. ^1H n.m.r. δ 2.23, m, 2H, H 2; 2.54, s, 3H, CH_3CO; 3.18, ABd, *J* 18.4 Hz, 1H, H 4; 3.02, ABd, *J* 18.4 Hz, 1H, H 4; 3.76, s, 3H, OCH_3; 3.89, s, 3H, OCH_3; 5.68, dd, *J* 2.8, 2.8 Hz, 1H, H 1; 6.74, s, 2H, H 6, H 7; 7.33, m, 3H, ArH; 7.81, m, 2H, ArH. ^{13}C n.m.r. δ 25.1, CH_3CO; 32.8, C2, 4; 34.4, C4, 2; 55.6, OCH_3; 56.7, OCH_3; 61.4, C1; 77.2, C3; 109.5, C7, 6; 110.0, C6, 7; 121.9, C8a, 4a; 126.4, C4a,8a; 127.5, 3C, aromatics; 130.9, aromatic; 133.9, 2C, aromatics; 151.2, C8, 5; 151.8, C 5, 8; 211.2, $COCH_3$. Mass spectrum m/z 353 (24%), 352 (M, 100), 351 (24), 231 (12), 230 (35), 205 (46), 177 (66), 43 (29) all other peaks less than 10%.

(±)-(1RS,3RS)-3-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronapthalene-1,3-diol (7). [6b]

A solution of the phenylboronate (6) (200 mg) in dichloromethane (50 ml) was stirred for 24 h with 2-methylpentane-2,4-diol (4.7 ml) and acetic acid (120 µl) at room temperature. The solution was washed successively with 5% aqueous sodium bicarbonate solution (50 ml), water (4x20 ml), and brine (20 ml), dried, and the solvent evaporated to yield *the title compound* (146 mg, 96.4%). Crystallization from a mixture of ether and light petroleum gave colorless needles, m.p. 94-5° (Found: C, 63.1; H, 7.1. $C_{14}H_{18}O_5$ requires C, 63.2; H, 6.8%). I.r. ν_{max} 3580 m, 3480 m, 2960 m, 2840 m, 1708 s, 1600 m, 1440 m, 1376 s, 1354 s, 1328 s, 1113 s, 1091 s, 1080 s, 1036 m, 1015 m, 969 m, 915 m cm^{-1}. ^1H n.m.r. δ 2.10, ABdd, *J* 4.3, 14.4 Hz, 1H, H 2; 2.26, ABddd, *J* 2.1, 2.1, 14.4 Hz, 1H, H 2; 2.39, s, 3H, CH_3CO; 2.79, ABd, *J* 17.7 Hz, 1H, H4; 3.04, ABdd, *J* 2.1, 17.7 Hz, 1H, H4; 3.43, d, *J* 4.3 Hz, 1H, C(1)OH; 3.78, s, 3H, OCH_3; 3.87, s, 3H, OCH_3; 4.59, s, 1H, C(3)OH; 5.22, ddd, *J* 2.1, 4.3, 4.3 Hz, 1H, H 1; 6.77, s, 2H, H 6, H 7. ^{13}C n.m.r. δ 24.6, $COCH_3$; 33.1, C 2, 4; 35.6, C 4, 2; 55.0, OCH_3; 55.9, OCH_3; 62.7, C1; 77.4, C 3; 107.9, C 7, 6; 109.6, C 6, 7; 122.4, C 8a, 4a; 125.8, C 4a, 8a; 151.5, C 8, 5; 151.8, C 5, 8; 212.9, $COCH_3$. Mass spectrum m/z 266 (M, 47%), 206 (13), 205 (68), 178 (14), 177 (100), 138 (11), 43 (31), all other peaks less than 10%.

(±)-(1RS,3RS)-3-Acetyl-5,8-dimethoxy-1,3-bis(methoxymethyloxy)-1,2,3,4-tetrahydronaphthelene (8).

A solution of the diol (7) (993 mg) in dry dichloromethane (100 ml) was stirred under reflux under an argon atmosphere with diisopropylethylamine (16.2 ml) and chloromethyl methyl ether (6.9 ml) for 28 h. The solution was poured onto sodium bicarbonate solution (100 ml, 5%) and the product extracted with dichloromethane (3x100 ml). The combined extracts were washed successively with water (100 ml), brine (100 ml), dried and solvent removed to give a brown oil. The oil was dissolved in ethyl acetate and the solution filtered through a pad of silica, which was washed with ethyl acetate to remove the product. Evaporation of the solvent from the filtrate gave *the title compound* (1.29 g, 97.8%) as off white crystals, a sample of which was recrystallized from a mixture of dichloromethane and light petroleum to give colourless crystals, m.p. 89-90° (Found: C, 60.7; H, 7.5. $C_{18}H_{26}O_7$ requires C, 61.0; H, 7.4%). I.r. (nujol) ν_{max} 1720 s, 1610 m, 1490 s, 1470 s, 1450 s, 1350 m, 1270 s, 1250 m, 1160 s, 1110 m, 1085 s, 1040 s, 1010 s, 905 m cm^{-1}. ^1H n.m.r. δ 2.18, ABdd, *J* 5.7, 14.9 Hz, 1H, H 2; 2.26, s, 3H, CH_3CO; 2.50, ABdm, *J* 14.9 Hz, 1H, H 2; 2.90, ABd, *J* 17.0 Hz, 1H, H 4; 3.20, ABd, *J* 17.0 Hz, 1H, H 4; 3.34, s, 3H, MOM CH_3; 3.45, s, 3H, MOM CH_3; 3.77, s, 6H, $(OCH_3)_2$; 4.65, ABd, *J* 7.2 Hz, 1H, OCH_2O; 4.71, ABd, *J* 6.8 Hz, 1H, OCH_2O; 4.77, ABd, *J* 7.2 Hz, 1H, OCH_2O; 4.94, ABd, *J* 6.8 Hz, 1H, OCH_2O; 5.03, dd, *J* 3.2, 5.7 Hz, 1H, H 1; 6.67, ABd, *J* 8.9 Hz, 1H, H 6, 7; 6.75, ABd, *J* 8.9 Hz, 1H, H 6, 7. ^{13}C n.m.r. δ 22.1, CH_3CO; 29.6, C 2, 4; 33.5, C 2, 4; 55.5, OCH_3; 55.9, 2C, $(OCH_3)_2$; 56.1, OCH_3; 68.9, C 1; 80.7, C 3; 92.8, OCH_2O; 97.4, OCH_2O; 108.2, C 6, 7; 110.1, C 6, 7; 123.8, C 8a, 4a; 125.0, C 4a, 8a; 150.8, C 8, 5; 151.9, C 5, 8; 209.5, $COCH_3$. Mass spectrum m/z 354 (M, 33%), 205 (100), 177 (72), all other peaks less than 10%.

(±)-(6RS,8RS)-6-Acetyl-4,4-dimethoxy-6,8-bis(methoxymethyloxy)-5,6,7,8-tetrahydronaphthalene-1(4H)-one (10)

A solution of the bis ether (8) (2.55g) in 2% methanolic potassium hydroxide (300 ml) was anodically oxidised in a single cell using platinum electrodes at a constant reference voltage (relative to a saturated calomel electrode) of 1.1 V until no starting material was detected by t.l.c. The reaction mixture was poured onto brine (200 ml), water was added to dissolve the salt and the product was extracted with ethyl acetate (3x200 ml). The combined extracts were washed with brine (3x200 ml), dried and the solvent evaporated to give the bisketal (9) which was used directly in the next step.

The bisketal (9) was dissolved in acetone (400 ml) and water (75 ml) was added. The solution was cooled to 0° before glacial acetic acid (3 ml) was added and the solution stirred at 0-4° for 60 h. Sodium bicarbonate solution (5%) was added to the reaction at 0° to neutralise the acid and the reaction allowed to warm to room temperature. The product was extracted with dichloromethane (3x400 ml) and the combined extracts washed with water and brine, dried and solvent evaporated to give a brown oil which was shown by n.m.r. spectroscopy to contain the dienones (10) and (11) in the ratio of 87:13. The major dienone (10) crystallized on standing at 4°C and was purified by recrystallization from a mixture of ether and light petroleum to give colourless crystals (1.62 g, 60.6%), m.p. 75-77° (Found: C, 58.3; H, 7.1. $C_{18}H_{26}O_8$ requires C, 58.4; H, 7.1%). I.r. ν_{max} 2810 m, 1705 s, 1670 s, 1645 s, 1625 m, 1350 m, 1280 m, 1085 vs, 1005 vs, 960 s, 905 m cm^{-1}. ^1H n.m.r. δ 2.28, s, 3H, CH_3CO; 2.06, ABddd, *J* 0.9, 5.9, 15.1 Hz, 1H, H 7; 2.38, ABddd, *J* 1.5, 4.0, 15.1 Hz, 1H, H 7; 2.49, bABd, *J* 19.0 Hz, 1H, H 5; 2.76, bABd, *J* 19.0 Hz, 1H, H 5; 3.20, s, 3H, OCH_3; 3.29, s, 3H, OCH_3; 3.35, s, 3H, OCH_3; 3.42, s, 3H, OCH_3; 4.69, m, 1H, H 8; 4.63, ABd, *J* 7.0 Hz, 1H, OCH_2O; 4.65, ABd, *J* 6.7 Hz, 1H, OCH_2O; 4.72, ABd, *J* 7.0 Hz, 1H, OCH_2O; 5.00, ABd, *J* 6.7 Hz, 1H, OCH_2O; 6.59, ABq, *J* 10.3 Hz, 2H, H 2, H 3. ^{13}C n.m.r. δ 24.2, CH_3CO; 30.6, C 5, 7; 32.7, C 5, 7; 51.1, 2C, $(OCH_3)_2$; 56.1, OCH_3; 56.3, OCH_3; 67.7, C 6, 8; 79.7, C 6, 8; 92.9, OCH_2O; 94.8, C 4; 98.1, OCH_2O; 132.7, C 3; 135.1, C 4a; 142.7, C 2; 149.6, C 8a; 183.3, C 1; 209.1, CH_3CO. Mass spectrum m/z 251 (58%), 221 (38), 189 (13), 163 (12), 162 (16), 161 (100), all other peaks less than 10%.

(±)-2-Acetyl-5,8-dimethoxy-4-methoxymethyloxy-3,4-dihydronaphthalene (12).

To a stirred solution of ketone (1) (1.50 g) and diisopropylethylamine (22 ml) in dry dichloromethane (220 ml) at room temperature under an argon atmosphere was added chloromethylmethyl ether (9.2 ml). Stirring was continued for 2 h, whereupon the mixture was shaken with dilute aqueous sodium bicarbonate (100 ml). The organic phase was washed with water (2x100 ml), brine (100 ml), dried and concentrated. The residue was flash chromatographed on a short t.l.c. silica column with 30% ethyl acetate in ether as eluant to give *the title compound* as a pale yellow solid (1.64 g, 93%). Crystallization from a mixture of ether and light petroleum afforded pale yellow prisms: m.p. 97-97.5° (Found: C, 66.0; H 7.2. $C_{16}H_{20}O_5$ requires C, 65.7; H, 6.9%). I.r. ν_{max} 2940 s, 2880 s, 2840 m, 1650 s, 1624 m, 1438 bm, 1355 s, 1320 s, 1258 bs, 1146 s, 1106 bs, 1014 s, 991 m, 905 m cm^{-1}. ^1H n.m.r. δ 2.22, ddd, *J* 2.9, 4.9, 18.4 Hz, 1H, H 3; 2.49, s, 3H, CH_3CO; 3.34, s, 3H, MOM CH_3; 3.41, dd, *J* 1.8, 18.4 Hz, 1H, H 3; 3.84, s, 3H, OCH_3; 3.87, s, 3H, OCH_3; 4.64, ABq, *J* 6.9 Hz, 2H, OCH_2O; 5.27, dd, *J* 1.8, 4.9 Hz, 1H, H 4; 6.89, ABq, *J* 9.0 Hz, 2H, H 6, H 7; 7.95, d, *J* 2.9 Hz, 1H, H 1. ^{13}C n.m.r. δ 25.4, $COCH_3$; 28.9, C 3; 55.4, OCH_3; 55.9, OCH_3; 56.1, OCH_3; 63.9, C 4; 94.7, OCH_2O; 111.3, C 7, 6; 113.4, C 7, 6; 122.3, C 8a, 4a; 124.3, C 4a, 8a; 130.3, C 1; 134.9, C 2; 150.8, C 8, 5; 151.0, C 5, 8; 198.8, C OCH_3. Mass spectrum m/z 292 (M, 32%), 249 (13), 231 (31), 230 (100), 215 (50), 189 (11), 188 (59), 187 (11), 173 (12), 172 (12), 115 (10), 45 (32), 43 (72), all other peaks less than 10%.

