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Enantioselective acylation of (±)-*cis*-flavan-4-ols catalyzed by lipase from *Candida cylindracea* (*CCL*) and the synthesis of enantiopure flavan-4-ones

Sathunuru Ramadas* and G. L. David Krupadanam

Department of Chemistry, Osmania University, Hyderabad 500 007, India

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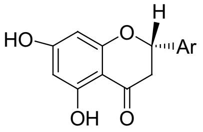
Abstract—Lipase *Candida cylindracea* (*CCL*) catalyzed acylation of (±)-*cis*-flavan-4-ols using vinyl acetate as the acyldonor in DME–toluene (1:2) gave (−)-(2*R*,4*R*)-4-acetoxyflavans **9a**–**m** and (+)-(2*S*,4*S*)-flavan-4-ols **10a**–**m** in high enantiomeric excess. (+)-(2*S*,4*S*)-Flavan-4-ols **10a**–**m** were converted to (−)-(2*S*)-flavan-4-ones **12a**–**m**.

1. Introduction

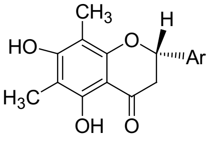
Flavan-4-ones are widely available in plants; several of these natural flavan-4-ones (−)-(2*S*)-pinocembrin[1] **1**, (−)-(2*S*)-farrero[2] **2**, (−)-(2*S*)-strobopinin[3] **3**, and (−)-(2*S*)-dihyrowogonin[4] **4** occur in enantiopure form and show levorotation. These have been assigned an (*S*)-configuration at the *C-2* stereogenic center. The absolute configuration at *C-2* was determined by chemical degradation. (−)-(2*S*)-Liquiritigenin **5** and (−)-(2*S*)-hesperetin **7** after ozonolysis gave (*S*)-malic acid **6**, indicating that *C-2* was of an (*S*)-configuration.[5,6]

Natural flavan-4-ones and flavan-4-ols are homochiral.[7–10] Enzymes have simplified the route to homochiral compounds, which are useful as drugs, synthetic intermediates, and chiral auxiliaries.[11] Among the enzymes, lipases have been extensively investigated as catalysts



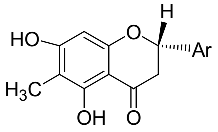
1

(-)-(2*S*)-Pinocembrin



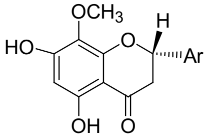
2

(-)-(2*S*)-Farrerol



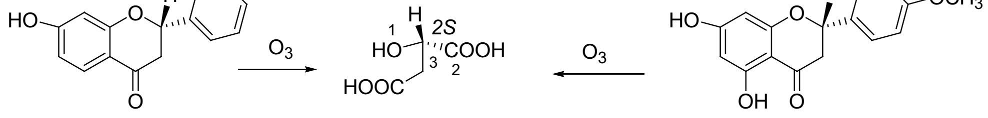
3

(-)-(2*S*)-Strobopinin



4

(-)-(2*S*)-Dihydrowognin



5 (-)-(2*S*)-Liquiritigenin

6 (*S*)-Malic acid

7 (-)-(2*S*)-Hesperetin

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[*] Corresponding author at present address: Department of Chemistry, Southern Methodist University, Foundern Science Bldg, 3215 Daniel Avenue, Dallas, TX 75275, USA. Tel.: +1 214 768 2735; fax: +1 214 768 4089; e-mail: rsathunu@mail.smu.edu

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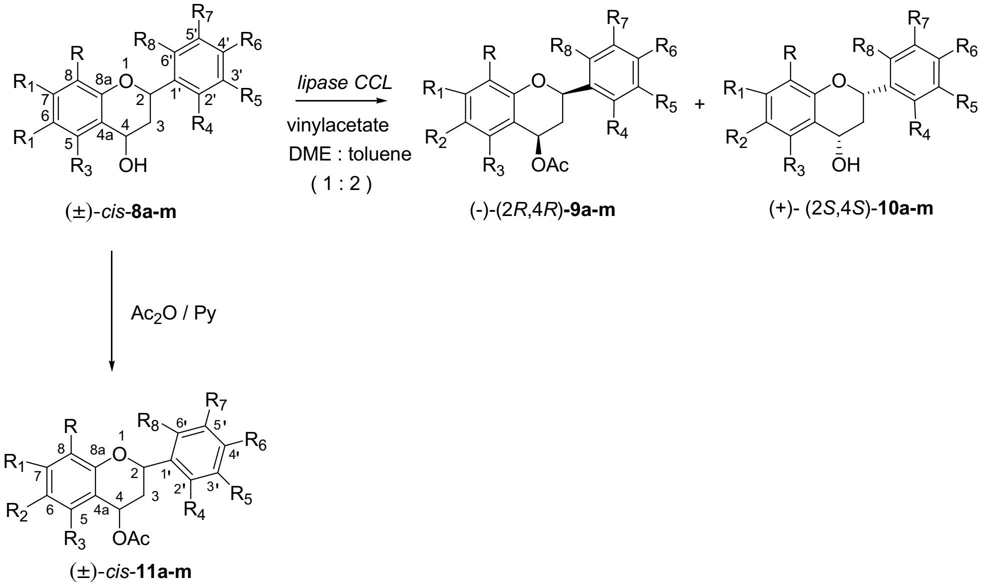
for either enantioselective acylation of racemic primary and secondary alcohols, or enantioselective hydrolysis of racemic primary or secondary esters.[11] The active site conformation, which accommodates the faster reacting enantiomer has been proposed for several lipases,[12] therefore making it possible to predict the absolute configuration of the products. Previously Izumi et al.[13] and Todoroki et al.[14] reported the enantioselective acylation and hydrolysis of unsubstituted flavan-4-ol **8a** and 4-acetoxyflavan **11a** with lipase from *Pseudomonas cepacia* and *lipase AY*. Herein we report the kinetic resolution by enantioselective acylation of unsubstituted and substituted flavan-4-ols with the lipase from *Candida cylindracea* (*CCL*) to give (−)-(2*R*,4*R*)-4-acetoxyflavans **9a–m** and (+)-(2*S*,4*S*)-flavan-4-ols **10a–m**. (−)-(2*S*,4*S*)-**10a–m** were oxidized to (−)-(2*S*)-flavan-4-ones **12a–m** with MnO_2.

2. Results and discussion

Racemic (±)-*cis*-flavan-4-ols **8a–m** were obtained by the $NaBH_4$ reduction of (±)-flavan-4-ones.[15–23] To monitor the enzyme mediated acylation of (±)-**8a–m**, these compounds were acetylated with acetic anhydride and pyridine to give *cis*-(±)-**11a–m**. *Candida cylindracea* lipase (*CCL*) catalyzed acylation of *cis* racemic flavan-4-ols **8a–m** was carried out with vinyl acetate as the acyl donor in 1,2-dimethoxyethane–toluene (1:2) at rt with the progress of the reaction monitored by TLC (Scheme 1). The reaction was terminated at or close to 50% conversion, at which point the enzyme was filtered off and the product containing the flavan-4-ol and its acetate separated by column chromatography on silica gel. The ee values of the product acetates **9a–m** and alcohols **10a–m** were determined by chiral HPLC (Table 1). The



8, 9, 10, 11, a-m a) $R = R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H$

b) $R = R_1 = R_2 = R_3 = R_4 = R_5 = R_7 = R_8 = H, R_6 = CH_3$

c) $R = R_1 = R_2 = R_3 = R_4 = R_5 = R_7 = R_8 = H, R_6 = OCH_3$

d) $R = R\ _1 = R_2 = R_3 = R_4 = R_5 = R_7 = R_8 = H, R_6 = Cl$

e) $R = R_1 = R_2 = R_3 = R_5 = R_6 = R_7 = R_8 = H, R_4 = Cl;$

f) $R = R_1 = R_2 = R\ _3 = R_4 = R_7 = R_8 = H, R_5 = R_6 = OCH_2O$

g) $R = R_1 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H, R_2 = Cl$

h) $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H, R = Cl$

i) $R = R_1 = R_3 = R_4 = R_5 = R_7 = R_8 = H, R_2 = Cl, R_6 = OMe$

j) $R = R_1 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H, R_2 = Br$

k) $R = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H, R_1 = OMe, R_2 = Br;$

l) $R_2 = R_3 = R_4 = R_5 = R_7 = R_8 = H, R_1 = R_3 = OMe, R_6 = OH$

m) $R = R_2 = R_4 = R_5 = H, R_1 = R_3 = R_6 = R_7 = R_8 = OMe$

Scheme 1.

Table 1.

Entry	Substrate	Reaction time (h)	(−)-(2*R*,4*R*)-Acetates **9a–m**			(+)-(2*S*,4*S*)-Alcohols **10a–m**		
			Yield (%)	$[\alpha]_D^{25}$	% Ee	Yield (%)	$[\alpha]_D^{25}$	% Ee
1	(±)-*cis*-**8a**	15	50	−58.2 (*c* 1.00)	91.6	50	+62.4 (*c* 1.24)	96.5
2	(±)-*cis*-**8b**	12	50	−71.6 (*c* 1.25)	69.2	50	+65.7 (*c* 1.49)	92.4
3	(±)-*cis*-**8c**	22	50	−78.4 (*c* 1.00)	75.2	50	+71.6 (*c* 1.26)	98.7
4	(±)-*cis*-**8d**	24	50	−54.2 (*c* 1.32)	95.6	50	+67.25 (*c* 1.26)	83.5
5	(±)-*cis*-**8e**	17	50	−97.3 (*c* 0.92)	68.3	50	+86.9 (*c* 1.01)	89.2
6	(±)-*cis*-**8f**	14	50	−61.85 (*c* 1.35)	>99	50	+94.5 (*c* 2.12)	>99
7	(±)-*cis*-**8g**	15	50	−44.6 (*c* 2.50)	54.8	50	+65.15 (*c* 2.15)	67.6
8	(±)-*cis*-**8h**	23	50	−78.35 (*c* 1.85)	>99	50	+51.75 (*c* 2.05)	90.7
9	(±)-*cis*-**8i**	19	50	−87.2 (*c* 1.50)	86.5	50	+67.45 (*c* 2.31)	>99
10	(±)-*cis*-**8j**	20	50	−48.4 (*c* 1.40)	79.9	50	+62.8 (*c* 1.95)	57.8
11	(±)-*cis*-**8k**	21	50	−56.8 (*c* 1.50)	93.5	50	+84.5 (*c* 2.31)	95.4
12	(±)-*cis*-**8l**	16	50	−69.35 (*c* 1.60)	>99	50	+78.2 (*c* 1.92)	>99
13	(±)-*cis*-**8m**	18	50	−85.6 (*c* 1.70)	95.4	50	+58.9 (*c* 1.74)	>99

resolved acetate **9a** showed a specific rotation of $[\alpha]_D^{25} = -58.2$ (*c* 1.00, $CHCl_3$). The CD spectrum of **9a** showed a negative cotton effect with maxima at 215, 225, 280, and 290 nm. The resolved alcohol **10a** showed a specific rotation $[\alpha]_D^{25} = +62.4$ (*c* 1.24, $CHCl_3$) The CD spectrum of **10a** showed a positive Cotton effect with maxima at 219, 229, 284, and 291 nm. Acetates **9b–m** showed negative Cotton effect bands similar to those of **9a**, while alcohols **10b–m** displayed positive Cotton effects similar to those of **10a**. The resolved acetates **9a–m** were considered to be (2*R*,4*R*) while flavan-4-ols **10a–m** were of a (2*S*,4*S*)-configuration. In this reaction, the (2*R*,4*R*)-enantiomer was considered to be reactive and therefore underwent acetylation while the (2*S*,4*S*)-enantiomer was less or even unreactive (Fig. 1).

