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Experiments Directed Towards the Synthesis of Anthracyclinones. XXVI* The Preparation of Chiral Intermediates for Anthracyclinone Synthesis

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Abstract

(2′*R*)-1,5-Dimethoxy-2(2′-methyloxiran-2′-ylmethyl)anthraquinone (8), an intermediate for the synthesis of fridamycin E, has been prepared enantioselectively via the diol (15). The diol (15) was prepared in high yield by asymmetric *cis*-hydroxylation of the alkene (11). The analogous diol (22), a vineomycinone B_2 precursor, was also prepared.

To date, several total syntheses of the anthracyclinone antibiotic fridamycin E (1)[1–3] and of the related compound vineomycinone B_2 (2)[4–7] have been reported. Most of these have followed a convergent approach in which the skeleton is assembled by the addition of two flanking aliphatic moieties of known stereochemistry to a tricyclic substrate of anthraquinonoid origin. For example, the commercial dyestuff anthrarufin (3) is a convenient starting material which has found wide use in the synthesis of vineomycins.[1,2,6,7] During his synthesis of fridamycin E from (3) Krohn investigated an approach based on the addition of nucleophilic acyl anion equivalents to the epoxide (8).[1] We now describe an enantioselective synthesis of the epoxide (8) and preparation of a related chiral enantio-enriched intermediate suitable for synthesis of vineomycinone B.

* Part XXV, *Aust. J. Chem.*, 1995, **48**, 531.

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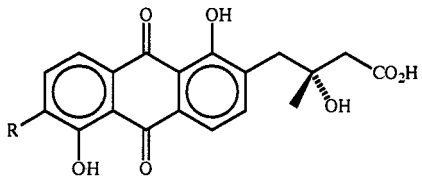
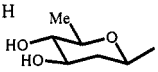
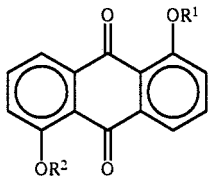


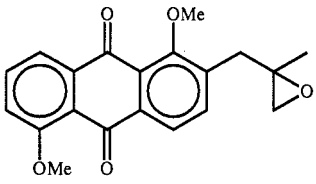
(1) R = H

(2) R = 

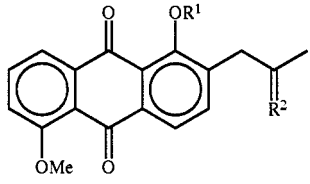


	R^1	R^2
(3)	H	H
(4)	H	Me
(5)	Me	Me

	R^1	R^2
(6)	$CH_2C(Me)=CH_2$	Me
(7)	$CH_2C(Me)=CH_2$	H

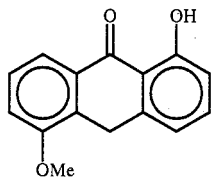


(8)

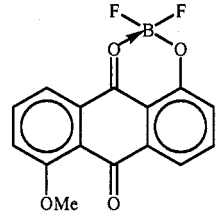


	R^1	R^2
(9)	H	CH_2
(10)	H	O
(11)	Me	CH_2

Krohn[1] prepared the racemic epoxide (8) from the alkene (9),* the preparation of which had been described previously by Baldwin and Rajeckas[8] who introduced dissymmetry between the aromatic rings of anthrarufin by preparing its monomethyl ether (4) from 1,5-dichloroanthraquinone via the anthrone (12). These workers indicated that the monomethyl ether (4) was not readily available either by partial demethylation of anthrarufin dimethyl ether (5) or by partial methylation of anthrarufin. However, Preston *et al.*[9] have subsequently reported a high yield (91%) of the monomethyl ether (4) by selective demethylation of the dimethyl ether (5) with boron trifluoride etherate via a highly insoluble difluoroboron chelate (13). Despite our inability to reproduce the reported yield for this demethylation, a yield of 45% in our hands and the ready availability of the dimethyl ether (5) still made this route to (4) more attractive than that via the anthrone (12).



(12)



(13)

* In the experimental section of ref. 1 and in a flow chart, compound (9) is erroneously referred to as compound (10).

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[9] Preston, P. N., Winwick, T., and Morley, J. O., *J. Chem. Soc., Perkin Trans. 1*, 1983, 1439.