(±)-(2RS,4RS,1'RS,)- and (2RS,4SR,1'RS)-2-(1'-Hydroxyethyl)-,5,-dimethoxy-4-methoxymethyloxy-1,2,3,4-tetrahydronaphthalen-2-ol (15) and (16).

To a solution of the ketone (12) (7.75 g) in tetrahydrofuran (100 ml) was added ethanol (600 ml) and the solution stirred at room temperature with sodium borohydride (4.16 g) for 2 h. The solvent was evaporated, the residue partitioned between chloroform (200 ml) and water (100 ml), and the aqueous phase extracted with chloroform (2x50 ml). The combined extracts were washed with water (4x100 ml), brine (100 ml), dried, and the solvent evaporated. The residue was dissolved in dry benzene (130 ml) under an argon atmosphere, vanadium (IV) bis (2,4-pentanedionate) oxide (155 mg) added, and the solution stirred at 6°, whereupon a solution of *t*-butyl hydroperoxide (3M, 36.4 ml) in dry benzene was introduced dropwise. The solution was stirred at 6° for 1 h, then at room temperature for 30 min, and then added dropwise to a stirred suspension of lithium aluminium hydride (10.8 g) in dry ether (1.2 l) at 0° under an argon atmosphere. The mixture was stirred under reflux for 1 h, cooled to 0°, and the excess hydride destroyed with ethyl acetate, followed by methanol. The suspension was poured into 50% saturated brine (1 l) and extracted with ethyl acetate (3x200 ml). The combined extracts were washed with brine (2x300 ml), dried, and the solvent evaporated. Flash column chromatography (50 → 60% ethyl acetate in light petroleum) of the residue afforded the (2RS,4RS,1'RS) isomer (15) (3.55 g, 43%) which was crystallized from a mixture of ethyl acetate and light petroleum to give colourless needles, m.p. 108.5-109.5° (Found: C, 61.8; H, 7.9. $C_{16}H_{24}O_6$ requires C, 61.5; H, 7.7%). I.r. ν_{max} 3490 m, 2940 s, 2840 m, 1600 m, 1460 s, 1436 s, 1331 s, 1250 bm, 1148 s, 1113 s, 1086 vs, 1017 vs, 995 s cm^{-1}. ^1H n.m.r. δ 1.29, d, *J* 6.4 Hz, 3H, H 2'; 1.67, dd, *J* 3.6, 14.7 Hz, 1H, H 3; 2.43, d, *J* 7.8 Hz, 1H, C(1')OH; 2.44, d, *J* 18.1 Hz, 1H, H 1; 2.60, ddd, *J* 2.0, 2.5, 14.7 Hz, 1H, H 3; 3.06, dd, *J* 2.0, 18.1 Hz, 1H, H 1; 3.48, s, 3H, MOM CH_3; 3.60, dq, *J* 6.4, 7.8 Hz, 1H, H 1'; 3.79, s, 3H, OCH_3; 3.82, s, 3H, OCH_3; 4.74, s, 1H, C(2)OH; 4.86, ABq, *J* 6.9 Hz, 2H, OCH_2O; 5.21, dd, *J* 2.5, 3.6 Hz, 1H, H 4; 6.75, ABq, *J* 8.9 Hz, 2H, H 6, H 7. ^{13}C n.m.r. δ 17.0, C 2'; 32.2, C 1, 3; 34.5, C 3, 1 55.6, OCH_3; 55.7, OCH_3; 56.2, OCH_3; 69.7, C 4; 72.1, C 2; 74.1, C 1'; 97.2, OCH_2O; 107.7, C 7, 6; 109.7, C 6, 7; 124.4, C 8a, 4a; 125.3, C 4a, 8a; 151.6, C 8, 5; 151.9, C 5, 8. Mass spectrum m/z 312 (M, 29%), 250 (10), 206 (36), 205 (100), 188 (22), 178 (14), 177 (60), 175 (12), 45 (35), all other peaks less than 10%.

Further elution from the column gave the (2RS,4SR,1'RS) isomer (16) (3.62 g, 44%) which upon crystallization from a mixture of ethyl acetate and light petroleum afforded colourless prisms, m.p. 126-8° (Found: C, 61.4; H, 7.9. $C_{16}H_{24}O_6$ requires C, 61.5; H, 7.7%). I.r. ν_{max} 3570 m, 3475 m, 2935 s, 2840 m, 1599 m, 1435 bs, 1355 m, 1322 s, 1258 bs, 1107 s, 1084 s, 1016 s, 946 s, 920 s cm^{-1}. ^1H n.m.r. δ 1.24, d, *J* 6.4 Hz, 3H, H 2'; 1.96, dd, *J* 5.0, 14.3 Hz, 1H, H 3; 2.11, s, 1H, C(2)OH; 2.48, ddd, *J* 1.9, 3.1, 14.3 Hz, 1H, H 3; 2.55, d, *J* 17.4 Hz, 1H, H 1; 3.05, dd, *J* 1.9, 17.4 Hz, 1H, H 1; 3.19, d, *J* 4.6 Hz, 1H, C(1')OH; 3.44, s, 3H, MOM CH_3; 3.78, s, 3H, OCH_3; 3.81, s, 3H, OCH_3; 3.98, dq, *J* 4.6, 6.4 Hz, 1H, H 1'; 4.87, ABq, *J* 6.2 Hz, 2H, OCH_2O; 5.01, dd, *J* 3.1, 5.0 Hz, 1H, H 4; 6.74, ABq, *J* 8.9 Hz, 2H, H 6, H 7. ^{13}C n.m.r. δ 16.0, C 2'; 31.9, C 3, 1; 39.2, C 1, 3; 55.7, OCH_3; 55.9, OCH_3; 56.0, OCH_3; 70.0, C 4; 71.9, C 1'; 72.9, C 2; 98.4, OCH_2O; 108.2, C 7, 6; 110.3, C 6, 7; 124.9, C 8a, 4a; 125.9, C 4a, 8a; 151.2, C 8, 5; 152.1, C 5, 8. Mass spectrum m/z 312 (M, 25%), 207 (18), 206 (100), 205 (81), 204 (12), 191 (11), 190 (12), 189 (52), 178 (11), 177 (61), 176 (13), 175 (38), 174 (14), 45 (52), 43 (10), all other peaks less than 10%.

(±)-(2RS,4SR,1'RS)-2-(1'-t-Butyldimethylsilyloxyethyl)-5,8-dimethoxy-4-methoxymethyloxy-1,2,3,4-tetrahydronaphthalen-2-ol (17).

A solution of the diol (16) (624 mg) in dry dimethyl formamide (20 ml) was stirred under an argon atmosphere with diisopropylethylamine (522 µl) and *t*-butyldimethylchlorosilane (362 mg) for 44 h at 22°. The mixture was poured into dilute sodium bicarbonate solution (50 ml) and extracted with ether (3x30 ml). The combined extracts were washed successively with water (2x30 ml), brine (30 ml), dried, and the solvent evaporated to give *the title compound* (816 mg, 96%) as a colourless syrup (Found: C, 61.9; H, 9.0. $C_{22}H_{38}SiO_6$ requires C, 61.9; H, 9.0%). I.r. ν_{max} 3550 m, 2930 s, 2885 s, 2835 s, 1598 m, 1445 bm, 1377 m, 1360 m, 1322 m, 1250 bm, 1135 s, 1087 vs, 1022 s, 962 s, 906 s cm^{-1}. ^1H n.m.r. δ 0.13, s, 6H, $Si(CH_3)_2$; 0.93, s, 9H, $SiC(CH_3)_3$; 1.23, d, *J* 6.2 Hz, 3H, H 2'; 1.94, dd, *J* 6.9, 13.9 Hz, 1H, H 3; 2.20, s, 1H, OH; 2.29, ddd, *J* 2.3, 6.9, 13.9 Hz, 1H, H 3; 2.51, d, *J* 16.8 Hz, 1H, H 1; 2.88, dd, *J* 2.3, 16.8 Hz, 1H, H 1; 3.38, s, 3H, MOM CH_3; 3.76, s, 3H, OCH_3; 3.78, s, 3H, OCH_3; 3.80, q, *J* 6.2 Hz, 1H, H 1'; 4.64, d, *J* 6.8 Hz, 1H, OCH_2O; 4.91, d, *J* 6.8 Hz, 1H, OCH_2O; 5.09, t, *J* 6.9 Hz, 1H, H 4; 6.72, ABq, *J* 8.3 Hz, 2H, H 6, H 7. ^{13}C n.m.r. δ -4.9, $SiCH_3$; -4.1, $SiCH_3$; 17.5, C 2'; 18.0, $SiC(CH_3)_3$; 25.8, 3C, $SiC(CH_3)_3$; 29.9, C 1; 39.5, C 3; 55.4, OCH_3; 55.7, OCH_3; 55.8, OCH_3; 70.6, C 4; 73.9, C 2; 74.8, C 1'; 96.9, OCH_2O; 108.4, C 6, 7; 109.9, C 7, 6; 125.8, C 8a, 4a; 126.3, C 4a, 8a; 151.4, C 5, 8; 152.0, C 8, 5. Mass spectrum m/z 426 (M, 15%), 346 (15), 308 (35), 275 (17), 264 (18), 234 (10), 217 (21), 216 (100), 208 (12), 207 (69), 206 (36), 191 (13), 190 (72), 178 (50), 160 (65), 119 (100), 115 (23), 111 (14), 103 (10), 75 (74), 73 (65), 45 (49), all other peaks less than 10%.

(±)-(1RS,3RS,1'RS)-3-(1'-t-Butyldimethylsilyloxyethyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-1,3-diyl benzeneboronate (19).

The silyl ether (17) (816 mg) was dissolved under an argon atmosphere in dry dichloromethane (15 ml) and cooled to -95°. A solution of dimethylboron bromide in dichloromethane (1.0 m, 1.67 ml) was added dropwise and the mixture stirred at -95° for 3 h. The solution was cannelated into a vigorously stirred suspension of saturated sodium bicarbonate solution (10 ml) and tetrahydrofuran (15 ml) and the mixture stirred for 15 min. The organic phase was removed and the aqueous phase extracted with dichloromethane (3x10 ml). The combined organic phase was washed with brine (20 ml), dried, and the solvent evaporated to give (±)-(1RS,3SR,1'SR)-3-(1'-*t*-butyldimethylsilyloxyethyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1,3-diol (18) (717 mg). An analytical sample was purified by flash column chromatography (40% ether in light petroleum) to give a colourless syrup (Found: C, 62.6; H, 8.7. $C_{20}H_{34}SiO_5$ requires C, 62.8; H, 9.0%). I.r. ν_{max} 3520 m, 2930 m, 2890 s, 2855 s, 2840 s, 1598 m, 1432 m, 1376 s, 1324 s, 1081 vs, 993 s, 951 s cm^{-1}. ^1H n.m.r. δ 0.13, s, 6H, $Si(CH_3)_2$; 0.92, s, 9H, $SiC(CH_3)_3$; 1.23, d, *J* 6.4 Hz, 3H, H 2'; 1.64, dd, *J* 9.6, 13.1 Hz, 1H, H 2; 2.27, m, 1H, C(1)OH; 2.35, ddd, *J* 2.5, 6.9, 13.1 Hz, 1H, H 2; 2.52, ABdd, *J* 1.1, 17.6 Hz, 1H, H 4; 2.79, ABdd, *J* 2.5, 17.6 Hz, 1H, H 4; 3.78, s, 3H, OCH_3; 3.80, q, *J* 6.4 Hz, 1H, H 1'; 3.86, s, 3H, OCH_3; 4.30, m, 1H, C(3)OH; 5.24, bdd, *J* 6.1, 9.6 Hz, 1H, H 1; 7.27, s, 2H, H 6, H 7. ^{13}C n.m.r. δ -4.7, $SiCH_3$; -4.0, $SiCH_3$; 17.6, C 2'; 18.1, $SiC(CH_3)_3$; 26.0, 3C, $SiC(CH_3)_3$; 31.0, C 4; 38.4, C 2; 55.7, 2C, $(OCH_3)_2$; 65.6, C 1; 73.5, C 3; 74.7, C 1'; 107.9, C 7, 6; 108.7, C 6, 7; 124.6, C 8a, 4a; 128.2, C 4a, 8a; 151.6, C 8, 5; 151.8, C 5, 8. Mass spectrum m/z 382 (M, 16%), 346 (10), 307 (18), 274 (14), 263 (19), 233 (11), 222 (15),

215 (34), 206 (10), 205 (36), 204 (11), 190 (16), 189 (95), 177 (34), 174 (12), 159 (33), 120 (13), 119 (100), 115 (16), 103 (10), 75 (67), 73 (62), all other peaks less than 10%.

