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Synthesis and biological evaluation of flavan-3-ol derivatives as positive modulators of $GABA_A$ receptors

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ABSTRACT

We herein describe the synthesis and positive modulatory activities of a small library of flavan-3-ol derivatives on $\alpha_1\beta_2\gamma_{2L}$ $GABA_A$ receptors. Structure–activity relationships of various substituents on the A, B and C rings were evaluated in a functional electrophysiological assay. A *trans* configuration and a 3-acetoxy moiety are essential for activity. Substitution of the B ring appears to be well tolerated, with substituents on the A ring playing a major role in determining activity.

1. Introduction

$GABA_A$ receptors are ligand-gated chloride channels consisting of a heteropentameric assembly of proteins derived from a family of 16 genes: α_{1-6}, β_{1-3}, γ_{1-3}, δ, π, ε and θ.[1] Although there are a vast number of possible subunit combinations, only 20 native combinations occur in the mammalian central nervous system; the most common receptor subtypes contain α_1, β_2 and γ_2 subunits in a 2:2:1 ratio.[2] $GABA_A$ receptors have a diverse range of allosteric binding sites and enhancement of the GABAergic responses at $GABA_A$ receptors is the mechanism of action for a range of important therapeutic agents such as benzodiazepines, barbiturates and some general anesthetics. Other allosteric modulators include steroids, ethanol and an extensive range of natural compounds including flavonoids.

Flavonoids were first linked to $GABA_A$ receptors as a result of their ability to inhibit the binding of benzodiazepines to brain membranes.[3] Many subsequent studies demonstrated that a range of naturally-occurring and synthetic flavonoids bind to this site with nanomolar affinity, displacing radiolabelled benzodiazepines from rat and bovine brain tissue.[4,5] These results in combination with behavioural studies, which indicated that many flavonoids exhibit anxiolytic activity in rodents, suggested that flavonoids mediate their activity via the benzodiazepine site at $GABA_A$ receptors. Subsequently, functional electrophysiological studies using recombinant receptors demonstrated that flavonoids modulate $GABA_A$ receptors at a site independent of the classical high-affinity, flumazenil-sensitive benzodiazepine binding site.[6–10]

Catechins are a group of naturally-occurring flavonoids that share the flavan (3,4-dihydro-2-phenyl-2*H*-1-benzopyran) basic backbone. Compared to flavones, catechins have a saturated bond between C2 and C3 of the C-ring (Fig. 1), which makes the molecule less planar and reportedly less able to bind to the high-affinity benzodiazepine binding site.[6,11–13] However, a number of catechins have demonstrated modulatory activity at $GABA_A$ receptors. (+)-Catechin and (−)-epicatechin, as well as their 3-gallate derivatives, have been reported to exhibit negative modulatory action at $\alpha_1\beta_2$ $GABA_A$ receptors.[14] Subsequently, (−)-epigallocatechin gallate (EGCG), a major component of green tea, was shown to inhibit GABA-elicited currents at $\alpha_1\beta_2\gamma_{2L}$ $GABA_A$ receptors in addition to

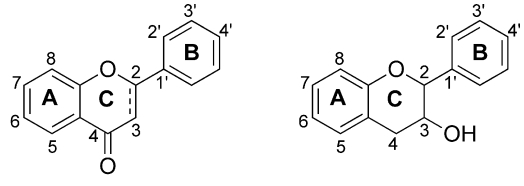

Figure 1. Structure and numbering of flavan skeleton.

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enhancing the positive modulatory effect of diazepam.[15] Recently, we described the flumazenil-insensitive positive modulatory action of 3-acetoxy-4′-methoxyflavans at human recombinant α_1, α_2, α_3 and α_5 containing $\alpha\beta\gamma$ $GABA_A$ receptors.[7]

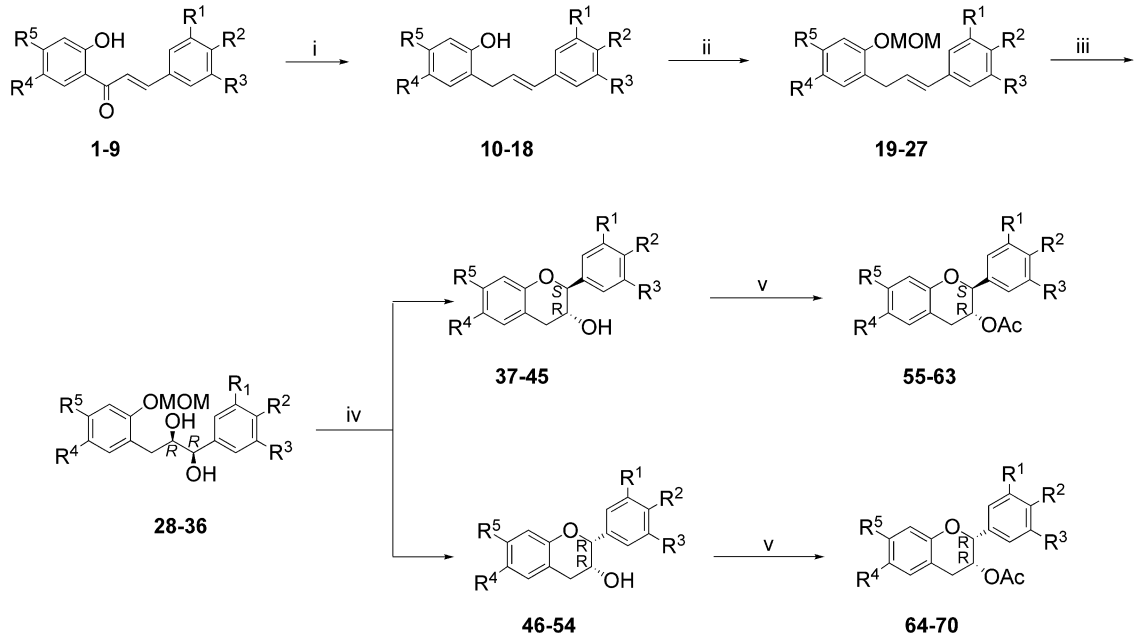
Many structure–activity studies of flavonoids acting at $GABA_A$ receptors have been described. However, these studies have been based on the results of ligand-binding assays on brain tissue, which includes a mixture of receptor subtypes that have different binding affinities for benzodiazepines.[11,12,16–18] The present study characterises the structure–activity of a series of relatively simple flavan-3-ol derivatives in a functional assay using human recombinant $\alpha_1\beta_2\gamma_{2L}$ $GABA_A$ receptors expressed in *Xenopus laevis* oocytes.

2. Results and discussion

The flavan-3-ol acetates were prepared by the synthetic route previously developed by van Rensberg et al.,[19] with some early modifications for the preparation of intermediate MOM-protected (*E*)-1,3-diarylpropenes. (*E*)-2′-Hydroxy-4-methoxychalcone (**1**) and a number of substituted analogues (**2**–**9**) were prepared by the base catalysed condensation of the appropriately substituted acetophenones and benzaldehdes. The chalcones were reduced to the unprotected (*E*)-1,3-diarylpropenes (**10**–**18**) as previously reported for **10**;[20] via protection of the 2′-hydroxy function, subsequent reduction with $NaBH_4$ and finally treatment with dilute acid (Scheme 1). While this reduction frequently afforded small yields of both the over-reduced product and the positional ene isomer, these could be removed by a combination of preparative chromatography and recrystallisation. Treatment of the unprotected (*E*)-1,3-diarylpropenes with methoxymethyl chloride (MOMCl) and an organic base afforded the corresponding MOM protected (*E*)-1,3-diarylpropenes (**19**–**27**) in high yields (Scheme 1). In the case of (**19**), NMR data were identical to those reported for this compound by van Rensburg, thereby establishing that the assignment of the position of the double bond was correct.

Treatment of the MOM-protected (*E*)-propenes (**19**–**27**) at initially 0 °C, then 2–4 °C, for ⩾2 days with AD-mix-β[21] in the standard 2-phase *t*-BuOH/water system afforded the (1*R*,2*R*)-*syn*-diols (**28a**–**35a**) in good yields (Scheme 1). On some occasions, small quantities of a second product, tentatively identified as the over-oxidised hydroxyketone by analysis of the ^1H and ^{13}C NMR spectra, could be isolated. The corresponding (1*S*,2*S*)-*syn*-diols (**28b**, **29b**, **31b**, **33b**, **35b** and **36b**) were obtained similarly using AD-mix-α.[21] Initially, the absolute configuration of the diols was tentatively assigned according to the Sharpless model.[21,22] However, the later determination of the absolute configuration of *trans*-(2*S*,3*R*)-3′-bromo-4′,5′-dimethoxyflavan-3-ol (**41a**) by X-ray analysis (vide infra) confirmed this tentative assignment, and, by extrapolation, the other assignments.

As observed by van Rensburg et al.,[19] the simultaneous deprotection and cyclisation of the diols (**28**–**36**) in the presence of 3 M HCl yielded a mixture of the *trans*- (**37**–**45**) and *cis*-flavan-3-ols (**46**–**54**) (Scheme 1).[19] While the ratio of *trans*:*cis* isomers varied slightly depending on the substitution patterns, a ratio of approximately 3:1 was obtained. Although the acetate derivatives of these compounds have been the most thoroughly investigated in our pharmacological assays to date, our eventual aims include the possible preparation of flavan-3-ol esters with a variety of acyl and aryl groups. Consequently, the *trans*- (**37**–**45**) and *cis*-flavan-3-ols (**46**–**54**) were separated with difficulty by chromatography at this stage rather than by the in situ conversion to and separation of the acetates derivatives. The acetates (**55**–**70**) were subsequently obtained from the corresponding isolated flavan-3-ols in near quantitative yields by treatment of the flavan-3-ols with acetic anhydride/pyridine. Following the precedent of van Rensburg et al.,[19] the optical purity of the acetates was determined by ^1H NMR spectroscopy using [Eu(hcf)$_3$] as the chiral shift reagent; as observed by the South African group, the acetates consistently showed the presence of only one detectable enantiomer, thereby indicating an excellent enantiomeric excess (nominally 99%). Deprotection of the benzyl ether protected acetates (**61a**, **62a**,**b**,



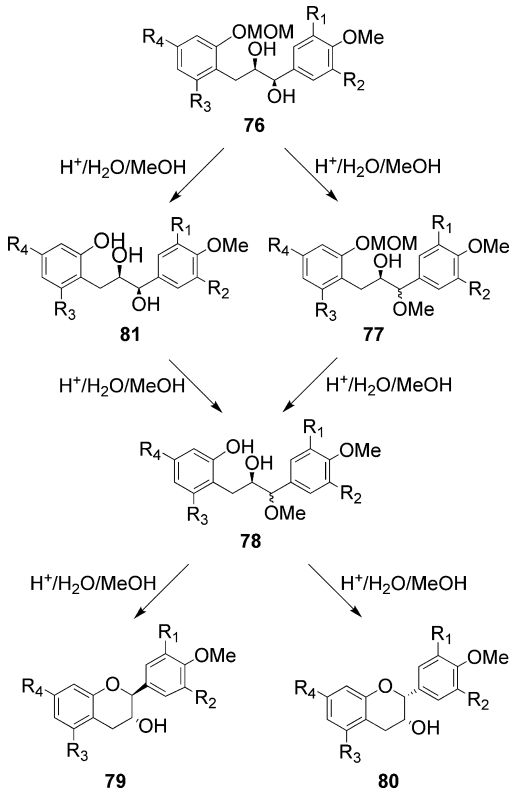
Scheme 1. Reagents and conditions: (i) EtOC(O)Cl/TEA/THF, then $NaBH_4/H_2O$, then H^+; (ii) MOMCl/$(i\text{-Pr})_2$NEt/THF; (iii) AD-mix-β or AD-mix-α/$MeSO_2NH_2/H_2O$/BuOH, 0–4 °C; (iv) 3 M HCl/MeOH–H_2O; (v) Ac_2O/pyridine. **1**, **10**, **19**, **28a**,**b**, **37a**,**b**, **46a**,**b**, **55a**,**b**, **64**,**a**,**b** $R^1 = R^3 = R^4 = R^5 = H$, R^2 = OMe; **2**, **11**, **20**, **29a**,**b**, **38a**,**b**, **47a**,**b**, **56a**,**b**, **65**,**a**,**b** $R^3 = R^4 = R^5 = H$, $R^1 = R^2$ = OMe; **3**, **12**, **21**, **30a**, **39a**, **48a**, **57a**, **66a** $R^1 = R^3 = R^5 = H$, $R^2 = R^4$ = OMe; **4**, **13**, **22**, **31a**,**b**, **40a**,**b**, **49a**,**b**, **58a**,**b**, **67b** $R^3 = R^5 = H$, $R^1 = R^2$ = OMe, R^4 = Me; **5**, **14**, **23**, **32a**, **41a**, **50a**, **59a** $R^4 = R^5 = H$, $R^2 = R^3$ = OMe, R^1 = Br; **6**, **15**, **24**, **33a**,**b**, **42a**,**b**, **51a**,**b**, **60a**,**b**, **68a**,**b** $R^3 = R^4 = R^5 = H$, $R^1 = R^2 = OCH_2O$; **7**, **16**, **25**, **34a**, **43a**, **52a**, **61a**, **69a** $R^1 = R^3 = R^4 = H$, R^2 = OMe, R^5 = OBn; **8**, **17**, **26**, **35a**,**b**, **44a**,**b**, **53a**,**b**, **62a**,**b** $R^3 = R^4 = H$, $R^1 = R^2$ = OMe, R^5 = OBn; **9**, **18**, **27**, **36b**, **45b**, **54b**, **63b**, **70b** $R^1 = R^3 = R^4 = R^5 = H$, R^2 = OBn. a: configuration shown, b: enantiomer.

63b, **69a**, **70b**) by hydrogenolysis over Pearlman's catalyst afforded (**71a**, **72a**,**b**, **73b**, **74a**, **75b**) (Scheme 2).

Analytical and spectroscopic data was consistent with the proposed structures. However, it is worth noting that although the enantiomerically pure *trans*-acetates (**56a**) and (**56b**) which had identical ^{1}H and ^{13}C NMR spectra gave different melting points. A repeat synthesis of both **56a** and **56b** from diols prepared using different batches of AD-mixes also resulted in products with melting points that were consistent with the original observations, and no problems were found with the melting points of either the parent 3-ols (**38a** and **38b**) or the corresponding *cis*-enantiomers. As a result, the different melting points of **56a** and **56b** were ascribed to polymorphism. However, this has not been confirmed as crystals suitable for X-ray diffraction have been unobtainable.

van Rensburg et al.[19] have proposed that the cyclisation of methoxylated diol (**76**) proceeds stepwise (Scheme 3); initially via a mixture of the *syn:anti* isomers (**77**) generated by an S_N1-type acid-catalysed methanolysis of the C-1 benzylic hydroxy group, a subsequent acid catalysed deprotection of the MOM ether on **77** to yield **78** and, in a final step, an S_N1 cyclisation of an incipient carbocation derived from **78** to afford predominantly the thermodynamically more stable *trans*-flavan-3-ol isomer (**79**) and smaller amounts of the *cis*-isomer (**80**). In the case of more highly substituted polymethoxylated compounds such as (**76**; $R^1 = R^3 = R^4 = OMe$, $R^2 = H$), intermediates (**77**; $R^1 = R^3 = R^4 = OMe$, $R^2 = H$) and (**78**; $R^1 = R^3 = R^4 = OMe$, $R^2 = H$) were reported as readily separated.

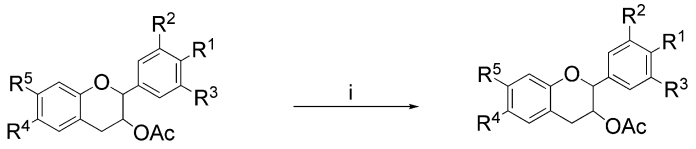
In the course of our investigation, we have found that with a *syn*-diol having both an unsubstituted A-ring and a highly substituted B-ring such as (**32a** (**76;** $R^1 = Br$, $R^2 = OMe$, $R^3 = R^4 = H$) Scheme 3), the cyclisation reaction, besides requiring protracted reaction times of up to several weeks to accomplish even a moderate conversion to the flavan-3-ol, appears to follow a different pathway with the 'triol' (**81**; $R^1 = Br$, $R^2 = OMe$, $R^3 = R^4 = H$) being both the first intermediate isolated and the major product after 3–5 days heating; (**81**; $R^1 = Br$, $R^2 = OMe$, $R^3 = R^4 = H$) was subsequently shown to be a precursor of (**78**; $R^1 = Br$, $R^2 = OMe$, $R^3 = R^4 = H$), and (**78**; $R^1 = Br$, $R^2 = OMe$, $R^3 = R^4 = H$) to be a precursor of the flavanols (**41a** (**79**; $R^1 = Br$, $R^2 = OMe$, $R^3 = R^4 = H$)) and (**50a** (**80**; $R^1 = Br$, $R^2 = OMe$, $R^3 = R^4 = H$)) by independent reactions. No species such as (**77**; $R^1 = Br$, $R^2 = OMe$, $R^3 = R^4 = H$) could be detected and this would suggest that, with these more hindered compounds, the acid catalysed hydrolysis of the MOM ether functionality, despite the suggestion by van Rensburg et al.[19] of a remarkably high stability towards acid hydrolysis in the compounds investigated, proceeds far more rapidly than methoxylation at C(1).



Scheme 3.

X-ray analyses of *trans*-(2*S*,3*R*)-4′-methoxyflavan-3-ol (**37a**), *trans*-(2*S*,3*R*)-3-acetoxy-4′-methoxyflavan (**55a**) and *cis*-(2*R*,3*R*)-3-acetoxy-4′-methoxyflavan (**64a**) confirmed the structure and relative stereochemistry for these products (Fig. 2A, C and D, respectively). In view of the fact that the absolute configuration of *trans*-(2*S*,3*R*)-3′-bromo-4′,5′-dimethoxyflavan-3-ol (**41a**, Fig. 2B), prepared by an identical route, was unambiguously established by X-ray analysis, it is reasonable to infer that the absolute configurations of both **37a** and **55a** are indeed *trans*-(2*S*,3*R*)- and that the assigned absolute configurations of other acetates are also correct.

The fused ring system of structures reported for **37a** and **41a** both exhibit similar features to the structure previously reported for 8-bromotetra-*O*-methyl-(+)-catechin.[23] The six aromatic carbons of the A-ring all lie close to their mean plane, with the maximum deviation of 0.6 picometres (pm) from the plane of ring A



61a (2*S*, 3*R*) R^1=OMe, R^2=R^3=R^4=H, R^5=OBn
62a (2*S*, 3*R*) R^1=R^2=OMe, R^3=R^4=H R^5=OBn
62b (2*R*, 3*S*) R^1=R^2=OMe, R^3=R^4=H R^5=OBn
63b (2*R*, 3*S*) R^1=OBn, R^2=R^3=R^4=R^5=H
69a (2*R*, 3*R*) R^1=OMe, R^2=R^3=R^4=H, R^5=OBn
70b (2*S*, 3*S*) R^1=OMe, R^2=R^3=R^4=H, R^5=OBn

71a (2*S*, 3*R*) R^1=OMe, R^2=R^3=R^4=H, R^5=OH
72a (2*S*, 3*R*) R^1=R^2=OMe, R^3=R^4=H R^5=OH
72b (2*R*, 3*S*) R^1=R^2=OMe, R^3=R^4=H R^5=OH
73b (2*R*, 3*S*) R^1=OH, R^2=R^3=R^4=R^5=H
74a (2*R*, 3*R*) R^1=OMe, R^2=R^3=R^4=H, R^5=OH
75b (2*S*, 3*S*) R^1=OMe, R^2=R^3=R^4=H, R^5=OH

Scheme 2. Reagents: (i) $Pd(OH)_2$–C/H_2 in MeOH/THF.

