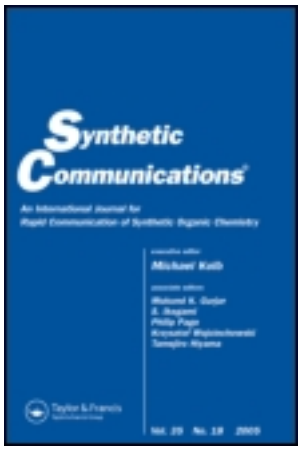

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First Synthesis of (±)-*C*-3-Prenylated Flavanones

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ABSTRACT

2,4,6-*tris*(Methoxymethoxy)acetophenone (**1**) was first mono-alkylated with 3-methylbut-2-enyl bromide to yield 5-methyl-1-(2,4,6-trimethoxymethoxyphenyl)hex-4-en-1-one (**2**). The base catalyzed aldol condensation of **2** and substituted benzaldehydes gave chalcones **3** in good yields. One pot cyclization and deprotection of the chalcones were accomplished in refluxing 4 N HCl in MeOH to afford (±)-*C*-3-prenylated flavanones.

Key Words: Prenylation; Chalcones; Flavanones.

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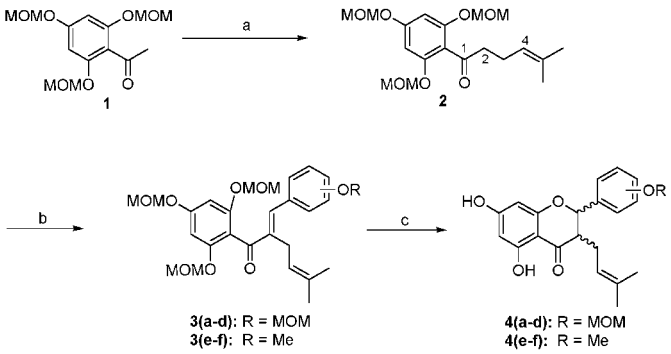
Flavonoids are naturally occurring compounds with important biological activities.[1] It is thought that the prenyl groups (including prenyl/isopentenyl, geranyl, and farnesyl side chains) in the flavonoids and isoflavonoids play an important role in their biological activities by increasing their lipophilicity and, consequently, enhancing their antimicrobial activities through interaction with cellular membrane.[2–4] Of the prenylated flavonoids, flavanone represents the most abundant class with a rich variety of structures.[5] Majority of the natural prenylated flavanones are *C*-prenylated derivatives. *C*-prenylation by regiospecific prenyltransferases is generated frequently at position 6/8 on ring A and at position 3′/5′ on ring B, which are usually *ortho* to a phenolic hydroxyl group with rich electrons,[6] and occasionally at C-3, which is also somewhat electron rich due to conjugation. To the best of our knowledge, *C*-3 prenylated flavanone has never been reported as synthetic or natural product, though there indeed exists small amount of naturally occurring *C*-3 prenylated flavones.[4,7]

The chemical syntheses of flavones and flavanones were generally carried out by oxidative cyclization and cyclization of chalcones respectively.[8,9] In the case of flavanol, the chalcones were epoxidized before cyclizations were conducted.[10] Flavonols were synthesized either by Algar–Flynn–Oyamada reaction[11] or by oxidation of flavone. Recently Brouillard and coworkers reported a new synthetic route to flavonols without using any oxidizing reagent.[12] The intermediate obtained via Baker–Venkataraman rearrangement[13] was concomitantly cyclized and dehydrated to yield the desired product. Of all the synthetic flavonoids reported, only a few were *C*-prenylated at C-6 and/or C-8 on ring A.[14] In view of the potential biological activities of *C*-3 prenylated flavanones, we herein report the first synthesis of (2,3-*cis*)- and (2,3-*trans*)-*C*-3-prenylated flavanones.

Alkylation of 2,4,6-*tris*(methoxymethoxy)acetophenone[10b] (**1**) with 3-methylbut-2-enyl bromide was carried out using different bases (Sch. 1). The most optimized condition was achieved by treating **1** with LDA in THF, as the desired mono-alkylated product **2** was obtained as the major product. Other bases such as NaH[15] and *t*BuOK gave mainly dialkylated products, whereas no reaction occurred when NaOEt was employed.

The MOM protected 4-hexenophenone **2** and the MOM protected hydroxybenzaldehydes or methoxybenzaldehydes were subjected to aldol condensation with spontaneous elimination to give chalcones **3**. Among the several bases utilized, NaHMDS/THF afforded the best yield (Table 1). Subsequent aldol condensations of **2** with various benzaldehydes were therefore carried out using NaHMDS in THF (Table 2).



Reagents and conditions: a) 3-methylbut-2-enyl bromide (2 equiv), fresh LDA (2.5 equiv), THF, -75°C to 4°C, 20 h, 50%; b) ArCHO (2 equiv), NaHMDS (3 equiv), THF, -75°C to reflux, 30 h, 13-46%; c) 4 N HCl, MeOH, reflux, 8-15 h, 22-63%.