The residue was taken up in dry toluene (45 ml) and stirred under an argon atmosphere at 28° with phenyl boronic acid (340 mg) and *p*-toluenesulphonic acid (15 mg) for 30 h. The solution was poured into dilute sodium bicarbonate solution (100 ml) and the aqueous phase extracted with ether (2x30 ml). The combined organic phase was washed with brine (30 ml), dried, and the solvent evaporated. Crystallization of the residue from methanol gave *the title compound* (581 mg, 67.3%) as colourless prisms, m.p. 137-8° (Found: C, 66.7; H, 7.9. $C_{26}H_{37}BO_5Si$ requires C, 66.7; H, 8.0%). Flash column chromatography of the mother liquors afforded a second crop (108 mg, 11.5%). Overall yield based on diol (16) was 73.6%. I.r. ν_{max} 2930 s, 2895 m, 2855 m, 1600 m, 1430 m, 1391 m, 1354 s, 1321 vs, 1393 s, 1110 vs, 1087 s, 979 m cm^{-1}. ^1H n.m.r. δ 0.14, s, 3H, $SiCH_3$; 0.16, s, 3H, $SiCH_3$; 0.89, s, 9H, $SiC(CH_3)_3$; 1.30, d, *J* 6.3 Hz, 3H, H 2'; 1.92, dd, *J* 2.4, 13.7 Hz, 1H, H 2; 2.27, ddd, *J* 1.3, 3.5, 13.7 Hz, 1H, H 2; 2.91, ABdd, *J* 1.3, 18.4 Hz, 1H, H 4; 3.02, ABd, *J* 18.4 Hz, 1H, H 4; 3.75, s, 3H, OCH_3; 3.87, s, 3H, OCH_3; 4.02, q, *J* 6.3 Hz, 1H, H 1'; 5.65, dd, *J* 2.4, 3.5 Hz, 1H, H 1; 6.71, s, 2H, H 6, H 7; 7.28, m, 3H, aromatics; 7.78, m, 2H, aromatics. ^{13}C n.m.r. δ -4.7, $SiCH_3$; -4.0, $SiCH_3$; 17.4, C 2'; 18.0, $SiC(CH_3)_3$; 25.9, 3C, $SiC(CH_3)_3$; 30.6, C 4; 34.4, C 2; 55.6, OCH_3; 56.7, OCH_3; 61.8, C 1; 73.7, C 1'; 73.8, C 3; 109.0, C 6, 7; 109.7, C 7, 6; 124.4, C 8a, 4a; 127.3, 3C, aromatics; 127.4, C 4a, 8a; 130.4, aromatic; 133.9, 2C, aromatics; 151.3, C 8, 5; 152.1, C 5, 8. Mass spectrum m/z 217 (12%), 216 (59), 191 (14), 190 (100), 180 (24), 138 (11), 120 (15), 105 (12), 75 (14), 73 (22), all other peaks less than 10%.

(±)-(1RS,3RS)-3-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-1,3-diylbenzeneboronate (6) from (19).

A mixture of the silyl ether (19) (550 mg) in dry tetrahydrofuran (5.5 ml) under an argon atmosphere was cooled to 0°. Tetra-*n*-butylammonium fluoride trihydrate (1.37 g) was added and the mixture stirred at 0° until homogenous, and then at room temperature for 4 h. The solution was poured into dilute sodium bicarbonate solution (75 ml), extracted with ethyl acetate (3x50 ml), and the combined extracts washed with brine, dried, and the solvent evaporated. The residue was taken up in dry dichloromethane (20 ml) and stirred at 30° under an argon atmosphere with pyridinium chlorochromate (1.28 g) and powdered 3Å molecular sieve (1.46 g) for 1.25 h, whereupon the suspension was cooled and stirred with dry ether (100 ml) for 0.5 h. The mixture was filtered through silica (Merck Art 7749), the solvent evaporated, and the residue flash column chromatographed (50% ether in light petroleum) to give *the title compound* (386 mg, 93.3%). Crystallization from a mixture of ether and light petroleum gave colourless needles, m.p. 101-3°, indistinguishable from material described above.

5-Fluoroisobenzofuran-1(3H)-one(22).

5-Aminoisobenzofuranone-1(3*H*)-one (21)[17] (8.0 g) was dissolved in water (20 ml) and hexafluorophosphoric acid (40%, 40 ml), cooled to 0°, and treated with a solution of sodium nitrite (8.0 g,) in water (50 ml). The resulting precipitate was collected by filtration, washed with cold methanol (20 ml) and ether (20 ml), and added to mesitylene (400 ml). This suspension was heated to reflux, cooled, decanted, and freed of solvent to yield a solid residue, which was purified by column chromatography (silica, dichloromethane) to afford *the product* as colourless needles (4.6 g, 56%), m.p. 117-119° (Found: C, 62.9; H, 3.3; F, 12.7. $C_8H_5O_2F$ requires C, 63.2; H, 3.3; F, 12.5%). I.r. ν_{max} 3048w, 1752bs, 1628w, 1600m, 1482m, 1330w, 1265s, 1258s, 1201w, 1144w, 1097m, 1064,s 1006s, 948w 892m, 854w, 797s, 784w, 762m, 748 m cm^{-1}. ^1H n.m.r. δ 5.34, s, 2H, H 3; 7.20-7.30, m, 2H, H 4, H 6; 7.91, dd ,*J* 4.8, 9.0 Hz, 1H, H 7. ^{19}F n.m.r. δ -103.5 to -103.4, m.

6-Aminoisobenzofuran-1(3H)-one (23).

A solution of 6-nitroisobenzofuran-1(3*H*)-one[17] (20.0 g) in ethyl acetate (700 ml) was stirred under a hydrogen atmosphere with 10% palladium on charcoal (500 mg) for 40 h. The mixture was filtered, and the filtrate freed of solvent to yield a pale yellow solid (16.5 g). Recrystallisation from ethyl acetate afforded *the product* as pale yellow prisms (12.9 g, 77%), m.p. 183.5-185.5° (lit[17] m.p. 182°).

6-Fluoroisobenzofuran-1(3H)-one (24).

The preceeding amine (23) (5.0 g) was dissolved in water (25 ml) and concentrated hydrochloric acid (10 ml), cooled to 0°, and diazotised with a solution of sodium nitrite (2.5 g) in water (15 ml). Fluoroboric acid (40%, 8 ml) was added, the resulting precipitate collected by filtration, washed with cold methanol (20 ml) and ether (20 ml) and added to xylene (100 ml). This solution was heated to reflux, cooled, and freed of solvent to yield a solid product. This was purified by column chromatography (silica, dichloromethane) to yield the crude product, (2.5 g, 49%), a sample of which was recrystallized from a mixture of ether and light petroleum to afford *the product* as colourless needles, m.p. 100-102° (Found: C, 63.2; H, 3.3; F, 12.6. $C_8H_5O_2F$ requires C, 63.2; H, 3.3; F, 12.5%). I.r. ν_{max} 1760bs, 1492m, 1311w, 1267s, 1239m 1190w, 1113w, 1045s, 998s, 918m, 875m, 822m, 810w, 767s, 728w, 688w cm^{-1}. ^1H n.m.r. δ 5.33, s, 2H, H 3; 7.43, ddd, *J* 2.3, 8.5, 8.6 Hz, 1H, H 5; 7.51, ddd, *J* 0.7, 4.4, 8.5 Hz, 1H, H 4; 7.57, dd, *J* 2.3, 7.3 Hz, 1H, H 7. ^{19}F n.m.r. δ -112.1, ddddd, *J* 1.5, 1.5, 4.4, 7.3, 8.6 Hz.

Fluorinated derivatives (25) and (26).of 3-cyanoisobenzofuran-1(3H)-one .

These compounds were all prepared from the parent fluoroisobenzofuran-1(3*H*)-ones (22) and (24) respectively by our previously described method.[18]

(±)-(7RS,9RS)-9-Acetyl-2-fluoro-6-hydroxy-11-methoxy-7,9-bis(methoxymethyloxy)-7,8,9,10-tetrahydronaphthacene-5,12,-dione (27).

Following the general procedure previously described[5c], dienone (10)(300 mg) in tetrahydrofuran (5 ml) was added to a solution of the phthalide anion prepared from diisopropylamine (148.2 µl) in tetrahydrofuran (3 ml), *n*-butyllithium (1.6 M, 630 µl), and phthalide (25) (156 mg) in tetrahydrofuran (7 ml), and the reaction mixture worked up as described. Crystallization of the product from methanol gave orange needles (351 mg, 85%), m.p. 153.5-155° (Found: C, 61.8; H, 5.1; F, 3.8. $C_{25}H_{25}FO_9$ requires C, 61.5; H, 5.2; F, 3.9%). Centrifugal t.l.c. of the mother liquors (25% ethyl acetate in light petroleum) gave a further crop (42 mg, total 393 mg, 95%). I.r. ν_{max} 3510 w, 2815 w, 1705 s, 1663 s, 1625 s, 1588 s, 1300 vs, 1317 s, 1275 bm, 1085 s, 995 s cm^{-1}. ^1H n.m.r. δ 2.23, dd, *J* 5.9, 15.0 Hz, 1H, H 8; 2.32, s, 3H, CH_3CO;

2.58, ddd, J 1.0, 3.3, 15.0 Hz, 1H, H 8; 3.20, ABd, J 17.9 Hz, 1H, H 10; 3.30, s, 3H, MOM CH_3; 3.37, ABdd, J 1.0, 17.9 Hz, 1H, H 10; 3.50, s, 3H, MOM CH_3; 3.91, s, 3H, C(11)OCH_3; 4.71, ABd, J 7.2 Hz, 1H, OCH_2O; 4.79, dd, J 6.9 Hz, 1H, OCH_2O; 4.79, ABd, J 7.2 Hz, 1H, OCH_2O; 5.07, d, J 6.9 Hz, 1H, OCH_2O; 5.16, dd, J 3.3, 5.9 Hz, 1H, H 7; 7.44, ddd, J 2.7, 8.6, J_F 7.9 Hz, 1H, H 3; 7.91, dd, J 2.7, J_F 8.6 Hz, 1H, H 1; 8.31, dd, J 8.6, J_F 5.4 Hz, 1H, H 4; 13.70, s, 1H, OH. ^{13}C n.m.r. δ 24.2, $COCH_3$; 29.7, C 10; 34.9, C 8; 56.0, 2C, MOM CH_3; 61.3,C(11)OCH_3 68.4, C 7; 81.2, C 9; 92.9, OCH_2; 98.0, OCH_2; 113.5, C 5a; 113.9, J 23.9 Hz, C 3; 121.1, J 22.8 Hz, C 1; 122.9, J 1.5 Hz, C 11a; 129.0, J 2.9 Hz, C 4a; 129.8, J 8.8 Hz, C 4; 133.3, C 6a; 137.4, J 8.4 Hz, C 12a; 141.5, C 10a; 152.2, C 11; 158.9, C 6; 166.8, J 257.5 Hz, C 2; 180.3, J 1.6 Hz, C 12; 187.1, C 5; 209.2, $COCH_3$. ^{19}F n.m.r. δ - 101.1, ddd, J 5.4, 7.9, 8.6 Hz.

