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Pigments of Fungi, Part 19.[1] A Degradative Method for the Determination of Central Chirality in Naturally Occurring 3-Hydroxy-3-methyl-3,4-dihydroanthracen-1(2*H*)-ones:[2a] Application to Pigments of the Flavomannin Type.[2b]

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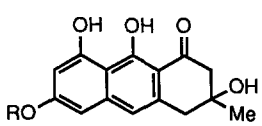
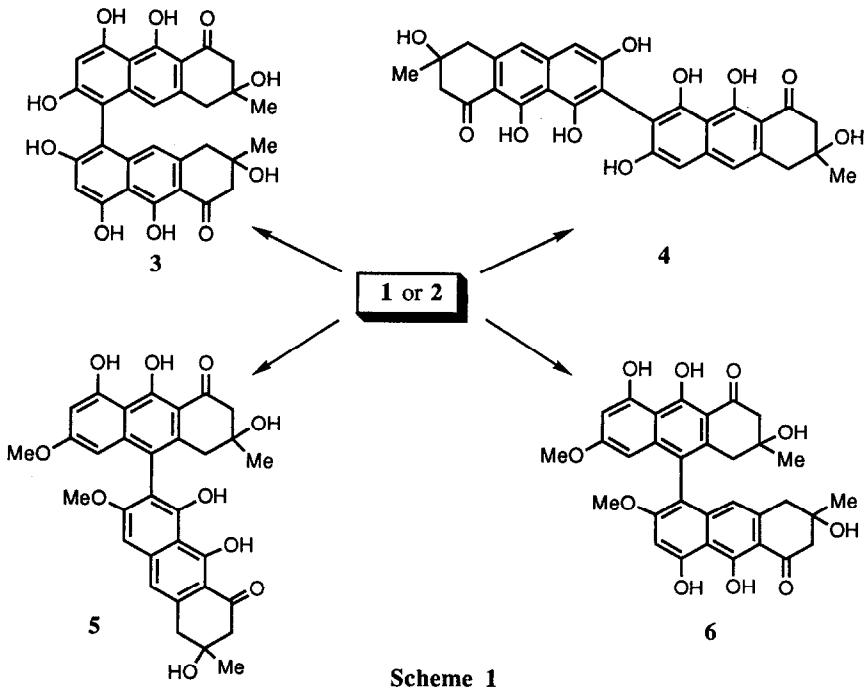
Abstract: The absolute stereochemistry at both chiral centres in the flavomannin-6,6'-di-*O*-methyl ethers A_1 (**23**) and B_1 (**24**) is determined as (*R*) by chemical correlation over six steps without the need for intermediate purification with methyl (*S*)-(-)-tetrahydro-2-methyl-5-oxo-2-furancetate (**25**); the methodology is developed using the fungal metabolite (*S*)-torosachrysone (**2**) as an initial substrate.

Atrochrysone (**1**) and torosachrysone (**2**) occupy pivotal positions in the biosynthesis of polyketide-derived pigments in fungi and higher plants. Atrochrysone occurs in both enantiomeric modifications in fungi belonging to the genus *Cortinarius* and its allies.[3-5] Torosachrysone was first isolated from the seeds of the leguminous plant *Cassia torosa*[6] and has recently been found in several toadstools of the genus *Dermocybe*.[5] The absolute stereochemistry of torosachrysone from *Cassia singueana* was established as (*S*) by application of the chiral exciton coupling method to the benzoate of torosachrysone-8,9-di-*O*-methyl ether (**11**)[7] and was subsequently confirmed by synthesis of torosachrysone-8-*O*-methyl ether (**9**) from (-)-quinic acid.[8] The absolute stereochemistry of fungal torosachrysone is also (*S*) as deduced by comparison of chiroptical data with those of the plant and synthetic materials.[5]



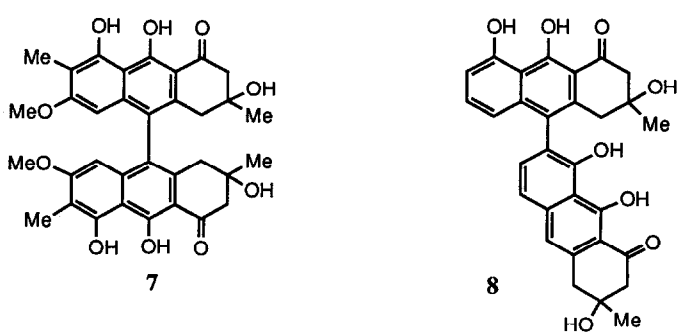
1 R = H
2 R = Me

Atrochrysone (**1**) and torosachrysone (**2**) serve as precursors to a large number of coupled pre-anthraquinone pigments found in great variety in *Cortinarius*. Thus, oxidative coupling at the various sites within the dihydroanthracenone nucleus of **1** or **2** gives rise, *inter alia*, to pigments of the atrovirin (**3**), flavomannin (**4**), phlegmacin (**5**), and pseudophlegmacin (**6**) types as shown in Scheme 1.[9] Coupled pre-anthraquinones closely related to these fungal metabolites have been isolated from medicinal plants of the genus *Cassia*. These include stereoisomers of the fungal phlegmacins from *C. torosa*,[10] and singueanol 1 (**7**) from *C. singueana* which exhibits antibacterial and papaverin-like antispasmodic activity.[7] Severe nervous disorders resulting from ingestion of the seeds of the Mexican shrub *Karwinskia humboldtiana* are directly attributable to the dihydroanthracenone **8**,[11] and similar toxic effects have been recorded for the flavomannins and phlegmacins.[4,8]



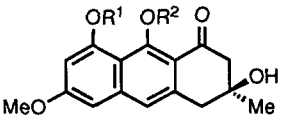
Scheme 1

Due to the presence of chiral centres within and an axis of chirality between the dihydroanthracenone subunits, the pigments **3-8** and their relatives have presented considerable stereochemical problems. Although the axial stereochemistry of singueanol 1 (**7**) has been deduced using CD spectroscopy[7] and kinetic resolution methods have been elegantly applied by Steglich and coworkers to the determination of axial configuration in the atrovirin series and for flavomannin (**4**), there exists to date no case in which the absolute stereochemistry at a chiral centre in any coupled pre-anthraquinone is known. We report here full details of a solution to this problem[2b] that involves the chemical degradation of 3-hydroxy-3-methyl-3,4-dihydroanthracen-1(2*H*)-ones to afford a chiral fragment of the type **22** or **25**. In the first instance the method was developed using (*S*)-torosachrysone (**2**) as the chiral substrate.[2a]