Allylation of the phenol (4) with methallyl chloride and potassium carbonate in *N*,*N*-dimethylformamide at 70° gave the methallyl ether (6) (90%), with a melting point (155·5–156·5°) somewhat higher than that reported (137–140°).[8] Alternatively, methylation of the monomethallyl ether (7)[10] of anthrarufin with dimethyl sulfate and potassium carbonate in refluxing acetone afforded the same compound (100%). Reductive Claisen rearrangement of the methallyl ether (6) with sodium dithionite in a mixture (1 : 1) of water and *N*,*N*-dimethylformamide rather than with zinc dust in acetic acid[1] afforded the phenol (9) in 94% yield (cf. 80% in ref. 1). Ozonolysis of the phenol (9) with a standardized solution of ozone in dichloromethane/methanol (20 : 1) afforded a 99% yield of the keto phenol (10), a key intermediate in Krohn's synthesis of fridamycin E. Correct ^{1}H and ^{13}C n.m.r. spectra were obtained for (10) but based on assignments for the related anthraquinones (5)[11] and (14)[12] (Fig. 1) the ^{13}C n.m.r. assignments for C 4 and C 7 reported in the literature (in parentheses in Fig. 1) should be interchanged. Despite the low yield for partial demethylation of (5), the above route offers an improved sequence for the formation of (10) from anthrarufin.

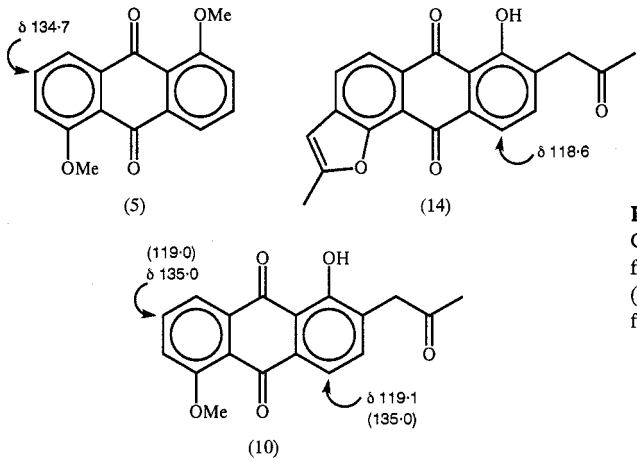

Fig. 1. ^{13}C n.m.r. assignments for C 4 and C 7 of (10) based on those for related anthraquinones (5)[11] and (14).[12] Values in parentheses are from ref. 1.

Treatment of the methyl ether (11) of the phenol (9) with the AD-mix β reagent[13,14] for 50 h at room temperature afforded the chiral optically active diol (15) (88%). Replacement of the characteristic H 3′ signals in the ^{1}H n.m.r. spectrum of the alkene (11) at δ 4·89 and 4·68 by a singlet at 3·40 was indicative of dihydroxylation. Under high resolution the singlet was resolved into a pair of doublets at δ 3·38 (J 11·3 Hz) and 3·41 (J 11·3 Hz) and the diastereotopic

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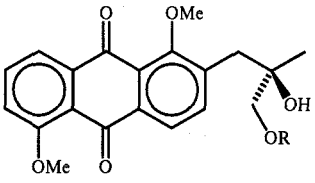
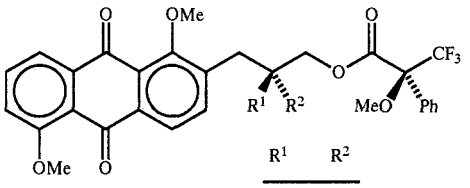
protons H3′ also gave rise to two doublets at 2·91 (J 13·3 Hz) and 3·09 (J 13·3 Hz). A full assignment of the ^{13}C n.m.r. signals was achieved by comparison with analogous fridamycin precursors[3] and by DEPT experiments. An attempt to determine the enantiomeric purity of the diol (15) by n.m.r. analysis in the presence of the π-donor chiral solvating reagent (*R*)-1-(9-anthryl)-2,2,2-ethanol[15] was unsuccessful, but conversion of (15) into the Mosher esters (17) and (18) by treatment with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and 4-dimethylaminopyridine for 24 h, afforded derivatives amenable to analysis. In addition to characteristic signals reported for Mosher esters[16] the ^1H n.m.r. spectrum showed that the H3′ signal of the diol (15) at δ 3·40 had been replaced by two doublets at 4·15 (J 11·0 Hz) and 4·29 (J 11·0 Hz). Also evident were two aliphatic methoxy signals at δ 3·90 and 3·85. Integration of these signals indicated an 87:13 ratio of the diastereomers (17) and (18) which equates to a 74% enantiomeric excess of the putative (*R*)-diol (15). The presence and integration of two signals in the ^{19}F n.m.r. spectrum of (17) and (18) at δ −71·75 and −71·82 relative to $CFCl_3$ indicated a 67% enantiomeric excess, which is considered to be more accurate than that obtained from the ^1H n.m.r. spectrum.



