# Chemical and enzyme-catalysed syntheses of enantiopure epoxide and diol derivatives of chromene, 2,2-dimethylchromene, and 7-methoxy-2,2-dimethylchromene (precocene-1)

**Derek R. Boyd,*[a] Narain D. Sharma,[a] Rosemary Boyle,[a] Timothy A. Evans,[a] John F. Malone,[a] Kenneth M. McCombe,[a] Howard Dalton*[b] and Jagdeep Chima[b]**

[a] *School of Chemistry, The Queen's University of Belfast, Belfast BT9 5AG, UK*
[b] *Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK*

**Procaryotic (bacterial) dioxygenase-catalysed asymmetric dihydroxylation of chromene and 2,2-dimethylchromene to yield the (4*S*)-enantiomers of the corresponding *cis*-diols exclusively is reported. The epoxide, and derived *cis*- and *trans*-diol products from the previously reported eucaryotic (mammalian) metabolism of precocene-1 (7-methoxy-2,2-dimethylchromene), and the corresponding epoxide and diol derivatives of chromene and 2,2-dimethylchromene, have now been obtained in enantiopure form by chemical resolution of the corresponding bromohydrins using methoxy-(trifluoromethyl)phenylacetic acid (MTPA) or camphanate esters. The absolute configurations of the epoxides, *cis*- and *trans*-diols have been determined by chemical synthesis from, and stereochemical correlation with, the corresponding camphanate and MTPA esters. X-Ray crystal structure analysis has provided an unequivocal method for assignment of the absolute stereochemistry in each case.**

## Introduction

Substituted forms of the chromene ring system **1** occur widely in plants.[1] Thus, the 2,2-dimethylchromene nucleus **2** is found in precocene-1 (7-methoxy-2,2-dimethylchromene) which inhibits juvenile hormone activity in insects.[2,3] The eucaryotic metabolism of precocene-1 **3** by insect and animal enzyme systems[4,5] involves oxidation to an unstable compound 3,4-epoxyprecocene-1 (3,4-epoxy-7-methoxy-2,2-dimethylchromene) **4** which, on subsequent hydrolysis, yields the corresponding *trans*-**5** and *cis*-**6**-diols.[6] Since the epoxide **4** readily forms adducts with water and a range of cellular thiols it has been used as a model for cytotoxic epoxide formation.[7] Although 3,4-epoxyprecocene-1 **4** is too unstable to be isolated after synthesis by peroxyacid oxidation[6] it has been obtained in racemic form by both indirect (from the bromohydrin precursor)[6] and direct methods (from dimethyldioxirane oxidation of precocene-1).[8] However the enantiopure forms of 3,4-epoxyprecocene-1 **4** are presently unavailable for cytotoxicity or other biological studies. In a preliminary report, we have shown how enantiopure forms of the *cis*- **6** and *trans*-diol **5** metabolites of precocene-1 can be obtained from resolved bromohydrin esters *via* the unstable epoxide **4** which could not be isolated in pure form.[5] The synthesis, purification and stereochemical assignments of the elusive 3,4-epoxyprecocene-1 enantiomers (+)-**4** and (−)-**4** and the derived *cis*- and *trans*-diols are reported herein.

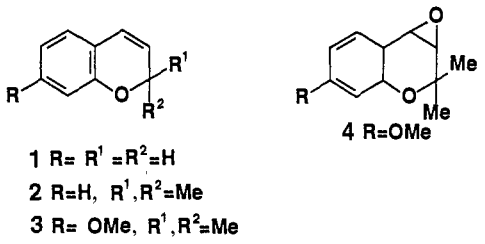
Enantiopure 2,2-dimethylchromene epoxides are important as intermediates in metabolism studies[2–5] and also in the synthesis of pharmaceuticals. Thus, epoxidation of 6-cyano-2,2-dimethylchromene **7** followed by nucleophilic ring-opening by amines has led to the synthesis of a new range of anti-hypertensive agents, *e.g.* cromakalim **8**, which act as potassium channel activators.[9]

In view of the continuing interest in the metabolism of chromenes from these and other laboratories,[4,6,10] and problems associated with the direct chemical resolution or asymmetric synthesis routes to the corresponding enantiopure epoxide and diol metabolites, alternative methods have been investigated. In the latter context a more detailed examination of the possible oxidation pathways occurring during metabolism of the chromenes **1–3**, by a mutant strain (UV4) of the soil bacterium *Pseudomonas putida* is also reported.

## Results and discussion

In earlier publications we reported[11,12] that the biotransformation of 1,2-dihydronaphthalene **10**, in cultures of *P. putida* UV4, resulted in monohydroxylation at the benzylic position to form the arene hydrate **12** (1*R*, >98% ee) and dihydroxylation to yield the *cis*-tetrahydro diol **11** (1*S*,2*R*, >98% ee). Enzyme-catalysed asymmetric dihydroxylation of the aryl ring of arene hydrate **12** followed by dehydration to yield naphthalene, or formation of naphthalene from enzyme-catalysed desaturation of the alkene **10** was followed by formation of the *cis*-dihydro diol metabolite **13** (1*R*,2*S* >98%) (Scheme 1). Although benzylic monohydroxylation appeared to be a major metabolic pathway for 1,2-dihydronaphthalene **10** in *P. putida* UV4, no evidence of allylic monohydroxylation was found.[11,12]

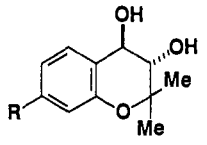
Replacement of the benzylic methylene group in 1,2-dihydronaphthalene **10** with an oxygen atom, as in the chromene **1**, will prevent benzylic monohydroxylation and, therefore, may facilitate a higher relative yield of the *cis*-dihydro diol during metabolism by *P. putida* UV4. In practice, however, the substitution of an oxygen atom was found to activate the allylic methylene group, for example when the chromene **1** was added as a substrate to growing cultures of *P. putida* UV4, allylic monohydroxylation to yield the hemiacetal **14** was observed. Although dioxygenase-catalysed benzylic monohydroxylation is common, allylic hydroxylation has not been reported using this bacterial strain. From the crude extract four metabolites were separated by preparative TLC on silica gel (Scheme 2). The least polar component ($R_F$ 0.66), obtained as a crystalline solid (10% yield), was identified as the coumarin **16**. A more polar ($R_F$ 0.59) and less stable minor component (*ca.* 2%) was identified, as the lactol **14**, by comparison with an authentic sample. Since benzylic monohydroxylation and dihydroxylation products from *P. putida* UV4 using 1,2-



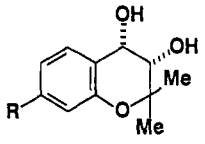
1 R= R¹ =R²=H
2 R=H, R¹,R²=Me
3 R= OMe, R¹,R²=Me



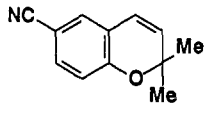
4 R=OMe



5 R=OMe



6 R = OMe
9 R = H



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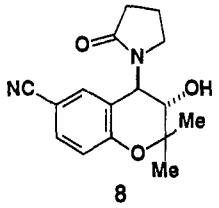

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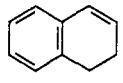
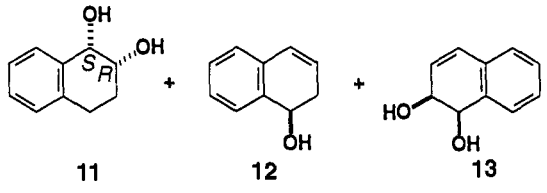


10

$O_2$ | *P.putida* UV4



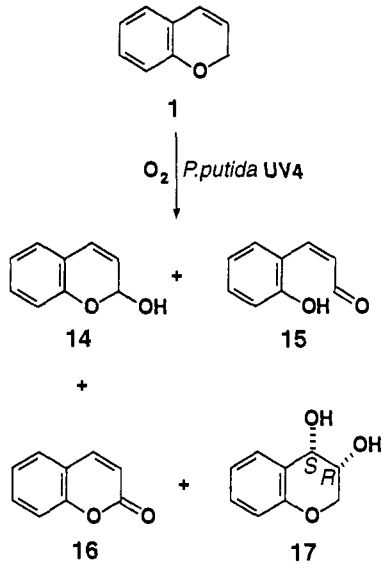
11 12 13

Scheme 1

dihydronaphthalene as substrate were enantiopure,[11,12] the possibility of stereoselectivity occurring during allylic hydroxylation of the chromene **1** was examined. The lactol **14** appeared to be racemic ($[\alpha]_D = 0$).† This may be due to either low stereoselectivity during allylic hydroxylation or a result of racemization by a reversible ring-opening process. Evidence for ring opening was provided by isolation of the achiral metabolite 3-(2′-hydroxyphenyl)prop-2-enal **15** as a minor product (3%, $R_F$ 0.55). Ring closure of the latter compound by the literature method[13] gave the lactol **14**.

The biotransformation of the chromene **1**, in *P. putida* UV4, to yield compounds **14**, **15** and **16**, is consistent with a metabolic sequence involving a dioxygenase-catalysed allylic monohydroxylation to form the hemiacetal **14** and its acyclic isomer **15**, and an alcohol dehydrogenase-catalysed oxidation of compound **14** to the coumarin **16**. The most polar metabolite ($R_F$ 0.14) was found to be the required *cis*-diol **17** ($[\alpha]_D$ +64, THF; 10% yield). Treatment of the *cis*-diol **17** with (+)-(*S*)-methoxy(trifluoromethyl)phenylacetyl chloride (MTPA-chloride) yielded a di-MTPA ester whose $^1$H NMR spectrum indicated that metabolite **17** was enantiopure (>98% ee). The 3*R*,4*S* configuration was assigned to the metabolite **17** ($[\alpha]_D$ + 64) by a stereochemical correlation method (see later).

† Throughout $[\alpha]_D$ values are quoted in units of $10^{-1}$ deg cm$^2$ g$^{-1}$.