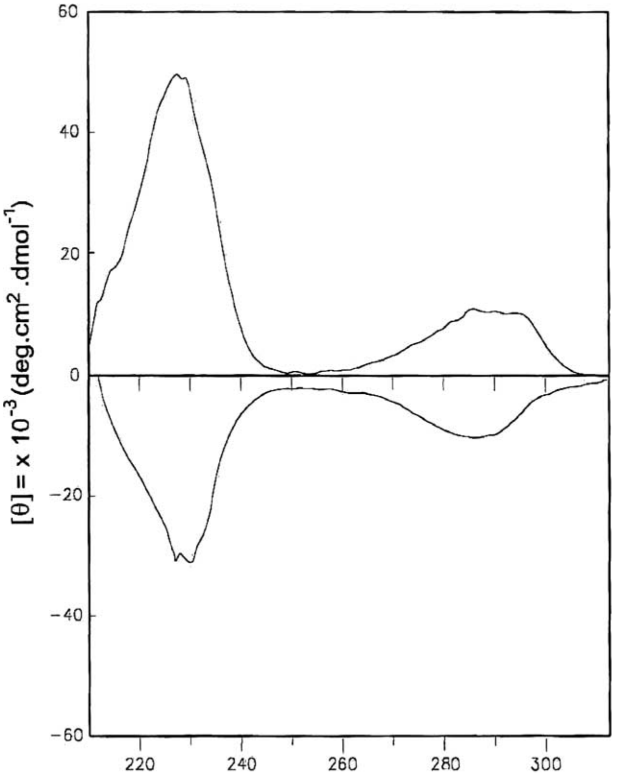


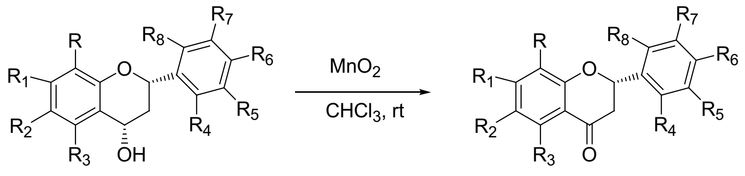
Figure 1. CD spectra of (−)-(2*R*,4*R*)-**9a** and (+)-(2*S*,4*S*)-**10a** in MeCN.

3. Determination of the absolute configuration of resolved alcohols 10a–m and acetates 9a–m by chemical correlation by use of the active site model

The configuration at *C-2* was established for alcohols **10a–m** by following Izumi's et al.[13] and Todoroki's et al. method.[14] (+)-(2*S*,4*S*)-Flavan-4-ols **10a–m** on oxidation with MnO_2 in $CHCl_3$ gave (−)-(2*S*)-flavan-4-ones **12a–m** (Scheme 2).

(−)-Flavan-4-ones are naturally occurring and have been established to have an (*S*)-configuration at the *C-2* by their oxidation to (*S*)-malic acid.[5,6] Therefore the (−)-flavan-4-ones **12a–m** obtained also have an (*S*)-configuration at *C-2*. In the MnO_2 oxidation of **10a–m**, the *C-4* chiral center is destroyed. The configuration at *C-4* is readily established as *S* because, these alcohols are already known to have a *cis* configuration. The *C-4*-OH in **12a–m** is α and quasiequatorial and is of an (*S*)-configuration. Thus alcohols **12a–m** were assigned as (2*S*,4*S*). Since the resolved acetates **9a–m** are enantiomeric to the resolved alcohols **12a–m**, and their specific rotations are levo, are assigned an (2*R*,4*R*) absolute configuration.

Majeric et al.[24] proposed an active site model for *Candida cylindracea* lipase transesterification reactions. This model explains the selectivity of enzymatic acetylation toward *R* secondary alcohols, for example, chroman-4-ol and 2,2-dimethylchroman-4-ol.[24] Since *cis*-flavan-4-ols are structurally similar to chroman-4-ols with respect to the C-4-OH, which is involved in the enzyme mediated acylation, it is considered reasonable to use the same active site model as that of 2,2-dimethylchroman-4-ols reaction with *CCL* lipase/vinyl acetate. Flavan-4-ols are considered to be bulkier substrates relative to chroman-4-ols. In the preferred conformation of the *cis*-(2*R*,4*R*) as well as *cis*-(2*S*,4*S*) the C-4-OH is quasiequatorial and the C-2 aryl group equatorial. The (2*R*,4*R*)-enantiomer of flavan-4-ols is considered to fit



(+)-(2*S*,4*S*)-**10a-m** (-)-(2*S*)-**12a-m**

10, 12, a-m a) $R = R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H$

b) $R = R_1 = R_2 = R_3 = R_4 = R_5 = R_7 = R_8 = H$, $R_6 = CH_3$

c) $R = R_1 = R_2 = R_3 = R_4 = R_5 = R_7 = R_8 = H$, $R_6 = OCH_3$

d) $R = R_1 = R_2 = R_3 = R_4 = R_5 = R_7 = R_8 = H$, $R_6 = Cl$

e) $R = R_1 = R_2 = R_3 = R_5 = R_6 = R_7 = R_8 = H$, $R_4 = Cl$;

f) $R = R_1 = R_2 = R_3 = R_4 = R_7 = R_8 = H$, $R_5 = R_6 = OCH_2O$

g) $R = R_1 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H$, $R_2 = Cl$

h) $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H$, $R = Cl$

i) $R = R_1 = R_3 = R_4 = R_5 = R_7 = R_8 = H$, $R_2 = Cl$, $R_6 = OMe$

j) $R = R_1 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H$, $R_2 = Br$

k) $R = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H$, $R_1 = OMe$, $R_2 = Br$;

l) $R_2 = R_3 = R_4 = R_5 = R_7 = R_8 = H$, $R_1 = R_3 = OMe$, $R_6 = OH$

m) $R = R_2 = R_4 = R_5 = H$, $R_1 = R_3 = R_6 = R_7 = R_8 = OMe$

Scheme 2.

better in the active site of *CCL* while the (2*S*,4*S*)-enantiomer does not fit properly in the active site.

4. Conclusion

Herein a new effective method has been developed for the resolution of (±)-*cis*-flavan-4-ols. The oxidation of the resolved alcohols with MnO_2 gives rise to chiral enantiopure natural flavan-4-ones.

5. Experimental

^{1}H NMR (200 MHz, $CDCl_3$), ^{13}C NMR (50.3 MHz, $CDCl_3$) spectra were recorded on a Varian Gemini 200 spectrometer with the chemical shifts expressed in δ ppm. Optical rotations were measured on a JASCO J-20 polarimeter (cell size 50 mm) in $CHCl_3$. Mass spectra were recorded on VG micro mass 7070-H and VG AUTOSPEC mass spectrometers. CD spectra were recorded on a JASCO J-715 spectropolarimeter. The progress of the acylation was monitored by TLC on silica gel ACME and column chromatography carried out 200 mesh silica gel ACME. The chiral HPLC of racemic (±)-*cis*-**8a**–**m** was carried out on a chiracel OD column (25 × 0.46 cm Daicel, Japan) under the following conditions: flow rate 0.5 mL min^{-1}, 10% isopropanol in *n*-hexane as the eluent. The retention times (min) are (±)-**8a** 21.7 and 23.5, (±)-**8b** 18.8 and 20.1, (±)-**8c** 17.5 and 19.6, (±)-**8d** 24.1 and 26.5, (±)-**8e** 14.6 and 15.8, (±)-**8f** 24.3 and 26.0, (±)-**8g** 19.1 and 20.4, (±)-**8h** 31.5 and 32.1, (±)-**8i** 14.6 and 16.5, (±)-**8j** 26.2 and 28.4, (±)-**8k** 13.6 and 15.5, (±)-**8l** 28.0 and 30.2, (±)-**8m** 25.2 and 26.5. The chiral HPLC of resolved alcohols **10a**–**m** was carried out on a chiracel OD column (25 × 0.46 cm Daicel, Japan) under the following conditions: flow rate 0.5 mL min^{-1}, 10% isopropanol in *n*-hexane as the eluent. The retention times (min) are (+)-**10a** 21.9 and 23.7, (+)-**10b** 18.9 and 20.3, (+)-**10c** 17.7 and 19.8, (+)-**10d** 24.3 and 26.7, (+)-**10e** 14.8 and 16.0, (+)-**10f** 24.5 and 26.2, (+)-**10g** 19.3 and 20.6, (+)-**10h** 31.7 and 32.3, (+)-**10i** 14.8 and 16.8, (+)-**10j** 26.4 and 28.7, (+)-**10k** 13.8 and 15.7, (+)-**10l** 28.2 and 30.4, (+)-**10m** 25.4 and 26.7. The chiral HPLC of racemic (±)-*cis*-**11a**–**m** was carried out on a chiracel OJ column (25 × 0.46 cm, Daicel, Japan) under the following conditions; flow rate 0.8 mL min^{-1}, 5% isopropanol in *n*-hexane as the eluent. The retention times (min) are (±)-**11a** 15.4 and 16.5, (±)-**11b** 18.5 and 19.6, (±)-**11c** 12.4 and 13.7, (±)-**11d** 24.1 and 25.4, (±)-**11e** 18.3 and 19.5, (±)-**11f** 15.8 and 16.7, (±)-**11g** 25.5 and 26.4, (±)-**11h** 17.2 and 18.7, (±)-**11i** 19.5 and 20.6, (±)-**11j** 26.3 and 27.4, (±)-**11k** 15.6 and 16.5, (±)-**11l** 25.8 and 26.5, (±)-**11m** 21.5 and 22.1. The chiral HPLC of resolved acetates **9a**–**m** was carried out on a chiracel OJ column (25 × 0.46 cm, Daicel, Japan) under the following conditions; flow rate 0.8 mL min^{-1}, 5% isopropanol in *n*-hexane as the eluent. The retention times (min) are (−)-**9a** 15.8 and 16.8, (−)-**9b** 18.7 and 19.8, (−)-**9c** 12.6 and 14.0, (−)-**9d** 24.5 and 25.7, (−)-

9e 18.6 and 19.8, (−)-**9f** 16.1 and 17.0, (−)-**9g** 25.7 and 26.6, (−)-**9h** 17.5 and 19.0, (−)-**9i** 19.8 and 20.9, (−)-**9j** 26.6 and 27.7, (−)-**9k** 15.8 and 16.7, (−)-**9l** 26.1 and 26.8, (−)-**9m** 21.8 and 22.4.

