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Synthesis and Reactions of Flav-3-en-3-ols

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Abstract—Flavan-3,4-diols are subject to facile conversion into flav-3-en-3-ols which are versatile precursors in flavonoid synthesis. The flavan-3-ones undergo a unique Lewis acid assisted α-sulfenylation reaction with benzyl mercaptan in the presence of $SnCl_4$. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

The absence of compelling evidence regarding the biosynthetic pathways to flavan-3-ols and proanthocyanidins has evoked much speculation about the key intermediate that could unequivocally explain the formation of these compounds.[1–8] A logical reductive sequence from the (+)-2,3-*trans*-dihydroflavonols to the flavan-3,4-diol and flavan-3-ol level for the 2,3-*trans* series of both the procyanidins (3,5,7,3′,4′-pentahydroxylation) and prodelphinidins (3,5,7,3′,4′,5′-hexahydroxylation) has been demonstrated in vitro and in vivo.[9–12] The latter enzymological studies have shifted the focus from the α-hydroxychalcone[2,3] and flav-3-en-3-ol[5–7,13] hypotheses to the stereospecific C-3 hydroxylation of flavanones and hence the intermediacy of 2,3-*trans*- and 2,3-*cis*-dihydroflavonols. This may explain why the synthesis[8,14] and synthetic potential[8] of the flav-3-en-3-ols were not extensively explored. Here we discuss the facile access to flav-3-en-3-ols and preliminary results relevant to their utilization in flavonoid synthesis.

Results and Discussion

Attempts at transforming 4′,7,8-tri-*O*-methylepioritin-4α-ol **1** with phosphorous tribromide (PBr_3) in THF at ca. 20°C into the 4β-bromoflavan-3-ol **2** for use as an intermediate in the synthesis of ether-linked proteracacinidin dimers,[15,16] invariably lead to the quantitative formation of the (2*R*)-4′,7,8-trimethoxyflavan-3-one **5** (Scheme 1). Monitoring of the reaction with ^{1}H NMR indicates that the flavan-3,4-diol **1** is first converted into the 4β-bromoflavan-3-ol **2** ($J_{2,3}$=1.0 (ca.), $J_{3,4}$=2.5 Hz) (Table 2). Since 2,3-*cis*-3,4-*cis*-flavan-3,4-diols are conspicuously resistant to S_N2 processes at C-4,[14,17] the inversion of configuration at this stereocenter probably results from neighbouring group participation by the axial C-3 hydroxyl function.[15,16] Evaporation of the solvent leads to spontaneous dehydrobromination of the 4β-bromo analogue **2** to afford the flav-3-en-3-ol **3**. The latter compound exists in solution as the keto tautomer **5** and is isolated in yields of ca. 80%. The ^{1}H NMR spectrum (Table 1) of the flavan-3-one **5** displays a singlet (δ 5.35) for H-2 and an AB spin system (δ 3.62, 3.73, both d, both J=20.0 Hz) for the diastereotopic C-4 methylene protons. Acetylation with acetic anhydride in pyridine leads to regioselective formation of the 3-enol acetate **4** which shows H-2 and H-4 as broadened singlets (δ 5.85, 6.53, resp.) in the ^{1}H NMR spectrum (Table 1).

The flavan-3-one **5** is reduced by sodium borohydride in ethanol to an epimeric mixture of 4′,7,8-tri-*O*-methyloritin **6** (27%) and 4′,7,8-tri-*O*-methylepioritin **8** (38%). This represents the first synthetic access to the hitherto naturally unknown oritin class of flavan-3-ols. The flavan-3-ols **6** and **8** were separated and identified as the 2,3-*trans*- and 2,3-*cis*-3-*O*-acetyl derivatives **7** ($J_{2,3}$=5.0 Hz) and **9** ($J_{2,3}$=1.0 Hz (ca.)) by comparison of ^{1}H NMR (Table 2) and CD data with those of similar derivatives of related flavan-3-ols having similar relative and absolute configurations.[18] Such a small coupling constant for the 2,3-*trans* derivative is reminiscent of a significant contribution of the E- as opposed to the A-form to the conformational itinerary of the heterocyclic ring.[19] The amplitudes of the Cotton effects in the ^1L_a and ^1L_b regions of the CD spectra of the flavan-3-ol derivatives **7** and **9** are of the same magnitude as those of enantiopure flavan-3-ols,[18] hence indicating that the reduction step occurs without racemization at C-2. The formation of an epimeric pair of flavan-3-ols **6** and **8** in moderate yields