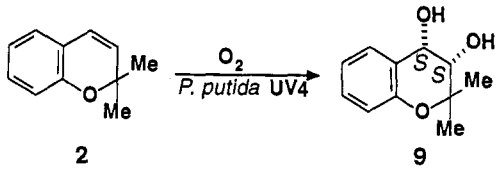
1

$O_2$ | *P.putida* UV4

14 15 16 17

Scheme 2

The presence of a *gem*-dimethyl group in naturally occurring chromenes prevents their oxidation at the allylic position. In the expectation that bacterial biotransformation of 2,2-dimethylchromene **2** would thus be confined to asymmetric *cis*-dihydroxylation, it was added to growing cultures of *P. putida* UV4. In accord with expectations, the sole metabolite isolated (18% yield) was identified as *cis*-3,4-dihydroxy-2,2-dimethylchromane **9** ($[\alpha]_D$ −15, $CHCl_3$) (Scheme 3). $^1$H NMR spectral



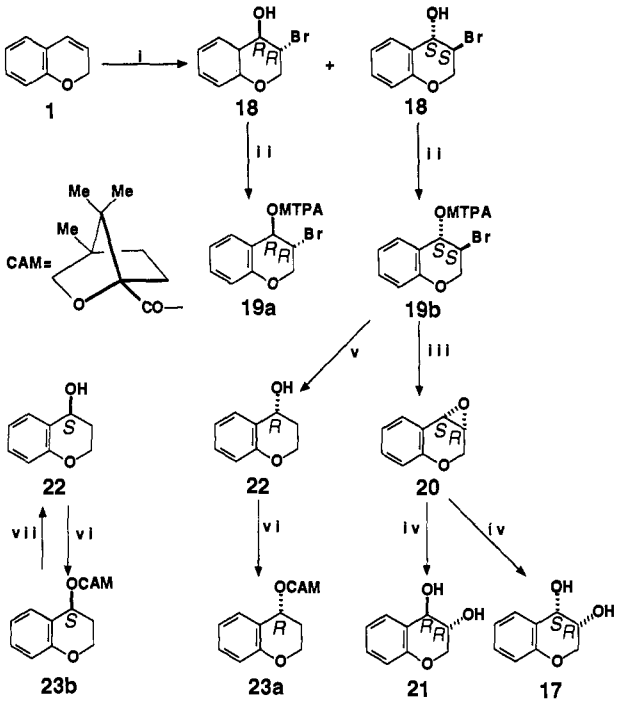
2 9

Scheme 3

analysis of the di-MTPA ester derivative of the metabolite **9** confirmed it to be enantiopure (>98% ee). The absolute configuration of the *cis*-diol **9** ($[\alpha]_D$ −15) was assigned as 3*S*,4*S* (see later). In contrast with the results obtained with the chromene substrates **1** and **2**, no *cis*-diol or other identifiable metabolites were found when precocene-1 **3** was added to growing cultures of *P. putida* UV4. Further studies are in progress in order to improve the relatively low yields of *cis*-diols and to obtain the alternative enantiomers.

It is noteworthy that the dioxygenase enzyme system in *P. putida* UV4 produced a single enantiomer of the *cis*-diol metabolite having the same *S* configuration at the benzylic chiral centre from all the cyclic alkene substrates we have studied so far (the only exception being indene). This enzyme-catalysed method of asymmetric dihydroxylation may be regarded as complementary to recently developed chemical methods of asymmetric dihydroxylation, using osmium tetroxide as oxidant in the presence of a chiral catalyst, although the chemical oxidation method appears to be less stereoselective for *cis*-diol enantiomers of cyclic alkenes[14–16] compared with the enzymatic method.

Earlier reports from these laboratories have shown that *cis*- and *trans*-diol enantiomers may be obtained *via* the resolved carbocyclic bromohydrin and epoxide precursors.[5,17] The latter method has been employed to obtain enantiopure samples of *cis*-diols **6**, **9**, **17** and *trans*-diols **5**, **21**, **28** (Schemes 4–7).



Scheme 4 *Reagents:* i, NBS–THF–$H_2O$; ii, (+)-(*S*)-MTPA-Cl–pyridine; iii, NaOMe–$Et_2O$; iv, $H^+$–$H_2O$; v, $LiAlH_4$–$Et_2O$; vi, (−)-(1*S*)-4,8,8-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carbonyl chloride–pyridine; vii, KOH–THF–$H_2O$

The racemic bromohydrin **18** was isolated in good yield (96%) by treatment of the chromene **1** with *N*-bromosuccinimide (NBS) in aqueous THF. Esterification of bromohydrin **18**, using (+)-(*S*)-MTPA chloride, gave a diastereoisomeric mixture **19a**/**19b** (96% yield). Chromatographic separation of the bromo-MTPA diastereoisomers by multi-elution preparative TLC, on silica gel, gave the low $R_F$ (**19a**, $[\alpha]_D$ −97, $CHCl_3$) and high $R_F$ (**19b**, $[\alpha]_D$ +129, $CHCl_3$) diastereoisomers as viscous oils. Although bromo-MTPA ester **19b** crystallized as a low-melting solid (mp 52–53 °C), a suitable crystal of it could not be obtained for X-ray crystallography.

Treatment of the bromo-MTPA ester **19b** ($[\alpha]_D$ +129, $CHCl_3$) with lithium aluminium hydride in refluxing diethyl ether yielded (+)-chroman-4-ol **22** (64% yield, ($[\alpha]_D$ +68.7, $CHCl_3$). Racemic chroman-4-ol **22** was esterified with (−)-(1*S*)-camphanic chloride in pyridine solvent to give a mixture of camphanate diastereoisomers **23a**/**23b**. Preparative TLC separation of the mixture, on silica gel, yielded a low $R_F$ compound **23b** ($[\alpha]_D$ −109, $CHCl_3$) and a less polar component **23a** ($[\alpha]_D$ +90, $CHCl_3$). The diastereoisomer **23b** was hydrolysed, with KOH in aqueous THF, to yield (−)-(4*S*)-chroman-4-ol **22** ($[\alpha]_D$ −69.1, $CHCl_3$). The more polar diastereoisomer **23b** ($[\alpha]_D$ −109, $CHCl_3$) formed a suitable crystal for X-ray structure analysis (Fig. 1). The ester substituent was found to adopt a pseudo-axial conformation and the absolute configuration of compound **23b** was deduced to be 4*S* relative to the established 1*S*′ absolute configuration of the camphanate group [derived from (1*S*)-camphanic acid]. This allows the absolute configuration of (−)-chroman-4-ol **22** to be unequivocally established as 4*S*.

By the process of stereochemical correlation, shown in Scheme 4, it was unequivocally established that the bromo-MTPA ester **19b** had a 3*S*,4*S* configuration. The epoxide **20** ($[\alpha]_D$ −71, $CHCl_3$), obtained in quantitative yield, from the bromo-MTPA ester **19b** ($[\alpha]_D$ +129, $CHCl_3$) by treatment with sodium methoxide in diethyl ether solution, was assigned a 3*R*,4*S* configuration. Acid-catalysed hydrolysis of the epoxide **20** ($[\alpha]_D$ −71, $CHCl_3$) gave a mixture of *cis*- and *trans*-diols, **17** and **21**, respectively, in the ratio 1 : 13. Earlier work on the acid-catalysed hydrolysis of epoxides similar to the epoxide **20** has shown that cleavage of the benzylic C–O bond occurs exclusively and thus the absolute configuration at the non-benzylic chiral centre remains unchanged. The (−)-(3*R*,4*R*)-*trans*-diol **21** ($[\alpha]_D$ −22.4, THF) and the (+)-(3*R*,4*S*)-*cis*-diol **17** ($[\alpha]_D$ +63.1, THF) were obtained from the (−)-(3*R*,4*S*)-epoxide **20**. Comparison with the *cis*-diol metabolite **17** ($[\alpha]_D$ +64, THF), obtained from chromene by bacterial metabolism, suggested that both diols were enantiopure. This was verified by $^1H$ NMR analysis of the di-MTPA esters.

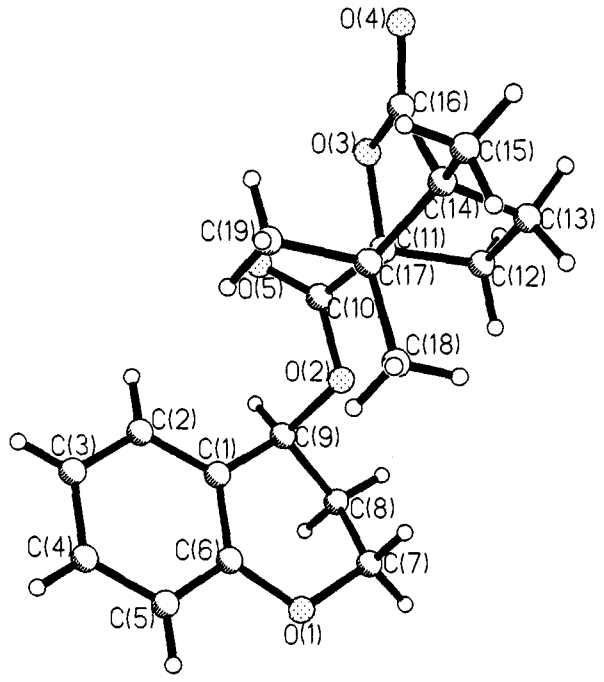
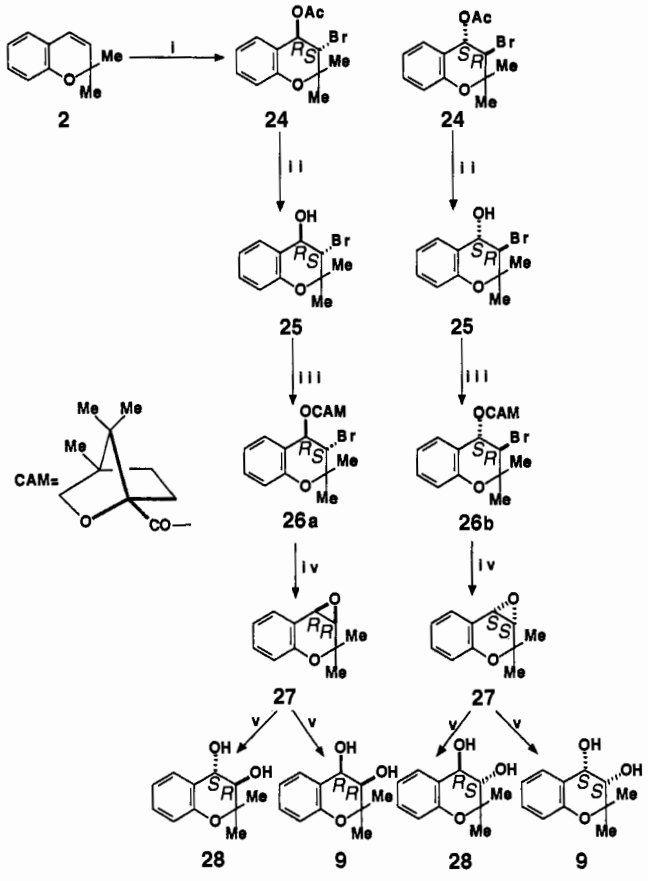