(15) R = H
(16) R = Ts



	R^1	R^2
(17)	Me	OH
(18)	OH	Me

Esterification of the enantiomerically enriched diol (15) with *p*-toluenesulfonyl chloride gave the primary *p*-toluenesulfonate (16) (52%) and unreacted diol (46%). Treatment of (16) with sodium hydride in tetrahydrofuran for 17 h effected cyclization to give the (*R*)-epoxide (8) (92%), which was also formed (72%) on treatment of the tosylate with potassium cyanide for 66 h.

Attempts to hydroxylate the mixed allyl substituted anthraquinone (19)[10] or the monoallyl-substituted compound (20)[11] with AD-mix β were unsuccessful. However, although asymmetric dihydroxylation of the methallyl furan (21)[17] with AD-mix β returned mainly starting material (59%) it also afforded a low yield (3%) of the chiral, optically active anthraquinonyl propanediol (22), a potentially useful intermediate for vineomycinone B_2 synthesis. Asymmetric dihydroxylation of the methallyl furan (21) was more successful when the reagents were added individually and an increased concentration of osmium and the PHAL(DHQD)$_2$ ligand was used. Under these conditions the anthraquinonyl propanediol (22) was isolated in 64% yield.

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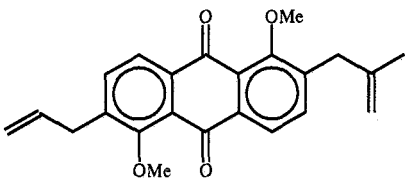
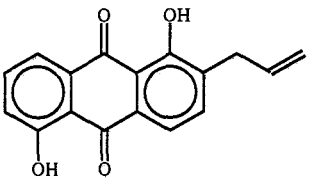
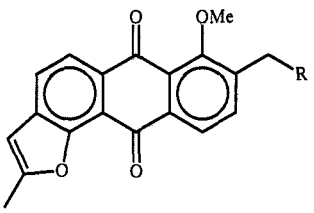


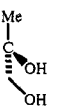
(19)



(20)



(21) R = C(Me)=CH$_2$

(22) R = 

Experimental

For general experimental details see ref. 18.

1-Hydroxy-5-methoxyanthraquinone (4)

A solution of the dimethoxyanthraquinone (5)[19] (1·00 g, 3·73 mmol) in *o*-dichlorobenzene (20 ml) was heated under reflux with boron trifluoride etherate (1·06 g, 7·46 mmol) under argon for 2 h. Solvent was removed under reduced pressure and the resulting purple solid was heated under reflux with methanol for 10 min, and the mixture was then cooled and filtered through Celite. Removal of solvent and column chromatography on silica (CH_2Cl_2/hexanes, 9:1) yielded starting material (0·18 g, 18%) and 1-hydroxy-5-methoxyanthraquinone (0·48 g, 48%) as yellow plates (from CH_2Cl_2/hexanes), m.p. 179–181·5° (lit.[8] 180–181·5°) (correct ^{1}H n.m.r. spectrum[8]).