The Determination of Central Chirality in "Monomeric" Pre-anthraquinones

Torosachrysone (**2**), which contains all of the relevant functionality present in its more complex antecedents **3-6** and their relatives **7** and **8**, is available from several Australian dermocybes[5] and has been used to develop the degradative methodology. In order to preclude the possibility of generating a symmetric, and consequently useless, fragment, the carbonyl oxygen atom in torosachrysone must first be removed. Numerous attempts to effect reduction of the carbonyl group in **2** were unsuccessful and served only to return the dihydroanthracenone unchanged or to cause extensive decomposition of this acid, air, and light sensitive pigment. Methylation of **2** imparts increased stability to the molecule but the reaction conditions must be carefully defined if yields are to be high and complex mixtures avoided. Thus, (*S*)-torosachrysone (**2**) forms the 8-*O*-methyl, 9-*O*-methyl, and the 8,9-di-*O*-methyl ethers **9**, **10**, and **11**, respectively, in varying proportions under different conditions (Table 1). In our hands, efficient generation of the fully methylated derivative **11** was best achieved by first treating **2** in chloroform with an excess of ethereal diazomethane for 15 minutes at room temperature whereupon a mixture containing a predominance of the 9-*O*-methyl ether **10**, $[\alpha]_D$ -5 (*c* 1.5, $CHCl_3$), m.p. 179-182°C, was obtained. When this mixture was subsequently exposed to dimethyl sulphate and potassium carbonate in acetone at reflux the 8,9-di-*O*-methyl ether **11** $[\alpha]_D$ -4 (*c* 1.0, $CHCl_3$), m.p. 194-197°C, could be isolated in 75% overall yield from torosachrysone (**2**).



9 R^1 = Me, R^2 = H
10 R^1 = H, R^2 = Me
11 $R^1 = R^2$ = Me

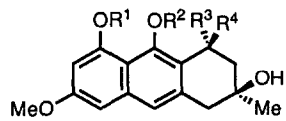
Table 1. Methylation of torosachrysone (**2**).

Conditions	Products (Isolated yields, %)		
	9	**10**	**11**
CH_2N_2/ $CHCl_3$ (10 h) (ref. 12)	14	38	-
CH_2N_2/Et_2O (10 h) (ref. 7)	-	-	54
CH_2N_2/Et_2O (16 h)	7	19	52
CH_2N_2/ $CHCl_3$ (15 min)	16	71	4
Me_2SO_4/K_2CO_3 (2 h)	57	-	40
MeI/K_2CO_3 (5 h)	46	-	31
(i) CH_2N_2/$CHCl_3$ (15 min) (ii) Me_2SO_4/K_2CO_3 (2 h)	19	-	75

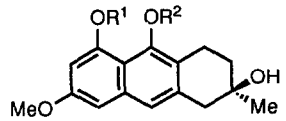
The ethers **9**, **10**, and **11** are readily distinguished by their physical and spectroscopic properties. They were identified here from inspection of their respective ^1H NMR spectra, particularly by the presence, or absence, of the characteristic chelated hydroxyl resonances ($\delta_{8\text{-}OH}$ ~10 and $\delta_{9\text{-}OH}$ ~16) and the number of discrete methoxy groups. Only limited data are available for these compounds in the literature.[7,12]

The 8-*O*-methyl ether **9**, $[\alpha]_{546}$ -15.5 (*c* 0.4, $CHCl_3$), m.p. 225-230°C, best prepared by treatment of **2** with dimethyl sulphate and potassium carbonate in acetone at reflux, proved to be identical in all respects, including specific rotation, with the pigment atrochrysone-6,8-di-*O*-methyl ether isolated by Oertel and Steglich from several *Cortinarius* and *Tricholoma* species.[3,4] This identity corroborates the assignment of (*S*) stereochemistry to both fungal torosachrysone (**2**)[5] and its naturally occurring 8-*O*-methyl ether.[8]

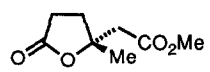
In contrast to the situation with torosachrysone (**2**) itself, reduction of the carbonyl group in the 8,9-di-*O*-methyl ether **11** posed no problems and with lithium borohydride in tetrahydrofuran during 2 h yielded a mixture of the diastereoisomeric alcohols **12** (76%), m.p. 142-143°C, and **13** (19%), m.p. 164-165°C, which could be separated by chromatography and their relative stereochemistries established from the corresponding ^1H NMR spectra.[13] With similar ease, and under the same conditions, the 8-*O*-methyl ether **9** gave a mixture of the alcohols **14** (66%) and **15** (21%), while the 9-*O*-methyl ether **10** furnished the diastereoisomeric alcohols **16** (57%) and **17** (39%).



12 $R^1 = R^2 = Me$, $R^3 = OH$, $R^4 = H$
13 $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = OH$
14 $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = OH$
15 $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = OH$
16 $R^1 = R^4 = H$, $R^2 = Me$, $R^3 = OH$
17 $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = OH$



18 $R^1 = R^2 = Me$
19 $R^1 = Me$, $R^2 = H$
20 $R^1 = H$, $R^2 = Me$



21 R = H
22 R = Me

Hydrogenolysis of **12** and **13**, either together or separately, in a Parr apparatus at 50 lb.p.s.i. in the presence of 10% palladium-on-carbon as catalyst gave the tetrahydroanthracene **18** (97%), m.p. 76-78°C. Similarly, hydrogenolysis of (**14** + **15**) and (**16** + **17**) gave the tetrahydroanthracenes **19** (97%), m.p. 121-122°C, and **20** (96%), m.p. 102-103°C, respectively.

Exposure of the tetrahydroanthracene **18** to ruthenium tetraoxide under Sharpless conditions[14] afforded after extractive work-up the carboxylic acid **21**, which was methylated using diazomethane without prior purification. The resulting (*R*)-ester **22** (6.8 mg, 30% from **18**), $[\alpha]_D$ + 7.6 (*c* 0.1, $CHCl_3$), was purified by high performance liquid chromatography and identified by spectroscopic and chiroptical comparison with a sample {$[\alpha]_D$ + 7.7 (*c* 0.1, $CHCl_3$)} prepared *via* Sharpless asymmetric epoxidation of geraniol.[15]

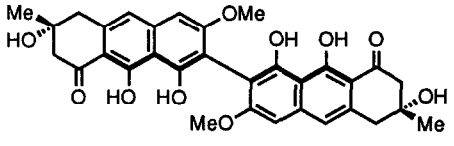
Similarly, oxidative degradation of both the tetrahydroanthracenes **19** and **20** gave the (*R*)-ester **22** after methylation in overall yields of 18% and 24%, respectively.

The correlation of torosachrysone (**2**) with the (*R*)-ester **22** confirms (*S*) stereochemistry for the fungal metabolite[5] and, more significantly, represents the first degradative method for the determination of absolute stereochemistry in a chiral dihydroanthracenone.

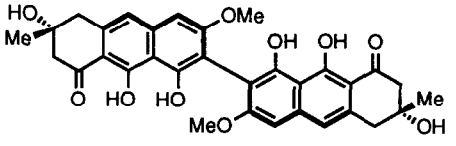
Although the intermediates **9-20** have been fully characterised **(Experimental)** it is significant that the degradation of torosachrysone (**2**) has also been carried out successfully without necessity for purification at any stage save final chromatographic isolation of the (*R*)-ester **22**. Thus, in contrast to chiroptical methods,[7,8] which are limited in their applicability to "monomeric" pre-anthraquinones such as torosachrysone,[16] chemical correlation with chiral esters of the type **22** offered for the first time a practical solution to the question of central chirality in coupled dihydroanthracenones.