Fig. 1 X-Ray crystal structure of the chromane **23b**, showing the crystallographic numbering

Employing a synthetic sequence similar to that shown in Scheme 4, 2,2-dimethylchromene **2** was converted into the corresponding bromohydrin **25** which was subsequently resolved by separation of the bromocamphanates **26a**/**26b** by fractional crystallization (Scheme 5). The less soluble isomer **26a** ($[\alpha]_D$ −72, $CHCl_3$) provided a suitable crystal for X-ray crystal structure analysis (Fig. 2). The bromine atom and ester group were found to adopt a *trans*-diaxial conformation in the crystalline state having a 3*S*,4*R* absolute configuration, determined *relative* to the known absolute configuration of the camphanate group and *independently* from the Flack absolute structure parameter. Treatment of the bromo ester **26a** ($[\alpha]_D$ −72, $CHCl_3$) with sodium methoxide yielded the corresponding epoxide (3*R*,4*R*)-**27** ($[\alpha]_D$ +31, THF) while the other diastereoisomer **26b** ($[\alpha]_D$ +70, $CHCl_3$) gave the enantiomeric epoxide **27** ($[\alpha]_D$ −31, THF). Hydrolysis of epoxide **27** ($[\alpha]_D$ −31, THF) with perchloric acid in aqueous dioxane buffer (pH 2.5) afforded the (+)-(3*S*,4*R*)-*trans*-diol **28** ($[\alpha]_D$ +38, $CHCl_3$) and the (−)-(3*S*,4*S*)-*cis*-diol **9** ($[\alpha]_D$ −15, $CHCl_3$) in the ratio 6 : 1 (*trans* : *cis*). Hydrolysis of the opposite epoxide enantiomer **27** ($[\alpha]_D$ +31, THF) yielded the *trans*- and *cis*-diols **28** and **9** respectively of opposite configurations.

The bromohydrin esters (**19a**/**19b** and **26a**/**26b**) and the corresponding derived epoxides (**20** and **27**) proved to be relatively stable compounds during chromatographic and other purification procedures. By contrast, the bromohydrin esters derived from precocene-1 (**30a**–**30d**) were unstable and decomposed during attempted separation of the diastereoisomers by chromatography (silica gel) (Scheme 6). The corresponding epoxide **4** was also very unstable and decomposed during attempted direct synthesis by peroxyacid oxidation.[6]

Esterification of a racemic sample of the bromohydrin **29**



**Scheme 5** *Reagents:* i, NBA–AcOH; ii, $BH_3$–THF; iii, (−)-(1*S*)-4,8,8-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carbonyl chloride–pyridine; iv, NaOMe–THF–$Et_2O$; v, $H^+$–$H_2O$

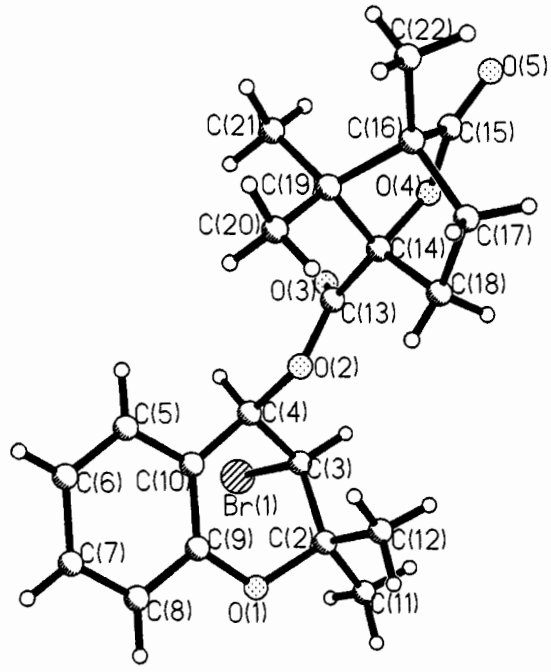
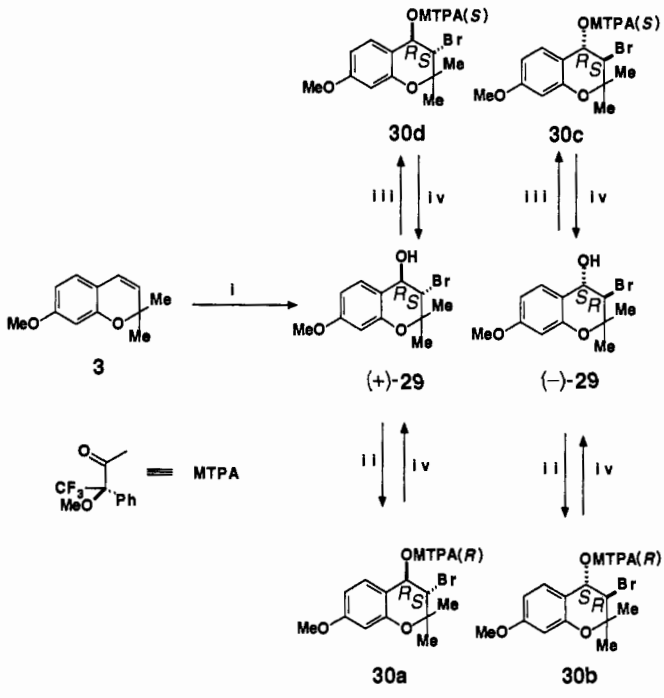


**Fig. 2** X-Ray crystal structure of the chromane **26a**, showing the crystallographic numbering

with (+)-(*S*)-MTPA-chloride [from (+)-*R*-MTPA] in pyridine solvent yielded a mixture of the diastereoisomers (**30a**/**30b**, Scheme 6). Fractional recrystallization yielded a pure sample of **30a** ($[\alpha]_D$ −42). The instability of the diastereoisomeric mixture (**30a**/**30b**) in aqueous THF (THF–water; 5:2) was found to be primarily due to hydrolysis to the parent bromohydrin, and this unexpected reaction was utilized to convert the mixture of



**Scheme 6** *Reagents:* i, NBA–THF–$H_2O$; ii, (+)-(*S*)-MTPA-Cl–pyridine; iii, (−)-(*R*)-MTPA-Cl–pyridine; iv, THF–$H_2O$

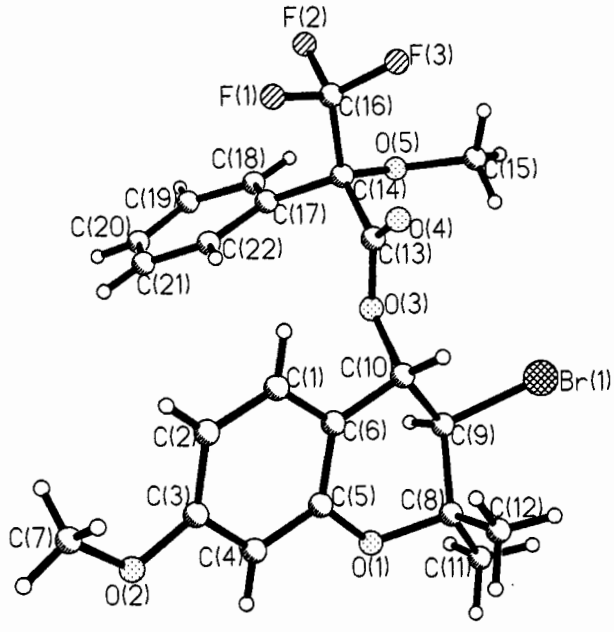
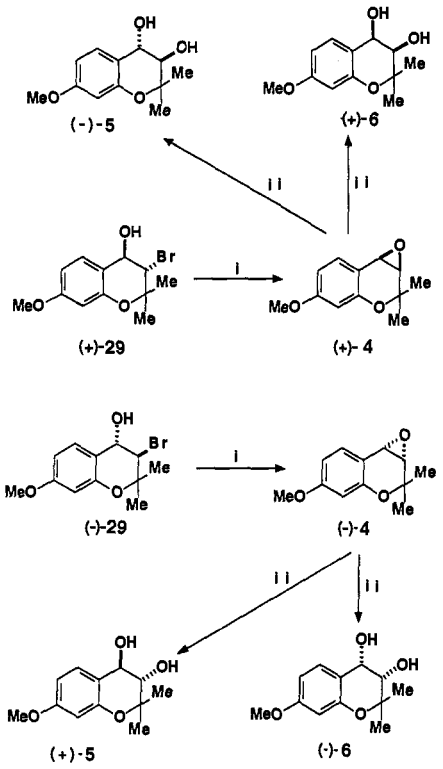


**Fig. 3** X-Ray crystal structure of the chromane **30c**, showing the crystallographic numbering

bromo-MTPA esters left in the mother liquors, after removal of the crystalline ester **30a**, to an optically enriched sample of the bromohydrin **29**. Treatment of the latter sample, in turn, with the (−)-(*R*)-MTPA chloride [from the (−)-(*S*)-MTPA] afforded a mixture of diastereoisomers (**30c**/**30d**; 7:3) from which a pure sample of the bromo-MTPA ester (**30c**, $[\alpha]_D$ +42) was isolated by crystallization. While the bromo-MTPA esters **30a** and **30c** were crystalline solids, the other diastereoisomers **30b** and **30d** proved to be non-crystalline.

A suitable crystal of the bromo-MTPA ester **30c** was selected for an X-ray crystallographic analysis (Fig. 3). Unlike the bromocamphanyl ester **26a**, the bromine atom and MTPA ester group in compound **30c** adopted a *trans*-diequatorial conformation in the crystalline state. The absolute configuration was unequivocally established as 3*S*,4*R* relative to the known *S* configuration of the MTPA group. The previously reported



Scheme 7 *Reagents:* i, NaH–THF; ii, THF–$H_2O$

configuration[5] was tentatively based on $^1$H NMR analysis alone.