Keywords: flavanoids; flav-3-en-3-ols; regioselection; stereoselection; α-sulfenylation.

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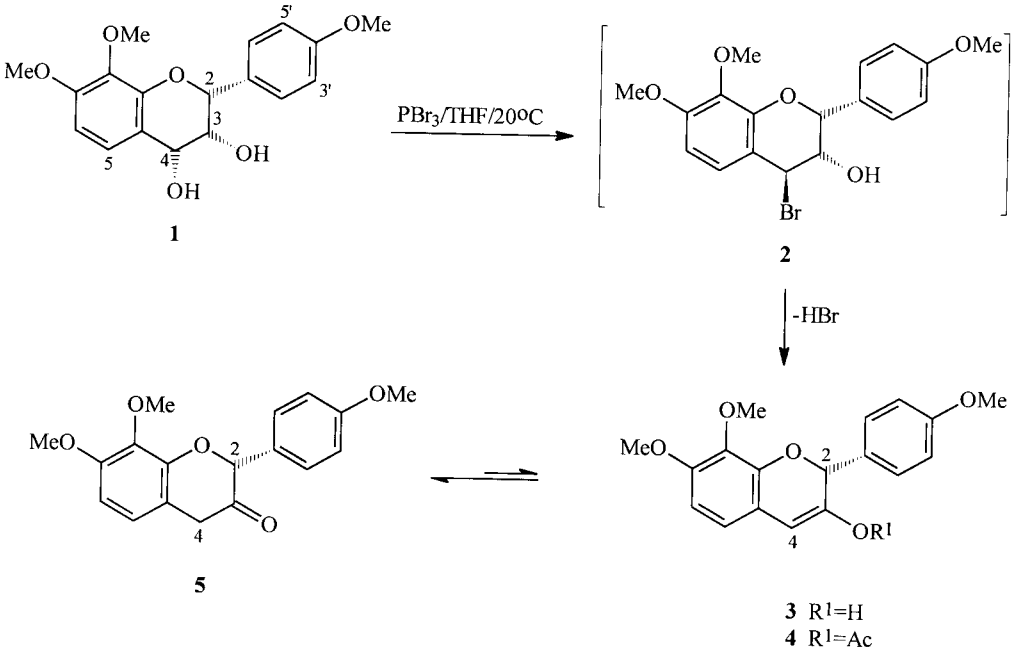


Scheme 1. Transformation of the flavan-3,4-diol **1** into flav-3-en-3-ol **3** and flavan-3-one **5** tautomers.

Table 1. ^{1}H NMR (300 MHz) data of flav-3-en-3-ol and flaven-3-one derivatives at 293 K. Splitting patterns and *J*-values (Hz) are given in parentheses