The Determination of Central Chirality in Coupled Pre-anthraquinones

Flavomannin-6,6'-di-*O*-methyl ether A_1 (FDM-A_1) (**23**) (no configuration at C-3 and C-3' yet implied) and its atropdiastereoisomer, FDM-B_1 (**24**), are representative of the large and stereochemically complex group of chiral biaryls that have been isolated from fungi,[4] and from medicinal[7] and toxic[11] plants (Scheme 1). FDM-A_1 has been isolated in homochiral form from fruit bodies of the toadstools *Cortinarius citrinus*[3] and *Dermocybe crocea*,[17] and in admixture to varying degrees with FDM-B_1 from *Cortinarius fulmineus*, *C. subfulgens*, and *Tricholoma auratum*.[17] In turn, FDM-B_1 (**24**) is found free from its stereoisomer (**23**) in *Cortinarius pseudosulphureus*[3] and *Tricholoma sulphureum*.[18] The parent phenol, flavomannin (**4**), was first isolated from *Penicillium wortmanni*.[19]



23



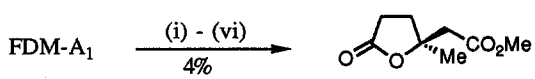
24

As mentioned earlier in this paper, the absolute stereochemistry at the chiral axis in members of the flavomannin series has recently been solved by Steglich and co-workers who have deduced an (*R*) configuration at the axis in flavomannin A (**4**) (from *Cortinarius odoratus*) by kinetic resolution studies and the synthesis of model compounds.[8] Consequently, comparison of the CD spectra of FDM-A_1 (**23**) and FDM-B_1 (**24**) with that of the *C. odoratus* metabolite[20] establishes the (*R*) and (*S*) axial configurations of (**23**) and (**24**), respectively.[21]

In seeking workable quantities of a suitable coupled pre-anthraquinone substrate on which to apply our degradative methodology we discovered a small, pale green *Dermocybe* toadstool growing in abundance during June 1989 in the Kinglake National Park, Victoria. Extraction and chromatography gave a green-yellow pigment, $C_{32}H_{30}O_{10}$, m.p. 203-205°C, $[\alpha]_{546}$ - 853 (*c* 0.2, $CHCl_3$), which was isolated in a yield of 0.1% of the fresh weight of the fungus and to which a flavomannin-6,6'-di-*O*-methyl ether structure was readily assigned from the mass, UV, and ^1H NMR spectra.[4] The CD spectrum exhibited an A-type couplet[21] indicating (*R*) axial stereochemistry. The identity of this pigment with FDM-A_1 as opposed to the alternative possibility, i.e., that it corresponds to the enantiomer of FDM-B_1, could be firmly established only by direct ^1H NMR spectroscopic comparison with authentic samples of FDM-A_1 (from *Cortinarius citrinus*) and FDM-B_1 (from *C. pseudosulphureus*) both generously provided by Professor W. Steglich. Thus, when the pigment was in

admixture with FDM-B_1 the spectrum showed discrete resonances from individual pairs of C-8 and C-8' hydroxyls and C-6 and C-6' methoxyls, one set of resonances originating from each atropdiastereoisomer. In contrast, the spectrum obtained from a mixture of the pigment and authentic FDM-A_1 exhibited only a single set of resonances.

In subjecting FDM-A_1 (**23**) thus obtained from the Australian toadstool to the degradative process previously applied to torosachrysone (**2**) we anticipated, from the outset, chemically complex mixtures and, potentially, a low overall yield. Consequently, we made no attempt to isolate any intermediates but remained secure in the belief that our experience in the torosachrysone series would be reproducible in more complex systems. Thus, FDM-A_1 (35 mg) was exposed without purification at any intermediate stage to the conditions defined in Scheme 2 designed to effect sequential methylation, reduction, hydrogenolysis, oxidative cleavage and esterification. Finally, HPLC purification of the complex reaction mixture gave methyl (*S*)-(-)-tetrahydro-2-methyl-5-oxo-2-furanacetate (**25**), the antipode of the lactone obtained from torosachrysone (**2**), in an overall yield of 4% from FDM-A_1 (**23**). The structure of the butanolide **25** was confirmed by spectroscopy but the limited quantity available (0.8 mg) precluded measurement of the specific rotation. Consequently, the (*S*) absolute stereochemistry was determined by ^{1}H NMR experiments at 400 MHz using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III) [Eu(hfc)$_3$] as chiral shift reagent. In preliminary experiments it was found that both the methoxyl (δ 3.70) and C-methyl (δ 1.52) resonances in the spectrum of the racemic butanolide (**22** + **25**) shift to *ca.* δ 4 and δ 2, respectively, and are each resolved ($\Delta\delta$ *ca.* 0.01 ppm) into two singlets (ratio 1:1) on addition of Eu(hfc)$_3$. That the higher field component of both signals corresponds to the (*S*)-butanolide **25** was established by comparison with the behaviour of synthetic samples of **22** and **25** (both 93% e.e.).[15] Shift experiments involving the lactone derived from FDM-A_1 both alone and in admixture with small amounts of the synthetic (*R*)- and (*S*)-butanolides **22** and **25** established unequivocally that the stereochemistry of the degradation product is (*S*).



23 **25**

Scheme 2. Degradation of FDM-A_1 (**23**) . Reagents and conditions : (i) CH_2N_2, $CHCl_3$, R.T., 15min, (ii) $(CH_3)_2SO_4$, acetone, reflux, 5h, (iii) $LiBH_4$, THF, R.T., 3h, (iv) H_2, Pd-C (10%), MeOH, 50 lb. p.s.i., 15h, (v) RuO_4, CH_3CN, CCl_4, H_2O, 24h, (vi) CH_2N_2, ether, R.T., 15 min.

Thus, the structure of FDM-A_1 is defined for the first time with complete stereochemical detail as (3*R*, 3'*R*, atrop-*R*), precisely as depicted in structure **23**. Since FDM-A_1 (**23**) and FDM-B_1 (**24**) differ only at the stereogenic axis (*vide supra*), the absolute configuration of FDM-B_1 must be (3*R*, 3'*R*, atrop-*S*).

The method described here is applicable, in principle, to many other coupled dihydroanthracenones such as the plant and fungal phlegmacins (**5**),[4] and biologically active plant products such as singueanol 1 (**7**)[7] and Karwinskia-toxin (**8**).[11] Work in these areas is continuing.