5.1. (±)-*cis*-4^1-Methylflavan-4-ol 8a

IR υ (KBr): 3629, 3586 cm^{-1} (OH). UV λ ($\log\varepsilon$) (MeOH): 215 (3.5), 235 (3.6), and 280 (3.5). ^{1}H NMR: δ 1.65 (d, $J = 10.0$ Hz, OH), 2.16 (m, $\mathrm{H_e}$-3), 2.37 (s, CH_3), 2.51 (m, $\mathrm{H_a}$-3), 5.09 (dd, $J = 10.36$, 6.20 Hz, H-4), 5.15 (dd, $J = 11.58$, 1.40 Hz, H-2), 6.90 (dd, $J = 8.0$, 2.0 Hz, H-8), 6.99 (m, H-6), 7.20 (m, H-7), 7.24 (d, $J = 8.0$ Hz, H-3^1, 5^1), 7.35 (d, $J = 8.0$ Hz, H-2^1, 6^1), and 7.51 (d, $J = 8.0$ Hz, H-5). ^{13}C NMR: δ 19.7 (CH_3), 39.0 (C-3), 63.3 (C-4), 75.5 (C-2), 114.0 (C-8), 119.0 (C-6), 124.7 (C-5), 125.0 (C-2^1, 6^1), 126.0 (C-4a), 126.3 (C-5), 127.7 (C-7), 129.0 (C-3^1, 5^1), 136.1 (C-4^1), 136.6 (C-1^1), and 153.1 (C-8a). MS (*m*/*z*) 240 (M$^+$). HRMS calcd for $C_{16}H_{16}O_2$ (M$^+$). 240.1236. Found: 240.1258.

5.2. (±)-*cis*-Flavan-4-ol 8b

IR υ (KBr): 3621, 3300 cm^{-1} (OH). UV λ ($\log\varepsilon$) (MeOH): 223 (3.6), 247 (3.5), and 296 (3.5). ^{1}H NMR: δ 1.60 (d, $J = 10.0$ Hz, OH), 2.08 (m, $\mathrm{H_e}$-3), 2.48 (m, $\mathrm{H_a}$-3), 5.05 (dd, $J = 10.50$, 6.50 Hz, H-4), 5.14 (dd, $J = 12.0$, 1.50 Hz, H-2), 6.85 (dd, $J = 10.0$, 2.0 Hz, H-8), 6.92 (dd, $J = 10.0$, 10. 0 Hz, H-6), 7.18 (m, H-7), 7.35 (m, H-2^1-6^1), and 7.45 (dd, $J = 10.0$, 2.0 Hz, H-5). ^{13}C NMR: δ 39.1 (C-3), 63.9 (C-4), 79.4 (C-2), 115.6 (C-8), 120.1 (C-6), 125.9 (C-4a), 127.1 (C-5), 127.3 (C-2^1, 6^1), 127.7 (C-4^1), 127.9 (C-3^1, 5^1), 128.2 (C-7), 140.9 (C-1^1), and 154.0 (C-8a). MS (*m*/*z*) 226 (M$^+$). HRMS calcd for $C_{15}H_{14}O_2$ (M$^+$), 226.1079. Found: 226.1094.

5.3. (±)-*cis*-4^1-Methoxyflavan-4-ol 8c

IR υ (KBr): 3659, 3481 cm^{-1} (OH). UV λ ($\log\varepsilon$) (MeOH): 251 (3.4), 292 (3.2), and 325 (3.8). ^{1}H NMR: δ 1.70 (d, $J = 10.0$ Hz, OH), 2.05 (m, $\mathrm{H_e}$-3), 2.35 (m, $\mathrm{H_a}$-3), 3.80 (s, OCH_3), 5.00 (dd, $J = 10.50$, 6.50 Hz, H-4), 5.13 (dd, $J = 12.0$, 1.50 Hz, H-2), 6.75 (dd, $J = 10.0$, 2.0 Hz, H-8), 6.92 (m, H-6), 6.95 (d, $J = 10.0$ Hz, H-3^1, 5^1), 7.12 (m, H-7), 7.40 (d, $J = 10.0$ Hz, H-2^1, 6^1), and 7.55 (dd, $J = 10.0$, 2.0 Hz, H-5). ^{13}C NMR: δ 39.5 (C-3), 55.4 (C-4^1, OCH_3), 65.0 (C-4), 77.8 (C-2), 114.0 (C-8), 126.0 (C-3^1, 5^1), 121.2 (C-6), 126.2 (C-4a), 127.5 (C-2^1, 6^1), 128.1 (C-5), 129.5 (C-7), 133.9 (C-1^1), 155.8 (C-8a), and 159.7 (C-4^1). MS (*m*/*z*) 256 (M$^+$). HRMS calcd for $C_{16}H_{16}O_3$ (M$^+$), 256.1145. Found: 256.1172.

5.4. (±)-*cis*-4^1-Chloroflavan-4-ol 8d

IR υ (KBr): 3665, 3355 cm^{-1} (OH). UV λ ($\log\varepsilon$) (MeOH): 228 (3.5), 271 (3.5), and 289 (3.6). ^{1}H NMR: δ 1.58 (d, $J = 10.0$ Hz, OH), 2.12 (m, $\mathrm{H_e}$-3), 2.51 (m, $\mathrm{H_a}$-3), 5.05 (dd, $J = 10.50$, 6.50 Hz, H-4), 5.15 (dd, $J = 12.0$, 1.50 Hz, H-2), 6.85 (dd, $J = 10.0$, 2.0 Hz, H-8), 6.96 (m, H-7), 7.20 (m, H-6), 7.38 (m, H-2^1, 3^1, 5^1, 6^1), and 7.50 (dd, $J = 10.0$, 2.0 Hz, H-5). ^{13}C NMR: δ 39.3 (C-3), 64.4 (C-4), 77.6 (C-2), 115.8 (C-8), 120.3 (C-6), 126.3 (C-4a), 126.8 (C-5), 127.1 (C-2^1, 6^1), 128.1 (C-3^1, 5^1), 128.2 (C-7), 133.1 (C-4^1), 139.1 (C-1^1), and 153.8 (C-8a). MS (*m*/*z*) 260 (M$^+$), 262 (M^{2+}). HRMS calcd for $C_{15}H_{13}ClO_2$ (M$^+$), 260.0676. Found: 260.0698.

5.5. (±)-*cis*-2^1-Chloroflavan-4-ol 8e

IR υ (KBr): 3486, 3163 cm^{-1} (OH). UV λ ($\log\varepsilon$) (MeOH): 224 (3.5), 244 (3.7), and 281 (3.6). ^{1}H NMR: δ 1.65 (d, $J = 10.0$ Hz, OH), 1.92 (m, $\mathrm{H_e}$-3), 2.70 (m, $\mathrm{H_a}$-3), 5.15 (dd, $J = 10.40$, 6.50 Hz, H-4), 5.68 (dd, $J = 12.0$, 1.50 Hz, H-2), 6.90 (dd, $J = 10.0$, 2.0 Hz, H-8), 7.00 (m, H-6), 7.15–7.45 (m, H-7, 3^1, 4^1, 5^1), 7.52 (dd, $J = 10.0$, 2.0 Hz, H-5), and 7.70 (dd, $J = 10.0$, 2.0 Hz, H-6^1). ^{13}C NMR: δ 38.3 (C-3), 65.4 (C-4), 76.2 (C-2), 116.5 (C-8), 121.0 (C-6), 125.7 (C-4a), 126.0 (C-5^1), 127.0 (C-5), 127.1 (C-4^1), 129.3 (C-7), 128.5 (C-6^1), 128.9 (C-3^1), 131.4 (C-2^1), 138.2 (C-1^1) and 154.2 (C-8a). MS (*m*/*z*) 260 (M$^+$), 262 (M^{2+}). HRMS calcd for $C_{15}H_{13}ClO_2$ (M$^+$), 260.0676. Found: 260.0651.

5.6. (±)-*cis*-3^1,4^1-Methylenedioxyflavan-4-ol 8f

IR υ (KBr): 3493, 3300 cm^{-1} (OH). UV λ ($\log\varepsilon$) (MeOH): 223 (3.6), 265 (3.7), and 295 (3.9). ^{1}H NMR: δ 1.75 (d, $J = 10.0$ Hz, OH), 2.10 (m, $\mathrm{H_e}$-3), 2.45 (m, $\mathrm{H_a}$-3), 5.05 (dd, $J = 10.5$, 6.50 Hz, H-4), 5.12 (dd, $J = 12.0$, 1.50 Hz, H-2), 6.00 (s, OCH_2O), 6.70–7.00 (m, H-6, 2^1, 5^1, 6^1), 6.92 (dd, $J = 10.0$, 2.0 Hz, H-8), 7.20 (m, H-7), and 7.45 (dd, $J = 10.0$, 2.0 Hz, H-5). ^{13}C NMR: δ 37.8 (C-3), 65.0 (C-4), 79.2 (C-2), 101.0 (OCH_2O), 128.1 (C-2^1), 110.3 (C-5^1), 116.5 (C-8), 120.7 (C-6), 122.5 (C-6^1), 125.8 (C-4a), 127.1 (C-5), 131.3 (C-7), 134.3 (C-1^1), 147.4 (C-4^1), 147.8 (C-3^1), and 154.5 (C-8a). MS (*m*/*z*) 270 (M$^+$). HRMS calcd for $C_{16}H_{14}O_4$ (M$^+$), 270.0936. Found: 270.0912.