Proton	**4**[a]	**5**[a]	**12**[b]	**14**[a]	**16/17**	**20/21**[a]
H-5(A)	6.75(d,9.0)	6.80(d,9.0)	7.01(d,8.5)	7.03(d,8.5)	7.04(d,8.5)	6.96(d,8.5)
H-6(A)	6.48(d,9.0)	6.65(d,9.0)	6.56(dd,2.5,8.5)	6.68(dd,2.5,8.5)	6.65(dd,2.5,8.5)	6.48(dd,2.5,8.5)
H-8(A)	–	–	6.54(d,2.5)	6.59(d,2.5)	6.70(d,2.5)	6.41(d,2.5)
H-2′(B)	–	–	6.87(d,2.5)	7.26(d,2.5)	6.92(d,2.5)	7.00(d,2.5)
H-5′(B)	–	–	6.81(d,8.5)	7.20(d,8.5)	6.86(d,8.5)	6.84(d,8.5)
H-6′(B)	–	–	6.73(dd,2.5,8.5)	7.35(dd,2.5,8.5)	6.95(dd,2.5,8.5)	6.99(dd,2.5,8.5)
H-2′/6′(B)	7.38(d,9.0)	7.32(d,9.0)	–	–	–	–
H-3′/5′(B)	6.86(d,9.0)	6.89(d,9.0)	–	–	–	–
H-2(C)	5.85(br.s)	5.35(br.s)	5.22(br.s)	5.90(br.s)	5.26(br.s)	3.85(br.s)
H-4(C)	6.53(s)	3.62(d,20.0) 3.73(d,20.0)	3.55(d,20.0) 3.68(d,20.0)	6.53(s)	3.61(d,20.0) 3.72(d,20.0)	6.47(s)
OMe	3.64,3.80,3.84 (each s)	3.80,3.85,3.88 (each s)	–	–	3.81,3.87,3.89 (each s)	3.75,3.87,3.89 (each s)
OAc	2.07(s)	–	–	(each s)	–	2.02(s)

[a] In $CDCl_3$.
[b] In $(CD_3)_2CO$.

Table 2. ^{1}H NMR (300 MHz) data of 4-bromoflavan-3-ol **2**, flavan-3-ol derivatives **7** and **9** and benzylthio-flavan-3-ones **18** and **19** in $CDCl_3$ at 393 K. Splitting patterns and *J*-values (Hz) are given in parentheses

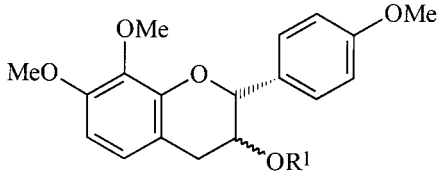
Proton	**2**	**7**	**9**	**18/19**
H-5(A)	7.11(d,9.0)	6.74(d,8.5)	6.79(d,8.5)	7.38(d,8.5)
H-6(A)	6.65(d,9.0)	6.55(d,8.5)	6.57(d,8.5)	6.86(dd,2.5,8.5)
H-8(A)	–	–	–	7.02(d,2.5)
H-2′(B)	–	–	–	7.00(d,2.5)
H-5′(B)	–	–	–	6.83(d,8.5)
H-6′(B)	–	–	–	6.97(dd,2.5,8.5)
H-2′/6′(B)	7.51(d,9.0)	7.28(d,9.0)	7.40(d,9.0)	–
H-3′/5′(B)	7.01(d,9.0)	6.88(d,9.0)	6.92(d,9.0)	–
Ph–CH_2–S–	–	–	–	7.27–7.36
H-2(C)	5.78(br.s)	5.29(d,5.0)	5.16(br.s)	5.00(br.s)
H-3(C)	4.39(dd,1.0,2.5)	5.33(m)	5.41(m)	–
H-4(C)	5.35(d,2.5)	2.80(dd,5.5,16.5) 2.95(dd,4.5,16.5)	2.95(dd,3.0,17.0) 3.27(dd,4.5,17.0)	6.55(s)
Ph–*CH_2*–S–	–	–	–	3.68(d,13.5) 3.75(d,13.5)
OMe	3.86,3.90,3.92(each s)	3.81,3.84,3.91(each s)	3.84,3.88,3.92(each s)	3.85,3.88,3.89(each s)
OAc		2.00(s)	1.92(s)	–

during reduction of the flavan-3-one **5** contrasts with the claimed quantitative and highly stereoselective reduction of the racemic flav-3-en-3-ol derivative **10** into an 'epicatechin-type flavan-3-ol' via catalytic hydrogenation.[8] Conversion of flavan-3-one **5** into the oritin and epioritin derivatives **6** and **8** represents the first protocol to manipulate the C-3 stereochemistry of flavan-3-ols, hence complementing the synthetic utility of their facile C-2 epimerization under alkaline conditions.[20] The high proportion of the epioritin derivative **8** is significant in view of the limited access to 2,3-*cis*-flavan-3-ols from natural sources (Scheme 2).