EXPERIMENTAL

NMR spectra were recorded using a JEOL-JNM GX-400 spectrometer (399.65 MHz ^1H, 100.40 MHz ^{13}C) for solutions in deuteriochloroform unless stated otherwise. ^{13}C NMR assignments are made by comparison with data available for torosachrysone[5] and compounds in the austrocortilutein series.[13,23] Commercial deuteriochloroform was washed with water, dried (K_2CO_3), distilled, and stored in the dark prior to use. IR spectra were recorded as KBr discs using a Perkin-Elmer 983 G grating spectrophotometer. UV spectra were recorded on a Varian SuperScan 3 spectrophotometer for ethanolic solutions; log ε is quoted in brackets after each absorption maximum. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter at 22°C; concentrations (*c*) refer to solutions in chloroform. CD spectra were obtained using a Cary 61 spectropolarimeter for solutions in methanol. Mass spectra (electron impact, probe) were recorded with a V.G. Micromass 7070F instrument. With the exception of the molecular ion (M^+) only ions of relative abundance >20% are cited. Analytical thin layer chromatography (TLC) used Merck Kieselgel 60 GF_{254} pre-coated glass plates. Preparative TLC was performed on layers (20 x 20 x 0.1 cm) of Merck Kieselgel GF_{254} or Machery Nagel UV_{254} silica gel. TLC employed toluene-ethyl formate-formic acid (50:49:1) as eluant and all R_F values are quoted in this solvent unless stated otherwise.

All reactions were performed using purified and dried solvents under an atmosphere of nitrogen. Solutions in organic solvents were routinely washed with water and brine and dried over sodium sulphate prior to concentration under reduced pressure (t < 35°C). Melting points are uncorrected. Combustion analyses were performed by Chemical and Analytical Services, Geelong.

Voucher specimens of the fungus used as the source of FDM-A_1 are held in the herbarium of the Royal Botanic Garden, Edinburgh, UK, under accession number WAT 20933.

Methylation of Torosachrysone (2).- (a) *With Diazomethane.* (i) Torosachrysone (**2**) (52 mg, 0.18 mmol) in chloroform (4 ml) was exposed to ethereal diazomethane (50 ml) at room temperature for 16 h. The reaction mixture was cooled on ice and the excess of diazomethane was destroyed with acetic acid. The mixture was diluted with aqueous phosphate buffer (pH 7.2) (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried and evaporated. The resulting pale brown residue (58 mg) was purified by prep. TLC to afford, in order of increasing polarity: (*S*)-torosachrysone-8-*O*-methyl ether (**9**) (R_F 0.32) (3.8 mg, 7%) as pale yellow needles, m.p. 227-230°C (from EtOAc-petrol) {Lit.[12] m.p. 229-231°C} (Found: M^+ 302.1153. Calc. for $C_{17}H_{18}O_5$: *M* 302.1154); $[\alpha]_{546}$ - 15.5 (*c* 0.4); ν_{max} 3396, 1638, and 1634 cm^{-1}; λ_{max} 225 (4.30), 269 (4.32), 320 (3.71), 332 (3.75), and 365 nm (3.92); δ_H 1.42 (3H, s, 3-Me), 2.82 (1H, d, *J* 16.5 Hz, 2-H_{ax}), 2.84 (1H, d, *J* 16.5 Hz, 2-H_e), 3.06 (2H, br s, 4-H_2), 3.91 (3H, s, 6-OMe), 3.98 (3H, s, 8-OMe), 6.43 (1H, d, *J* 2.2 Hz, 7-H), 6.56 (1H, d, *J* 2.2 Hz, 5-H), 6.87 (1H, br s, 10-H), and 15.08 (1H, s, 9-OH); δ_C 28.7 (q, *J* 126.5 Hz, 3-Me), 43.7 (t, *J* 129.0 Hz, C-4), 52.0 (t, *J* 129.3 Hz, C-2), 56.2 and 55.5 (each q, *J* 145.2 Hz, 8- and 6-OMe), 70.9 (m, C-3), 98.1 (dd, *J* 152.0 and 4.4 Hz, C-7), 99.0 (dt, *J* 163.2 and 4.4 Hz, C-5), 109.5 (m, C-9a), 110.5 (m, C-8a), 117.3 (dq, *J* 159.9 and 4.4 Hz, C-10), 136.4 (t, *J* 5.9 Hz, C-4a), 142.0 (br s, C-10a), 161.3 (pent, *J* 4.4 Hz, C-8), 162.3 (m, C-6), 165.9 (d, *J* 5.9 Hz, C-9), and 201.8 (t, *J* 5.9 Hz, C-1); *m/z* (70 eV) 302 (M^+, 100%), 284 (M^+ - H_2O, 11), 244 (40), and 18 (48), (*S*)-(-)-torosachrysone-9-*O*-methyl ether (**10**) (R_F 0.24) (10.3 mg, 19%) as yellow needles, m.p. 179-182 °C (from

EtOAc-petrol) {Lit.[12] m.p. 180-182°C} (Found: C, 67.4; H, 6.0. $C_{17}H_{18}O_5$ requires C, 67.5; H, 6.0%); $[\alpha]_D$ - 5 (*c* 1.5); ν_{max} 3396, 1665, and 1634 cm^{-1}; λ_{max} 225 (4.30), 267 (4.38), 324 (3.73), 337 (3.70), and 375 nm (3.83); δ_H 1.44 (3H, s, 3-Me), 1.71 (1H, br s, 3-OH), 2.78 (1H, d, *J* 16.6 Hz, 2-H_{ax}), 2.83 (1H, dd, *J* 16.6 and 1.5 Hz, 2-H_e), 3.14 and 3.18 (each 1H, d, *J* 16.1 Hz, 4-H_2), 3.88 (3H, s, 6-OMe), 4.04 (3H, s, 9-OMe), 6.53 (1H, d, *J* 2.2 Hz, 7-H), 6.59 (1H, d, *J* 2.2 Hz, 5-H), 7.28 (1H, br s, 10-H), and 9.98 (1H, s, 8-OH); δ_C 30.0 (q, *J* 128.0 Hz, 3-Me), 44.4 (t, *J* 130.0 Hz, C-4), 54.1 (t, *J* 131.0 Hz, C-2), 55.4 (q, *J* 145.2 Hz, 6-OMe), 64.1 (q, *J* 146.7 Hz, 9-OMe), 70.9 (m, C-3), 98.2 (dt, *J* 161.4 and 4.4 Hz, C-5), 102.3 (ddd, *J* 161.4, 7.3, and 5.9 Hz, C-7), 112.3 (m, C-8a), 117.1 (m, C-9a), 123.2 (dq, *J* 159.9 and 4.4 Hz, C-10), 137.7 (t, *J* 5.9 Hz, C-4a), 139.9 (br s, C-10a), 157.8 (t, *J* 4.4 Hz, C-8), 160.0 (q, *J* 4.4 Hz, C-9), 161.9 (m, C-6), and 195.1 (t, *J* 5.9 Hz, C-1); *m/z* (15 eV) 302 (M^+, 100%) and 284 (M^+ - H_2O, 18), and (*S*)-(-)-torosachrysone-8,9-di-*O*-methyl ether (**11**) (R_F 0.21) (29.7 mg, 52%) as pale orange needles, m.p. 194-197 °C (from EtOAc-petrol) (Found: C, 68.7; H, 6.6. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.3 %); $[\alpha]_D$ - 4 (*c* 1.0); ν_{max} 3384 and 1661 cm^{-1}; λ_{max} 224 (4.78), 265 (4.99), 317 (4.27), 330 (4.29), and 365 nm (4.36); δ_H 1.41 (3H, s, 3-Me), 1.68 (1H, br s, 3-OH), 2.79 and 2.82 (each 1H, d, *J* 16.5 Hz, 2-H_2), 3.15 (2H, br s, 4-H_2), 3.90 and 3.91 (each 3H, s, 6- and 8-OMe), 3.95 (3H, s, 9-OMe), 6.46 (1H, d, *J* 2.6 Hz, 7-H), 6.61 (1H, d, *J* 2.6 Hz, 5-H), and 7.32 (1H, br s, 10-H); δ_C 28.8 (q, *J* 126.0 Hz, 3-Me), 44.5 (t, *J* 129.0 Hz, C-4), 54.9 (t, *J* 129.0 Hz, C-2), 55.3 and 56.2 (each q, *J* 145.2 Hz, 6- and 8-OMe), 62.9 (q, *J* 145.3 Hz, 9-OMe), 70.8 (octet, *J* 4.4 Hz, C-3), 98.2 (dt, *J* 159.9 and 6.2 Hz, C-5), 99.2 (dd, *J* 154.0 and 4.4 Hz, C-7), 115.8 (q, *J* 5.9 Hz, C-8a), 120.4 (m, C-9a), 122.7 (dq, *J* 159.9 and 4.4 Hz, C-10), 138.1 (t, *J* 5.9 Hz, C-4a), 140.7 (br s, C-10a), 159.8 (pent, *J* 4.4 Hz, C-8), 160.8 and 160.7 (m, C-6 and C-9), and 195.1 (t, *J* 6.6 Hz, C-1); *m/z* (15 eV) 316 (M^+, 100%) and 298 (M^+ - H_2O, 32). (ii) To a solution of torosachrysone (**2**) (25 mg, 0.09 mmol) in chloroform (15 ml) was added an ethereal solution of diazomethane (2 ml) and the mixture was stirred at room temperature until consumption of starting material was complete by TLC (15 min.). Excess diazomethane was destroyed with acetic acid and the solvent was removed under reduced pressure. Prep. TLC gave **9** (4.2 mg, 16%), **10** (18.5 mg, 71%), and **11** (1 mg, 4%) identical with materials described above.