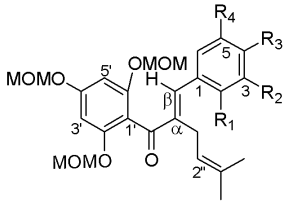
Scheme 1. Synthesis of *C*-3-prenylated flavanones (**4a–f**).

Table 1. Isolated yields of **3a**.

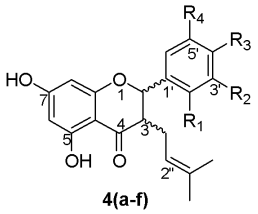
Reagent	Isolated yields of **3a** (%)
NaHMDS/THF	36
NaOH/EtOH	22
NaH/THF	12
LDA/THF	8
LiHMDS/THF	0

Since the benzaldehyde was readily reduced to benzyl alcohol as a result of Cannizzaro reaction,[16] excess amounts of benzaldehydes (2 equiv.) were added. The syntheses of chalcones **3c** and **3e** were also repeated using the commonly employed NaOH/EtOH condition. Although the yields of the chalcones obtained were comparable to those obtained using NaHMDS/THF, the amount of benzyl alcohol observed was significantly lower (decreased from 11 to 4%). We have found that the yields of the chalcone **3** are comparable to the hindered α-alkyl (*i*Pr, *c*-pentyl) substituted chalcones yields reported in the Lit.[17] Furthermore, it is correlated to the extent of substitution on the benzaldehyde. That is, condensation products (**3a–c**, **3e**) from mono- and di-substituted benzaldehydes afforded higher yields than those (**3d**, **3f**) from 2,4,5-trisubstituted benzaldehydes. Surprisingly, the yield of **3f** is lower than **3d** even though the benzaldehyde is protected with the less

Table 2. Isolated yields of chalcones **3** and flavanones **4**.



3(a-f)



4(a-f)

Entry	R_1	R_2	R_3	R_4	Yields of **3** (%) from NaHMDS/THF	Yields of **3** (%) from NaOH/EtOH	Yields of **4** (%)	Ratio of **4-I**:**4-II**[c]
(a)	X[a]	H	X	H	36	22	22	1:2
(b)	H	X	X	H	32	—[b]	50	5:4
(c)	H	H	X	H	30	42	55	5:3
(d)	X	H	X	X	24	—[b]	No reaction	—
(e)	H	H	OMe	H	46	50	63	3:2
(f)	OMe	H	OMe	OMe	13	—[b]	52	2:1

[a]For compounds **3(a–d)**, X = OMOM; for **4(a–d)**, X = OH.
[b]Synthesis was not carried out.
[c](2,3)-*cis* to *trans* ratio of **4** as determined by ^{1}**H NMR**.

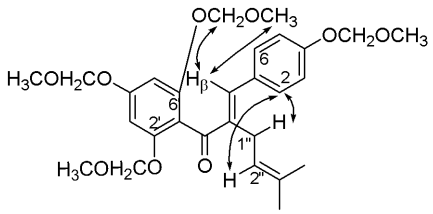


Figure 1. NOE enchancement of **3c**.

bulky methoxy group. The chalcones synthesized possess the expected *trans-E* configurations as determined by 1D NOE experiments.[18] For example, both H-1″ and H-2″ were enhanced when H-2 and H-6 of **3c** were irradiated, and similarly, both the CH_2 and CH_3 in 2′,6′-OMOM groups were enhanced when H-β was irradiated (Fig. 1).

We envisage that final cyclization with simultaneous deprotection of MOM should be achievable by refluxing chalcones **3** in acid. Thus, instead of using the commonly employed bases such as NaOAc (9a, 14a–b), NaOH[19] and piperidine,[19] 4 N HCl was used in

the cyclization for chalcones **3**. Using this approach, flavanones **4** were isolated with more than 50% yield except for **4a** and **4d**. The progress of **3d** ring closure reaction was monitored by TLC, MS and ^{1}H NMR. The intermediates were the partially deprotected chalcones. None of the MOM protected or deprotected flavanone was observed. The reaction gave rise to many unidentified polar mixtures upon further refluxing. The difficulty in the ring closure reaction of chalcones **3a** and **3d** might be caused by the sterically bulky 2′-MOM in ring B. On the contrary, chalcone **3f** cyclized with ease to give flavanone **4f**, most likely as a result of the smaller 2′-OMe group.

The final flavanones were obtained as mixtures of diastereomers (2,3)-*cis*- and (2,3)-*trans*-**4** (or **4-I** and **4-II**, respectively) with *cis* form being the major products (except **4a**) (Table 2). This is probably due to the addition of hydrogen on the opposite direction of ring B during cyclization. The relative configuration of **4** was determined by the ^{1}H NMR spectrum which showed that (2,3)-*cis*-**4** possesses an axial/equatorial coupling ($J = \sim 3$ Hz) while (2,3)-*trans*-**4** possesses a diaxial coupling ($J = 9$–10 Hz) for H-2 and H-3.[20] The diastereomeric ratio of **4-I** and **4-II** were assigned according to the integration of H-2. Full assignment (^{1}H and ^{13}C) of **4-I** and **4-II** was accomplished with 2D-NMR experiments (HMQC and HMBC).