(±)-4-Demethoxy-2-fluorodaunomycinone (28).

A solution of compound (27) (171 mg) in dry dichloromethane (30 ml) at -78° under an argon atmosphere was stirred with boron trichloride (1.05 M in dichloromethane, 4.1 ml, 12 equiv., introduced dropwise) for 0.5 h. The mixture was washed with 5% sodium bicarbonate solution (50 ml) and the aqueous phase extracted with chloroform (3x20 ml). The combined organic phase was washed successively with 5% sodium bicarbonate (50 ml), water (50 ml), and brine (50 ml), dried, and the solvent evaporated to give *the title compound* as a red solid (132 mg, 98%). Crystallization from methanol gave red prisms: sublimes 209°; m.p. 212-4°. (Found: C, 62.3; H, 4.0; F, 5.0. $C_{20}H_{15}FO_7$ requires C, 62.2; H, 3.9; F, 4.9%). I.r. ν_{max} 3570 w, 3465 bm, 2820 m, 1710 s, 1624 s, 1590 vs, 1295 s, 1368 vs, 1330 vs, 1268 bs, 1100 s, 1074 m, 997 m, 940 m, 920 m, 900 m cm^{-1}. ^1H n.m.r. δ 2.17, ABdd, J 4.4, 14.6 Hz, 1H, H 8; 2.35, ABdt, J 1.8, 14.6 Hz, 1H, H 8; 2.43, s, 3H, CH_3CO; 2.95, ABd, J 18.9 Hz, 1H, H 10; 3.19, ABdd, J 1.8, 18.9 Hz, 1H, H 10; 3.87, d, J 6.3 Hz, 1H, C(7)OH; 4.53, s, 1H, C(9)OH; 5.31, m, 1H, H 7; 7.50, ddd, J 2.5, 8.5, J_F 7.9 Hz, 1H, H 3; 7.97, dd, J 2.5, J_F 8.6 Hz, 1H, H1; 8.38, dd, J 8.5, J_F 5.5 Hz, 1H, H 4; 13.15, s, 1H, C(11)OH; 13.55, s, 1H, C(6)OH. ^{13}C n.m.r. (DMSO-d_6) δ 24.5, $COCH_3$; 32.1, C 10; 35.8, C 8; 60.5, C 7; 76.2, C 9; 109.5, C 11a, 5a; 110.6, C 5a, 11a; 112.8, d, J 23.9 Hz, C 3; 122.3, d, J 23.0 Hz, C 1; 129.7, d, J 2.7 Hz, C 4a; 130.3, d, J 9.6 Hz, C 4; 135.2, C 10a; 135.5, d, J 8.5 Hz, C 12a; 137.4, C 6a; 155.6, C 11; 156.4, C 6; 165.8, d, J 255.7 Hz, C 2; 184.7, C 5; 184.8, d, J 1.9 Hz, C 12; 211.8, CH_3CO. ^{19}F n.m.r. (40% $CDCl_3$ in CD_3OD) δ -101.3, ddd, J 5.5, 7.9, 8.5 Hz. Mass spectrum m/z 387 (10%), 386 (M, 47), 368 (10), 366 (11), 351 (18), 350 (64), 335 (20), 327 (21), 326 (30), 325 (100), 324 (12), 309 (10), 308 (16), 307 (11), 298 (18), 297 (73), 279 (12), 251 (12), 205 (50), 43 (26), all other peaks less than 10%.

(±)-(7RS,9RS)-9-Acetyl-3-fluoro-6-hydroxy-11-methoxy-7,9-bis(methoxymethyloxy)-7,8,9,10 tetrahydronaphthacenedione (29)

Following the general procedure previously reported[5c], a solution of the phthalide anion in dry tetrahydrofuran (15 ml), generated from phthalide (26) (260 mg, 1.25 equiv.), diisopropylamine (247 µl, 1.25 equiv.), and *n*-butyllithium (1.6 M, 1.05 ml, 1.2 equiv.), was treated with a solution of dienone (10) (500 mg) in dry tetrahydrofuran (3 ml) at -78°, and then stirred for 1 h at room temperature. Workup as described followed by crystallization from methanol gave *the title compound* (485 mg). Centrifugal t.l.c. (30% ethyl acetate in light petroleum) afforded a further crop (163 mg, total 94%). Recrystallization from methanol gave yellow needles, m.p. 126-7°. (Found: C, 61.2; H, 5.0; F, 3.7. $C_{25}H_{25}FO_9$ requires C, 61.5; H, 5.2; F, 3.9%). I.r. ν_{max} 3560 w, 2820 w, 1707 s, 1663 s, 1626 s, 1584 s, 1344 vs, 1318 s, 1260 bm, 1140 m, 1075 bm, 1001 s, 906 m cm^{-1}. ^1H n.m.r. δ 2.21, dd, J 5.8, 14.9 Hz, 1H, H 8; 2.29, s, 3H, CH_3CO; 2.55, ddd, J 1.2, 3.3, 14.9 Hz, 1H, H 8; 3.19, d, J 17.7 Hz, 1H, H 10; 3.25, dd, J 1.2, 17.7 Hz, 1H, H 10; 3.31, s, 3H, MOM CH_3; 3.49, s, 3H, MOM CH_3; 3.88, s, 3H, C(11)OCH_3; 4.69, d, J 7.2 Hz, 1H, OCH_2O; 4.76, d, J 7.2 Hz, 1H, OCH_2O; 4.77, d, J 6.9 Hz, 1H, OCH_2O; 5.05, d, J 6.9 Hz, 1H, OCH_2O; 5.14, dd, J 3.3, 5.8 Hz, 1H, H 7; 7.44, ddd, J 2.7, 8.8, J_F 7.9 Hz, 1H, H 2; 7.87, dd, J 2.7, J_F 8.6 Hz, 1H, H 4; 8.29, dd, J 8.8, J_F 5.3 Hz, 1H, H 1; 13.59, s, 1H, OH. ^{13}C n.m.r. δ 24.1, $COCH_3$; 29.6, C 10; 34.7, C 8; 55.9, 2C, MOM CH_3; 61.2, C(11)OCH_3; 68.3, C 7; 81.0, C 9; 92.8, C(9)OCH_2; 97.9, C(7)OCH_2; 112.6, J 23.6 Hz, C 2; 113.7, C 5a; 121.9, J 22.4 Hz, C 4; 122.4, C 11a; 130.5, J 8.8 Hz, C 1; 131.0, J 2.9 Hz, C 12a; 132.8, C 6a; 134.9, J 8.0 Hz, C 4a; 142.0, C 10a; 152.1, C 11; 158.6, C 6; 165.8, J 257.7 Hz, C 3; 180, C 12; 187.0, C 5; 209.1, $COCH_3$. ^{19}F n.m.r. - 103.0, ddd, J 5.3, 7.9, 8.6 Hz. Mass spectrum m/z 365 (24%), 364 (100), 350 (13), 349 (16), 339 (29), 336 (15), 335 (66), 322 (10), 321 (32), 319 (13), 311 (14), 294 (11), 293 (44), 278 (11), 250 (14), 194 (12), all other peaks less than 10%.

(±)-4-Demethoxy-3-fluorodaunomycinone (30)

To stirred a solution of (29) (615 mg) in dry dichloromethane (100 ml) at -78° under an argon atmosphere was added dropwise a solution of boron trichloride in dichloromethane (1.05 M, 12.1 ml, 10 equiv.), and the mixture stirred at -78° for 45 min. The solution was washed with dilute sodium bicarbonate solution (200 ml), and the aqueous phase extracted with chloroform (3x50 ml). The combined organic phase was washed successively with water (2x50 ml), brine (50 ml), dried and the solvent evaporated. Crystallization of the residue from a mixture of dichloromethane and methanol gave red prisms(440mg). Successive concentration of the mother liquors to give a second crop (21.7 mg), followed by column chromatography of the residual liquors (Sephadex LH-20, methanol) gave a total of 470 mg (96%). Recrystallization from tetrahydrofuran gave red prisms: sublimes to red needles ~215°, m.p. 280-2° (Sweats 278°). (Found: C, 62.1; H, 3.9; F, 5.0. $C_{20}H_{15}FO_7$ requires C, 62.2; H, 3.9; F, 4.9%). I.r. ν_{max} 3690 w, 3475 bm, 2990 w, 2870 w, 1710 s, 1626 s, 1592 vs, 1396 m, 1365 s, 1320 s, 1262 bm, 1092 m, 1076 m, 1000 m, 952 m, 900 m cm^{-1}. ^1H n.m.r. δ 2.20, dd, J 4.8, 14.8 Hz, 1H, H 8; 2.37, dt, J 2.1, 14.8 Hz, 1H, H 8; 2.43, s, 3H, CH_3CO; 2.97, d, J 18.8 Hz, 1H, H 10; 3.22, dd, J 2.1, 18.8 Hz, 1H, H 10; 3.81, d, J 6.2 Hz, 1H, C(7)OH; 5.31, s, 1H, C(9)OH; 5.34, m, 1H, H 7; 7.52, ddd, J 2.6, 8.7, J_F 7.8 Hz, 1H, H 2; 8.01, ddd, J 0.3, 2.6, J_F 8.6 Hz, 1H, H 4; 8.41, ddd, J 0.3, 8.7, J_F 5.2 Hz, 1H, H 1; 13.32, s, 1H, C(11)OH; 13.47, s, 1H, C(6)OH. ^{13}C n.m.r. (DMSO-d_6) δ 24.5, $COCH_3$; 32.2, C 10; 35.7, C 8; 60.4, C 7; 76.2, C 9; 109.9, 2C, C 5a, C 11a; 112.7, d, J 20.3 Hz, C 2; 122.2, d, J 21.3 Hz, C 4; 130.2, d, J 3.3 Hz, C 12a; 130.2, d, J 8.7 Hz, C 1; 135.6, d, J 7.1 Hz, C 4a; 135.7, C 10a; 136.8, C 6a; 155.6, C 11; 156.4, C 6; 167.8, J 257.5 Hz, C 3; 184.5, J 4.1 Hz, C 5; 184.7, C 12; 211.9, CH_3CO. ^{19}F n.m.r. (40% $CDCl_3$ in CD_3OD) δ -101.2, dt, J 5.4, 8.3 Hz. Mass spectrum m/z 386 (M, 41%), 351 (15), 350 (57), 335 (19), 327 (16), 326 (26), 325 (100), 324 (10), 308 (16), 307 (11), 298 (12), 297 (55), 279 (10), 251 (12), 205 (42), 91 (10), 43 (26), all other peaks less than 10%.