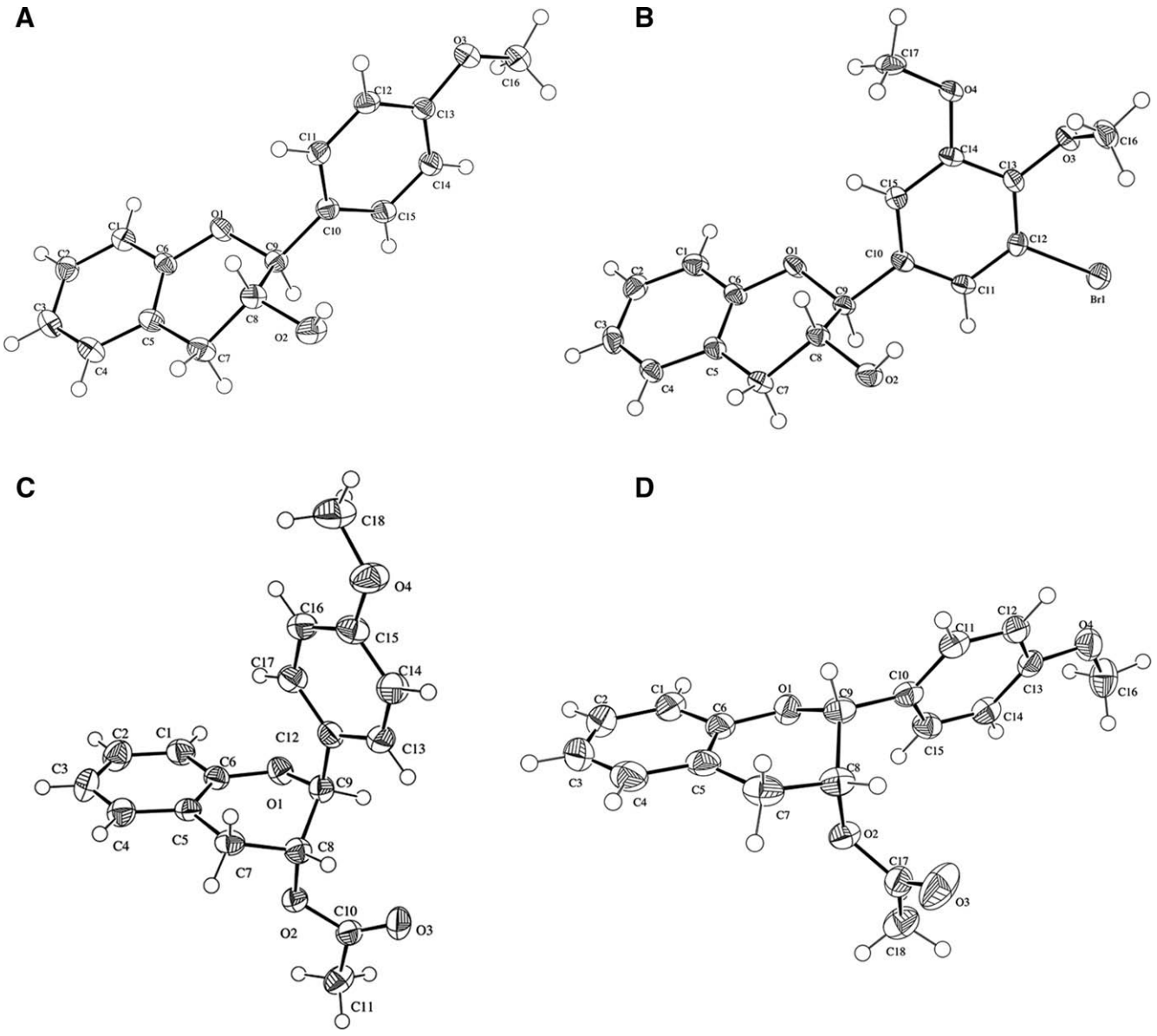


Figure 2. Structures of (A) **37a**, (B) **41a**, (C) **55a** and (D) **64a**. Displacement ellipsoids are drawn at the 50% probability level.

in compound **41a**. The puckering of the heterocyclic ring is most evident at C(2) and C(3). These two atoms lie on opposite sides of the mean plane of the aromatic ring with C(2) below the mean plane and C(3) above the plane. Equatorial positions are adopted by both the aromatic ring bonded to C(2) and the hydroxyl group bonded to C(3). In the solid state, 8-bromotetra-*O*-methyl-(+)-catechin exists in a conformation between a C(2)-sofa and a C-2,C-3-half-chair.[23] Similarly, both **37a** and **41a** exist in a conformation between a reverse C(2),C(3)-half-chair and a reverse C(2)-sofa.

In the case of **64a**, the six aromatic carbons also lie close to their mean plane with a maximum deviation of 1.5 pm. However, in contrast to compounds **37a** and **41a**, the C(2) lies above the mean plane and C(3) below the plane. The aromatic ring bonded to C(2) is in the equatorial position with the acetoxy group bonded to the C(3) position axial. This is consistent with the structure of (−)-epicatechin, which exists in the solid state in a half-chair distorted towards a C(2)-sofa.[24] Interestingly, the presence of an acetoxy group in the C3 position of **64a** results in a solid state structure that is closer to a half-chair conformation than (−)-epicatechin; with C(2) and C(3) deviations from the plane of 44.3 pm and −37.3 pm in **64a** compared to 26.3 pm and −49.5 pm in (−)-epicatechin.[24]

The six aromatic carbons of **55a** lie close to their mean plane with a maximum deviation of 1.0 pm, with the C(2) and C(3) lying below and above the plane, respectively. Both the aromatic ring bonded to C(2) and the acetoxy group bonded to the C(3) are in the axial positions, which is consistent with the structure reported for penta-*O*-acetyl-(+)-catechin,[25] indicating that the presence of the acetoxy group leads to the axial–axial conformation. In the solid state. The conformation of heterocyclic ring of **55a** is a reverse half-chair distorted towards a reverse C(3)-sofa, similar to that of **37a** and **41a**. However, penta-*O*-acetyl-(+)-catechin adopts a conformation that is close to a reverse half-chair.[25]

These structures confirm that the conformation of the heterocyclic ring in the solid state is determined by the nature of the C(2) and C(3) substituents. However, in solution, it has been demonstrated that it is likely that the heterocyclic ring undergoes a rapid interconversion of conformations,[25] and this is supported by the coupling constants determined for $J_{2,3}$, $J_{3,4a}$ and $J_{3,4b}$ of **37a** (8.3, 5.6 and 9.4 Hz, respectively), **41a** (8.3, 5.5 and 9.4 Hz, respectively),

64a (unresolved, 4.6 and 2.0 Hz, respectively) and **55a** (6.4, 5.0 and 6.6 Hz, respectively).

To determine the structural requirements for positive modulation of the GABA response at $\alpha_1\beta_2\gamma_{2L}$ $GABA_A$ receptors by flavans, the current study examines the effects of varying substitutions on simplified analogues of (−)-epigallocatechin gallate by determining the potentiation of the GABA EC_5 responses elicited by the coapplication of 30 μM flavan-3-ols and acetate derivatives. A dose of 30 μM was selected as some compounds used in this study were insoluble at higher doses. To account for inter-cell variability, all responses were normalised to the response of 30 μM **55a**, our lead compound, which enhances the response of the GABA EC_5 dose by 700%, with an EG_{50} of 13.7 ± 0.9 μM.[7]

Previous studies have indicated that EGCG is a negative modulator at $GABA_A$ receptors.[15] In contrast, all flavan compounds in this study were found to be positive modulators of $\alpha_1\beta_2\gamma_{2L}$ $GABA_A$ receptors and to effectively potentiate currents elicited by a low concentration (EC_5) of GABA (Fig. 3). Previous research on all four stereoisomers of 3-acetoxy-4′-methoxyflavan demonstrated that the *trans* isomers are more active than their *cis* counterparts with the *trans*-(2*S*,3*R*)-isomer being the most active stereoisomer.[7] Without exception, the *trans*-(2*S*,3*R*)-isomer was also found to be the most active isomer for all compounds in the current study.

The presence of an acetoxy group at the C3 position has been found to be a necessary requirement for activity. The parent hydroxy compounds, **37a** and **46a**, exhibited a 75% decrease in enhancement of the $GABA_A$ EC_5 response compared to the corresponding acetylated compounds **55a** and **55b**, respectively. A possible explanation for this is that the carbonyl of the acetoxy moiety interacts with the same residue in the binding site as the carbonyl of the pyranone ring in flavones and flavanones that are also positive modulators at $GABA_A$ receptors.[8,9]

The substitution pattern of the B-ring of the flavan was also found to be important for activity. The 3′,4′-dimethoxyl compounds **56a**, **56b** and **65b** demonstrated increased activity compared to that of the corresponding enantiomer of the 4′-methoxy compounds **55a**, **55b** and **64b**, respectively. One of the most efficacious compounds is **56a**, which elicited a maximal potentiation of approximately 1.2 times that of **55a** at a dose of 30 μM, when compared to the potentiation of **55a** on the same oocyte. The dose–response curve of **56a** demonstrates a maximal enhancement of 13.9 times the EC_5 of GABA with an EC_{50} value of 6.68 ± 1.38 μM (Fig. 4), approximately 1.7 times the maximal response of **55a**. This discrepancy is attributed to the receptors becoming unstable at maximal potentiation resulting in high variability. However, replacing the 3′,4′-dimethoxy substituents with the 3′,4′methylenedioxy moiety results in a decrease in activity of approximately 20% for **60a** and **60b** compared to **56a** and **56b**, respectively. Compound **59a**, which is essentially the 3′4′-dimethoxy compound **56a** with a bromo substituent *ortho* to the 4′-methoxy, showed a maximal efficacy similar to that of **55a**, but with increased potency (Fig. 4), having an EC_{50} of 3.17 ± 1.1 μM compared with 13.15 ± 1.00 μM.[7]

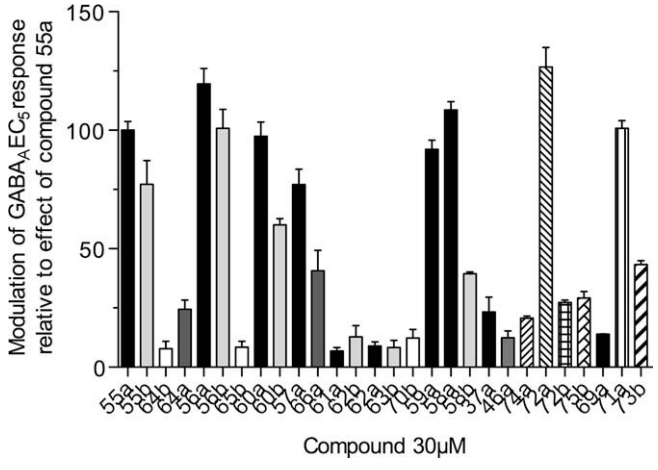


Figure 3. Comparison of enhancement of GABA EC_5 dose by compounds (30 μM) at $GABA_A$ $\alpha_1\beta_2\gamma_{2L}$ receptors relative to the effect of **55a** at 30 μM.

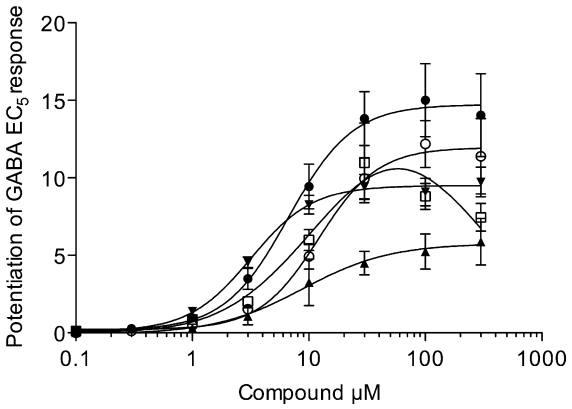


Figure 4. Enhancement of the response to EC_5 GABA dose GABA at $\alpha_1\beta_2\gamma_{2L}$ receptors by **56a** (●), **57a** (▲), **59a** (▼), **71a** (□) and **72a** (○) in the presence of GABA at $\alpha_1\beta_2\gamma_{2L}$. Data are expressed as mean ± SEM.

However, replacement of the 4′-methoxyl with a benzyloxy moiety resulted in a significant decrease in activity, with 30 μM **63b** and **70b** resulting in a maximal enhancement of 10% and 15%, respectively, of the enhancement resulting from 30 μM **55a**. This indicates that there are no large lipophilic pockets in the binding site surrounding the B-ring of the flavan. Replacement of the 4′-methoxyl of **55b** with a hydroxyl (**73b**) also resulted in significant loss of activity with **73b** only enhancing the GABA EC_5 response by 43% compared to 77% maximal enhancement by **55b**. Interestingly, in the case of the *cis*-(*S*,*S*) compound **64b** replacement of the 4′-methoxyl with a hydroxyl (**75b**) resulted in a fourfold increase in enhancement.

In the case of the *trans*-(2*S*,3*R*)-isomer, the presence of a methyl group at the C6 position, (**58a**), or a methoxyl group at the C6 position (**57a**), resulted in a decrease in the potentiation of the GABA EC_5 response, when compared to the potentiation of the corresponding compounds without a C6-substituent, **56a** and **55a**, respectively. However, there was little effect on the EC_{50} value for compound **57a** (EC_{50} = 14.95 ± 1.28 μM compared to EC_{50}=13.15 ± 1.00 μM for **55a**). In the case of the enantiomeric (2*R*,3*S*)-isomer (**58b**), C6 methyl substitution resulted in a 60% decrease in activity compared to that of (2*R*,3*S*)-3-acetoxy-3′,4′-dimethoxyflavan (**56b**).

In the *trans*-(2*S*,3*R*) compounds, a hydroxyl substituent at C7 is well tolerated, if not advantageous, with **71a** being equivalent in efficacy to **55a** at 30 μM and exerting a higher maximal enhancement than **55a** at a dose of 50 μM (10.5 vs 8.5-fold enhancement). Compound **72a** demonstrates a 10% increase in efficacy when compared to **56a**, the corresponding compound without the C7-hydroxyl. However, the dose–response curve of **72a** demonstrates a maximal enhancement of 12 times the EC_5 of GABA with an EC_{50} value of 12.15 ± 1.1 μM (Fig. 4), compared to a maximal enhancement of 14.7 times the EC_5 of GABA with an EC_{50} value of 6.68 ± 1.4 μM. These discrepancies are again attributed to the receptors becoming unstable at maximal potentiation resulting in high variability. Conversely, the *trans*-(2*R*,3*S*) compound **72b** exhibits a significant reduction in efficacy, having a maximal enhancement of 27% compared to the maximal enhancement by

56b of 100%. This suggests that the (2*S*,3*R*)- and the (2*R*,3*S*)-compounds bind in different orientations to each other. In the case of **74a**, the addition of a hydroxyl at the C-7 position resulted in a twofold increase in activity compared to compound **64a**.

Interestingly, **71a** displayed a bell-shaped dose–response curve with concentrations above 60 μM decreasing the potentiation of the GABA EC_5 response. Compound **55a** has previously been shown to exert a similar effect at high doses (>300 μM), possibly through open channel blockade.[7] The fact that **71a** exerts this blocking effect at lower concentrations suggests that manipulation of the affinity to this 'secondary' site may be achieved through appropriate substitutions at the C7 position. However, the precursor 7-benzyloxy compound **61a** and the other compounds incorporating a benzyloxy substituent, **62a**, **62b** and **69a** all displayed significantly decreased activity at 30 μM with a maximal enhancement of less than 12% of the activity of **55a** at the same concentration.

3. Conclusion

We have described the structure–activity relationships of a series of flavan-3-ol derivatives that enhance the response of $\alpha_1\beta_2\gamma_{2L}$ GABA receptors to GABA. Evaluation of the biological activity in a functional electrophysiological assay indicates that a *trans* configuration and a 3-acetoxy moiety is essential for activity. Although, substitution of the B ring appears to be well tolerated, substitution of the A ring plays a major role in determining activity. Compounds **56a** and 72a are two of the most efficacious positive modulators at $GABA_A$ $\alpha_1\beta_2\gamma_{2L}$ receptors. Further structure–activity studies and evaluation of flavan-3-ol derivatives as modulators of the GABA response is currently under investigation in our laboratories.

4. Experimental

4.1. General experimental

^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini-300 BB spectrometer at room temperature; for solutions in $CDCl_3$, TMS was employed as an internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75.5 MHz, referenced to the residual $CDCl_3$ signal at 77.0 ppm. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. High resolution mass spectra were recorded using atmospheric pressure chemical ionisation (APCI) on a Bruker 7T FTICR at The Mass Spectrometry Unit of the School of Chemistry, University of Sydney or electron ionisation (EI) on a Micromass Autospec at the Australian National University. All solvents were distilled before use. Anhydrous tetrahydrofuran (THF) was obtained by distillation from sodium/benzophenone ketal under an atmosphere of nitrogen. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} TLC aluminium plates; spots were visualised by UV light or by alkaline $KMnO_4$ spray. Short column vacuum chromatography (CC) was performed on Merck Kieselgel 60 H at water pump vacuum.

4.2. Crystallisation, data collection and refinement

X-ray crystallographic measurements were made with a Bruker Apex II diffractometer equipped with an Oxford Cryosystems Cobra. Graphite monochromated Mo Kα radiation (λ = 0.71073 Å) was used to collect the intensity data in the ω–2θ mode. Unit cell parameters and orientation matrix were obtained by least-squares refinement of the setting angles of 200 reflections. The structures were solved by direct methods (using SHELXS-97)[26] and refined using full-matrix least-squares on F^2 (using SHELXL-97),[26] using all unique data corrected for Lorentz and polarisation factors. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were refined in idealised positions, and given isotropic thermal parameters equal to 1.2 (or 1.5 for methyl groups) times the equivalent isotropic displacement parameter of the atom to which it is attached. For **41a** (Fig. 2B) the Flack Parameter (*X*) refined to 0.0000 with an esu of 0.0009, indicating the correct absolute configuration was refined. Material for publication was prepared using the WINGX suite of programs.[27]

4.3. General procedure for the preparation of (*E*)-4-methoxychalcones (1–9)

Aqueous KOH (7.0 g in 10 mL of H_2O) was added to a rapidly stirred solution of the appropriate 2′-hydroxyacetophenone (40 mmol) and the appropriately substituted 4-methoxybenzaldehyde (40 mmol) in EtOH (50–125 mL depending on solubility) at room temperature (or occasionally warmed slightly to facilitate solution). The mixture, which rapidly acquired a deep reddish colour and frequently deposited a copious, orange or orange-red precipitate, was stirred at room temperature for ⩾24 h, then poured into H_2O/ice (ca. 800 mL) and the mixture acidified (pH ⩽4) with vigorous stirring.

Where the resulting product was a yellow-orange precipitate, this was filtered, washed thoroughly with water and air-dried. Purification either by direct recrystallisation from EtOH or by CC and subsequent recrystallisation from EtOH gave the pure chalcone.

Where the resulting product was an oil or gum, the mixture was extracted with several portions of DCM, the combined DCM extracts washed in turn with H_2O and saturated brine, and the solution dried ($MgSO_4$). The residue obtained on concentration of the solution was purified as before by a combination of column chromatography and recrystallisation from EtOH to afford pure chalcone. Frequently, quantities of the corresponding flavanone could be recovered from the column upon further elution with a more polar solvent.

4.3.1. (*E*)-2′-Hydroxy-4-methoxychalcone (1)

Yellow-orange crystals; yield 79%; mp 93–94 °C (lit. mp 92 °C);[28] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.97 (1H, d of small coupling constant, O*H*), 7.93 (1H, dd, *J* = 1.7, 8.0 Hz, *H*-6′), 7.91 (1H, d, *J* = 15.5 Hz, CH=C*H*Ar), 7.64 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2 and *H*-6), 7.55 (1H, d with additional fine coupling, *J* = 15.5 Hz, CH=C*H*CO), 7.50 (1H, ddd with additional fine coupling, *J* = 1.7, 7.2, 8.3 Hz, *H*-4′), 7.03 (1H, dd with additional fine coupling, *J* = 1.2, 8.3 Hz, *H*-3′), 6.96 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3 and *H*-5), 6.95 (1H, ddd, *J* = 1.2, 7.2, 8.0 Hz, *H*-5′), 3.87 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 193.7, 163.6, 162.1, 145.3, 136.1, 130.5, 129.5, 127.5, 120.3, 118.72, 118.62, 117.9, 114.6, 55.4.