We have successfully synthesized (±)-*C*-3-prenylated flavanones via the α-prenylated chalcones. The ease of synthesis and the simultaneous deprotection and cyclization of the chalcones in acid provide a convenient route to the making of this class of compounds. Furthermore, the *C*-3 prenyl group is a versatile handle for further functional groups manipulation. Work is currently in progress to synthesize prenylated flavanones with more diversity.

EXPERIMENTAL

THF was distilled from sodium benzophenone ketyl prior to use. TLC was carried out on precoated plates: analytical (Merck Kieselgel 60 F_{254}); preparative scale (Aldrich, silica, 1 mm). Column chromatography was performed on silica (Merck, 230–400 mesh). All the 1D and 2D NMR experiments for ^{1}H (400.13 MHz) and ^{13}C (100.61 MHz) were obtained on a Bruker AVANCE-400 digital NMR spectrometer. ^{1}H and ^{13}C chemical shifts were expressed in ppm using their deuterated solvents' peak as internal standard (for $CDCl_3$: 7.26 ppm (^{1}H), 77.0 ppm (^{13}C); for acetone-d_6: 2.05 ppm (^{1}H), 29.5 ppm (^{13}C)). FTIR spectra were

performed on a Bio-Rad Excalibur FT 3000 spectrometer. HRESI-MS spectra were taken on a PerSeptive Biosystems Mariner TOF spectrometer at 70 eV. Elemental analyses were performed on Perkin Elmer 2400 CHN Elemental Analyzer.

Preparation of 5-methyl-1-(2,4,6-trimethoxymethoxyphenyl)hex-4-en-1-one (2). To a stirred solution of diisopropylamine (0.7 mL, 5 mmol) in dry THF (10 mL) was added BuLi (3.1 mL, 5 mmol, 1.6 M in hexane) at −75°C. The solution was stirred for 15 min before adding 2,4,6-*tris*-(methoxymethoxy)acetophenone (**1**) (600 mg, 2 mmol, in 5 mL THF). The mixture was stirred for 30 min at 0°C, and then 3-methylbut-2-enyl bromide (461 μL, 4 mmol) was added slowly. The reaction was allowed to react at 4°C for 20 h before it was quenched with ice and saturated $NaHCO_3$ (10 mL). The compound was extracted into EtOAc (3×20 mL), washed with brine (15 mL), and then water (15 mL), dried with $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (25% EtOAc in hexane) to give **2** (368 mg, 50%, R_f 0.65) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.49 (s, 2H, Ar), 5.13 (s, 2H, OCH_2O), 5.11 (t, 1H, $J = 7.2$ Hz, H-4), 5.10 (s, 4H, $2 \times OCH_2O$), 3.46 (s, 3H, OCH_3), 3.43 (s, 6H, $2 \times OCH_3$), 2.77 (t, 2H, $J = 7.2$ Hz, H-2), 2.35 (q, 2H, $J = 7.2$ Hz, H-3), 1.66, 1.61 (all s, 6H, $2 \times CH_3$). ^{13}C NMR ($CDCl_3$): δ 203.9, 159.2, 155.0 (2C), 132.1, 123.1, 116.5, 96.8 (2C), 94.6 (2C), 94.4, 56.2, 56.1 (2C), 44.9, 25.6, 22.4, 17.5. IR (KBr): 1698 cm^{-1} (C=O). Anal. calcd. for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.96; H, 7.33. HR-ESIMS: m/z $[M + H]^+$ calcd. for $C_{19}H_{29}O_7$: 369.1913. Found: 369.1910.

Preparation of α-(3″,3″-dimethylallyl)-2,4,2′,4′,6′-*pentakis*(methoxymethoxy)chalcone (3a). To a stirred solution of **2** (120 mg, 0.33 mmol) in dry THF (1.5 mL) was added NaHMDS (0.98 mL, 3 equiv., 1.0 M in THF) at −75°C. The solution was stirred for 30 min before adding 2,4-*bis*(methoxymethoxy)benzaldehyde (147 mg, 0.65 mmol, 2 equiv.) in THF (1 mL) at r.t. The mixture was refluxed for 30 h and then quenched with ice and saturated $NaHCO_3$, worked up as above. The residue was purified by flash column chromatography (30% EtOAc in hexane) to give **3a** (68.0 mg, 36%, R_f 0.24) as a yellow gum. ^{1}H NMR ($CDCl_3$): δ 7.44 (s, 1H, H-β), 7.34 (d, 1H, $J = 8.6$ Hz, H-6), 6.72 (d, 1H, $J = 2.3$ Hz, H-3), 6.69 (dd, 1H, $J = 8.6$, 2.3 Hz, H-5), 6.52 (s, 2H, H-3′, H-5′), 5.21 (br t, 1H, $J = 3.5$ Hz, H-2″), 5.16, 5.15, 5.08, 5.05 (all s, 10H, $5 \times OCH_2O$), 3.47, 3.46, 3.38, 3.31 (all s, 15H, $5 \times OCH_3$), 3.33 (br d, 2H, $J = 3.5$ Hz, H-1″), 1.72, 1.67 (all s, 6H, $2 \times CH_3$). ^{13}C NMR ($CDCl_3$): δ 196.9, 159.1, 158.9, 156.3, 155.5 (2C), 141.2, 137.6, 132.0, 130.9, 122.5, 119.7, 115.1, 108.8, 103.4, 97.0 (2C), 94.9, 94.6, 94.5 (2C), 94.3, 56.2 (3C), 56.1 (2C), 25.84, 25.79, 18.0. IR (KBr): 1649 cm^{-1} (C=C-C=O). Anal. calcd. for