5.7. (±)-*cis*-6-Chloroflavan-4-ol 8g

IR υ (KBr): 3476, 3271 cm^{-1} (OH). UV λ ($\log\varepsilon$) (MeOH): 221 (3.6), 251 (3.7), and 293 (3.6). ^{1}H NMR: δ 1.60 (d, $J = 10.0$ Hz, OH), 2.05 (m, $\mathrm{H_e}$-3), 2.45 (m, $\mathrm{H_a}$-3), 4.98 (dd, $J = 10.50$, 6.50 Hz, H-4), 5.10 (dd, $J = 12.0$, 1.50 Hz, H-2), 6.74 (d, $J = 10.0$ Hz, H-8), 7.08 (dd, $J = 10.0$, 2.0 Hz, H-7), 7.30 (m, H-2^1–6^1) and 7.42 (d, $J = 2.0$ Hz, H-5). ^{13}C NMR: δ 39.6 (C-3), 65.5 (C-4), 77.6 (C-2), 120.9 (C-8), 125.3 (C-5), 125.7 (C-4a), 126.6 (C-6), 127.4 (C-2^1, 6^1), 128.1 (C-3^1, 5^1), 128.6 (C-4^1), 129.9 (C-7), 140.0 (C-1^1) and 150.1 (C-8a). MS (*m*/*z*) 260 (M$^+$), 262 (M^{2+}). HRMS calcd for $C_{15}H_{13}ClO_2$ (M$^+$), 260.0676. Found: 260.0687.

5.8. (±)-*cis*-8-Chloroflavan-4-ol 8h

IR υ (KBr): 3479, 3253 cm^{-1} (OH). UV λ ($\log\varepsilon$) (MeOH): 221 (3.7), 254 (3.5), and 298 (3.8). ^{1}H NMR: δ 1.80 (d, $J = 10.0$ Hz, OH), 2.13 (m, $\mathrm{H_e}$-3), 2.60 (m, $\mathrm{H_a}$-3), 5.10 (dd, $J = 10.50$, 6.50 Hz, H-4), 5.30 (dd, $J = 12.0$, 1.50 Hz, H-2), 6.92 (dd, $J = 10.0$, 10.0 Hz, H-6), and 7.30–7.60 (m, H-5, 7, 2^1–6^1). ^{13}C NMR: δ 36.1 (C-3), 66.2 (C-4), 79.5 (C-2), 121.0 (C-6), 121.3 (C-8), 124.8 (C-5), 126.2 (C-2^1, 6^1), 127.1 (C-7), 127.5 (C-4a), 127.8 (C-4^1), 127.9 (C-3^1, 5^1), 142.4 (C-1^1), and 154.1 (C-8a). MS (*m*/*z*) 260 (M$^+$), 262 (M^{2+}). HRMS calcd for $C_{15}H_{13}ClO_2$ (M$^+$), 260.0676. Found: 260.0644.

5.9. (±)-*cis*-6-Chloro-4^1-methoxyflavan-4-ol 8i

IR υ (KBr): 3472, 3157 cm^{-1} (OH). UV λ (logε) (MeOH): 223 (3.9), 252 (3.5), and 295 (3.8). ^{1}H NMR: δ 1.65 (d, J = 10.0 Hz, OH), 2.10 (m, H$_e$-3), 2.45 (m, H$_a$-3), 3.82 (s, OCH$_3$), 5.00 (dd, J = 10.50, 6.50 Hz, H-4), 5.08 (dd, J = 12.0, 1.50 Hz, H-2), 6.75 (d, J = 10.0 Hz, H-8), 6.90 (d, J = 10.0 Hz, H-3^1, 5^1), 7.10 (dd, J = 10.0, 2.0 Hz, H-7), 7.30 (d, J = 10.0 Hz, H-2^1, 6^1), and 7.45 (d, J = 2.0 Hz, H-5). ^{13}C NMR: δ 37.2 (C-3), 55.1 (OCH$_3$), 66.5 (C-4), 78.5 (C-2), 113.2 (C-8), 125.5 (C-3^1, 5^1), 124.0 (C-5), 127.5 (C-4a), 129.3 (C-2^1, 6^1), 129.5 (C-6), 130.1 (C-7), 133.1 (C-1^1), 154.1 (C-8a), and 158.6 (C-4^1). MS (*m*/*z*) 290 (M$^+$), 292 (M^{2+}). HRMS calcd for $C_{16}H_{15}ClO_3$ (M$^+$), 290.0752. Found: 290.0776.

5.10. (±)-*cis*-6-Bromoflavan-4-ol 8j

IR υ (KBr): 3481, 3251 cm^{-1} (OH). UV λ (logε) (MeOH): 220 (3.5), 251 (3.7), and 295 (3.8). ^{1}H NMR: δ 1.56 (d, J = 10.0 Hz, OH), 2.10 (m, H$_e$-3), 2.48 (m, H$_a$-3), 4.95 (dd, J = 10.50, 6.50 Hz, H-4), 5.12 (dd, J = 12.0, 1.50 Hz, H-2), 6.75 (d, J = 10.0 Hz, H-8), 7.12 (dd, J = 10.0, 2.0 Hz, H-7), 7.32 (m, H-2^1–6^1), and 7.41 (d, J = 2.0 Hz, H-5). ^{13}C NMR: δ 38.5 (C-3), 64.2 (C-4), 76.1 (C-2), 120.5 (C-8), 124.6 (C-5), 125.4 (C-4a), 127.1 (C-6), 126.8 (C-2^1, 6^1), 127.9 (C-3^1, 5^1), 129.5 (C-4^1), 130.2 (C-7), 141.3 (C-1^1), and 150.5 (C-8a). MS (*m*/*z*) 304 (M$^+$), 305 (M^{2+}). HRMS calcd for $C_{15}H_{13}BrO_2$ (M$^+$), 304.0125. Found: 304.0156.

5.11. (±)-*cis*-6-Bromo-7-methoxyflavan-4-ol 8k

IR υ (KBr): 3621, 3515 cm^{-1} (OH). UV λ (logε) (MeOH): 225 (3.6), 269 (3.5), and 294 (3.6). ^{1}H NMR: δ 1.78 (d, J = 10.0 Hz, OH), 2.15 (m, H$_e$-3), 3.81 (s, OCH$_3$), 2.51 (m, H$_a$-3), 4.95 (dd, J = 10.50, 6.50 Hz, H-4), 5.14 (dd, J = 12.0, 1.50 Hz, H-2), 6.54 (s, H-8), 7.10 (s, H-5), and 7.51 (m, H-2^1–6^1). ^{13}C NMR: δ 37.5 (C-3), 57.4 (OCH$_3$), 66.2 (C-4), 76.5 (C-2), 118.5 (C-6), 121.6 (C-8), 126.3 (C-5), 126.2 (C-4a), 128.1 (C-2^1, 6^1), 129.4 (C-3^1, 5^1), 130.2 (C-4^1), 138.7 (C-1^1), 150.1 (C-8a), and 155.2 (C-7). MS (*m*/*z*) 334 (M$^+$), 335 (M^{2+}). HRMS calcd for $C_{16}H_{15}BrO_3$ (M$^+$), 334.0235. Found: 334.0218.

5.12. (±)-*cis*-7,8-Dimethoxy-4^1-hydroxyflavan-4-ol 8l

IR υ (KBr): 3695, 3455 cm^{-1} (OH). UV λ (logε) (MeOH): 228 (3.6), 279 (3.7), 294 (3.6), and 337 (3.8). ^{1}H NMR: δ 1.95 (d, J = 10 Hz, OH), 2.87 (m, H$_e$-3), 3.09 (m, H$_a$-3), 3.87 (s, 3H, OCH$_3$-8), 3.95 (s, 3H, OCH$_3$-7), 4.92 (dd, J = 10.50, 6.50 Hz, H-4), 5.45 (dd, J = 12.0, 1.50 Hz, H-2), 6.66 (d, J = 10.0 Hz, H-6), 6.85 (d, J = 10.0 Hz, H-3^1, 5^1), 7.35 (d, J = 10.0 Hz, H-2^1, 6^1), and 7.65 (d, J = 10.0 Hz, H-5). ^{13}C NMR: δ 43.6 (C-3), 56.7 (OCH$_3$-7), 61.8 (OCH$_3$-8), 64.8 (C-4), 80.2 (C-2), 111.3 (C-6), 112.2 (C-4a), 126.5 (C-3^1, 5^1), 128.4 (C- 2^1, 6^1), 129.4 (C-5), 130.1 (C-1^1), 158.7 (C-8), 158.4 (C-7), 159.5 (C-4^1), and 160.2 (8a). MS (*m*/*z*) 302 (M$^+$). HRMS calcd for $C_{17}H_{18}O_5$ (M$^+$), 302.1273. Found: 302.1259.

5.13. (±)-*cis*-5,7,4^1,5^1,6^1-Pentamethoxyflavan-4-ol 8m

IR υ (KBr): 3618, 3715 cm^{-1} (OH). UV λ (logε) (MeOH): 232 (3.5), 272 (3.7), and 297 (3.6). ^{1}H NMR: δ 1.78 (d, J = 10 Hz, OH), 2.15 (m, H$_e$-3), 2.51 (m, H$_a$-3), 3.58 (s, OCH$_3$-7), 3.70 (s, OCH$_3$-5^1), 3.74 (s, OCH$_3$-6^1), 3.81 (s, OCH$_3$-5), 3.87 (s, OCH$_3$-4^1), 4.91 (dd, J = 10.50, 6.50 Hz, H-4), 5.62 (dd, J = 12.0, 1.50 Hz, H-2), 6.04 (d, J = 2.0 Hz, H-6), 6.15 (d, J = 2.0 Hz, H-8). ^{13}C NMR: δ 43.7 (C-3), 55.8 (OCH$_3$-7), 56.5 (OCH$_3$-6^1), 56.7 (OCH$_3$-5), 60.1 (OCH$_3$-5^1), 61.8 (OCH$_3$-4^1), 66.2 (C-4), 75.1 (C-2), 117.2 (C-6), 94.6 (C-8), 115.7 (C-4a), 164.1 (C-5^1), 168.5 (C-6^1), 131.5 (C-1^1), 142.9 (C-3^1), 129.4 (C-2^1), 155.2 (C-4^1), 161.8 (5), 166.4 (C-8a), and 166.8 (C-7). MS (*m*/*z*) 376 (M$^+$). HRMS calcd for $C_{20}H_{24}O_7$ (M$^+$), 376.1562. Found: 376.1536.

5.14. (±)-*cis*-4^1-Methyl-4-acetoxyflavan 11a

^{1}H NMR: δ 2.10 (s, OCO*CH*$_3$), 2.15 (m, H$_e$-3), 2.38 (s, CH$_3$), 2.60 (m, H$_a$-3), 5.15 (dd, J = 14.0, 2.0 Hz, H-4), 6.16 (dd, J = 14.0, 8.0 Hz, H-2), 6.90 (m, H-6,8) and 7.10–7.40 (m, H-5, 7, 2^1–6^1). ^{13}C NMR: δ 20.1 (OCO*CH*$_3$), 21.0 (CH$_3$), 35.6 (C-3), 67.6 (C-4), 77.5 (C-2), 117.1 (C-8), 120.8 (C-6), 121.2 (C-4a), 126.2 (C-2^1, 6^1), 127.2 (C-5), 129.2 (C-3^1, 5^1), 129.4 (C-7), 137.2 (C-4^1), 137.9 (C-1^1), 155.3 (C-8a), and 170.9 (O*CO*CH$_3$). MS (*m*/*z*) 282 (M$^+$). HRMS calcd for $C_{18}H_{18}O_3$ (M$^+$), 282.1325. Found: 282.1357.