4.3.2. (*E*)-2′-Hydroxy-3,4-dimethoxychalcone (2)

Yellow-orange crystals; yield 83%; mp 116–117 °C (lit. mp 115–117 °C);[29] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.95 (1H, s, O*H*), 7.95 (1H, partly superimposed m (dd, *J* = 1.6, 8.2 Hz), *H*-6′), 7.90 (1H, d, *J* = 15.4 Hz, COCH=C*H*), 7.53 (1H, d, *J* = 15.4 Hz, COC*H*=CH), 7.50 (1H, partly superimposed m (ddd, *J* = 1.6, ca. 7.9, 8.4 Hz), *H*-4′), 7.28 (1H, dd, *J* = 2.1, 8.4 Hz, *H*-6), 7.18 (1H, d, *J* = 2.1 Hz, *H*-2), 7.04 (1H, dd, *J* = 1.1, 8.4 Hz, *H*-3′), 6.95 (1H, ddd, *J* = 1.2, ca. 7.9, 8.2 Hz, *H*-5′), 6.92 (1H, d, *J* = 8.4 Hz, *H*-5), 3.98 (3H, s, OCH_3), 3.95 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 193.7, 163.6, 152.0, 149.6, 145.6, 136.1, 129.6, 127.8, 123.5, 120.2, 118.73, 118.69, 118.1, 111.5, 110.8, 56.13, 56.09.

4.3.3. (*E*)-2′-Hydroxy-4,5′-dimethoxychalcone (3)

Orange crystals; yield 67%; mp 90–91 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.51 (1H, s, O*H*), 7.91 (1H, d, *J* = 15.4 Hz, COCH=C*H*),

7.64 (2H, aa′bb′ 'd', J = 8.8 Hz, H-2 and H-6), 7.48 (1H, dd, J = 15.4, <0.5 Hz, COCH=CH), 7.37 (1H, d, J = 3.0 Hz, H-6′), 7.14 (1H, dd, J = 3.0, 9.0 Hz, H-4′), 6.98 (1H, dd, J = <0.5, 9.0 Hz, H-3′), 6.96 (2H, aa′bb′ 'd', J = 8.8 Hz, H-3 and H-5), 3.88 (3H, s, OCH_3), 3.85 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ 193.4, 162.2, 158.0, 151.8, 145.5, 130.5, 127.5, 123.6, 119.9, 119.3, 117.9, 114.6, 113.2, 56.2, 55.5.

4.3.4. (*E*)-2′-Hydroxy-3,4-dimethoxy-5-methylchalcone (4)

Yellow-orange solid; yield 67%; mp 143–145 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.77 (1H, s, OH), 7.89 (1H, d, J = 15.3 Hz, C=CH-Ar), 7.70 (1H, dm (from decoupling experiment dq), J = 2.2 Hz, H-6′), 7.52 (1H, d, J = 15.3 Hz, C=CHCO), 7.32 (1H, dd (from decoupling experiment ddm), J = 2.2, 8.5 Hz, H-4′), 7.30 (1H, dd, J = 2.0, 8.3 Hz, H-6), 7.18 (1H, d, J = 2.0 Hz, H-2), 6.94 (1H, d, J = 8.5 Hz, H-3′), 6.93 (1H, d, J = 8.3 Hz, H-5), 3.98 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 2.37 (3H, s, ArCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 193.6, 161.6, 152.0, 149.5, 145.4, 137.2, 129.2, 127.9, 127.8, 123.4, 119.9, 118.4, 118.2, 111.5, 111.0, 56.2, 56.1, 20.6.

4.3.5. (*E*)-2′-Hydroxy-3-bromo-4,5-dimethoxychalcone (5)

Yellow-orange crystals; yield 37%; mp 131–133 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.77 (1H, s, OH), 7.93 (1H, dd, J = 1.6, 8.1 Hz, H-6′), 7.79 (1H, d, J = 15.4 Hz, COCH=CH), 7.55 (1H, d, J = 15.4 Hz, COCH=CH), 7.52 (1H, superimposed m (ddd, J = 1.6, ca. 7.4, 8.4 Hz), H-4′), 7.51 (1H, d, J = 2.0 Hz, H-2), 7.09 (1H, d, J = 2.0 Hz, H-6), 7.04 (1H, dd, J = 1.2, 8.4 Hz, H-3′), 6.97 (1H, ddd, J = 1.2, ca. 7.4, 8.1 Hz, H-5′), 3.95 (3H, s, OCH_3), 3.92 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 193.3, 163.6, 153.9, 148.7, 143.7, 136.5, 131.7, 129.6, 125.1, 120.4, 119.9, 118.9, 118.7, 118.3, 112.0, 60.8, 56.3.

4.3.6. (*E*)-2′-Hydroxy-3,4-methylenedioxychalcone (6)

Yellow crystals (EtOH); yield 62%, mp 139–141 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.92 (1H, s, OH), 7.92 (1H, dd, J = 1.6, 8.1 Hz, H-6′), 7.90 (1H, d, J = 15.4 Hz, COCH=CH), 7.50 (1H, superimposed m (ddd, J = 1.6, ca. 7.2, 8.4 Hz), H-4′), 7.50 (1H, d, J = 15.4 Hz, COCH=CH), 7.19 (1H, d, J = 1.6 Hz, H-2), 7.17 (1H, dd, J = 1.6, 8.1 Hz, H-6), 7.03 (1H, dd, J = 1.1, 8.4 Hz, H-3′), 6.95 (1H, ddd, J = 1.1, ca. 7.2, 8.1 Hz, H-5′), 6.87 (1H, d, J = 8.1 Hz, H-5), 6.05 (2H, s, OCH_2O); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 193.6, 163.6, 150.3, 148.6, 145.3, 136.2, 129.5, 129.2, 125.7, 120.2, 118.8, 118.7, 118.2, 108.8, 106.8, 101.8.

4.3.7. (*E*)-2′-Hydroxy-4-methoxy-4′-(phenylmethoxy)chalcone (7)

Yellow-orange crystals (EtOH); yield 35%; mp 135–136.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.56 (1H, s, OH), 7.87 (1H, d, J = 15.5 Hz, C=CH-Ar), 7.85 (1H, d, J = 9.7 Hz, H-6), 7.62 (2H, aa′bb′ 'd', J = 8.8 Hz, H-2′ and H-6′), 7.46 (1H, d, J = 15.5 Hz, C=CHCO), 7.46–7.28 (5H, m, 5 × benzyl Ar-H), 6.95 (2H, aa′bb′ 'd', J = 8.8 Hz, H-3′ and H-5′), 6.56 (1H, dd, J = 2.5, 9.7 Hz, H-5), 6.56 (1H, d, J = 2.5 Hz, H-3), 5.11 (2H, s, OCH_2), 3.87 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 192.0, 166.6, 165.2, 161.9, 144.3, 136.1, 131.2, 130.4, 128.7, 128.3, 127.7, 127.5, 118.1, 114.6, 114.5, 108.1, 102.3, 70.3, 55.4.

4.3.8. (*E*)-2′-Hydroxy-3,4-dimethoxy-4′-(phenylmethoxy)chalcone (8)

Yellow/orange crystals (EtOH); yield 68%; mp 131–133 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.55 (1H, s, OH), 7.86 (1H, m, H-6′), 7.855 (1H, d, J = 15.3 Hz, CH=CHCO), 7.46–7.32 (5H, m, 5 × benzyl Ar-H), 7.44 (1H, d, J = 15.3 Hz, CH=CHCO), 7.25 (1H, dd, J = 2.0, 8.3 Hz, H-6), 7.16 (1H, d, J = 2.0 Hz, H-2), 6.91 (1H, d, J = 8.3 Hz, H-5), 6.59–6.55 (2H, 2 × superimposed m, H-3′ and H-5′), 5.12 (2H, s, OCH_2), 3.97 (3H, s, OCH_3), 3.95 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 191.9, 166.6, 165.2, 151.8, 149.5, 144.6, 136.0, 131.2, 128.7, 128.3, 128.0, 127.5, 123.3, 118.2, 114.5, 111.4, 110.7, 108.1, 102.3, 70.3, 56.10, 56.06.

4.3.9. (*E*)-2′-Hydroxy-4-(phenylmethoxy)chalcone (9)

Yellow-orange crystals; yield 79%; mp 116.5–117 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.95 (1H, s, OH), 7.92 (1H, dd, J = 1.5, ca. 8.1 Hz, H-6′), 7.91 (1H, d, J = 15.6 Hz, COCH=CH), 7.64 (2H, aa′bb′ 'd', J = 8.8 Hz, H-2 and H-6), 7.55 (1H, d, J = 15.6 Hz, COCH=CH), 7.49 (1H, ddd, J = 1.5, ca. 7.5, ca. 7.5 Hz, H-4′), 7.46–7.32 (5H, m, 5 × benzyl Ar-H), 7.03 (1H, superimposed m (dd, J = 1.2, ca. 7.5 Hz), H-3′), 7.03 (2H, aa′bb′ 'd', J = 8.8 Hz, H-3 and H-5), 6.94 (1H, ddd, J = 1.2, ca. 7.5, ca. 8.1 Hz, H-5′), 5.13 (2H, s, OCH_2); ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ 193.7, 163.7, 161.3, 145.2, 136.5, 136.1, 130.5, 129.6, 128.7, 128.2, 127.8, 127.5, 120.3, 118.73, 118.65, 118.0, 115.5, 70.3.

4.4. General procedure for ene (10–18) preparation

Ethyl chloroformate (2.6 g, 24 mmol) in THF (5 mL) was added dropwise with stirring to a solution of TEA (2.4 g, 24 mmol) and the appropriate chalcone (20 mmol) in THF (25–70 mL depending on solubility) under N_2 at 0–5 °C over ca. 20 min. The resulting mixture was then stirred at the same temperature for ⩾30 min (a small amount of product intermediate (or other) occasionally precipitated early in a small minority of reactions; in these cases additional solvent was then added to dissolve as much precipitated material as possible, the stirring was immediately discontinued and the mixture filtered). The insoluble amine salt was filtered, the filter cake washed with an additional volume of THF (⩾25 mL) and the filtrate added slowly to a vigorously stirred solution of $NaBH_4$ (3.04 g, 80 mmol) in H_2O (~50 mL) over ca. 10 min. with the temperature being maintained at less than 15 °C. The mixture was stirred at <15 °C for 1–2 h, then allowed to warm slowly to room temperature (the yellow/orange colour rapidly fading to creamy/colourless) and stirred at room temperature overnight. The reaction mixture was diluted with H_2O, cooled and acidified/neutralised (to pH 3.0–4.0) with dilute HCl, and extracted with DCM (several portions). The combined DCM extracts were washed in turn with H_2O and brine, and dried ($MgSO_4$). Concentration under reduced pressure afforded crude *product* as a colourless or faintly coloured solid that consisted predominantly of product (⩾90%) with smaller quantities of both the C=C positional isomer and the fully reduced product; reported ratios were determined from the ^{1}H NMR spectra of crude samples. One or several CC separations (solvent systems varied for individual compounds) of the crude material afforded impurity free *product* but recovery was rarely, if ever, complete and consequently yields are reported as total recovered mixture after the first separation. Where possible, solid products were recrystallised from either hexane or hexane/EtOAc to afford pure product as colourless crystals. Fortunately, incompletely separated mixtures obtained from CC consisting only of product and fully reduced product could be protected concurrently in the subsequent protection step and the unreactive saturated impurity (as its protected derivative) removed during chromatography of the later dihydroxylation product.

4.4.1. 2-[(2*E*)-3-(4-Methoxyphenyl)-2-propen-1-yl]phenol (10)

Colourless needles (hexane); yield mixed products 83%, mole ratio product/positional isomer/saturated 100:5:5; mp 96.5–97.5 °C [lit mp 98.5–99.5 °C];[30] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (aa′bb′ 'd', J = 8.8 Hz, H-2″ and H-6″), 7.16 (1H, superimposed m (non-resolved dd), H-3), 7.15 (1H, superimposed m (non-resolved ddd, J = 1.7, 7.5, n/m Hz), H-5), 6.90 (1H, ddd, J = 1.2, 7.5, 7.5 Hz, H-4), 6.83 (1H, aa′bb′ 'd', J = 8.8 Hz, H-3″ and H-5″), 6.82 (1H, super-

imposed m (dd), *H*-6), 6.46 (1H, incompletely resolved td, *J* = ca. 1.1, 15.9 Hz, *H*-3′), 6.24 (1H, td, *J* = 6.6, 15.9 Hz, *H*-2′), 5.01 (1H, s, O*H*), 3.79 (3H, s, OCH_3), 3.54 (2H, dd, *J* = 1.1, 6.6 Hz, CH_2-1′); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 159.2, 154.2, 131.1, 130.5, 130.1, 127.9, 127.4, 126.0, 125.7, 121.0, 115.9, 114.1, 55.3, 34.1.

4.4.2. 2-[(*E*)-3-(3,4-Dimethoxyphenyl)-2-propen-1-yl]phenol (11)

Colourless solid (hexane/EtOAc); yield 83%, mole ratio product/positional isomer/saturated 100:4:5; ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.18 (1H, superimposed m (dd, *J* = 1.7, ca. 7.4 Hz), *H*-3), 7.16 (1H, superimposed m (ddd, *J* = 1.7, 7.4, 8.1 Hz), *H*-5), 6.91 (1H, superimposed m (ddd, *J* = 1.2, ca. 7.4, ca. 7.4 Hz), *H*-4), 6.91 (1H, superimposed m (d, *J* = 2.0 Hz), *H*-2″), 6.89 (1H, superimposed m (dd, *J* = 2.0, 8.1 Hz), *H*-6″), 6.83 (1H, dd, *J* = 1.2, 8.1 Hz, *H*-6), 6.79 (1H, d, *J* = 8.1 Hz, *H*-5″), 6.46 (1H, td, *J* = ca. 1.1 15.7, Hz, *H*-3′), 6.25 (1H, td, *J* = 6.5, 15.7 Hz, *H*-2′), 5.04 (1H, s, O*H*), 3.88 (3.876) (3H, s, OCH_3), 3.87(3.872) (3H, s, OCH_3), 3.56 (2H, dd, *J* = 1.1, 6.5 Hz, CH_2-1′); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 154.2, 149.3, 148.8, 131.2, 130.53, 130.47, 127.9, 126.1, 126.0, 121.0, 119.4, 115.8, 111.6, 109.2, 56.0, 55.9, 34.0.

4.4.3. 2-[(*E*)-3-(4-Methoxyphenyl)-2-propen-1-yl)-4-methoxyphenol (12)

Colourless oil; yield 90%, mole ratio product/positional isomer/saturated 100:5:5; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (2H, aa′bb′ ‘d’, *J* = 8.8 Hz, *H*-2″ and *H*-6″), 6.83 (2H, aa′bb′ ‘d’, *J* = 8.8 Hz, *H*-3″ and *H*-5″), 6.76 (1H, ‘d’ (unresolved dd), *J* = 8.5 Hz, *H*-6), 6.74 (1H, ‘d’ (unresolved dd, *J* = 2.9 Hz, *H*-3), 6.69 (1H, dd, *J* = 2.9, 8.5 Hz, *H*-5), 6.45 (1H, td, *J* = ca. 1.3, 15.8 Hz, *H*-3′), 6.22 (1H, td, *J* = 6.5, 15.8 Hz, *H*-2′), 4.70 (1H, br s, O*H*), 3.80 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.03 (2H, dd, *J* = 1.3, 6.5 Hz, CH_2-1′); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 159.1, 154.0, 148.1, 131.1, 130.1, 127.4, 127.2, 125.5, 116.5, 116.1, 114.1, 112.7, 55.8, 55.3, 34.3.

4.4.4. 2-[(*E*)-3-(3,4-Dimethoxyphenyl)-2-propen-1-yl]-4-methylphenol (13)

Colourless solid; yield mixed products 82%, mole ratio product/positional isomer/saturated 100:4:4; mp 121–123 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 [1H, superimposed m (d, *J* = ca. 2.1 Hz), *H*-3], 6.95 [1H, superimposed m (dd, *J* = 2.1, 8.0 Hz), *H*-5]. 6.91 (1H, superimposed m (d, *J* = ca. 1.9 Hz), *H*-2″], 6.89 (1H, dd, *J* = 1.9, 8.0 Hz, *H*-6″), 6.80 (1H, d, *J* = 8.0 Hz, *H*-5″), 6.73 (1H, d, *J* = 8.0 Hz, *H*-6), 6.45 (1H, td, *J* = ca. 1.0, 15.7 Hz, *H*-3′), 6.24 (1H, td, *J* = 6.5, 15.7 Hz, *H*-2′), 4.88 (1H, s, O*H*), 3.87 (3.874) (3H, s, OCH_3), 3.87 (3.870) (3H, s, OCH_3), 3.52 (2H, dd, *J* = 1.0, 6.5 Hz, CH_2-1′), 2.27 (1H, s, ArCH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 151.9, 149.1, 148.7, 131.03, 130.99, 130.4, 130.1, 128.2, 126.2, 125.6, 119.3, 115.7, 111.3, 108.9, 56.0, 55.9, 34.1, 20.5.

4.4.5. 2-[(*E*)-3-(3-Bromo-4,5-dimethoxyphenyl)-2-propen-1-yl]phenol (14)

Colourless oil; mole ratio product/positional isomer/saturated 100:5:5 ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.12 (3H, 3 × superimposed m, unassigned *H*-3, *H*-5 and *H*-2″), 6.91 (1H, ddd, *J* = 1.2, 7.5, ca. 8.2 Hz, *H*-4), 6.82 (1H, d, *J* = 2.0 Hz, *H*-6″), 6.81 (1H, dd, *J* = 1.2, 8.0 Hz, *H*-6), 6.40–6.25 (2H, m, *H*-3′ and *H*-2′), 4.97 (1H, br s, O*H*), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.55 (2H, d, *J* = 4.8 Hz, CH_2-1′); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 153.9, 153.6, 145.7, 134.6, 130.5, 129.6, 129.0, 127.9, 125.6, 122.6, 121.0, 117.8, 115.7, 109.4, 60.7, 56.1, 33.8.

4.4.6. 2-[(2*E*)-3-(4-Methylenedioxyphenyl)-2-propen-1-yl]phenol (15)

Colourless needles (hexane/EtOAc); yield mixed products 88% mole ratio product/positional isomer/saturated 100:5:5; mp 93–94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16 (1H, unresolved superimposed m, *H*-3), 7.15 (1H, unresolved superimposed m (ddd, *J* = 1.8, ca. 7.6, n/m Hz), *H*-5), 6.90 (1H, superimposed m (ddd, *J* = ca. 1.2, n/m, n/m Hz), *H*-4), 6.90 (1H, superimposed m (d, *J* = 1.6 Hz), *H*-2″), 6.82 (1H, dm, *H*-6), 6.78 (1H, dd, *J* = 1.6, 8.0 Hz, *H*-6″), 6.73 (1H, dd, *J* = ⩽0.5, 8.0 Hz, *H*-5″), 6.42 (1H, td, *J* = ca. 1.0, 15.9, Hz, *H*-3′), 6.21 (1H, td, *J* = 6.6, 15.9 Hz, *H*-2′), 5.94 (2H, s, OCH_2O), 4.98 (1H, s, O*H*), 3.54 (2H, dd, *J* = 1.0, 6.6 Hz, CH_2-1′); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 154.1, 148.0, 147.0, 131.7, 131.1, 130.5, 127.9, 126.2, 125.8, 121.0, 120.7, 115.8, 108.3, 105.7, 101.0, 34.0. n/m not measurable.

4.4.7. 2-[(*E*)-3-(4-Methoxyphenyl)-2-propen-1-yl]-5-(phenylmethoxy)phenol (16)

Off-white solid (hexane/EtOAc); yield mixed products 83% mole ratio product/positional isomer/saturated 100:2:8; mp 101–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.30 (5H, m, 5 × benzyl Ar-*H*), 7.28 (2H, aa′bb′ ‘d’, *J* = 8.8 Hz, *H*-2″ and *H*-6″), 7.04 (1H, d, *J* = 8.3 Hz, *H*-3), 6.83 (2H, aa′bb′ ‘d’, *J* = 8.8 Hz, *H*-3″ and *H*-5″), 6.54 (1H, dd, *J* = 2.5, 8.3 Hz, *H*-4), 6.50 (1H, d, *J* = 2.5 Hz, *H*-6), 6.45 (1H, td, *J* = 1.1, 15.8 Hz, *H*-3′), 6.21 (1H, td, *J* = 6.5, 15.8 Hz, *H*-2′), 5.06 (1H, s, O*H*), 5.03 (2H, s, OCH_2), 3.80 (3H, s, OCH_3), 3.48 (2H, dd, *J* = 1.1, 6.5 Hz, CH_2-1′); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 159.1, 158.9, 155.1, 137.1, 130.88, 130.85, 130.0, 128.6, 127.9, 127.5, 127.4, 126.0, 118.3, 114.0, 107.3, 103.1, 70.2, 55.3, 33.6.