Hydrolysis of the bromo-MTPA esters (−)-(3*S*,4*R*)-**30a** and (+)-(3*R*,4*S*)-**30b** occurred by stirring in aqueous THF at ambient temperature to yield the bromohydrin enantiomers **29** ([α]$_D$ +39 and −39 respectively). Treatment of the bromohydrin enantiomer **29** ([α]$_D$ +39) with sodium hydride in anhydrous THF afforded the corresponding 3*R*,4*R* enantiomer of precocene-1 3,4-epoxide **4** ([α]$_D$ +16) as an oil. Similar treatment of the other enantiomer of bromohydrin **29** ([α]$_D$ −39) gave (3*S*,4*S*)-precocene-1 3,4-epoxide **4** ([α]$_D$ −16). The precocene-1 epoxide enantiomers **4** were found to hydrolyse readily under aqueous conditions but proved to be sufficiently stable to allow further purification by distillation at low temperatures (65 °C, and 0.003 mmHg).

The conditions used to cleave the bromo-MTPA esters **30** (aqueous THF) were utilized again to hydrolyse the epoxide **4** ([α]$_D$ +16) to yield the high $R_F$ (3*R*,4*R*)-*cis*-diol **6** (19% yield, [α]$_D$ +6.6) and the low $R_F$ (3*R*,4*S*)-*trans*-diol-**5** (36% yield, [α]$_D$ −42) which were separated by preparative TLC and HPLC. Similarly, the corresponding *cis*-**6** and *trans*-**5** diols of opposite configuration were produced from the epoxide enantiomer **4** ([α]$_D$ −16). The stereochemical correlation sequence between bromohydrin **29**, epoxide **4**, and the *cis*-**6** and *trans*-**5** diols is shown in Scheme 7. The results of this study provide an unequivocal approach to absolute stereochemistry determination of the latter enantiopure compounds which had previously relied upon less rigorous methods. Furthermore, the study reveals additional evidence that the epoxide **4**, obtained when precocene-1 **3** is oxidized by animal liver enzymes (monooxygenases), has an excess of the 3*R*,4*R* enantiomer.

The chemical resolution of the bromohydrins (**18**, **25** and **29**) *via* their MTPA or camphanate esters appears to give a generally applicable route to the corresponding enantiopure epoxides (**20**, **27** and **4**), and their *cis*- (**17**, **9** and **6**) and *trans*-diols (**21**, **28** and **5**). A recent report[18] on the chiral epoxidation of 2,2-dimethylchromene **2** using NaOCl (as oxidant) and a Mn(salen) complex has provided a more convenient route to the enantiopure epoxide **27**. This method, however, was not found to be applicable to the synthesis of the epoxide **20**. The coumarin **16** was the only identifiable product and previous attempts to obtain epoxide **4** by direct epoxidation[6] were thwarted by product instability.

The foregoing results, obtained with chromene **1** and 2,2-dimethylchromene **2** as substrates for growing cultures of *P. putida* UV4, provide further evidence of dioxygenase-catalysed *cis*-dihydroxylation of bicyclic alkenes to yield exclusively one enantiomer. In common with several other bicyclic alkenes, *e.g.* 1,2-dihydronaphthalene,[11] and 6,7-dihydro-5*H*-benzocycloheptene,[11] a preference for the formation of one enantiomer of identical benzylic *S* configuration is shown using *P. putida* UV4.

## Conclusions

(i) The production of enantiopure bromohydrins by chemical resolution of their MTPA or camphanate esters has provided a generally applicable route to chromene epoxide enantiomers including relatively unstable epoxides, *e.g.* **4**.

(ii) X-Ray crystallographic analysis of the MTPA and camphanate esters, allied to stereochemical correlation, provides an unequivocal method for the absolute configuration assignment of a series of chromene epoxide, *cis*-diol, and *trans*-diol metabolites.

(iii) Dioxygenase-catalysed bacterial oxidation of chromenes **1** and **2** has been found to yield the corresponding enantiopure *cis*-diol metabolites (**17** and **9**).

## Experimental

$^1$H NMR spectra were recorded at 300 MHz with coupling constants (*J*) given in Hz using a General Electric QE 300 instrument. Mass spectra were recorded at 70 eV on an AEI-MS902 instrument updated by Autospec instruments. Accurate molecular weights were determined by the peak-matching method using perfluorokerosene as standard reference. Optical rotations were measured on a Perkin-Elmer precision polarimeter Model 241 and values are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$.

### Chromene 1

A solution of racemic chroman-4-ol **22** (8.0 g, 0.05 mmol) in benzene (150 cm$^3$), containing toluene-*p*-sulfonic acid (30 mg) and hydroquinone (5 mg), was heated under reflux using a Dean–Stark trap until dehydration was complete (1.5 h). The cooled benzene solution was washed with water, dried ($Na_2SO_4$) and concentrated under reduced pressure. Distillation of the residue *in vacuo* yielded chromene **1** (5.1 g, 74%), bp 30 °C/0.2 mmHg (lit.,[17] bp 51–53 °C/1.2 mmHg); $\delta_H$($CDCl_3$) 4.81 (2 H, m, 2-H), 5.76 (1 H, m, 3-H), 6.41 (1 H, d, $J_{4,3}$ 9.6, 4-H), 6.76 (1 H, d, $J_{8,7}$ 8.0, 8-H), 6.85 (1 H, dd, $J_{6,7}$ 8.6, $J_{6,5}$ 7.4, 6-H), 6.95 (1 H, dd, $J_{5,6}$ 7.4, $J_{5,7}$ 1.5, 5-H) and 7.09 (1 H, m, 7-H).

### 2,2-Dimethylchromene 2

A solution of the coumarin **16** (15.6 g, 0.11 mol) in diethyl ether (250 cm$^3$) was slowly added to an ethereal solution of methylmagnesium iodide [generated from magnesium (5 g, 0.21 mol) and methyl iodide (34 g, 0.24 mol) in diethyl ether (130 cm$^3$), following a literature method],[19] to afford 2-methyl-4-(2′-hydroxyphenyl)but-3-en-2-ol (19.2 g, 98%). Recrystallization of this from hexane gave white needles, mp 52–54 °C (lit.,[19] mp 53–55 °C); $\delta_H$($CDCl_3$) 1.34 (6 H, s, 2 × Me), 5.95 (1 H, d, $J_{3,4}$ 12.6, 3-H), 6.33 (1 H, d, $J_{4,3}$ 12.6, 4-H), 6.90 (2 H, m, ArH), 7.08 (1 H, m, ArH) and 7.16 (1 H, m, ArH).

4-(2′-Hydroxyphenyl)-2-methylbut-3-en-2-ol (7.29 g, 41 mmol) was dehydrated (2.5 h) in refluxing benzene (150 cm$^3$) containing toluene-*p*-sulfonic acid (25 mg) and hydroquinone (5 mg). Purification of the product by flash chromatography on silica gel (3% diethyl ether–97% hexane) gave 2,2-

dimethylchromene **2** (2.44 g, 37%); bp 69–70 °C/2.5 mmHg (lit.,[20] bp 96–97 °C/15 mmHg.); $\delta_H(CDCl_3)$ 1.42 (6 H, s, 2 × Me), 5.58 (1 H, d, $J_{3,4}$ 10.0, 3-H), 6.30 (1 H, d, $J_{4,3}$ 10.0, 4-H), 6.75–6.84 (2 H, m, 6-H and 8-H), 6.95 (1 H, dd, $J_{5,6}$ 7.4, $J_{5,7}$ 1.7, 5-H) and 7.11 (1 H, m, 7-H).

**Biotransformation of chromene 1 and 2,2-dimethylchromene 2**

With growing cultures of *Pseudomonas putida* UV4, and growth conditions as previously reported,[21] chromene **1** (0.19 g, 1.4 mmol) was added and incubated for 24 h by the shake-flask method. Extraction with ethyl acetate yielded a mixture which was separated into four compounds by preparative TLC (silica gel, diethyl ether–hexane, 1:1).

*Coumarin* **16**.—(0.02 g, 10%), $R_F$ 0.66, mp 66–69 °C (lit.,[22] mp 70 °C); $\delta_H(CDCl_3)$ 6.43 (1 H, d, $J_{4,3}$ 9.5, 4-H), 7.30 (2 H, m, ArH), 7.52 (2 H, m, ArH) and 7.72 (1 H, d, $J_{3,4}$ 9.5, 3-H).

*Chromen-2-ol* **14**.—(0.005 g, 2%), $R_F$ 0.59, low mp solid, $[\alpha]_D$ 0 (*c* 0.35, $CHCl_3$); $\delta_H(CDCl_3)$ 5.87 (1 H, dd, $J_{3,4}$ 9.5, $J_{3,2}$ 3.7, 3-H), 5.91 (1 H, d, $J_{2,3}$ 3.7, 2-H), 6.64 (1 H, d, $J_{4,3}$ 9.5, 4-H), 6.89 (2 H, m, 6-H and 8-H) and 7.05–7.19 (2 H, m, 5-H and 7-H). This sample was spectrally indistinguishable from an authentic sample.

3-(2'-*Hydroxyphenyl*)*prop*-2-*enal* **15**.—(0.007 g, 3%), $R_F$ 0.55, mp 120–121 °C (lit.,[22] mp 132–133 °C); $\delta_H(CDCl_3)$, 6.63 (1 H, br s, OH), 6.89 (1 H, d, $J_{3',4'}$ 7.7, 3'-H), 6.98 (1 H, m, 5'-H), 7.02 (1 H, dd, $J_{2,3}$ 15.9, $J_{2,1}$ 8.0, 2-H), 7.31 (1 H, m, 4'-H), 7.51 (1 H, dd, $J_{6',5'}$ 7.6, $J_{6',4'}$ 1.6, 6'-H), 7.79 (1 H, d, $J_{3,2}$ 15.9, 3-H) and 9.68 (1 H, d, $J_{1,2}$ 8.0, 1-H).