(b) *With Dimethyl Sulphate.* To a solution of torosachrysone (**2**) (20 mg, 0.07 mmol) in acetone (5 ml) was added potassium carbonate (10 mg) and dimethyl sulphate (20 µl), and the mixture was heated under reflux for 2 h. The reaction was cooled on ice, filtered, and the filtrate was diluted with water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layers were evaporated and the brown residue (24 mg) was purified by prep. TLC to afford **9** (12.1 mg, 57%) and **11** (8.9 mg, 40%), identical with materials described above.

(c) *With Methyl Iodide.* A mixture of torosachrysone (**2**) (25 mg, 0.09 mmol), potassium carbonate (21 mg), and methyl iodide (0.5 ml) in dry acetone (10 ml) was heated under reflux for 5 h. After cooling, the potassium carbonate was filtered off and the filtrate was evaporated to dryness. Prep. TLC gave **9** (12.1 mg, 46%) and **11** (8.6 mg, 31%).

Torosachrysone-8,9-di-*O*-methyl ether (11).- Torosachrysone (50 mg, 0.174 mmol) in chloroform (30 ml) was treated with ethereal diazomethane (5 ml) for 15 min. at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in dry acetone (10 ml), treated with dimethyl sulphate (10 drops) and potassium carbonate (100 mg), and heated under reflux for 2 h. Filtration, evaporation

of the solvent and prep. TLC gave **9** (9.9 mg, 19%) and **11** (42 mg, 76%), identical with materials described above.

Reduction of Torosachrysone-8,9-di-*O*-methyl ether.- A mixture of torosachrysone-8,9-di-*O*-methyl ether (**11**) (31 mg, 0.1 mmol) and lithium borohydride (100 µl, 2M in tetrahydrofuran) in tetrahydrofuran (5 ml) was stirred at room temperature for 2 h. Methanol (*ca.* 1 ml) was added to destroy excess reducing agent and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (3 x 10 ml) and water (15 ml) and the organic phase was dried and evaporated. The colourless oily residue (30.4 mg) was purified by prep. TLC using dichloromethane-ether (4:1) as eluant to give, in order of decreasing polarity: (*1*R, *3*S)-*1,2,3,4-tetrahydro-1,3-dihydroxy-6,8,9-trimethoxy-3-methylanthracene* (**12**) (R_F 0.10) (23.7 mg, 76%) as colourless needles, m.p. 142-143°C (from EtOAc-petrol) (Found: M^+ 318.1467.$C_{18}H_{22}O_5$ requires *M* 318.1467); $[\alpha]_D$ + 19.8 (*c* 0.1); ν_{max} 3528, 1625, 1574, 1329, 1163, and 1102 cm^{-1}; δ_H 1.44 (3H, s, 3-Me), 1.95 (1H, dd, *J* 13.9 and 7.3 Hz, 2-H_{ax}), 2.37 (1H , br dd, *J* 13.9 and 7.0 Hz, 2-H_e), 2.89 and 3.05 (each 1H, br d, *J* 16.1 Hz, 4-H_{ax} and 4-H_e, 3.89, 3.92, and 3.99 (each 3H, s, 6-, 8-, and 9-OMe), 5.42 (1H, br t, *J* *ca.* 7 Hz, 1-H), 6.49 (1H, br s, 7-H), 6.65 (1H, br s, 5-H), and 7.23 (1H, br s, 10-H); δ_C 29.8 (3-Me), 43.7 (C-4), 44.0 (C-2), 55.3, 56.2, and 62.1 (6-, 8-, and 9-OMe), 65.1 (C-1), 70.2 (C-3), 98.2 (C-5), 98.7 (C-7), 114.5 (C-8a), 123.3 (C-10), 126.9 (C-9a), 134.8 (C-4a), 137.6 (C-10a), 155.3 (C-6), 156.7 (C-9), and 158.2 (C-8); *m/z* (70 eV) 318 (M^+, 66%), 300 (M^+ - H_2O, 20), 285 (98), 283 (25), 282 (M^+ - 2 x H_2O, 100), 267 (31), 141 (27), 43 (21), and 18 (22), and its (*1*S, *3*S)-*diastereoisomer* (**13**) (R_F 0.21) (5.9 mg, 19%) as colourless needles, m.p. 164-165°C (from EtOAc - petrol) (Found: M^+ 318.1467. $C_{18}H_{22}O_5$ requires *M* 318.1467); $[\alpha]_D$ + 9.6 (*c* 0.11); ν_{max} 3476, 1625, 1573, 1340, 1162, and 1104 cm^{-1}; δ_H 1.42 (3H, s, 3-Me), 1.98 (1H, dd, *J* 14.7 and 4.9 Hz, 2-H_{ax}), 2.33 (1H, ddd, *J* 14.7, 2.3, and 2.3 Hz, 2-H_e), 2.89 (1H, dd, *J* 16.7 and 1.3 Hz, 4-H_{ax}), 3.07 (1H, dd, *J* 16.7 and 2.3 Hz, 4-H_e), 3.32 (1H, br s, 3-OH), 3.89, 3.95, and 3.99 (each 3H, s, 6-, 8-, and 9-OMe), 5.38 (1H, m, 1-H), 6.47 (1H, d, *J* 2.3 Hz, 7-H), 6.64 (1H, d, *J* 2.3 Hz, 5-H), and 7.26 (1H, s, 10-H); δ_C 29.9 (3-Me), 41.4 (C-2), 44.8 (C-4), 55.3, 56.0, and 63.1 (6-, 8-, and 9-OMe), 64.1 (C-1), 68.8 (C-3), 98.1 (C-5), 98.5 (C-7), 114.5 (C-8a), 123.6 (C-10), 126.1 (C-9a), 134.4 (C-4a), 137.9 (C-10a), 155.3 (C-6), 156.8 (C-9), and 158.3 (C-8); *m/z* (70 eV) 318 (M^+, 87%), 300 (M^+- H_2O, 36), 285 (38), 283 (25), 282 (M^+ - 2 x H_2O , 100), 269 (59), 267 (30), 141 (26), and 43 (20).