$C_{30}H_{40}O_{11}$: C, 62.49; H, 6.99. Found: C, 62.44; H, 7.40. HR-ESIMS: m/z $[M+H]^+$ calcd. for $C_{30}H_{41}O_{11}$. 577.2649. Found: 577.2652.

α-(3″,3″-Dimethylallyl)-3,4,2′,4′,6′-*pentakis*(methoxymethoxy)chalcone (3b). Prepared as **3a** from **2** (90 mg, 0.24 mmol) and 3,4-*bis*(methoxymethoxy)benzaldehyde (111 mg, 0.49 mmol). Column chromatography (30% EtOAc in hexane) gave **3b** (45.5 mg, 32%, R_f 0.24) as a yellow gum. ^{1}H NMR ($CDCl_3$): δ 7.19 (s, 1H, H-β), 7.17 (d, 1H, $J=2.0$ Hz, H-1), 7.12 (d, 1H, $J=8.0$ Hz, H-5), 7.01 (dd, 1H, $J=8.0$, 2.0 Hz, H-6), 6.52 (s, 2H, H-3′, H-5′), 5.25, 5.19, 5.17, 5.09 (all s, 10H, $5\times OCH_2O$), 5.08 (hidden, 1H, H-2″), 3.50, 3.49, 3.48, 3.37 (all s, 15H, $5\times OCH_3$), 3.46 (d, 2H, $J=3.4$ Hz, H-1″), 1.72, 1.70 (all s, 6H, $2\times CH_3$). ^{13}C NMR ($CDCl_3$): δ 196.7, 159.3, 155.5, 147.8, 146.8, 142.0, 141.7, 132.7, 130.2, 124.6, 122.1, 118.3, 116.0, 114.7, 96.9, 95.4, 95.1, 94.6, 94.4, 56.3, 56.2, 25.7, 25.5, 18.1. IR (KBr): 1649 cm^{-1} (C=C-C=O). HR-ESIMS: m/z $[M+H]^+$ calcd. for $C_{30}H_{41}O_{11}$: 577.2649. Found: 577.2641.

α-(3″,3″-Dimethylallyl)-4,2′,4′,6′-*tetrakis*(methoxymethoxy)chalcone (3c). Prepared as **3a** from **2** (250 mg, 0.68 mmol) and 4-methoxymethoxybenzaldehyde (225 mg, 1.36 mmol). Column chromatography (25% EtOAc in hexane) gave **3c** (105.2 mg, 30%, R_f 0.34) as a pale yellow gum. ^{1}H NMR ($CDCl_3$): δ 7.31 (dd, 2H, $J=8.8$, 2.0 Hz, H-2, H-6), 7.22 (s, 1H, H-β), 7.00 (dd, 2H, $J=8.8$, 2.0 Hz, H-3, H-5), 6.52 (s, 2H, H-3′, H-5′), 5.18 (hidden, 1H, H-2″), 5.19, 5.17, 5.09 (all s, 8H, $4\times OCH_2O$), 3.50, 3.47, 3.37 (all s, 12H, $4\times OCH_3$), 3.38 (d, 2H, $J=3.2$ Hz, H-1″), 1.73, 1.72 (all s, 6H, $2\times CH_3$). ^{13}C NMR ($CDCl_3$): δ 196.8, 159.2, 157.6, 155.5 (2C), 142.1, 141.2, 132.5, 131.3 (2C), 129.5, 122.1, 116.0 (2C), 114.7, 96.9 (2C), 94.6, 94.4 (2C), 94.2, 56.3, 56.2 (2C), 56.1, 25.8, 25.5, 18.0. IR (KBr): 1650 cm^{-1} (C=C-C=O). Anal. calcd. for $C_{28}H_{36}O_9$: C, 65.10; H, 7.02. Found: C, 64.82; H, 7.35. HR-ESIMS: m/z $[M+H]^+$ calcd. for $C_{28}H_{37}O_9$, 517.2438. Found: 517.2432.