4.4.8. 2-[(*E*)-3-(3,4-Dimethoxyphenyl)-2-propen-1-yl]-5-(phenylmethoxy)phenol (17)

Colourless solid; yield 80%, mole ratio product/positional isomer/saturated 100:5:5; mp 124–125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.45–7.29 (5H, m, benzyl Ar-*H*). 7.06 (1H, d, *J* = 8.3 Hz, *H*-3), 6.90 (1H, d, *J* = 1.9 Hz, *H*-2″), 6.89 (1H, dd, *J* = 1.9, 8.0 Hz, *H*-6″), 6.79 (1H, d, *J* = 8.0 Hz, *H*-5″), 6.55 (1H, dd, *J* = 2.5, 8.3 Hz, *H*-4), 6.51 (1H, d, *J* = 2.5 Hz, *H*-6), 6.44 (1H, td, *J* = ca. 1.1, 15.8 Hz, *H*-3′), 6.22 (1H, td, *J* = 6.5, 15.8 Hz, *H*-2′), 5.12 (1H, s, O*H*), 5.03 (2H, s, OCH_2), 3.88 (3.875) (3H, s, OCH_3), 3.87 (3.870) (3H, s, OCH_3), 3.56 (2H, dd, *J* = 1.1, 6.5 Hz, CH_2-1′); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 158.9, 155.1, 149.2, 148.8, 137.2, 131.1, 130.9, 130.4, 128.6, 127.9, 127.4, 126.4, 119.4, 118.3, 111.5, 109.1, 107.4, 103.2, 70.2, 56.0, 55.9, 33.5.

4.4.9. 2-[(*E*)-3-[(4-Phenylmethoxy)phenyl]-2-propen-1-yl]phenol (18)

Off-white solid (hexane/EtOAc); yield mixed products 84% mole ratio product/positional isomer/saturated 100:2:6; 92–93.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.30 (5H, m, 5 × benzyl Ar-*H*), 7.28 (2H, aa′bb′ ‘d’, *J* = 8.8 Hz, *H*-2″ and *H*-6″), 7.16 (1H, d (or superimposed, non-resolved dd), *J* = ca. 7.5 Hz, *H*-3), 7.14 (1H, superimposed m (ddd, *J* = ca. 1.5, ca. 7.5, ca. 7.8 Hz), *H*-5), 6.90 (2H, aa′bb′ ‘d’, *J* = 8.8 Hz, *H*-3″ and *H*-5″), 6.90 (1H, superimposed m (ddd, *J* = 1.2, 7.5, 7.5 Hz), *H*-4), 6.82 (1H, dm, *J* = ca. 7.8 Hz, *H*-6), 6.46 (1H, td, *J* = 1.0, 15.9 Hz, *H*-3′), 6.24 (1H, td, *J* = 6.6, 15.9 Hz, *H*-2′), 5.05 (2H, s, OCH_2) 4.99 (1H, s, O*H*), 3.54 (2H, dd, *J* = 1.0, 6.6 Hz, CH_2-1′), ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ 158.3, 154.1, 137.0, 131.0, 130.4, 130.3, 128.6, 128.0, 127.9, 127.5, 127.4, 125.9, 125.8, 121.0, 115.8, 115.0, 70.1, 34.1.

4.5. General procedure for the preparation of MOM protected propenes (19–27)

Di-isopropylethylamine (5 mL, 29 mmol) was added dropwise with stirring to a solution of the appropriate MOM-protected unsaturated precursor (12.5 mmol) in anhydrous THF (ca. 25 mL) under N_2 at room temperature and the resulting solution was stirred at this temperature for 15–20 min. A solution of MOM-Cl (1.85 mL, 24.3 mmol) in anhydrous THF (5 mL) was

then added dropwise at room temperature under N_2 and the solution stirred at room temperature for 1 h, then refluxed for $\geqslant$4 d. The reaction mixture was cooled and concentrated under reduced pressure. The residue was partitioned between H_2O (ca. 75 mL) and DCM (50 mL) and the aq layer extracted further with DCM (3 × 25 mL). The combined DCM extracts were washed in turn with H_2O and brine, and dried ($MgSO_4$). Concentration gave a tan, viscous oil. Purification of the crude product by short column vacuum chromatography (hexane/DCM mixtures with the polarity later increased to speed elution) afforded the desired compound as a colourless oil or occasionally as a colourless solid.

4.5.1. 1-(Methoxymethoxy)-2-[(*E*)-3-(4-methoxyphenyl)-2-propen-1-yl]benzene (19)

Colourless oil; yield 92–99%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2″ and *H*-6″), 7.20 (1H, unresolved superimposed dd, *H*-3) 7.19 (1H, unresolved superimposed ddd, *H*-5), 7.08 (1H, dd, J = ca. 1.2, 8.2 Hz, *H*-6), 6.96 (1H, ddd, J = ca. 1.2, 7.3, 7.3 Hz, *H*-4), 6.82 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3″ and *H*-5″), 6.37 (1H, d (unresolved t of d), J = 15.8 Hz, *H*-3′), 6.23 (1H, td, J = 6.6, 15.8 Hz, *H*-2′), 5.22 (2H, s, OCH_2O), 3.79 (3H, s, $ArOCH_3$); 3.54 (2H, d, J = 6.6 Hz, *H*-1′), 3.48 (3H, s, CH_2OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ 158.9, 155.1, 130.7, 130.2, 130.1, 129.7, 127.4, 127.2, 126.8, 121.9, 114.2, 114.0, 94.6, 56.1, 55.3, 33.5.

4.5.2. 1-(Methoxymethoxy)-2-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]benzene (20)

Colourless oil; yield 94%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (1H, superimposed m (dd, J = 1.7, 7.4 Hz), *H*-3), 7.20 (1H, ddd, J = 1.7, 7.4, 8.3 Hz, *H*-5), 7.09 (1H, dd, J = 1.2, 8.3 Hz, *H*-6), 6.97 (1H, ddd, J = 1.2, 7.4, 7.4 Hz, *H*-4), 6.90 (1H, d, J = 1.9 Hz, *H*-2″), 6.87 (1H, dd, J = 1.9, 8.2 Hz, *H*-6″), 6.79 (1H, d, J = 8.2 Hz, *H*-5″), 6.37 (1H, d (probably d of unresolved t), J = 15.8 Hz, *H*-3′), 6.24 (1H, td, J = 6.4, 15.8 Hz, *H*-2′), 5.23 (2H, s, OCH_2O), 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.55 (2H, d, J = 6.4 Hz, CH_2-1′), 3.48 (3H, s, CH_2OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ 155.1, 149.2, 148.6, 131.1, 130.5, 130.2, 129.7, 127.5, 127.1, 121.9, 119.1, 114.3, 111.6, 109.1, 94.6, 56.1, 56.0, 55.9, 33.5.

4.5.3. 1-(Methoxymethoxy)-2-[(*E*)-3-(4-methoxyphenyl)-2-propen-1-yl]-4-methoxybenzene (21)

Colourless, viscous oil; yield 90%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2″ and *H*-6″), 7.02 (1H, d, J = 8.9 Hz, *H*-6), 6.82 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3″ and *H*-5″), 6.78 (1H, d, J = 3.1 Hz, *H*-3), 6.70 (1H, dd, J = 3.1, 8.9 Hz, *H*-5), 6.38 (1H, d (d of unresolved t), J = 15.8, Hz, *H*-3′), 6.21 (1H, td, J = 6.7, 15.8 Hz, *H*-2′), 5.13 (2H, s, OCH_2O), 3.78 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.51 (2H, (d)d, J = (ca. 0.7), 6.4 Hz, CH_2-1′), 3.47 (3H, s, CH_2OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ 158.9, 154.7, 149.3, 131.3, 130.6, 130.4, 127.2, 126.5, 116.1 115.9, 114.0, 111.8, 95.6, 56.0, 55.7, 55.3, 33.7.

4.5.4. 1-(Methoxymethoxy)-2-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-4-methylbenzene (22)

Colourless oil; yield 98%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (1H, superimposed m (d, J = ca. 2.1 Hz), *H*-3), 6.95 (1H, superimposed m (dd, J = 2.1, 8.0 Hz), *H*-5). 6.91 (1H, superimposed m (d, J = ca. 2.1 Hz), *H*-2″), 6.89 (1H, dd, J = 1.9, 8.0 Hz, *H*-6″), 6.80 (1H, J = 8.0 Hz, *H*-5″), 6.73 (1H, d, J = 8.0 Hz, *H*-6), 6.45 (1H, td, J = ca. 1.0, 15.7 Hz, *H*-3′), 6.24 (1H, td, J = 6.5, 15.7 Hz, *H*-2′), 4.88 (1H, s, O*H*), 3.87 (3.874) (3H, s, OCH_3), 3.87 (3.870) (3H, s, OCH_3), 3.52 (2H, dd, J = 1.0, 6.5 Hz, CH_2-1′), 2.27 (1H, s, $ArCH_3$); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 151.9, 149.1, 148.7, 131.03, 130.99, 130.4, 130.1, 128.2, 126.2, 125.6, 119.3, 115.7, 111.3, 108.9, 56.0, 55.9, 34.1, 20.5.

4.5.5. 1-(Methoxymethoxy)-2-[(*E*)-3-(3-bromo-4,5-dimethoxyphenyl)-2-propen-1-yl]benzene (23)

Colourless oil; yield 88%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (1H, unresolved superimposed m (ddd), *H*-5), 7.19 (1H, unresolved superimposed m (dd), *H*-3), 7.11 (1H, d, J = 2.0 Hz, *H*-2″), 7.10 (1H, superimposed dm, J = ca. 8.0 Hz, *H*-6), 6.98 (1H, ddd, J = 1.2, 7.4, 8.0 Hz, *H*-4), 6.81 (1H, d, J = 2.0 Hz, *H*-6″), 6.39–6.25 (2H, m, *H*-3′ and *H*-2′), 5.19 (2H, s, OCH_2O), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.55 (2H, m, CH_2-1′), 3.48 (3H, s, CH_2OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.0, 153.6, 145.6, 135.1, 130.2, 129.8, 129.1, 128.9, 127.6, 122.5, 121.9, 117.7, 114.1, 109.3, 94.5, 60.6, 56.1, 56.1, 33.5.

4.5.6. 1-(Methoxymethoxy)-2-[(*E*)-3-(3,4-methylenedioxyphenyl)-2-propen-1-yl]benzene (24)

Colourless, viscous oil; yield 97%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (1H, superimposed m (dd, J = 1.7, ca. 7.4 Hz), *H*-3), 7.19 (1H, superimposed m (ddd, J = 1.7, ca. 7.4, ca. 8.3 Hz), *H*-5], 7.09 (1H, dd, J = 1.2, 8.3 Hz, *H*-6), 6.96 (1H, ddd, J = 1.2, 7.4, 7.4 Hz, *H*-4), 6.90 (1H, d, J = 1.5 Hz, *H*-2″), 6.76 (1H, dd, J = 1.5, 8.0 Hz, *H*-6″), 6.72 (1H, d, J = 8.0 Hz, *H*-5″), 6.34 (1H, d (unresolved t of d), J = 15.8 Hz, *H*-3′), 6.20 (1H, td, J = 6.5, 15.8 Hz, *H*-2′), 5.93 (2H, s, OCH_2O), 5.23 (2H, s, OCH_2OCH_3), 3.53 (2H, d, J = 6.5 Hz, CH_2-1′), 3.48 (3H, s, CH_2OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ 155.0, 148.0, 146.7, 132.4, 130.4, 130.1, 129.5, 127.5, 127.2, 121.9, 120.4, 114.2, 108.2, 105.6, 100.9, 94.5, 56.1, 33.5.

4.5.7. 1-(Methoxymethoxy)-2-[(*E*)-3-(4-methoxyphenyl)-2-propen-1-yl]-5-(phenylmethoxy)benzene (25)

Colourless, extremely viscous oil; yield 88%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.29 (5H, m, 5 × benzyl Ar-*H*), 7.27 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2″ and *H*-6″), 7.09 (1H, d, J = 8.3 Hz, *H*-3), 6.82 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3″ and *H*-5″), 6.79 (1H, d, J = 2.5 Hz, *H*-6), 6.58 (1H, dd, J = 2.5, 8.4 Hz, *H*-4), 6.34 (1H, d, J = 15.8 Hz, *H*-3′), 6.21 (1H, dt, J = 15.8, 6.5 Hz, *H*-2′), 5.19 (2H, s, OCH_2O), 5.03 (2H, s, OCH_2Ar), 3.79 (3H, s, OCH_3), 3.46 (3H, s, CH_2OCH_3), 3.46 (2H, broadened d, J = 6.5 Hz, CH_2-1′); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 158.8, 158.5, 155.8, 137.2, 130.7, 130.3, 129.9, 128.6, 127.9, 127.6, 127.1, 127.1, 122.2, 114.0, 107.2, 102.5, 94.6, 70.2, 56.1, 55.3, 33.0.

4.5.8. 1-(Methoxymethoxy)-2-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-5-(phenylmethoxy)benzene (26)

Colourless oil; yield 93%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.29 (5H, m, 5 × benzyl Ar-*H*), 7.10 (1H, d, J = 8.3 Hz, *H*-3), 6.90 (1H, d, J = 1.9 Hz, *H*-2″), 6.87 (1H, dd, J = 1.9, 8.2 Hz, *H*-6″), 6.80 (1H, d, J = 2.5 Hz, *H*-6), 6.78 (1H, d, J = 8.2 Hz, *H*-5″), 6.59 (1H, dd, J = 2.5, 8.3 Hz, *H*-4), 6.34 (1H, d (unresolved td), J = 15.7 Hz, *H*-3′), 6.21 (1H, td, J = 6.4, 15.7 Hz, *H*-2′), 5.19 (2H, s, OCH_2O), 5.04 (2H, s, OCH_2Ph), 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.48 (2H, d (unresolved dd), J = 6.4 Hz, CH_2-1′), 3.47 (3H, s, CH_2OCH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ 158.6, 155.9, 149.2, 148.5, 137.2, 131.2, 130.4, 130.1, 128.5, 127.9, 127.54, 127.49, 122.1, 119.1, 111.5, 109.1, 107.4, 102.6, 94.7, 70.3, 56.06, 56.03, 55.91, 32.9.

4.5.9. 1-(Methoxymethoxy)-2-[(*E*)-3-[4-(phenylmethoxy)-phenyl]-2-propen-1-yl]benzene (27)

Colourless solid; yield 93%; mp 67–68 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.30 (5H, m, 5 × benzyl Ar-*H*), 7.27 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2″ and *H*-6″), 7.20 (1H, unresolved superimposed m (dd), *H*-6) 7.18 (1H, unresolved superimposed m (ddd), *H*-4), 7.08 (1H, dd, J = ca. 1.0, 8.2 Hz, *H*-3), 6.96 (1H, ddd, J = ca. 1.0, 7.3, 7.3 Hz, *H*-5), 6.89 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3″ and *H*-5″), 6.37 (1H, d (unresolved t of d), J = 15.8 Hz, *H*-3′), 6.24 (1H, td, J = 6.6, 15.8 Hz, *H*-2′), 5.22 (2H, s, OCH_2O), 5.05 (2H, s, OCH_2Ph), 3.54 (2H, d, J = 6.6 Hz, *H*-1′), 3.48 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$,

75.45 MHz): δ 158.0, 155.0, 137.1, 130.9, 130.2, 130.1, 129.7, 128.6, 127.9, 127.45, 127.41, 127.2, 126.9, 121.8, 115.0, 114.1, 94.5, 70.1, 56.1, 33.5.

4.6. General procedure for the asymmetric dihydroxylation of the MOM-protected propenes (19–27)

AD-mix-β or AD-mix-α (11.2 g) in *t*-BuOH (40 mL) and H_2O (40 mL) was vigorously stirred at room temperature to give a 2-phase mixture. $MeSO_2NH_2$ (760 mg, ca. 8 mmol) was added at room temperature to the stirred mixture and stirring continued for ca. 5 min. At this stage the mixture was cooled to 0 °C and treated with a solution of the appropriate propene (**15**–**21**) (8 mmol) in acetone (ca. 4–5 mL) in one portion. The viscous reaction mixture was stirred vigorously at 0 °C for ⩾8 h then at 2–4 °C (cold room) for ca. 72 h (longer in the case of highly substituted ene compounds). Na_2SO_3 (12 g) was then added, the mixture allowed to warm to room temperature, and finally stirred at rt for ⩾30 min. EtOAc (⩾60 mL) was added (extra H_2O may also required to dissolve all inorganics) and the organic layer separated. The aqueous phase was extracted further with EtOAc (3 × ca. 60 mL), the combined organic extracts washed in turn with H_2O and brine, and dried ($MgSO_4$). The solvent was removed in vacuo to afford crude product (**22**–**28**) as either a colourless/pale yellow solid or a viscous oil. The crude product was purified by short column vacuum chromatography (eluting with DCM/EtOAc mixtures) followed, where possible with solid products, by recrystallisation from hexane/EtOAc. In some cases, a small quantity of hydroxyketone eluted prior to the diol product.

4.6.1. (1*R*,2*R*)-*syn*-1-(4-Methoxyphenyl)-3-[2-(methoxymethoxy)phenyl]propan-1,2-diol (28a)

Colourless oil; yield 92%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 7.19 (1H, ddd, *J* = 1.8, 7.5, 8.2 Hz, *H*-4″), 7.12 (1H, dd, *J* = 1.8, 7.5 Hz, *H*-6″), 7.06 (1H, dd, *J* = 1.2, 8.2 Hz, *H*-3″), 6.95 (1H, ddd as apparent 'dt', *J* = 1.2, 7.5, 7.5 Hz, *H*-5″), 6.90 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), ca. 5.15 and 5.14 merging to non-resolved br central peak (each 1H, each d of AB system, *J* = 6.7 Hz, OCH_2O), 4.48 (1H, dm, *J* = 6.5 Hz, *H*-1), 3.95 (1H, sym m (unresolved dddd), *H*-2), 3.81 (3H, s, OCH_3), 3.42 (3H, s, CH_2OCH_3), 3.02 (1H, d, *J* = ca. 2.5 Hz, ArCH(O*H*)), 2.79 (1H, dd, *J* = 4.0, 13.8 Hz, CH_2-3a), 2.69 (1H, dd, *J* = 8.8, 13.8 Hz, CH_2-3b), 2.62 (1H, d, *J* = 4.3 Hz, CH(O*H*)); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 159.4, 155.2, 133.1, 131.4, 128.2, 127.9, 127.5, 122.1, 114.2, 114.0, 94.6, 76.7, 76.1, 56.2, 55.3, 34.4.

4.6.2. (1*S*,2*S*)-*syn*-1-(4-Methoxyphenyl)-3-[2-(methoxymethoxy)phenyl]propan-1,2-diol (22b) and (2*S*)-1-(4-methoxyphenyl)-2-hydroxy-3-[2-(methoxymethoxy)phenyl]propan-1-one diol (28b)

Oil; yield 91%; NMR spectra of (**28b**) correspond to those reported above for the (1*R*,2*R*)-enantiomer (**28a**).

2-Hydroxypropan-1-one: colourless solid, yield 5%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 7.22 (1H, superimposed m (unresolved dm, *J* = ca. 7.5 Hz), *H*-6″), 7.21 (1H, superimposed m (ddd, *J* = 1.6, 7.5, n/d), *H*-4″), 7.06 (1H, dm, *J* = ca. 8.1 Hz, *H*-3″), 6.97 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 6.96 (1H, superimposed m (ddd), *H*-5″), 5.30 (1H, ddd, *J* = 3.4, 7.2, 8.9 Hz, *H*-2), 5.22 and 5.17 (each 1H, each d of AB system, *J* = 6.6 Hz, OCH_2O), 3.90 (3H, s, OCH_3), 3.73 (1H, d, *J* = 7.2 Hz, O*H*), 3.48 (3H, s, CH_2OCH_3), 3.35 (1H, dd, *J* = 3.4, 13.6 Hz, *H*-3a), 2.65 (1H, dd, *J* = 8.9, 13.6 Hz, *H*-3b); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 199.8, 164.2, 155.2, 131.9, 131.2, 128.1, 126.9, 126.5, 121.8, 114.0, 113.7, 94.7, 72.5, 56.2, 55.5, 38.1.