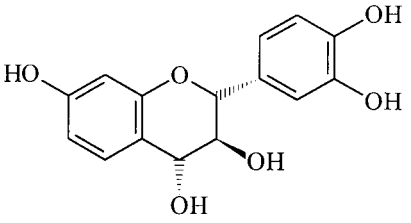
The conversion of the flavan-3,4-diol derivative **1** into the flav-3-en-3-ol **3** (see also below), together with the reduction of its keto tautomer **5** to give the 2,3-*trans*- and *cis*-flavan-3-ols **6** and **8**, are in agreement with the hypotheses regarding the role of flav-3-en-3-ols[4–7,13] and A-ring quinone methides[21,22] in flavan-3-ol and proanthocyanidin biosynthesis. Accordingly, the conversions provide direct in vitro evidence supporting the suggested in vivo role of keto-enol tautomers of types **5** and **3**.

Treatment of fisetinidol-4α-ol **11**, conveniently available from the heartwood of *Acacia mearnii* (black wattle),[23] with PBr_3 in THF at −78°C and warming to 0°C to facilitate dehydrobromination, also gives quantitative conversion into the (2*R*)-3′,4′,7-trihydroxyflavan-3-one **12**. It is again regioselectively converted into the enol acetate **14** (^{1}H NMR data—Table 1) via the flav-3-en-3-ol **13** by acetylation with acetic anhydride in pyridine. The free phenolic enol **13** is highly susceptible to aerial oxidation of its activated C_2–H bond and hence to conversion into the anthocyanidin, fisetinidin bromide **15**. Dehydrobromination and subsequent anthocyanidin formation already commenced at −78°C as is evident from the faint purple colour of the mixture which changes to a characteristic reddish at 0°C where the solvent is rapidly removed under a nitrogen current. Substantial conversion of flav-3-en-3-ol **13** into anthocyanidin during chromatography additionally accounts for the relative low isolated yield (ca. 40%) of the flavan-3-one **12**. The sequence, **11→12⇌13→15**, represents the first in vitro evidence of the intermediacy of a flav-3-en-3-ol in the transformation of a free phenolic leucoanthocyanidin into an anthocyanidin.

We next selected flavan-3-ones **16** and **17** (^{1}H NMR data, Table 1), readily available by treatment of, respectively, the 3′,4′,7-tri-*O*-methyl ethers of fisetinidol-4α-ol **11** and its enantiomer *ent*-fisetinidol-4β-ol with PBr_3 in THF, to assess the feasibility of using their enolic tautomers as electrophiles in flavonoid synthesis.



6 R1=H, ≡
7 R1=Ac, ≡
8 R1=H, ≡
9 R1=Ac, ≡



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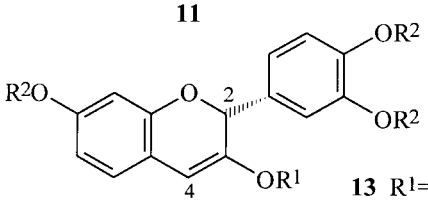
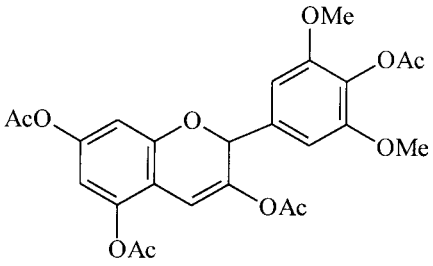