α-(3″,3″-Dimethylallyl)-2,4,5,2′,4′,6′-*hexakis*(methoxymethoxy)chalcone (3d). Prepared as **3a** from **2** (137 mg, 0.37 mmol) and 2,4,5-*tris*-(methoxymethoxy)benzaldehyde (213 mg, 0.74 mmol). Column chromatography (30% EtOAc in hexane) gave **3d** (56.8 mg, 24%, R_f 0.16) as a brown yellow gum. ^{1}H NMR ($CDCl_3$): δ 7.41 (s, 1H, H-β), 7.24 (s, 1H, H-6), 6.90 (s, 1H, H-3), 6.51 (s, 2H, H-3′, H-5′), 5.21, 5.14, 5.09, 5.08, 4.99 (all s, 12H, $6\times OCH_2O$), 5.19 (hidden, 1H, H-2″), 3.49, 3.474, 3.470, 3.38, 3.29 (all s, 18H, $6\times OCH_3$), 3.33 (d, 2H, $J=3.2$ Hz, H-1″), 1.71, 1.66 (all s, 6H, $2\times CH_3$). ^{13}C NMR ($CDCl_3$): δ 196.8, 159.1, 155.6, 151.2, 149.1, 141.6, 141.4, 137.4, 132.5, 122.4, 119.9, 119.5, 114.9, 104.8, 97.0, 96.2, 95.7, 95.3, 94.5, 56.3, 56.1, 25.7, 25.6, 18.0. IR (KBr): 1651 cm^{-1} (C=C-C=O). HR-ESIMS: m/z $[M+H]^+$ calcd. for $C_{32}H_{45}O_{13}$: 637.2860. Found: 637.2873.

α-(3″,3″-Dimethylallyl)-4-methoxy-2′,4′,6′-*tris*(methoxymethoxy)chalcone (3e). Prepared as **3a** from **2** (50 mg, 0.14 mmol) and 4-methoxybenzaldehyde (33 μL, 0.27 mmol). Column chromatography (25% EtOAc in hexane) gave **3e** (30.7 mg, 46%, R_f 0.42) as a pale yellow gum. ^{1}H NMR ($CDCl_3$): δ 7.33 (dd, 2H, $J = 8.6$, 1.7 Hz, H-2, H-6), 7.22 (s, 1H, H-β), 6.87 (dd, 2H, $J = 8.6$, 1.7 Hz, H-3, H-5), 6.52 (s, 2H, H-3′, H-5′), 5.18 (t, 1H, $J = 4.0$ Hz, H-2″), 5.17, 5.09 (all s, 6H, $3 \times OCH_2O$), 3.82, 3.50, 3.37 (all s, 12H, $4 \times OCH_3$), 3.40 (d, 2H, $J = 4.0$ Hz, H-1″), 1.74, 1.73 (all s, 6H, $2 \times CH_3$). ^{13}C NMR ($CDCl_3$): δ 196.7, 160.0, 159.2, 155.4 (2C), 142.4, 140.8, 132.5, 131.5 (2C), 128.4, 122.1, 114.8, 113.9 (2C), 96.9 (2C), 94.6, 94.3 (2C), 56.24, 56.18 (2C), 55.3, 25.8, 25.5, 18.1. IR (KBr): 1649 cm^{-1} (C=C-C=O). HR-ESIMS: m/z $[M + H]^+$ calcd. for $C_{27}H_{35}O_8$. 487.2332. Found: 487.2346.

α-(3″,3″-Dimethylallyl)-2,4,5-trimethoxy-2′,4′,6′-*tris*(methoxymethoxy)-chalcone (3f). Prepared as **3a** from **2** (250 mg, 0.68 mmol) and 2,4,5-trimethoxybenzaldehyde (266 mg, 1.36 mmol). Column chromatography (30% EtOAc in hexane) gave **3f** (50.0 mg, 13%, R_f 0.25) as a yellow gum. ^{1}H NMR ($CDCl_3$): δ 7.48 (s, 1H, H-β), 7.05 (s, 1H, H-6), 6.54 (s, 2H, H-3′, H-5′), 6.45 (s, 1H, H-3), 5.23 (br t, 1H, $J = 4.1$ Hz, H-2″), 5.17, 5.10 (all s, 6H, $3 \times OCH_2O$), 3.89, 3.77, 3.71 (all s, 9H, $3 \times OCH_3$), 3.49, 3.40 (all s, 9H, $3 \times OCH_3$), 3.35 (d, 2H, $J = 4.1$ Hz, H-1″), 1.73, 1.68 (all s, 6H, $2 \times CH_3$). ^{13}C NMR ($CDCl_3$): δ 196.8, 159.1, 155.5 (2C), 152.7, 150.6, 142.6, 140.5, 138.4, 132.6, 123.3, 116.4, 115.0, 113.6, 97.0 (2C), 96.6, 94.6, 94.5 (2C), 56.3, 56.2 (2C), 56.1 (2C), 56.0, 25.8, 25.7, 18.3. IR (KBr): 1656 cm^{-1} (C=C-C=O). HR-ESIMS: m/z $[M + H]^+$ calcd. for $C_{29}H_{39}O_{10}$: 547.2543. Found: 547.2538.

General Procedure for the Preparation of Flavanones 4

Chalcones **3** were treated with 4 N HCl in refluxing MeOH for 8–15 h. After concentration, the mixture was extracted into EtOAc, washed with brine and water, and then concentrated again. The residue was purified by preparative TLC to afford **4**.