(+)-(3*R*,4*S*)-cis-*Chromane*-3,4-*diol* **17**.—(0.025 g, 10%), $R_F$ 0.14, mp 152–153 °C [lit.,[21] mp 136 °C (rac.)], $[\alpha]_D$ +64 (*c* 0.52, THF); $\delta_H(CDCl_3)$ 2.47 (2 H, br s, OH), 4.14 (3 H, m, 2-H, 2'-H and 3-H), 4.77 (1 H, br s, 4-H), 6.85 (1 H, dd, $J_{8,7}$ 8.3, $J_{8,6}$ 0.9, 8-H), 6.98 (1 H, m, 6-H), 7.23 (1 H, m, 7-H) and 7.41 (1 H, dd, $J_{5,6}$ 7.6, $J_{5,7}$ 1.5, 5-H).

Biotransformation of 2,2-dimethylchromene **2** (0.1 g, 0.63 mmol; 24 h) and subsequent extraction of the culture medium with ethyl acetate yielded a single product which was identified as (−)-(3*S*,4*S*)-*cis*-2,2-dimethylchromane-3,4-diol **9** (0.022 g, 18%) after TLC purification (silica gel, THF–dichloromethane, 10:90). The *cis*-diol **9** was recrystallized from chloroform–hexane, and had mp 112–113 °C, $[\alpha]_D$ −15.2 (*c* 1.26, $CHCl_3$); $\delta_H(CDCl_3)$ 1.26 (3 H, s, Me), 1.45 (3 H, s, Me), 2.54 (1 H, br s, OH), 2.93 (1 H, br s, OH), 3.61 (1 H, d, $J_{3,4}$ 4.2, 3-H), 4.76 (1 H, d, $J_{4,3}$ 4.2, 4-H), 6.79 (1 H, d, $J_{8,7}$ 8.2, 8-H), 6.96 (1 H, m, 6-H), 7.18 (1 H, m, 7-H) and 7.50 (1 H, d, $J_{5,6}$ 7.6, 5-H).

**(±)-*trans*-3-Bromochroman-4-ol 18**

*N*-Bromosuccinimide (6.1 g, 34 mmol) was added to a solution of chromene **1** (4.1 g, 31 mmol) in THF (70 $cm^3$) and water (15 $cm^3$) and the reaction mixture was stirred at room temperature for 17 h after which the THF was removed under reduced pressure. The residue was diluted with water (50 $cm^3$) and extracted with diethyl ether. The combined extracts were washed with water, dried ($Na_2SO_4$) and concentrated to yield a residue (6.8 g, 96%) which was recrystallized from dichloromethane–hexane to give the title compound **18**, mp 108–109 °C (lit.,[25] mp 107–108 °C); $\delta_H(CDCl_3)$ 2.54 (1 H, br s, OH), 4.31 (2 H, m, 2-H and 2'-H), 4.49 (1 H, m, 3-H), 4.89 (1 H, d, $J_{4,3}$ 4.6, 4-H), 6.89 (1 H, d, $J_{8,7}$ 8.3, 8-H), 7.01 (1 H, m, 6-H), 7.26 (1 H, m, 7-H) and 7.39 (1 H, dd, $J_{5,6}$ 7.7, $J_{5,7}$ 1.6, 5-H).

**(−)-(3*R*,4*R*)-19a and (+)-(3*S*,4*S*)-*trans*-3-Bromo-4-[methoxy(phenyl)trifluoromethylacetoxy]chromane 19b**

(+)-(*S*)-MTPA chloride (2.74 g, 10.8 mmol) [derived from (+)-(*R*)-MTPA] was added to a solution of the racemic bromohydrin **18** (2.24 g, 9.8 mmol) in dry pyridine (6 $cm^3$) and the reaction mixture was stirred at room temperature for 17 h after which the pyridine was removed under reduced pressure. The residue, after dilution with water (50 $cm^3$), was extracted with diethyl ether (2 × 50 $cm^3$). The combined extracts were washed with aqueous sodium hydrogen carbonate, dried ($Na_2SO_4$), and concentrated to yield the diastereoisomeric mixture of bromo-MTPA esters (4.16 g, 96%), separation of which was achieved by preparative TLC [silica gel, diethyl ether–hexane, 5:95].

(−)-(3*R*,4*R*)-**19a**.—(1.73 g, 40%), low $R_F$ viscous oil, $[\alpha]_D$ −97 (*c* 1.9, $CHCl_3$) (Found: $M^+$, 444.0183. $C_{19}H_{16}BrF_3O_4$ requires 444.0184); $\delta_H(CDCl_3)$ 3.50 (3 H, s, OMe), 4.34–4.42 (3 H, m, 2-H, 2'-H and 3-H), 6.28 (1 H, d, $J_{4,3}$ 3.3, 4-H), 6.87–6.93 (2 H, m, ArH), 7.17–7.27 (2 H, m, ArH), 7.38 (3 H, m, ArH) and 7.51 (2 H, m, ArH).

(+)-(3*S*,4*S*)-**19b**.—2.11 g, 49%, high $R_F$, mp 52–53 °C (pentane); $[\alpha]_D$ +129 (*c* 2.2, $CHCl_3$) (Found: C, 51.1; H, 3.6. $C_{19}H_{16}BrF_3O_4$ requires C, 51.2; H, 3.6%); $\delta_H(CDCl_3)$ 3.50 (3 H, s, OMe), 4.26 (3 H, m, 2-H, 2'-H and 3-H), 6.27 (1 H, d, $J_{4,3}$ 3.2, 4-H), 6.91–6.98 (2 H, m, ArH), 7.28–7.36 (5 H, m, ArH) and 7.45 (2 H, m, ArH).

**(+)-(4*R*)-Chroman-4-ol 22**

An excess of lithium aluminium hydride (0.28 g, 7.4 mmol) was added to a solution of the bromo-MTPA ester **19b** (0.28 g, 0.63 mmol, $[\alpha]_D$ +129) in dry diethyl ether (20 $cm^3$) and the mixture was refluxed for 18 h. The cooled solution was treated with wet diethyl ether and then filtered, dried ($MgSO_4$) and concentrated to yield the chroman-4-ol **22** (0.061g, 64%), mp 77–78 °C; $[\alpha]_D$ +68.7 (*c* 0.49, $CHCl_3$) and $[\alpha]_D$ +69.0 (*c* 0.36, EtOH) (lit.,[26] $[\alpha]_D$ +67.0, EtOH). This compound was spectrally indistinguishable from an authentic sample.

**(−)-(4*S*)-and(+)-(4*R*)-4-(4,8,8-Trimethyl-2-oxabicyclo[2.2.1]heptane-1-carbonyloxy)chromane 23b and 23a**

Racemic chroman-4-ol **22**, (0.22 g, 1.4 mmol) was treated with (−)-(1*S*)-4,8,8-trimethyl-2-oxabicyclo [2.2.1]heptane-1-carbonyl chloride (0.41 g, 1.9 mmol) in dry pyridine (4 $cm^3$) and the mixture worked up in a similar manner to that for the bromo-MTPA esters (**19a**/**19b**) to yield the title compounds **23a**/**23b** (0.45 g, 95%). Preparative TLC separation [silica gel, diethyl ether–hexane, 35:65] gave (−)-(4*S*)-**23b**, $R_F$ 0.20, mp 136–137 °C (diethyl ether–hexane); $[\alpha]_D$ −109 (*c* 0.65, $CHCl_3$) (Found: C, 68.9; H, 6.6. $C_{19}H_{22}O_5$ requires C, 69.1; H, 6.7%); $\delta_H(CDCl_3)$ 0.93, 0.97, 1.10 (3 × 3 H, s, Me), 1.64–1.72 (1 H, m, $H_{cam}$),‡ 1.85–1.95 (1 H, m, $H_{cam}$), 2.00–2.15 (2 H, m, 3-H and $H_{cam}$), 2.25–2.46 (2 H, m, 3'-H and $H_{cam}$), 4.20–4.38 (2 H, m, 2-H and 2'-H), 6.12 (1 H, dd, $J_{4,3} = J_{4,3'}$ 3.4, 4-H), 6.90 (2 H, m, 6-H and 8-H) and 7.27 (2 H, m, 5-H and 7-H).

(+)-(4*R*)-**23a**, $R_F$ 0.25, mp 109–110 °C (diethyl ether–hexane), $[\alpha]_D$ +90 (*c* 0.55, $CHCl_3$) (Found: C, 69.2; H, 6.6. $C_{19}H_{22}O_5$ requires C, 69.1; H, 6.7%); $\delta_H(CDCl_3)$ 0.86, 1.03 and 1.10 (3 × 3 H, s, Me), 1.63–1.72 (1 H, m, $H_{cam}$), 1.85–1.95 (1 H, m, $H_{cam}$), 1.99–2.16 (2 H, m, 3-H and $H_{cam}$), 2.25–2.34 (1 H, m, 3'-H), 2.40–2.48 (1 H, m, $H_{cam}$), 4.22–4.38 (2 H, m, 2 H and 2'-H), 6.12 (1 H, dd, $J_{4,3} = J_{4,3'}$ 3.5, 4-H), 6.90 (2 H, m, 6-H and 8-H) and 7.27 (2 H, m, 5-H and 7-H).

Treatment of the ester **23b** (0.105 g, 0.32 mmol, $[\alpha]_D$ −109) in THF solution (5 $cm^3$) with KOH (0.053 g, 0.95 mmol) in water (0.5 $cm^3$), and heating of the reaction mixture under reflux for 2.5 h resulted in complete hydrolysis. THF solvent was removed under reduced pressure and the residue was diluted with water (10 $cm^3$), and extracted with diethyl ether. The extracts were dried ($Na_2SO_4$) and concentrated to yield the (4*S*)-chroman-4-ol **22** (0.025 g, 52%), mp 77–78 °C, $[\alpha]_D$ −69.1 (*c* 1.10, $CHCl_3$).

**X-Ray crystal structure analysis of compound 23b**

**Crystal data.** $C_{19}H_{22}O_5$, $M$ = 330.4, orthorhombic, space group $P2_12_12_1$ (no. 19), $a$ = 6.357(2), $b$ = 11.787(7), $c$ = 23.060(9) Å, $U$ = 1727.9(1.4) $Å^3$, $\mu$(Mo-K$\alpha$) = 0.91 $cm^{-1}$,

‡ For definition of cam see displayed formula in Scheme 5.