13 R1=R2=H
14 R1=R2=Ac
20 R1=Ac, R2=Me
21 C-2 epimer



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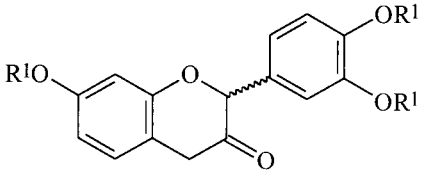
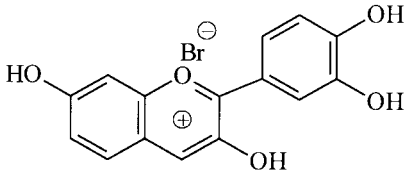
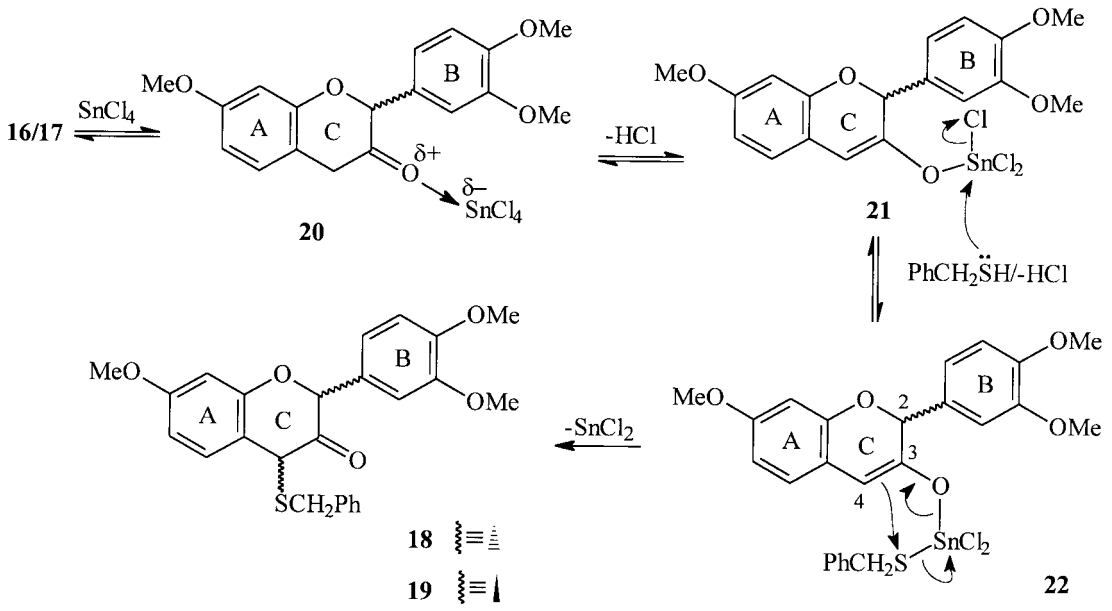


12 R1=H, ≡
16 R1=Me, ≡
17 R1=Me, ≡



15

Scheme 2.



Scheme 3. Proposed route to the formation of 4-benzylsulfanylflavan-3-ones **18**/**19** via α-sulfenylation of **16**/**17**.

Separate treatment of the flavan-3-ones **16** and **17** with tin(IV)chloride in dichloromethane containing benzyl mercaptan at 20°C affords the 2,4-*cis*-arylbenzylsulfanyl-flavan-3-ones **18** (52%) and **19** (63%) (Scheme 3). The 2,4-*cis* relative configurations of both compounds are confirmed by observation of a strong NOE association between the H-2(C) (δ 5.00) and H-4(C) (δ 6.55) resonances (^{1}H NMR data—Table 2). When taken in conjunction with the high amplitude negative Cotton effect at 239 nm in the CD spectrum of **18** and the positive Cotton effect at 244.6 nm in the spectrum of **19**, the NOE associations also confirm the absolute configurations at C-2 and C-4 as are depicted in **18** and **19**.