(2,3)-*cis* and (2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7,2′,4′-tetrahydroxyflavanone (4a). 4a, prepared from **3a** (18.5 mg, 0.032 mmol), was obtained as a yellow solid (2.5 mg, 22%, R_f 0.17, 5% MeOH in $CHCl_3$). IR (KBr): 3672 (OH), 3560-3300 (OH, br), 1637 (C=O) cm^{-1}. HR-ESIMS: m/z $[M + H]^+$ calcd. for $C_{20}H_{21}O_6$: 357.1338. Found: 357.1341.

(2,3)-*cis*-3-(3″,3″-Dimethylallyl)-5,7,2′,4′-tetrahydroxyflavanone (4a-I) ^{1}H NMR (acetone-d_6): δ 12.21 (s, 1H, OH-5), 7.36 (d, 1H, $J = 8.8$ Hz,

H-6′), 6.48 (d, 1H, $J = 2.2$ Hz, H-3′, overlap with H-3′ of **4a–II**), 6.46 (dd, 1H, $J = 8.8$, 2.2 Hz, H-5′), 6.05 (d, 1H, $J = 1.9$ Hz, H-8), 5.97 (d, 1H, $J = 1.9$ Hz, H-6), 5.75 (d, 1H, $J = 3.2$ Hz, H-2), 5.00 (t, 1H, $J = 6.6$ Hz, H-2″), 2.82–2.87 (m, 1H, H-3), 2.13–2.18 (m, 2H, H-1″), 1.53, 1.32 (all s, 6H, $2 \times CH_3$). ^{13}C NMR (acetone-d_6): δ 200.7, 167.2, 165.0, 164.4, 158.8, 155.5, 133.2, 128.5, 121.3, 116.0, 107.1, 103.1, 96.7, 95.4, 77.7, 49.3, 25.5, 25.1, 17.3.

(2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7, 2′,4′-tetrahydroxyflavanone (4a-II). ^{1}H NMR (acetone-d_6): δ 12.34 (s, 1H, OH-5), 7.19 (d, 1H, $J = 8.5$ Hz, H-6′), 6.48 (d, 1H, $J = 2.2$ Hz, H-3′, overlap with H-3′ of **4a-I**), 6.40 (dd, 1H, $J = 8.5$, 2.2 Hz, H-5′), 5.93 (d, 1H, $J = 2.2$ Hz, H-6), 5.89 (d, 1H, $J = 2.2$ Hz, H-8), 5.56 (d, 1H, $J = 11.0$ Hz, H-2), 5.10 (t, 1H, $J = 6.9$ Hz, H-2″), 3.30–3.35 (m, 1H, H-3), 2.45–2.52 (m, 1H, H-1″), 2.18–2.26 (m, 1H, H-1″), 1.59, 1.39 (all s, 6H, $2 \times CH_3$). ^{13}C NMR (acetone-d_6): δ 199.4, 167.2, 165.0, 164.1, 159.4, 157.2, 133.4, 130.2, 121.3, 115.9, 107.5, 103.3, 96.3, 95.2, 78.1, 49.3, 25.6, 25.1, 17.3.

(2,3)-*cis*- and (2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7,3′,4′-tetrahydroxyflavanone (4b). 4b, prepared from **3b** (45.5 mg, 0.079 mmol), was obtained as a yellowish brown solid (14.0 mg, 50%, R_f 0.26, 5% MeOH in $CHCl_3$). IR (KBr): 3670 (OH), 3560-3190 (OH, br), 1640 (C=O) cm^{-1}. HR-ESIMS: m/z $[M + H]^+$ calcd. for $C_{20}H_{21}O_6$: 357.1338. Found, 357.1143.

(2,3)-*cis*-3-(3″,3″-Dimethylallyl)-5,7,3′,4′-tetrahydroxyflavanone (4b-I) ^{1}H NMR (acetone-d_6): δ 12.18 (s, 1H, OH-5), 7.00 (d, 1H, $J = 2.0$ Hz, H-2′), 6.88 (d, 1H, $J = 8.0$ Hz, H-5′), 6.85 (overlap, 1H, H-6′), 6.04 (d, 1H, $J = 2.1$ Hz, H-8), 5.97 (d, 1H, $J = 2.1$ Hz, H-6), 5.58 (d, 1H, $J = 3.1$ Hz, H-2), 5.02 (t, 1H, $J = 7.2$ Hz, H-2″), 2.68–2.72 (m, 1H, H-3), 2.15–2.21 (m, 2H, H-1″), 1.55, 1.31 (all s, 6H, $2 \times CH_3$). ^{13}C NMR (acetone-d_6): δ 200.0, 166.9, 165.1, 163.3, 145.7, 145.4, 133.8, 129.4, 121.0, 118.1, 115.7, 113.8, 101.9, 96.6, 95.3, 81.2, 51.4, 25.5, 24.0, 17.2.