4.6.3. (1*R*,2*R*)-*syn*-1-(3,4-Dimethoxyphenyl)-3-[2-(methoxymethoxy)phenyl]propan-1,2-diol (29a)

Colourless solid; yield 94%; mp 130–132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (1H, ddd, *J* = 1.8, 7.3, 8.2 Hz, *H*-4″), 7.12 (1H, dd, *J* = 1.8, 7.5 Hz, *H*-6″), 7.06 (1H, dd, *J* = 1.2, 8.2 Hz, *H*-3″), 6.96 (1H, superimposed m (ddd, *J* = 1.2, 7.3, 7.5 Hz), *H*-5″), 6.96 (1H, superimposed m (d, *J* = 2.0 Hz), *H*-2′), 6.93 (1H, dd, *J* = 2.0, 8.0 Hz, *H*-6′), 6.86 (1H, d, *J* = 8.0 Hz, *H*-5′), 5.16 (2H, s, OCH_2O), 4.48 (1H, dd (when coupled to OH), *J* = 2.9, 6.2 Hz, *H*-1), 3.96 (1H, sym m (dddd (when coupled to OH), *J* = 4.2, 4.4, 6.2, 8.6 Hz), *H*-2), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.43 (3H, s, CH_2OCH_3), 3.07 (1H, d, *J* = 2.9 Hz, ArCH(O*H*)), 2.82 (1H, dd, *J* = 4.2, 13.7 Hz, *H*-3a), 2.72 (1H, dd, *J* = 8.6, 13.7 Hz, *H*-3b), 2.63 (1H, d, *J* = 4.4 Hz, CH_2CH(O*H*)); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.3, 149.3, 149.0, 133.8, 131.4, 128.0, 127.4, 122.1, 119.5, 114.4, 111.4, 110.5, 94.9, 76.9, 76.1, 56.2, 56.04, 56.02, 34.6.

4.6.4. (1*S*,2*S*)-*syn*-1-(3,4-Dimethoxyphenyl)-3-[2-(methoxymethoxy)phenyl]propan-1,2-diol (29b)

Colourless solid; yield 91%; mp 130–131 °C; NMR spectra correspond to those reported above for the (1*R*,2*R*)-enantiomer (**29a**).

4.6.5. (1*R*,2*R*)-*syn*-1-(4-Methoxyphenyl)-3-[2-(methoxymethoxy)-5-methoxyphenyl]propan-1,2-diol (30a)

Colourless, viscous oil; yield 85%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (2H, aa′bb′ 'd', *J* = 8.6 Hz, *H*-2′ and *H*-6′), 7.00 (1H, d, *J* = 8.8 Hz, *H*-3″), 6.90 (2H, aa′bb′ 'd', *J* = 8.6 Hz, *H*-3′ and *H*-5′) 6.71 (1H, dd, *J* = 3.1, 8.8 Hz, *H*-4″), 6.67 (1H, d, *J* = 3.1 Hz, *H*-6″), 5.07 (2H, s, OCH_2O), 4.48 (1H, d, *J* = 6.5 Hz, *H*-1), 3.94 (1H, sym m (ddd, *J* = 4.4, 6.5, 8.5 Hz), *H*-2), 3.81 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.42 (3H, s, CH_2OCH_3), 3.01 (1H, br s, O*H*), 2.75 (1H, dd, *J* = 4.4, 13.7 Hz, *H*-3a), 2.67 (1H, dd, *J* = 8.5, 13.7 Hz, *H*-3b), 1.64 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ 159.5, 154.8, 149.5, 133.2, 129.0, 128.2, 117.1, 116.0, 113.9, 112.5, 95.7, 76.7, 76.2, 56.1, 55.7, 55.3, 34.7.

4.6.6. (1*R*,2*R*)-*syn*-1-(3,4-dimethoxyphenyl)-3-[2-(methoxymethoxy)-5-methylphenyl]-propan-1,2-diol (31a)

Colourless solid; yield 91%; mp 112.5–114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01–6.90 (5H, 5 × superimposed m, unassigned *H*-3″, *H*-4″, *H*-6″, *H*-2′ and *H*-6′), 6.86 (1H, d, *J* = 8.0 Hz, *H*-5′), 5.13 (2H, s, OCH_2), 4.48 (1H, d, *J* = 6.4 Hz, *H*-1), 3.94 (1H, sym m (dddd, *J* = 4.6, 6.4, 6.2, 8.4 Hz, *H*-2], 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.42 (3H, s, CH_2OCH_3), 3.12 (1H, br s, ArCH(O*H*)), 2.77 (1H, dd, *J* = 4.6, 13.7 Hz, *H*-3a), 2.69 (1H, dd, *J* = 8.4, 13.7 Hz, *H*-3b), 2.69 (1H, br s, CH_2CH(O*H*)), 2.26 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 153.1, 149.1, 148.9, 133.7, 132.0, 131.5, 128.3, 127.1, 119.5, 114.4, 111.2, 110.3, 95.0, 76.9, 76.2, 56.2, 55.99, 55.96, 34.5, 20.5.

4.6.7. (1*S*,2*S*)-*syn*-1-(3,4-Dimethoxyphenyl)-3-[2-(methoxymethoxy)-5-methylphenyl]-propan-1,2-diol (31b)

Colourless solid; yield 88%; mp 112–114 °C; NMR spectra of (31b) correspond to those reported above for the (1*R*,2*R*)-enantiomer (**31a**).

4.6.8. (1*R*,2*R*)-*syn*-1-(3-Bromo-4,5-dimethoxyphenyl)-3-[2-(methoxymethoxy)phenyl]propan-1,2-diol (32a)

Colourless, viscous gum; yield 93%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (1H, ddd, *J* = 1.8, 7.4, 8.3 Hz, *H*-4″), 7.15 (1H, d, *J* = 1.9 Hz, *H*-2′), 7.15 (1H, dd, *J* = 1.8, 7.4 Hz, *H*-6″), 7.08 (1H, dd, *J* = 1.1, 8.3 Hz, *H*-3″), 6.97 (1H, ddd, *J* = 1.1, 7.4, 7.4 Hz, *H*-5″), 6.92 (1H, d, *J* = 1.9 Hz, *H*-6′), 5.18 (2H, s, OCH_2), 4.45 (1H, d, *J* = 5.9 Hz, *H*-1), 3.95 (1H, sym m (ddd, *J* = 4.5, 5.9, 8.5 Hz), *H*-2), 3.88 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.45 (3H, s, CH_2OCH_3), 3.14 (1H, br s, ArCH(O*H*)), 2.86 (1H, dd, *J* = 4.5, 13.6 Hz, *H*-3a), 2.74 (1H, dd,

J = 8.5, 13.6 Hz, *H*-3b), 2.58 (1H, br s, $CH_2CH(OH)$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.2, 153.6, 146.0, 138.3, 131.4, 128.2, 126.9, 123.2, 122.1, 117.5, 114.2, 110.5, 94.7, 76.0, 75.8, 60.6, 56.3, 56.1, 34.7.

4.6.9. (1*R*,2*R*)-*syn*-1-(3,4-Methylenedioxyphenyl)-3-[2-(methoxymethoxy)phenyl]propan-1,2-diol (33a)

Colourless solid (needles ex hexane/EtOAc); yield 89%; mp 93–95 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (1H, ddd, J = 1.7, 7.5, 8.3 Hz, *H*-4″), 7.13 (1H, dd, J = 1.7, 7.5 Hz, *H*-6″), 7.07 (1H, dd, J = 1.0, 8.3 Hz, *H*-3″), 6.95 (1H, ddd, J = 1.0, 7.5, 7.5 Hz, *H*-5″), 6.92 (1H, d, J = 1.2 Hz, *H*-2′), 6.85 (1H, dd, J = 1.2, 8.0 Hz, *H*-6′), 6.80 (1H, d, J = 8.0 Hz, *H*-5′), 5.963 and 5.960 (each 1H (of 'ab' system), d, J = 1.5 Hz, OCH_2O), 5.17 and 5.155 (each 1H (of 'ab' system), d, J = 6.8 Hz, OCH_2OCH_3), 4.45 (1H, d, J = 6.3 Hz, *H*-1), 3.93 (1H, sym m (ddd, J = 4.0, 6.3, 8.8 Hz), *H*-2), 3.44 (3H, s, OCH_3), 3.04 (1H, br s, ArCH(O*H*)), 2.81 (1H, dd, J = 4.0, 13.8 Hz, *H*-3a), 2.69 (1H, dd, J = 8.8, 13.8 Hz, *H*-3b), 2.60 (1H, br s, $CH_2CH(OH)$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.2, 147.8, 147.3, 135.0, 131.4, 128.0, 127.2, 122.1, 120.6, 114.2, 108.1, 107.4, 101.0, 94.7, 76.9, 76.1, 56.2, 34.5.

4.6.10. (1*S*,2*S*)-*syn*-1-(3,4-Methylenedioxyphenyl)-3-[2-(methoxymethoxy)phenyl]propan-1,2-diol (33b)

Colourless solid (needles ex hexane/EtOAc); yield 95%; mp 93–95 °C; NMR spectra correspond to those reported above for the (2*R*,3*R*)-enantiomer (**33a**).

4.6.11. (1*R*,2*R*)-*syn*-1-(4-Methoxyphenyl)-3-[2-(methoxymethoxy)-4-(phenylmethoxy)phenyl]propan-1,2-diol (34a)

Colourless oil; yield 89%; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.29 (5H, m, benzyl Ar-*H*), 7.31 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2′ and *H*-6′), 7.01 (1H, d, J = 8.3 Hz, *H*-6″), 6.90 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3′ and *H*-5′), 6.76 (1H, d, J = 2.5 Hz, *H*-3″), 6.57 (1H, dd, J = 2.5, 8.3 Hz, *H*-5″), 5.115 and 5.105 (each 1H of ab system, d, J = 6.7 Hz, OCH_2O), 5.02 (2H, s, OCH_2Ar), 4.47 (1H, dd, J = 3.3, 6.5 Hz, *H*-1), 3.91 (1H, sym m, *H*-2), 3.81 (3H, s, OCH_3), 3.41 (3H, s, CH_2OCH_3), 2.97 (1H, d, J = 3.3 Hz, ArCH(O*H*)), 2.72 (1H, dd, J = 4.2, 13.8 Hz, *H*-3a), 2.62 (1H, dd, J = 8.7, 13.8 Hz, *H*-3b), 2.54 (1H, d, J = 4.3 Hz, $CH_2CH(OH)$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 159.4, 158.8, 156.0, 137.0, 133.3, 131.6, 128.5, 128.2, 128.0, 127.5, 119.7, 113.8, 107.5, 102.6, 94.8, 76.6, 76.1, 70.2, 56.2, 55.3, 33.9.

4.6.12. (1*R*,2*R*)-*syn*-1-(3,4-Dimethoxyphenyl)-3-[2-(methoxymethoxy)-4-(phenylmethoxy)phenyl]propan-1,2-diol (35a)

Colourless solid; yield 82%; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.29 (5H, m, benzyl Ar-*H*). 7.02 (1H, d, J = 8.3 Hz, *H*-6″), 6.95 (1H, d, J = 1.9 Hz, *H*-2′), 6.93 (1H, dd, J = 1.9, 8.2 Hz, *H*-6′), 6.85 (1H, d, J = 8.2 Hz, *H*-5′), 6.77 (1H, d, J = 2.5 Hz, *H*-3″), 6.57 (1H, dd, J = 2.5, 8.3 Hz, *H*-5″), 5.12 (2H, s, OCH_2O), 5.02 (2H, s, OCH_2Ph), 4.47 (1H, dd, J = 3.0, 6.2 Hz, *H*-1), 3.91 (1H, superimposed sym m (dddd, J = 4.1, 4.3, 6.2, 8.6 Hz), *H*-2)), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.42 (3H, s, CH_2OCH_3), 3.04 (1H, d, J = 3.0 Hz, ArCH(O*H*)), 2.75 (1H, dd, J = 4.3, 13.9 Hz, *H*-3a), 2.65 (1H, dd, J = 8.6, 13.9 Hz, *H*-3b), 2.56 (1H, d, J = 4.1 Hz, $CH_2CH(OH)$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 158.9, 156.1, 149.2, 148.9, 137.0, 133.9, 131.6, 128.5, 128.0, 127.5, 119.7, 119.5, 111.3, 110.4, 107.7, 102.7, 94.9, 76.8, 76.1, 70.3, 56.2, 56.03, 56.01, 33.9.

4.6.13. (1*S*,2*S*)-*syn*-1-(3,4-Dimethoxyphenyl)-3-[2-(methoxymethoxy)-4-(phenylmethoxy)phenyl]propan-1,2-diol (35b)

Colourless solid; yield 89%; mp 120–121.5 °C; NMR spectra correspond to those reported above for the (1*R*,2*R*)-enantiomer (**35a**).

4.6.14. (1*S*,2*S*)-*syn*-1-[4-(Phenylmethoxy)phenyl]-3-[2-(methoxymethoxy)phenyl]propan-1,2-diol (36b)

Colourless oil; yield 89%; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.30 (5H, m, benzyl Ar-*H*), 7.32 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2′ and *H*-6′), 7.19 (1H, ddd, J = 1.8, 7.3, 8.3 Hz, *H*-4″), 7.12 (1H, dd, J = 1.8, 7.5 Hz, *H*-6″), 7.06 (1H, dd, J = 1.2, 8.3 Hz, *H*-3″), 6.98 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3′ and *H*-5′), 6.95 (1H, ddd, J = 1.2, 7.3, 7.5 Hz, *H*-5″), 5.14 and 5.12 (each 1H, d, J = 6.6 Hz, OCH_2O), 5.08 (2H, s, OCH_2Ar), 4.49 (1H, d, J = 6.3 Hz, *H*-1), 3.96 (1H, sym m (ddd with no coupling to O*H*, J = 4.2, 6.3, 8.7 Hz), *H*-2), 3.41 (3H, s, CH_2OCH_3), 2.98 (1H, br s or d (J = 2.2 Hz), ArCH(O*H*)), 2.80 (1H, dd, J = 4.2, 13.7 Hz, *H*-3a), 2.70 (1H, dd, J = 8.7, 13.7 Hz, *H*-3b), 2.6 (1H, br s or d (J = 4.0 Hz), $CH_2CH(OH)$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 158.7, 155.3, 137.1, 133.6, 131.4, 128.6, 128.3, 128.0, 128.0, 127.5, 127.4, 122.1, 115.0, 114.4, 94.8, 76.7, 76.1, 70.2, 56.2, 34.6.

4.7. General procedure for the preparation of *trans*- (37–45) and *cis*-flavan-3-ols (46–54)

Aqueous HCl (11 mL of 3 M) was added to a solution of the diol (**28**–**36**) (ca. 6.25 mmol) in MeOH/H_2O (3:1, total 120 mL; dissolved in MeOH prior to addition of H_2O) and the solution was heated at 75–80 °C for $\geqslant$48 h (longer reaction times were required for compounds having a highly substituted precursor B ring. The mixture was cooled, diluted with ice-H_2O (ca. 600 mL) (giving a white precipitate) and extracted with Et_2O (1 × >120 mL, 3 × ~75 mL). The combined extracts were washed in turn with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford crude *products* as a colourless or slightly coloured (usually pinkish increasing in intensity with time) gum or solid. Initial CC (eluting solvent DCM/hexane/EtOAc mixtures) separated the closely eluting mixed *cis*- and *trans*-isomers (yield, ratio) from impurities with the *cis*-isomer eluting immediately before, but partly overlapping with, the *trans*-isomer. Further repetitive CC employing the same solvent system gave a separation of adequate quantities of the *cis*- and *trans*-isomers that could be further purified by recrystallisation from hexane/EtOAc.

4.7.1. (2*S*,3*R*)-*trans*-4′-Methoxyflavan-3-ol (37a)

Colourless solid; yield for combined *trans*:*cis* 94%, ratio 3:1; mp 104–105 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2′ and *H*-6′), 7.15 (1H, superimposed m (ddd), *H*-7), 7.12 (1H, superimposed m (dd), *H*-5), 6.96 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3′ and *H*-5′), 6.92 (1H, m (superimposed ddd), *H*-6), 6.91 (1H, 'd' (superimposed/unresolved dd), J = 7.7 Hz, *H*-8), 4.74 (1H, d, J = 8.3 Hz, *H*-2), 4.11 (1H, sym m (dddd, J = 3.5, 5.6, 8.3, 9.4 Hz), *H*-3), 3.83 (3H, s, OCH_3), 3.12 (1H, dd, J = 5.6, 16.2 Hz, *H*-4a), 2.93 (1H, dd, J = 9.4, 16.2 Hz, *H*-4b), 1.73 variable (1H, d, J = 3.5 Hz variable, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 160.0, 154.0, 130.0, 129.9, 128.5, 127.7, 121.0, 120.2, 116.5, 114.3, 81.7, 68.1, 55.3, 33.1.

4.7.2. Crystal data for *trans*-(2*S*,3*R*)-4′-methoxyflavan-3-ol (37a)

$C_{16}H_{16}O_3$, M = 256.29. Orthorhombic, a = 5.8927(11), b = 10.2670(19), c = 21.264(4) Å (by least-squares refinement of the setting angles for 200 reflections within θ = 1.92–28.20), V = 1286.5(4) Å^3, space group $P2_12_12_1$, Z = 4, D_m = 1.323 g cm^{-1}, F(0 0 0) = 544. Colourless prisms. Crystal dimensions 0.15 × 0.12 × 0.12 mm, μ(Mo Kα) = 0.0091 mm^{-1}.

4.7.3. (2*R*,3*R*)-*cis*-4′-Methoxyflavan-3-ol (46a)

Colourless solid; mp 116–117 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2′ and *H*-6′), 7.17 (1H, non-resolved superimposed m (ddd), *H*-7), 7.13 (1H, non-resolved superimposed m (dd), *H*-5), 6.97 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3′ and *H*-5′), 6.97 (1H, superimposed m (dd), *H*-8), 6.93 (1H, ddd, J = 1.2, 7.4, 7.4 Hz, *H*-6), 5.06 (1H, m as broadened s, *H*-2), 4.28 (1H, sym m (dddd, J = $\leqslant$1.0, 2.4, 4.2, 6.0 Hz), *H*-3), 3.83 (3H, s, OCH_3), 3.26 (1H, dd, J = 4.2, 16.9 Hz, *H*-4a), 2.98 (1H, dd, J = 2.4, 16.9 Hz, *H*-

4b), 1.80 variable (1H, d, J = ca. 6.0 Hz variable, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 159.6, 154.2, 130.3, 130.3, 127.61, 127.59, 121.3, 118.9, 116.8, 114.1, 78.4, 66.7, 55.3, 33.5.

4.7.4. (2*R*,3*S*)-*trans*-4′-Methoxyflavan-3-ol (37b)

Colourless solid; yield for combined *trans*:*cis* 89%, ratio 2.7:1; mp 104–105 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**37a**).

4.7.5. (2*S*,3*S*)-*cis*-4′-Methoxyflavan-3-ol (46b)

Colourless solid; mp 115–117 °C; NMR spectra correspond to those reported above for the *cis*-(2*R*,3*R*)-enantiomer (**46a**).

4.7.6. (2*S*,3*R*)-*trans*-3′,4′-Dimethoxyflavan-3-ol (38a)

Colourless solid; yield for combined *trans*:*cis* 94%, ratio 2.7:1; mp 110–112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (1H, superimposed m (ddd), *H*-7), 7.14 (1H, superimposed m (dd), *H*-5), 7.02 (1H, superimposed m (dd, J = 2.0, 8.1 Hz), *H*-6′), 6.99 (1H, superimposed m (d, J = 2.0), *H*-2′), 6.96–6.89 (2H, 2 × superimposed m, *H*-6 and *H*-8), 6.91 (1H, d, J = 8.1 Hz, *H*-5′), 4.71 (1H, d, J = 8.3 Hz, *H*-2), 4.11 (1H, ddd, J = 5.6, 8.3, 9.5 Hz, *H*-3), 3.901 (3H, s, OCH_3), 3.896 (3H, s, OCH_3), 3.14 (1H, dd, J = 5.6, 16.0 Hz, *H*-4a), 2.94 (1H, dd, J = 9.5, 16.0 Hz, *H*-4b), 1.74 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 154.2, 149.6, 149.6, 130.6, 129.9, 127.7, 121.1, 120.3, 119.9, 116.5, 111.6, 110.4, 82.0, 68.2, 56.1, 56.0, 33.2.