5.15. (±)-*cis*-4-Acetoxyflavan 11b

^{1}H NMR: δ 2.10 (s, OCO*CH*$_3$), 2.15 (m, H$_e$-3), 2.60 (m, H$_a$-3), 5.16 (dd, J = 14.0, 2.0 Hz, H-4), 6.15 (dd, J = 14.0, 8.0 Hz, H-2), 6.90 (m, H-6,8), and 7.15–7.50 (m, H-5, 7, 2^1–6^1). ^{13}C NMR: δ 20.1 (OCOCH$_3$), 38.0 (C-3), 68.5 (C-4), 79.5 (C-2), 115.4 (C-8), 120.3 (C-4a), 120.5 (C-6), 125.9 (C-2^1, 6^1), 126.7 (C-5), 128.5 (C-3^1, 5^1), 135.7 (C-4^1), 131.0 (C-7), 137.8 (C-1^1), 154.7 (C-8a), and 170.5 (O*CO*CH$_3$). MS (*m*/*z*) 268 (M$^+$). HRMS calcd for $C_{17}H_{16}O_3$ (M$^+$), 268.1153. Found: 268.1176.

5.16. (±)-*cis*-4^1-Methoxy-4-acetoxyflavan 11c

^{1}H NMR: δ 2.12 (s, OCO*CH*$_3$), 2.15 (m, H$_e$-3), 2.60 (m, H$_a$-3), 3.80 (s, OCH$_3$), 5.13 (dd, J = 14.0, 2.0 Hz, H-4), 6.18 (dd, J = 14.0, 8.0 Hz, H-2), 6.90 (m, H-6,8, 3^1, 5^1), 7.20 (m, H-5,7), and 7.35 (d, J = 10.0 Hz, H-2^1, 6^1). ^{13}C NMR: δ 20.8 (OCO*CH*$_3$), 36.4 (C-3), 54.9 (OCH$_3$), 75.9 (C-4), 75.9 (C-2), 113.7 (C-8), 129.5 (C-3^1, 5^1), 120.5 (C-6), 121.1 (C-4a), 127.0 (C-5), 130.7 (C-7), 127.3 (C-2^1, 6^1), 138.3 (C-1^1), 155.1 (C-8a), 136.5 (C-4^1), and 170.5 (O*CO*CH$_3$). MS (*m*/*z*) 298 (M$^+$). HRMS calcd for $C_{18}H_{18}O_4$ (M$^+$), 298.1235. Found: 298.1218.

5.17. (±)-*cis*-4^1-Chloro-4-acetoxyflavan 11d

^{1}H NMR: δ 2.10 (s, OCOCH_3), 2.12 (m, H_e-3), 2.62 (m, H_a-3), 5.20 (dd, $J = 14.0$, 2.0 Hz, H-4), 6.18 (dd, $J = 14.0$, 8.0 Hz, H-2), 6.92 (m, H-6,8), 7.20 (m, H-5,7) and 7.40 (m, H-2^1, 3^1, 5^1, 6^1). ^{13}C NMR: 20.6 (OCOCH_3), 37.1 (C-3), 75.4 (C-4), 75.2 (C-2), 115.4 (C-8), 120.7 (C-6), 121.3 (C-4a), 126.5 (C-2^1, 6^1), 127.8 (C-3^1, 5^1), 128.7 (C-5), 130.0 (C-7), 138.3 (C-4^1), 138.1 (C-1^1), 154.9 (C-8a), and 170.2 (O*CO*CH$_3$). MS (*m*/*z*) 302 (M^+), 304 (M^{2+}). HRMS calcd for $C_{17}H_{15}ClO_3$ (M^+), 302.0763. Found: 302.0789.

5.18. (±)-*cis*-2^1-Chloro-4-acetoxyflavan 11e

^{1}H NMR: δ 2.12 (s, OCOCH_3), 2.08 (m, H_e-3), 2.81 (m, H_a-3), 5.18 (dd, $J = 14.0$, 2.0 Hz, H-4), 5.95 (dd, $J = 14.0$, 8.0 Hz, H-2), 6.91 (dd, $J = 10.0$, 2.0, H-8), 7.05 (m, H-6), 7.19–7.52 (m, H-7, 3^1, 4^1, 5^1), 7.58 (dd, $J = 10.0$, 2.0 Hz, H-5), and 7.74 (dd, $J = 10.0$, 2.0 Hz, H-6^1). ^{13}C NMR: δ 20.9 (OCOCH_3), 38.4 (C-3), 65.6 (C-4), 74.1 (C-2), 116.8 (C-8), 122.4 (C-6), 126.3 (C-4a), 127.5 (C-5^1), 128.0 (C- 5), 138.4 (C-4^1), 129.7 (C-7), 129.2 (C-6^1), 129.8 (C-3^1), 125.5 (C-2^1), 139.6 (1^1), 155.6 (C-8a), and 170.7 (O*CO*CH$_3$). MS (*m*/*z*) 302 (M^+), 304 (M^{2+}). HRMS calcd for $C_{17}H_{15}ClO_3$ (M^+), 302.0763. Found: 302.0738.

5.19. (±)-*cis*-3^1,4^1-Methylenedioxy-4-acetoxyflavan 11f

^{1}H NMR: δ 2.18 (s, OCOCH_3), 2.12 (m, H_e-3), 2.47 (m, H_a-3), 5.15 (dd, $J = 14.0$, 2.0 Hz, H-4), 5.92 (dd, $J = 14.0$, 8.0 Hz, H-2), 6.10 (s, OCH$_2$O), 6.87 (dd, $J = 10.0$, 2.0 Hz, H-8), 6.95–7.15 (m, H-6, 2^1, 5^1, 6^1), 7.25 (m, H-7), and 7.51 (dd, $J = 10.0$, 2.0 Hz, H-5). ^{13}C NMR: δ 20.1 (OCOCH_3), 38.1 (C-3), 65.8 (C-4), 76.4 (C-2), 101.5 (OCH$_2$O), 129.2, (C-2^1), 130.2 (C-5^1), 117.7 (C-8), 121.5 (C-6), 123.6 (C-6^1), 126.7 (C-4a), 128.2 (C-5), 132.6 (C-7), 137.8 (C-1^1), 136.9 (C-4^1), 148.2 (C-3^1), 155.4 (C-8a), and 171.4 (O*CO*CH$_3$). MS (*m*/*z*) 312 (M^+). HRMS calcd for $C_{18}H_{16}O_5$ (M^+), 312.1025. Found: 312.1048.

5.20. (±)-*cis*-6-Chloro-4-acetoxyflavan 11g

^{1}H NMR: δ 2.10 (s, OCOCH_3), 2.12 (m, H_e-3), 2.62 (m, H_a-3), 5.18 (dd, $J = 14.0$, 2.0 Hz, H-4), 6.10 (dd, $J = 14.0$, 8.0 Hz, H-2), 6.83 (d, $J = 10.0$ Hz, H-8), 7.15 (m, H-7), and 7.35 (m, H-5, 2^1–6^1). ^{13}C NMR: 20.9 (OCOCH_3), 35.3 (C-3), 77.6 (C-2), 79.5 (C-4), 118.0 (C-8), 121.8 (C-6), 129.0 (C-5), 125.6 (C-4a), 128.5 (C-3^1, 5^1), 128.0 (C-2^1, 6^1), 128.5 (C-7), 139.5 (C- 4^1), 139.7 (C-1^1), 150.8 (C-8a), and 170.7(O*CO*CH$_3$). MS (*m*/*z*) 302 (M^+), 304 (M^{2+}). HRMS calcd for $C_{17}H_{15}ClO_3$ (M^+), 302.0763. Found: 302.07776.

5.21. (±)-*cis*-8-Chloro-4-acetoxyflavan 11h

^{1}H NMR: δ 2.10 (s, OCOCH_3), 2.17 (m, H_e-3), 2.70 (m, H_a-3), 5.35 (dd, $J = 14.0$, 2.0 Hz, H-4), 6.17 (dd, $J = 14.0$, 8.0 Hz, H-2), 6.90 (dd, $J = 10.0$, 10.0 Hz, H-6), 7.13 (dd, $J = 10.0$, 2.0 Hz, H-7), and 7.25–7.55 (m, H-5, 2^1–6^1). ^{13}C NMR: δ 20.6 (OCOCH_3), 39.6 (C-3), 78.0 (C-4), 79.7 (C-2), 120.9 (C-6), 118.6 (C-8), 125.2 (C-4a), 128.2 (C-5), 126.6 (C-2^1, 6^1), 127.5 (C-3^1, 5^1), 135.6 (C-4^1), 130.3 (C-7), 140.3 (C-1^1), 152.3 (C-8a), and 170.5 (O*CO*CH$_3$). MS (*m*/*z*) 302 (M^+), 304 (M^{2+}). HRMS calcd for $C_{17}H_{15}ClO_3$ (M^+), 302.0763. Found: 302.0742.

5.22. (±)-*cis*-6-Chloro-4^1-methoxy-4-acetoxyflavan 11i

^{1}H NMR: δ 2.14 (s, OCOCH_3), 2.10 (m, H_e-3), 2.60 (m, H_a-3), 3.80 (s, OCH$_3$), 5.11 (dd, $J = 14.0$, 2.0 Hz, H-4), 6.10 (dd, $J = 14.0$, 8.0 Hz, H-2), 6.80 (d, $J = 10.0$ Hz, H-8), 6.86 (d, $J = 10.0$ Hz, H-3^1, 5^1), 7.15 (dd, $J = 10.0$, 2.0 Hz, H-7), 7.25 (d, $J = 2.0$ Hz, H-5), and 7.30 (d, $J = 10.0$ Hz, H-2^1, 6^1). ^{13}C NMR: 21.1 (OCOCH_3), 35.2 (C-3), 55.3 (OCH$_3$), 77.6 (C-2), 78.2 (C-4), 119.1 (C-8), 128.2, (C-3^1, 5^1), 128.5 (C-5), 125.7 (C-4a), 127.4 (C-2^1, 6^1), 121.4 (C-6), 138.9 (C-7), 131.9 (C-1^1), 153.9 (C-8a), 138.7 (C-4^1), and 170.7 (O*CO*CH$_3$). MS (*m*/*z*) 332 (M^+), 334 (M^{2+}). HRMS calcd for $C_{18}H_{17}ClO_4$ (M^+), 332.0826. Found: 332.0851.