(2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7, 3′,4′-tetrahydroxyflavanone (4b–II). ^{1}H NMR (acetone-d_6): δ 12.28 (s, 1H, OH-5), 6.97 (d, 1H, $J = 2.0$ Hz, H-2′), 6.86 (overlap, 1H, H-5′), 6.81 (dd, 1H, $J = 8.0$, 2.0 Hz, H-6′), 5.93 (d, 1H, $J = 2.2$ Hz, H-6), 5.91 (d, 1H, $J = 2.2$ Hz, H-8), 5.16 (d, 1H, $J = 10.3$ Hz, H-2), 5.10 (t, 1H, $J = 7.2$ Hz, H-2″), 3.12 (dt, 1H, $J = 10.3$, 5.1 Hz, H-3), 2.48–2.55 (m, 1H, H-1″), 2.09–2.15 (m, 1H, H-1″), 1.62, 1.40 (all s, 6H, $2 \times CH_3$). ^{13}C NMR (acetone-d_6): δ 198.4, 167.1, 165.0, 163.3, 146.1, 145.7, 133.4, 130.2, 121.0, 120.1, 115.6, 115.3, 102.7, 96.4, 95.3, 82.9, 50.2, 25.6, 25.1, 17.5.

(2,3)-*cis*- and (2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7,4′-trihydroxyflavanone (4c). 4c, prepared from **3c** (32.0 mg, 0.062 mmol), was obtained as a yellowish brown solid (11.7 mg, 55%, R_f 0.18, 3% MeOH in $CHCl_3$). IR (KBr): 3670 (OH), 3540–3197 (OH, br), 1640

(C=O) cm^{-1}. HR-ESIMS: m/z $[M+H]^+$ calcd. for $C_{20}H_{21}O_5$: 341.1389. Found: 341.1394.

(2,3)-*cis*-3-(3″,3″-Dimethylallyl)-5,7,4′-trihydroxyflavanone (4c-I). ^1H NMR (acetone-d_6): δ 12.16 (s, 1H, OH-5), 7.33 (d, 2H, $J=8.8$ Hz, H-2′, H-6′), 6.90 (d, 2H, $J=8.8$ Hz, H-3′, H-5′), 6.03 (d, 1H, $J=2.1$ Hz, H-8), 5.95 (d, 1H, $J=2.1$ Hz, H-6), 5.61 (d, 1H, $J=3.0$ Hz, H-2), 4.99 (br t, 1H, $J=7.5$ Hz, H-2″), 2.66–2.71 (m, 1H, H-3), 2.12–2.22 (m, 2H, H-1″), 1.53, 1.28 (all s, 6H, $2\times CH_3$). ^{13}C NMR (acetone-d_6): δ 200.2, 167.1, 165.1, 163.2, 157.8, 133.4, 128.4, 127.7 (2C), 120.9, 115.7 (2C), 101.8, 96.6, 95.3, 81.2, 51.4, 25.4, 23.9, 17.1.

(2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7,4′-trihydroxyflavanone (4c-II). ^1H NMR (acetone-d_6): δ 12.27 (s, 1H, OH-5), 7.30 (d, 2H, $J=8.8$ Hz, H-2′, H-6′), 6.87 (d, 2H, $J=8.8$ Hz, H-3′, H-5′), 5.92 (d, 1H, $J=2.1$ Hz, H-6), 5.88 (d, 1H, $J=2.1$ Hz, H-8), 5.20 (d, 1H, $J=9.9$ Hz, H-2), 5.06 (br t, 1H, $J=7.5$ Hz, H-2″), 3.12–3.18 (m, 1H, H-3, hidden), 2.47–2.53 (m, 1H, H-1″), 2.12–2.18 (m, 1H, H-1″), 1.60, 1.35 (all s, 6H, $2\times CH_3$). ^{13}C NMR (acetone-d_6): δ 199.9, 167.3, 164.9, 163.3, 158.5, 133.7, 129.7 (2C), 129.2, 120.8, 115.6 (2C), 102.7, 96.4, 95.3, 82.8, 49.9, 25.5, 24.8, 17.4.

(2,3)-*cis*- and (2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7-dihydroxy-4′-methoxyflavanone (4e). 4e, prepared from **3e** (30.7 mg, 0.063 mmol), was obtained as a yellow gum (14.0 mg, 63%, R_f 0.46, 25% EtOAc in hexane). IR (KBr): 3632 (OH), 3500-3200 (OH, br), 1639 (C=O) cm^{-1}. HR-ESIMS: m/z $[M+H]^+$ calcd. for $C_{21}H_{23}O_5$: 355.1546. Found: 355.1549.