4.7.7. (2*R*,3*R*)-*cis*-3′,4′-Dimethoxyflavan-3-ol (47a)

Colourless solid; mp 96.5–98 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17 (1H, superimposed m, *H*-7), 7.14 (1H, superimposed m, *H*-5), 7.08 (1H, superimposed m (d, J = ca. 2.0 Hz), *H*-2′), 7.06 (1H, superimposed m (ddd, J = ca. 0.7, 2.0, 8.1 Hz), *H*-6′), 6.99 (1H. superimposed m (dd), *H*-8), 6.97 (1H, superimposed m (ddd), *H*-6), 6.93 (1H, superimposed m (d, J = 8.1 Hz), *H*-5′), 5.05 (1H, m as slightly br s, *H*-2), 4.30 (1H, m, *H*-3), 3.93 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.28 (1H, dd, J = 4.2, 16.8 Hz, *H*-4a), 2.99 (1H, dd, J = 2.2, 16.8 Hz, *H*-4b), 1.71 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 154.2, 149.4, 149.1, 131.0, 130.3, 127.6, 121.3, 118.9, 118.7, 116.8, 111.6, 110.0, 78.5, 66.9, 56.1, 56.1, 33.5.

4.7.8. (2*R*,3*S*)-*trans*-3′,4′-Dimethoxyflavan-3-ol (38b)

Colourless solid; yield for combined *trans*:*cis* 94%, ratio 2.5:1; mp 109–111 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**38a**).

4.7.9. (2*S*,3*S*)-*cis*-3′,4′-Dimethoxyflavan-3-ol (47b)

Colourless solid; mp 97–98 °C; NMR spectra correspond to those reported above for the *cis*-(2*R*,3*R*)-enantiomer (**47a**).

4.7.10. (2*S*,3*R*)-*trans*-4′,6-Dimethoxyflavan-3-ol (39a)

Colourless solid; yield for combined *trans*:*cis* 88%, ratio 2.3:1; mp 117–118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2′ and *H*-6′), 6.94 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3′ and *H*-5′), 6.84 (1H, d, J = 8.9 Hz, *H*-8), 6.72 (1H, dd, J = 3.0, 8.9 Hz, *H*-7), 6.64 (1H, d, J = 3.0, *H*-5), 4.69 (1H, d, J = 8.2 Hz, *H*-2), 4.11 (1H, ddd, J = 5.4, 8.2, 9.0 Hz, *H*-3), 3.83 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.09 (1H, dd, J = 5.4, 16.2 Hz, *H*-4a), 2.91 (1H, dd, J = 9.0, 16.2 Hz, *H*-4b), 1.55 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 160.0, 154.0, 148.3, 130.3, 128.5, 121.0, 117.2, 114.39, 114.35, 113.9, 81.7, 68.2, 55.8, 55.4, 33.4.

4.7.11. (2*R*,3*R*)-*cis*-4′,6-Dimethoxyflavan-3-ol (48a)

Colourless solid; mp 153–155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (2H, aa′bb′ 'd', J = 8.9 Hz, *H*-2′ and *H*-6′), 6.96 (2H, aa′bb′ 'd', J = 8.9 Hz, *H*-3′ and *H*-5′), 6.90 (1H, d, J = 8.9 Hz, *H*-8), 6.74 (1H, dd, J = 2.9, 8.9 Hz, *H*-7), 6.66 (1H, d, J = 2.9, *H*-5), 4.99 (1H, m as broadened s, *H*-2), 4.25 (1H, sym m, *H*-3), 3.83 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.26 (1H, dd, J = 4.3, 17.0 Hz (possibly more accurately ddd with a further small J = ca. 0.5 Hz), *H*-4a), 2.95 (1H, dd, J = 2.2, 17.0 Hz, *H*-4b), 1.84 variable (1H, d, J = 6.2 Hz variable, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 159.6, 154.2, 148.3, 130.5, 127.6, 119.6, 117.4, 114.8, 114.1, 113.9, 78.4, 66.8, 55.8, 55.3, 34.0.

4.7.12. (2*S*,3*R*)-*trans*-3′,4′-Dimethoxy-6-methylflavan-3-ol (40a)

Colourless solid; yield for combined *trans*:*cis* 85%, ratio 2.6:1; mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.02 (1H, dd, J = 2.0, 8.1 Hz, *H*-6′), 6.99 (1H, d. J = 2.0 Hz, *H*-2′), 6.96 (1H, superimposed m (dd), *H*-7), 6.94 (1H, superimposed m (d), *H*-5), 6.91 (1H, d, J = 8.1 Hz, *H*-5′), 6.83 (1H, d, J = 8.0 Hz, *H*-8), 4.68 (1H, d, J = 8.5 Hz, *H*-2), 4.10 (1H, ddd, J = 5.5, 8.5, 9.4 Hz, *H*-3), 3.899 (3H, s, OCH_3), 3.896 (3H, s, OCH_3), 3.10 (1H, dd, J = 5.5, 16.0 Hz, *H*-4a), 2.91 (1H, dd, J = 9.4, 16.0 Hz, *H*-4b), 2.29 (3H, s, ArCH_3), 1.74 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 152.0, 149.4, 149.4, 130.5, 130.3, 130.2 128.3, 119.94, 119.91, 116.2, 111.3, 110.0, 81.9, 68.3, 56.0, 55.9, 33.2, 20.5.

4.7.13. (2*R*,3*R*)-*cis*-3′,4′-Dimethoxy-6-methylflavan-3-ol (49a)

Glassy solid (not recrystallised); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (1H, d, J = 2.0 Hz, *H*-2′) 7.05 (1H, ddd, J = ca. 0.6, 2.0, 8.1 Hz, *H*-6′), 6.98 (1H, dd (or ddm with possible additional coupling to ring methyl) J = ca. 1.8, ca. 8.2 Hz, *H*-7), 6.94 (1H, superimposed and unresolved d, J = ca. 1.8 Hz, *H*-5), 6.92 (1H, d, J = 8.1 Hz. *H*-5′), 6.88 (1H, d, J = 8.2 Hz, *H*-8), 5.01 (1H, sl. br s, *H*-2), 4.27 (1H, sym m (ddd, J = ca. 1.0, 2.4, 4.2 Hz), *H*-3), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.24 (1H, dd, J = 4.2, 16.9 Hz, *H*-4a), 2.94 (1H, dd, J = 2.4, 16.9 Hz, *H*-4b), 2.28 (3H, s, ArCH_3), 1.74 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 151.8, 149.2, 148.8, 130.9, 130.6, 130.5, 128.2, 118.5, 118.4, 116.4, 111.3, 109.7, 78.3, 66,9, 55.93, 55.92, 33.4, 20.5.

4.7.14. (2*R*,3*S*)-*trans*-3′,4′-Dimethoxy-6-methylflavan-3-ol (40b)

Fine, colourless needles (hexane/EtOAc); yield for combined *trans*:*cis* 85%, ratio 2.6:1; mp 119–121 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**40a**).

4.7.15. (2*S*,3*S*)-*cis*-3′,4′-Dimethoxy-6-methylflavan-3-ol (49b)

Colourless solid; mp 102–103 °C; NMR spectra correspond to those reported above for the *cis*-(2*R*,3*R*)-enantiomer (**49a**).

4.7.16. (2*S*,3*R*)-*trans*-3′-Bromo-4′,5′-Dimethoxyflavan-3-ol (41a)

Reaction time >15 d, colourless crystals (hexane/EtOAc); combined *trans:cis* ratio not determined with minimal *cis* isolated; mp 164–165 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (1H, d, J = 1.8 Hz, *H*-2′), 7.16 (1H, non-resolved ddd, *H*-7), 7.13 (1H, non-resolved dd, *H*-5), 6.96 (1H, d, J = 1.8 Hz, *H*-6′), 6.94 (1H. superimposed ddd, *H*-6) 6.93 (1H, superimposed dd, *H*-8), 4.68 (1H, d, J = 8.3 Hz, *H*-2), 4.09 (1H, ddd, J = 5.5, 8.3, 9.4 Hz, *H*-3), 3.87 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.14 (1H, dd, J = 5.5, 16.0 Hz, *H*-4a), 2.94 (1H, dd, J = 9.4, 16.0 Hz, *H*-4b), 1.74 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 153.8, 153.7, 146.4, 135.3, 129.9, 127.8, 123.4, 121.3, 120.2, 117.8, 116.4, 110.5, 81.4, 68.0, 60.5, 56.1, 33.3.

4.7.17. Crystal data for *trans*-(2*S*,3*R*)-3′-bromo-4′,5′-dimethoxyflavan-3-ol (41a)

$C_{17}H_{17}BrO_4$, M = 365.22. Orthorhombic, a = 7.9341(3), b = 10.4401(4), c = 18.6699(8) Å (by least-squares refinement of the setting angles for 200 reflections within θ = 2.18–28.25), V = 1546.48(11) Å^3, space group $P2_12_12_1$, Z = 4, D_m = 1.569 g cm^{-3}, F(0 0 0) = 744. Colourless needles. Crystal dimensions 0.30 × 0.20 × 0.20 mm, μ(Mo Kα) = 0.2673 mm^{-1}.

4.7.18. (2*R*,3*R*)-*cis*-3′-Bromo-4′,5′-dimethoxyflavan-3-ol (50a)

Colourless, viscous gum; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (1H, dd, J = ca. 0.6, 1.8 Hz, *H*-2′), 7.18 (1H, non-resolved ddd, *H*-7), 7.14 (1H, non-resolved dd, *H*-5), 7.06 (1H, d, J = 1.8 Hz, *H*-6′), 6.99 (1H, dd, J = 1.2, 8.1 Hz, *H*-8), 6.96 (1H, ddd, J = 1.2, 7.5, 7.5 Hz, *H*-6), 5.00 (1H, broadened s, *H*-2), 4.31 (1H, incompletely resolved sym m, *H*-3), 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.29 (1H, dd, J = 4.0, 16.9 Hz, *H*-4a), 3.00 (1H, dd, J = 1.8, 16.9 Hz, *H*-4b), 1.67 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 153.9, 153.7, 146.3, 135.5, 130.4, 127.8, 122.6, 121.7, 118.6, 117.9, 116.8, 109.9, 77.9, 66.7, 60.6, 56.3, 33.6.

4.7.19. (2*S*,3*R*)-*trans*-3′4′-Methylenedioxyflavan-3-ol (42a)

Colourless crystals (hexane/EtOAc); yield for combined *trans*:*cis* 92%, ratio 2.6:1; mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (1H, unresolved superimposed m, *H*-7), 7.12 (1H, unresolved superimposed m, *H*-5), 6.97–6.89 (3H, 3 × superimposed m, unassigned *H*-6, *H*-8, and *H*-2′), 6.92 (1H, superimposed m (ddd, J = ca. 0.5, 1.8, 8.0 Hz), *H*-6′), 6.84 (1H, d, J = 8.0 Hz, *H*-5′), 5.99 (2H, s, OCH_2O, 4.69 (1H, d, J = 8.3 Hz, *H*-2), 4.07 (1H, sym. m (dddd, J = 3.6, 5.5, 8.3, 9.4 Hz, *H*-3), 3.12 (1H, dd, J = 5.5, 16.0 Hz, *H*-4a), 2.92 (1H, dd, J = 9.2, 16.0 Hz, *H*-4b), 1.74 variable (1H, d, J = 3.6 Hz, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 154.0, 148.2, 148.0, 131.8, 129.9, 127.7, 121.2, 121.1, 120.2, 116.5, 108.4, 107.3, 101.3, 81.9, 68.1, 33.1.

4.7.20. (2*R*,3*R*)-*cis*-3′4′-Methylenedioxyflavan-3-ol (51a)

Colourless solid; mp 78–79 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17 (1H, unresolved superimposed m (ddd), *H*-7), 7.13 (1H, unresolved superimposed m (dd), *H*-5), 7.05 (1H, d, J = 1.7 Hz, *H*-2′), 6.97 (1H, superimposed m (ddd, J = ca. 0.6, 1.7, 8.0 Hz), *H*-6′), 6.95 (1H. superimposed m (dd), *H*-8), 6.94 (1H, superimposed m (ddd), *H*-6), 6.86 (1H, d, J = 8.0 Hz, *H*-5′), 5.99 (2H, s, OCH_2O), 5.01 (1H, m as slightly br s, *H*-2), 4.26 (1H, m, *H*-3), 3.27 (1H, dd, J = 4.0, 17.0 Hz, *H*-4a), 2.98 (1H, dd, J = 2.2, 17.0 Hz, *H*-4b), 1.71 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 154.0, 148.0, 147.4, 132.2, 130.4, 127.7, 121.4, 119.6, 118.7, 116.7, 108.4, 107.1, 101.2, 78.4, 66.8, 33.5.

4.7.21. (2*R*,3*S*)-*trans*-3′4′-Methylenedioxyflavan-3-ol (42b)

Colourless crystals (hexane/EtOAc); yield for combined *trans*:*cis* 95%, ratio 2.6:1; mp 101–102.5 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**42a**).

4.7.22. (2*S*,3*S*)-*cis*-3′4′-Methylenedioxyflavan-3-ol (51b)

Colourless solid; mp 77–78 °C; NMR spectra correspond to those reported above for the *cis*-(2*R*,3*R*)-enantiomer (**51a**).

4.7.23. *trans*-(2*S*,3*R*)-4′-Methoxy-7-(phenylmethoxy)flavan-3-ol (43a)

Colourless solid; yield for combined *trans*:*cis* 83%, ratio 2.8:1; mp 117–118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.28 (5H, m, benzyl Ar-*H*), 7.36 (2H, aa′bb′ 'd', J = 8.7 Hz, *H*-2′ and *H*-6′), 7.00 (1H, d, J = 8.3 Hz, *H*-5), 6.95 (2H, aa′bb′ 'd', J = 8.7 Hz, *H*-3′ and *H*-5′), 6.59 (1H, dd, J = 2.5, 8.3 Hz, *H*-6), 6.55 (1H, d, J = 2.5 Hz, *H*-8), 5.01 (2H, s, OCH_2), 4.73 (1H, d, J = 8.1 Hz, *H*-2), 4.09 (1H, incompletely resolved sym m, *H*-3), 3.82 (3H, s, OCH_3), 3.05 (1H, dd, J = 5.4, 15.8 Hz, *H*-4a), 2.84 (1H, dd, J = 9.0, 15.8 Hz, *H*-4b), 1.71 (1H, d, J = 3.8 Hz, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 160.0, 158.6, 154.9, 137.1, 130.4, 130.0, 128.54, 128.49, 127.9, 127.4, 114.3, 112.5, 108.9, 102.4, 81.7, 70.1, 68.3, 55.3, 32.4.

4.7.24. *cis*-(2*S*,3*R*)-4′-Methoxy-7-(phenylmethoxy)flavan-3-ol (52a)

Colourless solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.29 (5H, m, benzyl Ar-*H*), 7.44 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-2′ and *H*-6′), 7.02 (1H, 'd', J = 9.1 Hz, *H*-5), 6.96 (2H, aa′bb′ 'd', J = 8.8 Hz, *H*-3′ and *H*-5′), 6.61 (1H, d, J = 2.6 Hz, *H*-8), 6.61 (1H, dd, J = 2.6, 9.1 Hz, *H*-6), 5.04 (2H, s, OCH_2), 5.04 (1H, s, *H*-2), 4.25 (1H, sym m, *H*-3), 3.83 (3H, s, OCH_3), 3.19 (1H, dd, J = 4.0, 16.5 Hz, *H*-4a), 2.91 (1H, dd, J = 2.5, 16.5 Hz, *H*-4b), 1.77 (1H, d, J = 6.0 Hz, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 159.6, 158.7, 154.9, 137.2, 130.8 130.4, 128.5, 127.9, 127.7, 127.4, 114.1, 111.2, 109.3, 102.8, 78.5, 70.2, 66.8, 55.3, 33.0.

4.7.25. (2*S*,3*R*)-*trans*-3′,4′-Dimethoxy-7-(phenylmethoxy)-flavan-3-ol (44a)

Colourless solid; yield for combined *trans*:*cis* 70%, ratio 3:1; mp 124–125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.28 (5H, m, benzyl Ar-*H*), 7.02 (1H, d, J = 8.3 Hz, *H*-5), 7.01 (1H, dd, J = 2.0, 8.1 Hz, *H*-6′), 6.97 (1H, d, J = 2.0, *H*-2′), 6.91 (1H, d, J = 8.1 Hz, *H*-5′), 6.60 (1H, dd, J = 2.5, 8.3 Hz, *H*-6), 6.57 (1H, d, J = 2.5 Hz, *H*-8), 5.02 (2H, s, CH_2O), 4.70 (1H, d, J = 8.3 Hz, *H*-2), 4.09 (1H, ddd, J = 5.5, 8.3, 9.4 Hz, *H*-3), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.07 (1H, dd, J = 5.5, 15.7 Hz, *H*-4a), 2.86 (1H, dd, J = 9.4, 15.7 Hz, *H*-4b), ca. 1.70 variable (1H, variable d to br s, variable J = 3.5 to 0 depending on solvent acidity and dryness, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 158.7, 154.9, 149.6, 149.6, 137.1, 130.5, 130.4, 128.6, 127.9, 127.4, 119.9, 112.6, 111.6, 110.3, 109.0, 102.5, 82.0, 70.2, 68.3, 56.1, 56.0, 32.6.

4.7.26. (2*R*,3*R*)-*cis*-3′,4′-Dimethoxy-7(phenylmethoxy)flavan-3-ol (53a)

Colourless solid; mp 114–115 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.29 (5H, m, benzyl Ar-*H*), 7.07 (1H, superimposed d, J = ca. 2.0 Hz, *H*-2′), 7.05 (superimposed m (dd with additional fine coupling), *H*-6′), 7.02 (1H, superimposed d (or md), *H*-5), 6.92 (1H, d, J = 8.2 Hz, *H*-5′), 6.63 (1H, superimposed d, J = 2.6 Hz, *H*-8), 6.61 (1H, superimposed dd, J = ca. 8.2, 2.6 Hz, *H*-6), 5.04 (2H, s, OCH_2), 5.03 (1H, s, *H*-2), 4.27 (1H, sym m, *H*-3), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.20 (1H, dd, J = 4.1, 16.5 Hz, *H*-4a), 2.91 (1H, dd, J = 2.3, 16.5 Hz, *H*-4b), ca. 1.7 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 158.7, 154.9, 149.4, 149.2, 137.2, 130.9, 130.8, 128.6, 127.9, 127.4, 118.8, 111.6, 111.2, 110.1, 109.3, 102.9, 78.6, 70.2, 66.9, 56.1, 56.1, 32.9.

4.7.27. (2*R*,3*S*)-*trans*-3′,4′-Dimethoxy-7-(phenylmethoxy)flavan-3-ol (44b)

Colourless solid; yield for combined *trans*:*cis* 68%, ratio 3:1; mp 125–126 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**44a**).

4.7.28. (2*S*,3*S*)-*cis*-3′,4′-Dimethoxy-7-(phenylmethoxy)flavan-3-ol (53b)

Colourless solid; mp 113–114.5 °C; NMR spectra correspond to those reported above for the *cis*-(2*R*,3*R*)-enantiomer (**53a**).

4.7.29. *trans*-(2*R*,3*S*)-4′-(Phenylmethoxy)flavan-3-ol (45b)

Colourless solid; yield for combined *trans*:*cis* 86%, ratio 2.7:1; mp 119–120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.30 (5H, m, benzyl Ar-*H*), 7.38 (2H, superimposed aa′bb′ 'd', J = 8.7 Hz, *H*-2′ and *H*-6′), 7.15 (1H, superimposed m (unresolved ddd), *H*-7), 7.12 superimposed m (unresolved dd), *H*-5), 7.03 (2H, aa′bb′ 'd', J = 8.7 Hz, *H*-3′ and *H*-5′), 6.92 (1H, superimposed m (ddd), *H*-6), 6.91 (1H, 'd' (superimposed dd), J = ⩾7.5 Hz, *H*-8), 5.09 (2H, s, OCH_2), 4.73 (1H, d, J = 8.3 Hz, *H*-2), 4.11 (1H, ddd, J = 5.5, 8.3, 9.3 Hz, *H*-3), 3.12 (1H, dd, J = 5.4, 16.0 Hz, *H*-4a), 2.93 (1H, dd, J = 9.3, 16.0 Hz, *H*-4b), ca. 1.6 variable (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 159.3, 154.3, 137.0, 130.5, 130.0, 128.6, 128.5, 128.0, 127.7, 127.4, 121.0, 120.3, 116.5, 115.3, 81.7, 70.2, 68.2, 33.1.