Glycosidation of (±)-4-Demethoxy-2--fluorodaunomycinone

a. By Method of Terashima[15]:

A solution of the ester (31) (150 mg) in dry ether (3 ml) and dichloromethane (11 ml) was stirred with freshly activated 4Å molecular sieve (1.1 g) at -42° under an argon atmosphere, whereupon TMS triflate (104 µl) was introduced dropwise. The mixture was stirred at 0° for 1 h, cooled to -30°, and a solution of the aglycone (28) (52 mg) in dichloromethane (25 ml) added dropwise. After stirring at -30° overnight, the mixture was decanted and partitioned between ethyl acetate and dilute sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate until free of colour, and the combined organic phase washed with brine, dried, and the solvent evaporated. Column chromatography (Sephadex LH-20, methanol) of the residue, followed by centifugal thin layer chromatography of the glycoside fractions (0.5% methanol in dichloromethane) gave compounds (32) (29.0 mg, 28.3%) and (38) (29.1 mg, 28.4%), together with a β - isomer (1.2 mg, 1.2%) and the 7,9-bis-*O*-(daunosaminyl) derivative (44) (2.3 mg, 1.5%). Centrifugal t.l.c. (2% methanol in dichloromethane) of the non-glycoside fraction gave unreacted (31) (3.8 mg, 7.3%), preceeded by an unidentified compound (4.5 mg). Compound (32) crystallized from a mixture of dichloromethane and diisopropyl ether as red needles, m.p. 163-5°; $[\alpha]_D$ -90° (c, 0.15, dioxane) (Found: C, 55.2; H, 3.8; N, 3.4; F, 9.8. $C_{35}H_{28}F_4N_2O_{13}$ requires C, 55.3; H, 3.7; N, 3.7; F, 10.0%). I.r. ν_{max} 3520 w, 3420 w, 2960 w, 1752 bm, 1695 bm, 1618 s, 1583 s, 1481 m, 1435 m, 1318 bs, 1268 s, 1246 s, 1147 s, 1108 s, 1095 s, 999 s, 982 s, 954 s cm^{-1}. ^1H n.m.r. δ 1.29, d, *J* 6.4 Hz, 3H, H 6'; 2.08 - 2.27, m, 3H, H 8, C(2')H_2; 2.39, m, 1H, H 8; 2.47, s, 3H, CH_3CO; 3.00, d, *J* 19.1 Hz, 1H, H 10; 3.31, dd, *J* 1.3, 19.1 Hz, 1H, H 10; 4.27, s, 1H, C(9)OH; 4.51, m, 2H, H 3, H 5'; 5.34, m, 1H, H 7; 5.52, m, 1H, H 4'; 5.71, bs, 1H, H 1'; 6.44, bd, *J* 7.2 Hz, 1H, NH; 7.53, ddd, *J* 2.7, 8.7, J_F 7.7 Hz, 1H, H 3; 8.00, dd, *J* 2.6, J_F 8.6 Hz, 1H, H 1; 8.33, m, 4H, ArH; 8.39, dd, *J* 8.7, J_F 5.2 Hz, 1H, H 4; 13.17, s, 1H, C(11)OH; 13.63, s, 1H, C(6)OH. ^{13}C n.m.r.δ 17.1, C 6'; 24.9, CH_3CO; 30.1, C 2'; 33.6, C 10; 35.2, C 8; 45.7, C 3'; 66.2, C 5'; 70.0, C 7; 71.6, C 4'; 76.5, C 9; 100.0, C1'; 110.4, C 11a, 5a; 111.6, C 5a, 11a; 113.7, *J* 22.6 Hz, C 3; 115.3, q, *J* 288.3 Hz, CF_3; 122.0, *J* 22.6 Hz, C 1; 123.8, 2C, Ar; 129.9, *J* 3.2 Hz, C 4a; 130.3, *J* 9.2 Hz, C 4; 131.0, 2C, Ar; 133.6, C 10a; 134.2, Ar; 135.9, C 6a; 136.1, *J* 8.2 Hz, C 12a; 150.5, Ar; 156.6, q, *J* 37.5 Hz, $COCF_3$; 156.5, C 6, 11; 156.7, C 11, 6; 164.5, ArCO; 166.0, *J* 259.2 Hz, C 2; 185.4, C 5; 185.5, *J* 1.5 Hz, C 12; 211.5, $COCH_3$. ^{19}F n.m.r δ - 100.3, ddd, *J* 5.2, 7.7, 8.6 Hz, C(2)F; -76.2, s, CF_3.

Compound (38) crystallized as red prisms from a mixture of diisopropyl ether and dichloromethane: m.p. 165-8°; $[\alpha]_D$ -286° (c, 0.14, dioxane). (Found: C, 55.0; H, 3.8; N, 3.7; F, 9.7. $C_{35}H_{28}F_4N_2O_{13}$ requires C, 55.3; H, 3.7; N, 3.7; F, 10.0%). I.r. ν_{max} 3600 w, 2950 w, 2830 w, 1720 s, 1618 m, 1586 s, 1329 s, 1263 s, 1093 s, 998 m, 951 s cm^{-1}. ^1H n.m.r. δ 1.26, d, *J* 6.4 Hz, 3H, H 6'; 2.01, m, 2H, H 8, H 2'; 2.17, m, 1H, H 2'; 2.42, s, 3H, CH_3CO; 2.50, m, 1H, H 8; 3.03, d, *J* 19.5 Hz, 1H, H 10; 3.33, d, J 19.5 Hz, 1H, H 10; 4.48, s, 1H, C(9)OH; 4.51, m, 1H, H 3'; 4.72, q, *J* 6.4 Hz, 1H, H 5'; 5.42, m, 1H, H 7; 5.58, s, 1H, H 1'; 6.47, bd, *J* 7.3 Hz, 1H, NH; 7.53, ddd, *J* 2.6, 8.7, J_F 8.0 Hz, 1H, H 3; 7.99, dd, *J* 2.6, J_F 8.6 Hz, 1H, H 1; 8.29, m, 4H, ArH; 8.40, dd, *J* 8.7, J_F 5.2 Hz, 1H, H 4; 13.18, s, 1H, C(11)OH; 13.77, s, 1H, C(6)OH. ^{13}C n.m.r. δ 17.0, C 6'; 24.8, CH_3CO; 30.2, C 2', 10; 30.3, C 10, 2'; 34.3, C 8; 45.6, C 3'; 64.4, C 5'; 66.5, C 7; 72.0, C 4'; 76.5, C 9; 93.4, C 1'; 110.5, C 11a, 5a; 111.8, C 5a, 11a; 113.7, *J* 23.7 Hz, C 3; 115.4, q, *J* 287.5 Hz, CF_3; 122.1, *J* 22.8 Hz, C 1; 123.8, 2C, Ar; 129.9, *J* 3.0 Hz, C 4a; 130.4, *J* 9.1 Hz, C 4; 131.0, 2C, Ar; 132.8, C 10a; 134.3, Ar; 136.0, *J* 8.4 Hz, C 12a; 136.9, C 6a; 150.8, Ar; 156.3, C 6, 11; 156.5, q, *J* 38.1 Hz, $COCF_3$; 156.6, C 11, 6; 164.6, ArCO; 166.5, *J* 259.2 Hz, C 2; 185.4, C 5; 185.5, *J* 1.4 Hz, C 12; 211.4, $COCH_3$. ^{19}F n.m.r. δ -100.2, ddd, *J* 5.2, 8.0, 8.6 Hz, C(2)F; -76.2, s, CF_3.

The bis-*O*-daunosaminyl derivative (44) was obtained as an orange glass. ^1H n.m.r. δ 0.62, d, *J* 6.5 Hz, 3H, H 6"; 1.38, d, *J* 6.5 Hz, 3H, H 6'; 1.73 - 2.36, m, 5H, H 8, C(2')H_2, C(2")H_2; 2.38, s, 3H, CH_3CO; 2.64, m, H 8; 3.06, d, *J* 20.0 Hz, 1H, H 10; 3.64, d, *J* 20.0 Hz, 1H, H 10; 3.80 - 4.80, m, 4H, H 3', H 3", H 5', H 5"; 5.09, m, 1H, H 7; 5.15, bs, 1H, H 1"; 5.30, bs, 1H, H 4"; 5.46, bs, 1H, H 4'; 5.69, bs, 1H, H 1'; 6.96, bd, *J* 7.5 Hz, 1H, NH; 7.41, bd, *J* 5.9 Hz, 1H, NH; 7.52, ddd, *J* 2.6, 8.6, J_F 7.8 Hz, 1H, H 3; 8.00, dd, *J* 2.6, J_F 8.6 Hz, 1H, H 1; 8.29, m, 8H, Ar H; 8.43, dd, *J* 8.8, J_F 5.2 Hz, 1H, H 4; 13.34, s, 1H, C(11)OH; 13.68, s, 1H, C(6)OH. The β-glycoside was obtained as an orange glass. ^1H n.m.r. δ 1.32, d, *J* 6.3 Hz, 3H, H 6'; 1.60 - 2.40, m, 3H, H 8, C(2')H_2; 2.46, s, 3H, CH_3CO; 2.72, bd, *J* 15.2 Hz, 1H, H 8; 2.95, d, *J* 18.9 Hz, 1H, H 10; 3.30, d, *J* 18.9 Hz, 1H, H 10; 3.99, dq, *J* 1.1, 6.3 Hz, 1H, H 5'; 4.47, 2H, m, H 3', C(9)OH; 5.22, dd, *J* 2.1, 9.3 Hz, 1H, H 1'; 5.38, m, 2H, H 7, H 4'; 6.39, bd, *J* 6.8 Hz, 1H, NH; 7.51, ddd, *J* 2.6, 8.5, J_F 8.1 Hz, 1H, H 3; 7.99, dd, *J* 2.6, J_F 8.5 Hz, 1H, H 1; 8.30, m, 4H, Ar H; 8.40, dd, *J* 8.5, J_F 5.2 Hz, 1H, H 4; 13.17, s, 1H, C(11)OH; 13.60, s, 1H, C(6)OH.

b. Koenigs-Knorr method:

A solution of compound (28) (165 mg) in anhydrous tetrahydrofuran (50 ml) was stirred at 60° under an argon atmosphere with freshly activated powdered 3Å molecular sieve (2.0 g), mercuric bromide (400 mg), and mercuric cyanide (880 mg). At intervals of 1, 5, 23, and 48 h, aliquots of the glycosyl chloride, prepared from the ester (31) (230 mg) and dry hydrogen chloride in dichloromethane,[11] were introduced. Further aliquots of sieve and mercuric salts were introduced after 4 and 22 h, and stirring was continued for a total of 96 h. The mixture was cooled, filtered through celite, and the celite washed with hot tetrahydrofuran until colourless. The residue upon evaporation of the solvent was taken up in hot chloroform, cooled, filtered, and washed successively with 10% aqueous potassium iodide (100 ml), 5% aqueous sodium bicarbonate (100 ml), brine (100 ml), dried, and the solvent evaporated. Column chromatography of the residue (Sephadex LH-20, methanol) gave two fractions which upon further separation by centrifugal thin layer chromatography as described above yielded glycoside (32) (124 mg, 38%), glycoside (38) (126 mg, 39%), unreacted (28) (31.3 mg, 19%), and other minor products (25mg).

(+)-4-Demethoxy-2-fluoro-3'- N-trifluoroacetyldaunomycin (33).

A solution of compound (32) (52 mg) in dichloromethane (0.5 ml) and methanol (25 ml) was stirred at 0° under an argon stmosphere for 20 min with 0.1 M aqueous sodium hydroxide (0.7 ml). The solution was acidified with acetic acid, diluted with ethyl acetate (50 ml), washed with brine (3x30 ml), dried, and the solvent evaporated. Centrifugal t.l.c. of the residue (3% methanol in dichloromethane) gave compound (33) (41 mg, 99%) as an orange solid which crystallized with one mole of dichloromethane of crystallization from a mixture of dichloromethane and diisopropyl ether as orange prisms, m.p. 147-9°; $[\alpha]_D$ +159° (c, 0.15, dioxane) (Found: C, 50.3; H, 4.0; N, 2.0; F, 10.6; Cl 10.3. $C_{28}H_{25}F_4NO_{10}.CH_2Cl_2$ requires C, 50.0; H, 4.0; N, 2.0; F, 10.9; Cl, 10.2%). I.r. ν_{max} 3530 w, 3390 w, 2930 w, 1718 s, 1623 m, 1587 s, 1335 s, 1320 s, 1260 s, 1155 m, 1109 s, 996 m, 978 s cm^{-1}. ^1H n.m.r. δ 1.30, d, *J* 6.7 Hz, 3H, H 6'; 1.85, dd, *J* 4.0, 12.7 Hz, 1H, H 2'; 1.98, m, 2H, H 2', C(4')OH; 2.15, dd, *J* 3.3, 15.0 Hz, 1H, H 8; 2.36, dt, *J* 1.8, 15.0 Hz, 1H, H 8; 2.41, s, 3H, CH_3CO; 2.99, d, *J* 19.2 Hz, 1H, H 10; 3.30, dd, *J* 1.6, 19.2 Hz, 1H, H 10; 3.69, m, 1H, H 4'; 4.29, s, 1H, C(9)OH; 4.16 - 4.36, m, 2H, H 3', H

5'; 5.27, bs, 1H, H1'; 5.31, s, 2H, CH_2Cl_2; 5.51, dd, *J* 1.8, 3.3 Hz, 1H, H 7; 6.69, bd, *J* 8.4 Hz, 1H, NH; 7.51, ddd, *J* 2.6, 8.7, J_F 7.9 Hz, 1H, H 3; 8.00, dd, *J* 2.6, J_F 8.6 Hz, 1H, H 1; 8.40, dd, *J* 8.7, J_F 5.3 Hz, 1H, H 4; 13.17, s, 1H, C(11)OH; 13.57, s, 1H, C(6)OH. ^{13}C n.m.r. (20% DMSO - d_6 in $CDCl_3$) δ 15.8, C 6'; 23.5, CH_3CO; 27.9, C 2'; 31.4, C 10; 34.5, C 8; 45.9, C 3'; 65.9, C 5'; 66.6, C 4'; 68.7, C 7; 74.8, C 9; 99.4, C 1'; 108.7, C 5a, 11a; 109.8, C 11a, 5a; 111.1, *J* 23.6 Hz, C 3; 114.8, q, *J* 288.4 Hz, CF_3; 120.9, *J* 22.8 Hz, C 1; 128.7, *J* 2.7 Hz, C 4a; 129.2, *J* 9.2 Hz, C 4; 133.9, C 10a; 134.7, *J* 8.2 Hz, C 12a; 135.2, C 6a; 134.7, *J* 8.2 Hz, C 12a; 155.1, q, *J* 36.8 Hz, $COCF_3$; 155.2, C 6, 11; 156.0, C 11, 6; 164.1, *J* 257.8 Hz, C 2; 183.8, C 5; 184.0, *J* 1.5 Hz, C 12; 211.0, $COCH_3$. ^{19}F n.m.r. δ - 100.9, ddd, *J* 5.3, 7.9, 8.6 Hz, C(2)F; -76.5, s, $COCF_3$.