$F(000) = 704$, $Z = 4$, $D_c = 1.27$ Mg m$^{-3}$, $\theta/2\theta$ scan, scan range $3.5 < 2\theta < 55°$.

**Data collection, analysis and refinement.** Siemens P3/V2000 diffractometer, 2300 unique reflections measured, 1379 observed [$I > 2\sigma(I)$]; direct methods solution (SHELXS-86),[27] full-matrix least-squares refinement on $F^2$ (SHELXL-93),[28] non-hydrogen atoms anisotropic, hydrogen atoms included at geometrically calculated positions with common isotropic temperature factors for benzene, methyl, methylene and tertiary hydrogens which refined to final values of $U = 0.11(1)$, 0.11(1), 0.06(1) and 0.04(1) Å$^2$, respectively; in the final cycles data with $I > 2\sigma(I)$ gave $R_1 = 0.057$, $wR_2 = 0.150$ (all data); $GoF = 0.99$; maximum residual electron density was 0.17 e Å$^{-3}$. A projection of the molecule is shown in Fig. 1.§

### (−)-(3*R*,4*S*)-3,4-Epoxychromane 20

The bromo-MTPA ester **19b** (1.28 g, 2.9 mmol, $[\alpha]_D$ +129) was treated with an excess of sodium methoxide (0.5 g, 10 mmol) in diethyl ether (10 cm$^3$) and the reaction mixture stirred at room temperature for 2 h. It was then diluted with water (15 cm$^3$) and extracted with diethyl ether. The combined extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure to yield an oil (0.4 g, 95%) which solidified with time. Recrystallization of this (diethyl ether–hexane) gave the epoxide **20**, mp 57–59 °C, $[\alpha]_D$ −71 (*c* 0.8, $CHCl_3$) (Found: M$^+$, 148.0523. $C_9H_8O_2$ requires *M*, 148.0524); $\delta_H(CDCl_3)$ 3.82 (1 H, d, $J_{3,4}$ 4.4, 3-H), 3.92 (1 H, d, $J_{4,3}$ 4.4, 4-H), 4.16 (1 H, d, $J_{2,2'}$ 12.7, 2-H), 4.57 (1 H, d, $J_{2,2'}$ 12.7, 2′-H), 6.85 (1 H, d, $J_{8,7}$ 8.2, 8-H), 6.96 (1 H, m, 6-H), 7.26 (1 H, m, 7-H) and 7.36 (1 H, dd, $J_{5,6}$ 7.4, $J_{5,7}$ 1.4, 5-H).

### (+)-(3*R*,4*S*)-*cis*- and (−)-(3*R*,4*R*)-*trans*-Chromane-3,4-diol 17 and 21

Sodium perchlorate solution (0.1 mol dm$^{-3}$; 19 cm$^3$ 1.9 mmol) was added to dioxane–water (3:7; 555 cm$^3$) and the solution was adjusted to pH 2.5 with perchloric acid. A solution of epoxide **20** (0.46 g, 3.11 mmol, $[\alpha]_D$ −71) in dioxane (5 cm$^3$) was added to the sodium perchlorate solution and the reaction mixture was stirred for 20 h at room temperature. After treatment with sodium hydrogen carbonate (1 g), the solution was concentrated under reduced pressure and the residue was diluted with water (50 cm$^3$) and extracted with ethyl acetate. The combined extracts were dried ($Na_2SO_4$) and concentrated to yield a yellow oil consisting of the *cis*-diol **17** and *trans*-diol **21**. The diols were separated using preparative TLC [silica gel, methanol–chloroform, 4:96].

(+)-(3*R*,4*S*)-*cis*-Chromane-3,4-diol **17** (0.038 g, 7%), $R_F$ 0.26, mp 159–161 °C (chloroform–hexane) [lit.,[24] (rac.) mp 136 °C], $[\alpha]_D$ +63 (*c* 0.77, THF); $\delta_H(CDCl_3)$ 2.47 (2 H, br s, OH), 4.14 (3 H, m, 2-H, 2′-H and 3-H), 4.77 (1 H, br s, 4-H), 6.85 (1 H, dd, $J_{8,7}$ 8.3, $J_{8,6}$ 0.9, 8-H), 6.98 (1 H, m, 6-H), 7.23 (1 H, m, 7-H) and 7.41 (1 H, dd, $J_{5,6}$ 7.6, $J_{5,7}$ 1.5, 5-H).

(−)-(3*R*,4*R*)-*trans*-Chromane-3,4-diol **21** (0.41 g, 75%), $R_F$ 0.16, mp 97–98 °C (chloroform–hexane) [lit.,[24] (rac.) mp 102 °C], $[\alpha]_D$ −22 (*c* 0.49, THF); $\delta_H(CDCl_3)$ 2.66 (2 H, br s, OH), 3.99 (1 H, m, 3-H), 4.13 (1 H, dd, $J_{2,2'}$ 11.5, $J_{2,3}$ 5.8, 2-H), 4.28 (1 H, dd, $J_{2,2'}$ 11.5, $J_{2',3}$ 2.6, 2′-H), 4.59 (1 H, m, 4-H), 6.88 (1 H, dd, $J_{8,7}$ 8.2, $J_{8,6}$ 0.6, 8-H), 6.99 (1 H, m, 6-H), 7.24 (1 H, m, 7-H) and 7.37 (1 H, dd, $J_{5,6}$ 7.6, $J_{5,7}$ 1.5, 5-H).

### (±)-*trans*-4-Acetoxy-3-bromo-2,2-dimethylchromane 24

*N*-Bromoacetamide (3.27 g, 23.7 mmol) was added to a solution of 2,2-dimethylchromene **2** (3.80 g, 23.8 mmol) in glacial acetic acid (3.5 cm$^3$) containing lithium acetate (1.5 g) and the reaction mixture was stirred at room temperature for 3 h. It was then diluted with water (25 cm$^3$) and extracted with diethyl ether (3 × 25 cm$^3$). The combined extracts were washed with water, dried ($Na_2SO_4$) and concentrated and the residue was purified by flash chromatography on silica gel to give the bromoacetate **24** (4.64 g, 65%). A small sample of racemic *trans*-4-acetoxy-3-bromo-2,2-dimethylchromane **24** was recrystallized from hexane, mp 52–53 °C (lit.,[28] mp 63 °C); $\delta_H(CDCl_3)$ 1.48 (3 H, s, Me), 1.60 (3 H, s, Me), 2.20 (3 H, s, OAc), 4.26 (1 H, d, $J_{3,4}$ 8.3, 3-H), 6.30 (1 H, d, $J_{4,3}$ 8.3, 4-H), 6.83 (1 H, d, $J_{8,7}$ 8.2, 8-H), 6.93 (1 H, m, 6-H), 7.10 (1 H, d, $J_{5,6}$ 7.5, 5-H) and 7.23 (1 H, m, 7-H).

### (±)-*trans*-3-Bromo-2,2-dimethylchroman-4-ol 25

Borane–THF complex (1.0 mol dm$^{-3}$ solution in THF; 20 cm$^3$, 0.02 mol) was added slowly to a stirred solution of the racemic bromoacetate **24** (1.93 g, 6.5 mmol) in dry THF (5 cm$^3$) under an atmosphere of $N_2$ gas at 0 °C. The mixture was stirred at room temperature for 36 h after which excess of reagent was destroyed by careful treatment with water; most of the THF was then removed under reduced pressure. The aqueous residues were extracted with diethyl ether, and the combined extracts were washed with water, dried ($Na_2SO_4$) and concentrated to yield the bromohydrin **25**. Recrystallization of this from dichloromethane–hexane yielded compound **25** (1.60 g, 96%), mp 114–116 °C (lit.,[29] mp 106 °C); $\delta_H(CDCl_3)$ 1.41 (3 H, s, Me), 1.60 (3 H, s, Me), 2.50 (1 H, br s, OH), 4.14 (1 H, d, $J_{3,4}$ 9.4, 3-H), 4.92 (1 H, d, $J_{4,3}$ 9.4, 4-H), 6.80 (1 H, d, $J_{8,7}$ 8.2, 8-H), 6.98 (1 H, m, 6-H), 7.21 (1 H, m, 7-H) and 7.48 (1 H, d, $J_{5,6}$ 7.6, 5-H).

### (−)-(3*S*,4*R*)- and (+)-(3*R*,4*S*)-*trans*-3-Bromo-4-(4,8,8-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carbonyloxy)-2,2-dimethylchromane (26a and 26b)

(±)-*trans*-3-Bromo-2,2-dimethylchroman-4-ol **25** (2.02 g, 7.9 mmol) was treated with (−)-(1*S*)-4,8,8-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carbonyl chloride (2.22 g, 10.2 mmol) using the procedure outlined for the formation of the bromo-MTPA esters (**19a**/**19b**) from the corresponding bromohydrins **18**. The crude mixture of the diastereoisomers **26a**/**26b** was obtained as a white solid after purification by flash chromatography on silica gel (2.72 g, 79%) (Found: C, 57.5; H, 5.8. $C_{21}H_{25}BrO_5$ requires C, 57.7; H, 5.7%). Fractional recrystallization of this from diethyl ether gave the diastereoisomer **26a** as the less-soluble isomer (1.28 g, 37%), mp 147–148 °C, $[\alpha]_D$ −72, (*c* 1.56, $CHCl_3$); $\delta_H(CDCl_3)$ 1.07, 1.09 and 1.13 (3 × 3 H, s, $Me_{cam}$), 1.49 (3 H, s, 2-Me), 1.62 (3 H, s, 2′-Me), 1.73, 1.95, 2.14 and 2.53 (4 × 1 H, m, $H_{cam}$), 4.32 (1 H, d, $J_{3,4}$ 8.4, 3-H), 6.45 (1 H, d, $J_{4,3}$ 8.4, 4-H), 6.85 (1 H, d, $J_{8,7}$ 8.4, 8-H), 6.94 (1 H, m, 6-H), 7.08 (1 H, d, $J_{5,6}$ 7.4, 5-H) and 7.24 (1 H, m, 7-H).