Similarly prepared from torosachrysone-8-*O*-methyl ether (**9**) (30 mg, 0.1 mmol) was (*1*R, *3*S)-*1,2,3,4-tetrahydro-1,3,9-trihydroxy-6,8-dimethoxy-3-methylanthracene* (**14**) (R_F 0.10) (20.1 mg, 66%) as a colourless film; δ_H 1.45 (3H, s, 3-Me), 1.97 (1H, dd, *J* 13.6 and 7.0 Hz, 2-H_{ax}), 2.37 (1H, ddd, *J* 13.6, 7.0, and 2.2 Hz, 2-H_e), 2.86 and 3.03 (each 1H, br d, *J* 16.1 Hz, 4-H_{ax} and 4-H_e), 3.88 and 4.04 (each 3H, s, 6- and 8-OMe), 5.40 (1H, t, *J* 7.0 Hz, 1-H), 6.41 (1H, d, *J* 2.2 Hz, 7-H), 6.62 (1H, d, *J* 2.2 Hz, 5-H), 6.97 (1H, s, 10-H), and 9.70 (1H, s, 9-OH); *m/z* (12 eV) 286 (M^+ - H_2O, 33%), 269 (23), 268 (M^+ - 2 x H_2O, 100); (70 eV) 286 (27), 268 (100), 253 (68), 225 (24), 18 (38), and 15 (22), and its (*1*S, *3*S)-*diastereoisomer* (**15**) (R_F 0.20) (6.3 mg, 21%) as a colourless film; δ_H 1.42 (3H, s, 3-Me), 1.98 (1H, dd, *J* 14.6 and 5.0 Hz, 2-H_{ax}), 2.32 (1H, ddd, *J* 14.6, 2.4, and 2.4 Hz, 2-H_e), 2.86 (1H, dd, *J* 16.8 and 1.9 Hz, 4-H_{ax}), 3.04 (1H, dd, *J* 16.8 and 2.4 Hz, 4-H_e), 3.35 (1H, br s, 3-OH), 3.88 and 4.03 (each 3H, s, 6- and 8-OMe), 5.39 (1H, m, 1-H), 6.41 (1H, d, *J* 2.0 Hz, 7-H), 6.62 (1H, d, *J* 2.0 Hz, 5-H), 7.00 (1H, s, 10-H), and 9.58 (1H, s, 9-OH); *m/z* (15 eV) 269 (20%) and 268 (M^+ - 2 x H_2O, 100); (70 eV) 268 (100), 253 (51), 86 (43), 43 (41), and 18 (21).

Similarly, reduction of torosachrysone-9-*O*-methyl ether (**10**) (41.5 mg, 0.14 mmol) furnished (*1*R, *3*S)-*1,2,3,4-tetrahydro-1,3,8-trihydroxy-6,9-dimethoxy-3-methylanthracene* (**16**) (R_F 0.1) (24.2 mg, 57%) as a colourless waxy solid (from EtOAc-petrol) (Found: M^+ 304.1310. $C_{17}H_{20}O_5$ requires *M* 304.1311); δ_H 1.46 (3H, s, 3-Me), 1.94 (1H, dd, *J* 13.6 and 7.3 Hz, 2-H_{ax}), 2.36 (1H, ddd, *J* 13.6, 6.8, and 2.2 Hz, 2-H_e), 2.87 and 3.06 (each 1H, br d, *J* 16.3 Hz, 4-H_{ax} and 4-H_e), 3.86 and 4.02 (each 3H, s, 6- and 9-OMe), 5.44 (1H, br t, *J ca.* 7 H, 1-H), 6.55 (1H, d, *J* 2.2 Hz, 7-H), 6.61 (1H, d, *J* 2.2 Hz, 5-H), 7.25 (1H, br s, 10-H), and 9.01 (1H, s, 8-OH); δ_C 30.3 (3-Me), 43.8 and 43.9 (C-2 and C-4), 55.3 and 63.0 (6- and 9-OMe), 64.6 (C-1), 70.1 (C-3), 97.9 (C-5), 102.1 (C-7), 111.9 (C-8a), 124.0 (C-10), 125.1 (C-9a), 134.8 (C-4a), 137.0 (C-10a), 154.2 and 154.3 (C-6 and C-9), and 159.3 (C-8); *m/z* (70 eV) 304 (M^+, 100%), 286 (M^+- H_2O, 37), 271 (57), 268 (M^+- 2 x HO, 14), 253 (27), 229 (34), 228 (39), and 43 (35), and its (*1*S, *3*S)-*diastereoisomer* (**17**) (R_F 0.2) (16.1 mg, 39%) as pale yellow needles, m.p. 111-113°C (from EtOAc-petrol) (Found: M^+ 304.1310. $C_{17}H_{20}O_5$ requires *M* 304.1311); δ_H 1.46 (3H, s, 3-Me), 1.97 (1H, dd, *J* 14.5 and 4.6 Hz, 2-H_{ax}), 2.37 (1H, ddd, J 14.3, 2.4, and 2.4 Hz, 2-H_e), 2.83 (1H, br s, 3-OH), 2.94 (1H, dd, *J* 16.9 and 1.5 Hz, 4-H_{ax}), 3.09 (1H, dd, *J* 16.9 and 2.4 Hz, 4-H_e), 3.87 and 4.08 (each 3H, s, 6- and 9-OMe), 5.32 (1H, m, 1-H), 6.54 (1H, d, *J* 2.6 Hz, 7-H), 6.61 (1H, d, *J* 2.6 Hz, 5-H), 7.27 (1H, br s, 10-H), and 9.22 (1H, s, 8-OH); δ_C 30.6 (3-Me), 41.6 and 43.9 (C-2 and C-4), 55.3 and 63.6 (6- and 9-OMe), 64.6 (C-1), 70.0 (C-3), 97.8 (C-5), 101.9 (C-7), 112.2 (C-8a), 124.0 (C-10), 124.5 (C-9a), 133.8 (C-4a), 137.2 (C-10a), 154.6 and 155.0 (C-6 and C-9), and 159.4 (C-8); *m/z* (70 eV) 304 (M^+, 100%), 286 (M^+ - H_2O, 45), 271 (25), 268 (M^+- 2 x H_2O, 43), 255 (34), 253 (67), 229 (40), 228 (48), 43 (22), and 18 (21).