(2,3)-*cis*-3-(3″,3″-Dimethylallyl)-5,7-dihydroxy-4′-methoxyflavanone (4e-I). ^1H NMR ($CDCl_3$): δ 12.07 (s, 1H, OH-5), 7.33 (d, 2H, $J=8.8$ Hz, H-2′, H-6′), 6.94 (d, 2H, $J=8.8$ Hz, H-3′, H-5′), 6.03 (d, 1H, $J=1.9$ Hz, H-8), 6.01 (d, 1H, $J=1.9$ Hz, H-6), 5.52 (d, 1H, $J=2.9$ Hz, H-2), 4.96 (br t, 1H, $J=7.4$ Hz, H-2″), 3.83 (s, 3H, OCH_3), 2.64 (ddd, 1H, $J=8.8$, 5.7, 3.1 Hz, H-3), 2.20–2.25 (m, 1H, H-1″), 2.10–2.19 (m, 1H, H-1″), 1.57, 1.30 (all s, 6H, $2\times CH_3$). ^{13}C NMR ($CDCl_3$): δ 199.7, 164.8, 164.4, 162.6, 159.3, 134.2, 128.8, 127.0 (2C), 119.6, 113.9 (2C), 102.0, 96.7, 95.3, 80.7, 55.3, 51.2, 25.6, 23.5, 17.4.

(2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7-dihydroxy-4′-methoxyflavanone (4e-II). ^1H NMR ($CDCl_3$): δ 12.24 (s, 1H, OH-5), 7.29 (d, 2H, $J=8.7$ Hz, H-2′, H-6′), 6.91 (d, 2H, $J=8.7$ Hz, H-3′, H-5′), 5.97 (d, 1H, $J=2.0$ Hz, H-6), 5.92 (d, 1H, $J=2.0$ Hz, H-8), 5.21 (d, 1H, $J=9.7$ Hz, H-2), 5.03 (br t, 1H, $J=7.3$ Hz, H-2″), 3.82 (s, 3H, OCH_3), 3.04 (dt, 1H, $J=9.7$, 5.3 Hz, H-3), 2.52–2.60 (m, 1H, H-1″), 2.10–2.18 (m, 1H, H-1″), 1.65, 1.39 (all s, 6H, $2\times CH_3$). ^{13}C NMR ($CDCl_3$): δ 198.0, 164.9, 164.3, 162.4, 159.9, 134.5, 129.7, 128.8 (2C), 119.7, 114.0 (2C), 102.9, 96.5, 95.2, 81.9, 55.3, 49.8, 25.8, 24.9, 17.8.

(2,3)-*cis*- and (2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7-dihydroxy-2′,4′,5′-trimethoxyflavanone (4f). 4f, prepared from **3f** (50.0 mg, 0.092 mmol), was obtained as a yellow solid (19.7 mg, 52%, R_f 0.26, 10% MeOH in $CHCl_3$). IR (KBr): 3676 (OH), 3560–3190 (OH, br), 1640 (C=O) cm^{-1}. HR-ESIMS: m/z $[M+H]^+$ calcd. for $C_{23}H_{27}O_7$: 415.1757. Found: 415.1741.

(2,3)-*cis*-3-(3″,3″-Dimethylallyl)-5,7-dihydroxy-2′,4′,5′-trimethoxyflavanone (4f-I). ^{1}H NMR (acetone-d_6): δ 12.20 (s, 1H, OH-5), 7.23 (s, 1H, H-6′), 6.79 (s, 1H, H-3′), 6.06 (d, 1H, $J=2.2$ Hz, H-8), 5.98 (d, 1H, $J=2.2$ Hz, H-6), 5.75 (d, 1H, $J=2.9$ Hz, H-2), 4.93 (br t, 1H, $J=7.0$ Hz, H-2″), 3.86, 3.85 (hidden), 3.81 (all s, 9H, $3\times OCH_3$), 2.50–2.55 (m, 1H, H-3), 2.15–2.19 (m, 2H, H-1″, overlap with H-1″of **4f-II**), 1.52, 1.30 (all s, 6H, $2\times CH_3$). ^{13}C NMR (acetone-d_6): δ 200.3, 166.8, 165.2, 163.4, 150.8 (2C), 143.8, 133.2, 121.1, 116.9, 113.2, 101.7, 98.4, 96.7, 95.4, 77.3, 57.1, 56.2, 56.1, 50.7, 25.4, 24.5, 17.1.

(2,3)-*trans*-3-(3″,3″-Dimethylallyl)-5,7-dihydroxy-2′,4′,5′-trimethoxyflavanone (4f-II). ^{1}H NMR (acetone-d_6): δ 12.33 (s, 1H, OH-5), 7.11 (s, 1H, H-6′), 6.77 (s, 1H, H-3′), 5.94 (d, 1H, $J=2.2$ Hz, H-8), 5.89 (d, 1H, $J=2.2$ Hz, H-6), 5.60 (d, 1H, $J=11.5$ Hz, H-2), 5.03 (br t, 1H, $J=7.0$ Hz, H-2″), 3.87, 3.84, 3.76 (all s, 9H, $3\times OCH_3$), 2.75–2.80 (m, 1H, H-3), 2.15–2.19 (m, 2H, H-1″, overlap with H-1″of **4f-I**), 1.57, 1.32 (all s, 6H, $2\times CH_3$). ^{13}C NMR (acetone-d_6): δ 199.2, 167.0, 165.0, 164.0, 152.9, 151.5, 144.0, 137.0, 121.3, 117.2, 113.8, 102.6, 98.5, 96.3, 95.1, 77.5, 56.7, 56.4, 56.0, 49.3, 25.6, 24.5, 17.2.

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