4.7.30. *cis*-(2*S*,3*S*)-4′-(Phenylmethoxy)flavan-3-ol (54b)

Colourless solid; mp 103–105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47–7.30 (5H, m, benzyl Ar-*H*), 7.45 (2H, superimposed aa′bb′

'd', J = 8.8 Hz, H-2′ and H-6′), 7.17 (1H, unresolved superimposed ddd, H-7), 7.13 (1H, unresolved superimposed dd, H-5), 6.97 (2H, aa′bb′ 'd', J = 8.8 Hz, H-3′ and H-5′), 6.96 (1H, dd, J = ca. 1.2, 8.0 Hz, H-8), 6.93 (1H, ddd, J = ca. 1.2, ca. 7.4, ca. 7.4 Hz, H-6), 5.10 (2H, s, OCH_2), 5.05 (1H, s, H-2), 4.28 (1H, sym m as broadened s, H-3), 3.27 (1H, dd, J = 4.1, 17.0 Hz, H-4a), 2.98 (1H, dd, J = 2.4, 17.0 Hz, H-4b), 1.76 variable (1H, br s, OH); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 158.8, 154.3, 137.1, 130.7, 130.4, 128.6, 128.0, 127.67, 127.65, 127.4, 121.3, 118.9, 116.8, 115.2, 78.4, 70.2, 66.8, 33.6.

4.8. General procedure for the preparation of *trans*- (43–49) and *cis*-acetates (64–70)

To the precursor *trans*- (**37**–**45**) or *cis*-flavan-3-ol (**46**–**49**, **51**, **52** and **54**) (1.0 mmol) was added a mixture of pyridine (1 mL) and Ac_2O (1 mL) and the resulting solution was allowed to stand at room temperature for >24 h. The solution was poured into sat. $NaHCO_3$ solution ($\geqslant$75 mL) and the product extracted into EtOAc (3 × 25 mL). The combined organic extracts were washed in turn with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford crude product *trans*- (**55**–**63**) and *cis*-acetates (**64**–**70**) (usually in high to quantitative yield) as either a colourless solid or a colourless, extremely viscous gum that could not be induced to crystallise. Crude material was often sufficiently pure for pharmacological evaluation and was occasionally tested as the crude product.

More frequently, the crude material was purified by short column vacuum chromatography (various solvent systems including hexane/DCM/EtOAc) to afforded pure *product* as either a colourless solid or alternatively as a viscous gum that, with a few exceptions, slowly crystallised to a colourless or off-white solid. Where possible, solid products were purified further by recrystallisation from hexane or hexane/EtOAc.

When the amount of material available for acetylation was greater or less than 1 mmol, the amounts of acetic anhydride and pyridine were scaled accordingly.

4.8.1. (2*S*,3*R*)-*trans*-3-Acetoxy-4′-methoxyflavan (55a)

Colourless crystals; yield 95%; mp 77–78 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (2H, aa′bb′ 'd', J = 8.8 Hz, H-2′ and H-6′), 7.18 (1H, ddd (with additional fine structure), J = ca. 1.5, 7.5, 8.1 Hz, H-7), 7.05 (1H, dd, J = ca. 1.2, 7.5 Hz, H-5), 6.96 (1H, dd, J = ca. 1.2, 8.1 Hz, H-8), 6.92 (1H, superimposed m (possibly ddd, J = ca. 1.2, 7.5, 7.5 Hz), H-6), 6.88 (2H, aa′bb′ 'd', J = 8.8 Hz, H-3′ and H-5′), 5.35 (1H, incompletely resolved sym m (ddd, J = 5.0, 6.4, 6.6 Hz), H-3), 5.12 (1H, d, J = 6.4 Hz, H-2), 3.80 (3H, s, OCH_3), 3.05 (1H, dd, J = 5.0, 16.5 Hz, H-4a), 2.88 (1H, dd, J = 6.6, 16.5 Hz, H-4b), 1.97 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 170.1, 159.7, 153.9, 130.3, 129.7, 127.9, 127.7, 121.0, 119.2, 116.6, 114.0, 78.3, 69.4, 55.3, 29.2, 21.0; APCI-MS ($C_{18}H_{18}O_4$ requires MH^+, m/z 299.1278, found: MH^+, m/z 299.1287).

4.8.2. Crystal data for *trans*-(2*S*,3*R*)-3-acetoxy-4′-methoxyflavan (55a)

$C_{18}H_{18}O_4$, M = 298.34. Monoclinic, a = 6.1915(9), b = 8.2754(12), c = 15.049(2) Å, α = 99.092(2) (by least-squares refinement of the setting angles for 200 reflections within θ = 1.37– 24.87), V = 761.40(19) Å^3, space group $P2_1$, Z = 2, D_m = 1.301 g cm^3, F(0 0 0) = 316. Colourless prisms Crystal dimensions 0.25 × 0.20 × 0.20 mm, μ(Mo Kα) = 0.0091 mm^{-1}.

4.8.3. (2*R*,3*S*)-*trans*-3-Acetoxy-4′-methoxyflavan (55b)

Yield 88%; mp 76–77 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**55a**); APCI-MS ($C_{18}H_{18}O_4$ requires MH^+, m/z 299.1278, found: MH^+, m/z 299.1276).

4.8.4. (2*R*,3*R*)-*cis*-3-Acetoxy-4′-methoxyflavan (64a)

Colourless crystals (hexane/EtOAc); yield 99%; mp 145–146 °C [lit. mp 140 °C];[19] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (2H, aa′bb′ 'd', J = 8.8 Hz, H-2′ and H-6′), 7.18 (1H, unresolved ddd, H-7), 7.10 (1H, unresolved dd, J = ca. 7.5 Hz, H-5), 6.97 (1H, unresolved dd, J = ca. 8.4 Hz, H-8), 6.93 (1H, superimposed m (presumed ddd), H-6), 6.91 (2H, aa′bb′ 'd', J = 8.8 Hz, H-3′ and H-5′), 5.40 (1H, sym m (ddd), H-3), 5.11 (1H, br s, H-2), 3.82 (3H, s, OCH_3), 3.31 (1H, dd, J = 4.6, 17.6 Hz, H-4a), 2.99 (1H, dd, J = 2.0, 17.6 Hz, H-4b), 1.91 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.3, 159.6, 154.4, 130.1, 129.8, 127.8, 127.7, 121.1, 118.5, 116.9, 113.8, 77.3, 68.3, 55.3, 30.9, 20.9; APCI-MS ($C_{18}H_{18}O_4$ requires MH^+, m/z 299.1278, found: MH^+, m/z 299.1275).

4.8.5. Crystal data for *cis*-(2*R*,3*R*)-3-acetoxy-4′-methoxyflavan (64a)

$C_{18}H_{18}O_4$, M = 298.32. Orthorhombic, a = 5.6430(12), b = 14.644(3), c = 18.586(4) Å (by least-squares refinement of the setting angles for 200 reflections within θ = 1.77–26.84), V = 1535.9(6) Å^3, space group $P2_12_12_1$, Z = 4, D_m = 1.290 g cm^{-3}, F(0 0 0) = 632. Colourless prisms. Crystal dimensions 0.20 × 0.15 × 0.15 mm, μ(Mo Kα) = 0.0091 mm^{-1}.

4.8.6. (2*S*,3*S*)-*cis*-3-Acetoxy-4′-methoxyflavan (64b)

Colourless solid, yield 99%; mp 144–145.5 °C [lit. mp 142 °C];[19] NMR spectra correspond to those reported above for the *cis*-(2*R*,3*R*)-enantiomer (**64a**); APCI-MS ($C_{18}H_{18}O_4$ requires MH^+, m/z 299.1278, found: MH^+, m/z 299.1274).

4.8.7. (2*S*,3*R*)-*trans*-3-Acetoxy-3′,4′-dimethoxyflavan (56a)

Colourless solid; yield 98%; mp 76–77 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (1H, ddd (with additional fine structure), J = ca. 1.5, 7.3, 8.2 Hz, H-7), 7.06 (1H, dd (with additional fine structure), J = ca. 1.5, 7.5 Hz, H-5), 6.97 (1H, dd, J = ca. 1.0, 8.2 Hz, H-8), 6.92 (1H, superimposed m (ddd, J = ca. 1.0, 7.3, 7.5 Hz), H-6), 6.92 (1H, superimposed m (ddd, J = ca. 0.5, 2.0, 8.1 Hz), H-6′), 6.89 (1H, d, J = 2.0 Hz, H-2′), 6.84 (1H, d, J = 8.1 Hz, H-5′), 5.38 (1H, ddd, J = 5.1, 6.4, 6.8 Hz, H-3), 5.11 (1H, broadened d (d of unresolved m), J = 6.4 Hz, H-2), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.07 (1H, dd, J = 5.1, 16.5 Hz, H-4a), 2.89 (1H, dd, J = 6.8, 16.5 Hz, H-4b), 1.97 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.0, 153.8, 149.25, 149.22, 130.8, 129.7, 127.9, 121.0, 119.24, 119.17, 116.5, 111.4, 109.9, 78.5, 69.4, 56.0, 56.0, 29.3, 21.0; APCI-MS ($C_{19}H_{20}O_5$ requires MH^+, m/z 329.1384, found: MH^+, m/z 329.1380).

4.8.8. (2*R*,3*S*)-*trans*-3-Acetoxy-3′,4′-dimethoxyflavan (56b)

Colourless solid; quantitative yield; mp 92–93 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**56a**); APCI-MS ($C_{19}H_{20}O_5$ requires MH^+, m/z 329.1384, found: MH^+, m/z 329.1376).

4.8.9. (2*R*,3*R*)-*cis*-3-Acetoxy-3′,4′-dimethoxyflavan (65a)

Colourless solid; yield 92%; mp 93.5–95 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (1H, incompletely resolved ddm (or ddd with additional fine structure), J = ca. 7.4, 8.2 Hz, H-7), 7.10 (1H, incompletely resolved dm (or dd with additional fine structure), J = ca. 7.4 Hz, H-5), 7.05 (1H, d, J = 2.0 Hz, H-2′), 6.99 (1H, dd, J = ca. 1.2, 8.2 Hz, H-8), 6.98 (1H, ddd, J = ca. 0.6*, 2.0, 8.3 Hz, H-6′), 6.94 (1H, ddd, J = ca. 1.2, 7.4, 7.4 Hz, H-6), 6.87 (1H, d, J = 8.3 Hz, H-5′), 5.42 (1H, sym m (ddd, J = 1.4, 2.2, 4.4 Hz), H-3), 5.10 (1H, m as br s, H-2), 3.91 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.32 (1H, dd, J = 4.4, 17.7 Hz, H-4a), 2.99 (1H, dd, J = 2.2, 17.7 Hz, H-4b), 1.93 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.2, 154.3, 149.11, 149.06, 130.6, 129.8, 127.7, 121.2, 119.0, 118.5, 116.9, 111.2, 110.3, 77.3, 68.3, 56.02, 56.00, 31.0, 20.9; APCI-MS ($C_{19}H_{20}O_5$ requires MH^+, m/z 329.1384, found: MH^+, m/z 329.1380).

* shown to be coupled to H-2 by decoupling experiment.

4.8.10. (2*S*,3*S*)-*cis*-3-Acetoxy-3′,4′-dimethoxyflavan (65b)

Colourless solid; yield 95%; mp 94–95 °C; NMR spectra correspond to those reported above for the *cis*-(2*R*,3*R*)-enantiomer (**65a**); EI-MS ($C_{19}H_{20}O_5$ requires MH^+, *m/z* 328.1311, found: MH^+, *m/z* 328.1131).

4.8.11. (2*S*,3*R*)-*trans*-3-Acetoxy-4′,6-dimethoxyflavan (57a)

Colourless solid; quantitative yield; mp 84–85 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 6.89 (1H, d, *J* = 8.9 Hz, *H*-8), 6.87 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 6.75 (1H, dd, *J* = 3.0, 8.9 Hz, *H*-7), 6.58 (1H, d, *J* = 3.0 Hz, *H*-5), 5.33 (sym m as apparent td (ddd, *J* = 5.0, 6.5, 6.5 Hz), *H*-3), 5.06 (1H, d, *J* = 6.5 Hz, *H*-2), 3.80 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.03 (1H, dd, *J* = 5.0, 16.6 Hz, *H*-4a), 2.85 (1H, dd, *J* = 6.5, 16.6 Hz, *H*-4b), 1.97 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1, 159.6, 154.0, 147.9, 130.4, 127.8, 119.9, 117.2, 114.2, 114.1, 114.0, 78.2, 69.5, 55.8, 55.3, 29.5, 21.0; EI-MS ($C_{19}H_{20}O_5$ requires MH^+, *m/z* 328.1311, found: MH^+, *m/z* 328.1312).

4.8.12. (2*R*,3*R*)-*cis*-3-Acetoxy-4′,6-dimethoxyflavan (66a)

Colourless solid; yield 98%; mp 130–132 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.19 8.8 Hz, *H*-2′ and *H*-6′), 6.91 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 6.91 (1H, d, *J* = 8.9 Hz, *H*-8), 6.75 (1H, dd, *J* = 3.0, 8.9 Hz, *H*-7), 6.62 (1H, d, *J* = 3.0 Hz, *H*-5), 5.38 (1H, sym m (ddd), *H*-3), 5.04 (1H, unresolved m as broadened s, *H*-2)), 3.82 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.31 (1H, dd with additional fine coupling, *J* = 4.6, 17.7 Hz, *H*-4a), 2.95 (1H, dd, *J* = ca. 1.8, 17.7 Hz, *H*-4b), 1.92 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.3, 159.5, 154.1, 148.4, 130.2, 127.8, 119.0, 117.5, 114.3, 113.9, 113.8, 77.3, 68.3, 55.8, 55.3, 31.3, 20.9; EI-MS ($C_{19}H_{20}O_5$ requires MH^+, *m/z* 328.1311, found: MH^+, *m/z* 328.1316).

4.8.13. (2*S*,3*R*)-*trans*-3-Acetoxy-3′,4′-dimethoxy-6-methylflavan (58a)

Colourless solid; quantitative yield; mp 84–85 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (1H, dd, *J* = 1.8, 8.3 Hz, *H*-7), 6.92 (1H, ddd, *J* = <0.5, ca. 1.8, 8.2 Hz, *H*-6′), 6.90–6.84 (3H, 3 × superimposed m, *H*-5, *H*-2′ and *H*-8), 6.82 (1H, d, *J* = 8.2 Hz, *H*-5′), 5.37 (1H, ddd, *J* = 5.1, 6.4, 6.7 Hz, *H*-3), 5.11 (1H, d, *J* = 6.4 Hz, *H*-2), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.02 (1H, dd, *J* = 5.1, 16.6 Hz, *H*-4a), 2.84 (1H, dd, *J* = 6.7, 16.6 Hz, *H*-4b), 2.28 (3H, s, ArCH_3), 1.97 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.1, 151.5, 149.06, 149.00, 130.7, 130.2, 130.0, 128.5, 119.1, 118.8, 116.2, 111.1, 109.7, 78.3, 69.4, 55.9, 55.9, 29.2, 21.1, 20.5; EI-MS ($C_{20}H_{22}O_5$ requires MH^+, *m/z* 342.1467, found: MH^+, *m/z* 342.1464).

4.8.14. (2*R*,3*S*)-*trans*-3-Acetoxy-3′,4′-dimethoxy-6-methylflavan (58b)

Colourless solid; yield 98%; mp 83.5–85 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**58a**); EI-MS ($C_{20}H_{22}O_5$ requires MH^+, *m/z* 342.1467, found: MH^+, *m/z* 342.1469).

4.8.15. (2*S*,3*S*)-*cis*-3-Acetoxy-3′,4′-dimethoxy-6-methylflavan (67b)

Colourless solid; yield 88%; mp 123–124 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05 (1H, d, *J* = 2.0 Hz, *H*-2′), 6.99 (1H, ddm (ddq, *J* = ca. 1.9, 8.0, n/m Hz), *H*-7), 6.98 (1H, ddd, *J* = ca. 0.5, 2.0, 8.2 Hz, *H*-6′), 6.90 (1H superimposed m (unresolved d), *H*-5), 6.89 (1H, superimposed m (d, *J* = 8.0 Hz), *H*-8), 6.87 (1H, d, *J* = 8.2 Hz, *H*-5′), 5.40 (1H, sym m (ddd, *J* = 1.4, 2.2, 4.5 Hz), *H*-3), 5.06 (1H, m as broadened s, *H*-2), 3.91 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.29 (1H, dd, *J* = 4.5, 17.7 Hz, *H*-4a), 2.95 (1H, dd, *J* = 2.2, 17.7 Hz, *H*-4b), 2.29 (3H, s, ArCH_3), 1.92 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.4, 152.1, 148.90, 148.88, 130.6, 130.4, 130.1, 128.4, 118.9, 118.0, 116.6, 110.9, 109.9, 77.3, 68.5, 55.95, 55.94, 31.0, 21.0, 20.6; EI-MS ($C_{20}H_{22}O_5$ requires MH^+, *m/z* 342.1467, found: MH^+, *m/z* 342.1471). n/m not measurable.

4.8.16. (2*S*,3*R*)-*trans*-3-Acetoxy-3′-bromo-4′,5′-dimethoxyflavan (59a)

Colourless solid (glass); yield 93%; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.19 (1H, ddm, *J* = ca. 7.5, ca. 8.1, n/m Hz, *H*-7), 7.15 (1H, dd, *J* = ca. 0.6, 2.0 Hz, *H*-2′), 7.07 (1H, dd (or md) *J* = ca. 1.2, 7.5 Hz, *H*-5), 6.97 (1H, dd, *J* = ca. 1.2, ca. 8.1 Hz, *H*-8), 6.94 (1H, ddd, *J* = 1.2, 7.5, 7.5 Hz, *H*-6), 6.89 (1H, d, *J* = 2.0 Hz, *H*-6′), 5.32 (1H, ddd, *J* = 5.1, 6.5, 6.8 Hz, *H*-3), 5.07 (1H, d, *J* = 6.5 Hz, *H*-2), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.08 (1H, dd, *J* = 5.1, 16.5 Hz, *H*-4a), 2.89 (1H, dd, *J* = 6.8, 16.5 Hz, *H*-4b), 2.00 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.1, 153.8, 153.3, 146.4, 135.2, 129.8, 128.1, 123.0, 121.4, 119.0, 117.6, 116.5, 109.8, 77.7, 69.2, 60.6, 56.1, 29.2, 21.1; APCI-MS ($C_{19}H_{19}BrO_5$ requires MH^+, *m/z* 407.0489, found: MH^+, *m/z* 407.0489).

4.8.17. (2*S*,3*R*)-*trans*-3-Acetoxy-3′,4′-methylenedioxyflavan (60a)

Colourless, viscous gum; yield 97%; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (1H, ddm, *J* = 7.5, 8.1 Hz, *H*-7), 7.05 (1H, dm, *J* = 7.5 Hz, *H*-5), 6.95 (1H, dd, *J* = ca. 1.2, 8.1 Hz, *H*-8), 6.92 (1H, ddd, *J* = ca. 1.2, 7.5, 7.5 Hz, *H*-6), 6.86 (1H, dm, *J* = 1.7 Hz, *H*-2′), 6.84 (1H, ddd, *J* = ca. 0.6, 1.7, 7.9 Hz, *H*-6′), 6.78 (1H, d (with additional fine coupling), *J* = 7.9 Hz, *H*-5′), 5.958 and 5.956 (each 1H, d, *J* = ca. 1.4 Hz, OCH_2O), 5.31 (1H, sym m (ddd, *J* = 5.1, 6.4, 6.6 Hz), *H*-2), 5.07 (1H, broadened d (unresolved m of d), *J* = 6.4 Hz, *H*-3), 3.06 (1H, dd, *J* = 5.1, 16.4 Hz, *H*-4a), 2.87 (1H, dd, *J* = 6.6, 16.4 Hz, *H*-4b), 1.98 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.1, 153.6, 147.9, 147.5, 132.0, 129.7, 128.0, 121.1, 120.1, 119.1, 116.5, 108.2, 106.9, 101.2, 78.3, 69.3, 29.1, 21.1; APCI-MS ($C_{18}H_{16}O_5$ requires MH^+, *m/z* 313.1071, found: MH^+, *m/z* 313.1072).