5.23. (±)-*cis*-6-Bromo-4-acetoxyflavan 11j

^{1}H NMR: δ 2.11 (s, OCOCH_3), 2.15 (m, H_e-3), 2.50 (m, H_a-3), 4.91 (dd, $J = 14.0$, 2.0 Hz, H-4), 5.15 (dd, $J = 14.0$, 8.0 Hz, H-2), 6.72 (d, $J = 10.0$ Hz, H-8), 7.16 (dd, $J = 10.0$, 2.0 H-7), 7.35 (m, H-2^1–6^1), and 7.45 (d, $J = 2.0$ Hz, H-5). ^{13}C NMR: 21.8 (OCOCH_3), 37.4 (C-3), 63.6 (C-4), 76.5 (C-2), 117.6 (C-8), 123.5 (C-6), 126.0, (C-4a), 127.7 (C-5), 128.3 (C-2^1, 6^1), 128.7 (C-3^1, 5^1), 136.2 (C-4^1), 131.5 (C-7), 142.0 (C-1^1), 151.3 (C-8a) and 171.8 (O*CO*CH$_3$). MS (*m*/*z*) 346 (M^+), 348 (M^{2+}). HRMS calcd for $C_{17}H_{15}BrO_3$ (M^+), 346.0218. Found: 346.0245.

5.24. (±)-*cis*-6-Bromo-7-methoxy-4-acetoxyflavan 11k

^{1}H NMR: δ 2.18 (s, OCOCH_3), 2.16 (m, H_e-3), 2.48 (m, H_a-3), 3.87 (s, OCH$_3$), 4.90 (dd, $J = 14.0$, 2.0 Hz, H-4), 5.16 (dd, $J = 14.0$, 8.0 Hz, H-2), 6.64 (s, H-8), 7.12 (s, H-5), and 7.54 (m, H-2^1–6^1). ^{13}C NMR: 22.2 (OCOCH_3), 36.2 (C-3), 56.3 (OCH$_3$), 65.5 (C-4), 74.8 (C-2), 122.2 (C-6), 116.8 (C-8), 126.4, (C-5), 126.1 (C-4a), 127.9 (C-2^1, 6^1), 130.3 (C-3^1, 5^1), 137.5 (C-4^1), 137.6 (C-1^1), 150.3 (C-8a), 132.5 (C-7), and 171.4 (O*CO*CH$_3$). MS (*m*/*z*) 376 (M^+), 378 (M^{2+}). HRMS calcd for $C_{18}H_{17}BrO_4$ (M^+), 376.0335. Found: 376.0363.

5.25. (±)-*cis*-7,8-Dimethoxy-4^1-hydroxy-4-acetoxyflavan 11l

^{1}H NMR: δ 2.04 (s, OCOCH_3), 2.75 (m, H_e-3), 3.16 (m, H_a-3), 3.80 (s, OCH$_3$-8), 3.92 (s, OCH$_3$-7), 4.84 (dd, $J = 14.0$, 2.0 Hz, H-4), 5.41 (dd, $J = 14.0$, 8.0 Hz, H-2), 6.62 (d, $J = 10.0$ Hz, H-6), 6.78 (d, $J = 10.0$ Hz, H-3^1, 5^1), 7.31 (d, $J = 10.0$ Hz, H-2^1, 6^1), and 7.56 (d, $J = 10.0$ Hz, H-5). ^{13}C NMR: 19.5 (OCOCH_3), 38.6 (C-3), 55.7 (OCH$_3$-7), 59.2 (OCH$_3$-8) 65.5 (C-4), 78.4 (C-2), 124.8 (C-6), 127.3 (C-4a), 128.4 (C-3^1, 5^1), 126.8 (C-2^1, 6^1), 128.6 (C-5), 139.5 (C-1^1), 118.3 (C-8), 130.2 (C-7), 138.6 (C-4^1), 155.6 (C-8a), and 171.8 (O*CO*CH$_3$).

MS (*m*/*z*) 344 (M^+). HRMS calcd for $C_{19}H_{20}O_6$ (M^+), 344.1348. Found: 344.1362.

5.26. (±)-*cis*-5,7,4^1,5^1,6^1-Pentamethoxy-4-acetoxyflavan 11m

^1H NMR: δ 2.01 (s, OCOCH_3), 2.09 (m, H_e-3), 2.55 (m, H_a-3), 3.62 (s, OCH_3-7), 3.75 (s, OCH_3-5^1), 3.78 (s, OCH_3-6^1), 3.86 (s, OCH_3-5), 3.92 (s, OCH_3-4^1), 4.65 (dd, *J* = 14.0, 2.0 Hz, H-4), 5.51 (dd, *J* = 14.0, 8.0 Hz, H-2), 6.02 (d, *J* = 2.0 Hz, H-6), 6.12 (d, *J* = 2.0 Hz, H-8), 6.57 (d, *J* = 10.0 Hz, H-2^1), and 7.12 (d, *J* = 10.0 Hz, H-6^1). ^{13}C NMR: 19.7 (OCOCH_3), 34.7 (C-3), 53.5 (OCH_3-7), 54.6 (OCH_3-6^1), 54.8 (OCH_3-5), 59.2 (OCH_3-5^1), 60.7 (OCH_3-4^1), 65.4 (C-4), 75.8 (C-2), 93.1 (C-6), 118.5 (C-8), 123.2 (C-6), 126.5 (C-4a), 127.8 (C-5), 129.1 (C-2^1, 6^1), 130.2 (C-3^1, 5^1), 132.7 (C-7), 137.6 (C-1^1), 137.8 (C-4^1), 154.8 (C-8a), and 170.5 (O*CO*CH_3). MS (*m*/*z*) 418 (M^+). HRMS calcd for $C_{22}H_{26}O_8$ (M^+), 418.1664. Found: 418.1689.

5.27. General procedure for the lipase mediated enantioselective acylation of (±)-*cis*-flavan-4-ols 8a–m

(±)-*cis*-4^1-Methylflavan-4-ol **8a** (1.20 g, 5 mmol) was dissolved in 1,2-dimethoxyethane (DME)–toluene (1:2) (50 mL). Lipase *C. cylindracea* (*CCL*) (1.20 g) was added to this solution and the suspension thermostated at room temperature. After a few minutes, vinyl acetate (10 mL) was added and the reaction mixture stirred using a magnetic stirrer with the progress of the reaction monitored by TCL by comparing the amount of (±)-*cis*-**8a** present with the amount of (±)-*cis*-**11a**. After 50% conversion, the lipase was filtered off, the solvent evaporated and the resulting gum chromatographed on silica gel by eluting with petroleum ether–ethyl acetate (8:2 v/v) to give (−)-(2*R*,4*R*)-acetate **9a** and (+)-(2*S*,4*S*)-alcohol **10a**. Similarly, (±)-**8b–m** gave (−)-(2*R*,4*R*)-acetates **9b–m** and (+)-(2*S*,4*S*)-alcohols **10b–m** after lipase mediated kinetic resolution. The chemical yield, $[\alpha]_D^{25}$ and % ee of **9a–m** and **10a–m** are given in Table 1.

5.28. General procedure for the oxidation of (+)-(2*S*,4*S*)-flavan-4-ols 10a–m with MnO_2

Active manganese dioxide (2.10 g, 24 mmol) was added to a solution of (+)-(2*S*,4*S*)-4^1-methylflavan-4-ol **10a** (0.48 g, 2 mmol) in chloroform (10 mL) at room temperature and the mixture stirred in the dark for 24 h. After filtration to remove MnO_2 and evaporation to dryness under reduced pressure, the residue on chromatography over silica gel by eluting with petroleum ether–ethyl acetate (9:1 v/v) gave (−)-(2*S*)-4^1-methylflavan-4-one **12a**. Similarly, **11b–m** gave (−)-(2*S*)-flavan-4-ones **12b–m**. The chemical yield, IR, UV, CD data, ^1H, ^{13}C NMR spectra, and high-resolution mass spectra (HRMS) of the prepared (−)-(2*S*)-flavan-4-ones **12a–m** are reported below.

5.29. (−)-(2*S*)-4^1-Methylflavan-4-one 12a

White solid, mp 110 °C, yield 93%, $[\alpha]_D^{25} = -76.1$ (*c* 1.25, $CHCl_3$), ee: 94.5%, IR υ (KBr): 1690 cm^{-1} (C=O). UV λ (logε) (MeOH): 223 (3.6), 285 (3.7), and 315 (3.5). CD (CH_3CN): −225 nm ($\theta = -20.15 \times 10^{-3}$ deg cm^2 d mol^{-1}), −285 nm ($\theta = -25.91 \times 10^{-3}$ deg cm^2 d mol^{-1}) and −315 nm ($\theta = -0.31 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^1H NMR: δ 2.40 (s, CH_3), 2.86 (dd, *J* = 17.0, 3.0 Hz, H_e-3), 3.08 (dd, *J* = 17.0, 13.0 Hz, H_a-3), 5.45 (dd, *J* = 13.0, 3.20 Hz, H-2), 7.05 (m, H-8), 7.25 (m, H-6), 7.25 (d, *J* = 10.0 Hz, H-3^1, 5^1), 7.38 (d, *J* = 10.0 Hz, H-2^1, 6^1), 7.50 (m, H-7), and 7.92 (dd, *J* = 10.0, 2.0 Hz, H-5). ^{13}C NMR: δ 21.1 (CH_3), 44.3 (C-3), 79.7 (C-2), 118.1 (C-8), 118.2 (C-6), 121.3 (C-2^1, 6^1), 126.0 (C-4a), 127.0 (C-5), 129.1 (C-3^1, 5^1), 136.1 (C-4^1), 136.2 (C-7), 139.1 (C-1^1), 162.1 (C-8a), and 190.2 (C=O). MS (*m*/*z*) 238 (M^+). HRMS calcd for $C_{16}H_{14}O_2$ (M^+), 238.1035. Found: 238.1015.