Although α-sulfenylation of ketones using electrophilic sulphur reagents in basic medium and under Lewis acid catalysis is well documented,[24–28] the Lewis acid catalyzed process involving mercaptans is not precedented. Thus, the formation of the 4-benzylsulfanyl flavan-3-ones **18** and **19** is presumably triggered by the initial formation of a complex **20** between the $SnCl_4$ and the carbonyl oxygen of the 3-ketoflavans **16**/**17** (Scheme 3). Such a complex should readily equilibrate with the tin(IV)enolate **21** under the influence of the electron-rich resorcinol-type A-ring (see also below). The tin(IV)enolate may then complex with the benzyl mercaptan (free of dibenzyl disulphide as possible source of electrophilic sulphur) leading to 'umpohlung' of the nucleophilic properties of sulphur in intermediate **22**. The electrophilic sulphur in **22** is now susceptible to intramolecular attack by the nucleophilic C-4 centre to give the 4-benzylsulfanylflavan-3-ones **18** and **19**. Owing to the planarity of the enolic double bond in **22**, the stereochemistry of the transfer of the thiobenzyl group is evidently directed by the *axial* hydrogen at C-2. The proposal regarding the influence of the A-ring on enolization and hence the main impetus for this unique Lewis acid assisted α-sulfenylation by a nucleophilic sulphur source, was supported by the results of a control experiment using cyclohexanone[29] which was inert under conditions effecting the facile thiolation of the flavan-3-ones **16** and **17**.

The stereoselective formation of the 2,4-*cis*-arylbenzyl-sulfanylflavan-3-ones **18** and **19** provides considerable control in manipulating the stereochemistry at C-4. The 2,4-*cis* analogues **18** and **19** are currently being elaborated as intermediates in flavonoid synthesis.

A notable feature of the aforementioned enol-acetylations is the regioselective formation of the 3-*O*-acetylflav-3-enes, e.g. **4**, in spite of the presence of the alternative enolizable

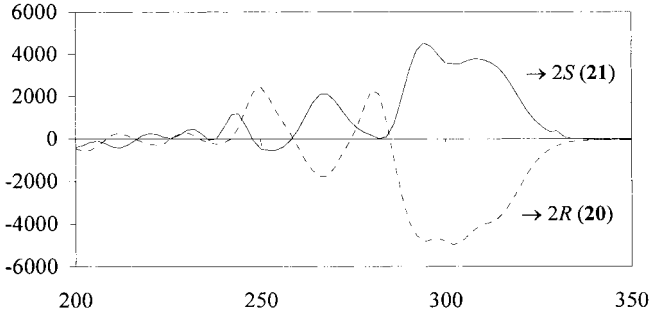


Figure 1. CD curves of (2*R*)-flav-3-en-3-ol acetate **20** and its (2*S*) enantiomer **21**.

proton at C-2 in e.g. **5**. Such selectivity is presumably attributable to the extended delocalization in the flav-3-en-3-ol, compared to a putative flav-2-en-3-ol, which permits additional delocalization of electron density of the more electron-rich ring A compared to the B-ring. The conservation of the optical integrity at C-2 of all the flav-3-en-3-ol acetates is evident from their CD spectra. These invariably display negative and positive Cotton effects for their $n\rightarrow\pi^*$ transitions in the 290–310 nm and $\pi\rightarrow\pi^*$ transitions near 240 nm, for analogues with 2*R* configuration **4**, **14** and **20**, and vice versa for compound **21** with 2*S* configuration (Fig. 1).

We have demonstrated a facile route to the flavan-3-one/flav-3-en-3-ol tautomers, which may serve as useful intermediates in flavonoid synthesis. Their further elaboration as synthetic precursors will be published elsewhere and may collectively stimulate renewed focus on their interesting chemical behaviour.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions as indicated, with Me_4Si as internal standard. FAB Mass spectra were recorded on a VG 70-70E instrument with a VG 11-250J data system and an iontech saddlefield FAB gun. TLC was performed on precoated Merck plastic sheets (silica gel 60 PF_{254} 0.25 mm) and the plates were sprayed with H_2SO_4–HCHO (40:1, v/v) after development. Preparative plates (PLC) [20×20 cm, Kieselgel PF_{254} (1.0 mm)] were air dried and used without prior activation. Methylations were performed with an excess of diazomethane in MeOH–diethyl ether over 48 h at −15°C, while acetylations were conducted in acetic anhydride–pyridine at ambient temperature. Evaporations were done under reduced pressure at ambient temperature in a rotary evaporator.