5-Methoxy-1-(2′-methylprop-2′-enyloxy)anthraquinone (6)

(A) A mixture of the monophenol (4) (0·13 g, 0·50 mmol) anhydrous potassium carbonate (0·69 g, 5·02 mmol) and methallyl chloride (0·25 g, 2·76 mmol) in *N*,*N*-dimethylformamide (7 ml) was stirred at 70° under nitrogen for 19 h. Water (10 ml) was added, the mixture was filtered, and the solvent was removed under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (30 ml), washed with water, concentrated and chromatographed on silica CH_2Cl_2/hexanes, 7:3) to yield 5-methoxy-1-(2′-methylprop-2′-enyloxy)anthraquinone (0·14 g, 90%) as yellow needles (from CH_2Cl_2), m.p. 148–149° (lit.[10] 138–140°). δ_H 1·91, s, 2′-CH_3; 4·02, s, 5-OCH_3; 4·62, s, 2H, H1′; 5·07, m, *J* 1·3 Hz, H3′ *cis* to Me; 5·33, m, unresolved, H3′ *trans* to Me; 7·23, dd, $J_{6,7}$ 8·4, $J_{6,8}$ 0·8 Hz, H6; 7·26, dd, $J_{2,3}$ 8·4, $J_{2,4}$ 0·6 Hz, H2; 7·64, dd, $J_{6,7}$ 8·2, $J_{7,8}$ 7·9 Hz, H7; 7·68, dd, $J_{2,3}$ 8·3, $J_{3,4}$ 7·9 Hz, H3; 7·88, dd, $J_{3,4}$ 7·7, $J_{2,4}$ 0·9 Hz, H4; 7·90, dd, $J_{7,8}$ 7·7, $J_{6,8}$ 0·9 Hz, H8. δ_C 19·3, 2′-CH_3; 56·5, 5-OCH_3; 72·6, C1′; 113·1, C3′; 116·6, C2; 118·1, C6; 119·7, C4; 119·8, C8; 120·9, C9a; 121·1, C10a; 134·8, C7; 135·0, C3; 137·4, C8a; 137·5, C4a; 139·8, C2′; 158·7, C5; 159·7, C1; 182·3, C10; 182·8, C9.

(B) A mixture of the monoether (7)[10] (0·78 g, 2·65 mmol), dimethyl sulfate (1·67 g, 13·2 mmol) and anhydrous potassium carbonate (1·83 g, 13·2 mmol) in acetone (150 ml) was heated under reflux for 24 h. Water (150 ml) was added and the solution was extracted with CH_2Cl_2 (300 ml). Workup and chromatography on magnesium carbonate (CH_2Cl_2/hexanes, 3:7) gave 5-methoxy-1-(2′-methylprop-2′-enyloxy)anthraquinone (0·82 g, 100%) as yellow needles (from ether), m.p. 155·5–156·5° (correct t.l.c. behaviour and ^{1}H n.m.r. spectrum).

[18] Cambie, R. C., Holroyd, S. E., Larsen, D. S., Rutledge, P. S., and Woodgate, P. D., *Aust. J. Chem.*, 1992, **45**, 1589.
[19] Cook, J. W., and Pauson, P. L., *J. Chem. Soc.*, 1949, 2726.

1-Hydroxy-5-methoxy-2-(2′-methylprop-2′-enyl)anthraquinone (9)

A solution of the ether (6) (0·16 g, 0·51 mmol) in *N*,*N*-dimethylformamide (10 ml) was added to a hot (90°) solution of sodium dithionite (0·16 g, 0·90 mmol) in water (30 ml) and *N*,*N*-dimethylformamide (20 ml) under argon, and the mixture was heated under reflux for 2 h. Water (50 ml) was added to the cooled solution and the resulting precipitate was collected and dissolved in CH_2Cl_2 (50 ml), and the solution was worked up to give 1-hydroxy-5-methoxy-2-(2′-methylprop-2′-enyl)anthraquinone (0·15 g, 94%) as orange prisms (from CH_2Cl_2/hexanes), m.p. 132·5–133·5° (lit.[10] 129–130°). δ_H 1·77, s, 2′-CH_3; 3·45, s, 2H, H1′; 4·04, s, 5-OCH_3; 4·73, m, unresolved, H3′ *cis* to Me; 4·88, m, unresolved, H3′ *trans* to Me; 7·33, dd, $J_{6,7}$ 8·4 Hz, $J_{6,8}$ unresolved, H6; 7·53, d, $J_{3,4}$ 7·8 Hz, H3; 7·70, dd, $J_{6,7}$ 8·1, $J_{7,8}$ 8·1 Hz, H7; 7·72, d, $J_{3,4}$ 7·8 Hz, H4; 7·95, dd, $J_{7,8}$ 7·8, $J_{6,8}$ 1·0 Hz, H8; 12·8, s, 1-OH. δ_C 22·4, 2′-CH_3; 37·2, C1′; 56·5, 5-OCH_3; 112·6, C3′; 115·0, C9a; 118·4, C6; 119·0, C4; 119·4, C8; 121·6, C10a; 133·3, C4a; 134·6, C2; 134·9, C7; 135·5, C8a; 137·3, C3; 143·2, C2′; 160·2, C5; 160·4, C1; 181·7, C10; 188·8, C9.