(*R*)-1,2,3,4-Tetrahydro-3-hydroxy-6,8,9-trimethoxy-3-methylanthracene (18).- A mixture of the alcohols **12** and **13** (50 mg, 0.157 mmol) in methanol (5 ml) containing palladium-on-carbon (10%, 10 mg) was shaken under an atmosphere of hydrogen (50 lb p.s.i.) in a Parr apparatus for 10 h. The catalyst was filtered off and washed with methanol and the solvent was removed under reduced pressure. Crystallisation of the colourless residue gave the *tetrahydroanthracene* (**18**) [R_F 0.39, dichloromethane-ether (4:1)] (46 mg, 97%) as colourless needles, m.p. 76-78°C (from EtOAc-petrol) (Found: M^+ 302.1519.$C_{18}H_{22}O_4$ requires *M* 302.1518); $[\alpha]_D$ + 17.9° (*c* 0.15); ν_{max} 3459, 1623, 1573, 1337, 1160, and 1105 cm^{-1}; δ_H 1.37 (3H, s, 3-Me), 1.83 and 1.94 (each 1H, m, 2-H_{ax} and 2-H_e), 2.95 (1H, br s, 3-OH), 3.04 (4H, m, 1-H_2 and 4-H_2), 3.80, 3.88, and 3.96 (each 3H, s, 6-, 8-, and 9-OMe), 6.45 (1H, d, *J* 2.2 Hz, 7-H), 6.62 (1H, d, *J* 2.2 Hz, 5-H), and 7.19 (1H, s, 10-H); δ_C 20.8 (C-2), 28.5 (3-Me), 35.9 (C-4), 43.9 (C-1), 55.2, 55.9, and 61.2 (6-, 8-, and 9-OMe), 69.2 (C-3), 97.9 (C-5), 98.2 (C-7), 114.6 (C-8a), 122.9 (C-10), 124.1 (C-9a), 135.6 (C-4a), 136.3 (C-10a), 153.7 (C-6), 156.8 (C-9), and 157.4 (C-8); *m/z* (70 eV) 302 (M^+, 100%), 284 (M^+- H_2O, 80), 282 (57), 269 (27), 253 (24), 245 (22), 238 (26), 28 (42), and 18 (70).

Similarly prepared from a mixture of the alcohols **14** and **15** (52 mg, 0.17 mmol) was *(R)-1,2,3,4-tetrahydro-3,9-dihydroxy-6,8-dimethoxy-3-methylanthracene* (**19**) [R_F 0.35, dichloromethane-ether (4:1)] (47.7 mg, 97%) as colourless needles, m.p. 121-122°C (from EtOAc-petrol) (Found: M^+ 288.1361. $C_{17}H_{20}O_4$ requires *M* 288.1362); ν_{max} 3405, 1632, 1614, 1582, 1358, 1204, 1162, 1104, and 1045 cm^{-1}; δ_H 1.36 (3H, s, 3-Me), 1.86 and 1.95 (each 1H, m, 2-H_{ax} and 2-H_e), 2.93 (4H, m, 1-H_2 and 4-H_2), 3.87 and 4.01 (each 3H, s, 6- and 8-OMe), 6.38 (1H, d, *J* 2.2 Hz, 7-H), 6.60 (1H, d, *J* 2.2 Hz, 5-H), 6.94 (1H, br s, 10-H), and 9.35 (1H, s, 9-OH); δ_C 20.7 (C-2), 28.2 (3-Me), 35.7 (C-4), 44.1 (C-1), 55.3 and 56.1 (6- and 8-OMe), 69.2 (C-3), 97.0 (C-7), 98.5 (C-5), 109.1 (C-9a), 115.5 (C-8a), 117.5 (C-10), 135.4 (C-4a), 136.3 (C-10a), 151.2

(C-9), 156.8 (C-6), and 157.0 (C-8); *m/z* (15 eV) 288 (M^+, 100%), 270 (M^+ - H_2O, 50), and 255 (43); (70 eV) 288 (M^+, 100%), 270 (38), 255 (77), 231 (51), 230 (38), and 18 (24). From a mixture of the alcohols **16** and **17** (28 mg, 0.09 mmol) was prepared *(R)-1,2,3,4-tetrahydro-3,8-dihydroxy-6,9-dimethoxy-3-methylanthracene* (**20**) [R_F 0.39, dichloromethane-ether (4:1)] (25 mg, 96%) as cream needles, m.p. 102-103°C (from EtOAc-petrol) (Found: M^+ 288.1362.$C_{17}H_{20}O_4$ requires 288.1362); δ_H 1.40 (3H, s, 3-Me), 1.83 and 1.96 (each 1H, m, 2-H_{ax} and 2-H_e), 3.01 (4H, m, 1-H_2 and 4-H_2), 3.86 and 3.92 (each 3H, s, 6- and 9-OMe), 6.52 (1H, d, *J* 2.4 Hz, 7-H), 6.59 (1H, d, *J* 2.4 Hz, 5-H), 7.23 (1H, br s, 10-H), and 9.51 (1H, s, 8-OH); δ_C 20.4 (C-2), 29.2 (3-Me), 35.7 (C-4), 43.8 (C-1), 55.2 and 61.8 (6- and 9-OMe), 69.1 (C-3), 97.5 (C-7), 101.5 (C-5), 111.9 (C-8a), 122.0 (C-9a), 123.6 (C-10), 135.5 (C-4a), 135.8 (C-10a), and 153.0, 154.4, and 158.6 (C-6, C-8, and C-9); *m/z* (70 eV) 288 (M^+, 100%), 270 (M^+-H_2O, 22), 255 (53), 231 (28), and 43 (33).

Oxidation of the Tetrahydroanthracene 18.- The tetrahydroanthracene **18** (40 mg, 0.13 mmol), sodium metaperiodate (850 mg) and a trace of ruthenium (III) chloride trihydrate were stirred vigorously in a heterogeneous mixture of carbon tetrachloride (4 ml), acetonitrile (4 ml), and water (6 ml) at room temperature for 24 h.[14] After this time *iso*-propanol (5 ml) was added to destroy the oxidising agent followed by an excess of barium chloride. After 30 min vigorous stirring, the mixture was filtered and the residue was washed thoroughly with dichloromethane. The filtrate was extracted with dichloromethane (3 x 15 ml), acidified (to Congo red) and continuously extracted (24 h) with ether. The dichloromethane and ether extracts were combined, dried, and evaporated to yield an oil that was immediately exposed to an excess of ethereal diazomethane. After 15 minutes the excess of diazomethane was destroyed by dropwise addition of acetic acid and the solution was evaporated to dryness. The residue was purified by high performance liquid chromatography [Ultrasphere-Si, 5μ, 1 x 25 cm, EtOAc-hexane (3:2)] to afford methyl (*R*)-(+)-tetrahydro-2-methyl-5-oxo-2-furanacetate (**22**) (6.8 mg, 30%) as a colourless oil; $[\alpha]_D$ + 7.6 (*c* 0.1) {lit.[15] $[\alpha]_D$ + 7.7 (*c* 0.1)}; other spectroscopic data are identical with those reported in the literature.[15]

Similarly, oxidation of the tetrahydroanthracenes **19** (21 mg, 0.073 mmol) and **20** (30 mg, 0.104 mmol) gave the (*R*)-ester **22** in yields of 18 and 24%, respectively.