(+)-4-Demethoxy -2- fluorodaunomycin hydrochloride (34).

A solution of compound (33) (225 mg) in 0.1 M aqueous sodium hydroxide (40 ml) was stirred at room temperature under an argon atmosphere for 2 h. The mixture was acidified to pH 4 with 5 M HCl, then added to saturated aqueous sodium bicarbonate , and extracted with chloroform (6x50 ml). The combined extracts were washed successively with water (50 ml) and brine (100 ml), dried (Na_2SO_4), and the solvent evaporated to give a red solid (175mg, 92%). I.r. ν_{max} 3600w, 3480m, 1717s, 1620s, 1583s, 1318s, 1260bm, 1100m, 992m, 975s cm^{-1}. The residue was taken up in a 9/1 mixture of chloroform and methanol, cooled, acidified to pH 3 with methanolic hydrogen chloride, and the solvent evaporated. The residue was freed of excess hydrogen chloride at 0.1mm,stirred with dry methanol (10ml), filtered, and the filtrate freed of impurities by column chromatography (Sephadex LH-20, methanol). Precipitation of *the hydrochloride* was effected by addition of anhydrous ether to a concentrated solution in dry methanol to give red prisms: m.p. 166-68°; $[\alpha]_D$ +131° (c, 0.05, methanol) . ^1H n.m.r. (DMSO-d_6) δ 1.15, d, *J* 6.5Hz, 3H, H 6'; 1.68, dd, *J* 3.6, 12.3 Hz, 1H, H 2'; 1.89, m, 1H, H 2'; 2.14, m, 2H, C(8)H_2; 2.27, s, 3H, CH_3CO; 2.96, bs, 2H, C(10)H_2; 3.23, bs, 8H, C(6)OH, C(11)OH, NH_3^+, H 3', H_2O; 3.58, m, 1H, H 4'; 4.20, q, *J* 6.5 Hz, 1H, H 5'; 4.94, bs, 1H, H 7; 5.29, bs, 1H, H 1'; 5.47, d, *J* 6.0 Hz, 1H, C(4')OH; 5.58, s, 1H, C(9)OH; 7.82, ddd, *J* 2.4, 8.7, J_F 8.2 Hz, 1H, H 3; 7.98, dd, *J* 2.4, J_F 8.9 Hz, 1H, H 1; 8.35, dd, *J* 8.7, J_F 5.4 Hz, 1H, H 4. ^{13}C n.m.r. (DMSO-d_6) δ 16.7, C 6'; 24.7, CH_3CO; 28.2, C 2'; 31.7, C 10; 35.9, C 8; 46.5, C 3'; 66.0, C 4'; 66.1, C 7; 70.0, C 5'; 74.9, C 9; 99.2, C 1'; 109.7, C 11a, 5a; 110.9, C 5a, 11a; 112.9, *J* 23.6 Hz, C 3; 122.2, *J* 23.1 Hz, C 1; 129.8, *J* 2.6 Hz, C 4a; 130.3, *J* 10.0 Hz, C 4; 135.3, C 10a; 135.8, *J* 8.2 Hz, C 12a; 136.2, C 6a; 155.2, C 11; 156.5, C 6; 165.8, *J* 255.5 Hz, C 2; 185.1, C 5; 185.2, *J* 1.3 Hz, C 12; 211.6, $COCH_3$. ^{19}F n.m.r. (DMSO-d_6) δ -101.2, ddd, *J* 5.4, 8.2, 8.9 Hz.

Glycosidation of (±)-4 - Demethoxy-3-fluorodaunomycinone (30)

a. Koenig-Knorr method:

A solution of compound (30) (386 mg) in dry tetrahydrofuran (150 ml) was stirred at 60° under an argon atmosphere with freshly activated powdered 3Å molecular sieve (4.6 g), mercuric cyanide (2.0 g), and mercuric bromide (912 mg). At intervals of 1, 5, and 23 h, a dichloromethane solution of the glycosyl chloride derived from ester (31) (520 mg) and dry hydrogen chloride[11] was introduced, and further additions of similar aliquots of sieve and mercuric salts were made after 4 and 22 h. Stirring was maintained for a total of 50 h, after which the solution was cooled and worked up in the manner described for the glycosidation of the 2-fluoro analogue (28). Chromatography as described afforded glycoside (35) (212 mg, 28%), glycoside (41) (233 mg, 31%), unreacted (30) (73.3 mg, 19%), and unidentified minor products (88 mg).

Glycoside (35) crystallized from a mixture of deuterochloroform and light petroleum as red prisms, m.p. 163-5°; $[\alpha]_D$ -72° (c, 0.10; dioxane) (Found: C, 54.9; H, 3.8; N, 3.5; F, 10.2. $C_{35}H_{28}F_4N_2O_{13}$ requires C, 55.3; H, 3.7; N, 3.7; F, 10.0%). I.r. ν_{max} 3670 w, 3520 w, 2825 w, 1726 s, 1620 m, 1588 s, 1334 s, 1266 m, 1107 m, 1095 m, 982 m, 958 s cm^{-1}. ^1H n.m.r. (DMSO - d_6) δ 1.10, d, *J* 6.4 Hz, 3H, H 6'; 1.70, m, 1H, H 2'; 2.04 - 2.36, m, 3H, H 2', C(8)H_2; 2.31, s, 3H, CH_3CO; 2.86, ABd, *J* 18.7 Hz, 1H, H 10; 2.98, ABd, *J* 18.7 Hz, 1H, H 10; 4.38, m, 1H, H 3'; 4.63, q, *J* 6.4 Hz, 1H, H 5'; 4.95, m, 1H, H 7; 5.30, s, 1H, C(9)OH; 5.45, bs, 1H, H 4'; 5.65, s, 1H, H 1'; 7.70 -7.88, m, 2H, H 2, H 4; 8.19 - 8.30, m, 3H, Ar H, H 1; 8.40, m, 2H, Ar H; 9.50, d, *J* 7.3 Hz, 1H, NH; 13.17, s, 1H, C(11)OH; 13.22, s, 1H, C(6)OH. ^{13}C n.m.r. (DMSO - d_6) δ 16.6, C 6'; 24.2, CH_3CO; 29.2, C 2'; 31.6, C 10; 35.8, C 8; 45.0, C 3'; 64.7, C 5'; 70.3, C 7; 71.1, C 4'; 74.8, C 9; 99.8, C 1'; 110.1, C 11a, 5a; 110.3, C 5a, 11a; 112.7, *J* 23.3 Hz, C 2; 115.4, q, *J* 289.3 Hz, CF_3; 122.2, *J* 22.6 Hz, C 4; 123.8, 2C, Ar; 129.5, *J* 2.4 Hz, C 12a; 130.4, *J* 9.8 Hz, C 1; 130.9, 2C, Ar; 134.8, C 10a; 134.9, Ar; 135.7, *J* 8.3 Hz, C 4a; 136.8, C 6a; 150.4, Ar; 155.3, C 11; 156.1, q, *J* 36.7 Hz, $COCF_3$; 156.7, C 6; 164.2, ArCO; 165.8, *J* 255.7 Hz, C 3; 184.8, C 5; 185.1, C 12; 211.9,$COCH_3$. ^{19}F n.m.r. (DMSO - d_6) δ -101.0, ddd, *J* 5.3, 7.9, 8.7 Hz, C(3)F; -78.7, s, CF_3.

Compound (41) crystallized from a mixture of diisopropyl ether and light petroleum as red prisms: m.p. 160-3°; $[\alpha]_D$ -284° (c, 0.10; dioxane) (Found: C, 54.7; H, 3.7; N, 4.0; F, 10.3. $C_{35}H_{28}F_4N_2O_{13}$ requires C, 55.2; H, 3.7; N, 3.7; F, 10.0%). I.r. ν_{max} 3470 w, 3410 w, 1712 s, 1618 m, 1582 s, 1339 s, 1265 bm, 1089 m, 995 m, 951 s cm^{-1}. ^1H n.m.r. δ 1.25, d, *J* 6.5 Hz, 3H, H 6'; 1.89 - 2.01, m, 2H, H 8, H 2'; 2.19, dt, *J* 3.3, 13.0 Hz, 1H, H 2'; 2.39, s, 3H, CH_3CO; 2.48, m, 1H, H 8; 2.98, d, *J* 19.5 Hz, 1H, H 10; 3.29, d, *J* 19.5 Hz, 1H, H 10; 4.45, s, 1H, C(9)OH; 4.60, m, 1H, H 3'; 4.70, q, *J* 6.5 Hz, 1H, H 5'; 5.41, bs, 1H, H 4; 5.48 - 5.60, m, 2H, H 1', H 7; 6.60, d, *J* 7.4 Hz, 1H, NH; 7.50, ddd, *J* 2.6, 8.7, J_F 7.9 Hz, 1H, H 2; 7.92, dd, *J* 2.6, J_F 8.6 Hz, 1H, H 4; 8.25, m, 4H, Ar H; 8.36, dd, *J* 8.7, J_F 5.3 Hz, 1H, H 1; 13.23, s, 1H, C(11)OH; 13.57, s, 1H, C(6)OH. ^{13}C n.m.r. δ 16.8, C 6'; 24.7, CH_3CO; 29.8, C 2'; 30.1, C 10; 34.2, C 8; 45.5, C 3'; 64.3, C 5'; 66.5, C 7; 72.0, C 4'; 76.5, C 9; 93.4, C 1'; 110.9, C 11a, 5a; 111.3, C 5a, 11a; 113.6, *J* 23.3 Hz, C 2; 115.4, q, *J* 287.7 Hz, CF_3; 122.1, *J* 22.6 Hz, C 4; 123.8, 2C, Ar; 129.8, *J* 2.8 Hz, C 12a; 130.5, *J* 9.1 Hz, C 1; 131.0, 2C, Ar; 132.3, C 10a; 134.4, Ar; 136.2, *J* 8.4 Hz, C 4a; 137.1, C 6a; 150.7, Ar; 156.2, C 11, 6; 156.7, C 6, 11; 156.8, q, *J* 37.6 Hz, $COCF_3$; 164.6, ArCO; 166.6, *J* 258.7 Hz, C 3; 185.4, *J* 1.5 Hz, C 5; 185.5, C 12; 211.6, $COCH_3$. ^{19}F n.m.r. δ -100.5, ddd, *J* 5.3, 7.9, 8.6 Hz, C(3)F; -76.5, s, CF_3.

b. Terashima Method:

A mixture of the ester (31) (358 mg) and freshly activated 4Å molecular sieve (1.81 g) in dry ether (23 ml) and dichloromethane (27 ml) was cooled to -42° under an argon atmosphere, whereupon TMS triflate (270 µl) was introduced dropwise. The mixture was stirred at 0° for 1 h, cooled to -15°, and a solution of the anthracyclinone (30) (200 mg) in dry

dichloromethane (100 ml) added dropwise. The solution was maintained at -15° for 8 h, quenched with methanol (2 ml), decanted, and partitioned between ethyl acetate (600 ml), and sodium bicarbonate solution (5%, 200 ml). The aqueous phase was extracted with ethyl acetate until free of colour, and the combined extracts washed successively with water (200 ml) and brine (200 ml), dried, and the solvent evaporated. Chromatography as described above yielded glycoside (35) (66.0 mg, 17%), glycoside (41) (124 mg, 31%), the bis-*O*-daunosaminyl derivative (45) (88.7 mg, 15%), unreacted (30) (65.6 mg, 33%) and a mixture of the β-derivatives (15.3 mg, 4%).