1-Hydroxy-5-methoxy-2-(2′-oxopropyl)anthraquinone (10)

A solution of the phenol (9) (0·21 g, 0·67 mmol) in methanol/CH_2Cl_2 (1:20, 50 ml) was treated with ozone (3·8 mmol) in CH_2Cl_2 (35 ml) at −78°, and the solution was stirred for 1 h and again treated with ozone (2·9 mmol) in CH_2Cl_2 (27·2 ml). After 12 min dimethyl sulfide (2·55 g, 41·0 mmol) was added and the mixture was warmed to room temperature and stirred for 14 h. Solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (50 ml), and the solution worked up to give 1-hydroxy-5-methoxy-2-(2′-oxopropyl)anthraquinone (0·21 g, 99%) as yellow needles (from CH_2Cl_2/hexanes), m.p. 193–194° (lit.[1] 182–183°) (correct ^1H and ^{13}C n.m.r. spectra[1]).

1,5-Dimethoxy-2-(2′-methylprop-2′-enyl)anthraquinone (11)

Dimethyl sulfate (1·19 g, 9·44 mmol), the methallyl anthraquinone (9) (0·29 g, 0·94 mmol) and anhydrous potassium carbonate (1·30 g, 9·44 mmol) in acetone (30 ml) were heated under nitrogen for 18 h. Solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (30 ml), and the solution washed successively with 5% aqueous hydrochloric acid and water. Chromatography on silica (CH_2Cl_2/hexanes, 1:1) yielded 1,5-dimethoxy-2-(2′-methylprop-2′-enyl)anthraquinone (0·28 g, 92%) as yellow needles, m.p. 81–81·5° (lit.[1] 93°) (Found: $M^{+\bullet}$, 322·1199. Calc. for $C_{20}H_{18}O_4$: $M^{+\bullet}$, 322·1205). (Correct ^1H n.m.r. spectrum.) δ_C 22·6, 2′-CH_3; 37·7, C1′; 56·6, 5-OCH_3; 62·0, 1-OCH_3; 112·9, C3′; 117·0, C6; 119·7, C8; 121·0, C10a; 123·2, C4; 125·0, C9a; 135·0, C7; 135·8, C4a; 136·2, C3; 137·2, C8a; 140·8, C2; 143·8, C2′; 158·4, C1; 159·8, C5; 182·5, C10; 182·9, C9.

(2′R)-2-(2′,3′-Dihydroxy-2′-methylpropan-1′-yl)-1,5-dimethoxyanthraquinone (15)