Isolation of FDM-A_1 (23) from WAT 20933.- Fresh fruit bodies (30g) were finely chopped and soaked in ethanol (200 ml) in the dark for 2 h. The extract was evaporated to dryness and the brown residue partitioned between ethyl acetate (3 x 100 ml) and water (200 ml). Evaporation of the dried organic phase yielded a brown-green residue (0.2 g) which was chromatographed (prep. TLC) to afford two minor orange-yellow zones (R_F 0.80 and 0.48), and a predominant green zone (R_F 0.30), which was further purified by gel permeation through Sephadex LH-20 in methanol to give flavomannin-6,6'-di-*O*-methyl ether A_1 (**23**) (33 mg, 0.10% fr. wt.) as a bright green-yellow powder, m.p. 203-205°C (decomp.) (from $CHCl_3$-petrol) {Lit.[20] 212°C (decomp.)} (Found: M^+, 574.1839. Calc. for $C_{32}H_{30}O_{10}$: *M* 574.1839); $[\alpha]_{546}$ - 853 (*c* 0.20) {Lit.[20] $[\alpha]_{546}$ - 860 (*c* 0.55)}; CD 330 (Δε 0.0), 287 (- 68.25), 277 (0.0), and 265 nm (+ 72.39); ν_{max} 3386 and 1630 cm^{-1}; λ_{max} 282 (4.48), 320sh (3.86), and 410 nm (4.07); δ_H 1.44 (6H, s, 3-Me and 3'-Me), 2.83 (4H, br s, 2-H_2 and 2'-H_2), 3.06 (4H, br s, 4-H_2 and 4'-H_2), 3.84 (6H, 6-OMe and 6'-OMe), 6.67 (2H, s, 5-H and 5'-H), 6.93 (2H, s, 10-H and 10'-H), 9.98 (2H, s, 8-OH and 8'-OH), and 16.15 (2H, s, 9-OH and 9'-OH); δ_H (Me_2CO-d_6) 1.42 (6H, s, 3-Me and 3'-Me), 2.77 (2H, dd, *J* 17.1 and 1.8 Hz, 2-H_e and 2'-H_e), 2.90 (2H, d, *J*

17.1 Hz, 2-H_{ax} and 2'-H_{ax}), 3.04 (2H, dd, *J* 16.1 and 1.8 Hz, 4-H_e and 4'-H_e), 3.12 (2H, d, *J* 16.1 Hz, 4-H_{ax} and 4'-H_{ax}), 3.82 (6H, s, 6-OMe and 6'-OMe), 6.80 (2H, s, 5-H and 5'-H), 7.04 (2H, s, 10-H and 10'-H), 9.89 (2H, s, 8-OH and 8'-OH), and 16.34 (2H, 9-OH and 9'-OH); δ_C 28.8 (3-Me and 3'-Me), 43.6 (C-4 and C-4'), 51.1 (C-2 and C-2'), 55.9 (6-OMe and 6'-OMe), 71.0 (C-3 and C-3'), 98.4 (C-5 and C-5'), 108.0 (C-7 and C-7'), 108.2 (C-9a and C-9a'), 108.3 (C-8a and C-8a'), 117.8 (C-10 and C-10'), 135.0 (C-4a and C-4a'), 140.7 (C-10a and C-10a'), 156.4 (C-8 and C-8'), 162.3 (C-6 and C-6'), 166.4 (C-9 and C-9'), and 201.5 (C-1 and C-1'); *m/z* 574 (M^+, 32%), 538 ($C_{32}H_{26}O_8$, 82), 507 ($C_{31}H_{23}O_7$, 100), and 254 (25);

Degradation of FDM-A_1.- Flavomannin-6,6'-di-*O*-methyl ether A_1 (**23**) (35 mg, 0.06 mmol) in chloroform (25 ml) was treated with ethereal diazomethane (5 ml) at room temperature for 15 min. The solvent was removed under reduced pressure and the residue was dissolved in acetone (10 ml) and heated under reflux with potassium carbonate (50 mg) and dimethyl sulphate (10 drops) for 5 h. The suspension was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ethyl actetate (15 ml), washed exhaustively with water, and the organic phase was dried and filtered through a short bed of silica gel. The solvent was removed under reduced pressure and the residue was dissolved in tetrahydrofuran (15 ml) and exposed to lithium borohydride (250 µl, 2M in tetrahydrofuran) at room temperature during 3 h. Methanol (2 ml) was added and the mixture was stirred for 15 min before the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (15 ml) and water (3 x 10 ml), and the organic phase was washed with brine, dried and evaporated to dryness. The residue was dissolved in methanol (5 ml) and shaken under an atmopsphere of hydrogen in a Parr assembly at 50 lb. p.s.i. in the presence of palladium-on-carbon (10%, 10 mg) for 15 h. The catalyst was filtered off and washed with methanol, and the filtrate was evaporated to dryness. To the residue, dissolved in a heterogeneous mixture of carbon tetrachloride (4 ml), acetonitrile (4 ml), and water (6 ml), was added sodium metaperiodate (850 mg) and a trace of ruthenium (III) chloride trihydrate, and the mixture was stirred vigorously at room temperature for 24 h. *Iso*-propanol (3 ml) was added followed by an excess of barium chloride and the mixture was worked up and methylated (CH_2N_2) as described above. The residue was purified by high performance liquid chromatography to afford methyl (*S*)-(-)-tetrahydro-2-methyl-5-oxo-2-furanacetate (**25**) (0.8 mg, 4% from **23**) as a colourless oil. The ^1H NMR spectrum (400 MHz) was identical with that of **22** and with data reported in the literature.[15]

The absolute configuration was determined by ^1H NMR spectroscopy as follows: to the butanolide **25** (0.8 mg) in deuteriochloroform (0.5 ml) in an NMR tube was added an aliquot (35 µl) of a solution of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III) [Eu(hfc)$_3$] (150 mg) in deuteriochloroform (1 ml). At that point the OMe and C-Me resonances had been shifted to δ 3.94 and δ 1.75, respectively, but neither signal was resolved. Addition of a solution of the synthetic (*S*)-butanolide **25**[15] (80 µg) in deuteriochloroform (50 µl) caused no change in the multiplicity of the spectrum. A solution of the synthetic (*R*)-butanolide **22**[15] (80 µg) in deuteriochloroform (50 µl) was then added, whereupon additional discrete resonances at δ 3.95 (OMe) and δ 1.76 (C-Me) appeared in the spectrum.

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