Compound **26b**, more-soluble isomer (1.14 g, 33%), mp 138–139 °C, $[\alpha]_D$ +70 (*c* 1.23, $CHCl_3$); $\delta_H(CDCl_3)$, 1.06, 1.13 and 1.15 (3 × 3 H, s, $Me_{cam}$), 1.49 (3 H, s, 2-Me), 1.63 (3 H, s, 2′-Me), 1.73, 1.95, 2.14 and 2.48 (4 × 1 H, m, $H_{cam}$), 4.32 (1 H, d, $J_{3,4}$ 8.5, 3-H), 6.48 (1 H, d, $J_{4,3}$ 8.5, 4 H), 6.85 (1 H, d, $J_{8,7}$ 8.3, 8-H), 6.94 (1 H, m, 6-H), 7.06 (1 H, d, $J_{5,6}$ 7.3, 5-H) and 7.24 (1 H, m, 7-H).

### X-Ray crystal structure analysis of compound 26a

**Crystal data.** $C_{21}H_{25}BrO_5$, $M = 437.3$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 12.905(6)$, $b = 14.438(3)$, $c = 10.683(2)$ Å, $U = 1990.3(1.0)$ Å$^3$, $\mu$(Mo-K$\alpha$) = 20.9 cm$^{-1}$, $F(000) = 904$, $Z = 4$, $D_c = 1.46$ Mg m$^{-3}$, $\theta/2\theta$ scan, scan range $4 < 2\theta < 50°$.

**Data collection, analysis and refinement.** Siemens P3/V2000 diffractometer, 2024 unique reflections measured, 1867 observed [$I > 2\sigma(I)$]; direct methods solution (SHELXS-86),[27] full-matrix least-squares refinement on $F^2$ (SHELXL-93),[28] non-hydrogen atoms anisotropic, hydrogen atoms included at

§ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/11.

geometrically calculated positions with common isotropic temperature factors for benzene, methyl, methylene and tertiary hydrogens which refined to final values of $U = 0.053(7)$, 0.068(5), 0.066(9) and 0.029(8) Å$^2$ respectively; data with $I > 2\sigma(I)$ gave $R_1 = 0.029$, $wR_2 = 0.087$ (all data); $GoF = 0.80$; Flack parameter $-0.02(1)$; maximum residual electron density was 0.51 e Å$^{-3}$. A projection of the molecule is shown in Fig. 2.§

**(+)-(3*R*,4*R*)- and (−)-(3*S*,4*S*)-3,4-Epoxy-2,2-dimethylchromane 27**

Treatment of the ester **26a** (0.77 g, 1.76 mmol, $[\alpha]_D$ −72) with sodium methoxide (0.64 g, 11.9 mmol) in a mixture of dry THF (10 cm$^3$) and dry diethyl ether (10 cm$^3$), using a similar procedure and work-up to that described for the bromo-MTPA ester (**19b**), yielded the epoxide **27** (0.30 g, 97%), bp 75 °C/0.1 mmHg, $[\alpha]_D$ +31 (*c* 0.65, THF) (Found: C, 74.7; H, 6.9. $C_{11}H_{12}O_2$ requires C, 75.0; H, 6.8%); $\delta_H$($CDCl_3$) 1.25 (3 H, s, Me), 1.58 (3 H, s, Me), 3.49 (1 H, d, $J_{3,4}$ 4.3, 3-H), 3.90 (1 H, d, $J_{4,3}$ 4.3, 4-H), 6.81 (1 H, d, $J_{8,7}$ 8.2, 8-H), 6.93 (1 H, m, 6-H), 7.23 (1 H, m, 7-H) and 7.33 (1 H, dd, $J_{5,6}$ 7.4, $J_{5,7}$ 1.6, 5-H).

The ester **26b** (0.69 g, 1.5 mmol, $[\alpha]_D$ +70) was treated in an identical manner to give the epoxide **27** (0.27 g, 97%), $[\alpha]_D$ −31 (*c* 0.47, THF).

**(−)-(3*S*,4*S*)- and (+)-(3*R*,4*R*)-*cis*-2,2-Dimethylchromane-3,4-diol 9 and (+)-(3*S*,4*R*)- and (−)-(3*R*,4*S*)-*trans*-2,2-dimethylchromane-3,4-diol 28**

Acid-catalysed hydrolysis of the epoxide **27** (0.268 g, 1.52 mmol, $[\alpha]_D$ −31) was carried out using the method described for epoxide **20** to yield a mixture of (+)-(3*S*,4*R*)-*trans*-2,2-dimethylchromane-3,4-diol **28** and (−)-(3*S*,4*S*)-*cis*-2,2-dimethylchromane-3,4-diol **9**. Separation by preparative TLC [silica gel, THF–dichloromethane, 10:90] yielded the more polar *trans*-**28**, ($R_F$ 0.16) and less polar *cis*-**9**, ($R_F$ 0.28) diols:

(+)-(3*S*,4*R*)-trans-2,2-*Dimethylchromane*-3,4-*diol* **28**.—(0.224 g, 76%); mp 93–94 °C (chloroform–hexane); $[\alpha]_D$ +38 (*c* 1.01, $CHCl_3$) (Found: C, 67.8; H, 7.2. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.2%); $\delta_H$($CDCl_3$) 1.14 (3 H, s, Me), 1.42 (3 H, s, Me), 3.58 (1 H, d, $J_{3,4}$ 8.7, 3-H), 4.52 (1 H, d, $J_{4,3}$ 8.7, 4-H), 4.72 (2 H, br s, OH), 6.75 (1 H, d, $J_{8,7}$ 8.2, 8-H), 6.91 (1 H, m, 6-H), 7.16 (1 H, m, 7-H) and 7.38 (1 H, d, $J_{5,6}$ 7.7, 5-H).

(−)-(3*S*,4*S*)-cis-2,2-*Dimethylchromane*-3,4-*diol* **9**.—(0.038 g, 13%), mp 113–114 °C (chloroform–hexane); $[\alpha]_D$ −15 (*c* 0.63, $CHCl_3$) (Found: C, 67.9; H, 7.0. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.2%); $\delta_H$($CDCl_3$) 1.26 (3 H, s, Me), 1.45 (3 H, s, Me), 2.54 (1 H, br s, OH), 2.93 (1 H, br s, OH), 3.61 (1 H, d, $J_{3,4}$ 4.2, 3-H), 4.76 (1 H, d, $J_{4,3}$ 4.2, 4-H), 6.79 (1 H, d, $J_{8,7}$ 8.2, 8-H), 6.96 (1 H, m, 6-H), 7.18 (1 H, m, 7-H) and 7.50 (1 H, d, $J_{5,6}$ 7.6, 5-H).

Similar treatment of the (+)-(3*R*,4*R*)-enantiomer of the epoxide **27** (0.150 g, 0.85 mmol) gave the (−)-(3*R*,4*S*)-*trans*-diol **28** (0.134 g, 81%), $[\alpha]_D$ −38 (*c* 1.14, $CHCl_3$) and the (+)-(3*R*,4*R*)-*cis*-diol **9** (0.024 g, 15%), $[\alpha]_D$ +16 (*c* 0.42, $CHCl_3$).

**(±)-*trans*-3-Bromo-7-methoxy-2,2-dimethylchroman-4-ol 29**

*N*-Bromoacetamide (3.45 g, 25 mmol) was added to a stirred, ice-cooled solution of precocene-1 **3** (Aldrich Chemical Co.) (4.39 g, 23 mmol) in THF (55 cm$^3$) and water (10 cm$^3$). The reaction mixture was protected from light and allowed to warm gradually to room temperature overnight. The THF was removed under reduced pressure and the residue was diluted with water (40 cm$^3$) and extracted with ether (2 × 80 cm$^3$). The combined extracts were washed with water (70 cm$^3$), dried ($Na_2SO_4$) and concentrated under reduced pressure to yield the product bromohydrin **29** (6.42 g, 97%), mp 67–69 °C (from ether–hexane) (lit.,[6] 77–78.5 °C); $\delta_H$($CDCl_3$) 1.38 (3 H, s, Me), 1.57 (3 H, s, Me), 2.78 (1 H, br s, OH), 3.75 (3 H, s, OMe), 4.01 (1 H, d, $J_{3,4}$ 9.2, 3-H), 4.83 (1 H, d, $J_{4,3}$ 9.2, 4-H), 6.32 (1 H, d, $J_{8,6}$ 2.6, 8-H), 6.55 (1 H, dd, $J_{6,5}$ 8.6, $J_{6,8}$ 2.6 Hz, 6-H) and 7.34 (1 H, d, $J_{5,6}$ 8.6, 5-H).

**(−)-(3*S*,4*R*)-*trans*-3-Bromo-7-methoxy-4-[(*R*)-methoxy-(phenyl)trifluoromethylacetoxy]-2,2-dimethylchromane 30a**

(+)-(*S*)-MTPA chloride [3.45 g, 14 mmol; derived from (+)-(*R*)-MTPA] was added to a solution of the bromohydrin **29** (3.52 g, 12 mmol) in dry pyridine (12 cm$^3$). The reaction mixture, protected from light, was stirred at room temperature overnight after which the pyridine was removed azeotropically with toluene under reduced pressure. Water (50 cm$^3$) was added to the residue and the product extracted with ether (2 × 100 cm$^3$). The combined ethereal fractions were washed with aqueous sodium hydrogen carbonate (1 mol dm$^{-3}$; 50 cm$^3$), dried ($Na_2SO_4$) and concentrated under reduced pressure to give the crude diastereoisomeric mixture, **30a**–**30b** as a yellow oil (6.0 g, 96%) which was unstable to chromatography on silica gel. Crystallization of the mixture, from ether–pentane, afforded the diastereoisomer **30a** as white needles (1.79 g, 29%), mp 101–103 °C; $[\alpha]_D$ −42 (*c* 1.50, $CHCl_3$) (Found: C, 52.4; H, 4.4. $C_{22}H_{22}BrF_3O_5$ requires C, 52.5; H, 4.4%); $\delta_H$(300 MHz, $CDCl_3$) 1.49 (3 H, s, Me), 1.52 (3 H, s, Me), 3.62 (3 H, s, MTPA-OMe), 3.74 (3 H, s, 7-OMe), 4.27 (1 H, d, $J_{3,4}$ 7.2, 3-H), 6.33–6.48 (3 H, m, 4-H, 6-H and 8-H), 6.83 (1 H, d, $J_{5,6}$ 8.7, 5-H), 7.41–7.44 (3 H, m, ArH) and 7.62–7.66 (2 H, m, ArOH).