4.8.18. (2*R*,3*S*)-*trans*-3-Acetoxy-3′,4′-methylenedioxyflavan (60b)

Colourless, viscous gum; yield 96%; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**60a**); APCI-MS ($C_{18}H_{16}O_5$ requires MH^+, *m/z* 313.1071, found: MH^+, *m/z* 313.1069).

4.8.19. (2*R*,3*R*)-*cis*-3-Acetoxy-3′,4′-methylenedioxyflavan (68a)

Colourless solid; yield 82%; mp 95–96 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 7.18 (1H, unresolved ddd, *H*-7), 7.10 (1H, unresolved dd, *J* = ca. 7.5 Hz, *H*-5), 6.97 (1H, unresolved dd, *J* = ca. 8.4 Hz, *H*-8), 6.93 (1H, superimposed m (presumed ddd), *H*-6), 6.91 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 5.40 (1H, sym m (ddd), *H*-3), 5.11 (1H, m as broadened s, *H*-2), 3.82 (3H, s, OCH_3), 3.31 (1H, dd, *J* = 4.6, 17.6 Hz, *H*-4a), 2.99 (1H, dd, *J* = 2.0, 17.6 Hz, *H*-4b), 1.91 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.3, 159.6, 154.4, 130.1, 129.8, 127.8, 127.7, 121.1, 118.5, 116.9, 113.8, 77.3, 68.3, 55.3, 30.9, 20.9; APCI-MS ($C_{18}H_{16}O_5$ requires MH^+, *m/z* 313.1071, found: MH^+, *m/z* 313.1069).

4.8.20. (2*S*,3*S*)-*cis*-3-Acetoxy-3′,4′-methylenedioxyflavan (68b)

Colourless solid; quantitative yield; mp 95–96 °C; NMR spectra correspond to those reported above for the *trans*-(2*R*,3*R*)-enantiomer (**68a**); APCI-MS ($C_{18}H_{16}O_5$ requires MH^+, *m/z* 313.1071, found: MH^+, *m/z* 313.1068).

4.8.21. (2*S*,3*R*)-*trans*-3-Acetoxy-4′-methoxy-7-(phenylmethoxy)flavan (61a)

Off-white solid; quantitative yield; mp 111–113 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.30 (5H, m, benzyl Ar-*H*), 7.28 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 6.94 (1H, md (possibly td with coupling to CH_2), *J* = 8.4 Hz, *H*-5), 6.88 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′

and *H*-5′), 6.60 (1H, d, *J* = 2.5 Hz, *H*-8), 6.59 (1H, dd, *J* = 2.5, 8.4 Hz, *H*-6), 5.32 (1H, ddd, *J* = 5.0, 6.3, 6.6 Hz, *H*-3), 5.10 (1H, broadened d, *J* = 6.3 Hz, *H*-2), 5.03 (2H, s, OCH_2), 3.80 (3H, s, OCH_3), 2.97 (1H, dd (with additional fine coupling), *J* = 5.0, 16.2 Hz, *H*-4a), 2.80 (1H, dd (with possible additional fine coupling), *J* = 6.6, 16.2 Hz, *H*-4b), 1.97 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.1, 159.7, 158.9, 154.6, 137.2, 130.3, 130.2, 128.6, 127.9, 127.8, 127.5, 114.0, 111.6, 108.9, 102.6, 78.4, 70.2, 69.6, 55.3, 28.5, 21.0; APCI-MS ($C_{25}H_{24}O_5$ requires MH^+, *m/z* 405.1697, found: MH^+, *m/z* 405.1691).

4.8.22. (2*R*,3*R*)-*cis*-3-Acetoxy-4′-methoxy-7-(phenylmethoxy)-flavan (69a)

Colourless solid (needles, hexane/EtOAc); yield 61%; mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.29 (5H, m, benzyl Ar-*H*), 7.37 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 6.98 (1H, 'm' (distorted d), *H*-5), 6.91 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 6.62 (1H, superimposed d, *J* = 2.5 Hz, *H*-8), 6.60 (1H, dd, *J* = 2.5, 7.5 Hz, *H*-6), 5.38 (1H, sym m (ddd, *J* = 1.4, 2.3, 4.5 Hz), *H*-3), 5.08 (1H, m (as broadened s), *H*-2), 5.04 (2H, s, OCH_2), 3.82 (3H, s, OCH_3), 3.23 (1H, dd, *J* = 4.5, 17.2 Hz, *H*-4a), 2.92 (1H, dd, *J* = 2.3, 17.2 Hz, H_2-4b), 1.92 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.3, 159.6, 158.8, 155.2, 137.2, 130.3, 130.1, 128.6, 127.9, 127.8, 127.5, 113.8, 110.9, 109.1, 102.9, 77.4, 70.3, 68.4, 55.3, 30.3, 20.9; APCI-MS ($C_{25}H_{24}O_5$ requires MH^+, *m/z* 405.1697, found: MH^+, *m/z* 405.1688).

4.8.23. (2*S*,3*R*)-*trans*-3-Acetoxy-3′,4′-dimethoxy-7-(phenylmethoxy)flavan (62a)

Colourless solid; yield 93%; mp 116–117.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.29 (5H, m, benzyl Ar-*H*), 6.95 (1H, dm, *J* = ca. 8.3 Hz, *H*-5), 6.91 (1H, partly superimposed m (ddd, *J* = ca. 0.5, 1.9, 8.5 Hz), *H*-6′), 6.87 (1H, d, *J* = 1.9 Hz, *H*-2′), 6.83 (1H, d, *J* = 8.5 Hz, *H*-5′), 6.61 (1H, d, *J* = 2.6 Hz, *H*-8), 6.59 (1H, dd, *J* = 2.6, 8.3 Hz, *H*-6), 5.35 (1H, ddd, *J* = 5.1, 6.4, 6.7 Hz, *H*-3), 5.08 (1H, broadened d (or d of unresolved m), *J* = 6.4 Hz, *H*-2), 5.04 (2H, s, OCH_2), 3.87 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 2.98 (1H, dd, *J* = 5.1, 16.1 Hz, *H*-4a), 2.81 (1H, dd, *J* = 6.7, 16.1 Hz, *H*-4b), 1.97 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.1, 158.8, 154.5, 149.26, 149.24, 137.1, 130.7, 130.2, 128.6, 127.9, 127.4, 119.2, 111.6, 111.4, 109.9, 108.9, 102.5, 78.5, 70.2, 69.5, 56.0, 56.0, 28.6, 21.0; APCI-MS ($C_{25}H_{24}O_5$ requires MH^+, *m/z* 435.1802, found: MH^+, *m/z* 435.1802).

4.8.24. (2*R*,3*S*)-*trans*-3-Acetoxy-3′,4′-dimethoxy-7-(phenylmethoxy)flavan (62b)

Colourless solid; quantitative yield; mp 115–117 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**62a**); APCI-MS ($C_{25}H_{24}O_5$ requires MH^+, *m/z* 435.1802, found: MH^+, *m/z* 435.1797).

4.8.25. *trans*-(2*R*,3*S*)-3-Acetoxy-4′-(phenylmethoxy)flavan (63b)

Colourless solid; yield 97%; mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.30 (5H, m, benzyl Ar-*H*), 7.29 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 7.18 (1H, ddd, *J* = ca. 1.6, 7.5, 8.1 Hz, *H*-7), 7.05 (1H, dd, *J* = ca. 1.6, 7.5 Hz, *H*-5), 6.96 (1H, superimposed m (dd), *H*-8), 6.95 (2H, aa′ bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 6.92 (1H, superimposed m (ddd, *J* = 1.2, 7.5, 7.5 Hz), *H*-6), 5.34 (1H, m (ddd, *J* = 5.0, 6.2, 6.5 Hz), *H*-3), 5.13 (1H, d, *J* = 6.2 Hz, *H*-2), 5.05 (2H, s, OCH_2), 3.05 (1H, dd, *J* = 5.0, 16.5 Hz, *H*-4a), 2.85 (1H, dd, *J* = 6.5, 16.5 Hz, *H*-4b), 1.96 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 170.1, 158.9, 153.9, 137.0, 130.7, 129.7, 128.6, 128.0, 127.9, 127.8, 127.5, 121.0, 119.2, 116.6, 115.1, 78.3, 70.2, 69.5, 29.2, 21.0; APCI-MS ($C_{19}H_{20}O_5$ requires MH^+, *m/z* 375.1591, found: MH^+, *m/z* 375.1591).

4.8.26. *cis*-(2*S*,3*S*)-3-Acetoxy-4′-(phenylmethoxy)flavan (70b)

Colourless solid; quantitative yield; mp 131–133 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47–7.30 (5H, m, benzyl Ar-*H*), 7.38 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 7.18 (1H, m (unresolved ddd), *H*-7), 7.09 (1H, br d (unresolved dd), *H*-5), 6.98 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 6.97 (1H, superimposed m (dd), *H*-8), 6.93 (1H, apparent td (ddd, *J* = ca. 1.2, 7.4, 7.4 Hz), *H*-6), 5.41 (1H, sym m, *H*-3), 5.10 (1H, m as broadened s, *H*-2), 5.08 (2H, s, OCH_2), 3.31 (1H, dd, *J* = 4.4, 17.5 Hz, *H*-4a), 2.98 (1H, dd, *J* = 2.2, 17.5 Hz, *H*-4b), 1.91 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.3, 158.8, 154.4, 137.1, 130.4, 129.8, 128.6, 128.0, 127.8, 127.7, 127.5, 121.1, 118.5, 116.9, 114.8, 77.3, 70.2, 68.3, 30.9, 20.9; APCI-MS ($C_{19}H_{20}O_5$ requires MH^+, *m/z* 375.1591, found: MH^+, *m/z* 375.1591).

4.9. General procedure for the deprotection of benzyloxy substituted 3-acetoxyflavans

A mixture of the precursor benzyloxy compound (**61a**, **62a**,**b**, **63b**, **69a**, **70a**) (1.0 mmol) and $Pd(OH)_2$–C (50 mg, 20% on C) in MeOH/THF (1:1, 20 mL) was stirred vigorously at room temperature under H_2 (1 atm) for 6 h. The reaction mixture was filtered through Celite to remove catalyst and the filtrate concentrated under reduced pressure to yield a glassy off-white solid. Column chromatography (DCM/EtOAc 19:1) afforded the pure product.

4.9.1. *trans*-(2*S*,3*R*)-3-Acetoxy-7-hydroxy-4′-methoxyflavan (71a)

Colourless foam; yield 99%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 6.89 (1H, md, *J* = 8.0 Hz, *H*-5), 6.87 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 6.46 (1H, d, *J* = 2.5 Hz, *H*-8), 6.43 (1H, dd, *J* = 2.5, 8.0 Hz, *H*-6), 5.32 (1H, sym m (ddd, *J* = 5.0, 6.2, 6.5 Hz), *H*-3), 5.10 (1H, d, *J* = 6.2 Hz, *H*-2), 5.1 variable (1H, br s, O*H*), 3.80 (3H, s, OCH_3), 2.95 (1H, dd (with additional fine coupling), *J* = 5.0, 16.2 Hz, *H*-4a), 2.79 (1H, dd, *J* = 6.5, 16.2 Hz, *H*-4b), 1.97 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.4, 159.6, 155.6, 154.6, 130.4, 130.2, 127.7, 114.1, 111.3, 108.8, 103.3, 78.3, 69.7, 55.3, 28.4, 21.0.

4.9.2. *trans*-(2*S*,3*R*)-3-Acetoxy-3′,4′-dimethoxy-7-hydroxyflavan (72a)

Faintly pink solid; quantitative yield; mp 64–66 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93–6.86 (3H, 3 × superimposed m, *H*-5, *H*-2′ and *H*-6′), 6.83 (1H, d, *J* = 8.2 Hz, *H*-5′), 5.47 (1H, d, *J* = 2.5 Hz, *H*-8), 6.44 (1H, dd, *J* = 2.5, 8.2 Hz, *H*-6), 5.34 (1H, sym m (ddd, *J* = 5.0, 6.3, 6.7 Hz), *H*-3), 5.10 (1H, br s, O*H*), 5.08 (1H, d, *J* = 6.3 Hz, *H*-2), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.96 (1H, dd, *J* = 5.0, 16.3 Hz, *H*-4a), 2.80 (1H, dd, *J* = 6.7, 16.3 Hz, *H*-4b), 1.97 (3H, s, C(O)CH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.4, 155.5, 154.4, 149.01, 148.98, 130.5, 130.4, 119.1, 111.2, 111.1, 109.5, 108.8, 103.2, 78.4, 69.5, 55.92, 55.91, 28.5, 21.1.

4.9.3. *trans*-(2*R*,3*S*)-3-Acetoxy-3′,4′-dimethoxy-7-hydroxyflavan (72b)

Faintly pink solid; quantitative yield; mp 63–65 °C; NMR spectra correspond to those reported above for the *trans*-(2*S*,3*R*)-enantiomer (**72a**).

4.9.4. *trans*-(2*R*,3*S*)-3-Acetoxy-4′-hydroxyflavan (73b)

Faintly pink solid; yield 98%; mp 50–52 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 7.18 (1H, m (non-resolved ddd), *H*-7), 7.06 (1H, non-resolved dd, *H*-5), 6.96 (1H, superimposed non-resolved dd, *H*-8), 6.92 (1H, superimposed non-resolved ddd, *H*-6), 6.79 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 5.44 (1H, br s, O*H*), 5.35 (1H, sym m (ddd, *J* = 5.2, 6.2, 6.9 Hz), *H*-3), 5.08 (1H, d, *J* = 6.5 Hz, *H*-2), 3.06 (1H, dd, *J* = 5.2,

16.0 Hz, *H*-4a), 2.89 (1H, dd, *J* = 6.9, 16.0 Hz, *H*-4b), 1.97 (3H, s, C(O)C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.4, 155.7, 153.7, 130.2, 129.8, 127.9, 127.9, 121.0, 119.1, 116.6, 115.4, 78.3, 69.4, 29.2, 21.1.

4.9.5. *cis*-(2*S*,3*S*)-3-Acetoxy-4′-methoxy-7-hydroxyflavan (74a)

Faintly pink solid; quantitative yield; mp 147–148.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-2′ and *H*-6′), 6.94 (1H, d, *J* = 8.2 Hz, *H*-5), 6.91 (2H, aa′bb′ 'd', *J* = 8.8 Hz, *H*-3′ and *H*-5′), 6.46 (1H, superimposed m (d, *J* = 2.5 Hz), *H*-8), 6.44 (1H, dd, *J* = 2.5, 8.2 Hz, *H*-6), 5.38 (1H, sym m, *H*-3), 5.08 (1H, s, *H*-2), 5.02 (1H, br s, O*H*), 3.82 (3H, s, OC*H*$_3$), 3.23 (1H, dd, *J* = 4.4, 17.2 Hz, *H*-4a), 2.90 (1H, dd, *J* = 2.2, 17.2 Hz, *H*-4b), 1.92 (3H, s, C(O)C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.6, 159.5, 155.3, 155.1, 130.5, 129.9, 127.8, 113.7, 110.6, 108.8, 103.5, 77.3, 68.4, 55.3, 30.3, 21.0.

4.9.6. *cis*-(2*S*,3*S*)-3-Acetoxy-4′-hydroxyflavan (75b)

Faintly pink solid; quantitative yield; mp 51–53 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (2H, aa′bb′ 'd', *J* = 8.6 Hz, *H*-2′ and *H*-6′), 7.18 (1H, m (non-resolved ddd), *H*-7), 7.10 (1H, non-resolved dd, *H*-5), 6.96 (1H, superimposed non-resolved dd, *H*-8), 6.93 (1H, ddd, *J* = 1.2, 7.4, 7.4 Hz, *H*-6), 6.82 (2H, aa′bb′ 'd', *J* = 8.6 Hz, *H*-3′ and *H*-5′), 5.43 (1H, sym m (ddd), *H*-3), 5.32 (1H, br s, O*H*), 5.10 (1H, s, *H*-2), 3.33 (1H, dd, *J* = 4.3, 17.5 Hz, *H*-4a), 2.98 (1H, dd, *J* = 1.8, 17.5 Hz, *H*-4b), 1.92 (3H, s, C(O)C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 170.7, 155.6, 154.3, 130.0, 129.8, 127.9, 127.7, 121.1, 118.4, 116.9, 115.2, 77.2, 68.3, 30.9, 21.0.

4.10. Biological protocol

cDNA for human α_1, β_2 and γ_{2L} $GABA_A$ receptor subunits subcloned into pCDM8 were provided by Dr. Paul Whiting (Merck, Sharpe and Dohme Research Labs, Harlow, UK). The protocol for in vitro transcription of cRNA has been previously described.[9,31] Briefly, cDNA vectors were linearised with the appropriate restriction endonucleases and capped transcripts were produced from linearised plasmids using the mMessage mMachine T7 transcription kit (Ambion, Austin, TX). cRNA was diluted and stored in diethylpyrocarbonate treated water at −80 °C. The procedure involving the extraction, separation, and enzymatic treatment of *X. laevis* oocytes was identical to that previously described.[9] Stage V–VI oocytes were selected and injected (Nanoject, Drummond Scientific Co., Broomali, PA) with 2–3 ng of cRNA in a 1:1:2 ratio of α:β:γ subunits to facilitate the incorporation of the γ subunit and to achieve the desirable level of expression (maximal response to GABA less than 1 μA). High-expressing oocytes were obtained by injection of 10 ng of RNA (maximal GABA activation 1.5–2.5 mA). After injection, oocytes were incubated at 16 °C in ND96 storage solution (96 mM NaCl, 2 mM KCl, 1 mM $MgCl_2{\cdot}6H_2O$, 1.8 mM $CaCl_2$, 5 mM HEPES, pH 7.5, supplemented with 2.5 mM pyruvate, 0.5 mM theophylline and 50 mg/ml gentamycin) for 3–4 days before use in electrophysiological studies.

Currents were recorded using the two-electrode voltage clamp technique as described previously.[9,31] Oocytes were placed in a 100 ml chamber connected to a reservoir bottle containing ND96 solution (96 mM NaCl, 2 mM KCl, 1 mM $MgCl_2{\cdot}6H_2O$, 1.8 mM $CaCl_2$, 5 mM HEPES, pH 7.5). Glass microelectrodes were made using a micropipette puller (Narishige Scientific Instrument Laboratory, Tokyo, Japan) and filled with 3 M KCl (0.5–2 MΩ). The oocytes were impaled and the membrane potential was clamped at −60 mV while continuously superfused with ND96 solution (10 ml/min). Stock solutions of the drug were prepared in DMSO, except for GABA where distilled water was used, and applied into the perfusate until a peak response was reached. DMSO concentration in the perfusate was 0.6% and did not produce any alteration in the recording. Current measurements were obtained using a Geneclamp 500 voltage clamp amplifier (Axon Instruments INC, Foster City, CA), a MacLab/8 recorder (ADInstruments, Sydney, NSW, Australia) and Chart program v3.6. Responses were graphed as mean ± SEM from at least three oocytes from at least two different batches.

Modulation of GABA-elicited currents was tested by applying the sample drugs at 30 μM with a concentration of GABA that produced 5% of maximal activation (EC_5). A 5–10 min washout period was allowed between drug applications to avoid receptor desensitisation. For comparison of doses at 30 μM, responses were normalised to the response to 30 μM **55a**[7] on the same cell ($n \leqslant 5$). For the dose–response curves the responses were recorded and normalised as: percentage potentiation = $(I_{drug} - I_{GABA}) \times 100/I_{GABA}$, where I_{drug} is the current in the presence of a given concentration of the drug, and I_{GABA} is amplitude of the control GABA current ($n \geqslant 8$).

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Supplementary data

^{1}H NMR data for compounds. Crystallographic data (excluding factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 733419, 733420, 733421 and 733425 for **55a**, **41a**, **64a** and **37a**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.08.062.

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