The methallyl anthraquinone (11) (0·12 g, 0·40 mmol) was added to a cooled (0°) mixture of AD-mix β (0·49 g) in t-butyl alcohol (1 ml) and water (1 ml), and the biphasic suspension was warmed to room temperature and stirred for 50 h. Sodium sulfite (0·10 g) was added and the mixture stirred for a further 1 h. The mixture was extracted with CH_2Cl_2 and the extract worked up and purified by p.l.c. (silica, ethyl acetate) to give *(2′R)-2-(2′,3′-dihydroxy-2′-methylpropan-1′-yl)-1,5-dimethoxyanthraquinone* (0·12 g, 88%) as a yellow oil, $[\alpha]_D$ −12° (*c*, 2·1 in CH_2Cl_2) (Found: $M^{+\bullet}$+1 (d.c.i., NH_3), 357·1321. $C_{20}H_{20}O_6$ requires $M^{+\bullet}$+1, 357·1338). λ_{max} 379 (log ϵ 3·83), 257 (4·50), 221 nm (5·07). ν_{max} 3476 (OH), 1667 (CO), 1586, 1574, 1264 cm^{-1}. δ_H 1·16, s, 2′-CH_3; 2·91, d, $J_{1'a,1'b}$ 13·3 Hz, H1′$_a$; 3·09, d, $J_{1'a,1'b}$ 13·3 Hz, H1′$_b$; 3·38, d, $J_{3'a,3'b}$ 11·3 Hz, H3′$_a$; 3·41, d, $J_{3'a,3'b}$ 11·3 Hz, H3′$_b$; 3·97, s, 1-OCH_3; 4·03, s, 5-OCH_3; 7·29, d, $J_{6,7}$ unresolved, H6; 7·67, d, $J_{3,4}$ 7·7 Hz, H3; 7·69, dd, $J_{6,7}$ 7·7, $J_{7,8}$ 7·7 Hz, H7; 7·86, d, $J_{7,8}$ 7·7 Hz, H8; 8·01, d, $J_{3,4}$ 7·9 Hz, H4. δ_C 23·6, 2′-CH_3; 38·6, C1′; 56·4, 5-OCH_3; 62·1, 1-OCH_3; 69·3, C3′; 73·6, C2′; 117·1, C6; 119·6, C8; 120·7, C10a; 123·4, C4; 124·7, C9a; 135·1, C7; 136·1, C4a; 136·9, C8a; 138·2, C3; 138·4, C2; 158·0, C1; 159·8, C5; 182·1, C10; 182·6, C9. *m/z* (d.c.i., NH_3) 337 (M+H), 339 (357 − H_2O), 325.

(2'R)-3'-(1'',5''-Dimethoxyanthraquinon-2''-yl)-2'-hydroxy-2'-methylpropan-1'-yl p-*Toluenesulfonate (16)*

A solution of the diol (15) (29 mg, 0·08 mmol), *p*-toluenesulfonyl chloride (22 mg, 0·11 mmol) and 4-dimethylaminopyridine (2 mg, 0·02 mmol) in pyridine (1 ml) was kept at room temperature under nitrogen for 124 h. The solution was diluted with CH_2Cl_2 (5 ml), and washed with 5% aqueous hydrochloric acid, and the solvent was removed under reduced pressure. P.l.c. (silica, ethyl acetate) gave starting material (13·5 mg, 46%) and *(2'R)-3'-(1'',5''-dimethoxyanthraquinon-2''-yl)-2'-hydroxy-2'-methylpropan-1'-yl* p-*toluenesulfonate* (23 mg, 52%) as a yellow oil, $[\alpha]_D$ −9·5°, (*c*, 2·4 in CH_2Cl_2) (Found: $M^{+\bullet}$, 510·1342. $C_{27}H_{26}O_8S$ requires $M^{+\bullet}$, 510·1335). λ_{max} 382 (log ϵ 3·63), 256 nm (4·32). ν_{max} 3470 (OH), 1668 cm^{-1} (CO). δ_H 1·15, s, 2'-CH_3; 2·43, s, tosyl-CH_3; 2·89, d, $J_{3'_a,3'_b}$ 13·7 Hz, H3'$_a$; 3·09, d, $J_{3'_a,3'_b}$ 13·7 Hz, H3'$_b$; 3·80, d, $J_{1'_a,1'_b}$ 9·5 Hz, H1'$_a$; 3·86, d, $J_{1'_a,1'_b}$ 9·3 Hz, H1'$_b$; 3·92, s, 1''-OCH_3; 4·04, s, 5'-OCH_3; 7·27–7·36, m; 7·54, d, $J_{3'',4''}$ 8·0 Hz, H3''; 7·67–7·81, m; 7·88, dd, $J_{7'',8''}$ 7·7, $J_{6'',8''}$ 0·8 Hz, H8''; 7·97, d, $J_{3'',4''}$ 8·0 Hz, H4''. δ_C 21·6, tosyl CH_3; 24·1, 2'-CH_3; 38·8, C3'; 56·5; 5''-OCH_3; 6·19, 1''-OCH_3; 71·9, C2'; 75·4, C1'; 117·2, C6''; 119·7, C8''; 120·8, C10a''; 123·5, C4''; 124·9, C9a''; 127·9, C3/5; 129·9, C2/6; 132·5, C4; 135·1, C7''; 136·4, C4a''; 137·0, C8a''; 137·1, C2'; 138·0, C3''; 145·1, C1; 158·1, C1''; 159·8, C5''; 182·0, C10''; 182·6, C9.'' *m/z* 510 (M), 338 (M − $C_7H_8O_3S$).