Compound (45) was obtained as orange prisms upon crystallization from aqueous methanol, m.p.185-7°; $[\alpha]_D$ -84° (c, 0.16; dioxane). I.r. ν_{max} 3590w, 2890w, 1719vs, 1621m, 1585s, 1346s, 1265bm, 1095m, 978m, 960s cm^{-1}. ^1H n.m.r. δ 0.60, d, *J* 6.4 Hz, 3H, H 6"; 1.36, d, *J* 6.5 Hz, 3H, H 6'; 1.97, dd, *J* 5.3, 15.1 Hz, 1H, H 8; 2.04-2.35, m, 4H, C(2')H_2, C(2")H_2; 2.38, s, 3H, CH_3CO; 2.63, dm, *J* 15.1 Hz, 1H, H 8; 3.03, d, *J* 19.3 Hz, 1H, H 10; 3.80, dd, *J* 1.9, 19.3 Hz, 1H, H 10; 3.97, q, *J* 6.4 Hz, 1H, H 5"; 4.50-4.82, m, 2H, H 3', H 3"; 4.74, q, *J* 6.5 Hz, 1H, H 5'; 5.06, bd, *J* 5.3 Hz, 1H, H 7; 5.12, bs, 1H, H 1"; 5.29, s, 1H, H 4"; 5.45, s, 1H, H 4'; 5.66, bs, 1H, H 1'; 6.95, d, *J* 7.5 Hz, 1H, NH; 7.39, d, *J* 5.9 Hz, 1H, NH; 7.49, ddd, *J* 2.7, 8.5, J_F 7.8 Hz, 1H, H 2; 7.99, dd, *J* 2.5, J_F 8.6 Hz, 1H, H 4; 8.24, m, 4H, ArH; 8.31, s, 4H, ArH; 8.39, dd, *J* 8.5, J_F 5.2 Hz, 1H, H 1;13.46, s, 1H, C(11)OH; 13.55, s, 1H, C(6)OH. ^{19}F n.m.r. δ -100.6, ddd, *J* 5.2,7.8,8.6 Hz, C(3)F; -77.1, s, CF_3; -76.9, s, CF_3.

(+)-4-Demethoxy-3-fluoro-3'-N-trifluoroacetyldaunomycin (36).

A solution of the *p*-nitrobenzoate (35) (153 mg) in a mixture of dichloromethane (4 ml) and methanol (80 ml) was stirred at 0° under an argon atmosphere with 0.1 M aqueous sodium hydroxide (2.0 ml) for 20 min. The solution was neutralized with acetic acid, diluted with ethyl acetate (400 ml), and washed with brine (3x200 ml). Evaporation afforded an orange solid which was purified on a short silica column eluted first with dichloromethane, followed by 10% methanol in dichloromethane to give *the title compound* as an orange solid (115 mg, 93%). Crystallization from a mixture of dichloromethane and light petroleum gave orange prisms: sublimes to red needles ~240°; m.p. 246-8°. $[\alpha]_D$ +195° (c, 0.11; dioxane) (Found: C, 54.7; H, 3.9; N, 2.1; F, 11.9. $C_{28}H_{25}F_4NO_{10}$ requires C, 55.0; H, 4.1; N, 2.3; F, 12.4%). I.r. ν_{max} 3500 w, 3390 w, 1710 vs, 1617 m, 1583 s, 1324 s, 1268 bm, 1105 m, 995 m, 975 m, 952 m cm^{-1}. ^1H n.m.r. (DMSO - d_6) δ 1.14, d, *J* 6.3 Hz, 3H, H 6'; 1.49, dd, *J* 4.1, 12.6 Hz, 1H, H 2"; 1.96-2.27, m, 3H, H 2', C(8)H_2; 2.28, s, 3H, CH_3CO; 2.89, s, 2H, C(10)H_2; 3.52, bd, *J* 5.2 Hz, 1H, H 4'; 4.04, m, 1H, H 3'; 4.24, q, *J* 6.3 Hz, 1H, H 5'; 4.85, m, 1H, H 7; 5.01, d, *J* 5.6 Hz, 1H, C(4')OH; 5.23, bs, 1H, H 1'; 5.54, s, 1H, C(9)OH; 7.71, ABdd, *J* 2.0, J_F 8.5 Hz, 1H, H 4; 7.73, ABddd, *J* 2.0, 8.4, J_F 7.9 Hz, 1H, H 2; 8.19, dd, *J* 8.4, J_F 5.5 Hz, 1H, H 1; 9.10, d, *J* 7.4 Hz, 1H, NH; 13.15, bs, 2H, C(6), C(11)OH. ^{13}C n.m.r. (DMSO - d_6) δ 16.9, C 6'; 24.1, CH_3CO; 28.8, C 2'; 31.7, C 10; 36.0, C 8; 47.0, C 3'; 66.5, C 5', 4'; 67.0, C 4', 5'; 70.1, C 7; 75.0, C 9; 100.1,C1'; 110.1, C 5a, 11a; 110.2, C 11a, 5a; 112.8, *J* 23.1 Hz, C 2; 115.8, q, *J* 288.1 Hz, CF_3; 122.2, *J* 22.7 Hz, C 4; 129.5, *J* 2.5 Hz, C 12a; 130.4, *J* 9.5 Hz, C 1; 135.1, C 10a; 135.8, *J* 8.3 Hz, C 4a; 136.8, C 6a; 155.3, C 11; 155.8, q, *J* 36.5 Hz, $COCF_3$; 156.8, C 6; 165.9, *J* 256.2 Hz, C 3; 184.7, C 5; 185.0, C 12; 211.9, $COCH_3$. ^{19}F n.m.r. (DMSO - d_6) δ -100.9, ddd, *J* 5.5, 7.9, 8.5 Hz, C(3)F; -73.5, s, CF_3.

(+)-4-Demethoxy-3-fluorodaunomycin hydrochloride (37).

Compound (36) (33.5 mg) was stirred under an argon atmosphere in 0.1 M aqueous sodium hydroxide (9 ml) for 2 h at room temperature, and the solution acidified with 5 M HCl (to pH 4). The mixture was poured into saturated sodium bicarbonate solution (10 ml) and extracted with chloroform (5x20 ml). The combined extracts were washed successively with water (20 ml), brine (20 ml), dried (Na_2SO_4) and the solvent evaporated to give an orange solid. I.r. ν_{max} 3750 w, 3570 w, 2860 w, 1706 m, 1620 m, 1583 s, 1320 s, 1280 bm, 1100 bm, 973 s cm^{-1}. The free amine was dissolved in a 9/1 mixture of chloroform and methanol (2 ml), cooled to 0°, acidified to pH 3 with methanolic HCl, and diluted with anhydrous ether. Filtration yielded *the hydrochloride* (37) as an orange powder (20.3 mg, 67%): m.p. 214-7° (dec); $[\alpha]_D$ +186° (c, 0.10; methanol) ^1H n.m.r. (DMSO-d_6) δ 1.15, d, *J* 6.5 Hz, 3H, H 6'; 1.68, dd, *J* 4.1, 12.5 Hz, 1H, H 2'; 1.88, dt, *J* 2.9, 12.5 Hz, 1H, H 2'; 2.14, m, 2H, C(8)H_2; 2.26, s, 3H, CH_3CO; 2.95, s, 2H, C(10)H_2; 3.32, m, 8H, C(6)OH; C(11)OH, H 3', NH_3^+, H_2O; 3.57, m, 1H, H 4'; 4.20, q, *J* 6.5 Hz, 1H, H 5'; 4.93, m, 1H, H 7; 5.28, bs, 1H, H 1'; 5.46, d, *J* 6.0 Hz, 1H, C(4')OH; 5.57, s, 1H, C(9)OH; 7.82, ddd, *J* 2.1, 8.9, J_F 8.0 Hz, 1H, H 2; 7.96, dd, *J* 2.1, J_F 8.7 Hz, 1H, H 4; 8.34, dd, *J* 8.9, J_F 5.6 Hz, 1H, H 1. ^{13}C n.m.r. (DMSO-d_6) δ 16.7, C 6'; 24.1, CH_3CO; 28.2, C 2'; 31.7, C 10; 35.9, C 8; 46.5, C 3'; 66.0, C 4'; 66.1, C 7; 70.1, C 5'; 74.9, C 9'; 99.4, C 1'; 110.3, C 11a, 5a; 110.6, C 5a, 11a; 113.0, *J* 23.4 Hz, C 2; 122.3, *J* 23.6 Hz, C 4; 129.9, *J* 2.6 Hz, C 12a; 130.5, *J* 9.6 Hz, C 1; 134.9, C 10a; 136.0, *J* 8.5 Hz, C 4a; 136.8, C 6a; 155.3, C 11; 156.7, C 6; 165.9, *J* 255.6 Hz, C 3; 185.2, *J* 1.5 Hz, C 5; 185.5, C 12; 211.8, $COCH_3$. ^{19}F n.m.r. (DMSO-d_6) δ -101.1, ddd, *J* 5.6, 8.0, 8.7 Hz.

(-)-4-Demethoxy- 2-fluoro-3'-N-trifluoroacetyl-7,9-bisepidaunomycin (39).

A solution of the ester (38) (146 mg) in dichloromethane (1.5 ml) and methanol (80 ml) at 0° under an argon atmosphere was stirred with 0.1 M aqueous sodium hydroxide (1.92 ml) for 20 min. The mixture was neutralized with acetic acid, diluted with ethyl acetate (200 ml), washed with brine (3x750 ml), dried, and the solvent evaporated. Flash column chromatography on a short silica column (dichloromethane, then 5% methanol in dichloromethane afforded *the title compound* as an orange solid (109 mg, 93%) which was precipitated from a dichloromethane solution with light petroleum to give an orange powder: m.p. 137.5 - 140°; $[\alpha]_D$ -355° (c, 0.11; dioxane) (Found: C, 54.6; H, 4.2; N, 2.2; F, 12.1. $C_{28}H_{25}F_4N_{10}$ requires C, 55.0; H, 4.1; N, 2.3; F, 12.4%). I.r. ν_{max} 3490 w, 3400 w, 2950 w, 1715 vs, 1619 m, 1588 s, 1573 s, 1336 s, 1321 s, 1266 m, 1106 m, 978 s cm^{-1}. ^1H n.m.r. δ 1.28, d, *J* 6.6 Hz, 3H, H 6'; 1.84, bdd, *J* 5.5, 13.3 Hz, 1H, H 2'; 1.91, m, 2H, H 2', C(4')OH; 1.93, dd, *J* 3.3, 15.1 Hz, 1H, H 8; 2.40, s, 3H, CH_3CO; 2.45, dt, *J* 2.1, 15.1 Hz, 1H, H 8; 3.03, d, *J* 19.4 Hz, 1H, H 10; 3.30, dd, *J* 1.5, 19.4 Hz, 1H, H 10; 3.60, m, 1H, H 4'; 4.29, m, 1H, H 3'; 4.47, s, 1H, C(9)OH; 4.49, q, *J* 6.6 Hz, 1H, H 5'; 5.34, d, *J* 3.4 Hz, 1H, H 1'; 5.52, dd, *J* 2.1, 3.3 Hz, 1H, H 7; 6.71, bd, *J* 8.4 Hz, 1H, NH; 7.50, ddd, *J* 2.7, 8.7, J_F 7.9 Hz, 1H, H 3; 7.98, dd, *J* 2.6, J_F 8.6 Hz, 1H, H 1; 8.38, dd, *J* 8.7, J_F 5.2 Hz, 1H, H 4; 13.16, s, 1H, C(11)OH; 13.71, s, 1H, C(6)OH. ^{13}C n.m.r. δ 16.5, C 6'; 24.8, CH_3CO; 29.4, C 2'; 30.1, C 10; 34.2, C 8; 46.0, C 3'; 64.2, C 5'; 67.1, C

4'; 68.9, C 7; 76.5, C 9; 93.5, C 1'; 110.2, C 5a, 11a; 111.6, C 11a, 5a; 113.6, *J* 23.5 Hz, C 3; 115.5, q, *J* 287.3 Hz, CF_3; 122.0, *J* 23.3 Hz, C 1; 129.9, *J* 2.8 Hz, C 4a; 130.2, *J* 9.2 Hz, C 4; 133.1, C 10a; 136.0, C 6a; 136.0, *J* 8.3 Hz, C 12a; 156.5, q, *J* 37.4 Hz, $COCF_3$; 156.4, C 6, 11; 156.8, C 11, 6; 166.5, *J* 258.3 Hz, C 2; 185.9, C 5; 185.4, *J* 1.3 Hz, C 12; 211.9, $COCH_3$. ^{19}F n.m.r. δ -100.7, ddd, *J* 5.2, 7.9, 8.6 Hz, C(2)F; -76.4, s, CF_3.