5.30. (−)-(2*S*)-Flavan-4-one 12b

White solid, mp 75 °C (lit.[13] mp 75–77 °C), yield 75%, $[\alpha]_D^{25} = -56.2$ (*c* 0.50, $CHCl_3$) {lit.[13] $[\alpha]_D = -54.1$ (*c* 1.00, $CHCl_3$)}, ee: 97.3%, IR υ (KBr): 1682 cm^{-1} (C=O). UV λ (logε) (MeOH): 215 (3.6), 255 (3.6), and 291 (3.7). CD (CH_3CN): −220 nm ($\theta = -16.00 \times 10^{-3}$ deg cm^2 d mol^{-1}), −281 nm ($\theta = -21.42 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −312 nm ($\theta = -28.00 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^1H NMR: δ 2.85 (dd, *J* = 17.0, 3.0 Hz, H_e-3), 3.08 (dd, *J* = 17.0, 13.0 Hz, H_a-3), 5.50 (dd, *J* = 13.0, 3.20 Hz, H-2), 7.05 (m, H-6,8), 7.30–7.60 (m, H-7, H-2^1, 6^1), and 7.93 (dd, *J* = 10.0, 2.0 Hz, H-5). ^{13}C NMR: δ 44.6 (C-3), 79.5 (C-2), 118.1 (C-8), 120.9 (C-4a), 121.5 (C-6), 126.1 (C-2^1, 6^1), 127.0 (C-5), 128.7 (C-4^1), 128.8 (C-3^1, 5^1) 136.1 (C-7), 138.7 (C-1^1), 161.5 (C-8a), and 191.9 (C=O). MS (*m*/*z*) 224 (M^+). HRMS calcd for $C_{15}H_{12}O_2$ (M^+), 224.0845. Found: 224.0858.

5.31. (−)-(2*S*)-4^1-Methoxyflavan-4-one 12c

Colorless solid, mp 85 °C, yield 81%, $[\alpha]_D^{25} = -36.7$ (*c* 1.81, $CHCl_3$), ee: >99%, IR υ (KBr): 1680 cm^{-1} (C=O). UV λ (logε) (MeOH): 224 (3.8), 278 (3.9), and 305 (3.8). CD (CH_3CN): −221 nm ($\theta = -25.10 \times 10^{-3}$ deg cm^2 d mol^{-1}), −278 nm ($\theta = -28.13 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −305 nm ($\theta = -0.41 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^1H NMR: δ 2.85 (dd, *J* = 17.0, 3.0 Hz, H_e-3), 3.10 (dd, *J* = 17.0, 13.0 Hz, H_a-3), 3.80 (s, OCH_3), 5.42 (dd, *J* = 13.0, 3.20 Hz, H-2), 7.15 (d, *J* = 10.0 Hz, H-3^1, 5^1), 7.05 (m, H-6, 8), 7.40 (d, *J* = 10.0 Hz, H-2^1, 6^1), 7.50 (m, H-7), and 7.98 (d, *J* = 10.0 H-5). ^{13}C NMR: δ 44.2 (C-3), 55.1 (OCH_3), 79.7 (C-2), 115.2 (C-3^1, 5^1), 117.8 (C-8), 119.5 (C-4a), 120.5 (C-6), 127.6 (C-5), 127.7 (C-2^1, 6^1), 132.5 (C-1^1), 135.9 (C-7), 150.2 (C-4^1), 161.7 (C-8a), and 190.1 (C=O). MS (*m*/*z*) 254 (M^+). HRMS calcd for $C_{16}H_{14}O_3$ (M^+), 254.0942. Found: 254.0954.

5.32. (−)-(2*S*)-4^1-Chloroflavan-4-one 12d

White solid, mp 120 °C, yield 79%, $[\alpha]_D{}^{25} = -43.75$ (*c* 2.51, $CHCl_3$), ee: 85.6%, IR υ (KBr): 1690 cm^{-1} (C=O). UV λ (MeOH): 223 (3.5), 269 (3.6), and 310 (3.5). CD (CH_3CN): −228 nm ($\theta = -15.22 \times 10^{-3}$ deg cm^2 d mol^{-1}), −275 nm ($\theta = -18.13 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −310 nm ($\theta = -0.85 \times 10^{-3}$ deg cm^2

d mol^{-1}). ^{1}H NMR: δ 2.91 (dd, J = 17.0, 3.0 Hz, H$_e$-3), 3.05 (dd, J = 17.0, 13.0 Hz, H$_a$-3), 5.43 (dd, J = 13.0, 3.0 Hz, H-2), 7.07 (m, H-8), 7.28 (m, H-6), 7.29 (d, J = 10.0 Hz, H-3^1, 5^1), 7.35 (d, J = 10.0 Hz, H-2^1, 6^1), 7.53 (m, H-7), and 7.95 (dd, J = 10.0, 2.0 Hz, H-5). ^{13}C NMR: δ 44.1 (C-3), 78.8 (C-2), 117.7 (C-8), 118.0 (C-4a), 121.3 (C-6), 127.1 (C-5), 127.2 (C-2^1, 6^1), 128.9 (C-3^1, 5^1), 133.6 (C-4^1), 135.3 (C-7), 138.1 (C-1^1), 162.5 (C-8a), and 192.5 (C=O). MS (*m*/*z*) 258 (M$^+$), 260 (M^{2+}). HRMS calcd for $C_{15}H_{11}ClO_2$ (M$^+$), 258.0423. Found: 258.0411.

5.33. (−)-(2*S*)-2^1-Chloroflavan-4-one 12e

White solid, mp 124 °C, yield 78%, $[\alpha]_D^{25} = -56.7$ (*c* 1.50, CHCl$_3$), ee: 92.1%, IR υ (KBr): 1686 cm^{-1} (C=O). UV λ (MeOH): 221 (3.6), 271 (3.6), and 310 (3.5). CD (CH$_3$CN): −222 nm ($\theta = -25.56 \times 10^{-3}$ deg cm^2 d mol^{-1}), −272 nm ($\theta = -28.43 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −310 nm ($\theta = -2.87 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^{1}H NMR: δ 2.85 (dd, J = 17.0, 3.0 Hz, H$_e$-3), 3.08 (dd, J = 17.0, 13.0 Hz, H$_a$-3), 5.90 (dd, J = 13.0, 3.0 Hz, H-2), 7.06 (m, H-8)7.23 (m, H-6), 7.48 (m, H-7), 7.60 (m, H-3^1, 4^1, 5^1), 7.75 (dd, J = 10.0, 2.0 Hz, H-6^1), and 7.95 (dd, J = 10.0, 2.0 Hz, H-5). ^{13}C NMR: δ 43.8 (C-3), 76.3 (C-2), 117.5 (C-8), 118.0 (C-4a), 121.8 (C-6), 125.1 (C-5^1), 127.1 (C-5), 127.4 (C-3^1, 4^1), 128.2 (C-6^1), 133.5 (C-2^1), 135.8 (C-1^1), 136.2 (C-7), 161.7 (C-8a), and 192.0 (C=O). MS (*m*/*z*) 258 M$^+$), 260 (M^{2+}). HRMS calcd for $C_{15}H_{11}ClO_2$ (M$^+$), 258.0423. Found: 258.0435.

5.34. (−)-(2*S*)-3^1,4^1-Methylenedioxyflavan-4-one 12f

Colorless solid, mp 138 °C, yield 92%, $[\alpha]_D^{25} = -72.3$ (*c* 1.50, CHCl$_3$), ee: >99%, IR υ (KBr): 1637 cm^{-1} (C=O). UV λ (MeOH): 225 (3.5), 275 (3.2), and 309 (4.1). CD (CH$_3$CN): −226 nm ($\theta = -45.16 \times 10^{-3}$ deg cm^2 d mol^{-1}), −273 nm ($\theta = -18.68 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −306 nm ($\theta = -0.92 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^{1}H NMR: δ 2.87 (dd, J = 17.0, 3.0 Hz, H$_e$-3), 3.09 (dd, J = 17.0, 13.0 Hz, H$_a$-3), 5.08 (dd, J = 13.0, 3.0 Hz, H-2), 6.00 (s, OCH$_2$O), 6.70–7.00 (m, H-6, 2^1, 5^1, 6^1), 7.09 (m, H-8), 7.30 (m, H-7), and 7.46 (dd, J = 10.0, 2.0 Hz, H-5). ^{13}C NMR: δ 44.2 (C-3), 79.0 (C-2), 102.1 (OCH$_2$O), 125.2 (C-2^1), 129.5 (C-5^1), 118.1 (C-8), 119.3 (C-4a), 120.2 (C-6), 127.3 (C-6^1), 126.7 (C-5), 132.5 (C-1^1), 134.7 (C-7), 145.5 (C-4^1), 148.2 (C-3^1), 161.2 (C-8a), and 190.1 (C=O). MS (*m*/*z*) 268 (M$^+$). HRMS calcd for $C_{16}H_{12}O_4$ (M$^+$), 268.0764. Found: 268.0785.

5.35. (−)-(2*S*)-6-Chloroflavan-4-one 12g

White solid, mp 128 °C, yield 65%, $[\alpha]_D^{25} = -65.7$ (*c* 1.75, CHCl$_3$), ee: 68.7%, IR υ (KBr): 1678 cm^{-1} (C=O). UV λ (MeOH): 226 (3.7), 274 (3.5), and 312 (3.7). CD (CH$_3$CN): −225 nm ($\theta = -19.14 \times 10^{-3}$ deg cm^2 d mol^{-1}), −275 nm ($\theta = -38.59 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −310 nm ($\theta = -1.95 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^{1}H NMR: δ 2.88 (dd, J = 17.0, 3.0 Hz, H$_e$-3), 3.05 (dd, J = 17.0, 13.0 Hz, H$_a$-3), 5.45 (dd, J = 13.0, 3.0 Hz, H-2), 7.00 (d, J = 10.0 Hz, H-8), 7.43 (dd, J = 10.0, 2.0 Hz, H-7), 7.51 (m, H-2^1–6^1), and 7.88 (d, J = 2.0 Hz, H-5). ^{13}C NMR: δ 43.2 (C-3), 79.5 (C-2), 118.5 (C-8), 122.8 (C-4a), 125.4 (C-2^1, 6^1), 125.7 (C-5), 128.5 (C-3^1, 4^1, 5^1), 133.9 (C-6), 122.3 (C-6), 135.1 (C-7), 137.5 (C-1^1), 158.1 (C-8a), and 190.5 (C=O). MS (*m*/*z*) 258 (M$^+$), 260 (M^{2+}). HRMS calcd for $C_{15}H_{11}ClO_2$ (M$^+$), 258.0423. Found: 258.0416.