General procedures for synthesis

Flavan-3-ones. The appropriate flavan-3,4-diol (50 mg) was dissolved in dry THF (10 ml) and treated with 0.35 equiv. of PBr_3 (0.049 ml). The reaction mixture was stirred under an N_2-atmosphere for 2 h at room temperature (22°C), the volume was reduced under vacuum and the products were separated by PLC. In the case of the free phenolic flavan-3-one **12** the reaction was conducted at −78°C under Ar. The temperature was allowed to reach 0°C and the volume reduced by bubbling Ar through the mixture followed by immediate PLC separation.

Lewis acid assisted benzyl mercaptan coupling. The appropriate flavan-3-one (100 mg) was dissolved in dry DCM (10 ml) and cooled to 0°C. Under a blanket of N_2 the $SnCl_4$ (0.06 ml) was added, followed by immediate addition of BnSH (0.28 ml). The mixture was stirred for 30 min at 0°C, the temperature was allowed to rise to 22°C and stirring was continued for another 2 h. The solvent was removed with N_2 and the mixture separated by PLC.

Reduction of flavan-3-one 5. Compound **5** (17 mg) was dissolved in EtOH (10 ml), $NaBH_4$ (4 mg) added and the mixture was stirred at room temperature (25°C) for 3 h. The mixture was quenched with 0.3 M HCl (10 ml), filtered and the solvent removed under vacuum. The epimeric mixture (16 mg) was acetylated and separated by PLC (hexane/Me_2CO/EtOAc; 23:1:1, ×5) to give compounds **7** (R_f 0.28, 7.3 mg) and **9** (R_f 0.36, 5.1 mg) as pure products.

(2*R*,3*S*,4*S*)-2,3-*cis*-3,4-*trans*-4-Bromo-3-hydroxy-4′,7,8-trimethoxyflavan 2. δ_H (Table 2).

(2*R*)-3-Acetoxy-4′,7,8-trimethoxyflav-3-ene 4. *Amorphous solid* R_f 0.66, 35.8 mg (eluent: benzene/Me_2CO, 9:1); δ_H (Table 1); FABMS Calcd for $C_{20}H_{20}O_6$: 356.1259. Found: 356.1260; CD $[\theta]_{260.7}$+219, $[\theta]_{267.0}$+1304, $[\theta]_{275.9}$+257, $[\theta]_{282.6}$+558, $[\theta]_{291.8}$−25, $[\theta]_{295.5}$+157, $[\theta]_{297.4}$+8, $[\theta]_{302.6}$−645, $[\theta]_{331.6}$−27.

(2*R*)-4′,7,8-Trimethoxyflavan-3-one 5. *Amorphous solid*, R_f 0.80, 37 mg (eluent: benzene/Me_2CO, 4:1); δ_H (Table 1); FABMS Calcd for $C_{18}H_{18}O_5$: 314.1154. Found: 314.1152; IR (ν_{max}/cm^{-1}, $CHCl_3$): 1740 (C=O).

(2*R*,3*S*)-2,3-*trans*-3-Acetoxy-4′,7,8-trimethoxyflavan 7. *Amorphous solid*, R_f 0.28, 7.3 mg (eluent: hexane/Me_2CO/EtOAc, 23:1:1, ×5); δ_H (Table 2); FABMS Calcd for $C_{20}H_{21}O_6$: 357.1338. Found: 357.1337; CD $[\theta]_{222.1}$+56, $[\theta]_{226.9}$+5330, $[\theta]_{234.9}$+2200, $[\theta]_{242.3}$+8239, $[\theta]_{249.2}$+39, $[\theta]_{283.3}$−7268, $[\theta]_{297.9}$+2.