(-)-4-Demethoxy-2-fluoro-7,9-bisepidaunomycin hydrochloride (40).

A solution of compound (39) (260 mg) in 0.1 M aqueous sodium hydroxide (50 ml) was stirred at room temperature under an argon atmosphere for 3 h. The solution was acidified to pH 4 with 5 M HCl, diluted with saturated aqueous sodium bicarbonate (5 ml) and extracted with chloroform (5x100 ml). The combined extracts were washed successively with water (100ml), brine (150 ml), dried (Na_2SO_4), and the solvent evaporated to yield a red solid (195 mg,89%). I.r. ν_{max} 3650 m, 2940 w, 1711 m, 1623 m, 1586 s, 1380 s, 1270 bm, 1105 m, 955 m, 975 s cm^{-1}. The residue was dissolved in a 9/1 mixture of chloroform and methanol , cooled and acidified to pH 3 with methanolic hydrogen chloride. The solvent was evaporated *in vacuo* at room temperature and the residue freed of excess hydrogen chloride at 0.1mm. The residue was dissolved in dry methanol filtered,and the filtrate subjected to column chromatography (Sephadex LH-20, methanol). The material thus obtained was precipitated from a concentrated solution in dry methanol by addition of anhydrous ether to give red prisms: m.p. 169-171° ; $[\alpha]_D$ -230° (c, 0.04; methanol). ^1H n.m.r. (DMSO-d_6) δ 1.12, d, *J* 6.1Hz, 3H, H6'; 1.66, dd, *J* 4.0, 13.5 Hz, 1H, H 2'; 1.89, m, 2H, H 8, H 2'; 2.29, s, 3H, CH_3CO; 2.40, dm, *J* 14.9 Hz, H 8; 2.92, ABd, *J* 18.6 Hz, 1H, H 10; 3.05, ABd, *J* 18.6 Hz, 1H, H 10; 3.42, m, 1H, H 3'; 3.58, m, 1H, H 4'; 4.19, q, *J* 6.1 Hz, 1H, H 5'; 5.16, bs, 1H, H 7; 5.29, bs, 1H, H 1'; 5.43, d, *J* 6.0 Hz, 1H, C(4')OH; 5.50, s, 1H, C(9)OH; 7.82, ddd, *J* 2.6, 8.6, J_F 8.1 Hz, 1H, H 3; 7.93, m, 4H, H 1, NH_3^+; 8.32, dd, *J* 8.6, J_F 5.4 Hz, 1H, H 4; 13.06, s, 1H, C(11)OH; 13.48, s, 1H, C(6)OH. ^{13}C n.m.r. (DMSO-d_6) δ 16.7, C 6'; 24.4, CH_3CO; 27.8, C 2'; 31.0, C 10; 32.1, C 8; 46.7, C 3'; 63.2, C 4'; 65.9, C 5'; 66.5, C 7; 75.2, C 9; 92.1, C 1'; 109.8, C 11a, 5a; 111.2, C 5a, 11a; 113.0, *J* 23.5 Hz, C 3; 122.4, *J* 23.0 Hz, C 1; 129.7, *J* 2.2 Hz, C 4a; 130.4, *J* 9.3 Hz, C 4; 135.1, C 10a; 135.8, *J* 8.5 Hz, C 12a; 137.3, C 6a; 155.2, C 11; 156.3, C 6; 165.8, *J* 255.1 Hz, C 2; 185.2, C 5; 185.3, *J* 1.0 Hz, C 12; 211.9, $COCH_3$. ^{19}F n.m.r. (DMSO-d_6) δ -101.1, ddd, *J* 5.4, 8.1, 8.8 Hz.

(-)-4-Demethoxy-3-fluoro-3'- N*-trifluoroacetyl-7,9-bisepidaunomycin (42).*

A solution of the *p*-nitrobenzoate (41) (155 mg) in methanol (30 ml) and dichloromethane (3 ml) was stirred at 0° under argon with 0.1 M aqueous sodium hydroxide (2.0ml) for 0.5 h. The mixture was neutralized with acetic acid, poured into ethyl acetate (100 ml), washed with brine (3x50 ml), dried, and the solvent evaporated. Centrifugal t.l.c.of the residue (3% methanol in dichloromethane) afforded *the title compound* as an orange solid (120 mg, 96%) which crystallized from a mixture of ether and dichloromethane to give red prisms: m.p. 138-140°; $[\alpha]_D$ -368° (c, 0.14; dioxane) (Found: C, 54.9; H, 4.3; N, 2.3; F, 12.3. $C_{28}H_{25}F_4NO_{10}$ requires C, 55.0; H, 4.1; N, 2.3; F, 12.4%). I.r. ν_{max} 3480 w, 3400 w, 1716 vs, 1620 m, 1585 s, 1331 s, 1266 m, 978 s cm^{-1}. ^1H n.m.r. δ 1.27, d, *J* 6.5 Hz, 3H, H 6'; 1.76-2.04, m, 3H, H 8, C(2')H_2; 2.23, bs, 1H, C(4')OH; 2.39, s, 3H, CH_3CO; 2.45, m, 1H, H 8; 2.99, d, *J* 19.5 Hz, 1H, H 10; 3.28, d, *J* 19.5 Hz, 1H, H 10; 3.61, m, 1H, H 4'; 4.29, m, 1H, H 3'; 4.47, q, *J* 6.5 Hz, 1H, H 5'; 4.49, s, 1H, C(9)OH; 5.32, bs, 1H, H 1'; 5.48, m, 1H, H 7; 6.78, d, *J* 8.4 Hz, 1H, NH; 7.48, ddd, *J* 2.6, 8.6, J_F 8.0 Hz, 1H, H 2; 7.90, dd, *J* 2.6,J_F 8.6 Hz, 1H, H 4; 8.34, dd, *J* 8.6, J_F 5.2 Hz, 1H, H 1; 13.23, s, 1H, C(11)OH; 13.52, s, 1H, C(6)OH. ^{13}C n.m.r. δ 16.5, C 6'; 24.8, CH_3CO; 29.5, C 2'; 30.2, C 10; 34.3, C 8; 46.0, C 3'; 64.2, C 5'; 67.1, C 7; 68.9, C 4'; 76.5, C 9; 93.4, C 1'; 110.8, C 5a, 11a; 111.2, C 11a, 5a; 113.8, *J* 23.8 Hz, C 2; 115.7, q, *J* 288.9 Hz, CF_3; 122.0, *J* 22.3 Hz, C 4; 129.8, *J* 3.0 Hz, C 12a; 130.5, *J* 9.1 Hz, C 1; 132.5, C 10a; 136.2, *J* 8.3Hz, C 4a; 137.8, C 6a; 156.4, C 11, 6; 156.5, q, *J* 37.4 Hz, $COCF_3$; 156.9, C 6, 11; 166.6, *J* 259.0 Hz, C 3; 185.2, *J* 1.6 Hz, C 5; 185.5, C 12; 211.3, $COCH_3$. ^{19}F n.m.r. δ -100.7, ddd, *J* 5.2, 8.0, 8.6 Hz , C(3)F; -76.5, s, CF_3.

(-)-4-Demethoxy-3-fluoro-7,9-bisepidaunomycin hydrochloride (43).

A solution of compound (42) (137 mg) in 0.1 M aqueous sodium hydroxide (28 ml) was stirred under an argon atmosphere at room temperature for 1.5 h. The solution was acidified to pH 4 with 5 M HCl, diluted with saturated aqueous sodium bicarbonate (10 ml), and extracted with chloroform (6x20 ml). The combined extracts were washed successively with water (30 ml), brine (30 ml), dried (Na_2SO_4) and the solvent evaporated to give a reddish powder. I.r. ν_{max} 3660 w, 3600 w, 2955 w, 1705 m, 1618 m, 1584 s, 1331 s, 1270 bm, 1107 m, 1075 bm, 973 s cm^{-1}. The free amine was taken up in a 9/1 mixture of chloroform and methanol (3 ml), cooled, acidified to pH 3 with methanolic hydrogen chloride, and diluted with anhydrous ether (30 ml). Filtration give *the title compound* as an orange powder (96 mg, 78%), m.p. 170-2°; $[\alpha]_D$ -270° (c, 0.10; methanol) . ^1H n.m.r. (DMSO - d_6) δ 1.13, d, *J* 6.4Hz, 3H, H 6'; 1.66, dd, *J* 3.8, 12.3 Hz, 1H, H 2'; 1.78 -1.98, m, 2H, H 8, H 2'; 2.30, s, 3H, CH_3CO; 2.41, dm, *J* 15.3 Hz, 1H, H 8; 2.94, s, 2H, C(10)H_2; 3.34, m, 1H, H 3'; 3.59, m, 1H, H 4'; 4.19, q, *J* 6.4 Hz, 1H, H 5'; 5.10, m, 1H, H 7; 5.30, bs, 1H, H 1'; 5.44, d, *J* 6.0 Hz, 1H, C(4')OH; 5.49, s, 1H, C(9)OH; 7.78, ddd, *J* 2.5, 8.7, J_F 8.0 Hz, 1H, H 2; 7.86, dd, *J* 2.5, J_F 8.9 Hz, 1H, H 4; 7.99, bs, 3H, NH_3^+; 8.24, dd, *J* 8.7, J_F 5.4 Hz, 1H, H 1; 13.12, s, 1H, C(11)OH; 13.26, s, 1H, C(6)OH. ^{13}C n.m.r. (DMSO-d_6) δ 16.7, C 6'; 24.5, CH_3CO; 27.8, C 2'; 30.7, C 10; 32.1, C 8; 46.7, C 3'; 62.9, C 4'; 65.9, C 7; 66.6, C 5'; 75.2, C 9; 92.0, C 1'; 110.1, C 11a, 5a; 113.3, C 5a, 11a; 112.9, *J* 23.0 Hz, C 2; 122.3, *J* 22.2 Hz, C 4; 129.8, *J* 2.6 Hz, C 12a; 130.4, *J* 9.0 Hz, C 1; 134.5, C 10a; 135.8, *J* 8.7 Hz, C 4a; 137.8, C 6a; 155.2, C 11; 156.4, C 6; 165.9, *J* 256.4 Hz, C 3; 184.8, *J* 1.2 Hz, C 5; 185.1, C 12; 212.3, $COCH_3$. ^{19}F n.m.r. (DMSO - d_6) δ -100.9, ddd, *J* 5.4, 8.0, 8.9 Hz.

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