5.36. (−)-(2*S*)-8-Chloroflavan-4-one 12h

White solid, mp 122 °C, yield 79%, $[\alpha]_D^{25} = -38.15$ (*c* 1.61, CHCl$_3$), ee: 69.5%, IR υ (KBr): 1690 cm^{-1} (C=O). UV λ (log ε) (MeOH): 224 (3.5), 276 (3.8), and 311 (3.5). CD (CH$_3$CN): −219 nm ($\theta = -41.26 \times 10^{-3}$ deg cm^2 d mol^{-1}), −270 nm ($\theta = -16.55 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −310 nm ($\theta = -1.23 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^{1}H NMR: δ 2.96 (dd, J = 17.0, 3.0 Hz, H$_e$-3), 3.12 (dd, J = 17.0, 13.0 Hz, H$_a$-3), 5.60 (dd, J = 13.0, 3.0 Hz, H-2), 7.00 (m, H-6), 7.45 (m, H-2^1–6^1), 7.60 (dd, J = 10.0, 2.0 Hz, H-7), and 7.85 (dd, J = 10.0, 2.0 Hz, H-5). ^{13}C NMR: δ 43.9 (C-3), 79.6 (C-2), 112.1 (C-8), 125.4 (C-6), 125.8 (C-5), 128.6 (C-2^1, 6^1), 128.7 (C-3^1, 5^1), 130.0 (C-4a), 123.0 (C-4^1), 133.5 (C-7), 138.0 (C-1^1), 156.8 (C-8a), and 190.9 (C=O). MS (*m*/*z*) 258 (M$^+$), 260 (M^{2+}). HRMS calcd for $C_{15}H_{11}ClO_2$ (M$^+$), 258.0423. Found: 258.0446.

5.37. (−)-(2*S*)-6-Chloro-4^1-methoxyflavan-4-one 12i

White solid, mp 154 °C, yield 85%, $[\alpha]_D^{25} = -48.4$ (*c* 2.71, CHCl$_3$), ee: 96.2%, IR υ (KBr): 1689 cm^{-1} (C=O). UV λ (log ε) (MeOH): 223 (3.5), 278 (3.6), and 305 (3.8). CD (CH$_3$CN): −219 nm ($\theta = -32.86 \times 10^{-3}$ deg cm^2 d mol^{-1}), −275 nm ($\theta = -26.45 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −308 nm ($\theta = -3.65 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^{1}H NMR: δ 2.80 (dd, J = 17.0, 3.0 Hz, H$_e$-3), 3.05 (dd, J = 17.0, 13.0 Hz, H$_a$-3), 3.80 (s, OCH$_3$), 5.37 (dd, J = 13.0, 3.20 Hz, H-2), 6.95 (d, J = 10.0 Hz, H-8), 7.35 (d, J = 10.0 Hz, H-2^1, 6^1), 7.40 (dd, J = 10.0 Hz, 2.0 Hz, H-7), 7.72 (d, J = 10.0 Hz, H-3^1–5^1), and 7.85 (d, J = 2.0 Hz, H-5). ^{13}C NMR: δ 55.3 (OCH$_3$), 44.0 (C-3), 79.5 (C-2), 137.6 (C-1^1), 125.6 (C-3^1, 5^1), 119.8 (C-8), 121.6 (C-4a), 127.0 (C-5), 127.7 (C-2^1, 6^1), 130.2 (C-6), 135.8 (C-7), 159.9 (C-4^1), 160.0 (C-8a), and 190.9 (C=O). MS (*m*/*z*) 288 (M$^+$). HRMS calcd for $C_{16}H_{13}ClO_3$ (M$^+$), 288.0637. Found: 288.0624.

5.38. (−)-(2*S*)-6-Bromoflavan-4-one 12j

Light brown solid, mp 146 °C, yield 74%, $[\alpha]_D^{25} = -75.1$ (*c* 1.12, CHCl$_3$), ee: >99%, IR υ (KBr): 1672 cm^{-1} (C=O). UV λ (log ε) (MeOH): 225 (3.5), 269 (3.7), and 303 (3.6). CD (CH$_3$CN): −224 nm ($\theta = -12.85 \times 10^{-3}$ deg cm^2 d mol^{-1}), −270 nm ($\theta = -34.51 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −303 nm ($\theta = -1.68 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^{1}H NMR: δ 2.71 (dd, J = 17.0, 3.0 Hz, H$_e$-3), 3.11 (dd, J = 17.0, 13.0 Hz, H$_a$-3), 5.45 (dd, J = 13.0, 3.20 Hz, H-2), 6.87 (d, J = 10.0 Hz, H-8), 7.31 (dd, J = 10.0, 2.0 Hz, H-7), 7. 59–7.64 (m, H-2^1–6^1), and 7.92 (d, J = 2.0 Hz, H-5). ^{13}C NMR: δ 41.2 (C-3), 77.4 (C-2), 121.5 (C-8), 128.7 (C-6), 126.4 (C-5), 127.2 (C-2^1, 6^1), 128.6 (C-3^1, 5^1), 120.7 (C-4a), 131.3 (C-7), 125.1 (C-4^1), 136.9 (C-4^1), 152.8 (C-8a), and 191.5

(C=O). MS (*m*/*z*) 302 (M^+), 304 (M^{2+}). HRMS calcd for $C_{15}H_{11}BrO_2$ (M^+), 302.9915. Found: 302.9931.

5.39. (−)-(2*S*)-6-Bromo-7-methoxyflavan-4-one 12k

Brown solid, mp 152 °C, yield 83%, $[\alpha]_D^{25} = -62.6$ (*c* 1.71, $CHCl_3$), ee: 63.6%, IR υ (KBr): 1681 cm^{-1} (C=O). UV λ (log ε) (MeOH): 232 (3.6), 275 (3.5), and 310 (3.6). CD (CH_3CN): −230 nm ($\theta = -52.03 \times 10^{-3}$ deg cm^2 d mol^{-1}), −272 nm ($\theta = -24.58 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −309 nm ($\theta = -2.26 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^1H NMR: δ 2.85 (dd, *J* = 17.0, 3.0 Hz, H_e-3), 3.15 (dd, *J* = 17.0, 13.0 Hz, H_a-3), 3.75 (s, OCH_3), 5.39 (dd, *J* = 13.0, 3.20 Hz, H-2), 6.72 (s, H-8), 7.15 (s, H-5), and 7.38–7.41 (m, H-2^1–6^1). ^{13}C NMR: δ 45.1 (C-3), 55.4 (OCH_3), 78.5 (C-2), 121.5 (C-6), 123.7 (C-8), 128.5 (C-5), 125.5 (C-4a), 126.1 (C-2^1, 6^1), 135.3 (C-3^1, 5^1), 152.3 (C-4^1), 139.5 (C-1^1) 155.2 (C-8a), 143.1 (C-7), and 193.2 (C=O). MS (*m*/*z*) 332 (M^+). HRMS calcd for $C_{16}H_{13}BrO_3$ (M^+), 332.0023. Found: 332.0016.

5.40. (−)-(2*S*)-7,8-Dimethoxy-4^1-hydroxyflavan-4-one{(−)-(2*S*)-heliannone B} 12l

White solid, mp 136 °C, yield 95%, $[\alpha]_D^{25} = -65.3$ (*c* 1.81, $CHCl_3$), ee: 97.2%, IR υ (KBr): 1650 cm^{-1} (C=O). UV λ (log ε) (MeOH): 235 (3.5), 282 (3.7), and 326 (3.6). CD (CH_3CN): −233 nm ($\theta = -25.86 \times 10^{-3}$ deg cm^2 d mol^{-1}), −280 nm ($\theta = -17.79 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −318 nm ($\theta = -4.85 \times 10^{-3}$ deg cm^2 d mol^{-1}). ^1H NMR: δ 2.78 (dd, *J* = 17.0, 3.0 Hz, H_e-3), 3.04 (dd, *J* = 17.0, 13.0 Hz, H_a-3), 3.85 (s, OCH_3-8), 3.95 (s, OCH_3-7), 5.42 (dd, *J* = 13.0, 3.2 Hz, H-2), 6.66 (d, *J* = 10.0 Hz H-6), 6.85 (d, *J* = 10.0 Hz, H-3^1, 5^1), 7.35 (d, *J* = 10.0 Hz, H-2^1, 6^1), and 7.64 (d, *J* = 10.0 Hz, H-5). ^{13}C NMR: δ 44.2 (C-3), 56.5 (OCH_3-7), 60.8 (OCH_3-8), 80.2 (C-2), 110.6 (C-6), 112.1 (C-4a), 116.2 (C-3^1, 5^1), 127.8 (C-2^1, 6^1), 128.3 (C-5), 130.5 (C-1^1), 131.2 (C-8), 158.5 (C-7) 158.9 (C-4^1), 160.3 (C-8a), and 195.4 (C=O). MS (*m*/*z*) 300 (M^+). HRMS calcd for $C_{17}H_{16}O_5$ (M^+), 300.0997. Found: 300.0993.

5.41. (−)-(2*S*)-5,7,4^1,5^1,6^1-Pentamethoxyflavan-4-one 12m

White solid, mp 167 °C (lit.[18] mp 166–168 °C), yield 93%, $[\alpha]_D^{25} = -84.15$ (*c* 1.61, $CHCl_3$) {lit.[18] $[\alpha]_D = -21.0$ (*c* 0.10, MeOH)}, ee: >99%, IR υ (KBr): 1671 cm^{-1} (C=O). UV λ (log ε) (MeOH): 231 (3.6), 283 (3.9), and 320 (3.5). CD (CH_3CN): −230 nm ($\theta = -35.21 \times 10^{-3}$ deg cm^2 d mol^{-1}), −281 nm ($\theta = -22.62 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −316 nm ($\theta = -5.74 \times 10^{-3}$ deg cm^2 d mol^{-1}). {(Lit.[19] CD (MeOH): 287 nm ($\theta = -0.23 \times 10^{-3}$ deg cm^2 d mol^{-1}), and −320 nm ($\theta = 0.07 \times 10^{-3}$ deg cm^2 d mol^{-1})}. ^1H NMR: δ 2.70 (dd, *J* = 17.0, 3.0 Hz, H_e-3), 3.05 (dd, *J* = 17.0, 13.0 Hz, H_a-3), 3.76 (s, OCH_3-7), 3.84 (s, OCH_3-5^1), 3.85 (s, OCH_3-6^1), 3.86 (s, OCH_3-5), 3.86 (s, OCH_3-4^1), 5.62 (dd, *J* = 13.0, 3.20 Hz, H-2), 6.04 (d, *J* = 2.0 Hz H-6), 6.10 (d, *J* = 2.0 Hz H-8), 6.70 (d, *J* = 10.0 Hz H-2^1), and 7.16 (d, *J* = 10.0 Hz H-3^1). ^{13}NMR: δ 44.2 (C-3), 55.4 (OCH_3-7), 56.1 (OCH_3-6^1), 56.3 (OCH_3-5), 61.4 (OCH_3-5^1), 61.7 (OCH_3-4^1), 74.5 (C-2), 105.2 (C-6), 94.3 (C-8), 110.5 (C-4a), 107.4 (C-5^1), 120.6 (C-6^1), 125.0 (C-1^1), 140.4 (C-3^1), 142.9 (C-2^1) 155.2 (C-4^1), 163.3 (C-5), 166.4 (C-8a), 166.8 (C-7), and 190.4 (C=O). MS (*m*/*z*) 374 (M^+). HRMS calcd for $C_{20}H_{22}O_7$ (M^+), 374.1438. Found: 374.1426.

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