(2'R)-1,5-Dimethoxy-2-(2'-methyloxiran-2'-ylmethyl)anthraquinone (8)

(A) A solution of the tosylate (16) (29 mg, 0·06 mmol) in dry tetrahydrofuran (8 ml) was stirred with sodium hydride (15 mg, 0·57 mmol) at room temperature for 17 h. The reaction was quenched with water (0·5 ml) and the solvent was removed under reduced pressure. P.l.c. (silica, CH_2Cl_2/ethyl acetate, 9:1) yielded (2'*R*)-1,5-dimethoxy-2-(2'-methyloxiran-2'-ylmethyl)anthraquinone (18 mg, 92%) as yellow crystals (from CH_2Cl_2), m.p. 129–130° (lit.[1] 130°) (correct i.r. and ^1H n.m.r. spectrum[1]), $[\alpha]_D$ +5·3° (*c*, 0·5 in CH_2Cl_2).

(B) Potassium cyanide (8 mg, 0·12 mmol) was added to a solution of the tosylate (16) (20 mg, 0·04 mmol) in *N*,*N*-dimethylformamide (1 ml) and the mixture was kept at room temperature for 66 h. Solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 ml) and washed with water. P.l.c. (silica, ethyl acetate) gave (2'*R*)-1,5-dimethoxy-2-(2'-methyloxiran-2'-ylmethyl)anthraquinone (10 mg, 72%) as yellow granules, m.p. 129–130°.

(2'R)-3'-(1'',5''-Dimethoxyanthraquinon-2''-yl)-2'-hydroxy-2'-methylpropan-1'-yl (2S)-α-Methoxy-α-(trifluoromethyl)phenylacetate (17)

The diol (15) (23 mg, 0·065 mmol) in dry pyridine (2 ml) was stirred with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (50 mg, 0·20 mmol) and 4-dimethylaminopyridine (2 mg, 0·016 mmol) at room temperature for 21 h. The reaction was quenched with water (2 ml) and the mixture was extracted with CH_2Cl_2. The solution was dried with magnesium sulfate and the solvent removed under reduced pressure. P.l.c. (silica, ethyl acetate) yielded the *(2'R)-3'-(1'',5''-dimethoxyanthraquinon-2''-yl)-2'-hydroxy-2'-methylpropan-1'-yl (2S)-α-methoxy-α-(trifluoromethyl)phenylacetate* (10 mg, 27%) as a yellow oil, $[\alpha]_D$ −15·6° (*c*, 0·2 in CH_2Cl_2) (Found: $M^{+\bullet}$ (d.e.i.), 572·1653. $C_{30}H_{27}F_3O_8$ requires 572·1658). δ_H 1·16, s, 2'-CH_3; 2·80, d, $J_{3'_a,3'_b}$ 13·5 Hz, H3'$_a$; 3·12, d, $J_{3'_a,3'_b}$ 13·5 Hz, H3'$_b$; 3·58, s, 1''-OCH_3; 3·85, s, (17) α-OCH_3; 3·90, s, (18) α-OCH_3; 4·05, s, 5''-OCH_3; 4·15, d, $J_{1'_a,1'_b}$ 11·0 Hz, H1'$_a$; 4·29, d, $J_{1'_a,1'_b}$ 11·0 Hz, H1'$_b$; 7·25–7·60, m, Ar; 7·65–7·80, m, Ar; 7·88–8·30, m, Ar. δ_F −71·82, 1F, CF_3; −71·75, 5F, CF_3.*

* Fluorine n.m.r. spectra were recorded on a Bruker AM 400 spectrometer with $CFCl_3$ as the internal reference. Spectra are reported in the following style: δ_F chemical shift, relative integral, assignment.