Efforts to obtain a pure sample of the diastereoisomer **30b** by chromatography of the residual yellow oil were unsuccessful owing to decomposition.

**(+)-(3*R*,4*S*)-*trans*-3-Bromo-7-methoxy-4-[(*S*)-methoxy-(phenyl)trifluoromethylacetoxy]-2,2-dimethylchromane 30c**

The residual diastereoisomeric mixture **30a**–**30b** (4.05 g, 8.05 mmol), enriched in compound **30b** after removal of a portion of the crystalline isomer **30a**, was reconverted into the bromohydrin **29** by stirring a solution of it in THF (100 cm$^3$) and water (40 cm$^3$) in the dark at room temperature for 5 days. Work-up furnished the bromohydrin **29** (2.26 g, 7.87 mmol) enriched in the (3*R*,4*S*)-enantiomer, which was dissolved in pyridine (8 cm$^3$) and treated with (−)-MTPA chloride (2.20 g, 8.70 mmol) in the dark for 12 h at room temperature. Crystallization of the diastereoisomeric mixture **30c**–**30d** yielded the pure bromo-MTPA ester **30c** (1.60 g, 40%), mp 101–103 °C (from ether–pentane) $[\alpha]_D$ +42 (*c* 1.36, $CHCl_3$) (Found: C, 52.4; H, 4.4. $C_{22}H_{22}BrF_3O_5$ requires C, 52.5; H, 4.4%). The spectral data for the enantiomeric bromo-MTPA esters **30a** and **30c** were identical.

**X-Ray crystal structure analysis of (+)-(3*R*,4*S*)-*trans*-3-bromo-7-methoxy-4-[(*S*)-methoxy(phenyl)trifluoromethylacetoxy]-2,2-dimethylchromane 30c**

**Crystal data.** $C_{22}H_{22}BrF_3O_5$, $M = 503.3$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 17.280(10)$, $b = 20.506(13)$, $c = 6.157(3)$ Å, $U = 2182(2)$ Å$^3$, $\mu$(Mo-K$\alpha$) = 19.4 cm$^{-1}$, $F(000) = 1024$, $Z = 4$, $D_c = 1.53$ Mg m$^{-3}$, $\theta/2\theta$ scan, scan range $3 < 2\theta < 45°$.

**Data collection, analysis and refinement.** Siemens P3/V2000 diffractometer, 1694 unique reflections measured, 1054 observed [$I > 2\sigma(I)$]; direct methods solution (SHELXS-86),[27] full-matrix least squares refinement on $F^2$ (SHELXL-93),[28] non-hydrogen atoms anisotropic, hydrogen atoms included at geometrically calculated positions with common isotropic temperature factors for benzene, methyl, and tertiary hydrogens which refined to final values of $U = 0.05(2)$, 0.09(2) and 0.13(7) Å$^2$ respectively; data with $I > 2\sigma(I)$ gave $R_1 = 0.063$, $wR_2 = 0.136$ (all data); $GoF = 1.07$, maximum residual electron density was 0.53 e Å$^{-3}$. The estimated standard deviations in this structure are relatively high, typically 0.02 Å for C–C bonds and 1.5° for angles, but this does not affect our

conclusions with regard to configurational assignment. A projection of the molecule is shown in Fig. 3.

**(+)-(3*S*,4*R*)- and (−)-(3*R*,4*S*)-*trans*-3-Bromo-7-methoxy-2,2-dimethylchroman-4-ol 29**

Hydrolysis of the crystalline bromo-MTPA diastereoisomer **30a**, $[\alpha]_D$ −42 (1.59 g, 3.16 mmol) in THF (50 $cm^3$) and water (20 $cm^3$) afforded (+)-(3*S*,4*R*)-*trans*-3-bromo-7-methoxy-2,2-dimethylchroman-4-ol **29**, in quantitative yield (0.97 g), as a pale yellow oil, which was used without further purification. A small sample of the crude product was purified by preparative TLC on silica gel (25% ether–pentane) to yield the bromohydrin **29** as a colourless oil, $[\alpha]_D$ +39 (*c* 2.75, $CHCl_3$).

Similar treatment of the bromo-MTPA ester **30c** $[\alpha]_D$ +42 (1.43 g, 2.84 mmol) gave the (−)-(3*R*,4*S*)-bromohydrin **29** (0.84 g), $[\alpha]_D$ −39 (*c* 2.74, $CHCl_3$). Both enantiomers of the bromohydrin **29** were spectrally indistinguishable from the racemic sample.

**(+)-(3*R*,4*R*)- and (−)-(3*S*,4*S*)-3,4-Epoxy-7-methoxy-2,2-dimethylchromane 4**

A solution of the bromohydrin **29**, $[\alpha]_D$ +39 (0.55 g, 1.92 mmol) in dry THF (12 $cm^3$) was added dropwise to a stirred suspension of sodium hydride (0.32 g, 8.0 mmol) in dry THF (12 $cm^3$) under nitrogen. After 1 h, the mixture was filtered through a pad of Celite and the solvent removed under reduced pressure to yield (+)-(3*R*,4*R*)-3,4-epoxy-7-methoxy-2,2-dimethylchromane **4** (0.38 g, 97%). A sample of the crude product was purified by distillation, under reduced pressure, to give the epoxide **4** as a colourless oil, bp 65 °C (oil bath)/0.003 mmHg [lit.,[6] mp 45–46 °C (racemate)]; $[\alpha]_D$ +16 (*c* 0.76, $CHCl_3$); $\delta_H(CDCl_3)$ 1.26 (3 H, s, Me), 1.58 (3 H, s, Me), 3.45 (1 H, d, $J_{3,4}$ 4.6, 3-H), 3.76 (3 H, s, OMe), 3.88 (1 H, d, $J_{4,3}$ 4.6, 4-H), 6.38 (1 H, d, $J_{8,6}$ 2.4, 8-H), 6.49 (1 H, dd, $J_{6,5}$ 8.3, $J_{6,8}$ 2.4, 6-H) and 7.23 (1 H, d, $J_{5,6}$ 8.3, 5-H).

Cyclization of the bromohydrin **29**, $[\alpha]_D$ −39 (0.52 g, 1.81 mmol) was carried out in an identical manner to yield (−)-(3*S*,4*S*)-3,4-epoxy-7-methoxy-2,2-dimethylchromane **4** (0.35 g, 95%), $[\alpha]_D$ −16 (*c* 0.42, $CHCl_3$). The spectral data for the (+)- and (−)-enantiomers of the epoxide **4** were identical.

**(+)-(3*R*,4*R*)-*cis*- and (−)-(3*R*,4*S*)-*trans*-7-Methoxy-2,2-dimethylchromane-3,4-diol 6 and 5**

The epoxide **4** $[\alpha]_D$ +16 (204 mg, 1.0 mmol) was stirred overnight in THF (35 $cm^3$) and water (35 $cm^3$) in the dark at room temperature. The THF was removed under reduced pressure and the residue was extracted with ethyl acetate (2 × 25 $cm^3$). The combined extracts were dried ($Na_2SO_4$), and evaporated under reduced pressure to afford the crude mixture of diols **5** and **6**. Separation of the diols was effected by preparative TLC on silica gel (10% THF–dichloromethane) to yield the less polar ($R_F$ 0.31) (+)-(3*R*,4*R*)-*cis*-7-methoxy-2,2-dimethylchromane-3,4-diol **6** (43 mg, 19%), and the more polar ($R_F$ 0.17) (−)-(3*R*,4*S*)-*trans*-7-methoxy-2,2-dimethylchromane-3,4-diol **5** (81 mg, 36%).

A sample of the (+)-(3*R*,4*R*)-*cis*-diol **6** was further purified by normal phase HPLC (Zorbax Sil, 25 × 0.94 cm, 20% THF–dichloromethane, 2.0 $cm^3$ $min^{-1}$) to yield a white solid, mp 79–81 °C [lit.,[6] mp 101–102 °C (racemate)]; $[\alpha]_D$ +6.6 (*c* 0.5, ethanol); $\delta_H(CDCl_3)$ 1.29 (3 H, s, Me), 1.47 (3 H, s, Me), 2.16 (1 H, br s, OH), 2.58 (1 H, br s, OH), 3.67 (1 H, d, $J_{3,4}$ 3.7, 3-H), 3.76 (3 H, s, OMe), 4.76 (1 H, d, $J_{4,3}$ 3.7, 4-H), 6.35 (1 H, d, $J_{8,6}$ 2.2, 8-H), 6.54 (1 H, dd, $J_{6,5}$ 8.5, $J_{6,8}$ 2.2, 6-H) and 7.40 (1 H, d, $J_{5,6}$ 8.5, 5-H).

A sample of the (−)-(3*R*,4*S*)-*trans*-diol **5** was further purified by normal phase HPLC (using the same column and conditions as for the *cis*-diol **6**) to yield a colourless oil [lit.,[6] mp 124.5–125.5 °C (racemate)]; $[\alpha]_D$ −42.0 (*c* 0.9, ethanol); $\delta_H(CDCl_3)$ 1.29 (3 H, s, Me), 1.47 (3 H, s, Me), 2.16 (1 H, br s, OH), 2.58 (1 H, br s, OH), 3.67 (1 H, d, $J_{3,4}$ 3.7, 3-H), 3.76 (3 H, s, OMe), 4.76 (1 H, d, $J_{4,3}$ 3.7, 4-H), 6.35 (1 H, d, $J_{8,6}$ 2.2, 8-H), 6.54 (1 H, dd, $J_{6,5}$ 8.5, $J_{6,8}$ 1.8, 6-H) and 7.33 (1 H, d, $J_{5,6}$ 8.5, 5-H).

**(−)-(3*S*,4*S*)-*cis* and (+)-(3*S*,4*R*)-*trans*-7-Methoxy-2,2-dimethylchromane-3,4-diol 6 and 5**

Hydrolysis of the epoxide (−)-**4**, $[\alpha]_D$ −16 (188 mg, 0.91 mmol) provided (−)-(3*S*,4*S*)-*cis*-diol **6** (37 mg, 18%), mp 79–81 °C; $[\alpha]_D$ −6.9 (*c* 0.6, ethanol) and (+)-(3*S*,4*R*)-*trans*-diol **5** (77 mg, 37%), $[\alpha]_D$ +43.9 (*c* 0.7, ethanol).

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