(2*R*,3*R*)-2,3-*cis*-3-Acetoxy-4′,7,8-trimethoxyflavan 9. *Amorphous solid*, R_f 0.36, 5.1 mg (eluent: hexane/Me_2CO/EtOAc, 23:1:1, ×5); δ_H (Table 2); FABMS Calcd for $C_{20}H_{21}O_6$: 357.1338. Found: 357.1338; CD $[\theta]_{237.9}$+8, $[\theta]_{243.8}$−9557, $[\theta]_{255.5}$−630, $[\theta]_{284.9}$−6532, $[\theta]_{299.2}$+6.

(2*R*)-3′,4′,7-Trihydroxyflavan-3-one 12. *Amorphous solid*, R_f 0.56, 20.4 mg (eluent: benzene/Me_2CO/MeOH, 7:2:1); δ_H (Table 1); IR (ν_{max}/cm^{-1}, $CHCl_3$): 1745 (C=O).

(2*R*)-3,3′,4′,7-Tetraacetoxyflav-3-ene 14. *Amorphous solid*, R_f 0.64, 24.3 mg (eluent: benzene/Me_2CO, 9:1); δ_H (Table 1); FABMS Calcd for $C_{23}H_{20}O_9$: 440.1107. Found: 440.1109; CD $[\theta]_{222.9}$+57, $[\theta]_{229.4}$+4491, $[\theta]_{234.5}$+2672, $[\theta]_{240.6}$+9083, $[\theta]_{246.0}$+4229, $[\theta]_{250.3}$+5861, $[\theta]_{264.4}$+17, $[\theta]_{284.7}$−4116, $[\theta]_{300.7}$−151.

(2*R*)-3′,4′,7-Trimethoxyflavan-3-one 16. *Amorphous solid*, R_f 0.78, 38.2 mg (eluent: benzene/Me_2CO, 4:1); δ_H (Table 1); FABMS Calcd for $C_{18}H_{18}O_5$: 314.1154. Found: 314.1154; IR (ν_{max}/cm^{-1}, $CHCl_3$): 1740 (C=O).

(2*S*)-3′,4′,7-Trimethoxyflavan-3-one 17. *Amorphous solid*, R_f 0.78, 40.6 mg (eluent: benzene/Me_2CO, 4:1); δ_H (Table 1); FABMS and IR as for **16**.

(2*R*,4*R*)-4-Benzylthio-3′,4′,7-trimethoxyflavan-3-one 18. *Amorphous solid*, R_f 0.78, 26.2 mg (eluent: benzene/Me_2CO, 19:1); δ_H (Table 2); FABMS Calcd for $C_{25}H_{24}O_5S$: 436.1344. Found: 436.1341; CD $[\theta]_{230.0}$+4033, $[\theta]_{239.0}$−8532, $[\theta]_{252.8}$−442, $[\theta]_{273.8}$−1736, $[\theta]_{291.8}$−24; IR (ν_{max}/cm^{-1}, $CHCl_3$): 1720 (C=O).

(2*S*,4*S*)-4-Benzylthio-3′,4′,7-trimethoxyflavan-3-one 19. *Amorphous solid*, R_f 0.72, 31.6 mg (eluent: benzene/Me_2CO, 19:1); δ_H (Table 2); FABMS and IR as for **18**; CD $[\theta]_{236.7}+17$, $[\theta]_{244.6}+47980$, $[\theta]_{267.9}+24$, $[\theta]_{284.4}-10530$, $[\theta]_{295.3}+12$.

(2*R*)-3-Acetoxy-3′,4′,7-trimethoxyflav-3-ene 20. *Amorphous solid*, R_f 0.63, 33.2 mg (eluent: benzene/Me_2CO, 9:1); δ_H (Table 1); FABMS Calcd for $C_{20}H_{20}O_6$: 356.1259. Found: 356.1259; CD (Fig. 1).

(2*S*)-3-Acetoxy-3′,4′,7-trimethoxyflav-3-ene 21. *Amorphous solid*, R_f 0.63, 36.2 mg (eluent: benzene/Me_2CO, 9:1); δ_H (Table 1); FABMS as for **20**. CD (Fig. 1).

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