Synthesis of (2'R)-8-(2',3'-Dihydroxy-2'-methylpropan-1'-yl)-7-methoxy-2-methyl-6,11-dihydroanthra[1,2-b]furan-6,11-dione (22)

(A) *By using preformulated* AD-*mix* β. A mixture of the furanoanthraquinone (21)[17] (30 mg, 0·087 mmol) and AD-mix β (0·10 g) in t-butyl alcohol (0·5 ml) and water (0·5 ml) was stirred at room temperature for 24 h. Sodium sulfite (75 mg) was added, stirring was continued for 1 h, and the mixture was diluted with CH_2Cl_2 (10 ml) and washed successively with brine and water. Removal of solvent and p.l.c. (silica, ethyl acetate/hexanes, 4:1) gave starting material (8 mg, 59%) and *(2'R)-8-(2',3'-dihydroxy-2'-methylpropan-1'-yl)-7-methoxy-2-methyl-6,11-dihydroanthra[1,2-b]furan-6,11-dione* (1·1 mg, 3%) as yellow needles, m.p. 157·5–160°, $[\alpha]_D$ −13·1° (*c*, 0·72 in CH_2Cl_2) (Found: $M^{+\bullet}+1$ (d.c.i., NH_3), 381·1336. $C_{22}H_{20}O_6$ requires $M^{+\bullet}+1$, 381·1338). λ_{max} 281 (log ϵ 4·43), 350 (4·03), 232 nm (4·41). ν_{max} 3416 (OH), 1668 (CO), 1598, 1579, 1323, 1277, 1217, 1091 cm^{-1}. δ_H 1·17, s, 2'-CH_3; 2·64, s, 2-CH_3; 2·93, d, $J_{1'_a,1'_b}$ 13·0 Hz, H 1$_a$; 3·12, d, $J_{1'_a,1'_b}$ 13·4 Hz, H 1'$_b$; 3·40, s, 2H, H 3'; 4·00, s, 7-OCH_3; 6·54, s, H 3; 7·68, d, $J_{9,10}$ 8·0 Hz, H 9; 7·84, d, $J_{4,5}$ 8·3 Hz, H 4; 8·14, d, $J_{9,10}$ 8·0 Hz, H 10; 8·17, d, $J_{4,5}$ 8·3 Hz, H 5. δ_C 14·51, 2-CH_3; 23·64, 2'-CH_3; 38·80, C 1'; 62·06, 7-OCH_3; 69·33, C 3'; 73·65 C 2'; 103·00 C 3; 117·07, C 6a; 122·04, C 5; 123·16, C 10; 125·22, C 11a; 125·77, C 4; 130·26, C 3a; 134·80, C 5a; 136·08, C 10a; 137·98, C 9; 139·55, C 8; 151·13, C 2; 158·53, C 7; 161·74, C 11b; 182·01, C 6; 182·37, C 11. *m/z* 381 (M+H), 363 (381 − H_2O), 349 (M − CH_2OH).

(B) *By using increased osmium concentration.* A solution of osmium tetroxide (0·82 mg, 0·003 mmol) in t-butyl alcohol (42 μl) was added to a mixture of the furanoanthraquinone (21)[17] (56 mg, 0·162 mmol), PHAL(DHQD)$_2$[13] (12·6 mg, 0·016 mmol), potassium ferricyanide (0·16 g, 4·85 mmol) and potassium carbonate (67 mg, 5·85 mmol). t-Butyl alcohol (1 ml) and water (1 ml) were added and the mixture was stirred at room temperature for 16 h. Sodium sulfite (0·14 g) was added, stirring was continued for 1 h, and the mixture was diluted with CH_2Cl_2 (20 ml) and washed successively with brine and water. Removal of solvent and p.l.c. (silica, ethyl acetate/hexanes, 4:1) gave (2'*R*)-8-(2',3'-dihydroxy-2'-methylpropan-1'-yl)-7-methoxy-2-methyl-6,11-dihydroanthra[1,2-*b*]furan-6,11-dione (39 mg, 64%).